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Synthesis of The Enantiomer of the Antidepressant Tranylcypromine

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Abstract: Both enantiomers of the antidepressant tranylcypromine, *trans* 2-phenyl-cyclopropylamine **1**, were prepared in enantiomerically pure form by a chemoenzymatic approach starting from racemic (±)-(1*RS*, 2*RS*)-*trans* ethyl 2-phenyl-cyclopropane carboxylate **(±)-3**.

INTRODUCTION

Racemic switches are chiral drugs that are already approved as racemates but have been redeveloped as single isomers. Sometimes the single isomer version lacks certain side effects that the racemate exhibits and where the two enantiomers are sufficiently different in pharmacological effects [1], it may be possible to get a patent on one or both isomers.[2] In a project dealing with the development of racemic switches for (pro-)drugs and drug intermediates by chemoenzymatic enantiodifferentiation we became interested in the monoaminooxidase inhibitor (MAOI) tranylcypromine (Parnate®, Jatrosom® N), (±)-(1*RS*, 2*SR*)-*trans* 2-phenyl-cyclopropylamine **(±)-1**. Tranylcypromine is an oral MAOI-type antidepressant and it is used to treat major depression in patients who have not responded to other antidepressant therapy and are either closely supervised or hospitalized. **1** is used in therapy as a racemate. It has been established, however, that the enantiomers of **1** show both qualitative and quantitative differences. Thus **(+)-(1 *S*, 2 *R*)-1** exhibits a five-fold higher MAOI activity than its enantiomer, whereas the latter inhibits significantly stronger the re-uptake of catecholamines. [3] In addition, the *trans*-2-phenylcyclopropyl-amine moiety is part of antibacterial active gyrase inhibitors and again a strong dependence of the antibacterial activity with the absolute configuration of the two stereogenic centers of this moiety was established.[4]

Several approaches for the synthesis of the two enantiomers of **(±)-1** or suitable precursors have been devised. Thus, (–)-(1 *R*, 2 *R*)-*trans* 2-phenyl-cyclopropane carboxylic acid **(–)-2** has been obtained from the racemate by crystallization of its (+)-dehydroabiethylamine [3] or brucine [5] salts whereas for the synthesis of **(+)-2** the diastereomeric quinine salts [6] have been used. In addition, enantioselective cyclopropanation of styrene with alkyl diazoacetates has been performed in the presence of semicorrin-metal (-triflate)[7, 8] complexes or of bis(oxazoline) copper complexes [9-11] to afford **(+)-2** or **(–)-2** with ee's of 90-99%.

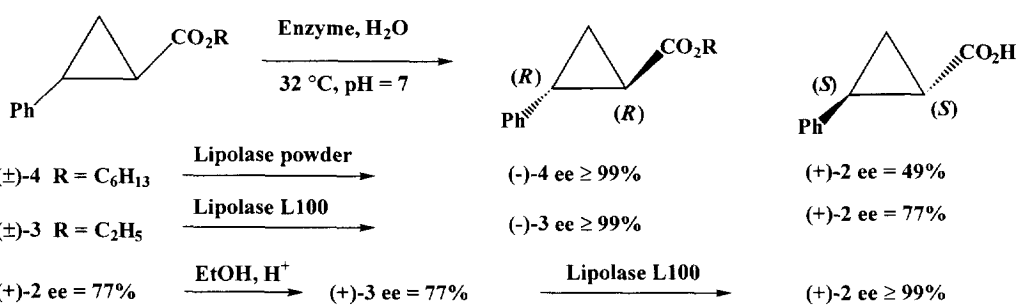
RESULTS AND DISCUSSION

A chemoenzymatic route was planed starting from racemic (±)-(1 *RS*, 2 *RS*)-*trans* ethyl 2-phenyl-cyclopropane carboxylate **(±)-3** and (±)-(1 *RS*, 2 *RS*)-*trans* hexyl 2-phenyl-cyclopropane carboxylate **(±)-4**; **(±)-4** was easily obtained from **(±)-3** by transesterification with *n*-hexanol in the presence of conc. sulfuric acid. It was another aim of this project to use rather inexpensive enzymes to allow a very economic synthesis of the enantiomers of **1**.

The two esters were subjected to chemoenzymatic hydrolysis reactions using pH-stat equipment maintaining the pH of the reactions constant at pH=7 throughout the reaction by the addition of 0.1 N NaOH. Both **(±)-3** and **(±)-4** were excellent substrates for the enzyme pig liver esterase (PLE), but unfortunately these hydrolyses proceeded without any selectivity.

Table 1: Enzymatic Hydrolysis of **(±)-3** and **(±)-4**

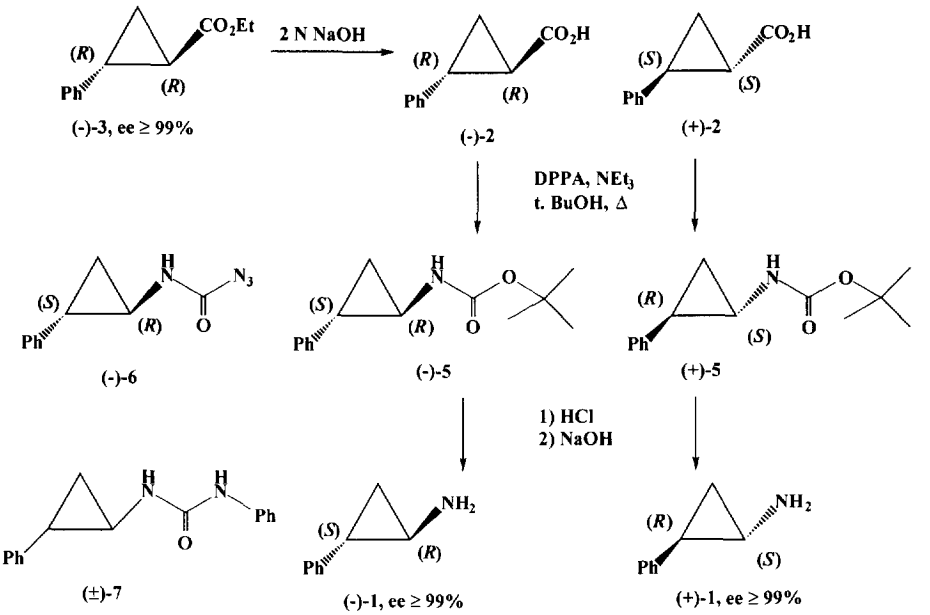
Enzyme	conversion of (±)-3 [%]	ee of (–)-3 [%]	ee of (+)-2 [%]	conversion of (±)-4 [%]	ee of (–)-4 [%]	ee of (+)-2 [%]
Lipolase -powder	0			73	> 99	49
Lipolase L100	55	> 99	77	47	86	78
Lipase P	62	92	43	68	92	50
Lipase PS	72	90	32	22	32	68
Novozym 435®	61	20	14	66	18	9
PLE	50	0	0	58	0	0
Lipase AY	29	24	67	0		
Lipase M	62	59	75	0		
Lipase F	0			10	0	0



The best results (*cf.* Table 1) were obtained with the lipolase powder (immobilized lipolase, E.C. 3.1.1.3) to afford enantiomerically pure **(–)-4** and with the lipolase L100 (as used in detergents) enantiomerically pure **(–)-3** was obtained. Interestingly, **(±)-3** was a non-substrate for the lipolase powder within a reaction time of 3 days. This represents a dramatic change of reactivity as a function of immobilization. Worthwhile to mention that lipolase has been obtained according to GMP procedures from a non-pathogen microorganism, it is not toxic, very cheap due its common-spread use in synthetic detergents and biosurfactants and is completely biodegradated.

The enantiomeric purity of **3** was determined by HPLC either directly using a (*S*, *S*)-Whelk O1® column or after transesterification with *n*-hexanol as its hexylester **4**; the HPLC investigation of the hexylester **4** showed a clean baseline separation of the corresponding enantiomers on a Chiralcel OD-R® column. The ee of **2** was measured after its re-esterification with ethanol (→ **3**).

Saponification of **(–)-3** with 2 N NaOH gave (–)-(1*R*, 2*R*)-*trans* 2-phenyl-cyclopropane carboxylic acid **(–)-2**. **(–)-2** was subjected to a modified *Curtius* degradation using diphenyl phosphorylazide, *tert.* butanol and triethylamine [12] to afford **(–)-5**.[13] As a byproduct the formation of the carbamoyl azide **(–)-6** was observed.[14] Treatment of **(–)-5** with conc. hydrochloric acid at room temperature gave enantiomerically pure (–)-tranylcypromine **(–)-1**.

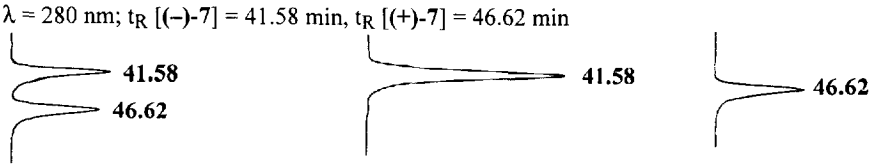


As for the synthesis of **(+)-1** the enantiomerically enriched **(+)-2** (ee = 77-78%) from the first enzymatic hydrolysis was subjected to a re-esterification to afford **(+)-3** (ee = 77-78%) that was used as a starting material for a second enzymatic hydrolysis with lipolase L100 using a conversion of 40% to yield enantiomerically pure **(+)-2**. *Curtius* degradation of **(+)-2** followed by acidic hydrolysis finally gave enantiomerically pure (+)-tranylcypromine **(+)-1**.

Since no suitable conditions for a direct HPLC determination of the enantiomeric purity of **1** could be found, the ee was established after *in-situ* transformation of **1** into its derivative **7**. A clean baseline separation of the two enantiomers could be achieved using a Chiralcel OD-R® column.[15]

Fig. 1: HPLC investigation of (±)-, (+)- and (–)-**3**: (*S*, *S*)-Whelk O1®, pentane/prop-2-OH/AcOH 98/2/05, 1 *ml*/min, λ = 270 nm; t_R [(–)-**3**] = 5.04 min, t_R [(+)-**3**] = 5.74 min

Fig. 2: HPLC investigation of (±)-, (+)- and (–)-**7**: Chiralcel OD-R®, AcCN/H_2O (pH=4) 50/50, 0.4 *ml*/min, λ = 280 nm; t_R [(–)-**7**] = 41.58 min, t_R [(+)-**7**] = 46.62 min



EXPERIMENTAL

General.– Melting points are uncorrected (*Reichert* hot stage microscope), optical rotations were obtained using a Perkin-Elmer 243B polarimeter (1 cm micro-cell), NMR spectra (internal Me_4Si) were

recorded using either a Bruker AM250 or a Varian XL300 instrument (δ given in ppm, *J* in Hz, internal Me_4Si, IR spectra (film or KBr pellet) on a Perkin-Elmer 298 instrument or on a Perkin-Elmer 1605 FT-IR, MS spectra were taken either on a MAT311A or a Varian-112S instrument; for elemental analysis a Foss-Heraeus Vario EL instrument was used. TLC was performed on silica gel (Merck 5554, detection by dipping in an ethanolic ninhydrin (1%) solution followed by gentle heating, or by treatment with iodine). HPLC was performed on a Merck-Hitachi L6200A/L4000/D2500 instrument; the pH-stat equipment was obtained from Metrohm. The enzymes were used as obtained: Lipolase and Lipolase L100 (Novo Nordisk), Lipase P (*Pseudomonas fluorescens*, Amano Ltd.), Lipase PS (*Pseudomonas sp.*, Amano Ltd.), Novozym 435 (*Candida antarctica*, Novo Nordisk), PLE (*porcine liver*, Boehringer Mannheim).

(±)-(1 *RS*, 2 *RS*)-*trans* Hexyl 2-phenyl-cyclopropane carboxylate [(±)-4].– A solution of **(±)-3** (5.0 g, 26.3 mmol, commercial, Lancaster, used as received) in *n*-hexanol (75 *ml*) and conc. sulfuric acid (0.5 *ml*) was heated for 12 h at 130 °C; the ethanol formed during this reaction was distilled off continuously by use of a distillation head attached onto the top of a 80 °C warm *Vigreux* column. After cooling to 25 °C the excess of hexanol was distilled off under reduced pressure and the residue was subjected to column chromatography (silica gel, hexane → ethyl acetate/hexane 1:20 → 1:10) to afford **(±)-4** (6.0 g, 93%) as a colorless oil. As a byproduct dihexylether (2.3 g; colorless oil; R_F (ethyl acetate/hexane 1:15) 0.42; n_D = 1.4180; IR (film) ν 2957*s*, 2932*s*, 2859*s*, 1603*w*, 1467*m*, 1377*w*, 1120*m*; ^{1}H NMR (250 MHz, $CDCl_3$): δ 3.39 (*t*, *J* = 6.7, 4 H, 2 x OCH_2), 1.59-1.51 (*m*, 4 H, 2 x CH_2), 1.36-1.30 (*m*, 12 H, 6 x CH_2), 0.89 (*t*, *J* = 6.4, 6 H, 2 x CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): δ 71.11 (*t*, 2 x OCH_2), 31.88, 29.91, 26.03, 22.78 (each *t*, 2 x CH_2), 14.14 (*q*, 2 x CH_3); MS (ei, 80 eV, 78 °C): 186 (5.4%), 185 (35.1%), 132 (1.1%), 131 (13.2%), 113 (3.2%), 101 (22.3%), 86 (6.3%), 85 (100.0%)) was formed. Data for **4**: R_F (ethyl acetate/hexane 1:15) 0.35; IR (film): ν 3030*m*, 2956*s*, 2931*s*, 2859*m*, 1726*s*, 1605*w*, 1499*m*, 1458*m*, 1437*m*, 1409*s*, 1337*m*, 1263*m*, 1220*m*, 1175*s*, 1078*m*, 1044*w*; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.30-7.07 (*m*, 5 H, H-C(phenyl)), 4.10 (*t*, *J* = 6.7, 2 H, OCH_2), 2.51 (*ddd*, *J* = 9.5, 6.1, 3.9, 1 H, H-C(2)), 1.93-1.86 (*m*, 1 H, H-C(1)), 1.66-1.55 (*m*, 1 H, H_A-C(3) and 2 H, CH_2), 1.41-1.26 (*m*, 1 H, H_B-C(3) and 6 H, 3 x CH_2), 0.89 (*t*, *J* = 6.3, 3 H, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): δ 173.48 (*s*, CO), 140.19 (*s*, C_q(phenyl)), 128.49, 126.48, 126.21 (*d*, C(phenyl)), 64.95 (*t*, OCH_2), 31.47, 28 68 (each *t*, CH_2), 26.16 (*d*, C(2)), 24.21 (*d*, C(1)), 25.62, 22.56 (each *t*, CH_2), 17.03 (*t*, C(3)), 14.00 (*q*, CH_3); MS (ei, 80 eV, 100 °C): 248 (0.4%), 247 (2.0%), 246 (12.6%), 215 (0.8%), 191 (5.4%), 163 (33.0%), 162 (69.6%), 145 (17.8%), 144 (23.6%), 117 (93.5%), 116 (23.9%), 115 (33.7%), 107 (27.1%), 91 (19.8%), 43 (100.0%); Anal. calcd. for $C_{16}H_{22}O_2$ (246.35): C, 78.01; H, 9.00; found: C, 77.72; H, 9.03.

(–)-(1 *R*, 2 *R*)-*trans* ethyl 2-phenyl-cyclopropane carboxylate (–)-3 and *trans* 2-phenyl-cyclopropane carboxylic acid (2).– To a solution of **(±)-3** (3.0 g, 15.8 mmol) in water (40 *ml*) at 30 °C lipolase L100 (100 mg) was added and the pH of the reaction mixture was kept constant in the pH-stat equipment at 7.0 by the addition of 0.1 N NaOH (86.73 *ml* corresponding to a conversion of 55%). The aqueous solution was diluted with dichloromethane (50 *ml*) and brought to pH ≈ 1-2 by the careful addition of 17% aqueous hydrochloric acid. The aqueous layer was extracted with dichloromethane (4 x 40 *ml*) and the combined organic phases were dried ($MgSO_4$), the solvent was evaporated and the residue subjected to chromatography (silica gel, ethyl acetate/hexane 1:10 → 1:5) to afford **(–)-3** (1.14 g, 38%) and **2** (1.25 g, 49%).

Data for **(–)-3**: colorless liquid, $[\alpha]_D^{20}$-308 (*c* 0.78, $CHCl_3$), ee ≥99% [lit.: $[\alpha]_D^{20}$-279 (ee 96%)[9], $[\alpha]_D^{20}$+236 (ee 75%) for **(+)-3** [16]]; R_F (ethyl acetate/hexane 1:15) 0.43; IR (KBr): ν 3415*m*, 3087*m*, 3065*m*, 3030*m*, 2982*m*, 1957*w*, 1879*w*, 1718*s*, 1675*m*, 1653*m*, 1636*m*, 1617*w*, 1603*m*, 1581*m*, 1560*m*, 1545*w*,

1507*w*, 1496*m*, 1473*m*, 1457*s*, 1437*m*, 1412*m*, 1387*m*, 1366*m*, 1336*s*, 1311*m*, 1286*m*, 1219*m*, 1190*s*, 1077*m*, 1040*m*, 1018*m*; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.30-7.07 (*m*, 5 H, H-C(phenyl)), 4.16 (*q*, *J* = 7.1, 2 H, OCH_2), 2.51 (*ddd*, *J* = 9.4, 6.1, 4.1, 1 H, H-C(2)), 1.89 (*ddd*, *J* = 8.4, 5.1, 4.1, 1 H, H-C(1)), 1.59 (*ddd*, *J* = 9.4, 5.1, 4.4, 1 H, H_A-C(3)), 1.33-1.24 (*m*, 1 H, H_B-C(3)), 1.27 (*t*, *J* = 7.1, 3 H, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): δ 173.39 (*s*, CO), 140.15 (*s*, C_q(phenyl)), 128.47, 126.48, 126.19 (*d*, C(phenyl)), 60.68 (*t*, OCH_2), 26.15 (*d*, C(2)), 24.16 (*d*, C(1)), 17.02 (*t*, C(3)), 14.27 (*q*, CH_3); MS (ei, 80 eV, 30 °C): 192 (0.5%), 191 (6.1%), 190 (47.9%), 162 (7.6%), 145 (23.2%), 144 (20.3%), 135 (18.9%), 133 (13.7%), 117 (100.0%); Anal. calcd. for $C_{12}H_{14}O_2$ (190.24): C, 75.76; H, 7.42; found: C, 75.44; H, 7.42. Determination of the ee: 1) HPLC, column Whelk O1® (Merck), pentane/2-propanol/acetic acid 98/2/0.5, flow 1.0 *ml*/min, pressure 24 bar, UV detection at λ = 270 nm, t_R **[(–)-3]** = 5.04 min, t_R **[(+)-3]** = 5.74 min; 2) after transesterification: **3** (1 mg) was dissolved in *n*-hexanol (0.1 *ml*) and catalytic amounts of conc. sulfuric acid (10 *µl*) were added. After warming to 120 °C for 60 min the reaction mixture was cooled to 25 °C, the solvents were removed under reduced pressure and the residue dissolved in methanol (3 *ml*, HPLC quality, Merck). After filtration (membrane filter 45 µm) this solution was directly used for HPLC: Chiralcel OD-R® (Daicel), methanol/water (pH = 4 by the addition of $HClO_4$) 80/20, flow 0.4 *ml*/min, pressure 27 kg/cm^2, UV detection at λ = 280 nm, t_R **[(–)-4]** = 54.03 min, t_R **[(+)-4]** = 65.76 min.

Data for **2**: white solid, mp 46-47 °C, $[\alpha]_D^{20}$+299.0 (*c* 1.05, $CHCl_3$), ee = 77% (by HPLC after esterification: A solution of **2** (1 mg) and *p*-TsOH (catalytic amounts) in dry ethanol (1 *ml*) was heated under reflux for 30 min, then the solvent was removed under reduced pressure, the remaining residue was redissolved in methanol (3 *ml*, HPLC quality, Merck), filtered (membrane filter, 45 µm) and this solution was directly used for the HPLC analysis).

(–)-(1 *R*, 2 *R*)-*trans* 2-phenyl-cyclopropane carboxylic acid (–)-2.– A solution of **(–)-3** (0.5 g, 2.63 mmol) in an aqueous solution of NaOH (2 N, 5 *ml*) was heated under reflux for 5 h. After cooling to 25 °C the pH was adjusted by the addition of 17% HCl to 1-2 and the mixture was extracted with ethyl acetate (4 x 30 *ml*). The combined organic layers were dried ($MgSO_4$), the solvent was removed under reduced pressure and **(–)-2** (0.41 g, 96%) was obtained as a white solid; mp 36-37 °C (lit.: colorless oil [17], 51-52 °C [5], 47-49 °C [3]); R_F (ethyl acetate/hexane 1:2) 0.29; $[\alpha]_D^{20}$-381.3 (*c* 0.96, $CHCl_3$) (lit.: $[\alpha]_D^{25}$-381.1 (*c* 1, $CHCl_3$) [3]); ee ≥ 99% (determined as ethyl ester by HPLC (Whelk O1®, *vide supra*); IR (KBr): ν 3032*s*, 2645*s*, 2365*m*, 1950*w*, 1874*w*, 1690*s*, 1602*m*, 1581*m*, 1560*w*, 1498*s*, 1461*s*, 1447*s*, 1432*s*, 1338*s*, 1326*s*, 1308*s*, 1289*s*, 1236*s*, 1182*m*, 1118*m*, 1080*m*, 1057*m*, 1048*m*, 1041*m*, 1024*m*; ^{1}H NMR (250 MHz, $CDCl_3$): δ 11.45 (*br s*, 1 H, OH), 7.31-7.08 (*m*, 5 H, H-C(phenyl)), 2.60 (*ddd*, *J* = 9.5, 6.5, 4.0, 1 H, H-C(2)), 1.90 (*ddd*, *J* = 8.3, 4.7, 4.0, 1 H, H-C(1)), 1.66 (*ddd*, *J* = 9.5, 4.7, 4.6, 1 H, H_A-C(3)), 1.39 (*ddd*, *J* = 8.3, 6.5, 4.6, 1 H, H_B-C(3)); ^{13}C NMR (63 MHz, $CDCl_3$): δ 180.03 (*s*, CO), 139.53 (*s*, C_q(phenyl)), 128.57, 126.75, 126.33 (*d*, C(phenyl)), 27.13 (*d*, C(2)), 24.00 (*d*, C(1)), 17.50 (*t*, C(3)); MS (ei, 80 eV, 61 °C): 162 (44.0%), 161 (1.0%), 145 (3.0%), 144 (15.6%), 118 (9.6%), 117 (100.0%); Anal. calcd. for $C_{10}H_{10}O_2$ (162.19): C, 74.06; H, 6.21; found: C, 73.97; H, 6.39.

(–)-(1 *R*, 2 *S*)-*trans* (2-phenyl-cyclopropyl)-carbaminic acid *tert.* butyl ester (–)-5 and (–)-(1 *R*, 2 *S*)-*trans* (2-phenyl-cyclopropyl)-carbamoyl azide (–)-6.– To a solution of **(–)-2** in dry *tert.* butanol (5 *ml*), triethylamine (0.22 g, 2.18 mmol) and diphenyl phosphoryl azide (0.60 g, 2.18 mmol) were added and the mixture was warmed to 90-95 °C for 5 h. Then the solvents were removed under reduced pressure and the residue subjected to chromatography (ethyl acetate/hexane 1:10) to afford **(–)-5** (0.26 g, 51%) and **(–)-6** (0.03 g, 9%).

Data for **(–)-5**: white solid; mp 81-83 °C; R_F (ethyl acetate(hexane 1:4) 0.48; $[\alpha]_D^{20}$-97.6 (*c* 0.8, $CHCl_3$); IR (KBr): ν 3370*s*, 3029*w*, 3011*w*, 2983*w*, 2934*w*, 1734*w*, 1688*s*, 1653*m*, 1617*w*, 1604*w*, 1560*w*, 1512*s*, 1457*w*, 1443*w*, 1391*w*, 1365*m*, 1338*w*, 1268*m*, 1252*m*, 1226*w*, 1213*m*, 1167*s*, 1113*w*, 1102*w*, 1079*w*, 1068*m*, 1045*m*, 1027*w*; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.29-7.10 (*m*, 5 H, H-C(phenyl)), 4.85 (*br s*, 1 H, NH), 2.72 (*m*, 1 H, H-C(1)), 2.03 (*ddd*, *J* = 9.4, 6.5, 3.0, 1 H, H-C(2)), 1.45 (*s*, 9 H, 3 x CH_3(*tert.* butyl)), 1.18-1.11 (*m*, 2 H, $H_{A,B}$-C(3)); ^{13}C NMR (63 MHz, $CDCl_3$): δ 156.35 (*s*, CO), 140.76 (*s*, C_q(phenyl)), 128.33, 126.51, 126.03 (each *d*, C(phenyl)), 79.64 (*s*, C_q(*tert.* butyl)), 32.57 (*d*, C(1)), 28.49 (*q*, 3 x CH_3(*tert.* butyl)), 25.11 (*d*, C(2)), 16.37 (*t*, C(3)); MS (ei, 80 eV, 54 °C): 234 (0.1%), 233 (0.5%), 219 (0.1%), 218 (0.6%), 177 (21.5%), 134 (5.4%), 133 (48.3%), 132 (28.3%), 116 (34.8%), 57 (100.0%); anal. calcd. for $C_{14}H_{19}NO_2$ (233.31): C, 72.07; H, 8.21; N, 6.00; found: C, 72.07; H, 8.17; N, 5.82.

Data for **(–)-6**: white solid; mp 65-83 °C (under decomposition); R_F (ethyl acetate/hexane 1:4) 0.40; $[\alpha]_D^{20}$-114.9 (*c* 0.74, $CHCl_3$); IR (KBr): ν 3319*s*, 3085*w*, 3028*m*, 2172*s*, 2146*s*, 1675*s*, 1605*m*, 1546*s*, 1499*s*, 1460*m*, 1387*w*, 1326*m*, 1281*s*, 1215*m*, 1193*m*, 1166*m*, 1090*m*, 1069*m*, 1058*m*, 1045*m*, 1033*m*, 1003*m*; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.30-7.03 (*m*, 5 H, H-C(phenyl)), 5.43 (*br s*, 1 H, NH), 2.85-2.75 (*m*, 1 H, H-C(1)), 2.15-2.05 (*m*, 1 H, H-C(2)), 1.30-1.19 (*m*, 2 H, $H_{A,B}$-C(3)); ^{13}C NMR (63 MHz, $CDCl_3$): δ 157.20 (*s*, CO), 139.80 (*s*, C_q(phenyl)), 128.47, 126.77, 126.63 (each *d*, C(phenyl)), 32.56 (*d*, C(1)), 25.01 (*d*, C(2)), 15.83 (*t*, C(3)); MS (ei, 80 eV, 59 °C): 202 (0.2%), 173 (15.4%), 159 (46.6%), 130 (100.0%), 116 (51.2%), 104 (42.5%), 103 (31.8%), 77 (43.7%); HRMS calcd. for $C_{10}H_{10}N_4O$: 202.0856; found: 202.0856.

(–)-(1 *R*, 2 *S*)-*trans* 2-phenyl-cyclopropylamine, (–)-tranylcypromine (–)-1.– To a solution of **(–)-5** (0.15 g, 0.65 mmol) in THF (1 *ml*) aqueous hydrochloric acid (33%, 1 *ml*) was added and the mixture was warmed to 40 °C for 30 min. After cooling to 25 °C the pH was adjusted to 13-14 by the careful addition of an aqueous solution of NaOH (20%) and the mixture was extracted with diethylether (3 x 20 *ml*). The combined organic phases were dried ($MgSO_4$), filtered through a short pad of basic aluminium oxide, evaporated and **(–)-1** (0.06 g, 68%) remained as an oil; R_F (ethyl acetate/methanol 3:1) 0.27; $[\alpha]_D^{20}$-135.4 (*c* 0.81, $CHCl_3$) (lit.: $[\alpha]_D^{25}$-115.8° (*c* 1.13, $CHCl_3$)[3]); IR (film): ν 2920s, 2728s, 2113w, 1946w, 1763w, 1735w, 1718w, 1701w, 1696w, 1685w, 1636m, 1605s, 1582s, 1561s, 1496s, 1466s, 1443m, 1404w, 1346w, 1247m, 1185s, 1156s, 1117s, 1023s; ^{1}H NMR (300 MHz, d_4-methanol): δ 7.22-6.98 (*m*, 5 H, H-C(phenyl)), 4.82 (*s*, 2 H, NH_2), 2.43 (*ddd*, *J* = 7.7, 4.4, 3.3, 1 H, H-C(1)), 1.84 (*ddd*, *J* = 9.1, 6.0, 3.3, 1 H, H-C(2)), 1.03-0.92 (*m*, 2 H, $H_{A,B}$-C(3)); ^{13}C NMR (75 MHz, d_4-methanol): δ 143.53 (*s*, C_q(phenyl)), 129.22, 126.67, 126.45 (each *d* C(phenyl)), 35.75 (*d*, C(1)), 26.36 (*d*, C(2)), 18.13 (*t*, C(3)); MS (ei, 80 eV, 30°C): 134 (8.7%), 133 (100.0%), 132 (79.9%), 130 (8.1%), 118 (4.0%), 117 (19.8%), 115 (36.6%), 104 (14.4%), 91 (17.4%), 77 (20.7%); Anal. calcd. for $C_9H_{11}N$ (133.20): C, 81.16; H, 8.32; N, 10.52; found: C, 80.93; H, 8.44; N, 10.63; ee ≥ 99% as determined by HPLC after derivatization with phenyl-isocyanate: **(–)-1** (1 mg) was dissolved in dry diethylether (1 *ml*), triethylamine (0.25 *ml*) and phenyl-isocyanate (5 *μl*) were added. After warming (50 °C, 30 min) and cooling to 25 °C, the volatile components were removed under reduced pressure and the residue was dissolved in methanol (3 *ml*, HPLC quality, Merck). This solution was filtered (membrane filter, 45 μm) and the filtrate was directly used for the HPLC investigations: column Chiralcel OD-R® (Daicel), eluent: acetonitrile/water (pH = 4 by the addition of $HClO_4$) 50:50, flow 0.4 *ml*/min, pressure 19 kg/cm^2, UV-detection at λ = 280 nm, t_R [(–)-7] = 41.58 min, t_R [(+)-7] = 46.62 min.

(±)-(1 *RS*, 2 *SR*)-*trans* 1-phenyl-3-(2-phenyl-cyclopropyl)-urea (±)-7.– To a solution of **(±)-1** (0.15 g, 1.13 mmol) in dry diethylether (1 *ml*), triethylamine (0.5 *ml*) and phenyl-isocyanate (0.12 *ml*, 1.13 mmol)

were added and the reaction mixture was stirred for 3 h at 25 °C. The solvent was removed under reduced pressure and the residue subjected to chromatography (ethyl acetate/hexane 1:10 → 1:5 → 1:2 → ethyl acetate) to afford **(±)-7** (0.24 g, 91%) as a white solid; mp 172-174 °C; R_F (ethyl acetate/hexane 1:3) 0.19; IR (KBr): ν 3290*m*, 3057*w*, 2979*w*, 1734*w*, 1718*w*, 1695*m*, 1642*s*, 1600*s*, 1572*s*, 1496*m*, 1464*w*, 1445*m*, 1401*w*, 1311*m*, 1244*m*, 1196*w*, 1183*w*, 1113*w*, 1076*w*, 1030*w*; ^{1}H NMR (300 MHz, d_6-DMSO): δ 8.37 (*s*, 1 H, NH), 7.42-7.39 (*m*, 2 H, H-C(phenyl)), 7.30-7.12 (*m*, 7 H, H-C(phenyl)), 6.93-6.87 (*m*, 1 H, H-C(phenyl)), 6.59 (*d*, *J* = 2.7, 1 H, NH), 2.77-2.71 (*m*, 1 H, H-C(1)), 1.97 (*ddd*, *J* = 9.0, 6.2, 3.0, 1 H, H-C(2)), 1.18-1.13 (*m*, 2 H, $H_{A,B}$-C(3)); ^{13}C NMR (75 MHz, d_6-DMSO): δ 155.56 (*s*, CO), 141.33, 140.09 (each *s*, C_q(phenyl)), 128.48, 128.02, 125.77, 125.39, 121.00, 117.70 (each *d*, C(phenyl)), 32.82 (*d*, C(1)), 24.59 (*d*, C(2)), 15.84 (*t*, C(3)); MS (ei, 80 eV, 138 °C): 253 (5.3%), 252 (26.8%), 137 (45.8%), 133 (68.9%), 132 (100.0%); Anal. calcd. for $C_{16}H_{16}N_2O$ (252.32): C, 76.17; H, 6.39; found: C, 75.87; H, 6.39.

(+)-(1 *S*, 2 *S*)-*trans* 2-phenyl-cyclopropane carboxylic acid (+)-2.– A solution of **2** (1.08 g, 6.66 mmol, ee = 77%, *vide supra*) in abs. ethanol (25 *ml*) was treated with catalytic amounts of *p*-TsOH and the mixture was heated under reflux for 8 h. The solvents were removed under reduced pressure, the residue was dissolved in ethyl acetate (100 *ml*), extracted in succession with a saturated aqueous solution of $NaHCO_3$ (2 x 5 *ml*) and brine (10 *ml*) and dried ($MgSO_4$). The solvent was evaporated and the residue subjected to chromatography (silica gel, hexane/ethyl acetate 10:1 5:1) to afford **3** (1.23 g, 96%), ee = 77% as determined by HPLC (Whelk O1®, vide supra). **3** (1.2 g, 6.31 mmol) was dissolved in water (80 *ml*) and treated with the enzyme lipolase L100 (600 mg) in the pH-stat equipment as described above (pH = 7, 30 °C). After addition of a total of 25.22 *ml* of 0.1 N NaOH (corresponding to a conversion of 40%) the reaction was stopped by extraction with dichloromethane (3 x 30 *ml*). The aqueous layer was adjusted to pH ≈ 1-2 by the careful addition of hydrochloric acid (0.1 N), extracted with dichloromethane (4 x 50 *ml*) and the combined organic phases were dried ($MgSO_4$), the solvent was removed under reduced pressure and the residue subjected to chromatography (silica gel, hexane/ethyl acetate 10:1 → ethyl acetate) to afford **3** (0.5 g, 45%, colorless liquid; $[\alpha]_D^{20}$ = 225.7 (*c* 0.86, $CHCl_3$; ee = 72% (by HPLC, Whelk O1®, *vide supra*)) and **(+)-2** (0.32 g, 32%): white solid, mp 46-47 °C; $[\alpha]_D^{20}$+377.1° (*c* 1.04, $CHCl_3$); ee ≥ 99% (determined as ethyl ester by HPLC, Whelk O1®); R_F, IR, ^{1}H NMR, ^{13}C NMR and MS as described for **(–)-2**; Anal. calcd. for $C_{10}H_{10}O_2$ (162.19): C, 74.06; H, 6.21; found: C, 73.86; H, 6.48.

(+)-(1 *S*, 2 *R*)-*trans* (2-phenyl-cyclopropyl)-carbaminic acid *tert.* butyl ester (+)-5.– Following the procedure given for the preparation of **(–)-5** from **(+)-2** (0.18 g, 1.09 mmol) **(+)-5** (0.15 g, 57%) was obtained together with a small amount of slightly impure **(+)-6** (11 mg). Data for **(+)-5**: white solid; mp 82-84 °C; $[\alpha]_D^{20}$ +97.0 (*c* 0.98, $CHCl_3$); analytical data as given for **(–)-6**; Anal. calcd. for $C_{14}H_{19}NO_2$ (233.31): C, 72.07; H, 8.21; N, 6.00; found: C, 71.93; H, 8.32; N, 6.18.

(+)-(1 *S*, 2 *R*)-*trans* 2-phenyl-cylopropylamine, (+)-tranylcypromine, (+)-1.– Following the procedure given for the preparation of **(–)-1** from **(+)-5** (0.15 g, 0.65 mmol) **(+)-1** (0.06 g, 67%) was obtained as an oil; $[\alpha]_D^{20}$ +134.9 (*c* 0.85, $CHCl_3$); analytical data as given for **(–)-1**; Anal. calcd. for $C_9H_{11}N$ (133.20): C, 81.16; H, 8.32; N, 10.52; found: C, 80.90; H, 8.21; N, 10.69; ee ≥ 99% (as determined by HPLC after derivatization with phenyl-isocyanate (→ **7**) on Chiralcel OD-R®, *vide supra*).

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