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Synthesis of 4(S)-(3,4-Dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone by SN2 Cuprate Displacement of an Activated Chiral Benzylic Alcohol

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Abstract: Two routes for the preparation of 4(S)-(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone are reported. The most efficient route generates a chiral benzylic alcohol by catalytic asymmetric oxazaborolidine reduction of a γ-ketoester that is subsequently activated and displaced in an SN2 manner with a higher order cuprate. Intramolecular Friedel-Crafts cyclization of the resulting t-butylester affords the title compound.

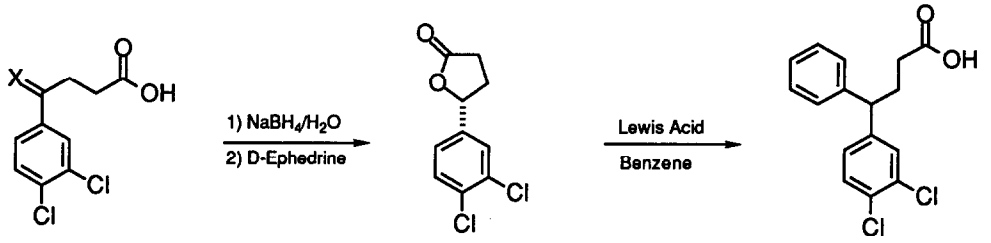
The number of new pharmaceutical agents being developed and marketed as single stereoisomers continues unabated.[1] Pure enantiomers now constitute over half of the drugs undergoing clinical evaluation.[2] Sertraline **1**, a novel competitive inhibitor of synaptosomal serotonin uptake, is a member of the drug class being developed as a pure enantiomer.[3] Sertraline was originally prepared by resolution of the racemate with D-mandelic acid.[4] This synthesis has been improved by a more efficient route to the intermediate racemic tetralone **2**.[5] An asymmetric synthesis of tetralone **2** was sought to eliminate processing the undesired enantiomer of Sertraline to the resolution stage. Enantioselective ketone reduction and SN2 cuprate displacement of a chiral benzylic mesylate with good stereochemical control are the hallmarks of the synthesis.

Results and Discussion

The initial route to tetralone **2** began with the known ketoacid **3**[6] that was reduced as its sodium salt in water with sodium borohydride to generate the racemic hydroxy acid **4**[7] (Scheme 1). Resolution of the hydroxy acid **4** with D-ephedrine and subsequent liberation of the resolved ephedrine salt with hydrochloric acid afforded a 55% overall yield of chiral lactone **5**. Conversion of lactone **5** into tetralone formally required the addition of benzene and loss of water. We believed this would be best achieved under "basic" conditions, as under acidic conditions the secondary benzylic carbocation would not have chiral memory, and the racemic product would be expected.[8] Literature precedent supported this contention as Friedel Crafts reaction of (S)-γ-valerolactone with benzene as solvent has been reported to give the (R)-γ-phenylvaleric acid with 40%

inversion.[9] Since the secondary chiral center in lactone **5** was also benzylic, the inversion was anticipated to be lower.[10] This expectation was born out by experiment. Reaction of lactone **5** in benzene with a variety of Lewis acid catalysts produced the diaryl acid **6** in racemic form.[11]

Scheme 1



3 X=O
4 X=OH,H

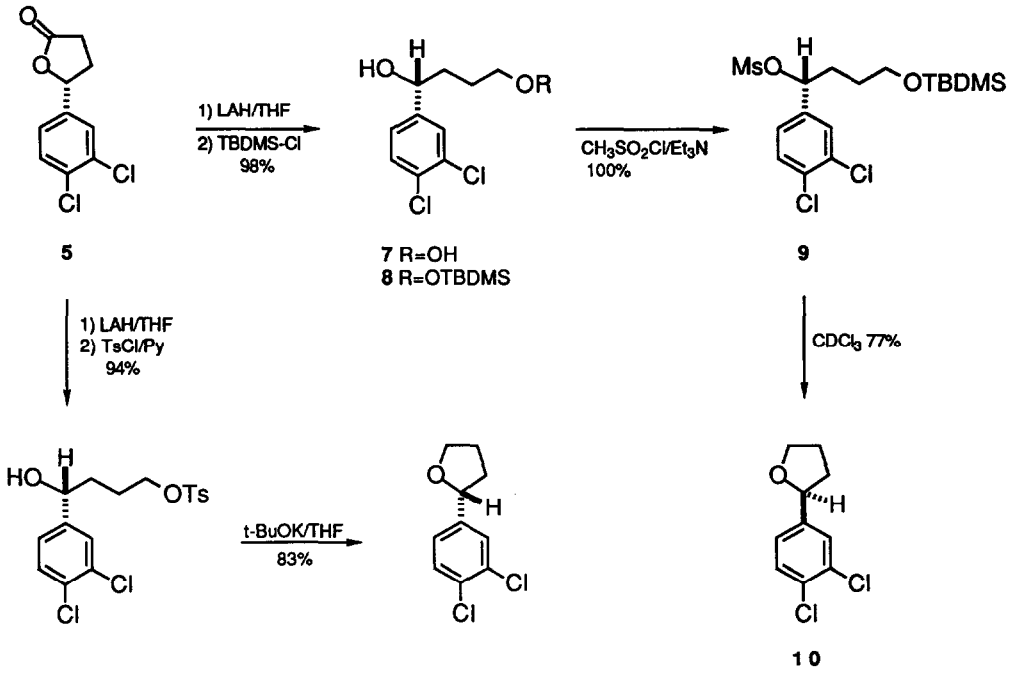
5

6

Conversion of **5** under basic conditions was investigated having verified that chirality transfer under acidic conditions was precluded by intervention of the carbocation. The plan was to employ an SN2 cuprate reaction to secure tetralone **2**.[12] Because cuprate displacement of a secondary benzylic leaving group with good chirality transfer was to our knowledge not known, and substitutions at secondary centers were reported to be limited to those cuprates prepared from either n-alkyl or vinyllithium precursors, this proposal was assessed with concern.[13] Furthermore, it was not clear from the literature which derivative of the secondary benzylic alcohol **8** would be best for the cuprate displacement. Tosylates and mesylates of secondary non-benzylic alcohols have been employed in lower order cuprate displacements affording predominate SN2 inversion.[14] By contrast, higher order cuprates have been reported to work best with secondary halides employing two equivalents of reagent, while secondary mesylates and tosylates also form the desired products but require ten equivalents of reagent.[15] The appropriate choice of copper salt was not perspicuous either,[16] and whether higher order cuprates, possessing cyanide ligands as opposed to lower order cuprates with halide ligands, exist as unique species has also been questioned.[17] Therefore, while numerous examples of SN2 cuprate displacement of secondary leaving groups affording the products in high optical purity exist in the literature, the understanding of these substitution reactions at benzylic sites and in other systems continues to evolve.[18]

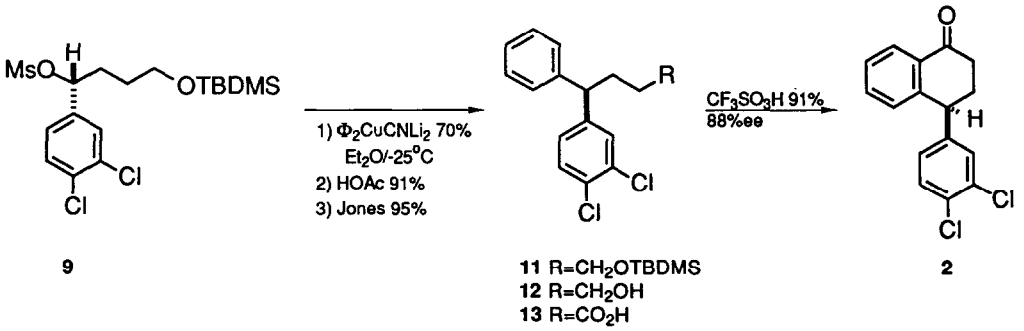
Transformation of lactone **5** into tetralone began with lithium aluminum hydride reduction to afford the diol **7**, which was selectively protected at the primary alcohol as its t-butyldimethyl silyl ether **8** in 98% yield (Scheme 2). Mosher's ester derivatization of **8** verified that the ephedrine resolution of **4** generated enantiomerically pure lactone **5**.[19] The mesylate was chosen as the leaving group on pragmatic grounds for the cuprate displacement since this derivative can be rapidly and quantitatively formed without racemization due to the intermediate sulfene. Under standard conditions, alcohol **8** was uneventfully converted into mesylate **9** and employed directly in the cuprate coupling.[20] On standing in deuterochlorform the mesylate reproducibly cyclized to the optically pure tetrahydrofuran **10** with inversion at the benzylic position. Cyclization with inversion was verified by mono tosylation of the diol **7** and cyclization with potassium t-butoxide affording the enantiomer of **10**.[21]

Scheme 2



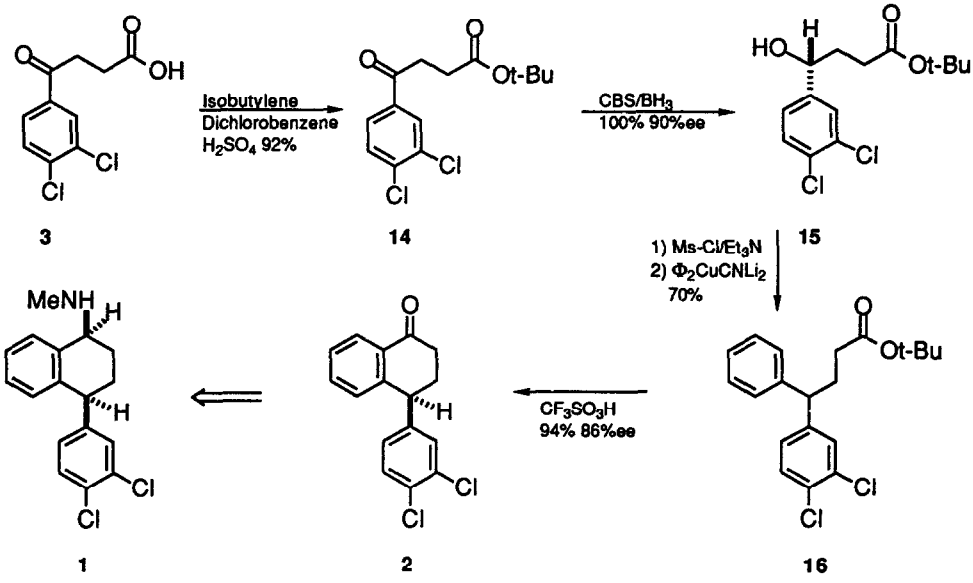
The higher order cuprate, derived from copper cyanide, was the best for coupling with mesylate **9** producing a 70% yield of diaryl **11** (Scheme 3).[22] The lower order cuprate formed from copper iodide yielded predominately alcohol **7** due to cleavage of the mesylate under the reaction conditions. Conversion of the diaryl **11** into tetralone **2** was achieved by hydrolysis of the silyl ether, Jones oxidation of the primary alcohol **12** to the carboxylic acid **13**, and intramolecular Friedel-Crafts acylation mediated by triflic acid. The enantiomeric excess obtained in the cuprate coupling was determined to be 90% ee at the tetralone stage.[23] Since the mesylate **9** in this synthesis was enantiomerically pure, only 10% of the higher order cuprate displacement proceeded through a non-SN2 mechanism. This synthesis provided tetralone **2** in ten steps and 28% overall yield from the ketoacid **3**.

Scheme 3



Enantioselective ketone reduction and maintaining the carboxylic acid oxidation state throughout the synthesis were targeted to improve the initial tetralone route. Ketoacid **3** was converted to the t-butyl ester **14** with isobutylene and sulfuric acid in 92% yield (Scheme 4). Catalytic enantioselective reduction of ketoester **14** with 0.05 equivalents of (S)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole[24] produced the desired hydroxyester **15** in quantitative yield and 90% ee.[18] The stoichiometric reducing reagent, (+)-chlorodiisopinocamphyl borane, reduced **14** to yield **15** with 88% ee. Alcohol **15** was mesylated and subjected to higher order cuprate displacement with the same conditions employed in the preceeding synthesis affording diarylbutyrate **16** in 70% yield. The judicious choice of protecting the carboxylic acid group as its t-butyl ester allowed **16** to be directly converted into tetralone **2** in 94% yield with triflic acid. Higher order cuprate SN2 chirality transfer on the t-butyl ester was identical to that secured with the silyl protected alcohol **9** mentioned earlier. This five step synthesis of **2** from ketoacid **3** proceeded in 63% overall yield and 86% ee.[22]

Scheme 4



In summary, two methods to prepare chiral tetralone **2** have been reported. The first route employed classical resolution of a γ-hydroxyacid to obtain an enantiomerically pure lactone. Reduction of the lactone to the diol, selective silylation of the primary alcohol, and mesylation of the secondary benzylic alcohol allowed for SN2 higher order cuprate displacement with good chirality transfer. Functional group manipulation of the cuprate product afforded tetralone **2** in 90% ee (28% overall yield) in ten steps. A more efficient route employed catalytic oxazaborolidine asymmetric reduction of a γ-ketoester to provide the benzylic alcohol in 90% ee. Mesylation and higher order cuprate displacement in an SN2 fashion gave the diaryl t-butyl ester again with good chirality transfer. Intramolecular Friedel-Crafts cyclization of the diaryl t-butylester yielded the tetralone **2** 86% ee (63% overall yield) in five steps. These routes detail classical resolution verses catalytic asymmetric oxazaborolidine reduction of a prochiral ketone to obtain the desired absolute stereochemistry at a

benzylic position. Inversion of the mesylated benzylic center by intramolecular displacement with a silyl ether, and intermolecularly with a higher order cuprate was achieved with good stereochemical control.

Experimental Section

Melting points were determined with Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ at 300MHz and infrared spectra were recorded in $CHCl_3$ unless noted otherwise. Microanalyses were performed by the Pfizer Analytical Department. Phenyllithium was prepared by the method of Schlosser.[25] Copper iodide was purified [26] and copper cyanide was dried under vacuum over phosphorus pentoxide. Deuterochloroform was purchased from Isotec Inc.

(5R)-(3,4-dichlorophenyl)dihydro-2(3H)-furanone (5) Ketoacid 3[7] (100 g, 0.40 mol) was dissolved in aqueous sodium hydroxide (1N, 610 mL) at ambient temperature. Sodium borohydride (8.53 g, 225 mmol) was added in portions maintaining the temperature < 35°C. After the addition was complete, stirring was continued for 18 h. The reaction was cooled to < 5°C and acidified with concentrated hydrochloric acid (73 mL) to pH 1. This solution was extracted with methylene chloride (2 X 500 mL), and the combined organic extracts were washed with water (2 X 150 mL), brine (2 X 50 mL), and dried with magnesium sulfate. The methylene chloride solution of hydroxy acid was added to a solution of D-ephedrine (69.68 g, 422 mmol) in methylene chloride (1660 mL) at ambient temperature, seeded, and stirred overnight. The ephedrine salt was filtered off, washed with methylene chloride (100 mL), and dried, to afford a white solid 108.6 g $[\alpha]_D$ +22.6° (c = 1 MeOH). The salt was dissolved in methylene chloride (4 L) and the solvent was distilled off until the volume was reduced to 2.1 L. A white solid precipitated and was stirred overnight. The salt was filtered off and dried to yield 46.4 g of a white solid $[\alpha]_D$ +30.2° (c = 1 MeOH). The salt was combined with a salt {25.3 g, $[\alpha]_D$ +30.7° (c = 1 MeOH)} from a previous preparation, dissolved in methylene chloride (9 L) and the methylene chloride volume reduced to 1450 mL by distillation. During the reduction of the solvent volume by distillation a white solid precipated and was stirred overnight, filtered off, washed with methylene chloride (200 mL), and dried under vacuum to yield a white solid (63 g, $[\alpha]_D$ +29.8° (c = 1 MeOH). The salt (56 g) was dissloved in water (122 mL), methylene chloride (110 mL), and concentrated hydrochloric acid (91 mL) were added and the contents stirred at ambient temperature for 1 h, and heated to 45° C for 1.75 h. Water (130 mL) and methylene chloride (130 mL) were added to the cooled solution and the contents filtered through celite. The phases were separated, the aqueous phase extracted with methylene chloride, the combined organic extracts were washed with aqueous sodium bicarbonate (saturated solution 130 mL), water (130 mL), dried with magnesium sulfate, and the solvent was removed under vacuum to yield the enantiomerically pure lactone as a white solid (30.1 g) mp 54-55°C $[\alpha]_D^{23}$ +12.3° (c = 1 MeOH). IR 2985, 1781, 1600, 1564, 1466, 1405, 1349, 1324, 1299, 1268, 1170, 1131, 1025 cm^{-1}. ^{13}C NMR δ 176.2, 139.7, 133.0, 132.5, 130.8, 127.3, 124.5, 79.6, 30.8, 28.7. Anal. Calcd for $C_{10}H_8Cl_2O_2$: C, 51.98; H, 3.49. Found: C, 52.12; H, 3.39.

(1R)-(3,4-dichlorophenyl)-1,4-butanediol (7) A suspension of lithium aluminum hydride (1.53 g, 40.2 mmol) in tetrahydrofuran (16 mL) was cooled in an ice bath under nitrogen. Lactone **5** (10 g, 40.3 mmol) in tetrahydrofuran (48 mL) was added dropwise to the hydride suspension. The reaction was stirred for

1 h in an ice bath, 1 h at 25° C, and then 1.5 h at 60° C. The reaction was cooled, quenched with water (1.53 mL), 15 % aqueous sodium hydroxide (1.53 mL), and water (4.6 mL). Tetrahydrofuran (30 mL) was added and stirring was continued for 16 h. The reaction was then vacuum filtered through magnesium sulfate and the solvent removed under vacuum to afford the diol product as a white semisolid 10.33 g (102% mass balance). mp 60-61° C $[\alpha]_D^{23}$ +36.7° (c = 1.76 acetone). IR 3594, 3370, 2931, 2876, 1466, 1391, 1196, 1129, 1026 cm^{-1}. ^1H NMR δ 7.45 (d, J = 2 Hz, 1 H), 7.39 (d, J = 8 Hz, 1 H), 7.16 (dd, J = 2 Hz, J = 8 Hz, 1 H), 4.69 (t, J = 7 Hz, 1 H), 3.68 (m, 2 H), 3.21 (bs, 1 H), 2.12 (bs, 1 H), 1.75 (m, 2 H), 1.62 (m, 2 H). ^{13}C NMR δ 145.0, 132.4, 131.0, 130.3, 127.8, 125.2, 72.9, 62.6, 36.6, 28.8. Anal. Calcd for $C_{10}H_{12}Cl_2O_2$: C, 51.09; H, 5.14. Found: C, 51.17; H, 5.12.

(1R)-(3,4-dichlorophenyl)-4-[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-butanol (8) A solution of diol **7** (10.33 g, 41 mmol) and imidazole (5.48 g, 80.6 mmol) in dimethylformamide (93 mL) under nitrogen was cooled with an ice bath. t-Butyldimethylsilyl chloride (6.99 g, 46.4 mmol) was added in one portion. Stirring was continued for 18 h, allowing the ice bath to melt under its own integrity. The reaction was inversely quenched into water (1000 mL) and extracted with hexane (4 X 100 mL). The combined organic layers were washed with water (2 X 200 mL), dried with magnesium sulfate, and the solvent removed under vacuum to afford a colorless oil (15.25 g). Chromatography on silica, eluting with ethyl acetate/hexane (1:3) provided **8** as a colorless oil 13.85 g (98%) $[\alpha]_D^{23}$ +21.49° (c = 1.24 acetone). IR 3595, 3340, 2923, 2878, 2853, 1590, 1564, 1465, 1388, 1362, 1253, 1233, 1126, 1092, 1025 cm^{-1}. ^1H NMR δ 7.47 (d, J = 2 Hz, 1 H), 7.38 (d, 8 Hz, 1 H), 7.17 (dd, J = 2 Hz, J = 8 Hz, 1 H), 4.66 (dd, J = 3 Hz, J = 4 Hz, 1 H), 3.84 (d, J = 3 Hz, 1 H), 3.68 (m, 2 H), 1.91-1.57 (m, 4 H), 0.91 (s, 9 H), 0.08 (s, 6 H). ^{13}C NMR δ 145.5, 132.3, 130.7, 130.2, 127.9, 125.2, 72.7, 63.5, 37.3, 29.0, 25.9, 25.6, 18.3. Anal. Calcd for $C_{16}H_{26}Cl_2O_2Si$: C, 55.01; H, 7.50. Found: C, 55.11; H, 7.48.

(1R)-(3,4-dichlorophenyl)-α-[3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]propyl]-methanesulfonate benzenemethanol (9) A solution of the monosilylated diol **8** (1.74 g, 4.98 mmol) in methylene chloride (24.9 mL) was cooled in an ice/salt bath. Triethylamine (1.04 mL, 7.48 mmol) was added dropwise followed by methanesulfonyl chloride (0.535 mL, 5.48 mmol). After stirring for 15 min, with ice/salt bath cooling, the reaction was quenched with ice cold water (25 mL). The phases were separated and the organic phase washed successively with cold aqueous hydrochloric acid (10%, 12 mL), saturated aqueous sodium bicarbonate (12 mL), and saturated aqueous sodium chloride (12 mL). The organic phase was dried with magnesium sulfate and the solvent removed under vacuum to yield the mesylate **9** as a colorless oil 2.15 g (97%) which was used without further purification. ^1H NMR δ 7.47 (d, J = 2 Hz, 1 H), 7.46 (d, J = 8 Hz, 1 H), 7.21 (dd, J = 2 Hz, J = 8 Hz, 1 H), 5.51 (dd, J = 6 Hz, J = 8 Hz, 1 H), 3.63 (m, 2 H), 2.80 (s, 3 H), 2.0 (m, 2 H), 1.57 (m, 2 H), 0.87 (s, 9 H), 0.02 (s, 6 H). ^{13}C NMR δ (C_6D_6) 139.6, 133.1, 132.8, 130.8, 128.6, 126.0, 81.7, 62.1, 38.2, 33.8, 28.4, 25.9, 18.3, -5.5.

(1R)-(3,4-dichlorophenyl)-4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-phenylbutane (11) A suspension of copper(I) cyanide (572 mg, 6.39 mmol) in ether (25.5 mL) was cooled to -20° C. Phenyllithium (1.56M in ether, 8.19 mL, 12.78 mmol) was added dropwise to the suspension over 10 min.

The reagent was stirred at -20° C for 20 min, and then at 0° C for 30 min (light yellow precipitate). The reaction was cooled to -50° C and the mesylate **9** (1.415 g, 3.19 mmol) in ether (3.2 mL) was added dropwise. Stirring was continued for 18h at -25° C, and then 5.5 h at ambient temperature. The reaction was inverse quenched onto ice (60 g), aqueous saturated ammonium chloride (60 mL), and stirred for 1h. Ether (2 X 50 mL) was added and the aqueous phase extracted. The organic phase was dried with magnesium sulfate and solvent removed to afford the crude product as a light yellow oil (1.92 g). Chromatography on silica eluting with ethyl acetate/hexane (1:99) afforded the product **11** as a colorless oil 911 mg (70%) $[\alpha]_D^{23}$ -4.81° (c = 1.06 $CDCl_3$). IR 2940, 2925, 2881, 2853, 1601, 1589, 1559, 1490, 1467, 1452, 1388, 1361, 1248, 1219, 1130, 1099, 1085.cm^{-1}. ^{1}H NMR δ 7.33-7.16 (m, 7 H,) 7.05 (dd, J = 2 Hz, J = 8 Hz, 1 H), 3.85 (t, J = 8 Hz, 1 H), 3.60 (t, J = 6 Hz, 2 H), 2.05 (m, 2 H), 1.46 (m, 2 H), 0.87 (s, 9 H), 0.01 (s, 6 H). ^{13}C NMR δ 145.6, 143.9, 132.3, 130.3, 130.0, 129.8, 128.7, 127.7, 127.3, 126.6, 62.8, 50.3, 31.7, 31.0, 26.0, 18.4, -5.3. Anal. Calcd for $C_{22}H_{30}Cl_2OSi$: C, 64.53; H, 7.39. Found: C, 64.44; H, 7.29.

(1R)-(3,4-dichlorophenyl)-1-phenyl-butane-4-ol (12) A solution of diarylsilylated butanol **11** (911 mg, 2.23 mmol), in acetic acid (12 mL), tetrahydrofuran (4 mL), and water (4 mL) was stirred at ambient temperature for 24h. The solvents were removed under vacuum, aqueous sodium bicarbonate (5%, 10 mL) and methylene chloride were added. The phases were separated, and the organic phase dried with magnesium sulfate. Upon solvent removal under vacuum, a colorless oil (838 mg) was obtained. Chromatography of the oil on silica with ethyl acetate/hexane (1:3) for elution yielded **12** as a colorless oil 690 mg (91%) $[\alpha]_D^{23}$ -2.71° (c = 1.36 acetone). IR 3600, 3454, 2989, 2931, 2867, 1601, 1589, 1557, 1489, 1466, 1452, 1396, 1346, 1327, 1253, 1191, 1130, 1044 cm^{-1}. ^{1}H NMR δ 7.43-7.05 (m, 8 H), 3.85 (t, J = 8 Hz, 1 H), 3.62 (t, J = 6 Hz, 2 H), 2.25 (s, 1 H), 2.07 (m, 2 H), 1.52 (m, 2 H). ^{13}C NMR δ 145.4, 143.6, 132.4, 130.4, 130.1, 129.8, 128.7, 127.7, 127.3, 126.7, 62.6, 50.3, 31.6, 31.0. Anal. Calcd for $C_{16}H_{16}Cl_2O$: C, 65.10; H, 5.46. Found C, 64.88; H, 5.22.

(4R)-(3,4-dichlorophenyl)-4-phenylbutanoic acid (13) Jones reagent (6.0 mL) was added to a solution of the alcohol **12** (690 mg, 2.34 mmol) in acetone (45 mL) at ambient temperature. The reaction was stirred for 2 h and then quenched by the addition of isopropyl alcohol (5 mL). After stirring the quenched reaction for 30 min the solvents were removed under vacuum. Water was added to the green solid and the solution extracted with methylene chloride (2 X 25 mL). The organic phases were combined, dried with magnesium sulfate, and the solvent removed under vacuum to yield **13** as a colorless oil 689 mg (95%) $[\alpha]_D^{23}$ -12.75° (c = 1.16 benzene). IR 2926, 1711, 1590, 1558, 1464, 1399, 1239, 1129 cm^{-1}. ^{13}C NMR δ (C_6D_6O) 174.4, 146.3, 143.9, 131.5, 131.0, 130.1, 129.1, 128.4, 128.0, 127.0, 49.2, 32.5, 30.0. Anal. Calcd for $C_{16}H_{14}Cl_2O_2$: C, 62.15; H, 4.56. Found: C, 62.31; H, 4.44.

(4S)-(3,4-Dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone (2) Trifluoromethanesulfonic acid (5.0 mL) was added to a solution of acid **13** (689 mg, 2.23 mmol) in benzene (5.0 mL) at ambient temperature. The reaction was heated to 70° C for 2 h, cooled and quenched with ice (20 g). The pH of the solution was adjusted to 12 with aqueous sodium hydroxide (4N, 14.5 mL). This solution was extracted with methylene chloride (2 X 30 mL), the organic phases combined, dried with magnesium sulfate, and the solvent

removed under vacuum to afford the crude product as a light yellow oil (692 mg) which began crystallizing on standing. The product was chromatographed on silica with ethyl acetate/hexane (1:5.6) to yield the tetralone product as a white solid 592 mg (91%) $[\alpha]_D^{23}$ +58.3° (c = 1.01 acetone) 88.6% ee. IR 2993, 2942, 2865, 1687, 1597, 1560, 1467, 1452, 1398, 1346, 1330, 1285, 1188, 1145, 1131 cm^{-1}. ^1H NMR δ 8.1 (dd, J = 1.5 Hz, J = 8 Hz, 1 H) 7.49-7.31 (m, 3 H), 7.21 (d, J = 2 Hz, 1 H), 6.93 (dd, J = 2 Hz, J = 8 Hz, 2 H), 4.26 (dd, J = 4.5 Hz, J = 8 Hz, 1 H), 2.74-2.18 (m, 4 H). ^{13}C NMR δ 197.3, 144.9, 144.0, 133.9, 132.8, 132.7, 131.0, 130.6, 130.5, 129.3, 128.0, 127.6, 127.4, 44.6, 36.5, 31.7. Anal. Calcd for $C_{16}H_{12}Cl_2O$: C, 66.00; H, 4.15. Found: C, 66.20; H, 3.91.

(2S)-(3,4-Dichlorophenyl)tetrahydrofuran (10) Mesylate **9** (1.1 g, 2.48 mmol) was dissolved in deuterochloroform (15 mL) and allowed to stand for 16 h. Proton nmr showed complete reaction occurred. The solution was washed with aqueous sodium bicarbonate (25 mL), and dried with magnesium sulfate. Removal of the solvent under vacuum provided a colorless oil (691 mg). Chromatography on silica (21 g) eluting with 10% ethylacetate/hexane gave **10** as a colorless oil 415 mg (77%) $[\alpha]_D^{23}$ -29.33° (c = 1.05 acetone). IR 2948, 2867, 1595, 1563, 1462, 1388, 1346, 1214, 1128, 1058, 1028, 948 cm^{-1}. ^1H NMR δ 7.41 (d, J = 2 Hz, 1 H), 7.37 (d, J = 8 Hz, 1 H), 7.13 (dd, J = 2 Hz, J = 8 Hz, 1 H), 4.82 (t, J = 7 Hz, 1 H), 3.99 (m, 2 H), 2.31 (m, 1 H), 1.98 (m, 2 H), 1.71 (m, 1 H) ^{13}C NMR δ 144.0, 132.3, 130.8, 130.2, 127.6, 125, 79.4, 68.8, 34.7, 25.9. Anal. Calcd for $C_{10}H_{10}Cl_2O$: C, 55.33; H, 4.64. Found: C, 55.33; H, 4.65.

4-(3,4-Dichlorophenyl)-4-oxo-butanoic acid-1,1-dimethylethyl ester (14) Isobutylene (31 g, 0.5 mol) was condensed into a mixture of ketoacid **3** (5.0 g, 20 mmol), 1,2-dichlorobenzene (100 mL), t-butanol (1.0 mL), and sulfuric acid (1.0 mL) with the aid of a dry ice cold finger. The contents were stirred for 18 h and the excess isobutylene was distilled out. Saturated aqueous sodium bicarbonate (100 mL) was added and after stirring the contents for 30 min, the pH of the media was 8. The layers were separated, the organic layer was dried with magnesium sulfate, and the solvent was removed under vacuum to afford the crude product (8.31 g). Chromatography on silica (90 g) eluting with 10% ethyl acetate/hexane yielded the keto-t-butyl ester **14** as a colorless oil 5.64 g (92%). IR 2965, 2923, 1720, 1693, 1586, 1555, 1465, 1391, 1369, 1354, 1325, 1280, 1230, 1151 cm^{-1}. ^{13}C NMR δ 196.3, 171.9, 137.7, 136.3, 133.4, 130.8, 130.1, 127.1, 80.9, 33.5, 29.3, 28.1. Anal. Calcd for $C_{14}H_{16}Cl_2O_3$: C, 55.46; H, 5.32. Found: C, 55.32; H, 5.29.

4-(3,4-Dichlorophenyl)-(4R)-hydroxy-butanoic acid-1,1-dimethylethyl ester (15) Keto-t-butyl ester **14** (3.0 g, 9.9 mmol) in tetrahydrofuran (3.0 mL) was added simultaneously with borane (1M in THF, 5.94 mL, 5.94 mmol) via double syringe pump over 40 min to a 0° C solution of (S)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo[1,2-c][1,3,2]oxazaborole[27] (137 mg, 0.5 mmol) in tetrahydrofuran (6 mL). The reaction was stirred 30 min after the double concurrent addition was complete, quenched with methanol (9.6 mL), and stirred 30 min. The solvents were removed under vacuum, methylene chloride was added (30 mL), the organic phase washed with pH 4 buffer (2 X 25 mL), and water (25 mL). The organic phase was dried with magnesium sulfate and the solvents removed under vacuum to provide the crude

hydroxy-t-butylester **15** as an oil 3.17 g (105% mass balance) which was used without further purification. IR 3595, 2924, 1715, 1600, 1563, 1462, 1367, 1229, 1143 cm^{-1}. ^1H NMR δ 7.47 (d, J = 2 Hz, 1 H), 7.41 (d, J = 8 Hz, 1 H), 7.18 (dd, J = 2 Hz, J = 8 Hz, 1 H), 4.75 (t, J = 6 Hz, 1 H), 2.35 (t, J = 7 Hz, 2 H), 1.99 (m, 2 H), 1.59 (bs, 1 H), 1.45 (s, 9 H). Anal. Calcd for $C_{14}H_{18}Cl_2O_3$: C, 55.10; H, 5.94. Found: C, 54.85; H, 5.61.

(4R)-(3,4-dichlorophenyl)benzenebutanoic acid-1,1-dimethylethyl ester (16) Methanesulfonyl chloride (1.04 mL, 10.6 mmol) was added dropwise to a solution of 3,4-dichloro-(4R)-hydroxy-benzenebutanoic acid 1,1-dimethylethyl ester **15** (2.96 g, 9.70 mmol), triethylamine (2.02 mL, 14 mmol) in methylene chloride (48 mL) at 0° C. After stirring 20 min, the reaction was quenched with ice cold water (25 mL), and the phases were separated. The organic layer was washed with 3N aqueous HCl (25 mL), saturated aqueous sodium bicarbonate (25 mL), brine (25 mL), and dried with magnesium sulfate. Removal of the solvent under vacuum provided the crude mesylate (3.90 g, 97%) which was employed directly in the copper coupling. A suspension of copper(I) cyanide (867 mg, 9.68 mmol) in ether (30 mL) at -20° C was treated with phenyllithium in ether (0.96M, 20mL, 19.2 mmol) dropwise over 10 min. The reaction was stirred at -20° C for 30 min, at 0° C for 30 min, and then cooled to -45° C. The mesylate (2.0 g, 4.84 mmol) in ether (5.0 mL) was added over 10 min to the reaction, which was stirred for 16 h at -45° C. The reaction was quenched with saturated aqueous ammonium chloride (90 mL), ice (90 g) and stirred for 1h. The phases were separated and the aqueous layer extracted again with ether. The combined ether extracts were dried with magnesium sulfate, and the solvent removed under vacuum to provide a pale yellow oil (2.15 g). Chromatography of the oil on silica (63 g) eluting with 5% ethyl acetate/hexane provided 1.25 g (70%) of the diaryl-t-butyl ester **16** as a colorless oil. $[\alpha]_D^{23}$ -4.00 (c = 1.15 benzene). IR 2971, 2930, 1722, 1601, 1490, 1463, 1454, 1393, 1368, 1344, 1204 cm^{-1}. ^{13}C NMR δ 172.4, 144.7, 143.0, 132.5, 130.45, 130.43, 129.8, 128.8, 127.8, 127.3, 126.8, 80.4, 49.6, 33.6, 30.4, 28.1. Anal. Calcd for $C_{20}H_{22}Cl_2O_2$: C, 65.76; H, 6.07. Found: C, 65.82; H, 5.92.

(4S)-(3,4-Dichlorophenyl)-3,4-dihydro-1(2H)-naphthalenone (2) To a solution of the t-butyl ester **16** (668 mg, 1.83 mmol) in benzene (5.0 mL) at ambient temperature was added trifluoromethanesulfonic acid (5.0 mL, 56.5 mmol). The reaction was heated to 70° C for 2 h, cooled, quenched onto ice (20 g), and the pH adjusted to 13 with aqueous 4N sodium hydroxide (15 mL). The contents were extracted with methylene chloride which was dried with magnesium sulfate and the solvent removed under vacuum to afford a light yellow oil (612 mg). Chromatography on silica (18 g) eluting with 15% ethyl acetate/hexane produced the desired tetralone 500 mg (94%). mp 83-84°C $[\alpha]_D^{23}$ = +55.7 (c = 1.01 acetone). Thus the tetralone was obtained in 84% ee or a 92:8 ratio of enantiomers. Anal. Calcd for $C_{16}H_{12}Cl_2O$: C, 66.00; H, 4.15. Found C, 65.97; H, 4.15.

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