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Dibromomethane as one-carbon source in organic synthesis: total synthesis of (±)-canadensolide

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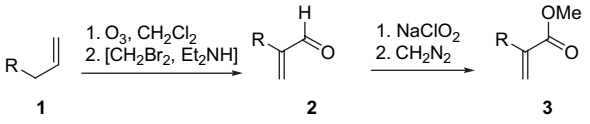
Abstract—A diastereoselective total synthesis of (±)-canadensolide is described. The key step is to introduce the α-methylene group by the ozonolysis of mono-substituted alkenes followed by reaction with a preheated mixture of CH_2Br_2–Et_2NH.

1. Introduction

We have reported that the ozonolysis of mono-substituted alkenes **1** followed by reaction with a preheated mixture of CH_2Br_2–Et_2NH affords α-substituted acroleins **2** in good yields.[1] The α-substituted acroleins **2** were easily oxidized by $NaClO_2$ and then treated with CH_2N_2 to give α-substituted acrylate **3** in excellent yields (Scheme 1).[2] This methodology was also applied to prepare the α-methylene lactones with different ring sizes from the corresponding alkenol.[3]



Scheme 1.

Various bioactive α-methylene-γ-butyrolactones and bislactones have been isolated from microorganisms and some specific examples are shown in Figure 1.[4] The structures **4**–**6** contain α-methylene, β-carboxylic acid, and γ-alkyl groups in different chain lengths. Both the β- and γ-substituents are *trans* to each other. We have successfully applied the methodology described in Scheme 1 in the total synthesis of the (±)- and (−)-methylenolactocin (**4**).[4]

Naturally occurring bislactones such as canadensolide (**7**),[5] xylobovide (**8**),[6] and sporothriolide (**9**)[7] are metabolites of *Penicillium canadense*, *Xylaria obovata*, and *Sporothrix* sp., respectively. They are closely related natural products that differ simply in the length of their side chain (Fig. 1). The interest in these compounds lies not only in their significant biological activities but also their unique stereochemical features. The fungicidal activity of canadensolide (**7**), the phytotoxic activity of xylobovide (**8**), and the antibacterial, fungicidal, algicidal, and herbicidal activities of sporothriolide (**9**) are noteworthy. These compounds contain all *cis* stereochemistry of the three adjacent methine protons and the alkyl substituent is interestingly situated in the sterically less accessible concave face. These structures have received considerable attention as synthetic targets, with several reported total syntheses of canadensolide,[8,9] xylobovide,[10] and sporothriolide[11] appearing in the literature.

In continuation of our interest in the synthetic applications of the α-methylenation methodology in natural product synthesis,[4] we want to develop a general synthetic pathway, which is applicable to prepare natural products **7**–**9**. In this article, our effort in the stereoselective total synthesis of canadensolide (**7**) will be described.

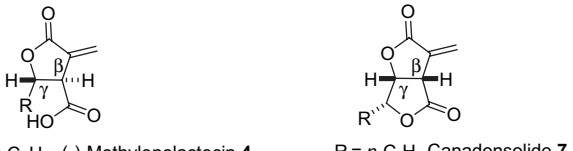


Figure 1. Natural products with β,γ-disubstituted-α-methylene-γ-butyrolactone moiety and α-methylene-furofurandione moiety.

Keywords: Canadensolide; α-Methylene-γ-butyrolactones; Bislactones; α-Methylenation.
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2. Results and discussions

2.1. The retrosynthetic analysis of bislactone-type natural product

The retrosynthetic analysis of bislactone-type natural product **A** is shown in Figure 2. The bislactone **A** should be easily prepared by the bislactonization of the diester **B**. The methyl

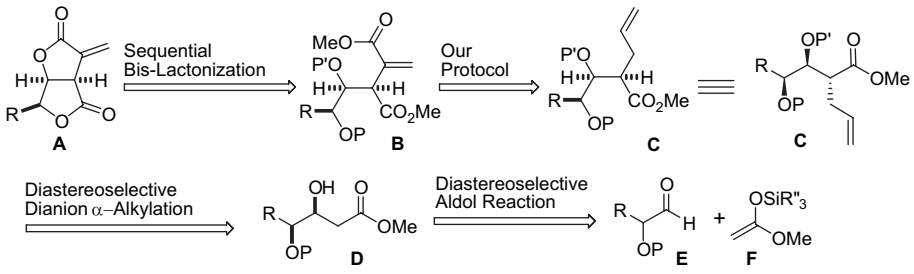


Figure 2. Retrosynthetic analysis of the total synthesis of bislactone natural products.

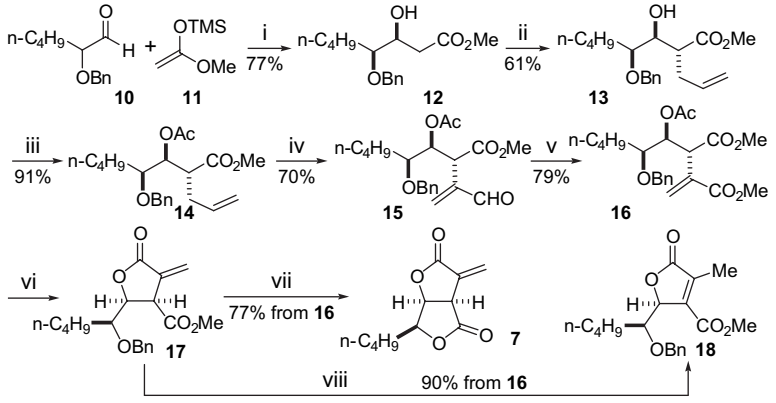
acrylate **B** should be easily prepared from allylacetate **C** by our methodology as shown in Scheme 1. The stereoselective introduction of the α-stereogenic center of compound **C** from the allylation of the dianion of β-hydroxy ester **D** is a well known procedure in the literature.[12] The *syn*-β-hydroxy-γ-alkoxy ester **D** formed from the Lewis acid-catalyzed addition of the silyl enol ether **F** to α-alkoxy aldehyde **E** via chelation-controlled intermediate should be a diastereoselective process (Fig. 2).[13]

2.2. The total synthesis of canadensolide

The readily available α-benzyloxyhexanal (**10**)[14] undergoes aldol additions with trimethylsilyl ketene acetal **11** catalyzed by $TiCl_4$ at −78 °C to give the chelation-controlled 1,2-asymmetric induction[13] *syn* product **12** in 77% yield (Scheme 2). Essentially only one of two possible diastereomers is formed. The allylation of β-hydroxy ester **12** following the procedure of Frater[12] gave the 2,3-*anti*-β-hydroxy ester **13** in 61% yield. The acetylation of the secondary alcohol **13** gave the corresponding acetate **14** in 91% yield. The ozonolysis of terminal olefin **14** followed by addition of of the crude product. However, we found that compound **17** undergoes isomerization to the endocyclic olefin **18** during the silica gel column chromatography. Fortunately, the debenzylation of the crude product **17** with a stoichiometric amount of $SnCl_4$[15] was tried and canadensolide (**7**) was isolated in 77% yield for two steps as a white solid. Presumably, the isomerization to the extended conjugated product is a facile process only for the monocyclic compound **17** but not the bicyclic compound **7**.

3. Conclusions

The special features of our synthetic design are described as follows. The relative stereochemistry of γ- and δ-substituents was established by the $TiCl_4$-catalyzed aldol reaction via chelation-controlled intermediate. The relative stereochemistry of β- and γ-substituents was established by the stereoselective allylation of the dianion of β-hydroxy ester **12**. Furthermore, the α-methylene-γ-butyrolactone moiety was derived from the corresponding terminal alkene by the methodology developed in our laboratory (Fig. 3). We



Scheme 2. Reagents and conditions: (i) $TiCl_4$, −78 °C, CH_2Cl_2, 8 h; (ii) (a) 2.2 equiv LDA, −78 °C, 6 h; (b) $H_2C{=}CHCH_2Br$; (iii) Ac_2O, Et_3N, cat. DMAP; (iv) (a) O_3, CH_2Cl_2, −78 °C; (b) preheated mixture of Et_2NH and CH_2Br_2, 2 h; (v) (a) $NaClO_2$, *t*-BuOH, $NaH_2PO_4{\cdot}2H_2O$, $MeCH{=}CMe_2$, 8 h; (b) CH_2N_2; (vi) cat. MeCOCl, MeOH, 24 h; (vii) $SnCl_4$, CH_2Cl_2, reflux, 2.5 h; (viii) silica gel column chromatography.

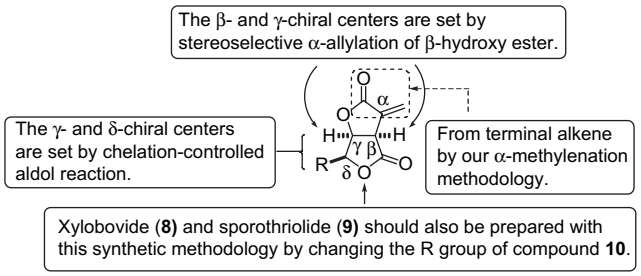


Figure 3. Summary of the special features of our natural product synthesis.

complete the total synthesis of canadensolide (**7**) in nine operation steps in 18% overall yield starting from α-benzyloxy aldehyde **10**.

Our synthetic design should be extendable to the total synthesis of xylobovide (**8**) and sporothriolide (**9**) by replacing the α-substituent of compound **10** from *n*-butyl to ethyl and *n*-hexyl, respectively.

4. Experimental

4.1. General

All reactions were carried out under nitrogen. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting points were determined by using a Thomas–Hoover melting point apparatus and were uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX400 spectrometer, and chemical shifts were given in parts per million downfield from tetramethylsilane (TMS). IR spectra were taken with a Perkin–Elmer 682 spectrophotometer and only noteworthy absorptions were listed. Mass spectra were measured on a Micromass Trio-2000 GC–MS spectrometer (National Chiao-Tung University) by electronic impact at 70 eV (unless otherwise indicated). High Resolution Mass Spectroscopy (HRMS) was measured on a Finnigan/Thermo Quest MAT (National Chung Hsing University) mass spectrometer. 3-Nitrobenzyl alcohol (NBA) was used as FAB Mass matrix. Compound **10** was prepared by the reported procedure.[14]

4.2. (3*S**,4*S**)-4-(Benzyloxy)-3-hydroxyoctanoic acid methyl ester (12)

To a mixture of aldehyde **10** (1.2 g, 5.82 mmol) and enol silyl ether **11** (1.02 g, 6.98 mmol) in 23 mL of CH_2Cl_2 was added $TiCl_4$ (6.4 mmol, 6.4 mL, 1.0 M in CH_2Cl_2) by syringe pump at −78 °C over 1 h. The reaction mixture was warmed to rt and continued to stir for another 8 h. The reaction mixture was neutralized slowly by saturated aqueous $NaHCO_3$ at 0 °C and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4, filtered, and concentrated to give the crude product. The crude product was purified by silica gel column chromatography to give β-hydroxy ester **12** (1.26 g, 4.49 mmol) as a pale yellow oil in 77% yield. R_f=0.39 (hexane/EtOAc=5:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28–7.38 (m, 5H, Ph-H), 4.64 (ABq, J=11.4 Hz, 1H, –CH_2Ph), 4.51 (ABq, J=11.4 Hz, 1H, –CH_2Ph), 4.08–4.14 (m, 1H, –C*H*OH), 3.68 (s, 3H, OMe), 3.37 (td, J=6.1 and 4.1 Hz, 1H, –C*H*OBn), 2.70 (d, J=5.8 Hz, 1H, OH), 2.53–2.55 (m, 2H, –CH_2CO$_2$Me), 1.32–1.67 (m, 6H), 0.91 (t, J=7.0 Hz, 3H, –CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.8, 138.2, 128.3, 127.8, 127.7, 80.8, 72.2, 69.0, 51.6, 38.0, 29.4, 27.6, 22.8, 13.9; IR (thin film, NaCl plates): 3471, 2953, 2930, 2859, 1736, 1455, 1437, 1275, 1170, 1072, 736, 699 cm^{-1}; FAB Mass (*m*/*z*): 281 (M$^+$+l, 30), 280 (M$^+$, 0.2), 263 (4), 249 (2), 173 (12), 91 (100); HRMS calcd for $C_{16}H_{24}O_4$: 280.1675, found: 280.1673.

4.3. (2*R**,3*S**,4*S**)-2-Allyl-4-(benzyloxy)-3-hydroxyoctanoic acid methyl ester (13)

n-Butyllithium (4.9 mL, 7.85 mmol, 1.6 M in hexane) was added to a stirring solution of diisopropylamine (1.10 mL, 7.85 mmol) in THF (12 mL) at −78 °C. To the LDA solution, β-hydroxy ester **11** (1.0 g, 3.57 mmol) in 5 mL of THF was added at −78 °C and stirred at this temperature for 1 h. At −78 °C, a mixture of allyl bromide (0.37 mL, 4.27 mmol) and HMPA (1.2 mL) in THF (4.8 mL) was added to the reaction mixture. After stirring at −78 °C for 1 h, the reaction mixture was partitioned between 40% ethyl acetate/petroleum ether and saturated aqueous NH_4Cl. The combined organic phase was dried (Na_2SO_4), concentrated, and chromatographed on silica gel column to afford product **13** (698 mg, 2.44 mmol) in 61% yield as a colorless oil. TLC R_f=0.58 (hexane/EtOAc=5:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29–7.37 (m, 5H, Ph-H), 5.62–5.73 (m, 1H, –C*H*=CH$_2$), 5.01–5.07 (m, 2H, –CH=CH_2), 4.66 (ABq, J=11.4 Hz, 1H, –CH_2Ph), 4.42 (ABq, J=11.4 Hz, 1H, –CH_2Ph), 3.70 (ddd, J=9.4, 5.8, and 2.7 Hz, 1H, –C*H*OH), 3.54 (s, 3H, OMe), 3.38 (ddd, J=7.7, 5.2, and 2.6 Hz, 1H, –C*H*OBn), 2.85 (d, J=9.5 Hz, 1H, OH), 2.64 (dt, J=9.0 and 5.8 Hz, 1H, –C*H*CO$_2$Me), 2.22–2.41 (m, 2H, –CH_2CH=CH$_2$), 1.29–1.64 (m, 6H), 0.91 (t, J=7.0 Hz, 3H, –CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.8, 138.1, 134.7, 128.4, 127.9, 127.7, 117.2, 79.3, 72.8, 71.5, 51.6, 48.5, 33.8, 29.3, 27.6, 22.9, 14.0; IR (thin film, NaCl plates): 3481, 2953, 2932, 2861, 1736, 1455, 1437, 1267, 1195, 1167, 1069, 916, 734, 699 cm^{-1}; FAB Mass (*m*/*z*): 321 (M$^+$+l, 31), 320 (M$^+$, 0.2), 281 (28), 213 (32), 207 (21), 147 (28), 91 (100), 73 (42); HRMS calcd for $C_{19}H_{28}O_4$: 320.1988, found: 320.1990.

4.4. (2*R**,3*S**,4*S**)-3-Acetoxy-2-allyl-4-(benzyloxy)octanoic acid methyl ester (14)

To a solution of the alcohol **13** (500 mg, 1.56 mmol), *N*,*N*-dimethylaminopyridine (DMAP, 19.0 mg, 0.156 mmol) and Et_3N (0.26 mL, 1.87 mmol) in 3.1 mL of CH_2Cl_2 was added acetic anhydride (0.17 mL, 1.87 mmol) at rt and stirred for 2 h. The reaction mixture was concentrated and chromatographed on silica gel column to afford the acetate **14** (515 mg, 1.42 mmol) in 91% yield as a pale yellow oil. TLC R_f=0.67 (hexane/EtOAc=3:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28–7.37 (m, 5H, Ph-H), 5.67–5.69 (m, 1H, –C*H*=CH$_2$), 5.24 (dd, J=8.3 and 3.7 Hz, 1H, –C*H*OAc), 4.99–5.03 (m, 2H, –CH=CH_2), 4.64 (ABq, J=11.7 Hz, 1H, –CH_2Ph), 4.54 (ABq, J=11.7 Hz, 1H, –CH_2Ph), 3.64 (s, 3H, OMe), 3.52 (td, J=6.4 and 3.7 Hz, 1H, –C*H*OBn), 2.96 (td, J=8.3 and 6.3 Hz, 1H, –C*H*CO$_2$Me), 2.24–2.28 (m, 2H, –CH_2CH=CH$_2$), 2.03 (s, 3H, –COCH_3), 1.28–1.51

(m, 6H), 0.88 (t, J=7.2 Hz, 3H, –CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.9, 169.9, 138.0, 134.2, 128.3, 127.9, 127.7, 117.3, 77.3, 73.4, 71.7, 51.4, 46.5, 32.8, 29.2, 27.4, 22.6, 20.8, 13.8; IR (thin film, NaCl plates): 2954, 2935, 2871, 1746, 1455, 1436, 1372, 1233, 1169, 1026, 918, 736, 699 cm^{-1}; EI Mass (m/z): 362 (M^+, 1), 255 (74), 177 (24), 155 (20), 143 (65), 135 (40), 123 (45), 105 (93), 91 (100), 77 (49), 55 (19); HRMS calcd for $C_{21}H_{30}O_5$: 362.2093, found: 362.2101.

4.5. (2*S**,3*R**,4*R**)-3-Acetoxy-4-(benzyloxy)-2-(1-formylvinyl)octanoic acid methyl ester (15)

A two-necked flask fitted with a glass tube to admit ozone, a $CaCl_2$ drying tube, and a magnetic stirring bar were charged with terminal alkene **14** (400 mg, 1.10 mmol) in CH_2Cl_2 (20 mL). The flask was cooled to −78 °C and ozone was bubbled through the solution. When the solution turned blue, ozone addition was stopped. Nitrogen was passed through the solution until the blue color was discharged. A mixture of Et_2NH (0.62 mL, 16.7 mmol) and CH_2Br_2 (1.2 mL, 5.6 mmol) was heated to 55 °C for 1.5 h to give a yellow solution and then cooled to rt. To a solution of ozonide in CH_2Cl_2 generated above was added a preheated mixture of Et_2NH and CH_2Br_2 at −78 °C. After the addition, the cooling bath was removed and the reaction mixture was stirred at rt. The reaction was complete in 2.5 h and the reaction mixture was concentrated. To the crude mixture, ether was added and most of the ammonium salts were precipitated out. After filtration, the filtrate was concentrated, chromatographed on the silica gel column to give the desired acrolein **15** (290 mg, 0.77 mmol) in 70% yield as a pale yellow oil; TLC R_f=0.32 (hexane/EtOAc=5:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.40 (s, 1H, CHO), 7.26–7.35 (m, 5H, Ph-H), 6.59 (s, 1H, –C=CH_2), 6.14 (s, 1H, –C=CH_2), 5.52 (dd, J=8.8 and 3.8 Hz, 1H, –CHOAc), 4.49 (ABq, J=11.5 Hz, 1H, –CH_2Ph), 4.42 (ABq, J=11.5 Hz, 1H, –CH_2Ph), 4.20 (d, J=8.8 Hz, 1H, –CHCO$_2$Me), 3.64 (s, 3H, OMe), 3.44 (ddd, J=7.2, 5.5, and 3.8 Hz, 1H, –CHOBn), 2.05 (s, 3H, –COCH_3), 1.28–1.49 (m, 6H), 0.87 (t, J=7.0 Hz, 3H, –CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.9, 170.7, 169.9, 144.2, 137.9, 136.5, 128.2, 127.7, 127.5, 77.8, 72.7, 71.6, 52.1, 43.2, 29.1, 27.5, 22.5, 20.8, 13.8; IR (thin film, NaCl plates): 2955, 2934, 2870, 1747, 1696, 1455, 1435, 1372, 1232, 1168, 1027, 914, 734, 699 cm^{-1}; FAB Mass (m/z): 376 (M^+, 1), 316 (17), 284 (88), 270 (16), 230 (51), 210 (65), 199 (81), 177 (90), 157 (98), 139 (91), 125 (95), 109 (22), 91 (100), 65 (84), 55 (27); HRMS calcd for $C_{21}H_{29}O_6$ (M^++1): 377.1964, found: 377.1956.

4.6. (2*R**)-[(1*S**,2*S**)-1-Acetoxy-2-(benzyloxy)hexyl]-3-methylenesuccinic acid dimethyl ester (16)

To a solution of acrolein **15** (200 mg, 0.53 mmol), *tert*-butyl alcohol (2.7 mL), and 2-methyl-2-butene (0.18 mL, 111.7 mg, 1.59 mmol) was added dropwise a solution of sodium chlorite (110.7 mg, 1.21 mmol) and sodium dihydrogenphosphate dihydrate (163.7 mg, 1.06 mmol) in 0.8 mL of water. The pale yellow reaction mixture was stirred at rt for 2.5 h. The reaction mixture was concentrated, the residue then dissolved in 1.6 mL of water, and this extracted with 6 mL of hexane. The aqueous layer was acidified to pH 3 with 2 N HCl and extracted with two 5 mL portions of ether. The combined ether layers were washed with 6 mL of water, dried with Na_2SO_4, concentrated to give the crude carboxylic acid. To a solution of α-substituted acrylic acid in 2 mL of CH_2Cl_2 was added a solution of CH_2N_2 in ethyl ether at rt. The progress of the reaction should be monitored carefully by TLC. Excess of the CH_2N_2 will cause further 1,3-dipolar cycloaddition on the double bond. The reaction mixture was concentrated and the residue was chromatographed on silica gel column to give methyl acrylate **16** (171 mg, 0.42 mmol) as a pale yellow oil in 79% yield. TLC R_f=0.6 (hexane/EtOAc=3:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27–7.35 (m, 5H, Ph-H), 6.38 (s, 1H, –C=CH_2), 5.90 (s, 1H, –C=CH_2), 5.59 (dd, J=9.0 and 3.4 Hz, 1H, –CHOAc), 4.51 (ABq, J=11.5 Hz, 1H, –CH_2Ph), 4.41 (ABq, J=11.5 Hz, 1H, –CH_2Ph), 4.17 (d, J=9.0 Hz, 1H, –CHCO$_2$Me), 3.68 (s, 3H, OMe), 3.65 (s, 3H, OMe), 3.49 (td, J=6.4 and 3.4 Hz, 1H, –CHOBn), 2.05 (s, 3H, –COCH_3), 1.28–1.35 (m, 6H), 0.86 (t, J=7.1 Hz, 3H, –CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.1, 170.0, 166.0, 138.1, 135.2, 128.8, 128.1, 127.5, 127.4, 77.9, 72.9, 71.6, 52.1, 47.2, 29.0, 27.4, 22.5, 20.8, 13.8; IR (thin film, NaCl plates): 2953, 2932, 2860, 1748, 1455, 1436, 1372, 1229, 1172, 1027, 917, 736, 699 cm^{-1}; EI Mass (m/z): 406 (M^+, 5), 375 (18); HRMS calcd for $C_{22}H_{30}O_7$: 406.1992, found: 406.1990.

4.7. (2*R**)-[(1*R**)-1-(Benzyloxy)pentyl]-2,5-dihydro-4-methyl-5-oxofuran-3-carboxylic acid methyl ester (18)

To a mixture of acetoxy-acrylate **16** (40 mg, 0.098 mmol) in 1 mL of MeOH was added a catalytic amount of acetyl chloride (2 μL, 29 μmol) and stirred at rt for 24 h. The reaction mixture was concentrated to give the crude α-methylene-γ-butyrolactone **17**. The crude product **17** was chromatographed on silica gel column to give the isomerized product **18** (29.3 mg, 0.088 mmol) in 90% yield as a pale yellow oil. TLC R_f=0.33 (hexane/EtOAc=10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.14–7.35 (m, 5H, Ph-H), 5.10–5.11 (m, 1H, CHOCO), 4.50 (ABq, J=11.9 Hz, 1H, –CH_2Ph), 4.27 (ABq, J=11.9 Hz, 1H, –CH_2Ph), 3.89 (td, J=7.0 and 1.7 Hz, 1H, –CHOBn), 3.75 (s, 3H, OMe), 2.16 (d, J=2.0 Hz, 3H, =CCH_3), 1.28–1.49 (m, 6H), 0.92 (t, J=7.0 Hz, 3H, –CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.8, 162.6, 144.7, 138.3, 137.8, 128.3, 127.6, 81.9, 76.4, 72.3, 52.2, 31.2, 27.9, 22.6, 13.9, 10.8; IR (thin film, NaCl plates): 2955, 2931, 2862, 1768, 1728, 1455, 1438, 1339, 1225, 1098, 1026, 737, 699 cm^{-1}; EI Mass (m/z): 332 (M^+, 1), 258 (58), 215 (88), 199 (66), 187 (69), 156 (95), 145 (52), 127 (56), 124 (88), 105 (100), 91 (97), 65 (73), 55 (63); HRMS calcd for $C_{19}H_{24}O_5$: 332.1624, found: 332.1626.

4.8. (3a*S**,6*R**,6a*R**)-6-Butyl-tetrahydro-3-methylene-furo[3,4-*b*]furan-2,4-dione [i.e., (±)-canadensolide] (7)

To a solution of acetoxy-acrylate **16** (40 mg, 0.098 mmol) in 1 mL of MeOH was added a catalytic amount of acetyl chloride (2 μL, 29 μmol) and stirred at rt for 24 h. The reaction mixture was neutralized by $NaHCO_3$, filtered, and the filtrate was concentrated to give the crude α-methylene-γ-butyrolactone **17**. To a solution of the crude product **17** in 2 mL of anhydrous CH_2Cl_2 was added $SnCl_4$ (0.1 mmol, 0.1 mL,

1 M in CH_2Cl_2) at rt. The solution was refluxed for 2.5 h, and then saturated aqueous $NaHCO_3$ was added at 0 °C. The mixture was extracted with CH_2Cl_2 and the organic layer was washed with brine and dried over Na_2SO_4. After filtration of the mixture and evaporation of the solvent, the crude product was purified by silica gel column chromatography to afford 15.9 mg of canadensolide (**7**) as a white solid in 77% yield. TLC R_f=0.68 (hexane/EtOAc=l:2), mp 95.3–96.7 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.47 (d, J=2.0 Hz, 1H, –C=CH_2), 5.16 (d, J=1.9 Hz, 1H, –C=CH_2), 5.15 (dd, J=6.8 and 4.7 Hz, 1H, –C*H*OCO), 4.65 (ddd, J=7.6, 6.6, and 4.8 Hz, 1H, –C*H*OCO), 4.01 (dt, J=6.7 and 2.0 Hz, 1H, –C*H*CO_2), 1.40–1.90 (m, 6H), 0.94 (t, J=7.2 Hz, 3H, –CH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.1, 167.4, 129.9, 127.2, 82.8, 77.2, 46.2, 28.5, 27.5, 22.4, 13.8; IR (thin film, NaCl plates): 2954, 2928, 2858, 1762, 1664, 1464, 1363, 1306, 1269, 1118, 1069, 934, 727 cm^{-1}; EI Mass (*m*/*z*): 211 (M^++1, 1), 156 (12), 124 (30), 110 (45), 96 (100), 85 (16), 68 (53), 55 (18); HRMS calcd for $C_{11}H_{15}O_4$ (M^++1): 211.0970, found: 211.0975.

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