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Stereoselective Reactions. X.[1] Total Synthesis of Optically Pure Antitumor Lignan, Burseran[2]

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Optically pure *trans*- and *cis*-burseran (**4**, **10**) were stereoselectively synthesized in an unequivocal manner. Comparison of their behaviors on gas chromatography indicated that naturally occurring antitumor lignan, burseran, is the *trans*-isomer.

Keywords——antitumor lignan; relative configuration; absolute configuration; asymmetric synthesis; burseran; isodeoxypodophyllotoxin; deoxypodorhizon

In previous papers[3,4] we have reported the development of novel asymmetric reactions on the basis of the novel use of optically pure (*S*)-γ-hydroxymethyl γ-butyrolactone, easily available in quantity from L-glutamic acid, and its successful application to the asymmetric total synthesis of an antitumor lignan lactone steganacin. In the present paper we describe the stereoselective total synthesis of optically pure *trans*- and *cis*-burseran, and the determination of the relative configuration of naturally occurring antitumor lignan burseran as the *trans*-isomer.

Burseran was isolated as an antitumor compound from *Bursera microphylla* (Burseraceae) and has been characterized as a lignan, 3-(3,4-methylenedioxybenzyl)-4-(3,4,5-trimethoxybenzyl)tetrahydrofuran.[5] Although Trumbull and Cole undertook a synthetic study of burseran in order to determine its stereochemistry, a mixture of *trans*- and *cis*-burseran (**4** and **10**) was obtained. Gas chromatographic analysis, however, showed that naturally occurring burseran had a retention time identical to that of the faster-moving component of the synthetic mixture.[6] Thus, in order to establish the relative configuration of natural burseran, it is necessary to achieve a stereoselective synthesis of both *trans*- and *cis*-burseran in an unequivocal manner.

(−)-*trans*-Burseran ((−)-**4**) was synthesized from (−)-deoxypodorhizon ((−)-**2**), available from (+)-(*R*)-**1**,[4c,f] as shown in Chart 1. Reduction of (−)-**2** with $LiAlH_4$ in tetrahydrofuran (THF) afforded the diol ((−)-**3**) in 84% yield. Treatment of (−)-**3** with *para*-toluenesulfonyl chloride (*p*-TsCl) in pyridine resulted in concomitant tetrahydrofuran ring formation to afford *trans*-burseran ((−)-**4**) in 72% yield. The optical antipode ((+)-**4**) was synthesized starting from (+)-**2**.[4f,g] The infrared (IR) and mass spectra (MS) of (−)- and (+)-**4** are identical with reported spectra of natural burseran.[5]

(+)-*cis*-Burseran ((+)-**10**) was stereoselectively synthesized from (+)-(*R*)-**1**[4c,f] as shown in Chart 1. Lithioenolate derived from (+)-**1** was allowed to react with 3,4,5-trimethoxybenzaldehyde to give a mixture of (−)-podorhizol ((−)-**5a**) and (−)-epipodorhizol ((−)-**5b**).[7] Attempted dehydration of the mixture (**5a**, **b**) in refluxing xylene in the presence of *para*-toluenesulfonic acid (*p*-TsOH) according to the Matsui's procedure,[8] however, afforded a cyclization product, (−)-isodeoxypodophyllotoxin ((−)-**6**,[7] in 76% yield. Successful dehydration of **5** was achieved by tosylation followed by elimination reaction of the tosylate to afford (−)-anhydropodorhizol ((−)-**7**)[7] in 80% yield. Catalytic hydrogenation of (−)-**7** over

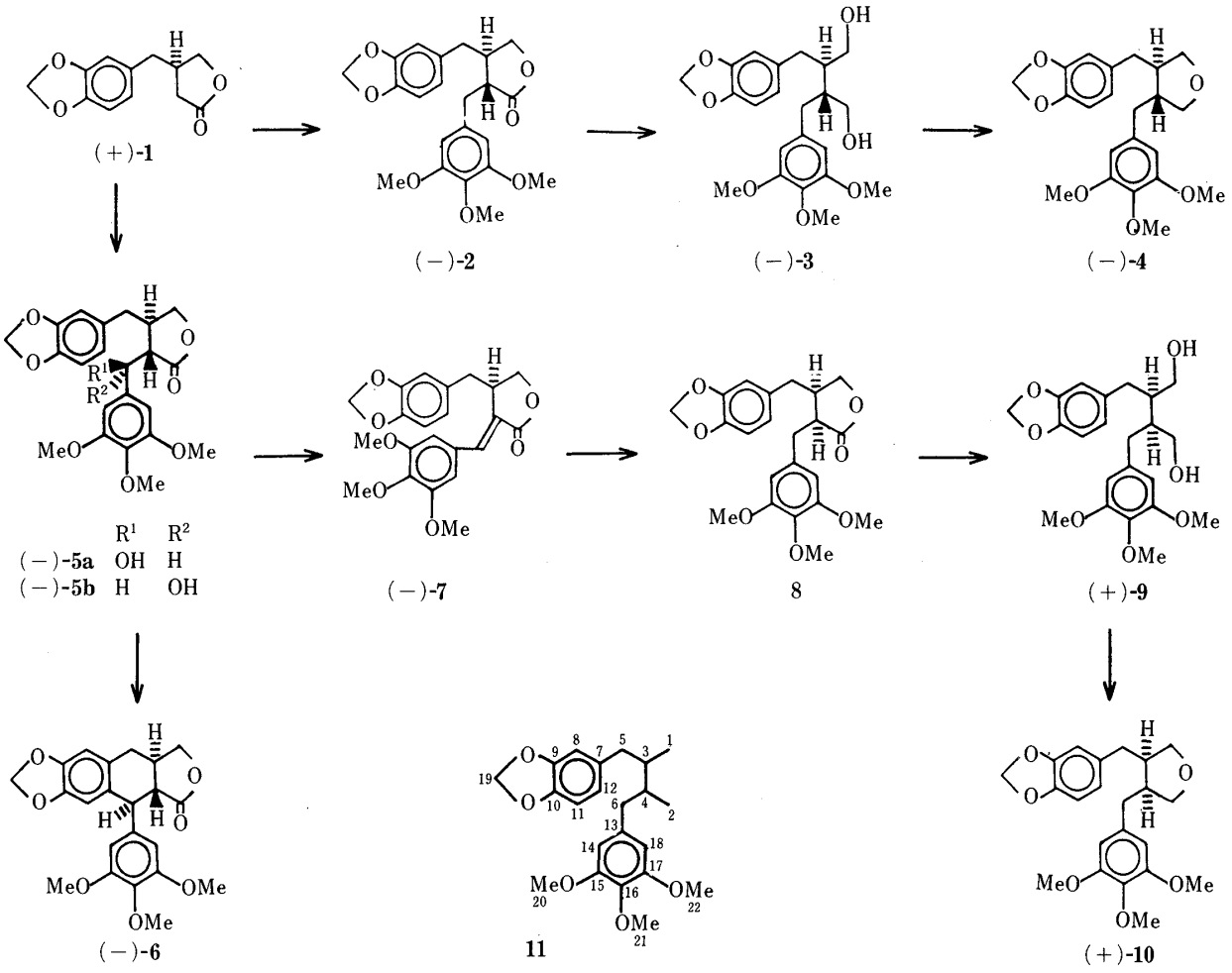

Chart 1

5% Pd–C in AcOH gave a mixture of the expected *cis*-dihydroanhydropodorhizol (**8**)[7] and (−)-**2** in a ratio of 7 : 3 (determined by carbon 13 nuclear magnetic resonance (NMR) analysis (Table I)). Reduction of the mixture (**8** and (−)-**2**) with $LiAlH_4$ in THF gave, after purification by column chromatography, the pure diol ((+)-**9**) and (−)-**3**, in 50 and 15% yields, respectively. In the same way as described for the preparation of the *trans*-isomer ((−)-**4**), the diol ((+)-**9**) was converted to (+)-*cis*-burseran ((+)-**10**). The IR and MS spectra of (+)-**10** were also indistinguishable from those reported for natural burseran.[5]

The relative configurations of (−)-**4** and (+)-**10** were unambiguous on the basis of the stereoselective synthetic pathway, and were also supported by ^{13}C-NMR analyses as shown in Table I. It was, as expected, found that the peaks derived from the *cis*-compound ((+)-**10**) appeared at higher field than those of the *trans*-isomer ((−)-**4**).

Finally, gas chromatographic analysis using the same type of column as reported[5] showed that synthetic *trans*-isomer ((−)-**4**) moved faster (retention time: 1.5 min) than the *cis*-isomer ((+)-**10**) (retention time: 2.2 min). Therefore, it was concluded that naturally occurring antitumor burseran is the *trans*-isomer. The absolute stereochemistry of natural burseran still remains unknown, because the optical rotation of natural burseran is not available.[9] However, since the novel method for the asymmetric synthesis developed by us has the advantage that either enantiomer is available,[3,4] both (−)- and (+)-**4** could be synthesized as described above.

TABLE I. ^{13}C-NMR Data for **2**, **3**, **4**, **8**, **9**, **10**[a]

Carbon[b]	**2**	**8**	**3**	**9**	**4**	**10**
1	71.1 t	69.4 t	60.2 t	63.0 t	73.2 t	71.9 t[c]
2	178.4 s	177.7 s	60.2 t	63.0 t	73.2 t	72.0 t[c]
3 or 4	41.0 d	40.2 d	43.7 d	44.8 d	46.3 d	43.6 d
4 or 3	46.4 d	45.3 d	44.1 d	45.3 d	46.6 d	43.8 d
5 or 6	35.2 t	31.2 t	35.9 t	33.7 t	39.2 t	33.3 t
6 or 5	38.3 t	32.8 t	36.6 t	33.7 t	39.9 t	33.9 t
7 or 13	131.6 s	132.0 s	134.3 s	134.1 s	134.1 s	134.3 s
8 or 11	108.2 d	108.4 d	108.0 d	108.1 d	108.0 d	108.2 d
9 or 10	146.3 s	146.3 s	145.7 s	145.8 s	145.8 s	145.9 s
10 or 9	147.8 s	147.9 s	147.6 s	147.7 s	147.6 s	147.7 s
11 or 8	108.8 d	109.0 d	109.3 d	109.3 d	108.9 d	108.9 d
12	121.5 d	121.8 d	121.8 d	121.8 d	121.4 d	121.4 d
13 or 7	133.4 s	134.4 s	136.4 s	136.3 s	136.1 s	136.3 s
14, 18	106.3 d	105.5 d	106.0 d	106.0 d	105.6 d	105.7 d
15, 17	153.2 s	153.3 s	153.0 s	153.0 s	153.1 s	153.2 s
16	136.8 s	136.8 s	136.1 s	136.2 s	136.4 s	136.3 s
19	101.0 t	101.0 t	100.8 t	100.8 t	100.8 t	100.8 t
20, 22	56.0 q	56.2 q	56.0 q	56.0 q	56.0 q	56.1 q
21	60.7 q	60.8 q	60.8 q	60.9 q	60.8 q	60.8 q

a) Taken in $CDCl_3$. Tetramethylsilane as an internal standard. *b*) For numbering, see **11** in Chart 1. *c*) Assignments may be reversed.

Experimental[10]

(−)-(2*R*,3*R*)-2-(3,4-Methylenedioxybenzyl)-3-(3,4,5-trimethoxybenzyl)-1,4-butanediol ((−)-3)——A solution of (−)-**2** ($[\alpha]_D^{25}$ −22.2° (*c*=0.410, $CHCl_3$))[4c,f] (200 mg, 0.5 mmol) in THF (5 ml) was added to a suspension of $LiAlH_4$ (38 mg, 1.0 mmol) at room temperature. The whole was stirred for 1 h, then water (0.04 ml), 15% aq. NaOH (0.04 ml), and water (0.12 ml) were added successively. Filtration and concentration *in vacuo* afforded a yellow oil (230 mg). Purification by silica gel column chromatography (ether–$CHCl_3$ (3 : 1)) afforded (−)-**3** (170 mg, 84%) as colorless fine needles of mp 94—95 °C (from ether–*n*-hexane). $[\alpha]_D^{20}$ −29.9° (*c*=0.976, $CHCl_3$). IR ν_{max}^{KBr} cm^{-1}: 3420, 3230, 1589. ^{1}H-NMR ($CDCl_3$) δ: 1.6—2.0 (2H, m, $ArCH_2C\underline{H}\times2$), 2.5—2.8 (4H, m, $ArC\underline{H}_2\times2$), 3.0—3.2 (2H, br s, $O\underline{H}\times2$), 3.3—3.9 (4H, m, $C\underline{H}_2OH\times2$), 3.80 (9H, s, $OC\underline{H}_3\times3$), 5.87 (2H, s, $OC\underline{H}_2O$), 6.31 (2H, s, aromatic H), 6.5—6.7 (3H, m, aromatic H). ^{13}C-NMR (Table I). MS *m/z*: 404 (M^+). *Anal.* Calcd for $C_{22}H_{28}O_7\cdot1/3H_2O$: C, 64.37; H, 7.04. Found: C, 64.38; H, 7.13.

(+)-3——Reduction of (+)-**2** ($[\alpha]_D^{25}$ +21.3° (*c*=0.400, $CHCl_3$))[4f,g] afforded (+)-**3** as colorless fine needles of mp 93.5—94.5 °C (from ether–*n*-hexane). $[\alpha]_D^{20}$ +31.6° (*c*=0.950, $CHCl_3$). *Anal.* Calcd for $C_{22}H_{28}O_7\cdot1/3H_2O$: C, 64.37; H, 7.04. Found: C, 64.42; H, 6.93. IR, ^{1}H-NMR, MS, and thin layer chromatography (TLC) behavior were identical with those for (−)-**3**.

(−)-(3*R*,4*R*)-3-(3,4-Methylenedioxybenzyl)-4-(3,4,5-trimethoxybenzyl)tetrahydrofuran ((−)-*trans*-Burseran) ((−)-4)——A solution of *p*-TsCl (74.3 mg, 0.39 mmol) in pyridine (3 ml) was added to (−)-**3** ($[\alpha]_D^{20}$ −29.9° (*c*=0.976, $CHCl_3$)) (150 mg, 0.37 mmol) and the whole was stirred at room temperature for 4 h, then at reflux for 3 h. The mixture was diluted with a mixture of benzene (200 ml) and $CHCl_3$ (50 ml), then washed with satd. aq. $CuSO_4$, water, satd. aq. $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to leave a yellow oil (150 mg). Purification by silica gel column chromatography (ether–$CHCl_3$ (1 : 4)) gave (−)-**4** (103 mg, 72%) as a pale yellow oil. $[\alpha]_D^{20}$ −34.8° (*c*=0.926, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1591. ^{1}H-NMR ($CDCl_3$) δ: 1.9—2.6 (6H, m, $ArC\underline{H}_2C\underline{H}\times2$), 3.3—4.0 (4H, m, $C\underline{H}_2OC\underline{H}_2$), 3.82 (9H, s, $OC\underline{H}_3\times3$), 5.8—5.9 (2H, m, $OC\underline{H}_2O$), 6.28 (2H, s, aromatic H), 6.4—6.7 (3H, m, aromatic H). ^{13}C-NMR (Table I). MS *m/z*: 386 (M^+), 182, 181, 167, 151, 136, 135, 77, 69. *Anal.* Calcd for $C_{22}H_{26}O_6$: C, 68,38; H, 6.78. Found: C, 68.08; H, 6.72.

(+)-4——Cyclization of (+)-**3** ($[\alpha]_D^{20}$ +31.6° (*c*=0.950, $CHCl_3$)) afforded (+)-**4** as a pale yellow oil. $[\alpha]_D^{20}$ +37.5° (*c*=0.982, $CHCl_3$). IR, ^{1}H-NMR, MS, and TLC behavior were identical with those for (−)-**4**.

(−)-Podorhizol ((−)-5a) and (−)-Epipodorhizol ((−)-5b)——A solution of (+)-**1**[4c,f] ($[\alpha]_D^{20}$ +5.22° (*c*=1.13, $CHCl_3$)) (110 mg, 0.50 mmol) in THF (3 ml) was added to a solution of lithium diisopropylamide (0.55 mmol) in THF (5 ml) at −78 °C and the mixture was stirred at −78 °C for 25 min. A solution of 3,4,5-trimethoxybenzaldehyde (108 mg, 0.55 mmol) in THF (3 ml) was added, and the whole was stirred at −78 °C for 2 h and quenched with AcOH

(0.5 ml). After dilution with AcOEt (150 ml), the organic solution was washed with 10% aq. HCl, 15% aq. NaOH, and brine, then dried over $MgSO_4$. Concentration *in vacuo* gave a yellow oil (220 mg). Purification by preparative TLC (SiO_2, iso-PrOH–$CHCl_3$ (0.5 : 99.5)) afforded (−)-**5a** (85.9 mg, 42%) (*Rf*: 0.25) and (−)-**5b** (84.1 mg, 41%) (*Rf*: 0.30).

(−)-**5a**: A yellow glass. $[\alpha]_D^{21}$ −51.7° (*c* = 0.944, $CHCl_3$) (lit.,[7]) $[\alpha]_D^{21}$ −51.8° (*c* = 1.046, $CHCl_3$)). IR $\nu_{max}^{CH_2Cl_2}$ cm^{-1}: 3600, 3480, 1760, 1598. ^{1}H-NMR ($CDCl_3$) δ: 2.0—3.0 (4H, m, C$\underline{H}_2$, C$\underline{H}$ × 2), 3.2 (1H, br s, O$\underline{H}$), 3.84 (9H, s, OC$\underline{H}_3$ × 3), 3.8—4.5 (2H, m, C$\underline{H}_2$O), 5.25 (1H, d, *J* = 2 Hz, C$\underline{H}$OH), 5.92 (2H, s, OC$\underline{H}_2$O), 6.24 (1H, s, aromatic H), 6.3—6.8 (4H, m, aromatic H). MS *m/z*: 416 (M^+).

(−)-**5b**: Amorphous powder of mp 49—51 °C (lit.,[7]) 51—53 °C), $[\alpha]_D^{21}$ −32.3° (*c* = 0.600, $CHCl_3$) (lit.,[7]) $[\alpha]_D^{21}$ −32.6° (*c* = 0.628, $CHCl_3$)). IR $\nu_{max}^{CH_2Cl_2}$ cm^{-1}: 3500, 1760, 1598. ^{1}H-NMR ($CDCl_3$) δ: 2.0—2.8 (5H, m, C$\underline{H}_2$, C$\underline{H}$ × 2, O$\underline{H}$), 3.81 (3H, s, OC$\underline{H}_3$), 3.85 (6H, s, OC$\underline{H}_3$ × 2), 4.06 (2H, m, C$\underline{H}_2$O), 4.81 (1H, d, *J* = 6.6 Hz, C$\underline{H}$OH), 5.89 (2H, s, OC$\underline{H}_2$O), 6.0—6.4 (2H, m, aromatic H), 6.4—6.8 (3H, m, aromatic H). MS *m/z*: 416 (M^+).

Spectroscopic data for (−)-**5a**, **b** were identical with those reported.[7] The mixture was directly used for the next step.

(−)-Isodeoxypodophyllotoxin ((−)-6)——A solution of the mixture of **5a** and **5b** (460 mg), obtained from (+)-**1** (220 mg, 1.0 mmol) as above, and *p*-TsOH (30 mg) in xylene (60 ml) was stirred at reflux for 2 h.[8] The whole was washed with satd. aq. $NaHCO_3$ and brine, then dried over $MgSO_4$. Concentration *in vacuo* afforded a brown solid (450 mg). Purification by silica gel column chromatography (ether–$CHCl_3$ (1 : 5)) afforded ( )-**6** (300 mg, 76% from (+)-**1**) as a white solid of mp 250—253 °C (from AcOEt) (lit.,[7] mp 252—254 °C). $[\alpha]_D^{21}$ −80.8° (*c* = 0.624, $CHCl_3$) (lit.,[7]) $[\alpha]_D^{21}$ −84.6° (*c* = 0.614, $CHCl_3$)). IR $\nu_{max}^{CH_2Cl_2}$ cm^{-1}: 1783, 1592. ^{1}H-NMR (d_6-DMSO) δ: 3.68 (3H, s, OC$\underline{H}_3$), 3.74 (6H, s, OC$\underline{H}_3$), 5.90 (2H, s, OC$\underline{H}_2$O), 6.20 (1H, s, aromatic H), 6.50 (2H, s, aromatic H), 6.71 (1H, s, aromatic H). MS *m/z*: 398 (M^+). *Anal.* Calcd for $C_{22}H_{22}O_7$: C, 66.32; H, 5.57. Found: C, 66.02; H, 5.59.

(−)-Anhydropodorhizol ((−)-7)——A solution of *n*-BuLi (0.70 mmol) in *n*-hexane (0.44 ml) was added to a solution of **5a**, **b**, obtained from (+)-**1** (110 mg, 0.50 mmol), in THF (4 ml) and the mixture was stirred at −78 °C for 30 min. A solution of *p*-TsCl (133 mg, 0.70 mmol) in THF (1 ml) was added, and the whole was stirred at room temperature for 2.5 h, then poured into satd. aq. NH_4Cl (10 ml) and extracted with AcOEt (50 ml × 2). The organic solution was washed with 10% HCl, satd. aq. $NaHCO_3$, and brine, then dried over $MgSO_4$. Concentration *in vacuo* gave a yellow oil (270 mg). A solution of the above yellow oil and *tert*-BuOK (78.4 mg, 0.70 mmol) in MeOH (5 ml) was stirred at room temperature for 12 h and poured into 10% aq. HCl (5 ml). The mixture was extracted with AcOEt (50 ml × 2). The combined extracts were washed with satd. aq. $NaHCO_3$, and brine, then dried over $MgSO_4$. Concentration *in vacuo* gave a yellow oil (210 mg). Purification by silica gel column chromatography (ether–$CHCl_3$ (1 : 99)) afforded (−)-**7** (160 mg, 80%) as a pale yellow oil. $[\alpha]_D^{21}$ −54.1° (*c* = 0.54, $CHCl_3$) (lit.,[7]) $[\alpha]_D^{21}$ −55.2° (*c* = 0.598, $CHCl_3$)). IR $\nu_{max}^{CH_2Cl_2}$ cm^{-1}: 1755, 1650, 1587. ^{1}H-NMR ($CDCl_3$) δ: 2.68 (1H, dd, *J* = 10 and 15 Hz, $ArCH_2$), 3.11 (1H, dd, *J* = 5 and 15 Hz, $ArC\underline{H}_2$), 3.92 (9H, s, OC$\underline{H}_3$ × 3), 3.6—4.1 (1H, m, C$\underline{H}$), 4.1—4.5 (2H, m, C$\underline{H}_2$O), 6.00 (2H, s, OC$\underline{H}_2$O), 6.5—6.8 (3H, m, aromatic H), 6.86 (2H, s, aromatic H), 7.60 (1H, d, *J* = 2 Hz, CH). MS *m/z*: 398 (M^+). IR and ^{1}H-NMR data were in good agreement with those reported for (−)-**7**.[7]

(+)-(2*R*,3*S*)-2-(3,4-Methylenedioxybenzyl)-3-(3,4,5-trimethoxybenzyl)-1,4-butanediol ((+)-9)——A mixture of (−)-**7** (240 mg, 0.60 mmol) and 5% Pd–C (100 mg) in AcOH (3 ml) was stirred at room temperature for 12 h under an atmosphere of hydrogen. The mixture was filtered and concentrated to leave a colorless oil. Purification by silica gel column chromatography (ether–$CHCl_3$ (0.5 : 9.5)) gave *cis*-dihydroanhydropodorhizol (**8**) (150 mg, 63%)[7] containing deoxypodorhizon ((−)-**2**) (30% by ^{13}C-NMR (Table I)). A mixture of **8** and (−)-**2** (120 mg, 0.3 mmol), obtained above, in THF (10 ml) was added to a suspension of $LiAlH_4$ (23 mg, 0.6 mmol) in THF (5 ml) and the whole was stirred at room temperature for 1 h. Water (0.02 ml), 15% aq. NaOH (0.02 ml), and water (0.06 ml) were added, then the mixture was filtered. The filtrate was concentrated *in vacuo* to give a colorless glass (110 mg). Purification by silica gel TLC (ether–$CHCl_3$ (4 : 6)) gave (−)-**3** (30 mg, 15%) and (+)-**9** (60 mg, 50%) as a pale yellow oil. $[\alpha]_D^{20}$ +9.65° (*c* = 0.974, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 3300, 1580. ^{1}H-NMR ($CDCl_3$) δ: 1.8—2.4 (2H, m, C$\underline{H}$), 2.5—2.9 (4H, m, $ArC\underline{H}_2$ × 2), 3.2—4.0 (6H, m, C$\underline{H}_2$O$\underline{H}$ × 2), 3.80 (9H, s, OC$\underline{H}_3$ × 3), 5.90 (2H, s, OC$\underline{H}_2$O), 6.40 (2H, s, aromatic H), 6.70 (3H, s, aromatic H). ^{13}C-NMR (Table I). MS *m/z*: 404 (M^+).

(+)-*cis*-Burseran ((+)-10)——A solution of (+)-**9** (90 mg, 0.22 mmol) and *p*-TsCl (45 mg, 0.23 mmol) in pyridine (4 ml) was stirred at −18 °C for 4 h and at room temperature for 1 h, then diluted with a mixture of benzene (50 ml) and $CHCl_3$ (50 ml). The whole was washed with satd. aq. $CuSO_4$, satd. aq. $NaHCO_3$, and brine, then dried over $MgSO_4$. Concentration *in vacuo* gave a yellow oil (80 mg). Purification by silica gel column chromatography (ether–$CHCl_3$ (1 : 9)) afforded (+)-**9** (60 mg, 67% recovery) and (+)-**10** (28 mg, 33%) as a colorless oil. $[\alpha]_D^{20}$ +5.4° (*c* = 0.558, $CHCl_3$). IR ν_{max}^{film} cm^{-1}: 1580. ^{1}H-NMR ($CDCl_3$) δ: 2.4—3.1 (6H, m, $ArC\underline{H}_2C\underline{H}$ × 2), 3.6—4.1 (4H, m, $C\underline{H}_2OC\underline{H}_2$), 3.84 (9H, m, OC$\underline{H}_3$ × 2), 5.91 (2H, s, OC$\underline{H}_2$O), 6.38 (2H, s, aromatic H), 6.68 (3H, s, aromatic H). ^{13}C-NMR (Table I). MS *m/z*: 386 (M^+), 182, 181, 167, 151, 136, 135, 77, 69. *Anal.* Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.18; H, 6.85. IR, ^{1}H-NMR, and MS were indistinguishable from those reported for burseran,[5] but were clearly different from those of (−)-**4**.

Gas Chromatography of *trans*- and *cis*-Burseran ((−)-4 and (+)-10)——The retention times of (−)-**4** and (+)-**10** were 1.5 and 2.2 min, respectively (stainless steel column, 1 m, 15% QF-1 on Diasolid A, 258 °C, carrier gas N_2 1 kg/cm^2).

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9) More information on natural burseran was not available from Drs. J. R. Cole and E. R. Trumbull.
10) Melting points were measured using Büchi 510 melting point apparatus and are not corrected. Optical rotations were taken with a JASCO DIP-181 automatic polarimeter. IR spectra were taken with a JASCO Infrared Spectrometer Model DS-402 G and a JASCO IRA-I Grating Infrared Spectrometer. ^{1}H-NMR spectra were taken with a JNM-PS 100 Spectrometer, with a JEOL FX-100 Spectrometer at 100 MHz, or with a Hitachi R-24 Spectrometer at 60 MHz. ^{13}C-NMR spectra were taken with a JEOL FX-100 Spectrometer at 25 MHz. Chemical shift values are expressed in ppm relative to internal tetramethylsilane. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. MS were taken with a JEOL-01, SG-2 Mass Spectrometer.