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]

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada for a predoctoral studentship (R.C.A.) and for financial support. We are also grateful to Dr. W. B. Turner of Imperical Chemical Industries for an authentic sample of natural (-)-avenaciolide.

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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(1) Part 4: Anderson, R. C.; Fraser-Reid, B. *J. Org. Chem.*, previous paper in this issue.

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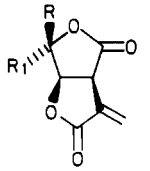
tivity against fungi. The compound was isolated by



1a, R = C_4H_9; R_1 = H
b, R = H; R_1 = C_4H_9

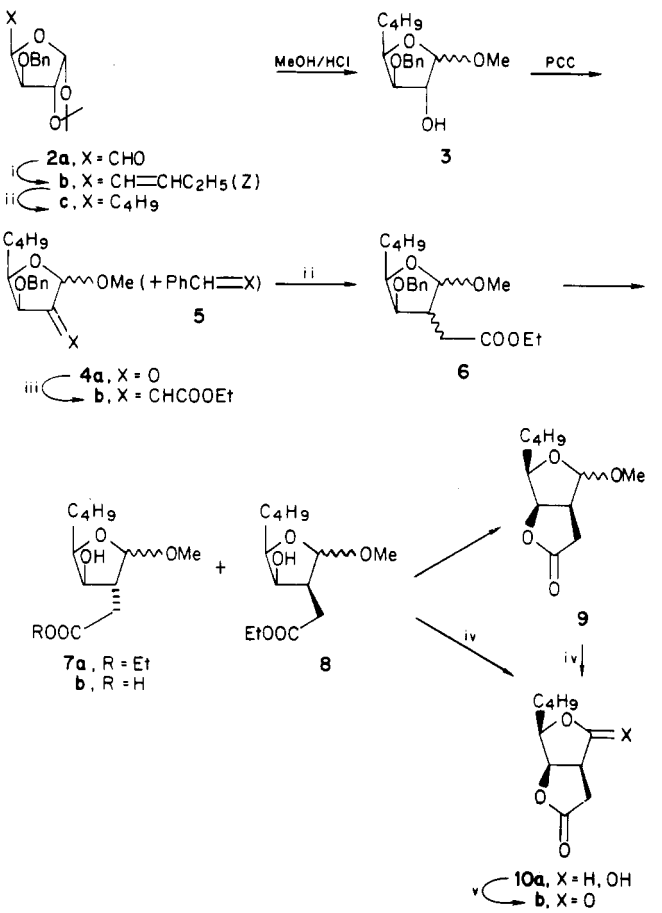
McCorkindale[4] and co-workers who used spectroscopic and degradative studies to assign the relative stereochemistry shown in **1b**. However, synthesis of racemic **1b** by Yoshikoshi and co-workers[5] showed that this assignment was incorrect and they reassigned the *relative* stereochemistry as shown in **1a**. At the outset of our studies, the *absolute* stereochemistry had not been determined and the obtainment of this piece of information was one reason for undertaking the synthesis. More recent syntheses[6] have also afforded the optically active material.[7]

In designing a route to optically active **1a**, the bis-lactone **10b**, which had been prepared in racemic form by Yoshikoshi,[5] was viewed as a reasonable objective, since it could conceivably be α-methylenated by the procedure utilized in the previous bis-lactone syntheses.[1] The aldehyde **2a**,[1] which is available from the avenaciolide synthesis, was considered an appropriate precursor, and indeed compound **2c** was obtained therefrom by using the previously tested procedures.

Acid-catalyzed methanolysis of **2c** gave a 1:1 mixture of the methyl furanosides **3**, in which the C-2 hydroxyl was now available for oxidation; however, this undertaking proved to be surprisingly difficult. A number of reagents[9-14] were tried, all of which gave low yields and/or were unreliable (Scheme I). The problem appeared to result both from inherent difficulties with the oxidation of **3** as well as from the facile degradation of the resulting ketone **4a**. This may be best illustrated by the following account. Oxidations of **3** (24 g) in refluxing dry benzene with pyridinium chlorochromate[14] for 4 to 5 h gave a crude oil (10 g) whose infrared spectrum showed carbonyl absorption. The NMR and IR spectra showed that an aromatic aldehyde was present, and the odor of the oil confirmed the presence of benzaldehyde. The crude oil contained 6 g of ketone **4a** (25%) and 4 g of benzaldehyde as determined by integration of the NMR spectrum. This suggests that ketone **4a** underwent elimination of benzyl alcohol which was subsequently oxidized to benzaldehyde. Attempts to separate ketone **4a** from benzaldehyde **5a** merely caused further decomposition of the labile ketone and hence it was found best to proceed with the mixture.

The crude oil from the oxidation was allowed to react with (carbethoxymethylene)triphenylphosphorane[15] in

Scheme I[a]



[a] (i) $Ph_3P=CHC_2H_5$/THF (64%); (ii) stir with Raney Ni/EtOH, then H_2/Pd; (iii) $Ph_3P=CHCOOEt$/THF; (iv) H_2SO_4/dioxane/H_2O; (v) Jones' reagent[15] (87%).

acetonitrile, and the resulting product containing **4b** and **5b** was directly hydrogenated over Raney nickel. The stereochemical course of the addition of hydrogen to **4b** was crucial since the reaction generated one of the chiral centers of canadensolide. However, a quantitative analysis of the diastereomers in **6** was not possible since the mixture was not resolved on TLC.

Hydrogenolytic cleavage of the benzyl ether of **6** was undertaken in the hope that separation of the resulting alcohol from ethyl dihydrocinnamate would be facilitated. This indeed proved to be the case. We had also hoped that the *cis*-hydroxy ester **8** would spontaneously give the lactone **9** and thereby facilitate isolation from the trans counterpart, **7a**. This expectation was only partially realized since substantial amounts of **8** remained unlactonized. The mixture of **7a**, **8**, and **9** was therefore subjected to acid hydrolysis in order to convert **8** and **9** into the hemiacetal **10a** which would then be readily freed from the *trans*-hydroxy acid **7b** by sodium bicarbonate washing. Indeed, the hemiacetal **10a** was readily obtained free of contaminants, and although the α and β anomers were separable, they were oxidized directly to the bis lactone **10b**.

The crystalline bis-lactone **10b** was subjected to the conditions utilized for α-methylenations of the other bis-lactones[1,8] (Scheme II). This, however, did not result in the formation of **12**. Soon after this disappointing experience, Kosugi and co-workers reported a similar failure

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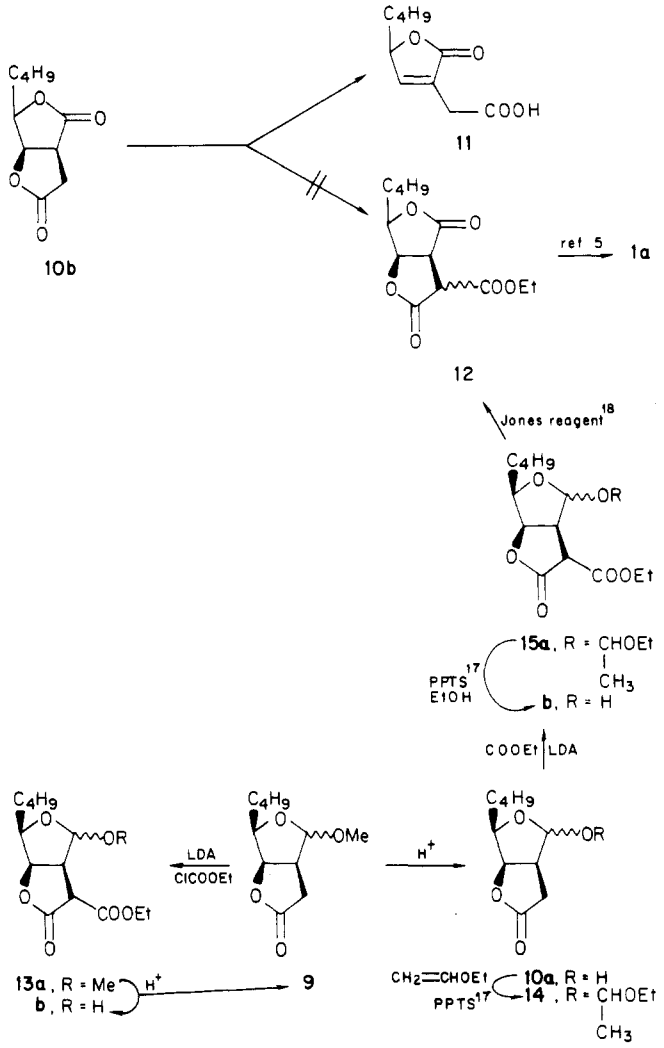
Scheme II



using racemic **10b**.[16] Thus their attempts at introducing a one carbon unit at the methylene position were thwarted owing to preferential abstraction of the proton from C-2 by LDA to give the ring opened product **11**.

With this avenue to canadensolide closed, we turned our attention to the synthesis of **12**, a compound whose racemic modification had been successfully utilized by Yoshikoshi and co-workers in their synthesis of (±)-canadensolide.[5] A promising, expeditious route should be available from lactone **9**. Indeed treatment of **9** with lithium diisopropylamide and acylation with ethyl chloroformate gave, judging from the NMR spectrum, the carbethoxylated product **13a**. A variety of attempts to hydrolyze the glycosidic methoxyl of **13a** selectively gave either unchanged material, or regenerated the lactone **9** or the lactol **10a**.

It was therefore apparent that a more acid-labile group was required at the glycosidic center. Accordingly, we attempted to glycosylate **10a** with ethyl vinyl ether to afford **14**. When *p*-toluenesulfonic acid was used as catalyst, severe decomposition was observed; however, with pyridinium *p*-toluenesulfonate,[17] the desired transformation went smoothly.

Carbethoxylation of **14** proceeded well (87%) with lithium diisopropylamide and ethyl chloroformate to give **15a** which appeared as a single substance on TLC. The oil exhibited two carbonyl absorptions in the infrared, one at 1790 cm^{1} (γ-lactone) and one at 1740 cm^{-1} (saturated ester), and the NMR spectrum showed the presence of an ethoxy group and the absence of the lactone methylene protons.

Removal of the α-ethoxyethyl group was readily achieved by heating **15a** at 55 °C for 8 h in absolute ethanol containing a catalytic amount of pyridinium *p*-toluenesulfonate.[17] Oxidation of the resulting hemiacetal **15b** with Jones' reagent[18] afforded the crystalline bislactone **12** whose 220-MHz NMR spectrum was fully congruent with that of the known methyl ester.[5] The orientation of the ethoxycarbonyl group was assigned as exo because of the small coupling constant ($J_{2,9}$ = 1.2 Hz).

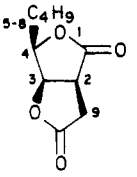
A slight modification (see Experimental Section) of the procedure employed by Yoshikoshi and co-workers[5] in their synthesis was used to convert compound **12** into canadensolide **1a** (41% from **12**). The canadensolide so produced did not crystallize, but its optical rotation, infrared, and 220-MHz NMR spectra were identical with those displayed by the natural (−)-canadensolide obtained from Drs. McCorkindale[4] and Yoshikoshi,[5] and its mass spectrum was identical with that of the racemic material.[19]

In conclusion, natural (−)-canadensolide has been synthesized and its absolute configuration determined to be 2*S*,3*R*,4*R*.

Experimental Section

General Methods. See previous paper, this issue.

For the purpose of NMR interpretation, the following numbering scheme was used:



3-*O*-Benzyl-5,6-dideoxy-6-*C*-ethyl-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (2b). Using the standard Wittig reaction procedures (see General Methods),[1] the aldehyde **2a**[1] (40 g) was treated with propenyltriphenylphosphorane (1.2 equiv) in DME to give the alkene **2b** (27 g, 64% after chromatography) as a homogeneous oil: TLC R_f 0.36 (B); IR ν_{max} 1500, 1455, 1388, 1375, 1160, 1065, 880, 855 cm^{-1}; MS, *m/e* 303 (M^+ − 1), 289 (M^+ − CH_3), 91 (tropyllium); 60-MHz ^1H NMR δ 0.97 (t, 3, CH_2CH_3), 1.30 (s, 3, $C(CH_3)_2$), 1.83–2.33 (m, 2, OCH_2CH_3), 3.84 (d, 1, $J_{3,4}$ = 3.0 Hz, H-3), 4.60 (s, 2, $PhCH_2$), 4.63 (d, 1, H-2), 4.80–5.13 (m, 1, H-4), 5.60–5.83 (m, 2, vinyl), 5.98 (d, 1, $J_{1,2}$ = 4.0 Hz, H-1), 7.35 (s, 5, $PhCH_2$).

3-*O*-Benzyl-5-deoxy-1,2-*O*-isopropylidene-5-*C*-(*n*-propyl)-α-D-xylofuranose (2c). Standard hydrogenation (see General Methods) of **2b** using Raney nickel gave **2c** (100%) as an oil: TLC R_f 0.36 (G); $[\alpha]^{22}_D$ −55.3° (*c*, 3.84 in $CHCl_3$); IR ν_{max} 1501, 1458, 1378, 1160, 882, 855 cm^{-1}; MS, *m/e* 306 (M^+), 305 (M^+ − 1), 291 (M^+ − CH_3), 91 (tropylium); 60-MHz ^1H NMR δ 0.67–1.03 (m, 3, CH_2CH_3), 1.03–2.0 (m, 6, $CH_2CH_2CH_2CH_3$), 1.30 (s, 3, $C(CH_3)_2$), 1.5 (s, 3, $C(CH_3)_2$), 3.73 (d, 1, $J_{3,4}$ = 3.0 Hz, H-3), 3.83–4.23 (m, 1, H-4), 4.53 (AB q, 2, $PhCH_2$), 4.58 (d, 1, H-2), 5.85 (d, q, $J_{1,2}$ = 4.0 Hz, H-1), 7.23 (s, 5, $PhCH_2$).

Methyl 3-*O*-Benzyl-5-deoxy-5-*C*-(*n*-propyl)-α,β-D-xylofuranoside (3). Compound **2c** (29.5 g, 96.4 mmol) was dissolved in dry methanol (900 mL) containing hydrogen chloride (18 g), and after 2 h at room temperature, the solution was neutralized by the careful addition of solid sodium bicarbonate. Filtration and evaporation gave an oily residue which was processed in the usual way to give a 1:1 mixture of **3** (α) and **3** (β) as an oil (24

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g, 90%). These were separated by column chromatography (solvent G). **3**(α): TLC R_f 0.33 (G); $[\alpha]^{22}_D$ +54.3° (*c*, 3.12 in $CHCl_3$); IR ν_{max} 3460–3620 (OH), 1500, 1468, 1454, 1120, 1030 cm^{-1}; MS, *m/e* 220, 181, 165, 91 (tropylium); 220-MHz ^1H NMR β 0.89 (t, 3, $(CH_2)_3CH_3$), 1.14–1.5 (m, 4, H-6a,b,7a,b), 1.66 (q, 2, H-5a,b), 2.90 (d, 1, J = 6.5 Hz, OH), 3.45 (s, 3, OCH_3), 3.81 (q, 1, J = 2.75 Hz, J = 5.0 Hz, H-3), 4.07–4.17 (m, 1, H-4), 4.20–4.30 (m, 1, H-2), 4.53 (d, AB q, 1, J_{AB} = 12.0 Hz, $PhCH_AH_BO$), 4.74 (d, AB q, 1, $PhCH_AH_BO$), 4.99 (d, 1, $J_{1,2}$ = 4.5 Hz, H-1), 7.32 (s, 5, $PhCH_2O$). **3**(β): TLC R_f 0.27 (G); $[\alpha]^{22}_D$ +53.8° (*c*, 3.07 in $CHCl_3$); IR ν_{max} 3620 (s, OH), 3400 (br, OH), 1500, 1460, 1452, 1080, 1030 cm^{-1}; MS, *m/e* 249, ($M^+ - OCH_3$), 220, 181, 163, 91 (tropylium); 220-MHz ^1H NMR δ 0.89 (t, 3, $-(CH_2)_3CH_3$), 1.14–1.5 (m, 4, H-6a,-b,7a,b), 1.55–1.82 (m, 2, H-5a,b), 2.57 (s, 1, OH), 3.39 (s, 3, OCH_3), 3.83 (q, 1, J = 5.5 Hz, J = 3.25 Hz, H-3), 4.10–4.82 (m, 2, H-2,4), 4.53 (d, AB q, 1, J_{AB} = 11.75 Hz, $PhCH_AH_BO$), 4.67 (d, AB q, 1, $PhCH_AH_BO$), 4.75 (d, 1, $J_{1,2}$ = 1.75 Hz), 7.32 (s, 5, $PhCH_2O$-).

Methyl 3-*O*-Benzyl-5-deoxy-5-*C*-(*n*-propyl)-α,β-D-*threo*-pentofuranosid-2-ulose (4a). The mixture of anomers **3** (217.4 mg, 0.775 mmol) was dissolved in dry methylene chloride (10 mL). Sodium acetate (19 mg) and pyridinium chlorochromate[14] (1.5 g) were added, and the reaction mixture was shaken for 4 h, poured into diethyl ether (200 mL), and then filtered through a bed of Celite and Florisil. The filtrate was evaporated to an oil which was purified by PTLC (H) to give **4a** (100 mg, 46%) as an oil.

Methyl 3-*O*-Benzyl-2-*C*-(carbethoxymethylene)-2,5-dideoxy-5-*C*-(*n*-propyl)-α,β-D-*threo*-pentofuranoside (4b). The crude oily oxidation product (10 g, containing 6 g of **4a** (21.5 mmol) and 4 g of benzaldehyde **5a** (37.7 mmol)) was dissolved in acetonitrile (125 mL), and (carbethoxymethylene)triphenylphosphorane[15] (24.7 g, 71.0 mmol) was added. The reaction mixture was shaken overnight and then evaporated to give a semisolid residue which was processed in the usual way. The product was then chromatographed on a silica gel column (H) and the material which was eluted between R_f 0.25 and R_f 0.42 was collected (9.2 g). The presence of the α,β-unsaturated ester was indicated by a strong infrared absorption at 1720 cm^{-1} and by the appearance of the distinctive ethyl ester triplet and quartet in the NMR.

2-*C*-(Carboxymethyl)-2,5-dideoxy-5-*C*-(*n*-propyl)-D-lyxono-1,4-lactone 2,3-γ-Lactone (10b). Standard hydrogenation (see General Methods)[1] of the mixture of unsaturated esters **4b** and **5b** (9.2 g) with Raney nickel gave **6** and ethyl dihydrocinnamate as a homogeneous oil: TLC (R_f 0.50 (G)); IR 1649 cm^{-1} (saturated ester). The mixture of esters (8.7 g) was hydrogenolyzed with 10% Pd/C (see General Methods) and the oily residue was chromatographed on a silica gel column (solvent C) to give four major fractions: i (1.9 g), ii (0.3 g), iii (0.75 g), and iv (1.0 g). R_f (D): 0.61, 0.44, 0.30, 0.12, respectively. Fraction i was identified as ethyl dihydrocinnamate on the basis of its 60-MHz ^1H NMR spectrum: δ 1.2 (t, 3, OCH_2CH_3), 2.78 (AA'BB' m, 4, $PhCH_2CH_2CO_2$), 4.12 (q, 2, OCH_2CH_3), 7.22 (s, 5, $PhCH_2CH_2CO_3$); fraction ii was not identifiable. Fractions iii and iv were considered to contain **9**, **7a**, and/or **8** as both fractions exhibited hydroxyl (ν_{max} 3520 cm^{-1}), γ-lactone (ν_{max} 1780 cm^{-1}), and saturated ester (ν_{max} 1735 cm^{-1}) absorptions in their infrared spectra, as well as methoxy and ethoxy patterns in their NMR spectra.

The oily residue containing **9** [1.9 g, fractions ii, iii, and iv] was dissolved in dioxane (20 mL) and 2% sulfuric acid (10 mL) was added. The reaction mixture was refluxed for 5 h, cooled, and diluted with methylene chloride. The organic phase was separated, washed twice with saturated $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated to give an oil (1.25 g). A portion (104 mg) was purified by PTLC (B) to give a mixture of the hemiacetals **10a** (59.2 mg, R_f 0.31 (E), R_f 0.38 (E)) as an oil. That this oil contained the desired hemiacetals was substantiated by NMR (absence of OMe singlets) and IR [(ν_{max} 3450 br (OH), 1780 (γ-lactone) cm^{-1}.]

The purified hemiacetals **10a** (47.6 mg) were dissolved in acetone (5 mL) and Jones' reagent[18] was added dropwise until a brown color persisted for 5 min. The reaction was then quenched by the addition of methanol. The reaction mixture was diluted with methylene chloride which was then washed with water, saturated $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated to give crystalline **10b** (41.0 mg, 87%): mp 84.5–86.0 °C (lit.[16] (±)-**10b**, mp 85.0–85.5 °C); $[\alpha]^{23}_D$ −18.9° (*c*, 4.79 in $CHCl_3$); IR (KBr) ν_{max} 1772 (bis-γ-lactones), 1470, 1418, 1318, 1200, 1155, 1075, 1012, 982 cm^{-1}; 220-MHz ^1H NMR δ 0.94 (t, 3, CH_2CH_3), 1.45 (m, 4, $CH_2CH_2CH_2CH_3$), 1.86 (m, 2, $CH_2CH_2CH_2CH_3$), 2.93 (d, 1, $J_{2,9}$ = 5.1 Hz, H-9), 2.94 (d, 1, $J_{2,9}$ = 7.5 Hz, H-9′), 3.55 (qd, 1, $J_{2,3}$ = 6.0 Hz, H-2), 4.62 (qd, 1, $J_{3,4}$ = 4.2 Hz, $J_{4,5}$ = 7.0 Hz, $J_{4,5'}$ = 8.0 Hz, H-4), 5.14 (dd, 1, H-3). These NMR and IR data are in good agreement with those reported for (±)-**10b**.[16] Anal. Calcd for $C_{10}H_{14}O_4$: C; 60.59; H; 7.12. Found: C; 60.54; H; 7.00.

Formation and Attempted Hydrolyses of Methyl 2-*C*-(Carboxycarbethoxymethyl)-2,5-dideoxy-5-*C*-(*n*-propyl)-α,β-D-lyxofuranoside 2,3-γ-Lactone (13a). A dry 10-mL two-necked flask equipped with a gas inlet, a serum cap, and a stirring bar was charged with dry THF (5 mL), diisopropylamine (266 mg, 2.68 mmol), and flushed with argon. After *n*-butyllithium (2.68 mmol) was added dropwise with stirring, the reaction mixture was left standing at room temperature for 15 min, at which time it was cooled to −78 °C. The acetals **9** (192.6 mg, 0.89 mmol) in dry THF (1 mL) were slowly injected into the lithium diisopropylamide solution and the reaction mixture was left stirring for 1 h. Ethyl chloroformate (290 mg, 2.68 mmol) was then added dropwise, and after 1 h the cooling bath was removed and the reaction mixture was allowed to warm to room temperature and then diluted with methylene chloride for processing in the usual manner. Compound **13a** was an oil (208.3 mg, 81%, TLC R_f 0.58 (E)) which showed methoxyl and ethoxyl patterns in its NMR and the absence of lactone methylene protons in the 2.0–3.0-ppm region.

Several attempts to hydrolyze the acetals **13a** in dioxane and dilute mineral acids (H_2SO_4, HCl) under a wide variety of conditions and temperatures led only to regeneration of the lactol **10a**.

α-Ethoxyethyl 2-*C*-(Carboxymethyl)-2,5-dideoxy-5-*C*-(*n*-propyl)-α,β-D-lyxofuranoside 2,3-γ-Lactone (14). The crude oil containing hemiacetals **10a** (1.17 g, 5.85 mmol) was dissolved in dry methylene chloride (15 mL), and ethyl vinyl ether (0.55 mL, 5.85 mmol) and a catalytic amount of pyridinium *p*-toluenesulfonate[17] were added. The reaction mixture was stirred at room temperature for 2 h at which time it was diluted with methylene chloride, washed twice with water, dried over sodium sulfate, and evaporated to give **14** as an oil (1.41 g, 88%) which was homogeneous on TLC (R_f 0.47 (D)) and showed an ethoxyl pattern in its NMR. In the IR hydroxyl was absent but γ-lactone (ν_{max} 1782 cm^{-1}) was present.

2-*C*-(Carboxycarbethoxymethyl)-2,5-dideoxy-5-*C*-(*n*-propyl)-α,β-D-lyxofuranose 2,3-γ-Lactone (15b). The ethoxycarbonylation of **14** (1.41 g, 5.18 mmol), carried out in a manner as described above for the formation of **13a**, gave **15a** (1.55 g, 87%) as a homogeneous oil: TLC R_f 0.50 (D); IR 1790 (γ-lactone) and 1740 (saturated ester) cm^{-1}; NMR, absence of lactone methylene protons in the 2.0–3.0 ppm and presence of an ethoxy pattern. The material was dissolved in absolute ethanol (20 mL) and a catalytic amount of pyridinium *p*-toluenesulfonate[17] was added. The reaction mixture was heated on an oil bath at 55 °C for 8 h and then processed in the usual way to give an oil (1.31 g, 100%) that showed several components on TLC (R_f 0.17 to 0.33 (D)). NMR analysis indicated the loss of the α-ethoxyethyl group, and IR analysis indicated the presence of a γ-lactone (ν_{max} 1790 cm^{-1}), a saturated ester (ν_{max} 1740 cm^{-1}), and a hydroxyl group (ν_{max} 3500 (br) cm^{-1}).

Bis-γ-lactone 12. Oxidation of **15b** (1.31 g, 4.58 mmol) as described above for **10a** gave **12** as an oil, which crystallized upon trituration with absolute ethanol (270.2 mg, 21%). After recrystallization (EtOH): 107.5–108.5 °C; $[\alpha]^{23}_D$ −28.1° (*c*, 3.39 in $CHCl_3$); IR ν_{max} 1775 (γ-lactone), 1735 (CO_2Et), 1468, 1370, 1285, 1245, 1010, 942 cm^{-1}; 220-MHz NMR δ 0.93 (t, 3, CH_2CH_3), 1.33 (t, 3, OCH_2CH_3), 1.43 (m, 4, $CH_2CH_2CH_2CH_3$), 1.86 (m, $CH_2CH_2CH_2CH_3$), 3.87 (d, q, $J_{2,3}$ = 6.0 Hz, $J_{2,9}$ = 1.2 Hz, H-2), 3.92 (d, q, H-9), 4.30 (q, 1, OCH_2CH_3), 4.31 (q, 1, OCH_2CH_3), 4.65 (qd, 1, $J_{3,4}$ = 4.2 Hz, $J_{4,5}$ = 7.0 Hz, $J_{4,5'}$ = 8.0 Hz, H-4), 5.25 (dd, 1, H-3). Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.90; H, 6.78.

2-*C*-(Carboxymethylenemethyl)-2,5-dideoxy-5-*C*-(*n*-propyl)-D-lyxono-1,4-lactone 2,3-γ-Lactone (Canadensolide, 1). To a solution of ester **12** (20.2 mg, 0.95 mmol) in dioxane (15 mL) was added 6 N hydrochloric acid (15 mL), and the mixture was heated at 60 °C, under argon with stirring, for 8 h. The reaction mixture was extracted with methylene chloride (2 × 50

mL) which was then dried over sodium sulfate and evaporated to give an oil. The oil was dissolved in acetic acid (2.7 mL) and diethylamine (0.56 mL) was added dropwise with stirring. Aqueous formalin (0.95 mL) and sodium acetate (0.84 g) were added after a further 15 and 45 min, respectively, and the solution was then heated on an oil bath at 80 °C for 10 min. Upon cooling, standard workup afforded a residue, purification of which [PTLC (I)] gave canadensolide as an oil (82 mg, 41% from **12**) which could not be induced to crystalline $[\alpha]^{23}_D$ −162° (*c*, 3.20 in $CHCl_3$) (lit.[16] $[\alpha]_D$ −168.9° (*c*, 1.02 in pyridine); IR (neat) ν_{max} 1780, 1670, 1470, 1350, 1295, 1262, 1180, 1102, 1060, 1010, 950, 912, 902, 790 cm^{-1}; MS *m/e* 124, 123, 110, 109, 96; 220-MHz NMR δ 0.93 (t, 3, CH_2CH_3), 1.44 (m, 4, $CH_2CH_2CH_2CH_3$), 1.86 (m, 2, $CH_2CH_2CH_2CH_3$), 4.05 (dt, 1, $J_{2,3}$ = 7.0 Hz, $J_{2,A}$ = 2.0 Hz, $J_{2,B}$ = 2.0 Hz, H-2), 4.67 (dt, 1, $J_{3,4}$ = 4.2 Hz, $J_{4,5}$ = 7.0 Hz, $J_{4,5'}$ = 7.0 Hz, H-4), 5.18 (dd, 1, H-3), 6.16 (d, q, *J* = 2.0 Hz, H-A), 6.46 (d, q, *J* = 2.0 Hz, H-b). The NMR and IR data are in excellent agreement with those in the literature[4,5] and the mass spectrum is identical with that displayed by (±)-canadensolide.[19]

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Registry No. **1a**, 20421-31-2; **2a**, 23558-05-6; **2b**, 98760-37-3; **2c**, 79448-72-9; α-**3**, 98760-38-4; β-**3**, 79431-88-2; α-**4a**, 98760-39-5; β-**4a**, 79431-89-3; α-**4b**, 98760-40-8; β-**4b**, 98760-41-9; **5a**, 100-52-7; **5b**, 103-36-6; **6** (isomer 1), 98760-42-0; **6** (isomer 2), 98819-38-6; **6** (isomer 3), 98819-39-7; **6** (isomer 4), 98819-40-0; α-**7a**, 69681-87-4; β-**7a**, 69744-49-6; α-**8**, 98819-41-1; β-**8**, 98819-42-2; **9** (isomer 1), 69681-88-5; **9** (isomer 2), 69744-50-9; **10a** (isomer 1), 69681-89-6; **10a** (isomer 2), 69744-40-7; **10b**, 69744-41-8; **12** (isomer 1), 98819-44-4; **12** (isomer 2), 69681-93-2; **13a**, 98819-43-3; **14**, 70048-75-8; **15a**, 69681-91-0; **15b**, 69681-92-1; propenyltriphenylphosphorane, 16666-78-7; (carbethoxymethylene)triphenylphosphorane, 1099-45-2; ethyl dihydrocinnamate, 2021-28-5; ethyl chloroformate, 541-41-3; ethyl vinyl ether, 109-92-2.

Studies in Biomimetic Alkaloid Syntheses. 13. Total Syntheses of Racemic Aspidofractine, Pleiocarpine, Pleiocarpinine, Kopsinine, *N*-Methylkopsanone, and Kopsanone

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Syntheses of the title alkaloid structures **1** (R = CHO, CO_2CH_3, CH_3, H; X = H_2) and **2** (R = CH_3, H; X = H_2) were based on generation of pentacyclic diene intermediates **17**, **18**, and **23** and their Diels–Alder reactions with phenyl vinyl sulfone.

Reports of synthetic studies leading to the hexacyclic aspidosperma alkaloids of the kopsinine (**1**, R = H; X = H_2)–pleiocarpinine (**1**, R = CH_3; X = H_2) class and to those of the heptacyclic kopsanone (**2**, R = H; X = H_2) group are relative sparse. To this end, an obvious biogenetic relationship of such alkaloids to the simpler pentacyclic vincadifformine (**3**, X = H_2) type alkaloids is provocative of a biomimetic cyclization of minovincine (**3**, X = O) as a synthetic approach. We had established three synthetic paths to minovincine,[1,2] but, while its decarbomethoxylation and cyclization provides 19-oxoaspidofractinine and then aspidofractinine (decarbomethoxy **1**, R = H),[3-5] its direct cyclization leads, alas, to an anticipated hexacyclic product, which is C-16 epimeric with 19-oxokopsinine (**1**, R = H; X = O).[6]

For an alternative synthetic strategy, the central bicyclo[2.2.2]octane moiety of these alkaloids suggests, of course, a Diels–Alder addition as a route to the C-2 to C-20 ethylene-bridged compounds **1** or **2**. In accord with broad experience in terpene chemistry, where, for bicyclooctanes this synthetic approach is generally preferred to biomimetic cyclizations of substituted cyclohexanes, synthetic planning for the target structures is then reduced to a choice of desirable diene and dienophile components.

Such an approach was first investigated in the C-16 decarbomethoxy series **4** leading, with nitroethylene and subsequent reduction and deamination steps, to another synthesis of aspidofractinine (decarbomethoxy **1**, R = H).[7] This concept was then used in an intramolecular sense for formation of the heptacyclic kopsane skeleton from a pentacyclic intermediate **5** (Scheme I). Introduction of the C-22 oxygen function of kopsanone (**2**, X = H_2) through a remarkable rearrangement reaction, cleavage of the C-6 to C-22 bond and esterification of the resultant acid then provided kopsinine (**1**, R = H; X = H_2), after reduction of the lactam function.[8b]

Extension of the intermolecular Diels–Alder reaction of the $\Delta^{2,16:17,20}$ diene **4**, to a synthesis of pleiocarpinine (**1**, R = CH_3; X = H_2) by a reaction of the diene with methyl acrylate, can be expected to lead to addition of the acrylic ester to the wrong face of the diene component **4**. Thus, an alternative, ethylene equivalent, reactive dienophile and the incorporation of the carbomethoxy function into the diene **4** were required for this synthesis.

In the present report we describe such a reaction scheme. By reversal of the last stages of the Magnus strategy this provides first syntheses of kopsinine and pleiocarpinine (**1**, R = H, CH_3; X = H_2) and then, in a possibly biomimetic formation of the C-6 to C-22 bond,[9] the generation of kopsanone and *N*-methylkopsanone (**2**, R = H, CH_3; X = H_2).

The key ring E diene intermediates **6** were obtained from an adaptation of our biomimetic secodine cyclization

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