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An Efficient Synthesis of the Constrained Peptidomimetic 2-Oxo-3-(*N*-9-fluorenyloxycarbonylamino)-1-azabicyclo[4.3.0]nonane-9-carboxylic Acid from Pyroglutamic Acid

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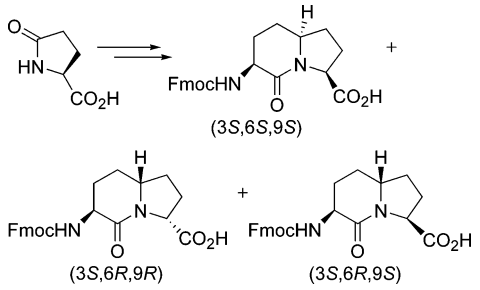

Azabicyclo[*X*.*Y*.0]alkane amino acids are rigid dipeptide mimetics that are useful tools for structure−activity studies in peptide-based drug discovery. Herein, we report an efficient synthesis of three diastereomers of 9-*tert*-butoxycarbonyl-2-oxo-3-(*N*-*tert*-butoxycarbonylamino)-1-azabicyclo-[4.3.0]nonane (3*S*,6*S*,9*S*, 3*S*,6*R*,9*R*, and 3*S*,6*R*,9*S*). Methyl *N*-Boc-pyroglutamate is cleaved with vinylmagnesium bromide to produce an acyclic γ-vinyl ketone. Michael addition of *N*-diphenylmethyleneglycine *tert*-butyl ester produces the *N*-Boc-δ-oxo-α,ω-diaminoazelate intermediate, which, on hydrogenloysis, gives the fused ring system. Acidolytic deprotection followed by Fmoc-protection provided building blocks suitable for solid-phase synthesis.

Considerable effort has been applied to the synthesis of conformationally restricted peptides and peptidomimetics and the study of their effects on biological activity.[1] In this area, azabicyclo[*X*.*Y*.0]alkane amino acids (Figure 1, AZABIC Type **I**) are particularly attractive

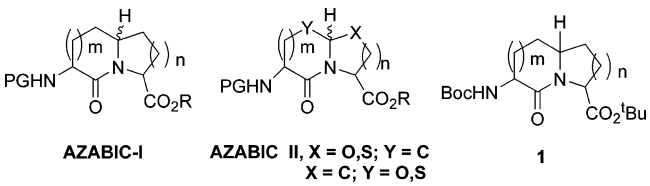

FIGURE 1. Structure of azabicyclo[*X*.*Y*.0]-alkane amino acids.

because of their rigid conformations that are able to constrain the φ_i, ω, and ψ_{i+1} backbone dihedral angles within the bicyclic framework.[2] Heterosubstituted AZABIC analogues (type **II**) have also been reported.[3] The growing use of these mimetics in the investigation of stucture-activity relationships of biologically active peptides has created a demand for new, efficient methodology for their synthesis. In connection with an ongoing program on the development of peptide-based inhibitors of signal transduction enzymes, we were interested in dipeptide mimetics of AZABIC type I, where $m = 1$, $n = 1$, and azabicyclo[4.3.0]nonane **1** and its homologues where $m = 2$, 3 and $n = 1$.[4]

Though many methods have been reported for the synthesis of azabicyclo[4.3.0]nonane **1** and its analogues,[2,5] the majority of approaches suffer from relatively long reaction sequences, thus limiting practical accessibility. Here we report an efficient strategy for synthesis of three stereoisomers of lactam **1** starting with inexpensive and commercially available pyroglutamic acid.

A number of the published methods for the synthesis of **1** center on intramolecular reductive amination and lactam cyclization of appropriately *N*-deprotected δ-oxo-α,ω-diaminoazelates (**2**, Scheme 1). Thus, the preparation of **2** is the key to the synthetic scheme.

Two general methods have been reported for the synthesis of **2**. In the first, symmetrical ketones, protected as 1,3-dioxolanes, were alkylated with glycine equivalents, which were then unmasked to provide 5-oxodiaminoazelates. Mueller and Revesz[5a] alkylated 2 mol of the

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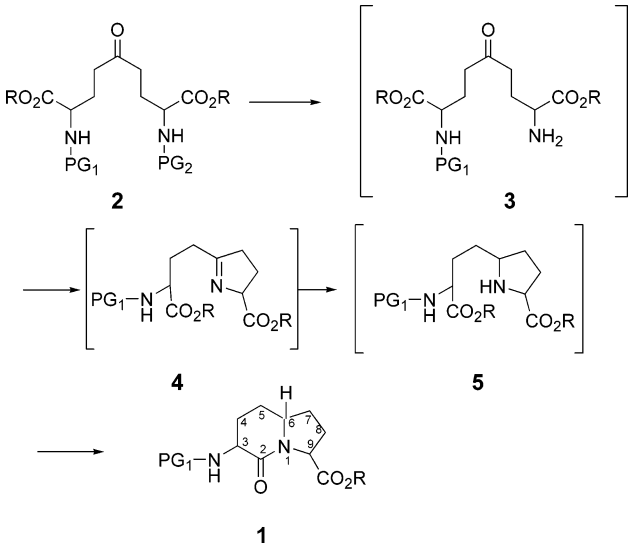
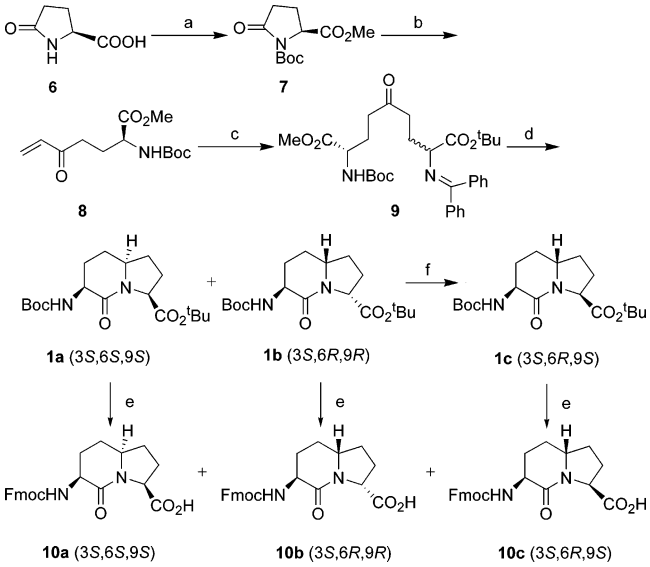
SCHEME 1



SCHEME 2[a]



[a] Key: (a) (i) MeOH, $SOCl_2$, DMF(cat), rt, 4 h, (ii) $(Boc)_2O$, DIEA, DMAP, dry DMF, rt 3 h, 90%; (b) vinylmagnesium bromide, THF, −40°C to rt, 3 h, 80%; (c) $(Ph)_2{=}NCH_2CO_2{}^tBu$, Cs_2CO_3, THF, 74%; (d) 10% Pd−C, 9:1 EtOH/AcOH, 24 h, 68% (e) (i) TFA, Et_3SiH, CH_2Cl_2, (ii) Fmoc-OSu, 10% Na_2CO_3, 1,4-dioxane, 12 h, 74%; (f) NaHMDS (50%).

Schöllkopf bislactim ether with bis-iodethyl 1,3-dioxolane to prepare a masked azelate. Acid hydrolysis gave dimethyl 5-oxo-2,6-diamino azelate ready for reductive amination/ring closure. This methodology required multistep preparation of the diiodoethyl dioxolane, and although the alkylation was highly stereoselective, it was not stereospecific. In a similar method, Wang et al.[5g] reduced 1,3-dioxolane-protected diethyl 1,3-acetonedicarboxylate to the corresponding dialdehyde, which was extended with Horner−Emmons olefination with $(MeO)_2P(O)CH(NHCbz)CO_2Me$ to give 2,7-didehydro **2**. The diene was reduced to (2*S*,7*S*) or (2*R*,7*R*) diastereomers by stereoselectve hydrogenation using Burk's chiral rhodium catalysts. Conversion to **1** was accomplished by hydrogenation over palladium on charcoal. The second approach involved Claisen condensation of glutamic acid derivatives. Lubell and colleagues[5b] condensed two identical *N*-[9-(9-phenylfluorenyl)}glutamate molecules which was followed by decarboxylation of the β-ketoester to achieve the 5-oxoazelate. Hydrogenolysis of the 9-(9-phenylfluorenyl) protecting groups was accompanied by reductive amination and cyclization to give **1**. Kahn et al.[5f] adopted a similar approach, but condensed glutamates with different amino group protection to give an asymmetric azelate, which was then taken on to azabic synthesis. While these methods were elegant, the multistep sequences, expensive catalysts, and "nonstandard" protecting groups (in some cases) can limit practical application.

Our approach to the synthesis of diaminoazelate **(2)** is based on a simple Michael addition of glycine ester to an enone analogue of glutamic acid, derived from commercially available, inexpensive pyroglutamic acid (Scheme 2). Thus, Michael acceptor **8** was prepared by ring opening of methyl *N*-Boc-pyroglutamate **7**[6] with vinyl Grignard (1.1 equiv).[7] The reaction occurred regiospecifically to give exclusively the enone amino acid derivative. Freshly prepared vinyl Grignard reagent gave cleaner products and better yields than commercially available material.

Michael addition of Schiff base, *tert*-butyl *N*-(diphenylmethylene)glycinate,[8] to **8** in the presence of Cs_2CO_3 in THF[9] gave the target 5-oxo diaminoazelate, **9**. This compound, being very susceptible to acidolysis of the diphenylmethylene group, was obtained in 74% yield after rapid neutral alumina chromatography as a mixture of two inseparable diastereomers with >95% purity. Hydrogenation with 10% palladium-on-carbon in 9:1 EtOH/AcOH for 24 h accomplished amino group deprotection, reductive amination of the ketone, and lactamization to give a 1:1 diastereomeric mixture of fully protected azabicycloalkane, *tert*-butyl-2-oxo-3-[*N*-*tert*-butoxycarbonylamino]-1-azabicyclo[4.3.0]nonane-9-carboxylate **1a** and **1b** in 70% overall yield. The two diastereomers were readily separated by silica gel chromatography with 40% EtOAc/hexanes as the eluant.

Crystallization of **1a** was fruitless, thus precluding stereochemical assignment by X-ray crystallography. However, NMR and optical rotation data were in excellent agreement with that of the (3*S*,6*S*,9*S*) isomer reported by Scolastico and colleagues.[5j] Diastereomer **1b** gave good crystals from hexanes−ether, and its structure was determined by X-ray crystallography to be (3*S*,6*R*,9*R*) (Figure S1, Supporting Information). The stereochemistry of the hydrogenation of the five-membered ring of these mimetics provided *cis* arrangement of the 2 and 5 substituents, in agreement with that reported by Werf and Kellog for 1,5-dehydropyrrolidines.[9]

The (3*S*,6*R*,9*S*) diastereomer (**1c**) was prepared by epimerization of C(9) of **1b** using NaHMDS in a 1:1

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diastereomeric ratio.[3c] These isomers were inseparable using standard silica gel chromatography but were readily separated using C18 reversed-phase HPLC. NMR and optical rotation were in excellent agreement with the (3*S*,6*R*,9*S*) diastereomer reported by Scolastico and colleagues.[5j]

Each diastereomer of **1** was then converted to the corresponding *N*-Fmoc derivative (**10**) by TFA hydrolysis of the Boc and *tert*-butyl ester groups followed by treatment with Fmoc-OSu.[10]

In conclusion, we have described an efficient route to synthesize three stereoisomers of azabicyclo[4.3.0]nonane amino acid ester **1** through a facile pyroglutamate ring opening, followed by Michael addition, reductive amination, and lactam cyclization. Further research on asymmetric synthesis of stereoisomers of **1** and their application in a series of azabicyclic dipeptide analogues is in progress and will be reported in due course.

Experimental Section

Synthesis of Methyl 5-Oxo-2-(*tert*-butoxycarbonylamino)hept-6-enoate 8. Freshly prepared vinylmagnesium bromide (8 mL, 5.0 mmol) in THF was added to methyl *N*-Boc-pyroglutamate, prepared as in ref 5 (**7**, 1.0 g, 4.11 mmol), in dry THF (20 mL) at −40 °C under argon. After 3 h of stirring, the reaction was quenched with AcOH−MeOH (1:1, 5.0 mL) and the mixture diluted with ether. The phases were separated, and the Et_2O layer was washed with water, dried ($MgSO_4$), and evaporated. The residue was purified by silica gel chromatography (25% EtOAc−hexane) yielding 890 mg of **8** (80%) as an oil: IR $\nu^{CH_2Cl_2}$ 3300, 1744, 1711, 1680, 1616; ^{1}H NMR (300 Hz, $CDCl_3$) δ1.43 (s, 9H), 1.92−1.99 (m, 1H), 2.15−2.22 (m, 1H), 2.66−2.78 (m, 2H), 3.74 (s, 3H), 4.32 (m, 1H), 5.14 (brs, 1H), 5.85 (dd, 1H, J = 1.2 and 9.00 Hz), 6.2−6.4 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.6, 28.3, 35.4, 52.4, 53.0, 80.0, 128.4, 136.3, 155.4, 172.8, 199.2.

Synthesis of (2*S*,8*R*/*S*)-Methyl 2-*tert*-Butoxycarbonylamino-5-oxo-8-(diphenylmethylenimino)nonanoate 9. To a stirred solution of enone **8** (1.0 gm, 3.68 mmol) and *tert*-butyl *N*-(diphenylmethylene)glycinate (1.2gm, 4.05 mmol) in dry THF (20 mL) was added Cs_2CO_3 (1.2 gm, 3.68 mmol). The reaction was monitored by TLC. Upon completion, THF was removed in vacuo and the residue diluted with 200 mL of ether. The organic layer was washed with water, followed by brine, and dried (Na_2SO_4), and the solvents were evaporated. Quick neutral alumina filtration resulted in an equimolar mixture of diasteromers **9** (1.55 gm, 74%) as a viscous oil: ^{1}H NMR (300 Hz, $CDCl_3$) δ 1.42 (s, 9H), 1.43 (s, 9H), 1.79−1.87 (m, 1H), 2.04−2.18(m, 3H), 2.42−2.56(m, 4H), 3.71 (s, 3H), 3.94 (t, 1H, J = 6.0 Hz), 4.24 (m, 1H), 5.07 (brs, 1H), 7.15−7.17(m, 2H), 7.31−7.45 (m, 6H), 7.60−7.63 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.4, 27.7, 28.0, 28.3, 38.4, 39.0, 52.3, 52.9, 64.7, 79.9, 81.1, 127.7, 128.0, 128.5, 128.6, 128.7, 130.0, 136.4, 139.4, 155.4, 170.5, 170.9, 172.9, 208.8; mass calcd for $C_{32}H_{42}N_2O_7$ 566.3, found 566.9.

Synthesis of (2*S*,6*S*,9*S*)/(2*S*,6*R*,9*R*)-*tert*-Butyl 2-Oxo-3-(*tert*-butoxycarbonylamino)-1-azabicyclo[4.3.0]nonane-9-carboxylate 1a and 1b. A solution of ketone **9** (1.0 gm, 1.76 mmol) in 20 mL of 9:1 EtOH/AcOH was hydrogenated under 30 psi pressure of H_2 in the presence of palladium-on-carbon (100 mg, 10 wt %) for 24 h. The reaction mixture then diluted with 20 mL of EtOH, filtered through a pad of Celite, and washed with additional EtOH. After the solvent was removed, AcOH was removed azeotropically by adding and evaporating toluene (3 × 10 mL). The crude mixture of diasteromers was separated by silica gel chromatography (40% EtOAc−hexane).

1a: yield 208 mg (33%) $[\alpha]^{20}_D$ −12.1 (*c* 1.32, $CHCl_3$); ^{1}H NMR (300 Hz, $CDCl_3$) δ 1.44 (s, 9H), 1.46(s, 9H), 1.66−1.72 (m, 3H), 2.00−2.21 (m, 4H), 2.43−2.48 (m, 1H), 3.69 (m, 1H), 4.11 (m, 1H), 4.37 (d, 1H, J = 7.8 Hz), 5.58 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.8, 27.1, 27.9, 28.3, 29.1, 32.1, 49.9, 56.3, 59.1, 79.3, 81.4, 155.6, 168.8, 170.7; mass calcd for $C_{18}H_{30}N_2O_5$ (M + H^+) 355.215, found 355.206; HPLC t_R 25.54 (A).

1b: yield 242 mg (38%); $[\alpha]^{20}_D$ 32.7 (*c* 1.32, $CHCl_3$); ^{1}H NMR (300 Hz, $CDCl_3$) δ 1.37 (s, 9H), 1.39 (s, 9H), 1.56−2.07 (m, 7H), 2.44 (m, 1H), 3.54 (m, 1H), 3.83 (m, 1H), 4.26 (d, 1H, J = 9.3 Hz), 5.23 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.8, 27.9, 28.3, 28.5, 31.5, 52.250, 59.6, 60.6, 81.6, 155.9, 168.8, 170. 7; mass calcd for $C_{18}H_{30}N_2O_5$ (M + H^+) 355.215, found 355.214; HPLC t_R 22.63 (A).

Synthesis of (2*S*,6*R*,9*S*)-*tert*-Butyl 2-Oxo-3-(*tert*-butoxycarbonylamino)-1-azabicyclo[4.3.0]nonane-9-carboxylate 1c. To a stirred solution of **1b** (400 mg, 1.12 mmol) in 10 mL of dry THF, at −78 °C, was added $NaN(SiMe_3)_2$ (2.24 mL, 2.24 mmol, 1 M in THF) over a period of 10 min. Stirring was continued for 2 h. The reaction was quenched with 1 M NaH_2PO_4 (10 mL) followed by 10 mL of EtOAc. The aqueous portion was extracted with EtOAc (3 × 10 mL). The combined organic parts were then washed with brine, dried (Na_2SO_4), and evaporated. A gummy oil, as a 1:2 ratio of **1b** (3*S*,6*R*,9*R*)/**1c** (3*S*,6*R*,9*S*), as determined by ^{1}H NMR and by HPLC, was obtained. Product **1c** was then purified by C18 reversed-phase HPLC: yield 140 mg (35%); $[\alpha]^{20}_D$ −92.1 (*c* 1.6, $CHCl_3$); mass calcd for $C_{18}H_{30}N_2O_5$ (M + H^+) 355.215, found 355.22; ^{1}H NMR (300 Hz, $CDCl_3$) δ 1.44 (s, 9H), 1.47(s, 9H), 1.72−1.82 (m, 3H), 2.05−2.15 (m, 3H), 2.33−2.56 (m, 2H) 3.70(m, 1H), 4.02 (m, 1H), 4.35 (t, 1H, J = 7.8 Hz), 5.30 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 27.5, 27.8, 27.9, 28.3, 28.7, 32.8, 52.1, 58.6, 60.1, 79.4, 81.4, 156.1, 167.6, 171.4; HPLC t_R 24.74 (A).

Synthesis of (2*S*,6*S*,9*S*)-2-Oxo-3-(9-fluorenyloxycarbonylamino)-1-azabicyclo[4.3.0]nonane-9-carboxylic Acid 10a. Compound **1a** (300 mg, 0.85 mmol) was treated with 3.0 mL of 95:5 TFA/:TES in 2.0 mL of dichloromethane for 1 h. The solvent was removed, and excess TFA was stripped off with toluene (3 × 5 mL). The residue was dissolved in 10 mL of 1,4-dioxane. Fmoc-OSu (320 mg, 0.94 mmol) was added followed 10 mL of 10% aqueous Na_2CO_3. Stirring was continued overnight. The dioxan was removed in vacuo, and the aqueous solution was extracted with ether (2 × 20 mL). The aqueous solution was acidified, and the product was extracted with EtOAc (3 × 20 mL). The organic phase was washed with brine, dried (Na_2SO_4), and evaporated. Tituration with ether−hexane gave **6a** (265 mg, 74%) as white solid: ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.52−1.60 (m, 2H), 1.64−1.70 (m, 1H), 1.91−2.05 (m, 2H), 2.08−2.16 (m, 3H), 3.75 (m, 1H), 4.12 (m, 1H), 4.22−4.44 (m, 4H), 7.32−7.35 (m, 2H), 7.41−7.45 (m 3H), 7.73−7.76 (m, 2H), 7.895 (d, 2H, J = 8 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 26.2, 27.4, 29.2, 32.1, 47.1, 50.1, 56.5, 58.4, 66.2, 120.5, 125.9, 127.5, 128.1, 141.2, 144.3, 144.4, 156.6, 168.7, 173.5; mass calcd for $C_{24}H_{25}N_2O_5$ (M + H^+) 421.176, found 421.165; HPLC t_R 16.81 (B).

10b. Prepared as for **10a**: yield 82%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.45−1.55 (m, 2H), 1.80−1.87 (m, 2H), 1.97−2.12 (m, 4H), 3.53 (m, 1H), 3.83 (m, 1H), 4.15 (d, 1H, J = 9.5 Hz), 4.21−4.31 (m, 3H), 7.32−7.35 (m, 2H), 7.38−7.45 (m, 2H), 7.55 (d, 1H, J = 8.00 Hz), 7.70 (d, 2H, J = 2.5 Hz), 7.89 (d, 2H, J = 7.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 26.7, 27.3, 28.5, 31.7, 46.3, 51.2, 56.4, 58.8, 66.0, 120.6, 125.7, 127.5, 128.1, 141.2, 144.3, 144.5, 156.5, 167.8, 173.4; mass calcd for $C_{24}H_{25}N_2O_5$ (M + H^+) 421.176, found 421.170; HPLC t_R 17.60 (B).

10c. Prepared as for **10a**: yield 68%; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.40−1.53 (m, 2H), 1.69−1.73 (m, 1H), 1.76−1.87 (m, 4H), 2.26−2.32 (m, 1H), 3.61 (m, 1H), 4.04 (m, 1H), 4.21−4.28 (m, 4H), 7.32−7.35 (m, 2H), 7.38−7.45 (m, 2H), 7.55 (d, 1H, J = 8.00 Hz), 7.70 (d, 2H, J = 2.5 Hz), 7.89 (d, 2H, J = 7.5 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 28.0, 28.2, 28.4, 32.6, 47.1, 51.9, 58.7, 59.6, 66.1, 120.5, 125.8, 127.4, 128.0, 141.2, 144.3, 144.4, 156.7, 167.6, 174.2; mass calcd for $C_{24}H_{25}N_2O_5$ (M + H^+) 421.176, found 421.210; HPLC t_R 17.25 (B).

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Supporting Information Available: CIF file and ORTEP diagram of the X-ray structure of compound **1b**, general experimental methods, ^{1}H and ^{13}C NMR spectra for compounds **8** and **9**, ^{1}H and ^{13}C NMR spectra and analytical HPLC chromatograms for **1a**−**c**, and ^{1}H NMR spectra and analytical HPLC chromatograms for **10a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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