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Diastereoselective Pictet−Spengler Approach for the Synthesis of Pyrrolo[3,2-*e*][1,4]diazepin-2-one Peptide Turn Mimics

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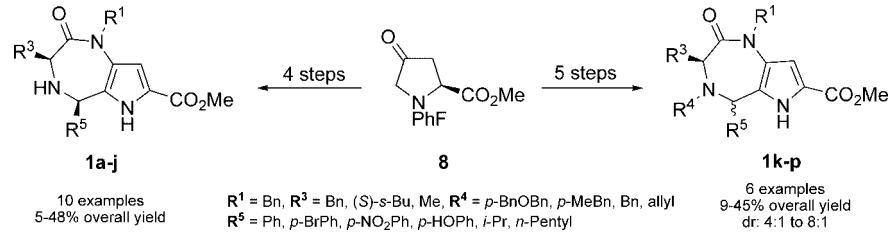
ABSTRACT



Sixteen pyrrolo[3,2-*e*][1,4]diazepin-2-ones 1 were synthesized in 4−5 steps and 5−48% overall yields from 4-oxoproline 8 by a route featuring a diastereoselective Pictet−Spengler reaction to close the seven-membered diazepinone ring. Crystallographic analysis of pyrrolo[3,2-*e*][1,4]diazepin-2-one 1b by X-ray diffraction demonstrated that the α-amino acid residue adopted dihedral angle geometry similar to an ideal γ-turn, illustrating the potential for employing these novel heterocycles as peptide turn mimics.

Aryldiazepine ring systems have been called "privileged structures" because of their capacity to bind at multiple receptor types with high affinity.[1,2] For example, they act as antagonists on G-protein coupled receptors,[2,3] block protein−DNA interactions,[2,4] and function as scaffolds in enzyme inhibitors.[2,5] Their affinity for various receptors is likely due to their capacity to mimic peptide turn geometry. For example, benzodiazepinones can position peptide side-chain and backbone residues in orientations that mimic β-turns.[6] 1,4-Diazepinones have been shown by X-ray analysis to mimic γ-turns.[7]

Among diverse aryl and heteroaryl systems fused to the diazepine ring, few pyrrole analogs have been synthesized,

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yet their activity has been remarkable. For example, pyrrolo[1,2-*b*][1,2]diazepine **2** and pyrrolo[1,2-*d*][1,4]benzodiazepine **3** inhibit, respectively, angiotensin-converting enzyme and HIV-1 reverse transcriptase (Figure 1).[8,9]

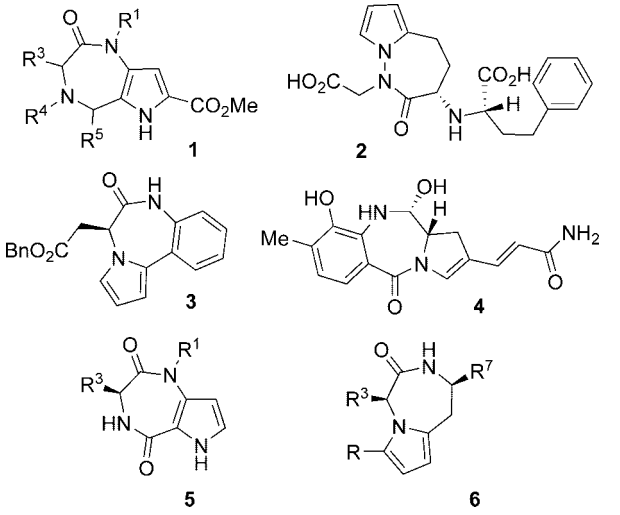


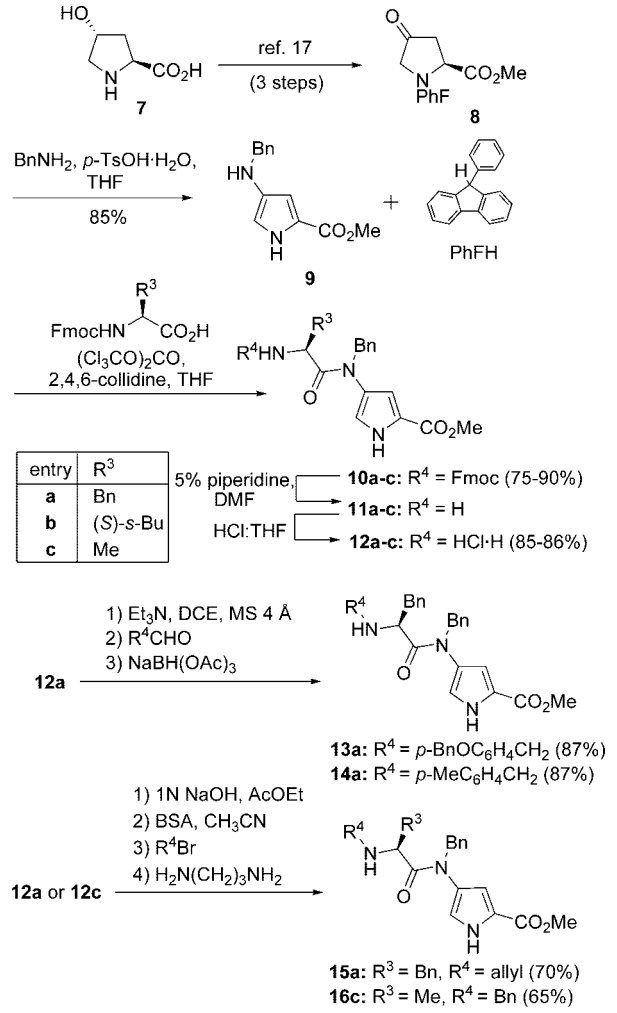
Figure 1. Representative pyrrolodiazepinones.

Pyrrolo[2,1-*c*][1,4]benzodiazepines, such as anthramycin **4**, are antitumor antibiotics.[10] Their promising activity has inspired new chemistry to expand pyrrolodiazepinone diversity, including multicomponent Ugi reactions,[11] as well as rearrangements of cyclopropylketimines[12] and intramolecular Paal−Knorr condensations,[7] which have, respectively, delivered pyrrolodiazepines **5** and **6**. In this vein, we report now a diastereoselective Pictet−Spengler[13] route to pyrrolo[3,2-*e*][1,4]diazepin-2-ones **1**. Although formaldehyde was recently employed in a Pictet−Spengler reaction to make pyrimido[4,5-*b*][1,4]benzodiazepines,[14] to the best of our knowledge, this reaction has never been used in pyrrolodiazepinone synthesis.[15]

In light of our previous approach for making 4-aminopyrrole-2-carboxylates with various 4-alkylamino substituents,[16] efforts were focused on diazepinone assembly using different α-amino acids and aldehydes. Thus, we restricted our study to 4-benzylaminopyrrole **9**, which was prepared from 4-oxoproline **8** (Scheme 1).[17]

Methyl 4-[*N*-(Fmoc)aminoacyl]benzylamino-1*H*-pyrrole-2-carboxylates (**10a**−**c**) were isolated in 75−90% yields from acylation of benzylaminopyrrole **9** with *N*-(Fmoc)amino acid chlorides (Ala, Ile, and Phe), generated using bis(trichloromethyl)carbonate and 2,4,6-collidine in THF at rt.[18] The Fmoc group removal using 5% piperidine in DMF[19] gave amines **11a**−**c** after filtration through a pad of silica gel to separate the dibenzofulvene−piperidine adduct. Hydrochlorides **12a**−**c** were obtained in 85−86% yields by treating amines **11** with 12 N HCl in THF (1:100 v/v) and freeze-drying.

Scheme 1. Synthesis of Aminoamidopyrroles **10**−**16**



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Alkylation of amine **12a** was performed by reductive amination[20] and by way of a silylamide intermediate.[21] Hydrochloride **12a** was treated with triethylamine and, respectively, condensed with *p*-benzyloxybenzaldehyde and tolualdehyde (90 mol %), in the presence of molecular sieves to yield imines, which were reduced with sodium triacetoxyborohydride (150 mol %) in dichloroethane providing secondary amines **13a** and **14a**, both in 87% yield. Allylamine **15a** and benzylamine **16c** were, respectively, prepared in 70% and 65% yields by a sequence featuring silylation of amine **11a** and **11c** with *N*,*O*-bis(trimethylsilyl)acetamide (BSA, 160 mol %), alkylation with allyl and benzyl bromide (200 mol %), and treatment with propylenediamine to scavenge excess alkyl halide.

With primary and secondary amino pyrroles in hand, we explored diazepinone annulation. The Pictet−Spengler reaction refers commonly to the condensation of a tryptamine analog with an aldehyde or ketone to yield a β-carboline;[22] however, this intramolecular annulation via an imminium ion intermediate has been accomplished with a variety of amines tethered to electron-rich aromatic and heteroaromatic ring systems. Few reports have, however, described Pictet−Spengler reactions with pyrrole as the nucleophile.[23–27] For example, pyrrolo[3,2-*e*]pyrimidines were made from the Pictet−Spengler reactions of ureidopyrroles and arylaldehydes.[27]

To explore the Pictet−Spengler cyclization for adding substituents to the 5-position of the diazepinone ring, we initially heated *N*-(phenyalaninyl)aminopyrrole **12a** with a set of aldehydes and TFA at 70 °C in toluene (condition A, Figure 2). Analysis by LC-MS showed masses corresponding to diazepinone **1** and starting material. Diazepinones **1a**−**j** were purified on silica gel and isolated as pure diastereomers in 8−83% yields (Figure 2). Although the electron-rich *p*-hydroxybenzaldehyde gave diazepinone **1f** in 47% yield, benzaldehyde and the electron-poor *p*-nitro- and *p*-bromobenzaldehydes all reacted with aminoamidopyrrole **12a** to give **1a**,**d**,**e** in 75−83% yields, suggesting that electron-deficient iminium ions were more reactive in the cyclization. Hexanal reacted to give diazepinone **1h** in 22% yield, accompanied by diazepinone **1j** (8%) from a homoaldol reaction prior to cyclization.[28] On the contrary, *iso*-butyraldehyde gave diazepinone **1g** in 72% yield.

With primary amino pyrroles **12**, our best Pictet−Spengler reaction yields and purity were obtained using the aldehyde as the limiting reagent (90 mol %) with **12** (100 mol %) at low concentration (0.01 M) in toluene. A sealed system and

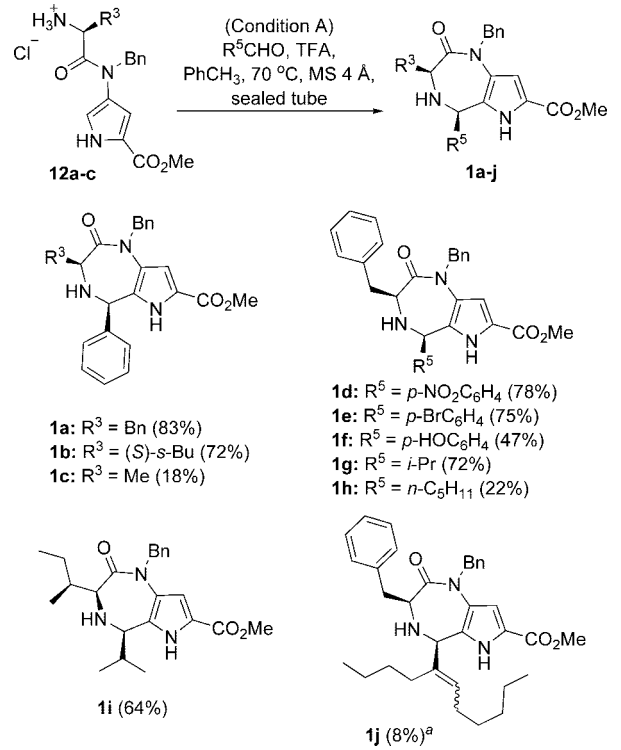

Figure 2. Diazepinones **1a**−**j** (isolated yields) *a*. **1j** was obtained as a side product from the synthesis of **1h** as a single olefin isomer.

degassed solvent avoided oxidation to the corresponding 4,5-unsaturated diazepinone, such as **17** (Figure 3), which formed on air oxidation of **1g**.[29]

Condition A (Figure 2) was also used to react *N*-(isoleucinyl)aminopyrrole **12b** with benzaldehyde and *iso*-butyraldehyde to give diazepinones **1b** and **1i** in 72% and 64% yields, respectively. On the other hand, the less sterically demanding *N*-(alaninyl)aminopyrrole **12c** reacted with benzaldehyde to give **1c** in only 18% yield.

In the case of secondary amines, *p*-substituted benzylamines and allylamine **13a**−**15a** reacted with benzaldehyde under condition B (excess aldehyde in toluene at reflux using a Dean−Stark apparatus) to give diazepinones **1k**−**m** in 62−90% yields, respectively (Figure 3). *p*-Benzyloxybenzylamine **13a** reacted, respectively, with *p*-hydroxybenzaldehyde and *iso*-butyraldehyde to give diazepinone **1p** in 42% yield and diazepinone **1o** in 40% yield, likely due to the volatility of *iso*-butyraldehyde. Alaninylaminopyrrole **16c** also reacted with benzaldehyde to provide diazepinone **1n** in 45% yield.

Diastereoisomerically pure and enriched diazepinones **1** were, respectively, isolated after cyclization of primary (**12a**−**c**) and secondary amines **13**−**16**. The *cis* relative stereochemistry of the major product was assigned based on the observed nuclear Overhauser effect between the signals for the C-5 and C-3 protons in the NOESY spectra of **1a** and the major diastereoisomer of diazepinone **1l**.

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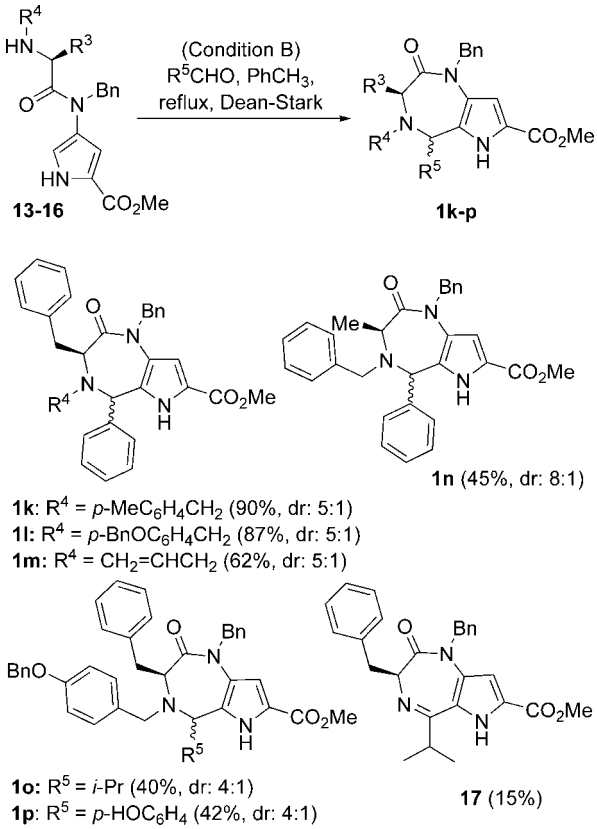

Figure 3. Diazepinones **1k**−**p** (isolated yields) and **17**.

Although unaware of prior art in stereoselective diazepinone synthesis by iminium ion cyclization, we note that *cis* diastereoselectivity was reported in Pictet−Spengler reactions leading to fuzed azepinone systems and suggest a similar mechanism featuring endo attack of the *E*-iminium ion in a transition state having a preferred equatorial conformer of the amino acid side chain.[30]

Crystals of diazepinone **1b** (Figure 4) were grown from ethyl ether and analyzed by X-ray diffraction, which showed an ordered cubic matrix and confirmed the relative cis stereochemistry. In the crystal structure of **1b**, the amino acid residue dihedral angles ($\psi = 72°$, $\phi = -93°$) compared favorably to those of an ideal reverse γ-turn ($\psi = 60°$ to 70°, $\phi = -70°$ to $-85°$).[31] Hence, pyrrolodiazepinones **1** may serve as reverse γ-turn peptide mimics.

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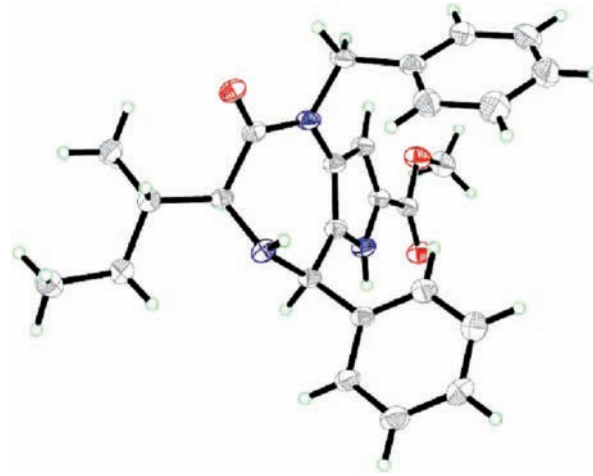

Figure 4. X-ray crystal structure of diazepinone **1b**.

1,3,5-Tri- and 1,3,4,5-tetrasubstituted pyrrolo[3,2-*e*][1,4]diazepin-2-ones **1** were synthesized from *N*-(aminoacyl)aminopyrroles **12**−**16** using diastereoselective Pictet−Spengler annulations. The dihedral angle geometry observed in the crystal structure of pyrrolodiazepinone **1b** compared favorably with an ideal peptide γ-turn, suggesting potential for turn mimicry. In light of the remarkable biological activity of diazepinones, this diversity-oriented methodology should find use for peptide mimicry and medicinal chemistry.

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Supporting Information Available: Experimental procedures, characterizations, and NMR spectras of compounds **1**, **9**, **10**, **12**, and **13**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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