and extracted with ether (30 ml) to remove traces of nitrobenzene. The sodium hydrogen carbonate extract was acidified to pH <1 by dropwise addition of concentrated hydrochloric acid and reextracted with chloroform (4 × 15 ml). The pooled chloroform extracts were dried ($Na_2SO_4$) and the solvent was removed in vacuo to leave 1.20 g of viscous brown oil, which after standing for 2 days at 5° crystallized. Attempted recrystallization from benzene at this stage failed and the crude product was chromatographed on a 1-in. column packed with 60 g of silica gel with chloroform–acetic acid (19:1) as eluent. This procedure afforded a product which when recrystallized from benzene gave 0.7 g (68%) of pure **28:** mp 119–121°; NMR ($CDCl_3$) δ 2.00–2.59 (2 H, m, five lines), 2.63–3.26 (2 H, m), 3.45 (2 H, t, $J$ = 8 Hz), 3.70 (3 H, s), 4.82 (2 H, t, $J$ = 7 Hz), 4.70–4.96 (1 H, m); uv $\lambda_{max}$ 221 nm (log ε 3.65) and 274 (4.25).

Anal. Calcd for $C_{11}H_{12}O_6$: C, 55.00; H, 5.04. Found: C, 54.95; H, 5.13.

**(±)-Carlic Acid (1a).** Carlic acid methyl ester (0.70 g) was dissolved in 3 *N* potassium hydroxide (10 ml) and left at room temperature for 72 hr. The solution was acidified with concentrated hydrochloric acid to pH <1 and evaporated to dryness in vacuo. The remaining solid mass was extracted with boiling chloroform (8 × 10 ml) and the chloroform was removed, leaving 0.54 g of crystalline material, mp 176–180°. One recrystallization from ethyl acetate–ethanol gave 0.50 g (76%) of pure carlic acid: mp 177–180° [lit.[22] mp of (−)-carlic acid 176°]; NMR (DMSO-$d_6$) δ 1.90–2.48 (2 H, m, five lines), 2.50–3.15 (2 H, m), 3.36 (2 H, t, $J$ = 8 Hz), 4.70 (2 H, t, $J$ = 7.5 Hz), 4.55–5.00 (1 H, m); uv $\lambda_{max}$ 226 nm (log ε 3.73) and 273 (4.23).[26]

Anal. Calcd for $C_{10}H_{10}O_6$: C, 53.10; H, 4.46. Found: C, 52.90; H, 4.57.

**Registry No.**—**1,** 55088-89-6; **1a,** 55088-90-9; **2,** 54423-52-8; **3,** 54397-56-7; **4,** 54397-59-0; **5,** 55088-91-0; **6,** 55088-92-1; **7,** 55088-93-2; **8,** 54397-58-9; **9,** 40421-01-0; **10,** 55088-94-3; **10a,** 55088-95-4; **11,** 55088-96-5; **15,** 54423-53-9; **16,** 55088-97-6; **17,** 54397-60-3; **19,** 55088-98-7; **20,** 55088-99-8; **23,** 55089-00-4; **24,** 41479-98-5; **26,** 33177-29-6; **27** (R = $CH_3$), 53252-38-3; **28,** 54397-61-4; ethyl chlorocarbonylacetate, 36239-09-5; ethyl hydrogen malonate, 1071-46-1; thionyl chloride, 7719-09-7; diethyl malate, 7554-12-3; fumaric acid, 110-17-8; bromine, 7726-95-6; ethyl acetoacetate, 141-97-9; *trans*-3-ethoxycarbonylacrylyl chloride, 26367-48-6; ethyl 3-oxohexanoate, 3249-68-1; 3-oxodecanoate, 13195-66-9; ethyl 6-chloro-3-oxohexanoate, 54362-87-7.

## References and Notes


(1) Part of this material has been presented in a preliminary communication, Part VII: A. Svendsen and P. M. Boll, *Tetrahedron Lett.*, 2821 (1974).
(2) L. J. Haynes and J. W. M. Jamieson, *J. Chem. Soc.*, 4132 (1958).
(3) F. H. Andresen, A. Svendsen, and P. M. Boll, *Acta Chem. Scand., Ser. B,* **28,** 130 (1974).
(4) J. L. Bloomer and F. E. Kappler, *J. Org. Chem.*, **39,** 113 (1974).
(5) R. Nicoletti and L. Baiocchi, *Ann. Chim. (Rome)*, **54,** 170–179 (1964).
(6) R. N. Lacey, *J. Chem. Soc.*, 832 (1954).
(7) L. J. Haynes and A. H. Stanners, *J. Chem. Soc.*, 4103 (1956).
(8) A. Svendsen and P. M. Boll, *Tetrahedron*, **29,** 4251 (1973).
(9) G. S. Skinner, *J. Am. Chem. Soc.*, **59,** 322 (1937).
(10) G. S. Skinner and R. de V. Huber, *J. Am. Chem. Soc.*, **73,** 3321 (1951).
(11) R. P. Linstead and H. N. Rydon, *J. Chem. Soc.*, 580 (1933).
(12) U. Eisner, J. A. Elvidge, and R. P. Linstead, *J. Chem. Soc.*, 1501 (1951).
(13) This mechanism is adopted on suggestion of one of the referees. We gratefully acknowledge this improvement.
(14) L. J. Haynes and J. R. Plimmer, *Q. Rev., Chem. Soc.*, **14,** 292 (1960).
(15) E. Benary, *Ber.*, **40,** 1079 (1907).
(16) T. P. C. Mulholland, R. Foster, and D. B. Haydock, *J. Chem. Soc., Perkin Trans. 1,* 1225 (1972).
(17) E. B. Reid and W. R. Ruby, *J. Am. Chem. Soc.*, **73,** 1054 (1951).
(18) H. G. Viehe and M. Reinstein, *Chem. Ber.*, **95,** 2557 (1962).
(19) S. Gelin and A. Galliaud, *C. R. Acad. Sci.*, **275,** 897 (1972).
(20) During the preparation of this manuscript a paper appeared in which essentially the same synthetic idea is presented: S. Gelin and P. Pollet, *C. R. Acad. Sci., Ser. C,* 345 (1974).
(21) A. Svendsen and P. M. Boll, *Acta Chem. Scand., Ser. B,* **29,** 197 (1975). Recently an alternative route to this compound has been devised: *C. R. Acad. Sci., Ser. C,* 263 (1974).
(22) P. W. Clutterbuck, W. N. Haworth, H. Ralstrick, G. Smith, and M. Stacey, *Biochem. J.*, **28,** 94 (1933).
(23) D. S. Breslow, E. Baumgarten, and C. R. Hauser. *J. Am. Chem. Soc.*, **66,** 1286 (1944).
(24) P. W. Clutterbuck, H. Ralstrick, and F. Reuter, *Biochem. J.*, **29,** 300 (1935).
(25) J. H. Birkinshaw and M. S. Samant, *Biochem. J.*, **74,** 369 (1960).
(26) The synthetic compound has not been compared with the naturally occurring one, but carlosic acid as well as viridicatic acid have been degraded to 3-bromo-5-carboxylmethyltetronic acid (**6**) according to ref 25 as further evidence for the synthesis of the racemic forms of the natural products.


# Synthetic Study of (±)-Canadensolide and Related Dilactones. Double Lactonization of Unsaturated Dicarboxylic Acids via Acyl Hypoiodite Intermediates


Michiharu Kato, Masanori Kageyama, Reiko Tanaka, Kozo Kuwahara, and Akira Yoshikoshi*

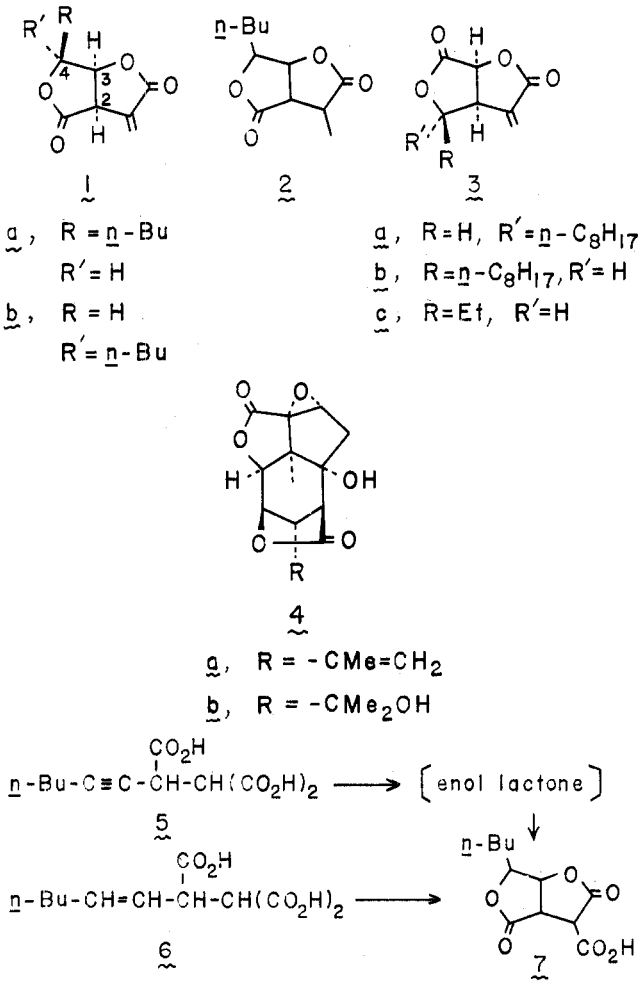
*Chemical Research Institute of Non-Aqueous Solutions, Tohoku University, Sendai 980, Japan*


*Received February 4, 1975*


Stereospecific oxidation of **12a** and **12b,** followed by methylenation, yielded **1b** and **1a,** respectively. The latter product was identified as (±)-canadensolide and has resulted in a revision of the stereochemistry previously proposed for this natural dilactone. Furthermore, a new stereospecific double lactonization reaction of olefinic dicarboxylic acids has been found. Besides a demonstration with some model compounds, it has been used to lactonize **54** and **57** giving **1b** and **1a,** respectively.


Canadensolide (**1a**) is a mold metabolite produced by *Penicillium canadense* and has an antigerminative activity against fungi, e.g., *Botrytis alii.* It was isolated from the culture filtrate, along with other closely related compounds, and their structures were assigned by McCorkindale et al.[1] A structural feature of canadensolide is its di-γ-lactone system, and the analogous di-γ-lactone structure has been found in other acetogenins, dihydrocanadensolide[1] (**2**), avenaciolide[2] (**3a**), 4-isoavenaciolide[3] (**3b**), and ethisolide[3] (**3c**), and in the sesquiterpenoids picrotoxinine[4] (**4a**) and picrotine[4] (**4b**).

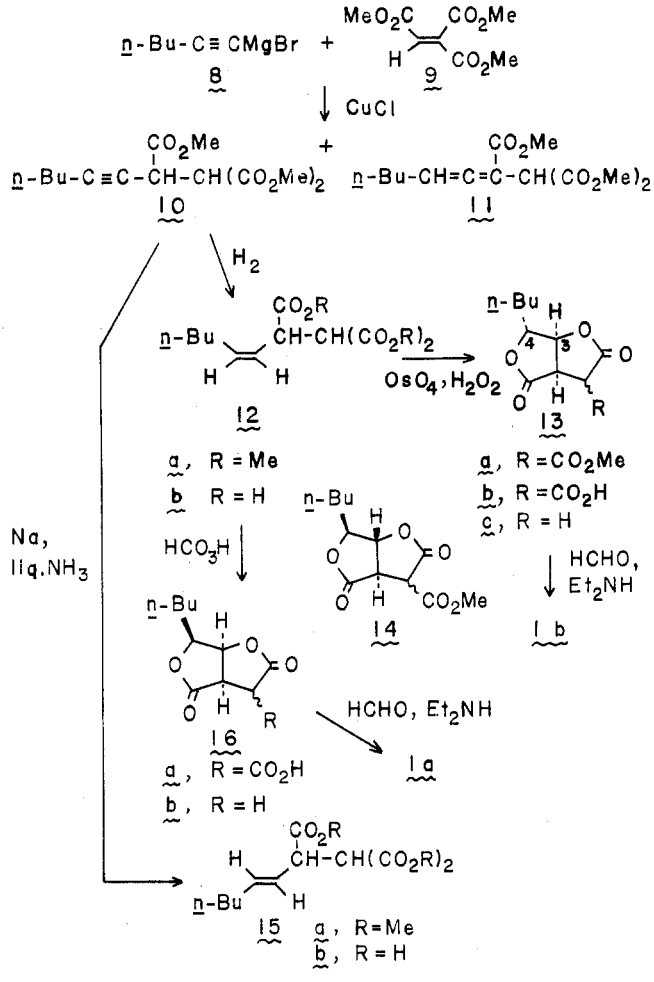
We were interested in the synthesis of canadensolide and related di-γ-lactone systems.[5] Our synthetic design envisaged a double lactonization of unsaturated tricarboxylic acids, such as **5** or **6,** which would lead to the dilactonic carboxylic acid (**7**). The extra carboxyl group in **7** might then be utilized for the introduction of an exocyclic methylene group.



**Stereochemistry of Canadensolide.** The original stereochemistry of canadensolide (**1b**) was assigned on the basis of NMR evidence.[1] Alignments of protons at C(2), C(3), and C(4) have been given on their NMR coupling constants, i.e., $J_{2,3}$ = 6.5 and $J_{3,4}$ = 4.5 Hz, respectively. However, it is recognized that the Karplus relation between coupling constants and dihedral angles largely depends upon the electronegativity of substituents, bond angles, and bond lengths.[6] Thus to confirm the stereochemistry of canadensolide assigned by McCorkindale et al.,[1] we attempted the synthesis according to formula **1b** via stereochemically well-documented reactions.[7]

1-Hexynylmagnesium bromide (**8**) was allowed to react with trimethoxycarbonylethylene[8] (**9**) in the presence of cuprous chloride and gave an adduct (**10**) (73% yield) accompanied by a minor amount of the allene derivative[9] (**11**) in a ratio of 20:1 (GLC) (Chart I). Hydrogenation of **10** over Lindlar catalyst yielded the cis olefinic ester (**12a**) in 74% yield, which when submitted to oxidation with Milas' reagent afforded a crystalline dilactone (22% yield). The structure (**13a**) depicted for this dilactone was supported by its spectra. The lack of stereoselectivity presumed for this oxidation led us to anticipate the formation of two diastereomeric cis oxidation intermediates, one of which should give **13a** upon lactonization. The other diastereomer should give largely strained trans dilactone (**14**), provided that its double lactonization were possible under reaction conditions used. Nevertheless, we did not encounter the latter lactone or its progenitors and, in fact, the facile formation of a single dilactone, obtained under such mild reaction conditions, suggested the product to be an unstrained cis-fused compound (**13a**). When lactone **13a** was hydrolyzed by heating with dilute hydrochloric acid at 55°,

**Chart I**



the corresponding carboxylic acid (**13b**) was obtained; on the other hand, heating with the same mineral acid at 100–110° resulted in the formation of the decarboxylation product (**13c**). The latter compound was also obtained from the cis olefinic acid (**12b**), itself prepared by alkaline hydrolysis of **12a**, upon treatment with Milas' reagent followed by acetic anhydride (29% yield). The dilactone **13c** has been prepared by Mukaiyama et al.[10] using an alternative route, and our compound was identified by comparison with their compound. To introduce an exo methylene group, the carboxylic acid **13b** was treated, according to Parker and Johnson,[5b] with formalin and diethylamine in acetic acid and then with sodium acetate. The unsaturated lactone **1b** was obtained in 64% yield. The NMR spectrum of **1b** was similar to that of canadensolide, but they were distinctly different. A prominent difference was that the coupling constant between protons at C(3) and C(4) for this compound is 1.5 Hz, whereas 4.5 Hz has been reported for the corresponding proton coupling of natural product. These results raised doubts about the orientation assigned to the *n*-butyl group in canadensolide and therefore we turned to a synthesis of its epimer (**1a**) by analogous routes.

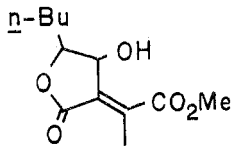
The acetylenic ester **10** yielded the trans olefinic ester **15a** on treatment with sodium in liquid ammonia (69% yield). A similar cis oxidation of **15a** with Milas' reagent then afforded a mixture from which we failed to separate the desired dilactonic ester. Trans oxidation of the cis olefinic ester **12a** with performic acid also gave an inseparable mixture. However, when the former product was heated with dilute sulfuric acid, crystals could be isolated, whose spectra seemed to be consistent with formula **16b**. In addi-

**Table I**
**Double Lactonization of Norbornenedicarboxylic Acid (22)**

| Run | Salt of 22 | Reaction conditions: Solvent | Reagent | Temp, °C (time, hr) | Yield of 23, % |
|---|---|---|---|---|---|
| 1 | Na[a] | DMSO | $I_2$ | Room temp (12) | 0 |
| 2 | K[b] | *t*-BuOH | $I_2$ | Room temp (15) and then 50 (2) | 0 |
| 3 | K[b] | DMSO + $H_2O$ (40:1) | $I_2$, KI | 50 (18) | 27 |
| 4 | Na[a] | DMSO | $I_2$, AgOAc | 50 (15) | 64 |
| 5 | Ag[c] | DMSO[d] | $I_2$, AgOAc | 60 (12) | 92 |

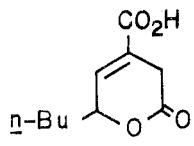
[a] Neutralized with sodium bicarbonate. [b] Neutralized with potassium *tert*-butoxide. [c] Prepared from the sodium salt by an exchange reaction with silver nitrate. [d] When dimethylformamide was used as solvent, 23 was obtained in 88% yield.

tion the coupling constant between C(3) and C(4) protons in the NMR spectrum was 4.0 Hz. The performic acid oxidation product of **12a** was then heated with dilute hydrochloric acid at 55°, and the resulting thick oily hydrolysis product, probably consisting of dilactonic acid (**16a**) for the most part, was treated with formalin and diethylamine as in the previous case. The unsaturated dilactone (**1a**) obtained was completely identical with natural canadensolide by spectral comparison.[11] We thus conclude that the relative stereochemistry of canadensolide should be revised to that depicted in **1a**.[12] Consequently, the configuration of the butyl groups assigned to other mold metabolites correlated to canadensolide, i.e., dihydrocanadensolide[1] (**2**) and the monolactonic ester[1] (**17**), should also be revised.

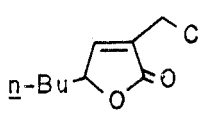


**17**

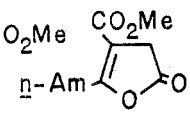
**Double Lactonization.** At the outset we examined the double lactonization of the acetylenic acid **5**, which was obtained in 85% yield by alkaline hydrolysis of **10** under mild conditions. The hydrolysis product was accompanied by a minor amount of δ-lactone **18**, which was probably formed



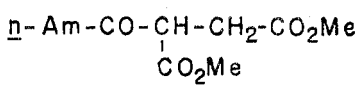
**18**



**19**



**20**



**21**

by partial lactonization of **5** upon acidification or during silica gel chromatography of the hydrolysis product. Attempted double lactonization of **5** failed to lead to dilactones. Treatment of **5** with silver nitrate in aqueous dioxane followed by diazomethane provided the butenolide **19** in good yield, which was also obtained by heating **5** followed by esterification. The acetylenic acid lactonized in cold sulfuric acid giving an enol-γ-lactone in good yield, and the product was characterized as its ester **20**. On the other hand, treatment of **5** with dilute sulfuric acid in the presence of mercuric salt followed by esterification yielded the major hydration product **21**, along with **19** and unidentified compounds. Although it was of interest that the acetylenic acid underwent lactonization and decarboxylation at different positions depending upon reaction conditions, such attempts to form the desired dilactone seemed to be hopeless. We then decided to examine the oxidation of related olefinic acids.

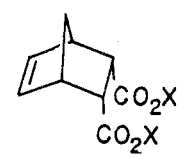
**Table II**
**Double Lactonization of Some Olefinic Dicarboxylic Acids via Acyl Hypoiodites**

| Acid | Product | Yield, % |
|---|---|---|
| **22a**[13] | **23**[14] | 92 |
| **24** | **25**[16] | 56 |
| **26** | **27**[16] | 60 |
| **28**[17] | **29** | 52 |
| **30**[18] | **31** | 77 |
| **32** | **33** | 47 |
| **34**[19] | **35**[b] | 32 |

[a] The yields were not optimized. [b] Dimethylformamide was used as solvent for convenience of work-up.

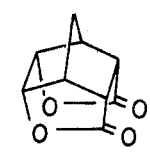
When an olefinic polycarboxylic acid undergoes halolactonization, the halogen atom of the initially formed halolactone may then serve as a leaving group for the intramolecular attack of carboxylate ion in the second lactonization that leads to the dilactone, provided that stereochemical requirements are satisfied.

Prior to the examination of the olefinic acids, such as **48**, we began with norbornenedicarboxylic acid[13] (**22a**) as a



**22**

**a**, X = H
**b**, X = I



**23**

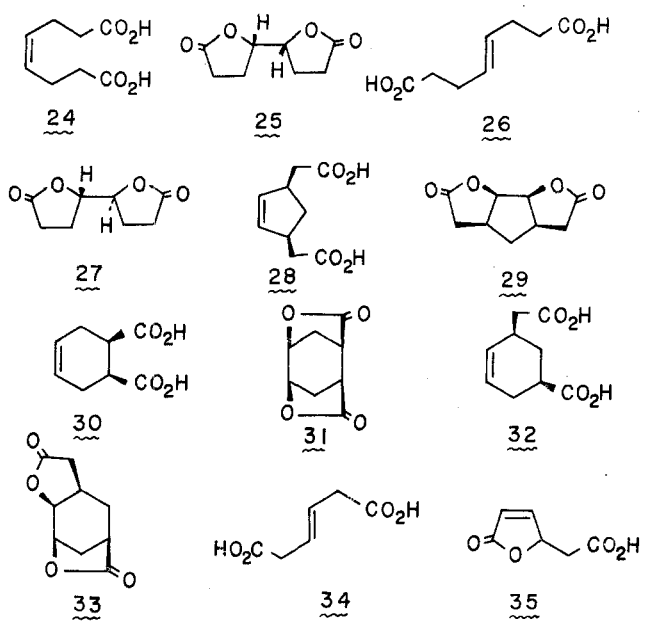
model compound. Some typical runs are summarized in Table I.

Under anhydrous conditions aprotic (run 1) or protic solvent (run 2) did not effect double lactonization, while addition of water (run 3) gave dilactone[14] **23** in low yield.[15] Addition of silver acetate to promote the ionization of iodine atom of the intermediate iodolactone improved the yield of **23** remarkably (run 4). An almost quantitative yield was obtained when the silver salt of the acid was treated with iodine and silver acetate in dimethyl sulfoxide (run 5). Under the last-mentioned reaction conditions diacyl dihypoiodite (**22b**) is likely involved as a reactive intermediate.

This double lactonization using silver salts was examined with some other olefinic dicarboxylic acids, and the results are summarized in Table II.

It was found that this reaction is general in nature and results in good yields of dilactones. An exception, however, is the silver salt of *trans*-dihydromuconic acid (**34**), which gave the butenolide **35** upon treatment with iodine and silver acetate but no lactone. Its formation can be rationalized in terms of a faster elimination of hydrogen iodide than the rate of the second lactonization, since the inter-

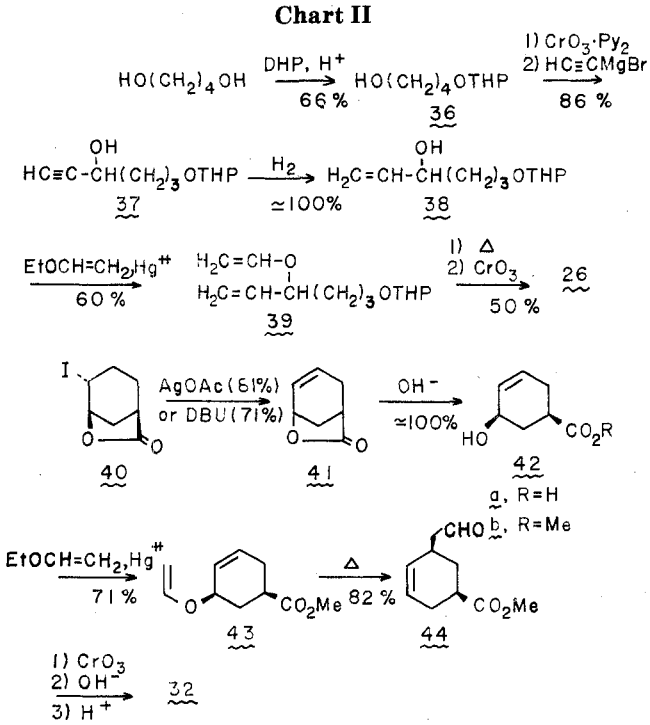
mediate is anticipated to be a β-iodobutyrolactone. Dilactone **33** involves a dilactonic structure which has been



found in some picrotoxane sesquiterpenoids, e.g., picrotoxinine[4] (**4a**) and picrotine[4] (**4b**).

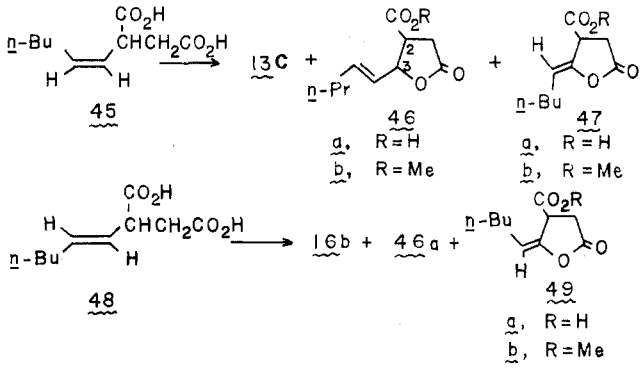
The synthesis of the new olefinic acids used is as follows. The dimethyl ester of (*Z*)-4-octenedioic acid (**24**) was prepared by hydrogenation of dimethyl 4-octynedioate[20] over Lindlar catalyst. Dicarboxylic acids **26**[22] and **32** were prepared as shown in Chart II.

**Chart II**



Next we utilized the above double lactonization reaction for the synthesis of canadensolide and related dilactones. Cis and trans olefinic dicarboxylic acids, **45** and **48**, were prepared by decarboxylation of the tricarboxylic acids **12b** and **15b**, respectively. The latter tricarboxylic acid was obtained by alkaline hydrolysis of the corresponding ester **15a**. Under standard conditions, silver salts of **45** and **48** yielded 4-*epi*-norcanadensolide (**13c**) and norcanadensolide (**16b**) in 30 and 41% yields, respectively (Chart III). As

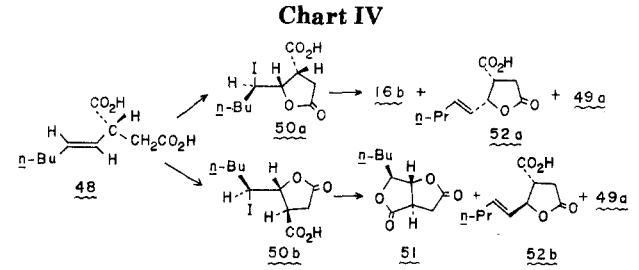
**Chart III**



acidic by-products, the former silver salt gave butyrolactones **46a** and **47a**, while the latter provided **46a** and butyrolactone **49a** isomeric with **47a**. These by-products were characterized as methyl esters (**46b**, **47b**, and **49b**). It is noteworthy that the same butyrolactone (**46a**) was obtained from both of the silver salts, and that isomeric butyrolactones, **47a** and **49a**, were formed in respective reactions. Stereochemical assignments for **47a** and **49a** were made on the basis of the difference in chemical shift values in the NMR spectra of their esters, **47b** and **49b**; i.e., the former ester showed an olefinic proton signal at a distinctly higher field than did the corresponding proton of the latter ester (Δδ 0.47 ppm).

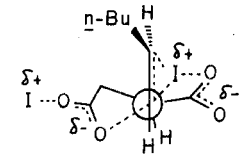
These results suggested the following mechanistic pathway for the formation of the lactones. The carboxyl group that participated in the first lactonization is the less substituted one, because we observed no formation of $\Delta^{\alpha,\beta}$-butenolide, which would be a possible product if the more substituted carboxyl formed the first lactone ring, as we saw in the case of **34**. This is simply explained in terms of the sterically hindered approach of the more substituted carboxyl group. Chart IV demonstrates the reaction of the

**Chart IV**



trans olefinic acid **48** (silver salt). Two diastereomeric iodolactone intermediates, **50a** and **50b**, may be formed. Assuming that the second lactonization proceeds by bimolecular substitution, the former intermediate (**50a**) would give norcanadensolide (**16b**), whereas **50b** would lead to the formation of strained dilactone **51**. Either of the intermediates should afford the same butyrolactone (**49a**) by trans elimination of hydrogen iodide with methine proton, whereas by trans elimination of hydrogen iodide with one of methylene protons they would produce butyrolactones **52a** and **52b**, respectively. A similar discussion leads us to assume the formation of 4-*epi*-norcanadensolide (**13c**), butyrolactones **52a** and **52b**, and **47a** from the cis olefinic acid **45**. The stereochemistry of the butyrolactone **46b** could not be assigned directly from the coupling constant (6 Hz) between protons at C(2) and C(3). It should be noticed, however, that only one isomer (**46a**) was obtained from both of the cis and trans olefinic acids (**45** and **48**). This fact allowed us to conclude that in the first iodolactonization step, the iodine atom of the more substituted hypoiodite group partic-

ipated in the transition state of this reaction as shown in **53.** Such a fixation of the conformation in the transition

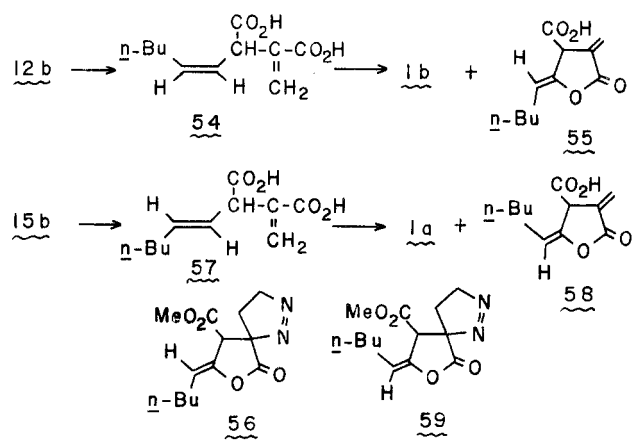


53

state accounts well for the formation of the same butyrolactone (**46a**) from either of the olefinic acids. If this mechanism is operative, the butyrolactone must be cis disubstituted, i.e., **52a,** although we did not verify it.

Finally the double lactonization reaction was applied to the synthesis of (±)-canadensolide and its 4 epimer (Chart V). Cis and trans olefinic tricarboxylic acids, **12b** and **15b,**

**Chart V**



were treated with formalin and dimethylamine, affording unsaturated dicarboxylic acids **54** and **57** in yields of 43 and 42%, respectively. When the silver salt of **54** was treated under similar conditions, (±)-4-*epi*-canadensolide (**1b**, 14% yield) and an acidic product were obtained. Similarly **57** gave (±)-canadensolide (**1a**, 21% yield) accompanied by an acidic product. Although lower yields than those of the corresponding nordilactones were obtained in the above reactions, it may be partly ascribed to an increased strain in the formation of lactone rings due to the replacement of $sp^3$ by $sp^2$ carbon atoms. The acidic by-products were treated with diazomethane, giving pyrrazolines **56** and **59,** respectively. This indicated that the acidic products in the above reactions were unsaturated butyrolactones **55** and **58,** respectively.

## Experimental Section

All melting points and boiling points are uncorrected. IR spectra were taken on a Hitachi EPI-S2 or a G-2 spectrometer. NMR spectra were obtained by a Jeol Model C-60HL spectrometer using $Me_4Si$ ($\delta$ 0) as an internal standard and $CDCl_3$ as the solvent unless otherwise indicated. Coupling constants ($J$) are given in hertz. Mass spectra were obtained on a Hitachi RMU-6D spectrometer. GLC analyses were performed on a Jeol Model JGC-750 instrument using the following columns: A (20% PEG, 2 m × 3 mm) and B (10% SE-30, 2 m × 3 mm).

**1,1,2-Tricarbomethoxy-3-octyne (10).** A solution of 1-hexyne[23] (2.83 g) in dry tetrahydrofuran (20 ml) was added to a stirred Grignard reagent solution, prepared from ethyl bromide (3.71 g) and magnesium (816 mg) in the same solvent (20 ml), at room temperature. After the mixture had been stirred overnight, anhydrous cuprous chloride (15 mg) was added. Tricarbomethoxyethylene[8] (**9,** 5.39 g) in dry tetrahydrofuran (100 ml) was then added dropwise to the above solution in an ice bath. The reaction mixture was stirred at room temperature overnight, and then water (150 ml) and 3 *N* hydrochloric acid (10 ml) were added. The product was extracted with ether, and the combined extracts were washed with water and brine and dried. Removal of the solvent gave a brownish-red oil,[24] which was chromatographed on silica gel. Elution with petroleum ether–ether (3:1) afforded **10** (5.79 g, 73%) as a colorless oil. An analytical sample was obtained by distillation (bath temperature, 120°) in vacuo (0.3 mm). The distillate gradually crystallized on standing: mp 26–27.5°; ir (KBr) 2220 and 1760–1740 $cm^{-1}$; NMR ($CCl_4$) $\delta$ 0.89 (t, 3 H, $J$ = 6.0 Hz), 1.1–1.6 (br m, 4 H), 2.14 (br t, 2 H, $J$ = 6.0 Hz, $CH_2C\equiv$), 3.75 and 3.78 (s, 3 H each), and 4.0 (br s, 2 H, $CHCO_2Me$).

Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.38; H, 6.92.

**Methyl 2,3-Dimethoxycarbonyl-3,4-nonadienoate (11).** The ester **10** (300 mg) was added to a solution of sodium amide prepared from sodium (70 mg) and liquid ammonia (200 ml), and the mixture was stirred for 2 hr. After evaporation of liquid ammonia, water (50 ml) was added to the residue. The product was extracted with ether, and the combined extracts were washed with water and brine and dried. Removal of the solvent gave a yellow oil (300 mg), which was chromatographed on silica gel. Elution with petroleum ether–ether gave the recovered acetylenic ester **10** (150 mg) and then oily **11** (70 mg, 23%). An analytical sample was obtained by distillation (bath temperature, 120°) in vacuo (0.3 mm): ir (liquid film) 1960, 1755 (sh), and 1710 $cm^{-1}$; NMR $\delta$ 0.91 (t, 3 H, $J$ = 6 Hz), 1.1–1.6 (m, 4 H), 1.97–2.35 (m, 2 H, $CH_2CH{=}C{=}C$), 3.78 (s, 9 H), 4.55 (d, 1 H, $J$ = 1.5 Hz, $CHCO_2Me$), and 5.80 (dt, 1 H, $J$ = 7.0 and 1.5 Hz, $CH{=}C{=}C$).

Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.34; H, 7.34.

**Methyl 2,3-Dimethoxycarbonyl-(*Z*)-4-nonenoate (12a) and Its Parent Acid (12b).** The ester **10** (470 mg) was hydrogenated over 5% palladium on barium sulfate (20 mg) in methanol (3 ml) containing synthetic quinoline (20 mg). After 1 equiv of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated in vacuo. The residual oil was chromatographed on silica gel. Petroluem ether–ether (3:1) eluted **12a** (350 mg, 74%). An analytical sample was obtained by distillation (bath temperature, 150–160°) in vacuo (0.3 mm): ir (liquid film) 1760 (sh) and 1745 $cm^{-1}$; NMR 0.92 (t, 3 H, $J$ = 6 Hz), 1.1–1.6 (m, 4 H), 1.9–2.4 (m, 2 H), 3.75 and 3.72 (s, 3 H each), 4.0 [m, 2 H, $CHCO_2Me$ and $CH(CO_2Me)_2$], 5.25 (m, 1 H, $J$ = 10.5, 10, and 1.2 Hz, Bu-CH=CH), and 5.72 (m, 1 H, $J$ = 10.5, 7.2, and 1.0 Hz, BuCH=C).

Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.75. Found: C, 58.93; H, 7.52.

A suspension of the ester **12a** (685 mg) in an aqueous solution (10 ml) of sodium hydroxide (396 mg) was stirred for 5 hr at room temperature and then at 60–70° for 1 hr. After cooling, ether (10 ml) was added, and the stirred mixture was carefully acidified with dilute hydrochloric acid in an ice bath until the aqueous layer turned slightly acidic. The ether layer was washed with water and brine and then dried. Removal of the solvent gave a crystalline mass (ca. 600 mg). Recrystallization from ether afforded colorless crystals: mp 146.5° dec; ir (KBr) 3400–2500 and 1704 $cm^{-1}$.

Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.48; H, 6.48.

**1-Methoxycarbonyl-4-*epi*-norcanadensolide (13a).** A solution of osmium tetroxide (150 mg) in *tert*-butyl alcohol (3 ml) was added dropwise to a stirred mixture of the cis olefinic ester **12a** (3.0 g) and a hydrogen peroxide–*tert*-butyl alcohol solution[25] (30 ml) in an ice bath. After the exothermic reaction had subsided, the mixture was kept in a refrigerator overnight and then at room temperature for 20 hr. The mixture was poured into water (200 ml) containing a small amount of sodium bisulfite and extracted with ether. The combined extracts were washed with water and brine and then dried. Removal of the solvent left a pale yellow oil, which was chromatographed on silica gel. Petroleum ether–ether (1:2) eluted a semisolid material. Recrystallization from ether gave **13a** (550 mg, 22%) as colorless platelets: mp 117–118°; ir (KBr) 1800 (sh), 1778, 1742, 1180, and 965 $cm^{-1}$; NMR $\delta$ 0.93 (t, 3 H, $J$ = 6 Hz), 1.2–1.9 (m, 6 H), 3.8–3.9 [m, 2 H, C(1) and C(2) protons], 3.90 (s, 3 H), 4.73 [t, 1 H, $J$ = 6.0 Hz, C(3) proton], 5.05 [br d, 1 H, $J$ = 6.7 Hz, C(4) proton]. The NMR spectrum in DMSO-$d_6$ demonstrated that despite the narrow melting range, this compound was a mixture of epimers regarding the methoxycarbonyl group.

Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.24; H, 6.29. Found: C, 56.42; H, 6.03.

**4-*epi*-Norcanadensolide (13c). From 13a.** A suspension of **13a** (350 mg) and 6 *N* hydrochloric acid (10 ml) was heated at 100–110° for 1.5 hr. After cooling, brine (5 ml) was added, and the mix-

ture was extracted three times with ether. The combined extracts were washed with brine and dried. Removal of the solvent gave a yellow syrup (350 mg), which gradually crystallized on standing. Recrystallization from ether gave needles: mp 85–86°; ir (KBr) 1780, 1200, 1180, 1050, 1010, 1000, and 990–970 $cm^{-1}$; NMR $\delta$ 0.93 (t, 3 H), 1.1–1.9 (m, 6 H), 2.88 (d, 1 H, $J$ = 5.3 Hz), 2.9 (d, 1 H, $J$ = 7.5 Hz), 3.5 (m, 1 H, $J$ = 7.5, 6.0, and 5.3 Hz), 4.90 (d, $J$ = 6.0 Hz), and 4.70 (t, 1 H, $J$ = 6.0 Hz).

This compound was identified by comparison of its ir and NMR spectra with those of an authentic sample.[10]

**From 12b.** Osmium tetroxide (70 mg) in *tert*-butyl alcohol (1 ml) was added to a stirred mixture of **12b** (3.00 g) and a hydrogen peroxide–*tert*-butyl alcohol solution[25] (15 ml). The reaction was exothermic. The mixture was allowed to react in a refrigerator for 20 hr and then for 12 hr at room temperature with occasional swirling. Ether (20 ml) and sodium bisulfite (ca. 2 g) were added to the reaction mixture, and the mixture was stirred for 10 min in an ice bath. The mixture was filtered, and the ether layer was separated and dried. Removal of the solvent left a yellow oil (2.85 g). A mixture of the oil and acetic anhydride (20 ml) was heated at 110–120° for 3 hr, and excess acetic anhydride was distilled off to leave a dark red oil. The oily residue was dissolved in ether (50 ml), and the solution was washed with aqueous sodium bicarbonate, water, and brine, and then dried. Removal of the solvent gave a neutral oil (870 mg), which was chromatographed on silica gel. Elution with petroleum ether–ether (1:4) afforded colorless crystals (588 mg, 29%). Recrystallization from ether gave **13c** as colorless needles, mp 85–86°.

**4-*epi*-Canadensolide (1b).** A suspension of **13a** (190 mg) in 6 $N$ hydrochloric acid (9 ml) was warmed at 55° until a clear solution was obtained. The resulting solution was diluted with water (10 ml) and extracted with ether. The extracts were washed with brine and dried. Evaporation of the solvent gave **13b** as an oil (150 mg), which yielded **13a** by treatment with diazomethane.

To a solution of **13b** (270 mg) in acetic acid (1.5 ml) was added diethylamine (250 mg) and then 30% formaline (0.7 ml) in an ice bath. After the mixture was stirred until the evolution of carbon dioxide ceased, sodium acetate (400 mg) was added, and the mixture was heated at 90–100° for 10 min. The reaction mixture was diluted with water and extracted with ether. The extracts were washed with water and brine and dried. Removal of the solvent gave a pale yellow oil (190 mg), which was then chromatographed on silica gel. Petroleum ether–ether (2:3) eluted **1b** (150 mg, 64%). Recrystallization from ether gave colorless needles: mp 47.5–48.5°; ir (KBr) 1780 and 1665 $cm^{-1}$; NMR $\delta$ 0.95 (t, 3 H, $J$ = 6 Hz), 1.2–1.9 (m, 6 H), 4.09 [dt, 1 H, $J$ = 6.8 and 2.2 Hz, C(2) proton], 4.75 [dt, 1 H, $J$ = 1.5 and 7.0 Hz, C(4) proton], 4.98 [dd, 1 H, $J$ = 1.5 and 6.8 Hz, C(3) proton], and 6.23 and 6.54 (d, 1 H, $J$ = 2.2 Hz each, $=CH_2$).

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.64; H, 6.30.

**Methyl 2,3-Dimethoxycarbonyl-(*E*)-4-nonenoate (15a) and Its Parent Acid (15b).** To a stirred solution of **10a** (6.0 g) in liquid ammonia (500 ml) were added pieces of sodium (6 g) over 10 min, and the mixture was stirred for 5 hr. Excess ammonium chloride was added cautiously. After the mixture turned pale yellow, stirring was continued at room temperature to allow the ammonia to evaporate. The pasty residue was dissolved in water and extracted with ether. The combined extracts were washed with water and brine and dried. An oily fraction (4.12 g, 69%) boiling at 130° (bath temperature) in vacuo (0.2 mm) was collected. GLC analysis (column B) showed the fraction to be greater than 95% in purity: ir (liquid film) 1740 and 970 $cm^{-1}$; NMR $\delta$ 0.90 (t, 3 H), 1.1–1.6 (m, 4 H), 1.9–2.3 (m, 2 H, allylic methylene), 3.72 and 3.74 (s, 3 H each, OMe), 3.6–3.9 [m, 2 H, $CHCO_2Me$ and $CH(CO_2Me)_2$], 5.42 (dt, 1 H, $J$ = 15.0 and 7.0 Hz, $CH_2CH{=}C$), and 5.81 (dd, 1 H, $J$ = 15.0 and 6.0 Hz, $CH_2CH{=}CH$).

Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.75. Found: C, 58.55; H, 7.53.

A mixture of **15a** (2.95 g) and a solution of sodium hydroxide (1.59 g) in water (15 ml) was stirred at room temperature for 10 hr and then at 70° for 3 hr. The resulting clear solution was washed with ether, and the aqueous layer was acidified with 6 $N$ hydrochloric acid in an ice bath. After saturating with sodium chloride, the liberated acid was extracted with ether, and the extracts were washed with brine. Removal of the solvent left **15b** as crystals (2.50 g), which when recrystallized from ether gave an analytical sample: mp 166° dec; ir (KBr) 3500–2500, 1700, 970, and 900 $cm^{-1}$.

Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.38; H, 6.82.

**(±)-Canadensolide (1a) and Dilactone 16b from Cis Olefinic Ester (12a) *via* Performic Acid Oxidation.** Hydrogen peroxide (30%, 1.0 g) was added in one portion to a stirred solution of **12a** (2.0 g) in formic acid (6.0 ml) at room temperature. After stirring for 5 min at the same temperature, the mixture was stirred at 40–50° for 7 hr. The reaction mixture was poured into ice water and extracted with ether. The combined extracts were washed with water and brine and dried. Evaporation of the solvent left a pale yellow oil (1.98 g), which was chromatographed on silica gel (60 g). Ether eluted an oily fraction (1.17 g), which showed an ir absorption at 1780 $cm^{-1}$.

After the above lactonic fraction (170 mg) and 50% aqueous sulfuric acid (10 ml) had been heated at 120° for 2 hr with stirring, the reaction mixture was diluted with water (10 ml) and then saturated with sodium chloride. The product was extracted with ether, and the extracts were washed with cold water and then brine and dried. Work-up in a usual manner left a semisolid (ca. 50 mg), which was recrystallized from ether, giving **16b** (24 mg) as colorless needles: mp 81–82.5°; ir (KBr) 1770 $cm^{-1}$; NMR $\delta$ 0.93 (t, 3 H), 1.45 (m, 4 H), 1.85 (m, 2 H), 2.91 [1 H, d, $J$ = 7 Hz, C(1) proton], 2.93 [1 H, d, $J$ = 6 Hz, C(1) proton], 3.50 [q, 1 H, $J$ = 6.0 Hz, C(2) proton], 4.70 [dt, 1 H, $J$ = 4.0 and 7.0 Hz, C(4) proton], 5.09 [dd, $J$ = 6.0 and 4.0 Hz, C(3) proton].

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.34; H, 6.60.

A heterogeneous mixture of the lactone fraction (1.0 g) and 6 $N$ hydrochloric acid (55 ml) was stirred at 55° for 5 hr under nitrogen. The resulting clear solution was saturated with sodium chloride and then extracted with ether. The combined extracts were washed with brine and dried. Removal of the solvent left a pale yellow viscous oil (855 mg), whose ir spectrum (liquid film) showed broad absorptions at 3400–2500 and 1780–1720 $cm^{-1}$. The oil was dissolved in acetic acid (10 ml), and diethylamine (2.1 ml) was added dropwise with stirring. After stirring for 15 min, aqueous formalin (3.5 ml) was added. Stirring was continued for an additional 30 min, and then sodium acetate (3.0 g) was added. The mixture was heated at 80° for 10 min. Work-up in a usual manner afforded a semisolid (102 mg), which was purified by preparative silica gel TLC, giving **1a** (84 mg). Recrystallization from ether gave an analytical sample as colorless needles: mp 92.5–93.5°; ir (KBr) 1770 and 1666 $cm^{-1}$; NMR $\delta$ 0.95 (t, 3 H), 1.5 (m, 4 H), ca. 1.9 (br q, 2 H), 4.07 [dt, 1 H, $J$ = 6.8 and 2.1 Hz, C(2) proton], 4.70 [dt, 1 H, $J$ = 4.5 and 6.7 Hz, C(4) proton], 5.22 [dd, 1 H, $J$ = 6.8 and 4.5 Hz, C(3) proton], and 6.18 and 6.49 [d, 1 H, $J$ = 2.1 Hz each, C(1) protons].

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.63; H, 6.68.

The ir and NMR spectra were superimposable with those of natural canadensolide.

**Hydrolysis of Acetylenic Ester 10.** A suspension of **10** (5.7 g) in a solution of sodium hydroxide (4.08 g) in water (50 ml) was stirred at room temperature for 7 hr under nitrogen. The mixture was extracted with ether to remove the neutral portion, and the aqueous layer was separated. Ether was added to the aqueous layer, and the mixture was carefully acidified with 3 $N$ hydrochloric acid with stirring in an ice bath. The aqueous layer was extracted with ether. The combined organic layers were washed with cold water and brine and dried. Removal of the solvent at room temperature left a semisolid (5.2 g), which was chromatographed on silica gel. Elution with petroleum ether–ether (6:4) gave **18** (610 mg). Recrystallization from ether afforded colorless needles: mp 122–123°; ir (KBr) 3400–2500, 1740, 1698, and 1670 $cm^{-1}$; NMR[26] $\delta$ 0.96 (t, 3 H), 1.2–1.7 (m, 4 H), 1.7–2.1 (m, 2 H), 3.38 (dd, 2 H, $J$ = 3.0 and 1.7 Hz, $CH_2CO$), 5.22 (octet, 1 H, $J$ = 6.0, 3.1, and 3.0 Hz, OCH), 7.15 (dt, 1 H, $J$ = 3.1 and 1.7 Hz, =CH), and 11.1 (s, 1 H, $CO_2H$). The NMR assignments were verified by DNMR experiments.

Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.82; H, 7.14.

Successive elution with petroleum ether–ether (2:8) gave **5** (3.95 g, 85%). Recrystallization from ether yielded colorless crystals: mp 157°; ir (KBr) 3550–2400 and 1720 $cm^{-1}$; NMR $\delta$ 0.9 (t 3 H), 1.05–1.4 (m, 4 H), 2.2 (br t, 2 H), 3.55 and 3.77 [d, $J$ = 7 Hz each, 2 H in total, $CH(CO_2H)CH(CO_2H)_2$], and 6.68 (s, 3 H, $CO_2H$).

Anal. Calcd for $C_{11}H_{14}O_6$: C, 54.54; H, 5.83. Found: C, 54.64; H, 5.90.

Treatment of **5** with ethereal diazomethane gave **10.**

**Silver Salt Catalyzed Lactonization of 5.** A mixture of **5** (560 mg), silver nitrate (10 mg), water (1 drop), and dioxane (6 ml) was stirred at 40–50° for 15 hr under nitrogen. The reaction mixture was poured into distilled water (20 ml) and extracted with ether

three times. The combined extracts were washed with water and then dried. Evaporation of the solvent left a pale yellow oil (560 mg), which was treated with ethereal diazomethane. An oil obtained was chromatographed on silica gel. Elution with petroleum ether–ether (2:1) afforded **19** (489 mg, 98%) as a colorless oil. An analytical sample was obtained by distillation (bath temperature 105°) in vacuo (0.8 mm): ir ($CHCl_3$) 1750–1740 and 880 $cm^{-1}$; NMR $\delta$ 0.95 (t, 3 H), 1.1–1.8 (m, 6 H), 3.25 (br t, 2 H, $J$ = 1.5 Hz), 3.73 (s, 3 H), 4.93 (m, 1 H, CHO), and 7.40 (q, 1 H, $J$ = 1.5 Hz, =CH).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.22; H, 7.77.

This butenolide was also obtained by heating **5** at 175–180° for 1 hr followed by treatment with diazomethane.

**Lactonization of 5 with Sulfuric Acid.** The acetylenic acid **5** (800 mg) was added to concentrated sulfuric acid (4 ml) in an ice bath, and the solution was stirred for 1 hr with cooling and then at room temperature for an additional 1 hr. The mixture was poured into ice water and extracted with ether. The combined extracts were washed with brine and dried. Concentration in vacuo left a semisolid (600 mg). The latter material was treated with a slight excess of diazomethane. After work-up, the product was purified by silica gel chromatography. Petroleum ether–ether (8:2) eluted **20** (574 mg, 82%), whose analytical sample was obtained by distillation (bath temperature 110°) in vacuo (0.4 mm) as a colorless oil: ir ($CHCl_3$) 1821, 1718, and 1660 $cm^{-1}$; NMR $\delta$ 0.92 (t, 3 H), 1.1–1.9 (m, 6 H), 2.83 (t, 2 H, $J$ = 7.5 Hz, $CH_2C$=), 3.35 (br s, 2 H, $CH_2CO$), and 3.75 (s, 3 H).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.11; H, 7.75.

**Lactonization of 5 with Dilute Sulfuric Acid Containing Mercuric Salt.** Red mercuric oxide (10 mg) was added to a stirred mixture of **5** (760 mg), 60% sulfuric acid (1 ml), and dioxane (1 ml). After stirring had been continued at room temperature for 12 hr, the reaction mixture was poured into ice water. The product was extracted with ether, and the combined extracts were washed with brine and dried. Removal of the solvent in vacuo yielded an oil, which was then treated with diazomethane in slight excess. Work-up gave a yellow oil (ca. 750 mg). GLC analysis (column B) showed a main peak and three minor peaks, one of which was identified as **19** by peak enhancement experiments. Petroleum ether–ether (2:8) eluted the main product **21** (395 mg) as a colorless oil: ir ($CHCl_3$) 1745 and 1728 $cm^{-1}$; NMR (benzene) $\delta$ 0.80 (t, 3 H), 0.95–1.7 (m, 6 H), 2.10 (t, 2 H, $J$ = 6 Hz, $CH_2CO$), 2.85 (d, 2 H, $J$ = 7.5 Hz, $CH_2CO_2Me$), 3.39 (s, 6 H), and 3.93 (t, 1 H, $J$ = 7.5 Hz, $CO\text{-}CHCO_2Me$); MS $m/e$ 145 (base peak), 99, and 55.

Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found: C, 59.36; H, 7.99.

**Dilactone (23) from Norbornene-*endo*-dicarboxylic Acid (22a).** Finely pulverized **22a**[13] (183 mg, 1 mmol) was dissolved in a solution of sodium hydroxide (104 mg, 2.6 mmol) in water (3 ml). A solution of silver nitrate (357 mg, 2.1 mmol) in water (5 ml) was added with stirring to the above solution, and the mixture was stirred for an additional 30 min. The silver salt was collected by filtration and washed with water and then with ether. The salt was dried in vacuo at room temperature in the dark. Iodine (507 mg, 4 mmol) was added to a stirred suspension of the pulverized silver salt in dry dimethyl sulfoxide (5 ml). After stirring for 30 min, silver acetate (527 mg, 2.1 mmol) was added, and the mixture was stirred at 60° for 12 hr. Chloroform (10 ml) was added to the cooled mixture, and inorganic materials were filtered off. The filtrate was concentrated under reduced pressure at 60° to small bulk. The residue then was dissolved in chloroform (30 ml) and washed with water. The solution was dried and evaporated to give **23** (166 mg, 92%). Trituration of the product with hot ether gave an analytical sample as colorless, fine needles: mp 265–266° (lit. mp 274–275°,[14b] 264–265° [14a]); ir (KBr) 1800 and 1780 $cm^{-1}$ (lit. 5.53 and 5.60 $\mu$,[14b] 1795 and 1770 $cm^{-1}$ [14c]); NMR[26] (DMSO-$d_6$) $\delta$ 1.80 (t, 2 H, $J$ = 2 Hz), 3.06 (m, 2 H), 3.39 (m, 2 H), and 4.78 (t, 2 H, $J$ = 2 Hz).

Anal. Calcd for $C_9H_8O_4$: C, 60.00; H, 4.48. Found: C, 60.19; H, 4.71.

**Dimethyl Ester of (*Z*)-4-Octenedioic Acid (24).** A solution of methyl 4-octynedioate[20] (1.60 g) in methanol containing synthetic quinoline (0.2 ml) was hydrogenated over 5% palladium–barium sulfate (150 mg) at room temperature. Hydrogen uptake ceased after 1 equiv of hydrogen had been absorbed. After filtration of the catalyst, the filtrate was concentrated in vacuo. The oily residue was dissolved in ether, and the solution was washed with water and brine and dried. Evaporation of the solvent left the dimethyl ester of **24** (1.12 g) as an oil. An analytical sample was obtained by distillation (bath temperature 130°) in vacuo (8 mm): ir (liquid film) 1735 $cm^{-1}$; NMR $\delta$ 2.46 (m, 8 H), 3.70 (s, 6 H), and 5.45 (br m, 2 H).

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.70; H, 8.06.

***meso*-4,5-Dihydroxyoctanedioic Acid Di-γ-lactone (25).** A heterogeneous mixture of the above dimethyl ester of **24** (1.27 g), sodium hydroxide (762 mg), and water (15 ml) was stirred at room temperature for 1 hr under nitrogen, and then at 60° for 4 hr. The resultant solution was washed once with ether. Ether was added to the aqueous layer, and the mixture was acidified with dilute hydrochloric acid with stirring in an ice bath. The aqueous layer was saturated with sodium chloride and extracted with ether. The combined organic layers were washed with brine and dried. Evaporation of the solvent left a solid, which was washed with a small amount of a mixture of ether and petroleum ether (1:1) to give crude **24** (813 mg, ca. 73%) as an amorphous powder. The crude acid was used without further purification.

To a stirred suspension of the silver salt of **24** [prepared in a similar manner from **24** (1.14 g) and silver nitrate (2.48 g)] in dimethyl sulfoxide (10 ml), iodine (3.37 g) and then silver acetate (2.22 g) were added. The mixture was then stirred at 65° for 12 hr. Work-up gave **25** (620 mg, 56%) as the neutral product. Recrystallization from ethyl acetate gave colorless needles: mp 104–105° (lit.[16a] mp 106°); ir (KBr) 1785 (sh) and 1765 $cm^{-1}$; NMR $\delta$ 1.8–2.7 [m, 8 H, C(2) and C(3) protons] and 4.60 [m, 2 H, C(4) proton].

Anal. Calcd for $C_8H_{10}O_4$: C, 56.46; H, 5.92. Found: C, 56.45; H, 5.87.

**Monotetrahydropyranyl Ether (36) of 1,4-Butanediol.** A solution of 1,4-butanediol (3.0 g), freshly distilled dihydropyran (2.8 g), and *p*-toluenesulfonic acid (20 mg) in tetrahydrofuran (100 ml) was stirred at −25° for 3 hr. The mixture was then allowed to warm to room temperature during a 1-hr period and was stirred for an additional 10 hr at the same temperature. A few drops of pyridine were added to the mixture to quench the catalyst. The mixture was diluted with ether, washed with water and brine, and dried. Evaporation of the solvent left an oil, which was chromatographed on a silica gel column. Ether–petroleum ether (1:2) eluted an oily diether of 1,4-butanediol (1.25 g, 15%): ir (liquid film) 1120, 1060, 1030, 900, 860, and 810 $cm^{-1}$; NMR $\delta$ 1.6 (m, 16 H), 3.2–4.1 (m, 8 H), and 4.60 (br t, 2 H).

Anal. Calcd for $C_{14}H_{26}O_4$: C, 65.08; H, 10.14. Found: C, 64.85; H, 10.09.

Further elution with the same solvent gave **36** (3.85 g, 66%) as a colorless oil: ir (liquid film) 3400, 1060, 1030, 900, 860, and 810 $cm^{-1}$; NMR $\delta$ 1.70 (m, 10 H), 3.20 (br s, 1 H, OH), 3.3–4.1 (m, 6 H, $CH_2O$), and 4.68 (br t, 1 H, OCHO).

Anal. Calcd for $C_9H_{18}O_3$: C, 62.04; H, 10.41. Found: C, 61.68; H, 10.48.

**Ethynyl Carbinol (37).** To an ice-cooled and stirred suspension of chromic anhydride–dipyridine complex[27] (29.9 g) and Celite 535 (25 g) in dry methylene chloride (150 ml) was added dropwise a solution of **36** (2.18 g) in methylene chloride (50 ml) under an argon atmosphere. After stirring for 15 min, sodium hydrogen sulfate monohydrate (30 g) was added, and the resultant mixture was stirred for an additional 15 min at room temperature. The organic layer was separated, and the solid was washed with a small amount of methylene chloride. The combined methylene chloride solutions were evaporated at 0° to leave an oil, which was dissolved in a small amount of ether. The solution was filtered through a Celite 535 column. The filtrate was evaporated in vacuo to give an aldehyde (2.06 g) as a colorless oil: ir (liquid film) 2750 and 1720 $cm^{-1}$; NMR $\delta$ 1.3–2.2 (m, 8 H), 2.60 (t, 2 H, $J \simeq$ 7.5 Hz with fine splittings, $CH_2CHO$), 3.3–4.1 (m, 4 H, $CH_2O$), 4.65 (br t, 1H, OCHO), and 9.80 (t, 1 H, $J$ = 1.5 Hz, CHO).

Although the crude product showed a single spot on TLC, no analytically pure sample was obtained because of its instability.

After dry tetrahydrofuran (100 ml) had been saturated with acetylene with stirring, ethylmagnesium bromide solution, prepared from magnesium (350 mg) and ethyl bromide (1.57 g) in the same solvent, was added dropwise at room temperature. Stirring was continued for an additional 30 min while the reaction flask was cooled in an ice bath, and then a solution of the above aldehyde (2.06 g) in the same solvent (15 ml) was added dropwise. Stirring was further continued, while the solution was allowed to warm to room temperature. The resultant brown mixture was poured into a cold saturated ammonium chloride solution. The aqueous layer was extracted with ether several times, and the combined organic layers were washed with water and brine and dried. Evapora-

tion of the solvent left an oil, which was purified by passing through a short silica gel column to give **37** (2.04 g, 86% from **36**) as a pale yellow oil: ir (liquid film) 3400, 3210, 1120, 1070, 1020, 910, 900, and 865 $cm^{-1}$; NMR $\delta$ 1.3–2.0 (m, 10 H), 2.50 (d, 1 H, $J \simeq 1.5$ Hz, ≡CH), 3.2–4.1 (m, 5 H), 4.5 (br s, 1 H, OH), 4.68 (br t, 1 H, OCHO).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.98; H, 9.34.

**Allylic Carbinol (38).** The ethynyl carbinol (**37**, 2.04 g) in methanol (20 ml) containing synthetic quinoline (0.15 ml) was hydrogenated over 5% palladium–barium sulfate (200 mg). Hydrogen uptake ceased after 1 equiv of hydrogen had been absorbed. The catalyst was filtered off, and the filtrate was concentrated in vacuo to leave an oil, which was dissolved in ether (30 ml). The solution was washed with water and brine and dried. Removal of the solvent in vacuo gave **38** (2.05 g) as a colorless oil, which showed a single spot on TLC: ir (liquid film) 3400, 3050, 1640, 1110, 1070, 1030, 900, 860, and 810 $cm^{-1}$; NMR $\delta$ 1.4–2.0 (m, 10 H), 2.76 (br s, 1 H, OH), 3.3–4.4 (m, 5 H, $CH_2O$ and CHO), 4.65 (br t, 1 H, OCHO), 4.5–5.0 (m, 2 H, $=CH_2$), 5.95 (dq, 1 H, $J$ = 17.3, 10.5, and 6.0 Hz, =CH).

Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.98; H, 10.15.

**Vinyl Ether 39.** A mixture of **38** (2.00 g), freshly distilled ethyl vinyl ether (4 ml), and mercuric acetate (100 mg) was gently refluxed for 48 hr under nitrogen. After cooling to 0°, saturated sodium bicarbonate solution (4 ml) was added and the mixture was stirred for 15 min. The reaction mixture was extracted with ether three times, and the combined extracts were washed with water and brine and dried. The solvent was removed, and the residual oil was chromatographed on a short silica gel column using methylene chloride as eluent to give **39** (1.10 g, 60%) as a pale yellow oil: ir (liquid film) 3050, 1636, 1615, 1130, 1120, 1070, 1030, 985, and 900 $cm^{-1}$; NMR $\delta$ 1.1–2.0 (m, 10 H), 3.2–4.4 (m, 5 H, $CH_2O$ and CHO), 4.0 (dd, 1 H, $J$ = 7.5 and 1.3 Hz, $OCH{=}CH_cH_t$), 4.32 (dd, 1 H, $J$ = 14.0 and 1.3 Hz, $OCH{=}CH_cH_t$), 4.60 (br t, 1 H, OCHO), 5.02–5.4 (m, 2 H, $CH{=}CH_2$), 5.85 (dq, 1 H, $J$ = 18.0, 9.0, and 5.7 Hz, $CH{=}CH_2$), and 6.34 (q, 1 H, $J$ = 14.0 and 7.5 Hz, $OCH{=}CH_2$).

Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.74; H, 9.71.

Further elution with ether gave the unreacted **38** (821 mg).

***(E)*-4-Octenedioic Acid (26).** The vinyl ether **39** (2.00 g) in a sealed tube was heated at 190° for 20 min to give an oily aldehyde quantitatively: ir (liquid film) 2720, 1720, 1130, 1120, 1070, 1030, and 970 $cm^{-1}$. The oil was dissolved in acetone (30 ml) and Jones reagent was added at 0° until the orange color of the reagent persisted for 5 min. After the excess reagent was destroyed by the addition of 2-propanol, the reaction mixture was diluted with brine (30 ml) and extracted with ether. The combined extracts were washed with brine and evaporated to leave an oil. The oil was dissolved in acetone (10 ml), and 10% sulfuric acid (2 ml) was added. After warming at 55° for 30 min, the solution was cooled in an ice bath and treated with a slight excess of Jones reagent. Work-up in a usual manner gave a semisolid (1.15 g), which was washed with a small amount of cold ether to give a colorless solid. Recrystallization from ether gave **26** (750 mg, 50%) as a colorless powder: mp 174.5–176° (lit.[22] mp 175–176°); ir (KBr) 3500–2300, 1700, 980, and 940 $cm^{-1}$; NMR[26] (DMSO-$d_6$) $\delta$ 1.24 (br m, 8 H), 5.41 (br m, 2 H), and 12.4 (br s, 2 H).

Anal. Calcd for $C_8H_{12}O_4$: C, 55.80; H, 7.03. Found: C, 55.60; H, 7.07.

***dl*-4,5-Dihydroxyoctanedioic Acid Di-γ-lactone (27).** To a stirred suspension of the silver salt, prepared from **26** (150 mg) in a similar manner, in dimethyl sulfoxide (3 ml) was added iodine (454 mg). After stirring had been continued for an additional 15 min, silver acetate (301 mg) was added, and the mixture was stirred at 60° for 15 hr. Work-up in a usual manner afforded colorless crystals (98 mg, 60%), whose recrystallization from ethyl acetate gave an analytical sample as colorless needles: mp 55–56° (lit.[16b] mp 55–56°); ir (KBr) 1780 $cm^{-1}$; NMR $\delta$ 2.1–2.9 (br m, 4 H) and 4.63 (m, 2 H).

Anal. Calcd for $C_8H_{10}O_4$: C, 56.46; H, 5.92. Found: C, 56.16; H, 5.91.

**Dilactone 29.** The dimethyl ester of **28**[17] (250 mg) was heated with a solution of sodium hydroxide (125 mg) in a mixture of water (3 ml) and methanol (3 drops) at 60°. The resultant homogeneous solution was washed with ether, and the aqueous layer was treated with a solution of silver nitrate (408 mg) in water (1 ml) to give a silver salt. Iodine (610 mg) was added to a stirred suspension of the dried silver salt in dimethyl sulfoxide (8 ml), and then silver acetate (400 mg) was added. The mixture was stirred at 60° for 12 hr. Work-up in a usual manner gave a semisolid, which was poured on a short silica gel column, and the product was eluted with methylene chloride to give **29** (115 mg, 52%). An analytical sample was obtained by recrystallization from ethyl acetate as colorless needles: mp 116–117°; ir (KBr) 1770 $cm^{-1}$; NMR $\delta$ 1.2–3.2 (br m, 8 H) and 5.02 (m, 2 H).

Anal. Calcd for $C_9H_{10}O_4$: C, 59.33; H, 5.53. Found: C, 59.34; H, 5.60.

**Dilactone 31.** To a stirred suspension of the silver salt of **30**[18] (170 mg), iodine (508 mg) and then silver acetate (351 mg) were added at 50–60°. The mixture was stirred for 5 hr and worked up to give crystals (129 mg, 77%), whose recrystallization from ether afforded colorless needles: mp 205–206°; ir (KBr) 1840 and 1770 $cm^{-1}$; NMR[26] $\delta$ 2.22 (dq, 2 H, $J$ = 19.2, 4.8, and 2.0 Hz, exo methylene protons), 2.73 (d, 2 H, $J$ = 19.2 with fine splittings, endo methylene protons), 2.98 (q, 2 H, $J$ = 4.8 and 2.0 Hz, CHC=O), and 3.23 (m, 2 H, CHO).

Anal. Calcd for $C_8H_8O_4$: C, 57.14; H, 4.80. Found: C, 57.03; H, 4.91.

**5-Hydroxy-3-cyclohexenecarboxylic Acid Lactone (41). A. With Silver Acetate.** A suspension of **40**[21] (4.03 g) and silver acetate (3.51 g) in dry dimethyl sulfoxide (50 ml) was heated at 130–140° for 2 hr under nitrogen. The reaction mixture was diluted with chloroform (100 ml) and filtered. The filtrate was washed with water and brine and dried. After removal of the solvent, the residue was distilled (bath temperature ca. 150°) in vacuo (20 mm) to give **41** (1.61 g, 81%) as an oil: ir (liquid film) 1800 (sh), 1770, and 1735 $cm^{-1}$ (sh); NMR $\delta$ 2.0–2.8 (m, 4 H), 2.89 (m, 1 H, CHC=O), 4.77 (br t, 1 H, $J$ = 4.5 Hz, CHO), 5.7–6.5 (m, 2 H, =CH).

Anal. Calcd for $C_7H_8O_2$: C, 67.73; H, 6.50. Found: C, 67.93; H, 6.37.

**B. With 1,5-Diazabicyclo[5.4.0]undecene-5.** A solution of **40** (20.16 g) and 1,5-diazabicyclo[5.4.0]undecene-5 (18.24 g) in dry benzene (300 ml) was refluxed for 6 hr under nitrogen. The solution was washed with water and dried. The oil obtained by evaporation of the solvent was distilled in vacuo to afford **41** (6.1 g, 71%).

**Hydroxy Acid 42a and Its Methyl Ester 42b.** A suspension of **41** (2.48 g) and a solution of sodium hydroxide (1.04 g) in water (4 ml) was stirred at room temperature for 3 hr. The solution obtained was washed with ether. Chloroform (10 ml) was added to the aqueous layer, the mixture was acidified with powdered oxalic acid with stirring, and then sodium chloride and magnesium sulfate were added until the mixture became pasty. The paste was packed in a column and eluted with chloroform. The combined chloroform eluents were concentrated. The residual solid was washed with hot ether to give **42a** (2.5 g, quantitative yield) as a colorless powder: ir (KBr) 3350, 2600, 1710, and 950 $cm^{-1}$; NMR $\delta$ 1.0–1.6 (m, 1 H), 1.95–2.5 (m, 5 H), 4.2 (m, 1 H, CHOH), 5.68 (br s, 2 H, =CH).

Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 58.85; H, 7.09.

Treatment of **42a** with a slight excess of ethereal diazomethane gave oily **42b:** ir (liquid film) 3350, 1725, and 1650 $cm^{-1}$; NMR $\delta$ 2.0–3.0 (m, 6 H), 3.74 (s, 3 H), 4.38 (m, 1 H, CHO), and 5.85 (br s, 2 H, =CH(/

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.75. Found: C, 61.18; H, 8.17.

**Vinyl Ether 43.** A mixture of **42b** (435 mg), ethyl vinyl ether (10 ml), and mercuric acetate (150 mg) was refluxed for 3 days under nitrogen. The reaction mixture was diluted with ether (ca. 30 ml), washed with 5% sodium bicarbonate, water, and brine, and then dried. After removal of the solvent, the residue was distilled (bath temperature ca. 120°) in vacuo (25 mm) to give **43** (367 mg, 71%) as a colorless oil: ir (liquid film) 3010, 1730, 1630, and 1610 $cm^{-1}$; NMR $\delta$ 2.0–3.0 (m, 5 H), 3.70 (s, 3 H), 4.5 (m, 1 H, CHO), 4.08 (dd, 1 H, $J$ = 6.8 and 1.5 Hz, $OCH{=}CH_cH_t$), 4.35 (dd, 1 H, $J$ = 14.5 and 1.5 Hz, $OCH{=}CH_cH_t$), 5.82 (m, 2 H, $CH{=}CH$ in the cyclohexene ring), and 6.40 (dd, $J$ = 14.5 and 6.8 Hz, $OCH{=}CH_2$).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.52; H, 7.62.

**Formyl Ester 44.** The vinyl ether **43** (1.31 g) was heated in a sealed tube at 200° for 1 hr. Distillation (bath temperature ca. 130°) in vacuo (10 mm) gave **44** (1.08 g, 82%) as a colorless oil: ir (liquid film) 2710, 1730–1720, and 1650 $cm^{-1}$; NMR $\delta$ 1.0–3.0 (m, 8 H), 3.65 (s, 3 H), 5.62 (m, 2 H, =CH), and 9.25 (t, 1 H, $J$ = 2 H, 2 Hz, CHO).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.96; H, 8.31.

**Dicarboxylic Acid 32.** A solution of **44** (273 mg) in acetone (10 ml) was treated with slightly excess Jones reagent at 0°. Work-up in a usual manner afforded the monomethyl ester of **32** (232 mg) as a colorless oil: ir (liquid film) 3500–2500, 1725, and 1705 $cm^{-1}$; NMR $\delta$ 1.0–3.0 (m, 8 H), 3.67 (s, 3 H), 5.68 (m, 2 H, =CH), and 10.6 (br s, 1 H, $CO_2H$).

The monomethyl ester (207 mg) was dissolved in a solution of sodium hydroxide (52 mg) in water (2 ml), and the solution was stirred overnight at room temperature under nitrogen. The reaction mixture was acidified with 6 *N* hydrochloric acid in an ice bath and then saturated with sodium chloride. The product was extracted with methylene chloride, and the combined extracts were washed with cold brine and dried. Removal of the solvent gave **32** (173 mg, 67% from **44**) as a colorless powder: ir (KBr) 3350, 1700, and 1650 $cm^{-1}$.

Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.58. Found: C, 58.94; H, 6.87.

**Dilactone 33.** A suspension of the silver salt (587 mg), prepared from **32** (347 mg) in a similar manner, was successively treated with iodine (813 mg) and silver acetate (551 mg). Work-up gave **33** (143 mg, 47%). Recrystallization from ethyl acetate afforded colorless needles: mp 159–160°, ir (KBr) 1775 $cm^{-1}$; NMR[26] $\delta$ 1.0–2.1 (5 H), 2.4–2.8 (4 H), 4.60 (dd, 1 H, $J$ = 9 and 2 Hz, CHO), and 5.05 (dd, 1 H, $J$ = 6.4 and 2 Hz, CHO(/

Anal. Calcd for $C_9H_{10}O_4$: C, 59.33; H, 5.53. Found: C, 59.07; H, 5.50.

**Butenolide 35.** Iodine (1.27 g) was added to a stirred suspension of the silver salt, prepared from dihydromuconic acid[19] (**34**, 350 mg), in dimethylformamide (5 ml). After stirring for 20 min, silver acetate (835 mg) was added, and the mixture was stirred at 70° for 24 hr. The reaction mixture was diluted with wet ether (10 ml), and the organic layer was separated and concentrated to leave a brown oil. An ethereal solution of the oil was treated with slightly excess diazomethane in an ice bath. The solvent was removed to leave an oil, which was poured on a short silica gel column. Ether eluted **35** (120 mg, 32%) as an oil: ir ($CHCl_3$) 1760 and 1735 $cm^{-1}$; NMR $\delta$ 2.80 (dd, 2 H, $J$ = 7.5 and 1.5 Hz, C**H**$_2$CO$_2$Me), 3.75 (s, 3 H, OMe), 5.50 (tdd with fine splittings, 1 H, $J$ = 7.5, 2.3, and 1.5 Hz, CHO), 6.23 (dd, 1 H, $J$ = 6.0 and 2.3 Hz, =CHC=O), and 7.67 (dd, 1 H, $J$ = 6.0 and 1.5 Hz, C**H**=CHC=O).

Anal. Calcd for $C_7H_8O_4$: C, 53.84; H, 5.16. Found: C, 53.98; H, 5.34.

**2-[(*Z*)-1-Hexenyl]butanedioic Acid (45).** A mixture of **12b** (5.3 g) and xylene (20 ml) was gently refluxed for 2 hr under nitrogen. After evolution of carbon dioxide had ceased, the solution was stirred for an additional 1 hr with heating. Removal of the solvent in vacuo gave a colorless solid, whose ir spectrum showed it to be a mixture of dicarboxylic acid (1710 $cm^{-1}$) and anhydride (1860 and 1790 $cm^{-1}$). The mixture was refluxed with water (15 ml) for 1 hr. The resulting solution was saturated with sodium chloride and extracted with ether. The combined extracts were dried. Evaporation of the solvent gave colorless crystals (3.91 g, 88%). Recrystallization from ether–petroleum ether (1:1) afforded an analytical sample as colorless leaflets: mp 112–113°; ir (KBr) 3400–2500, 1695, and 950 $cm^{-1}$; NMR $\delta$ 0.90 (t, 3 H), 1.1–1.6 (m, 4 H), 1.9–2.4 (m, 2 H, $CH_2C$=), 2.52 (dd, 1 H, $J$ = 18 and 6 Hz, one of C**H**$_2$CO$_2$H), 2.99 (dd, 1 H, $J$ = 18 and 9 Hz, one of C**H**$_2$CO$_2$H), 3.82 (m, 1 H), 5.37 (t, 1 H, $J$ = 10.5 Hz, =C**H**CHCO$_2$H), 5.75 (dt, 1 H, $J$ = 10.5 and 4.7 Hz, $CH_2$C**H**=), and 11.6 (br s, 2 H, $CO_2H$).

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.23; H, 8.43.

**2-[(*E*)-1-Hexenyl]butanedioic Acid (48).** A suspension of **15b** (2.5 g) in xylene (25 ml) was refluxed for 4 hr. Evaporation of the solvent at 70° in vacuo gave an oil. The oil was refluxed with water (10 ml) for 1 hr. The solution was extracted with ether, and the combined extracts were dried. Removal of the solvent afforded an oil (2.00 g), which gradually crystallized on standing to give colorless crystals. The crystals were chromatographed on silica gel, and ether eluted **48** (1.50 g, 73%). Recrystallization from petroleum ether containing a small amount of ether gave colorless needles: mp 86–87°; ir (KBr) 3400–2600, 1695, 970, and 950 $cm^{-1}$; NMR $\delta$ 0.90 (t, 3 H), 1.1–1.6 (m, 4 H), 1.9–2.3 (m, 2 H, $CH_2C$=), 2.55 (dd, 1 H, $J$ = 16.5 and 6 Hz, one of C**H**$_2$CO$_2$H), 2.95 (dd, 1 H, $J$ = 16.5 and 8.3 Hz, one of C**H**$_2$CO$_2$H), 3.53 (br m, 1 H, C**H**CO$_2$H), 5.42 (dd, 1 H, $J$ = 17 and 6 Hz, =C**H**CHCO$_2$H), 5.78 (dt, 1 H, $J$ = 17 and 5.7 Hz, $CH_2$C**H**=), and 11.75 (s, 2 H, $CO_2H$).

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.12; H, 7.92.

**Silver Salt Double Lactonization of 45.** To a stirred suspension of the silver salt (3.44 g), prepared from **45** (1.660 g), in dimethyl sulfoxide (25 ml) there was added iodine (4.24 g), and then after stirring for 30 min silver acetate (2.84 g) was added. Stirring was continued for an additional 4 hr at room temperature, and then at 60° for 12 hr. The reaction mixture was diluted with methylene chloride (70 ml) and filtered. The filtrate was concentrated in vacuo at 50–60°, and the residue was dissolved in methylene chloride (100 ml). The solution was washed with sodium bicarbonate solution (20 ml), water, and brine. Evaporation of the organic layer left a brown oil, which was chromatographed on a silica gel column using methylene chloride–ether (1:1) as eluent, giving **13c** (493 mg, 30%).

The sodium bicarbonate extracts were acidified with 6 *N* hydrochloric acid. Extraction of the mixture with ether, followed by evaporation of the extracts, gave an acidic, oily product (463 mg). Treatment of the oil with ethereal diazomethane gave a mixture of methyl esters (470 mg). The mixture was separated by preparative silica gel TLC using ether–petroleum ether (1:2) as solvent, affording two oily butyrolactones, **46b** (340 mg, 19%) and **47b** (130 mg, 7%).

**46b:** ir (liquid film) 1785 and 1740 $cm^{-1}$; NMR[26] $\delta$ 0.90 (t, 3 H), 1.38 (quintet, 2 H, $J$ = 7 Hz), 2.05 (q, 2 H, $J$ = 7 Hz, C**H**$_2$CH=), 2.73 [dd, 1 H, $J$ = 17 and 10 Hz, CHCO$_2$ (lactone)], 2.94 [dd, 1 H, $J$ = 17 and 7.6 Hz, CHCO$_2$ (lactone)], 3.1 (m, 1 H, C**H**CO$_2$Me), 3.75 (s, 3 H, OMe), 4.96 (t, 1 H, $J$ = 6.0 Hz, CHO), 5.45 (dd, 1 H, $J$ = 16 and 6 Hz, =CHCO), and 5.85 (dt, 1 H, $J$ = 16 and 7 Hz, $CH_2$C**H**=).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 61.85; H, 7.22.

**47b:** ir (liquid film) 1810, 1740, and 1700 $cm^{-1}$; NMR[26] $\delta$ 0.90 (t, 3 H), 1.1–1.5 (m, 4 H), 2.15 (m, 2 H), 2.78 [dd, 1 H, $J$ = 18 and 9.6 Hz, CHCO$_2$ (lactone)], 3.12 [dd, 1 H, $J$ = 18 and 5.6 Hz, CHCO$_2$ (lactone)], 3.78 (s, 3 H, OMe), 3.9 (m, 1 H, C**H**CO$_2$Me), 4.85 (dt, 1 H, $J$ = 6.8 and 1.2 Hz, CH=).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.17; H, 7.37.

**Silver Salt Double Lactonization of 48.** A suspension of the silver salt, prepared from **48** (500 mg), in dimethyl sulfoxide (5 ml) was treated similarly with iodine (1.27 g) and silver acetate (835 mg). Work-up of the neutral product gave **16b** (205 mg, 41%). After the treatment of the acidic product with ethereal diazomethane, preparative silica gel TLC gave two oily esters, **46a** (84 mg, 16%) and **49b** (18 mg, 3%): ir (liquid film) 1805, 1740, and 1695 $cm^{-1}$; NMR[26] $\delta$ 0.91 (t, 3 H), 1.2–1.5 (m, 4 H), 2.06 (m, 2 H, $CH_2C$=), 2.84–2.92 [m, 2 H, $CH_2CO_2$ (lactone)], 3.75 (s, 3 H, OMe), 3.95 (m, 1 H, C**H**CO$_2$Me), and 5.32 (dt, 1 H, $J$ = 7 and 1.7 Hz, CH=).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.28; H, 7.67.

**2-[(*Z*)-1-Hexenyl]-3-methylenebutanedioic Acid (54).** To a stirred solution of **12b** (3.66 g) and 40% aqueous dimethylamine (1.69 g) in methanol (2.5 ml) there was added a solution of 37% aqueous formalin (2.5 g) in methanol (2.5 ml) at −20°. Carbon dioxide evolution was observed during the addition. The resulting mixture was stirred for 7 hr, while the temperature was allowed to rise gradually to room temperature. The reaction mixture was finally refluxed for 1 hr. After removal of the solvent in vacuo, the residue was dissolved in water (5 ml). Ether was added to the solution, which was then acidified with 6 *N* hydrochloric acid, with stirring in an ice bath. After the mixture had been saturated with sodium chloride, the product was extracted with ether. Removal of the solvent gave **54** (1.377 g, 43%) as a semisolid, which was recrystallized from ether–petroleum ether (1:4) to give a pure sample as colorless crystals: mp 105–106°; ir (KBr) 3500–2500, 1705, 1625, 970, 945, and 770 $cm^{-1}$; NMR $\delta$ 0.90 (t, 3 H), 1.1–1.5 (m, 4 H), 2.1 (m, 2 H), 4.25 (br d, 1 H, $J$ = 7.5 Hz, C**H**CO$_2$H), 5.4–6.0 (m, 2 H, C**H**=C**H**), 5.85 and 6.51 (s, 1 H each, =$CH_2$), and 11.60 (s, 2 H, $CO_2H$).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.43; H, 7.85.

**2-[(*E*)-1-Hexenyl]-3-methylenebutanedioic Acid (57).** A solution of 37% aqueous formalin (1.25 g) in methanol (3 ml) was added to a stirred solution of **15b** (2.78 g) and 40% aqueous dimethylamine (1.23 g) in methanol (3 ml) at −20°. The mixture was stirred for 7 hr; meanwhile the temperature was allowed to rise gradually to room temperature, and then the mixture was refluxed for 1 hr. Work-up as described above gave a colorless semisolid (ca. 1.8 g), whose recrystallization from ether–petroleum ether (1:4) afforded analytically pure **57** (1.04 g, 42%) as colorless needles: mp 84–85°; ir (KBr) 3500–2500, 1965, 1625, and 980 $cm^{-1}$; NMR $\delta$ 0.90

(t, 3 H), 1.1–1.5 (m, 4 H), 2.05 (m, 2 H), 4.05 (br d, 1 H, $J$ = 7 Hz, $CHCO_2H$), 5.3–5.9 (m, 2 H, CH=CH), 5.83 and 6.47 (s, 1 H each, $CH_2$=), and 10.5 (s, 2 H, $CO_2H$).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.03; H, 7.80.

**Silver Salt Double Lactonization of 54.** Iodine (2.28 g) was added to a stirred suspension of the silver salt, prepared from **54** (950 mg), in dimethyl sulfoxide (10 ml) at room temperature, and then silver acetate (1.50 g) was added after 10 min. The mixture was stirred at 70° for an additional 15 hr. After most of the solvent was removed, the residue was diluted with methylene chloride (10 ml) and filtered. The filtrate was successively washed with water, aqueous sodium thiosulfate, and water. The acidic product was extracted with aqueous sodium bicarbonate solution. Removal of the solvent from the organic layer left a semisolid, which was purified by preparative silica gel TLC using methylene chloride as solvent, giving **1b** (125 mg, 14%) as colorless needles.

Ether was added to the above sodium bicarbonate extracts, and the mixture was carefully acidified with 6 $N$ hydrochloric acid with stirring in an ice bath. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were evaporated in vacuo at 0° to give an oil (470 mg), which was immediately treated with excess diazomethane. Removal of the solvent in vacuo at 0° left an oil. The oil was purified by preparative silica gel TLC using petroleum ether–ether (2:1) as solvent, giving **56** (100 mg, 8%) as an unstable oil: ir (liquid film) 1785, 1730, and 1550 $cm^{-1}$; NMR $\delta$ 0.90 (t, 3 H), 1.1–1.6 (m, 6 H), 1.6–2.2 (m, 3 H, $CH_2CH$= and $CHCO_2Me$), 3.65 (s, 3 H, OMe), and 4.65–5.05 (m, 3 H, $CH_2N$= and CH=).

No analytical sample was obtained owing to its instability.

**Silver Salt Double Lactonization of 57.** Iodine (1.22 g) was added to a stirred suspension of the silver salt, prepared from **57** (500 mg), in dimethyl sulfoxide (4 ml) at room temperature, and then silver acetate (802 mg) was added after 10 min. The mixture was stirred at 60° overnight. Work-up of the reaction mixture as described for the double lactonization of **54** gave **1a** (114 mg, 21%).

An acidic product obtained was treated with excess diazomethane and purified by preparative silica gel TLC, giving **59** (79 mg, 13%) as a colorless oil: ir (liquid film) 1785, 1725, and 1550 $cm^{-1}$; NMR $\delta$ 0.93 (t, 3 H), 1.1–1.6 (m, 6 H), 1.6–2.4 (m, 3 H, $CH_2CH$= and $CHCO_2Me$), 3.63 (s, 3 H, OMe), and 4.85–5.15 (m, 3 H, CH= and $CH_2N$=).

Anal. Calcd for $C_{13}H_{18}O_4N_2$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.75; H, 7.07; N, 10.36.

**Registry No.—1a,** 35093-30-2; **1b,** 35093-28-8; **5,** 54911-70-5; **10,** 54984-23-5; **11,** 35093-25-5; **12a,** 54911-71-6; **12b,** 54911-72-7; **13a** epimer 1, 36283-63-3; **13a** epimer 2, 36283-62-2; **13b,** 51016-86-5; **13c,** 35093-27-7; **15a,** 54911-73-8; **15b,** 54911-74-9; **16b,** 35093-29-9; **18,** 54911-75-0; **19,** 54911-76-1; **20,** 54911-77-2; **21,** 54911-78-3; **22a,** 3853-88-1; **23,** 5826-27-7; **24** dimethyl ester, 54432-94-9; **25,** 54933-62-9; **26,** 48059-97-8; **27,** 54933-63-0; **28** dimethyl ester, 39590-03-9; **29,** 54911-79-4; **30** silver salt, 55000-29-8; **31,** 54911-80-7; **32,** 54911-81-8; **32** monomethyl ester, 54911-82-9; **33,** 54911-83-0; **34,** 29311-53-3; **35** methyl ester, 54911-84-1; **36,** 51326-51-3; **36** diether, 15057-13-3; **36** aldehyde analog, 54911-85-2; **37,** 54911-86-3; **38,** 54985-60-3; **39,** 54911-87-4; **40,** 19914-92-2; **41,** 4720-83-6; **42a,** 54911-88-5; **42b,** 54911-89-6; **43,** 54911-90-9; **44,** 54911-91-0; **45,** 54911-92-1; **46a,** 54911-93-2; **46b,** 54911-94-3; **47b,** 54911-95-4; **48,** 54911-96-5; **49b,** 54911-97-6; **54,** 54911-98-7; **56,** 54911-99-8; **57,** 54912-00-4; 1-hexyne, 693-02-7; tricarbomethoxyethylene, 51175-48-5; performic acid, 107-32-4; silver nitrate, 7761-88-8; silver acetate, 563-63-3; dimethyl 4-octynedioate, 23542-39-4; 1,4-butanediol, 110-63-4; dihydropyran, 25512-65-6; ethyl vinyl ether, 109-92-2; 1,5-diazabicyclo[5.4.0]undecene-5, 6674-22-2.

## References and Notes


(1) N. J. McCorkindale, J. L. C. Wright, P. W. Brian, S. M. Clarke, and S. A. Hutchinson, *Tetrahedron Lett.*, 727 (1968).
(2) D. Brookes, B. K. Tidd, and W. B. Turner, *J. Chem. Soc.*, 5385 (1963); D. Brookes, S. Sternhell, B. K. Tidd, and W. B. Turner, *Aust. J. Chem.*, **18,** 373 (1965).
(3) D. C. Aldridge and W. B. Turner, *J. Chem. Soc. C,* 2341 (1971).
(4) For a review, see L. A. Porter, *Chem. Rev.*, **67,** 441 (1967).
(5) Avenaciolide (**3a**) [(a) J. L. Herrmann, M. H. Berger, and R. H. Schlessinger, *J. Am. Chem. Soc.*, **95,** 7923 (1973); (b) W. L. Parker and F. Johnson, *ibid.*, **91,** 7208 (1968); *J. Org. Chem.*, **38,** 2489 (1973)] and 4-isoavenaciolide [(c) K. Yamada, M. Kato, M. Iyoda, and Y. Hirata, *Chem. Commun.*, 499 (1973)] have been synthesized.
(6) For a review, see N. S. Bhacca and D. H. Williams, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Holden-Day, San Francisco, Calif., 1964, pp 49–54.
(7) For a preliminary communication regarding part of this work, cf. M. Kato, R. Tanaka, and A. Yoshikoshi, *Chem. Commun.*, 1561 (1971).
(8) H. O. House, F. J. Sauter, W. G. Kenyon, and J. J. Riehl, *J. Org. Chem.*, **33,** 957 (1968).
(9) This allene derivative (**11**) was independently prepared from **10** by isomerization with sodium amide. See Experimental Section.
(10) T. Mukaiyama, K. Hagio, H. Takei, and K. Saigo, *Bull. Chem. Soc. Jpn.*, **44,** 161 (1971). We thank Professor T. Mukaiyama for his generous gift of an authentic sample.
(11) We thank Dr. N. J. McCorkindale for the identification of (±)-canadensolide.
(12) McCorkindale has independently revised the stereochemistry of canadensolide as **1a,** including the absolute configurations, by a degradative work: personal communication.
(13) (a) O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, **460,** 98 (1928); (b) R. S. Monson, "Advanced Organic Synthesis", Academic Press, New York, N.Y., 1972, p 78.
(14) (a) K. Alder and G. Stein, *Justus Liebigs Ann. Chem.*, **514,** 1 (1934); (b) A. Winston and P. Wilder, Jr., *J. Am. Chem. Soc.*, **76,** 3045 (1954); (c) L. H. Zalkov and C. D. Kennedy, *J. Org. Chem.*, **28,** 3309 (1963).
(15) We have found that iodolactonization occurred much faster in dimethyl sulfoxide than in aqueous media which have been usually used.
(16) These dilactones **25** and **27** have been reported without assignment of their steric configurations. The higher melting meso isomer was obtained as an oxidation product of a butadiene copolymer [(a) T. Handa, *Chem. High Polym.*, **6,** 382 (1949); *Chem. Abstr.*, **46,** 1794*d* (1952)]. The lower melting racemic isomer and the above meso isomer have been prepared by catalytic hydrogenation of 4,6-dihydroxy-2,4,6-octatrienedioic acid di-γ-lactones [(b) H. E. Holmquist, F. D. Marsh, J. C. Sauer, and V. A. Engelhardt, *J. Am. Chem. Soc.*, **81,** 3681 (1959)].
(17) For the preparation of the methyl ester of this acid, see P. G. Gassman and X. Creary, *Chem. Commun.*, 1214 (1972).
(18) L. F. Fieser and F. C. Novello, *J. Am. Chem. Soc.*, **64,** 802 (1942). See also ref 13b, p 72.
(19) E. H. Farmer, *J. Chem. Soc.*, **123,** 2541 (1923).
(20) E. R. H. Jones, G. M. Mansfield, and M. C. Whiting, *J. Chem. Soc.*, 3208 (1954).
(21) R. Grewe, A. Heinke, and C. Sommer, *Chem. Ber.*, **89,** 1978 (1956).
(22) This acid has been prepared by an alternative route: K. Shishido, K. Sei, and H. Nozaki, *J. Org. Chem.*, **27,** 2681 (1962).
(23) K. W. Campbell and B. K. Campbell, "Organic Systheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 117.
(24) This oil was contaminated with a minor amount (ca. 5% in GLC analysis) of the allene derivative (**11**) as shown in the ir spectrum (1960 $cm^{-1}$). The identification was made by GLC peak enhancement experiments using the authentic compound (vide post).
(25) Prepared according to F. D. Gunstone, *Adv. Org. Chem.*, **1,** 137 (1960).
(26) Recorded on a Jeol PS-100 spectrometer (100 MHz).
(27) J. C. Collins, *Tetrahedron Lett.*, 3363 (1968).