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Novel Stereoselective Synthesis of (-)-Enterolactone Employing Chiral Unsaturated Lactam

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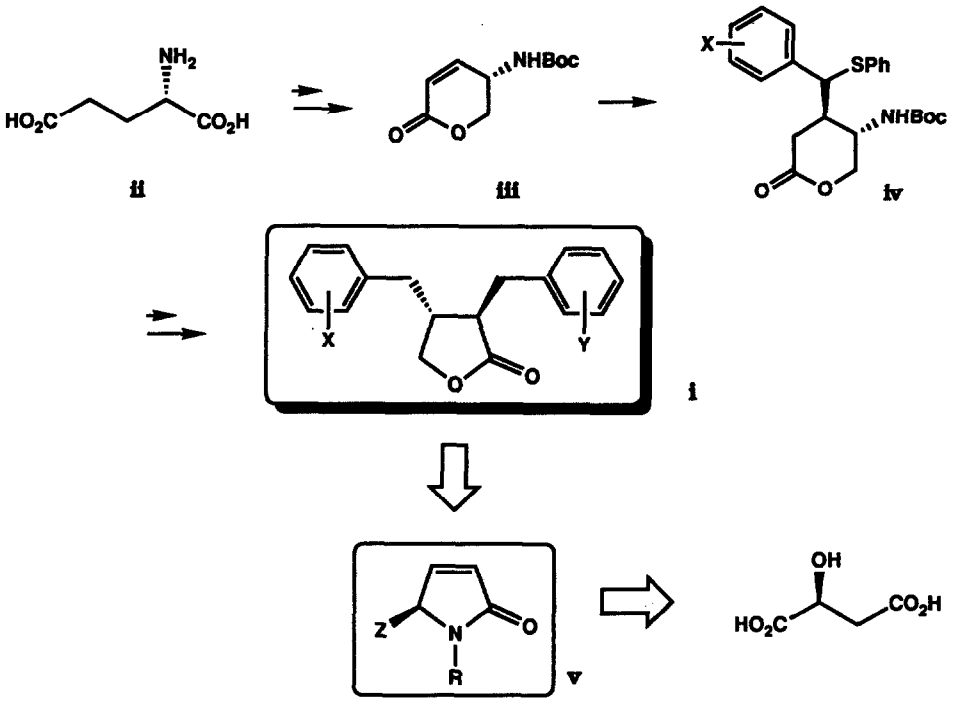
Abstract: *A novel convergent synthetic methodology of chiral antileukemic lignan lactones was developed by the use of optically active N-alkyl-α,β-unsaturated lactam elaborated from L-malic acid and the asymmetric synthesis of (-)-enterolactone was accomplished in short and simple steps.*

INTRODUCTION

Plant lignans exhibit a variety of useful biological activities such as cytotoxic, fungitoxic, and growth inhibitory activity[1] and are used for the development of chemotherapeutic agents.[2] Cosequently, a great deal of effort for the synthesis of this class of compounds has been expended[3] and impressive reviews have appeared.[4] We also revealed an efficient method for the synthesis of optically active hinokinin (i; X=Y=-OCH_2O-) employing stereoselective Michael addition of the anion of phenylthioether to unsaturated δ-lactone (iii) derived from L-glutamic acid (ii) (scheme 1).[5] Furthermore, recent discovery of enterolactone in human and various animal excretions[6] has prompted a renewed interest in the lignan chemistry. Although as mentioned above a large number of methods have been already studied,

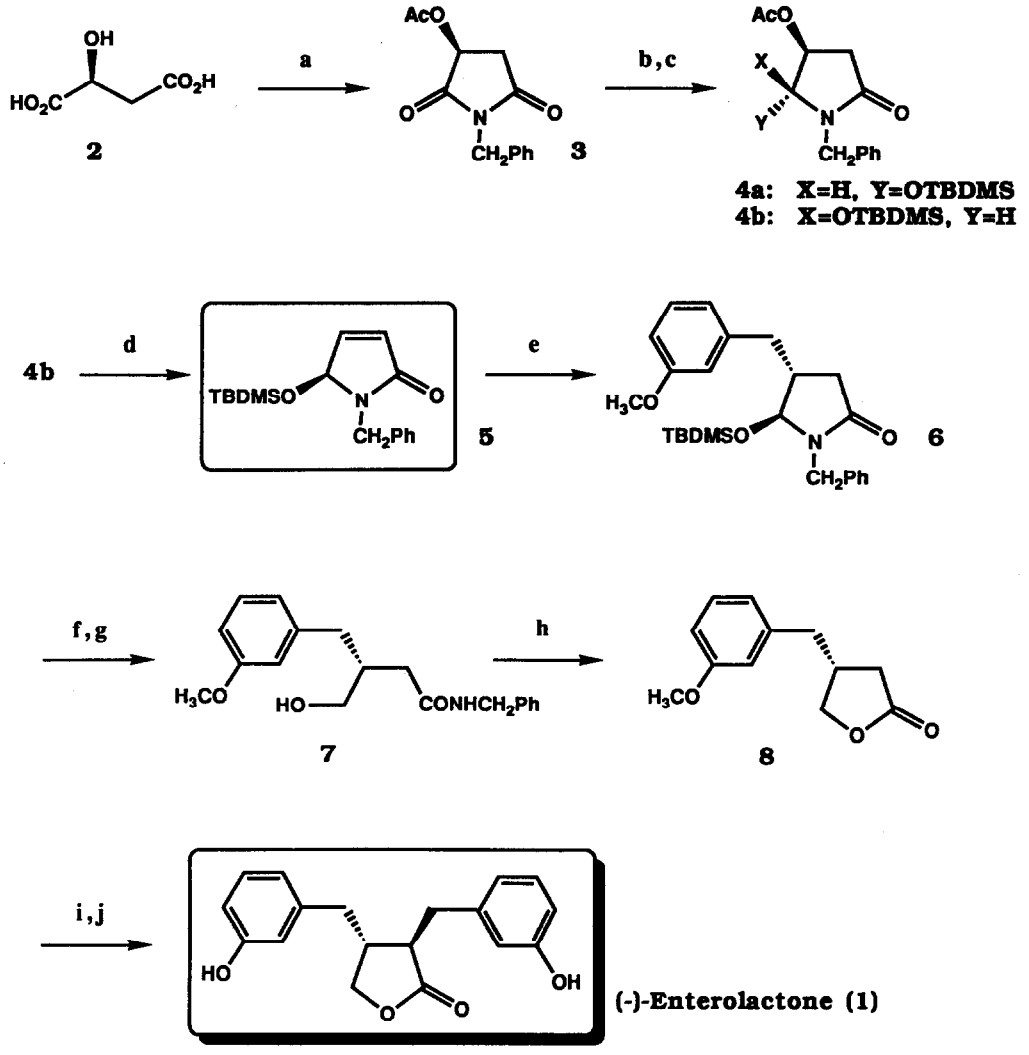
these methods generally required multistage and were not necessarily satisfactory. We report herein a simple and short synthetic strategy of such compounds and the synthesis of (-)-enterolactone (I; X=Y=OH), in which asymmetric conjugate addition to chiral lactam (v) without an electron-attracting group such as COOR or SO_2Ar on the nitrogen atom is the essential step.



Scheme 1.

RESULTS AND DISCUSSION

Imide **3** was readily prepared by treating L-malic acid (**2**), with, successively, acetyl chloride, benzylamine, and again acetyl chloride along the lines reported in the literature[7] (scheme 2). Regio- and stereoselective reduction of **3** with sodium borohydride ($NaBH_4$),[7] followed by protection with tert-butyldimethylsilyl chloride (TBDMSCl)[8] afforded silyl ether **4** as a 78:22 mixture of C-5 epimers[9] which were demonstrated to be separable by using column chromatography on silica gel. The more polar, major diastereomer **4b** was effected by olefination with sodium hydride (NaH) in THF[10] to give desired chiral unsaturated lactam **5** in moderate yield.



(a) 1, AcCl, reflux; 2, $PhCH_2NH_2$; 3, AcCl, reflux; (b) $NaBH_4$, MeOH, -4 °C; (c) TBSCl, imidazole, DMF; (d) NaH, THF; (e) m-$MeOPhCH_2MgCl$, CuI, TMSCl, THF, -78 °C; (f) Bu_4NF, THF; (g) $NaBH_4$, EtOH; (h) TsOH, benzene, reflux; (i) LDA, *m*-$MeOPhCH_2Cl$, HMPA, THF, -78--20 °C; (j) BBr_3, CH_2Cl_2, 0 °C.

Scheme 2.

According to our previous communication which disclosed asymmetric conjugate addition of a variety of organometallic reagents to **5**,[11] we treated **5** with *m*-methoxybenzylmagnesium chloride in THF activated by CuI in the presence of trimethylsilyl chloride (TMSCl). The reaction smoothly proceeded at -78 °C for 1 h to provide the addition product **6** in 41% isolated yield in spite of the absence of an electron-attracting group on the nitrogen atom.[12] Of particular interest is that this reaction gave **6** with virtually complete diastereoselectivity and the other stereoisomer was not detected by HPLC. At this point, the absolute configuration of the newly created chiral center of **6** could not be determined, but was easily predicted to be *R* on the basis of reaction mechanism in which conjugate addition of Grignard reagent took place from the less hindered side of **5**.[9] Apparently, this procedure is applicable to introduce a wide range of chiral β-alkyl side chains of lignan lactones in short steps from **2**.

With compound **6** in hand, we next performed desilylation of **6** with 1.1 equiv of tetrabutylammonium fluoride in THF[13] followed by subsequent reduction of corresponding labile hydroxylactam intermediate with $NaBH_4$ in ethanol[14] at room temperature leading to hydroxyamide (**7**) without difficulty. Treatment of **7** thus obtained with *p*-toluenesulfonic acid (*p*-TsOH) in refluxing benzene for 3 h resulted in smooth cyclization to (*R*)-γ-butyrolactone (**8**) ($[\alpha]_D^{20}$+6.41°(c 2.08, $CHCl_3$))[3e,g] in 63% yield from **6**. Fortunately, it has become apparent that no racemization was observed during the crucial steps of desilylation and reduction of the corresponding hydroxylactam which existed as a mixture of itself and the equilibrated open formylamide on TLC.[15]

Finally, stereoselective introduction of *m*-methoxybenzyl group at α-position of the lactone ring of **8** and deprotection of the two methoxy groups using boron tribromide in CH_2Cl_2 accomplished the asymmetric synthesis of (-)-enterolactone (**1**) ($[\alpha]_D^{20}$-40.5°(c 0.62, $CHCl_3$)) whose spectral data were identical in all respects with those of reported **1**.[3e,g]

As a final remark, our procedures represent a short and efficient alternative to existing asymmetric synthesis of lignan lactones and we anticipate that chiral lactam **5** will serve as a template for the synthesis of the other natural products.

EXPERIMENTAL SECTION

Melting points were recorded on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO Model A-3 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL Model EX-90 spectrometer (operated at 90 and 22.4 MHz, respectively) in $CDCl_3$ referenced to

internal tetramethylsilane (TMS) at 0.0 ppm. Optical rotations were measured in 1-dm path legth cell of 2 mL capacity using a JASCO Model DIP-140 polarimeter. Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm Merck silica gel 60-F_{254} precoated silica gel plates. Column chromatography or flash chromatography was performed on Merck silica gel (70-230 or 230-400 mesh ASTM, respectively) eluting with the indicated solvent system. High-pressure liquid chromatography (HPLC) was carried out on a Shimazu Model LC-6A liquid chromatograph equipped with a refractive index detector using reversed-phase (Cosmosil 5PYE and 5C_{18}) columns. Yields refer to chromatographically and spectroscopically (^1H and ^{13}C NMR) homogeneous materials.

(*S*)-2,5-pyrrolidinedione (3)

A mixture of L-malic acid (20.0 g, 149 mmol) and acetyl chloride (200 mL) was refluxed for 10 h and then concentrated in vacuo to give an oil (23.5 g) of the anhydride. To a solution of 2.95 g (18.7 mmol) of the above product in 60 mL of dichloromathane was added benzylamine (2.00 g, 18.7 mmol) slowly. After the solution was stirred for 1 h, it was concentrated in vacuo, and the residue was refluxed with acetyl chloride (100 mL) for another 10 h. After concentration of the reaction mixture in vacuo, the residue was purified by using flash chromatography (4:1 hexane-ethyl acetate) to afford 4.62 g (100%) of **3** as a white solid: mp 61-64 °C; $[\alpha]_D^{24}$ -39.6°(c 1.46, EtOH); IR (CCl_4) 1750, 1720, 1220 cm^{-1}; ^1H NMR δ 7.29 (5H, s), 5.38 (1H, dd, J = 8.6, 5.0 Hz), 4.63 (2H, s), 3.09 (1H, dd, J = 18.4, 8.6 Hz), 2.58 (1H, dd, J = 18.4, 5.0 Hz), 2.10 (3H, s); ^{13}C NMR δ 173.3, 173.0, 169.7, 135.3, 128.8, 128.7, 128.1, 67.5, 42.6, 35.6, 20.4. Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.14; H, 5.27; N, 5.64.

(4*S*,5*R*)-*N*-Benzyl-4-acetoxy-5-(tert-butyldimethylsilyl)oxy-2-pyrrolidinone (4a) and (4*S*,5*S*) epimer (4b)

To a solution of **3** (3.59 g, 14.5 mmol) in MeOH (200 mL) at -4 °C was added $NaBH_4$ (2.91 g, 76.6 mmol). After the reaction mixture was stirred for 15 min at -4 °C, it was poured into a stirred mixture of saturated aqueous $NaHCO_3$ (150 mL) and CH_2Cl_2 (150 mL). Extraction with CH_2Cl_2 (3 x 50 mL), followed by drying (Na_2SO_4), and concentration of the combined organic layers in vacuo gave 2.35 g (65%) of a mixture of two diastereomeric hydroxylactams, which were used in the following reaction without separation.

To a solution of 2.11 g (8.47 mmol) of the above hydroxylactams and imidazole (1.15 g, 16.9 mmol) in 15 mL of DMF was added TBDMSCl (1.91 g, 12.7 mmol) at room temperature. After the solution was stirred for 12 h, it was diluted with water (10 mL) and extracted with ether (3 x 50 mL). The organic extracts were dried (Na_2SO_4) and concentrated in vacuo, and the crude products of two diastereomers were separated by chromatography on silica gel (9:1 hexane-ethyl acetate) to give **4a**

(0.52 g, 17%), Rf 0.48 (minor isomer) and **4b** (1.85 g, 60%), Rf 0.39 (major isomer) (2:1 hexane-ethyl acetate) as a colorless oil and a white solid, respectively. **4a**: $[\alpha]_D^{25}$ -6.31°(c 1.54, EtOH); IR (thin film) 1750, 1720, 1230 cm^{-1}; ^1H NMR δ 7.24 (5H, s), 5.04 (1H, d, J = 15.5 Hz), 4.90 (1H, d, J = 6.0 Hz), 4.87 (1H, s), 3.94 (1H, d, J = 15.5 Hz), 2.99 (1H, dd, J = 17.7, 6.0 Hz), 2.50-2.20 (1H, m), 1.99 (3H, s), 0.89 (9H, s), 0.01 (6H, s); ^{13}C NMR δ 172.5, 169.8, 136.2, 128.6, 127.5, 85.9, 73.4, 42.9, 35.4, 25.5, 20.6, 17.8, -4.7, -5.3. Anal. Calcd for $C_{19}H_{29}NO_4Si$: C, 62.78; H, 8.04; N, 3.85. Found: C, 62.68; H, 8.35; N, 3.65. **4b**: mp 65-67 °C; $[\alpha]_D^{22}$ -20.0°(c 1.54, EtOH); IR ($CHCl_3$) 1750, 1720, 1250 cm^{-1}; ^1H NMR δ 7.25 (5H, s), 5.30-4.90 (2H, m), 5.05 (1H, d, J = 15.8 Hz), 3.95 (1H, d, J = 15.8 Hz), 2.66 (2H, d, J = 7.6 Hz), 2.06 (3H, s), 0.91 (9H, s), 0.02 (6H, s); ^{13}C NMR δ 171.4, 170.1, 136.4, 128.7, 127.4, 81.5, 68.6, 42.9, 34.2, 25.6, 20.9, 18.0, -4.4, -4.7. Anal. Calcd for $C_{19}H_{29}NO_4Si$: C, 62.78; H, 8.04; N, 3.85. Found: C, 62.49; H, 8.08; N, 3.73.

(*S*)-*N*-Benzyl-5-(tert-butyldimethylsilyl)oxy-3-pyrrolin-2-one (5)

To a stirred solution of NaH (0.40 g, 16.5 mmol) in THF (3 mL) under a nitrogen atmosphere at 0 °C was added a solution of **4b** (0.40 g, 1.10 mmol) in THF (5 mL). After the reaction mixture was stirred for 5 h at the same temperature, it was quenched by the addition of water (10 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed (6:1 hexane-ethyl acetate) to give **5** (0.16 g, 48%) as a white solid: mp 30-34 °C; $[\alpha]_D^{21}$ +39.6°(c 2.63, EtOH); IR ($CHCl_3$) 1710, 1100 cm^{-1}; ^1H NMR δ 7.26 (5H, s), 6.84 (1H, dd, J = 6.0, 1.5 Hz), 6.19 (1H, d, J = 6.0 Hz), 5.37 (1H, d, J = 1.5 Hz), 5.02 (1H, d, J = 1.5 Hz), 4.12 (1H, d, J = 1.5 Hz), 0.90 (9H, S), 0.04 (6H, s); ^{13}C NMR δ 169.1, 145.7, 137.4, 128.6, 128.2, 127.8, 127.4, 82.6, 42.3, 30.8, 25.6, 18.0, -4.2, -4.4. Anal. Calcd for $C_{17}H_{25}NO_2Si$: C, 67.28; H, 8.30; N, 4.62. Found: C, 66.99; H, 8.38; N, 4.52.

(4*R*,5*S*)-*N*-Benzyl-5-(tert-butyldimethylsilyl)oxy-4-(3-methoxyphenyl)-methyl-2-pyrrolidinone (6)

To a solution of CuI (2.12 g, 11.1 mmol) in THF (15 mL) under nitrogen at -78 °C were added a 1 M solution of *m*-methoxybenzylmagnesium chloride in THF (9.24 mL, 9.24 mmol) and TMSCl (1.00 g, 9.24 mmol) in THF (10 mL). After the mixture was stirred for 5 min, a solution of **5** (0.28 g, 0.924 mmol) in THF (10 mL) was added, and the reaction mixture was stirred for 1 h at -78 °C. Then the mixture was quenched by the addition of water (5 mL) and filtered through a pad of Celite. The filtrate was extracted with ether (3 x 20 mL), and the organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by using flash chromatogrophy (19:1 hexane-ehtyl acetate) to afford 0.16 g (41%) of **6** as a white sold: mp 100-102 °C; $[\alpha]_D^{23}$ -16.9°(c 2.00, EtOH); IR (thin film) 1690, 1260, 780 cm^{-1}; ^1H NMR δ 7.20 (5H, s), 7.20-6.30 (4H, m), 4.96 (1H, d, J = 15.3 Hz), 4.64 (1H,

s), 3.74 (1H, d, J = 15.3), 3.55 (3H, s), 2.60-1.70 (5H, m), 0.72 (9H, s), -0.35 (6H, s); ^{13}C NMR δ 176.6, 159.7, 140.0, 137.4, 129.4, 128.5, 128.2, 127.8, 127.3, 121.5, 114.6, 112.2, 85.4, 55.0, 45.7, 42.6, 41.7, 39.6, 25.6, 17.8, -4.8, -5.5. Anal. Calcd for $C_{25}H_{35}NO_3Si$: C, 70.55; H, 8.29; N, 3.29. Found: C, 70.42; H, 8.38; N, 3.43.

(*R*)-*N*-Benzyl-4-hydroxy-3-(3-methoxyphenyl)methylbutanamide (7)

To a solution of **6** (0.266 g, 0.626 mmol) in THF (4 mL) at 0 °C was added a 1 M solution of tetrabutylammonium fluoride in THF (0.69 mL, 0.69 mmol). After the reaction mixture was stirred for 20 min, it was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was immediately dissolved in EtOH (15 mL) and was added $NaBH_4$ (0.24 g, 6.34 mmol) at 0 °C. After the solution was stired for 21 h at room temperature, it was diluted with water (10 mL) and extracted with ethyl acetate (3 x 50 mL). The organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by using flash chromatogrophy (1:1 hexane-ethyl acetate) to afford 0.14 g (71%) of **7** as a colorless viscous oil: $[\alpha]_D^{20}$ -11.2°(c 1.16, EtOH); IR (thin film) 3300, 1650, 1590, 790 cm^{-1}; ^1H NMR δ 7.30-6.60 (9H, m), 4.29 (2H, d, J = 5.7 Hz), 3.80-3.40 (2H, m), 3.71 (3H, s), 3.52 (1H, bs), 2.60-1.90 (3H, m), 1.99 (2H, bs); ^{13}C NMR δ 173.1, 159.6, 141.5, 138.2, 129.3, 128.6, 127.6, 127.4, 121.5, 115.0, 111.5, 78.6, 77.2, 75.8, 64.6, 55.1, 43.6, 39.9, 38.6, 37.6, 30.8. Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.96; H, 7.54; N, 4.13.

(*R*)-Dihydro-4-(3-methoxyphenyl)methyl-2(3H)-furanone (8)

A solution of **7** (0.104 g, 0.33 mmol) and *p*-TsOH (0.063 g, 0.33 mmol) in benzene (5 mL) was refluxed for 3 h and then poured into water (10 mL). The aqueous layer was extracted with ether (3 x 50 mL), and the combined organic extracts were dried (Na_2SO_4). After concentration of the reaction mixture in vacuo, flash chromatographic purification (3:1 hexane-ethyl acetate) gave **8** (0.061 g, 89%) as a colorless oil: $[\alpha]_D^{20}$ +6.41°(c 2.08, $CHCl_3$); IR (thin film) 1780, 790 cm^{-1}; ^1H NMR δ 7.30-6.50 (4H, m), 4.40-3.60 (2H, m), 3.78 (3H, s), 2.90-2.10 (5H, m); ^{13}C NMR δ 176.8, 159.1, 139.9, 129.8, 121.0, 114.6, 111.9, 78.6, 77.2, 75.8, 72.6. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.94; H, 7.01.

(3*R*,4*R*)-3,4-Bis[(3-hydroxyphenyl)methyl]dihydro-2(3H)-furanone ((-)-Enterolactone, 1)

To a stirred solution of LDA [prepared from diisopropylamine (0.08 g, 0.82 mmol) and *n*-BuLi (1.50 M in hexane, 0.51 mL, 0.76 mmol) in THF (2 mL) under nitrogen at -78 °C] were added a solution of **8** (0.04 g, 0.19 mmol) in THF (2 mL) and HMPA (0.10 g, 0.56 mmol) in THF (1 mL). After the mixture was stirred for 0.5 h, a solution of *m*-methoxybenzylmagnesium chloride (0.09 g, 0.57 mmol) in THF (2 mL)

was added, and the reaction mixture was stirred for 20 h at -78 to -20 °C. Then the mixture was quenched by the addition of saturated aqueous NH_4Cl (3 mL), and H_2O (10 mL) was added. The product was extracted with ether (3 x 50 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by using flash chromatography (30:1 benzene-ethyl acetate) to afford dimethylether (0.052 g, 84%) of (-)-enterolactone (**1**) as a colorless oil: $[\alpha]_D^{23}$ -42.3°(c 0.98, $CHCl_3$); IR (thin film) 1770, 1260, 1160, 780, 700 cm^{-1}; ^1H NMR δ 7.40-6.41 (8H, m), 4.20-3.50 (2H, m), 3.75 (6H, s), 3.10-2.11 (6H, m); ^{13}C NMR δ 178.2, 159.6, 139.4, 139.1, 129.5, 129.4, 121.4, 120.6, 114.7, 114.2, 112.1, 111.7, 70.9, 54.8, 46.0, 41.0, 38.2, 34.8, 30.5. Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.80. Found: C, 73.36; H, 6.49.

Subsequent demethylation was performed as follows;
a solution of dimethylether of **1** (0.092 g, 0.28 mmol) and BBr_3 (0.28 g, 1.12 mmol) in CH_2Cl_2 (4 mL) was stirred for 38 h at 0 °C and diluted with water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL), and the combined organic layers were dried (Na_2SO_4), and concentrated in vacuo. The crude enterolactone was purified by using flash chromatography (2:1 hexane-ethyl acetate) to yield 0.081 g (0.27 mmol) of pure (-)-enterolactone (**1**) as a gum. The spectral data of **1** thus obtained were identical in all aspects with those of natural origin:[5a] $[\alpha]_D^{20}$ -40.5°(c 0.62, $CHCl_3$); IR (thin film) 3350, 1750, 790, 700 cm^{-1}; ^1H NMR (acetone-d_6) δ 8.26 (2H, s), 7.35-6.35 (8H, m), 4.30-3.65 (2H, m), 3.50-2.20 (6H, m); ^{13}C NMR (acetone-d_6) δ 178.7, 158.1, 140.9, 140.5, 130.2, 130.1, 121.2, 120.4, 116.9, 116.3, 114.3, 114.1, 71.4, 46.6, 41.9, 38.5, 35.2. Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.59; H, 6.39.

Acknowledgement: We thank Mr. K. Kimata and Dr. K. Hosoya, Kyoto Institute of Technology, for measurement of diastereomeric excess of the compound **6** by HPLC.

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13. When desilylation of **6** was undertaken in methanol in the presence of catalytic hydrochloric acid, a 7.7:1 mixture of C_5 epimers of 5-methoxy-4-(3-methoxyphenyl)methyl-2-pyrrolidinone was obtained by way of *N*-acyliminium

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