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# Synthesis of the Novel Antidepressant (R)-(-)-Rolipram

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# SYNTHESIS OF THE NOVEL ANTIDEPRESSANT (*R*)-(-)-ROLIPRAM

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**Abstract :** Enantioselective synthesis of (*R*)-Rolipram **1** has been achieved through a conjugate addition of cyanide to enantiomerically pure 2-(2-aryl ethenyl)oxazoline **2**, followed by selective reduction of the adduct with $NaBH_4$-$NiCl_2$.

Rolipram, (*R,S*)-4-(3-cyclopentyloxy-4-methoxyphenyl)-pyrrolidin-2-one is an antidepressant drug known to be a selective phosphodiesterase type IV inhibitor, which has significant advantages over other antidepressants.[1,2] The (*R*)-(-) enantiomer **1**, the most active one,[3] was obtained by chiral HPLC resolution,[4] and several enantioselective syntheses have been described recently.[1,5,6]

We report here a novel route to synthesize (*R*)-Rolipram following the Scheme 1. The stereoselective conjugate addition of cyanide to the suitable activated α,ß-unsaturated oxazoline **2** could afford the 2-(2-aryl-2-cyanoethyl)-4-phenyl-4,5 dihydrooxazole **3a**. A suitable reduction of the nitrile function of **3a**[7,8] led to the amidinic precursor **4** of (*R*)-Rolipram.

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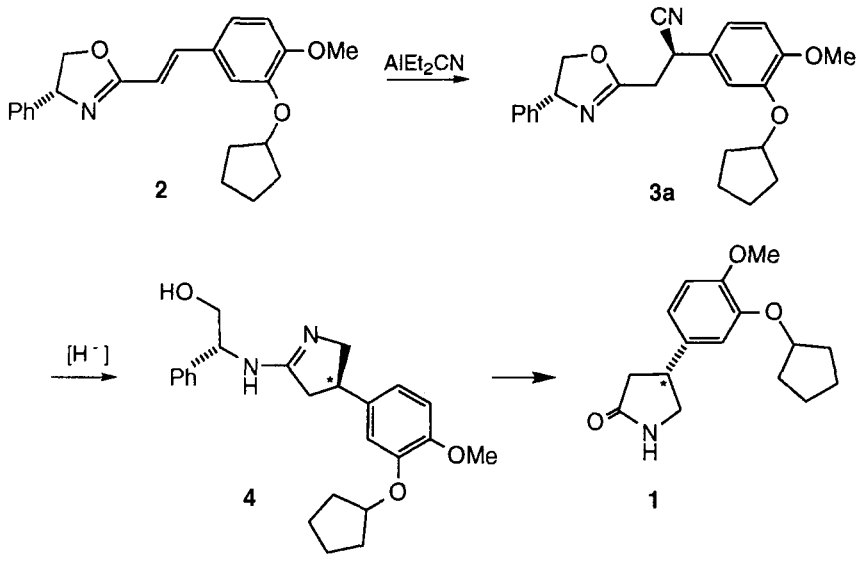
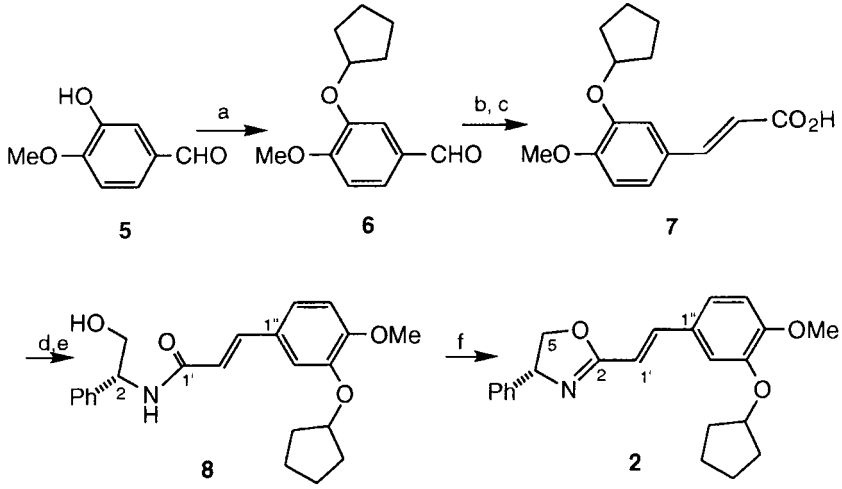



Scheme 1

The preparation of the α,ß-unsaturated oxazoline **2** is depicted in Scheme 2. (*E*)-3-Cyclopentyloxy-4-methoxycinnamic acid **7** was synthesized from isovanillin **5** in 90% yield for a three-step sequence involving *O*-alkylation with cyclopentylbromide[6] and Wittig-Horner reaction with methyl diethylphosphono acetate[9] followed by saponification. The reaction of *(R)*-phenylglycinol with acid chloride prepared from 1 equiv. of the acid **7** in the Schotten-Baumann conditions (aqueous $Na_2CO_3$-$CH_2Cl_2$, r.t., 3.5 h) led to the amide **8** in 72% yield. Under anhydrous conditions ($CH_2Cl_2$-$Et_3N$ 3 equiv., 2 h) the yield was lightly improved and reached 93% in the presence of DMAP, using 1.15 equiv. of acid **7** and prolonged reaction time [$CH_2Cl_2$, $Et_3N$ (3 equiv.), DMAP (0.2 equiv.), 22.5 h]. The (4*R*)-2-(*E*)-[2-(3-cyclopentyloxy-4-methoxyphenyl)ethenyl]-4-phenyl-4,5-dihydrooxazole **2** was obtained from the amide **8** in 92% yield by treatment with $POCl_3$ in excess at room temperature.[10]



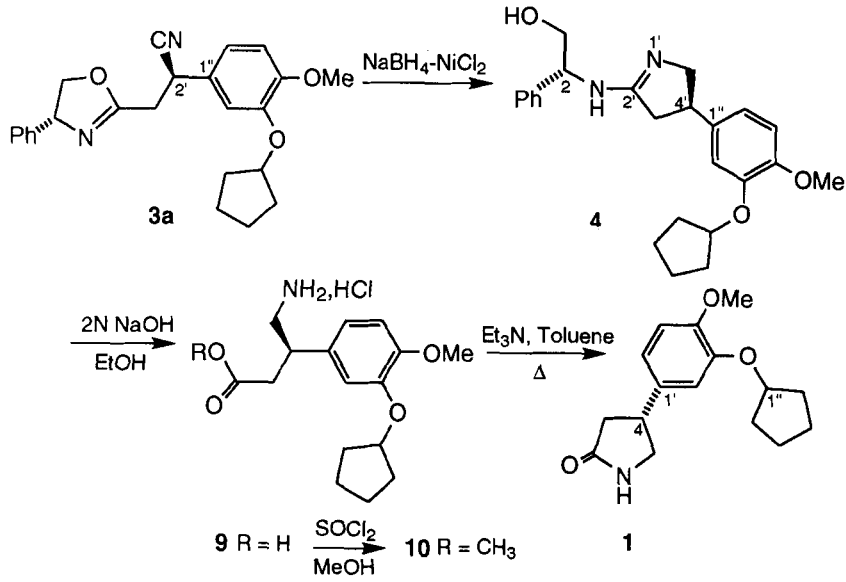

a : $C_5H_9Br$-$K_2CO_3$ ; b : $(EtO)_2P(O)CH_2CO_2Me$ ; c : 2N NaOH ; d : $SOCl_2$ ; e : (*R*)-phenylglycinol-$Et_3N$-DMAP ; f : $POCl_3$-toluene

Scheme 2

This 2-(2-arylethenyl)oxazoline **2** was subjected to conjugate addition of cyanide by means of $AlEt_2CN$ acting also as a complexant of the oxazoline function.[11,12] The reaction was slow at 18°C. As the formation of by-products was observed using higher temperature (+35°C), an incomplete (c.a. 50%) but clean conversion into the 2-(2-aryl-2-cyanoethyl) oxazolines **3** at 18°C was preferred. The diastereomers **3a** and **3b** were obtained in the ratio 63:37 as shown by $^1H$ NMR spectrum which displays two distinct signals for one of the protons at C-5. The configuration 2*R* was assigned to the newly created asymmetric center of the major diastereomer, by analogy with our prior results,[8,12] and was confirmed by subsequent synthesis.

The cyano group of the pure major diastereomer **3a**, isolated by chromatography on silica gel, was selectively reduced with $NaBH_4$-$NiCl_2$ into the amidine **4**.

After alkaline hydrolysis of **4** (2N NaOH, 95% EtOH), the reaction mixture was extracted with dichloromethane to remove the chiral auxiliary (*R*)-phenylglycinol. The aqueous phase was acidified to give, after evaporation to dryness, the crude aminoacid hydrochloride **9**, which was converted to its methylester **10** by treatment with $SOCl_2$ in methanol. This aminoacid ester was not isolated but directly cyclized into (*R*)-Rolipram **1** by heating in toluene in the presence of triethylamine (Scheme 3).




Scheme 3

Thus, (*R*)-Rolipram was synthesized in this way in 55% yield from the nitrile **3a**, in four steps with only one stage of purification.

## Experimental section

Optical rotations were measured on a Perkin-Elmer 241 ; the concentrations in

$CHCl_3$ solution (unless otherwise indicated) were given in g/100 mL. IR spectra ($\nu$ $cm^{-1}$, $CHCl_3$) were recorded on a Nicolet 205 (FT). $^1H$ NMR spectra were obtained ($CDCl_3$ unless otherwise indicated, $Me_4Si$, $\delta$ = 0 ppm) from Bruker AC200, AC250, AM300 ; coupling constants *J* values are given in Hertz (s, d, t, dd, and m indicate singlet, doublet, triplet, doublet of doublets, and multiplet respectively). $^{13}C$ NMR spectra were recorded on AC200 (50.0 MHz), AC250 (62.5 MHz) or AM300 (75.0MHz). Mass spectra and high resolution mass spectra were respectively measured on an AEI MS50 and on a Kratos MS80 spectrometer. Flash chromatography was performed on silica gel (SDS 230-400 mesh) and preparative thin layer chromatography on silica gel (Merck HF 254 + 366). Usual workup means that organic layer was dried over magnesium sulfate, filtered, and evaporated under vacuum.

**3-Cyclopentyloxy-4-methoxybenzaldehyde 6**[6,9]

Potassium carbonate (16.7 g, 120.8 mmol) and cyclopentylbromide (13.0 mL, 121 mmol) were successively added to a solution of isovanillin **5** (6.12 g, 40.2 mmol) in dry DMF (120 mL). The mixture was stirred at 100°C for 1.6 h. and the solvent and excess reagent were removed under reduced pressure. Water was added to the residue and the product was extracted with $CH_2Cl_2$ to give **6** as a yellow oil (8.80 g, 90%). IR : 2969, 1681, 1588, 1509, 1434. $^1H$ NMR (300 MHz) : 9.84 (s, 1H, CHO), 7.43 (dd, 1H, J = 8.1, J' = 1.8, H-6), 7.40 (d, 1H, J = 1.8, H-2), 6.97 (d, 1H, J = 8.1, H-5), 4.86 (m, 1H, H-1'), 3.93 (s, 3H, $OCH_3$), 2.10-1.57 (8H, cyclopentyl). $^{13}C$ NMR (75.0 MHz) : 190.52 (CO), 155.13, 147.90, 129.71 (qC-Ar), 125.93, 111.85, 110.57 (CH-Ar), 80.11 (C-1'), 55.75 ($OCH_3$), 32.42 (C-2', C-5'), 23.76 (C-3', C-4').

**(*E*)-3-Cyclopentyloxy-4-methoxy cinnamic acid 7**

Methyl diethylphosphonoacetate (7.75 mL, 42.2 mmol) was added in 20 min. under argon to a stirred suspension of NaH (55-65% in oil, 1.86 g, 46.5 mmol) in anhydrous toluene (15.0 mL) at 0°C After being stirred at room temperature for additional 30 min., a solution of aldehyde **6** (8.48 g, 38.5 mmol) in anhydrous toluene (11.0 mL) was added dropwise to the reaction mixture. The gum formed after 20 min. was filtered on a short column of silica gel (eluent : $CH_2Cl_2$-MeOH 9:1) to give the crude methylester[9] which was directly saponified. To a solution of the crude ester in methanol (190 mL) was added 2N NaOH (60 mL) and the mixture was stirred at room temperature for 15 h. After evaporation to dryness, the residue was acidified with 2N HCl (80 mL) and extracted with $CH_2Cl_2$. The solid obtained after usual workup was recrystallized from ether-pentane to give the acid **7** as white crystals (9.09 g, 90%). mp : 188-190°C. IR : 3625, 2970, 1685, 1628, 1600, 1510, 1440, 1430. $^1$H NMR (200 MHz) : 7.73 (d, 1H, J = 15.9, HC=), 7.11 (d, 1H, H-6'), 7.09 (1H, H-2'), 6.87 (d, 1H, J = 8.1, H-5'), 6.30 (d, 1H, HC=), 4.80 (m, 1H, H-1"), 3.89 (s, 3H, $OCH_3$), 1.92, 1.63 (8H, cyclopentyl). $^{13}$C (50 MHz) : 172.9 (CO), 152.7, 148.0 (qC-Ar), 147.3 (C-3), 127.0 (qC-Ar), 122.9, 114.8, 113.7, 111.7 (CH-Ar, C-2), 80.7 (C-1"), 56.2 ($OCH_3$), 32.9 (C-2", C-5"), 24.2 (C-3", C-4").

**(2*R*)-2-[*N*-(*E*)-3-Cyclopentyloxy-4-methoxycinnamoyl]amino-2-phenylethanol 8**

The acid **7** (602 mg, 2.3 mmol) was converted into acid chloride by heating in anhydrous toluene (5.0 mL) with $SOCl_2$ (0.5 mL) at 95°C for 2.5 h, followed by evaporation to dryness under reduced pressure. A solution of this crude acid

chloride in dry $CH_2Cl_2$ (4.0 mL) was added under argon to a stirred solution of (*R*)-phenylglycinol (271.4 mg ; 1.98 mmol) and *N,N*-dimethylaminopyridine (57 mg, 0.47 mmol) in dry $CH_2Cl_2$ (6.0 mL) at -40°C. After addition of triethylamine (1.0 mL, 7.17 mmol), the mixture was stirred at r.t. for 22.5 h. before addition of 2N HCl (10 mL) and extraction with $CH_2Cl_2$. To a solution of the crude product obtained after usual workup in $CH_2Cl_2$ (3 mL) was added MeOH (7 mL) and 2N NaOH (1.2 mL) and the mixture was stirred at r.t. for 20 min. The solvents were removed under reduced pressure below 40°C and the residue was extracted with $CH_2Cl_2$ to give an oil which was purified by flash chromatography (eluent : $CH_2Cl_2$-MeOH 98:2 to 95:5). Amide **8** (701 mg, 93%) was obtained as a white solid. mp : 155-157°C. $[\alpha]_D^{24}$ = + 45 (c = 1.02). IR : 3431, 3017, 2963, 1665, 1623, 1600, 1511. $^1H$ NMR (300 MHz) : 7.58 (d, 1H, J = 15.5, H-3'), 7.36 (m, 5H, Ar-H), 7.05 (dd, 1H, J = 8.2, J' = 1.7, H-6"), 7.02 (1H, H-2"), 6.83 (d, 1H, H-5"), 6.32 (d, 1H, J = 15.5, H-2'), 6.32 (d, 1H, J = 7, exch., NH), 5.20 (m, 1H, H-2), 4.77 (m, 1H, H-1"'), 3.96 (m, 2H, $H_2$-1), 3.86 (s, 3H, $OCH_3$), 2.97 (m, 1H, exch., OH), 1.91, 1.85, 1.64 (8H, cyclopentyl). $^{13}C$ NMR (50 MHz) : 167.0 (CO), 151.72, 147.8 (qC-Ar), 141.8 (C-3'), 139.1 (qC-Ar), 128.9, 127.8, 127.5, 126.8, 121.7, 118.0, 113.6, 111.7 (CH-Ar, C-2'), 80.5 (C-1"'), 66.5 (C-1), 56.3, 56.0 ($OCH_3$, C-2), 32.8 (C-2"', C-5"'), 24.1 (C-3"', C-4"'). Anal. Calcd for $C_{23}H_{27}NO_4$ : C, 72.42; H, 7.13; N, 3.67. Found : C, 72.42; H, 7.12; N, 3.63.

**(4*R*)-2-(*E*)-[2-(3-Cyclopentyloxy-4-methoxyphenyl)ethenyl]-4-phenyl-4,5-dihydrooxazole 2**

$POCl_3$ (9.6 mL, 103 mmol) was slowly added at r.t. under argon to a sitrred mixture of amide **8** (3.84 g, 10.0 mmol) and anhydrous toluene (60 mL). The solution was stirred at r.t. for additional 45 min. Solvent and excess reagent were

evaporated under reduced pressure. The residue was dissolved in dichloromethane (60 mL) before addition of 2N NaOH (30 mL). After being stirred at r.t. for 1 h., the mixture was extracted with $CH_2Cl_2$. The crude product was purified by flash chromatography (eluent : heptane-EtOAc 2:1) to afford oxazoline (3.35 g, 92%) as a white solid. mp : 57-59°C. $[\alpha]_D^{25} = +31$ (c = 1.82). IR : 2966, 1654, 1597, 1512 ,1263. $^1H$ NMR (300 MHz) : 7.38 (d, 1H, J = 16, H-2'), 7.36-7.26 (5H, Ar-H), 7.06 (H-2"), 7.04 (dd, 1H, J = 8, J' = 1.8, H-6"), 6.85 (d, 1H, J = 8, H-5"), 6.60 (d, 1H, J = 16, H-1'), 5.31 (dd, 1H, J = 9.9, J' = 8.2, H-4), 4.79 (m, 1H, H-1'"), 4.71 (dd, 1H, J = 9.9, J' = 8.4, Ha-5), 4.19 (dd, 1H, J ~ J' ~ 8.2, Hb-5), 3.87 (s, 3H, $OCH_3$), 1.92, 1.62 (8H, cyclopentyl). $^{13}C$ NMR (75.0 MHz) : 164.49 (C-2), 151.40, 147.70, 142.27 (qC-Ar), 140.28 (C-2'), 127.87 (qC-Ar), 128.53, 127.34, 126.44, 121.38, 112.58, 112.46, 111.52 (CH-Ar, C-1'), 80.23 (C-1'"), 74.14 (C-5), 69.74 (C-4), 55.76 ($OCH_3$), 32.62 (C-2'", C-5"'), 23.87 (C-3"'-C-4"'). (CI) MS : 364 $(M + H)^+$, 296. Anal. Calcd for $C_{23}H_{25}NO_3$ : C, 76.00; H, 6.93; N, 3.85. Found : C, 76.33; H, 7.06, N, 3.81.

**(4*R*,)-2-[2'-Cyano-2'-(3-cyclopentyloxy-4-methoxyphenyl)ethyl]-4-phenyl-4,5-dihydrooxazoles 3**

Anhydrous $CH_2Cl_2$ (12.0 mL) was added to a mixture of oxazoline **2** (2.11 g, 5.81 mmol) and dried powdered 3Å molecular sieves (1.89 g). To the mixture stirred at -70°C under argon was added $Et_2AlCN$ (1M in toluene, 9.0 mL, 9.0 mmol). The cooling bath was removed after 0.5 h. and the mixture was stirred at r.t. for 24 h. before a second addition of $Et_2AlCN$ (1M, 4.0 mL). After being stirred for additional 70 h., the reaction was quenched by addition of $CH_2Cl_2$ (15 mL) and aqueous solution of $Na_2CO_3$ (10% w/v, 15 mL) at -10°C. Extraction with $CH_2Cl_2$ and usual workup afforded crude product (2.3 g). Diastereomeric

excess of the nitriles **3** was determinated by $^1$H NMR after preparative TLC (yield 49%, d.e. 26%) and starting oxazoline **2** was recovered in 49% yield. The diastereomers **3a** and **3b** were separated by flash chromatography (eluent : pentane-ether 1:1 to 2:3).

Major diastereomer (4*R*, 2'*R*)-**3a** : mp : 99-100°C ($Et_2O$-pentane), $[\alpha]_D^{25}$ = + 16 (c = 1.25). IR : 2966, 2244, 1669, 1594, 1516. $^1$H NMR (300 MHz) : 7.28 (m, 3H, H-Ar), 7.08 (m, 2H, H-Ar), 6.93-6.83 (m, 3H, H-Ar), 5.19 (dd, 1H, J = 10', J' = 8.4, H-4), 4.76 (m, 1H, H-1'''), 4.64 (dd, 1H, J = 10, J' = 8.4, Ha-5), 4.30 (dd, 1H, J = 8.5, J' = 7.5, H-2'), 4.07 (dd, 1H, J = J' = 8.4, Hb-5), 3.86 (s, 3H, $OCH_3$), 3.05 (ddd, 1H, J = 16, J' = 8.5, J'' = 1.5, $H_a$-1'), 2.93 (ddd, 1H, J = 16, J' = 7, J'' = 1.5, Hb-1'), 1.87, 1.60 (8H, cyclopentyl). $^{13}$C NMR (75.0 MHz) : 164.15 (C-2), 150.16, 148.13, 141.69 (qC-Ar), 128.66, 127.58 (CH-Ar), 126.58 (qC-Ar), 126.42 (CH-Ar), 120.27 (CN), 119.62, 113.91, 112.21 (CH-Ar), 80.50 (C-1'''), 75.17 (C-5), 69.54 (C-4), 56.03 ($OCH_3$), 34.24 (C-1'), 33.89 (C-2'), 32.71 (C-2''', C-5'''), 23.97 (C-3''', C-4'''). (CI) MS (isobutane) : 447 $(M + 57)^+$, 391 $[M + H]^+$, 364, 323, 197. Anal. Calcd for $C_{24}H_{26}N_2O_3$ : C, 73.82; H, 6.71; N, 7.18. Found : C, 73.65; H, 6.69; N, 7.11.

Minor diastereomer(4*R*, 2'*S*)-**3b** : mp : 68-70°C ($Et_2O$-pentane). $[\alpha]_D^{25}$ = + 25 (c = 1.47). IR : 2965, 2244, 1668, 1516. $^1$H NMR (300 MHz) : 7.36-7.24 (m, 3H, H-Ar), 7.13 (2H, H-Ar), 6.95-6.83 (m, 3H, H-Ar), 5.20 (dd, 1H, J = 10, J' = 8.5, H-4), 4.73 (m, 1H, H-1'''), 4.65 (dd, 1H, J = 10, J' = 8.5, Ha-5), 4.31 (dd, 1H, J = 8.6, J' = 6.8, H-2'), 4.10 (dd, J = J' = 8.5, Hb-5), 3.85 (s, 3H, $OCH_3$), 3.05 (dd, 1H, J = 15.7, J' = 8.7, Ha-1'), 2.91 (dd, 1H, J = 15.7, J' = 6.7, Hb-1'), 1.87, 1.83 and 1.60 (cyclopentyl). $^{13}$C NMR (62.5 MHz) : 164.2 (C-2), 150.2, 148.2, 141.7 (qC-Ar), 128.8, 127.7 (CH-Ar), 126.8 (qC-Ar), 126.7 (CH-Ar), 120.3 (CN), 119.6, 114.1, 112.4 (CH-Ar), 80.6 (C-1'''), 75.2 (C-5), 69.8 (C-4), 56.2 ($OCH_3$),

34.2 (C-1'), 33.9 (C-2'), 32.8 (C-2"', C-5"'), 24.1 (C-3"', C-4"'). Anal. Calcd for $C_{24}H_{26}N_2O_3$ : C, 73.82; H, 6.71: N, 7.18. Found : C, 73.72; H, 6.61; N, 7.07.

**(2*R*, 4*R*)-2-[4-(3-Cyclopentyloxy-4-methoxyphenyl)pyrrolin-2-yl]amino-2-phenylethanol 4**

$NiCl_2$-$6H_2O$ (418 mg, 1.76 mmol) was added to a solution of major nitrile **3a** (336.2 mg, 0.86 mmol) in THF-$H_2O$ 2:1 (17 mL), and $NaBH_4$ (117 mg, 3.09 mmol) was added in portions under vigorous stirring over 35 min. at r.t.. After being stirred for additional 25 min., $NH_4OH$ (32%, 3 mL) and MeOH (20 mL) were added to the reaction mixture, which was stirred for 25 min. before filtration on a short column of silica gel (eluent : $CH_2Cl_2$-MeOH-$NH_4OH$ 4:1:0.1). The filtrate was evaporated to dryness *in vacuo* and a solution of the residue in $CH_2Cl_2$-MeOH 9:1 was filtered again. The solvents were removed under reduced pressure to give the crude amidine **4** as a yellowish foam (431 mg). This crude material could be used in the next step without any purification or purified in 69% yield by preparative TLC (eluent : $CH_2Cl_2$-MeOH-$NH_4OH$ 9:1:0.2) as a white foam. $[\alpha]_D^{25}$ = - 90 (c = 1.10). IR : 3200 (br), 2966, 1682, 1518. $^1H$ NMR (300 MHz, $CDCl_3$ + $D_2O$-NaOD) : 7.4-7.3 (5H, H-Ar), 6.8-6.7 (3H, H-Ar), 4.73 (m, 2H, H-4, H-1"'), 4.05 (m, 1H, H-5'), 3.93 (dd, 1H, J = 11.2, J' = 8.0, Ha-1'), 3.81 (s + m, 4H, $OCH_3$ + Hb-1'), 3.56 (m, 2H, Hb-5', H-4'), 2.91 (dd, 1H, J = 15.7, J' = 9.6, Ha-3'), 2.56 (dd, 1H, J = 15.7, J' = 7.8, Hb-3'), 1.87, 1.60 (8H, cyclopentyl). $^{13}C$ NMR (62.5 MHz) : 166.4 (C-2'), 148.8, 147.8, 140.5, 136.5 (qC-Ar), 129.0, 127.9, 126.8, 118.9, 113.9, 112.3 (CH-Ar), 80.6 (C-1"'), 68.6 (C-1), 62.8 (C-5'), 61.6 (C-2), 56.2 ($OCH_3$), 43.2 (C-4'), 41.4 (C-3'), 32.9 (C-2"', C-5"'), 24.1 (C-3"', C-4"'). (IC) MS : 395 $[M + H]^+$, 275, 262, 194, 138. (IC) HRMS : $(M + H)^+$ Calcd for $C_{24}H_{31}N_2O_3$ : 395.2335. Found : 395.2349.

**(4*R*)-4-(3-Cyclopentyloxy-4-methoxy)phenyl-pyrrolidin-2-one [(*R*)-Rolipram]**

To a solution of the crude amidine **4** obtained from 0.7 mmol of nitrile **3a** (352 mg) in 95% ethanol (4 mL) was added 2N NaOH (10 mL) and the mixture was heated at 100°C for 16 h. Ethanol was removed under reduced pressure and the residue was extracted with $CH_2Cl_2$ to remove (*R*)-phenylglycinol (100%). The aqueous phase was acidified with 2N HCl (15 mL), extracted with $CH_2Cl_2$ and evaporated to dryness. A solution of the product in methanol was filtered and the solvent was removed *in vacuo* to afford the crude aminoacid hydrochloride. To a solution of this crude aminoacid hydrochloride in anhydrous methanol (22.5 mL) was added $SOCl_2$ (2.5 mL) and the mixture was stirred at room temperature for 22 h. The solvent and reagent in excess were removed *in vacuo*, $CH_2Cl_2$ (20 mL) and aqueous $Na_2CO_3$ (10%, 6 mL) were added and the mixture was stirred at room temperature for 1.5 h and then extracted 4 times with $CH_2Cl_2$. A solution of the crude product obtained after usual workup in toluene (5 mL) and $Et_3N$ (0.2 mL) was heated at 110°C for 21 h. After evaporation to dryness, the crude (*R*)-Rolipram was purified by preparative TLC (eluent : $CH_2Cl_2$-MeOH 93:7) to give **1** as white crystals (85.1 mg, 55% from the nitrile). mp : 131.5-132.5 ($Et_2O$-pentane), lit. 131-133°C.[4] $[\alpha]_D^{26}$ = - 32 (0.53, MeOH), lit. $[\alpha]_D^{24}$ = - 31.0 (c = 0.5, MeOH).[4] IR : 3438, 2963, 1697, 1517. $^1H$ NMR (300 MHz) : 6.85-6.76 (m, 3H, H-Ar), 6.34 (br s, 1H, NH), 4.77 (m, 1H, H-1"), 3.83 (s, 3H, $OCH_3$), 3.76 (dd, 1H, J ~ J' ~ 8.6, Ha-5), 3.63 (m, 1H, H-4), 3.38 (dd, J = 9, J' = 7.3, Hb-5), 2.71 (dd, 1H, J = 16.9, J' = 8.8, Ha-3), 2.48 (dd, 1H, J = 16.9, J' = 8.9, Hb-3), 1.89, 1.62 (8H, cyclopentyl). $^{13}C$ (50 MHz) : 177.8 (CO), 149.3, 148.0, 134.7 (qC-Ar), 118.9, 114.0, 112.3 (CH, Ar), 80.7 (C-1'), 56.3 ($OCH_3$), 49.8 (C-5), 40.1 (C-4), 38.2 (C-3), 32.9 (C-2", C-5"), 24.1 (C-3", C-4").

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