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A Catalytic Enantioselective Synthesis of Antidepressant Tranylcypromine

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SYNTHETIC COMMUNICATIONS, 29(4), 567-572 (1999)

A CATALYTIC ENANTIOSELECTIVE SYNTHESIS OF ANTIDEPRESSANT TRANYLCYPROMINE

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Abstract: An efficient catalytic enantioselective synthesis of the antideprssant trnylcypromine is described.

trans-2-Phenylcyclopropylamine, tranylcypromine (**1**) is a commercially pharmaceutical agent for treatment of depression, acting as a monoamine oxidase inhibitor. **1** is used in therapy as a racemate. It has been found, however, that the two enantiomers of **1** have different biological activities[1-3]. Synthesis of enantiomerically pure **1** involves resolution of (±)-*trans*-2-phenycyclopropane carboxylic acid ±(**2**) followed by *Curtius* degradation[2,4]. To our knowledge, no enantioselective synthesis of **1** has been previously reported.

We herein describe a highly enantioselective and diastereoselective method for the synthesis of tranylcypromine that involves catalytic asymmetric cyclopropanation of styrene with dicyclohexylmethyl diazoacetate.

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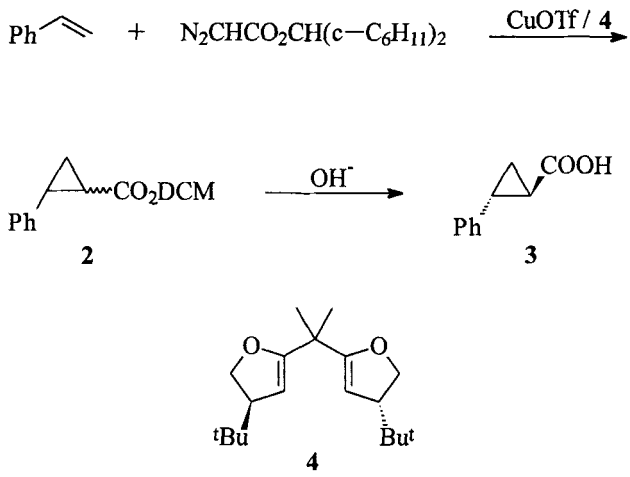
Scheme 1



Asymmetric cyclopropanation of styrene with diazoacetates catalyzed by chiral copper complexes has been well established[5-8]. Evans' chiral bisoxazoline ligand **4** was used in our experiment mainly for its excellent ability in enantioselective induction and feasibility to prepare. The cyclopropanation reaction was carried out in CH_2Cl_2 by slow addition of dicyclohexylmethyl diazoacetate over 2 h at 0°C to the solution of CuL* which was prepared *in situ* by complexation of $Cu(OTf)(C_6H_6)_{0.5}$ with optically pure ligand **4** and the resulting solution was stirred for an additional 10 h at r.t.. Chromatography on silica gel provided dicyclohexylmethyl 2-phenylcyclopropane carboxylate (**2**) in 83% yield with a 88:12 trans/cis ratio and 97% ee for trans isomer[9].

It was known that trans isomer of **2** could be hydrolyzed selectively under basic condition[10]. Control experiments showed that trans/cis ratio of **3** depended on the time of hydrolysis. Reflux of **2** with aq. 25% NaOH in C_2H_5OH for 10 h gave 130:1 trans/cis ratio in 79% yield, whereas 200:1 trans/cis ratio in 37% yield and 90:10 trans/cis ratio in 89% yield were given at 4 h reflux and at 24 h reflux respectively.

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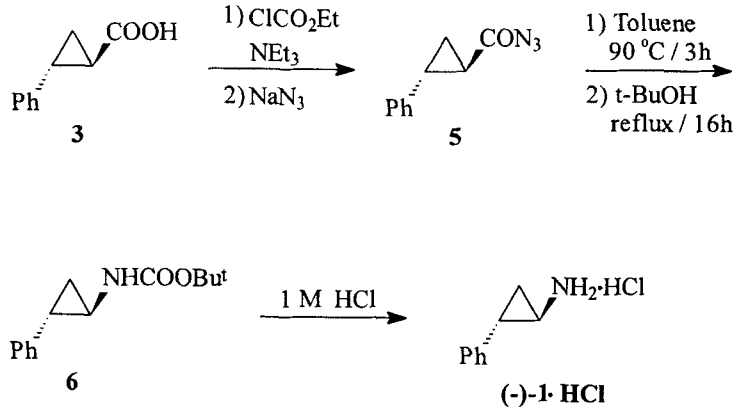
Scheme 2



A modified *Curtius* degradation of **3** followed by acidic hydrolysis finally gave (1*R*,2*S*)-(-)-tranylcypromine hydrochloride (-)-**1•HCl** in 36% yield, m.p. 179.5-180.5°C, $[\alpha]_D^{20}$ –75.3 (C 1.0, H_2O) [lit.[1] m.p. 180-181°C, $[\alpha]_D^{25}$ –75.5 (C 1.0, H_2O)]. In the transformation of acid **3** to acid chloride, ethyl chloroformate, instead of thionyl chloride, was used, which avoided the decomposition of formed acid chloride[11]. When benzyl alcohol was applied as a replacement of *tert*-butyl alcohol, the same result was obtained in *Curtius* degradation of **3**, which needed Pd-C catalyzed hydrogenation to remove protection in amino group.

It is apparent that (1*S*,2*R*)-(+)-tranylcypromine could be prepared with this methodology by using a chiral bisoxazoline ligand which has an opposite configuration to ligand **4**.

Experiments for the synthesis of (-)-**1•HCl**

Dicyclohexylmethyl 2-phenylcyclopropane carboxylate (2). To a suspension of $CuOTf(C_6H_6)_{0.5}$ (36.0 mg, 0.143 mmol) in 40 ml CH_2Cl_2, a solution of ligand **4** (44 mg, 0.149 mmol) in 10 ml CH_2Cl_2 was added. The resulting mixture was stirred at r.t. for 1 h and filtered through a glass filter cannula under

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argon, 10 ml (87.5 mmol) styrene was added, and then a solution of dicyclohexylmethyl diazoacetate (4.5 g, 17.0 mmol) in CH_2Cl_2 (50 ml) was added dropwise by a syringe pump at 0°C over 2 h. The mixture was allowed to warm slowly to room temperature (25°C) and stirred for additional 10 h. Filtration through a short silica gel column (to remove catalyst), concentration in vacuum (to remove solvent and excess styrene) and flash chromatography using petroleum ether/ethyl acetate (95/5) as eluent provided compound **2** as a white solid (4.8 g, 14.1 mmol, 83% yield, 88/12 trans/cis ratio, 97% ee for trans isomer). The trans/cis ratio was determined by capillary GC analysis on a 50 m OV-17 column operated at 100°C for 10 min., then programmed at 2°C/min. to 270°C [T_R = 119.7 min. and 124.4 min (trans isomer)]. Enantiomerical excess of trans isomer was determined by capillary GC, after re-esterification with (-)-menthol, on a 50 m OV-17 column operated at 100°C for 10 min, then programmed at 2°C /min to 230°C [T_R = 108.19 min (desired enatiomer) and 109.93 min]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30-7.10 (m, 5H), 4.66 (t, J = 5.8 Hz, 0.88H), 4.39 (t, J = 5.8 Hz, 0.12H), 2.59–0.71 (m, 26H).

(1*R*, 2*R*)-(-)-*trans*-2-Phenylcyclopropane carboxylic acid (3). A mixture of **2** (4.1 g, 12.1 mmol), ethyl alcohol (25 ml) and aq. NaOH (25%, 25 ml) was heated under reflux for 10 h. After the most of ethyl alcohol was removed, the remaining residue was diluted by the addition of 60 ml water, and then washed with ethyl ether (15 ml). The pH of aqueous phase was adjusted by addition of 6 M HCl to 1-2, and was extracted with ethyl ether (3 X 50 ml). Drying of combined organic phase over $MgSO_4$ and concentration gave (-)-**3** as a white solid (1.55 g, 9.57 mmol, 79% yield, 130:1 trans/cis ratio, 97% ee for trans isomer). The trans/cis ratio and enantiomerical excess were determined by capiliary GC of (-)-menthyl ester as described in the case of **2**. According to the minus optical rotation, the configuration of **3** is (1R, 2R)[2]. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.78 (s, 1H), 7.31-7.08 (m, 5H), 2.60(ddd, J = 9.37, 6.60, 4.15 Hz, 1H, H-C(2)), 1.90 (ddd, J = 8.32, 4.63, 4.15 Hz, 1H, H-C(1)), 1.66 (app. p, J = 4.63 Hz, 1H, H_A-C(3)), 1.39 (ddd, J = 8.32, 6.60, 4.40 Hz, 1H, H_B-C(3)).

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(1*R*, 2*S*)-(-)-*trans*-2-Phenylcyclopropylamine hydrochloride, (-)-tranylcypromine (-)-1•HCl. Ethyl chloroformate (0.55 g, 5.07 mmol) was added to a stirred cold solution (ice-salt bath) of the acid **2** (0.56 g, 3.46 mmol) and triethyl amine (0.45 g, 4.46 mmol) in dry acetone (25 ml). After stirring for 2 h, aq. NaN_3 (0.36 g, 5.54 mmol in 1.1 ml H_2O) was added and the mixture was stirred for an additional hour, and 10 ml of H_2O was added. The resulting mixture was extracted with ether (4 X 20 ml), and the extract was dried with $MgSO_4$, concentrated under reduced pressure. The crude acyl azide **5** thus obtained was dissolved in dry toluene (22 ml), and heated at 90°C for 3 h. The reaction mixture was concentrated and the residue was dissolved in dry *tert*-butyl alcohol (25 ml) and resulting solution was heated under reflux for 16 h. Concentration followed by chromatography (Et_2O/petroleum 1:4 as eluent) gave pure carbamate **6**. A mixture of **6**, *tert*-butyl alcohol (5 ml) and 1 M HCl (20 ml) was heated at 100 °C for 20 min.. The resulting solution was concentrated under reduced pressure and the residue acidic aqueous solution was washed with Et_2O (10 ml), alkalinized by addition of sodium carbonate, and extracted with Et_2O (4 X 20 ml). The combined organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was dissolved in Et_2O and treated with ethereal HCl. The precipitate was collected and recrystallized from 2-propyl alcohol / Et_2O to provided pure (-)-**1•HCl** (0.21 g, 1.25 mmol, 36% yield, m. p. 179.5-180.5°C, $[\alpha]_D^{20}$ –75.3 (c 1.0, H_2O) (lit[1]. m.p. 180-181°C; $[\alpha]_D^{25}$ –75.5 (c 1.0, H_2O)). ^1H NMR (D_2O, 300 MHz) δ 7.32-7.10 (m, 5H), 2.81 (ddd, J = 7.90, 4.29, 3.58 Hz, 1H, H-C(1)), 2.36 (ddd, J = 10.22, 6.64, 3.58 Hz, 1H, H-C(2)), 1.39-1.23 (m, 2H, $H_{A,B}$-C(3)).

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