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Design and synthesis of 6-amino-5-oxo-1,2,3,5-tetrahydro-3-indolizinecarboxylic acids as β-sheet peptidomimetics

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Abstract—6-Amino-5-oxo-1,2,3,5-tetrahydro-3-indolizinecarboxylic acid was designed as a novel scaffold that can effectively mimic the extended conformation of a peptide. The key reaction in the synthesis of the scaffold involved a [3+2]-cycloaddition of a dicarbonyl stabilized isomünchnone intermediate. Its effectiveness as a β-sheet mimetic was demonstrated by the preparation of a potent HCV NS3 protease inhibitor.

One challenging aspect of medicinal chemistry is the design of highly potent, target selective, and metabolically stable peptidomimetics. An important step in this effort is the development of molecular scaffolds inducing conformational constraints.[1,2] Within this field, β-sheet and reverse-turn templates are of special interest because a large number of small peptides having regulatory roles adopt either extended or turn conformations. While many bicyclic scaffolds have been designed and synthesized to mimic the turn conformations,[3–6] bicyclic β-sheet mimetics are scarce. We report herein a design and synthesis of 6-amino-5-oxo-1,2,3,5-tetrahydro-3-indolizinecarboxylic acid (**3**, Fig. 1) as a novel scaffold that can effectively mimic the extended conformation of peptides.[20]

A recent Hepatitis C virus (HCV) NS3 serine protease program prompted us to design a molecular scaffold to replace a hexapeptide lead. Based on the assumption that proteases typically bind their substrate in an extended conformation, we looked for β-sheet scaffolds that have been reported. Among them, pyridones **1** and pyrazinones **2** have been successfully employed against a wide variety of protease targets, e.g. elastase,[7] thrombin,[8,9] and interleukin-1β-converting enzyme.[10,11] It was postulated and subsequently confirmed by X-ray crystal structures that the CO and NH off the ring could form a pair of β-sheet H-bonds with the enzyme backbone.[12,13] However, neither **1** nor **2** worked well against HCV NS3. We reasoned that by a constraint using a bicyclic pyridone as in compound **3**, a more

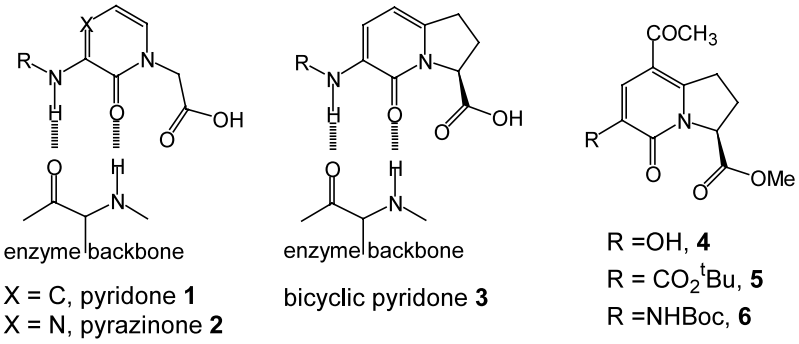

Figure 1. From monocyclic heterocycles to bicyclic pyridones as a conformational constraint.

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rigid conformation could be generated, which in turn should produce a more potent compound. This letter reports the synthesis of derivatives of **3** (Scheme 1).

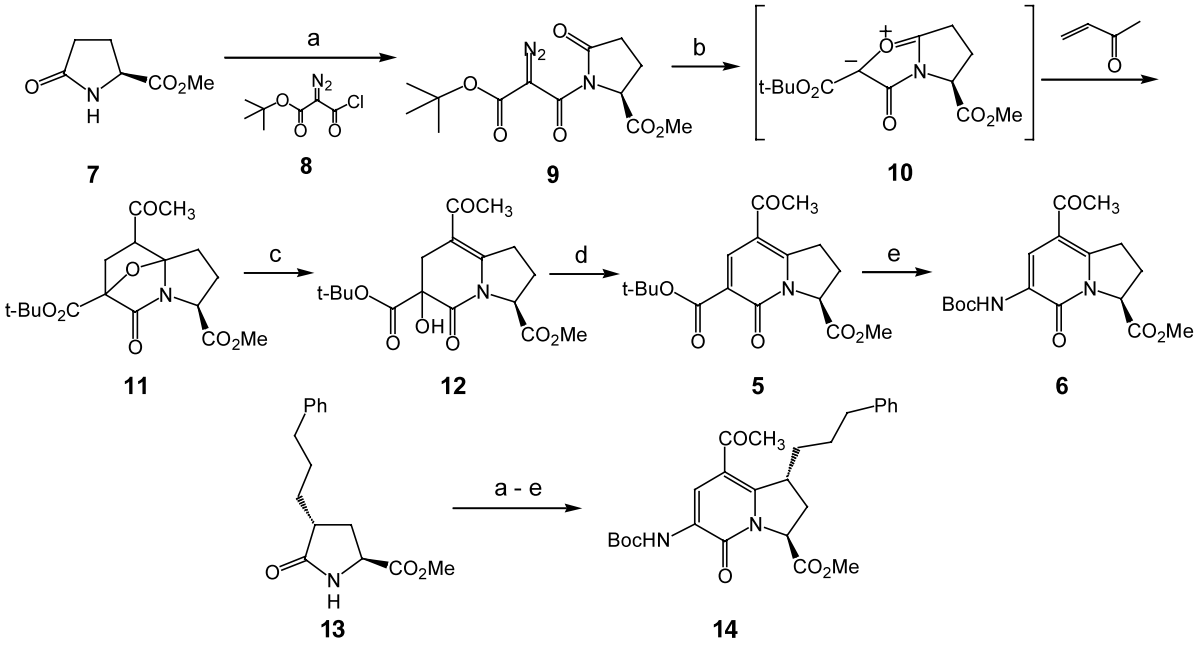
Our synthesis took advantage of a recent elegant report by Padwa et al. on the synthesis of 8-acetyl-6-hydroxyl indolizinecarboxylic ester **4** by a [3+2]-cycloaddition of a phenylsulfonyl stabilized isomünchnone intermediate.[14,15] In principal, the hydroxy of **4** could be transformed to an amino group by a palladium-catalyzed amination reaction of its triflate. In consideration of the strongly basic conditions typically found for this transformation, we opted to prepare the 6-carboxyl analog **5** through a dicarbonyl stabilized isomünchnone intermediate (e.g. **10** in Scheme 1). The carboxylate **5** could be readily converted to the protected amino analog **6** by a Curtius rearrangement.

The lithium salt of **7** reacted with *t*-butyl diazomalonyl chloride **8**[16] to give diazo imide **9** in 90% yield. $Rh_2(OAc)_4$ (2–5% mol) catalyzed decomposition of **9** to isomünchnone intermediate **10**, followed by in situ trapping with methyl vinyl ketone gave tricyclic compound **11** as a mixture of three diastereomers in high yield. Although each diastereomer was isolated and characterized, the stereochemistry had no significance for the preparation of the target molecules because the two newly formed chiral centers would be converted to sp^2 carbons. Treatment of **11** with a catalytic amount of PTSA in CH_2Cl_2 cleaved one of the ether bonds to give a mixture of two diastereomeric alcohols **12** in 74% yield. Dehydration of **12** to **5** was effected with $POCl_3$ in pyridine. Burgess reagent[17] was also effective for dehydration of **12**, but $POCl_3$/pyridine is more convenient to use. Deprotection of the *t*-butyl ester in **5** to its acid, followed by a Curtius rearrangement of the acyl azide, gave Boc-protected amino bicyclic pyridone **6** in good yields.[21] Starting from a phenylpropyl substituted pyroglutamate **13**, bicyclic pyridone **14** was prepared in similar yields following the same chemistry.

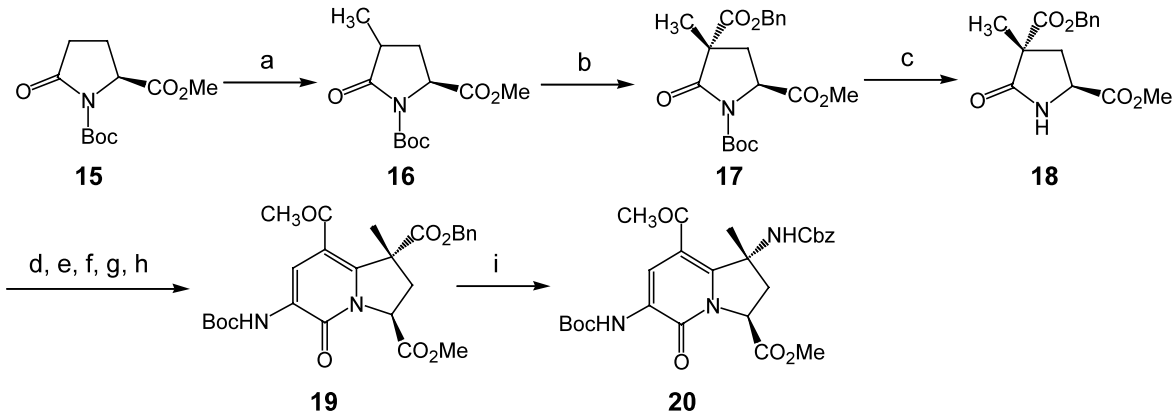
This synthetic sequence is versatile in terms of functional group tolerance, as demonstrated by the preparation of a heavily functionalized pyridone **20** (Scheme 2). Monomethylation of **15** was performed in high yield with MeOTf. Carbonylation of **16** with benzyl chloroformate was achieved stereospecifically to give **17**.[18,19] Deprotection of the Boc group in **17** gave precursor **18**. Following the same chemistry described above, compound **18** was converted to a Boc-protected amino bicyclic pyridone **19**. Hydrogenolysis of **19** and a second Curtius reaction afforded a differentially protected diaminopyridone **20**.

Compounds **6**, **14** and **20** can be further modified through the amino and carboxyl groups (Scheme 3). For example, deprotection of **14** and **20**, followed by reaction with *m*-toluenesulfonyl chloride gave sulfonamides **21** and **23**. Saponification of **21** and coupling of the free acid with $NH_2CH(Et)B(C_{10}H_{16}O_2)\cdot HCl$ afforded a potent HCV NS3 protease inhibitor with $IC_{50}=0.12$ μM in the enzymatic assay. On the other hand, hydrogenation of **23** and reaction of the corresponding free amine with isocyanates gave rise to ureas **24** in high yields.

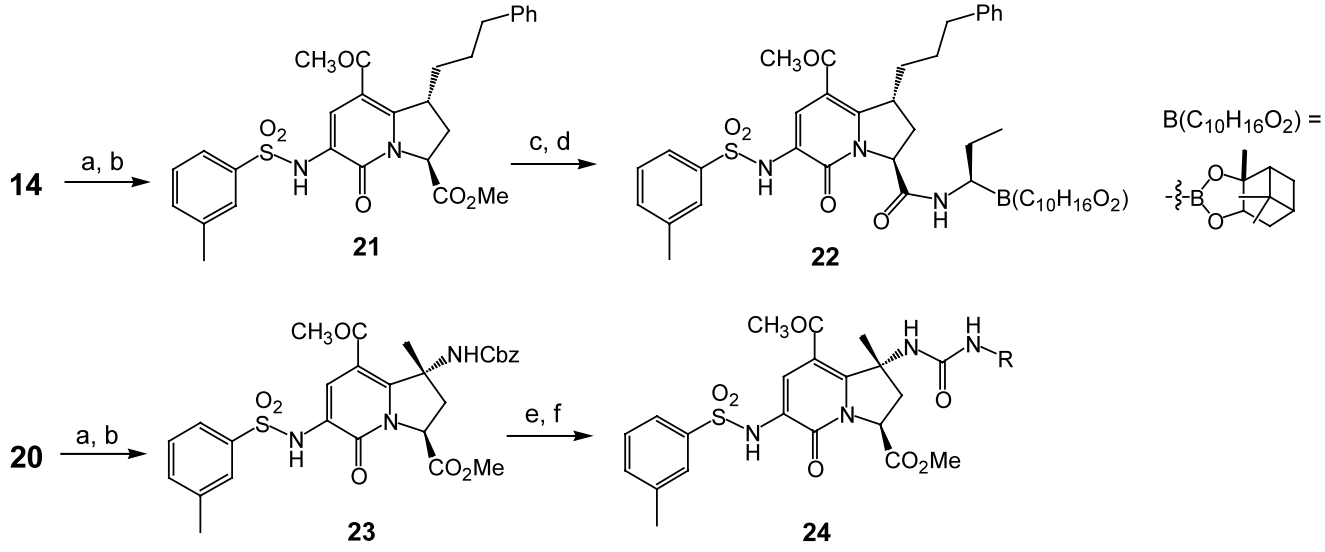
In summary, we have designed 6-amino-5-oxo-1,2,3,5-tetrahydro-3-indolizinecarboxylic acid as a novel molecular scaffold that can mimic the extended conformation of a peptide. The key reaction in the synthesis of the scaffold involved a [3+2]-cycloaddition of a dicarbonyl stabilized isomünchnone intermediate. The synthetic sequence is versatile, giving highly functionalized templates that can be further elaborated. Furthermore, we demonstrated that by incorporation of the correct side chains into the scaffold, a potent non-peptidic HCV NS3 serine protease inhibitor could be obtained.



Scheme 1. *Reagents and conditions*: (a) LHMDS, THF, −78°C, 90%; (b) $Rh_2(OAc)_4$, benzene, 90°C; (c) PTSA, CH_2Cl_2, 75% for two steps; (d) $POCl_3$, pyridine, 65%; (e) (1) TFA, CH_2Cl_2, (2) EtOCOCl, Et_3N, THF, −5°C, NaN_3, (3) toluene, *t*-BuOH, 90°C, 60%.



Scheme 2. *Reagents and conditions*: (a) KHMDS, toluene, −78°C, MeOTf, >90%; (b) LHMDS, THF, −78°C, BnOCOCl, 92%; (c) TFA, CH_2Cl_2, 90%; (d) LHMDS, THF, −78°C, then **8**, 89%; (e) $Rh_2(OAc)_4$, methyl vinyl ketone, benzene, 90°C; (f) PTSA, CH_2Cl_2, 50°C, 70% for two steps; (g) $POCl_3$, pyridine, 55%; (h) (1) TFA, CH_2Cl_2, (2) EtOCOCl, Et_3N, THF, −5°C, NaN_3, (3) toluene, *t*-BuOH, 90°C, 60%. (i) (1) Pd/C, H_2, MeOH, (2) EtOCOCl, Et_3N, THF, −5°C, NaN_3, (3) toluene, BnOH, 90°C, 80%.



Scheme 3. *Reagents and conditions*: (a) TFA, CH_2Cl_2; (b) *m*-toluenesulfonyl chloride, pyridine, Et_3N, 65%; (c) LiOH, THF/H_2O; (d) $NH_2CH(Et)B(C_{10}H_{16}O_2)\cdot HCl$, DIEA, PyAOP, DMF, 60%; (e) Pd/C, H_2, MeOH; (f) RNCO, CH_2Cl_2, Et_3N, 80–90%.

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21. Experimental for compound **6**: To compound **9** (1.1 g, 5.52 mmol) in benzene (40 mL) was added methyl vinyl ketone (1.3 mL, 15.4 mmol) and $[Rh(OAc_2)]_2$ (3 mg). The reaction was heated to 90°C for 6 h. *p*-TsOH (130 mg, 0.68 mmol) was then added and the mixture was heated to 50°C overnight. Flash chromatography gave product **12** (1.46 g, 75%). Compound **12** (1.2 g, 3.42 mmol) was dissolved in pyridine and $POCl_3$ was added. The reaction was allowed to stir overnight. The mixture was diluted with ethyl acetate and washed with 5% citric acid, sat. aqueous $CuSO_4$, brine and dried with $MgSO_4$. Flash chromatography gave product **5** (560 mg, 50%). Compound **5** (560 mg, 1.66 mmol) was dissolved in ethyl acetate (5.0 mL) and treated with 4.0 M HCl/dioxane (4.2 mL, 16.8 mmol) for 3 h. Concentration under vacuum gave the intermediate acid (460 mg, 99%). The acid (460 mg, 1.64 mmol) was dissolved in THF (10 mL) and cooled to −20°C. To this solution was added NMM (272 μL, 2.48 mmol) followed by ethyl chloroformate (174 μL, 1.81 mmol) and let stir for 40 min at −20°C. The reaction was allowed to warm to −5°C and NaN_3 (268 mg, 4.12 mmol) in water (1.2 mL) was added and allowed to stir for 40 min. The mixture was then diluted with ethyl acetate, washed with brine, dried with $MgSO_4$ and concentrated. The concentrate was dissolved in 10 mL toluene and heated to 70°C for 0.5 h. *t*-Butyl alcohol (470 μL, 4.90 mmol) and *p*-TsOH (26 mg, 0.13 mmol) were added and the reaction heated to 85°C overnight. Flash chromatography (25–50% ethyl acetate/hexanes) gave product **6** (340 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.3 (s, 9H), 2.3–2.6 (m, 5H), 3.5 (m, 1H), 3.7 (m, 1H), 3.8 (s, 3H), 5.18 (dd, 1H, $J=3.3$ 9.9 Hz), 8.62 (bs, 1H). MS *m*/*e* 351.3 [M+H].