Reaction of Benzenesulfenyl Chloride with Ethylene Glycol. To the stirred solution of benzenesulfenyl chloride (7.25 g, 0.05 mol) in tetrahydrofuran (50 mL) at −40 °C was added ethylene glycol (1.55 g, 0.025 mol) and triethylamine (5.02 g, 0.05 mol). The reaction mixture was allowed to warm to room temperature, and it was stirred for an additional 2 h. The solid was removed by filtration, and the filtrate was concentrated at reduced pressure. The residual oil was molecularly distilled [T_{block} = 70 °C (0.25 mm)] to yield **14**. Anal. Calcd for $C_{14}H_{14}O_2S_2$: C, 60.43; H, 5.03. Found: C, 60.81; H, 4.85.

Preparation of 16. To a stirred solution of 1,1,1,3,3,3-hexafluoro-2-propanol (2.69 g, 0.016 mol) and triethylamine (1.62 g, 0.016 mol) in pentane (25 mL) at −30 °C was added benzenesulfenyl chloride (2.31 g, 0.016 mol). The reaction mixture was allowed to warm to room temperature, and it was then stirred for an additional 1 h. The solid was removed by filtration. To the filtrate at −75 °C was added **13** (1.032 g, 0.004 mol) in pentane (10 mL). The reaction mixture was allowed to warm to room temperature, and it was stirred for an additional 1 h. The mixture was cooled to −20 °C, and it was filtered. The filtrate was concentrated at reduced pressure, and the residual oil was molecularly distilled [T_{block} = 50° (0.01 mm)] to yield 1.0 g (42%) of product **16**.

Preparation of 15. To a stirred solution of 1,2-ethanediyl bis[benzenesulfenate] (**14**; 2.17 g, 0.0078 mol) in pentane (20 mL) and tetrahydrofuran (5 mL) at −70 °C was added **13** (2.01 g, 0.0078 mol). The reaction mixture was allowed to warm to room temperature and it was stirred for an additional 1 h. The reaction mixture was concentrated at reduced pressure and the residual solid was sublimed (50 °C, 0.05 mm).

Reaction of 6 with Potassium 1,1,1,3,3,3-Hexafluoroisopropoxide. To a stirred solution of **6** (0.7 g, 0.001 mol) in toluene (1 mL), at 10 °C was added a solution of potassium 1,1,1,3,3,3-hexafluoroisopropoxide (0.4 g, 0.002 mol) and 18-crown-6 ether (0.53 g, 0.002 mol) in toluene (1 mL). The reaction mixture was allowed to warm to room temperature. The ^{31}P NMR spectrum of this solution showed only one absorption at δ 27.5 (external lock).

Reaction of 15 with Potassium 1,1,1,3,3,3-Hexafluoroisopropoxide. To a stirred solution of **15** (0.25 g, 0.0008 mol) in benzene-d_6 was added potassium 1,1,1,3,3,3-hexafluoroisopropoxide (0.32 g, 0.0016 mol) and 18-crown-6 ether (0.42 g, 0.0016 mol) in benzene-d_6 (2 mL). After the mixture was stirred at room temperature for 30 min, the ^{31}P NMR spectrum of the reaction mixture showed resonances at δ −86.7, −1.5, −1.0, −0.9, −0.2 (C_6D_6).

Reaction of 16 with Potassium 1,1,1,3,3,3-Hexafluoroisopropoxide. To a stirred solution of **16** (1.0 g, 0.0017 mol) at 10 °C were added potassium 1,1,1,3,3,3-hexafluoroisopropoxide (0.7 g, 0.0034 mol) and 18-crown-6 ether (0.89 g, 0.0034 mol) in benzene-d_6 (1.5 mL). The reaction mixture was allowed to warm to room temperature. The ^{31}P NMR spectrum of the reaction mixture showed two absorptions at δ −109.5 and 0.8 (C_6D_6).

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Registry No. **2**, 66489-70-1; **4**, 69128-00-3; **6**, 85762-85-2; **7**, 85762-86-3; **8**, 66470-81-3; **9**, 85762-87-4; **10**, 67091-88-7; **11**, 53772-43-3; **12**, 603-35-0; **13**, 85762-88-5; **14**, 6099-21-4; **15**, 85762-89-6; **16**, 85762-90-9; **19**, 66559-58-8; 1,1,1,3,3,3-hexafluoro-2-propanol, 920-66-1; benzenesulfenyl chloride, 931-59-9; diphenylphosphinous chloride, 1079-66-9; diphenyl disulfide, 882-33-7; triphenylphosphine oxide, 791-28-6; phosphorous trichloride, 7719-12-2; phenylphosphonous dichloride, 644-97-3; ethylene glycol, 107-21-1; potassium 1,1,1,3,3,3-hexafluoroisopropoxide, 85762-91-0.

Riccardin A and Riccardin B, Two Novel Cyclic Bis(bibenzyls) Possessing Cytotoxicity from the Liverwort *Riccardia multifida* (L.) S. Gray

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Riccardin A (**1**) and riccardin B (**4a**), two novel cyclic bis(bibenzyls) possessing cytotoxic activity, were isolated from the liverwort *Riccardia multifida* (L.) S. Gray together with 6-(3-methyl-2-butenyl)indole (**9**). Proof for the proposed structure and definite evidence for the stereochemistry of **1** were provided by X-ray analysis of the acetate of **1**. The structure of **4a** was suggested by the analysis of 400-MHz ^1H NMR spectral data.

Some liverworts contain potent allergenic, cytotoxic, and antifeedant sesquiterpenoids.[1] On the other hand, various prenylbibenzyls[2,3] and prenyl benzoates[4] have been isolated from a few liverworts belonging to the Jungermanniales. In our continuing search of biologically active substances of the liverworts, we investigated the chemical constituents of *Riccardia multifida* (L.) S. Gray, belonging to the Metzgeriales, and isolated two structurally unique cyclic bis(bibenzyl) derivatives, named riccardin A (**1**) and B (**4a**) (Chart I), which possessed cytotoxic activity vs. KB cells.

Silica gel chromatography of the ether extract of the ground material resulted in the isolation of **1** (8% of the total extract) and **4a** (7%), together with the previously known 6-(3-methyl-2-butenyl) indole (**9**, 8%).[5]

(1) Asakawa, Y. *J. Hattori Bot. Lab.* **1981**, *60*, 123.
(2) Asakawa, Y.; Toyota, M.; Takemoto, T. *Phytochemistry* **1978**, *17*, 2005.
(3) Asakawa, Y.; Kusube, E.; Takemoto, T.; Suire, C. *Phytochemistry* **1978**, *17*, 2115.
(4) Asakawa, Y.; Toyota, M.; Takemoto, T.; Mues, R. *Phytochemistry* **1981**, *20*, 2695.
(5) Benesova, V.; Samek, Z.; Herout, V.; Sorm, F. *Collect. Czech. Chem. Commun.* **1969**, *34*, 582.

0022-3263/83/1948-2164$01.50/0

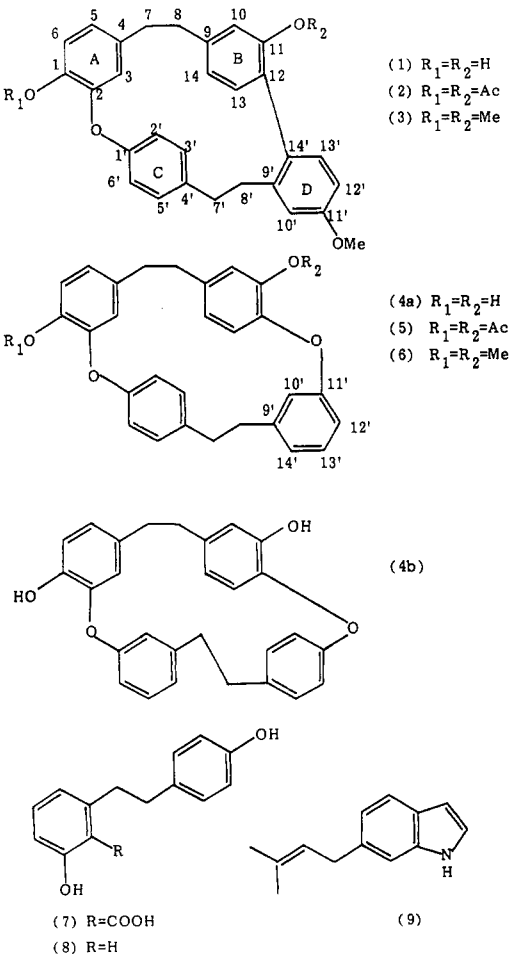
Table I. ^{1}H NMR Spectral Data[a] (400 MHz) of Riccardin A (1) and Riccardin B (4a) and Their Methyl Ethers (3 and 6)

	1	3	4a	6
H-3	5.33 (d, J = 1.9)	5.36 (d, J = 2.2)	6.02 (d, J = 2.1)	6.02 (d, J = 2.1)
H-5	6.69 (dd, J = 8.1, 1.9)	6.77 (dd, J = 8.1, 2.2)	6.90 (dd, J = 8.3, 2.1)	7.00 (dd, J = 9.3, 2.1)
H-6	6.88 (d, J = 8.1)	6.87 (d, J = 8.1)[c]	6.95 (d, J = 8.3)	6.94 (d, J = 8.3)[c]
H-7	2.60 (m)	2.84 (m)	2.70 (s)	2.77 (s)
H-8	2.70 (m)	2.61 (m)	2.70 (s)	2.77 (s)
H-10	6.36 (d, J = 1.5)	6.43 (d, J = 1.5)[c]	6.67 (d, J = 1.9)	6.66 (d, J = 1.2)[c]
H-13	6.75 (d, J = 7.7)	6.82 (d, J = 7.7)	6.17 (d, J = 8.3)	6.17 (d, J = 8.0)
H-14	6.18 (dd, J = 7.7, 1.5)	6.23 (dd, J = 7.7, 1.5)	5.98 (dd, J = 8.3, 1.9)	5.99 (dd, J = 8.0, 1.9)
H-2′	6.70 (br)[b]	6.67 (br d, J = 8.6)	6.63 (d, J = 8.6)	6.59 (d, J = 8.6)
H-3′	6.83 (br)[b]	6.73 (br d)[b]	6.70 (d, J = 8.6)	6.71 (d, J = 8.6)
H-5′	6.75 (br)[b]	6.88 (br d)[b]	6.70 (d, J = 8.6)	6.71 (d, J = 8.6)
H-6′	6.70 (br)[b]	6.73 (br d)[b]	6.63 (d, J = 8.6)	6.59 (d, J = 8.6)
H-7′	2.88 (m)	2.84 (m), 2.92 (m)	2.78 (m)	2.80 (br s)
H-8′	2.65 (m), 3.04 (m)	2.62 (m), 3.09 (m)	2.78 (m)	2.80 (br s)
H-10′	6.98 (d, J = 2.9)	6.96 (d, J = 2.9)[c]	6.03 (dd, J = 2.4, 2.4)	5.98 (dd, J = 2., 2.4)
H-12′	6.82 (dd, J = 8.5, 2.9)	6.81 (dd, J = 8.5, 2.9)[c]	6.93 (ddd, J = 7.8, 2.4, 0.8)	6.95 (ddd, J = 8.0, 2.4, 1.1)
H-13′	7.05 (d, J = 8.5)	7.05 (d, J = 8.5)	7.32 (dd, J = 7.8, 7.8)	7.31 (dd, J = 8.0, 8.0)
H-14′			7.06 (ddd, J = 7.8, 2.4, 0.8)	7.04 (ddd, J = 8.0, 2.4, 1.1)
Ar-OH	5.35 (s, C_{11}OH), 5.98 (s, C_1OH)		5.64 (s, C_{11}OH), 5.77 (s, C_1OH)	
Ar-OMe	3.82 (s, C_{11}OMe)	3.65 (s, C_{11}OMe), 3.86 (s, C_{11}OMe), 3.92 (s, C_1OMe)		3.77 (s, C_1OMe), 3.85 (s, C_{11}OMe)

[a] All assignments were performed by double-resonance experiments. The chemical shifts are given as δ values, and the J values are in hertz. [b] Overlapped signals. [c] A 15% NOE was observed between each proton and each OMe group. [d] No data were obtained for H-11′.

The compound 1 was shown to possess the molecular formula $C_{29}H_{26}O_4$ (high-resolution electron-impact mass spectrum, m/e 438.1831). The infrared and ultraviolet spectra showed the presence of a hydroxyl group (3400 cm^{-1}) and an aromatic ring [1605, 1560 and 1500 cm^{-1}; 283 nm (log ϵ 3.90)]. The ^{1}H NMR spectrum (Table I) of 1 contained four benzylic methylenes, a methoxyl group, two broad singlet signals at δ 5.35 and 5.98 which disappeared on addition of D_2O, due to two phenolic hydroxyl groups, three meta coupled protons (H-3, H-10, and H-10′), one of which was heavily shielded, three sets of ortho protons in which three protons (H-5, H-14, and H-12′) were coupled with meta protons (H-3, H-10, and H-10′), and an additional two sets of ortho protons (H-2′, H-3′, H-5′, and H-6′). The presence of two phenolic hydroxyl groups was also confirmed as follows. Acetylation of 1 with acetic anhydride in pyridine gave a diacetate (2): mp 203–204 °C; $C_{33}H_{30}O_6$; mass spectrum, m/e 522 (M$^+$); IR 1770, and 1270 cm^{-1}; ^{1}H NMR δ 1.96 and 2.29 (each s, 3 H). Methylation of 1 with methyl iodide in acetone gave riccardin A trimethyl ether (3): $C_{31}H_{30}O_4$; mass spectrum, m/e 466 (M$^+$); ^{1}H NMR δ 3.65, 3.86 and 3.92 (each s, 3 H). In the infrared spectrum of 3, the absorption bands of carbonyl and hydroxyl groups could not be observed, indicating the additional oxygen atom of 1 to be an ether. The above spectral and chemical evidence coupled with the molecular formula indicated that 1 was a cyclic bis(bibenzyl) derivative with two phenolic hydroxyl groups, one methoxyl group, a biphenyl ether and a biphenyl linkage. The arrangement of the substituents of four benzene rings was suggested by the NOE and double-resonance experiments of 3. A 15% NOE was observed between C_1 OMe and H-6, between C_{11}OMe and H-10, and between $C_{11'}$OMe and H-10′ and H-12′. The long-range coupling was also observed between a benzylic methylene (H-7) and H-3 and H-5, between a benzylic methylene (H-8) and H-10 and H-14, between a benzylic methylene (H-7′) and H-3′ and H-5′, and between a benzylic methylene (H-8′) and H-10′, respectively. Since the interpretation of the complex ^{1}H NMR spectral data could not be accommodated by any known naturally occurring phenolic compounds, the acetate 2 was subjected to single-crystal X-ray diffraction analysis which led to the stereostructure of 1.

Chart I



Crystals of 2 were triclinic, space group $P\bar{1}$, with a = 8.711 (3) Å, b = 12.905 (7) Å, c = 12.903 (5) Å, α = 95.05 (4)°, β = 107.03 (3)°, γ = 86.35 (4)°, and d_x = 1.26 g cm^{-3}

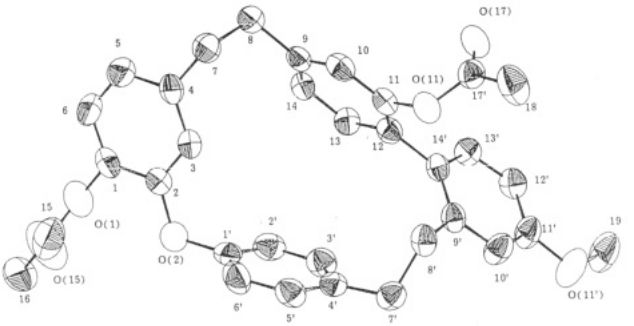


Figure 1. Stereoscopic view of riccardin A diacetate (**2**).

for $Z = 2$. The diffraction intensities were collected in the ω scan by using graphite-monochromated Mo Kα radiation on a Syntex R3 diffractometer, and data were corrected for Lorentz, polarization, and background effects. The structure was solved by direct methods with the MULTAN program[6] and refined by full-matrix least-squares methods with anisotropic temperature factors. The final value is 0.067 for 3379 refrections. Tables of final atomic and anisotropic thermal parameters for nonhydrogen atoms, bond distances, and bond angles can be found in the supplemental material.

Figure 1 shows a computer-generated perspective drawing of **2**. As anticipated from the spectral and chemical data, riccardin A (**1**) is a monocyclic bis(bibenzyl), connected with an ether oxygen between the benzene rings A and B and with a biphenyl bond between the benzene rings C and D. The strongly shielded doublet signal at δ 5.33 (1 H) in **1** is assigned to be an inner proton (H-3) on benzene ring A which lies over the plane of benzene ring B.

Riccardin B (**4a**; $C_{28}H_{24}O_4$; high-resolution electron-impact mass spectrum, m/e 424.1674) showed the presence of a hydroxyl group (3350 cm^{-1}) and an aromatic ring (1600 and 1508 cm^{-1}). The ^1H NMR spectrum (Table I) indicated the signals of four benzylic methylenes, two protons (H-3 and H-10) coupled with meta protons (H-5 and H-14), four sets of ortho protons in which two protons (H-5 and H-14) were coupled with meta protons (H-3 and H-10), a proton (H-10') coupled with two meta protons (H-12' and H-14'), and three protons (H-12', H-13', and H-14') on a 1,3-disubstituted benzene ring.

Treatment of **4a** with acetic anhydride in pyridine afforded a diacetate [**5**: mp 148–149 °C; $C_{32}H_{28}O_6$; mass spectrum, m/e 508 (M^+); IR 1770, 1240 cm^{-1}; ^1H NMR δ 2.13 and 2.16 (each s, 3 H)], indicating the presence of two phenolic hydroxyl groups in **4a**. Methylation of **4a** gave a dimethyl ether [**6**: mp 147–148 °C; $C_{30}H_{28}O_4$; mass spectrum, m/e 466 (M^+); ^1H NMR δ 3.77 and 3.85 ppm (each s, 3 H)], which had no absorption bands for carbonyl and hydroxyl groups in the infrared spectrum. The above spectral and chemical evidence together with the molecular formula showed that riccardin B was a cyclic bis(bibenzyl) with two phenolic hydroxyl groups and two bibenzyl groups which were linked with two ether oxygens. The presence of two 1,2,4-trisubstituted benzene rings, a para-substituted benzene ring, and a meta-substituted benzene ring in riccardin B was suggested by the combination of the double-resonance experiments of the protons on each benzene ring and the observation of the long-range coupling between each benzylic methylene and each proton of the benzene rings and by the observation of an NOE between two methoxyl groups and two protons (H-6 and H-10; see Table I). The infrared and ^1H NMR spectra of **4a**, **5**, and **6** quite resembled those of **1**–**3**, showing that riccardin B might be the demethoxy derivative (**4a**) of **1** and that an additional ether oxygen might be linked between C-12 and C-11' in place of a biphenyl bond. However, an alternative structure (**4b**) is possible for riccardinB, and the structure **4a** could not be distinguished from **4b** only by spectral data. The structure **4a** for riccardin B may be suggested by the coexistence of riccardin A (**1**).

Riccardin A (**1**) and riccardin B (**4a**) are structurally unique phenolic compounds which show cytotoxicity against KB cells at the concentration of 10 and 12 μg/mL, respectively. Riccardins may be biosynthesized from lunularic acid (**7**) or lunularin (**8**) which are widespread in the leafy and thalloid liverworts.[7]

Work in progress indicates that we have isolated several compounds having the same carbon skeleton from the liverwort species *Marchantia*, *Radula*, *Reboulia*, and *Wiesnerella* in high yield[8]

Experimental Section

General Methods. ^1H NMR spectra were recorded on Varian EM-360 and Brucker WH-400 instruments, and ^{13}C NMR spectra were obtained on a Brucker WH-400 spectrometer at 50.28 MHz. Chemical shifts are reported as parts per million downfield from Me_4Si. IR spectra were recorded on a Shimadzu IR-27G as a thin film (neat) on sodium chloride plates or in CCl_4 solution. UV spectra were obtained on a Shimadzu UV-300 spectrophotometer as EtOH solutions. Electron-impact mass spectra (EIMS) were measured on a Shimadzu LKB-9000 spectrometer with MAS PAC 300. High-resolution electron-impact mass spectra (HREIMS) were obtained on a MAT-312 spectrometer. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel plates (250 μm) with a fluorescent indicator (Merck). Visualization was effected with ultraviolet light (254 nm) and 30% H_2SO_4. Merck SG-60 (70–230 mesh) silica gel was used for column chromatography.

Extraction Procedure. *Riccardia multifida* (L.) S. Gray was collected in Gotaki, Tokushima, in 1979 (Tokushima Bunri University, Institute of Pharmacognosy Herbarium voucher specimen No. 0087). The sample was dried for 5 days and mechanically powdered. A 620-g sample of the ground material was extracted with 5 L of Et_2O for 2 weeks. The ether extract was evaporated in vacuo to yield 10.20 g of green residue which was subjected to silica gel chromatography (*n*-hexane–EtOAc gradient) and divided into seven fractions: fraction 1 (*n*-hexane, 100%), fraction 2 (*n*-hexane–EtOAc, 19:1), fraction 3 (9:1), fraction 4 (4:1), fraction 5 (1:1), fraction 6 (1:4), and fraction 7 (EtOAc, 100%). The third fraction (1.50 g) was rechromatographed on silica gel with *n*-hexane–EtOAc (19:1) as the eluant to yield riccardin A (**1**): 810 mg; UV λ_{max} 213 nm (logϵ, 4.59), 283 (3.90); ^{13}C NMR ($CDCl_3$)δ 35.13, 36.98, 37.71, 38.13, 55.28, 112.53, 114.53, 115.14, 116.19*, 121.62, 122.35*, 124.66, 128.55, 129.32*, 131.52, 132.67, 133.14, 139.88, 141.84*, 143.46*, 146.46, 152.06, 152.67, 159.80 (an asterisk indicates two carbon signals were overlapped); IR (liquid film) 3420, 1610, 1565, 1520, 1509, 1446, 1435, 1342, 1275, 1230, 1195, 1170, 1113, 1050, 1020, 1008, 985, 910, 854, 816, 760, 645 cm^{-1}; EIMS, m/e (relative intensity) 439 ($M^+ + 1$, 36), 438 (M^+, 89), 226 (31), 225 (100), 213 (25), 211 (38); HREIMS, calcd for $C_{29}H_{26}O_4$ m/e 438.1831, found m/e 438.1836. The fourth fraction (2.05 g) was rechromatographed on silica gel with *n*-hexane–EtOAc (4:1) to give 6-(3-methyl-2-butenyl)indole (9^5 813 mg) and riccardin B (**4a**): 717 mg; UV λ_{max} 233 nm (log ϵ, 3.74), 280 (3.64); ^{13}C NMR ($CDCl_3$) δ 37.32*, 37.90, 38.02, 115.30, 116.15*, 116.84*, 118.54, 120.85, 121.23*, 125.12, 125.32, 130.09, 130.36*, 134.06, 135.37, 136.30, 141.69, 143.30, 143.69, 149.89*, 154.60, 155.17; IR (liquid film) 3550, 3040, 1600, 1508, 1435, 1345, 1275, 1230, 1110, 1015, 975, 909, 820, 805, 755, 730, 695, 648 cm^{-1}; EIMS, m/e (relative intensity) 425 ($M^+ + 1$, 16), 424 (M^+,46), 225 (5), 213 (16), 212

(6) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystalogr., Sect. A* **1971**, *27*, 368.

(7) Gorham, J. *Phytochemistry* **1977**, *16*, 249.

(8) Asakawa, Y.; Toyota, M.; Taira, Z.; Takemoto, T. "Symposium Papers", 25th Symposium on the Chemistry of Natural Products, Tokyo, Oct 19–22, 1982; Chemical Society of Japan: Tokyo, 1982; p 337.

(31), 211 (100), 107 (9), 106 (7), 105 (11), 91 (6), 90 (7), 83 (12), 77 (6); HREIMS, calcd for $C_{28}H_{24}O_4$ m/e 424.1674, found m/e 424.1700.

Riccardin A Diacetate (2). Riccardin A (1, 40 mg) was dissolved in 3 mL of pyridine and 3 mL of acetic anhydride. The mixture was allowed to stand overnight. The reaction mixture was treated in usual manner to give riccardin A diacetate (2): 45 mg; mp 209–210 °C (from petroleum ether); UV λ_{max} 218 nm (log ϵ, 4.62), 250 (4.38); ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.96 (s, 6 H), 2.29 (s, 3 H), 2.70, 2.79, 2.93 (m, 8 H), 3.83 (s, 3 H), 5.42 (d, J = 2 Hz, 1 H), 6.43–7.02 (m, 12 H); IR (CCl_4) 1770, 1610, 1505, 1425, 1370, 1270, 1200, 1115; EIMS, m/e (relative intensity) 522 (M^+, 28), 480 (67), 438 (100), 226 (22), 225 (66), 213 (14), 211 (32), 43 (38).

Riccardin A Trimethyl Ether (3). To riccardin A (1, 60 mg) in 5 mL of dry acetone was added 3 mL of MeI and 2 g of dry K_2CO_3. The mixture was kept at reflux for 10 h, and then the reaction mixture was filtered. The solvents were evaporated in vacuo, and the residue was purified by silica gel PLC to afford riccardin A trimethyl ether (3, 40 mg) as viscous liquid: UV λ_{max} 210 nm (log ϵ, 4.77), 280 (3.96); ^{13}C NMR ($CDCl_3$) δ 35.7, 37.2, 38.1, 38.3, 55.2*, 56.2, 111.4, 111.6, 112.2*, 115.5, 116.9, 121.5, 121.8, 122.4, 127.8, 122.4, 127.8, 129.5*, 131.1, 132.5*, 134.0, 139.8, 141.3, 143.4, 147.2, 148.9, 153.0, 156.2, 159.3; IR (CCl_4) 1610, 1580, 1510, 1490, 1455, 1440, 1420, 1265, 1235, 1165, 1130, 1040, 1020, 905, 870, 855 cm^{-1}; EIMS, m/e (relative intensity) 466 (M^+, 90), 240 (20), 239 (100), 233 (14), 227 (12), 225 (15), 211 (16), 105 (11), 90 (18).

Riccardin B Diacetate (5). Riccardin B (4a, 38 mg) was treated in the same manner as described above to yield riccardin B diacetate (5): 40 mg; UV λ_{max} 215 nm (log ϵ, 4.31), 273 (3.50); ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.13 (s, 3 H), 2.16 (s, 3 H), 2.80 (s, 8 H), 6.23–7.20 (complex m, 14 H); IR (CCl_4) 1770, 1590, 1505, 1485, 1445, 1425, 1370, 1265, 1240, 1220, 1190, 1170, 1150, 1110, 1010, 900; EIMS, m/e (relative intensity) 508 (M^+, 11), 466 (31), 424 (100), 213 (13), 212 (20), 211 (92), 105 (15), 43 (27).

Riccardin B Dimethyl Ether (6). Riccardin B (4a, 60 mg) was methylated in the same manner as described above to give riccardin B dimethyl ether (6): 58 mg; mp 151–152 °C (petroleum ether); UV λ_{max} 217 nm (log ϵ, 4.41), 277 (3.79); IR (CCl_4) 1607, 1585, 1505, 1470, 1440, 1415, 1265, 1215, 1155, 1125, 1035, 690, 670; EIMS, m/e (relative intensity) 452 (M^+, 100), 239 (11), 226 (19), 213 (11), 211 (25), 105 (11), 90 (24), 85 (17), 83 (28).

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Registry No. 1, 85318-25-8; 2, 85318-26-9; 3, 84575-09-7; 4a, 85318-27-0; 5, 85318-28-1; 6, 85318-29-2.

Supplementary Material Available: Tables II–V containing final atomic and anisotropic thermal parameters for nonhydrogen atoms, bond lengths, and bond angles for compound 2 (5 pages). Ordering information is given on any current masthead page.

A Triply Convergent Total Synthesis of L-(-)-Prostaglandin E_2[1]

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This paper details a versatile and efficient total synthesis of *l*-(-)-PGE_2 (3). The key step is a triply convergent conjugate-addition/alkylation reaction involving the 1,4-addition of chiral vinyllithium reagent **7b** to chiral vinyl sulfone D-**47** to afford sulfone-stabilized anion [**57**], which is subsequently alkylated to produce the basic prostaglandin E_2 skeleton **70**. The synthesis of chiral vinyl sulfone D-**47** involves a five-step sequence with an enantioconvergent resolution process as one step and produces vinyl sulfone D-**47** from readily available sulfide alcohol DL-**11** in an overall yield of 36%. The preparation of D-**47** features two steps that utilize stereospecific S_N2' reactions. The synthesis of *l*-(-)-PGE_2 (3) involves a seven-step sequence from vinyl sulfone D-**47** using mild conditions with an overall yield of 40% and features an efficient peracetic acid oxidation of secondary amino acid **120** to oximino acid **121**, which is, in turn, desulfonylated by 1,4-elimination of phenylsulfinic acid to generate a vinyl nitroso species that undergoes stereospecific 1,4-reduction by sodium borohydride to yield oxime **131**. The hydrolysis of oxime **131** to *l*-(-)-PGE_2 (3) using boron trifluoride and paraformaldehyde is the first reported high-yield method (84%). This gives an overall yield for the synthesis of *l*-(-)-PGE_2 (3) from racemic sulfide alcohol DL-**11** of 14.5%, including the resolution process.

The wide range of biological activity exhibited by the prostaglandin family combined with the lack of good natural source has elicited an immense effort dedicated to the total synthesis of these important materials. Particularly important in recent years is prostacyclin (PGI_2, 1)[2] and its analogues[3] because of their ability to inhibit blood platelet aggregation. The efficient conversion of PGE_2 **3** to prostacyclin **1** (through $PGF_{2\alpha}$ **2**) interconnects all three of these important prostaglandin cogeners.

The synthetic activity in the prostaglandin area covers a vast number of papers and has been extensively reviewed.[5] The only previous synthetic efforts that have direct relevance to this paper deal with a strategy involving

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(1) Syntheses via Vinyl Sulfones. 11. For paper 10, see P. Hamann and P. L. Fuchs, *J. Org. Chem.*, **48**, 914 (1983). Synthetic Utilization of the Imine Moiety. 9. For papers 8, 7, and 6 in this series, see S. G. Pyne; et al., *ibid.*, **104**, 5728 (1982); ref 1a; D. A. Clark, C. A. Bunnell, and P. L. Fuchs, *J. Am. Chem. Soc.*, **100**, 7777 (1978). This work has been published in part: (a) R. E. Donaldson and P. L. Fuchs, *ibid.*, **103**, 2108 (1981); (b) J. C. Saddler, R. E. Donaldson, and P. L. Fuchs, *ibid.*, **103**, 2110 (1981); (c) R. E. Donaldson, Ph.D. Thesis, Purdue University (1981).

(2) (a) R. A. Johnson, D. R. Morton, J. H. Kinner, R. R. Gorman, J. C. McGuire, F. F. Son, N. Whittaker, S. Bunting, J. Salmon, S. Moncada, and J. R. Vane, *Prostaglandins*, **12**, 915 (1976); (b) E. J. Corey, G. E. Keck, and I. Szekely, *J. Am. Chem. Soc.*, **99**, 2006 (1977); (c) K. C. Nicolaou, *J. Chem. Soc., Chem.* 630 (1977); (d) J. G. Kelton; et al., *Can. Med. Assoc. J.* **122**, 175 (1980).

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