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A Catalytic Enantioselective Synthetic Route to the Important Antidepressant Sertraline

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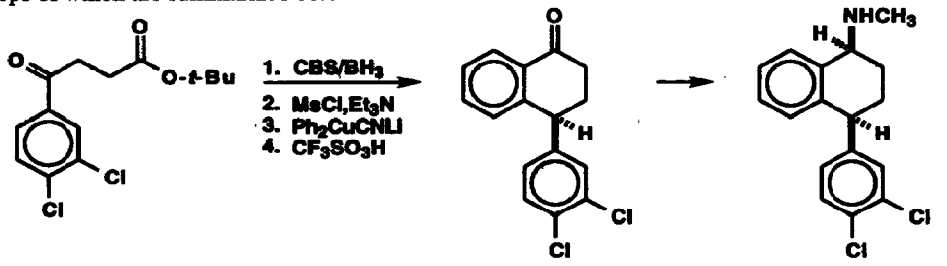
Summary: *An efficient catalytic enantioselective synthesis of the important antidepressant sertraline is described (Scheme I).*

(+)-*cis*-(1*S*,4*S*)-1-Methylamino-4-(3,4-dichlorophenyl)tetralin, sertraline (Zoloft®) (**1**), is a major commercial pharmaceutical agent for the treatment of depression, acting in the central nervous system as a serotonin uptake inhibitor.[1,2] The current commercial process for the production of sertraline involves the synthesis of (±)-**1** followed by resolution.[3] At present only one enantioselective synthesis of **1** has been reported, the key steps of which are summarized below.[4]



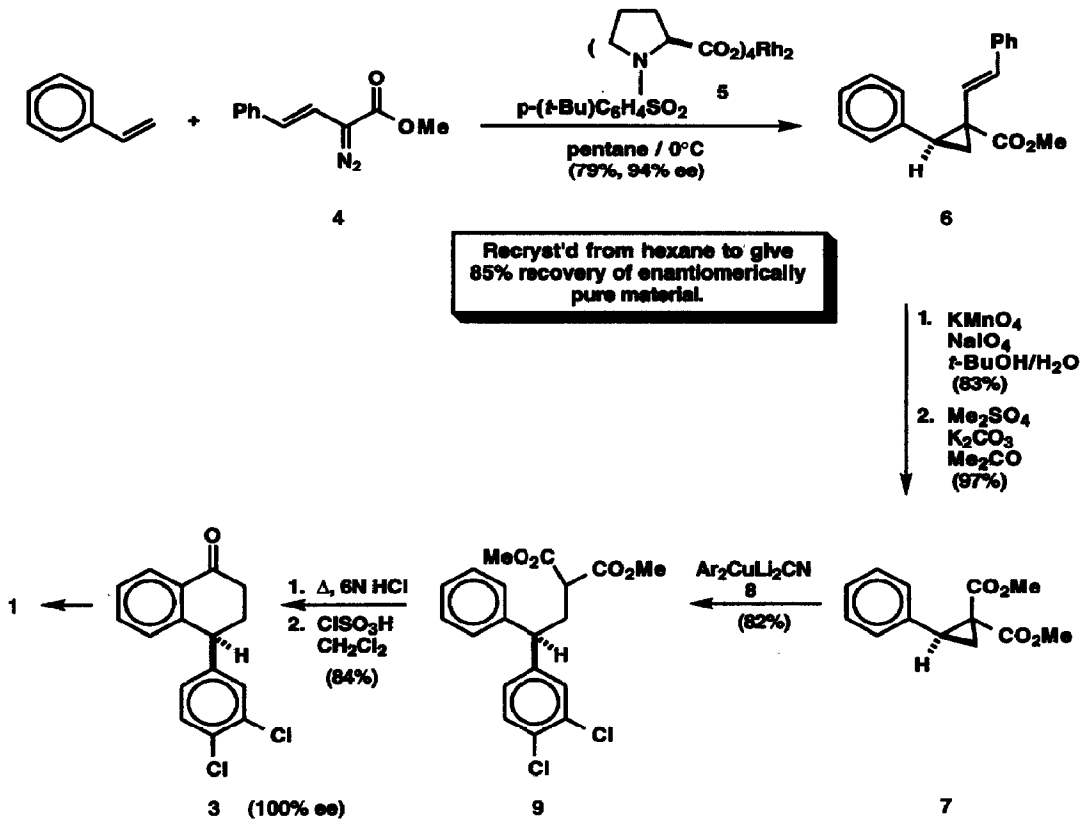
2 **3** (86% ee) **1**

In this synthesis, chirality is introduced by means of the oxazaborolidine-catalyzed (CBS) reduction of ketone **2** which affords product of 90% ee. The penultimate intermediate, tetralone **3** was obtained in 86% enantiomeric purity.

Described herein is a different approach to the synthesis of sertraline which involves catalytic asymmetric synthesis and which produces tetralone **3** of 100% ee in excellent yield. The reaction sequence is summarized in Scheme I.

Reaction of methyl (*E*)-2-diazo-4-phenyl-3-butenoate[5] (**4**) with 3.3 equiv of styrene and 0.1 mole % of catalyst **5**[5] in pentane solution at 0 °C for 18 h afforded cyclopropane **6**[5] in 94% ee and 79% yield. Recrystallization of this product from hexane gave enantiomerically pure **6** (85% recovery), mp 77-78 °C, $[\alpha]_D^{23}$

Scheme I



-169° (c=1.1, $CHCl_3$). Oxidation of **6** to the malonic acid mono ester and methylation provided the dimethyl ester **7** cleanly, mp 61-62 °C, $[\alpha]_D^{23}$ -124° (c=2.2, C_6H_6). The cuprate reagent **8** was prepared from 3,4-dichlorophenyl iodide by iodine–lithium exchange (2 equiv of *t*-butyllithium, ether, -78 °C) and reaction with cuprous cyanide (-78 °C initially and then at 23 °C for 15 min), and then treated with diester **7** in ether at 23 °C for 1 h. After quenching with aqueous ammonium chloride, extractive isolation and silica gel chromatography, the homoconjugate addition product **9**, $[\alpha]_D^{23}$ -11.3° (c=1.2, C_6H_6), was obtained as a colorless oil in 82% yield. The malonic ester **9** was hydrolyzed and decarboxylated to the corresponding 4,4-diarylbutyric acid by heating at reflux with 6 N HCl. Cyclization of this acid occurred smoothly upon reaction at 23 °C with 3 equiv of chlorosulfonic acid in CH_2Cl_2 for 40 min to give the crystalline tetralone **3**, mp 84 °C, $[\alpha]_D^{23}$ +71.3° (c=1.1, C_6H_6) of 100% ee. The conversion of **3** to sertraline (**1**) by reductive amination has already been described.[3]

Experimental detail is provided below for the sequence **4** → **6** → **7** → **9** → **3**.

(1*S*,2*S*)-(*E*)-1-Methoxycarbonyl-2-phenyl-1-(*trans*-styryl)cyclopropane (6). A 0 °C solution of rhodium catalyst **5**[5a] (35 mg, 0.1 mol%) and styrene (10.2 mL, 89 mmol, 3.3 equiv) in pentane (500 mL) was treated dropwise with a 0 °C solution of methyl (*E*)-2-diazo-4-phenyl-3-butenoate[5b] (5.42 g, 26.8 mmol) in pentane (500 mL) over 2 h. The mixture was stirred overnight, concentrated, and purified via radial chromatography using hexanes/ethyl acetate (20/1) as eluent to afford a white solid (5.91 g, 21.2 mmol, 79%, 94% ee). The enantiomeric purity of **6** was determined by HPLC analysis with a Daicel Chiralcel OJ column; flow rate = 1 mL/min, 2% isopropanol in hexane, UV 254 nm, T_R = 21.1 [desired enantiomer] and 25.7 min. Recrystallization from hexane afforded 85% recovery of enantiomerically pure material: mp 77-78 °C (lit. 77-78°C); $[\alpha]_D^{23}$ -169 (c = 1.10, $CHCl_3$) and -161° (c = 1.10, PhH) (lit. for ent.: +157.1° (c = 1.1, $CHCl_3$)); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.82 (dd, J = 5.3, 7.2 Hz, 1H), 2.02 (dd, J = 5.0, 9.1 Hz, 1H), 3.01 (app. t, J = 8.2 Hz, 1H), 3.75 (s, 3H), 6.13 (d, J = 16.0 Hz, 1H), 6.34 (d, J = 16.0 Hz, 1H), 7.10-7.26 (m, 10H).

(1*R*,2*S*)-(*E*)-1-Carboxyl-1-methoxycarbonyl-2-phenylcyclopropane. A mixture of $NaIO_4$ (6.91 g, 32.3 mmol) in water (125 mL) was treated with $KMnO_4$ (113 mg, 0.718 mmol) and stirred 0.5 h at ambient temperature. The purple suspension was treated sequentially with K_2CO_3 (521 mg, 3.77 mmol), *t*-BuOH (35 mL), and a solution of alkene (1.00 g, 3.59 mmol) in *t*-BuOH (35 mL). After stirring an additional 3 h, ethylene glycol (0.88 mL, 15.8 mmol) was added and stirred 1 h to destroy excess oxidant. The brown suspension was acidified to pH 4 with 1 N HCl and extracted with EtOAc. Drying ($MgSO_4$), concentration, and purification via radial chromatography (4 mm plate) using hexanes/ethyl acetate/acetic acid (100/10/1) gave a white solid (656 mg, 2.98 mmol, 83%): mp 83-86 °C; $[\alpha]_D^{23}$ -104° (c = 0.89, PhH); IR ($CHCl_3$) 2958, 1760, 1726, 1708, 1679 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.09 (dd, J = 4.9, 9.5 Hz, 1H), 2.41 (dd, J = 4.9, 8.7 Hz, 1H), 3.31 (app. t, J = 9.1 Hz, 1H), 3.83 (s, 3H), 7.20-7.31 (m, 5H), 10.7 (br. s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.30, 34.86, 37.26, 53.15, 127.59, 128.02, 128.93, 133.19, 168.26, 172.83. HRMS calcd for $C_{12}H_{12}O_4$ 220.0736, found 220.0740.

(*S*)-1,1-*Bis*-(methoxycarbonyl)-2-phenylcyclopropane (7). A suspension of K_2CO_3 (412 mg, 3.05 mmol) and carboxylic acid (610 mg, 2.77 mmol) in acetone (50 mL, freshly distilled from B_2O_3) was treated with Me_2SO_4 (0.288 mL, 3.05 mmol, freshly distilled) and stirred 3 h. The mixture was poured into ether and water, the organic layer separated, dried ($MgSO_4$) and concentrated. Purification via radial chromatography (4 mm plate) using hexane/ethyl acetate (10/1) as eluent afforded a white solid (630 mg, 2.69 mmol, 97%): mp 61-62 °C; $[\alpha]_D^{23}$ -124° (c = 2.23, PhH); IR (neat) 2954, 1733, 1438 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.74 (dd, J = 5.2, 9.2 Hz, 1H), 2.20 (dd, J = 5.2, 8.1 Hz, 1H), 3.23 (app. t, J = 8.7 Hz, 1H), 3.35 (s, 3H), 3.78 (s, 3H), 7.16-7.28 (m, 5H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.90, 32.36, 37.15, 51.93, 52.54, 127.24, 128.02, 128.37, 134.58, 166.84, 170.04. HRMS calcd for $C_{13}H_{14}O_4$ 234.0891, found 234.0897.

(*R*)-Methyl 4-(3,4-dichlorophenyl)-4-phenyl-2-methoxycarbonylbutanoate (9). A solution of 3,4-dichlorophenyl iodide (499 mg, 1.83 mmol) in Et_2O (5 mL) was cooled to -78 °C, treated with *t*-BuLi (2.17 mL of a 1.77 M sol'n in pentane, 3.66 mmol) and stirred 1 h. The freshly generated aryllithium was cannulated into a suspension of rapidly stirred cuprous cyanide (81.9 mg, 0.915 mmol) in Et_2O (5 mL), warmed

quickly to ambient temperature and stirred 15 min to form **8**. At this point the reaction had become biphasic, each layer being completely translucent. The mixture was treated with a solution of the cyclopropane **7** (204 mg, 0.871 mmol) in Et_2O (4 mL) and stirred 45 min at ambient temperature. The reaction was then quenched with NH_4Cl (sat'd aq. sol'n), stirred 1 h, and partitioned between Et_2O and water. The organic layer was dried ($MgSO_4$), filtered, concentrated, and purified via radial chromatography (4 mm plate) using hexanes/ethyl acetate (20/1 → 10/1) as eluent to yield a clear colorless oil (273 mg, 0.716 mmol, 82%): $[\alpha]_D^{23}$ -11.3° (c = 1.18, PhH); IR (neat) 2954, 1752, 1735, 1436 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.62 (t, J = 7.8 Hz, 2H), 3.25, (t, J = 7.4 Hz, 1H), 3.70 (s, 3H), 3.72 (s, 3H), 3.91 (t, J = 8.0 Hz, 1H), 7.07 (dd, J = 2.1, 8.3 Hz, 1H), 7.15-7.38 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.05, 47.76, 49.67, 52.58, 127.04, 127.17, 127.70, 128.83, 129.71, 130.45, 130.52, 132.48, 141.82, 143.76, 169.35. HRMS calcd for $C_{19}H_{18}Cl_2O_4$ 380.0582, found 380.0591.

(*S*)-4-(3,4-Dichlorophenyl)-1-tetralone (3). The *bis*(ester) (224 mg, 0.588 mmol) was treated with 6N HCl (5 mL) and heated at reflux for 20 h. The mixture was cooled, added to ether and 1 N NaOH. The aqueous layer was washed (ether) and acidified (6 N HCl). Extraction with CH_2Cl_2, drying ($MgSO_4$), and concentration gave 4-phenyl-4-(3,4-dichlorophenyl)butanoic acid $[\alpha]_D^{23}$ -12.5° (c = 2.8, PhH); ^1H NMR ($CDCl_3$, 400 MHz) δ 2.28-2.39 (m, 4H), 3.91 (t, J = 7.2 Hz, 1H), 7.07 (dd, J = 2.1, 8.3 Hz, 1H), 7.16-7.25 (m, 3H), 7.27-7.38 (m, 4H). The acid was dissolved in CH_2Cl_2 (25 mL) and treated dropwise with $ClSO_3H$ (0.117 mL, 1.76 mmol). After 30 min stirring, the cloudy mixture was added to ether and dilute aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$), concentrated, and purified via radial chromatography (4 mm plate) using hexanes/ethyl acetate (20/1 → 10/1) as eluent to afford a white solid, mp 84 °C, $[\alpha]_D^{23}$ +71.3° (c = 1.1, C_6H_6) (136 mg, 0.491 mmol, 84%, 100% ee). The enantiomeric purity of **3** was determined to be 100% by HPLC analysis with a Daicel Chiralcel OD column; flow rate = 1 mL/min, 2% isopropanol in hexane, UV 254 nm, T_R = 15.7 [desired enantiomer]; T_R values for the enantiomers of **3** were measured on racemic **3** (gift of Pfizer Inc.) as 15.7 and 18.5 min under these conditions. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.20-2.32 (m, 1H), 2.42-2.53 (m, 1H), 2.57-2.78 (m, 2H), 4.28 (dd, J = 4.6, 8.1 Hz, 1H), 6.95 (dd, J = 2.1, 7.6 Hz, 2H), 7.23 (d, J = 2.0 Hz, 1H), 7.37-7.50 (m, 3H), 8.13 (d, J = 7.6 Hz, Hz, 1H).[6]

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