Synthesis of Bis-γ-lactones from "Diacetone Glucose". 4.[1-3] Optically Active Avenaciolide and Isoavenaciolide†

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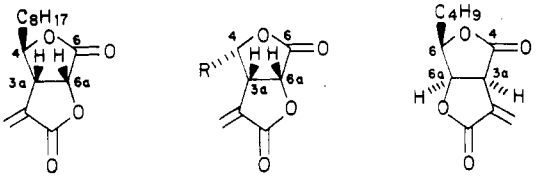
Full details are given on the use of "diacetone glucose" for the preparation of optically active avenaciolide (1). Two routes are outlined involving nine and ten steps, the corresponding yields being 5.2% and 14.5%, respectively. The syntheses show that the absolute configuration of naturally occurring levorotatory avenaciolide is 2*R*,3*R*,4*R*, in contradiction of the initial assignment. Isoavenaciolide (**2a**) has also been synthesized (3% overall from "diacetone glucose") and the absolute configuration of the naturally occurring levorotatory enantiomer has been corrected as being 2*R*,3*R*,4*S*. The latter synthesis reveals problems associated with the direct or indirect epimerization at C-4 of 3-ketofurano sugars and also reemphasizes the lack of uniformity in selective hydrolyses of 1,2:5,6-di-*O*-isopropylidenefuranoses.

Avenaciolide (1), an antifungal mold metabolite, was first isolated from *Aspergillus avenaceus* G. Smith by Brookes, Tidd, and Turner[4] and subsequently from *A. fischeri* var. *glaber* Fennell and Raper, by Ellis, Stodola, Vesonder, and Glass.[5] The former group determined the relative configuration by the use of degradative and spectroscopic techniques, and an assignment of absolute configuration was also made on the basis of a degradative study (vide infra). Subsequently, a minor metabolite was isolated



during the accumulation of stocks from *A. avenaceus*, whose structure was determined to be 4-isoavenaciolide (**2a**).[6] The molecule was levorotatory, and an assignment of absolute stereochemistry was made on the basis of comparisons with avenaciolide (**1**). A similar assignment was made for ethisolide **2b**[6] which had been isolated from an unidentified penicillium species. *Penicillum canadense* also yielded a metabolite, **3**, termed canadensolide,[7] which, being a bis-γ-lactone, is reminiscent of **1**, **2a**, and **2b**.

At the outset of our work, two syntheses[8,9] of racemic avenaciolide (**1**) had been published.[10] Routes to optically active modifications from "diacetone glucose" **4a**[11] were carried out independently by Ohrui and Emoto[12] and ourselves.[1] Brookes et al.[4] had assigned the configuration of naturally occurring (−)-avenaciolide as 2*S*,3*S*,4*S* on the basis of which we expected that our proposed synthesis would have given the unnatural (+) enantiomer. This turned out *not* to be the case,[1] and it is an indication of the versatility of diacetone glucose as a synthon that *both* (+) and (−) enantiomers of avenaciolide were prepared from it by Ohrui.[12] In light of this misassignment, a reexamination of other members of the family was necessary since their absolute stereochemistries had been assigned in relation to the forerunner, avenaciolide. In this and the accompanying[13] manuscript we give complete details of our synthetic studies on avenaciolide (**1**), isoavenaciolide (**2**), and canadensolide.

Results and Discussion

Our synthetic target was the bis-lactone **7b**, the racemic form of which had featured in Johnson's synthesis.[8b] The starting material chosen for initial examination was the known aldehydic ester **5a**,[14] whose conversion to the *cis*-alkene **5b** [$J_{5,6}$ = 10.7 Hz] was found to be dependent on the solvent [THF (70%), diethyl ether (29%), THF/Me_2SO 4:1 (66%)]. Hydrogenation to **6a** followed by hydrolysis led directly to lactol **7a**, which could be oxidized either by Collins'[15] (63%) or Jones' reagent[16] (77%) to give the target intermediate **7b** as an oil, the ^1H NMR and IR data of which were in excellent agreement with those of the authentic racemic material obtained from Professor Johnson.[8]

α-Methylenation of **7b** according to the published procedure[8b] then afforded avenaciolide (**1**), which was identical with a sample of the naturally occurring material in every respect—*including optical rotation*, $[\alpha]_D$ −41°. Since the

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(11) Compound **4a** (1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose) is commercially available. For preparation, see: Schmidt, O. T. In "Methods in Carbohydrate Chemistry"; Whistler, R. L., Wolfrom, M. L., Eds.; Academic Press Inc.: New York, 1963; Vol 2, p 318.
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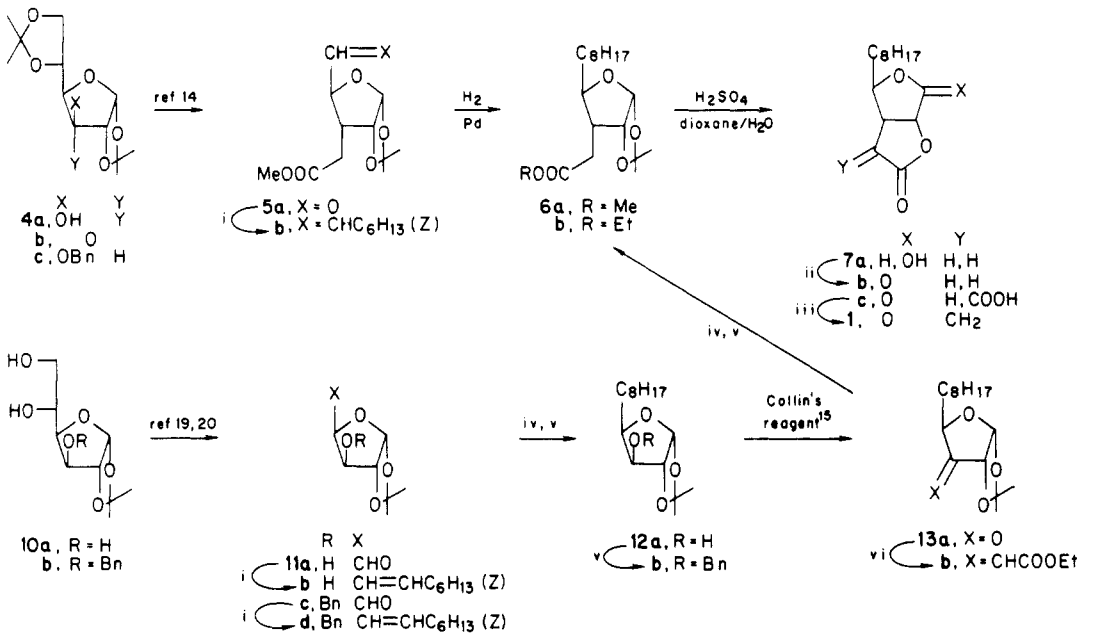
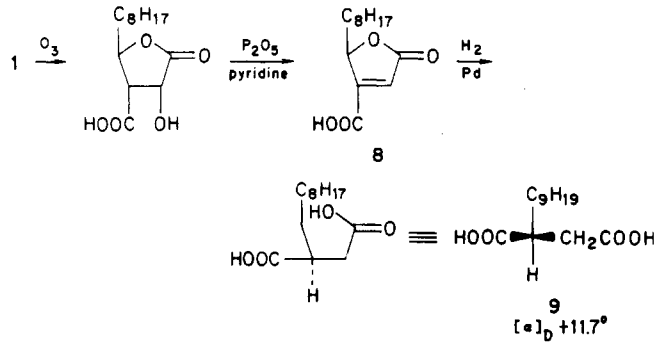
Scheme I[a]



[a] (i) n-$C_6H_{13}CH{=}PPh_3$, THF (70–80%); (ii) Jones' reagent[16] (77%); (iii) ref 8b; (iv) stir with Raney nickel in EtOH; (v) H_2/Pd; (vi) $Ph_3P{=}CHCOOEt$.

Scheme II[4]



synthetic plan in Scheme I must have provided the 2*R*,3*R*,4*R* enantiomer unambiguously, we had in fact prepared the naturally occurring modification, which meant that the original assignment[4] was incorrect.

At this point, an account of the manner in which the optical rotation had been originally assigned is warranted. Brooks et al. had degraded avenaciolide as indicated in Scheme II. The crucial reaction was the hydrogenation of the double bond in **8** which was assumed, reasonably, to occur anti to the *n*-octyl side chain, leading to what was said to be dextrorotatory nonylsuccinic acid, **9**. Fredga[17] had examined a number of alkyl succinic acids and found that the *R* enantiomers were all dextrorotatory and hence it was concluded that levorotatory avenaciolide was 2*S*,3*S*,4*S*.

Our studies do not pinpoint the source of the error in the foregoing assignment.

In spite of the brevity of the route outlined in Scheme Ia, there was a major operational problem. In our hands, the oxidation of "diacetone glucose" to ketone **4b** was, at that time, problematic. (For an excellent new procedure for carrying out this oxidation (96% yield), see the recent work of Anderson and Samuelsson.[18]) In the course of our studies we had found that the C4-alkyl derivatives did not suffer these problems, and hence the plan outlined in Scheme Ib was designed in which the olefinations at C3 and C5 were carried out in the reverse order to that shown in Scheme Ia.

By use of 2 equiv of the ylide; the hydroxy aldehyde **11a**[19] (readily available via triol **10a**) could be converted into the olefin **11b** in 78% yield. However, there were difficulties in isolation (a) because **11a** is a thick intractable syrup and (b) because the second equivalent of ylide made chromatographic purification of the product tedious. Hence for large-scale work, the 3-*O*-benzyl analogue **11c**[20] proved a more amenable precursor.

The transformations shown in Scheme Ib require no comment except for the hydrogenation of the olefinic products **11d** and **13b** which initially proved to be very difficult. However, we found that the reaction proceeded much more rapidly if the product of the Wittig reaction was stirred first with Raney nickel [presumably to remove traces of phosphorus impurities] prior to the hydrogenation with the palladium catalyst. Compound **6b** obtained in Scheme Ib was similar to the previously described ester **6a** in all respects except for the signals due to the ethyl instead of the methyl ester.

In view of the foregoing studies on avenaciolide (**1**), the assignment of absolute stereochemistry for isoavenaciolide (**2a**), which had been based on comparisons of data,[6] had to be questioned. Two syntheses of racemic isoavenaciolide had been reported when our work was initiated. The first, patterned after Parker and Johnson's avenaciolide synthesis,[8] was by Yamada and co-workers[21] and the second, a succinct endeavor, was by Schlessinger's group.[22]

We had hoped to utilize intermediates **13a** and **13b** which offer the possibility of epimerization at C-4. How-

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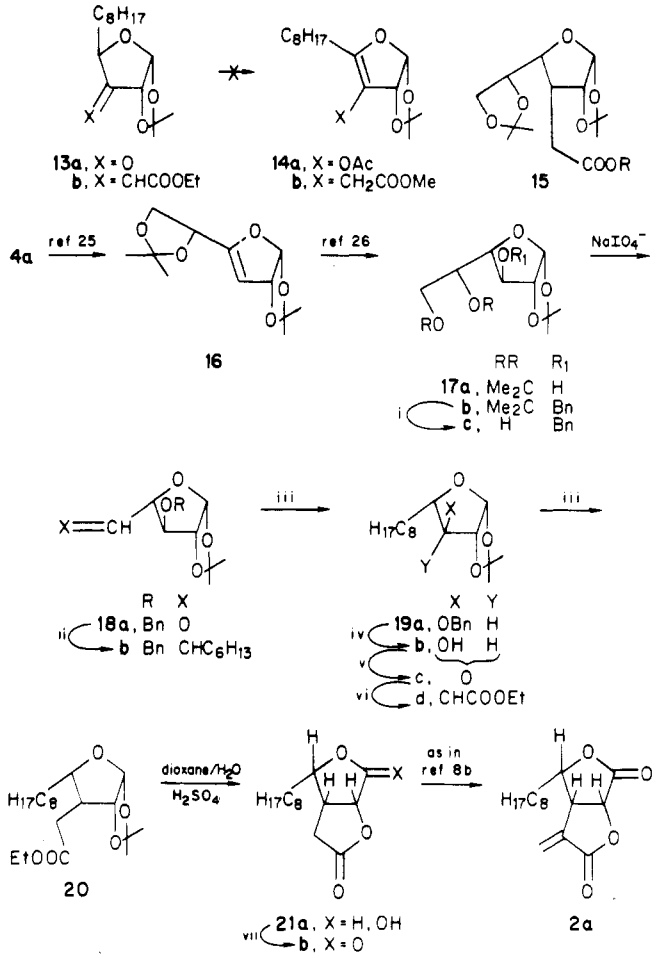
Scheme III[a]



[a] (i) HOAc/H_2O (80%); (ii) *n*-$C_6H_{13}CH$=PPh (65%); (iii) stir with Raney nickel in EtOH, then H_2/Pd; (iv) H_2/Ni (quantitative); (v) Collins' reagent[15] (47%); (vi) Ph_3P=CHCOOEt (75%); (vii) Jones' reagent[16] (74%).

ever, treatment of **13a** with sodium methoxide caused gross decomposition, and we therefore tried an indirect route which had been used for **4b**, by hydrogenation of the corresponding enol acetate.[23] However, we were unable to prepare the enol acetate **14a** from **13a** (Scheme III) by means of the procedure that had succeeded in the case of **4b**.[23] Deconjugation of ester **13b** to give **14b** was also unsuccessful in spite of the excellent precedent by Tronchet and co-workers[24] for a cyano analogue of **13b**.

As a result of these failures, "diacetone galactose" **17a**[25,26] (Scheme III) was examined. The sequence of the subsequent alkylations was crucial. Thus we found that if the C3 substituent was introduced first, thereby affording the D-*gulo* derivative **15**, selective hydrolysis of the 5,6-*O*-isopropylidene ring was difficult. (Similar problems with other D-*gulo* analogues have been observed.[27]) Accordingly, the 3-*O*-benzyl-D-*galacto* derivative **17b** was prepared, and as expected from the literature,[28] hydrolysis proceeded smoothly and the resulting diol **17c** was cleaved with sodium metaperiodate. Epimerization at C4 of the resulting aldehyde **18a** had not occurred, since the product had a different NMR spectrum and optical rotation from the material, **11c**, shown in Scheme IIb.

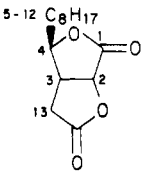
The synthetic pathway developed in Scheme IIb for avenaciolide was then applied to **18a**, the stereochemical integrity of the potentially vulnerable intermediates being ascertained by comparison of NMR data and optical rotations of the corresponding epimers described above. The standard processing of ester **20** led to lactone **21b**, known hitherto in racemic form,[5] and α-methylenation afforded isoavenaciolide which proved to be levorotatory.

In conclusion, syntheses of avenaciolide (**1**) from "diacetone glucose" have been achieved by two routes in 5.2% and 14.5% yield, respectively, and the naturally occurring levorotatory enantiomer is established to be of 2*R*,3*R*,4*R* configuration. Natural (−)-isoavenaciolide (**2a**) was synthesized in 3% overall yield from diacetone glucose and its absolute configuration has been shown to be 2*R*,3*R*,4*S*.

Experimental Section

Melting points were determined in capillary tubes and are uncorrected. Nuclear magnetic resonance (NMR) spectra were determined, unless otherwise stated, in $CDCl_3$ containing 1% tetramethylsilane (Me_3Si) as internal standard. Coupling constants were obtained by measuring the spacings of spectra judged to be first order. Infrared (IR) spectra were determined by using 0.1-mm sodium chloride cells and $CHCl_3$ as solvent. The progress of reactions was monitored by thin layer chromatography (TLC) which was performed on 2.0 cm × 6.6 cm aluminum sheets precoated with silica gel 60 to a thickness of 0.25 mm. The following solvent systems were used to develop the plates. Et_2O–PhH mixtures: A (1:9); B (1:1); C (1:4); D (1:3); E (3:7). EtOAc–petroleum ether (30–60 °C) mixtures: F (1:1); G (1:4); H (1:9); I (2:3). The chromatograms were viewed under an ultraviolet light, sprayed with concentrated sulfuric acid, and briefly heated with a hot-air gun. For column chromatography, silica gel was used. Preparative thick layer chromatography (PTLC) was done on glass plates (20 cm × 20 cm) coated with silica gel to a depth of 2.0 mm.

For the purpose of NMR interpretation, the following numbering scheme has been adopted:



Standard Procedure for Wittig Reaction on Aldehydes. A dried three-necked, round-bottomed flask was fitted with a rubber serum cap, a vacuum adapter equipped with a stopcock, a magnetic stirring bar, and a glass stopper. The flask was then charged with dry solvent (about 15 mL/g of carbonyl compound) and the appropriate Wittig salt (the number of molar equivalents will be specified). The suspension was stirred and the flask was successively evacuated and flushed with either dry nitrogen or argon. *n*-Butyllithium (1 mol/mol of Wittig salt) was then injected via syringe and the resultant mixture was stirred for 0.5 h by which time a colored solution had formed. The carbonyl compound was dissolved in the same solvent (about 2 mL/g of substrate) and slowly injected into the reaction flask through the serum cap. The reaction mixture was then allowed to stir at room temperature for 1.5 h at which point it was quenched by the addition of a small amount of water. The solvents were then evaporated and the residue was processed in the usual way to give a semisolid mass, which was chromatographed on a silica gel column. The particular solvent system is specified in each case.

Standard Hydrogenation and Hydrogenolysis. The hydrogenations were accomplished in absolute EtOH (200 mL) on a Parr hydrogenator with 50 psi of hydrogen. The catalyst will be specified. The reaction mixture was filtered through Celite and the filtrate was evaporated, and the resulting residue was processed in the usual manner to give the desired product.

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3-*C*-(Carbomethoxymethyl)-6-*C*-(*n*-hexyl)-1,2-*O*-isopropylidene-3,5,6-trideoxy-α-D-*ribo*-hex-5(*Z*)-enofuranose (5b). (a) Using the standard Wittig reaction procedure (see General Methods), 3-*C*-(carbomethoxymethyl)-3-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose (**5a**)[14] (250 mg, 1.02 mmol) was treated with n-$C_6H_{13}CH{=}PPh_3$[29] (1.2 equiv) in THF to give a residue from which crystalline **5b** (257 mg, 70%) was isolated after column chromatography (solvent A). After recrystallization from *n*-pentane: TLC R_f 0.41 (A); mp 60.0–60.5 °C; $[\alpha]^{23}_D$ −31.8° (*c*, 1.05 in $CHCl_3$); IR ν_{max} 1735 (saturated ester), 1438, 1375, 1328, 1162, 1012, 865 cm^{-1}; 220-MHz ^{1}H NMR δ 0.89 (m, 3, CH_2CH_3), 1.31 (m, 8, -$(CH_2)_4$-), 1.32 (s, 3, $C(CH_3)_2$), 1.36 (s, 3, $C(CH_3)_2$), 1.95–2.18 (m, 3, CH=CH—CH_2, H-3), 2.27 (dd, 1, $J_{13a,13b}$ = 17.0 Hz, $J_{3,13b}$ = 4.0 Hz, H-13b), 2.51 (dd, 1, $J_{3,13a}$ = 10.7 Hz, H-13a), 3.68 (s, 3, CO_2CH_3), 4.42 (t, 1, $J_{3,4}$ = 4.9 Hz, $J_{4,5}$ = 9.5 Hz, H-4), 4.65 (t, 1, $J_{2,3}$ = 4.0 Hz, H-2), 5.23 (ddt, 1, $J_{5,6}$ = 10.7 Hz, $J_{5,7}$ = 1.5 Hz, H-5), 5.68 (dt, 1, $J_{6,7ab}$ = 7.0 Hz, H-6), 5.70 (d, 1, $J_{1,2}$ = 3.75 Hz, H-1). Anal. Calcd. for $C_{18}H_{30}O_5$: C, 66.23; H, 9.26. Found: C, 66.29; H, 9.42.

Use of Et_2O and THF–Me_2SO (4:1) as solvents afforded compound **5b** in 29% and 66% yields, respectively.

3-*C*-(Carbomethoxymethyl)-3,5-dideoxy-5-*C*-(*n*-heptyl)-1,2-*O*-isopropylidene-α-D-ribofuranose (6a). The alkene **5b** (312 mg, 0.956 mmol) was hydrogenated (see General Methods) to give **6a** (272 mg, 87%) as a homogeneous oil: TLC R_f 0.75 (B); $[\alpha]^{23}_D$ +87.0° (*c*, 1.01 in $CHCl_3$); IR ν_{max} 1735 (saturated ester), 1438, 1372, 1162, 1010, 868 cm^{-1}; MS, *m/e* 328 (M^+), 327 (M^+ – 1), 313 ($M^+ - CH_3$), 253 ($M^+ - CH_3$ – HOAc); 60-MHz ^{1}H NMR δ 0.66–1.00 (m, 3, CH_2CH_3), 1.16–1.40 (br s, 17, $C(CH_3)_2$, -$(CH_2)_7$-), 1.44 (s, 3, $C(CH_3)_2$), 1.8–2.8 (m, 3, $CH_2CO_2CH_3$, H-3), 3.6–4.0 (m, 1, H-4), 3.68 (s, 3, CO_2CH_3), 4.76 (t, 1, $J_{1,2}$ = 4.0 Hz, H-2), 5.85 (d, 1, H-1).

5-Deoxy-5-*C*-(*n*-heptyl)-1,2-*O*-isopropylidene-α-D-xylofuranose (12a). Using the standard Wittig procedure (see General Methods), the aldehyde **11a**[19] (1.0 g, 5.3 mmol) was converted into **11b** (as described for **5b**) as a mixture of isomers (1.1 g, 78%) [R_f 0.55, 0.50 (F)], which with standard hydrogenation over 10% Pd/C gave **12a** as an oil in quantitative yield: TLC R_f 0.30 (G); $[\alpha]^{22}_D$ −13.0° (*c*, 2.49 in $CHCl_3$); IR ν_{max} 3400 (OH), 1462, 1580, 1162, 1070, 1010 cm^{-1}; MS, *m/e* 257 ($M^+ - CH_3$), 197 ($M^+ - CH_3$, HOAc), 179 ($M^+ - CH_3$, HOAc, H_2O): 60-MHz ^{1}H NMR δ 0.65–1.10 (m, 3, $(CH_2)_7CH_3$), 1.33 (m 17, $C(CH_3)_2$, $(CH_2)_7$, 1.52 (s, 3, $C(CH_3)_2$), 4.0–4.4 (m, 2, H-3,4), 4.53 (d, 1, H-2), 5.90 (s, 1, $J_{1,2}$ = 4.0 Hz, H-1).

3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose (11c). 3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**10c**)[20] (40 g, 130 mmol) was dissolved in dioxane (300 mL) and a solution of sodium metaperiodate (33 g, 155 mmol) in water (300 mL) was added. The reaction mixture was placed on a shaker for 2 h and then filtered. The filtrate was extracted twice with CH_2Cl_2 (500 mL, 200 mL), and the combined organic fractions were washed with water (300 mL) and dried (Na_2SO_4). Evaporation of the solvent and azeotropic drying of the residue for 3 h in a Dean–Stark trap using toluene gave **11c** as an oil (36 g, 100%): TLC R_f 0.5 (F); $[\alpha]^{20}_D$ −29.3° (*c*, 3.38 in $CHCl_3$); IR ν_{max} 1735 (aliphatic aldehyde), 1450, 1372, 1158, 880, 850 cm^{-1}; MS, *m/e* 263 ($M^+ - CH_3$), 249 (M^+ – CHO); 220-MHz ^{1}H NMR δ 1.30 (s, 3, $C(CH_3)_2$), 1.45 (s, 3, $C(CH_3)_2$), 4.33 (d, 1, $J_{3,4}$ = 4.25 Hz, H-3), 4.6 (d, AB q, $J_{A,B}$ = 12 Hz, CH_2Ph), 4.50–4.63 (m, 1, H-4), 4.59 (d, AB q, 1, CH_2Ph), 4.64 (d, 1, $J_{1,2}$ = 3.75 Hz, H-2), 6.11 (d, 1, H-1), 7.27 (s, 5, CH_2Ph), 9.64 (d, 1, J = 1.5 Hz, CHO).

3-*O*-Benzyl-5,6-dideoxy-6-*C*-(*n*-hexyl)-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (11d). Using the standard Wittig reaction procedure (see General Methods) the aldehyde **11c**[20] (5 g, 18.0 mmol) in DME was converted into **11d** as described for **5b**. Column chromatography (H) gave **11d** (5.0 g, 77%) as an oil: TLC R_f 0.55 (G); IR ν_{max} 1455, 1378, 1160, 1070, 1020, 880, 860 cm^{-1}; MS, *m/e* 359 (M^+ – 1), 345 ($M^+ - CH_3$), 327, 302, 231, 91 (tropylium); 220-MHz^1 NMR δ 0.87 (t, 3, $(CH_2)_5CH_3$), 1.27 (s, 8, -$(CH_2)_4$-), 1.34 (s, 3, $C(CH_3)_2$), 1.52 (s, 3, $C(CH_3)_2$, 2.09 (t, 2, CH=CH—CH_2), 3.82 (d, 1, $J_{3,4}$ = 3.0 Hz, H-3), 4.56 (d, AB q, 1, J_{AB} = 11.75 Hz, $PhCH_AH_B$), 4.63 (d, 1, H-2), 4.65 (d, AB q, 1, $PhCH_AH_B$), 4.94 (q, 1, $J_{4,5}$ = 7.5 Hz, H-4), 5.61–5.78 (m, 2, H-5, 6), 5.96 (d, 1, $J_{1,2}$ = 3.75 Hz, H-1), 7.31 (s, 5, $PhCH_2$-).

3-*O*-Benzyl-5-deoxy-*C*-(*n*-heptyl)-1,2-*O*-isopropylidene-α-D-xylofuranose (12b). Standard hydrogenation (see General Methods) of alkene **11d** (4.8 g, 13.3 mmol) with Raney nickel gave oily **12b** in quantitative yield: TLC R_f 0.36 (H); $[\alpha]^{22}_D$ −43.3° (*c*, 3.03 in $CHCl_3$); IR ν_{max} 1452, 1382, 1372, 1159, 1063, 1008, 880, 850 cm^{-1}; MS, *m/e* 362 (M^+), 361 (M^+ – 1), 347 ($M^+ - CH_3$), 91 (tropylium); 220-MHz ^{1}H NMR δ 0.27 (t, 3, $(CH_2)_7CH_3$), 1.05–1.43 (s, 15, $C(CH_3)_2$, -$(CH_2)_6$-), 1.48 (s, 3, $C(CH_3)_2$), 1.59–1.82 (m, 2, -(CH_2)-), 3.78 (d, 1, $J_{3,4}$ = 2.5 Hz, H-3), 4.12 (dt, 1, $J_{4,5}$ = 7.0 Hz, H-4), 4.48 (d, AB q, 1, $J_{A,B}$ = 12.75 Hz, $PhCH_AH_B$), 4.62 (d, 1, H-2), 4.71 (d, AB q, 1, $PhCH_AH_B$), 5.55 (d, 1, $J_{1,2}$ = 3.75 Hz, H-1), 7.30 (s, 5, $PhCH_2$).

5-Deoxy-5-*C*-(*n*-heptyl)-1,2-*O*-isoproylidene-α-D-*erythro*-pentofuran-3-ulose (13a). Under standard hydrogenolysis with 10% Pd/C (see General Methods), the benzyl ether **12b** (3.5 g, 9.67 mmol) was reductively cleaved to give the alcohol **12a** (2.6 g, 100%) as an oil (2.07 g, 7.61 mmol) which was dissolved in dry CH_2Cl_2 (100 mL) and Collins' reagent[15] (12 g) was added. After being shaken for 8 h, the mixture was poured into anhydrous Et_2O (600 mL) and filtered through Florisil and Celite. The filtrate was concentrated (300 mL) was washed with 3 N HCl (3 × 75 mL) and saturated $NaHCO_3$ solution (100 mL). The organic layer was dried (Na_2SO_4) and evaporated to give an oily residue which was passed through a small silica gel column with Et_2O as eluant. Ketone **13a** was obtained as an oil (1.66 g, 80%): TLC R_f 0.61 (E); $[\alpha]^{20}_D$ +111.3° (*c*, 2.46 in $CHCl_3$); IR ν_{max} 1780 (ketone), 1460, 1380, 1155, 865 cm^{-1}; MS, *m/e* 255 ($M^+ - CH_3$); 60-MHz ^{1}H NMR δ 0.65–1.10 (m, 3, $(CH_2)_7CH_3$), 1.25 (s, 14, -$(CH_2)_7$-), 1.38 (s, 3, $C(CH_3)_2$), 1.48 (s, 3, $C(CH_3)_2$), 4.32 (d, 2, H-2,4), 6.05 (d, 1, $J_{1,2}$ = 4.0 Hz, H-1).

3-(*E,Z*)-*C*-(Carbethoxymethylene)-3,5-dideoxy-5-*C*-(*n*-heptyl)-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose (13b). The ketone **13a** (568.1 mg, 2.10 mmol) was dissolved in acetonitrile (925 mL) and (carbethoxymethylene)triphenylphosphorane (878 mg, 2.52 mmol) was added. The reaction mixture was placed on a shaker for 4 h at which time the solvent was evaporated to give an oily residue. Processing of the residue in the usual manner afforded an oil (465 mg, 65%) which consisted of the α,β-unsaturated esters **13b**. The isomers, which were separated by PTLC (G), gave the following data. **Isomer 1**: TLC R_f 0.64 (G); 100 mg (14%); $[\alpha]^{20}_D$ +149.8° (*c*, 3.03 in $CHCl_3$); IR ν_{max} 1710 (conjugated ester), 1458, 1372, 1152, 1015, 860 cm^{-1}; MS, *m/e* 325 ($M^+ - CH_3$), 311, 283, 265 ($M^+ - CH_3$, HOAc), 227 ($M^+ - C_8H_{17}$), 169; 60-MHz ^{1}H NMR δ 0.65–1.10 (m, 3, $(CH_2)_7CH_3$), 1.30 (s, 20, -$CH_2)_7$-, OCH_2CH_3, $C(CH_3)_2$), 1.42 (s, 3, $C(CH_3)_2$), 4.23 (q, 2, OCH_2CH_3), 5.00–5.10 (m, 1, H-2), 5.40–5.70 (m, 1, H-4), 5.90 (d, 1, $J_{1,2}$ = 4.5 Hz, H-1), 6.10 (t, 1, $J_{allylic}$ = 2 Hz, vinyl proton). **Isomer 2**: TLC R_f 0.53 (G); 365 mg (51%); $[\alpha]^{20}_D$ +151.7° (*c*, 3.05 in $CHCl_3$); IR ν_{max} 1720 (conjugated ester), 1458, 1375, 1150, 1020, 865 cm^{-1}; MS, *m/e* 325 ($M^+ - CH_3$), 311, 283, 265 ($M^+ - CH_3$, HOAc), 227 ($M^+ - C_8H_{17}$); 60-MHz ^{1}H NMR δ 0.65–1.10 (m, 3, $(CH_2)_7CH_3$), 1.33 (s, 17, -$(CH_2)_7$-, OCH_2CH_3), 1.43 (s, 3, $C(CH_3)_2$), 1.50 (s, 3, $C(CH_3)_2$), 4.23 (q, 2, OCH_2CH_3), 4.6–5.2 (m, 2, H-2,4), 5.6–5.9 (m, 2, vinyl proton, H-1).

3-*C*-(Carbethoxymethyl)-3,5-dideoxy-5-*C*-(*n*-heptyl)-1,2-*O*-isopropylidene-α-D-ribofuranose (6b). Standard hydrogenation with 10% Pd/C (See General Methods) of **13b** (154 mg, 0.453 mmol) gave ester **6b** (147 mg, 95%) as the only product detectable by TLC and NMR: TLC R_f 0.50 (G); $[\alpha]^{20}_D$ +50.1° (*c*, 3.97 in $CHCl_3$); IR ν_{max} 1730 (saturated ester), 1455, 1372, 1330, 1160, 1010, 865 cm^{-1}; MS, *m/e* 327 ($M^+ - CH_3$), 267 ($M^+ - CH_3$, HOAc), 239, 221, 171; 60-MHz ^{1}H NMR δ 0.65–1.10 (m, 3, $(CH_2)_7CH_3$), 1.10–1.43 (q, 20, -$(CH_2)_7$-, OCH_2CH_3, $C(CH_3)_2$), 1.50 (s, 3, $C(CH_3)_2$), 1.95–2.8 (m, 3, H-3, CH_2CO_2Et), 3.6–4.0 (m, 1, H-4), 4.17 (q, 2, OCH_2CH_3), 4.73 (t, 1, $J_{2,3}$ = 4.5 Hz, H-2), 5.79 (d, 1, $J_{1,2}$ = 4.5 Hz, H-1).

3-*C*-(Carboxymethyl)-3,5-dideoxy-5-*C*-(*n*-heptyl)-α-D-ribofuranose 2,3-δ-Lactone (7a). The acetonide **6a** or **6b** (291.5 mg, 0.888 mol) was dissolved in *p*-dioxane (15.8 mL), and 2% aqueous sulfuric acid (6.2 mL) was added. The mixture was refluxed for 2 h at which point TLC (solvent B) showed that the reaction was complete. After cooling, the reaction mixture was diluted with Et_2O (150 mL), and the organic layer was then washed with water (2 × 15 mL) and saturated $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated to give crystalline **7a** (216 mg, 95%).

(29) Wittig, G.; Haag, W. *Chem. Ber.* **1955**, *88*, 1654.

Compound **7a** was recrystallized from methanol: mp 73.5–74.0 °C; TLC R_f 0.5 (B); $[\alpha]^{23}_C$ −59.05° (*c*, 1.12 in $CHCl_3$); IR ν_{max} 3610 (OH free), 3380 (OH, H bonded), 1788 (γ-lactone), 1155, 1040 cm^{-1}; MS, *m/e* 25 ($M^+ + 1$), 239 ($M^+ + 1 - H_2O$); 60-MHz ^1H NMR δ 0.66–1.06 (m, 3, $-(CH_2)_7CH_3$), 1.06–1.66 (s, 14, $-(CH_2)_7-$), 2.20–3.20 (m, 3, $-CH_2CO_2$, H-3), 3.40–4.20 (m, 1, H-4), 4.92 (d, 1, $J_{2,3}$ = 6 Hz, H-2), 5.46–5.66 (s, 1, H-1). Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.50; H, 9.47.

3-*C*-(Carboxymethyl)-3,5-dideoxy-5-*C*-(*n*-heptyl)-D-ribono-1,4-lactone 2,3-γ-Lactone (7b). (a) The hemiacetal **7a** (114.2 mg, 0.445 mmol) was dissolved in methylene chloride (30 mL) and Collins' reagent[15] (500 mg) was added. The heterogeneous reaction mixture was then shaken for 0.75 h at which time it was diluted with Et_2O (200 mL) and filtered through Celite. The filtrate was then evaporated to a volume of approximately 50 mL, washed with 3 N HCl (2 × 30 mL) and saturated $NaHCO_3$ solution (30 mL), dried over sodium sulfate containing decolorizing carbon, and filtered again through Celite. Evaporation of the solvent gave **7b** (88 mg, 63%) as an oil.

(b) The hemiacetal **7a** (36.5 mg, 0.143 mmol) was dissolved in acetone (2 mL), and Jones' reagent[16] (0.1 mL) was added with stirring. After 5 min, more Jones' reagent (0.1 mL) was added and stirring was continued for another 10 min at which time the reaction was quenched with methanol (5 mL). The reaction mixture was then diluted with Et_2O (30 mL) and water (20 mL). The organic layer was separated, washed with saturated $NaHCO_3$ solution (5 mL) and water (2 × 10 mL), and dried (Na_2SO_4). Evaporation of the solvent gave **7b** (27.7 mg, 77%) as an oil: TLC R_f 0.23 (97.5:2.5, C_6H_6–CH_3OH); $[\alpha]^{23}_D$ +204.85° (*c*, 1.01 in $CHCl_3$); IR ν_{max} 1795 (γ-lactones), 1460, 1243, 1140, 1071, 970 cm^{-1}; 60-MHz ^1H NMR γ 0.66–1.66 (m, 3, $(CH_2)_7CH_3$), 1.66–1.80 (s, 14, $-(CH_2)_7-$), 2.2–3.2 (m, 3, $-CH_2CO_2-$, H-3), 4.1–4.5 (m, 1, H-4), 5.00 (d, 1, $J_{2,3}$ = 7 Hz, H-2).

The IR and NMR data described above were in good agreement with those obtained from the racemic analogue prepared by Parker and Johnson.[8]

3-*C*-(Carboxymethylenemethyl)-3,5-dideoxy-5-*C*-(*n*-heptyl)-D-ribono-1,4-lactone 2,3-γ-Lactone ((−)-Avenaciolide (1)). The bis-lactone **7b** (1 g, 3.9 mmol) was dissolved in a 2.5 M solution of methyl methoxymagnesium carbonate[30] in DMF (20 mL) and heated under dry nitrogen for 5 h at 112 °C. The reaction mixture was poured into ice cold 6 N HCl and Et_2O and shaken until all of the precipitated solids had dissolved. The organic layer was then washed with water and dried (Na_2SO_4). Evaporation of the solvent gave **7c** as an oil that was used directly in the next step. Sodium acetate (1.0 g) was dissolved in acetic acid (40 mL) and mixed with a solution of formalin (29.2 mL) and diethylamine (10 mL). A portion of this solution (10 mL) was added to the oily bis-lactonic acid **7c** obtained above. This mixture was then heated on a steam bath for 5 min, cooled, and poured into diethyl ether and water. The organic layer was separated, washed with water, and dried (Na_2SO_4). Evaporation gave an oil that was chromatographed on a silica gel column (solvent A) to give crystalline 1 (651 mg, 63% from **7b**) which, after recrystallization from ether–pentane, gave the following data: mp 50–51 °C (lit.[4] mp 49–50 °C and 54–56 °C); TLC R_f 0.55 (B); $[\alpha]^{29.5}_D$ −41.07° (*c*, 0.274 in ethanol[31] (lit.[4] $[\alpha]^{26.5}_D$ −41.6° (*c*, 1.2)); IR ν_{max} 1795 (γ-lactones), 1465, 1295, 1100, 1061, 955 cm^{-1}; 60-MHz ^1H NMR δ 0.66–1.66 (m, 3, $-(CH_2)_7CH_3$), 1.66–2.0 (s, 14, $-(CH_2)_7-$), 3.2–3.8 (m, 1, H-3), 4.3–4.7 (m, 1, H-4), 5.12 (d, 1, $J_{2,3}$ = 8.5 Hz, H-2), 5.92 (d, 1, J_{gem} = 2.5 Hz, H-b), 6.48 (d, 1, H-a). This data is in excellent agreement with that for natural (−)-avenaciolide.[4] Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.76; H, 8.35.

1,2:5,6-Di-*O*-isopropylidene-α-D-galactofuranose (17a). To a cold (0 °C) solution of the olefin **16**[25,26] (17.40 g, 71.9 mmol) in dry THF (100 mL), a THF solution of diborane (86.3 mL, 8.63 mmol) was slowly added. After 4 h a mixture of 2 N NaOH (30.96 mL) and 30% H_2O_2 (13.76 mL) was carefully added, and the reaction mixture was allowed to warm to room temperature. The solvents were evaporated and the residue was diluted with water (150 mL) and extracted with Et_2O (4 × 100 mL). Drying (Na_2SO_4) and evaporation gave crystalline **17a** (11.79 g, 63%), mp 97–98 °C.[25,26] A portion of the "diacetone galactose" **17a** (137 mg, 0.530 mmol) was dissolved in dry DMF (10 mL), and sodium hydride (25 mg, 1.05 mmol) and benzyl chloride (146 mg, 1.17 mmol) were added. After 24 h, the solvent was removed and the residue was taken up in methylene chloride, washed several times with water, dried over (Na_2SO_4), and evaporated to an oil, which was chromatographed (PTLC (B)) to give **17b** (129 mg, 73%) as a syrup: TLC R_f 0.42 (B); MS, *m/e* 335 ($M^+ - CH_3$), 292, 277 ($M^+ - CH_3$ – acetone), 249 ($M^+ - C_5H_9O_2$), 91 (tropylium); 60-MHz ^1H NMR δ 1.3–1.5 (m, 9, 3-C$(CH_3)_2$), 1.54 (s, 3, C$(CH_3)_2$), 3.6–4.4 (m, 5, H-3,4,5,6a,6b), 4.4–4.85 (m, 3, OCH_2Ph, H-2), 5.85 (d, 1, $J_{1,2}$ = 4 Hz, H-1), 7.33 (s, 5, OCH_2Ph).

3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-galactofuranose (17c). The diacetonide **17b** (13.0 g, 37.1 mmol) was dissolved in a mixture of acetic acid and water (7:3, 200 mL) and left at room temperature for 24 h. The reaction mixture was then concentrated by evaporation and methylene chloride (200 mL) was added. The mixture was neutralized with saturated sodium bicarbonate and then separated. The aqueous layer was extracted three more times with methylene chloride (3 × 200 mL) and the organic fractions were combined, dried over sodium sulfate, and evaporated to give crystalline **17c** (9.3 g, 80%): mp 104.0–104.5 °C, recrystallized from EtOAc/petroleum ether; TLC R_f 0.25 (Et_2O); $[\alpha]^{20}_D$ −32.6° (*c*, 1.10 in $CHCl_3$); IR ν_{max} 3600 (OH), 1390, 1380, 1070 cm^{-1}; MS, *m/e* 295 ($M^+ - CH_3$), 279, 249 ($M^+ - C_2H_5O_2$), 221, 193, 91 (tropylium); 60-MHz ^1H NMR δ 1.37 (s, 3, C$(CH_3)_2$), 3.8–4.25 (m, 5, H-3,4,5,6a,6b), 4.67 (s, 2, OCH_2Ph), 4.73 (d, 1, H-2), 5.97 (d, 1, $J_{1,2}$ = 4 Hz,H-1), 7.33 (s, 5, OCH_2Ph). Anal. Calcd. for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 61.74; H, 6.89.

3-*O*-Benzyl-1,2-*O*-isopropylidene-β-L-*arabino*-pentodialdo-1,4-furanose (18a). Cleavage of diol **17c** (9.270 g, 29.9 mmol) with sodium metaperiodate (10.0 g, 46.7 mmol) was carried out for 4 h as described for preparation of **11c**. For **18a**: TLC R_f 0.25 (G); $[\alpha]^{20}_D$ +14.7° (*c*, 2.90 in $CHCl_3$); IR ν_{max} 1738 (CHO), 1460, 1390, 1380, 1045, 855 cm^{-1}; MS, *m/e* 279 ($M^+ + 1$), 277 ($M^+ - 1$), 263 ($M^+ - CH_3$), 249 ($M^+ - CHO$), 91 (tropylium); 60-MHz ^1H NMR δ 1.23 (s, 3, C$(CH_3)_2$), 1.40 (s, 3, C$(CH_3)_2$), 4.2–4.8 (m, 5, OCH_2Ph, H-2,3,4), 6.03 (d, 1, $J_{1,2}$ = 3.75 Hz, H-1), 7.28 (s, 5, OCH_2Ph), 9.78 (s, 1, CHO).

3-*O*-Benzyl-5,6-dideoxy-6-*C*-(*n*-hexyl)-1,2-*O*-isopropylidene-β-L-*arabino*-hex-5-enofuranose (18b). Using the standard Witting reaction procedure (see General Methods), aldehyde **18a** (9.241 g) in DME gave **18b** (7.721 g, 65%) as an oil: TLC R_f 0.54 (G); IR ν_{max} 1455, 1385, 1372, 1158, 1065 cm^{-1}; MS, *m/e* 345 ($M^+ - CH_3$), 302, 277, 91 (tropylium); 60-MHz ^1H NMR δ 0.83–1.17 (s, 3, $(CH_2)_5CH_3$), 1.17–1.50 (s, 11, $-(CH_2)_4-$, C$(CH_3)_2$), 1.53 (s, 3, C$(CH_3)_2$), 1.86–2.40 (m, 2, $-=-CH_2-$), 3.90 (d, 1, $J_{3,4}$ = 3.75 Hz, H-3), 4.57–4.73 (m, 3, OCH_2Ph, H-2), 4.73–5.00 (m, 1, H-4), 5.50–5.83 (m, 2, vinyl), 5.93 (d, 1, $J_{1,2}$ = 4 Hz, H-1), 7.37 (s, 5, OCH_2Ph).

5-Deoxy-5-*C*-(*n*-heptyl)-1,2-*O*-isopropylidene-β-L-arabinofuranose (19b). Standard hydrogenation with Raney nickel (see General Methods) of compound **18b** (7.72 g) gave **19a** (6.31 g, 82%): TLC R_f 0.38 (H); $[\alpha]^{20}_D$ −22.3° (*c*, 3.82 in $CHCl_3$); IR ν_{max} 1455, 1388, 1375, 1160, 1065, 1010 cm^{-1}; MS, *m/e* 362 (M^+), 361 ($M^+ - 1$), 347 ($M^+ - CH_3$), 225, 197, 91 (tropylium); 220-MHz ^1H NMR δ 0.89 (t, 3, $(CH_2)_7CH_3$), 1.25 (s, 14,-$(CH_2)_7-$), 1.34 (s, 3, C$(CH_3)_2$), 1.52 (s, 3, CH$(CH_3)_2$), 3.79 (d, 1, $J_{3,4}$ = 3.0 Hz, H-3), 3.95–4.07 (m, 1, H-4), 4.55 (d, AB q, 1, OCH_2Ph), 4.64 (d, 1, H-2), 4.65 (d, AB q, 1, OCH_2Ph), 5.87 (d, 1, $J_{1,2}$ = 4.75 Hz, H-1), 7.32 (s, 5, OCH_2Ph). The standard hydrogenolysis procedure (see General Methods) and 10% Pd/C as the catalyst led to the alcohol **19b** (100%): TLC R_f 0.22 (G); $[\alpha]^{20}_D$ −21.6° (*c*, 1.95 in $CHCl_3$); IR ν_{max} 3450 (OH), 1460, 1390, 1380, 1163, 1065, 1015, 858 cm^{-1}; MS, *m/e* 257 ($M^+ - CH_3$), 243, 201, 197 ($M^+ - CH_3$ – HOAc), 159 ($M^+ - C_8H_{17}$); 60-MHz ^1H NMR δ 0.83–1.03 (s, 3, $(CH_2)_7CH_3$), 1.03–1.43 (s, 17, $-(CH_2)_7-$, C$(CH_3)_2$), 1.53 (s, 3, C$(CH_3)_2$), 3.7–4.2 (m, 2, H-3,4), 4.53 (d, 1, H-2), 5.88 (d, 1, $J_{1,2}$ = 4.25 Hz, H-1).

5-Deoxy-5-*C*-(*n*-heptyl)-1,2-*O*-isopropylidene-β-L-*threo*-pentofuran-3-ulose (19c). Alcohol **19b** (4.821 g, 17.7 mmol) was oxidized with Collins' reagent[15] (30 g) as described for **13a**. The product **19c** (2.255 g, 47%) was an oil: TLC R_f 0.55 (G); $[\alpha]^{20}_D$ −4.93° (*c*, 3.77 in $CHCl_3$); IR ν_{max} 1772 (carbonyl), 1390, 1380, 1155, 1060 cm^{-1}; MS, *m/e* 271 ($M^+ + 1$), 255 ($M^+ - CH_3$), 243, 214;

(30) Finkbeiner, H. L.; Stiles, M. *J. Am. Chem. Soc.* **1963**, *85*, 616.
(31) We are indebted to Professor R. Roche of the Department of Chemistry, University of Calgary, Calgary, Alberta, for determining this value by ORD procedures.

60-MHz ^{1}H NMR δ 0.76–1.07 (m, 3, $(CH_2)_7CH_3$), 1.23–1.36 (s, 14, $-(CH_2)_7-$), 1.40 (s, 3, $C(CH_3)_2$), 1.52 (s, 3, $C(CH_3)_2$), 3.9–4.1 (m, 1, H-4), 4.38 (d, 1, H-2), 5.97 (d, 1, $J_{1,2}$ = 4.25 Hz, H-1).

3-*C*-(Carbethoxymethylene)-3,5-dideoxy-5-*C*-(*n*-heptyl)-1,2-*O*-isopropylidene-β-L-lyxofuranose (20). Ketone **19c** (2.152 g, 7.96 mmol) was dissolved in acetonitrile (50 mL) and Ph_3P=CHCOOEt (3.326 g, 9.55 mmol) was added. After being stirred overnight, the reaction was processed in the usual manner to give **19d** (1.919 g, 71%) as a syrup: TLC R_f 0.44 (G); IR ν_{max} 1712 (carbonyl), 1455, 1372, 1152, 1020, 900, 860 cm^{-1}; MS, *m/e* 341 (M^+ + 1), 325 ($M^+ - CH_3$), 265 ($M^+ - CH_3$ - HOAc); 60-MHz ^{1}H NMR δ 0.73–1.07 (m, 3, $(CH_2)_7CH_3$), 1.07–1.50 (m, 20, $-(CH_2)_7-$, OCH_2CH_3, $C(CH_3)_2$), 1.57 (s, 3, $C(CH_3)_2$), 4.20 (q, 2, OCH_2CH_3), 4.88 (d, 1, H-2), 5.0–5.4 (m, 1, H-4), 5.88 (d, 1, $J_{1,2}$ = 4.25 Hz, H-1), 6.03 (d, 1, J = 1.75 Hz, vinyl). Standard hydrogenation (see General Methods) of **19a** gave **20** (1.820 g, 95%): TLC R_f 0.42 (G); $[\alpha]^{20}_D$ -19.6° (*c*, 2.65 in $CHCl_3$); IR ν_{max} 1730 (carbonyl), 1458, 1375, 1160, 1010, 868 cm^{-1}; MS, *m/e* 327 ($M^+ - CH_3$), 267 ($M^+ - CH_3$ - HOAc), 239, 221; 60-MHz ^{1}H NMR δ 0.73–1.07 (m, 3, $(CH_2)_7CH_3$), 1.07–1.47 (m, 20, $-(CH_2)_7-$, OCH_2CH_3, $C(CH_3)_2$), 1.50 (s, 3, $C(CH_3)_2$), 2.0–2.8 (m, 3, $-CH_2CO_2-$, H-3), 4.15 (q, 2, OCH_2CH_3), 4.67 (t, 1, H-2), 5.78 (d, 1, $J_{1,2}$ = 4.0 Hz, H-1).

3-*C*-(Carboxymethyl)-3,5-dideoxy-5-*C*-(*n*-heptyl)-L-lyxono-1,4-lactone 2,3-δ-Lactone (21b). Compound **20** (1.783 g, 5.21 mmol) was converted into **21a** as described above for preparation of **7a**. Lactol **21a** (1.391 g, 100%) was a waxy material: TLC R_f 0.33 (I); $[\alpha]^{20}_D$ -34.5° (*c*, 2.91 in $CHCl_3$); IR ν_{max} 3400 (OH), 1781 (γ-lactone), 1465, 1345, 1165, 1035 cm^{-1}; MS, *m/e* 257 (M^+ + 1), 256 (M^+), 255 (M^+ - 1), 227, 210, 143 ($M^+ - C_8H_{17}$); 60-MHz ^{1}H NMR δ 0.77–1.10 (m, 3, $(CH_2)_7CH_3$), 1.30 (s, 14, $-(CH_2)_7-$), 2.2–2.9 (m, 3, $-CH_2CO_2-$, H-3), 4.2–4.7 (m, 1, H-4), 5.02 (d, 1, $J_{2,3}$ = 7 Hz,H-2), 5.53 (s, 1, H-1). A portion of **21a** (1.303 g, 5.08 mmol) was oxidized with Jones' reagent[16] (6.50 mL) as described for **7b**. For the bis-lactone **21b** (954 mg, 74%): mp 110.5-111.5 °C (recrystallized from EtOAc/petroleum ether); TLC R_f 0.37 (C); $[\alpha]^{20}_D$ -7.52° (*c*, 1.08 in $CHCl_3$); IR ν_{max} 1795 (γ-lactones), 1600, 1460, 1282, 1148, 1070 cm^{-1}; MS, *m/e* 255 (M^+ + 1), 254 (M^+), 253 (M^+ - 1), 210, 182, 179, 167; 60-MHz ^{1}H NMR δ 0.77–1.08 (m, 3, $(CH_2)_7CH_3$), 1.27 (s, 14, $-(CH_2)_7-$), 2.1–2.7 (m, 3, $-CH_2CO_2-$, H-3), 4.4–4.9 (m, 1, H-4), 5.20 (d, 1, $J_{2,3}$ = 8Hz, H-2). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 65.96; H, 8.74.

3-*C*-(Carboxymethylenemethyl)-3,5-dideoxy-5-*C*-(*n*-heptyl)-L-lyxono-1,4-lactone 2,3-γ-Lactone ((-)-Isoavenaciolide) (2a). The bis-lactone **21b** (209.3 mg, 0.823 mmol) was dissolved in Stiles' reagent[30] (3 mL) and heated at 125 °C for 5.5 h under argon and was then processed as described above for 1. This gave crude crystalline isoavenaciolide (113.7 mg, 52% from **21b**) which was recrystallized from diethyl ether: mp 127–128 °C (lit.[6] mp 129–130 °C); $[\alpha]^{27}_D$ -167° (*c* 1.20 in ethanol) (lit.[6] $[\alpha]^{27}_D$ -154° (*c*, 1.1% in ethanol)); IR ν_{max} 1790 (lactones), 1285, 1102, 1062, 9095, 960 cm^{-1}; MS, *m/e* 266 (M^+), 193, 191, 141; 60-MHz ^{1}H NMR δ 0.73–1.10 (m, 3, $(CH_2)_7CH_3$), 1.30 (s, 14, $-(CH_2)_7-$), 4.0 (m, 1, H-3), 4.6–5.0 (m, 1, H-4), 5.17 (d, 1, $J_{2,3}$ = 9 Hz, H-2), 5.87 (d, 1, J = 2.0 Hz, α-methylene), 6.62 (d, 1, J = 2.25 Hz, α-methylene). The IR and NMR data were in good agreement with those in the literature.[6]

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Registry No. 1, 20223-76-1; **2a**, 33644-09-6; **5a**, 56777-87-8; **5b**, 98779-29-4; **6a**, 56765-04-9; **6b**, 98855-08-4; **7a**, 58846-04-1; **7b**, 56816-44-5; **7c**, 50708-46-8; **10b**, 22529-61-9; **11a**, 53167-11-6; **11b** (isomer 1), 98779-30-7; **11b** (isomer 2), 98855-03-9; **11c**, 23558-05-6; **11d**, 98855-04-0; **12a**, 68853-81-6; **12b**, 98779-31-8; **13a**, 98855-05-1; (*E*)-**13b**, 98855-06-2; (*Z*)-**13b**, 98855-07-3; **16**, 2774-28-9; **17a**, 10368-86-2; **17b**, 65451-98-1; **17c**, 65434-49-3; **18a**, 65462-15-9; **18b**, 65434-50-6; **19a**, 98855-09-5; **19b**, 65434-51-7; **19c**, 65434-52-8; **19d**, 65434-53-9; **20**, 65434-54-0; **21a**, 98855-10-8; **21b**, 65451-99-2; n-$C_6H_{13}CH$=PPh_3, 55367-56-1; Ph_3P=CHCOOEt, 1099-45-2; methyl methoxymagnesium carbonate, 4861-79-4; diacetone glucose, 582-52-5.

Synthesis of Bis-γ-lactones from "Diacetone Glucose". 5. Optically Active Canadensolide†

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Details are given for the synthesis of optically active canadensolide. Use of "diacetone glucose" as the precursor affords the naturally occurring levorotatory enantiomer in 16 steps. The absolute configuration has been determined to be 2*S*,3*R*,4*R*. The investigation has revealed that the readily obtainable bis-lactone **10b** is not a suitable intermediate for α-methylenation, since deprotonation with kinetic bases occurs preferentially at the methine position (C-2), which results in β-elimination. In the successful synthesis, the lactonic hemiacetal **10a** emerges as the precursor of choice.

In the accompanying manuscript[1] we discussed the use of "diacetone glucose" and "diacetone galactose" for "cyclic transfer"[2] of the tetrahydrofuran moiety into the bis-γ-lactones avenaciolide and isoavenaciolide, respectively. Our success in these enterprises served to establish the correct absolute stereochemistry for these compounds by routes that were also totally stereoselective. In this manuscript, we give full details of our work on canadensolide, which also is a bis-γ-lactone, although of different skeletal arrangement than the former two.[3]

(-)-Canadensolide, **1a**, is a mold metabolite produced by *Penicillium canadense* which has antigerminative ac-

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(3) For preliminary account, see: Anderson, R. C.; Fraser-Reid, B. *Tetrahedron Lett.* **1978**, 3233.

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