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Short Synthesis of (3S,6S,9S)-2-Oxo-3-(N-Boc-amino)-1-azabicyclo[4.3.0]nonane-9-carboxylic Acid Methyl Ester: Tandem Cyclization Protocol

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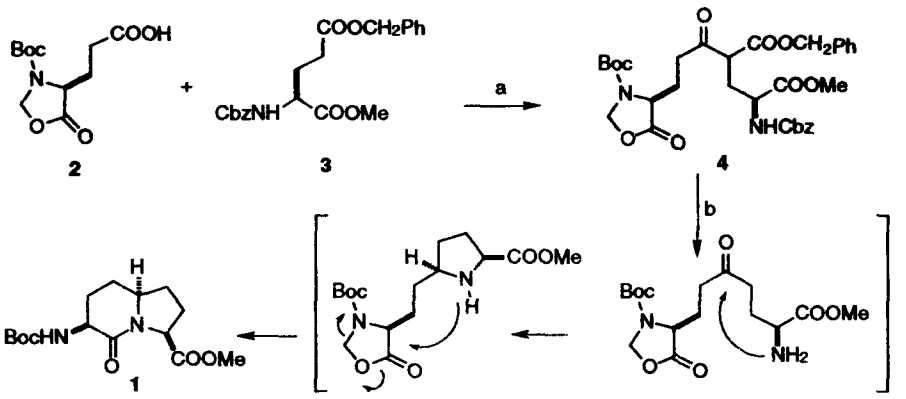
Abstract: A concise enantioselective synthesis of (3S,6S,9S)-2-oxo-3-(N-Boc-amino)-1-azabicyclo[4.3.0]nonane-9-carboxylic acid methyl ester from N-protected glutamic acid is described. © 1997 Elsevier Science Ltd.

In the course of our continuing research in the area of peptide secondary structure mimetics,[1] we required a rapid and convenient synthetic route to (3S,6S,9S)-2-oxo-3-amino-1-azabicyclo[4.3.0]nonane-9-carboxylic acid ester **1**. While there are several published protocols for the synthesis of azabicyclo nonane **1** and its analogues,[2] the majority of the approaches suffer from relatively long reaction sequences. In order to achieve an efficient synthesis of compound **1**, we envisioned that we would employ a Claisen-type condensation and tandem cyclization.

The oxazolidinone[3] protected N-Boc-Glu-OH (**2**) was activated by reaction with 1,1'-carbonyldiimidazole to form the imidazolide active ester. Its subsequent Claisen condensation[4] with the lithium enolate of Cbz-Glu(OBn)-OMe (**3**) afforded the desired β-keto ester **4** in 58% yield. With β-keto ester **4** in hand, we attempted a *one-pot* reductive cyclization to provide **1**. When the β-keto ester **4** was treated under hydrogen atmosphere (20 atm) in the presence of 10% Pd/C (MeOH/AcOH (10/1)), the azabicyclic nonane **1** was produced as a single enantiomer in 19% yield.[5] These conditions were selected after an extensive effort was devoted to improve the chemical yield by changing catalyst, pressure, and/or solvent. A plausible mechanism for the *in situ* formation of **1** involves i) debenzylation/decarboxylation ii) deprotection of the amino group/imine formation/reduction to give the proline ring iii) second cyclization, followed by loss of formaldehyde. The stereochemistry of the newly created chiral center at C-6 in **1** is presumably induced by steric repulsion during the reduction of the imine to form the proline ring. The low yield of this reaction is likely due to the competition between debenzylation/decarboxylation of the benzyl ester and imine formation/reduction of the proline ring.

Scheme



Reagents and Conditions: a) 1,1'-CDI with **2**, THF, 20 min then LiHMDS (2.5 eq.) with **3**, -78 °C, THF b) H_2/20 atm, 10% Pd/C, MeOH/AcOH (10:1).

In summary, we have demonstrated a facile route to synthesize the azabicyclo[4.3.0]nonane amino acid ester **1** by Claisen condensation and tandem cyclization. Further research and application of this work is in progress and will be reported in due course.

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References and Notes

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5. Compound **1**; NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.6-1.8 (m, 3H), 2.0-2.5 (m, 5H), 3.72 (s and m, 3H and collapsed 1H), 4.13 (m, 1H), 4.50 (d, 1H, *J*=8.5 Hz), 5.50 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.1, 27.4, 28.5, 29.3, 32.3, 50.2, 52.6, 56.7, 58.4, 79.7, 155.9, 169.4, 172.4. MS (CI/NH_3) m/z 313.4 ($M+H^+$). All spectral data were in good agreement with literature; ref. 2a.

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