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Ex-chiral pool synthesis and pharmacological aspects of 3-pyrrolidinyl-isoxazoles

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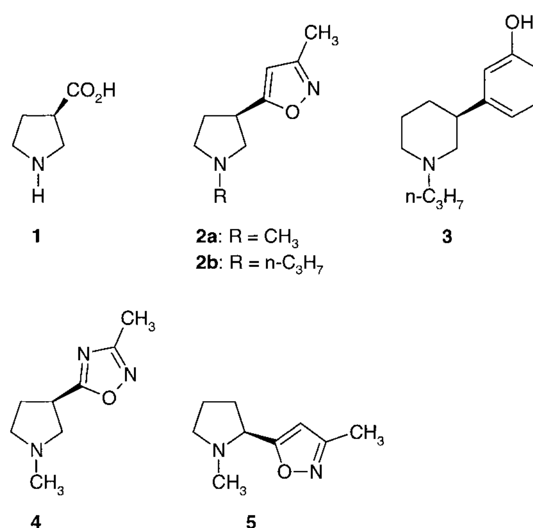
Employing the dopamine autoreceptor agonist (−)-3-PPP (**3**) as well as the cholinergic receptor ligands **4** and **5** as lead compounds the 3-pyrrolidinylisoxazoles **2a**,**b** as well as its optical antipodes ent-**2a**,**b** were synthesized from (*R*)-aspartic acid (**6**) and (*S*)-aspartic acid (ent-**6**), respectively. Pharmacological properties of the target compounds were evaluated employing dopamine D2 receptor binding studies and functional experiments on muscarinic M2 receptors.

1. Introduction

EPC-syntheses of β-amino acids [1] and their applications for bioorganic and medicinal chemistry have become research topics of rapidly increasing interest. Thus, it could be shown that β-peptides can adopt remarkably well ordered conformations [2, 3]. Furthermore β-amino acids can serve as useful building blocks for the construction of bioactive compounds including β-lactams [4, 5], peptidomimetics [6, 7], anti-tumor agents (e.g. taxol) [8] and dopamine autoreceptor agonists [9, 10]. In recent work, we have described a practical synthesis of the glycine receptor agonist β-proline (**1**) in enantiomerically pure form [11–13]. Employing the carboxylate function as a synthetic precursor for the construction of an isoxazole heterocycle, β-proline (**1**) should give access to the 3-pyrrolidinyl-isoxazoles **2**. The *N*-propyl derivative **2b** can be regarded as a heterocyclic surrogate for the dopamine autoreceptor agonist (−)-3-PPP (**3**) [1]. Furthermore, the structural similarity of the methylpyrrolidine **2a** with the aza-analog **4**, which is known as a highly active agonist for cerebrocortical muscarinic receptors [14], and the regioisomer ABT-418 (**5**), a potent neuronal nicotinic acetylcholine receptor activator [15–18] intrigued us to investigate the synthesis as well as the pharmacological properties of **2a**,**b** and the optical antipodes ent-**2a**,**b**.

Scheme 1

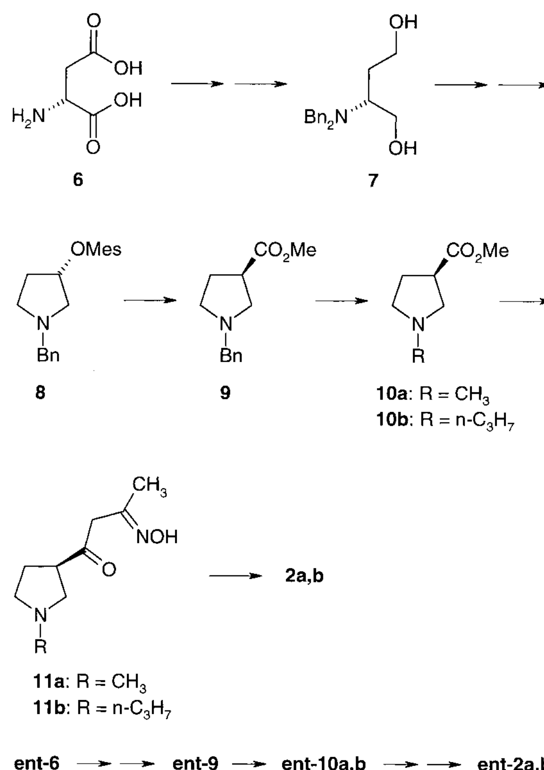


2. Investigations, result and discussion

2.1. Synthesis

For the preparation of the (*R*)-configurated target compounds **2a**,**b** the *N*-benzyl protected β-proline ester **9** should serve as a central intermediate. According to our previously reported protocol the synthesis of **9** was performed in 76% overall yield [11, 12]. In practice, unnatural (*R*)-aspartic acid (**6**) was perbenzylated and reduced to afford the diol **7**. Subsequent activation by methanesulfonyl chloride, rearrangement and hydrogenolysis gave the pyrrolidine mesylate **8** which could be readily transformed into the ester **9** by displacement with NaCN/Bu_4NCN and methanolysis. For an exchange of the *N*-benzyl protecting group by a methyl substituent **9** was hydrogenated using Pearlman's catalyst followed by reductive methylation (formaldehyde, $NaCNBH_3$). Thus, the *N*-methylpyrrolidine **10a** could be obtained. For the synthesis of the *N*-propyl analog **10b** slightly modified reaction conditions using $Zn(BH_4)_2$ instead of $NaCNBH_3$ turned out to be advantageous [19, 20]. The construction of the isoxazole subunit was performed by employing the methodology developed by Hauser et al. [21]. Thus, the methyl esters **10a**,**b** were reacted with the dianion derived from acetone oxime and

Scheme 2



BuLi resulting in formation of the β-keto oximes **11a** and **11b**, respectively. Finally, cyclization was accomplished by treatment of crude **11a**,**b** with methanesulfonyl chloride and triethylamine. Under these conditions, the target compounds **2a** and **2b** could be synthesized in pure form. Analogously, the optical antipodes ent-**2a**, **b** were prepared from natural (*S*)-aspartic acid (ent-**6**) through the intermediates ent-**9a**,**b**, ent-**10a**,**b** and ent-**11a**,**b**.

2.2. Pharmacological investigations

Due to the structural analogy between the isoxazoles **2** and the classical dopamine D2 autoreceptor agonist (−)-3-PPP (**3**), D2 receptor binding studies were performed. Employing bovine striatal membranes the ability of the test compounds to displace the specific radioligand [^{3}H]-pramipexole was evaluated [22]. It turned out, that the isoxazoles **2a**, **2b**, ent-**2a** and ent-**2b** revealed significant but only modest affinity at D2 receptors labelled with [^{3}H]-pramipexole (Table). The (*R*)-configured substrates **2a**,**b** with an isoxazole substituent identically positioned to the 3-hydroxyphenyl moiety of (*S*)-(−)-3-PPP (**3**) displayed a higher activity than the optical antipodes ent-**2a**,**b**.

Table: Dopamine D2 receptor binding, [^{3}H]-ligand: pramipexole

Compound	2a	2b	ent-2a	ent-2b	3
K_i (μM)	32	34	120	65	0.052

The structural similarity of **2a** with the muscarinic agonist **4** prompted us to check for an interaction of **2a** with muscarinic receptors in a functional test system, i.e. in electrically stimulated guinea pig atria [23]. The agonist oxotremorine M reduced the force of contraction concentration-dependently (means ± S.E.M., n = 14) down to 12 ± 3% of the pre-drug contractile force; the half maximum effect of oxotremorine M was attained at $EC_{50} = 0.009$ μM ($pEC_{50} = 8.04 \pm 0.06$, slope factor of the curve $n_H = -1.61 \pm 0.17$). Compound **2a** left the contractile activity of the atria almost unaffected; in the presence of 3.00 μM **2a**, the force of contraction still amounted to 69 ± 6% of the predrug value (mean ± S.E.M., 4 preparations). Compounds ent-**2a** and **2b** did not reveal any inotropic effect up to 100 μm and 1000 μM, respectively (2 preparations for each compound). It was checked whether the compounds might have a muscarinic receptor affinity without intrinsic activity. Therefore, the concentration-effect curve of oxotremorine was measured first in the absence and thereafter in the presence of 100 μM of the test compounds. Compound **2a** did not induce a significant shift of the oxotremorine curve ($p > 0.05$, 3 preparations). Compounds ent-**2a** and **2b** at 100 μM shifted the oxotremorine curve in a parallel fashion to higher concentrations by factors of 3 and 5, respectively ($p < 0.01$, 2–3 preparations). In view of the low potency of the compounds, no attempt was made to further elucidate the mode of antagonism. In any case, we did not find evidence for a relevant interaction of the compounds with muscarinic acetylcholine receptors.

3. Experimental

3.1. General

THF and Et_2O were distilled from Na immediately before use. All liquid reagents were also purified by distillation. Unless otherwise noted reactions were conducted under dry Ar. Evaporations of product solutions were done in vacuo with a rotary evaporator. Flash chromatography was carried out with 230–400 mesh silica gel. Melting points: Büchi apparatus. IR spectra: Perkin-Elmer 1420 spectrometer. MS: Hewlett Packard 5989 A. NMR spectra: Bruker AM-400 at 400 MHz, spectra were measured as $CDCl_3$ solutions. Elemental analyses: Heraeus CHN Rapid, Vario EL instruments. Optical rotations: Zeiss 83204 polarimeter. Light petroleum used had a bp of 40–60 °C.

3.2. (R)-1-Methyl pyrrolidine-3-carboxylic acid methyl ester (10a)

A solution of **9** (1.56 g, 7.12 mmol) in methanol (5 ml) was hydrogenated in a Parr hydrogenation apparatus (14 h, 1010 mbar, 210 ml H_2) using 20% $Pd(OH)_2/C$ (0.40 g) as a catalyst. Then, the reaction mixture was filtered (Celite), the solvent evaporated, and the residue was purified by bulb to bulb distillation (20–30 °C, 0.01 mbar) to give (3*R*)-pyrrolidine-3-carboxylic acid methyl ester as a colorless oil, which was dissolved in methanol (23 ml) and CH_2O (36% in H_2O, 4.5 ml). Subsequently, $NaBH_3CN$ (0.65 g, 10.2 mmol) was added at −20 °C. The reaction mixture was slowly warmed to RT (1 h), stirred for 20 h, acidified with HCl (10%, 45 ml), and extracted with Et_2O (2 × 60 ml). The aqueous layer was basified (K_2CO_3, pH = 11–12) and extracted with $CHCl_3$ (4×60 ml). The organic layer was dried ($MgSO_4$), evaporated, and the residue was purified by bulb to bulb distillation (50–80 °C, 0.001 mbar) to give **10a** (0.496 g, 48.6%) as a colorless oil: $[\alpha]_D^{21} = -5.3°$ (c = 5.0, $CHCl_3$). IR (NaCl, cm^{-1}): 2940/2870 (C−H), 2830 (C−H, NCH_3, OCH_3), 2770 (C−H, NCH_2), 1730 (C=O), 1445 (C−H), 1195/1170 (C−O). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 2.00–2.10 (m, 2 H, 4-H), 2.29 (s, 3 H, $N\underline{CH_3}$), 2.46 (ddd, $^2J = 9.0$ Hz, $^3J = 7.2/7.2$ Hz, 1 H, 5-H), 2.53 (ddd, $^2J = 9.0$ Hz, $^3J = 7.1/6.5$ Hz, 1 H, 5-H), 2.60 (dd, $^2J = 9.4$ Hz, $^3J = 6.7$ Hz, 1 H, 2-H), 2.73 (dd, $^2J = 9.4$ Hz, $^3J = 8.2$ Hz, 1 H, 2-H), 2.98 (dddd, J = 8.2/7.8/7.8/6.7 Hz, 1 H, 3-H), 3.63 (s, 3 H, OCH_3). Ent-**10a** ($[\alpha]_D^{20} = +5.7°$, c = 1.0, $CHCl_3$) was prepared under the same reaction conditions starting from ent-**9**.

3.3. (R)-1-Propyl pyrrolidine-3-carboxylic acid methyl ester (10b)

A solution of **9** (0.433 g, 1.98 mmol) in methanol (5 ml) was hydrogenated in a Parr hydrogenation apparatus (14 h, 1010 mbar, 60 ml H_2) using 20% $Pd(OH)_2/C$ (0.10 g) as a catalyst. The reaction mixture was filtered (Celite), stirred after addition of freshly distilled propionaldehyde (0.715 ml, 9.88 mmol) for 0.5 h, and cooled (0 °C). Then, $Zn(BH_4)_2$ (prepared from 0.44 g $ZnCl_2$, 2.5 g Et_2O and 0.116 g $NaBH_4$, according to ref. [19]) was added to the reaction mixture. The solution was warmed to RT, stirred for 4 h, acidified with aq. HCl (15%, 7 ml), and extracted with Et_2O (5 × 3 ml). The aqueous layer was basified (K_2CO_3, pH = 10–11) and extracted with $CHCl_3$ (5 × 5 ml). Then, the organic layer was dried ($MgSO_4$), evaporated and the residue was purified by flash chromatography ($CH_2Cl_2/MeOH$, 9 : 1) to give **10b** (0.2106 g, 62.3%) as a colorless oil: $[\alpha_D^{21}] = -8.5°$, c = 3.0 in $CHCl_3$. IR (NaCl, cm^{-1}): 2960/2935 (C−H), 2875 (C−H, OCH_3), 2790 (C−H, NCH_2), 1735 (C=O), 1455 (C−H), 1205/1170 (C−O). ^{1}H NMR ($CDCl_3$, 400 MHz, δ ppm): 0.85 (t, $^3J = 7.4$ Hz, 3 H, $NCH_2CH_2\underline{CH_3}$), 1.45 (ddq, $^3J = 7.9/7.6/7.4$ Hz, 2 H, $NCH_2\underline{CH_2}CH_3$), 2.02 (ddd, $^3J = 8.0/7.6/6.3$ Hz, 2 H, 4-H), 2.30 (dt, $^2J = 11.8$ Hz, $^3J = 7.6$ Hz, 1 H, $N\underline{CH_2}CH_2CH_3$), 2.36 (dt, $^2J = 11.8$ Hz, $^3J = 7.9$ Hz, 1 H, $N\underline{CH_2}CH_2CH_3$), 2.41 (dt, $^2J = 9.3$ Hz, $^3J = 7.6$ Hz, 1 H, 5-H), 2.51 (dd, $^2J = 9.4$ Hz, $^3J = 7.1$ Hz, 1 H, 2-H), 2.63 (dt, $^2J = 9.3$ Hz, $^3J = 6.3$ Hz, 1 H, 5-H), 2.84 (dd, $^2J = 9.4$ Hz, $^3J = 8.3$ Hz, 1 H, 2-H), 2.98 (ddt, J = 8.3/8.0/7.1 Hz, 1 H, 3-H), 3.63 (s, 3 H, OCH_3). HRMS: m/z $C_9H_{17}NO_2$: calcd.: 171.1259, found: 171.1259. EI-MS: 171.0 ($M^{+\cdot}$), 170.0 (M−H), 156.0 ($M-CH_3$), 142.0 ($M-CH_2CH_3$), 140.0 ($M-OCH_3$), 128.0 ($M-CH_2CH_2CH_3$), 112.0 ($M-COOCH_3$), 84.0 ($CH_3NC_4H_7$), 70.0 (HNC_4H_7), 43.0 (C_3H_7), 41.9 (C_3H_6 Onium-Reaction). Ent-**10b** ($[\alpha]_D^{20} = +7.8°$, *c* = 1.0, $CHCl_3$) was prepared under the same reaction conditions starting from ent-**9**.

3.4. (R)-3-Methyl -5-(1-methyl-3-pyrrolidinyl)-isoxazole (2a)

To a solution of acetone oxime (3.12 g, 43.2 mmol) in THF (50 ml) was added BuLi (1.6 M in hexane, 54 ml, 86 mmol) at −20 °C over a period of 10 min. Then, the reaction mixture was stirred for 2 h at 0 °C before a solution of **10a** in THF (20 ml) was added at −20 °C. After stirring for additional 20 h the reaction mixture was cannulated into aq. HCl (10%, 100 ml) at 0 °C. After separation the aqueous layer was washed with EtOAc (2 × 100 ml), basified with K_2CO_3 (pH = 10–11), and extracted with CH_2Cl_2 (4 × 100 ml). The organic layers were dried ($MgSO_4$) and the solvent was evaporated to afford the crude oxime **11a**, which was used without further purification. To a solution of **11a** (complete) in CH_2Cl_2 (50 ml) at 0 °C were added Et_3N (2.49 ml, 18,0 ml, 18.0 mmol) and mesyl chloride (1.24 ml, 15.3 mmol). The reaction mixture was stirred for 24 h at 0 °C and subsequently for 5 h at RT before being extracted with aq. HCl (10%, 80, 40, 40 ml). The combined aqueous layers were basified (K_2CO_3, pH = 10–11) and extracted with CH_2Cl_2 (4 × 50 ml). Then, the organic layers were dried ($MgSO_4$). The solvent was evaporated and the residue distilled (bulb to bulb, 85 °C, 0.16 mbar). To obtain analytically

pure **2a**, the distillate was purified by flash chromatography ($CHCl_3$/MeOH, 95 : 5 to 9 : 1) to give 0.547 g (24.7%) **2a** as a colorless oil: $[\alpha]_D^{20} = -13.8°$, (c = 5.0, $CHCl_3$). IR (NaCl, cm^{-1}): 2980/2940/2890 (C−H), 2830 (C−H, NCH_3), 2770 (C−H, NCH_2), 1730 (C=O), 1610/1490 (C=C, C=N), 1450 (C−H). ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 1.98 (dddd, ^2J = 12.9, ^3J = 8.3/6.2/5.9, 1H, 4-H), 2.26 (s, 3 H, $C\underline{CH_3}$), 2.31 (dddd, ^2J = 12.9, ^3J = 10.0/8.2/6.2, 1 H, 4-H), 2.39 (s, 3 H, $N\underline{CH_3}$), 2.59 (dd, ^2J = 9.2 Hz, ^3J = 6.6 Hz, 1 H, 2-H), 2.61 (ddd, ^2J = 8.8 Hz, ^3J = 8.3/6.2 Hz, 1 H, 5-H), 2.69 (ddd, ^2J = 8.9 Hz, ^3J = 8.2/5.9 Hz, 1 H, 5-H), 2.94 (dd, ^2J = 9.2 Hz, ^3J = 7.9 Hz, 1 H, 2-H), 3.50 (dddd, J = 10.0/7.9/6.6/6.2 Hz, 1 H, 3-H), 5.86 (s, 1 H, CH). $C_9H_{14}N_2O \cdot {}^1/_2\,H_2O$ (175.23): calcd.: C 61.69, H 8.63, N 15.99, found: C 61.63, H 8.42, N 15.86. HRMS: m/z $C_{11}H_{18}N_2O$: calcd.: 166.1106, found: 166.1114. EI-MS: 166.2 ($M^{+\cdot}$), 165.2 (M−H), 84.2 ($C_5H_{10}N^+$), 82.2 (M−$C_5H_{10}N$), 57.2 ($C_3H_7N^+$), 42.2 ($C_2H_4N^+$). Ent-**2a** ($[\alpha]_D^{26} = +13.6°$, c = 10, $CHCl_3$) was prepared under the same reaction conditions starting from ent-**10a**.

3.5. *(R)-3-Methyl-5-(1-propyl-3-pyrrolidinyl)-isoxazole* (**2b**)

Compound **10b** (0.386 g, 2.26 mmol) was obtained under analogous reaction conditions as described for the preparation of **2a**. Flash chromatographic purification (Et_2O/MeOH/$EtNMe_2$, 98 :2 : 0.5) of the crude product gave pure **2b** (0.084 g, 19.8%) as a pale yellow oil: ($[\alpha]_D^{26} = -20.70$, c = 0.6, $CHCl_3$). IR (NaCl, cm^{-1}): 2970/2940/2890 (C−H), 2800 (C−H, NCH_2)m 1730 (C=O), 1605 (C=C, C=N), 1450 (C−H). ^1H NMR ($CDCl_3$, 400 MHz) [ppm]: 0.93 (t, J = 7.4 Hz, 3 H, $CH_2CH_2\underline{CH_3}$), 1.54 (ddq, J = 7.8/7.6/7.4 Hz, 2 H, $CH_2\underline{CH_2}CH_3$), 1.96 (dddd, ^2J = 12.9, ^3J = 8.5/6.5/5.5, 1 H, 4-H), 2.26 (s, 3 H, $C\underline{CH_3}$), 2.30 (dddd, ^2J = 12.9, ^3J = 10.0/8.0/6.4, 1 H, 4-H), 2.42 (t, J = 7.6 Hz, 1 H, $N\underline{CH_2}CH_2CH_3$), 2.46 (t, J = 7.8 Hz, 1 H, $N\underline{CH_2}CH_2CH_3$), 2.56 (dd, ^2J = 9.2 Hz, ^3J = 7.3 Hz, 1 H, 2-H), 2.58 (ddd, ^2J = 8.9 Hz, ^3J = 8.5/6.4 Hz, 1 H, 5-H), 2.78 (ddd, ^2J = 8.9 Hz, ^3J = 8.0/5.5 Hz, 1 H, 5-H), 3.03 (dd, ^2J = 9.2 Hz, ^3J = 8.1 Hz, 1 H, 2-H), 3.50 (dddd, J = 10.0/8.1/7.3/6.5 Hz, 1 H, 3-H), 5.86 (s, 1 H, CH). $C_{11}H_{18}N_2O \cdot {}^1/_2\,H_2O$ (203.29): calcd.: C 64.99, H 9.42, N 13.78, found: C 65.41, H 9.03, N 13.56. HRMS: m/z $C_{11}H_{18}N_2O$: calcd. 194.1419, found: 194.1418. Ent-**2b** ($[\alpha]_D^{21} = +19.2°$, c = 0.8, $CHCl_3$) was prepared under the same reaction conditions starting from ent-**10**.

3.6. *Dopamine receptor binding assay*

Dopamine D2 receptor binding studies were performed as described using [^{3}H]-pramipexole as a radioligand in a concentration of 0.5 nM and bovine striatal membranes [22]. Briefly, the [^{3}H]-pramipexole binding assays were carried out using a bovine striatal membrane preparation (~300 µg protein), [^{3}H]-pramipexole (0.5 nM final concentration) and competing drug in a range of concentrations from 10^{-9} M to 10^{-4} M diluted in incubation buffer (50 mM Tris, 1 mM EDTA, 5 mM $MgCl_2$, 0.1 mM dithiothreitol, 100 µg/ml bacitracin and 5 µg/ml soybean trypsin inhibitor, pH 7.4). Non specific binding was determined in the presence of 1 µM (+)-butaclamol. After incubation for 2 h at 23 °C the bound and free ligand were separated by rapid filtration on Whatman GF/B filters. The filters were washed three times with 5 ml of ice-cold Tris-HCl buffer pH 7.4 containing 1 mM EDTA. The radioactivity trapped on the filters was determined by placing them into a scintillation cocktail (ReadyProtein Beckman) and counting them in a Beckman Scintillation Counter. The binding data were analysed using the nonlinear curve-fitting PRISM program (GraphPad Software, San Diego, CA). The IC_{50} values obtained from the competition curves were transformed to K_i values according to the equation of Cheng and Prusoff.

3.7. *Interaction with muscarinic receptors in guinea pig atria*

The procedure has been described previously [23]. In short, isolated guinea pig atria were suspended in modified Tyrode's solution, electrically stimulated at a frequency of 3 Hz, and the force of contraction was recorded isometrically. After an equilibration period of 60 min, a concentration-effect curve of oxotremorine M was measured. Subsequently, oxotremorine M was washed out in drug free Tyrode's solution for 60 min. Thereafter, to test for an agonist action, the test compounds were added in a cumulative fashion starting at 1 nM with an exposure time of 10 min for each concentration. To test for an antagonist action, 100 µM of a test compound were applied for 60 min before the oxotremorine concentration-effect curve was measured in the presence of the compound.

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References

1 Juaristi, E. (Ed.): Enantioselective Synthesis of β-Amino Acids, Wiley-VCH, New York 1997
2 Seebach, D.; Overhand, M.; Kühnle, F. N. M.; Martinoni, B.; Oberer, L.; Hommel, U.; Widmer, H.: Helv. Chim. Acta **79**, 913 (1996)
3 Seebach, D.; Ciceri, P. E.; Overhand, M.; Jaun, B.; Rigo, D.: Helv. Chim. Acta **79**, 2043 (1996)
4 Hart, D. J.; Ha, D.-C.: Chem. Rev. **89**, 1447 (1989) and references cited therein
5 Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A.: J. Am. Chem. Soc. **102**, 6161 (1980)
6 Drey, C. N. C.; in: Barret, G. C. (Ed.): Chemistry and Biochemistry of Amino Acids, Chapman and Hall, London−New York 1985
7 Amblard, M.; Rodriguez, M.; Lignon, M.-F.; Galas, M.-C.; Bernard, N.; Artis.-Noel, A.-M.; Hauad, L.; Laur, J.; Califano, J.-C.; Aumelas, A.; Martinez, J.: J. Med. Chem. **36**, 3021 (1993)
8 For review, see: Nicolaou, K. C.; Dai, W.-M.; Guy, R. K.: Angew. Chem. **106**, 38 (1994)
9 Gmeiner, P.; Mierau, J.; Höfner, G.: Arch. Pharm. (Weinheim) **325**, 57 (1992)
10 Gmeiner, P.; Hummel, E.; Mierau, J.: Bioorg. Med. Chem. Lett. **4**, 2589 (1994)
11 Gmeiner, P.; Orecher, F.; Thomas, C.; Weber, K.: Tetrahedron Lett. **36**, 381 (1995)
12 Thomas, C.; Orecher, F.; Gmeiner, P.: Synthesis 1491 (1998).
13 For pharmacological investigations on racemic β-proline, see: Johnson, G.; Drummond, J. T.; Boxer, P. A.; Bruns, R. F.: J. Med. Chem. **35**, 233 (1992)
14 Street, L. J.; Baker, R.; Book, T.; Kneen, C. O.; MacLeod, A. M.; Merchant, K. J.; Showell, G. A.; Saunders, J.; Herbert, R. H.; Freedman, S. B.; Harley, E. A.: J. Med. Chem. **33**, 2690 (1990)
15 Garvey, D. S.; Wasicak, J. T.; Decker, M. W.; Brioni, J. D.; Buckley, M. J.; Sullivan, J. P.; Carreara, G. M.; Holladay, M. W.; Arneric, S. P.; Williams, M. J.: J. Med. Chem. **37**, 1055 (1994)
16 Elliott, R. E.; Kopecka, H.; Lin, N.-H.; Garvey, D. S.: Synthesis 772 (1995)
17 Lin, N.-H.; He, Y.; Kopecka, H.: Tetrahedron Lett. **36**, 2563 (1995)
18 Wittenberger, S. J.: J. Org. Chem. **61**, 356 (1996)
19 Crabbe, P.; Garcia, G. A.; Rius, C.: J. Chem. Soc., Perkin Trans. **1**, 810 (1973)
20 Bhattacharyya, S.; Chatterjee, A.; Kantha, S.; Duttachowdhury, S. K.: J. Chem. Soc., Perkin Trans. **1**, 1 (1994)
21 Beam, C. F.; Dyer, M. C. D.; Schwarz, R. A.; Hauser, C. R.: J. Org. Chem. **35**, 1806 (1970)
22 Ohnmacht, U.; Tränkle, C.; Mohr, K.; Gmeiner, P.: Pharmazie **54**, 294 (1999)
23 Maaß, A.; Kostenis, E.; Mohr, K.: Eur. J. Pharmacol. **272**, 103 (1995)

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