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Hyperolactones A (**1**) and C (**3**) have been synthesized starting from (*S*)-malic acid by a straightforward route. The unique spirolactone skeleton was efficiently constructed by one-pot reaction as a key step. The absolute stereochemistry of hyperolactones was unambiguously established by this synthesis.

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(-)-Hyperolactone A (**1**) was isolated from the leaves and stems of the Chinese plant *Hypericum chinense* L. by M. Tada and co-workers in 1989 [1]. Later, two structural relatives of **1**, (+)-hyperolactone B (**2**) and (-)-hyperolactone C (**3**), were also isolated from the same plant as minor components in 1995 [2]. The gross structure of **1** and its relative stereochemistry were determined by means of extensive spectroscopic studies and chemical transformation, and was finally confirmed by X-ray crystallographic analysis. These compounds possess a common spirolactone skeleton (anti-orientation at the stereogenic center C-5 in **2** as compared with **1** and **3**), and some novel characteristics of the structure are (1) a highly substituted 1,7-dioxaspiro[4,4]non-2-ene-4,6-dione skeleton; (2) a strained 2,2,5-trisubstituted 3(2*H*)furanone ring system. Owing to their structural uniqueness, compound **1** and structurally related natural products are good targets for total synthesis [3]. We now describe herein the synthesis of **1** and **3** in a stereoselective fashion, which enables us to establish their absolute stereochemistry unambiguously.

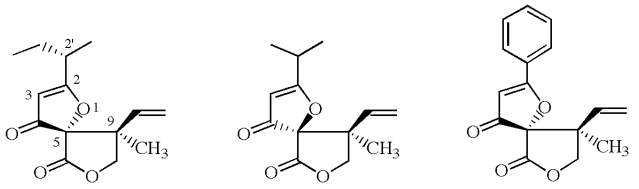
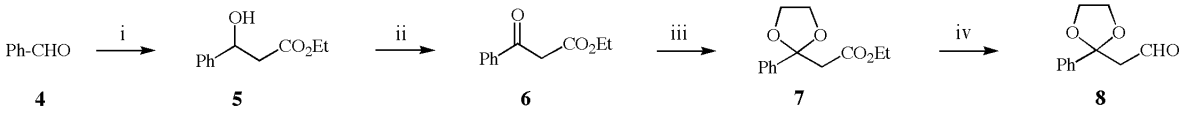


Figure 1

Synthesis of the Side Chain Units **8** and **14**.

The requisite aldehyde **8** was synthesized as shown in Scheme 1. The β-keto ester **6** was obtained by the Collins oxidation of the β-hydroxy ester **5**, which was prepared from ethyl bromoacetate and benzaldehyde **4** by the Reformatsky reaction [4]. The keto ester **6** was heated with ethylene glycol containing a small amount of *p*-toluenesulfonic acid in benzene to give the ketal **7** in 73% yield. Diisobutylaluminium hydride reduction of **7** afforded the aldehyde **8** in 78% yield.

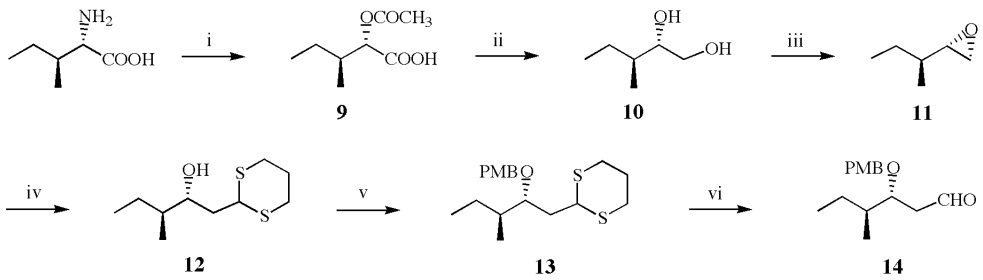
Scheme 1



4 **5** **6** **7** **8**

Reagents and conditions: i, Zn, $BrCH_2CO_2CH_2CH_3$, benzene, reflux, 85%; ii, CrO_3, pyridine, CH_2Cl_2, rt, 82%; iii, ethyleneglycol, *p*-TsOH, benzene, reflux, 73%; iv, diisobutylaluminium hydride, toluene, -78°, 78%.

Scheme 2



9 **10** **11** **12** **13** **14**

PMB=*p*-methoxybenzyl

Reagents and conditions: i, ref. 5; ii, $LiAlH_4$, tetrahydrofuran, reflux, 83%; iii, $[PhCH_2NEt_3]^+Cl^-$, MsCl, NaOH, CH_2Cl_2, 62%; iv, 1,3-dithiane, n-BuLi, tetrahydrofuran, -40° to 0°, 79%; v, NaH, *p*-methoxybenzyl chloride, dimethylformamide, 84%. vi, $HgCl_2$, HgO, CH_3CN, reflux, 84%.

Since the X-ray crystallographic analysis of **1** suggests (2'*S*)-configuration, a synthetic plan for the requisite (4*S*)-aldehyde **14** as a coupling partner is shown in Scheme 2. Reduction of (2*S*, 3*S*)-acetoxy-3-methylvaleric acid **9** [5], prepared from (2*S*, 3*S*)-isoleucine, with lithium aluminium hydride afforded the diol **10** in 83% yield, which was converted [6] into the volatile epoxide **11** in 62% yield. The lithiation of 1,3-dithiane with *n*-butyllithium and subsequent addition to the epoxide **11** gave the dithiane **12** in 79% yield. *p*-Methoxybenzyl protection of the hydroxyl group in **12** and subsequent oxidative cleavage of the dithiane afforded the desired aldehyde **14**.

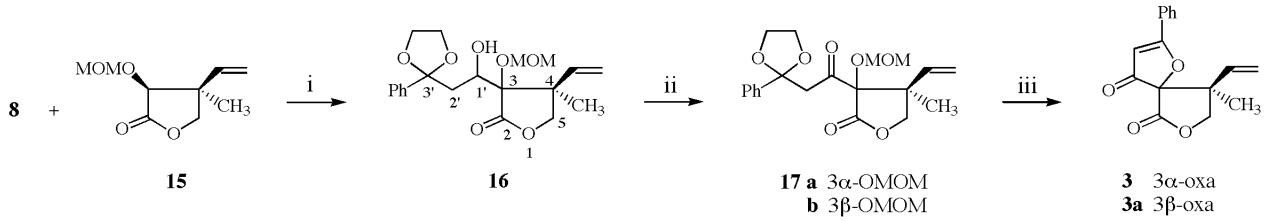
Synthesis of **3** (Scheme 3).

The aldol reaction of the lithium enolate of (3*S*,4*S*)-3-methoxymethyloxy-4-methyl-4-vinyl-γ-butyrolactone **15** (Scheme 5, see experimental section) [3b] with the aldehyde **8** afforded **16** as an inseparable mixture of four diastereomers in 83% yield. Although a multitude of isomers is formed, in the light of the subsequent steps this factor is of minor significance. Successive treatment of **16** with the Jones reagent provided **17** in 92% yield (a:b = 2:3) as a separable mixture.

The stereochemistries of **17** were confirmed by ^{1}H NMR analysis and NOE experiments of **17a** and **17b** (Figure 2). Both in **17a** and **17b**, a NOE was observed between the 4-methyl group (4-CH_3) and a higher-field hydrogen (5-Ha) of the 5-methylene, but not observed between the 4-CH_3 and a lower-field hydrogen (5-Hb). In **17a**, a small NOE was observed between the 4-CH_3 and a methylene hydrogen of the methoxymethyloxy group, whereas a NOE was not observed in **17b**. By the anisotropic effect of the methoxymethyloxy group, the signals of 4-CH_3 and 5-Ha for **17a** appeared in the lower field than the corresponding signals for **17b**, and 5-Hb signal for **17b** was observed in the lower field than that for **17a**. These results indicate that the methoxymethyloxy group and the 4-CH_3 in **17a** were located in the *syn* relationship. From these considerations, it was found that the stereochemistry of **17a** was (3*S*,4*S*)- configuration and **17b** was its 3*R*-epimer.

Acid-catalyzed hydrolysis of **17a** in boiling tetrahydrofuran containing 3 *M* hydrochloric acid furnished **3** (93% yield) consequently *via* a subsequent ring closure and dehydration (Scheme 3). The compound **3** was found to be identical with the natural product [2] by comparing the mp, $[\alpha]_D$, ms, ^{1}H and ^{13}C NMR spectra with those reported, while the physical data of compound **3a** derived from **17b** were all different except the hrms.

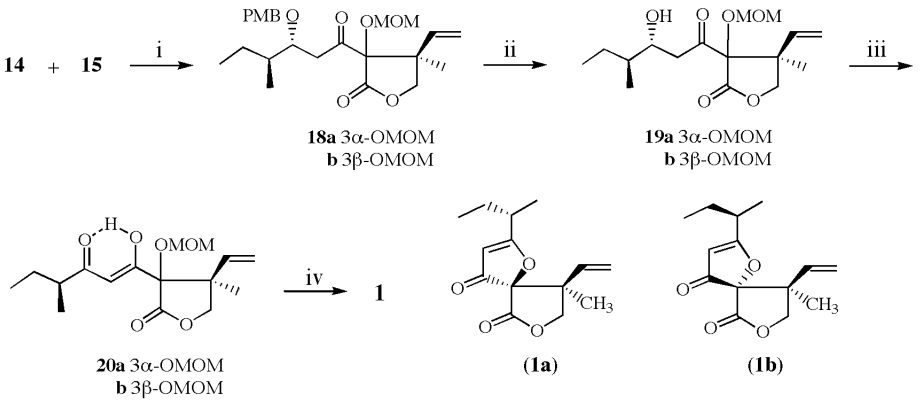
Scheme 3



MOM = methoxymethyl

Reagents and conditions: i, lithium diisopropylamide, tetrahydrofuran, -78°, 83%; ii, CrO_3, H_2SO_4, acetone, 0°, 92%; iii, 3M HCl, tetrahydrofuran, reflux, **3** (93%); **3a** (100%).

Scheme 4



Reagents and conditions: i, (a) lithium diisopropypamide, tetrahydrofuran, -78°, 84% (b) Dess-Martin periodinane, CH_2Cl_2, 100%; ii, dichlorodicyanobenzoquinone, CH_2Cl_2-H_2O, 94%; iii, CrO_3, H_2SO_4, acetone, -20°, 66%; iv,trimethylsilyl bromide, CH_2Cl_2, -20°, 98%.

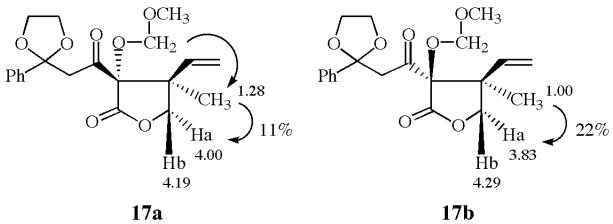
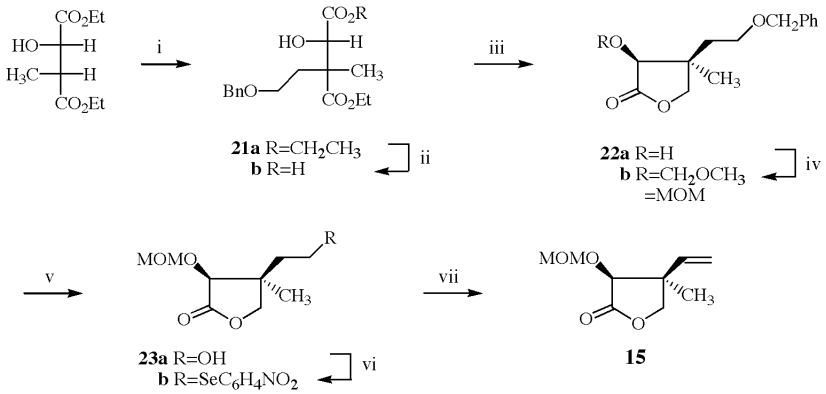


Figure 2

ms, ^1H and ^{13}C NMR spectra with those reported [1]. The β-methoxymethyloxy isomer **20b** was treated with bromotrimethylsilane to afford a 5*R*-isomer **1a** as a single product in 95% yield.

Thus, we have completed the total synthesis of **1** and **3**. This synthesis discloses that the stereochemistry should be depicted as (2'*S*,5*S*,9*S*)-2-(2'-butyl)-9-ethenyl-9-methyl-1,7-dioxaspiro-[4,4]non-2-ene-4,6-dione for (-)-hyperolactone A and (5*S*,9*S*)-configuration for (-)-hyperolactone C, respectively.

Scheme 5
Preparation of **15**



Reagents and conditions: i, lithium diisopropylamide, $PhCH_2OCH_2CH_2I$, tetrahydrofuran, -78°, 67%; ii, KOH, MeOH-H_2O, rt, 97%; iii, $LiB(C_2H_5)_3H$, tetrahydrofuran, rt, 74%; iv, CH_3OCH_2Cl, *i*-Pr_2EtN, CH_2Cl_2, reflux, 93%; v, 10% Pd-C, H_2, EtOH, 96%; vi, *o*-$O_2NC_6H_4SeCN$, Bu_3P, tetrahydrofuran, rt, 88%; vii, 30% H_2O_2, tetrahydrofuran, rt, 76%.

Synthesis of **1** (Scheme 4).

A similar coupling reaction of **15** with the aldehyde **14** gave an inseparable mixture of four diastereomers of the hydroxyl compound in 84% yield, which on oxidation with Dess-Martin periodinane provided **18** in quantitative yield (a:b = 1:1). The two diastereoisomers **18a** and **18b** were separated by chromatography. By similar ^1H NMR analysis and NOE experiments of **18**, a 2.2% enhancement was observed in the signal for the 4-methyl group upon irradiation of the methylene proton of the methoxymethyloxy group in **18a**, thereby confirming that the desired stereochemistry had been established. Deprotection of the *p*-methoxybenzyl group in the lactone **18a** was accomplished using dichlorodicyanobenzoquinone in dichloromethane to give the β-hydroxy ketone **19a** in 94% yield. The Jones oxidation of **19a** under mild condition resulted in enol formation of the diketone **20a**, the structure of which was elucidated by NMR.

An acid-catalyzed reaction of **20a** with boiling tetrahydrofuran in the presence of 3 *M* hydrochloric acid gave a mixture of diastereomers of **1** and its 2'-isomer **1b** (1:1 by NMR) in 70% yield. Such drastic conditions indeed would be inappropriate for the delicate ketone. Finally and much to our relief, deprotection of **20a** was achieved using bromotrimethylsilane in dichloromethane at -20° to give the spirolactone **1** as a single product in 98% yield. The synthetic **1** was found to be identical with the natural product by comparing the mp, $[\alpha]_D$,

The advantages of this strategy are the short and efficient steps in one-pot direct construction of spirolactone by acid-catalysis *via* deprotection, cyclization and elimination.

EXPERIMENTAL

Melting points were measured with a Yanagimoto MP apparatus and are uncorrected. Specific rotations were measured with a JASCO Model DIP-370 polarimeter. Ir spectra were obtained on a JASCO A-102 infrared spectrophotometer. ^1H and ^{13}C nmr spectra were recorded on a JEOL LA-300 (300 MHz) in deuterio chloroform solution, unless stated otherwise. Chemical shifts (ppm) are given downfield of tetramethylsilane. Mass spectra were determined on a JEOL AX-500 spectrometer. Elemental analyses were performed with a JMS AX-500 elemental analyzer by the staff at our Instrumental Measurement Center. Thin-layer chromatography (TLC) was performed with a glass plate coated Kieselgel 60 GF_{254} (Merck). Column chromatography was carried out on silica gel 60 (Merck No. 7734; 63-200 μm). Solvents were dried (drying agent in parenthesis) and distilled prior to use: tetrahydrofuran and diethyl ether (sodium/benzophenone ketyl), benzene and dichloromethane (phosphorous pentoxide), and dimethylsulfoxide (calcium hydride). Organic solutions were dried over anhydrous sodium sulfate.

Ethyl 3-hydroxy-3-phenylpropanoate (**5**).

This compound was prepared from benzaldehyde and ethyl bromoacetate by the Reformatsky reaction in 85% yield as a colorless oil; bp 120-123°/2 mm Hg; (lit [4] 105°/0.2 mm Hg).

Ethyl 3-Phenyl-3-oxopropanoate (**6**).

This compound was prepared by the Collins oxidation [7] of **5** in 82% yield as a colorless oil: bp 115°/1 mm Hg; (lit [7] 95°/0.2 mm Hg); ir (film) 1725, 1670, 1620 cm^{-1}; ^1H nmr: δ 1.25 (t, 3H, J = 7.1 Hz), 3.99 (s, 2H), 4.21 (q, 2H, J = 7.1 Hz), 7.37-7.96 (m, 5H); ^{13}C nmr: δ 14.1 (q), 46.0 (t), 61.5 (t), 126.0 (d), 128.5 (d), 128.8 (d), 133.7 (s), 167.5 (s), 192.5 (s). hrms: Calcd. for $C_{11}H_{12}O_3$: (M^+) 192.0786. Found: m/z 192.0775.

Ethyl 3,3-Ethylenedioxy-3-phenylpropanoate (**7**).

A solution of **6** (10 mmoles), ethyleneglycol (20 mmoles) and *p*-toluenesulfonic acid (20 mg) in benzene (50 ml) was refluxed for 15 hours. The cooled mixture was poured onto saturated aqueous sodium bicarbonate (50 ml), and the organic layer was washed with water and dried. The solvent was removed and the residue was distilled to give **7** in 73% yield as a colorless oil; bp 121°/2 mm Hg; ir (film) 1720 cm^{-1}; ^1H nmr: δ 1.15 (t, 3H, J = 7.1 Hz), 2.96 (s, 2H), 3.80-3.84 (m, 2H), 4.03-4.11 (m, 2H), 4.07 (q, 2H, J = 7.1 Hz), 7.27-7.52 (m, 5H); ^{13}C nmr: δ 14.0 (q), 45.8 (t), 60.4 (t), 64.8 (t), 107.8 (s), 125.6 (d), 128.1 (d), 128.2 (d), 141.4 (s), 168.5 (s). hrms: Calcd. for $C_{13}H_{17}O_4$: $(M + H)^+$ 237.1129. Found: m/z 237.1127.

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.00; H, 6.88.

3,3-Ethylenedioxy-3-phenylpropanal (**8**).

To a solution of **7** (1.0 mmol) in toluene (10 ml) was added diisobutylaluminium hydride (1.5 *M* in toluene, 1.01 mmoles) at -78°. After stirring for 10 minutes the reaction mixture was quenched by addition of water. The precipitate was removed by filtration through celite. The filtrate was washed with water, dried and distilled to give **8** in 78% yield as white crystals; mp 87°; ir (nujol) 1710 cm^{-1}; ^1H nmr: δ 2.90 (d, 2H, J = 2.9 Hz), 3.78-3.90 (m, 2H), 4.03-4.14 (m, 2H), 7.29-7.50 (m, 5H), 9.76 (t, 1H, J = 2.9 Hz); ^{13}C nmr: δ 52.7 (t), 64.7 (t), 108.2 (s), 125.3 (d), 128.5 (d x 2), 141.2 (s), 199.8 (d). MS (EI) m/z 192 (M^+, 15%), 149 (90), 115 (100).

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.48; H, 6.33.

(2*S*,3*S*)-3-Methyl-1,2-pentanediol (**10**).

To a stirred suspension of lithium aluminium hydride (4.36 g, 115 mmoles) in tetrahydrofuran (60 ml) was added a solution of (2*S*,3*S*)-2-acetoxy-3-methylvaleric acid **9** [5] (5.0 g, 28.7 mmoles) in tetrahydrofuran (30 ml) at 0°. After refluxing for 5 hours a small amount of water was added dropwise to decompose excess lithium aluminium hydride, and the precipitate was filtered off through celite and washed with ethyl acetate. The combined filtrates were dried and concentrated to give **10** as a colorless oil (2.8 g, 83%); bp 87°/9 mm Hg; $[\alpha]_D^{24}$ +5.9 (c 1.13, methanol); ir (film) 3400 cm^{-1}; ^1H nmr: δ 0.87 (d, 3H, J = 6.7 Hz), 0.91 (t, 3H, J = 7.3 Hz), 1.04-1.24 (m, 1H), 1.50-1.64 (m, 2H), 3.23 (br s, 2H), 3.49 (dd, 2H, J = 8.2 Hz, J = 17.1 Hz), 3.64-3.70 (m, 1H); ^{13}C nmr: δ 11.2 (q), 14.6 (q), 25.0 (t), 37.6 (d), 64.2 (t), 76.0 (d).

(2*S*,3*S*)-3-Methyl-1,2-epoxypentane (**11**).

A mixture of **10** (2.5 g, 21.2 mmoles), benzyltriethylammonium chloride [6] (139 mg, 3 mol%) and 20% aqueous sodium hydroxide (25 ml) in 25 ml of dichloromethane was heated under reflux, and a solution of mesyl chloride (3.6g, 31.8 mmoles) in 40 ml of dichloromethane was added in portion. Heating and stirring was continued until complete consumption of the starting diol. The mixture was cooled to room temperature, and was poured into 25 ml of water. The organic layer was dried and distilled to give **11** (1.3 g, 62%) as a colorless liquid; bp 95°/760 mm Hg; $[\alpha]_D^{21}$ +3.8 (c 2.10, ethanol); ^1H nmr: δ 0.92 (d, 3H, J = 6.7 Hz), 0.96 (t, 3H, J = 7.3 Hz), 1.15-1.66 (m, 3H), 2.46-2.56 (m, 1H), 2.64-2.78 (m, 2H); ^{13}C nmr: δ 11.2 (q), 15.1 (q), 27.2 (t), 37.6 (d), 45.6 (t), 56.9 (d).

(2*R*,3*S*)-2-(2-Hydroxy-3-methylpentyl)-1,3-dithiane (**12**).

To a solution of 1,3-dithiane (3.01 g, 25.1 mmoles) in tetrahydrofuran (40 ml) was added *n*-butyllithium (1.6 *M* in hexane, 14.2 ml, 22.9 mmols) at -40° under nitrogen and the mixture was stirred for 2 hours. A solution of **11** (2.09 g, 20.9 mmoles) in tetrahydrofuran (15 ml) was added to the reaction mixture, and stirred for additional 5 hours at -40°. After standing overnight at 0°, the reaction mixture was quenched with saturated aqueous ammonium chloride, and extracted with ether (4 x 100 ml). The combined organic layer was dried and concentrated. The residue was purified by column chromatography (hexane/ethyl acetate, 5:1) to give **12** (3.63 g, 79%) as a pale yellow oil; $[\alpha]_D^{20}$ +28.3 (c 0.91, ethanol); ir (film) 3350 cm^{-1}; ^1H nmr: δ 0.89 (d, 3H, J = 6.8 Hz), 0.92 (t, 3H, J = 7.3 Hz), 1.12-1.21 (m, 1H), 1.44-1.53 (m, 2H), 1.80-1.96 (m, 3H), 2.02-2.19 (m, 1H), 2.84-2.94 (m, 4H), 3.78-3.90 (m, 1H), 4.28 (dd, 1H, J = 5.5 Hz, J = 8.3 Hz); ^{13}C nmr: δ 11.6 (q), 14.4 (q), 24.8 (t), 26.0 (t), 30.0 (t), 30.4 (t), 38.8 (d), 40.7 (t), 44.7 (d), 72.0 (d). MS (EI) m/z 220 (M^+, 60%), 145 (100), 119 (75); hrms: Calcd. for $C_{10}H_{20}OS_2$: $(M)^+$ 220.0956. Found: m/z 220.0982.

(2*R*,3*S*)-2-[2-(4-Methoxybenzyloxy)-3-methylpentyl]-1,3-dithiane (**13**).

To a suspension of sodium hydride (158 mg, 3.96 mmoles) in dimethylformamide (15 ml) was added **12** (581 mg, 2.64 mmoles) in dimethylformamide (3 ml) at room temperature, and the mixture was stirred for 1 hour. To the mixture was added *p*-methoxybenzyl chloride (1.07 ml, 7.90 mmoles), and the mixture was stirred for 21 hours at 50°. The reaction mixture was quenched with water, and extracted with ether (3 x 30 ml). The combined organic layer was dried and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/ethyl acetate, 10/1) to give **13** (751 mg, 84%) as a colorless oil; $[\alpha]_D^{25}$ +43.0 (c 0.56, ethanol); ^1H nmr: δ 0.88 (d, 3H, J = 7.0 Hz), 0.92 (t, 3H, J = 7.3 Hz), 1.10-1.41 (m, 2H), 1.70-1.93 (m, 4H), 2.05-2.15 (m, 1H), 2.70-2.92 (m, 4H), 3.62-3.68 (m, 1H), 3.81 (s, 3H), 4.13 (dd, 1H, J = 4.2 Hz, J = 10.2 Hz), 4.39 (d, 1H, J = 11.0 Hz), 4.54 (d, 1H, J = 11.0 Hz), 6.88 (d, 2H, J = 8.8 Hz), 7.29 (d, 2H, J = 8.8 Hz); ^{13}C nmr: δ 12.1 (q), 13.6 (q), 25.8 (t), 26.1 (t), 29.9 (t), 30.5 (t), 35.8 (t), 36.8 (d), 44.5 (d), 55.3 (q), 71.3 (t), 78.5 (d), 113.7 (d), 129.4 (d), 131.2 (s), 159.1 (s). MS (EI) m/z 340 (M^+, 5%), 219 (74), 133 (100). hrms: Calcd. for $C_{18}H_{28}O_2S_2$: $(M)^+$ 340.1531. Found: m/z 340.1509.

(3*R*,4*S*)-3-(4-Methoxybenzyloxy)-4-methylhexanal (**14**).

To a solution of **13** (1.10 g, 3.24 mmoles) in aqueous 80% acetonitrile (30 ml) was added mercury (II) chloride (2.19 g, 8.10 mmoles) and mercury (II) oxide (1.75 g, 8.10 mmoles) at room temperature. The mixture was heated at 60° with stirring for 2 hours. The cooled mixture was filtered through celite, and the filtrate was dried and concentrated. The residue was purified by chromatography (hexane/ethyl acetate, 10:1) to give **14** (680 mg, 84%) as a colorless oil; $[\alpha]_D^{23}$ +18.5 (c 0.73, ethanol); ir (film) 1724 cm^{-1}; ^1H nmr: δ 0.91 (d, 3H, J = 6.8 Hz), 0.94 (t, 3H, J = 7.3 Hz), 1.08-1.23

(m, 1H), 1.34-1.48 (m, 1H), 1.77-1.88 (m, 1H), 2.42 (ddd, 1H, J = 1.7 Hz, J = 3.5 Hz, J = 16.3 Hz), 2.60 (ddd, 1H, J = 2.7 Hz, J = 8.8 Hz, J = 16.3 Hz), 3.80 (s, 3H), 3.85-3.90 (m, 1H), 4.42 (d, 1H, J = 11.0 Hz), 4.52 (d, 1H, J = 11.0 Hz), 6.88 (d, 2H, J = 8.8 Hz), 7.24 (d, 2H, J = 8.8 Hz), 9.78 (dd, 1H, J = 1.8 Hz, J = 8.8 Hz). ^{13}C nmr: δ 11.8 (q), 13.6 (q), 25.6 (t), 36.9 (d), 44.3 (t), 55.2 (q), 70.9 (t), 77.3 (d), 113.7 (d), 129.3 (d), 130.3 (s), 159.1 (s), 202.2 (d). hrms: Calcd. for $C_{15}H_{22}O_3$: $(M)^+$ 250.1569. Found: m/z 250.1545.

(3*S*,4*S*) and (3*R*,4*S*)-3-[3',3'-(Ethylenedioxy)-3'-phenylpropanoyl]-3-methoxymethyloxy-4-methyl-4-vinyl-γ-butyrolactone (**17a**) and (**17b**).

To a solution of lithium diisopropylamide, prepared from diisopropylamine (0.12 ml, 0.86 mmol) in tetrahydrofuran (10 ml) and *n*-butyllithium (1.6 *M* in hexane, 0.49 ml, 0.79 mmol), was added a solution of **15** (123 mg, 0.66 mmol) in tetrahydrofuran (5 ml) at -78° under nitrogen, and the mixture was stirred for 30 minutes. A solution of **8** (165 mg, 0.86 mmol) in tetrahydrofuran (5 ml) was added to the reaction mixture. After stirring for 3.5 hours at -78°, the mixture was quenched by addition of saturated aqueous ammonium chloride, and extracted with ether (4 x 10 ml). The combined extracts were dried and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/ethyl acetate, 20:1) to give **16** (207 mg, 83%) as an inseparable mixture of four diastereomers; ir (film) 3500, 1765, 1620 cm^{-1}; To a solution of **16** (37 mg) in acetone (30 ml) was added Jones reagent (8 *M*, 0.04 ml) at 0°. After stirring for 1.5 hours, the mixture was quenched by addition of 2-propanol, followed by solid sodium bicarbonate. The mixture was filtered through celite and the filtrate was concentrated. The residue was chromatographed on silica gel (hexane/ethyl acetate, 2:1) to give **17a** (14 mg, 38%) and **17b** (20 mg, 54%) as colorless needles, respectively. **17a**: mp 76°; $[\alpha]_D^{23}$ -29.3 (c 0.40, ethanol); ir (nujol) 1770, 1715 cm^{-1}; ^{1}H nmr: δ 1.28 (s, 3H), 3.17 (d, 1H, J = 17.2 Hz), 3.39 (s, 3H), 3.48 (d, 1H, J = 17.2 Hz), 3.73-3.85 (m, 2H), 4.00 (d, 1H, J = 8.8 Hz), 4.02-4.12 (m, 2H), 4.19 (d, 1H, J = 8.8 Hz), 4.97 (d, 1H, J = 6.0 Hz), 5.05 (d, 1H, J = 6.0 Hz), 5.12 (d, 1H, J = 17.0 Hz), 5.17 (d, 1H, J = 10.8 Hz), 5.58 (dd, 1H, J = 10.8 Hz, J = 17.4 Hz), 7.27-7.37 (m, 3H), 7.48-7.52 (m, 2H); ^{13}C nmr: δ 18.1 (q), 48.7 (t), 50.6 (s), 56.7 (q), 64.8 (t x 2), 73.6 (t), 88.8 (s), 94.6 (t), 108.3 (s), 117.7 (t), 125.8 (d), 128.1 (d), 128.2 (d), 135.7 (d), 141.9 (s), 171.6 (s), 203.0 (s). MS m/z 377 [$(M + H)^+$, 5%], 317 (11), 271 (59), 185 (91), 149 (100), 93 (78). hrms: Calcd. for $C_{20}H_{25}O_7$: $(M + H)^+$ 377.1600. Found: m/z 377.1579.

Anal. Calcd for $C_{20}H_{24}O_7$: C, 63.82; H, 6.43. Found: C, 63.75; H, 6.47.

Compound **17b** has mp 76°; $[\alpha]_D^{23}$ -30.2 (c 2.0, ethanol); ir (nujol) 1770, 1715 cm^{-1}; ^{1}H nmr: δ 1.00 (s, 3H), 3.17 (d, 1H, J = 17.3 Hz), 3.35 (s, 3H), 3.37 (d, 1H, J = 17.3 Hz), 3.74-3.82 (m, 2H), 3.83 (d, 1H, J = 8.5 Hz), 3.99-4.13 (m, 2H), 4.29 (d, 1H, J = 8.5 Hz), 4.79 (d, 1H, J = 6.4 Hz), 4.85 (d, 1H, J = 6.4 Hz), 5.17 (d, 1H, J = 17.6 Hz), 5.33 (d, 1H, J = 11.0 Hz), 6.15 (dd, 1H, J = 11.0 Hz, J = 17.6 Hz), 7.26-7.35 (m, 3H), 7.47-7.52 (m, 2H); ^{13}C nmr: δ 17.7 (q), 48.7 (t), 49.3 (s), 56.5 (q), 64.7 (t), 64.9 (t), 74.6 (t), 87.3 (s), 94.6 (t), 108.1 (s), 117.7 (t), 125.8 (d), 128.0 (d), 128.1 (d), 135.2 (d), 141.9 (s), 170.2 (s), 200.7 (s). hrms: Calcd. for $C_{20}H_{25}O_7$: $(M + H)^+$ 377.1600. Found: m/z 377.1583.

(-)-Hyperolactone C (**3**).

To a solution of **17a** (9 mg, 0.024 mmol) in tetrahydrofuran (10 ml) was added a few drops of 3 *M* hydrochloric acid, and the mixture was heated at reflux for 11 hours. The mixture was cooled and poured into aqueous sodium bicarbonate, and extracted with ether (3 x 20 ml). The combined extracts were dried and concentrated. The residue was purified by column chromatography (hexane/ethyl acetate, 10:1) to give a crystalline **3** (6 mg, 93%); mp 106°; (lit [2] mp 104°); $[\alpha]_D^{25}$ -390 (c 0.018, ethanol) [lit [2] -356 (c 0.018, ethanol)]; ^{1}H nmr: δ 1.53 (s, 3H), 4.11 (d, 1H, J = 8.4 Hz), 4.97 (d, 1H, J = 8.4 Hz), 5.26 (d, 1H, J = 17.6 Hz), 5.27 (d, 1H, J = 10.8 Hz), 5.98 (s, 1H), 5.99 (dd, 1H, J = 10.8 Hz, J = 17.6 Hz), 7.49-7.54 (m, 2H), 7.58-7.63 (m, 1H), 7.83-7.86 (m, 2H); ^{13}C nmr: δ 19.6 (q), 48.9 (s), 74.1 (t), 93.1 (s), 100.3 (d), 119.0 (t), 127.4 (d), 127.7 (s), 129.0 (d), 133.6 (d), 134.3 (d), 168.0 (s), 187.2 (s), 196.6 (s). MS (EI) m/z 270 (M^+, 35%), 252 (8), 225 (15), 211 (23), 197 (4), 187 (100), 173 (11), 147 (15), 105 (5), 129 (9), 102 (56). hrms: Calcd. for $C_{16}H_{14}O_4$: $(M)^+$ 270.0892. Found: m/z 270.0909.

5-Epi-hyperolactone C (**3a**).

The similar reaction of the β-methoxymethyloxy isomer **17b** (41 mg) as in the synthesis of **3** gave, after chromatography, **3a** (29.4 mg, 100%) as a wax; $[\alpha]_D^{20}$ +283 (c 0.054, ethanol); ^{1}H nmr: δ 1.30 (s, 3H), 4.38 (d, 1H, J = 8.6 Hz), 4.78 (d, 1H, J = 8.6 Hz), 5.34 (d, 1H, J = 17.4 Hz), 5.37 (d, 1H, J = 10.8 Hz), 6.04 (s, 1H), 6.06 (dd, 1H, J = 10.8 Hz, J = 17.4 Hz), 7.48-7.54 (m, 2H), 7.58-7.64 (m, 1H), 7.83-7.86 (m, 2H); ^{13}C nmr: δ 15.4 (q), 48.9 (s), 73.3 (t), 92.3 (s), 100.4 (d), 116.2 (t), 127.4 (s), 127.5 (d), 129.0 (d), 133.6 (d), 136.8 (d), 168.1 (s), 187.4 (s), 196.6 (s). MS (EI) m/z 270 (M^+, 46%), 252 (8), 211 (25), 187 (100), 173 (16), 147 (14), 129 (9), 102 (58). hrms: Calcd. for $C_{16}H_{14}O_4$: $(M)^+$ 270.0892. Found: m/z 270.0880.

(3S,4*S*, 3'*R*, 4'*S*) and (3*R*,4*S*,3'*R*,4'*S*)-3-[3'-(4-Methoxybenzyloxy)-4'-methylhexanoyl]-3-methoxymethyloxy-4-methyl-4-vinyl-γ-butyrolactone (**18a**) and (**18b**).

The procedure for **16** was employed with **14** and **15** gave an alcohol as an inseparable mixture of four diastereomers in 84% yield. To a solution of the resulting alcohol (269 mg, 0.62 mmol) in dichloromethane (20 ml) was added Dess-Martin periodinane (915 mg, 2.16 mmoles), and the mixture was stirred for 2 hours at room temperature. The reaction was quenched by addition of 2-propanol, and the precipitate was filtered off. The filtrate was washed with 10% sodium thiosulfate solution, and concentrated. The residue was purified by column chromatography (hexane/ethyl acetate, 20:1) to give **18a** (134 mg, 50%) and **18b** (134 mg, 50%). **18a** (colorless oil); $[\alpha]_D^{21}$ -0.20 (c 2.7, ethanol); ^{1}H nmr: δ 0.89 (d, 3H, J = 6.8 Hz), 0.91 (t, 3H, J = 7.3 Hz), 1.03-1.18 (m, 1H), 1.30 (s, 3H), 1.23-1.40 (m, 1H), 1.68-1.80 (m, 1H), 2.59 (dd, 1H, J = 2.7 Hz, J = 19.0 Hz), 2.99 (dd, 1H, J = 9.0 Hz, J = 19.0 Hz), 3.43 (s, 3H), 3.79 (s, 3H), 3.94-3.97 (m, 1H), 4.00 (d, 1H, J = 8.6 Hz), 4.18 (d, 1H, J = 8.6 Hz), 4.41 (d, 1H, J = 10.8 Hz), 4.48 (d, 1H, J = 10.8 Hz), 4.99 (s, 2H), 5.11 (d, 1H, J = 10.8 Hz), 5.14 (d, 1H, J = 17.4 Hz), 5.75 (dd, 1H, J = 10.8 Hz, J = 17.4 Hz), 6.84 (d, 2H, J = 8.4 Hz), 7.22 (d, 2H, J = 8.4 Hz); ^{13}C nmr: δ 12.0 (q), 13.9 (q), 17.7 (q), 25.6 (t), 37.1 (d), 41.6 (t), 50.7 (s), 55.2 (q), 56.6 (q), 71.6 (t), 73.9 (t), 77.3 (d), 88.8 (s), 94.5 (t), 113.5 (d), 117.5 (t), 129.2 (d), 131.1 (s), 135.7 (d), 158.9 (s), 171.8 (s), 206.4 (s). hrms: Calcd. for $C_{24}H_{34}O_7$: $(M)^+$ 434.2304. Found: m/z 434.2328. **18b** (colorless oil); $[\alpha]_D^{22}$ -11.3 (c 3.76, ethanol); ^{1}H nmr: δ 0.88 (d, 3H, J = 6.8 Hz), 0.91 (t, 3H, J = 7.3 Hz), 1.11 (s, 3H), 1.23-1.41 (m, 2H), 1.70-1.78 (m, 1H), 2.31 (dd, 1H, J = 2.8 Hz, J = 18.1 Hz), 3.00 (dd, 1H, J = 9.4 Hz, J = 18.1 Hz), 3.35 (s, 3H), 3.78 (s, 3H), 3.88 (d, 1H, J = 8.4 Hz), 3.96-4.03 (m, 1H), 4.36 (d, 1H, J = 8.4 Hz), 4.41 (d, 1H,

J = 10.6 Hz), 4.45 (d, 1H, J = 10.6 Hz), 4.77 (d, 1H, J = 6.4 Hz), 4.81 (d, 1H, J = 6.4 Hz), 5.17 (d, 1H, J = 17.8 Hz), 5.34 (d, 1H, J = 11.0 Hz), 6.23 (dd, 1H, J = 11.0 Hz, J = 17.8 Hz), 6.84 (d, 2H, J = 8.6 Hz), 7.22 (d, 2H, J = 8.6 Hz); ^{13}C nmr: δ 12.0 (q), 13.9 (q), 18.3 (q), 26.0 (t), 37.0 (d), 41.4 (t), 49.5 (s), 55.2 (q), 56.5 (q), 72.0 (t), 74.9 (t), 77.9 (d), 87.2 (s), 94.7 (t), 113.6 (d), 117.6 (t), 129.5 (d), 130.8 (s), 135.1 (d), 159.0 (s), 170.7 (s), 204.8 (s). hrms: Calcd. for $C_{24}H_{34}O_7$: $(M)^+$ 434.2304. Found: m/z 434.2281.

(3*S*,4*S*,3'*R*,4'*S*) and (3*R*,4*S*,3'*R*,4'*S*)-3-(3'-Hydroxy-4'-methylhexanoyl)-3-methoxymethyloxy-4-methyl-4-vinyl-γ-butyrolactone (**19a**) and (**19b**).

A mixture of **18a** (131 mg, 0.3 mmol), dichlorodicyanobenzoquinone (DDQ) (177 mg, 0.76 mmol) in dichloromethane (9 ml) and water (0.5 ml) was stirred at room temperature for 90 minutes. The mixture was diluted with saturated aqueous sodium bicarbonate solution and extracted with dichloromethane (3 x 30 ml). The organic layer was dried and concentrated. The residue was chromatographed on silica gel (hexane/ethyl acetate, 10:1) to give **19a** (84 mg, 94% yield) as a colorless oil; $[\alpha]_D^{23}$ +1.87 (c 1.65, ethanol); ir (film) 3545, 1790, 1710 cm^{-1}; ^{1}H nmr: δ 0.87 (d, 3H, J = 6.6 Hz), 0.90 (t, 3H, J = 7.1 Hz), 1.04-1,26 (m, 1H), 1.34 (s, 3H), 1.43-1.57 (m, 2H), 2.74 (d, 1H, J = 9.5 Hz), 2.79 (dd, 1H, J = 4.2 Hz, J = 15.0 Hz), 3.43 (s, 3H), 3.88-3.95 (m, 1H), 4.12 (d, 1H, J = 8.8 Hz), 4.25 (d, 1H, J = 8.8 Hz), 4.96 (s, 2H), 5.23 (d, 1H, J =17.4 Hz), 5.29 (d, 1H, J = 10.8 Hz), 5.78 (dd, 1H, J = 10.8 Hz, J = 17.4 Hz); ^{13}C nmr: δ 11.4 (q), 14.4 (q), 17.0 (q), 24.8 (t), 39.7 (d), 44.3 (t), 50.6 (s), 56.6 (q), 70.8 (d), 74.0 (t), 87.7 (s), 94.5 (t), 117.7 (t), 135.9 (d), 171.5 (s), 208.8 (s). hrms (FAB): Calcd. for $C_{16}H_{26}O_6Na^+$: $(M + Na)^+$ 337.1627. Found: m/z 337.1640.

The β-methoxymethyloxy isomer **18b** was treated as in the synthesis of **19a** to give a colorless oil **19b** (94% yield); $[\alpha]_D^{23}$ -11.1 (c 2.55, ethanol); ^{1}H nmr: δ 0.87 (d, 3H, J = 6.6 Hz), 0.90 (t, 3H, J = 7.3 Hz), 1.14 (s, 3H), 1.10-1.17 (m, 1H), 1.41-1.56 (m, 2H), 2.63-2.77 (m, 2H), 2.92 (d, 1H, J = 3.3 Hz, OH), 3.42 (s, 3H), 3.90 (d, 1H, J = 8.6 Hz), 3.90-3.96 (m, 1H), 4.36 (d, 1H, J = 8.6 Hz), 4.86 (s, 2H), 5.24 (d, 1H, J = 17.6 Hz), 5.38 (d, 1H, J = 10.8 Hz), 6.25 (dd, 1H, J = 10.8 Hz, J = 17.6 Hz); ^{13}C nmr: δ 11.4 (q), 14.4 (q), 18.2 (q), 24.8 (t), 39.5 (d), 43.6 (t), 49.3 (s), 56.6 (q), 70.6 (d), 74.8 (t), 87.1 (s), 94.6 (t), 118.0 (t), 134.9 (d), 170.2 (s), 207.3 (s). hrms (FAB): Calcd. for $C_{16}H_{26}O_6Na^+$: $(M + Na)^+$ 337.1627. Found: m/z 337.1640.

(3*S*,4S,4'*S*) and (3*R*, 4*S*, 4'*S*)-3-(3'-Oxo-4'-methylhexanoyl)-3-methoxymethyloxy-4-methyl-4-vinyl-γ-butyrolactone (**20a**) and (**20b**).

To a solution of **19a** (28.1 mg, 0.09 mmol) in acetone (5 ml) was added an excess amount of Jones reagent (8 *M* solution) at -20°. After stirring for 2 hours, the reaction mixture was quenched by addition of 2-propanol and solid sodium bicarbonate. The mixture was filtered through Celite, and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography (hexane/ethyl acetate, 9:1) to give **20a** (18.3 mg, 66% yield) as a pale yellow oil; $[\alpha]_D^{21}$ -11.7 (c 0.63, ethanol); ir (film) 2970, 1790, 1600 cm^{-1}; ^{1}H nmr: δ 0.89 (t, 3H, J = 7.5 Hz), 1.14 (d, 3H, J = 7.0 Hz), 1.36 (s, 3H), 1.42-1.54 (m, 1H), 1.59-1.73 (m, 1H), 2.22-2.34 (m, 1H), 3.47 (s, 3H), 4.12 (d, 1H, J = 8.6 Hz), 4.33 (d, 1H, J = 8.6 Hz), 4.94 (d, 1H, J = 5.9 Hz), 5.09 (d, 1H, J = 5.9 Hz), 5.13 (d, 1H, J = 17.4 Hz), 5.16 (d, 1H, J = 11.0 Hz), 5.73 (dd, 1H, J = 11.0 Hz, J = 17.4 Hz), 5.92 (s, 1H); ^{13}C nmr: δ 11.6 (q), 17.2 (q), 17.9 (q), 27.1 (t), 43.6 (d), 50.7 (s), 56.8 (q), 73.9 (t), 85.8 (s), 94.4 (t), 97.8 (d), 116.3 (t), 136.4 (d), 172.2 (s), 190.8 (s), 196.5 (s). hrms: Calcd. for $C_{16}H_{24}O_6$: $(M)^+$ 312.1573. Found: m/z 312.1563.

The β-methoxymethyloxy isomer **19b** was treated as in the synthesis of **20a** to give pale yellow crystals **20b** (65%); mp 54.5 °C; $[\alpha]_D^{20}$ +13.6 (c 0.89, ethanol); ^{1}H nmr: δ 0.90 (t, 3H, J = 7.5 Hz), 1.15 (d, 3H, J = 6.8 Hz), 1.16 (s, 3H), 1.41-1.55 (m, 1H), 1.59-1.73 (m, 1H), 2.25-2.37 (m, 1H), 3.43 (s, 3H), 3.99 (d, 1H, J = 8.4 Hz), 4.43 (d, 1H, J = 8.4 Hz), 4.83 (d, 1H, J = 6.2 Hz), 4.92 (d, 1H, J = 6.2 Hz), 5.17 (d, 1H, J = 17.6 Hz), 5.32 (d, 1H, J = 11.0 Hz), 5.95 (s, 1H), 6.17 (dd, 1H, J = 11.0 Hz, J = 17.6 Hz); ^{13}C nmr: δ 11.6 (q), 17.0 (q), 18.9 (q), 27.1 (t), 43.8 (d), 49.9 (s), 56.7 (q), 74.8 (t), 84.9 (s), 94.4 (t), 98.2 (d), 116.9 (t), 135.6 (d), 171.2 (s), 188.2 (s), 197.9 (s).

(2'*S*,5*S*,9*S*)-Isomer (1): (-)-Hyperolactone A.

To a cooled solution of **20a** (7.5 mg) in dichloromethane (5 ml) was added trimethylsilyl bromide (0.03 ml, 0.22 mmol) at -20°, and the mixture was stirred for 14 hours. The reaction was quenched by addition of saturated aqueous sodium bicarbonate and the mixture was extracted with dichloromethane (3 x 10 ml). The combined extracts were washed with water, dried and concentrated. The residue was chromatographed on silica gel (hexane/ethyl acetate, 10:1) to give **1** (5.9 mg, 98%) as a single product; mp 57° (recrystallized from ether and *n*-hexane); [lit [1] mp 57° for natural hyperolactone A]; $[\alpha]_D^{24}$ -265 (c 0.13, methanol); [lit [1] $[\alpha]_D^{24}$ -229 (c 0.13, methanol)]; ^{1}H nmr: δ 0.96 (t, 3H, J = 7.5 Hz), 1.25 (d, 3H, J = 6.8 Hz), 1.41 (s, 3H), 1.59-1.78 (m, 2H), 2.63-2.75 (m, 1H), 4.05 (d, 1H, J = 8.4 Hz), 4.90 (d, 1H, J = 8.4 Hz), 5.24 (d, 1H, J = 17.4 Hz), 5.28 (d, 1H, J = 10.8 Hz), 5.38 (s, 1H), 5.94 (dd, 1H, J = 10.8 Hz, J = 17.4 Hz). ^{13}C nmr: δ 11.0 (q), 16.9 (q), 19.3 (q), 27.1 (t), 37.1 (d), 48.4 (s), 74.0 (t), 92.5 (s), 102.1 (d), 118.8 (t), 134.3 (d), 168.0 (s), 197.3 (s), 200.2 (s). MS (EI) m/z 250 (M^+, 31%), 193 (53), 177 (42), 167 (100). hrms: Calcd. for $C_{14}H_{18}O_4$: $(M)^+$ 250.1205. Found: m/z 250.1216.

(2'*S*,5*R*,9*S*)-Isomer (**1a**).

The β-methoxymethyloxy isomer **20b** was treated as in the synthesis of **1** to give a colorless wax **1a** (89% yield) as a single product; $[\alpha]_D^{21}$ +194 (c 0.20, ethanol); ^{1}H nmr: δ 0.99 (t, 3H, J = 7.3 Hz), 1.23 (s, 3H), 1.27 (d, 3H, J = 7.0 Hz), 1.54-1.68 (m, 1H), 1.67-1.79 (m, 1H), 2.61-2.73 (m, 1H), 4.31 (d, 1H, J = 8.6 Hz), 4.71 (d, 1H, J = 8.6 Hz), 5.27 (d, 1H, J = 17.4 Hz), 5.30 (d, 1H, J = 10.8 Hz), 5.43 (s, 1H), 5.93 (dd, 1H, J = 10.8 Hz, J = 17.4 Hz); ^{13}C nmr: δ 11.3 (q), 15.4 (q), 17.2 (q), 27.1 (t), 37.3 (d), 48.4 (s), 73.2 (t), 90.3 (s), 102.2 (d), 116.0 (t), 136.8 (d), 168.0 (s), 197.4 (s), 200.5 (s). MS (EI) m/z 250 (M^+, 23%), 193 (42), 177 (47), 167 (100). hrms: Calcd. for $C_{14}H_{18}O_4$: $(M)^+$ 250.1205. Found: m/z 250.1215.

(2'*R*,5*S*,9*S*)-Isomer (**1b**).

The α-methoxymethyloxy isomer **20a** was treated with boiling tetrahydrofuran containing 3 *M* hydrochloric acid to give a mixture of **1** and its 2'-isomer **1b** (88% yield), which was separated by HPLC [Shimadzu LC-3A; column: Cosmosil 5SI; *n*-hexane-diethyl ether (95:5); 5 ml/minute]. The first peak (Rt 21.25 minutes) gave **1** and second peak (Rt 21.75 minutes) gave **1b** as a colorless wax. **1b**: ^{1}H nmr: δ 0.97 (t, 3H, J = 7.3 Hz), 1.25 (d, 3H, J = 7.3 Hz), 1.41 (s, 3H), 1.50-1.62 (m, 1H), 1.62-1.80 (m, 1H), 2.69 (sextet, 1H, J = 7.3 Hz), 4.04 (d, 1H, J = 8.5 Hz), 4.89

(d, 1H, J = 8.5 Hz), 5.24 (d, 1H, J = 17.1 Hz), 5.28 (d, 1H, J = 11.0 Hz), 5.37 (s, 1H), 5.93 (dd, 1H, J = 11.0 Hz, J = 17.1 Hz); ^{13}C nmr: δ 11.3 (q), 17.3 (q), 19.3 (q), 27.2 (t), 37.3 (d), 48.4 (s), 74.0 (t), 92.5 (s), 102.2 (d), 118.9 (t), 134.4 (d), 168.0 (s), 197.4 (s), 200.2 (s). hrms: Calcd. for $C_{14}H_{18}O_4$: $(M)^+$ 250.1205. Found: m/z 250.1195.

Preparation of the Key Intermediate **15.**

(2*S*,3*R*)-5-Benzyloxy-3-ethoxycarbonyl-2-hydroxy-3-methylpentanoic acid (**21b**).

To a solution of lithium diisopropylamide, prepared from diisopropylamine (11.3 ml, 80.4 mmoles) and *n*-butyllithium (1.6 *M* in hexane, 45.6 ml, 73.7 mmoles) in tetrahydrofuran (200 ml), was added a solution of diethyl (2*S*,3*R*)-(+)-2-hydroxy-3-methylsuccinate [8] (6.8 g, 33.4 mmoles) in tetrahydrofuran (12 ml) at -78° and the mixture was stirred for 3 hours. To the cooled (-78) solution was added benzyl 2-iodoethyl ether [9] (13.1 g, 50 mmoles) within 5 minutes and the mixture was stirred for 8 hours, then at 0° for 13 hours. After quenching by addition of a solution of acetic acid (8 ml) in 15 ml of ether, the mixture was poured into water and extracted with ether (4 x 100 ml). The combined extracts were washed with aqueous sodium bicarbonate, dried and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/ethyl acetate, 10:1) to give **21a** (12.46 g, 67%) as a pale yellow oil; $[\alpha]_D^{27}$ +12.9 (c 0.70, ethanol); ir (film) 3490, 1715 cm^{-1}; ^{1}H nmr: δ 1.21 (t, 3H, J = 7.1 Hz), 1.22 (s, 3H), 1.27 (t, 3H, J = 7.1 Hz), 1.80-1.99 (m, 1H), 2.10-2.22 (m,1H), 3.55 (t, 2H, J = 6.5 Hz), 3.65 (d, 1H, J = 9.8 Hz, OH), 4.12 (q, 2H, J = 7.1 Hz), 4.24 (q, 2H, J = 7.1 Hz), 4.32 (d, 1H, J = 9.8 Hz), 4.47 (s, 2H), 7.27-7.33 (m, 5H); MS (EI) m/z 338 (M^+, 15%), 293 (4), 231 (16), 204 (23), 157 (35), 131 (30), 91 (100); hrms: Calcd. for $C_{18}H_{26}O_6$: $(M)^+$ 338.1729. Found: m/z 338.1728. To the resulting diester **21a** (5.11 g) in methanol (40 ml) was added a solution of potassium hydroxide (2.85 g, 3.4 equivalents) in methanol (30 ml) and water (2 ml) at -40°, and the mixture was stirred for 1 hour, then at room temperature for 3 days. The mixture was acidified by addition of 3 *M* hydrochloric acid to pH-2 and extracted with ether (4 x 100 ml). The combined extracts were dried and concentrated *in vacuo* to give **21b** (4.55 g, 97%) as a pale yellow syrup; $[\alpha]_D^{27}$ +8.4 (c 0.71, ethanol); ir (film) 3400, 1700 cm^{-1}; ^{1}H nmr: δ 1.21 (t, 3H, J = 7.1 Hz), 1.25 (s, 3H), 1.99-2.15 (m, 2H), 3.57-3.66 (m, 2H), 4.13 (q, 2H, J = 7.1 Hz), 4.51 (s, 2H), 7.27-7.33 (m, 5H); ^{13}C nmr: δ 13.9 (q), 18.6 (q), 34.8 (t), 49.0 (s), 60.9 (t), 61.4 (t), 66.4 (t), 73.4 (t), 74.4 (d), 128.0 (d), 128.5 (d x 2), 137.0 (s), 174.4 (s), 174.9 (s). hrms: Calcd. for $C_{16}H_{22}O_6$: $(M)^+$ 310.1416. Found: m/z 310.1429.

(3*S*,4*S*)-4-(2-Benzyloxyethyl)-3-hydroxy-4-methyl-γ-butyrolactone (**22a**).

To a solution of **21b** (2.29 g, 7.4 mmoles) in tetrahydrofuran (100 ml) was added lithium triethylborohydride (1.0 *M* in tetrahydrofuran, 44.3 ml, 44.3 mmoles) at -78°, and the mixture was stirred for 3 hours, then at room temperature for 40 hours. To the reaction mixture was added 17 ml of water at -10°, and the aqueous layer was extracted with ether (3 x 50 ml). The combined extracts were dried and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/ethyl acetate, 2:1) to give **22a** (1.37 g, 74%) as a colorless oil; $[\alpha]_D^{27}$ +6.0 (c 0.80, ethanol); ir (film) 3400, 1760, 1620 cm^{-1}; ^{1}H nmr: δ 1.26 (s, 3H), 1.58-1.94 (m, 2H), 3.48 (dt, 1H, J = 2.4 Hz, J = 10.1 Hz), 3.57-3.66 (m, 1H), 3.97 (d, 1H, J = 9.3 Hz), 4.08 (s, 1H), 4.19 (d, 1H, J = 9.3 Hz), 4.31 (d, 1H, J = 11.7 Hz), 4.59 (d, 1H, J = 11.7 Hz), 7.30-7.38 (m, 5H); ^{13}C nmr: δ 23.5 (q), 33.8 (t), 42.5 (s), 66.0 (t), 73.1 (t), 74.7 (t), 75.4 (d), 127.9 (d), 128.1 (d), 128.4 (d), 136.7 (s), 176.5 (s). hrms: Calcd. for $C_{14}H_{18}O_4$: $(M)^+$ 250.1205. Found: m/z 250.1219.

(3*S*,4*S*)-4-(2-Benzyloxyethyl)-3-methoxymethyloxy-4-methyl-γ-butyrolactone (**22b**).

To a solution of **22a** (730 mg, 2.92 mmoles) and diisopropylethylamine (5.1 ml, 29.0 mmoles) in dichloromethane (50 ml) was added chloromethoxymethane (1.11 ml, 14.6 mmoles), and the mixture was heated at reflux for 48 hours. The mixture was cooled, diluted with water, and extracted with dichloromethane (4 x 20 ml). The combined extracts were dried and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/ethyl acetate, 3:1) to give **22b** (795 mg, 93%) as a pale yellow oil; $[\alpha]_D^{27}$ -47.7 (c 2.3, ethanol); ir (film) 1770 cm^{-1}; ^{1}H nmr: δ 1.19 (s, 3H), 1.72-1.95 (m, 2H), 3.41 (s, 3H), 3.57-3.62 (m, 2H), 3.88 (d, 1H, J = 9.0 Hz), 3.99 (s, 1H), 4.39 (d, 1H, J = 9.0 Hz), 4.47 (s, 2H), 4.69 (d, 1H, J = 6.8 Hz), 4.99 (d, 1H, J = 6.8 Hz), 7.28-7.35 (m, 5H); ^{13}C nmr: δ 21.1 (q), 31.3 (t), 42.1 (s), 56.0 (q), 66.4 (t), 73.2 (t), 75.1 (t), 78.3 (d), 95.9 (t), 127.6 (d x 2), 128.4 (d), 138.1 (s), 175.0 (s). MS (EI): m/z 249 ($[M\text{-}CH_2OCH_3]^+$, 40%), 143 (65), 91 (100).

(3*S*,4*S*)-4-(2-Hydroxyethyl)-3-methoxymethyloxy-4-methyl-γ-butyrolactone (**23a**).

A mixture of **22b** (622 mg, 2.11 mmoles) and 10% palladium on carbon (300 mg) in ethanol (25 ml) was vigorously stirred under an atmosphere of hydrogen at room temperature for 44 hours. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (hexane/ethyl acetate, 1:1) to give **23a** (414 mg, 96%) as a colorless oil; $[\alpha]_D^{22}$ -94.6 (c 0.65, ethanol); ir (film) 3425, 1760 cm^{-1}; ^{1}H nmr: δ 1.24 (s, 3H), 1.79 (t, 2H, J = 6.6 Hz), 2.21 (br s, 1H, OH), 3.44 (s, 3H), 3.70-3.82 (m, 2H), 3.93 (d, 1H, J = 9.0 Hz), 4.05 (s, 1H), 4.35 (d, 1H, J = 9.0 Hz), 4.73 (d, 1H, J = 6.8 Hz), 5.01 (d, 1H, J = 6.8 Hz); ^{13}C nmr: δ 21.1 (q), 34.6 (t), 42.1 (s), 56.0 (q), 58.7 (t), 75.0 (t), 78.3 (d), 96.0 (t), 175.0 (s). MS (EI) m/z ($[M\text{-}OCH_2OCH_3]^+$, 16%), 129 (11), 113 (43), 99 (100), 91 (11), 85 (27). hrms: Calcd. for $C_7H_{11}O_3$: $(M - OCH_2OCH_3)^+$ 143.0708. Found: m/z 143.0722.

(3*S*,4*S*)-3-Methoxymethyloxy-4-methyl-4-[2-(2-nitrophenyl)-seleno]-γ-butyrolactone (**23b**).

A mixture of **23a** (673 mg, 3.3 mmoles), 2-nitrophenylselenocyanate (1.05 g, 4.62 mmoles) and *n*-tributylphosphine (1.15 ml, 4.62 mmoles) in 30 ml of tetrahydrofuran was stirred at room temperature for 1 hour. The reaction mixture was diluted with water and extracted with ether (5 x 20 ml). The combined extracts were dried and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/ethyl acetate, 4/1) to give **23b** (1.13 g, 88%) as yellow crystals; mp 74-75°; $[\alpha]_D^{27}$ -37.0 (c 0.24, ethanol); ir (nujol) 1770, 1590, 1560, 1510 cm^{-1}; ^{1}H nmr: δ 1.29 (s, 3H), 1.87-2.06 (m, 2H), 2.85-3.00 (m, 2H), 3.46 (s, 3H), 4.01 (d, 1H, J = 9.4 Hz), 4.18 (s, 1H), 4.26 (d, 1H, J = 9.4 Hz), 4.78 (d, 1H, J = 6.8 Hz), 5.08 (d, 1H, J = 6.8 Hz), 7.30-7.35 (m, 1H), 7.50-7.59 (m, 3H), 8.28 (dd, 1H, J = 1.3 Hz, J = 8.3 Hz). ^{13}C nmr: δ 20.4 (t), 22.2 (q), 33.3 (t), 44.7 (s), 56.2 (q), 74.3 (t), 77.5 (d), 96.2 (t), 125.5 (d), 126.5 (d), 128.9 (d), 132.8 (d), 133.7 (s), 146.7 (s), 174.8 (s). hrms: Calcd. for $C_{15}H_{19}NO_6Se$: $(M)^+$ 389.0377. Found: m/z 389.0399.

Anal. Calcd for $C_{15}H_{19}NO_6Se$: C, 46.40; H, 4.93; N, 3.61. Found: C, 46.45; H, 4.98; N, 3.61.

(3*S*,4*S*)-3-Methoxymethyloxy-4-methyl-4-vinyl-γ-butyrolactone (**15**).

To a solution of **23b** (1.11 g, 2.85 mmoles) in tetrahydrofuran (40 ml) was added dropwise 30% hydrogen peroxide (1.58 ml, 17.2 mmoles) at 0°, and the mixture was warmed to room temperature. After stirring for 5 hours, the reaction mixture was diluted with water and extracted with ether (4 x 50 ml). The combined extracts were washed with sodium thiosulfate solution, dried and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/ethyl acetate, 6:1) to give **15** (403 mg, 76%) as an oil; $[\alpha]_D^{25}$ -64.7 (c 2.20, ethanol); ir (film) 1780, 1630 cm^{-1}; ^1H nmr: δ 1.32 (s, 3H), 3.43 (s, 3H), 3.98 (d, 1H, J = 9.0 Hz), 4.13 (s, 1H), 4.28 (d, 1H, J = 9.0 Hz), 4.71 (d, 1H, J = 6.8 Hz), 4.98 (d, 1H, J = 7.0 Hz), 5.23 (d, 1H, J = 17.6 Hz), 5.27 (d, 1H, J = 10.8 Hz), 5.97 (dd, 1H, J = 10.8 Hz, J = 17.5 Hz); ^{13}C nmr: δ 20.4 (q), 45.6 (s), 55.9 (q), 74.1 (t), 78.4 (d), 96.0 (t), 115.9 (t), 136.3 (d), 174.2 (s). hrms (CI): Calcd. for $C_9H_{15}O_4$: $(M + H)^+$ 187.0934. Found: m/z 187.0954.

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