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ENANTIOSPECIFIC SYNTHESIS AND ABSOLUTE CONFIGURATION OF (+)-RP 66803 A NEW NON-PEPTIDE CCK ANTAGONIST

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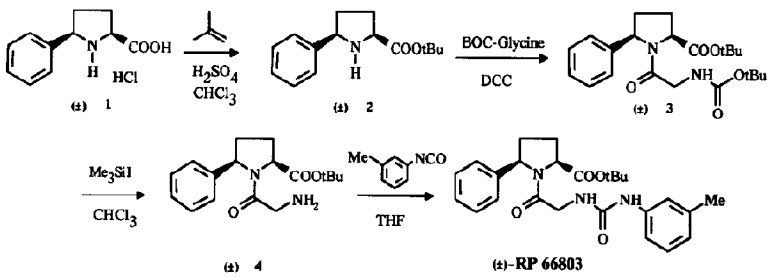
Abstract : Pyrrolidine derivatives have been identified as a new class of non-peptide CCK antagonists. Enantiomers of **RP 66803**, a representative compound of this chemical family were previously prepared by chiral chromatography of the racemate. In order to determine the absolute configuration of each one, we report herein an enantiospecific synthesis leading to the (+)-isomer using anodic methoxylation as key step.

Cholecystokinin (CCK) is a brain-gut peptide that is found in a number of mammalian species where it is putatively involved in the modulation of many physiological processes[1,2]. Considerable efforts have been expanded over recent years on the research of non-peptide CCK antagonists[2-5]. Recently we described a new class of non-peptide antagonists[6] in which **(±)-RP 66803** is a representative compound.

The synthesis of the racemate has been published[6] : esterification of the starting material 1[7] using isobutene in acidic medium, followed by coupling reaction with BOC-glycine gives **3** which, after deprotection of the amino function and condensation with meta-tolylisocyanate, leads to **(±)-RP 66803**.

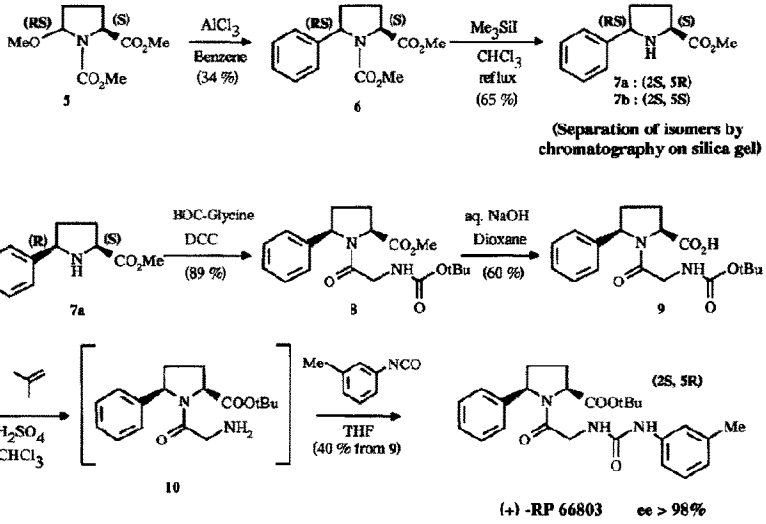


(±) 1 (±) 2 (±) 3 (±) 4 (±)-RP 66803

The enantiomers of **RP 66803** have been previously prepared by chiral HPLC of the racemate. This work has been performed using a Pirkle-modified chiral stationary phase[6]. The (+)-enantiomer exhibits the higher affinity for the CCK receptors[16]. In order to determine the absolute configuration of this enantiomer we report in this paper a simple enantioselective route to **(+)-RP 66803** using an optically pure proline derivative as starting material.

Anodic methoxylation[8] allows the easy preparation of α-methoxyamides and α-methoxycarbamates. This reaction has been recently extensively exploited for introducing a wide range of nucleophiles at the α-position of the carbamate-nitrogen atom, thus giving access to a variety of alkaloids[9-11]. The α-methoxycarbamates obtained can react in the presence of Lewis acid with carbon nucleophiles to form a new C-C bond. This electrochemical reaction is regiospecific and can be illustrated by the methoxylation at C-5 position of a protected L-proline derivative to give **5**[12]. This methoxylated compound **5** formed has been largely used for introducing a chain in this position[9-13].

The same chemical strategy was chosen to introduce a phenyl ring moiety in this position *via* a Friedel-Crafts reaction[14]. This reaction performed on **5** with benzene in the presence of aluminium trichloride at room temperature gave the arylated product **6** as a mixture of diastereoisomers (*cis:trans* 1:1, 34 % yield). When the reaction was performed at higher temperature, the yield decreased with formation of oligomers. Deprotection of the amino function by means of trimethylsilyl iodide gave the two isomers **7a** and **7b** which are easily separable by chromatography on silica gel. Coupling reaction of the *cis* isomer **7a** with BOC-glycine affords the adduct **8** (89 % yield) which upon saponification under classical conditions gave the corresponding acid **9** (60% yield). Esterification of compound **9** and deprotection of its amino function were performed in a one-pot reaction using isobutene under acidic medium to afford the free amino-ester derivative **10** as crude product. Finally, condensation of **10** with meta-tolylisocyanate afforded an enantiomerically pure compound (40 % overall yield from **9**) which proved to be identical with **(+)-RP 66803** prepared by chiral chromatography (ee > 98 % [15], $[\alpha]_D^{25}$ = + 36 (1%, MeOH)).



In summary **(+)-RP 66803** has been prepared in a pure form and its absolute configuration (2S,5R) has been unambiguously determinated by a simple synthesis of enantiomerically pure 5-phenylproline derivative. This synthetic application of anodic methoxylation of carbamates is an additional example showing that organic electrochemistry is an area of growing interest in organic synthesis.

Experimental:

Experiments sensitive to moisture and oxygen were performed under inert atmosphere. All chemicals used were of the highest commercial purity and were used without further purification. NMR spectra were recorded on a Brücker WM (250 MHz), a Brücker WP 200 (200 MHz) or a Brücker AM 400 (400 MHz) spectrometer (δ scale). MS data were obtained with a Finnigan 3300 spectrometer. IR spectra were taken on a Perkin-Elmer Model 938G or 580 B. Optical rotation was determinated with a Perkin Elmer Model 241 polarimeter.

(2S, 5RS)-Methyl 1-methoxycarbonyl-5-phenyl-pyrrolidine-2-carboxylate 6. To a solution of the α-methoxycarbamate **5** (2.45 g, 11 mmol) in benzene (200 ml) was added in small portions $AlCl_3$ (3.0 g, 22 mmol). The mixture was then stirred at room temperature for 6 hours. Hydrolysis was performed at 0°C by addition of a 5% aqueous solution of $NaHCO_3$ (30 ml) and the aluminium hydroxide removed by filtration

over celite. After decantation the aqueous layer was extracted with CH_2Cl_2 (3 x 40 ml). The combined organic phases were washed with brine, dried over $MgSO_4$ and evaporated. Silica gel chromatography (cyclohexane : ethyl acetate 80:20) gave 1,0 g (34 %) of **6** as a yellow oil (mixture of C-5 diastereoisomers). **^{1}H NMR** (DMSO D_6, 200 MHz), δ (ppm): at room temperature, a mixture of isomers and rotamers is observed ; from 1.60 to 2.50 (m, 4H: -C<u>H</u>$_2$-C<u>H</u>$_2$-), 3.43 - 3.54 - 3.70 - 3.72 and 3.75 (5s, 6H: -COO-C<u>H</u>$_3$), from 4.30 to 4.70 (m, 1H: N-C<u>H</u>-CO-), from 4.80 to 5.10 (m, 1H: N-C<u>H</u>-Ph), from 7.10 to 7.60 (m, 5H: -<u>H</u> Aromatics). **MS** (70 eV), m/z (%) : 263 (M^+, 5); 204 (100).

(2S, 5R)-Methyl 5-phenyl-pyrrolidine-2-carboxylate 7a and (2S, 5S)-methyl 5-phenyl-pyrrolidine-2-carboxylate 7b. To a solution of **6** (0.6 g, 2.2 mmol) in $CHCl_3$ (15 ml) was added using a syringe trimethylsilyl iodide (0.45 ml, 3.1 mmol), the mixture was heated at reflux for 18 hours and then allowed to cool at room temperature. Water (20 ml) is added at 20°C and after stirring for another 30 minutes the reaction mixture was decanted and the aqueous layer extracted with $CHCl_3$ (2 x 30 ml). The combined organic phases were washed with brine, dried over $MgSO_4$ and evaporated. Silica gel chromatography (cyclohexane : ethyl acetate 70:30) gave 0.12 g (26 %) of *cis* isomer (2S, 5R) **7a** and 0.18 g (39 %) of *trans* isomer (2S, 5S) **7b** (eluted first) as syrups.

<u>**7a**</u> **: ^{1}H NMR** (DMSO D_6, 250 MHz), δ (ppm): from 1.50 to 1.70 and from 1.90 to 2.20 (2m, respectively 1H and 3H: -C<u>H</u>$_2$-C<u>H</u>$_2$-), 3.68 (s, 3H: -COO-C<u>H</u>$_3$), 3.87 and 4.16 (2dd, respectively J=8,0 - 5,0 Hz and J=8.5 - 6,0 Hz, 1H each: N-C<u>H</u>-CO- and N-C<u>H</u>-Ph), from 7.15 to 7.50 (m, 5H: -<u>H</u> Aromatics). **MS** (70 eV), m/z (%) : 205 (M^+, 5); 146 (100); 129 (50).

<u>**7b**</u> **: ^{1}H NMR** (DMSO D_6, 250 MHz), δ (ppm): 1.53 - 1.86 and from 2.05 to 2.30 (3m, respectively 1H, 1H and 2H: -C<u>H</u>$_2$-C<u>H</u>$_2$-), from 3.00 to 3.25 (bb, 1H: -N<u>H</u>-), 3.67 (s, 3H: -COO-C<u>H</u>$_3$), 3.97 and 4.28 (2dd, respectively J=8,0- 5.5 Hz and J=8,0 - 7,0 Hz, 1H each: N-C<u>H</u>-CO-and N-C<u>H</u>-Ph), from 7.15 to 7.45 (m, 5H: -<u>H</u> Aromatics). **MS** (70 eV), m/z (%) : 205 (M^+, 10); 146 (100); 129 (95).

(2S, 5R)-Methyl 1-[2-(tert-butoxycarbonylamino)-1-oxo-ethyl]-5-phenyl-pyrrolidine-2-carboxylate 8. DCC (0.1 g, 0.6 mmol) was added at 5 °C to a solution of **7a** (0.1 g, 0.5 mmol) and BOC-Glycine (0.1 g, 0.6 mmol) in CH_3CN (10 ml). The reaction mixture was then stirred at room temperature for 12 hours and the precipitate removed by filtration. After evaporation of the solvent the oily product was purified by silica gel chromatography (cyclohexane/ethyl acetate (70:30)) giving 0.16 g (89 %) of **8** as a colourless syrup. **^{1}H NMR** (DMSO D_6, 250 MHz), δ (ppm): at ambient temperature, we observe a mixture of rotamers, only the major rotamer is described: 1.35 [s, 9H: -C(-C<u>H</u>$_3$)$_3$], from 1.50 to 2.40 (m, 4H: -C<u>H</u>$_2$-C<u>H</u>$_2$-), 2.98 and 3.78 (respectively bd J=15,0 Hz and m, 1H each: N-CO-C<u>H</u>$_2$-N), 3.78 (s, 3H: -COO-C<u>H</u>$_3$), 4.47 (m, 1H: N-C<u>H</u>-CO-), 5.15 (m, 1H: N-C<u>H</u>-Ph), 6.62 (m, 1H: -N<u>H</u>-), from 7.20 to 7.80 (m, 5H: -<u>H</u> Aromatics). **MS** (70 eV), m/z (%) : 362 (M^+, 2); 306 (13); 204 (100).

(2S, 5R)-1-[2-(tert-butoxycarbonylamino)-1-oxo-ethyl]-5-phenyl-pyrrolidine-2-carboxylic acid 9. 1N NaOH (0.5 ml) was added to a solution of **10** (160 mg, 0.44 mmol) in dioxane (10 ml) and water (5 ml). After 12 hours at room temperature the reaction mixture was extracted with ether (2 x 10 ml). The aqueous phase was acidified (pH 2) at 5 °C with 0.1 N HCl and extracted with EtOAc (3 x 40 ml). The combined EtOAc phases were washed with brine, dried over $MgSO_4$. Evaporation of the solvent gave 90 mg (60 %) of **9** as an oil, used without any further purification in the next step. **^{1}H NMR** ($CDCl_3$, 200 MHz), δ (ppm): at ambient temperature, we observe a mixture of rotamers 80/20; 1.32 and 1.36 [2s, 9H: respectively -C(-C<u>H</u>$_3$)$_3$ of major and minor rotamers], from 1.90 to 2.50 (m, 4H: -C<u>H</u>$_2$-C<u>H</u>$_2$-), 3.10 and 3.88 [respectively bd (J=18,0 Hz) and m: N-CO-C<u>H</u>$_2$-N of major rotamer], 3.55 (m: N-CO-C<u>H</u>$_2$-N of minor rotamer), 4.50 and 4.65 [respectively m and t (J=7.5 Hz), 1H: respectively N-C<u>H</u>-CO- of minor and major rotamers], 4.90 and 5.02 [respectively bt (J=6.5 Hz) and m, 1H: respectively N-C<u>H</u>-Ph of major and minor rotamers), 5.26 and 5.60 (2bb, 1H: respectively -N<u>H</u>- major and minor rotamers), from 7.15 to 7.50 (m, 5H: -<u>H</u> Aromatics). **MS** (70 eV), m/z (%) : 349 (M,H^+, 100); 293 (70); 249 (60).

(2S, 5R)-tert-Butyl 1-{2-[3-(3-methylphenyl)-ureido]-1-oxo-ethyl}-5-phenyl-pyrrolidine-2-carboxylate. RP (+)-66803. Isobutene was passed through an ice-cooled solution of **9** (80 mg, 0.2 mmol) in $CHCl_3$ (20 ml) containing a few drops of concentrated H_2SO_4 over a 2 hours period. The reaction mixture was allowed

to reach room temperature, stirred 16 hours and neutralized by addition of a 10 % aqueous solution of $NaHCO_3$ (30 ml). After decantation the aqueous layer was extracted with $CHCl_3$ (3 x 30 ml). The combined organic phases were washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave 90 mg (100 %, crude product) of **10** used without any further purification in the next step.

To a solution of freshly prepared **10** (90 mg, 0.23 mmol) in THF (20 ml) was added meta-tolylisocyanate (50 µl, 0.23 mol). The solution was stirred for 3 hours at room temperature then evaporated. Purification of the crude product by silica gel chromatography (methylene chloride / methanol (98 : 2)) gave 40 mg (40 %, 3 steps from **11**) of **RP (+)-66803**. **^{1}H NMR** (DMSO D_6, 200 MHz), δ (ppm): at ambient temperature, we observe a mixture of rotamers 80/20; 1.43 and 1.46 [2s, 9H: respectively -C(-C$\underline{H}_3$)$_3$ of major and minor rotamers], from 1.60 to 2.50 (m, 4H: -C$\underline{H}_2$-C$\underline{H}_2$-), 2.20 and 2.22 (2s, 3H: Ar-C$\underline{H}_3$ of major and minor rotamers), 3.18 and 3.90 (2dd, J=18,0 and 5,0 Hz: N-CO-C$\underline{H}_2$-N of major rotamer), from 3.70 to 4.10 (m: N-CO-C$\underline{H}_2$-N of minor rotamer), 4.29 and 4.98 (2t, respectively J=8,0 Hz and J=7.5 Hz, 1H: respectively N-C$\underline{H}$-CO- of major and minor rotamers], 4.67 and 5.12 (2dd, respectively J=8.5 - 5,0 Hz and J=8.5 - 3.5 Hz, 1H: respectively N- C$\underline{H}$-Ph of minor and major rotamers), 6.23 (t, J=5,0 Hz, 1H: -N$\underline{H}$-), 6.65 and 6.71 [2bd, J=7.5 Hz, 1H: respectively -$\underline{H}$ Aromatics (in ortho of -CH_3 and para of -NH-) of major and minor rotamers], from 6.90 to 7.70 (m, 8H: -$\underline{H}$ Aromatics), 8.62 and 8.70 (2s, 1H: respectively -CO-N$\underline{H}$-Ar of minor and major rotamers). **MS** (70 eV), m/z (%) : 437 (M^+, 15); 381 (10); 190 (30); 146 (100); 107 (90); 57 (28). **IR** (KBr, cm^{-1}) γ_{NH}: 3370; $\gamma_{CH\ Ar}$: 3100-3000, 780, 755, 700 ; γ_{CH}: 3000-2825 ; $\gamma_{C=O\ ester}$: 1735 ; $\gamma_{C=O\ amide,\ urea}$ 1640. $[\alpha]_D^{25} = +36$ (C = 1 % ; MeOH).

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