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3-Aminopyrrolidines from α-Aminoacids: Total Synthesis of (+)-Nemonapride from D-Alanine

Cam Thuy Hoang, Viet Hoang Nguyen, Valérie Alezra, and Cyrille Kouklovsky*

Laboratoire de Chimie des Procédés et Substances Naturelles, Institut de Chimie Moléculaire et des Matériaux d'Orsay (UMR CNRS No. 8182), Université Paris-Sud, F-91405 Orsay, France

cykouklo@icmo.u-psud.fr

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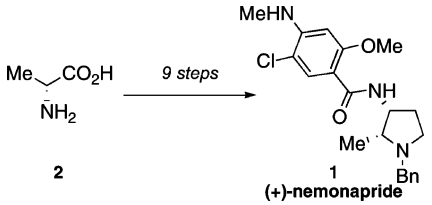
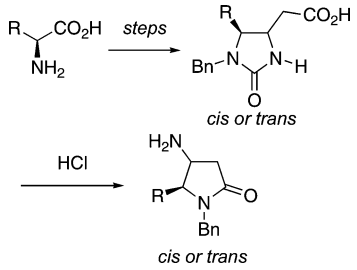


The antipsychotic compound nemonapride **1** was synthesized in nine steps from D-alanine **2**. The key steps for the synthesis of the 3-aminopyrrolidine moiety include a Birch reduction of a cyclic enaminoester and the reduction of a pyrrolidinone to the pyrrolidine **7**. Final coupling with the benzoic acid derivative **9** gave **1** as a single enantio- and diastereomer.

In the search for new benzamide-derived neuroleptic agents, the Yammanouchi company reported in 1978 the structure of nemonapride **1**, a highly active antipsychotic compound.[1] Nemonapride (formerly called emonapride) has been commercialized (under its racemic form) since 1991, and further studies underlined its activity as a dopamine receptor antagonist.[2] The structure of **1** consists of a 3-benzoylated 2,3-*cis*-3-amino-1-benzyl-2-methylpyrrolidine. Since the first synthesis of racemic nemonapride **1**, two enantioselective syntheses of the pyrrolidine moiety have been disclosed, one from L-malic acid[3] and the other one by using a catalytic asymmetric Mannich reaction.[4] In this note, we wish to report a new synthesis of (+)-nemonapride **1** from D-alanine.

We have recently reported a new method for aminoacid homologation, consisting of the Blaise condensation of α-bromoesters onto α-aminoacid-derived aminonitriles, followed by reduction of the subsequent cyclic enaminoester.[5] Depending on the reduction conditions (cyanoborohydride reduction or Birch reduction), this synthetic sequence led to *cis*- or *trans*-disubstituted cyclic ureas, the hydrolysis of which gives rise to enantio- and diastereomerically defined 4-amino-5-alkylpyrrolidinones (Scheme 1). Since pyrrolidinones are obvious precursors to pyrrolidines, the whole synthetic sequence could provide a short and efficient access to the enantiomerically pure pyrrolidine subunit of nemonapride by hydrolysis of a *trans*-alanine-derived urea.[6]

SCHEME 1. Synthesis of 4-Aminopyrrolidinones from α-Aminoacids



The synthesis started by transformation of D-alanine **2** into the cyclic enaminoester **3** in five steps without loss of enantiomeric purity (Scheme 2). Reduction under Birch conditions (sodium, ammonia in anhydrous THF) gave a mixture of reduced compounds; the crude mixture was immediately treated with an aqueous sodium hydroxide solution to give a mixture of the carboxylic acid **4** and the overreduced alcohol **5**. Both compounds were obtained as single diastereomers and could be easily separated by chromatography. The alcohol **5** may be recycled by oxidation to **4** (PDC, DMF, quantitative yield).

Hydrolysis of the *trans*-disubstituted cyclic urea **4** proved to be more difficult than its *cis* counterpart. Nevertheless, treatment of **4** with 3 N HCl solution at 140 °C for 5 days gave a quantitative yield of the aminopyrrolidinone hydrochloride **6**. Standard reduction ($LiAlH_4$, THF, reflux) gave the target 3-aminopyrrolidine **7** in excellent yield. This compound was identical in all respects to those previously described in the literature.[7]

The total synthesis of nemonapride **1** requires the synthesis of 5-chloro-4-methylamino-2-methoxybenzoic acid **9** and its coupling with **7**. Since compound **8** is commercially available at a low price, it was selected as the starting material for the synthesis of **9**. Thus, N-methylation of **8** with methyl sulfate in acetone followed by N-deacetylation and ester hydrolysis by acidic treatment gave the target benzoic acid derivative **9** (as its sulfate salt) in good overall yield. Final coupling was achieved using a slight modification of literature conditions[4] ($ClCO_2Et$, Et_3N, CH_2Cl_2, 0 °C) to give nemonapride **1** in 74% yield.[8]

(1) (a) Murakami, K.; Takahashi, M.; Hirata, Y.; Takashima, M.; Iwanami, S.; Hasegawa, O.; Nozaki, Y.; Tashikawa, S.; Takeda, M.; Usuda, S. U.S. Patent 4097487, 1978. (b) Takashima, M.; Iwanami, S.; Usuda, S. U.S. Patent 4210660, 1980. (c) Iwanami, S.; Takashima, H.; Hirata, Y.; Hasagewa, O.; Usuda, S. *J. Med. Chem.* **1981**, *24*, 1224.

(2) (a) Furuya, T.; Iwanami, S.; Takenaka, A.; Sasada, Y. *Bull. Chem. Soc. Jpn* **1982**, *55*, 2321. (b) Yamamoto, M.; Usuda, S.; Tachikawa, S.; Maeno, H. *Neurophamacology* **1982**, *21*, 945.

(3) Huang, P. Q.; Wang, S. L.; Zheng, H.; Fei, X. S. *Tetrahedron Lett.* **1997**, *38*, 271.

(4) Shibugushi, T.; Mihara, H.; Kuramochi, A.; Ohshima, T.; Shibasaki, M. *Chem. Asian J.* **2007**, *2*, 794.

(5) Hoang, C. T.; Alezra, V.; Guillot, R.; Kouklovsky, C. *Org. Lett.* **2007**, *9*, 2521.

(6) For the synthesis and properties of 3-aminopyrrolidines, see: (a) Davies, S. G.; Garner, A. C.; Goddard, E. C.; Kruchinin, D.; Roberts, P. M.; Rodriguez-Solla, H.; Smith, A. D. *Chem. Commun.* **2006**, 2664 and references cited therein. (b) See also: Vargas-Sanchez, M.; Couty, F.; Evano, G.; Prim, D.; Marrot, J. *Org. Lett.* **2005**, *7*, 5861.

(7) The enantiomeric purity of **8** was checked by HPLC analysis on a chiral column and comparison with a racemic standard (prepared according to the same synthetic sequence from racemic alanine) and was found to be >99%.

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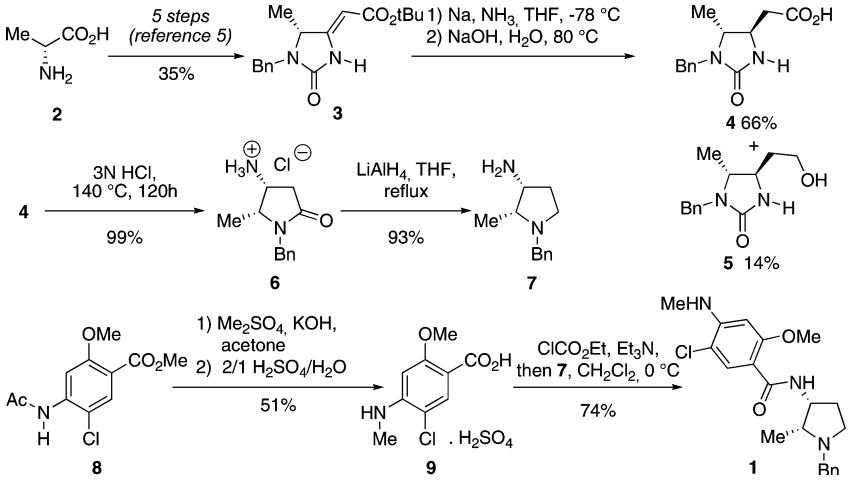
SCHEME 2. Total Synthesis of (+)-Nemonapride 1 from D-alanine



Nemonapride **1** was synthesized as a single enantio- and diastereomer in nine steps from D-alanine **2**, with an overall yield of 16%. Furthermore, this synthesis illustrates a new route to 3-aminopyrrolidines from aminoacids by organometallic condensation. Further applications of this synthetic strategy are currently under investigation.

Experimental Section

General Methods: Unless otherwise stated, all reactions were performed under argon atmosphere. All commercially available reagents were used without further purification. Triethylamine and dichloromethane were distilled from CaH_2 under argon. THF was distilled from benzophenone ketyl under argon prior to use. Reagent grade acetone was used from a freshly opened bottle. Column chromatography was performed using silica gel (230−400 mesh). NMR spectra were recorded with 250 or 360 MHz spectrometers. Chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane. Coupling constants (J values) are reported in hertz. IR spectra were recorder on a FT-IR spectrometer. MS and HRMS experiments were performed on a high/low-resolution magnetic sector mass spectrometer. Optical rotations were performed on a precision automated polarimeter. HPLC experiments were performed using a diode array detector.

(4*R*,5*R*)-4-Amino-1-benzyl-5-methyl-2-pyrrolidone hydrochloride (6). A solution of the urea **4**[5] (150 mg, 6 mmol) in 3 M hydrochloric acid solution (10 mL) was heated at reflux (oil bath temperature = 140 °C) for 120 h. After cooling to rt, the volatiles were removed in vacuo to give the pyrrolidone hydrochloride **6** as a yellow foam: yield 99% (144 mg); ^{1}H NMR (360 MHz, D_2O) δ 1.16 (3H, d, J = 7 Hz), 2.59 (1H, dd, J = 4.4 Hz, 17.5 Hz), 2.89 (1H, dd, J = 7.9 Hz, 17.5 Hz), 3.83 (1H, m), 4.0 (1H, m), 4.02 (1H, d, J = 15.8 Hz), 4.70 (1H, d, J = 15.8 Hz), 7.14−7.3 (5H, br s); ^{13}C NMR (90, MHz, D_2O) δ 12.0, 35.0, 43.8, 47.5, 54.8, 127.7, 128.0, 129.0, 135.3, 173.3; IR (NaCl) ν (cm^{-1}) 3395, 1683, 1645; HRMS (ESI) calcd for $C_{12}H_{17}N_2O$ (MH^+) 205.1346; found 205.1353; $[\alpha]_D$ = −17 (c = 0.4, H_2O).

(2*R*,3*R*)-3-Amino-1-benzyl-2-methyl pyrrolidine (7). $LiAlH_4$ (67 mg, 1.76 mmol) was added portionwise to a solution of pyrrolidone **6** (120 mg, 0.59 mmol) in anhydrous THF (5 mL). The solution was stirred at reflux for 4 h, then cooled to rt and treated with MeOH (5 mL). The solvents were removed in vacuo to give a yellow residue which was redissolved in water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to give the pyrrolidine **7** as a white solid, which was sufficiently pure for the next reaction: yield 93% (106 mg); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.10 (3H, d, J = 7 Hz), 1.45 (1H, m), 1.78 (2H, br s, exchange with D_2O), 2.03 (1H, m), 2.13 (1H, m), 2.35 (1H, m), 2.91 (1H, m), 3.13 (1H, d, J = 13 Hz), 3.25 (1H, m), 3.98 (1H, d, J = 13 Hz), 7.13−7.32 (5H, br s); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 13.5, 32.8, 51.7, 54.4, 57.8, 62.9, 126.8, 128.1, 128.8, 139.3; HRMS (EI) calcd for $C_{12}H_{18}N_2$ 190.1465; found 190.1465. HPLC analysis: Chiralpack AD column (hexane/EtOH 9/1 with 0.1% Et_2NH), 1 mL/min, λ = 254 nm; retention times = 9.69 min (*R*,*R* enantiomer), 11.07 min (*S*,*S* enantiomer).

5-Chloro-2-methoxy-4-methylamino benzoic acid sulfate (9). A solution of ester **8** (300 mg, 1.16 mmol) and potassium hydroxide (196 mg, 3.5 mmol) in acetone (4 mL) was stirred at rt for 20 min. Dimethylsulfate (0.33 mL, 3.5 mmol) was then added, and the mixture was stirred at reflux for 90 min. After cooling to rt, the volatiles were removed in vacuo. The residue was redissolved in water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was dissolved in water (0.5 mL) and concentrated sulfuric acid (1 mL), and the resulting solution was stirred for 15 min at 80 °C. After cooling to 0 °C, water (2 mL) was added, giving an white precipitate, which was filtered, washed with cold water, and dried under vacuum: yield 51% (158 mg); ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.02 (3H, s), 4.09 (3H, s), 5.02 (1H, br s), 6.15 (1H, s), 8.07 (1H, s), 10.2 (1H, br s); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 30.1, 56.7, 92.5, 105.7, 112.2, 133.5, 149.9, 158.9, 165.0; HRMS (ESI) calcd for $C_9H_{10}NClO_3Na$ (M + Na − H_2SO_4) 238.0241; found 238.0237.

(+)-Nemonapride (1). Triethylamine (0.24 mL, 1.74 mmol) and ethyl chloroformate (65 μL, 0.65 mmol) were added to a cooled (0 °C) solution of acid **9** (140 mg, 0.65 mmol) in anhydrous CH_2Cl_2 (1 mL). The reaction was stirred for 30 min, and a solution of aminopyrrolidine **7** (82 mg, 0.43 mmol) in dry CH_2Cl_2 (1 mL) was added. The mixture was stirred at 0 °C for 2 h, then quenched with water (3 mL) and extracted with EtOAc (3 × 4 mL). The combined organic layer was washed with water (5 mL) and brine and dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (heptane/EtOAc 1/1 followed by EtOAc/MeOH 9/1) to give nemonapride **1** as a colorless solid: yield 74% (124 mg); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.17 (3H, d, J = 6.3 Hz), 1.69 (1H, m), 2.22 (2H, m), 2.68 (1H, m), 2.97 (3H, d, J = 5.1 Hz), 3.04 (1H, m), 3.24 (1H, d, J = 13.3 Hz), 4.01 (3H,

(8) Since there is a slight difference in the optical rotation of synthetic nemonapride **1** and literature data, the enantiomeric purity of **1** was checked by HPLC analysis on a chiral column with comparison to a racemic standard (prepared according to the same synthetic sequence from racemic alanine) and was found to be >99%.

s), 4.08 (1H, d, J = 13.3 Hz), 4.72 (2H, m), 6.15 (1H, s), 7.25−7.43 (5H, br s), 8.06 (1H, d, J = 8.8 Hz), 8.13 (1H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 13.9, 30.2, 31.1, 51.7, 52.2, 56.1, 57.5, 61.9, 93.2, 110.6, 111.4, 127.0, 128.3, 132.3, 139.6, 148.1, 158.2, 164.3; IR (NaCl) ν (cm^{-1}) 3389, 1634, 1603, 1520, 1282; HRMS (ESI) calcd for $C_{21}H_{27}ClN_3O_2$ (MH^+) 388.1786; found 388.1788; $[\alpha]_D$ = +2.3 (c = 0.6, $CHCl_3$); lit.[4] $[\alpha]_D$ = +4 (c = 0.6, $CHCl_3$). HPLC analysis: Chiralpack AD column (hexane/EtOH 9/1), 1 mL/min, λ = 278 nm; retention times = 17.28 min (*R*,*R* enantiomer), 26.41 min (*S*,*S* enantiomer).

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Supporting Information Available: Copies of NMR spectra for compounds **6**, **7**, **9**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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