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

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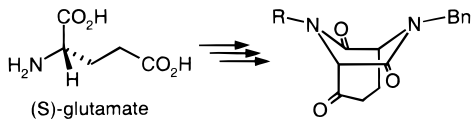
ABSTRACT



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 examples, which display very high affinity for σ,[1] κ,[2] and neurokinin[3] (NK_1) receptors, respectively.

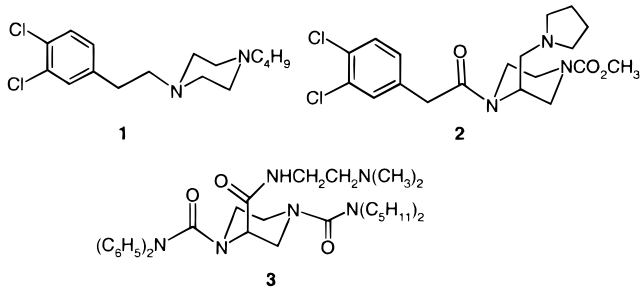


Figure 1. Piperazines with very high receptor affinities.

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., bicyclomycine[6]).

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

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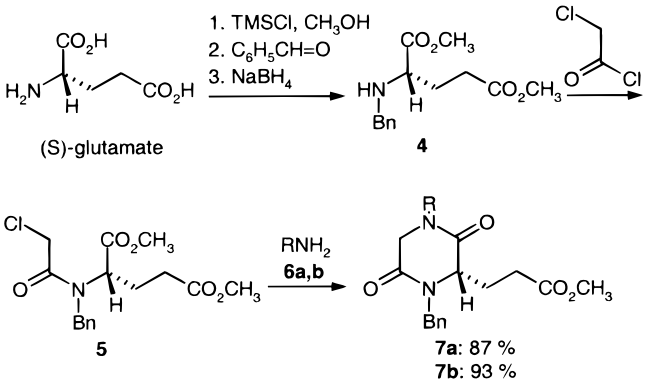
tramolecular aminolysis of 2,6-diaminopimelic acid derivatives leads to racemic 6,8-diazabicyclo[3.2.2]nonanes without further substituents in the propano bridge.[7] The second approach starts with a racemic homoserine derivative using an intramolecular enolate epoxide cyclization as the key step, which 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*-monobenzylation[9] afforded

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



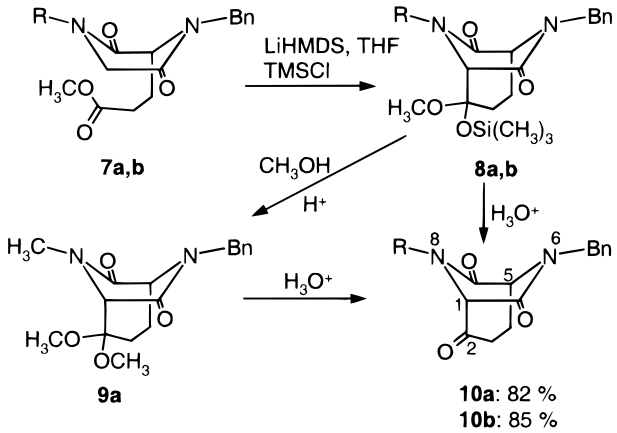
6,7	R
a	CH_3
b	$CH_2CH_2C_6H_5$

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.

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 ($NaOCH_3$ 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



7-10	R
A	CH_3
b	$CH_2CH_2C_6H_5$

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 ^{1}H NMR spectroscopy (singulet 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 $NaBH_4$ reduction of ketone **10a** to afford diastereoselectively the (*R*)-configurated alcohol, which was subsequently acylated with (*R*)- and (*S*)-Mosher's acid chloride to yield diastereomeric esters. ^{1}H as well as ^{19}F 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

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

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(*S*)-glutamate is presented. Modification of the ketone functional group of **10** and, subsequently, the nitrogen protective groups (substituents) will lead to conformationally restricted receptor ligands (compare **1**−**3**) or aza-analogues and/or homologues of bicyclic alkaloids.

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(15) **Typical procedure for the synthesis of 10a from 7a:** At −78 °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 °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 °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 in vacuo. Since further purification was not necessary, the residue (**8a**) was dissolved in THF/H_2O (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%).