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Stereoselective Reactions. V.[1] Design of the Asymmetric Synthesis of Lignan Lactones. Synthesis of optically Active Podorhizon and Deoxypodorhizon by 1,3-Asymmetric Induction[2]

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A novel method for the asymmetric synthesis of both enantiomers of 2,3-disubstituted-butanolides (**8**) was devised using a readily available (*S*)-4-hydroxymethyl-4-butanolide 4-derivative (**6**) as a chiral source in the asymmetric induction and as the carbon framework of **8**. Application of this method to the asymmetric total synthesis of podorhizon (**23**) and deoxypodorhizon (**4**) is described.

Keywords——asymmetric synthesis; lignan lactone; podorhizon; deoxypodorhizon; lactone carbonyl transposition; enantiomeric enrichment; antileukemic natural product; 1,3-asymmetric induction; diastereoselectivity

It is generally recognized that biologically active chiral natural products exist in nature as optically active forms, and their biological activities are highly dependent on their absolute configurations. In studies aimed at the total synthesis of these compounds, therefore, the targets should be optically active compounds having the desired absolute configurations.

Lignans are compounds composed of two phenylpropane (C_6–C_3) units linking at their side chains.[3] They are a group of very attractive compounds as synthetic targets, because some of them, such as podophyllotoxin (**1**),[4] steganacin (**2**),[5,6] burseran (**3**),[7,8] *etc.*, are known to exhibit antileukemic activity.[9,10] The present paper describes our general strategy for the synthesis of these biologically active lignan lactones in optically active forms by asymmetric synthesis and its application to the synthesis of optically active podorhizon (**24**)[11] and deoxypodorhizon (**4**).[12]

Design of the Asymmetric Synthesis of Lignans

The retrosynthetic analysis of lignan is shown in Chart 1. Optically active deoxypodorhizon (**4**) having *trans*-configuration seems to be a convenient intermediate, because non-phenolic oxidative coupling of **4** is expected to give the steganacin skeleton, while generation of a carbonium ion at the benzylic position of **4** is expected to result in cyclization to the podophyllotoxin skeleton. It was necessary to obtain both enantiomers of **4** ((2*S*, 3*S*)-**4** and (2*R*, 3*R*)-4), because we wanted to synthesize both enantiomers of the target compounds.[6,8] As **4** is expected to be prepared from the corresponding optically active β-substituted γ-lactone (**5**), the first problem in the present synthesis is to develop a method for preparing both enantiomers of **5** in optically active forms.

This problem was solved by the idea shown in Chart 2, starting from optically active γ-lactone (**6**). This strategy has two key steps, *i.e.*, carbon–carbon bond formation at the α- and/or β-position of the lactone carbonyl of **6** to give **7** in predictable stereochemical courses, and removal of the original chiral center in **7** to give the objective optically active γ-lactone (**8**). This means that the chiral center in **6** is used as a chiral source in the asymmetric induction, and the carbon framework of **6** is used as that of **8**. The present method was designed based on the esay accessibility of optically pure γ-lactone (**6**), because we had our own method to prepare it in quantity starting from L-glutamic acid,[13] one of the most inexpensive optically active compounds that are commercially available. This optically active lactone (**6**) was found

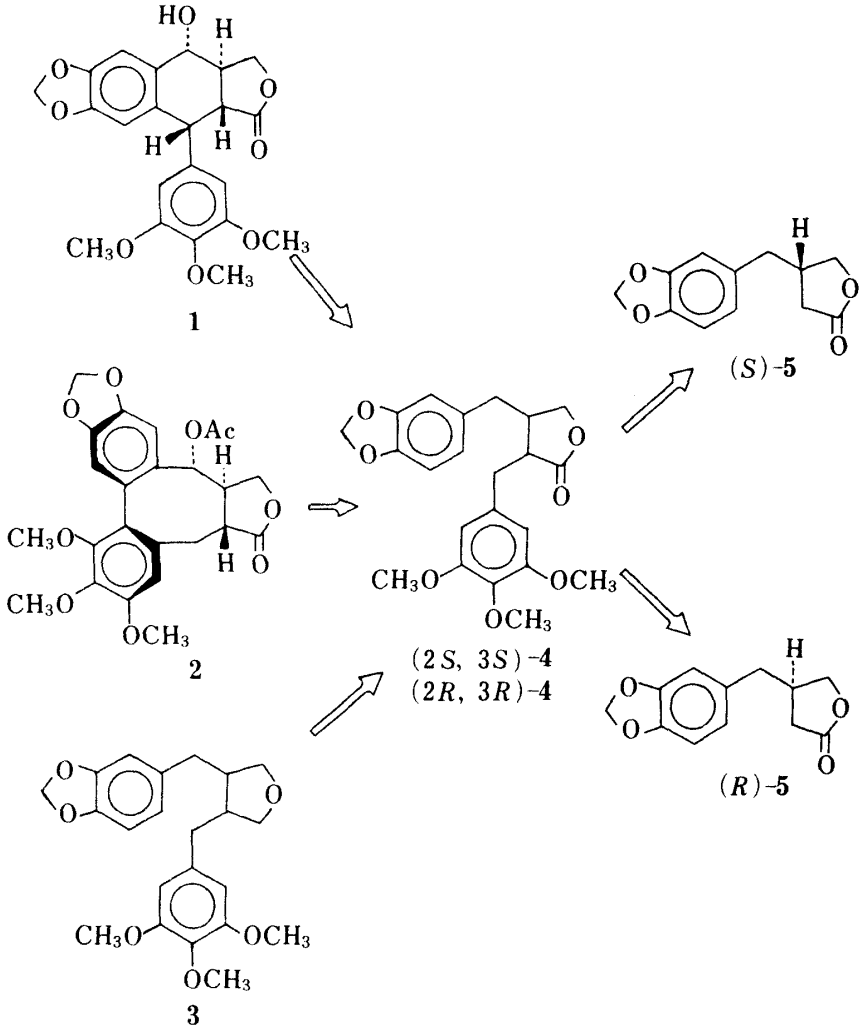

Chart 1

to be very useful, as ahown in this and the following papers of this series.[14]

The methods of carbon-carbon bond formation at the α-position of the γ-lactone (**6**) *via* 1,3-asymmetric induction are shown in Chart 3. Thus, conversion of **6** to the corresponding alkylidene or arylidene derivative (**9**) followed by catalytic hydrogenation is expected to give the α-substituted γ-lactone (**10**).[15] The enolate anion (**13**) of **6** is also expected to give an α-alkylated product (**14**) with a variety of electrophiles.[16] It is highly probable that hydrogenation of **9** will take place from the less hindered β-side to give **10** predominantly, while direct alkylation of **13** will also take place from the less hindered β-side to give **14** predominantly. Therefore, after the sequence of reactions involving reduction to triol, sodium metaperiodate oxidation to lactol, and then Collins oxidation to lactone as described below, both enantiomers (**11** and **15**) of the objective optically active β-substituted lactones are expected to be obtainable. Furthermore, these lactones (**11** and **15**) will give the corresponding *trans*-2,3-disubstituted γ-lactones (**12** and **16**) preferentially by direct alkylation, or

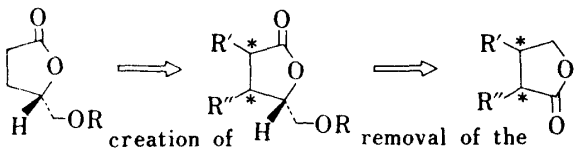

Chart 2

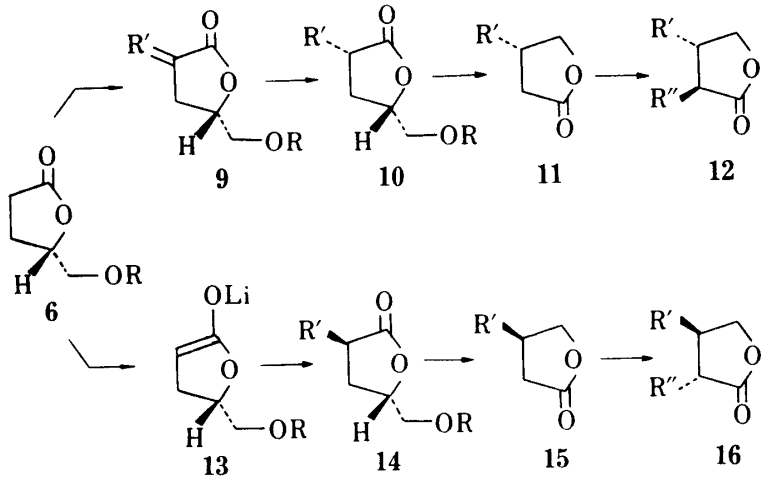

Chart 3

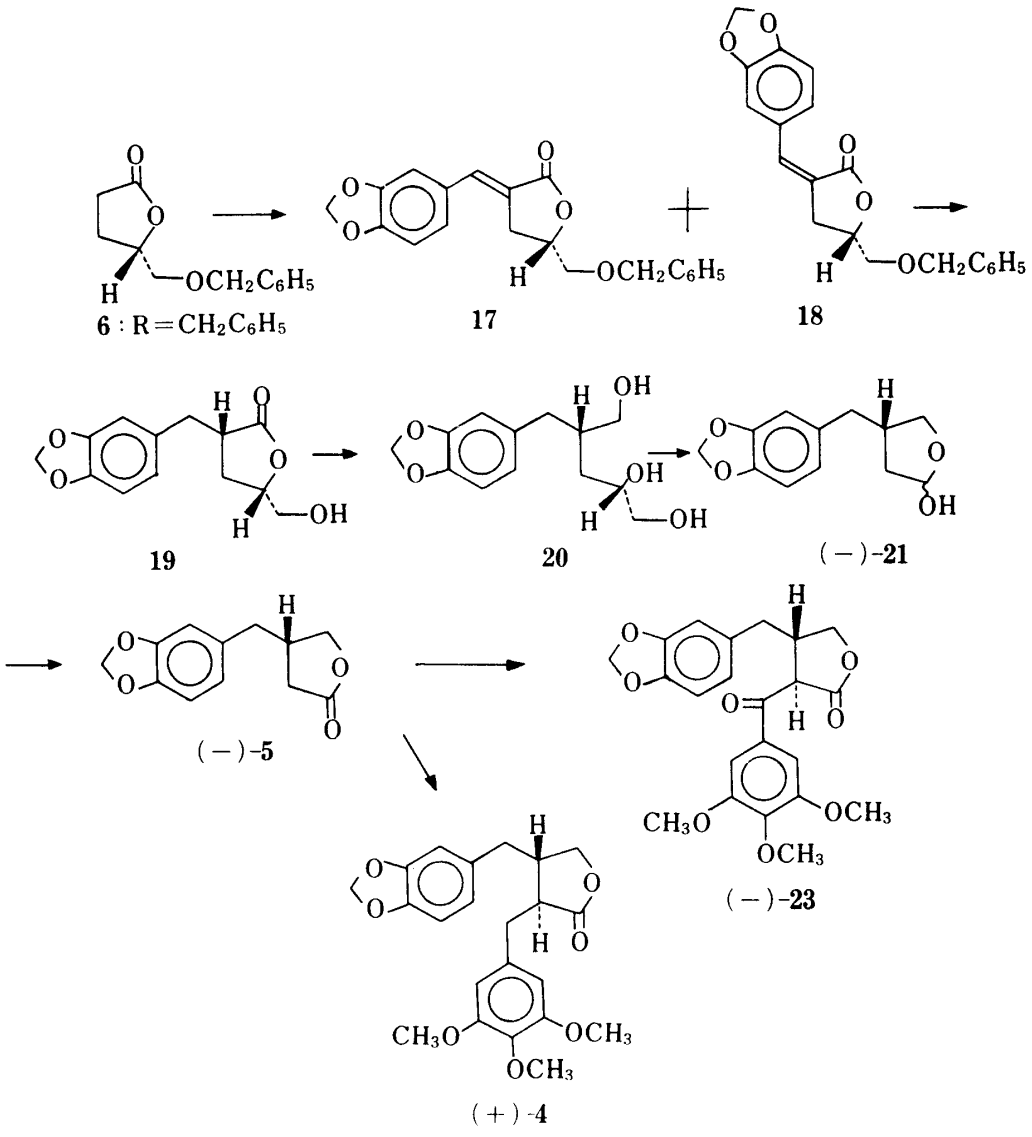

Chart 4

cis-2,3-disubstituted γ-lactones preferentially by catalytic hydrogenation of the corresponding alkylidene or arylidene derivatives, as above.

Asymmetric Synthesis of optically Active Podorhizon (23) and Deoxypodorhizon (4) by 1,3-Asymmetric Induction

The utility of the method based on the 1,3-asymmetric induction described above was proved by the synthesis of optically active podorhizon (**23**) and deoxypodorhizon (**4**) as shown in Charts 4 and 5. Condensation of **6** ($R=CH_2Ph$) with piperonal was undertaken under various conditions as summarized in Table I. Thus, the condensation of **6** ($R=CH_2C_6H_5$) with piperonal using lithiun diisopropylamide (LDA) and diethyl phosphorochloridate[17] gave a mixture of *trans*- and *cis*-isomer (**17** and **18**) in 57% yield. The *trans*-isomer (**17**) was isolated by column chromatography and its configuration about the double bond was confirmed by comparison of its ^1H nuclear magnetic resonance (NMR) spectrum with those of similar compounds in the literature.[11] After several examinations, a two-step procedure was found to give **17** in as high as 84% yield. Thus, aldol-type reaction of **6** ($R=CH_2Ph$) with piperonal in the presence of LDA in tetrahydrofuran (THF) at $-78°C$ afforded a diastereomeric mixture of alcohols, which was dehydrated in boiling toluene in the presence of *p*-toluenesulfonic acid[18] to give a mixture of **17** and **18** (10: 1) in 92% yield. The *trans*-isomer (**17**) was easily isolated, if necessary, by simple recrystallization.

Table I. Condensation of **6** ($R=CH_2C_6H_5$) with Piperonal

	Condition	Yield (**17**) (%)	**17**/**18**
1	THF–MeOH–NaOMe	26	—
2	2xLDA, $ClPO(OEt)_2$-THF	54	20/1
3	LDA, TsCl–THF	62	13/1
4	LDA–THF/TsOH–xylene	84	10/1

Catalytic hydrogenation of **17** using a palladium catalyst gave the corresponding saturated lactone (**19**) as a mixture of diastereomers. Without fractionation, this mixture was reduced with lithium aluminum hydride to the corresponding triol mixture (**20**), which was subjected to oxidative cleavage of the glycol function with sodium metaperiodate followed by oxidation of the resulting lactol ((−)-**21**) to give the target lacotne ((−)-**5**) in 45% overall yield from **6** ($R=CH_2Ph$). Although the absolute configuration and maximum rotation of **5** are already known,[11] the rotational value is too small for calculation of the optical purity. Therefore, the lactone (−)-**5** obtained above was acylated with the mixed anhydride (**22**) prepared from 3,4,5-trimethoxybenzoic acid and ethyl chloroformate to yield (−)-podorhizon ((−)-**23**) of $[\alpha]_D^{21}$ $-50.5°$ ($CHCl_3$), corresponding to be 64% optically pure based on the reported value.[11] It has now become apparent that asymmetric reduction had occurred, as we expected, from the less hindered β-side of **17** predominantly to give a mixture of **19** and its diastereomer in a ratio of 82: 18.[19] Single recrystallization of (−)-**23** prepared above from methanol afforded almost optically pure (−)-podorhizon, an antipode of natural (+)-podorhizon.

On the other hand, the anion of the chiral lactone (**6**, $R=CPh_3$) having a bulky trityl group was alkylated with piperonyl bromide to give the piperonyl derivative (**24**) as a diastereomeric mixture. Without fractionation, **24** was subjected to lithium aluminum hydride reduction followed by catalytic hydrogenation or by treatment with acid to give the triol (**26**) as a mixture of diastereomers. According to the procedure described above, this triol mixture (**26**) was converted as shown in Chart 5 to (+)-podorhizon ((+)-**23**) of $[\alpha]_D^{21}$ $+45.7°$ ($CHCl_3$), corresponding to be 57% optically pure.[11] This means that alkylation of **6** ($R=CPh_3$) with piperonyl bromide had taken place from the less hindered β-side to give a mixture of **24** and

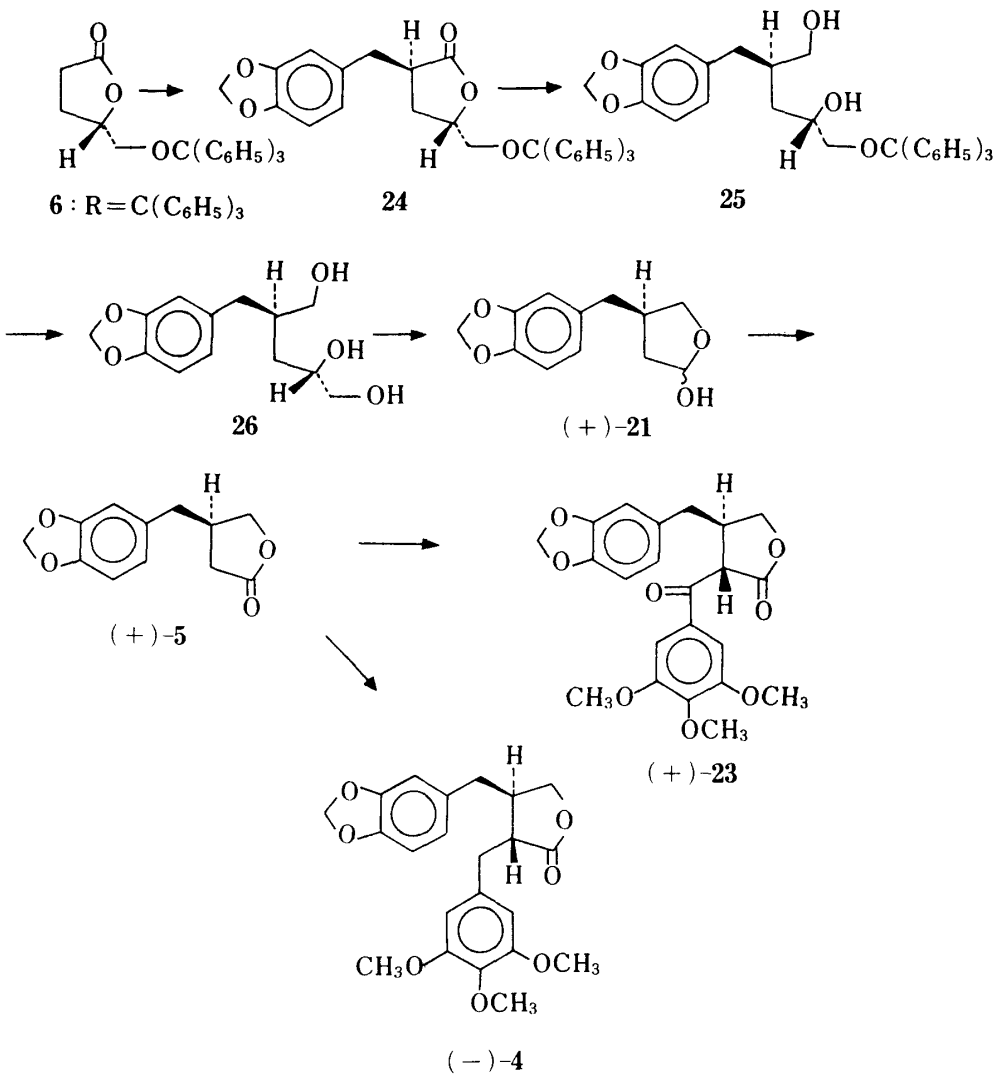

Chart 5

its diastereomer in a ratio of 79: 21. Optically pure (+)-podorhizon having the natural configuration was obtained by simple recrystallization.

Although recrystallization of the final products was necessary to increase optical purities for the synthesis of both enantiomers ((−)-**23** and (+)-**23**) of podorhizon, enantiomeric enrichment at the key intermediate (**5**) stage could also be achieved by recrystallization of the triols (**20**, **26**). Optically pure (+)- and (−)-deoxypodorhizon (**4**)[12] were obtained by this method.

This first successful asymmetric total synthesis of optically active podorhizon (**23**) and deoxypodorhizon (**4**) in high optical purity starting from the easily available chiral synthon (**6**) holds promise for the asymmetric total syntheses of various lignans.

Experimental[20]

(*S*)-(+)-4-Benzyloxymethyl-4-butanolide (6, R=CH_2Ph)——Sodium hydride (50% in oil, 5.28 g, 0.11 mol) was washed with toluene and suspended in dimethylformamide (DMF) (10 ml). A solution of (*S*)-(+)-4-hydroxymethyl-4-butanolide (**6**, R=H)[13a] (11.6 g, 0.1 mol) in DMF (10 ml) was added to the above suspension, and the whole was stirred at room temperature for 1 h. Benzyl bromide (13 ml, 0.11 mol) was added dropwise under ice-cooling, and the mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with benzene (200 ml), and the whole was washed successively with water (50 ml), 10% aq. HCl (30 ml), water (30 ml), satd. aq. $NaHCO_3$ (50 ml), and satd. aq. NaCl (50 ml). The organic layer

was dried over $MgSO_4$ and concentrated to give a yellow oil (18.4 g), which was distilled to give **6** (R=CH_2Ph) (12.7 g, 62%) as a pale yellow oil of bp 152—160°C (0.04 mmHg), $[\alpha]_D^{15}$ +18.1° (c=2.70, EtOH). ^1H NMR and infrared (IR) data were identical with those reported earlier.[13a]

***trans*- and *cis*-(*S*)-2-Piperonylidene-4-benzyloxymethyl-4-butanolide (17 and 18)**——i) Run 2 in Table I: A solution of *n*-BuLi in hexane (15 ml, 22 mmol) was added to a solution of diisopropylamine (3.1 ml, 22 mmol) in THF (20 ml). After stirring for 15 min, a solution of **6** (R=CH_2Ph) (2.1 g, 10 mmol) and HMPA (3.8 ml, 22 mmol) in THF (4 ml) was added, and the whole was stirred for 15 min at −78°C. Diethyl phosphorochloridate (1.6 ml, 11 mmol) was added dropwise over a period of 10 min, and the resulting mixture was stirred at −78°C for 1 h, allowed to warm to −20°C during 3 h, and held at −20°C for 1 h. A solution of piperonal (1.7 g, 11 mmol) in THF (5 ml) was added. The mixture was stirred at −78°C for 2 h and at room temperature for 15 h, then quenched with satd. aq. NH_4Cl (20 ml), and the whole was extracted with AcOEt (200 ml). The extract was washed successively with water (20 ml), 10% aq. HCl (20 ml), water (20 ml), 10% aq. NaOH (20 ml), water (20 ml), and satd. aq. NaCl (20 ml), then dried over $MgSO_4$. Evaporation of the solvent *in vacuo* gave a brown oil, which was subjected to silica gel column chromatography using $CHCl_2$–hexane (2:1) to give the *cis*-isomer (**18**) (90 mg, 3%) and *trans*-isomer (**17**) (1.83 g, 54%).

18: Pale yellow oil. IR ν_{max}^{film} cm^{-1}: 1740 (lactone), 1638 (C=C). ^1H NMR ($CDCl_3$) δ: 2.8—3.3 (2H, m, –C–C$\underline{H}_2$–CH–), 3.60 (2H, d, J=5 Hz, –O–C$\underline{H}_2$–CH), 4.55 (2H, s, OC$\underline{H}_2$Ph), 4.4—4.9 (1H, m, –C$\underline{H}$–), 5.94 (2H, s, OC$\underline{H}_2$O–), 6.68—6.95 (3H, m, aromatic $\underline{H}$ of methylenedioxyphenyl), 7.10 (1H, m, C$\underline{H}$=C), 7.31 (5H, s, $C_6\underline{H}_5$–). MS m/z: 338 (M^+).

17: Colorless needles of double mp 92.5—94.5°C and 100—101.5°C from ether–hexane. $[\alpha]_D^{20}$ +167° (c=1.148, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1745 (lactone), 1648 (C=C). ^1H NMR ($CDCl_3$) δ: 3.2—3.6 (2H, m, –C–C$\underline{H}_2$–CH), 3.64 (2H, d, J=4 Hz, –O–C$\underline{H}_2$–CH–), 4.55 (2H, s, –OC$\underline{H}_2$Ph), 4.7 (1H, m, –C$\underline{H}$–), 5.98 (2H, s, –O–C$\underline{H}_2$–O–), 6.76—7.02 (3H, m, aromatic $\underline{H}$ of methylenedioxyphenyl), 7.24 (5H, s, $C_6\underline{H}_5$–), 7.39 (1H, t, J=3 Hz, –C$\underline{H}$=C). MS m/z: 338 (M^+), 247 (M^+-CH_2Ph). *Anal.* Calcd for $C_{20}H_{18}O_5$: C, 70.99; H, 5.36. Found: C, 70.94; H, 5.37.

ii) Run 3 in Table I: A solution of LDA (2.6 mmol) in THF (5 ml)–hexane (1.4 ml) was prepared as in i). A solution of **6** (R=CH_2Ph) (495 mg, 2.4 mmol) in THF (2 ml) was added, and the whole was stirred at −78°C for 30 min. A solution of piperonal (390 mg, 2.6 mmol) in THF (2 ml) was added, and the mixture was stirred at −78°C for 2 h. A solution of *p*-toluenesulfonyl chloride (545 mg, 2.9 mmol) in THF (1 ml) was then added and the mixture was stirred at room temperature for 30 h. Evaporation of the solvent *in vacuo* gave a residue, which was diluted with benzene, and the whole was washed successively with 10% aq. HCl (5 ml), satd. aq. NaCl (5 ml), satd. aq. $NaHCO_3$ (5 ml), and satd. aq. NaCl (5 ml), then dried over $MgSO_4$. Evaporation of the solvent gave a pale brown oil (880 mg), which was subjected to silica gel column chromatography as in i) to give **18** (37 mg, 4.6%) and **17** (540 mg, 62%).

iii) Run 4 in Table I: A solution of LDA (96 mmol) in THF (300 ml)–hexane (53 ml) was prepared as in i). A solution of **6** (R=CH_2Ph) (19.7 g, 96 mmol) in THF (50 ml) was added and the mixture was stirred at −78°C for 20 min. A solution of piperonal (14.3 g, 96 mmol) in THF (50 ml) was then added, and the whole was stirred at −78°C for 1.5 h. The reaction mixture was quenched with conc. HCl (30 ml), then extracted twice with 100 ml portions of AcOEt. The combined extracts were washed successively with satd. aq. NaCl (50 ml), satd. aq. $NaHCO_3$ (50 ml) and satd. aq. NaCl (50 ml). The dried ($MgSO_4$) organic layer was concentrated *in vacuo* to give a diastereomeric mixture of alcohols as a brown viscous oil (33.7 g, 99%). IR ν_{max}^{film} cm^{-1}: 3450 (OH), 1760 (lactone). MS m/z: 356 (M^+), 338 (M^+-H_2O).

The above crude oil (1.16 g, 3.3 mmol) was heated in the presence of *p*-TsOH (20 ml) in boiling xylene (30 ml) for 1 h. After cooling, the solution was washed with satd. aq. $NaHCO_3$ (5 ml), and satd. aq. NaCl (5 ml), then dried over $MgSO_4$. Evaporation of the solvent *in vacuo* gave a brown viscous oil (1.08 g), which was recrystallized from EtOH to give **17** (930 mg, 84%) as colorless needles of mp 91.5—101°C (double melting).

(2*S*,4*S*)-4-Hydroxymethyl-2-piperonyl-4-butanolide (19) and Its 2-Epimer——Catalytic hydrogenation of **17** (9.33 g) was carried out with 5% Pd-C (2.0 g), $PdCl_2$ (10 mg) and a small amount of conc. HCl in AcOEt (180 ml) under atmospheric pressure of H_2 as usual.[21] The mixture was filtered and the filtrate was concentrated *in vacuo* to give a pale yellow oil (6.74 g, 98%), which crystallized on standing, mp 60—74°C, $[\alpha]_D^{20}$ +93.6° (c=1.06, EtOH), IR ν_{max}^{film} cm^{-1}: 3400 (OH), 1775 (lactone). ^1H NMR (60 MHz, $CDCl_3$) δ: 1.9—4.3 (8H, m, –C$\underline{H}_2$–CH–C$\underline{H}_2$–CH), 4.46 (1H, m, –CH–O–), 5.89 (2H, s, –O–C$\underline{H}_2$–O–), 6.68 (3H, s, aromatic $\underline{H}$). MS m/z: 250 (M^+). This sample was used in the next step without purification.

An analytical sample was prepared by several recrystallizations from AcOEt as colorless needles of mp 79—81°C. ^{13}C NMR ($CDCl_3$) δ: 29.2 (t), 35.8 (t), 42.7 (d), 63.5 (t), 79.1 (d), 100.9 (t), 108.3 (d), 109.1 (d), 121.8 (d), 132.2 (s), 146.2 (s), 147.8 (s), 178.2 (s). *Anal.* Calcd for $C_{13}H_{14}O_5$: C, 62.40; H, 5.64. Found: C, 62.13; H, 5.65.

(2*S*,4*S*)-2-Piperonyl-1,4,5-pentanetriol (20) and Its 4-Epimer——A THF solution (20 ml) of a mixture (4.0 g, 16 mmol) of **19** and its 2-epimer obtained above was added dropwise to a suspension of $LiAlH_4$ (0.61 g, 6 mmol) in THF (120 ml) under ice-cooling. The mixture was stirred at room temperature for 1 h, then water (0.61 ml), 15% aq. NaOH (0.61 ml), and water (1.8 ml) were added successively, and the whole was filtered. The filtrate was concentrated *in vacuo* to give a pale yellow oil (3.23 g, 79%) of $[\alpha]_D^{20}$ −17.5° (c=

0.938, EtOH), IR ν_{max}^{film} cm^{-1}: 3350 (OH). ^1H NMR ($CDCl_3$) δ: 1.44 (2H, br m, -CH-C$\underline{H}_2$-CH-), 1.7—2.2 (1H, m, Ar-CH_2-C$\underline{H}$-), 2.48 (2H, t, J=7 Hz, Ar-C$\underline{H}_2$-CH-), 3.1—3.8 (5H, m, two -C$\underline{H}_2$-OH, -C$\underline{H}$-OH), 3.8—4.8 (3H, br m, three -O$\underline{H}$), 5.85 (2H, s, -O-CH_2-O-), 6.4—6.8 (3H, m, aromatic $\underline{H}$). MS m/z: 254 (M^+), 236 (M^+-H_2O). This diastereomeric mixture of triols was used in the next step without further purification.

An analytical sample of **20** was prepared by recrystallization of the above diastereomeric mixture from AcOEt as colorless needles of mp 64—66°C, $[\alpha]_D^{20}$ −12.9° (c=0.94, EtOH). *Anal.* Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.38; H, 7.07.

(4*S*)-(−)-2-Hydroxy-4-piperonyl-tetrahydrofuran ((−)-**21**)——i) From a Mixture of **20** and Its 4-Epimer: A solution of a mixture (1.32 g, 5.2 mmol) of **20** and its 4-epimer obtained above in *tert*-BuOH (20 ml) was added to a solution of $NaIO_4$ (2.22 g, 10 mmol) in water (20 ml)–*tert*-BuOH (20 ml).[22] The reaction mixture was stirred at room temperature for 2 h, and then extracted three times with 50 ml portions of AcOEt. The combined extracts were washed successively with 10% aq. $NaHSO_3$ (20 ml), satd. aq. $NaHCO_3$ (20 ml), and satd. aq. NaCl (20 ml), then dried over $MgSO_4$. Concentration *in vacuo* afforded the objective lactol ((−)-**21**) (1.06 g, 92%) as a pale yellow oil of $[\alpha]_D^{20}$ −13.6° (c=1.12, $CHCl_3$), IR ν_{max}^{film} cm^{-1}: 3400 (OH). ^1H NMR ($CDCl_3$) δ: 1.78 (2H, m, -CH-C$\underline{H}_2$-CH-), 1.8—2.3 (1H, m, Ar-CH_2-C$\underline{H}$-), 2.4—2.8 (2H, m, Ar-C$\underline{H}_2$-), 2.85 and 3.0 (total 1H, each br s, -O$\underline{H}$), 3.4—4.2 (2H, m, CH-C$\underline{H}_2$-O), 5.5 (1H, m, -C$\underline{H}$-(OH)-O-), 5.88 (2H, s, -O-C$\underline{H}_2$-O-), 6.4—6.8 (3H, m, aromatic $\underline{H}$). MS m/z: 222 (M^+), 204 (M^+-H_2O).

ii) From **20**: Crystalline **20** (mp 64—66°C) obtained above was treated as in i) above to give the loctol ((−)-**21**) of $[\alpha]_D^{20}$ −17.1° (c=1.07, $CHCl_3$) as a colorless oil in 98% yield.

(*S*)-(−)-3-Piperonyl-4-butanolide ((−)-**5**)——i) A solution of the above lactol ((−)-**21**) (170 mg, 0.77 mmol) of $[\alpha]_D^{20}$ −13.6° ($CHCl_3$) in CH_2Cl_2 (70 ml) was added to a suspension of Collins reagent, prepared from CrO_3 (770 mg, 7.7 mmol) and pyridine (1.25 ml, 15.4 mmol),[23] in CH_2Cl_2 (70 ml). The reaction mixture was stirred at room temperature for 20 min, then diluted with ether–hexane (1: 1) (200 ml), and the whole was stirred for an additional 10 min. The mixture was filtered through celite, and the filtrate was concentrated *in vacuo* to give a pale yellow oil. Purification by column chromatography (silica gel, CH_2Cl_2) afforded (−)-**5** (130 mg, 77%) as a pale yellow oil of $[\alpha]_D^{20}$ −3.2° (c=1.14 $CHCl_3$), (reported[11] $[\alpha]_D^{20}$ +4.8° (c=1.142, $CHCl_3$) for optically pure antipode). IR $\nu_{max}^{CH_2Cl_2}$ cm^{-1}: 1775 (lactone). ^1H NMR ($CDCl_3$) δ: 2.1—3.0 (5H, m, Ar-C$\underline{H}_2$-C$\underline{H}$-C$\underline{H}_2$-CO-), 3.95 (1H, q of ABX, J_{AB}=9 Hz, J_{BX}=5 Hz, CH-C$\underline{H}_2$-O-), 4.30 (1H, q of ABX, J_{AB}=9 Hz, J_{AX}=6 Hz, CH-C$\underline{H}_2$-O-), 5.89 (2H, s, -O-C$\underline{H}_2$-O-), 6.4—6.7 (3H, m, aromatic $\underline{H}$). ^{13}C NMR ($CDCl_3$) δ: 34.0 (t), 37.2 (d), 38.4 (t), 72.5 (t), 101.0 (t), 108.3 (d), 108.9 (d), 121.6 (d), 132.3 (s), 146.2 (s), 147.8 (s), 176.8 (s). MS m/z: 220 (M^+), 135 (M^+−γ-butyrolactone). *Anal.* Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 65.24; H, 5.45. This sample was found to be 64% optically pure by conversion to (−)-**23** described below.

ii) The lactol ((−)-**21**) of $[\alpha]_D^{20}$ −17.1° ($CHCl_3$) was treated as in i) above to give (−)-**5** of $[\alpha]_D^{20}$ −4.1° (c=1.14, $CHCl_3$) as a colorless oil in 53% yield. This sample was found to be 93% optically pure by conversion to (−)-**23** as described below.

3,4,5-Trimethoxybenzoic Ethoxycarbonic Anhydride (**22**)——Ethyl chloroformate (0.49 ml, 5.1 mmol) was added dropwise to a cooled (−78°C) solution of 3,4,5-trimethoxybenzoic acid (990 mg, 4.7 mmol) and triethylamine (0.78 ml, 5.6 mmol) in THF (10 ml). The mixture was stirred at −78°C for 1 h and then at room temperature for 15 h. The whole was filtered and the filtrate was concentrated *in vacuo* to give **22** (1.34 g) in quantitative yield. Recrystallization from hexane gave colorless leaflets of mp 94°C, IR ν_{max}^{KBr} cm^{-1}: 1823, 1730 (anhydride), ^1H NMR ($CDCl_3$) δ: 1.43 (3H, t, J=7 Hz, -C$\underline{H}_3$), 3.91 (9H, s, three -OC$\underline{H}_3$), 4.41 (2H, q, J=7 Hz, -O-C$\underline{H}_2$-CH_3), 7.26 (2H, s, aromatic $\underline{H}$). *Anal.* Calcd for $C_{13}H_{16}O_7$: C, 54.93; H, 5.67. Found: C, 55.04; H, 5.70.

(−)-Podorhizon ((−)-**23**)——i) A solution of LDA (1.24 mmol) in THF (7 ml)–hexane (0.84 ml) was prepared at −78°C as above. Haxamethylphosphoramide (HMPA) (0.22 ml, 1.24 mmol) was added and the mixture was stirred at −78°C for 10 min. A solution of (−)-**5** ($[\alpha]_D^{20}$ −3.2° ($CHCl_3$)) (130 mg, 0.59 ml) obtained above in THF (1 ml) was added and the mixture was stirred at −78°C for 25 min. A solution of mixed anhydride (**22**) (200 mg, 0.71 mmol) was added. The whole was stirred at −78°C for 1.5 h, then quenched with satd. aq. NH_4Cl (10 ml), and extracted three times with 50 ml portions of AcOEt. The combined extracts were washed successively with 10% aq. HCl (20 ml), water (20 ml), and satd. aq. NaCl (20 ml), then dried over $MgSO_4$. Evaporation of the solvent afforded a yellow oil (340 mg), which was purified by preparative thin-layer chromatography (TLC) (silica gel, $CHCl_3$) to give (−)-podorhizon ((−)-**23**) (180 mg, 74%) as a yellow solid of mp 110—123°C, $[\alpha]_D^{21}$ −50.5° (c=0.56, $CHCl_3$), corresponding to be 64% optically pure.[11] IR $\nu_{max}^{CH_2Cl_2}$ cm^{-1}: 1775 (lactone), 1675 (ketone). ^1H NMR ($CDCl_3$) δ: 2.75 (1H, d, J=8 Hz, Ar-C$\underline{H}_2$-CH-), 3.2—3.6 (1H, m, Ar-CH_2-C$\underline{H}$-), 3.88 (6H, s, two -OC$\underline{H}_3$), 3.92 (3H, s, -OC$\underline{H}_3$), 4.0—4.9 (3H, m, -C$\underline{H}_2$-O-, -CO-C$\underline{H}$-CO-), 5.92 (2H, s, -O-C$\underline{H}_2$-O-), 6.5—6.8 (3H, m, aromatic $\underline{H}$ of methylenedioxyphenyl), 7.16 (2H, s, aromatic $\underline{H}$ of trimethoxyphenyl). MS m/z: 414 (M^+). Recrystallization from MeOH gave (−)-podorhizon ((−)-**23**) of mp 125—127°C, $[\alpha]_D^{21}$ −75.6° (c=0.566, $CHCl_3$) (reported[11] mp 129—130°C, $[\alpha]_D^{21}$ +79.5° (c=0.588, $CHCl_3$) for optically pure (+)-podorhizon). *Anal.* Calcd for $C_{22}H_{22}O_8$: C, 63.79; H, 5.43. Found: C, 63.76; H, 5.35.

ii) The lactone ((−)-**5**) of $[\alpha]_D^{20}$ −4.1 ($CHCl_3$) obtained above was treated as in i) to give (−)-podorhizon

((−)-**3**) of $[\alpha]_D^{21}$ −73.7° (c=0.57, $CHCl_3$).

(*S*)-(+)-4-Trityloxymethyl-4-butanolide (6, R=CPh$_3$)——A solution of (*S*)-4-hydroxymethyl-4-butanolide (**6**, R=H)[13a] (715 mg, 6.2 mmol) and trityl chloride (1.89 g, 6.8 mmol) in pyridine (30 ml) was stirred at 50°C for 18 h. The whole was diluted with AcOEt (300 ml) and washed successively with satd. aq. $CuSO_4$ (50 ml×3), water (50 ml×2), satd. aq. $NaHCO_3$ (50 ml), and satd. aq. NaCl (50 ml), then dried over $MgSO_4$. The solvent was evaporated off *in vacuo* to afford a colorless solid, which was recrystallized from AcOEt to give (+)-**6** (R=CPh$_3$) (1.47 g, 67%) as colorless needles of mp 149.5—150°C, $[\alpha]_D^{20}$ +28.6° (c=1.05, $CHCl_3$), IR ν_{max}^{KBr} cm^{-1}: 1775 (lactone). ^1H NMR ($CDCl_3$) δ: 1.7—2.7 (4H, m, CH_2×2), 3.09 (1H, dd (A of ABX), J_{AB}=13 Hz, J_{AX}=4 Hz, $CH_AH_BOCPh_3$), 3.37 (1H, dd (B of ABX), J_{AB}=13 Hz, J_{BX}=3 Hz, $CH_AH_BOCPh_3$), 4.4—4.7 (1H, m, CH), 6.9—7.5 (15H, m, three C_6H_5–). MS m/z: 358 (M^+), *Anal.* Calcd for $C_{24}H_{22}O_3$: C, 80.42; H, 6.19. Found: C, 80.64; H, 6.18.

(2*R*,4*S*)-2-Piperonyl-4-trityloxymethyl-4-butanolide (24) and Its 2-Epimer——A solution of LDA (5.5 mmol) in THF (25 ml)–hexane (4 ml) was prepared as above. A solution of **6** (R=CPh$_3$) (1.79 g, 5.0 mmol) in THF (5 ml) was added and the mixture was stirred at −78°C for 25 min. A solution of piperonyl bromide[24] (1.29 g, 6.0 mmol) in THF (7.5 ml) was added and the mixture was stirred at −78°C for 3 h. The mixture was quenched with satd. aq. NH_4Cl (20 ml) and extracted three times with 70 ml portions of AcOEt. The combined AcOEt layers were washed with 10% aq. HCl (20 ml), water (20 ml), satd. aq. $NaHCO_3$ (20 ml), and satd. aq. NaCl (20 ml), then dried over $MgSO_4$. Concentration *in vacuo* afforded a pale yellow glass (2.5 g), which was purified by silica gel column chromatography using benzene–ether (9.5: 0.5) to give a mixture of **24** and its 2-epimer (1.70 g, 69%) as a colorless viscous oil of $[\alpha]_D^{20}$ +11.3° (c=0.936, $CHCl_3$), IR ν_{max}^{film} cm^{-1}: 1752 (lactone). ^1H NMR (60 MHz, $CDCl_3$) δ: 1.7—2.2 (2H, m, CH_2), 2.4—3.6 (5H, m, CH, two CH_2), 4.2—4.6 (1H, m, CH–O), 5.77 (2H, s, OCH_2O), 6.4—6.9 (3H, m, aromatic H), 7.0—7.6 (15H, m, three C_6H_5). MS m/z: 492 (M^+), 415 ($M^+-C_6H_5$).

(2*R*,4*S*)-2-Piperonyl-5-trityloxy-1,4-pentanediol (25) and Its 2-Epimer——A solution of the mixture (**24** and its 2-epimer) (1.40 g, 2.84 mmol) obtained above in THF (30 ml) was added to a suspension of $LiAlH_4$ (0.43 g, 11.4 mmol) in THF (70 ml) over a period of 5 min and the whole was stirred at room temperature for 2 h. The reaction mixture was quenched by successive additions of water (0.43 ml), 15% aq. NaOH (0.43 ml), and water (1.3 ml), then filtered. The filtrates were concentrated *in vacuo* to give a pale yellow oil (1.9 g), which was purified by preparative thin-layer chromatography (TLC) (silica gel, ether–hexane (4: 1), extraction with $CHCl_3$) to give the diols (**25** and its 2-epimer) (0.83 g, 59%) as a colorless viscous oil of $[\alpha]_D^{20}$ −2.7° (c=1.106, $CHCl_3$), IR ν_{max}^{film} cm^{-1}: 3350 (OH). ^1H NMR (60 MHz, $CDCl_3$) δ: 1.47 (2H, t, J=5 Hz, CH_2), 1.9 (1H, m, CH), 2.3—2.9 (4H, m, CH_2Ar, two OH), 3.13 (2H, d, J=5 Hz, CH_2), 3.57 (2H, d, J=4 Hz, CH_2OH), 3.95 (1H, m, CH–O), 5.87 (2H, s, OCH_2O), 6.4—6.8 (3H, m, aromatic H), 7.1—7.6 (15H, m, three C_6H_5). MS m/z: 496 (M^+).

(2*R*,4*S*)-2-Piperonyl-1,4,5-pentanetriol (26) and Its 2-Epimer[25]——i) A solution of the above diols (**25** and its 2-epimer) (0.80 g, 1.61 mmol) and five drops of acetic acid in EtOH (30 ml) was catalytically hydrogenated in the presence of 10% Pd-C (100 mg) and $PdCl_2$ (25 mg). The mixture was filtered and the filtrate was concentrated to leave oily crystals (0.87 g), which were purified by preparative TLC (silica gel, MeOH–AcOEt (3: 97), extraction with AcOEt) to give the triols (**26** and its 2-epimer) (0.22 g, 54%) as colorless leaflets of mp, 82—85°C, $[\alpha]_D^{20}$ −18.1° (c=0.930, EtOH), IR ν_{max}^{Nujol} cm^{-1}: 3250 (OH). ^1H NMR (60 MHz, $CDCl_3$) δ: 1.48 (2H, t, J=6 Hz, CH_2), 1.8—2.3 (1H, m, CH), 2.4—2.8 (2H, m, CH_2Ar), 3.3—3.7 (4H, m, two CH_2O), 3.8 (1H, m, CH–O), 4.16 (3H, br s, three OH), 5.89 (2H, s, OCH_2O), 6.4—6.8 (3H, m, aromatic H). MS m/z: 254 (M^+), 236 (M^+-H_2O).

ii) Synthesis of **26**:[26] A solution of **6** (R=CPh$_3$) (3.58 g, 10 mmol) in THF (20 ml) was added to an LDA (11 mmol) solution in THF (50 ml)–hexane (7 ml) at −78°C. The mixture was stirred for 25 min at −78°C, then a solution of piperonyl bromide (3.01 g, 14 mmol) in THF (15 ml) was added and the mixture was stirred at −78°C for 3 h. The mixture was quenched with satd. aq. NH_4Cl (20 ml) and extracted three times with 100 ml portions of AcOEt. The combined extracts were washed with 10% aq. HCl (30 ml), water (30 ml), satd. aq. $NaHCO_3$ (30 ml), and satd. aq. NaCl (50 ml), then dried over $MgSO_4$. Concentration *in vacuo* afforded a pale yellow oil (6.27 g).

A solution of this yellow oil (6.27 g) in THF (150 ml) was added to a suspension of $LiAlH_4$ (1.90 g, 50 mmol) in THF (30 ml) and the mixture was stirred at room temperature for 2 h, then treated successively with water (1.9 ml), 15% aq. NaOH (1.9 ml), and water (5.7 ml), and filtered. The filtrate was concentrated to give a pale yellow oil (6.37 g), which was dissolved in EtOH (130 ml) and hydrogenated in the presence of $PdCl_2$ (100 mg) and 5% Pd-C (20 mg) under H_2.[25] The reaction mixture was filtered, and the filtrates were concentrated *in vacuo* to yield the crude triol (6.28 g) as a pale yellow caramel. Crystallization of this caramel from chloroform afforded the pure triol (**26**) (1.53 g, 60% overall yield) of mp 90.5—91.5°C, $[\alpha]_D^{20}$ −21.7° (c=0.904, EtOH), IR ν_{max}^{Nujol} cm^{-1}: 3250 (OH). ^1H NMR (60 MHz, CD_3OD) δ: 1.3—1.7 (2H, m, CH_2), 1.7—2.3 (1H, m, CH), 2.5—3.0 (2H, m, CH_2Ar), 3.3—3.7 (4H, m, two CH_2O), 3.7—4.0 (1H, m, CH–O), 5.85 (2H, s, OCH_2O), 6.6—6.8 (3H, m, aromatic H). *Anal.* Calcd for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.38; H, 7.22.

(4*R*)-(+)-2-Hydroxy-4-piperonyl-tetrahydrofuran ((+)-21)——i) A solution of the above triols (**26** and its epimer) (100 mg, 0.39 mmol) in *tert*-BuOH (4 ml) was added to a solution of $NaIO_4$ (169 mg, 0.79

mmol) in water (4 ml) and *tert*-BuOH (4 ml). The mixture was stirred for 2 h at room temperature and extracted three times with 50 ml portions of AcOEt. The extracts were washed with 10% aq. $NaHSO_3$ (20 ml), satd. aq. $NaHCO_3$ (20 ml), and satd. aq. NaCl (20 ml), then dried over $MgSO_4$. Concentration *in vacuo* afforded a yellow oil (85 mg), which was purified by silica gel column chromatography (ether) to give the lactol (**21**) (80 mg, 92%) as a colorless oil of $[\alpha]_D^{20}$ +15.8° (c=1.602, $CHCl_3$), IR ν_{max}^{film} cm^{-1}: 3400 (OH). MS m/z: 222 (M^+). TLC behavior and spectral data of this lactol were identical with those of (−)-**21** described above.

ii) The reaction of the pure triol ((−)-**26**) (762 mg, 3.0 mmol) was carried out under the same condition described in i) above to give optically pure lactol (+)-**21** (650 mg, 98%) as a colorless oil of $[\alpha]_D^{20}$ +20.3° (c=1.258, $CHCl_3$). ^1H NMR, infrared (IR), and mass (MS) spectra were identical with those obtained above.

(*R*)-(+)-3-Piperonyl-4-butanolide ((+)-**5**)——i) The lactol ((+)-**21**) of $[\alpha]_D^{20}$ +15.8° ($CHCl_3$) obtained above was oxidized with Collins reagent under the same condition described above for (−)-**21** to give (+)-**5** as a pale yellow oil of $[\alpha]_D^{20}$ +2.9° (c=1.40, $CHCl_3$), in 88% yield. IR, NMR and TLC behavior of this lactone were identical with those of (−)-**5** described above. The optical purity of this lactone was determined to be 57% by converting it to podorhizon as described below.

ii) Optically pure lactone ((+)-**5**) was synthesized under the same condition described above from (+)-**21** of $[\alpha]_D^{20}$ +20.3° ($CHCl_3$) as a pale yellow oil (89%) of $[\alpha]_D^{20}$ +5.2° (c=1.13, $CHCl_3$). ^1H NMR, IR, and MS spectra were identical with those of (−)-**5** described above.

(+)-Podorhizon ((+)-**23**)——The lactone ((+)-**5**) of $[\alpha]_D^{20}$ +2.9° ($CHCl_3$) was treated under the same condition described above for the synthesis of (−)-**23** to give (+)-**23** as a pale yellow glass of $[\alpha]_D^{21}$ +45.7° (c=0.60, $CHCl_3$), corresponding to be 57% optically pure.[11] IR ν_{max}^{film} cm^{-1}: 1760 (lactone), 1633 (ketone). ^1H NMR (60 MHz, C_6D_6) δ: 2.1—2.5 (2H, m, $C\underline{H}_2$), 3.48 (6H, s, two $OC\underline{H}_3$), 3.77 (3H, s, $OC\underline{H}_3$), 4.0—4.4 (2H, m, $C\underline{H}_2O$), 5.35 (2H, s, $OC\underline{H}_2O$), 6.2—6.7 (3H, m, aromatic $\underline{H}$), 7.15 (2H, br s, aromatic $\underline{H}$). TLC behavior of this sample was identical with that of (−)-**23** described above.

(−)-Deoxypodorhizon ((−)-**4**)——A solution of (+)-**5** ($[\alpha]_D^{20}$ +5.2° (c=1.13, $CHCl_3$)) (220 mg, 1.0 mmol) in THF (3 ml) was added to a cooled (−78°C) solution of LDA (1.2 mmol) in THF (7 ml)–hexane (0.76 ml). The mixture was stirred for 15 min, then a solution of HMPA (0.21 ml, 1.2 mmol) and 3,4,5-trimethoxybenzyl bromide[27] (340 mg, 1.3 mmol) in THF (3 ml) was added and the whole was stirred at −78°C for 4 h. The mixture was quenched with satd. aq. NH_4Cl (10 ml) and then extracted three times with 100 ml portions of AcOEt. The combined extracts were washed successively with 10% aq. HCl (50 ml), water (50 ml), satd. aq. $NaHCO_3$ (50 ml), and satd. aq. NaCl, then dried over $MgSO_4$. Concentration *in vacuo* afforded a yellow oil (400 mg), which was purified by silica gel column chromatography (ether–$CHCl_3$) (5: 95) to give (−)-**4** (330 mg, 83%) as a pale yellow glass of $[\alpha]_D^{25}$ −25.2° (c=0.410, $CHCl_3$) (reported[12] $[\alpha]_D^{25}$ −21.6° ($CHCl_3$)), IR ν_{max}^{film} cm^{-1}: 1775 (lactone). ^1H NMR (60 MHz, $CDCl_3$) δ: 2.2—2.7 (2H, br s, $C\underline{H}_2$), 2.7—3.0 (2H, br s, $C\underline{H}_2$), 3.80 (9H, s, three $OC\underline{H}_3$), 3.8—4.4 (2H, m, $C\underline{H}_2O$), 5.90 (2H, s, $OC\underline{H}_2O$), 6.38 (2H, s, aromatic $\underline{H}$), 6.3—6.8 (3H, m, aromatic $\underline{H}$). ^{13}C NMR ($CDCl_3$) δ: 35.2 (t), 38.3 (t), 41.0 (d), 46.4 (d), 56.0 (q), 60.7 (q), 71.7 (t), 77.4 (d), 101.0 (t), 106.3 (d), 108.2 (d), 108.8 (d), 121.5 (d), 131.6 (s), 133.4 (s), 136.8 (s), 146.3 (s), 147.8 (s), 153.2 (s), 178.4 (s). MS m/z: 400 (M^+). *Anal.* Calcd for $C_{22}H_{24}O_7$: C, 65.99; H, 6.04. Found: C, 65.86; H, 6.12. All spectral data were identical with those of natural deoxypodorhizon.[12]

(+)-Deoxypodorhizon ((+)-**4**)——The lactone ((−)-**5**) of $[\alpha]_D^{20}$ −4.1° ($CHCl_3$) obtained above was treated in the same way as in the synthesis of (−)-**4** above to give (+)-**4** of $[\alpha]_D^{25}$ +26.3° (c=0.40, $CHCl_3$). Spectral data of this compound were identical with those of (−)-**4** described above.

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