Synthesis and Absolute Configuration of (*S*)-(−)- and (*R*)-(+)-2,3-Dihydro-2-(1-methylethenyl)-6-methoxybenzofuran

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Resolution of racemic 2,3-dihydro-2-carboxy-6-methoxybenzofuran (**2**) by recrystallizations of diastereomeric salts prepared with (*S*)-(−)-α-methylbenzylamine and (*R*)-(+)-α-methylbenzylamine gave the starting materials for the four-step total syntheses of (*S*)-(−)-2,3-dihydro-2-(1-methylethenyl)-6-methoxybenzofuran (**1a**) and (*R*)-(+)-2,3-dihydro-2-(1-methylethenyl)-6-methoxybenzofuran (**1b**). Their absolute configuration was established by chemical correlation.

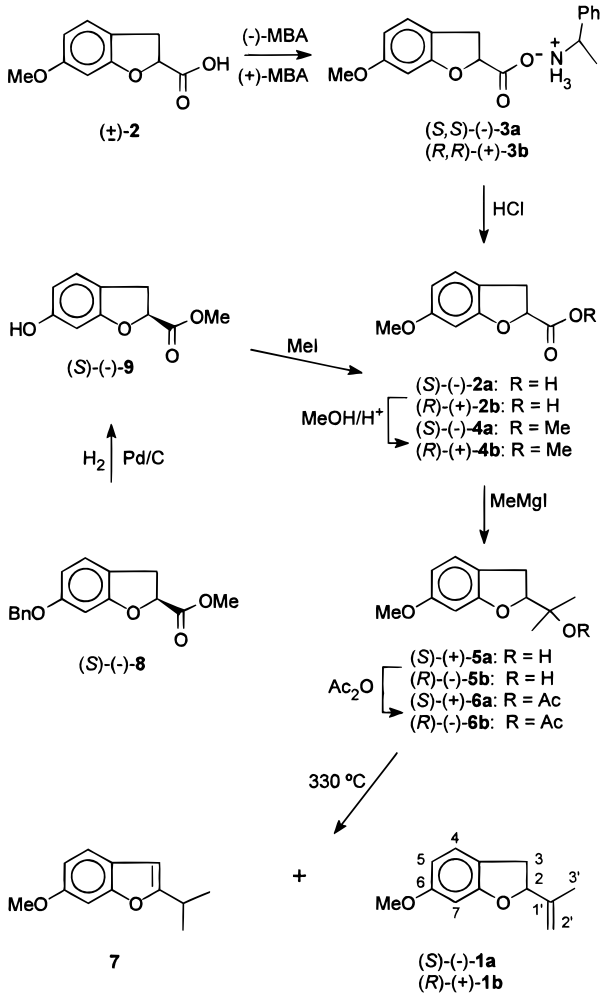
A *Chemical Abstracts* search for (*S*)-(−)-2,3-dihydro-2-(1-methylethenyl)-6-methoxybenzofuran (**1a**) and (*R*)-(+)-2,3-dihydro-2-(1-methylethenyl)-6-methoxybenzofuran (**1b**) revealed that these compounds appear in indexes[1,2] as natural products isolated from *Eupatorium gruppe*[3] and *Eupatorium aschembornianum*,[4] respectively. When one carefully looks at the papers referenced, it becomes clear that the absolute configuration of the (*S*)-(−)-**1a** isomer was suggested tentatively based on analogy to other compounds[5] and that the absolute stereochemistry of the (*R*)-(+)-**1b** isomer derives just from the drawing of the molecule; that is, the authors[4] indicate that their compound is equal to the one published previously[3] but have drawn the reverse stereochemistry. Neither of these papers[3,4] reports optical activity data for either isomer. Therefore, we report here the synthesis and the absolute configuration of both (*S*)-(−)-**1a** and (*R*)-(+)-**1b**.

Results and Discussion

The preparation of (*S*)-(−)-**1a** and (*R*)-(+)-**1b** is shown in Scheme 1 using dihydrobenzofuran **2**[6] as the starting material. This racemic molecule was resolved using the commercially available enantiomers of α-methylbenzylamine (α-MBA). Thus, compound **2** was dissolved in acetone, and one equivalent of (*S*)-(−)-α-MBA was added. The resultant precipitate was recrystallized several times from acetone to give the enantiomerically pure salt (−)-**3a**, mp 164−166 °C and $[\alpha]_D$ −72.6°. The mother liquors were concentrated and treated with hydrochloric acid to afford the acid **2**, which, in turn, was treated with (*R*)-(+)-α-MBA to give the enantiomerically pure salt (+)-**3b**, mp 165−166 °C and $[\alpha]_D$ +73°. Treatment of (−)-**3a** with diluted hydrochloric acid yielded acid (−)-**2a** as an amorphous solid, 122−123 °C and $[\alpha]_D$ −75°, while treatment of (+)-**3b** with diluted hydrochloric acid gave (+)-**2b** with $[\alpha]_D$ +75.5°.

Each acid, (−)-**2a** and (+)-**2b**, was subjected to the following sequence of reactions: Treatment of (−)-**2a**/(+)-**2b** with methanol and *p*-toluenesulfonic acid gave the methyl esters[7] (−)-**4a**/(+)-**4b**, which were treated with methylmagnesium iodide, yielding the tertiary alcohols (+)-**5a**/(−)-**5b**. Acetylation of (+)-**5a**/(−)-**5b** in boiling acetic anhydride afforded the corresponding acetates (+)-**6a**/(−)-**6b** as amorphous solids. Fast pyrolysis[8] of (+)-**6a** at 330 °C for 10 min afforded 2-isopropyl-6-methoxybenzofuran (**7**) and the desired (−)-2,3-dihydro-2-(1-methylethenyl)-6-methoxybenzofuran (**1a**)[9,10] in a 1:8 ratio. When (+)-**6a** was heated for longer periods at 330 °C, compound **7** became the main product. Similarly, treatment of (−)-**6b** under the same conditions gave (+)-**1b** and **7**, also in an 8:1 ratio. Comparison of spectroscopic data of (−)-**1a**

Scheme 1. Synthetic Route for (*S*)-(−)-**1a** and (*R*)-(+)-**1b**



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obtained by us with those reported for the natural product isolated from *E. gruppe*[3] and *E. aschembornianum*[4] revealed that they are identical.

The absolute configuration of (−)-**4a** and (+)-**4b** was established by chemical correlation using the (*S*)-(−)-methyl coumarancarboxylate (**8**) of known configuration,[11] which was debenzylated by catalytic hydrogenolysis[12] in the presence of palladium on charcoal in ethanol to give the phenol (*S*)-(−)-**9**. Treatment of (*S*)-(−)-**9** with iodomethane in acetone and K_2CO_3 afforded (*S*)-(−)-**4a**. Comparison of the spectroscopic and optical activity data of (*S*)-(−)-**4a** obtained from methyl ester (*S*)-(−)-**8** with that prepared from salt (−)-**3a** revealed that they are identical. Therefore, the series of compounds prepared from salt (−)-**3a** have the *S* absolute configuration, while those prepared from (+)-**3b** are *R*.

The two protons at C-3 were stereochemically assigned after generating minimum energy structures using MMX force-field calculations as implemented in the PCMODEL program[13] V4.00. The obtained dihedral angles for the dihydrofuran ring protons were used to estimate vicinal coupling constants using Karplus-type calculations by means of a computer program we developed almost a decade ago.[14] The agreement between experimental and estimated values allowed individual assignment of H-3α and H-3*β* for **2a**, **4a**, **6a**, and **9**. In these four cases H-3*β* has a large coupling constant due to the trans orientation of H-2 and H-3*β*, in which H-3α has a smaller coupling constant due to the cis orientation of H-2 and H-3α. Because, in the latter four cases, H-3*β* appears at higher fields than H-3α, we assigned by chemical-shift analogy the two protons at C-3 in **1a**, where $J_{2,3\alpha} = J_{2,3\beta} = 8.8$ Hz. Finally, in the case of **5a**, instead of the ABX spin−spin system[15] shown in all previously discussed ^{1}H NMR spectra, the dihydrofuran protons appear as an AX_2 system,[15] characterized by chemical shifts and a single vicinal coupling constant, due to chemical shift coincidence of H-3α and H-3*β*. To gain evidence supporting a similar conformation of the five-membered 2,3-dihydrofuran ring in **5a**, the ^{1}H NMR spectrum was determined in benzene-d_6, where it gave an ABX system, the pertinent data being in the Experimental Section.

Experimental Section

General Experimental Procedures. Organic layers were dried using anhydrous Na_2SO_4. Columns for chromatographic separations were packed with Merck Si gel 60 (230−400 mesh ASTM). Melting points were measured on a Melt-Temp II and are uncorrected. Specific rotations $[\alpha]_D$ were measured at the sodium-D line using a Perkin−Elmer 241 polarimeter at 25 °C. The concentration, *c*, given after specific rotations is indicated in g/100 mL. IR spectra were recorded on a Perkin−Elmer 16F PC FT−IR spectrophotometer. UV spectra were recorded on a Perkin−Elmer Lambda 2S spectrometer. ^{1}H and ^{13}C NMR measurements were performed on a Varian XL-300GS spectrometer using $CDCl_3$ solutions containing TMS as internal standard. MS were obtained on a Hewlett−Packard 598A spectrometer at 20 eV. The ^{1}H, ^{13}C NMR, UV, IR, and MS data for the **b** series are not described herein; they are identical to those of the **a** series.

(*S*)-(−)-Methylbenzylammonium (*S*)-2,3-Dihydro-6-methoxybenzofuran-2-carboxylate (3a). To a stirred solution of **2**[6] (10 g, 51.6 mmol) in Me_2CO (40 mL) was added 6.7 mL (51.6 mmol) of (*S*)-(−)-α-MBA and further stirred for 1 min. The white crystalline precipitate formed was filtered and washed with Me_2CO. Six recrystallizations from Me_2CO gave 5 g of the homogeneous salt (*S*)-(−)-**3a** as a white cotton-like material, mp 164−166 °C; $[\alpha]_D$ −72.6° (*c* 2.3, MeOH).

(*R*)-(+)-Methylbenzylammonium (*R*)-2,3-Dihydro-6-methoxybenzofuran-2-carboxylate (3b). The mother liquors remaining from the above recrystallizations were concentrated, treated with 12 mL of 5 N HCl and extracted with EtOAc. The organic layer was washed with H_2O, dried, and concentrated under vacuum to give a brown solid that was dissolved in CH_2Cl_2 and treated with activated carbon. After filtration of the charcoal and evaporation of the filtrate, a white solid was obtained, which was dissolved in Me_2CO, and 1 equiv of (*R*)-(+)-α-MBA was added, as in the previous case. The white crystalline precipitate formed was filtered, washed with Me_2CO, and, after four recrystallizations from Me_2CO, gave 5 g of (*R*)-(+)-**3b** as a white cotton-like material, mp 165−166 °C; $[\alpha]_D$ +73° (*c* 3.0, MeOH).

(*S*)-(−)-2,3-Dihydro-2-carboxy-6-methoxybenzofuran (2a). A vigorously stirred mixture of the salt (−)-**3a** (5 g), H_2O (50 mL), and EtOAc (50 mL) was cooled in an ice-H_2O bath and acidified dropwise with 5.3 mL of 5 N HCl over a period of 10 min. The separated organic layer was washed with H_2O, dried, and evaporated under vacuum to afford (*S*)-(−)-**2a** (3 g) as a white amorphous solid: mp 122−123 °C; $[\alpha]_D$ −75° (*c* 0.92, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 201 (1.64), 286 (0.66) nm; IR (KBr) ν_{max} 3502, 1710, 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 10.55 (1H, s, COOH), 7.03 (1H, d, J = 8.2 Hz, H-4), 6.50 (1H, d, J = 2.3 Hz, H-7), 6.45 (1H, dd, J = 8.2, 2.3 Hz, H-5), 5.23 (1H, dd, J = 10.8, 6.4 Hz, H-2), 3.75 (3H, s, OCH_3), 3.53 (1H, dd, J = 15.5, 10.8 Hz, H-3*β*), 3.31 (1H, dd, J = 15.5, 6.4 Hz, H-3α); ^{13}C NMR ($CDCl_3$, 74.5 MHz) δ 176.72 (s, C-1′), 160.54 (s, C-6), 159.98 (s, C-7a), 124.66 (d, C-4), 116.08 (s, C-3a), 107.30 (d, C-5), 96.47 (d, C-7), 79.09 (d, C-2), 55.50 (q, OCH_3), 33.24 (t, C-3); EIMS *m*/*z* 194 $[M]^+$ (98), 176 (38), 148 (100), 133 (34).

(*R*)-(+)-2,3-Dihydro-2-carboxy-6-methoxybenzofuran (2b). Using the previous procedure, acidification of 5 g of salt (+)-**3b** gave (*R*)-(+)-**2b** (2.9 g) as a white amorphous solid: mp 121−122 °C; $[\alpha]_D$ +75.5° (*c* 2.9, $CHCl_3$).

(*S*)-(−)-2,3-Dihydro-2-carboxymethyl-6-methoxybenzofuran (4a). A solution of (*S*)-(−)-**2a** (3 g, 15.5 mmol) and *p*-toluenesulfonic acid (100 mg) in 30 mL of anhydrous MeOH was refluxed for 3 h. The solution was concentrated to a small volume under vacuum and extracted with EtOAc. The organic layer was washed with 10% aqueous K_2CO_3 (2 × 30 mL) and H_2O and dried. Evaporation of the solvent under reduced pressure yielded (*S*)-(−)-**4a** (3.04 g, 95%) as a colorless oil: bp 90 °C/0.04 mmHg; $[\alpha]_D$ −52.2° (*c* 4.4, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 202 (1.50), 286 (0.68) nm; IR (dry film) ν_{max} 1742, 1148 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.03 (1H, d, J = 8.2 Hz, H-4), 6.50 (1H, d, J = 2.3 Hz, H-7), 6.44 (1H, dd, J = 8.2, 2.3 Hz, H-5), 5.22 (1H, dd, J = 10.5, 6.8 Hz, H-2), 3.80 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.49 (1H, dd, J = 15.4, 10.5 Hz, H-3*β*), 3.30 (1H, dd, J = 15.4, 6.8 Hz, H-3α); ^{13}C NMR ($CDCl_3$, 74.5 MHz) δ 171.66 (s, C-1′), 160.61 (s, C-6), 160.30 (s, C-7a), 124.66 (d, C-4), 116.48 (s, C-3a), 107.05 (d, C-5), 96.50 (d, C-7), 79.84 (d, C-2), 55.53 (q, OCH_3), 52.54 (q, OCH_3), 33.24 (t, C-3); EIMS *m*/*s* 208 $[M]^+$ (100), 176 (81), 148 (99), 121 (68).

(*R*)-(+)-2,3-Dihydro-2-carboxymethyl-6-methoxybenzofuran (4b). The ester (*R*)-(+)-**4b** (2.95 g, 95%) was obtained from (*R*)-(+)-**2b**, using the previous procedure, as a colorless oil; bp 92 °C/0.04 mmHg, $[\alpha]_D$ +52.6° (*c* 2.5, $CHCl_3$).

(*S*)-(+)-2,3-Dihydro-2-(2-hydroxyisopropyl)-6-methoxybenzofuran (5a). A solution of (*S*)-(−)-**4a** (3.0 g, 14.4 mmol) in 20 mL of dry Et_2O was added dropwise to a solution of methylmagnesium iodide, prepared from iodomethane (4.5 mL, 72.3 mmol) and magnesium turnings (1.4 g, 57.6 mmol) in dry Et_2O (20 mL), at room temperature under a nitrogen atmosphere. After stirring for 12 h at room temperature, the mixture was quenched with a saturated NH_4Cl solution. The reaction was extracted with Et_2O (2 × 50 mL), the combined organic layer was washed with H_2O, dried, and concentrated. The residue was purified by column chromatography eluting with hexane−EtOAc (98:2) to afford (*S*)-(+)-**5a** (2.1 g, 70%) as a colorless oil: bp 106 °C/0.04 mmHg; $[\alpha]_D$ +33.5° (*c* 5.1, $CHCl_3$); UV (EtOH) λ_{rnax} (log ϵ) 202 (1.58) nm; IR (dry film) ν_{max} 3582 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.01 (1H, d, J = 8.8 Hz, H-4), 6.38 (1H, d, J = 2.3 Hz, H-7), 6.38 (1H, dd, J = 8.8, 2.3 Hz, H-5), 4.60 (1H, t, J = 9.0 Hz, H-2), 3.74 (3H, s, OCH_3), 3.06 (2H, d, J = 9.0 Hz, CH_2-3), 2.17 (1H, s, OH), 1.31

(3H, s, CH_3-2′), 1.19 (3H, s, CH_3-3′); ^{1}H NMR (C_6D_6, 300 MHz) δ 6.87 (1H, d, J = 8.1 Hz, H-4), 6.55 (1H, d, J = 2.3 Hz, H-7), 6.43 (1H, dd, J = 8.1, 2.3 Hz, H-5), 4.33 (1H, t, J = 9.0 Hz, H-2), 3.34 (3H, s, OCH_3), 2.94 (1H, dd, J = 15.1, 9.0 Hz, H-3β), 2.64 (1H, dd, J = 15.1, 9.0 Hz, H-3α), 2.04 (1H, s, OH), 1.16 (3H, s, CH_3-2′), 1.02 (3H, s, CH_3-3′); ^{13}C NMR ($CDCl_3$, 74.5 MHz) δ 160.64 (s, C-6), 160.10 (s, C-7a), 124.68 (d, C-4), 118.90 (s, C-3a), 105.86 (d, C-5), 95.92 (d, C-7), 90.15 (d, C-2), 71.71 (s, C-1′), 55.35 (q, OCH_3), 29.94 (t, C-3), 25.89 (q, C-2′), 23.90 (q, C-3′); EIMS m/z 208 $[M]^+$ (82), 149 (98), 148 (11), 59 (50).

(*R*)-(−)-2,3-Dihydro-2-(2-hydroxyisopropyl)-6-methoxybenzofuran (5b). Using the previous procedure, the Grignard reaction with the ester (*R*)-(+)-**4b** (2.9 g) gave carbinol (*R*)-(−)-**5b** (2.03 g, 70%) as a colorless oil: $[\alpha]_D$ −33° (*c* 2.8; $CHCl_3$).

(*S*)-(+)-2,3-Dihydro-2-(2-acetoxyisopropyl)-6-methoxybenzofuran (6a). A solution of (*S*)-(+)-**5a** (2 g, 9.6 mmol) in 5 mL of Ac_2O was heated under reflux for 2 h. The solution was poured over ice and extracted with Et_2O. The organic layer was washed with 2% aqueous NaOH (2 × 50 mL) and H_2O, dried, and evaporated. The residue was chromatographed, eluting with hexane−EtOAc (99:1), to yield (*S*)-(+)-**6a** (1.92 g, 80%) as an amorphous solid: mp 88−90 °C; $[\alpha]_D$ +42.8° (*c* 1.5, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 202 (1.71), 287 (0.81) nm; IR (KBr) ν_{max} 1732, 1198 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.01 (1H, d, J = 8.8 Hz, H-4), 6.39 (1H, d, J = 2.5 Hz, H-7), 6.39 (1H, dd, J = 8.8, 2.5 Hz, H-5), 4.98 (1H, dd, J = 9.6, 8.1 Hz, H-2), 3.75 (3H, s, OCH_3), 3.13 (1H, dd, J = 15.5, 9.6 Hz, H-3β), 3.03 (1H, dd, J = 15.5, 8.1 Hz, H-3α), 1.99 (3H, s, $COCH_3$), 1.55 (3H, s, CH_3-2′), 1.49 (3H, s, CH_3-3′); ^{13}C NMR ($CDCl_3$, 74.5 MHz) δ 170.23 (s, $COCH_3$), 160.94 (s, C-6), 160.29 (s, C-7a), 124.54 (d, C-4), 118.23 (s, C-3a), 105.94 (d, C-5), 95.89 (d, C-7), 87.48 (d, C-2), 82.56 (s, C-1′), 55.39 (q, OCH_3), 30.07 (t, C-3), 22.27 (q, $COCH_3$), 21.88 (q, C-2′), 20.88 (q, C-3′); EIMS m/z 250 $[M]^+$ (10), 175 (100), 149 (7), 43 (8).

(*R*)-(−)-2,3-Dihydro-2-(2-acetoxyisopropyl)-6-methoxybenzofuran (6b). Using the previous procedure, the acetylation of (*R*)-(−)-**5b** (2.5 g, 12 mmol) gave (*R*)-(−)-**6b** (2.34 g, 78%) as a white amorphous solid: mp 88−90 °C; $[\alpha]_D$ −42.5° (*c* 1.3, $CHCl_3$).

(*S*)-(−)-2,3-Dihydro-2-(1-methylethenyl)-6-methoxybenzofuran (1a) and 6-Methoxy-2-isopropylbenzofuran (7). A sample of (*S*)-(+)-**6a** (1.5 g, 6 mmol) was heated in a muffle furnace at 330 °C for 10 min. The evolution of HOAc began at about 280 °C. The residue was allowed to cool to room temperature, dissolved in Et_2O, washed with 5% aqueous $NaHCO_3$ and H_2O, dried, and evaporated. The residue was purified by flash column chromatography eluting with petroleum ether−EtOAc (98:2) to give (*S*)-(−)-**1a** (800 mg, 70%, R_f 0.45, hexane−EtOAc 95:5) and **7** (100 mg, 8.2%, R_f 0.54.).

Olefin (*S*)-(−)-1a: colorless oil; $[\alpha]_D$ −5.8° (*c* 2.0, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 202 (4.27), 248 (3.97), 255 (3.95), 290 (3.68) nm; IR (dry film) ν_{max} 1654 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.01 (1H, dd, J = 7.7, 1.2 Hz, H-4), 6.40 (1H, d, J = 2.2 Hz, H-7), 6.38 (1H, dd, J = 7.7, 2.2 Hz, H-5), 5.17 (1H, t, J = 8.8 Hz, H-2), 5.07 (1H, m, H-2′a), 4.89 (1H, m, H-2′b), 3.75 (3H, s, OCH_3), 3.26 (1H, dd, J = 15.1, 8.8 Hz, H-3β), 2.95 (1H, ddd, J = 15.1, 8.8, 1.2 Hz, H-3α), 1.75 (3H, t, J = 1.3 Hz, CH_3-3′); ^{13}C NMR ($CDCl_3$, 74.5 MHz) δ 161.00 (s, C-6), 160.39 (s, C-7a), 144.09 (s, C-1′), 124.68 (d, C-4), 118.50 (s, C-3a), 111.87 (t, C-2′), 105.85 (d, C-5), 96.03 (d, C-7), 86.63 (d, C-2), 55.48 (q, OCH_3), 34.10 (t, C-3), 17.19 (q, C-3′); EIMS m/z 190 $[M]^+$ (85), 175 (100), 160 (17), 41 (4).

Benzofurane 7: colorless oil; UV (EtOH) λ_{max} (log ϵ) 202 (4.27), 248 (3.97) 255 (3.95), 290 (3.68) nm; IR (dry film) ν_{max} 2964, 1490, 1030, 820, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 (1H, d, J = 8.5 Hz, H-4), 6.96 (1H, d, J = 2.3 Hz, H-7), 6.80 (1H, dd, J = 8.5, 2.3 Hz, H-5), 6.23 (1H, t, J = 1.0 Hz, H-3), 3.78 (3H, s, OCH_3), 3.01 (1H, dh, J = 6.9, 1.0 Hz, H-1′), 1.30 (6H, d, J = 6.9 Hz, CH_3-2′ and CH_3-3′); ^{13}C NMR ($CDCl_3$, 74.5 MHz) δ 163.96 (s, C-2), 157.23 (s, C-6), 155.49 (s, C-7a), 122.18 (s, C-3a), 120.27 (d, C-4), 111.01 (d, C-5), 99.34 (d, C-3), 95.88 (d, C-7), 55.63 (q, OCH_3), 28.20 (d, C-1′), 20.96 (q, C-2′ and C-3′); EIMS m/z 190 $[M]^+$ (48), 175 (100), 160 (7), 132 (8), 43 (28).

(*R*)-(+)-2,3-Dihydro-2-(1-methylethenyl)-6-methoxybenzofuran (1b). The olefin (*R*)-(+)-**1b** was prepared from (*R*)-(−)-**6b** (2 g, 8.0 mmol) in the same way as described above, giving (*R*)-(+)-**1b** (1.03 g, 68%) as a colorless oil: $[\alpha]_D$ +5.4° (*c* 2.2, $CHCl_3$).

(*S*)-(−)-2,3-Dihydro-2-carboxymethyl-6-hydroxybenzofuran (9). A mixture of 100 mg of prehydrogenated 5% palladium on charcoal catalyst in EtOH and 1 g of the ester (*S*)-(−)-**8**,[11] $[\alpha]_D$ −53° (*c* 2.5, $CHCl_3$), dissolved in EtOH, was shaken in a hydrogen atmosphere over 15 h. The catalyst was filtered off and the EtOH evaporated under vacuum to give (*S*)-(−)-**9** (531 mg, 80%) as an amorphous solid: mp 125−127 °C; $[\alpha]_D$ −44° (*c* 1.9, $CHCl_3$); UV (EtOH) λ_{max} (log ϵ) 221 (4.42), 289 (4.16) nm; IR (KBr) ν_{max} 3376, 1742, 1244, 1142 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.97 (1H, d, J = 8.0 Hz, H-4), 6.48 (1H, d, J = 2.2 Hz, H-7), 6.37 (1H, dd, J = 8.0, 2.2 Hz, H-5), 5.70 (1H, s, OH), 5.22 (1H, dd, J = 10.5, 6.7 Hz, H-2), 3.81 (3H, s, $COOCH_3$), 3.49 (1H, dd, J = 15.4, 10.5 Hz, H-3β), 3.27 (1H, dd, J = 15.4, 6.7 Hz, H-3α); ^{13}C NMR ($CDCl_3$, 74.5 MHz) δ 172.12 (s, C-1′), 160.15 (s, C-6), 156.57 (s, C-7a), 124.83 (d, C-4), 116.30 (s, C-3a), 108.24 (d, C-5), 98.18 (d, C-7), 79.76 (d, C-2), 52.69 (q, $COOCH_3$), 33.27 (t, C-3); EIMS m/z 194 $[M]^+$ (68), 162 (45), 134 (100), 107 (100), 77 (20).

(*S*)-(−)-2,3-Dihydro-2-carboxymethyl-6-methoxybenzofuran (4a). A mixture of K_2CO_3 (712 mg, 5.16,mmol), (*S*)-(−)-**9** (500 mg, 2.58 mmol) and iodomethane (0.16 mL, 2.58 mmol) in anhydrous Me_2CO (30 mL) was refluxed for 3 h. The reaction mixture was concentrated to a small volume under vacuum, extracted with Et_2O, washed with H_2O, dried, and evaporated. The residue was purified by column chromatography eluting with hexane−EtOAc (98:2) to afford (*S*)-(−)-**4a** (429 mg, 80%) as a colorless oil, $[\alpha]_D$ −51.6° (*c* 2.0, $CHCl_3$), identical by IR, ^{1}H NMR, and ^{13}C NMR comparison to a sample obtained as described above.

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References and Notes

(1) (a) Formula Index, A−C_{15}, *Chem. Abstr.* **1978**, *88*, 849F, left column, ninth line from bottom. (b) Tenth Collective Index, Formula $C_{11}H_{12}O_5$−$C_{13}H_{16}FN_5$, *Chem. Abstr.* **1977**−**1981**, *86*−*95*, 6195F, left column, 12th line from bottom.

(2) (a) Formula Index, A−C_{15}, *Chem. Abstr.* **1983**, *98*, 985F, left column, 33rd line from bottom. (b) Eleventh Collective Index, Formula $C_{10}H_{13}NOS$−$C_{12}H_{15}NO_5V$, *Chem. Abstr.* **1982**−**1986**, *96*−*105*, 6950F, central column, 11th line from bottom.

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