

Synthesis of 6,8-Diazabicyclo[3.2.2]nonanes: Conformationally Restricted Piperazine Derivatives

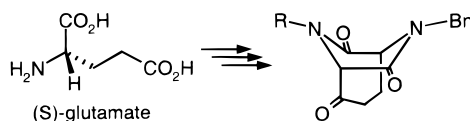
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ABSTRACT



Starting with the proteinogenic amino acid (S)-glutamate, a general method for the synthesis of 3-(piperazin-2-yl)propionic acid esters **7** with various substituents at N-4 of the piperazine ring system is presented. An intramolecular ester condensation of **7** is the key step in the formation of the 6,8-diazabicyclo[3.2.2]nonane derivatives **8–10**, which are of interest as conformationally restricted piperazines.

Several compounds with considerable biological activity belong to the piperazine substance class. The piperazine derivatives **1–3** depicted in Figure 1 represent three ex-

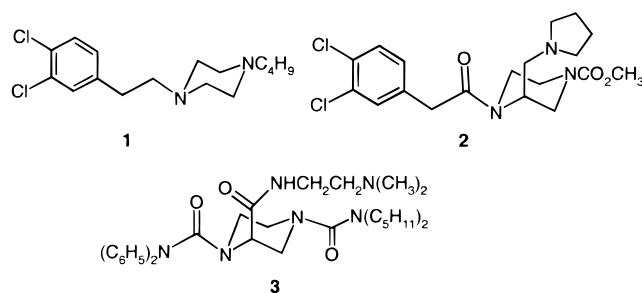


Figure 1. Piperazines with very high receptor affinities.

amples, which display very high affinity for σ_1 , κ_2 , and neurokinin³ (NK₁) receptors, respectively.

(1) deCosta, B. R.; He, X.; Linders, J. T. M.; Dominguez, C.; Gu, Z. Q.; Williams, W.; Bowen, W. D. *J. Med. Chem.* **1993**, *36*, 2311–2320.

(2) Naylor, A.; Judd, D. B.; Lloyd, J. E.; Scopes, D. I. C.; Hayes, A. G.; Birch, P. J. *J. Med. Chem.* **1993**, *36*, 2075–2083.

To study structure–activity relationships, bridges may be introduced into conformationally flexible receptor ligands. The enhanced rigidity may result in an increased receptor affinity, giving insight into the biologically active conformation.^{1,4,5}

Hence, our interest has been focused on the synthesis of 6,8-diazabicyclo[3.2.2]nonane derivatives (e.g., **10**), which are regarded as conformationally constrained piperazine derivatives. Suitable nitrogen protective groups (or substituents) should enable the synthesis of bicyclic analogues of the biologically active piperazines **1–3**. Moreover, bicyclic piperazinones **10** might be employed for the synthesis of aza analogues and homologues of bicyclic alkaloids (e.g., epibatidine, anatoxine, or cocaine) and antibiotics (e.g., bicyclomycin⁶).

In the literature two procedures for the synthesis of 6,8-diazabicyclo[3.2.2]nonanes are described: First, 2-fold in-

(3) Mills, S. G.; Wu, M. T.; MacCoss, M.; Budhu, R. J.; Dorn, C. P.; Cascieri, M. A.; Sadowski, S.; Strader, C. D.; Greenlee, W. J. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2707–2712.

(4) Silverman, R. B. *Medizinische Chemie*, VCH Verlagsgesellschaft mbH, Weinheim **1995**, pp 12–14 and 86–90.

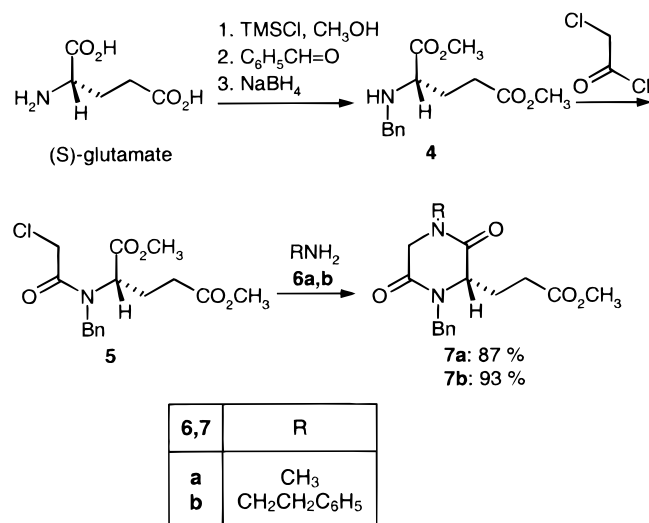
(5) Costantino, G.; Macchiarulo, A.; Pellicciari, R. *J. Med. Chem.* **1999**, *42*, 2816–2827.

(6) Williams, R. M.; Armstrong, R. W.; Dung, K.-S. *J. Med. Chem.* **1985**, *28*, 733.

tramolecular aminolysis of 2,6-diaminopimelic acid derivatives leads to racemic 6,8-diazabicyclo[3.2.2]nonanes without further substituents in the propano bridge.⁷ The second approach starts with a racemic homoserine derivative using an intramolecular enolate epoxide cyclization as the key step, which occurs with unfavorable regioselectivity.⁸

Therefore, we designed a novel synthesis of the chiral, *nonracemic* diazabicyclo[3.2.2]nonane ring system starting with the proteinogenic amino acid (*S*)-glutamate (Scheme 1). Esterification followed by *N*-monobenylation⁹ afforded

Scheme 1. Synthesis of 3-(Piperazin-2-yl)propionic Acid Esters



monobenzylamino diester **4**, which was acylated with chloroacetyl chloride to yield chloroacetamide **5**.¹⁰ Reaction of chloroacetyl derivative **5** with primary amines **6** led to S_N2 substitution of the chloro substituent and, subsequently, intramolecular aminolysis to furnish piperazinediones **7**.¹¹ The employment of exactly 1 equiv of the primary amines **6** is crucial for high yields of **7**, because an excess of primary amines would react with the second ester moiety. Thus, we have developed a facile, high-yielding access to 3-(dioxopiperazin-2-yl)propionic acid esters **7**. In comparison with reported procedures,^{12–14} the presented chiral-pool synthesis furnishes chiral nonracemic piperazines **7** with various substituents at both piperazine nitrogen atoms.

(7) (a) Eastwood, F. W.; Gunawardana, D.; Wernert, G. T. *Aust. J. Chem.* **1982**, *35*, 2289–2298. (b) Kiely, J. S.; Hutt, M. P.; Culbertson, T. P.; Bucsh, R. A.; Worth, D. F.; Lesheski, L. E.; Goglotti, R. D.; Sessie, J. C.; Solomon, M.; Mich, T. F. *J. Med. Chem.* **1991**, *34*, 656–663.

(8) Williams, R. M.; Maruyama, L. K. *J. Org. Chem.* **1987**, *52*, 4044–4047.

(9) Quitt, P.; Hellerbach, J.; Vogler, K. *Helv. Chim. Acta* **1963**, *46*, 327–333.

(10) All new compounds gave satisfactory spectroscopic and analytical data.

(11) An analogous piperazine synthesis is described by: Soukara, S.; Wunsch, B. *Synthesis* **1999**, 1739–1746.

(12) Williams, L.; Booth, S. E.; Undheim, K. *Tetrahedron* **1994**, *50*, 13697–13708.

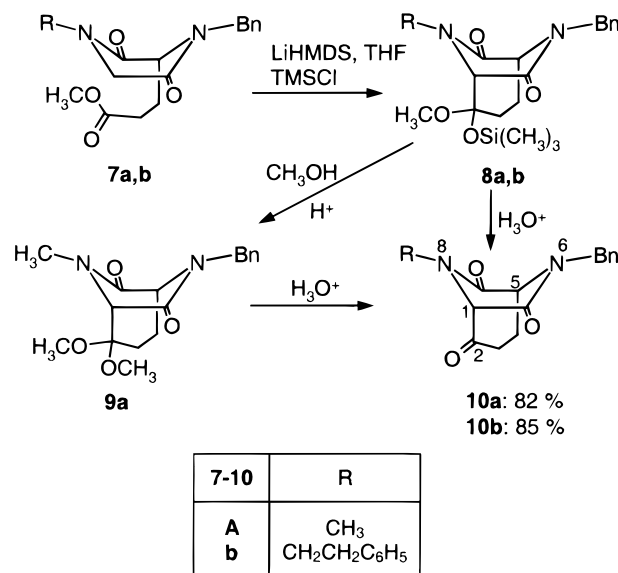
(13) Fukushi, H.; Mabuchi, H.; Terasgita, Z.; Nishikawa, K.; Sugihara, H. *Chem. Pharm. Bull.* **1994**, *42*, 551–559.

(14) Jerumanis, S.; Lefebvre, J. *Bull. Soc. Chim. Belg.* **1994**, *103*, 127–130.

Having afforded the 3-(piperazinyl)propionic acid esters **7**, we next investigated the intramolecular ester condensation. However, all attempts to obtain cyclization products from esters **7** under equilibrating conditions (NaOCH₃ in methanol, NaH in toluene) failed. Obviously, an anion to shift the equilibrium toward the cyclization products could not be formed due to the low acidity of the bridgehead proton in position 1 between the carbonyl moieties of **10**. This explanation is supported by the facile ring opening of **10a** with nucleophilic bases (e.g., methanolate) to yield 3-(piperazinyl)propionic acid ester **7a**.

Finally, the ester condensation of propionic acid esters **7** succeeded by using the nonnucleophilic base lithium hexamethyldisilazane (LiHMDS) and trapping of the primary cyclization products with trimethylsilyl chloride to furnish mixed acetals **8** (Scheme 2). By means of methanol and

Scheme 2. Synthesis of 6,8-Diazabicyclo[3.2.2]nonanes



p-toluenesulfonic acid, mixed acetal **8a** was transformed into dimethyl acetal **9a**. Careful hydrolysis of both, mixed acetals **8** and dimethyl acetal **9a**, provided bicyclic ketones **10** in good yields (82–85% with regard to **7**). The structure of ketones **10** is unequivocally proven by ¹H NMR spectroscopy (singlet at 4.2 ppm caused by 1-H) and IR spectroscopy (valence bond at 1728 cm⁻¹ for the ketone carbonyl group).

The enantiomeric purity of the bicyclic products was shown by NaBH₄ reduction of ketone **10a** to afford diastereoselectively the (*R*)-configured alcohol, which was subsequently acylated with (*R*)- and (*S*)-Mosher's acid chloride to yield diastereomeric esters. ¹H as well as ¹⁹F NMR spectra of the diastereomeric Mosher acid esters revealed a diastereomeric ratio of greater than 98:2. Therefore, racemization at the C-5 position during the base-induced cyclization can be ruled out.¹⁵

In conclusion, the synthesis of chiral nonracemic 6,8-diazabicyclo[3.2.2]nonane derivatives **8–10** starting from

(*S*)-glutamate is presented. Modification of the ketone functional group of **10** and, subsequently, the nitrogen protective groups (substituents) will lead to conformationally

(15) **Typical procedure for the synthesis of 10a from 7a:** At $-78\text{ }^{\circ}\text{C}$ a solution of lithium hexamethyldisilazane (LiHMDS, 1 M in THF, 18.5 mL, 18.5 mmol) was added to a solution of **7a** (4.92 g, 16.2 mmol) in THF (100 mL). After 30 min of stirring at $-78\text{ }^{\circ}\text{C}$ a solution of trimethylsilyl chloride (TMSCl, 5.5 g, 50.7 mmol) in THF (14 mL) was added and the reaction mixture was stirred for 30 min at $-78\text{ }^{\circ}\text{C}$ and for 3 h at room temperature. Then, the solvent was removed in vacuo, the residue was dissolved in ethyl acetate, and the organic layer was washed with HCl (0.5 M), NaOH (0.5 M), and a saturated solution of NaCl and finally concentrated

restricted receptor ligands (compare **1–3**) or aza-analogues and/or homologues of bicyclic alkaloids.

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in vacuo. Since further purification was not necessary, the residue (**8a**) was dissolved in THF/H₂O (10:1; 50 mL), *p*-toluenesulfonic acid (250 mg) was added, and the mixture was stirred for 12 h at room temperature. The solvent was removed in vacuo, and the residue was purified by flash chromatography (ethyl acetate, $R_f = 0.43$) to yield a colorless solid (3.62 g, 82%).