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An Efficient Route to All Stereoisomeric Enantiopure 6-Amino-3-alkyl-3-azabicyclo[3.2.1]octane-6-carboxylic Acids

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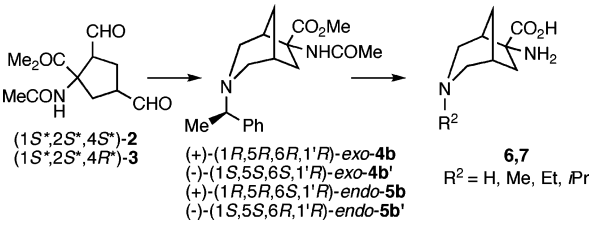

A single-step synthesis on a gram scale of four pure stereoisomers of the 6-amino-3-azabicyclo[3.2.1]octane-6-carboxylic acid was carried out using (*R*)-1-phenylethylamine to confer chirality. The phenylethyl group, and the *p*-methoxy group linked to the N-atom, are easily removed by hydrogenolysis to afford the corresponding NH-3 derivatives. A series of N-3-alkyl compounds were prepared by way of a "one-pot" deprotection−alkylation procedure starting from the above key compounds. Their biological activity has been evaluated on the GABA receptor.

Compounds containing the 3-azabicyclo[3.2.1]octane scaffold are of biological interest as evidenced by recent literature[1] and a large number of patents. Recently,[2] we reported on the synthesis of diastereoisomeric 6-amino-3-azabicyclo[3.2.1]-octane-6-carboxylic acid derivatives *exo*-**4a** and *endo*-**5a** (Scheme 1), as well as of the corresponding *NH*-3 derivatives. Compounds **4** and **5** are constrained analogues of γ-aminobutyric acid (GABA),[3] the major inhibitory neurotransmitter in the vertebrate central nervous system implicated in many physiological and pathological events.[4] The $GABA_A$ receptor gates a Cl^--selective channel in response to the binding of the transmitter as well as of benzodiazepines, barbiturates, and steroids.[5] Selective targeting and modulation of GABA transporter subtypes is of biological interest and additionally of importance for the elucidation of their specialized physiological function and individual structure. Different constrained amino acids have been prepared and tested on GABA receptors such as nipecotic acid and guvacine,[6,7] tiagabine,[8] compound SK&F 89976-A,[9] and the pyrrolidine-2-alkanoic acids.[10]

Considering the general biological interest in new derivatives possessing affinity for GABA receptors, we planned the biological evaluation of amino acids **6** and **7** (Schemes 2 and 3) containing the azabicycloctane skeleton. The fact that the stereochemistry plays a fundamental role in the interaction between a bioactive molecule and the receptor prompted us to revisit the previous synthetic procedure, aiming to make available all the possible stereoisomers of **4** and **5** which themselves were prepared in a single step. Furthermore, a series of *N*-alkyl derivatives were directly prepared from the *N*-benzyl derivatives **4a**,**b** and **5a**,**b** taking advantage of a "one-pot" reaction consisting in the deprotection and reductive alkylation of N-3.

The synthetic strategy previously adopted[2] to obtain compounds **4a** and **5a** took advantage of the use of exo and endo norbornene amino esters **1**, which were transformed into cyclopentyl amino esters **2** and **3** functionalized on C_2 and C_4 with two formyl groups with the required cis stereochemistry (Scheme 1). Their reactions with *p*-methoxybenzylamine, as the nitrogen donor, and $NaBH(OAc)_3$, as the reducing agent, allowed the preparation of compounds **4a** and **5a**. The corresponding enantiopure compounds were also prepared starting from norbornene derivatives related to **1**, containing the (−)-8-phenylmenthyl group as the chiral auxiliary, which were obtained in very high de and exo selectivity (exo/endo, 83:17) through a Diels−Alder reaction. This result obviously disfavored the preparation of the endo series of compounds **5** when starting from the (−)-8-phenylmenthyl ester of *endo*-**1**. For this reason and also with the objective of synthesizing all stereoisomers of compounds **4** and **5**, we chose to start from the racemic methyl

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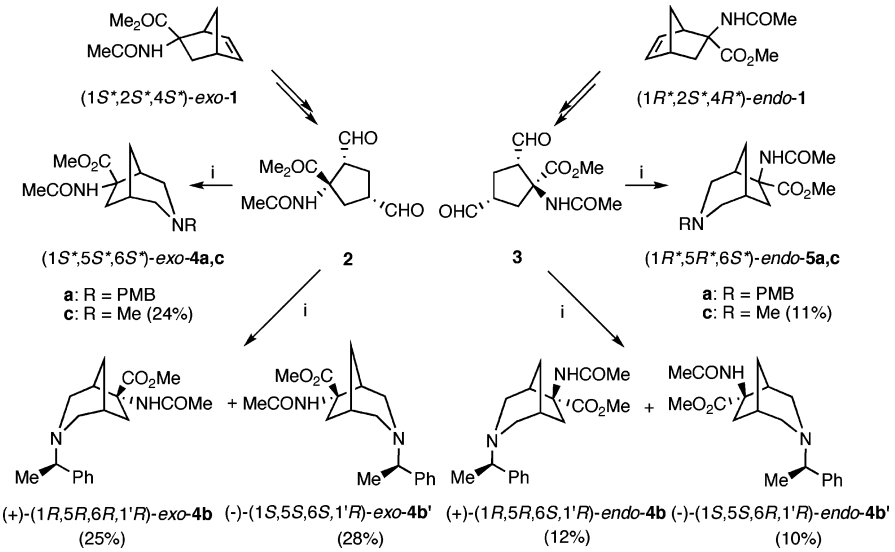
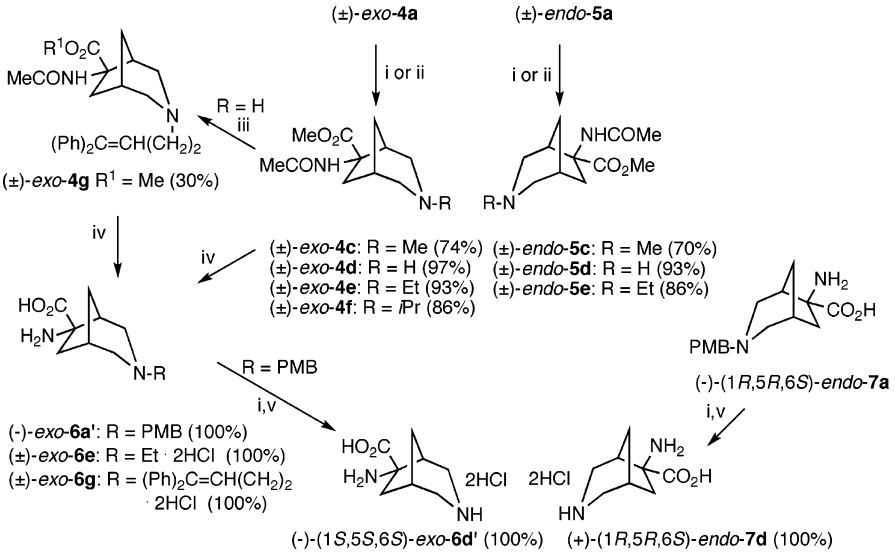
SCHEME 1. Synthesis of 3-*N*-Alkyl-6-amino-3-azabicyclo[3.2.1]octane-6-carboxylic Acids by Reductive Amination Procedure[a]



[a] Reagents and conditions: (i) RNH_2, $NaBH(OAc)_3$, AcOH (cat.), $ClCH_2CH_2Cl$, 25 °C.

SCHEME 2. Synthesis of 3-*N*-Alkyl-6-amino-3-azabicyclo[3.2.1]octane-6-carboxylic Acids by a "One-Pot" Deprotection−Alkylation Procedure[a]



[a] Reagents and conditions: (i) **4d**,**5d**,**6d′**,**7d**: H_2, Pd/C, MeOH; (ii) H_2, Pd/C (**4c**,**5c**: MeOH/HCHO; **4e**,**5e**: EtOH/MeCHO; **4f**: MeCOMe); (iii) $(Ph)_2C{=}CH(CH_2)_2Br$, K_2CO_3, NaI, DMF; (iv) 6 N HCl, Δ; (v) anhydrous HCl, EtOH.

esters of *exo*-**1** and *endo*-**1** which have been prepared in a 70:30 ratio and on a multigram scale.[11] Following the same synthetic protocol adopted for the preparation of compounds **4a** and **5a**,[2] all enantiopure stereoisomers *exo*-**4b**/**4b′** and *endo*-**5b**/**5b′** were prepared starting from a mixture of racemic bis-aldehydes **2** and **3** and performing the reductive amination in the presence of (+)-(*R*)-1-phenylethylamine and $NaBH(OAc)_3$ in dichloroethane (25 °C, 12 h) while using AcOH as catalyst. Using an efficient chromatographic separation, the diastereoisomeric azabicycloderivatives *exo*-**4b** (25%), *exo*-**4b′** (28%), *endo*-**5b** (12%), and *endo*-**5b′** (10%) were isolated (Scheme 1). The preparation of the above amino acids was performed on the gram scale (7 g), thus ensuring the availability of enantiopure materials, using a cheaper chiral reagent such as (*R*)-1-phenylethylamine in place of (−)-8-phenylmenthol. The above method was applied to the preparation of the 3-*N*-methyl compounds (±)-*exo*-**4c** (24%) and (±)-*endo*-**5c** (11%), which were obtained in poor yields from the mixture of aldehydes **2** and **3** and methylamine. The *p*-methoxybenzyl derivatives **4a** and **5a** were then selected as key reagents aiming to find a general procedure to minimize the number of the synthetic steps. This allowed the *NH*-compounds as well as a series of *N*-alkyl compounds to be synthesized efficiently. The deprotection of *N*-3 was performed by hydrogenolysis which made possible an easy purification of the reaction product (Scheme 2). The hydrogenolysis of (±)-*exo*-**4a** and (±)-*endo*-**5a** (Pd/C, MeOH, 25 °C, 1 atm, 2 days) gave the *NH* derivative (±)-*exo*-**4d** (97%) and (±)-*endo*-**5d** (93%), respectively.

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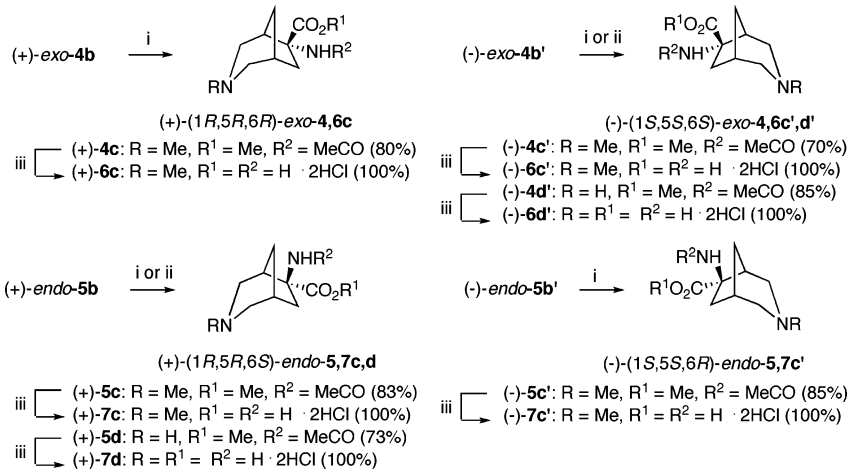
SCHEME 3. Enantiopure 6-Amino-3-azabicyclo[3.2.1]octane-6-carboxylic Acids and Their 3-*N*-Methyl Derivatives[a]



[a] Reagents and conditions: (i) R = Me: H_2, Pd/C, MeOH, HCHO; (ii) R = H: H_2, Pd/C, MeOH; (iii) 6 N HCl, Δ.

The same protocol was used efficiently (36 h) to deprotect (-)-*exo*-**4b′** and (+)-*endo*-**5b**, and the pure *NH* enantiomers (-)-*exo*-**4d′** (85%) and (+)-*endo*-**5d** (73%) were isolated (Scheme 3). In principle, compounds of the **d** series could also be precursors for the preparation of *N*-alkyl compounds using well-known methods. Here, we report on the use of an alternative strategy to achieve this synthetic target consisting in a "one pot" deprotecton and alkylation reaction of the nitrogen atom on *N*-3, taking advantage of the use of catalytic hydrogenation in presence of a carbonyl compound, starting from reagents **4a** and **5a** or enantiopure compounds **4b**/**4b′** and **5b**/**5b′**. When the hydrogenolysis was performed in presence of a methanolic solution of formaldehyde (37%), the *N*-methyl derivatives (±)-*exo*-**4c** (74%) and (±)-*endo*-**5c** (70%) were isolated, respectively, from (±)-*exo*-**4a** and (±)-*endo*-**5a** (Scheme 2). It has to be emphasized that this synthetic approach is a valuable alternative to the reductive amination of *bis*-aldehydes **2** and **3** in the presence of $MeNH_2$ which gave the same *N*-methyl derivatives **4c** and **5c** but in very low yield (Scheme 1). The reductive alkylation of (±)-*exo*-**4a** was also performed in EtOH/acetaldehyde and in acetone and the expected *N*-ethyl and *N*-isopropyl derivatives (±)-*exo*-**4e** (93%) and (±)-*exo*-**4f** (86%) were isolated, respectively (Scheme 2). Compound (±)-*endo*-**5e** (85%) was obtained from (±)-*endo*-**5a**.

The "one-pot" deprotection-methylation reaction of the *N*-3 atom of the four stereoisomers (+)-*exo*-**4b**, (−)-*exo*-**4b′**, (+)-*endo*-**5b**, and (−)-*endo*-**5b′** using formaldehyde gave the pure enantiomers (+)-*exo*-**4c** (80%), (−)-*exo*-**4c′** (70%), (+)-*endo*-**5c** (83%), and (−)-*endo*-**5c′** (85%), respectively (Scheme 3).

Finally, considering that the 4,4-diphenylbut-3-en-1-yl group is a typical residue that increases selectivity (see compound SK&F 89976-A[9]) on GABA receptors and taking into account that the appropriate aldehyde is not available, compound (±)-*exo*-**4g** (30%) was prepared starting from (±)-*exo*-**4d** and 4,4-diphenylbut-3-en-1-yl bromide operating in DMF and in the presence of K_2CO_3 and NaI (Scheme 2).

Aiming to ensure the correct stereochemistry of each stereoisomer of the **b** series, isomers (−)-*exo*-**4d′** and (+)-*endo*-**5d** were hydrolyzed in 6 N HCl (100 °C, 24 h) to give (−)-*exo*-**6d′** and (+)-*endo*-**7d**, respectively, in quantitative yield as the bishydrochlorides (Scheme 3). Compounds (−)-*exo*-**6d′** ($[\alpha]_D = -9.3$) and (+)-*endo*-**7d** ($[\alpha]_D = +4.9$) were correlated to the same compounds (−)-*exo*-**6d′** ($[\alpha]_D = -9.0$) and (+)-*endo*-**7d** ($[\alpha]_D = +4.0$) derived from the catalytic hydrogenolysis (Scheme 2) of the known amino acids (−)-*exo*-**6a′**[2] and (−)-*endo*-**7a**[2] followed by their treatment with anhydrous HCl in EtOH.

The hydrolysis of (+)-*exo*-**4c**, (−)-*exo*-**4c′**, (+)-*endo*-**5c**, and (−)-*endo*-**5c′** as well as of (±)-*exo*-**4e**,**g** performed as described before gave the corresponding amino acids (+)-*exo*-**6c**, (−)-*exo*-**6c′**, (+)-*endo*-**7c**, (−)-*endo*-**7c′**, and (±)-*exo*-**6e**,**g** in quantitative yields.

Amino acids *exo*-**6** and *endo*-**7**, as well as some of the corresponding *N*-acetyl derivatives (see Table TS1 in the Supporting Information) were tested for their binding ability to $GABA_A$ receptors in rat cerebral cortical membranes using labeling tests with [^{3}H]muscimol (for $GABA_A$ sites) and [^{3}H]-flunitrazepam (for the benzodiazepine site). In general, these compounds did not display an appreciable affinity for the $GABA_A$ receptor. Only the *N*-Me compounds displayed low affinity for $GABA_A$ receptors but the biological activity resides solely in the (+) enantiomers (i.e., (+)-(1*R*,5*R*,6*R*)-*exo*-**6c** and (+)-(1*R*,5*R*,6*S*)-*endo*-**7c**), thus confirming that the stereochemistry of the skeleton is an important feature in the binding to GABA receptors.

In conclusion, a very efficient method to prepare the four stereoisomers of 6-amino-3-azabicyclo[3.2.1]octane-6-carboxylates on the gram scale in a single step is described using (*R*)-1-phenylethylamine as the chiral-inducing moiety. The phenylethyl and the *p*-methoxy groups are easily removed by hydrogenolysis to give the corresponding *NH*-3 derivatives. By way of a "one-pot" deprotection−alkylation reaction, a series of *N*-3-alkyl compounds were synthesized. It can be concluded that compounds of the **b** series are valuable synthons for the preparation of enantiopure *N*-3-alkyl substituted derivatives.

Experimental Section

Compounds **2**, **3**, (±)-*exo*-**4a**, (±)-*endo*-**5a**, (-)-*exo*-**6a′**, and (-)-*endo*-**7a** are known compounds.[2]

General Procedure for the Reductive Amination from Aldehydes 2 and 3: Synthesis of 3-Azabicyclo[3.2.1]octane *exo*-4b,b′,c and *endo*-5b,b′,c. A mixture of aldehydes **2** and **3** (241 mg, 1 mmol) was dissolved in anhydrous dichloroethane (4 mL) under N_2 with stirring at 25 °C. (*R*)-1-Phenylethylamine (50 μL, 1.1 mmol) or $MeNH_2$ (32.6 mg, 1.05 mmol), $NaBH(OAc)_3$ (530 mg, 2.5 mmol), and AcOH (catalytic amount) were added. After

36 h, the solvent was removed, and the mixture was taken up with CH_2Cl_2 (5 mL), washed with H_2O (5 mL), and dried over $MgSO_4$. In the case of phenylethylamine (1.45 mL, 31.9 mmol), the reaction has been scaled up starting from aldehydes **2**,**3** (7 g, 29 mmol) to give a mixture of diastereoisomers (7.6 g, 80%), which were chromatographed on silica gel (CH_2Cl_2/MeOH, 20:1). This afforded a mixture of *exo*-**4b**/**4b′** (5.3 g, 56%) and *endo*-**5b**/**5b′** (2.3 g, 24%). Using a Biotage chromatographic system (column: FLASH 65i, KP-SIL, 65 × 200 mm; *exo*-**4b**/**4b′**: cyclohexane/AcOEt, 3:2; *endo*-**5b**/**5b′**: CH_2Cl_2/MeOH, 10:1) pure (+)-*exo*-**4b** (2.3 g, 25%) was separated from (−)-*exo*-**4b′** (2.65 g, 28%) and (+)-*endo*-**5b** (1.15 g, 12%) from (−)-*endo*-**5b′** (0.95 g, 10%). Pure (±)-*exo*-**4c** (57 mg, 24%) and (±)-*endo*-**5c** (21.6 mg, 11%) were isolated after column chromatography (CH_2Cl_2/MeOH, 50:1) and crystallization.

General Procedure for the Deprotection of *N*-3. Compound (±)-*exo*-**4a** or (±)-*endo*-**5a** (346 mg, 1 mmol), (−)-*exo*-**4b′** or (+)-*endo*-**5b** (330 mg, 1 mmol), or (−)-*exo*-**6a′** or (−)-*endo*-**7a** (290 mg, 1 mmol) was dissolved in MeOH (10 mL). Pd/C (10%, 100 mg, 0.1 mmol) was added, and the mixture was hydrogenated (25 °C, 1 atm; *exo*-**4a** and *endo*-**5a**: 48 h; *exo*-**4b′** and *endo*-**5b**: 36 h; *exo*-**6a′** and *endo*-**7a**: 24 h). The mixture was filtered through a Celite pad, the solvent was removed, and the residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 1 : 1). The pure compounds [from (±)-*exo*-**4a**: (±)-*exo*-**4d** (165 mg, 73%); from (±)-*endo*-**5a**: (±)-*endo*-**5d** (158 mg, 70%); from (−)-*exo*-**4b′**: (−)-*exo*-**4d′** (192 mg, 85%); from (+)-*endo*-**5b**: (+)-*endo*-**5d** (165 mg, 73%), from (−)-*exo*-**6a′**: (−)-*exo*-**6d′** (142 mg, 84%); from (−)-*endo*-**7a**: (+)-*endo*-**7d** (160 mg, 95%)] were obtained after crystallization. Spectroscopic data of known compounds are in agreement with literature.[2]

6-Amino-3-azabicyclo[3.2.1]octane-6-carboxylic Acids *exo*-6d′ and *endo*-7d·2HCl. The hydrochloride salts were obtained after treating compounds (−)-*exo*-**6d′** and (+)-*endo*-**7d** individually with a solution of anhydrous HCl in EtOH.

(−)-(1*S*,5*S*,6*S*)-*exo*-6d′·2HCl: $[\alpha]^{25}_D$ −9.0 (*c* 0.5, MeOH).

(+)-(1*R*,5*R*,6*S*)-*endo*-7d·2HCl: $[\alpha]^{25}_D$ +4.0 (*c* 0.5, MeOH).

General Procedure for the "One-Pot" Deprotection−Alkylation Reaction of *N*-3. Compound (±)-*exo*-**4a** or (±)-*endo*-**5a** (150 mg, 0.432 mmol), (+)-*exo*-**4b** or (−)-*exo*-**4b′**, or (+)-*endo*-**5b** or (−)-*endo*-**5b′** (100 mg, 0.303 mmol) was dissolved in the appropriate solvent (see below: 10 mL). A catalytic amount of AcOH and a carbonyl compound were added [for **c**: MeOH and formaldehyde (37% MeOH solution, 200 μL, 1.2 mmol); for **e**: EtOH and acetaldehyde (25 μL, 0.476 mmol); for **f**: acetone and water 1:3]. The mixture was hydrogenated over a Pd/C catalyst (10%, 47 mg, 0.044 mmol) at 25 °C and 1 atm for 24 h. The catalyst was removed by filtration through celite and the solvent was eliminated affording the expected compounds of the **c** series [from (±)-*exo*-**4a**: (±)-*exo*-**4c** (90 mg, 88%); from (±)-*endo*-**5a**: (±)-*endo*-**5c** (88 mg, 85%); from (+)-*exo*-**4b**: (+)-*exo*-**4c** (50 mg, 70%); from (−)-*exo*-**4b′**: (−)-*exo*-**4c′** (58 mg, 80%); from (+)-*endo*-**5b**: (+)-*endo*-**5c** (60 mg, 83%); from (−)-*endo*-**5b′**: (−)-*endo*-**5c′** (62 mg, 85%)] or (±)-*exo*-**4e** (from (±)-*exo*-**4a**: 100 mg, 90%) or (±)-*endo*-**5e** (from (±)-*endo*-**5a**: 75 mg, 68%) or (±)-*exo*-**4f** (from (±)-*exo*-**4a**: 81 mg, 70%) after crystallization.

Synthesis of Methyl (±)-(1*S,5*S**,6*S**)-6-Acetamido-3-(4,4-diphenylbut-3-enyl)-3-azabicyclo[3.2.1]octane-6-carboxylate *exo*-4g.** To a solution of (±)-*exo*-**4d** (297 mg, 1.3 mmol) in DMF (20 mL) were added 4-bromo-1,1-diphenylbut-1-ene (565 mg, 1.96 mmol), K_2CO_3 (370 mg, 2.68 mmol), and NaI (78 mg, 0.52 mmol). The reaction was stirred at reflux for 48 h (TLC: CH_2Cl_2/*n*-hexane, 4:1) and then poured into water (10 mL) and extracted with Et_2O (3 × 10 mL). The organic layer was washed with a saturated solution of NaCl (3 × 10 mL) and dried over Na_2SO_4. After flash column chromatography on silica gel (CH_2Cl_2/MeOH, 40:1) pure compound (±)-*exo*-**4g** was obtained (170 mg, 30%).

General Hydrolysis Procedure to obtain Amino Acid Dihydrochlorides. Operating in a sealed tube, compound (+)-*exo*-**4c** or (−)-*exo*-**4c′**, (+)-*endo*-**5c** or (−)-*endo*-**5c′**, (+)-*exo*-**4d** or (−)-*exo*-**4d′**, (+)-*endo*-**5d** or (−)-*endo*-**5d′**, or (±)-*exo*-**4e** or (±)-*exo*-**4g** (1 mmol) was suspended in 6 N HCl (1 mL), and the mixture was heated at 120 °C for 14 h. The solvent was removed, and the corresponding acids *exo*-**6**, *exo*-**6′**, *endo*-**7**, and *endo*-**7′** were isolated in quantitative yield. The spectroscopic data of the known compounds are in agreement with the literature.[2]

(−)-(1*S*,5*S*,6*S*)-6-Amino-3-azabicyclo[3.2.1]octane-6-carboxylic Acid *exo*-6d′·2HCl: $[\alpha]^{25}_D$ −9.3 (*c* 0.5, MeOH).

(+)-(1*R*,5*R*,6*S*)-6-Amino-3-azabicyclo[3.2.1]octane-6-carboxylic Acid *endo*-7d·2HCl: $[\alpha]^{25}_D$ +4.9 (*c* 0.5, MeOH).

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Supporting Information Available: General technique. Analytical, spectroscopic data, ^{1}H and ^{13}C NMR spectra of compounds *exo*-**4b**−**g**, *exo*-**4b′**−**d′**, *endo*-**5b**−**e**, *endo*-**5b′**−**c′**, *exo*-**6c**,**e**,**g**, *exo*-**6c′**, *endo*-**7c**, and *endo*-**7c′**. Biological activity of compounds *exo*-**6a**,**c**,**c′**,**d**,**g**, *endo*-**7a**,**c**,**c′**,**d**, *exo*-**8**, and *endo*-**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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