Synthesis of Enantiopure α,ω-Diamino Dicarboxylates and Azabicycloalkane Amino Acids by Claisen Condensation of α-[*N*-(Phenylfluorenyl)amino] Dicarboxylates

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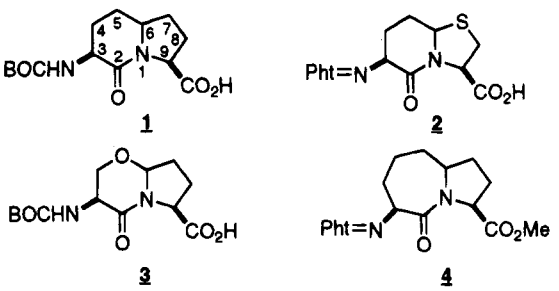
Summary: Enantiomerically pure (3*S*,6*S*,9*S*)-2-oxo-3-(*N*-BOC-amino)-1-azabicyclo[4.3.0]nonane-9-carboxylic acid ((3*S*,6*S*,9*S*)-**1**) was prepared in 39% overall yield from α-*tert*-butyl γ-methyl *N*-(9-(9-phenylfluorenyl))glutamate (**5**) using a Claisen condensation/reductive amination/lactam cyclization sequence.

Peptidomimetics, rationally designed conformationally rigid analogues of natural peptides, have emerged as important tools for studying the central roles peptides and proteins play in the communication, regulation, and replication of biological systems.[1] Azabicyclo[*X*.*Y*.0]-alkane amino acids are particularly attractive targets to those engaged in the rational design and synthesis of peptidomimetics because of their ability to serve as conformationally fixed surrogates of peptide turn secondary structures.[1-9] Pioneered by the preparation of 2-oxo-3-phthalimido-7-thia-1-azabicyclo[4.3.0]nonane-9-carboxylic acid (**2**, Figure 1) and its use to prepare peptidomimetics of the $i + 1$ and $i + 2$ residues of type II′ β-turn conformations,[3] efforts have intensified to synthesize azabicycloalkane amino acids in order to develop optimal peptidomimetics of different biologically active peptide turn conformations.[4-9] Recent reports on the synthesis of 2-oxo-3-(*N*-BOC-amino)-5-oxa-1-azabicyclo-[4.3.0]nonane-9-carboxylic acid (**3**) and methyl 2-oxo-3-phthalimido-1-azabicyclo[5.3.0]decane-10-carboxylate (**4**) have prompted us to reveal our approach to prepare azabicyclo[*X*.*Y*.0]alkane amino acid derivatives.[5-7]



1 **2** **3** **4**

Figure 1. 1-Azabicyclo[X.3.0]alkane amino acid analogues.[2]

Our strategy to synthesize azabicyclo[*X*.*Y*.0]alkane amino acids employs configurationally stable α-[*N*-(phenylfluorenyl)amino] dicarboxylates in a Claisen condensation/reductive amination/lactam cyclization sequence (Scheme 1). This strategy expands on our previously reported route to synthesize enantiopure δ-oxo α-amino esters and 5-alkylprolines via acylation of the γ-ester enolate of α-*tert*-butyl γ-methyl *N*-(9-(9-phenylfluorenyl))-glutamate (**5**) and subsequent reductive amination.[10] By employing readily available, natural α-amino dicarboxylates as chiral educts for azabicycloalkane amino acid synthesis, this method avoids complications associated with previous approaches that have required amination after heterocycle synthesis,[7a,8] as well as the preparation of optically active allylglycine starting materials.[6a] The synthesis of α,ω-diamino dicarboxylates by Claisen condensation of α-amino dicarboxylates adds value to our approach in light of their importance as antibacterials,[11] as well as replacements for cystine in macrocyclic peptides in which a reducible disulfide linkage is converted into an ethylene chain.[12] In addition, azabicycloalkane amino acids such as **1** are not susceptible to degradation by mechanisms that may ring-open the masked alde-

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(5) Baldwin, J. E.; Hulme, C.; Schofield, C. J.; Edwards, A. J. *J. Chem. Soc., Chem. Commun.* **1993**, 935.

(6) (a) Robl, J. A. *Tetrahedron Lett.* **1994**, *35*, 393. This work also describes preparation of methyl 2-oxo-3-phthalimido-1-azabicyclo[5.4.0]-undecane-11-carboxylate. (b) Thorsett, E. D. *Actual. Chim. Thér.* **1986**, *13*, 257. This work also describes preparation of methyl 2-oxo-3-amino-8-thia-1-azabicyclo[5.3.0]decane-10-carboxylate. (c) A radical cyclization approach to 2-oxo-3-*N*-(acetylamino)-1-azabicyclo[5.3.0]decane-10-carboxylate is presented in: Colombo, L.; Di Giacomo, M.; Papeo, G.; Carugo, O.; Scolastico, C.; Manzoni, L. *Tetrahedron Lett.* **1994**, *35*, 4031.

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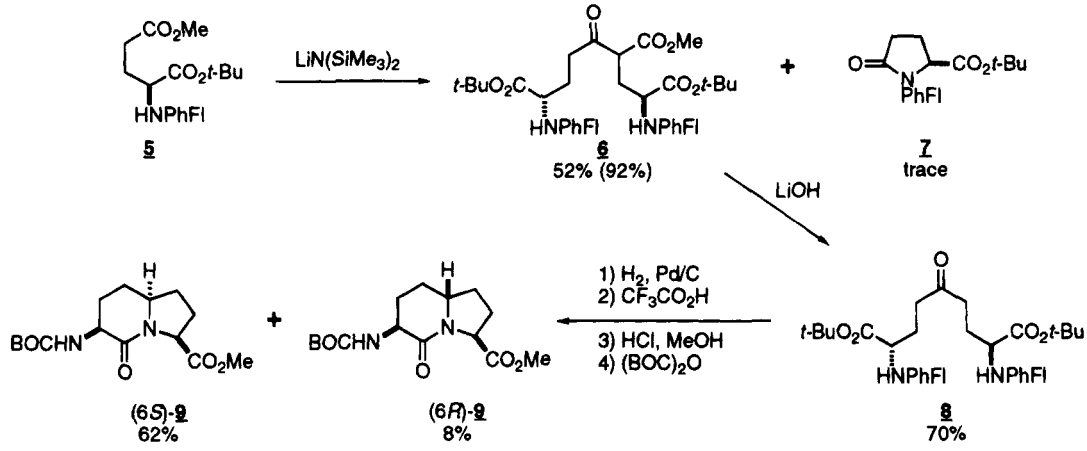
Scheme 1. Synthesis of (*N*-Boc-amino)indolizidinone Esters 9



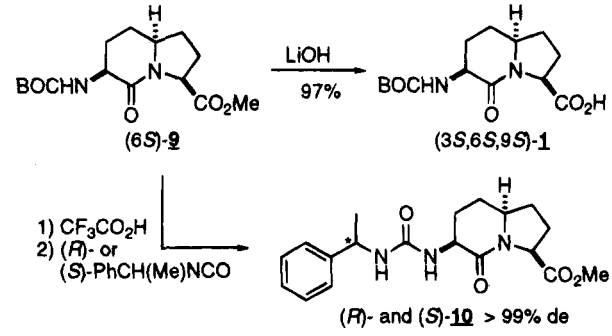
hydes present in derivatives **2** and **3**. This strategy is also designed to allow for side-chain functionality to be added to different positions of the α,ω-diamino dicarboxylate and azabicycloalkane amino acid peptidomimetics via subsequent alkylations and additions on *N*-(PhFl)-amino ketone intermediates.[13]

We have demonstrated the potential of our approach by the synthesis of >99% enantiomerically pure (3*S*,6*S*,9*S*)-2-oxo-3-(*N*-BOC-amino)-1-azabicyclo[4.3.0]-nonane-9-carboxylic acid ((3*S*,6*S*,9*S*)-**1**) in 39% overall yield from glutamate **5**. Slow addition of lithium bis-(trimethylsilyl)amide (110 mol %) to a −78 °C solution of glutamate **5** in THF (0.3 M) gave rise to Claisen condensation of the γ-methyl esters to produce after extraction and chromatography a 1:1 mixture of diastereomeric β-keto esters **6** (52%) and recovered **5** (45%). At elevated temperatures intramolecular cyclization competed with the condensation, and minor amounts of *tert*-butyl *N*-(PhFl)pyroglutamate (**7**) were isolated from the mixture. Hydrolysis and decarboxylation of the γ-methyl ester of **6** with 2 M lithium hydroxide (1500 mol %) in THF at reflux for 12 h furnished symmetrical δ-oxo α,ω-diaminoazelate **8** in 70% yield after chromatography.

The fully protected azabicycloalkane, methyl 2-oxo-3-(*N*-BOC-amino)-1-azabicyclo[4.3.0]nonane-9-carboxylate (**9**), was synthesized from azelate **8** in four steps and a single purification in 70% overall yield. Hydrogenation of **8** with palladium-on-carbon (10 mol % of 10 wt %) in a 10:1 ethanol:acetic acid solution at 5 atm of hydrogen provided the 5-substituted proline as an 8:1 mixture of *cis*:*trans* diastereomers. Treatment of the proline mixture with trifluoroacetic acid (20 vol %) in CH_2Cl_2 for 5 h at room temperature removed the *tert*-butyl esters, and esterification in methanolic HCl proceeded with lactam cyclization giving the desired indolizidinone ring system. The amino ester hydrochloride was then protected with di-*tert*-butyl dicarbonate (500 mol %) and triethylamine (200 mol %) in CH_2Cl_2 (0.06 M) to furnish the (*N*-BOC-amino)indolizidinone methyl esters **9** that were readily separable by purification using column chromatography on silica gel with 1:1 ethyl acetate:hexane as eluant. Concave (3*S*,6*S*,9*S*)-**9** (62%; R_f = 0.23, 1:1 EtOAc:hexane) eluted first from the column followed by convex (3*S*,6*R*,9*S*)-**9** (8%; R_f = 0.08).

Observation of Ruhemann's purple after removal of the *N*-BOC group by heating **9** on a silica gel coated TLC plate with ninhydrin indicated the presence of a primary

Scheme 2. Synthesis and Enantiomeric Purity of (3*S*,6*S*,9*S*)-1



amine and demonstrated that the 6-membered lactam had formed instead of an 8-membered lactam resulting from cyclization of the proline ester onto the primary amine.[14] The 6-membered lactam structure was further elucidated by a series of ^1H and ^{13}C NMR two-dimensional experiments.[15] The bridgehead stereochemistry of major product (6*S*)-**6** was assigned based on analogy with previous work[10] and on NMR experiments in which irradiation of the bridgehead proton produced a significant nuclear Overhauser effect on the C-3 proton. Enantiomeric purity of (6*S*)-**6** was determined after conversion to (*R*)- and (*S*)-*N*-(α-methylbenzyl)ureas **10** (Scheme 2). Trifluoroacetic acid in CH_2Cl_2 quantitatively removed the *N*-BOC protecting group, and the TFA salt was then acylated with either (*R*)- or (*S*)-α-methyl benzyl isocyanate in THF with triethylamine.[10] Observation of the diastereomeric methyl ester singlets by 400 MHz ^1H NMR spectroscopy in C_6D_6 during incremental additions of the opposite isomer demonstrated **10** to be of >99% de. Hence esters **9**, azelate **8**, and 2-oxo-3-(*N*-BOC-amino)-1-azabicyclo[4.3.0]nonane-9-carboxylic acids (**1**) are all presumed to be of >99% enantiomeric purity.

Hydrolysis of the methyl ester of (6*S*)-**9** using 2 M lithium hydroxide (1500 mol %) in THF (0.5 M) at reflux for 12 h provided an 81% yield of a 1.8:1 mixture of (3*S*,6*S*,9*S*)- and (3*S*,6*S*,9*R*)-2-oxo-3-(*N*-BOC-amino)-1-azabicyclo[4.3.0]nonane-9-carboxylic acids ((3*S*,6*S*,9*S*)- and (3*S*,6*S*,9*R*)-**1**) which were readily separable by chromatography on silica gel with 20:1 ethyl acetate: acetic acid as eluant. Since epimerization of (6*S*)-**9** during ester hydrolysis was presumed to provide

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(15) The structures of lactam **9** were confirmed by H,H-COSY, H,C-COSY, DEPT, NOE difference, NOESY, ^1H and ^{13}C NMR spectroscopy (see supplementary material).

(3*S*,6*S*,9*R*)-**1**, the hydrolysis was next performed under milder conditions. Methyl ester (6*S*)-**9** was thus subjected to 1 M lithium hydroxide (200 mol %) in THF (0.12 M) at room temperature for 16 h, and acid (3*S*,6*S*,9*S*)-**1** was isolated in 97% yield and >95% diastereomeric purity after aqueous extraction.

Conformational analysis of (3*S*,6*S*,9*S*)-*N'*-methyl 2-oxo-3-(*N*-acetylamino)-1-azabicyclo[4.3.0]nonane-9-carboxamide and its (6*R*)-stereoisomer predicts that both diastereomers exhibit ϕ and ψ torsion angles similar to the $i + 1$ and $i + 2$ residues of ideal type II' β-turn conformations.[16,17] We are now working to incorporate amino acid **1** into peptides in order to explore its ability to induce type II' β-turn conformations and β-hairpin structures.[16,18] Alkylation of ketone **8** and related intermediates is also under investigation to add side chains with stereocontrol at different positions on these peptidomimetic analogues. Having recently reported an enantioselective hydrogenation approach to synthesize both L- and D-α-amino dicarboxylates of six to eight carbon chain lengths with high enantiomeric purities,[19] we are now employing these different length α-amino dicarboxylates in our strategy in order to synthesize and study the conformations of a series of azabicyclic dipeptide analogues.

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Supplementary Material Available: Experimental details as well as ^{1}H and ^{13}C NMR spectra of **5**–**9** and ^{1}H NMR spectra of **10** (37 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(17) Conformational analyses were performed with Macromodel version 3.5x and the AMBER force field using solvent (water) treatment according to: McDonald, D. Q.; Still, W. C. *Tetrahedron Lett.* **1992**, *33*, 7743. The torsion angles for the minimum energy conformer of (3*S*,6*S*,9*S*)-*N'*-methyl 2-oxo-3-*N*-(acetylamino)-1-azabicyclo[4.3.0]nonane-9-carboxamide were $\phi_2 = -113°$ and $\psi_3 = -56°$. The torsion angles for the minimum energy conformer of its (6*R*)-stereoisomer were $\phi_2 = -137°$ and $\psi_3 = -69°$.

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