Highly Stereo- and Regioselective Alkylation of Alkylidenemalonates. Its Application to the Synthesis of (±)-Canadensolide

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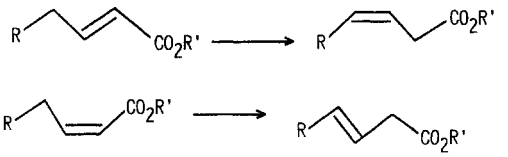
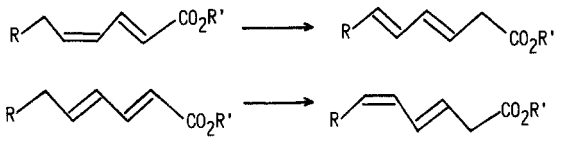
Deconjugative alkylation of *n*-alkylidenemalonates in the presence of lithium diisopropylamide (LDA) gave (*E*)-2-(alkoxycarbonyl)-2-alkyl-3-alkenoates in 53–99% yield with high stereoselectivity. The total synthesis of (±)-canadensolide is established in five steps with high stereoselectivity.

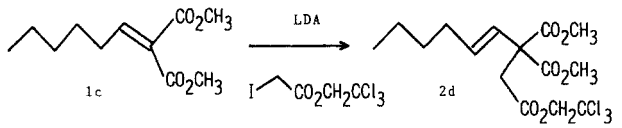
Recently, base-catalyzed deconjugation of conjugated olefinic esters has attracted the attention of organic chemists on the viewpoint of stereochemical study as well as the synthetic utility for natural products. Deconjugative alkylation of (*E*)- and (*Z*)-2-alkenoates with strong bases such as lithium diisopropylamide[1,2] and potassium disilazide[3] gave respectively (*Z*)- and (*E*)-3-alkenoates with high stereoselectivities. We recently reported deconjugative



protonations of 2(*E*),4(*Z*)- and 2(*E*),4(*E*)-alkadienoates give respectively 3*E*,5*E* and 3*E*,5*Z* isomers.[4]



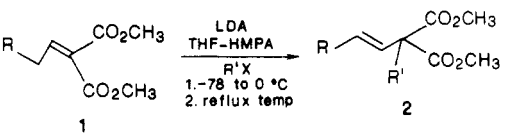
In the previous work,[5] we needed 2,2,2-trichloroethyl (*E*)-3,3-bis(methoxycarbonyl)-4-nonenoate (**2d**) for the stereoselective synthesis of (±)-canadensolide. Compound **2d** was stereospecifically prepared by the base-catalyzed condensation of dimethyl hexylidenemalonate (**1c**) with 2,2,2-trichloroethyl iodoacetate. In this paper the gen-



eralization of this stereospecific alkylation[6] for various alkylidenemalonates was attempted. The synthetic approach of (±)-canadensolide published in the preliminary communication[5] is also described in detail.

Various alkylidenemalonates **1** were prepared by Knoevenagel condensation.[7] Deconjugation of **1** to 2-(alkoxycarbonyl)-3-alkenoates **2** (R′ = H) with lithium diisopropylamide (LDA) was carried out by a slightly modified method of the literature.[1] Compound **1** was treated with a 0.29 M solution of LDA in THF/HMPA from −78 °C to room temperature. The results are summarized in Table I. The reaction gave a 3*E* isomer exclusively. Deconjugative alkylation of the enolate of **1** with alkyl halide was attempted to yield α-alkylated (*E*)-2-(alkoxycarbonyl)-3-alkenoates **2** as a single product. γ-Alkylated products were negligible in ^{1}H NMR analysis. When the reaction was carried out at −78 °C–room temperature, a small amount of the starting material was recovered. On the other hand, when the reaction mixture was heated up to the reflux temperature of the solvent, the yields increased greatly.

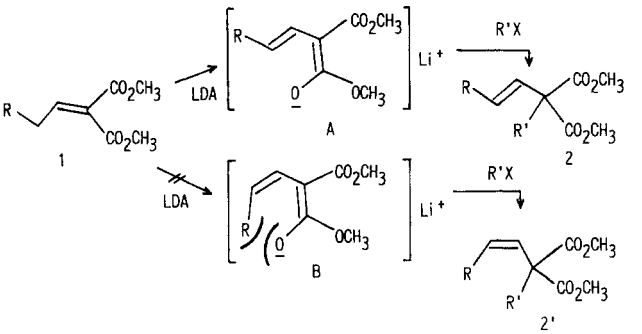
Table I



no.	R	R′	yield (%) of **2**[a]
a	CH_3	CH_3	59
b	C_4H_9	H	99
c	C_4H_9	CH_3	91
d	C_4H_9	$CH_2CO_2CH_2CCl_3$	90
e	C_6H_{13}	H	99
f	C_6H_{13}	CH_3	95
g	C_6H_{13}	$CH_2CO_2CH_2CCl_3$	78
h	C_4H_9	CH_2CO_2-menthyl	53

[a] Pure by ^{1}H NMR analysis.

Scheme I



The mechanism of this stereospecific deconjugation and alkylation was discussed as shown in Scheme I. Reflecting the fact that ester dienolate anions are known to adopt the *E* (s-cis) configuration with respect to the unsubstituted oxygen and α-carbon,[2,8] intermediates A and B in the reaction of **1** with LDA can be postulated. It is well-known

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(3) (a) Ikeda, Y.; Yamamoto, H. *Tetrahedron Lett.* **1984**, *25*, 5181. (b) Ikeda, Y.; Ukai, J.; Ikeda, N.; Yamamoto, H. *Tetrahedron Lett.* **1984**, *25*, 5177.
(4) Tsuboi, S.; Kuroda, A.; Masuda, T.; Takeda, A. *Chem. Lett.* **1984**, 1541.
(5) Tsuboi, S.; Fujita, H.; Muranaka, K.; Seko, K.; Takeda, A. *Chem. Lett.* **1982**, 1909.
(6) The deconjugative alkylation of alkylidenemalonates in the presence of NaOEt or $NaNH_2$ has been reported. However, the stereochemistry of the products was not accounted for: Cope, A. C.; Hartung, W. H.; Hancock, E. M.; Crossley, F. S. *J. Am. Chem. Soc.* **1940**, *62*, 314.
(7) Johnson, J. R. *Org. React. (N.Y.)* **1942**, *1*, 210.
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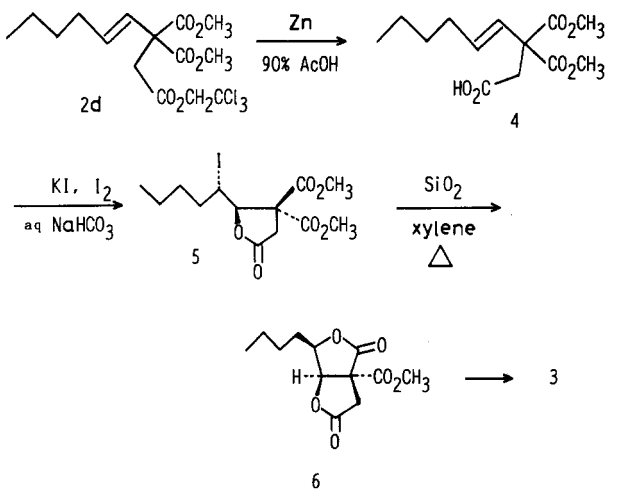
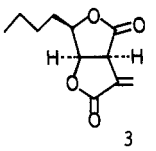
Scheme II



that the cis form is more stable than the trans form in the crotyl anion system.[2,9] However, in this case the steric hindrance between R and methoxycarbonyl groups of the intermediate B is pretty large. Therefore, presumably the reaction gives **2** via the intermediate A.

As an application of the present method for the synthesis of natural products, the alkylated product **2d** was used for the synthesis of (±)-canadensolide **3**.[10-13] The



reaction sequences are outlined in Scheme II. Hydrolysis of **2d** with Zn–CH_3CO_2H gave the acid **4** in 63% yield. Attempts of one-step synthesis of **4** from dimethyl hexylidenemalonate by the alkylations with sodium bromoacetate and also with sodium iodoacetate resulted in the deconjugative protonation to yield methyl (*E*)-2-(methoxycarbonyl)-3-octenoate (**2b**). Iodolactonization of **4** afforded erythro-γ-butyrolactone **5** stereospecifically. Previously we reported that silica gel promotes the lactonization of γ-halo esters.[5] This simple and economically feasible lactonization method was applied to **5**, giving cis-substituted γ-bislactone **6** in 78% yield. Finally, the introduction of exo-methylene group and demethoxycarbonylation were accomplished by similar procedures to those reported by Parker and Johnson.[14,15] Treatment of bislactone **6** with a 2 M solution of magnesium methyl crabonate (MMC) in DMF at 120 °C and the subsequent Mannich condensation at 60 °C for 5 min afforded (±)-canadensolide (**3**) in 10% yield.[16] The melting point and IR and ^1H NMR spectral data were consistent with those of the authentic sample.[10-12] In this total synthesis, the stereochemically desirable structures were obtained in all of the steps.

We conclude that the stereochemistry of deconjugative alkylation of alkylidenemalonates is now well understood and that this knowledge forms the basis of a simple and stereospecific synthesis of bis-γ-butyrolactone units.

Experimental Section

The melting points and boiling points are uncorrected. Elemental analyses were carried out by Mr. Eiichiro Amano of our laboratory. ^1H NMR spectra (60 MHz) were recorded with a JEOL LTD JNM-PMX60SI apparatus. ^{13}C NMR spectra were obtained with a JEOL LTD JNM-FX100 apparatus, with $CDCl_3$ as a solvent. All chemical shifts are reported in δ units downfield from internal Me_4Si, and the *J* values are given in hertz. IR spectra were recorded with a JASCO LTD A-102 apparatus. Column chromatography was done on SiO_2 (Wako-gel C-200). Thin-layer chromatography (TLC) was done on precoated silica gel 60 F_{254} plates (E. Merk). Preparative TLC was accomplished on silica gel PF_{254} (E. Merk). Alkylidenemalonates were prepared according to procedures reported in the literature.[17] Compounds, boiling points, and yields are as follows: **1a**,[17] bp 77–78 °C (4 mm), 19%; **1c**,[17] bp 102 °C (2 mm), 76%.

Deconjugative Protonation and Alkylation of 1 to 2. All glassware must be dried. The reaction was carried out under an atmosphere of dry nitrogen to protect from moisture. Some representative preparations of **2** are described below.

Methyl (*E*)-2-(Methoxycarbonyl)-3-octenoate (2b). Procedures published by Kende and Toder[2] were slightly modified. A stirred solution of 0.16 mL (1.14 mmol) of diisopropylamine in 1 mL of dry THF under an N_2 atmosphere was cooled to −15 °C, followed by slow, dropwise addition of 0.7 mL (1.16 mmol) of 1.65 M butyllithium in hexane. After 20 min, 0.5 mL of hexamethylphosphoric triamide (HMPA) was added, and then the mixture was cooled to −78 °C. Dimethyl hexylidenemalonate (0.206 g, 0.96 mmol) was added dropwise with stirring and the mixture was allowed to warm to 0 °C during 1 h. After 1 mL of water was added, the mixture was poured into ice–water and acidified with dilute HCl. The organic layer was extracted with ether. The combined organic layers were washed with water and dried over $MgSO_4$. Removal of the solvent gave 0.204 g (99%) of **2b** as a clean oil: TLC (hexane/acetone, 4:1) R_f 0.77; IR (neat) 1742 (C=O), 1647 cm^{-1}; ^1H NMR (CCl_4) δ 0.90 (t, *J* = 6 Hz, 3 H, $CH_3(CH_2)_3$), 1.1–1.6 (m, 4 H, $CH_3(CH_2)_2$), 2.05 (m, 2 H, CH_2CH=CH), 3.70 (s, 6 H, $2CO_2CH_3$), 3.80 (m, 1 H, $CH(CO_2CH_3)_2$), 5.62 (m, 2 H, —CH=CH—); ^{13}C NMR ($CDCl_3$) δ 13.9 (q), 22.3 (t), 31.2 (t), 32.3 (t) 52.4 (q), 55.3 (d), 121.9 (d), 136.7 (d), 168.6 (s). Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.75; H, 8.39.

2,2,2-Trichloroethyl (*E*)-3,3-Bis(methoxycarbonyl)-4-nonenoate (2d). A stirred solution of 0.16 mL (1.14 mmol) of diisopropylamine in 1 mL of dry THF under an N_2 atmosphere was cooled to −15 °C, followed by slow, dropwise addition of 0.7 mL (1.16 mmol) of 1.65 M butyllithium in hexane. After 20 min, 0.5 mL of HMPA was added, and then the mixture was cooled to −78 °C. Dimethyl hexylidenemalonate (0.206 g, 0.96 mmol) was added dropwise and the mixture was stirred for 30 min. After the dropwise addition of 0.556 g (1.8 mmol) of 2,2,2-trichloroethyl iodoacetate, the mixture was allowed to warm up to room temperature during 1 h. It was heated at reflux temperature for 30 min, cooled to room temperature, and worked up in the usual manner. Concentration of the ethereal extract gave 0.513 g of a crude product, which was purified by column chromatography (SiO_2, hexane/ethyl acetate, 10:1) to give 0.348 g (90%) of **2d**: TLC (hexane/ether, 5:1) R_f 0.54; IR (neat) 1740 (C=O), 1640 cm^{-1} (C=C); ^1H NMR ($CDCl_3$) δ 0.89 (t, *J* = 6 Hz, 3 H, $CH_3(CH_2)_3$), 1.3 (m, 4 H, $CH_3(CH_2)_2$), 2.05 (m, 2 H, CH_2CH=C), 3.30 (s, 2 H, CH_2CO_2), 3.72 (s, 6 H, $2CO_2CH_3$), 4.68 (s, 2 H, $CO_2CH_2CCl_3$), 5.55 (dt, *J* = 15.5 and 6 Hz, 1 H, CH_2CH=CH), 6.07 (d, *J* = 15.5 Hz,

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(15) Sakai, T.; Yoshida, M.; Kohmoto, S.; Utaka, M.; Takeda, A. *Tetrahedron Lett.* **1982**, *23*, 5185.

(16) Introduction of exo-methylene group in the synthesis of **3** has been poorly established. See ref 10, 12, 13, and 15.

(17) Cope, A. C.; Hofmann, C. M.; Wyckoff, C.; Hardenbergh, E. *J. Am. Chem. Soc.* **1941**, *63*, 3452.

1 H, CH=C*H*C<). Anal. Calcd for $C_{15}H_{21}Cl_3O_6$: C, 44.63; H, 5.24. Found: C, 44.71; H, 5.38.

Methyl (*E*)-2-(Methoxycarbonyl)-2-methyl-3-octenoate (2c). Diester **1c** (0.192 g, 0.9 mmol) was treated at −78 °C with 1.1 mmol of LDA and allowed to react with 0.1 mL (1.6 mmol) of methyl iodide as described above. Standard workup gave 193 mg of crude product, which was purified by column chromatography (SiO_2, hexane/ethyl acetate, 10:1–1:1) to give 0.187 mg (91%) of **2c**: TLC (hexane/ethyl acetate, 4:1) R_f 0.64; IR (neat) 1740 (C=O), 1640 cm^{-1} (C=C); ^1H NMR (CCl_4) δ 0.90 (t, J = 6 Hz, 3 H, $CH_3(CH_2)_3$), 1.1–1.6 (m, 4 H, $CH_3(CH_2)_2$), 1.44 (s, 3 H, CH_3), 2.09 (m, 2 H, CH_2CH=CH), 3.66 (s, 3 H, CO_2CH_3), 5.40 (dt, J = 5 Hz, 16 Hz, 1 H, CH_2CH=CH), 5.84 (d, J = 16 Hz, 1 H, CH=C*H*C<). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.29; H, 8.87.

Methyl (*E*)-2-(Methoxycarbonyl)-3-decenoate (2e). Diester **1e** (0.196 g, 0.81 mmol) was treated at −78 °C with 0.86 mmol of LDA, as described in **2b**. Standard workup gave 0.194 mg (99%) of **2e** as a clean oil: TLC (hexane/ethyl acetate, 4:1) R_f 0.70; IR (neat) 1740 (C=O), 1645 cm^{-1} (C=C); ^1H NMR (CCl_4) δ 0.7–1.6 (m, 11 H, $CH_3(CH_2)_4$), 2.0 (m, 2 H, CH_2CH=CH), 3.70 (s, 6 H, $2CO_2CH_3$), 3.85 (m, 1 H, $CH(CO_2CH_3)_2$), 5.60 (m, 2 H, CH=CH). Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.64; H, 9.02.

Methyl (*E*)-2-(Methoxycarbonyl)-2-methyl-3-decenoate (2f). Diester **1f** (0.23 g, 0.95 mmol) was treated at −78 °C with 1.1 mmol of LDA and then was allowed to react with 0.1 mL (1.6 mmol) of methyl iodide, as described in **2d**. Standard workup gave 0.23 g (95%) of **2f** as a clean oil: TLC (hexane/ether, 5:1) R_f 0.72; IR (neat) 1740 (C=O), 1645 cm^{-1} (C=C); ^1H NMR (CCl_4) δ 0.7–1.6 (m, 11 H, $CH_3(CH_2)_4$), 1.46 (s, 3 H, CH_3), 3.66 (s, 6 H, $2CO_2CH_3$), 5.40 (dt, 1 H, J = 6 and 16 Hz, CH_2CH=CH), 5.83 (d, J = 16 Hz, 1 H, CH_2CH=C<). Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.45; H, 9.43.

2,2,2-Trichloroethyl (*E*)-3,3-Bis(methoxycarbonyl)-4-undecenoate (2g). Diester **1g** (0.232 g, 0.96 mmol) was treated at −78 °C with 1.1 mmol of LDA and then was allowed to react with 0.514 g (1.62 mmol) of 2,2,2-trichloroethyl iodoacetate, as described in **2d**. Standard workup gave 0.321 g (78%) of **2g** as a clean oil; TLC (hexane/ether, 5:1) R_f 0.60; IR (neat) 1740 (C=O), 1645 cm^{-1}; ^1H NMR (CCl_4) δ 0.89 (t, J = 6 Hz, 3 H, $CH_3(CH_2)_5$), 1.29 (m, 8 H, $CH_3(CH_2)_4$), 1.7–2.4 (m, 2 H, CH_2CH=CH), 3.22 (s, 2 H, CH_2CO_2), 3.70 (s, 6 H, $2CO_2CH_3$), 4.65 (s, 2 H, $CO_2CH_2CCl_3$), 5.48 (dt, J = 6 and 16 Hz, 1 H, CH_2CH=CH), 6.00 (d, J = 16 Hz, 1 H, CH=C*H*C<). Anal. Calcd for $C_{17}H_{23}Cl_3O_6$: C, 47.52; H, 5.39. Found: C, 47.63; H, 5.43.

(−)-Menthyl (*E*)-3,3-Bis(methoxycarbonyl)-4-nonenoate (2h). Diester **1h** (1.11 g, 5.2 mmol) was treated at −78 °C with 6.1 mmol of LDA and then allowed to react with (−)-menthyl iodoacetate, as described in **2d**. The usual workup and column chromatography on silica gel (10:1 hexane–acetone) gave 1.19 g of **2h** as a clean oil: TLC (hexane/ether, 4:1) R_f 0.65; $[\alpha]^{14}_D$ − 34.1° (*c* 7.9, $CHCl_3$); IR (neat) 1740 cm^{-1} (C=O). Anal. Calcd for $C_{23}H_{38}O_6$: C, 67.29; H, 9.33. Found: C, 67.12; H, 9.18.

(*E*)-3,3-Bis(methoxycarbonyl)-4-nonenoic Acid (4). To a mixture of 0.144 g (2.2 mmol) of zinc powder and 20 mL of 90% acetic acid was added 0.60 g (1.5 mmol) of **2d**, and the resulting mixture was stirred for 6 h at room temperature. After filtration, the filtrate was made weakly basic to litmus with saturated $NaHCO_3$ and the mixture was washed with CH_2Cl_2. The aqueous layer was acidified with 10% HCl, and the organic layer was extracted with CH_2Cl_2. The combined extracts were washed with water and dried over $MgSO_4$. The solvent was evaporated to give 0.258 g (63%) of **4** as a clean oil: TLC (hexane/ethyl acetate, 1:1) R_f 0.56; IR (neat) 3700–2200 (CO_2H), 1735 and 1715 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.89 (t, J = 6 Hz, 3 H, $CH_3(CH_2)_3$), 1.1–1.6 (m, 4 H, $CH_3(CH_2)_2$), 1.7–2.3 (m, 2 H CH_2CH=CH), 3.20 (s, 2 H, CH_2CO_2), 3.75 (s, 6 H, $2CO_2CH_3$), 5.56 (dt, J = 6 and 16 Hz, 1 H, CH_2CH=CH), 6.08 (d, J = 16 Hz, 1 H, CH=C*H*C<), 10.25 (s, 1 H, CO_2H). Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34 H, 7.40. Found: C, 57.45; H, 7.51.

4,5-*erythro*-3,3-Bis(methoxycarbonyl)-5-iodo-4-nonanolide (5). To a mixed solution of 0.426 g (1.6 mmol) of **4** in 8 mL of 0.5 N $NaHCO_3$ was added a solution of I_2 (0.813 g, 3.2 mmol) and KI (1.6 g, 9.6 mmol) in 5 mL of water. The mixture was stirred for 48 h at room temperature in a dark room and then washed with CH_2Cl_2. After the usual workup, the methylene chloride extracts gave 18 mg of the starting material **4**. The aqueous layer was acidified with 10% HCl, and the organic layer was extracted with CH_2Cl_2. The combined extracts were washed with 5% $Na_2S_2O_3$ and water and dried over $MgSO_4$. The evaporation of the solvent gave 0.396 g (63%) of crude **5**: TLC (hexane/acetone, 3:1) R_f 0.36; IR (neat) 1800, 1790 (lactone C=O), 1750 cm^{-1} (ester C=O); ^1H NMR ($CDCl_3$) δ 0.9 (t, J = 6 Hz, 3 H, $CH_3(CH_2)_3$), 1.1–2.2 (m, 6 H, $CH_3CCH_2)_3$), 3.08 (m, 2 H, lactone CH_2), 3.68 (s, 6 H, $2CO_2CH_3$), 3.5–3.9 (m, 1 H, –CHI–), 4.68 (m, 1 H, lactone >CHO–). This sample was used for the next step without further purification.

2-(Methoxycarbonyl)-1,3:2,4-octanebiscarbolactone (6). To a mixture of 2.5 mL of dry xylene and 2 g of silica gel was added a solution of 0.258 g (0.95 mmol) of **5** in 2.5 mL of dry xylene. The mixture was heated at reflux temperature for 3 h and then cooled. After filtration, the evaporation of the solvent gave 0.227 g of crude **6**. Preparative TLC (chloroform/hexane, 1:2, developed two times, R_f 0.14) gave 0.157 g (62%) of pure **6**: IR (neat) 1800, 1790 (lactone C=O), 1750 cm^{-1} (ester C=O); ^1H NMR ($CDCl_3$) δ 0.91 (t, J = 6 Hz, 3 H, $CH_3(CH_2)_3$), 1.1–2.2 (m, 6 H, $CH_3(CH_2)_3$), 3.05 (d, J = 18 Hz, 1 H, C_1-H), 3.42 (d, J = 18 Hz, 1 H, C_1-H), 3.85 (s, 3 H, CO_2CH_3), 4.78 (m, 1 H, C_4-H), 5.06 (d, J = 4 Hz, 1 H, C_3-H); ^{13}C NMR ($CDCl_3$) δ 13.8 (q), 22.4 (t), 27.4 (t), 28.4 (t), 34.7 (t), 54.3 (q), 58.6 (s), 81.9 (d), 82.6 (d), 165.6 (s), 171.5 (s). Anal. Calcd for $C_{12}H_{16}O_6$: C, 56.25: H, 6.29. Found: C, 56.41; H, 6.35.

(±)-(3aα,6α,6aα)-Tetrahydro-6-butyl-3-methylenefuro[3,4-*b*]furan-2,4-dione (Canadensolide) (3). This experiment was carried out by a procedure similar to that reported by Johnson.[14] Bislactone **6** (333 mg, 1.30 mmol) was added to 4 mL of a 2 M solution of magnesium methyl carbonate (MMC) in dimethylformamide. After being stirred for 3 h at 120 °C, the mixture was poured into water and acidified with 10% HCl. The ether extract was washed with brine, dried ($MgSO_4$), and concentrated under vacuum. To the residue (270 mg) were added acetic acid (1 mL), sodium acetate (26 mg, 0.32 mmol), 37% aqueous formaldehyde solution (0.37 mL, 4.9 mmol), and then diethylamine (0.25 mL, 2.45 mmol), successively. The mixture was heated at 60 °C for 5 min with stirring and poured into water. The organic layer was extracted with ether, washed with aqueous $NaHCO_3$ and water, dried, and concentrated. The residual oil was purified by preparative TLC (hexane/ether, 1:2, R_f 0.33–0.44) to give (±)-canadensolide (27 mg, 10% yield). One recrystallization from carbon tetrachloride afforded pure **3**: mp 95–96.5 °C (lit.[11] 96–96.5 °C). IR and ^1H NMR spectral data were consistent with those reported.[10-12] Mixtures of some components at R_f 0–0.2 and 0.5–0.9 could not be purified and were not further investigated.