and 448 [(M-35)$^+$]. Alcohol **24** decomposes on standing.

Aldehyde 25. Silver nitrate (100 mg in 1 mL of water) and sodium hydroxide (300 mg in 2 mL of water) were mixed under nitrogen. To this mixture was immediately added **23** (50 mg, 0.1 mmol) in ethanol (6 mL). The mixture was stirred for 5 h with careful heating to 55 °C. Most of the solvent was evaporated at near 55 °C, and the residue extracted with chloroform. Workup, including TLC, gave 28 mg (60%) of yellow crystals: mp >200 °C dec (MeOH); R_f 0.51; UV λ_{max} 243 (sh), 275 (sh), 326, 407 nm (log ϵ 4.19, 3.93, 3.70, 3.10); NMR (200 MHz) δ 2.78–4.19 (m, 4 H, H-5 and -6), 3.89 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 6.06 and 6.08 (dd, 2 H, J = 2 Hz, OCH_2O), 6.79 (s, 1 H, H-4), 7.12 (s, 1 H, H-1), 7.08 and 8.26 (AB q, 2 H, J = 8.8 Hz, H-11 and -12), 9.53 (s, 1 H, CHO); high-resolution mass spectrum, calcd for $C_{22}H_{17}NO_5Cl_2$ 445.0483, found 445.0506.

Conversion of Keto Lactam 17 to 18. Keto lactam **17** (100 mg, 0.29 mmol) in acetic acid (3 mL) was treated with bromine (3–4 drops) in acetic acid (0.5 mL). The solution was stirred for 4 h at near 5 °C, poured into ice water, and extracted with chloroform. The organic layer was dried and the solvent evaporated. Me_2SO (6 mL) was added to the residue, and the solution heated on a steam bath for 10 h. Workup, including TLC, provided a light orange powder, fluorescent under long-wavelength ultraviolet light: 25 mg (25%); mp 276 °C ($CHCl_3$–MeOH), R_f 0.63; UV λ_{max} 212, 265, 430 nm (log ϵ 4.23, 3.85, 3.63); NMR (200 MHz) δ 3.20 (t, 2 H, J = 4.5 Hz, H-5), 3.93 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 4.35 (br t, 2 H, H-6), 6.72 (s, 1 H, H-4), 7.04 (s, 1 H, H-1), 7.37 (s, 1 H, H-14), 7.72–7.87 (m, 2 H, H-10 and -11), 8.26–8.40 (m, 2 H, H-9 and H-12); high-resolution mass spectrum, calcd for $C_{20}H_{17}NO_4$ 335.1158, found 335.1168.

Oxidation of 15 to Imide 19. To **15** (50 mg, 0.13 mmol) in methylene chloride (10 mL) was added excess pyridinium chlorochromate in portions. The mixture was stirred for 12 h and then extracted with sodium bicarbonate solution. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with chloroform. Workup gave **19** (5 mg, 10%), spectrally identical with an authentic sample.[8]

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Registry No. 1 chloride, 633-65-8; **2**, 549-21-3; **5**, 75767-28-1; **7**, 75767-29-2; **9**, 75767-30-5; **10**, 75767-31-6; **11**, 75767-32-7; **14**, 75767-33-8; **15**, 75767-34-9; **17**, 75767-35-0; **18**, 75767-36-1; **19**, 75767-37-2; **22**, 75767-38-3; **23**, 75767-39-4; **24**, 75767-40-7; **25**, 75767-41-8; dichlorocarbene, 1605-72-7.

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Atropisomerism of Biphenyl Compounds. An Important Role of Ortho-Substituted Methoxy Groups and Fluorine Atoms

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Optically stable atropisomers of 2,2′-difluoro-3,3′-dicarboxy-6,6′-dimethoxybiphenyl (**1**), 2,2′,6,6′-tetramethoxy-3,3′-dicarboxybiphenyl (**3**), and 2,2′,6,6′-tetramethoxy-3,3′-diaminobiphenyl (**4**) were obtained, indicating that ortho-substituted methoxy groups and fluorine atoms are sufficient to allow optical resolution. Furthermore, 2,2′,6-trimethoxy-3-carboxybiphenyl (**6**) was also optically resolvable though less stable than **1** (Tables III and VI).

Some optically active biflavones belonging to the cupressuflavone,[1] agathisflavone,[2] or amentoflavone[3] series have been isolated from natural sources. In these compounds the ortho positions of the pivot linkage are substituted by hydroxy, methoxy, or pyrone-ring oxygen. These facts were inconsistent with the old findings established by Adams and co-workers that fluorine atoms and methoxy groups at the ortho positions of biphenyl compounds do not interfere sufficiently to allow optical resolution. 2,2′-Difluoro-3,3′-dicarboxy-6,6′-dimethoxybiphenyl (**1**),[4] 2,2′,6,6′-tetrafluoro-3,3′-dicarboxy-5,5′-dichlorobiphenyl (**2**),[5] 2,2′,6,6′-tetramethoxy-3,3′-dicarboxybiphenyl (**3**),[6] and 2,2′,6,6′-tetramethoxy-3,3′-diaminobiphenyl (**4**)[6] have been reported to be nonresolvable and these observations are generally accepted.[7] Nevertheless, in the case of optically active amentoflavone (**5**)[3] one of the four ortho positions is unsubstituted (hydrogen). For the settlement of the discrepancy we reinvestigated the optical resolution of these biphenyls (**1**, **3**, and **4**).

Resolution of **3** was first reinvestigated. Contrary to the old report[6] an optically active acid, $[\alpha]^{22}_D$ −18.5° and $[\alpha]^{22}_{400}$ −31.5° ($CHCl_3$), was isolated from a brucine salt. Its dimethyl ester was also optically active, $[\alpha]^{23}_D$ +10.5° and $[\alpha]^{23}_{400}$ +29.5° ($CHCl_3$). Optical purity of the ester was found to be satisfactory from a ^1H NMR study carried out with use of a chiral shift reagent (CSR), tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium (III).[8] As shown in Table I the active ester showed only one set of signals, while the racemic ester gave two sets of signals. Racemization was not noticeable after the active ester was kept for 90 min at 215 °C in a β-phenylethanol solution. When treated with boiling 0.5 N ethanolic potassium hydroxide the (+)-ester was hydrolyzed to give (−)-acid, identical in rotation with the starting acid.

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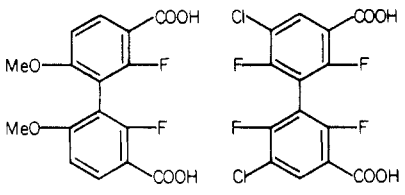

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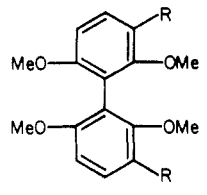
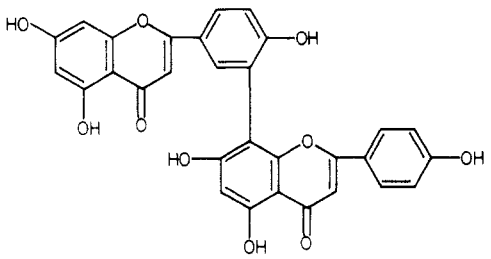


3, R = COOH
4, R = NH_2



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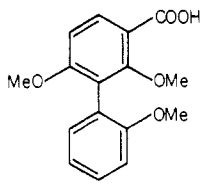

6

These observations indicate that the optical stability of the acid (3) is much different from the reported facts.[6]

It has also been reported[6] that the dicamphor sulfonate salt of 4 shows mutarotation in a solution even at −17 °C. However, present work showed that 4 is resolvable although the dicamphor sulfonate salt is not suitable for the resolution. Optically active amine, $[\alpha]^{18}_{D}$ +11.8° and $[\alpha]^{18}_{400}$ +110.6° ($CHCl_3$), was obtained from the optically active (−)-3 through the Schmidt reaction[9] with hydrazoic acid. The CSR[8] was used for the determination of optical purity of the active amine and showed no signal due to optical antipode, while inactive amine showed two sets of signals as given in Table II.

In order to compare the optical stability of the tetramethoxybiphenyl system with that of the trimethoxybiphenyl system, 2,2′,6-trimethoxy-3-carboxybiphenyl (6) was prepared from 2,2′,6-trimethoxybiphenyl[10] by acetylation followed by oxidation with sodium hypochlorite. Optical resolution of 6 through a brucine salt afforded an optically active acid, $[\alpha]^{15}_{D}$ −12.3° and $[\alpha]^{15}_{400}$ −58.5° ($CHCl_3$). Its methyl ester showed $[\alpha]^{15}_{D}$ −34.9° and $[\alpha]^{15}_{400}$ −112° ($CHCl_3$). However, the optical stability of the ester was much less than that of the dimethyl ester of 3. Complete racemization was observed on keeping the active ester at 125 °C for 15 min in a β-phenylethanol solution. The half-life times of the active ester for racemization were estimated in a dioxane solution at various temperatures and the results are given in Table III. The activation energy estimated graphically from these results was 28.2 kcal/mol.

Compound 1 was prepared along the lines reported by Becker and Adams.[4] However, 2,2′-difluoro-6,6′-dimethoxybiphenyl was obtained by a coupling reaction of 2-lithio-3-methoxyfluorobenzene with copper(II) chloride. The monobrucine salt of the dicarboxylic acid (1) was used for the optical resolution. The active acid showed the optical rotations given in Table IV. Although the $[\alpha]_D$ value in a pyridine solution was zero as reported earlier[4] +15° was observed in a methanol solution. A dimethyl ester of the active acid was prepared with diazomethane and showed $[\alpha]^{17}_{D}$ +37.5°, $[\alpha]^{17}_{400}$ +104.2°, and $[\alpha]^{17}_{326}$ +172.9° (dioxane). The CSR[8] was used for the determination of the optical purity of the dimethyl ester as shown in Table V and it was found to be satisfactory. The half-life times of the active ester for racemization in a β-phenylethanol solution were estimated as given in Table VI. The activation energy of the ester calculated graphically was 39.4 kcal/mol.

There are some reports in which the anomalously large steric effect on the o-methoxy group[11] or the easily detectable steric effect of the o-fluorine atom[12] in biphenyl compounds is discussed. Although they should be aware of the discrepancy nothing has been reported on the optically active atropisomer of 1, 3, or 4 so far. Anyway, the steric size of the fluorine atom and methoxy group seems to be large enough for obtaining restricted rotation, though one or two of these gorups are buttressed by the other (carboxy or amino) group at the meta position.

Experimental Section

All melting points are uncorrected. ^1H NMR spectra were recorded on a JEOL PS-100 instrument for solutions in $CDCl_3$. Mass spectra were obtained from a JEOL O1SG double-focusing high-resolution instrument. Optical rotations were measured with a Nihon-Bunko (JASCO) ORD/UV-5 spectropolarimeter unless otherwise stated. IR spectra were taken with a JASCO DS-301 spectrometer and UV spectra on a Hitachi ESP-2 recording spectrophotometer.

2,2′,6,6′-Tetramethoxy-3,3′-dicarboxybiphenyl (3). 3 was prepared by the reported method.[6] However, it is necessary to purify the acid through recrystallization of its dimethyl ester: mp 138–139 °C (EtOAc); UV λ_{max} (EtOH) 224 nm (ε 35 400), 258 (27 400). The ester (3.6 g) was hydrolyzed with 8% sodium hydroxide solution (25 mL) at 85 °C to give colorless acid (3 g): mp 239–240 °C (lit.[6] mp 231–232 °C); UV λ_{inf} (EtOH) 250 nm (ε 22 950).

(−)-2,2′,6,6′-Tetramethoxy-3,3′-dicarboxybiphenyl. Racemic acid 3 (724 mg, 2 mmol) and brucine dihydrate (1.77 g, 4.1 mmol) were dissolved in hot ethanol (7 mL) and left to stand overnight. Brucine salt obtained (650 mg) was recrystallized three times from ethanol to afford colorless sand crystals (300 mg), mp 203–204 °C dec, which were decomposed with 10% hydrochloric acid and recrystallized from ethyl acetate to give optically active acid (100 mg): mp 183–184 °C; $[\alpha]^{22}_{D}$ −18.5° and $[\alpha]^{22}_{400}$ −31.5° (5%, $CHCl_3$). The (−)-acid (15 mg) was dissolved in pyridine (1 mL) and kept for 40 min at the boiling point. After pyridine was removed it was methylated with diazomethane and dried ($MgSO_4$), and the ether was distilled off to give an ester (13.7 mg), whose ^1H NMR spectrum was taken after addition of the CSR[8] (19.0 mg). No signal due to the antipode was observed (Table I). The (−)-acid (40 mg) was dissolved in acetic acid (2 mL) and kept for 24 h at the boiling point. After acetic acid was removed at reduced pressure the residue was dissolved in chloroform (2.00 mL) for ORD measurement: $[\alpha]^{22}_{D}$ −17.5° and $[\alpha]^{22}_{400}$ −21.3°. A quarter of the chloroform solution was methylated with diazomethane and the ^1H NMR spectrum of the methyl ester (12 mg) taken after addition of the CSR (17.7 mg) showed no signal due to the optical antipode.

(+)-2,2′,6,6′-Tetramethoxy-3,3′-dicarbomethoxybiphenyl. The above described (−)-acid (80 mg) was methylated with diazomethane to give active ester (86 mg), $[\alpha]^{23}_{D}$ +10.5° and $[\alpha]^{23}_{400}$ +29.5° (5%, $CHCl_3$). The (+)-ester (70 mg) was hydrolyzed with 0.5 N ethanolic potassium hydroxide solution at 70 °C for 1 h. Usual workup and recrystallization from ethyl acetate gave an active acid (40 mg): mp 183–184 °C; $[\alpha]^{23}_{D}$ −18.5° and $[\alpha]^{23}_{400}$

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Table I. ^{1}H NMR Data (δ)[a] of the Dimethyl Ester of 3 with CSR[b]

protons	active or inactive ester without CSR	(+)-ester with 0.46 mol ratio of CSR	inactive ester with 0.32 mol of CSR	
OMe	3.52 (s)	4.33	3.87[c]	4.05
	3.73 (s)	4.36	4.03[c]	4.08
COOMe	3.85 (s)	6.25	4.86	5.37[c]
Ar H	6.75 (d, J = 9 Hz)	7.64	7.17	7.28[c]
	7.95 (d, J = 9 Hz)	9.91	8.86	8.96[c]

[a] ^{1}H NMR spectra were obtained from a solution of 10–15 mg of ester in 0.5 mL of $CDCl_3$. [b] NMR chiral shift reagent.[8] [c] Signals due to (−)-ester. The data obtained from a mixed sample of (+)-ester (4.5 mg), racemic ester (4.5 mg), and CSR (12.4 mg).

Table II. ^{1}H NMR Data (δ)[a] of Diamine 4 with CSR[b]

protons	active or inactive 4 without CSR	molar ratio of CSR: inactive 4 with CSR 0.49	0.73	active 4 with CSR 0.59	0.84
MeO-2,2′	3.44 (6 H, s)	4.89	5.82	6.05	7.18
		5.20	6.14		
MeO-6,6′	3.66 (6 H, s)	4.40	4.76	4.82	5.27
		4.50	4.92		
H-4,4′	6.59 (2 H, d)	7.46	7.81	7.88	8.3[c]
		7.49	7.88		
H-5,5′	6.76 (2 H, d)	8.5[c]		9.1[c]	

[a,b] See Table I. [c] Difficult to read exact values due to signal broadening.

Table III. Racemization of (−)-Methyl Ester of 6[a]

temp, °C	time, min	α^{25}_D, deg	log k	half-life time, min
66.8	90	−0.223	−4.759	663
77.4	60	−0.197	−4.218	191
88.2	30	−0.150	−3.565	42.5
101.0	10	−0.144	−3.053	13.0

[a] A solution of 101.58 mg of (−)-ester in dioxane (5.50 mL) was used. Initial rotation: α^{25}_D −0.245° (l = 10.00 cm).

Table IV. Optical Rotations of Active Acid 1

λ, nm	589 (D)	550	500	450	400	350	330
$[\alpha]^{20}$ (3.0%, pyridine), deg	0	−1.5	−6.0	−12.5	−30	−87	−155
$[\alpha]^{20}$ (2.3%, methanol), deg	+15	+17	+20	+23	+21	−7.8	−68

Table V. ^{1}H NMR Data (δ)[a] of the Dimethyl Ester of 1 with CSR[b]

protons	molar ratio of CSR: racemic ester 0	1.05	active ester 1.57	2.14
MeO	3.80 (6 H, s)	4.04	4.05	4.16
		4.11		
COOMe	3.88 (6 H, s)	7.20	7.58	9.47
		7.29		
H-4,4′	8.02 (2 H, dd, J = 9, 8 Hz)	11.00	11.6[c]	13.7[c]
		11.09		
H-5,5′	6.78 (2 H, d, J = 9 Hz)	7.11	7.16	7.34

[a,b] See Table I. [c] See Table II.

−31.0° (2%, $CHCl_3$). The (+)-dimethyl ester (17.67 mg) dissolved in β-phenylethanol (2.00 mL) showed α^{25}_D +0.455° (Perkin-Elmer Polarimeter 241). After the solution was kept at 215 °C for 90 min it showed α^{25}_D +0.458°. The ^{1}H NMR spectrum of the (+)-ester after addition of the CSR showed only one set of signals (middle column of Table I).

Table VI. Racemization of the Active Dimethyl Ester of 1[a]

temp, °C	time, min	$\alpha^{14.5}_D$, deg	log k	half-life time, min
177.9	120	+0.095	−4.034	125
189.3	60	+0.070	−3.569	42.8
200.4	30	+0.050	−3.139	15.9
211.2	15	+0.030	−2.694	5.7

[a] A solution of 60.2 mg in β-phenylethanol (10.00 mL) was used. Initial rotation, $\alpha^{14.5}_D$ +0.185° (l = 10.00 cm).

(+)-2,2′,6,6′-Tetramethoxy-3,3′-diaminobiphenyl (4). (−)-3 (150 mg) was dissolved in chloroform (9 mL) and mixed with concentrated sulfuric acid (3 mL). Sodium azide (250 mg) was added to the mixture under stirring at 43 °C and stirring was continued for 15 min; during that time nitrogen was evolved and the color of the solution became brown. The reaction mixture was poured into ice water (20 mL) containing sodium bisulfite (50 mg) and extracted with chloroform three times to recover the starting material (active acid, 16 mg). The water layer was neutralized with sodium hydroxide solution and again extracted three times with chloroform. The chloroform layer was washed with water, dried (K_2CO_3), and evaporated to give pale brown crystals (56 mg), which were recrystallized from ethanol: mp 149–151 °C; $[\alpha]^{18}_D$ +11.8° and $[\alpha]^{18}_{400}$ +110.6° (17.0 mg in 2.0 mL of $CHCl_3$); UV λ_{max} (EtOH) 304 nm (ε 7100), 230 λ_{inf} (24 000); ^{1}H NMR data in Table II.

2,2′,6-Trimethoxybiphenyl. 2,6-Dimethoxybromobenzene (6.5 g), 2-iodoanisol (7.0 g), active copper powder[13] (40 g), and a few milligrams of iodine were well mixed and kept for 2 h in an oil bath at 180–200 °C and then at 225–230 °C for 3 h. The cooled reaction mixture was extracted with chloroform completely by using a Soxhlet apparatus. The reaction products obtained (8.2 g) were a mixture of di-, tri- and tetramethoxybiphenyls. Repeated chromatography on silicic acid followed by recrystallizations from ethanol gave 2,2′,6-trimethoxybiphenyl (0.3 g): mp 134–135 °C; UV λ_{max} (EtOH) 244 nm (ε 6100), 281 (4700).

2,2′,6-Trimethoxy-3-acetylbiphenyl. 2,2′,6-Trimethoxybiphenyl (1 g) was dissolved in anhydrous CS_2 (10 mL) and mixed with powdered anhydrous $AlCl_3$ (2 g) and diethyl ether (40 mL). Under mechanical stirring acetyl chloride (1.5 mL) was added to the mixture dropwise and refluxing was continued for 2 h; during that time the color of the reaction mixture was changed to dark red. It was poured into ice–water containing hydrochloric acid and extracted with ether. The ether-soluble part was dissolved in methyl ethyl ketone (30 mL) and refluxed for 5 h with dimethyl sulfate (2.0 mL) and potassium carbonate (5 g). Further dimethyl sulfate (0.5 mL) and potassium carbonate (1 g) were added to the reaction mixture and refluxing was continued until no more phenolic compound was detected on a TLC plate. The methylated product was extracted with chloroform and subjected to chromatographic separations on silicic acid, using $CHCl_3$ as an eluting solvent. The main product (0.5 g) was obtained as colorless rods from ethanol: mp 82–83 °C; IR (KBr) 1657 (C=O), 1581, 1462, 1399, 1267, 1082, 806, 747 cm^{-1}; UV λ_{max} (EtOH) 277 nm (ε 15 000); mass spectrum, m/e 286.1127 (calcd for $C_{17}H_{18}O_4$ 286.1205), 271, 255, 239; ^{1}H NMR δ 2.60 (3 H, s), 3.34 (3 H, s),

(13) R. Q. Brewster and T. Groening, "Organic Syntheses", Collect. Vol. 2, Wiley, New York, 1950, p 446.

3.71 (6 H, s), 6.75, 7.75 (1 H, d each, J = 9 Hz), 6.9–7.4 (4 H, m). Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.08; H, 6.33.

2,2′,6-Trimethoxy-3-carbomethoxybiphenyl. The above acetyl compound (850 mg) was dissolved in methanol (20 mL) and mixed with 10% sodium hydroxide solution (5 mL). Sodium hypochlorite solution (5%, 16 mL) was dropwise added to the mixture under stirring at room temperature. After no more hypochlorite was consumed acetone was added to decompose excess hypochlorite. Methanol and excess acetone were distilled off under reduced pressure. The insoluble substance (230 mg) from the cooled reaction mixture was filtered, washed with water, and recrystallized from ethanol to give colorless rods (150 mg): mp 76–77 °C; IR (KBr) 1691 (C=O), 1585, 1456, 1400, 1306, 1270, 1210, 1090, 799, 745 cm^{-1}; UV λ_{max} (EtOH) 215 nm (ϵ 29 200), 237 (sh, 16 250), 262 (13 200); mass spectrum, m/e 302.1226 (calcd for $C_{17}H_{18}O_5$ 302.1154), 286, 271, 257, 240; ^1H NMR δ 3.45 (3 H, s), 3.75 (6 H, s), 3.87 (3 H, s), 6.71, 7.87 (1 H, d each), 6.9–7.4 (4 H, m). Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.75; H, 6.08. The filtrate and washings separated from the methyl ester were acidified with HCl and extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried ($MgSO_4$), and evaporated to give crude acid (720 mg), which was recrystallized from ethyl acetate to afford white minute crystals (470 mg), mp 156–158 °C. A methyl ester of the acid was obtained by treatment with diazomethane and identified by comparison with the above described methyl ester (melting point and ^1H NMR spectrum).

Racemic 2,2′,6-Trimethoxy-3-carboxybiphenyl (6). The above methyl ester was hydrolyzed with 10% NaOH solution. Usual workup and recrystallizations from ethyl acetate afforded **6**: mp 159–160 °C; UV λ_{max} (EtOH) 213 nm (ϵ 34 700), 241 (sh, 16 350), 260 (sh, 11 000), 282 (sh, 6050).

(−)-2,2′,6-Trimethoxy-3-carboxybiphenyl. Racemic acid (424 mg) and brucine dihydrate (630 mg) were dissolved in acetone (8 mL) and left to stand overnight. The brucine salt (550 mg) produced was recrystallized two times from acetone to give 400 mg of salt, mp 117–120 °C, which was dissolved in water (15 mL) and acidified with HCl. White precipitates (155 mg) were recrystallized from a mixture of benzene and hexane (1:1 v/v) to give colorless minute crystals (120 mg): mp 151–153 °C; $[\alpha]^{15}_D$ −12.3° and $[\alpha]^{15}_{400}$ −58.5° (1.3%, $CHCl_3$).

(−)-2,2′,6-Trimethoxy-3-carbomethoxybiphenyl. (−)-Acid (100 mg) was treated with a diazomethane ethereal solution. Evaporation of ether followed by recrystallization from ethyl acetate gave an active methyl ester (70 mg): mp 71–73 °C; $[\alpha]^{15}_D$ −34.9° and $[\alpha]^{15}_{400}$ −112° (1.2%, $CHCl_3$). Racemization data are given in Table III.

2,2′-Difluoro-6,6′-dimethoxybiphenyl. 3-Methoxyfluorobenzene[4] (12.6 g) was dissolved in anhydrous tetrahydrofuran (100 mL) and cooled by an ice–salt mixture. To the cooled and stirred solution was dropwise added 15% n-butyllithium–hexane solution (50 mL) during 30 min. Stirring was continued for a further 6 h and then dried $CuCl_2$ (18 g) was added. After the mixture was stirred for 10 min at the cooled temperature for a further 2 h, stirring was continued at room temperature. Water was added and the mixture was extracted with chloroform. The chloroform layer was washed with water, dried ($MgSO_4$), and evaporated. Recrystallizations from methanol gave colorless needles (9.3 g), mp 132–133 °C (lit.[4] mp 135–136 °C).

2,2′-Difluoro-3,3′-dicarboxy-6,6′-dimethoxybiphenyl (1). Acetylation and oxidation were carried out according to the reported method.[4] Crude acid (6 g) was converted to dimethyl ester with diazomethane and recrystallized from ethyl acetate to give colorless sand crystals (5.5 g): mp 160–161 °C; UV λ_{max} 221 nm (ϵ 31 500), 233 (34 350), 253 (31 000). The methyl ester was dissolved in methanol (30 mL) and hydrolyzed with 8% NaOH solution (40 mL) on a steam bath. Usual workup and recrystallizations from ethanol gave minute white crystals: mp 286–287 °C (lit.[4] mp 285–289 °C); UV λ_{max} 221 nm (ϵ 32 200), 231 (33 600), 248 λ_{inf} (26 900).

Optical Resolution of 1. The racemic 1 (675 mg, 2 mmol) was dissolved in a hot mixture of ethanol (20 mL) and acetone (5 mL) and mixed with brucine dihydrate (861 mg, 2 mmol) to give a clear solution, which was left standing for 2 h. The salt obtained (1.4 g) was washed with ethanol and recrystallized four times from a mixture of pyridine and acetone (1:1 v/v). The salt obtained (190 mg) melted at 272–273 °C. Decomposition of the salt with HCl followed by recrystallization from methanol gave an optical active acid (50 mg), mp 276–277 °C. The active acid was methylated with diazomethane and the ester obtained was recrystallized from methanol to give colorless sand crystals: mp 157–158 °C; $[\alpha]^{17}_D$ +37.5°, $[\alpha]^{17}_{400}$ +104.2°, and $[\alpha]^{17}_{326}$ +172.9° (1.44% dioxane). The other data are given in Tables IV–VI.

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Registry No. (±)-1, 75700-37-7; (+)-1, 75700-40-2; (±)-1 dimethyl ester, 75700-38-8; (+)-1 dimethyl ester, 75700-39-9; (+)-1 brucine salt, 75700-41-3; (±)-3, 70388-56-6; (−)-3, 70388-54-4; (+)-3 dimethyl ester, 70388-55-5; (±)-3 dimethyl ester, 70388-52-2; (−)-3 brucine salt, 75700-42-4; (+)-4, 75700-43-5; (±)-6, 70388-57-7; (−)-6, 70388-61-3; (−)-6 methyl ester, 70388-62-4; (−)-6 brucine salt, 75700-44-6; (±)-6 methyl ester, 70388-59-9; (±)-2,2′,6-trimethoxy-3-acetylbiphenyl, 75700-45-7; 2,2′,6-trimethoxybiphenyl, 19718-53-7; (±)-2,2′-difluoro-6,6′-dimethoxybiphenyl, 75700-46-8; 2,6-dimethoxybromobenzene, 16932-45-9; 2-iodoanisol, 529-28-2; acetyl chloride, 75-36-5; 3-methoxyfluorobenzene, 456-49-5.