

A Stereoselective Synthesis of (*R*)-(-)-Rolipram from L-Glutamic Acid

Adolfo Diaz, Jorge G. Siro, José L. García-Navío, Juan J. Vaquero, Julio Alvarez-Builla*

Departamento de Química Orgánica, Universidad de Alcalá, E-28871 Alcalá de Henares, Madrid, Spain

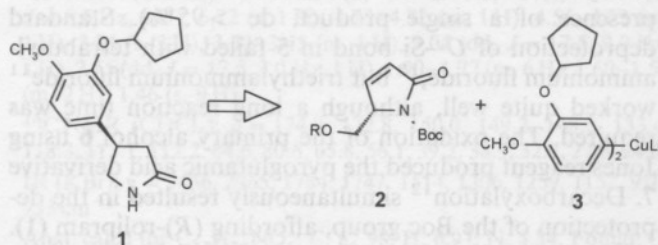
Fax +34(1)8854686; Internet: jalvarez@quimor.alcala.es

Received 20 September 1996; revised 13 November 1996

A stereoselective synthesis of (*R*)-(-)-rolipram from L-glutamic acid is described. The key step is a stereoselective Michael addition of an arylcuprate to a modified pyroglutamic derivative which acts as the template to induce the stereoselectivity. Facile manipulation of the enantiomerically pure Michael product afforded the expected therapeutic agent.

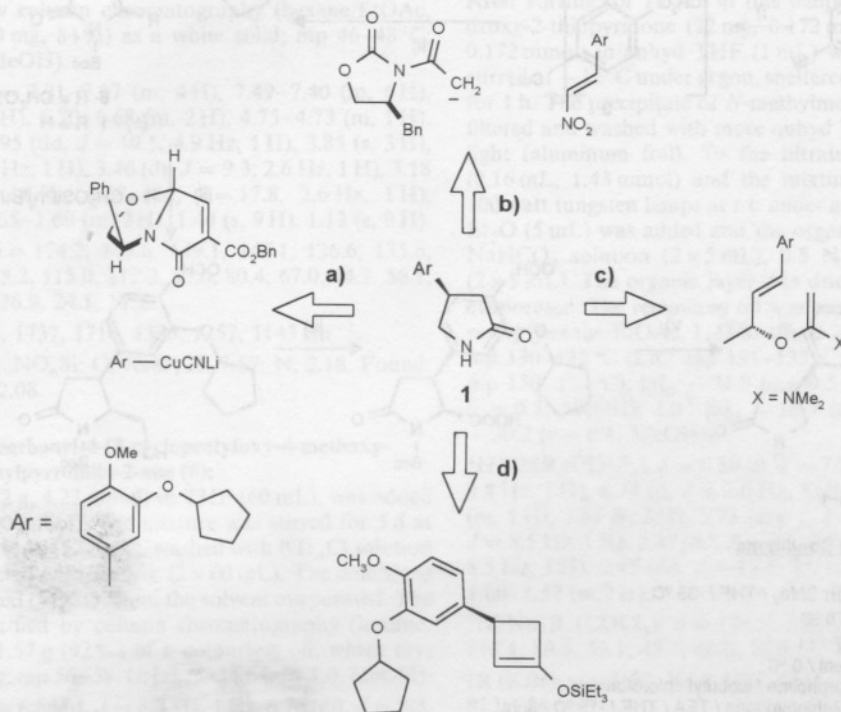
(*R*)-(-)-Rolipram (**1**), a potent inhibitor of the cardiac cyclic AMP phosphodiesterase (cAMP PDE) enzyme found in brain tissue, is of great interest as a therapeutic agent for the treatment of central nervous system disorders.¹ In a recent paper² some of the enantioselective syntheses of this compound have been reviewed. In Scheme 1, four retrosynthetic disconnections are shown for (*R*)-(-)-rolipram (**1**). Disconnections **a** and **b** are based on the same concept, where a conjugated Michael addition is employed as the key step. Whereas in route **a**, the stereochemistry of the final product is controlled by the stereoselective conjugate addition of RCuCNLi to a chiral α,β -unsaturated bicyclic lactam,³ the diastereoselectivity in route **b** is controlled by the chirality of the enolate of a *N*-acetyloxazolidone, which behaves as the nucleophile in the reaction with a suitable nitrostyrene.⁴ In route **c**, two synthetic approaches developed by Mulzer et al.,⁵ using a suprafacial Claisen rearrangement are summarized. Finally, route **d** shows the most recent approach which involves an enantioselective deprotonation of a cyclobutanone derivative using (*S,S'*)- α,α' -dimethylidibenzylamide as a chiral base.⁶

In the present communication we describe a Michael-type approach using a modified pyroglutamic derivative as the template to induce the stereoselectivity. The use of natural α -amino acids as starting materials for the synthesis of enantiomerically pure compounds has gained interest in recent times since the single chiral center provides a useful building block.⁷ L-Glutamic acid, the least expensive of all amino acids, is, due to its versatility and availability, one of the most used in synthesis. A simple retrosynthetic analysis (Scheme 2) led us to consider a modified pyroglutamic acid derivative **2**⁸ as a useful starting material for an asymmetric synthesis of (*R*)-(-)-rolipram (**1**).



Scheme 2

The key step for the planned synthesis should be the stereoselective introduction of the aryl moiety. The electron-withdrawing Boc group, attached to the amide



Scheme 1

nitrogen, activates the α,β -unsaturated system toward the conjugate addition of organocuprates and a bulky protected alcohol **2** ($R = \text{CH}_2\text{OSiPh}_2\text{Bu}$ -*t*) provides the steric hindrance necessary to control the stereoselectivity in the conjugate addition of the aryl cuprate **3**.

The preparation of the chiral doubly protected α,β -unsaturated γ -lactam **2** from L-glutamic acid is well documented in the literature.⁸ The required bromoarene **4**³ was obtained in a 4 step synthesis from 2-methoxyphenol via: a) *O*-benzoylation, b) regioselective electrophilic bromination of the *O*-protected 2-methoxyphenol, c) deprotection of the benzoyl moiety and finally, d) *O*-alkylation with cyclopentyl bromide.

The reaction of the aryl cuprate **3**, produced in situ from aryl bromide **4**, BuLi and a suspension of CuBr·SMe₂, with the unsaturated lactam **2** in the presence of trimethylsilyl chloride⁹ took place in good yield to produce the expected isomer **5** (Scheme 3) where the bulky protected silyloxy group induces the newly formed stereocenter, which could be confirmed by ¹H NMR spectroscopy (analysis of the crude reaction mixture showed the presence of a single product, de >95%). Standard deprotection of *O*-Si bond in **5** failed with tetrabutylammonium fluoride,¹⁰ but triethylammonium fluoride¹¹ worked quite well, although a long reaction time was required. The oxidation of the primary alcohol **6** using Jones reagent produced the pyroglutamic acid derivative **7**. Decarboxylation¹² simultaneously resulted in the deprotection of the Boc group, affording (*R*)-rolipram (**1**). Although the direction and magnitude of the optical ro-

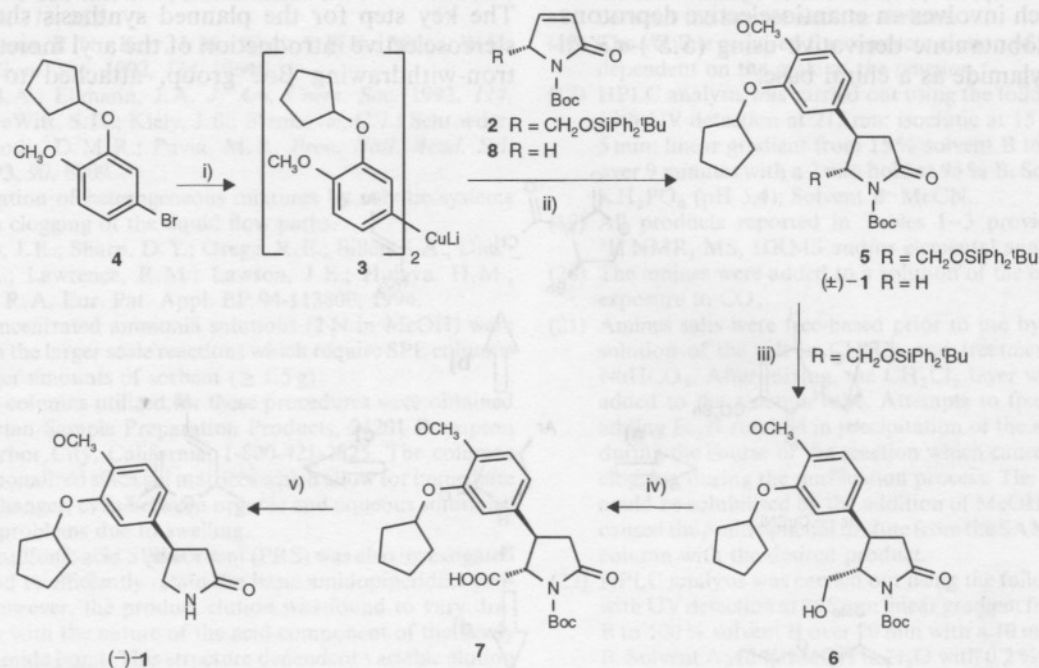
tation for this compound is identical to previously reported values, we carried out a chiral HPLC analysis¹³ for this synthetic material and the racemate, indicating more than 99% enantiomeric purity. The racemate (\pm)-**1** was simultaneously obtained from achiral 1-*tert*-butoxycarbonyl-1,5-dihydro-2*H*-pyrrol-2-one (**8**)¹⁴ by reaction with the aryl cuprate **3**.

In conclusion, this work represents an enantioselective synthesis of *R*-(-)-rolipram using a Michael-type approach from readily available starting materials. The synthesis of alternatively modified pyroglutamic precursors are now in progress in order to shorten the process and results will be reported in due course.

All solvents and reagents were purchased from commercial sources and used as received unless otherwise indicated. Reactions with organometallics were run in flame dried glassware under an argon atmosphere. THF and Et₂O were dried over sodium wire and distilled under argon prior to use. ¹H NMR and ¹³C NMR data were recorded on a Varian Unity (300 MHz) using CDCl₃ as solvent. Melting points were determined on a Büchi apparatus and are not corrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter using MeOH as solvent. Chromatographic separations were performed by using 230–400 mesh silica gel. (5*S*)-1-*tert*-Butoxycarbonyl-5-(*tert*-butyldiphenylsiloxy)methyl-1,5-dihydro-2*H*-pyrrol-2-one (**2**)⁸ and 1-*tert*-butoxycarbonyl-1,5-dihydro-2*H*-pyrrol-2-one **8**¹⁴ were prepared as described in the literature.

4-Bromo-2-cyclopentyloxyanisole (**4**):

2-Methoxyphenyl Benzoate: An ice cooled solution of 2-methoxyphenol (15 g, 0.12 mol) in H₂O (75 mL) was treated with an aqueous solution of NaOH (75 mL 20%), then benzoyl chloride (16.99 g, 0.12 mmol) was added dropwise. The mixture was stirred in an ice



Reagents and Conditions

- i) *n*-BuLi / CuBr·SMe₂ / THF / -35 °C
- ii) Me₃SiCl / -78 °C
- iii) TEAF / THF / r.t
- iv) Jones reagent / 0 °C
- v) N-methylmorpholine / isobutyl chloroformate / N-hydroxy-2-thiopyridone / TEA / THF / -15 °C / light

Scheme 3

bath for 1 h and then at r.t. for 2 h. The solution was extracted with CH_2Cl_2 (2×100 mL) and subsequently washed with H_2O (2×50 mL). The organic layer was dried (MgSO_4) and on removal of the solvent 2-methoxyphenyl benzoate was obtained as a solid (14.14 g, 51%); mp 58–60°C.

5-Bromo-2-methoxyphenol: A solution of Br_2 (10.03 g, 0.063 mol) in AcOH (10 mL) was slowly added to a solution of the above benzoate (13.02 g, 0.057 mol) in AcOH (65 mL). The mixture was stirred at r.t. for 24 h and then more Br_2 (3.22 g, 0.020 mol) in the same solvent (15 mL) was added, and the mixture stirred for 24 h. The residue which was obtained by removal of the solvent at r.t. was dissolved in CH_2Cl_2 (100 mL) and washed with a satd solution of KHCO_3 . The organic layer was dried and evaporated in vacuo to give an oily product which on standing in pentane yielded 5-bromo-2-methoxyphenol as a solid (10.98 g, 70%); mp 62–64°C (Lit.³ mp 60–62°C).

4-Bromo-2-cyclopentylxyanisole (4): To a solution of the above phenol (6.23 g, 0.038 mol) in anhyd DMF (50 mL), were added successively powdered anhyd K_2CO_3 (6.36 g, 0.046 mol) and cyclopentyl bromide (6.63 g, 0.046 mol). The mixture was stirred at 60°C for 24 h. The solvent was evaporated in vacuo and the residue triturated with H_2O and the inorganic residue removed by filtration. The solution was extracted with CH_2Cl_2 (40 mL), dried (MgSO_4) and the solvent was removed in vacuo to yield **4** as an oily product (7.24 g, 87%), which was used without further purification in the next step.

$^1\text{H NMR}$ (CDCl_3): $\delta = 7.01$ – 6.97 (m, 2H), 6.72 (d, 1H, $J = 8.4$ Hz), 4.74–4.72 (m, 1H), 3.73 (s, 3H), 1.94–1.79 (m, 6H), 1.64–1.58 (m, 2H).

(4R,5S)-1-tert-Butoxycarbonyl-5-tert-butylidiphenylsilyloxymethyl-4-(3-cyclopentylxy-4-methoxyphenyl)pyrrolidine-2-one (5):

To a cooled (-35°C) solution of **4** (1.79 g, 6.6 mmol) in anhyd Et_2O was added a 1.6 M solution of BuLi in hexanes (4.13 mL, 6.6 mmol). The precipitate formed was redissolved by the slow addition of anhyd THF and siphoned to a suspension of $\text{CuBr}\cdot\text{SMe}_2$ (0.682 g, 3.3 mmol) in anhyd Et_2O (20 mL). After 1 h the suspension was cooled at -78°C and a solution of **2** (300 mg, 0.66 mmol) and Me_3SiCl (0.17 mL, 1.32 mmol) in anhyd Et_2O (10 mL) was added. The mixture was stirred for 1.5 h at -78°C , and then quenched with NH_4Cl solution. The organic layer was washed with NH_4Cl solution, until the blue color of the water phase disappeared, and then dried (MgSO_4). Evaporation of the solvent gave an oily residue which was purified by column chromatography (hexane/ EtOAc , 4:1) to furnish **5** (360 mg, 84%) as a white solid; mp 46–48°C; $[\alpha]_{\text{D}}^{20} - 19.8$ ($c = 0.5$, MeOH).

$^1\text{H NMR}$ (CDCl_3): $\delta = 7.71$ – 7.67 (m, 4H), 7.49–7.40 (m, 6H), 6.82 (d, $J = 8.8$ Hz, 1H), 6.70–6.68 (m, 2H), 4.75–4.73 (m, 1H), 4.13–4.10 (m, 1H), 3.95 (dd, $J = 10.5$, 4.9 Hz, 1H), 3.85 (s, 3H), 3.84 (dd, $J = 10.5$, 2.4 Hz, 1H), 3.46 (dt, $J = 9.3$, 2.6 Hz, 1H), 3.18 (dd, $J = 17.8$, 9.3 Hz, 1H), 2.57 (dd, $J = 17.8$, 2.6 Hz, 1H), 1.94–1.81 (m, 6H), 1.65–1.60 (m, 2H), 1.44 (s, 9H), 1.12 (s, 9H).

$^{13}\text{C NMR}$ (CDCl_3): $\delta = 174.2$, 149.6, 149.1, 148.1, 136.6, 135.6, 133.0, 130.0, 127.9, 118.2, 113.0, 112.2, 83.0, 80.4, 67.0, 64.2, 56.1, 39.9, 38.2, 32.8, 28.0, 26.9, 24.1, 19.2.

IR (CHBr₃): $\nu = 1778$, 1737, 1710, 1305, 1257, 1143 cm^{-1} .

Anal. calcd for $\text{C}_{39}\text{H}_{49}\text{NO}_6\text{Si}$: C, 70.88; H, 7.67; N, 2.18. Found: C, 70.70; H, 7.80; N, 2.08.

(4R,5S)-1-tert-Butoxycarbonyl-4-(3-cyclopentylxy-4-methoxyphenyl)-5-hydroxymethylpyrrolidin-2-one (6):

To a solution of **5** (2.72 g, 4.22 mmol) in THF (60 mL), was added $\text{Et}_3\text{N}\cdot\text{HF}$ (2.05 g, 16.90 mmol). The mixture was stirred for 5 d at r.t. and diluted with EtOAc (120 mL), washed with NH_4Cl solution (3×60 mL) and extracted with EtOAc (2×60 mL). The combined organic layers were dried (MgSO_4) and the solvent evaporated. The remaining oil was purified by column chromatography (hexane/ EtOAc , 1:1) to give 1.57 g (92%) of a colourless oil, which crystallized upon standing; mp 56–58°C; $[\alpha]_{\text{D}}^{20} - 34.6$ ($c = 1.0$, MeOH).

$^1\text{H NMR}$ (CDCl_3): $\delta = 6.84$ (d, $J = 8.3$ Hz, 1H), 6.76 (dd, $J = 8.3$,

2.2 Hz, 1H), 6.73 (d, $J = 2.2$ Hz, 1H), 4.77–4.71 (m, 1H), 4.14–4.10 (m, 1H), 4.00–3.96 (m, 1H), 3.85 (s, 3H), 3.85–3.81 (m, 1H), 3.32–3.26 (m, 1H), 3.08 (dd, $J = 17.8$, 9.2 Hz, 1H), 2.56 (dd, $J = 17.8$, 4.6 Hz, 1H), 2.42 (t, $J = 5.5$ Hz, 1H), 1.97–1.83 (m, 6H), 1.64–1.60 (m, 2H), 1.57 (s, 9H).

$^{13}\text{C NMR}$ (CDCl_3): $\delta = 173.7$, 150.8, 149.2, 148.1, 135.1, 118.6, 113.2, 112.3, 83.7, 80.5, 67.3, 64.0, 56.1, 40.1, 38.5, 32.9, 28.0, 24.1. IR (KBr): $\nu = 3411$, 1778, 1711, 1515, 1365, 1303, 1254, 1151 cm^{-1} . Anal. calcd for $\text{C}_{22}\text{H}_{31}\text{NO}_6$: C, 65.15; H, 7.71; N, 3.46. Found: C, 64.95; H, 7.70; N, 3.28.

(2S,3R)-1-tert-Butoxycarbonyl-3-(3-cyclopentylxy-4-methoxyphenyl)-5-oxopyrrolidine-2-carboxylic Acid (7):

To a solution of the alcohol **6** (0.44 g, 1.09 mmol) in acetone (10 mL) was added Jones reagent¹⁵ (1.87 mL) at 0°C . The mixture was stirred for 90 min at 0°C and for 90 min at r.t. before the addition of propan-2-ol (1 mL). A satd aq solution of NaHCO_3 (10 mL) was added and the mixture was extracted with EtOAc (3×10 mL). The aqueous layer was acidified with 1 N HCl and extracted with EtOAc (3×10 mL). The combined organic layers were dried (MgSO_4) filtered and concentrated in vacuo to give **7** (0.23 g; 50%) as a white solid; mp 63–65°C; $[\alpha]_{\text{D}}^{20} + 37.7$ ($c = 0.5$, MeOH).

$^1\text{H NMR}$ (CDCl_3): $\delta = 6.81$ (d, $J = 8.5$ Hz, 1H), 6.74 (d, $J = 8.5$ Hz, 1H), 6.72 (s, 1H), 4.75–4.72 (m, 1H), 4.56–4.52 (m, 1H), 3.81 (s, 3H), 3.50–3.45 (m, 1H), 3.04 (dd, $J = 17.5$, 9.0 Hz, 1H), 2.65 (dd, $J = 17.5$, 3.0 Hz, 1H), 1.90–1.77 (m, 6H), 1.60–1.56 (m, 2H), 1.46 (s, 9H).

$^{13}\text{C NMR}$ (CDCl_3): $\delta = 174.9$, 172.8, 150.0, 149.2, 148.0, 133.4, 118.3, 113.1, 112.2, 84.6, 80.6, 65.8, 56.1, 39.2, 38.9, 32.7, 27.8, 24.0. IR (KBr): $\nu = 3436$, 2965, 1784, 1747, 1514, 1306, 1259, 1152, 910, 733 cm^{-1} .

Anal. calcd for $\text{C}_{22}\text{H}_{29}\text{NO}_6$: C, 62.98; H, 6.97; N, 3.34. Found: C, 62.65; H, 6.97; N, 3.19.

4-(3-Cyclopentylxy)-4-methoxyphenylpyrrolidin-2-one [(R)-(–)-Rolipram (–)-1]:

To a solution of acid **7** (60 mg, 0.143 mmol) in anhyd THF (1 mL) under argon at -15°C was added *N*-methylmorpholine (0.016 mL, 0.143 mmol) and isobutyl chloroformate (0.018 mL, 0.143 mmol). After stirring for 15 min at this temperature, a solution of *N*-hydroxy-2-thiopyridone (22 mg, 0.172 mmol) and Et_3N (0.024 mL, 0.172 mmol) in anhyd THF (1 mL) was added. The mixture was stirred at -15°C under argon, sheltered from light (aluminum foil), for 1 h. The precipitate of *N*-methylmorpholine hydrochloride was filtered and washed with more anhyd THF under protection from light (aluminum foil). To the filtrate was added *tert*-butylthiol (0.16 mL, 1.43 mmol) and the mixture was irradiated with two 100 watt tungsten lamps at r.t. under argon in a water bath for 1 h. Et_2O (5 mL) was added and the organic layer washed with 0.1 N NaHCO_3 solution (2×5 mL), 0.5 N HCl (2×5 mL) and brine (2×5 mL). The organic layer was dried (MgSO_4) and the solvent evaporated. The remaining oil was purified by column chromatography (hexane/ EtOAc , 1:1) to afford 25 mg (64%) of a white solid; mp 130–132°C (Lit.¹ mp 131–133°C; Lit.³ mp 126–128°C; Lit.⁶ mp 130–132°C); $[\alpha]_{\text{D}}^{20} - 31.8$ ($c = 0.5$, MeOH). (Lit.¹ $[\alpha]_{\text{D}}^{20} - 31.0$ ($c = 0.5$, MeOH); Lit.³ $[\alpha]_{\text{D}}^{20} - 19.5$ ($c = 1.15$, MeOH); Lit.⁶ $[\alpha]_{\text{D}}^{20} - 30.2$ ($c = 0.1$, MeOH)).

$^1\text{H NMR}$ (CDCl_3): $\delta = 6.80$ (d, $J = 7.8$ Hz, 1H), 6.75 (dd, $J = 7.8$, 2.0 Hz, 1H), 6.74 (d, $J = 2.0$ Hz, 1H), 5.95 (br s, 1H), 4.77–4.72 (m, 1H), 3.81 (s, 3H), 3.73 (app t, $J = 8.5$ Hz, 1H), 3.61 (app p, $J = 8.5$ Hz, 1H), 3.35 (dd, $J = 9.0$, 7.5 Hz, 1H), 2.69 (dd, $J = 18.5$, 8.5 Hz, 1H), 2.45 (dd, $J = 18.5$, 9.0 Hz, 1H), 1.90–1.79 (m, 6H), 1.60–1.57 (m, 2H).

$^{13}\text{C NMR}$ (CDCl_3): $\delta = 177.5$, 149.1, 147.9, 134.4, 118.7, 113.7, 112.1, 80.5, 56.1, 49.7, 40.0, 38.0, 32.8, 24.0.

IR (KBr): $\nu = 3199$, 2960, 1687, 1515, 1263, 1237, 1163, 1140, 1028, 813, 736 cm^{-1} .

**4-(3-Cyclopentyloxy)-4-methoxyphenylpyrrolidin-2-one [(±)-Roli-
pram, (±)-1]:**

The experimental procedure was identical to that described above for **5**. In this way the racemate (±)-**1** (0.29 g, 81%) was obtained as a white solid; mp 130–131°C (Lit.¹ mp 130°C).

We gratefully acknowledge ZAMBON GROUP for studentships (to A.D. and J.S.) and financial support.

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