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α,γ-Diamino Acids: Asymmetric Synthesis of New Constrained 6-Amino-3-azabicyclo[3.2.1]octane-6-carboxylic Acids

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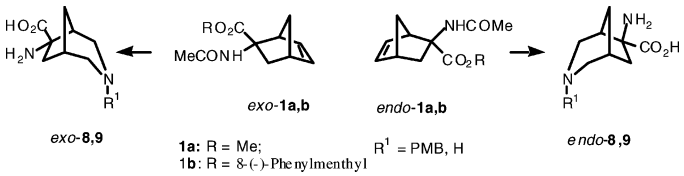

The synthesis of two new diastereomeric 6-amino-3-azabicyclo[3.2.1]octane-6-carboxylic acids *exo*- and *endo*-**8**,**9** is reported using *exo*- and *endo*-norbornene amino acids as chiral building blocks. This method provides a fast access to optically pure amino acids **8** and **9** which can be considered both α,γ- and α,δ-diamino acids containing sterical constraints and characterized by α,α-disubstitution.

Introduction

The syntheses and the biological activities of molecules containing the 3-azabicyclo[3.2.1]octane scaffold are documented by more than 250 patents which indicates that this ring could be the pharmacophore of a bioactive molecule or a substituent of a different bioactive scaffold. Depending on the substitution pattern of the 3-azabicyclo[3.2.1]octane ring, different activities were reported, and many of these compounds were used for treating central nervous system disorders. Among these molecules, the amino-substituted compounds are of relevance,[1] as well as the carboxylic acid derivatives.[2]

The diastereo- and enantioselective preparation of new constrained amino acids has been one of our synthetic targets since the 1999s.[3] Conformationally restricted amino acids are of great interest and have assumed a prominent role in drug design and development.[4] Going on our research program and considering the general biological importance of 3-azabicyclo-[3.2.1]octane derivatives and in view of their use in peptidomimetic synthesis, we planned the preparation of compounds *exo*- and *endo*-**8**,**9** (Scheme 1) functionalized both with amino and carboxy groups on C-6 which, to our knowledge, are unknown compounds. 6-Amino-3-azabicyclo[3.2.1]octane-6-carboxylic acids can be considered both α,γ- and α,δ-diamino acids containing sterical constraints and characterized by α,α-disubstitution. Their features, such as the α,α-disubstitution, which gives metabolic stability, the conformational rigidity, and the presence of two amino groups and one carboxy group, make them very interesting substrates to be used in peptidomimetic syntheses. Constrained amino acids are able to modulate the conformation and, as a consequence, the properties of peptides and their biological activity.[4c,5] In particular, few examples of δ-amino acids are reported even if they seem to be very promising in view of the synthesis of peptidomimetics.[5a,b]

To ensure the preparation of both diastereomers of the title compounds **8** and **9**, in enantiopure form too, our retrosynthetic

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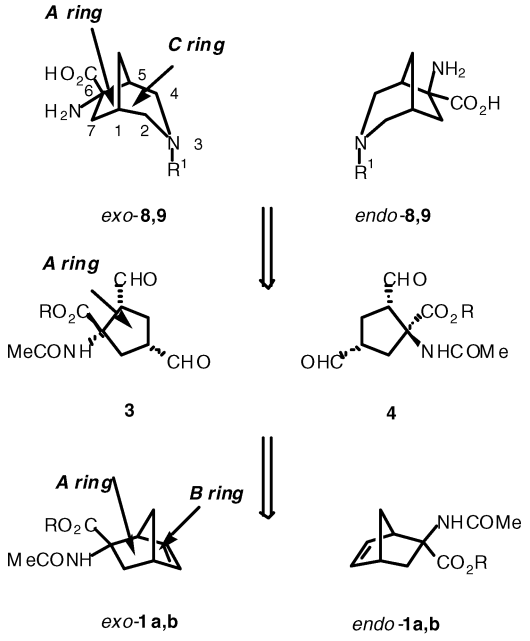
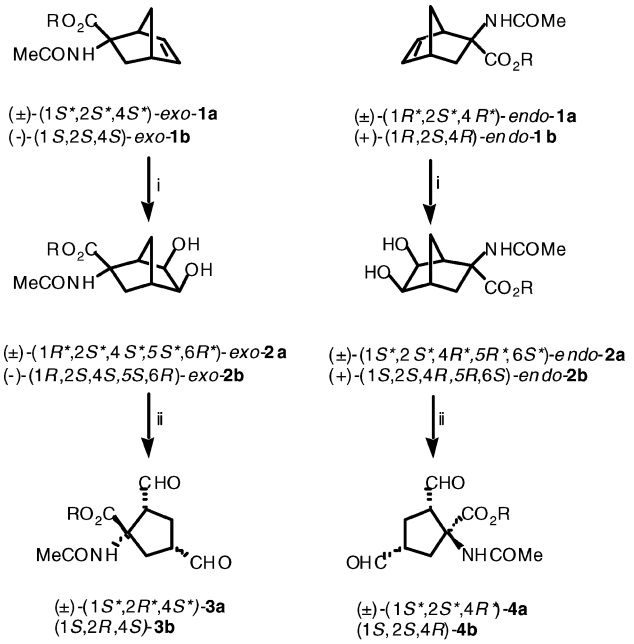
SCHEME 1. Retrosynthetic Analysis



SCHEME 2. Synthesis of Bisaldehydes 3 and 4[a]



[a] Reagents and conditions: (i) OsO_4, NMO, acetone/H_2O, 25 °C; (ii) $NaIO_4$, dioxane/H_2O, 25 °C.

plan features the norbornene amino acids **1** as suitable starting materials (Scheme 1).

Compounds **1** are readily prepared as endo/exo diastereomers, both in racemic[6] and in enantiopure form,[3b] by using the Diels–Alder reaction starting from 2-aminoacrylate derivatives and cyclopentadiene. The disconnection of ring B of norbornenes **1** by an oxidative reaction (C_5–C_6 cleavage) yields the cyclopentyl derivatives **3/4** (ring A in both compounds **1** and **3/4**) substituted with the amino acid function and with two formyl groups with the proper regiochemistry and *cis* configuration. From these key intermediates, the formation of ring C of the 3-azabicyclo[3.2.1]-octane skeleton was assured by a reductive amination reaction. By using a very efficient protocol, starting from a mixture of protected norbornene amino acids *exo*-**1** and *endo*-**1**, the new diastereomeric 6-amino-3-azabicyclo[3.2.1]octane-6-carboxylic acids *exo*-**8**,**9** and *endo*-**8**,**9** were prepared in good yields. Amino acids **8** and **9** are orthogonally protected, allowing the selective deprotection of both the acid and the two different amino groups.

Results

The key starting reagents for the preparation of the amino acids containing the 3-azabicyclo[3.2.1]octane skeleton were the norbornene derivatives *exo*-**1a** and *endo*-**1a** as well as the corresponding enantiopure compounds *exo*-**1b** and *endo*-**1b**. The C_4–C_5 double bond of the norbornene ring was cleaved by a two-step oxidative process. First, racemic compounds *exo*-**1a** and *endo*-**1a** were transformed into the corresponding dihydroxy derivatives **2** by allowing **1** to react with *N*-methylmorpholine-*N*-oxide (NMO) in acetone/H_2O, in the presence of a catalytic amount of osmium tetroxide (Scheme 2). The diol derivatives *exo*-**2a** (86%) and *endo*-**2a** (84%) were obtained in pure form as single diastereomers characterized by the *cis* relationship between both the hydroxy groups and the bridge, as demonstrated by a NOESY experiment on *exo*-**2a**. In fact, spatial proximity between *endo* H-3 (δ 1.34) and H-5 (δ 3.73) and between H-6 (δ 3.97) and the methyl group of the acetyl group (δ 1.94) was observed.

The cyclopentyl derivatives functionalized with two formyl groups with the proper stereochemistry were obtained by

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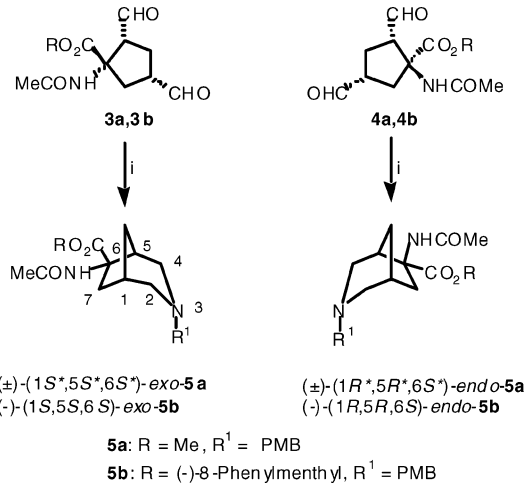
SCHEME 3. Synthesis of 3-Azabicyclo[3.2.1]octane Ring[a]



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

cleaving the C_4-C_5 bond of compounds **2** with sodium periodate as the oxidant in dioxane/H_2O (8:1) at room temperature (4 h). Bisaldehydes **3a** and **4a** were quantitatively obtained from *exo*-**2a** and *endo*-**2a**, respectively (Scheme 2).

Their structure was confirmed by ^1H NMR, which showed the presence of two singlets in the δ 9.7−9.8 region.

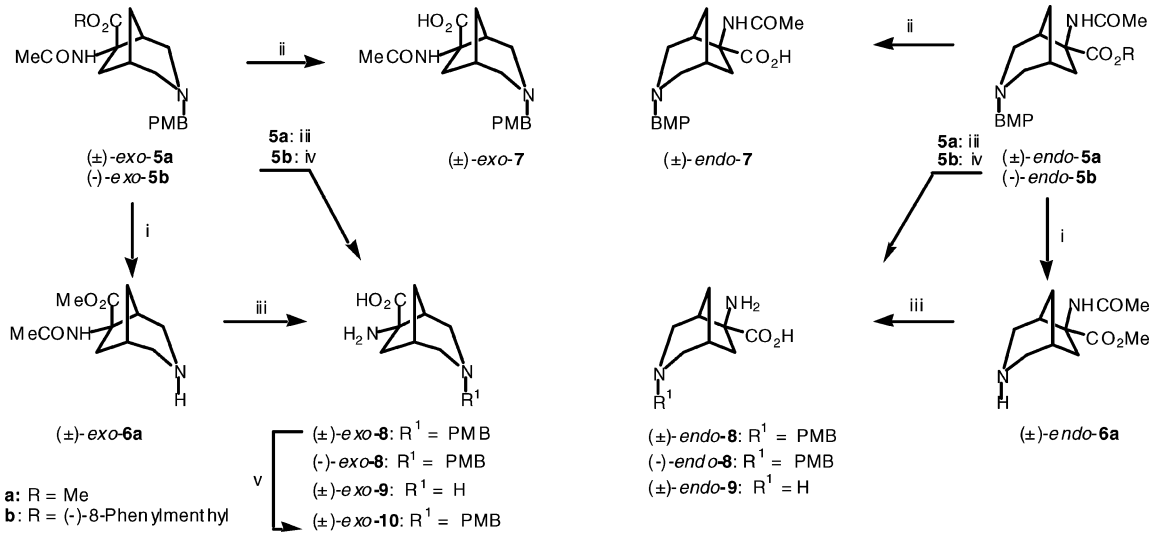
The bisaldehydes are not very stable, and it was chosen to transform the crude reaction mixtures directly into the corresponding 3-azabicyclo[3.2.1]octane derivatives. A reductive amination was performed using *p*-methoxybenzylamine, as the nitrogen donor, and sodium triacetoxyborohydride, as reducing agent (1.3 equiv). The reaction was performed at room temperature (4 h) in 1,2-dichloroethane and in the presence of a catalytic amount of acetic acid. Methyl 6-acetamido-3-azabicyclo-[3.2.1]octane-6-carboxylate derivative *exo*-**5a** (61%) was obtained from **3a**. Compound *endo*-**5a** was isolated in 53% yield starting from **4a** (Scheme 3).

This synthetic protocol suffers from some limitations related to (i) the efficiency of the exo/endo norbornenes **1** separation, and (ii) the necessity to perform the reaction twice, both starting from the exo and the endo norbornenes. A more efficient synthetic protocol was developed consisting of the preparation of the exo/endo mixture of compounds **5a** by using the same synthetic procedure described for pure diastereomers and in their easy separation by column chromatography in the final step. The mixture of *exo*- and *endo*-**1a** (7:3) was transformed into a mixture of *exo*/*endo*-3-azabicyclo[3.2.1]octane amino acid derivatives *exo*-**5a** (41%) and *endo*-**5a** (15%), through the diol derivatives **2a** and bisaldehydes **3a**/**4a**.

The enantiopure amino acids (−)-*exo*-**5b** (57%) and (−)-*endo*-**5b** (58%) (Scheme 3) were prepared following the same synthetic scheme starting from enantiopure compounds (−)-*exo*-**1b** and (+)-*endo*-**1b**, transformed into the diol derivatives (−)-*exo*-**2b** and (+)-*endo*-**2b**, oxidized to bisaldehyde **3b** and **4b**, respectively (Scheme 2).

Compounds **5** are orthogonally protected diamino acids which are selectively deprotected to each functional group. Compound *exo*-**5a** was selected to study the orthogonal deprotection. The 3-aza group was first deprotected, aiming to prepare the NH azabicyclo[3.2.1]octane derivatives which are valuable and alternative starting materials for the preparation of other 3-*N*-substituted amino acids. To remove the *N*-*p*-methoxybenzyl group (PMB), an oxidative process was performed using cerium ammonium nitrate (CAN) in acetone/H_2O (9:1) at room temperature. This method is reported in the literature, but its straightforward application in the present case caused difficulties because of the solubility of the amino acid derivative in water. The problem was overcome by treating the reaction mixture with solid $NaHCO_3$ followed by its chromatography on silica gel. Compound *exo*-**6a** was isolated in 90% yield. The same synthetic protocol allowed us to transform *endo*-**5a** into amino acid *endo*-**6a** (62%). The methyl ester group of *exo*-**5a** and *endo*-**5a** was selectively hydrolyzed using basic conditions (EtOH/KOH). The corresponding acids *exo*-**7** (95%) and *endo*-**7** (99%) were isolated, respectively. Both the amino and the carboxy functions were deprotected in acid conditions (6 N HCl at 100 °C, 24 h). Amino acids *exo*-**8**,**9** and *endo*-**8**,**9** were obtained in quantitative yield, as bishydrochlorides, from *exo*-**5a**,**6a** and *endo*-**5a**,**6a**, respectively.

SCHEME 4. Orthogonal Deprotection[a]



[a] Reagents and conditions: (i) CAN, acetone/H_2O, 25 °C; (ii) KOH, EtOH (95%), 120 °C; (iii) 6 N HCl, 100 °C; (iv) MeOH, Na, 0 °C, then **5b**, 100 °C; (v) $SOCl_2$, MeOH, reflux.

The hydrolysis of ester and amido functions of enantiopure compounds *exo*-**5b** and *endo*-**5b** was successfully achieved with MeONa in methanol at reflux for 50 h. Acids (−)-*exo*-**8** (45%) and (−)-*endo*-**8** (60%) were obtained, respectively. Finally, the reaction of amino acid *exo*-**8** with $SOCl_2$ and MeOH gave the corresponding methyl ester *exo*-**10** in 89% yield. All compounds were characterized by spectroscopic data, and as examples, the NMR discussion on the conformation of compounds **5** is reported in the Supporting Information (Figure S1).

In conclusion, a very efficient protocol for the preparation of two new diastereomeric constrained diamino acids containing the 3-azabicyclo[3.2.1]octane skeleton was developed. They were prepared in good yields and in enantiopure form starting from readily available enantiopure norbornene amino acids.

Amino acid derivatives **5** are orthogonally protected, and this allowed the selective deprotection of the *N*-3 atom or of the amino group on C-6. In particular, the NH compounds **6** are expected to be valuable starting materials for the selective functionalization of amino acid groups on the N-3 atom. Furthermore, these compounds are very promising amino acids to be used for peptidomimetic synthesis.

Experimental Section

Compounds *exo*-**1a**,[6] *endo*-**1a**,[6] *exo*-**1b**,[3b] and *endo*-**1b**[3b] were prepared according to a known procedure.

General Procedure for the Synthesis of Diols 2. Compound **1** [*exo*-**1a** or *endo*-**1a** or a mixture of *exo*-**1a**/*endo*-**1a** (7:3) (209 mg, 1 mmol); *exo*-**1b** or *endo*-**1b** (409.6 mg, 1 mmol)] was suspended in a mixture of acetone/H_2O (6 mL, 10:1). After addition of *N*-methylmorpholine-*N*-oxide (176 mg, 1.5 mmol) and OsO_4 (1.35 mg, 0.005 mmol), the solution turned brown. The reaction mixture was stirred at room temperature for 8 h after which the solvent was evaporated. The crude reaction mixture was filtered on silica gel (CH_2Cl_2/MeOH = 5:1). Pure compound **2** (*exo*-**2a**, 209 mg, 86%; *endo*-**2a**, 204 mg, 84%; *exo*-**2a**/*endo*-**2a**, 202 mg, 83%) was obtained after crystallization. The crude reaction mixture containing **2b** was taken up with a saturated solution of $Na_2S_2O_4$ (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). After drying of the organic layer with Na_2SO_4 and column chromatography on silica gel (CH_2Cl_2/MeOH = 20:1), pure compound **2b** (*exo*-**2b**, 404 mg, 90%; *endo*-**2b**, 430 mg, 97%) was isolated.

Methyl (1*R,2*S**,4*S**,5*S**,6*R**)-2-Acetylamino-5,6-dihydroxybicyclo[2.2.1]heptane-2-carboxylate *exo*-2a:** Mp 161 °C (MeOH/iPr_2O); IR ν_{max} 3500−3100, 1735, 1651 cm^{-1}; ^1H NMR (CD_3OD) δ 3.97 (d, J = 6.2 Hz, 1 H), 3.73 (d, J = 5.0 Hz, 1 H), 3.67 (s, 3 H), 2.71 (br s, 1 H), 2.22 (dd, J = 13.8, 5.0 Hz, 1 H), 2.09 (br s, 1 H), 1.94 (s, 3 H), 1.94−1.91 (m, 1 H), 1.64 (d, J = 10.9 Hz, 1 H), 1.34 (dd, J = 13.8, 2.9 Hz, 1 H); ^{13}C NMR (CD_3OD) δ 174.6, 172.9, 73.9, 69.3, 62.6, 51.8, 50.4, 43.3, 38.3, 31.3, 21.0; *m*/*z* 244.2 [M^+]. Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.28; H, 7.10; N, 5.68.

Methyl (1*S,2*S**,4*R**,5*R**,6*S**)-2-Acetylamino-5,6-dihydroxybicyclo[2.2.1]heptane-2-carboxylate *endo*-2a:** Mp 186 °C (MeOH/iPr_2O); IR ν_{max} 3346, 1731, 1694 cm^{-1}; ^1H NMR (CD_3OD) δ 3.74 (dd, J = 6.2, 1.4 Hz, 1 H), 3.66 (s, 3 H), 3.57 (dd, J = 5.8, 1.4 Hz, 1 H), 2.38 (dd, J = 13.9, 2.5 Hz, 1 H), 2.23 (br s, 1 H), 2.16−2.14 (m, 1 H), 1.97 (dt, J = 10.6, 1.1 Hz, 1 H), 1.88 (s, 3 H), 1.65 (dt, J = 10.6, 1.5 Hz, 1 H), 1.54 (ddd, J = 14.0, 5.1, 0.7 Hz, 1 H); ^{13}C NMR (CD_3OD) δ 173.1, 171.5, 72.8, 68.9, 63.8, 52.3, 51.6, 43.9, 38.8, 31.8, 20.8; *m*/*z* 244.2 [M^+]. Anal. Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.25; H, 7.12; N, 5.67.

(−)-8-Phenylmenthyl (1*R*,2*S*,4*S*,5*S*,6*R*)-2-Acetylamino-5,6-dihydroxybicyclo[2.2.1]heptane-2-carboxylate *exo*-2b: Mp 235 °C (CH_2Cl_2/*i*-Pr_2O); $[\alpha]^{25}_D$ = −9.1° (*c* 0.5, MeOH); IR ν_{max} 3360−3300, 1715, 1647 cm^{-1}; ^1H NMR (CD_3OD) δ 7.34−7.11 (m, 5 H), 4.83−4.71 (m, 1 H), 3.97 (d, J = 6.2 Hz, 1 H), 3.66 (d, J = 5.5 Hz, 1 H), 2.61 (br s, 1 H), 2.26 (dd, J = 13.9, 5.1 Hz, 1 H), 2.05−1.77 (m, 3 H), 1.90 (s, 3 H), 1.55−0.72 (m, 9 H), 1.35 (s, 3 H), 1.24 (s, 3 H), 0.86 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (CD_3OD) δ 172.9, 171.6, 153.3, 128.5, 125.9, 124.9, 77.4, 73.8, 69.3, 62.6, 50.8, 50.2, 43.7, 40.9, 39.7, 38.1, 35.0, 31.5, 29.9, 29.6, 26.8, 24.1, 23.5, 21.9; *m*/*z* 466.4 [+Na]. Anal. Calcd for $C_{26}H_{37}NO_5$: C, 70.40; H, 8.41; N, 3.16. Found: C, 70.33; H, 8.45; N, 3.10.

(−)-8-Phenylmenthyl (1*S*,2*S*,4*R*,5*R*,6*S*)-2-Acetylamino-5,6-dihydroxybicyclo[2.2.1]heptane-2-carboxylate *endo*-2b: Mp 249 °C; $[\alpha]^{25}_D$ = +13° (*c* 0.5, MeOH); IR ν_{max} 3375, 1704, 1649 cm^{-1}; ^{1} H NMR ($CDCl_3$) δ 7.40−7.16 (m, 5 H), 5.00 (s, 1 H, exch.), 4.69−4.59 (m, 1 H), 3.90 (d, J = 5.9 Hz, 1 H), 3.82 (d, J = 6.3 Hz, 1 H), 2.22−2.00 (m, 3 H), 2.00−1.80 (m, 4 H), 1.81 (s, 3 H), 1.79−1.42 (m, 4 H), 1.34 (s, 3 H), 1.30−0.80 (m, 2 H), 1.17 (s, 3 H), 0.87 (d, J = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.8, 169.9, 152.9, 128.4, 125.9, 125.1, 77.7, 73.2, 69.4, 63.7, 52.3, 49.8, 44.4, 41.0, 39.8, 39.2, 35.0, 32.5, 31.6, 28.9, 27.0, 25.1, 23.3, 22.0; *m*/*z* 466.4 [+Na]. Anal. Calcd for $C_{26}H_{37}NO_5$: C, 70.40; H, 8.41; N, 3.16. Found: C, 70.47; H, 8.39; N, 3.13.

General Procedure for the Preparation of Bisaldehydes 3 and 4. Compound **2** (**2a**, 243 mg, 1 mmol; **2b**, 443 mg, 1 mmol) was dissolved in a mixture of dioxane/H_2O (5 mL, 8:1). $NaIO_4$ was added (1.7 g, 7.92 mmol), and the mixture was stirred at room temperature for 2 h. The solvent was evaporated, and the reaction mixture was taken up with $CHCl_3$ (10 mL), and the salts were filtered and washed with $CHCl_3$. The organic solution was collected, and after solvent elimination, the crude aldehydes **3** or **4** [*exo*/*endo*-**2a**, **3a**,**4a** (240 mg); *exo*-**2a**, **3a** (232 mg); *endo*-**2a**, **4a** (234 mg); *exo*-**2b**, **3b** (395 mg); *endo*-**2b**, **4b** (398 mg)] were isolated and used without further purification.

Methyl (1*S,2*R**,4*S**)-1-Acetylamino-2,4-diformylcyclopentanecarboxylate 3a:** crude compound; IR ν_{max} 3346, 1731, 1694 cm^{-1}; ^{1} H NMR ($CDCl_3$) δ 9.76 (s, 1 H), 9.71 (s, 1 H), 6.50 (s, 1 H, exch.), 3.77 (s, 3 H), 3.25−3.05 (m, 1 H), 2.50 (dd, J = 13.9, 3.7 Hz, 1 H), 2.40−1.90 (m, 4 H), 1.91 (s, 3 H); ^{13}C NMR δ 202.7, 172.0, 170.8, 66.6, 57.2, 53.3, 47.4, 37.0, 24.7, 22.9; *m*/*z* 242.1 [M^+].

Methyl (1*S,2*S**,4*R**)-1-Acetylamino-2,4-diformylcyclopentanecarboxylate 4a:** crude compound; IR ν_{max} 3391, 1728, 1658 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.68 (s, 1 H), 9.67 (s, 1 H), 6.70 (s, H, exch.), 3.69 (s, 3 H), 3.20−2.90 (m, 1 H), 2.60−1.90 (m, 4 H), 2.01 (s, 3 H); ^{13}C NMR δ 201.7, 200.0, 173.0, 170.5, 65.7, 58.4, 53.2, 48.9, 36.8, 27.2, 23.9; *m*/*z* 242.1 [M^+].

(−)-8-Phenylmenthyl (1*S*,2*R*,4*S*)-1-Acetylamino-2,4-diformylcyclopentanecarboxylate 3b: crude compound; IR ν_{max} 3428, 1759, 1633 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.73 (s, 1 H), 9.48 (d, J = 0.81 Hz, H), 7.39−7.11 (m, 5 H), 6.35 (s, 1 H, exch.), 4.93−4.88 (m, 1 H), 3.02−2.92 (m, 1 H), 2.40−2.31 (m, 1 H), 2.25 (dd, J = 14.0, 2.3 Hz, 1 H), 2.20−2.13 (m, 1 H), 2.12−1.75 (m, 5 H), 1.84 (s, 3 H), 1.68 (dd, J = 14.0, 10.1 Hz, 1 H), 1.60−1.50 (m, 1 H), 1.32 (s, 3 H), 1.28−1.18 (m, 1 H), 1.14 (s, 3 H), 1.10−0.97 (m, 2 H), 0.93 (d, J = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 202.2, 197.3, 169.6, 168.8, 152.1, 127.4, 124.9, 124.3, 76.6, 65.5, 55.9, 48.5, 45.3, 40.1, 38.7, 35.0, 34.0, 30.7, 30.3, 25.8, 23.3, 21.7, 21.1, 20.8; *m*/*z* 442.5 [M^+].

(−)-8-Phenylmenthyl (1*S*,2*S*,4*R*)-1-Acetylamino-2,4-diformylcyclopentanecarboxylate 4b: crude compound; IR ν_{max} 3390, 1727, 1651 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.69 (d, J = 1.5 Hz, 1 H), 9.61 (d, J = 1.3 Hz, 1 H), 7.32−7.15 (m, 5 H), 6.05 (s, 1 H, exch.), 5.04−4.95 (m, 1 H), 3.27−3.12 (m, 1 H), 2.43 (dd, J = 14.0, 10.0 Hz, 1 H), 2.33 (dd, J = 9.3, 9.2 Hz, 1 H), 2.12−1.95 (m, 2 H), 1.97 (s, 3 H), 1.90−1.80 (m, 2 H), 1.72−1.55 (m, 3 H), 1.50−1.40 (m, 1 H), 1.36 (s, 3 H), 1.22 (s, 3 H), 1.18−0.80 (m, 3 H), 0.90 (d, J = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 202.0, 200.1, 171.5, 170.3, 151.7, 128.7, 125.9, 78.8, 67.1, 57.9, 50.3, 48.9, 41.8, 40.3, 35.6, 34.6, 31.8, 27.7, 27.3, 27.0, 26.5, 24.5, 22.1; *m*/*z* 442.5 [M^+].

General Procedure for the Reductive Amination: Synthesis of 3-Azabicyclo[3.2.1]octane Derivatives 5a,b. Aldehyde [**3a**/**4a**

(242 mg, 1 mmol); **3b**/**4b** (442 mg, 1 mmol)] was dissolved in anhydrous dichloroethane (4 mL) under nitrogen. Operating under stirring at room temperature, *p*-methoxybenzylamine (137.2 mg, 1 mmol), $NaBH(OAc)_3$ (487.0 mg, 2.3 mmol), and a catalytic amount of AcOH were added. After 4 h, the solvent was evaporated, and the crude reaction mixture was taken up with CH_2Cl_2 (5 mL). The organic layer was washed with H_2O (5 mL) and dried over $MgSO_4$. The crude reaction was chromatographed on silica gel (**5a**, CH_2Cl_2/MeOH = 20:1; **5b**, CH_2Cl_2/MeOH = 50:1) giving pure 3-azabicyclo-[3.2.1]octane derivatives **5** after crystallization [**3a**, *exo*-**5a** (211 mg, 61%); **4a**, *endo*-**5a** (183 mg, 53%); **3a**/**4a**, *exo*-**5a** (141 mg, 41%); *endo*-**5a** (52 mg, 15%); **3b**; *exo*-**5b** (311 mg, 57%); **4b**, *endo*-**5b** (317 mg, 58%)].

Methyl (1*S,5*S**,6*S**)-6-(Acetylamino)-3-(4-methoxybenzyl)-3-azabicyclo[3.2.1]octane-6-carboxylate *exo*-5a:** Mp 143−145 °C (benzene); IR ν_{max} 3344, 1737, 1637 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16, 6.84 (AA′XX′ system, J = 8.4 Hz, 4 H), 6.44 (s, 1 H, exch.), 3.78 (s, 3 H), 3.67 (s, 3 H), 3.55, 3.17 (AB system, J = 12.5 Hz, 2 H), 2.83−2.75 (m, 1 H), 2.72 (br s, 1 H), 2.56−2.50 (m, 1 H), 2.40−2.30 (m, 2 H), 2.20 (br s, 1 H), 2.03−1.98 (m, 2 H), 1.72 (dd, J = 13.5, 2.5 Hz, 1 H), 1.57 (s, 3 H), 1.50 (dd, J = 11.1, 2.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 174.4, 171.0, 159.2, 130.6, 130.6, 114.2, 65.9, 62.2, 61.0, 55.6, 54.9, 52.5, 43.0, 40.0, 37.1, 34.7, 22.5; *m*/*z* 347.3 [M^+]. Anal. Calcd for $C_{19}H_{26}N_2O_4$: C, 65.87; H, 7.56; N, 8.09. Found: C, 65.85; H, 7.55; N, 8.06.

Methyl (1*R,5*R**,6*S**)-6-(Acetylamino)-3-(4-methoxybenzyl)-3-azabicyclo[3.2.1]octane-6-carboxylate *endo*-5a:** Mp 155−157 °C (benzene); IR ν_{max} 3265, 1747, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23, 6.84 (AA′XX′ system, J = 8.5 Hz, 4 H), 5.72 (s, 1 H, exch.), 3.80 (s, 3 H), 3.69 (s, 3 H), 3.42, 3.33 (AB system, J = 13.0 Hz, 2 H), 3.01 (dd, J = 13.9, 1.8 Hz, 1 H), 2.84 (d, J = 10.2 Hz, 1 H), 2.71 (d, J = 8.4 Hz, 1 H), 2.30 (br s, 1 H), 2.30−1.85 (m, 5 H), 1.96 (s, 3 H), 1.51 (dd, J = 11.3, 2.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 172.5, 169.7, 159.0, 131.1, 130.4, 113.9, 68.5, 62.0, 59.0, 55.9, 55.6, 52.5, 46.8, 39.9, 37.1, 35.1, 23.7; *m*/*z* 347.3 [M^+]. Anal. Calcd for $C_{19}H_{26}N_2O_4$: C, 65.87; H, 7.56; N, 8.09. Found: C, 65.91; H, 7.54; N, 8.08.

(−)-Phenylmenthyl (1*S*,5*S*,6*S*)-6-(Acetylamino)-3-(4-methoxybenzyl)-3-azabicyclo[3.2.1]octane-6-carboxylate *exo*-5b: Mp 186 °C (*i*-Pr_2O); $[\alpha]^{25}_D$ = −46.5° (*c* 5.24, $CHCl_3$); IR ν_{max} 3400, 1730, 1657 cm^{-1}; ^{1} H NMR ($CDCl_3$) δ 7.28−7.08 (m, 6 H), 7.08−6.98 (m, 1 H), 6.86 (d, J = 8.4 Hz, 2 H), 5.94 (s, 1 H, exch.), 4.81−4.65 (m, 1 H), 3.80 (s, 3 H), 3.54, 3.16 (AB system, J = 12.5 Hz, 2 H), 2.90−2.70 (m, 1 H), 2.65−2.00 (m, 4 H), 2.00−1.80 (m, 2 H), 1.60−0.70 (m, 11 H), 1.58 (s, 3 H), 1.30 (s, 3 H), 1.19 (s, 3 H), 0.83 (d, J = 6.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.3, 170.6, 159.2, 151.7, 131.0, 130.5, 128.1, 125.9, 125.2, 114.1, 76.7, 66.2, 62.2, 60.9, 55.6, 54.8, 50.4, 42.1, 41.1, 40.3, 36.7, 34.9, 34.7, 31.5, 28.4, 27.6, 25.0, 23.1, 22.7, 22.0; *m*/*z* 547.3 [M^+]. Anal. Calcd for $C_{34}H_{46}N_2O_4$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.53; H, 8.50; N, 5.09.

(−)-Phenylmenthyl (1*R*,5*R*,6*S*)-6-(Acetylamino)-3-(4-methoxybenzyl)-3-azabicyclo[3.2.1]octane-6-carboxylate *endo*-5b: Mp 86 °C (CH_2Cl_2/*i*Pr_2O); $[\alpha]^{25}_D$ = −3.5° (*c* 6.4, $CHCl_3$); IR ν_{max} 3400, 1730, 1657 cm^{-1}; ^{1} H NMR ($CDCl_3$) δ 7.42−7.05 (m, 6 H), 7.05−6.95 (m, 1 H), 6.88 (d, J = 8.8 Hz, 2 H), 5.42 (s, 1 H, exch.), 4.78−4.66 (m, 1 H), 3.82 (s, 3 H), 3.55, 3.22 (AB system, J = 13.0 Hz, 2 H), 2.90−2.80 (m, 1 H), 2.58−162 (m, 10 H), 1.57 (s, 3H), 1.58−0.70 (m, 7 H), 1.29 (s, 3 H), 1.15 (s, 3 H), 0.84 (d, J = 6.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.0, 169.4, 158.8, 152.3, 131.0, 130.2, 128.1, 125.8, 125.2, 113.7, 77.3, 68.5 61.5, 58.1, 55.7, 55.4, 50.2, 41.1, 40.3, 39.1, 37.1, 35.0, 34.6, 31.6, 28.3, 27.6, 25.4, 23.5, 23.1, 22.1; *m*/*z* 547.3 [M^+]. Anal. Calcd for $C_{34}H_{46}N_2O_4$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.50; H, 8.51; N, 5.07.

General Procedure for the Oxidative Deprotection of 5a. To a solution of compound **5a** (346 mg, 1 mmol) in acetone/H_2O (23 mL, 9:1) at 0 °C was added $(NH_4)_2Ce(NO_3)_6$ (2.19 g, 4 mmol) in several portions in 1 h. The mixture was stirred at room temperature for 3 h and quenched with a saturated solution of $NaHCO_3$ (pH 10). A solid was formed. Acetone was evaporated, and the aqueous layer was filtered through a Celite pad. After elution with warm EtOH, the organic solution was concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (CH_2Cl_2/MeOH/NH_4OH = 5:1:0.025). Compound **6** (*exo*-**6a**, 204 mg, 90%; *endo*-**6a**, 141 mg, 62%) was isolated after recrystallization.

Methyl (1*S,5*S**,6*S**)-6-(Acetylamino)-3-azabicyclo[3.2.1]-octane-6-carboxylate *exo*-6a:** Mp 110 °C dec (EtOH); IR ν_{max} 3400, 1727, 1632 cm^{-1}; ^1H NMR (D_2O) δ 3.58 (s, 3 H), 3.10 (br s, 4 H), 2.86 (br s, 1 H), 2.55 (dd, J = 15.4, 7.3 Hz, 1 H), 2.39 (br s, 1 H), 2.11−1.98 (m, 1 H), 1.92 (s, 3 H), 1.83 (dd, J = 15.4, 3.0 Hz, 1 H), 1.71 (dd, J = 12.5, 2.6 Hz, 1 H); ^{13}C NMR (D_2O) δ 176.5, 175.5, 65.0, 53.5, 49.2, 45.9, 39.2, 38.8, 34.2, 32.0, 21.9; *m*/*z* 227.2 [M^+]. Anal. Calcd for $C_{11}H_{18}N_2O_3$: C, 58.39; H, 8.02; N, 12.38. Found: C, 58.21; H, 8.18; N, 12.22.

Methyl (1*R,5*R**,6*S**)-6-(Acetylamino)-3-azabicyclo[3.2.1]-octane-6-carboxylate *endo*-6a:** Mp 99 °C dec (EtOH); IR ν_{max} 3420, 1720, 1645 cm^{-1}; ^1H NMR (D_2O) δ 3.66 (s, 3 H), 3.21 (d, J = 12.5 Hz, 1H), 3.18−3.00 (m, 3 H), 2.56 (d, J = 15.7 Hz, 1 H), 2.47 (br s, 2 H), 2.21−2.00 (m, 2 H), 1.93 (s, 3 H), 1.75 (d, J = 12.5 Hz, 1 H); ^{13}C NMR (D_2O) δ 175.1, 173.9, 66.9, 53.9, 49.6, 45.8, 42.3, 39.8, 34.4, 32.5, 21.7; *m*/*z* 227.1 [M^+]. Anal. Calcd for $C_{11}H_{18}N_2O_3$: C, 58.39; H, 8.02; N, 12.38. Found: C, 58.30; H, 8.20; N, 12.14.

6-Acetylamino-3-(4-methoxybenzyl)-3-azabicyclo[3.2.1]octane-6-carboxylic Acid (±)-7: Operating in a sealed tube, compound **5a** (346 mg, 1 mmol) was dissolved in EtOH (95%, 5 mL), and KOH (112.2 mg, 2 mmol) was added. The solution was heated at 120 °C under stirring for 2 h. The reaction mixture was treated with HCl (6 N, pH 7), and the solvent was removed. The crude material was filtered through a pad of silica gel with CH_2Cl_2/CH_3-OH (5:2). Crystallization from absolute EtOH afforded the pure carboxylic acid derivative **7** [(±)-*exo*-**7** (315 mg, 95%); (±)-*endo*-**7** (330 mg, 99%)].

(1*S,5*S**,6*S**)-(±)-*exo*-7:** Mp 200 °C (EtOH); IR ν_{max} 3412, 1740, 1661 cm^{-1}; ^1H NMR (CD_3OD) δ 7.61, 7.00 (AA′XX′ system, J = 8.4 Hz, 4 H), 4.42, 4.01 (AB system, J = 11.0 Hz, 2 H), 3.83 (s, 3H), 3.56, 3.17 (AB system, J = 11.0 Hz, 2 H), 3.10−1.90 (br s, 2 H), 2.81 (d, J = 12.2 Hz, 1 H), 2.63 (d, J = 14.2 Hz, 1 H), 2.50 (br s, 1 H), 2.41 (dd, J = 14.7, 7.0 Hz, 1 H), 2.38−2.29 (m, 1 H), 1.92 (s, 3 H), 1.78 (d, J = 11.2 Hz, 1 H); ^{13}C NMR (CD_3-OD) δ 176.9, 172.7, 160.2, 131.5, 120.9, 113.4, 65.0, 59.7, 57.6, 53.8, 53.0, 40.0, 36.4, 33.9, 32.8, 20.9; *m*/*z* 333.2 [M^+]. Anal. Calcd for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43. Found: C, 65.12; H, 7.38; N, 8.50.

(1*R,5*R**,6*S**)-(±)-*endo*-7:** Mp 202 °C dec (EtOH); IR ν_{max} 3435, 1613, 1516 cm^{-1}; ^1H NMR (CD_3OD) δ 7.42, 6.98 (AA′XX′ system, J = 8.4 Hz, 4 H), 4.16, (br s, 2 H), 3.80 (s, 3 H), 3.40−3.20 (m, 3 H), 3.11 (d, J = 12.1 Hz, 1 H), 2.66 (d, J = 15.0 Hz, 1 H), 2.53 (br s, 2 H), 2.30−2.02 (m, 2 H), 1.92 (s, 3 H), 1.88 (d, J = 11.5 Hz, 1 H); ^{13}C NMR (CD_3OD) δ 177.2, 170.9, 160.2, 131.1, 120.7, 113.6, 67.6, 58.7, 56.2, 54.4, 53.8, 42.3, 41.2, 33.8, 33.6, 20.8; *m*/*z* 333.3 [M^+]. Anal. Calcd for $C_{18}H_{24}N_2O_4$: C, 65.04; H, 7.28; N, 8.43. Found: C, 65.00; H, 7.30; N, 8.39.

General Procedure for the Hydrolysis of Amino Acid Function. (i) Operating in a sealed tube, compounds (±)-*exo*-**5a**,**6a or** (±)-*endo*-**5a**,**6a** (1 mmol) were suspended in HCl (1 mL, 6 M), and the mixture was heated at 120 °C for 24 h. The solvent was removed, and the crude amino acids (±)-*exo*-**8** (mixture of conformers 7:1), *exo*-**9**, and (±)-*endo*-**8**,**9** were isolated as bischlorohydrate in quantitative yield. (ii) Operating in a sealed tube, MeOH (5 mL) was cooled at 0 °C, and Na (161 mg, 7 mmol) was added. Compound **5b** (546.7 mg, 1 mmol) was added, and the mixture was heated at 100 °C under stirring for 50 h (TLC, CH_2-Cl_2/MeOH, 50:1). The solvent was removed, and the crude reaction mixture was taken up with distilled H_2O (5 mL) and extracted with AcOEt (3 × 10 mL). The aqueous solution was treated with HCl (6 N, pH 1) and was purified by a Dowex 50W × 4−50

ion-exchange resin which was first activated with NH_4OH (2 N) then with AcOH (2 N, pH 4) followed by washing with H_2O (pH 7). The reaction mixture was deposited on the resin which was rinsed with water. The amino acid was eluted with aqueous NH_4OH (2 N). Ninhydrin positive fractions (TLC, CH_2Cl_2/MeOH/NH_4OH-(15%) = 5:3:0.9) were pooled and evaporated to give (−)-*exo*-**8** (130 mg, 45%) from (−)-*exo*-**5b** and (−)-*endo*-**8** (172 mg, 60%) from (−)-*endo*-**5b**.

6-Amino-3-(4-methoxybenzyl)-3-azabicyclo[3.2.1]octane-6-carboxylic Acids: (1*S,5*S**,6*S**)** (±)-***exo*-8·2 HCl:** mixture of isomers (8:1); mp 176 °C (acetone/H_2O); IR ν_{max} 3470−3370, 1742, 1614 cm^{-1}; ^1H NMR (D_2O) δ (major isomer) 7.32, 6.92 (AA′BB′ system, J = 8.8 Hz, 4 H), 4.29, 4.13 (AB system, J = 12.8 Hz, 2 H), 3.70 (s, 3 H), 3.52, 3.37 (AB system, J = 14.3 Hz, 2 H), 3.15 (br s, 2 H), 2.70−2.55 (m, 2 H), 2.52−2.48 (m, 1 H), 2.30−2.10 (m, 1 H), 1.62 (d, J = 4.0 Hz, 1 H), 1.56 (d, J = 8.4 Hz, 1 H); (minor isomer (significative signals)) 7.18, 6.80 (AA′BB′ system, J = 8.8 Hz, 4 H); ^{13}C NMR (D_2O) δ 173.1, 160.5, 133.3 (133.5), 120.3, 114.5 (115.9), 64.6, 61.9, 57.5, 55.5, 52.5, 41.5, 33.8, 33.0, 32.5; *m*/*z* 291.8 [M^+]. Anal. Calcd for $C_{16}H_{24}Cl_2N_2O_3$: C, 52.90; H, 6.66; N, 7.71. Found: C, 52.50; H, 7.00; N, 7.28.

(1*S*,5*S*,6*S*) (−)-*exo*-8: $[\alpha]^{25}_D$ = −36.3° (*c* 3.7, MeOH).

(1*R,5*R**,6*S**) (±)-*endo*-8·2 HCl:** mixture of isomers (3:1); mp 220−221 °C (EtOH); IR ν_{max} 3405−2950, 1725, 1614 cm^{-1}; ^1H NMR (D_2O) δ (major isomer) 7.35, 7.01 (AA′BB′ system, J = 8.8 Hz, 4 H), 4.18, 4.12 (AB system, J = 13.1 Hz, 2 H), 3.79 (s, 3 H), 3.44, 3.16 (AB system, J = 11.2 Hz, 2 H), 3.28−3.13 (m, 2 H), 2.71 (br s, 1 H), 2.66 (br s, 1 H), 2.46 (dd, J = 15.7, 2.1 Hz, 1 H), 2.17 (dd system, J = 15.7, 7.2 Hz, 1 H), 2.09−2.07 (m, 1 H), 1.94 (d, J = 13.5 Hz, 1 H); (minor isomer (significative signals)) 7.28, 6.90 (AA′BB′ system, J = 8.8 Hz, 4 H); ^{13}C NMR (D_2O) δ 174.6, 160.3, 132.4 (132.2), 121.3 (120.6), 114.9 (116.2), 67.1, 59.96 (60.03), 56.99 (56.93), 55.5, 54.5, 42.8, 38.9, 34.2, 33.9; *m*/*z* 291.8 [M^+]. Anal. Calcd for $C_{16}H_{24}Cl_2N_2O_3$: C, 52.90; H, 6.66; N, 7.71. Found: C, 52.53; H, 7.69; N, 7.29.

(1*R*,5*R*,6*S*) (−)-*endo*-8: $[\alpha]^{25}_D$ = −14.0° (*c* 4.25, MeOH).

(1*S,5*S**,6*S**)-6-Amino-3-azabicyclo[3.2.1]octane-6-carboxylic Acid 2 HCl (±)-*exo*-9:** IR ν_{max} 3600−2950, 1695, 1626 cm^{-1}; ^1H NMR (2·HCl salt D_2O) δ 3.51 (dd, J = 14.6, 3.1 Hz, 1 H), 3.45 (dt, J = 14.6, 2.2 Hz, 1 H), 3.37−3.24 (m, 2 H), 2.89 (dd, J = 15.9, 8.0 Hz, 1 H), 2.78 (br s, 1 H), 2.62 (br s, 1 H), 2.45−2.28 (m, 1 H), 1.85 (dd, J = 15.9, 1.9 Hz, 1 H), 1.79 (dd, J = 13.0, 2.1 Hz, 1 H); ^{13}C NMR δ 172.6, 63.1, 48.9, 42.9, 39.6, 33.6, 32.2, 31.0; *m*/*z* 172.2 [M^+]. Anal. Calcd for $C_8H_{16}Cl_2N_2O_2$: C, 39.52; H, 6.63; N, 11.52. Found: C, 39.05; H, 6.96; N, 11.30.

(1*R,5*R**,6*S**)-6-Amino-3-azabicyclo[3.2.1]octane-6-carboxylic Acid 2 HCl (±)-*endo*-9:** IR ν_{max} 3600−2950, 1697, 1627 cm^{-1}; ^1H NMR (D_2O) δ 3.35 (dt, J = 12.7, 2.4 Hz, 1 H), 3.27 (br s, 2 H), 3.23 (d, J = 12.7 Hz, 1 H), 2.71 (br s, 1 H), 2.68 (br s, 1 H), 2.57 (dd, J = 15.9, 2.1 Hz, 1 H), 2.24 (dd, J = 15.9, 7.4 Hz, 1 H), 2.20−2.12 (m, 1 H), 1.98 (dd, J = 13.2, 2.1 Hz, 1 H); ^{13}C NMR (D_2O) δ 173.2, 66.3, 48.4, 45.7, 41.4, 37.7, 33.2, 32.6; *m*/*z* 172.2 [M^+]. Anal. Calcd for $C_8H_{16}Cl_2N_2O_2$: C, 39.52; H, 6.63; N, 11.52. Found: C, 39.01; H, 6.98; N, 11.28.

(1*S,5*S**,6*S**) Methyl 6-Amino-3-azabicyclo[3.2.1]octane-6-carboxylate (±)-*exo*-10:** Amino acid *exo*-**9** (53 mg, 0.31 mmol) was dissolved in MeOH (3 mL), and $SOCl_2$ was added (100 μL, 0.62 mmol), and the mixture was refluxed for 5 h. After cooling, the reaction mixture was treated with a saturated solution of $NaHCO_3$ (pH 10). The solid was filtered, and the solution, after solvent evaporation of the solvent, was chromatographed on silica gel (CH_2Cl_2/MeOH/NH_4OH(15%) = 25:5:0.1). Compound (±)-*exo*-**10** was isolated and crystallized (51 mg, 89%): Mp 250 °C dec (EtOH); IR ν_{max} 3466, 1731, 1637 cm^{-1}; ^1H NMR (D_2O) δ 3.77 (s, 3 H), 3.30−3.05 (m, 4 H), 2.57 (br s, 1 H), 2.40−1.95 (m, 4 H), 1.75 (dd, J = 12.4, 1.8 Hz, 1 H); ^{13}C NMR δ 175.8, 81.3, 53.0, 49.0, 44.8, 44.3, 40.9, 33.4, 31.8. Anal. Calcd for $C_9H_{16}N_2O_2$: C, 58.67; H, 8.75; N, 15.21. Found: C, 56.60; H, 8.78; N, 15.18.

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Supporting Information Available: General technique, NMR discussion for compounds **5a**, and ^1H and ^{13}C NMR spectra of **2**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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