A Chiral Catechol with C_2 Symmetry

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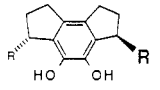
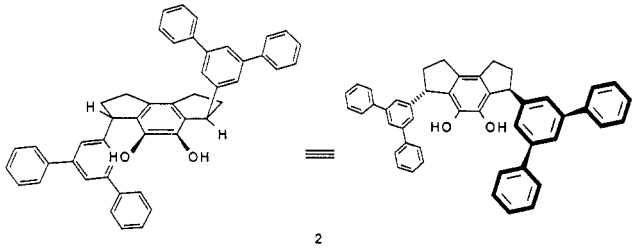
C_2-symmetric units figure prominently as the chiral element in a variety of asymmetric processes.[1,2] By virtue of their potential to function as either bidentate ligands or covalently bound auxiliaries, chiral, C_2-symmetric catechols would appear to have a diversity of possible applications in asymmetric synthesis. To date, however, no such catechols have been reported. We now describe the synthesis of the first representative of this new family of chiral substances.

Examination of molecular models suggested that catechols of the general type **1** possess several attractive features. Specifically, in addition to **1** being chiral and C_2 symmetric, the two R groups give rise to an asymmetric cavity within which the two potentially ligating oxygens are embedded. Appropriate choice of R allows one to dictate the steric and electronic contours of the cavity.



1

The derivative of **1** where R = *m*-terphenyl, i.e. **2**, was selected as a prototype for synthesis. We herein describe the preparation of (±)-**2** and the resolution of (±)-**2** into its enantiomers. Both the synthesis of **2** and its resolution

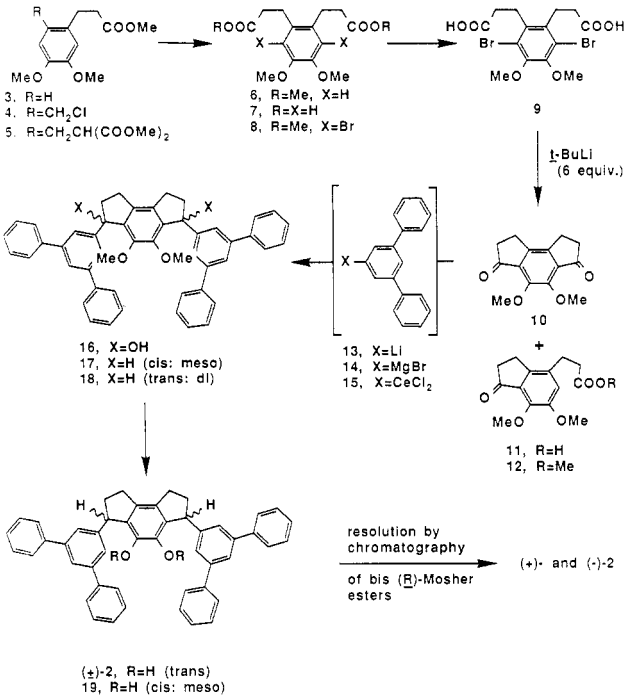


2

entail sequences that are essentially generic and should, by minor extension, provide access to a variety of variously functionalized members of this new class of catechols.

The synthesis of **2** is outlined in Scheme I. Originally, it had been anticipated that **10** might be available by biscyclization of diacid **7**.[3] The latter (**7**) is accessible from **3** in straightforward fashion, but attempts to convert **7** directly into **10** proved unsatisfactory.[4] Fortunately, however, the derived dibromo diacid **9** undergoes double Parham[5] cyclization upon treatment with 6 equiv of *t*-BuLi

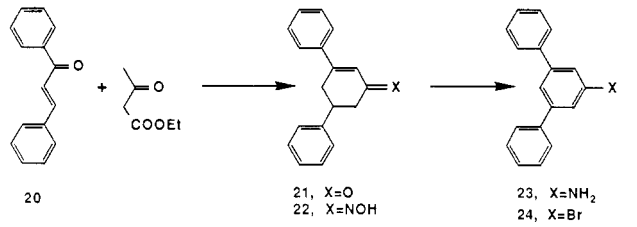
Scheme I



to provide the desired tricyclic diketone **10** along with keto acid **11**.

The terphenyl unit was originally prepared in abundance by the sequence in eq 1 which is based on the known[6] Semmler-Wolff[7] conversion of **22** to **23**. The synthesis of **24** outlined in eq 1 has recently been superceded by a convenient one-pot preparation.[8]

(eq 1)



Attempted coupling of **10** with the terphenyllithium or magnesium derivatives **13** and **14** gave none of **16**, presumably because of competing enolization, but reaction of **10** with the terphenylcerium[9] reagent **15** gives **16** in 61% yield as a cis/trans mixture. Reduction of this mixture with Et_3SiH/CF_3COOH provides in 87% yield a mixture of **17** and **18** in which the desired trans isomer (**18**) is the major component. Demethylation of **18** with BBr_3 gives the racemic ligand **2** in 90% yield.

Resolution of (±)-**2** into its antipodes is achieved by chromatographic separation of the diastereomeric mixture of bis Mosher[10,11] esters. Assignment of cis and trans

(1) For a review of chiral organic molecules with high symmetry, see: Nakazaki, M. *Top. Stereochem.* **1984**, *15*, 199-251.

(2) For an earlier paper on asymmetric catalysis from this laboratory, see: Kelly, T. R.; Whiting, A.; Chandrakumar, N. S. *J. Am. Chem. Soc.* **1986**, *108*, 3510-3512.

(3) Compare Bell, W. L.; Curtis, J. C.; Elgenbrot, C. W., Jr.; Pierpont, G. P.; Robbins, J. L.; Smart, J. C. *Organometallics* **1987**, *6*, 266-273.

(4) In small scale reactions **7** could be cyclized to **10** in approximately 16% yield with polyphosphate ester (PPE), but attempts to conduct the biscyclization on a practical scale were frustrated by lower yields. A variety of other reagents (e.g., PPA, PPA/P_2O_5, molten $AlCl_3/NaCl$, $POCl_3/P_2O_5/H_3PO_4$, and P_2O_5/CF_3SO_3H) were even more unsatisfactory. Attempts to cyclize the diacid chloride derived from **7** with $AlCl_3$ or CF_3SO_3H did not provide useful amounts of **10**.

(5) Parham, W. F.; Jones, L. D.; Sayed, Y. A. *J. Org. Chem.* **1975**, *40*, 2394-2399.

(6) Polaczkowa, W.; Porowska, N. *Roczniki Chem.* **1960**, *34*, 1659-1665; *Chem. Abstr.* **1962**, *56*, 5865*g*.

(7) For a review, see: Conley, R. T.; Ghosh, S. In *Mechanisms of Molecular Migrations*; Thyagarajan, B. S., Ed.; Interscience: New York, 1971; Vol. 4, pp 197-308 (see section III).

(8) Du, C.-J. F.; Hart, H.; Ng, K.-K. D. *J. Org. Chem.* **1986**, *51*, 3162-3165.

(9) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233-4236.

(10) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543-2549.

(11) The absolute stereochemistry of (+)-**2** and (−)-**2** remains to be established.

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relative stereochemistry to **17** and **18** follows from the finding that the catechol (**2**) derived from **18** can be resolved (the catechol derived from **17** is meso and, hence, not resolvable).

The synthesis and resolution of **2** demonstrate the feasibility of the overall synthetic scheme. By virtue of the central position of *as*-indacenedione **10** in the sequence, numerous other members of this family should be straightforwardly available.

Experimental Section[12]

Methyl 3-[2-(Chloromethyl)-4,5-dimethoxyphenyl]propanoate (4).[13] To a stirred, ice-cold solution of 27.0 g (0.120 mol) of ester **3**[14] in 200 mL of dry dichloromethane was added 13.5 mL (0.177 mol) of chloromethyl methyl ether followed by dropwise addition of 4.5 mL (0.038 mol) of stannic chloride over 1 h. The resulting blue solution was stirred for 1 h at 0 °C and then for 15 min at room temperature and poured into 200 mL of ice water. The mixture was stirred vigorously until the color of the organic layer became pale yellow. The organic layer was separated, washed with water, dried by gravity filtration, and diluted with 100 mL of toluene. Concentration in vacuo provided 32.9 g of crude **4** as a brown oil, which was normally used immediately in the next reaction.

A sample of pure **4** was obtained as a colorless solid, mp 69–70 °C, by Kugelrohr distillation (bp 150 °C/0.05 Torr): IR (film) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.83 (1 H, s), 6.71 (1 H, s), 4.63 (2 H, s), 3.87 (6 H, s), 3.68 (3 H, s), 2.85 (4 H, m); MS, *m/e* 272, 274 (M^+).

Methyl 3-[2-[2-(Methoxycarbonyl)ethyl]-4,5-dimethoxyphenyl]-2-(methoxycarbonyl)propanoate (5). To a dry, three-necked, 500-mL, round-bottomed flask equipped with a reflux condenser and magnetic stirring was added 0.125 mol of sodium hydride (5.00 g of a 60% suspension in oil) under nitrogen. After the NaH was washed with two 30-mL portions of petroleum ether, 200 mL of dry THF was added, and the suspension was cooled to 0 °C. To the stirred suspension was added 21 mL (0.18 mol) of dimethyl malonate dropwise over 15 min. Once H_2 evolution had ceased, a solution of 32.9 g of crude **4** in 100 mL of dry THF was added over 10 min. The mixture was heated at reflux under nitrogen for 3 h, cooled to room temperature, and allowed to stir overnight. Cautiously (residual NaH) water (15 mL) and then anhydrous $MgSO_4$ were added; the mixture was stirred for 15 min and filtered. Removal of the solvent provided 40 g of crude triester **5** as a dark brown oil, which was ordinarily used in the next reaction without further purification.

An analytical sample (a yellow oil) of **5** was prepared by flash column chromatography with 1:1 petroleum ether/ether as eluant: IR (film) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.68 (2 H, s), 3.83 (6 H, s), 3.70 (6 H, s), 3.68 (3 H, s), 2.88 (7 H, m). Anal. Calcd for $C_{18}H_{24}O_8$: C, 58.69; H, 6.52. Found: C, 58.95; H, 6.67.

Methyl 3-[2-[2-(Methoxycarbonyl)ethyl]-4,5-dimethoxyphenyl]propanoate (6). To a solution of 40 g of crude triester **5** in 100 mL of methanol was added a solution of 32 g of NaOH in 200 mL of water. After being heated at reflux for 5 h, the reaction mixture was cooled to room temperature, washed with ether to remove any neutral material, acidified with concentrated HCl (→pH 1), and extracted with four 200-mL portions of ethyl acetate. The combined ethyl acetate extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo to give 39 g of crude triacid as a brown solid, which was directly converted to **6** without purification. Thus, the triacid (39 g) was heated at 200 °C for 30 min at which time gas evolution had subsided. After being cooled to room temperature, the oil was dissolved in 200 mL of anhydrous methanol and stirred under reflux with 2 mL of concentrated H_2SO_4 for 4 h. After being cooled to room temperature and diluted with 400 mL of cold water, the mixture was extracted with four 200-mL portions of ether. The combined ether extracts were washed with two 100-mL portions of 5% NaOH solution, dried (Na_2SO_4), and concentrated in vacuo. The residual 31 g of brown oil was purified by flash column chromatography with 3:2 ether/petroleum ether as eluant to provide 22.0 g (54.7% from **3**) of pure diester **6** as a viscous, pale yellow oil: IR (film) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.67 (2 H, s), 3.83 (6 H, s), 3.68 (6 H, s), 2.70 (8 H, m); ^{13}C NMR ($CDCl_3$) δ 174.67, 148.86, 131.68, 113.81, 57.29, 53.03, 37.01, 28.75. Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.93; H, 7.09. Found: C, 62.08; H, 7.11.

3-[2-(2-Carboxyethyl)-4,5-dimethoxyphenyl]propanoic Acid (7). To a stirred solution of 8.0 g (26 mmol) of diester **6** in 100 mL of THF was added 100 mL of 1 N NaOH. After 1.5 h at room temperature, the two layers were separated, and the aqueous layer was acidified with ca. 1.5 M HCl and extracted with four 100-mL portions of ether. The extracts were combined, dried (Na_2SO_4), and concentrated in vacuo to give 7.2 g (98%) of diacid **7** as an off-white solid, mp 125–128 °C: IR (film) 3300 (br), 1740, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.50 (2 H, s), 3.74 (6 H, s), 2.67 (8 H, m); ^{13}C NMR ($CDCl_3$) δ 178.60, 147.64, 130.14, 112.49, 55.95, 35.65, 27.18.

Methyl 3-[3,6-Dibromo-2-[2-(methoxycarbonyl)ethyl]-4,5-dimethoxyphenyl]propanoate (8). To a stirred, gently refluxing mixture of 12.0 g (38.7 mmol) of diester **6** and 12.5 g (77.1 mmol) of anhydrous $FeCl_3$ in 1 L of CCl_4 was added dropwise a solution of 12.5 g (78.0 mmol) of Br_2 in 50 mL of CCl_4 at a rate that prevented bromine vapor from coloring the condenser. The addition required ca. 2 h. The reaction mixture was then cooled to room temperature, poured onto 1 kg of ice, and extracted with three 200-mL portions of CH_2Cl_2. The combined CH_2Cl_2 extracts were sequentially washed with water, 10% $Na_2S_2O_3$ solution (2 × 200 mL), and water. After the CH_2Cl_2 solution was dried by gravity filtration, removal of solvent and recrystallization of the residual brown solid from methanol provided 13.0 g (72%) of pure dibromo diester **8** as white needles: mp 132–134 °C; IR (film) 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.87 (6 H, s), 3.72 (6 H, s), 2.84 (8 H, m). Anal. Calcd for $C_{16}H_{20}Br_2O_6$: C, 41.02; H, 4.27; Br, 34.18. Found: C, 41.13; H, 4.36; Br, 34.08.

3-[3,6-Dibromo-2-(2-carboxyethyl)-4,5-dimethoxyphenyl]propanoic Acid (9). A mixture of 12.7 g (27 mmol) of dibromo diester **8**, 50 mL of ethanol, and 100 mL of 15% NaOH was heated at reflux for 2 h, cooled, and acidified (→pH 1) with concentrated HCl. The white precipitate was collected, dried, and recrystallized from acetone to give 11.9 g (99%) of dibromo diacid **9**, mp 240–241 °C.

An analytical sample, white crystals melting at 240–240.5 °C, was prepared by recrystallization from methanol: IR (KBr) 3400 (br), 1735 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.80 (6 H, s), 3.00 (4 H, m), 2.50 (4 H, m). Anal. Calcd for $C_{14}H_{16}Br_2O_6$: C, 38.18; H, 3.63. Found: C, 37.92; H, 3.77.

1,2,7,8-Tetrahydro-4,5-dimethoxy-*as*-indacene-3,6-dione (10). (a) From Dibromo Diacid 9. To a stirred solution of 9.60 g (21.8 mmol) of dibromo diacid **9** in 1 L of dry THF at −78 °C under argon was added 76.0 mL (129 mmol) of 1.7 M *t*-BuLi in hexane. After 20 h at −78 °C, 100 mL of 5 N HCl was added. The organic layer was separated, and the aqueous layer was extracted with two 250-mL portions of ethyl acetate. The combined organic phases were washed with saturated $NaHCO_3$ solution (2 × 200 mL) and water, dried ($MgSO_4$), and concentrated in vacuo. The residual off-white solid was triturated with 25 mL of 7:3 ether/petroleum ether to give 1.20 g of crystalline **10**. The mother liquor was concentrated and purified by flash column chromatography with 1:3 petroleum ether/ether to provide an additional 0.21 g (26% combined yield) of diketone **10** as a light-yellow solid, identical with the material prepared from **7** (see below).

In the course of a reaction conducted on half of the above scale, the combined $NaHCO_3$ extracts were acidified with concentrated HCl and extracted with three 300-mL portions of ethyl acetate. The ethyl acetate extracts were combined, washed with two 200-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residual solid (2.47 g) was purified by flash column chromatography with ethyl acetate as eluant to provide 2.0 g (70%) of keto acid **11** as an off-white solid, mp 119–121 °C: IR (film) 3200 (br), 1740, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.01 (1 H,

(12) For general experimental considerations, see: Kelly, T. R.; Ananthasubramanian, L.; Borah, K.; Gillard, J. W.; Goerner, R. N., Jr.; King, P. F.; Lyding, J. M.; Tsang, W.-G.; Vaya, J. *Tetrahedron* **1984**, *40*, 4569–4577.

(13) Compare Durand-Dran, R.; Lecocq, M.; Quelet, R. *Compt. Rend.* **1960**, *250*, 2727–2729.

(14) Prepared in 94% yield by BF_3-catalyzed esterification[15] of the corresponding dihydrocinnamic acid.[13]

(15) Marshall, J. L.; Erickson, K. C.; Folsom, T. K. *Tetrahedron Lett.* **1970**, 4011–4012.

s), 3.94 (3 H, s), 3.85 (3 H, s), 2.80 (8 H, m). The keto acid **11** was further characterized as its methyl ester (**12**) by esterification with methanol in the presence of a catalytic amount of concentrated sulfuric acid. After purification by flash column chromatography with 7:3 petroleum ether/ether as eluant, **12** melted at 79–80 °C: IR (film) 1735, 1705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.04 (1 H, s), 3.95 (3 H, s), 3.89 (3 H, s), 3.69 (3 H, s), 2.75 (8 H, m). Anal. Calcd for **12** ($C_{15}H_{18}O_5$): C, 64.75; H, 6.47. Found: C, 64.69; H, 6.75.

(b) From Diacid 7.[3,4] To a mixture of 430 mg (1.52 mmol) of the diacid **7** and 50 mL of dry dichloromethane was added 6 g of polyphosphate ester.[16] The reaction mixture was heated at reflux for 21 h under nitrogen, cooled to room temperature, poured into 200 mL of water, and extracted with three 150-mL portions of ether. The combined ether extracts were washed with three 60-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residual yellow oil was purified by flash column chromatography with 1:2 petroleum ether/ether as eluant to provide 62 mg (16%)[4] of diketone **10** as an off-white solid.

An analytical sample of **10**, mp 186–187 °C, was prepared by recrystallization from ether: IR (film) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.99 (6 H, s), 2.90 (8 H, m); ^{13}C NMR ($CDCl_3$) δ 203.87, 149.57, 147.66, 134.01, 62.23, 37.43, 22.98. Anal. Calcd for **10** ($C_{14}H_{14}O_4$): C, 68.29; H, 5.69. Found: C, 68.30; H, 5.60.

3,6-Bis(3,5-diphenylphenyl)-1,2,3,6,7,8-hexahydro-4,5-dimethoxy-*as*-indacene-3,6-diol (16). To a solution of 6.42 g (20.7 mmol) of terphenyl bromide **24** in 120 mL of dry THF was added dropwise 24.4 mL (41.3 mmol) of 1.7 M *t*-BuLi in pentane at −78 °C under argon, and the mixture was stirred for 24 h at −78 °C.

In a 1-L, round-bottomed, side-arm flask equipped with a magnetic stirring bar was placed 8.46 g (22.7 mmol) of $CeCl_3 \cdot 7H_2O$, which was then heated at 145 °C under vacuum (0.5 Torr) for 3 h. After being cooled to room temperature and placed under argon, the white powder was suspended in 200 mL of dry THF and stirred for 2 h. The suspension was cooled to −78 °C, and the freshly prepared solution of terphenyllithium (see preceding paragraph, still at −78 °C) was added via cannula. The mixture was allowed to stir for 30 min at −78 °C, during which time the white suspension became amber in color.

A solution of 1.33 g (5.41 mmol) of diketone **10** in 25 mL of THF was added, and the reaction mixture was stirred for 60 h at −78 °C and for 48 h at 4 °C. The reaction was quenched by addition of 200 mL of saturated NH_4Cl solution, and the mixture was filtered through Celite. The filtrate was diluted with 200 mL of water and extracted three times with ethyl acetate. The combined ethyl acetate extracts were dried (Na_2SO_4) and concentrated in vacuo. The residual brown mass (5.08 g) was purified by flash column chromatography with 1:1 petroleum ether/ether as eluant to provide 2.31 g (61%)[17] of diol **16** as a light-yellow solid, mp 111–113 °C, presumably a mixture of cis/trans isomers: IR (film) 3400 (br) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42 (26 H, m), 3.60 (6 H, s), 3.25 (2 H, br s), 3.1–2.4 (8 H, m).

***meso*- and *dl*-3,6-Bis(3,5-diphenylphenyl)-1,2,3,6,7,8-hexahydro-4,5-dimethoxy-*as*-indacene [17 (cis) and 18 (trans)].** A solution of 2.17 g (3.07 mmol) of diol **16** and 13 mL of triethylsilane in 130 mL of dry dichloromethane was added over 5 min to 45 mL of trifluoroacetic acid with stirring at room temperature under nitrogen. During the addition of each drop, a red color formed and disappeared immediately. Ten minutes after the addition of **16** was complete, 250 mL of water was added to the reaction mixture, which was then stirred for an additional 5 min. The organic layer was separated, and the aqueous layer was extracted with three 100-mL portions of dichloromethane. The combined organic phases were washed with three 200-mL portions of brine, dried (Na_2SO_4), and concentrated in vacuo. The residual off-white solid (2.84 g) was purified by flash column chromatography with 95:5 petroleum ether/ether as eluant to provide 0.99 g (48%) of the less polar trans isomer **18** and 0.80 g (39%) of the more polar cis isomer **17**.

An analytical sample of the *dl* (trans) isomer **18**, mp 167–168 °C, was prepared by recrystallization from petroleum ether/ether: IR (film) 1600, 1580, 1500, 1465, 1420, 1030, 1010, 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50 (26 H, m), 4.65 (2 H, m), 3.32 (6 H, s), 2.57 (8 H, m). Anal. Calcd for **18** ($C_{50}H_{42}O_2$): C, 89.02; H, 6.23. Found: C, 89.13; H, 6.14.

The *meso* (cis) isomer **17** melted at 192 °C after recrystallization from ether: MS, *m/e* 674 (M^+); IR (film) 1700, 1600, 1580, 1500, 1470, 1438, 1420, 1030 (sh), 1020, 990 (sh) cm^{-1}; ^1H NMR ($CDCl_3$) δ (26 H, m), 4.60 (2 H, m), 3.48 (6 H, s), 2.60 (8 H, m). Anal. Calcd for **17** ($C_{50}H_{42}O_2 \cdot 1H_2O$): C, 86.70; H, 6.35. Found: C, 86.64; H, 6.29.

(±)-3,6-Bis(3,5-diphenylphenyl)-1,2,3,6,7,8-hexahydro-*as*-indacene-4,5-diol (2). To a solution of 696 mg (1.03 mmol) of (±)-**18** in 8 mL of dry dichloromethane at −78 °C was added 1.1 mL (1.1 mmol) of a 1 M solution of boron tribromide in dichloromethane (Aldrich). The reaction mixture was allowed to warm to room temperature and stirred for 12 h. Water (20 mL) was added, and stirring was continued for a further 5 min. The organic layer was separated, and the aqueous layer was extracted with three 10-mL portions of dichloromethane. The combined organic phases were washed with 20 mL of brine, dried (Na_2SO_4), and concentrated in vacuo. The residual foamy off-white solid (650 mg) was purified by flash column chromatography with 1:1 petroleum ether/dichloromethane as eluant, to give 600 mg (90%) of the pure trans catechol (±)-**2** as a foamy white solid: mp 114 °C dec; IR (film) 3520 (br), 1600, 1580, 1500, 1480, 1460, 1438, 1415, 1290 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45 (26 H, m), 4.60 (4 H, br s), 3.10–2.05 (8 H, m).

***meso*-3,6-Bis(3,5-diphenylphenyl)-1,2,3,6,7,8-hexahydro-*as*-indacene-4,5-diol (19 (cis)).** Treatment of the cis isomer (**17**) with BBr_3 in a procedure analogous to that used to convert **18** to **2** gave the cis (*meso*) catechol **19**: mp 123–124 °C (from hexane/CH_2Cl_2); IR (film) 3520 (br), 1600, 1580, 1500, 1480, 1460, 1440, 1415, 1280 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45 (26 H, m), 4.60 (4 H, br s), 3.05–2.05 (8 H, m).

Preparation and Separation of the (*R*)-Mosher Diesters of (+)- and (−)-2. To a solution of 1.00 g (1.55 mmol) of the racemic catechol **2** in 14 mL of anhydrous pyridine was added 1.8 mL of Mosher acid chloride [prepared from (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (Aldrich) according to the literature[10]] at room temperature, and the reaction mixture was stirred for 4 days. The solvent was evaporated, and 50 mL each of water and dichloromethane were added. The layers were separated, and the aqueous layer was extracted with three 30-mL portions of dichloromethane. The combined organic extracts were washed with 5% $NaHCO_3$ solution (2 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo. The residual solid (1.14 g) was submitted to flash column chromatography with 3:1 petroleum ether/dichloromethane as eluant to give 634 mg (38%, 76% of theory) of one diester (the less polar diastereomer) as a foamy white solid and 644 mg (39%, 78% of theory) of the other diester, also as a foamy white solid.

The less polar isomer melted at 97 °C: IR (film) 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.70–6.75 (36 H, m), 4.61 (2 H, m), 3.06 (4 H, m), 2.84 (2 H, m), 2.30 (6 H, s), 2.20 (2 H, m); $[\alpha]^{23}_D$ +175° (c = 0.25, CH_2Cl_2).

The more polar isomer melted at 280–281 °C: IR (film) 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.51–6.70 (36 H, m), 4.35 (2 H, m), 3.02 (6 H, s), 2.98 (4 H, m), 2.78 (2 H, m), 2.12 (2 H, m); $[\alpha]^{23}_D$ −123° (c = 0.25, CH_2Cl_2).

(+)- and (−)-3,6-Bis(3,5-diphenylphenyl)-1,2,3,6,7,8-hexahydro-*as*-indacene-4,5-diol [(+)-2 and (−)-2]. To a solution of 396 mg (0.38 mmol) of the less polar Mosher diester from above in 40 mL of dry ether was added over 3 min 6 mL (6 mmol) of a 1 M solution of lithium aluminum hydride in THF at room temperature. After 18 h of stirring, the excess lithium aluminum hydride was destroyed by slow addition of 20 mL of ethyl acetate. The mixture was poured into 50 mL of 1 N HCl. The organic layer was separated, and the aqueous layer was extracted with three 30-mL portions of ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residual solid (360 mg) was purified by radial chromatography with 1:1 dichloromethane/petroleum ether as eluant to give 206 mg (86%) of enantiomerically pure (+)-**2** as a foamy white solid: mp 112 °C dec; $[\alpha]^{23}_D$ +127.1° (c = 1, CH_2Cl_2).

(16) The PPE was prepared by the method described in Cava, M. P.; Lakshmikantham, M. V.; Mitchell, M. J. *J. Org. Chem.* **1969**, *34*, 2665–2667.

(17) Increasing the **15**:**10** ratio gives a somewhat higher (based on **10**) yield of **16**.

Similar treatment of the more polar Mosher diester with lithium aluminum hydride gave after radial chromatography (−)-**2** as a white solid: mp 107 °C dec; $[\alpha]^{23}_D$ −128.3° (c = 1, CH_2Cl_2).

3,5-Diphenylcyclohex-2-en-1-one Oxime (22). To a stirred solution of 40 g (0.16 mol) of ketone **21**[18] in 1 L of ethanol was added a solution of 22.5 g (0.39 mol) of hydroxylamine hydrochloride in 150 mL of water. The solution was neutralized with 1 N alcoholic KOH to pH 7 and stirred for 4 days at 4 °C, which led to precipitation of a light yellow solid. The heterogeneous mixture was poured into 1 N HCl and thrice extracted with ether. The combined ether extracts were dried (Na_2SO_4) and concentrated in vacuo. The residual yellow solid (42 g) was purified by recrystallization from ethanol. Purification of the mother liquor by flash column chromatography (eluting with 4:1 petroleum ether/ethyl acetate) gave additional **22**; total yield = 38.5 g (91%) of oxime **22** as a white solid: mp 167–170 °C (lit.[19] mp 163–164 °C); IR (film) 3200 (br) 1650, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20 (10 H, m), 6.65 (1 H, s), 2.75 (5 H, m).

3,5-Diphenylaniline (23).[20] To a stirred mixture of 25.0 g (95 mmol) of oxime **22**, 62 mL (0.66 mol) of acetic anhydride, and 13.5 mL (0.167 mol) of pyridine at 0 °C was added dropwise (over 2 min) 10.5 mL (0.14 mol) of acetyl chloride, during which time a white solid precipitated. The mixture was warmed slowly to 90 °C, at which time the mixture became homogeneous, and then heated at reflux under nitrogen for 2 h. After being cooled to room temperature, the resulting brown solution was poured onto ice and thrice extracted with ether. The combined ether extracts were washed with water, dried (Na_2SO_4), and concentrated in vacuo to give 38 g of a yellow solid, which was not purified (it is a mixture primarily of the amide and imide of **23**) but subjected directly to hydrolysis.

Thus to a mixture of the yellow solid (38 g) and 400 mL of ethanol was added 400 mL of concentrated HCl, and the resulting mixture was heated under reflux for 3.5 h. After being cooled to 0 °C, the crystals were collected by filtration, suspended in 400 mL of water, treated with 350 mL of 5 M NaOH, and stirred at 100 °C for 15 min. The mixture was then cooled to 0 °C, and the crude amine was collected by filtration to give 19.5 g of a light gray solid after washing with cold water and air drying. Recrystallization from ethanol and flash column chromatography (eluting with 6:1 petroleum ether/ethyl acetate) of the mother liquor gave 19 g (81%) of aniline **23** as a gray-white solid: mp 92–95 °C (lit.[6] mp 109–110 °C); IR (film) 3400, 3290, 3180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (11 H, m), 6.90 (2 H, s), 3.50 (2 H, br).

1-Bromo-3,5-diphenylbenzene (24).[21,8] To an ice-cold, vigorously stirred mixture of 15.0 g (61.5 mmol) of **23** in 150 mL of 48% HBF_4 was added dropwise a solution of 75 g of sodium nitrite in 150 mL of water over 2 h. The mixture was then left to stir at 0 °C. The diazonium salt was collected by filtration and washed sequentially with ice-cold water (2×), ice-cold ethanol, and ether (*CAUTION*: although we have experienced no problems with this diazonium salt, diazonium salts have been known to explode, especially in the solid form).

The terphenyldiazonium fluoborate was immediately dissolved in 105 mL of dimethyl sulfoxide, and the resulting solution was added slowly to a vigorously stirred solution of 28.2 g (0.126 mol) of cupric bromide in 60 mL of dimethyl sulfoxide at room temperature over 20 min. After the addition was complete, the reaction mixture was diluted with 750 mL of water and thrice extracted with benzene. The combined benzene extracts were twice washed with water, dried (Na_2SO_4), and concentrated in vacuo to give 22.5 g of yellow solid. Purification by flash column chromatography (eluting with petroleum ether) gave a white solid, which was recrystallized from 95% ethanol to provide 13.7 g (72%) of terphenyl bromide **24**: mp 107–108 °C (after the fact lit.[8] mp 107.5–109 °C); IR (film) 3050, 3020, 2910, 1590, 1580, 1555, 1495 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.5. Anal. Calcd for $C_{18}H_{13}Br$: C, 69.90; H, 4.20. Found: C, 69.77; H, 4.31.

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Registry No. (±)-**2**, 118357-17-8; (+)-**2**, 118397-99-2; (−)-**2**, 118357-18-9; **2** (bis (*R*)-Mosher ester isomer 1), 118357-19-0; **2** (bis (*R*)-Mosher ester isomer 2), 118396-92-2; **3**, 27798-73-8; **4**, 118357-03-2; **5**, 118357-04-3; **5** (triacid derivative), 118357-10-1; **6**, 118357-05-4; **7**, 118357-06-5; **8**, 118357-07-6; **9**, 118357-08-7; **10**, 118357-09-8; **11**, 118357-11-2; **12**, 118357-12-3; **16** (cis isomer), 118357-13-4; **16** (trans isomer), 118357-20-3; **17**, 118357-14-5; **18**, 118357-15-6; **19**, 118357-16-7; **21**, 10346-08-4; **22**, 30240-38-1; **23**, 63006-66-6; **24**, 103068-20-8; chloromethyl methyl ether, 107-30-2; dimethyl malonate, 108-59-8.

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Conversion of Antibiotic A82846B to Orienticin A and Structural Relationships of Related Antibiotics

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Until recently the clinically important antibiotic, vancomycin, was structurally unique among the class of glycopeptide antibiotics in possessing five aromatic rings with a *N*-methylleucine as the N-terminal amino acid residue. However, several close structural analogues have been reported lately, and these include A51568 factors A and B,[1] the M43 group of antibiotics,[2] A82846 factors A, B, and C,[3] orienticin A, B, and C,[4] and eremomycin.[5] Here we report on the structural relationship of antibiotic A82846B with orienticin A and the structural identity of A82846A to eremomycin.

Amycolatopsis orientalis NRRL 18090 (formerly designated *Nocardia orientalis*) produces glycopeptide antibiotics A82846 factors A, B, and C,[6] and their structures were established as **2**, **3**, and **4**, respectively.[7] Orienticin A, the major component of *Nocardia orientalis* PA42867 has been assigned the structure **5**[4] (Figure 1). Catalytic dechlorination of vancomycin (*1*) occurs initially on the aromatic ring C, and on prolonged reaction the second chlorine on ring A is removed.[8] We undertook a catalytic

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