On the Verge of Axial Chirality: Atroposelective Synthesis of the AB-Biaryl Fragment of Vancomycin

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SUPPORTING INFORMATION

General Methods. Melting points were determined on a Reichert-Jung Thermovar hot-plate and are uncorrected. Optical rotations were taken on a Perkin-Elmer 241MC polarimeter (25°C, 10 cm cell) or a Perkin-Elmer 341 polarimeter (25°C, 10 cm cell). IR spectra were measured with a Perkin-Elmer 1429 spectrophotometer or a Jasco FT/IR-430 spectrometer. CD spectra (25°C, EtOH, 0.1-cm cell) were taken on a Jasco J-715 spectropolarimeter. ^{1}H NMR and ^{13}C NMR spectra were obtained on Bruker AC 200, AC 250, AMX 400, DMX 600, and Varian Inova 400 machines using $CDCl_3$ (δ 7.26 and δ 77.01) and CD_3SOCD_3 (δ 2.49 and

δ 39.70) as the solvents and internal ^{1}H and ^{13}C standards. EIMS and HRMS were determined on a Finnigan MAT 8200, Finnigan MAT 90 (70 eV), or VG70 Magnetic Sector instruments. Positive Electron Impact (EI) or Chemical Ionization (CI) probes were used to produce ions and fragments of the samples. Isobutane and NH_3 were used as reagent gas in CI measurements. LRMS and HRMS (ESI-TOF) were determined on a PE Sciex QStar quadrapole/time-of-flight tandem mass spectrometer. For TLC, precoated silica gel 60 F_{254} plates (Merck, 5 × 10 cm) were used. Spots were detected under UV light. Column chromatography was carried out on silica gel 60 (60-200 mesh, Merck). HPLC was performed using the following system: Waters HPLC Pump 510, Rheodyne 7125 Syringe Loading sample injector, ERC-7215 UV detector, Shimadzu C-R6-A integrator. Column: Chiralcel OD-H (Daicel Chem. Ind. Ltd., 4.6 mm x 250 mm), solvent: hexane/*i*-PrOH = 90:10 (0.5 mL/min) for **12** [t_R = 22 min for (*P*)-**12**, t_R = 33 min for (*M*)-**12**] and for **17** [t_R = 12 min for (*P*)-**17**, t_R = 15 min for (*M*)-**17**] and hexane/*i*-PrOH = 90:10 (0.6 mL/min) for **27** [t_R = 9 min for (*M*)-**27**, t_R = 15 min for (*P*)-**27**]. Melting points were obtained with a Fisher-Johns Melting Point Apparatus and are uncorrected. Source of compounds: methyl 2-iodo-3,5-dimethoxybenzoate,[1] methyl 3,5-dihydroxybenzoate,[2] and (4*R*)-*N*-(*tert*-butoxycarbonyl)-2,2'-dimethyl-4-[4-hydroxyphenyl]-1,3-oxazoline (**9**)[9] were prepared according to literature procedures. Their physical and spectroscopic properties were identical to the published data. For the synthesis of **10-12**, **16**, **17**, and **19-29**, all manipulations were performed under argon unless otherwise mentioned. THF was distilled under argon from sodium benzophenone ketyl. All other solvents were distilled under argon from sodium benzophenone ketyl (toluene) or from CaH_2 (CH_2Cl_2, DMA, and DMF). All other reagents were purified when necessary using standard procedures. All palladium-catalyzed coupling reactions were performed in carefully baked flasks (heating by a heatgun for 5 min under vacuum).

2-Iodo-3,5-dimethoxybenzoic Acid (8). A suspension of methyl 2-iodo-3,5-dimethoxybenzoate[1] (2.00 g, 6.21 mmol) in a mixture of MeOH (10 mL) and EtOH (5 mL) was treated with 6.5 mL of 5% aqueous NaOH and stirred at 70-80 °C for 1 h. The solvent was evaporated in vacuum and the residue was suspended in a mixture of 5 mL CH_2Cl_2 and 5 mL aqueous 2 M HCl. Filtration and recrystallization from EtOH gave 2-iodo-3,5-dimethoxybenzoic acid (1.75 g, 5.71 mmol, 92%) as colorless crystals: mp 211-213 °C (lit.[1] 212-216 °C); IR (KBr) ν 2960, 2928, 1680, 1575, 1403, 1318, 1315, 1160, 850 cm^{-1}; ^1H NMR (250 MHz, CD_3SOCD_3) δ 3.79 (s, 3H), 3.83 (s, 3H), 6.67 (d, J = 2.4 Hz, 1H), 6.73 (d, J = 2.4 Hz, 1H); ^{13}C NMR (63 MHz, CD_3SOCD_3) δ 55.59, 56.70, 74.41, 100.23, 105.81, 140.96, 140.96, 158.85, 160.53, 168.92; MS (EI) *m/z* 308 (100) [M^+], 166 (18), 151 (17).

***tert*-Butyl (*R*)-2,2-Dimethyl-4-[-4-(2'-iod-3',5'-dimethoxybenzoyloxy)-phenyl]-oxazolidine-*N*-carboxylate (10).** A solution of **8** (906 mg, 2.94 mmol) in a mixture of dry DMF (0.5 mL) and dry CH_2Cl_2 (0.5 mL) was treated with DMAP (33 mg, 270 μmol) and **9** (784 mg, 2.67 mmol). At 0 °C DCC (660 mg, 3.20 mmol) was added and the resulting mixture was stirred at 0 °C for 5 min and at rt for 45 min. After filtration, the solvent was removed in vacuum. The residue was dissolved in CH_2Cl_2 and washed twice with aqueous 0.5 M HCl and twice with saturated aqueous $NaHCO_3$. Drying of the combined organic phases ($MgSO_4$), evaporation of the solvent in vacuum, and flash chromatography on deactivated (7.5% NH_3) silica gel (CH_2Cl_2/MeOH = 100:1) gave **10** (1.53 g, 2.62 mmol, 89%) as a colorless oil, which crystallized from petroleum ether: mp 96-97 °C; $[\alpha]^{22}_D$ = -46 (*c* 1.0, MeOH); IR (KBr) ν 2960, 2920, 2860, 1730, 1675, 1570, 1490, 1440, 1370, 1200, 1080, 1040 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.22 (s, 6H), 1.45 (s, 3H), 1.59 (s, 3H), 1.76 (s, 3H), 3.77 (s, 1H), 3.84 (s, 3H), 3.88 (s, 3H), 4.28 (dd, J = 9.1 Hz, J = 6.8 Hz, 1H), 4.81 (s, 0.6H), 4.94 (s, 0.4H), 6.56 (d, J = 2.8 Hz, 1H), 6.97 (d, J = 2.6 Hz, 1H), 7.25 (m, 2H), 7.34-7.38 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 23.65, 24.52, 25.09, 25.37, 25.99, 26.15, 26.96, 28.14, 55.69,

56.71, 60.54, 70.08, 70.55, 75.89, 79.86, 80.35, 94.05, 94.52, 101.54, 106.96, 121.30, 127.44, 137.89, 139.80, 140.31, 149.75, 151.87, 152.11, 159.42, 160.94, 165.83; MS (EI) *m/z* 583 (1) [M^+], 468 (1), 291 (100), 165 (95). Anal. Calcd for $C_{25}H_{30}O_7NI$: C, 51.47; H, 5.18; N, 2.40. Found: C, 51.57; H, 5.27; N, 2.50.

***tert*-Butyl (*R*)-2,2-Dimethyl-4-[3',5'-dimethoxy-6H-dibenzo[b,d]pyran-7'-on]-oxazolidine-*N*-carboxylate (11).** A mixture of **10** (857 mg, 1.45 mmol), $PdCl_2(PPh_3)_2$ (309 mg, 441 μmol), and NaOPiv (547 mg, 4.41 mmol) was dried in vaccum (10^{-2} mbar) at 60 °C for 2 h, treated with 20 mL of dry DMA, degassed three times, and stirred under argon at 120 °C for 6 h. After cooling, the reaction mixture was diluted with EtOAc and washed with aqueous 2 M HCl and saturated aqueous NaCl. Drying ($MgSO_4$) of the organic phase, evaporation of the solvent in vacuum and flash chromatography on silica gel (CH_2Cl_2/MeOH = 100:0.5) gave **11** (600 mg, 1.32 mmol, 90%), which was crystallized from CH_2Cl_2/petroleum ether: mp 195 °C; $[\alpha]^{22}_D$ = -106 (*c* 1.14, CH_2Cl_2); IR (KBr) ν 2960, 1710, 1670, 1600, 1360, 1230, 1070, 1050 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.18 (s, 6H), 1.46 (s, 3H), 1.63 (s, 3H), 1.86 (s, 3H), 3.88 (m, 1H), 3.92 (s, 3H), 4.01 (s, 3H), 4.34 (dd, *J* = 9.1 Hz, *J* = 6.7 Hz, 1H), 4.89 (s, 0.66H), 5.02 (s, 0.33H), 6.89 (s, 1H), 7.29 (s, 2H), 7.52 (s, 1H), 8.90 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 23.70, 24.65, 25.94, 26.88, 28.10, 28.40, 55.20, 55.92, 60.97, 70.51, 70.84, 79.80, 80.42, 94.14, 94.54, 103.36, 106.26, 116.68, 117.01, 117.62, 117.84, 117.98, 118.25, 123.89, 124.94, 126.67, 138.01, 138.42, 148.88, 151.94, 152.19, 158.68, 160.24, 161.39; MS (EI) *m/z* 455 (34) [M^+], 399 (5), 384 (20), 340 (100). Anal. Calcd for $C_{25}H_{29}O_7N$: C, 65.92; H, 6.42; N, 3.09. Found: C, 65.62; H, 6.18; N, 3.08.

***tert*-Butyl (*P/M,R*)-2,2-Dimethyl-4-[(4-hydroxy-3',5'-dimethoxy-1'-hydroxymethyl)-(3,2'-biphenyl)-1-yl]-oxazolidine-*N*-carboxylate [(*P/M*)-12].** A solution of (*P*)-binaphthol (553 mg, 1.93 mmol) in 5 mL of dry THF was added under argon to 1.76 ml (1.76 mmol) of a 1 M LAH solution (in THF) and stirred at rt for 30 min. After addition of dry EtOH (113 μl,

1.93 mmol) the mixture was stirred for 45 min at rt and cooled to 0 °C, at which temperature lactone **11** (200 mg, 439 μmol) was added. After another 5 h at 0 °C, H_2O (1 mL) and aqueous 2 M HCl (1 mL) were added and the THF was removed in vacuum. The aqueous phase was extracted thoroughly with EtOAc. Drying of the combined organic phases ($MgSO_4$), evaporation of the solvent in vacuum, and flash chromatography on deactivated (7.5 % NH_3) silica gel (CH_2Cl_2/MeOH = 100:0 → 100:2) gave (*P*):(*M*)-**12** (192 mg, 417 μmol, 98%, dr 69:31). The atropoisomeric mixture (dr = 50:50) was characterized as an amorphous powder: $[\alpha]^{22}_D$ = -56 (*c* 0.12, CH_2Cl_2); IR (KBr) ν 3429, 2977, 2934, 1683, 1607, 1462, 1387, 1151, 1092, 845 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 5H), 1.43 (s, 4H), 1.58 (s, 3H), 1.71 (s, 3H), 3.70 (s, 2H), 3.75 (s, 1H), 3.87 (s, 3H), 3.89 (m, 1H), 4.12 (m, 0.5H), 4.25 (dd, *J* = 8.9 Hz, *J* = 6.3 Hz, 1H), 4.33 (m, 1.5H), 4.68-4.91 (m, 1H), 6.52 (d, *J* = 2.3 Hz, 1H), 6.77 (d, *J* = 2.3 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.99 (s, 0.7H), 7.16 (s, 0.2H), 7.21 (dd, *J* = 8.3 Hz, *J* = 2.3 Hz, 0.5H), 7.27 (s, 0.3H), 7.43 (m, 0.3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 23.75, 24.55, 25.96, 27.08, 28.13, 28.28, 53.36, 55.34, 55.64, 55.84, 60.27, 60.56, 62.86, 63.18, 63.28, 69.76, 70.46, 70.75, 70.84, 79.65, 80.84, 93.88, 94.36, 98.23, 98.35, 104.64, 106.18, 115.57, 115.82, 116.37, 117.06, 122.16, 122.50, 122.67, 126.65, 127.07, 127.25, 129.42, 129.93, 132.49, 133.06, 134.14, 142.26, 142.78, 152.09, 152.75, 152.89; MS (EI) *m/z* 459 (29) [M^+], 441 (11), 403 (3), 385 (23), 340 (43), 84 (100). Anal. Calcd for $C_{25}H_{33}O_7N$: C, 65.34; H, 7.24; N, 3.05. Found: C, 64.20; H, 7.32; N, 3.08.

Resolution of *tert*-Butyl (*P/M,R*)-2,2-Dimethyl-4-[(4-hydroxy-3',5'-dimethoxy-1'-hydroxymethyl)-(3,2'-biphenyl)-1-yl]-oxazolidine-*N*-carboxylate [(*P/M*)-12]. The atropisomeric mixture (*P/M*)-**12** (23.0 mg, 50.1 μmol) was resolved by preparative thin layer chromatography (CH_2Cl_2/MeOH = 100:4) to give (*P*)-**12** (11.0 mg, 24.0 μmol) and (*M*)-**12** (10.3 mg (22.4 μmol).

tert-Butyl (*P*,*R*)-2,2-Dimethyl-4-[(4-hydroxy-3',5'-dimethoxy-1'-hydroxymethyl)-(3,2'-biphenyl)-1-yl]-oxazolidine-*N*-carboxylate [(*P*)-**12**]: $[\alpha]^{22}_D$ = +18 (*c* 0.15, CH_2Cl_2, dr 97:3); CD (EtOH) $\Delta\varepsilon_{251}$ +2.57, $\Delta\varepsilon_{229}$ –13.41, $\Delta\varepsilon_{209}$ +16.60, $\Delta\varepsilon_{202}$ –16.21; ^{1}H NMR (400 MHz, $CDCl_3$, dr 97:3) δ 1.26 (s, 5.5H), 1.44 (s, 3.5H), 1.54-1.58 (m, 3H), 1.66-1.71 (m, 3H), 3.69-3.77 (m, 3H), 3.86-3.92 (m, 1H), 3.88 (s, 3H), 4.23-4.34 (m, 2H), 4.25 (dd, *J* = 8.8 Hz, *J* = 6.7 Hz, 1H), 4.72-4.92 (m, 1H), 6.52 (d, *J* = 2.4 Hz, 1H), 6.77 (d, *J* = 2.2 Hz, 1H), 6.95 (d, *J* = 8.5 Hz, 1H), 6.99 (m, 1H), 7.22 (dd, *J* = 8.3 Hz, *J* = 2.3 Hz, 0.4H), 7.28 (s, 0.3H), 7.44 (m, 0.3H).

tert-Butyl (*M*,*R*)-2,2-Dimethyl-4-[(4-hydroxy-3',5'-dimethoxy-1'-hydroxymethyl)-(3,2'-biphenyl)-1-yl]-oxazolidine-*N*-carboxylate [(*M*)-**12**]: $[\alpha]^{22}_D$ = -72 (*c* 0.023, CH_2Cl_2, dr 97:3); CD (EtOH) $\Delta\varepsilon_{252}$ –0.77, $\Delta\varepsilon_{232}$ +9.07, $\Delta\varepsilon_{210}$ –19.53, $\Delta\varepsilon_{201}$ +21.38; ^{1}H NMR (400 MHz, $CDCl_3$, dr 96:4) δ 1.24 (s, 5H), 1.43 (s, 4H), 1.54-1.57 (m, 3H), 1.66-1.70 (m, 3H), 3.70-3.76 (m, 3H), 3.85-3.92 (m, 0.6H), 3.87 (m, 3H), 4.10-4.12 (m, 0.3H), 4.23-4.36 (m, 3H), 4.75-4.92 (m, 1H), 6.52 (d, *J* = 2.3 Hz, 1H), 6.77 (d, *J* = 2.3 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 6.99 (s, 1H), 7.16-7.17 (m, 0.2H), 7.21 (dd, *J* = 8.5 Hz, *J* = 2.4 Hz, 0.4H), 7.27 (s, 0.2H), 7.43 (m, 0.4H).

Atropoisomerization of *tert*-Butyl (*P*,*R*)-2,2-Dimethyl-4-[(4-hydroxy-3',5'-dimethoxy-1'-hydroxymethyl)-(3,2'-biphenyl)-1-yl]-oxazolidine-*N*-carboxylate. (*P*)-**12** (1.10 mg, 2.40 μmol, dr > 99.5:0.5) was dissolved in 2 mL hexane/*i*-propanol (90:10) and kept at 23 °C. At the times indicated (Table 1) the diastereomeric ratio was determined by HPLC. Isomerization proceeded with an half-life of approximately 12 h.

Table 1. Isomerization of (*P*)-**12** in Hexane/Isopropanol (90:10) at Rt

time [h]	de [%]
0	> 99
8	64
13	45

27	27
64	3

Oxidation of (*M*)-12 Back to Lactone 11. A solution of (*M*)-**12** (10.0 mg, 21.8 μmol) in CH_2Cl_2 (5mL) was treated at rt with activated MnO_2 (10.0 mg, 119 μmol) and stirred vigorously for 3 h. Filtration of the reaction mixture through a silica plug (CH_2Cl_2/MeOH = 100:5) gave **11** (9.72 mg, 21.4 μmol, 98%), chromatographically (TLC) and spectroscopically (^{1}H NMR) identical to the material obtained above.

Methyl 3,5-Di-*tert*-butoxybenzoate. According to a known method,[10] isobutene (50 mL) was added to a suspension of methyl 3,5-dihydroxybenzoate[2] (5.00 g, 29.8 mmol) in 25 ml CH_2Cl_2 and 1 mL concd H_2SO_4. The resulting mixture was stirred at 40 °C for 20 h while cooling with a condenser (-25 °C, EtOH). The resulting solution was washed three times with 20 mL 5% NaOH. Evaporation of the solvent under vacuum gave methyl 3,5-di-*tert*-butoxybenzoate (7.31 g, 26.1 mmol, 87%) as a colorless oil: IR (KBr) ν 2940, 1704, 1570, 1425, 1305, 1120, 1003 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.33 (s, 18H), 3.86 (s, 3H), 6.82 (t, J = 2.4 Hz, 1H), 7.39 (d, J = 2.4 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 28.78, 52.07, 79.10, 120.21, 124.74, 130.84, 155.83, 166.57; MS (CI, isobutane) *m/z* 281 (2) [MH^+], 224 (2) [M], 168 (61), 57 (100). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.55; H, 8.63. Found: C, 68.50; H, 8.35.

Bromination of Methyl 3,5-Di-*tert*-butoxybenzoate. NBS (2.92 g, 16.4 mmol) was added in portions to a solution of methyl 3,5-di-*tert*-butoxybenzoate (3.84 g, 13.69 mmol) in 20 mL of CH_3CN at 0 °C and stirred at rt for 12 h. Another 975 mg (5.48 mmol) of NBS were added at 0 °C. After 45 min at rt 10 mL of a saturated solution of Na_2SO_3 was added and the mixture was filtered. H_2O (10 mL) was added and the aqueous phase was thoroughly extracted with Et_2O. Evaporation of the dried ($MgSO_4$) organic phases and flash chromatography on

deactivated (7.5% NH_3) silica gel (CH_2Cl_2/MeOH = 100:0 → 100:2) gave methyl 2,6-dibromo-3,5-di-*tert*-butoxybenzoate (1.37 g, 3.12 mmol, 19%), which was obtained as colorless crystals from petroleum ether, and methyl 2-bromo-3,5-di-*tert*-butoxybenzoate (4.02 g, 11.2 mmol, 68%), which gave a colorless oil.

Methyl 2,6-dibromo-3,5-di-*tert*-butoxybenzoate: mp 124-125 °C; IR (KBr) ν 2945, 2904, 1720, 1543, 1395, 1325, 1135, 990 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.43 (s, 18H), 3.95 (s, 3H), 6.94 (s, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 28.96, 52.96, 82.41, 109.66, 118.28, 139.07, 152.94, 166.64; MS (EI) *m/z* 440/438/436 (1/1/1) [M^+], 384/382/380 (1/3/1), 328/326/324 (32/68/33), 297/295/293 (11/21/10), 57 (100). Anal. Calcd for $C_{16}H_{22}Br_2O_4$: C, 43.86; H, 5.06. Found: C, 44.04; H, 5.05.

Methyl 2-Bromo-3,5-di-*tert*-butoxybenzoate: IR (KBr) ν 2974, 1731, 1640, 1542, 1420, 1018, 836 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.20 (s, 9H), 1.29 (s, 9H), 3.74 (s, 3H), 6.75 (d, J = 2.8 Hz, 1H), 6.89 (d, J = 2.8 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 28.32, 28.57, 50.08, 79.22, 81.59, 103.60, 111.52, 119.86, 121.21, 133.96, 153.98, 154.16, 166.67; MS (EI) *m/z* 360/358 (0.3/0.2) [M^+], 248/246 (9/8), 57 (100); HRMS (EI) calcd for $C_{16}H_{23}BrO_4$ 358.0782, found: 358.0784.

2-Bromo-3,5-di-*tert*-butoxybenzoic Acid (15). A solution of methyl 2-bromo-3,5-di-*tert*-butoxybenzoate (1.75 g, 4.87 mmol) in EtOH (20 mL) was treated with 10 mL of a 5% aqueous solution of NaOH in H_2O and stirred at 80 °C for 2 h. The reaction mixture was concentrated in vacuum, acidified with aqueous 2 M HCl, and extracted thoroughly with Et_2O. Drying of the combined organic phases ($MgSO_4$), evaporation of the solvent in vacuum, and crystallization from petroleum ether gave 2-bromo-3,5-di-*tert*-butoxybenzoic acid (**15**) (1.62 g, 4.69 mmol, 95%) as colorless needles: mp 67 °C; IR (KBr) ν 2948, 1690, 1563, 1350, 1300, 1130 1010 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.37 (s, 9H), 1.46 (s, 9H), 6.96 (d, J = 2.7 Hz, 1H), 7.28 (d, J = 2.7 Hz, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 28.75, 29.01, 79.88,

82.26, 113.09, 121.53, 122.85, 132.28, 154.48, 154.74, 171.61; MS (EI) *m/z* 346/244 (1/1) [M^+], 290/288 (3/3), 234/232 (65/68), 57 (100). Anal. Calcd for $C_{15}H_{21}BrO_4$: C, 52.19; H, 6.13. Found: C, 52.42; H, 6.08.

***tert*-Butyl (*R*)-2,2-Dimethyl-4-[-4-(2'-bromo-3',5'-di-*tert*-butoxybenzoyloxy)-phenyl]-oxazolidine-*N*-carboxylate.** A solution of **15** (500 mg, 1.45 mmol) in dry CH_2Cl_2 (1.5 mL) was treated under argon with DMAP (15.0 mg, 123 μmol) and phenol **9** (425 mg, 1.45 mmol). At 0 °C DCC (329 mg, 1.60 mmol) was added and the resulting mixture was stirred for 5 min at 0 °C and for 60 min at rt. After filtration, the solvent was evaporated in vacuum. The residue was dissolved in CH_2Cl_2 (30 mL) and washed twice with aqueous 0.5 M HCl and a saturated solution of $NaHCO_3$. Drying of the organic phase ($MgSO_4$), evaporation of the solvent in vacuum, and flash chromatography on deactivated (7.5% NH_3) silica gel (petroleum ether/EtOAc = 8:1) gave *tert*-butyl (*R*)-2,2-dimethyl-4-[-4-(2'-bromo-3',5'-di-*tert*-butoxybenzoyloxy)-phenyl]-oxazolidine-*N*-carboxylate (819 mg, 1.32 mmol, 91%) as an oil, which crystallized from petroleum ether as colorless needles: mp 70 °C; $[\alpha]^{22}_D$ = -46 (*c* 1.0, MeOH); IR (KBr) ν 2940, 2900, 1728, 1670, 1555, 1350, 1080, 945 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.23 (s, 6H), 1.38 (s, 9H), 1.47 (s, 12H), 1.60 (s, 3H), 1.77 (s, 3H), 3.90 (m, 1H), 4.29 (dd, *J* = 9.2 Hz, *J* = 6.7 Hz, 1H), 4.81 (s, 0.6H), 4.95 (s, 0.4H), 6.96 (d, *J* = 2.4 Hz, 1H), 7.23 (m, 3H), 7.34-7.38 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 22.30, 22.59, 23.73, 24.93, 25.59, 28.20, 28.78, 29.02, 33.93, 60.63, 70.19, 70.63, 77.01, 79.83, 82.23, 94.61, 112.49, 120.68, 121.39, 122.13, 127.49, 133.43, 140.10, 149.84, 152.01, 154.63, 154.67, 165.03; MS (EI) *m/z* 621/619 (1/1) [M^+], 509/507 (3/3), 453/451 (9/9), 409/407 (1/1), 394/392 (20/19), 57 (100). Anal. Calcd for $C_{21}H_{42}BrO_7N$: C, 60.00; H, 6.82; N, 2.26. Found: C, 60.31; H, 6.83; N, 2.54.

***tert*-Butyl (*R*)-2,2-Dimethyl-4-[3',5'-di-*tert*-butoxy-6H-dibenzo[b,d]pyran-7'-on]-oxazolidine-*N*-carboxylate (16).** *tert*-Butyl (*R*)-2,2-dimethyl-4-[-4-(2'-bromo-3',5'-di-*tert*-

butoxybenzoyloxy)-phenyl]-oxazolidine-*N*-carboxylate (20.0 mg, 32.2 μmol), $PdCl_2(PPh_3)_2$ (2.26 mg, 3.22 μmol), and NaOAc (5.28 mg, 64.4 μmol) were dissolved in dry DMA and stirred at 130 °C for 3 h. A solution of $PdCl_2(PPh_3)_2$ (2.26 mg, 3.22 μmol) was added and the resulting mixture was stirred for another 3 h at 130 °C. Evaporation of the solvent and flash chromatography on deactivated (7.5% NH_3) silica gel (CH_2Cl_2/MeOH = 100:1) gave a mixture of unreacted starting material (5.28 mg, 8.50 μmol, 26%) and **16** (10.4 mg, 19.3 μmol, 60%), from which **16** was obtained in pure form as colorless needles by crystallization from petroleum ether: mp 165 °C; $[\alpha]^{22}_D$ = -17 (*c* 0.48, EtOH); IR (KBr) ν 2977, 2933, 1739, 1695, 1601, 1390, 1257, 1173, 1080, 853 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 6H), 1.45 (s, 9H), 1.51 (s, 9H), 1.56 (s, 3H), 1.62 (s, 3H), 1.80 (s, 3H), 3.89 (s, 1H), 4.33 (dd, *J* = 9.1 Hz, *J* = 6.8 Hz, 1H), 4.87 (s, 0.7H), 5.00 (s, 0.3H), 7.15 (d, *J* = 2.5 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.80 (d, *J* = 2.5 Hz, s, 1H), 9.01 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 23.75, 26.15, 28.32, 28.82, 28.91, 29.07, 29.12, 61.25, 70.63, 70.81, 80.07, 82.30, 94.87, 117.19, 117.71, 117.96, 121.41, 123.36, 123.95, 124.15, 125.97, 126.39, 127.47, 138.19, 149.28, 154.49, 155.69, 161.34; MS (CI, NH_3) *m/z* 557 (100) [MNH_4^+], 540 (22) [MH^+], 501 (44), 484 (4). Anal. Calcd for $C_{31}H_{41}O_7N$: C, 68.99; H, 7.66; N, 2.60. Found: C, 68.43; H, 7.63; N, 2.61.

***tert*-Butyl (*P/M,R*)-2,2-Dimethyl-4-[(4-hydroxy-3',5'-di-*tert*-butoxy-1'-hydroxymethyl)-(3,2'-biphenyl)-1-yl]-oxazolidine-*N*-carboxylate [(*P/M*)-17].** A solution of **16** (30.0 mg, 55.7 μmol) in 5 mL dry THF was treated at rt with 150 μL (150 μmol) of a 1 M solution of LAH in Et_2O. After 10 min the reaction mixture was cautiously hydrolyzed with H_2O and aqueous 2 M HCl and extracted thoroughly with EtOAc. Drying of the combined organic phases ($MgSO_4$), evaporation of the solvent, and flash chromatography on deactivated (7.5% NH_3) silica gel (CH_2Cl_2/MeOH = 100:0 → 100:2) gave [(*P/M*)-**17**] (22.5 mg, 41.8 μmol, 75%, dr 48:52), which was crystallized from petroleum ether: mp 165 °C; $[\alpha]^{22}_D$ = -26

(*c* 1.42, CH_2Cl_2); IR (KBr) ν 3426, 2981, 2924, 2874, 1704, 1597, 1477, 1384, 1365, 1254, 1174, 1130, 1094, 1054, 849 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.11 (s, 8H), 1.26-1.43 (m, 18H), 1.58 (s, 6H), 1.73 (s, 3H), 3.85 (s, 1H), 4.12 (m, 0.5H), 4.27 (dd, J = 9.1 Hz, J = 6.6 Hz, 1H), 4.31-4.33 (m, 1.5H), 4.77-4.94 (m, 1H), 6.19 (s, 0.38H), 6.58 (s, 0.28H), 6.76-6.78 (m, 1H), 6.98-7.03 (m, 1.6H), 7.10-7.18 (m, 1.1H), 7.40-7.47 (m, 0.7H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 23.83, 24.53, 24.70, 26.06, 26.96, 27.28, 28.23, 28.35, 28.77, 28.91, 28.95, 30.91, 60.44, 60.67, 63.06, 63.47, 63.68, 69.85, 70.83, 79.05, 79.75, 80.14, 80.48, 80.74, 93.97, 94.45, 107.19, 115.12, 115.71, 117.66, 118.49, 118.54, 122.21, 127.45, 127.68, 127.78 128.54, 128.67, 132.06, 132.16, 133.30, 141.63, 152.20, 152.33, 152.90, 155.09, 155.69, 156.29; MS (EI) *m/z* 543 (7) [M^+], 487 (25), 431 (21), 375 (100), 57 (63). Anal. Calcd for $C_{31}H_{45}O_7N$: C, 68.74; H, 8.00; N, 2.59. Found: C, 68.68; H, 7.73; N, 2.71.

Resolution of *tert*-Butyl (*P*/*M*,*R*)-2,2-Dimethyl-4-[(4-hydroxy-3',5'-di-*tert*-butoxy-1'-hydroxymethyl)-(3,2'-biphenyl)-1-yl]-oxazolidine-*N*-carboxylate. (*P*/*M*)-**17** (1.80 mg, 3.31 μmol) was separated by preparative thin layer chromatography (CH_2Cl_2/MeOH = 100:4) to give (*P*)-**17** (0.82 mg, 1.51 μmol) and (*M*)-**17** (0.72 mg, 1.33 μmol)

tert-Butyl (*P*,*R*)-2,2-dimethyl-4-[(4-hydroxy-3',5'-di-*tert*-butoxy-1'-hydroxymethyl)-(3,2'-biphenyl)-1-yl]-oxazolidine-*N*-carboxylate [(*P*)-**17**]: $[\alpha]^{22}_D$ = +14 (*c* 0.010, CH_2Cl_2, dr 97:3); CD (EtOH) $\Delta\varepsilon_{288}$ –2.19, $\Delta\varepsilon_{268}$ –0.27, $\Delta\varepsilon_{215}$ -10.63, $\Delta\varepsilon_{198}$ +13.33; ^1H NMR (400 MHz, $CDCl_3$, dr 97:3) δ 1.11 (s, 8H), 1.26-1.28 (m, 4H), 1.41-1.43 (m, 12H), 1.57 (s, 5H), 1.66-1.73 (m, 3H), 3.85 (s, 1H), 4.10 (d, J = 9.1 Hz, 0.3H), 4.26 (dd, J = 9.1 Hz, J = 6.6 Hz, 1H), 4.22-4.40 (m, 2H), 4.77-4.83 (m, 0.7H), 6.18 (s, 0.4H), 6.58 (s, 0.3H), 6.76 (s, 1H), 6.98-7.03 (m, 1.6H), 7.10-7.16 (m, 1.1H), 7.40-7.46 (m, 0.7H).

tert-Butyl (*M*,*R*)-2,2-dimethyl-4-[(4-hydroxy-3',5'-di-*tert*-butoxy-1'-hydroxymethyl)-(3,2'-biphenyl)-1-yl]-oxazolidine-*N*-carboxylate [(*M*)-**17**]: $[\alpha]^{22}_D$ = -43 (*c* 0.010, CH_2Cl_2, dr 96:4); CD (EtOH) $\Delta\varepsilon_{291}$ +0.61, $\Delta\varepsilon_{228}$ –3.91, $\Delta\varepsilon_{220}$ –2.39, $\Delta\varepsilon_{201}$ –9.22; ^1H NMR (400 MHz, $CDCl_3$, dr

96:4) δ 1.11 (s, 7H), 1.26-1.43 (m, 17H), 1.56-1.57 (m, 6H), 1.66-1.73 (m, 2H), 3.86 (s, 1H), 4.10 (d, J = 9.1 Hz, 0.3H), 4.22-4.40 (m, 1.7H), 4.27 (dd, J = 9.1 Hz, J = 6.6 Hz, 1H), 4.77-4.94 (m, 1H), 6.19 (s, 0.4H), 6.58 (s, 0.3H), 6.75-6.78 (m, 1H), 6.95-7.03 (m, 1.6H), 7.10-7.16 (m, 1.1H), 7.40-7.47 (m, 0.7H).

Atropoisomerization of *tert*-Butyl (*P*,*R*)-2,2-Dimethyl-4-[(4-hydroxy-3',5'-di-*tert*-butoxy-1'-hydroxymethyl)-(3,2'-biphenyl)-1-yl]-oxazolidine-*N*-carboxylate [(*P*)-17]. *tert*-Butyl (*P*/*M*,*R*)-2,2-dimethyl-4-[(4-hydroxy-3',5'-di-*tert*-butoxy-1'-hydroxymethyl)-(3,2'-biphenyl)-1-yl]-oxazolidine-*N*-carboxylate (0.82 mg, 1.51 μmol, dr > 99.5:0.5) was dissolved in 2 mL hexane/isopropanol (90:10) and kept at 23 °C. At the times indicated (Table 2) the diastereomeric ratio of **17** was determined by HPLC. Isomerization proceeded with a half-life of approximately 15 h.

Table 2. Isomerization of (*P*)-**17** in Hexane/Isopropanol (90:10) at Rt

time [h]	de [%]
0	> 99
5	78
13	52
25	32
40	16
65	6

1-(*tert*-Butyldimethylsilyl)oxy-3,5-dichlorobenzene (19). To a solution of 3,5-dichlorophenol (4.90 g, 30.0 mmol) and imidazole (4.50 g, 66.0 mmol) in DMF (15 mL) was added TBDMSCl (5.00 g, 33.0 mmol) at 0 °C, and the mixture was stirred at rt for 20 min. Water was added at 0 °C, and the aqueous layer was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by

silica gel flash column chromatography (hexane/EtOAc = 20:1) to give **19** (8.2 g, quant.) as a colorless oil. IR (neat) ν 2933, 2895, 2860, 1586, 1432, 978, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.23 (s, 6 H), 0.99 (s, 9 H), 6.74 (m, J = 1.6, 0.4 Hz, 2H), 6.98 (t, J = 1.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ -4.3, 18.4, 25.7, 119.3, 122.0, 135.2, 157.1; LREIMS LREIMS 276(8), 223(24), 222(14), 221(69), 220(21), 219(100), 93(12); HREIMS calcd for $C_{12}H_{18}Cl_2OSi$ 276.0506, found 276.0504.

4-Benzyloxy-2,6-dichlorobenzaldehyde (21). To a solution of **19** (8.2 g, 30 mmol) in THF (100 mL), *sec*-BuLi (1.35 M solution in cyclohexane, 23 mL, 31 mmol) was slowly added at -78 °C, and the mixture was stirred at the same temperature for 30 min. To the mixture DMF (3.5 mL, 45 mmol) was added at -78 °C, and the mixture was stirred at the same temperature for 1.5 h. Then 10% aqueous HCl was added and the mixture was allowed to warm to rt. The aqueous layer was extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated. To a solution of crude aldehyde **20** (5.7 g, 30.0 mmol), K_2CO_3 (6.22 g, 45.0 mmol), KI (6.47 g, 39 mmol) and BnBr (3.9 mL, 32.8 mmol) were added at 0 °C, and the mixture was stirred at rt for 16 h, diluted with Et_2O, and the precipitate was filtered off. The filtrate was washed with water, brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 10:1) to give **21** (7.8 g, 93%, 4 steps) as a colorless solid: mp 85 °C; IR (nujol) ν 2727, 1695, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.11 (s, 2H), 6.99 (s, 2H), 7.28-7.51 (m, 5H), 10.4 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 71.0, 116.6, 123.1, 127.7, 127.7, 128.9, 128.9, 129.0, 135.0, 139.2, 162.0, 187.8; MS (EI) *m/z* 280(1), 91(100); HMRS (ESI-TOF) calcd for $C_{14}H_{11}O_2Cl_2$ 281.0136 $(M+H)^+$, found 281.0149.

4-Benzyloxy-2,6-dichlorostyrene (22). To a suspension of methyltriphenylphosphonium bromide (8.6 g, 24 mmol) in THF (80 mL) *n*-BuLi (2.4 M solution in hexane, 9.2 mL, 22

mmol) was slowly added at 0 °C, and the mixture was stirred at 0 °C for 30 min. After addition of a solution of **21** (5.6 g, 20 mmol) in THF (20 mL) at 0 °C, the whole was stirred at rt for 1 h. Then saturated aqueous NH_4Cl was added, and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel flash column chromatography (hexane/CH_2Cl_2 = 20:1 → 10:1) to give **22** (4.8 g, 85%) as a colorless solid: mp 30-32 °C; IR (nujol) ν 1632, 1595, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.03 (s, 2H), 5.64 (dd, *J* = 11.8, 1.4 Hz, 1H), 5.74 (dd, *J* = 17.8, *J* = 1.4 Hz, 1H), 6.66 (dd, *J* = 17.8, *J* = 11.8 Hz, 1H), 6.97 (s, 2H), 7.33-7.45 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) *δ* 70.5, 122.1, 125.5, 127.7, 127.8, 1128.5, 128.9, 130.7, 134.8, 136.0, 157.6; MS (EI) *m/z* 278(3), 91(100); HRMS (EI) calcd for $C_{15}H_{12}Cl_2O$ 278.0265, found 278.0168.

(1*S*)-1-[4-(Benzyloxy)-2,6-dichlorophenyl]-2-(*tert*-butyldimethylsilyl)oxy-1-ethylalcohol (23). A flask was charged with *t*-BuOH (25 mL), water (25 mL), and AD-mix α (7.0 g). Then **22** (1.39 g, 4.98 mmol) was added at 0 °C, and the resulting mixture was stirred at the same temperature for 48 h. Solid Na_2SO_3 was added. After stirring at rt for 1 h, the mixture was diluted with EtOAc, and the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. To a solution of crude product (1.43 g, 4.56 mmol) in CH_2Cl_2 (23 mL) Et_3N (0.96 mL, 6.89 mmol), TBDMSCl (824 mg, 5.47 mmol), and DMAP (27.9 mg, 0.228 mmol) were added at 0 °C, and the whole was stirred at rt for 7 h. After addition of water, the aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 5:1) to give **23** (1.93 g, 91%, 2 steps, 90% ee) as a colorless oil: $[\alpha]_D^{25}$ -2.4 (*c* 1.3, $CHCl_3$, 90% ee); IR (neat) ν 3447, 1599, 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.06, (s, 3H), 0.89 (s, 9H), 2.94 (br s, 1H), 3.81 (dd, *J* = 10.4, *J* = 5.2 Hz, 1H), 4.07 (dd, *J* = 10.4, *J* = 8.0 Hz, 1H),

5.03 (s, 2H), 5.35 (dd, J = 8.0, J = 5.2 Hz, 1H), 6.93 (s, 2H), 7.31-7.45 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ -5.2, -5.3., 18.4, 26.0, 63.5, 63.7, 70.7, 116.3, 124.2, 127.7, 128.6, 129.0, 135.7, 136.2, 158.7; MS (EI) *m/z* $(M-C_4H_9)^+$ 369(11), 91(100), 75(29), 75(15); HRMS (ESI-TOF) calcd for $C_{21}H_{28}Cl_2O_3SiNa$ 449.1082 $(M+Na)^+$, found 449.1083.

[2-Azido-2-(4-benzyloxy-2,6-dichloro-phenyl)-ethoxy]-tert-butyl-dimethyl-silane (24). A mixture of the chiral benzylic alcohol **23** (4.23 g, 9.90 mmol) and triphenylphosphine (3.89 g, 14.85 mmol) was dissolved in 16 mL of dry THF under an argon atmosphere. The reaction mixture was cooled to 0 °C, to which was added a mixture of diphenylphosphoryl azide (3.2 mL, 14.85 mmol) and diisopropyl azodicarboxylate (2.9 mL, 14.85 mmol) in 36 mL of dry THF. After 10 h TLC analysis indicated completion of the reaction. A few drops of water were added to the reaction mixture and the solvent was removed *invacuo*. A silica gel column (2-10 % Et_2O/Pet. Ether) was run on the crude oil to yield 3.84 g of azide **24** in an 86% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.7 (s, 3 H), 0.11 (s, 3 H), 0.91 (s, 9 H), 3.86 (m, J = 5.4, J = 2.8 Hz, 1H), 4.25 (m, J = 8.4, J = 2.8 Hz, 1H), 5.05 (s, 2 H), 5.47 (m, J = 5.4, J = 2.4 Hz, 1H), 6.89 (2 H, s), 7.45-7.37 (5 H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ -5.3, -5.2, 18.4, 26.0, 63.5, 70.7, 116.3, 124.2, 127.7, 128.6, 129.0, 135.7, 136.2, 158.7; MS (EI) *m/z* $(M-C_4H_9)^+$ 394(8), 91(100), 73(26); HRMS (ESI-TOF) $(M+Na)^+$ calcd for $C_{21}H_{27}Cl_2N_3O_2SiNa$ 474.1144, found 474.1147.

(1*R*)-*N*-(*tert*-Butoxycarbonyl)-1-[4-(benzyloxy)-2,6-dichlorophenyl]-2-hydroxyethylamine (25). A solution of azide **24** (10.60 g, 23.5 mmol) and 235 mL (0.1 M) of a 20:1 THF:H_2O was stirred at room temperature for 5 min. To this solution triphenylphosphine (24.60 g, 94.0 mmol) was added and the reaction was stirred for 12 h. At that time TLC analysis indicated no starting material was present so the solvent was removed *invacuo*. To the crude oily product was added 118 mL of dry CH_2Cl_2 (0.2 M) and $NaHCO_3$

(2.96 g, 35.25 mmol). This mixture was cooled to 0 °C and stirred for 10 min. At that time di-*t*-butyl dicarbonate (8.59 g, 30.55 mmol) was added and the reaction mixture was allowed to warm to room temperature. After 1 h 150 mL of deionized water was added to the reaction. The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL) and the organics were combined, dried over Na_2SO_4, and concentrated. The crude oil was dissolved in 24 mL of dry THF and stirred at 0 °C. Once the reaction mixture was cooled a 1 M solution of TBAF in THF (28 mL, 28.2 mmol) was added slowly. The reaction was allowed to warm to room temperature and stirring continued for 5 h. At that time 100 mL of deionized water was added and the organic layer was extracted with EtOAc (3 x 100 mL). The organic layers were combined, dried over Na_2SO_4, concentrated, and a silica gel column was run in 30% EtOAc/petroleum ether to yield 8.78 g (91%) of primary alcohol **25**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.65 (br s, 1H), 3.84 (m, 1H), 4.01 (m, 1H), 5.02 (s, 2H), 5.52-6.92 (m, 2H) 6.95 (s, 2H), 7.35-7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 156.1, 135.8, 128.9, 128.6, 127.7, 126.5, 116.5, 80.2, 70.7, 63.7, 53.8, 28.5; MS (CI) *m/z* ($M+H^+$) 414(8), 412(11), 382(12), 380(18), 358(15), 356(22), 324(11), 314(11), 312(17), 295(13), 282(45), 281(12), 280(70), 190(11), 104(20), 91(100), 60(11), 57(28); HRCIMS ($M+H^+$) calcd for $C_{20}H_{24}Cl_2NO_4$ 412.1075, found 412.1082.

(4*R*)-*N*-(*tert*-Butoxycarbonyl)-2,2'-dimethyl-4-[(4-hydroxy)-2,6-dichlorophenyl]-1,3-oxazoline (26). A solution of **25** (8.22 g, 5.36 mmol) in EtOAc/EtOH (10:1, 74 mL) was stirred in the presence of 5% Pd-C (958.5 mg, 0.60 mmol) at rt for 1 h under H_2. After the catalyst was filtered off, the filtrate was concentrated. To the crude product and 2,2-dimethoxypropane (9.8 mL, 80.0 mmol) in CH_2Cl_2 (100 mL) was added $TsOH{\cdot}H_2O$ (190.2 mg, 1.0 mmol) and MS 4Å (beads, 20.4 g), and the mixture was stirred at rt for 24 h. After the molecular sieves were filtered off, the filtrate was diluted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$, and brine, and dried over Na_2SO_4, and concentrated.

The residue was purified by silica gel flash column chromatography (hexane/EtOAc = 2:1) to give **26** (6.19 g, 86%, 2 steps) as a colorless solid: mp 153.5-156 °C; $[\alpha]_D^{25}$ -3.4 (*c* 1.8, EtOH, 90% ee); IR (nujol) ν 3213, 1657, 1168 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (for major rotamer) 1.52 (s, 9H), 1.62 (s, 3H), 1.74 (s, 3H), 3.91 (dd, *J* = 9.2, *J* = 8.8 Hz, 1H), 4.19 (m, 1H), 5.54 (m, 1H), 6.52 (br s, 1H), 6.56 (br s, 1H), 7.91 (s, 1H); δ (for minor rotamer) 1.14 (s, 9H), 1.62 (s, 3H), 1.74 (s, 3H), 4.05 (dd, *J* = 8.4, *J* = 7.6 Hz, 1H), 4.19 (m, 1H), 5.52 (m, 1H), 6.84 (s, 2H), 8.09 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.3, 27.3, 28.1, 28.8, 58.1, 67.1, 81.6, 95.9, 114.4, 116.7, 121.4, 152.9, 156.5; MS (CI) *m/z* 362 (1.3), 348(11), 346(17), 306(13), 292(22), 290(34), 264(11), 262(20), 250(12), 248(28), 246(22), 144(100), 58(20), 57(58); HRMS (ESI-TOF) calcd for $C_{16}H_{21}Cl_2NO_4Na$ 384.0745 $(M+Na)^+$, found 384.0728.

***tert*-Butyl (*R*)-2,2-Dimethyl-4-[2,6-dichloro-4-(2'-iodo-3',5'-dimethoxybenzoyloxy)-phenyl]-oxazolidine-*N*-carboxylate (27).** A solution of **8** (100 mg, 325 μmol) in dry DMF (2 mL) was treated with DMAP (3.74 mg, 30.6 μmol) and phenol **24** (106 mg, 293 μmol). At 0 °C DCC (73.9 mg, 358 μmol) was added. The mixture was stirred at 0 °C for 5 min and at rt for 45 min. Filtration, evaporation of the solvent in vacuum, and flash chromatography of the residue on silica gel (CH_2Cl_2/MeOH = 100:1) gave **27** (162 mg, 248 μmol, 85%), which was crystallized from petroleum ether: mp 47-48 °C; $[\alpha]^{22}_D$ = +16 (*c* 0.14, CH_2Cl_2); IR (KBr) ν 3084, 2972, 2936, 1757, 1704, 1593, 1455, 1343, 1205, 1170, 1040, 952, 854, 769 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 7H), 1.44 (s, 2H), 1.60 (s, 3H), 1.77 (s, 3H), 3.84 (s, 3H), 3.88 (s, 3H), 4.06 (m, 1H), 4.20 (m, 1H), 5.57 (m, 1H), 6.57 (d, *J* = 2.5 Hz, 1H), 6.94 (d, *J* = 2.5 Hz, 1H), 7.30 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.63, 25.82, 28.31, 56.24, 57.20, 57.64, 66.86, 76.52, 80.35, 96.43, 102.48, 107.71, 131.73, 137.32, 149.77, 152.21, 159.62, 160.01, 161.53, 162.01, 165.38; MS (EI) *m/z* 653/651 (1/1) $[M^+]$, 638/636 (6/8), 582/580 (5/8), 538/536 (26/38), 291 (100). Anal. Calcd for $C_{25}H_{28}Cl_2INO_7$: C, 46.03; H, 4.33; N, 2.15. Found: C, 64.35; H, 4.33; N, 2.19.

***tert*-Butyl (*R*)-2,2-Dimethyl-4-[2,6-dichloro-3',5'-dimethoxy-6H-dibenzo[b,d]pyran-7'-on]-oxazolidine-*N*-carboxylate (28).** A mixture of **27** (328 mg, 503 μmol), $Pd(OAc)_2$ (35.0 mg, 156 μmol), PPh_3 (80.0 mg, 305 μmol), and NaOPiv (126 mg, 1.02 mmol) was dried in vacuum (10^{-2} mbar) for 1 h at rt. Dry DMA (2 mL) was added, the resulting suspension was degassed three times, and subsequently stirred at 100 °C for 1 h. The cooled reaction mixture was diluted with EtOAc and washed with aqueous 2 M HCl. Drying ($MgSO_4$), evaporation of solvent in vacuum, and flash chromatography on silica gel (CH_2Cl_2/EtOAc = 50:1) afforded **28** (170 mg, 324 μmol, 64%) as an amorphous oil: $[\alpha]^{22}_D$ = -5 (*c* 0.13, CH_2Cl_2); IR (KBr) ν 2981, 2936, 1753, 1704, 1602, 1459, 1352, 1094, 1037, 858 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (s, 7H), 1.44 (m, 2H), 1.60 (m, 3H), 1.77 (s, 3H), 3.94 (s, 6H), 4.05 (m, 1H), 4.19 (m, 1H), 5.55 (m, 1H), 6.89 (d, *J* = 2.4 Hz, 1H), 7.29 (s, 1H), 7.40 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.12, 25.51, 27.92, 28.31, 56.01, 57.22, 60.47, 66.48, 79.82, 96.09, 103.53, 105.97, 125.72, 130.92, 148.90, 149.37, 151.88, 157.52, 160.32, 161.71, 168.44, 171.10; MS (EI) *m/z* 527/525/523 (1/3/4) [M^+], 510/508 (1/1), 490/488 (4/9), 454/452 (8/11), 434/432 (34/94), 410/408 (45/67), 57 (100); HRMS (EI) calcd for $C_{25}H_{27}Cl_2NO_7$ 523.1165, found: 523.1164.

***tert*-Butyl (*M*,*R*)-2,2-Dimethyl-4-[(2,6-dichloro-4-hydroxy-3',5'-dimethoxy-1'-hydroxymethyl)-(3,2'-biphenyl)-1-yl]-oxazolidine-*N*-carboxylate [(*M*)-29].** The solvent was removed in vacuum from a commercial (Aldrich) solution of (*S*)-**13** (1.0 M in toluene, 180 μmol, 180 μL) and a solution of the residue in 1 mL dry THF was treated at 0 °C with the BH_3-THF complex (1.0 M in THF, 240 μL). This mixture was stirred at rt for 30 min and subsequently cooled to –25 °C. A likewise precooled (-25 °C) solution of lactone **29** (30.0 mg, 57.1 μmol) in 1 mL dry THF was added dropwise and stirred at this temperature for 1.5 h. After cautious hydrolysis with H_2O and aqueous 0.1 M HCl the solvent was removed in vacuum. Flash chromatography of the residue on silica gel (CH_2Cl_2/MeOH = 100:5) gave

(*M*)-**29** (19.0 mg, 36.0 μmol, 63%, dr 94:6)[11] as an amorphous solid, which was obtained atropoisomerically pure by preparative HPLC on chiral phase [column: chiralcel OD-H (Daicel Chem. Ind. Ltd., 4.6 mm x 250 mm); pump: waters HPLC pump 510; injector: Rheodyne 7125 Syringe loading sample injector, ERC-7215 UV; detector: Shimadzu C-R6-A integrator; detection at λ = 280 nm; solvent: hexane/*i*-PrOH = 90:10 (0.6 mL/min); t_R = 9 min for (*M*)-**29**]: $[\alpha]^{22}_D$ = -22 (*c* 0.18, CH_2Cl_2); IR (KBr) ν 3423, 2971, 2941, 1696, 1449, 1154, 1099, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 ppm (s, 7H), 1.43 (m, 2H), 1.59 (s, 3H), 1.70-1.76 (m, 3H), 3.68 (s, 3H), 3.88 (s, 3H, OCH_3), 3.97-3.98 (s, 1H), 4.24-4.33 (m, 3H), 5.59 (s, 1H), 6.52 (d, *J* = 2.3 Hz, 1H), 6.78 (s, 1H), 6.99 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 25.37, 26.27, 28.05, 53.41, 55.39, 58.23, 63.10, 63.27, 64.51, 66.67, 66.84, 79.48, 95.18, 95.79, 98.13, 98.39, 104.44, 116.47, 117.60, 125.45, 125.81, 126.40, 127.67, 128.26, 142.07, 145.17, 147.63, 151.97, 158.41, 161.42; MS (EI) *m/z* 529/527 (1/1) [M^+], 514/512 (1/2), 494/492 (1/3), 438/436 (5/12), 414/412 (14/22), 57 (100). Anal. Calcd for $C_{25}H_{31}Cl_2NO_7$: C, 56.82; H, 5.91; N, 2.65. Found: C, 57.13; H, 5.63; N, 2.82.

Reductive Hydrogenation of (*M*)-29. (A) Preparative Scale. A mixture of (*M*)-**29** (30.0 mg, 56.7 μmol, dr 86:14), $Pd(OAc)_2$ (2.60 mg, 11.6 μmol), and tri-(*O*-tolyl-)-phosphine (14.1 mg, 46.4 μmol) was treated in a well baked flask with NEt_3 (500 μl, 363 mg, 3.58 mmol) and formic acid (115 μl, 138 mg, 3.00 mmol) and stirred under argon at 80 °C for 2 h. Aqueous HCl (2 M, 1 mL) was added and the aqueous phase was thoroughly extracted with EtOAc. Drying ($MgSO_4$) of the combined organic phases and preparative thin layer chromatography (CH_2Cl_2/MeOH = 100:4) gave (*P*/*M*)-**12** (412 μg, 0.898 μmol, 1.6%, dr 47:53), which was chromatographically (HPLC) and spectroscopically (^1H NMR) identical to the material obtained above. **(B) Analytical Scale.** (*M*)-**29** (12.1 mg, 22.9 μmol, dr 94:6) was treated as described above and stirred at 80 °C for 15 min. After aqueous workup (see above),

(*P*)-**12** (dr 66:34) was detected in the organic phase by chiral HPLC. Identity with (*P*)-**12** was confirmed by HPLC coelution and CD spectroscopy.

Computational Methods. The absolute configuration of **12** was established through quantum chemical CD calculations, which had proven to be a valuable tool in earlier studies.[3,4] Because of the high degree of rotational flexibility at the biaryl axis, the CD calculations were based on molecular dynamics (MD) investigations of the conformational behavior of **12**, using the Tripos force field.[5] Arbitrarily starting with the (*P*)-atropo-diastereomer of the compound, the simulation was performed for a total time period of 500 ps, recording the structure every 0.5 ps for further calculations. For the 1000 structures thus collected for each compound, single CD spectra were calculated and then averaged arithmetically to give theoretical overall spectra. In order to take into account systematic shifts of the calculated CD spectra, a 'UV correction' was carried out for each calculated spectrum as introduced earlier.[5] The experimental CD spectrum (Figure 2) of the main product [obtained when using (*P*)-**14** as the reductant] showed a good agreement with the overall CD spectrum calculated for the (*P*)-isomer of **12** thus permitting an unambiguous attribution of its absolute configuration as (*P*). In agreement with this attribution, the curve of the likewise obtained minor (*M*)-atropo-diastereomer of **12** was nearly opposite to that calculated for (*P*)-**12**.

The molecular dynamics simulations of (*P*,*R*)-**12** and (*M*,*S*)-**12** were performed on an SGI Octane R10000 workstation using the Tripos[5] force field as implemented in the molecular modeling package Sybyl 6.7,[5] with a time step of 0.5 fs. The molecule was weakly coupled to a virtual thermal bath at $T = 1100$ K,[6] with a temperature relaxation time $\tau = 0.1$ ps.

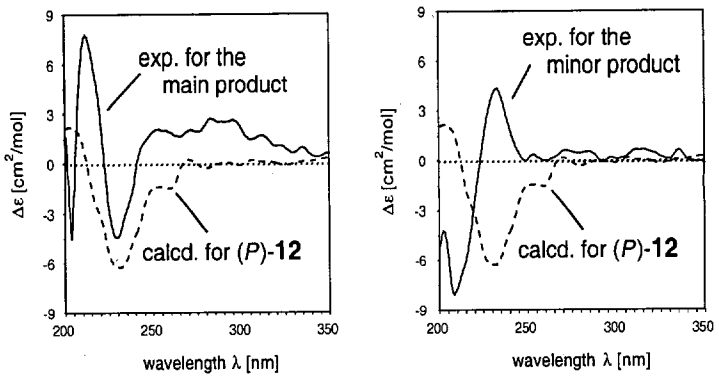

Figure 2. Elucidation of the absolute axial configurations of the major and the minor product of the ring cleavage of **11** using (*P*)-**14**, by comparison of their experimental CD spectra (—) with the one quantum chemically calculated for (*P*)-**12** (---)

The wavefunctions for the calculation of the rotational strengths for the electric transitions from the ground state to excited states were obtained by CNDO/S-CI calculations[7,8] with a CI expansion including 576 singly occupied configurations and the ground state determinant. These calculations were carried out on *i*PII and *i*PIII Linux workstations by the use of the BDZDO/MCDSPD[8] program package. For a better visualization, the rotational strengths were transformed into Δε values and superimposed with a Gaussian band shape function.

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(11) The dr value may not be totally accurate due to the fact that educt **28** is not optically pure, as it contains 5% of the 'wrong' (*S*)-enantiomer. Nonetheless, this should give the same (*M*):(*P*)-ratio using the enantiomeric oxazaborolidine for the ring cleavage, since (*R*)-**13** again affords the same 94:6 ratio, now in favor of (*P*)-**29**. This suggests that the asymmetric induction observed is independent of the configuration at the remote center in the B ring. Consequently, ring cleavage of the minor (*S*)-enantiomer of lactone **28** using (*S*)-**13** should give mainly the (*M*)-cleavage product, *i.e.* the (*S*)-diastereomer of (*M*)-**29** or, in other words, the enantiomer of (*P*)-**29**. Since the stereoanalysis was possible only on a chiral phase, whether this additional product is hidden under the larger peak of (*R*,*M*)-**29**, or (more

probably) under the smaller (*R*,*P*)-peak, cannot be determined with certainty at this stage. As a result, the 94:6 level of selectivity could be higher or lower by as much as ca. 5%.