Direct Methods for α-Methylene Lactone Synthesis Using Itaconic Acid Derivatives

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Received June 18, 1976

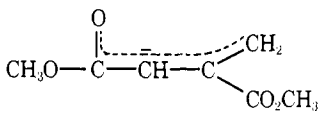
Anions of itaconic acid derivatives [$RO_2C\bar{C}HC(=CH_2)CO_2$] are versatile intermediates for the synthesis of α-methylene lactones. The addition of these anionic species to aldehydes or ketones and subsequent lactonization and hydrolysis have been utilized for the synthesis of a variety of compounds including protolichesterinic acid, nephrosterinic acid, and canadensolide.

α-Methylene lactones have recently attracted much synthetic effort[1] owing to the isolation of several cytotoxic and/or antitumor agents that possess this characteristic system.[2] Although several direct procedures have been developed for the synthesis of α-methylene lactones, the current methodology rests primarily upon techniques for the introduction and subsequent elimination of a heteroatom attached to the β carbon.[1]

Structural analysis of several naturally occurring β-carboxy-α-methylene lactones such as protolichesterinic acid,[3] nephrosterinic acid,[4] and canadensolide[5] suggested that these compounds could be obtained by the addition of an itaconic acid derivative to an aldehyde[6] (Scheme I). This synthesis would offer the advantages of broad scope and the ready availability of starting materials.[7]

Results and Discussion

Stable enolate anions could not be generated from dimethyl itaconate (1, $R_1 = R_2 = CH_3$) even at reduced temperatures (−78 °C).[8] The polymeric products that resulted from such attempts appeared to be derived from a Claisen condensation of the desired anion with the carboxymethyl not directly involved in the resonance stabilized system. Therefore, in order to avoid nucleophilic addition to the affected carbonyl carbon a carboxylate anion was used as a convenient protecting group (1, R_2 = Li).[9]



Attempts to generate the trianion of itaconic acid (1, $R_1 = R_2$ = Li) and to add it to carbonyl compounds were only moderately successful. Thus, treatment of itaconic acid with 3 equiv of lithium diisopropylamide[10] (LDA) at −78 °C in tetrahydrofuran (THF) followed by the addition of 1 equiv of aldehyde or ketone gave, upon acidification, low yields (~30%) of the desired α-methylene lactone **2** (R_1 = H).[11] The use of higher reaction temperatures and/or hexamethylphosphoramide (HMPA) decreased the yield of **2**.

In contrast, the dianions derived from monoesters of itaconic acid **1** ($R_1 = CH_3$, $ArCH_2$; R_2 = Li) were generated and observed to be viable nucleophiles in addition reactions to both aldehydes and ketones (Table I). For example, treatment of methyl itaconate (prepared by the addition of methanol to itaconic anhydride[7,12]) with 2 equiv of LDA[10] gave the dianion which upon addition to cyclohexanone and acid-catalyzed cyclization provided a 71% yield of the desired α-methylene lactone **2** [$R_1 = CH_3$; $R_3R_4 = (-CH_2-)_5$]. However, the use of methyl itaconate in the synthesis of protolichesterinic acid and its carboxy analogues **3** was precluded by the inability to hydrolyze the methyl ester without isomerization to the butenolide (Scheme II).

The problem of selective hydrolysis vs. isomerization in this overall scheme was overcome by utilizing the dianion of *p*-methoxybenzyl itaconate (1, $R_1 = ArCH_2$; R_2 = Li).[13] Hydrolysis of the ester without concurrent isomerization was then effected with trifluoroacetic acid. The overall sequence of addition, cyclization, and hydrolysis successfully generated a number of α-methylenebutyrolactones **3**, including protolichesterinic and nephrosterinic acids (Table I).

Scheme I

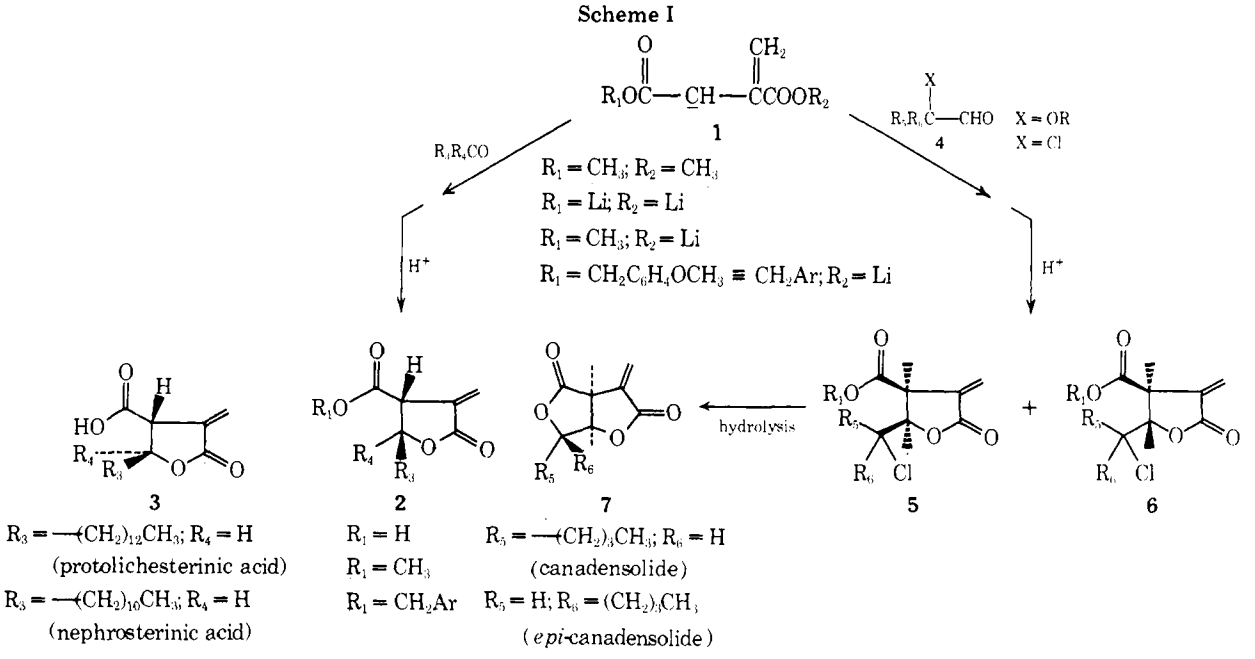
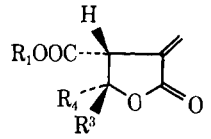


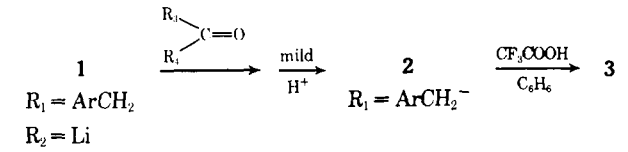
Table I.[a] Compounds Prepared from Monoesters of Itaconic Acid



2 and 3

Compd (registry no.)	R_1	R_4	R_3	% yield	Mp, °C	NMR, δ
2a (60427-56-7)	p-$CH_3OC_6H_4CH_2$	CH_3	CH_3	78[a]	54.5–55.5[b]	1.22 (3 H, s), 1.55 (3 H, s), 3.72 (1 H, t), 3.81 (3 H, s), 5.19 (2 H, s), 5.85 (1 H, d, J = 2.5 Hz), 6.48 (1 H, d, J = 2.5 Hz), 6.95 (2 H, m), 7.32 (2 H, m)[c]
3a (60427-57-8)	H	CH_3	CH_3	69[a]	150–151.8[b]	1.37 (3 H, s), 1.55 (3 H, s), 3.85 (1 H, t), 5.90 (1 h, d, J = 2.2 Hz), 6.05 (1 H, broad), 6.30 (1 H, d, J = 2.8 Hz)[d]
3b (60427-58-9)	p-$CH_3OC_6H_4CH_2$	$-CH_2CH_2CH_2CH_2-$		73[a]	[e]	1.7 (8 H, m), 3.78 (3 H, s), 3.90 (1 H, t), 5.12 (2 H, s), 5.75 (1 H, d, J = 2.2 Hz), 6.32 (1 H, d, J = 2.8 Hz), 6.9 (2 H, m), 7.3 (2 H, m)[c]
3b (60427-59-0)	H	$-CH_2CH_2CH_2CH_2-$		54[a]	107–109[b]	1.9 (8 H, m), 3.92 (1 H, t), 5.90 (1 H, d, J = 2.2 Hz), 6.47 (1 H, d, J = 2.5 Hz), 8.5 (1 H, s)[c]
2c (60427-60-3)	p-$CH_3OC_6H_4CH_2$	CH_3CH_2	CH_3CH_2	30[a]	[e]	0.9 (6 H, m), 1.7 (4 H, m), 3.8 (2 H, s), 3.8 (1 H, m), 5.15 (2 H, s), 5.8 (1 H, d, J = 2.5 Hz), 6.4 (1 H, d, J = 2.5 Hz), 6.9 (2 H, m), 7.28 (2 H, m)[c]
3c (60427-61-4)	H	CH_3CH_2	CH_3CH_2	17[a]	74–75[b]	1.0 (6 H, m), 1.85 (4 H, m), 3.9 (1 H, t), 5.95 (1 H, d, J = 2.5 Hz), 6.52 (1 H, d, J = 2.5 Hz), 8.5 (1 H, s)[c]
2d (60427-62-5)	p-$CH_3OC_6H_4CH_2$	H	$CH_3(CH_2)_{12}$	25[f]	53.5–54.5[b]	0.91 (3 H, t), 1.28 (24 H, m), 3.65 (1 H, m), 3.90 (3 H, s), 4.83 (1 H, m), 5.28 (2 H, s), 5.98 (1 H, d, J = 2.1 Hz), 6.50 (1 H, d, J = 2.5 Hz), 7.1 (2 H, m), 7.4 (2 H, m)[c]
2e (60427-63-6)	p-$CH_3OC_6H_4CH_2$	$CH_3(CH_2)_{12}$	H	16[f]	38–39.5[b]	0.89 (3 H, t), 1.25 (24 H, m), 3.9 (3 H, s), 4.08 (1 H, d, t, J = 8 and 1 Hz), 4.7 (1 H, m), 5.25 (2 H, s), 5.9 (1 H, d, J = 2 Hz), 6.5 (1 H, d, J = 2 Hz), 7.08 (2 H, m), 7.4 (2 H, m)[c]
3d (51260-32-3)	H	H	$CH_3(CH_2)_{12}$	20[g]	91–92[b]	0.9 (3 H, t), 1.3 (24 H, m), 3.7 (1 H, m), 4.85 (1 H, m), 6.1 (1 H, d, J = 2.1 Hz), 6.55 (1 H, d, J = 2.8 Hz), 8.3 (1 H, s)[c]
3e (60478-54-8)	H	$CH_3(CH_2)_{12}$	H	13[g]	87–88[b]	0.9 (3 H, t), 1.25 (24 H, m), 4.08 (1 H, d, t, J = 7.6 and 2 Hz), 4.7 (1 H, m), 6.0 (1 H, d, J = 2 Hz), 6.55 (1 H, d, J = 2 Hz), 9.75 (1 H, s)[c]
2f (60427-64-7)	p-$CH_3OC_6H_4CH_2$	H	$CH_3(CH_2)_{10}$	13[f]	46.8–47[b]	0.88 (3 H, t), 1.25 (20 H, m), 3.58 (1 H, m), 3.8 (3 H, s), 4.75 (1 H, m), 5.13 (2 H, s), 6.83 (1 H, d, J = 2.3 Hz), 6.37 (1 H, d, J = 3 Hz), 6.9 (2 H, m), 7.3 (2 H, m)[c]
2g (60427-65-8)	p-$CH_3OC_6H_4CH_2$	$CH_3(CH_2)_{10}$	H	13[f]	34–35[b]	0.89 (3 H, t), 1.23 (20 H, m), 3.8 (3 H, s), 3.95 (1 H, d, t, J = 7.6 and 2 Hz), 4.55 (1 H, m), 5.12 (2 H, s), 5.78 (1 H, d, J = 2.1 Hz), 6.38 (1 H, d, J = 2.5 Hz), 6.9 (2 H, m), 7.2 (2 H, m)[c]
3f (60427-66-9)	H	H	$CH_3(CH_2)_{10}$	11[g]	83.5–84.5[b]	0.88 (3 H, t), 1.28 (20 H, m), 3.65 (1 H, m), 4.8 (1 H, m), 6.0 (1 H, d, J = 2.7 Hz), 6.49 (1 H, d, J = 2.8 Hz), 9.5 (1 H, s)[c]
3g (60427-10-0)	H	$CH_3(CH_2)_{10}$	H	5[g]	81.5–82.5[b]	0.9 (3 H, t), 1.28 (20 H, m), 4.05 (1 H, d, t, J = 8 and 2.1 Hz), 4.65 (1 H, m), 5.92 (1 H, d, J = 1.9 Hz), 6.5 (1 H, d, J = 2.1 Hz), 9.3 (1 H, s)[c]
2h (60427-67-0)	CH_3	$-CH_2CH_2CH_2CH_2CH_2-$		71[a]	63–65[b]	1.6 (10 H, m), 3.62 (1 H, t, J = 2.1 Hz), 3.88 (3 H, s), 5.86 (1 H, d, J = 2.8 Hz), 6.58 (1 H, d, J = 2.5 Hz)[c]

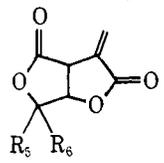
[a] Initial yield based on itaconic acid ester; >90% pure by NMR and/or HPLC. [b] A satisfactory elemental analysis (±0.3%) was obtained for this compound. [c] Solvent: $CDCl_3$. [d] Solvent: acetone-d_6. [e] This compound gave satisfactory mass spectral analysis. [f] Yield of single diastereomer, based on itaconic ester, after separation and purification by HPLC. [g] Yield based on itaconic acid ester; includes separation of intermediate ester diastereomers by HPLC and subsequent hydrolysis. [h] Lit.[3a] mp of (±)-protolichesterinic acid is 92–93.5 °C. [i] (±)-Alloprotolichesterinic acid.[3a,16] [j] "(±)-*trans*-Nephrosterinic acid".[4,16] [k] "(±)-*cis*-Nephrosterinic acid".[4,16]



The synthesis of canadensolide and related bislactones 7 (Table III) could be visualized as emanating from the previously developed synthetic sequence by the use of aldehydes 4 possessing an α-hydroxyl equivalent (Scheme I).

Symmetrically substituted α-chloro aldehydes were found

Table II. Physical Properties of Compounds Prepared from Symmetrical α-Chloro Aldehydes and Methyl Itaconate

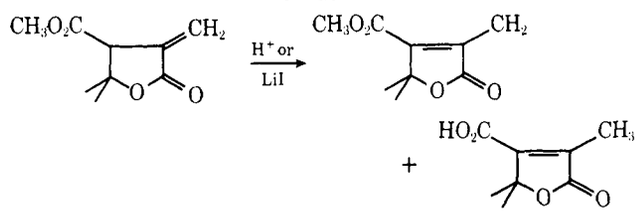


7

Compd (registry no.)	R_5	R_6	Mp, °C	NMR, δ ($CDCl_3$)
7a (60451-45-8)	$-CH_2CH_2CH_2CH_2CH_2-$		174–175[a]	1.7 (m, 10 H), 4.2 (d, t, 1 H, J = 7, 2 Hz), 5.0 (d, 1 H, J = 7 Hz), 6.4 (d, 1 H, J = 2 Hz), 6.7 (d, 1 H, J = 2 Hz)
7b (60427-68-1)	$-CH_2CH_2CH_2CH_2CH_2CH_2-$		148–151[a]	1.7 (m, 12H), 4.25 (d, t, 1 H, J = 7, 2 Hz), 5.0 (d. 1 H, J = 7 Hz), 6.3 (d, 1 H, J = 2 Hz), 6.65 (d, 1 H, J = 2 Hz)
7c (60427-69-2)	$CH_3CH_2CH_2$	$CH_3CH_2CH_2$	80.5–82[a]	1.0 (t, 3 H), 1.6 (m, 8 H), 4.15 (d, t, 1 H, J = 7, 2 Hz), 5 (d, 1 H, J = 7 Hz), 6.35 (d, 1 H, J = 2 Hz), 6.65 (d, 1 H, J = 2 Hz)

[a] A satisfactory elemental analysis (±0.3%) was obtained for this compound.

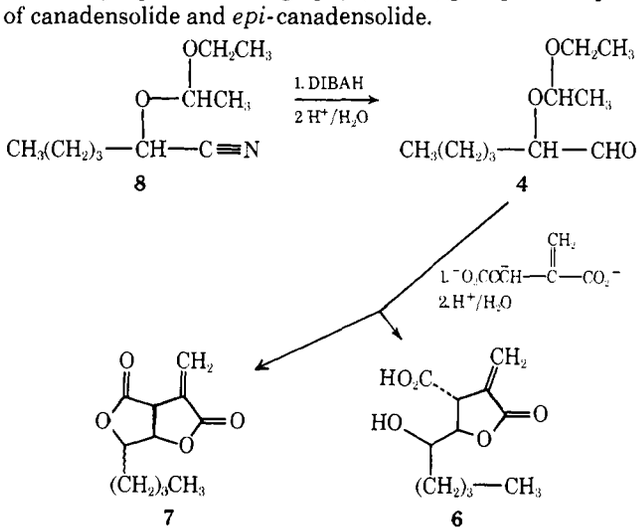
Scheme II



to provide an entry into the desired bislactone system by the addition of methyl itaconate dianion, the formation of the cis chloro lactone **5** (contaminated with 0–20% of the trans lactone **6**) by treatment with acid, and the generation of the bislactone by the silver ion promoted solvolysis of the tertiary halide (Scheme III, Table II).

However, the synthesis of canadensolide itself from α-chlorovaleraldehyde could not be accomplished utilizing this procedure since the requisite cis chloro lactone **5** was not formed during the initial addition step.

The successful synthesis of canadensolide involved the addition of the itaconic acid trianion (**1**, $R_1 = R_2 = Li$)[14] to α-hydroxyvaleraldehyde protected as the ethoxyethyl ether [**4**, $R_5 = CH_3(CH_2)_3$; $R_6 = H$; $X = OCH(OCH_2CH_3)CH_3$]. Moreover, the ease of isolation of the canadensolide isomers by the extraction of the uncyclized acidic products **6** ($R_1 = H$) from the itaconic acid trianion addition provided significant consolation for the relatively low yields. Separation of the isomers by liquid chromatography (HPLC) gave pure samples of canadensolide and *epi*-canadensolide.

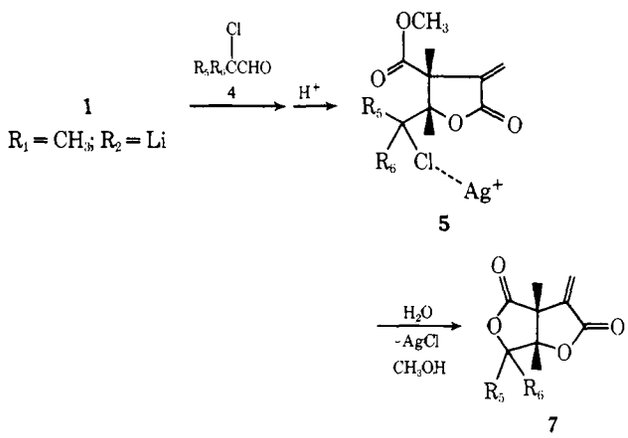


8 **4** **7** **6**

Experimental Section

General. Melting points (uncorrected) were obtained on a Thomas-Hoover capillary apparatus. Infrared spectra were recorded on a Beckman IR-33. NMR spectra were obtained with a Varian EM-360 instrument using Me_4Si as an internal standard. Preparative liquid chromatography (HPLC) was carried out on Waters Associates equipment using two 610 × 9.5 mm columns packed with Porasil A. In most cases ether–hexane mixtures were used at a flow rate of 9.9 ml/min.

Scheme III



5 **7**

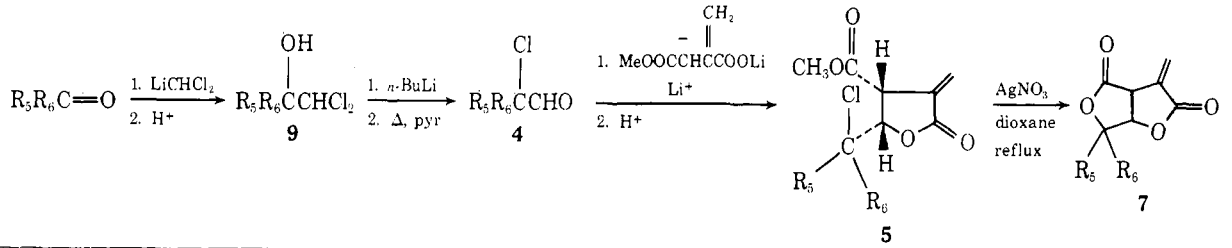
The THF (Aldrich Gold Label, <0.003% H_2O) was maintained under N_2 in septum-capped bottles and removed via syringe. The *n*-butyllithium and the diisobutylaluminum hydride (DIBAH) in hexane were obtained from Alfa Products. The diisopropylamine was distilled from CaH_2 and stored under N_2. The itaconic acid was obtained from Aldrich. The methyl itaconate was prepared by literature methods.[12]

All reactions involving organometallic reagents were carried out under N_2 in septum-capped flasks with introduction of reagents via syringe.

Elemental analyses were performed by Robertson Laboratories, Florham Park, N.J. Mass spectra were run on a Varian CH5 by Mr. Douglas Kuehl, National Water Quality Laboratory, Duluth, Minn.

General Procedure for the Preparation and Addition Reactions of Dianions of Monoesters of Itaconic Acid. The preparation of protolichesterinic acid (**3d**) using *p*-methoxybenzyl itaconate provides a typical example of the experimental procedure for the compounds listed in Table I. LDA[10] was prepared from *n*-butyllithium (4.2 ml of a 2.4 M solution in hexane, 0.010 mol) and diisopropylamine (1.4 ml, 0.010 mol) in 25 ml of THF contained in a septum-capped flask with nitrogen atmosphere at −10 °C. After stirring for 15 min the solution was cooled to −78 °C and *p*-methoxybenzyl itaconate[13] (1.25 g, 0.0050 mol) dissolved in 3 ml of THF was added. After 1.5 h tetradecylaldehyde (1.06 g, 0.0050 mol) in 3 ml of THF was added and the resulting mixture stirred for 7 h at −78 °C before quenching at this temperature with 25 ml of cold 6 M H_2SO_4. Immediate extraction with ether followed by overnight treatment with $MgSO_4$ afforded 2.05 g of a 3:1 mixture (by NMR) of the desired diastereomeric lactones (**2**) and *p*-methoxybenzyl itaconate. After removal of the starting material with a saturated $NaHCO_3$ wash, 1.4 g (64%) of an approximately 1:1 mixture of the two diastereomers remained. Separation of 1.0 g of this mixture by HPLC[15] gave 0.39 g

Table III. Preparation of Bislactones 7. Yield Data



	R_5	R_6	9[e]	4[e]	5[e]	7	Overall yield, %
a	$-CH_2CH_2CH_2CH_2CH_2-$		56% (52183-64-9) bp 55–56 °C (0.2 mm)	70% (53627-10-4) bp 56–60 °C[b] (5.5 mm)	65%[c] (60427-72-7)	31%	8
b	$-CH_2CH_2CH_2CH_2CH_2CH_2-$		74% (52183-65-0) bp 75 °C (0.3 mm)	76% (60464-11-1) bp 55–57 °C (1.4 mm)	29% (60427-73-8)	65%	11
c	$CH_3CH_2CH_2$	$CH_3CH_2CH_2$	49% (60427-70-5) bp 65–68 °C (1.3 mm)	64%[d] (60427-71-6) bp 38–42 °C (1.8 mm)	69%[c] (60427-74-9)	48%	10

[a] Yields represent material of 95% purity (by NMR) unless stated otherwise. [b] Lit. bp 47–50 °C (6 mm): G. Stork et al., *J. Am. Chem. Soc.*, **82**, 4315 (1960). [c] 60–75% pure. [d] 90% pure. [e] Registry no. in parentheses.

(25% overall) of the *p*-methoxybenzyl ester of protolichesterinic acid[16] (**2d**) and 0.26 g (16% overall) of the *p*-methoxybenzyl ester of alloprotolichesterinic acid[16] (**2e**).

The *p*-methoxybenzyl ester of protolichesterinic acid (**2d**) (0.159 g, 0.357 mmol) and trifluoroacetic acid[17] (0.05 ml, 0.714 mmol) in 2 ml of benzene were stirred for 7 h at 25 °C. The reaction mixture was then extracted with a saturated $NaHCO_3$ solution. The combined aqueous extracts were washed with ether, acidified to ~pH 1 with 6 M H_2SO_4, and extracted with ether to give 0.093 g (80%) of (±)-protolichesterinic acid (**3d**).[3]

General Procedure for the Preparation of the Bislactones (7, $R_5 = R_6$ = Alkyl). The general procedure for the preparation of the bislactones shown in Table II is illustrated below for the case of the lactone **7b** [R_5, R_6 = $(CH_2)_6$]. In all cases, the intermediates in the reaction sequence were not isolated in an analytically pure form, but rather, they were used in the subsequent step with little or no purification (see Table III).

Modified literature methods were used to prepare the α-chloro aldehyde.[18] Dichloromethane (11.6 ml, 0.18 mol) was dissolved in 300 ml of dry THF at −78 °C under N_2. *n*-Butyllithium (62.5 ml, 0.15 mol of a 2.4 M solution in hexane) was added dropwise from an addition funnel over a 1-h period. After the resulting solution had stirred for 40 min at −78 °C, cycloheptanone (16.3 ml, 0.138 mol) was added over a 5-min period. The reaction mixture was stirred for 2 h at −78 °C and then was allowed to gradually warm to −35 °C before it was poured into a cold solution of 15 ml of sulfuric acid in 600 ml of water. The resulting mixture was immediately extracted with 1 l. of ether in three portions. The combined ether extracts were dried over $MgSO_4$ and evaporated to yield 33 g of oil. Distillation afforded **9b** [20 g, 74%, bp 75–79 °C (0.3 mm); NMR ($CDCl_3$) δ 1.4–2.2 (broad multiplet, 12 H), 2.3 (s, 1 H), 5.7 (s, 1 H)]. A portion of the alcohol (**9b**) (14.5 g, 0.0738 mol) was dissolved in 180 ml of THF at −78 °C under N_2 and *n*-butyllithium (29.5 ml, 0.0738 mol of a 2.5 M solution in hexane) was added dropwise. After stirring for 20 min at −78 °C, 0.06 ml (0.74 mmol) of pyridine was added and the solution was gradually warmed to reflux and maintained at reflux for 18 h. The mixture was cooled, filtered, diluted with 200 ml of water, and extracted three times with 250-ml portions of ether. The combined ether extracts were dried over $MgSO_4$ and evaporated to give 12.6 g of crude α-chloro aldehyde which was distilled to provide a colorless liquid **4b** [bp 55–57 °C (1.4 mm), 9.03 g, 76% based on alcohol or 56% based on cycloheptane].

The addition of methyl itaconate to the α-chloro aldehyde **4b** was carried out as described below. Diisopropylamine (4.61 ml, 0.0329 mol) was dissolved in 125 ml of dry THF under N_2 at −10 °C and *n*-butyllithium (13.2 ml, 0.0329 mol of a 2.5 M solution in hexane) was added dropwise. After stirring for 15 min at −10 °C, the solution was cooled to −78 °C in a dry ice–acetone bath and 2.37 g (0.016 mol) of methyl itaconate[12] dissolved in 6 ml of THF was added slowly. After stirring for 2 h at −78 °C, 2.6 g (0.016 mol) of the α-chloro aldehyde **4b** in 2 ml of THF was added. After stirring for an additional 4.5 h at −78 °C, the reaction mixture was quenched at this temperature with 100 ml of 6 M H_2SO_4. The dry ice–acetone bath was removed, and after stirring for 5 min the mixture was extracted with 650 ml of ether in three portions. The combined ether extracts were dried overnight with $MgSO_4$. Evaporation of the solvent gave 5.5 g of an oil which contained the addition product, the starting aldehyde, and methyl itaconate (by NMR). This mixture was dissolved in ether and washed with saturated $NaHCO_3$ solution. After drying over $MgSO_4$, the organic layer was slowly evaporated to yield a solid which was purified by hexane trituration. The yield of solid amounted to 1.36 g (29%) and gave an NMR spectrum consistent with structure **5b**: NMR ($CDCl_3$) δ 1.65 (m, 8 H), 2.25 (m, 4 H), 3.85 (s, 3 H), 4.25 (d, t, *J* = 8, 2 Hz, 1 H), 4.8 (d, *J* = 7 Hz, 1 H), 5.95 (d, *J* = 2 Hz, 1 H), 6.6 (d, *J* = 2 Hz, 1 H).

Closure to the bislactone **7b** was effected with silver nitrate. Silver nitrate (0.8 g, 0.0047 mol) was dissolved in 12 ml of water and 20 ml of dioxane and heated to reflux. The product **5b** (0.67 g, 0.00235 mol) dissolved in 5 ml of dioxane was then added and the resulting mixture was maintained at reflux for 15 min. After cooling, the mixture was filtered and concentrated on a rotary evaporator. The residue was diluted with water and extracted three times with methylene chloride. The combined organic extracts were washed twice with brine and dried over $MgSO_4$. Evaporation gave 0.49 g (88%) of white solid of mp 142–146 °C (>85% pure by NMR). Recrystallization from THF gave analytically pure **7b** (0.362 g, 65%, mp 148–151 °C).

Preparation of Canadensolide. To the ethyl vinyl ether adduct[19] of valeraldehyde cyanohydrin[20,21] (**8**) (18.3 g, 0.099 ml), dissolved in 100 ml of hexane at −78 °C under nitrogen, was added 108 ml (0.105 mol) of a 0.97 M solution of DIBAH in hexane over a period of 40 min. After stirring for an additional 30 min, the reaction mixture was poured into 690 ml (6.9 mol) of 10 M acetic acid cooled to 0 °C. The resulting mixture, after stirring for 30 min at 0 °C, was extracted three times with hexane (1250 ml total). The combined extracts were diluted with 200 ml of a saturated sodium bicarbonate solution and solid sodium bicarbonate was added to the resulting mixture until carbon dioxide ceased to be liberated. The organic layer was separated, washed one time with 200 ml of saturated sodium bicarbonate solution, and dried over $MgSO_4$. The crude yield of product, which amounted to 12.2 g (66%), was shown by NMR to be 75–83% pure. Distillation afforded analytically pure aldehyde 4 [$R_5 = CH_3(CH_2)_3$; R_6 = H; X = $OCH(OCH_2CH_3)CH_3$;[22,23] 8.7 g, 47% yield, bp 46 °C (0.8 mm); NMR ($CDCl_3$) δ 0.8–2.0 (m, 15 H), 3.4–4.2 (m, 3 H), 4.8 (m, 1 H), 9.75 (m, 1 H); ir (neat) 1750 cm^{-1} (C=O)].

LDA[10] in 140 ml of THF was prepared from 6.06 ml (0.0432 mol) of diisopropylamine and 17.3 ml (0.0432 mol) of a 2.5 M *n*-butyllithium solution in hexane at −10 °C under nitrogen. After 15 min the pale-yellow solution was cooled to −78 °C and 1.87 g (0.0144 mol) of itaconic acid in 9 ml of THF was added. After 4 h at −78 °C, the 2-(1-ethoxy)ethoxyvaleraldehyde (**4**) was added to the finely divided suspension. After an additional 4 h at −78 °C, the reaction mixture was quenched at this temperature with 87 ml of 6 M H_2SO_4. The dry ice–acetone bath was then removed and the reaction mixture stirred vigorously for 25 min before extraction with 400 ml of ether in three portions. The ether extracts were combined and dried overnight with $MgSO_4$.[24] Evaporation yielded 3.5 g of a complex mixture which included itaconic acid, canadensolide (and its epimer), and unidentified

products. In order to remove itaconic acid and uncyclizable trans products **6** (R_1 = H), the mixture was dissolved in ether and washed three times with a saturated solution of sodium bicarbonate. After drying over $MgSO_4$, the ether was evaporated to yield 1.01 g of a mixture containing canadensolide. This mixture was separated by HPLC using 9:1 ether–hexane and columns deactivated as previously described.[15] The first peak, which appeared after 5 min, amounted to 0.48 g of material which presumably was largely derived from the unreacted aldehyde (based on NMR). The second peak, which appeared after 6.9 min, amounted to 0.225 g (7.4% based on starting aldehyde) of slightly impure (±)-*epi*-canadensolide. The third peak, which appeared after 12.5 min, amounted to 0.134 g (4.4% based on starting aldehyde) of impure (±)-canadensolide.

The material derived from the second peak was recrystallized once from ether–hexane to yield (±)-*epi*-canadensolide [0.179 g, 5.9%, mp 47–48 °C (lit.[5b] mp 47.5–48.5 °C); NMR ($CDCl_3$) δ 0.95 (t, J = 6 Hz, 3 H), 1.2–1.9 (m, 6 H), 4.1 (dt, J = 7 and 2 Hz, 1 H), 4.75 (dt, J = 7 and 1 Hz, 1 H), 5.1 (dt, J = 8 and 1 Hz, 1 H), 6.3 (d, J = 2 Hz, 1 H), 6.6 (d, J = 2 Hz, 1 H)].

The material derived from the third peak was recrystallized once from ether to yield (±)-canadensolide [0.071 g, 2.3%, mp 96–96.5 °C (lit.[5b] mp 92.5–93.5 °C); NMR δ 0.92 (t, J = 6 Hz, 3 H), 1.1–2.2 (m, 6 H), 4.05 (dt, J = 7 and 2 Hz, 1 H), 4.7 (m, 1 H), 5.22 (m, 1 H), 6.2 (d, J = 2 Hz, 1 H), 6.51 (d, J = 2 Hz, 1 H)].

Acknowledgment. We wish to express our appreciation to Professor A. Yoshikoshi, Tohoku University, Sendai, Japan, for providing ir and NMR spectra of authentic canadensolide and *epi*-canadensolide and to Professor N. J. McCorkindale, the University of Glasgow, Glasgow, Scotland, for unpublished information on canadensolide and canadensic acid. Technical support for certain aspects of this research effort was provided by Mr. Brian Kobilka and Mr. William Schmidt.

Registry No.—**4** [R_5 = $CH_3(CH_2)_3$; R_6 = H; X = $OCH(OCH_2CH_3)CH_3$], 60427-75-0; **7** [R_5 = H; R_6 = $(CH_2)_3CH_3$], 35093-30-2; **7** [R_5 = $(CH_2)_3CH_3$; R_6 = H], 35093-28-8; **8**, 60427-76-1; *p*-methoxybenzyl itaconate, 60427-77-2; methyl itaconate, 7338-27-4; cyclohexanone, 108-94-1; cycloheptanone, 502-42-1; heptan-4-one, 123-19-3; acetone, 67-64-1; cyclopentanone, 120-92-3; pentan-3-one, 96-22-0; tetradecanal, 124-25-4; dodecanal, 112-54-9.

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(14) The use of dianions **1** (R_1 = CH_3, R_2 = Li; R_1 = $ArCH_2$, R_2 = Li) provided only trace amounts of candensolide and its epimer.
(15) The Porasil A columns were deactivated with a 3:2 mixture of ether–2-propanol before the preparative separation was carried out using a 5:1.5:93.5 ether–2-propanol–hexane mixture. Failure to deactivate the columns resulted in extensive isomerization of the double bond of these α-methylene lactones to form α-methyl butenolides.
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(22) A satisfactory elemental analysis (±0.3%) was obtained for this compound.
(23) NMR showed the distilled product to be an approximately 1:1 mixture of two diastereomers. HPLC analysis was not possible owing to apparent decomposition on "μ Porasil" column.
(24) Traces of acid in the ether apparently account for a substantial amount of ring closure. Experiments in which the ether extracts were washed with brine before drying resulted in greatly decreased amounts of ring closed products.