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Practical Syntheses of a Novel Tricyclic Dipeptide Mimetic Based on a [6H]-Azepino Indoline Nucleus : Application to Angiotensin-Converting Enzyme Inhibition[1]

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(Dedicated to Professor Léon Ghosez on the occasion of his 60th birthday)

Abstract: Two stereocontrolled synthetic approaches towards 5-*(S)*-amino-1,2,4,5,6,7-hexahydro-azepino [3,2,1-hi] indole-4-one-2-*(S)*-carboxylic acid **1**, based on intramolecular Friedel-Crafts acylations, are reported. This conformationally restricted tricyclic dipeptidomimetic has been applied to the design of a potent and orally active inhibitor of angiotensin-converting enzyme (ACE).

Peptidomimetics are valuable tools to probe receptor binding domains and enzyme active sites, and can be applied to induce specific turns within larger peptide fragments. To the medicinal chemist, they offer means to rapidly improve the intrinsic potency, oral bioavailability or metabolic stability of a peptide lead, and to optimize the physical properties and pharmacokinetic profile of a potential drug. Unfortunately, the synthetic complexity associated with highly functionalized polycyclic templates bearing multiple chiral centers can be a serious practical limitation, stressing the need for new and more accessible structures. To date, few classes of therapeutic agents have benefited more from the peptidomimetic design than the inhibitors of angiotensin I-converting enzyme (ACE; EC 3.4.15.1), a zinc metallopeptidase involved in the regulation of blood pressure.[2] Several of these inhibitors, such as L-155,212[3] and benazeprilat,[4,5] exploit a fused ε-lactam as a conformationally restricted alanyl-proline surrogate.[6-11]

In this Letter, we report two convenient synthetic routes towards 5-*(S)*-amino-1,2,4,5,6,7-hexahydro-azepino [3,2,1-hi] indole-4-one-2-*(S)*-carboxylic acid **1** as a novel dipeptide mimetic, and its application for the design of ACE inhibitors. This tricyclic template combines the key structural elements of benazeprilat plus a fused five-membered ring restricting the conformational space accessible to the C-terminal carboxylic acid group (Figure 1).

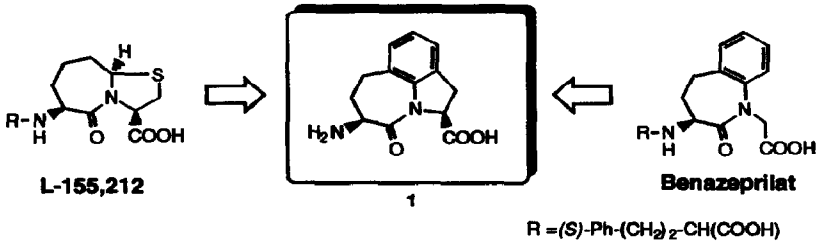
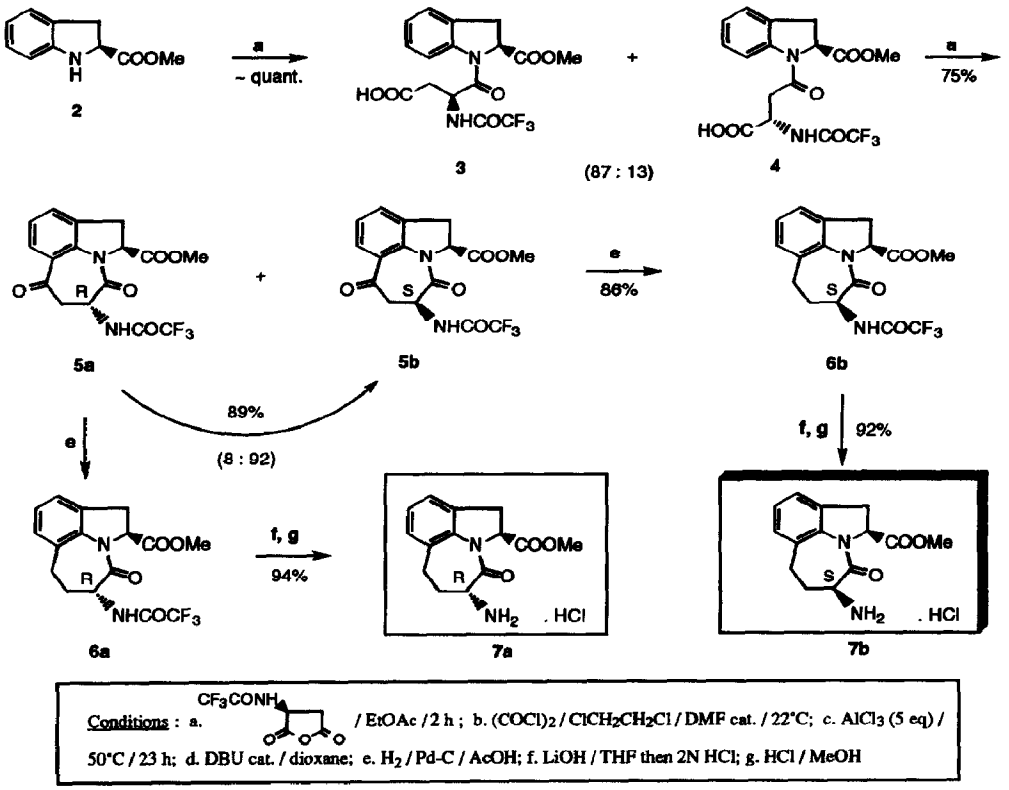


Figure 1

From a retrosynthetic analysis of **1**, the most appealing strategy involved the elaboration of the ε-lactam by the Friedel-Crafts cyclization of an indoline-containing dipeptide derivative (Scheme 1). Thus, *(S)*-indoline-2-carboxylic acid methyl ester **2**[12] was acylated regioselectively and in excellent yield with *(S)*-*N*-trifluoroacetyl aspartic anhydride[13] (**3**:**4** = 87:13). The mixture of regioisomers was conveniently carried on to the next step.[14] Activation of **3** as the acid chloride,[15] followed by aluminum trichloride-induced cyclization, afforded the desired tricyclic azepine derivative in good yield (75% based on **3**), albeit as a mixture of diastereomers **5a** and **5b**.[16] This undesired epimerization was inconsequential since equilibration of **5a**, or the mixture of epimers, with a catalytic amount of DBU strongly favored the 5-*(S)* diastereomer (**5a**:**5b** = 8:92). The stereoisomers were easily separated by crystallization and independently hydrogenated to give the more conformationally flexible lactams **6a** and **6b**. Basic equilibration of **6a** occurred with less selectivity as compared to **5a** (**6a**:**6b** = 1:2).



Scheme 1

The stereochemical assignments were confirmed by single x-ray analyses of **6b** and **7a** (as the hydrobromide). Interestingly, both diastereomers displayed similar values for the ψ torsion angle due to an alternate folding pattern of the 7-membered ring (Figure 2). This observation suggests that *both* epimeric templates could possibly adopt a suitable conformation for the binding to ACE.[17]

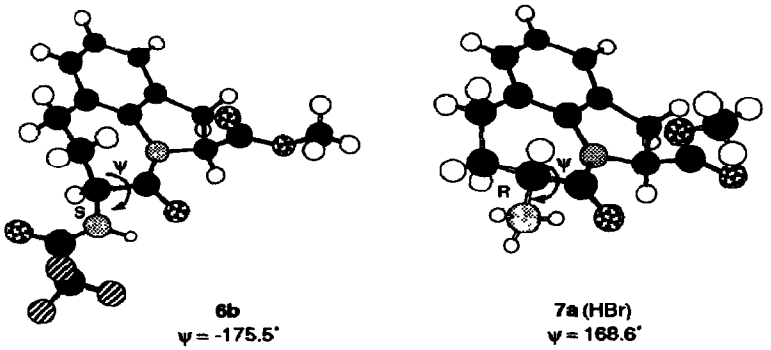
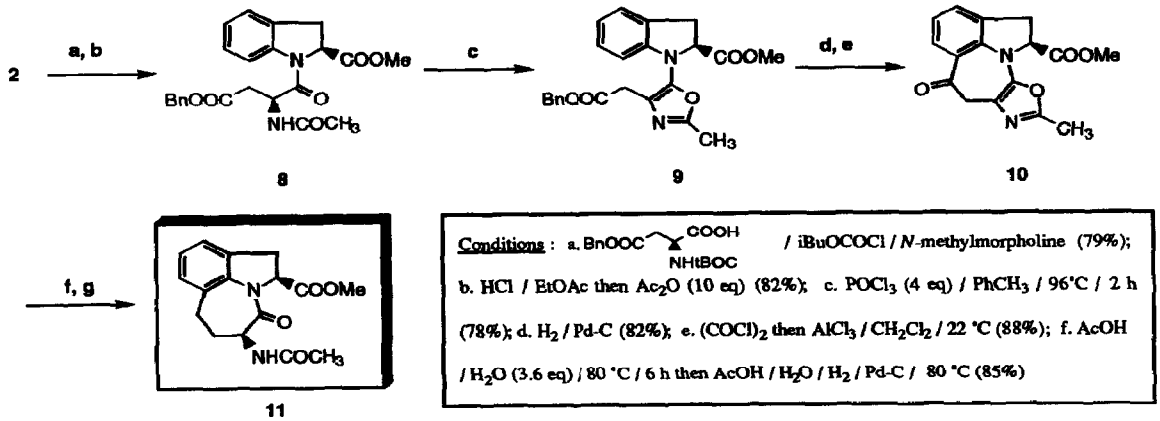


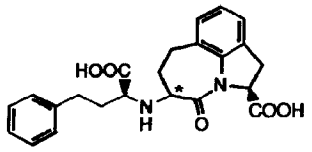
Figure 2

Since the absolute configuration at C5 could be efficiently controlled by epimerization *after* the cyclization, we considered favoring the ring closure by introducing a rigid constraint within the aspartyl chain. The possibility of temporarily masking dipeptides as oxazoles[18] constituted an attractive strategy. Although the oxazole formation failed with the *N*-trifluoroacetyl dipeptide, the corresponding acetamide precursor **8** was smoothly converted to **9** with phosphorus oxychloride. Hydrogenolysis of the benzyl ester, followed by activation to the acid chloride, afforded an intermediate which, upon treatment with aluminum trichloride, cyclized readily to the tetracyclic lactam **10**. Sequential acid hydrolysis of the oxazole moiety and reduction of the carbonyl group regenerated the dipeptide motif in **11** with excellent stereoselectivity (de ≥ 90%) (Scheme 2).



Scheme 2

To demonstrate the usefulness of the [6H]-azepino indoline template as a conformationally restricted alanyl-proline surrogate, **7a** and **7b** were further elaborated in 2 steps (N-alkylation / saponification) into the rigid analogues of benazeprilat, **12a** and **12b**, by the method of Effenberger.[19]



12a : 5-*(R)*
12b : 5-*(S)*

As expected, **12b** was found to be a potent inhibitor of ACE from rabbit lung (IC_{50} = 5.2 nM).[20] Furthermore, when administered orally to rats (10 mg/kg), **12b** produced a sustained (> 6 h) and efficient blockade of the angiotensin I-induced pressor response. This observation, which parallels one reported earlier with L-155,212,[3] is remarkable considering that most dicarboxylic acid ACE inhibitors require derivatization to a prodrug to achieve suitable oral activity. As predicted from the x-ray analysis, the 5-*(R)* epimer **12a** was also a potent ACE inhibitor (IC_{50} = 15 nM), similar in potency to captopril.[2]

In conclusion, using intramolecular Friedel-Crafts acylations, we have achieved short, efficient and stereocontrolled syntheses of the novel dipeptide mimetic **1**.[21] This tricyclic template has conferred interesting biological properties to ACE inhibitors. Additional applications of **1** will be reported in due course.

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References and Notes

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(12) Readily prepared from the commercially available acid (Aldrich Chemical Co.) according to: Stanton, J. L.; Gruenfeld, N.; Barbiaz, J. E.; Ackerman, M. H.; Friedmann, R. C.; Yuan, A. M.; Macchia, W. *J. Med. Chem.* **1983**, *26*, 1267-1277.
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(14) The presence of small amounts of **4**, otherwise separable by column chromatography, did not affect significantly the yield of the subsequent cyclization.
(15) Initial attempts to directly cyclize **3** to the desired 7-membered lactam via the mixed anhydride methods (trifluoroacetic anhydride, PPA, PPSE, trifluoromethanesulfonic anhydride) failed to provide substantial amount of the desired aryl ketone.
(16) Products resulting from the cyclization of **4** could not be identified.
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(21) We have been recently aware of a similar peptidomimetic design at Bristol-Myers Squibb (EP 0595610 A).

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