Pergamon

Tetrahedron Letters 43 (2002) 5087–5088

TETRAHEDRON LETTERS

Synthesis of an azabicycloalkane amino acid scaffold as potential rigid dipeptide mimetic

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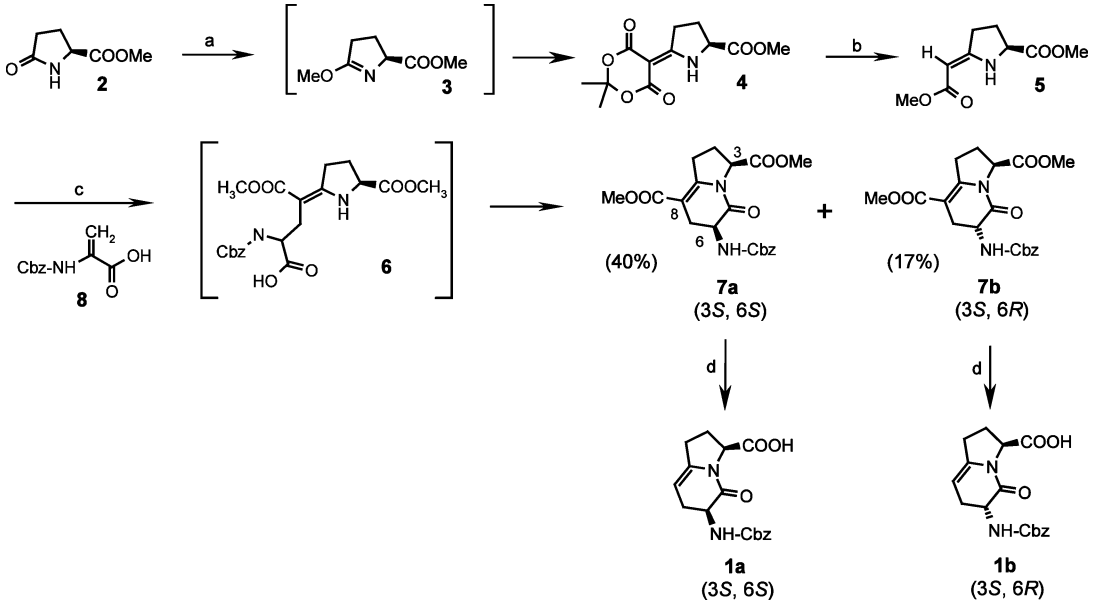
Received 27 March 2002; revised 22 May 2002; accepted 24 May 2002

Abstract—Short syntheses are presented of the pseudo-dipeptide (3*S*,6*S*)-6-[(benzyloxy)carbonyl]amino-5-oxo-1,2,3,5,6,7-hexahydro-3-indolizinecarboxylic acid (**1a**) and of its (3*S*,6*R*) diastereoisomer (**1b**). The key step involves adding vinylogous β-enaminoester derived from pyroglutamic acid on an acrylate derivative. The 6,5-fused bicyclic lactam obtained may be viewed as a conformationally restricted Ala-Pro mimetic.

The rational design of conformationally rigid analogs of natural peptides, usually named peptidomimetics,[1] has became important in the study of the central role of peptides and proteins in the communication, regulation and metabolism of biological systems. Moreover, it offers a better understanding of the interaction of ligands with their receptors such as enzymes or proteins. In the course of our continuing research on dipeptido heterocycle-containing mimetics,[2] we focused our interest on the design of the indolizine ring that encompasses the Ala-Pro dipeptide.[3] We report here an efficient synthesis of new analogous derivatives **1** that include an



Scheme 1. *Reagents and conditions*: (a) (i) Me_2SO_4, NEt_3, 60°C, 12 h, (ii) Meldrum's acid, 24 h, rt, 83%; (b) $BF_3{\cdot}Et_2O$, benzene, MeOH, reflux, 24 h, 60%; (c) WSC, HOBt, CH_2Cl_2, rt, 48 h; (d) (i) LiOH (2N), dioxane/H_2O, rt, 4 h, (ii) HCl (2N) 100%.

Keywords: 6,5-fused bicyclic lactam; indolizine; peptidomimetic.

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0040-4039/02/$ - see front matter
PII: S0040-4039(02)00992-9

unsaturated bond in their structure, a determined stereochemistry, and mimic Ala-Pro.

The synthesis of the 6,5-fused bicyclic skeleton (**1a**,**b**) is outlined in Scheme 1 and represents an extension of the previously described chemistry.[4] The strategy adopted to synthesize enantiomerically pure azabicycloalkanes **1a** and **1b** uses configurationally pure enaminoesters **7** coming from a Michael addition[5] on Cbz-protected dihydroalanine **8** followed by an in situ cyclization promoted by 1-ethyl-3-(3′-dimethylaminopropyl)-carbodiimide (WSC).[6]

Enantiomerically pure enaminoester **5** was obtained by modifying a previously described[7] procedure which used L-methyl pyroglutamate **2** as starting material. The conversion of lactame **2** into iminoether **3** was achieved with dimethyl sulfate and triethylamine and the following condensation with Meldrum's acid afforded good yield of the enaminoester **4**. The next step applied the procedure of Nagasaka[7] to break the Meldrum's ring of compound **5**. This method which used boron trifluoride etherate in refluxing benzene with MeOH afforded no racemization and enaminoester **5** was proved to be the *Z*-isomer, in accordance with reported results.[8] Cyclization into bicyclolactame **7** was performed in CH_2Cl_2 at room temperature with *N*-benzyloxycarbonyl dehydroalanine **8**[9] and WSC to accelerate the cyclization of carboxylic acid **6** into lactames **7**. The diastereoisomeric mixture **7a**,**b** was detected by ^1H NMR and HPLC[10a] and easily separated by preparative HPLC[10b] performed by an isocratic run. Configurational assignments of the two diastereoisomers **7a** and **7b** were supported by ROESY ^1H NMR. A cross-peak between H_3 and H_6 was detected for **7a** making it possible to distinguish the *cis* (**7a**) from the *trans* isomer (**7b**). In addition, the NMR analysis revealed that the former was predominant.

The azabicycloalkanes[11] **1a**,**b** were finally obtained via hydrolysis of diesters **7a**,**b** with LiOH in dioxane/H_2O followed by neutralization and regioselective decarboxylation of the 8-carboxylic function with 2N HCl. The reaction was monitored by HPLC: after 4 h, a single isomer **1a** or **1b** was formed, indicating that no epimerization occurred at C-3 or C-6 of the indolizine ring.

In conclusion, we described a convenient and efficient method to prepare a stereochemically pure 6,5-bicyclic lactam peptidomimetic that can be incorporated as a building unit into the drug design peptidic block.

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10. (a) HPLC were performed at flow rates of 1 mL/min, using three different conditions: condition A, a gradient run from 100% eluent A (0.05% TFA in H_2O) to 100% eluent B (0.05% TFA, 20% H_2O, 80% CH_3CN) over the next 30 min with C_{18} Vydac column (4×300 mm, 5 μm, 100 Å); condition B, an isocratic run from eluent (0.1% TFA, 50% H_2O, 50% MeOH) with C_{18} Kromasil column (4.6×150 mm, 5 μm, 100 Å); condition C, an isocratic run from eluent (0.1% TFA, 54% H_2O, 46% MeOH) with C_{18} Kromasil column (4.6×150 mm, 5 μm, 100 Å); (b) Separation of diastereoisomeric mixture **7a**,**b** was performed by preparative HPLC at flow rates 20 mL/min using C_{18} Kromasil column (21×250 mm, 10 μm, 100 Å) with an isocratic run from eluent (0.1% TFA, 50% H_2O, 50% MeOH).
11. Compound **7a**: ^1H NMR (DMSO-d_6, 300 MHz): δ 1.85–2.01 (m, 1H), 2.17–2.24 (m, 1H), 2.42–2.54 (m, 1H), 2.68–2.82 (m, 2H), 3.10–3.18 (m, 1H), 3.57 (s, 3H), 3.58 (s, 3H), 4.09–4.16 (m, 1H), 4.62 (dd, 1H, $J=9.5$ Hz, $J'=2.0$ Hz), 4.96 (s, 2H), 7.20–7.31 (m, 5H), 7.61 (d, 1H, $J=8.2$ Hz); MS (ESI) m/z 403 $[M+H]^+$, 425 $[M+Na]^+$, 441 $[M+K]^+$; HPLC (condition A) t_R 19.9 min, (condition B) t_R 17.4 min.
Compound **7b**: ^1H NMR (DMSO-d_6, 300 MHz): δ 1.89–2.01 (m, 1H), 2.17–2.24 (m, 1H), 2.42–2.54 (m, 1H), 2.68–2.82 (m, 2H), 3.05–3.18 (m, 1H), 3.57 (s, 3H), 3.58 (s, 3H), 4.19–4.27 (m, 1H), 4.55 (dd, 1H, $J=9.2$ Hz, $J'=3.7$ Hz), 4.96 (s, 2H), 7.21–7.28 (m, 5H), 7.58 (d, 1H, $J=8.2$ Hz); MS (ESI) m/z 403 $[M+H]^+$, 425 $[M+Na]^+$, 441 $[M+K]^+$; HPLC (condition A) t_R 19.9 min, (condition B) t_R 16.3 min.
Compound **1a**: ^1H NMR (DMSO-d_6, 300 MHz): δ 1.80–2.00 (m, 1H), 2.05–2.20 (m, 2H), 2.27–2.35 (m, 1H), 2.38–2.44 (m, 1H), 2.75–2.95 (m, 1H), 4.10–4.20 (m, 1H), 4.42–4.45 (m, 1H), 4.60–4.65 (m, 1H), 4.97 (s, 2H), 7.23–7.34 (m, 5H), 7.64 (d, 1H, $J=8.3$ Hz); MS (ESI) m/z 331 $[M+H]^+$, 353 $[M+Na]^+$, 369 $[M+K]^+$; HPLC (condition A) t_R 12.0 min, (condition C) t_R 13.7 min.
Compound **1b**: ^1H NMR (DMSO-d_6, 300 MHz): δ 1.80–2.00 (m, 1H), 2.05–2.20 (m, 2H), 2.27–2.35 (m, 1H), 2.38–2.44 (m, 1H), 2.75–2.95 (m, 1H), 4.10–4.20 (m, 1H), 4.42–4.45 (m, 1H), 4.60–4.65 (m, 1H), 4.97 (s, 2H), 7.23–7.34 (m, 5H), 7.61 (d, 1H, $J=8.3$ Hz); MS (ESI) m/z 331 $[M+H]^+$, 353 $[M+Na]^+$, 369 $[M+K]^+$; HPLC (condition A) t_R 12.0 min, (condition C) t_R 12.9 min.