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"Conformationally Restricted β-Amino Acid Isosteres Prepared Through Regioselectively Controlled Aza-Annulation."

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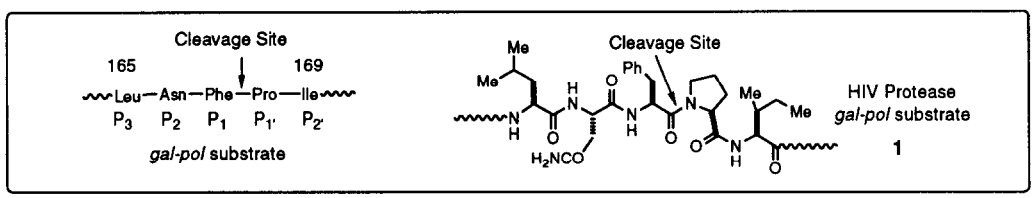
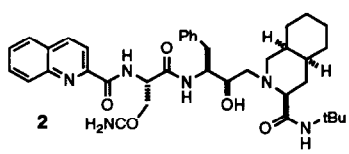
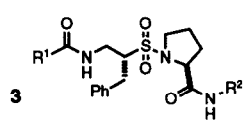
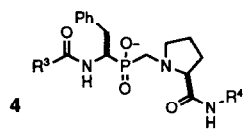
Abstract: A variety of electron withdrawing substituents were used to enhance the aza-annulation of enamines with acryloyl chloride, to direct the regioselectivity of alkene formation, and to facilitate hydrogenation of the unsaturated annulation product. The resulting δ-lactam products were β-amino acid analogs with structural features similar to those of established peptide isosteres.

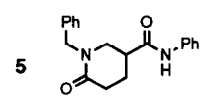
Many important biological processes rely on hydrogen bonding as the key to substrate binding and transition state stabilization. For peptide substrates, specificity of molecular recognition is dependent upon the functional groups present, and their relative topological arrangement. In rational drug design, each of these factors is critical in the evolution of small molecules into natural substrate mimics that will attenuate targeted biological processes through competitive inhibition or enzyme inactivation. For example, this chemotherapeutic strategy has been used in the inhibition of HIV protease, which is essential for viral maturation and infectivity.[1] Peptide isosteres specifically designed for inhibition of this enzyme include **2**,[2] **3**,[3] and **4**,[4] and in each case, these peptide mimics contain a 1,3 substitution pattern of nitrogen or oxygen heteroatoms. In order to design greater structural control into these amino acid analogs, synthetic routes to compounds related in structure to **5**, **6**, and **7** have been investigated. This work represents an approach to the synthesis of conformationally restricted β-amino acid isosteres prepared through regioselectively controlled aza-annulation of enamines with acryloyl chloride.

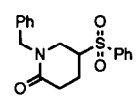


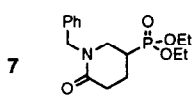








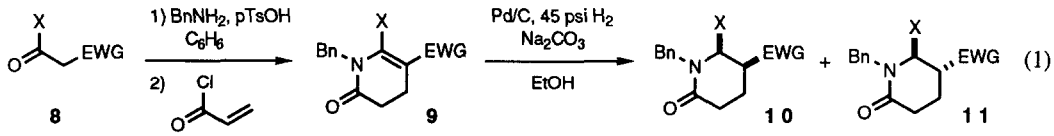




A number of research programs have focused their efforts on preparing peptidomimetic molecules.[5] Several approaches achieved conformational control of the backbone through the incorporation of ring systems,[6] which controlled the spatial arrangement of functional groups by substitution pattern, stereochemistry, and rotational constraints. In these studies, nonpeptidal peptidomimetics have been prepared that imitate naturally occurring β-pleated sheet conformations[7] and β-turns,[8] in which cyclic systems constrain the conformations of 1,2- and 1,3-heteroatom relationships. Other peptide analogs, which have greater potency and increased enzymatic stability, have been prepared by substitution of β-amino acids for α-amino acids in biologically active peptides.[9] Herein, a convergent aza-annulation approach to the synthesis of δ-lactams, through stepwise *C*-alkylation (conjugate addition) and *N*-acylation, is described for the preparation of 1,3-heteroatom substitution patterns similar to β-amino acid derivatives and isosteres **5**, **6**, and **7**.

The placement of an electron withdrawing group (EWG) in a position β to the ketimine has several key advantages in the aza-annulation reaction (eq. 1). In the absence of an electron withdrawing group, such as reported for the benzyl imine of cyclohexanone, treatment with acryloyl chloride produced a mixture of the *N*-acylation product (15%) and aza-annulation products (85%) as an 85:15 mixture of two olefin regioisomers.[10] In the presence of an electron withdrawing group, however, the tautomeric equilibrium shifts from the ketimine form to that of β-enamino functionality. Enhancement of the enamine form produced significant increases in both reaction yield and selectivity under similar aza-annulation conditions.[11]

Table. Aza-Annulation of β-Enamino Derivatives and Subsequent Hydrogenation to δ-Lactams.



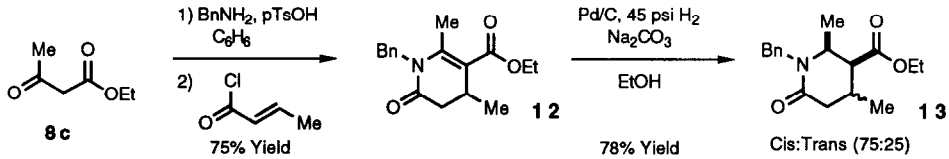
8 **9** **10** **11** (1)

Substrate (8)			Isolated Yield (%)		Selectivity
Compound	X	EWG	9	(10+11)	(10:11)
a	Me	C(O)Me	84	87	72:28
b	Me	C(O)Ph	96	*see text*	
c	Me	CO_2Et	94	91	>99:1
d	CO_2Me	CO_2Me	74	80	>99:1
e	-$CH_2OC(O)$-		48	83	>95:5
f	Me	C(O)NHPh	53	56	>95:5
g	Me	$P(O)(OEt)_2$	72	67	78:22
h	Me	SO_2Me	45	*see text*	
i	Me	SO_2Ph	69	*see text*	

The reaction of β-diketones **8a** and **8b** in the two-step enamine condensation/aza-annulation procedure produced **9a** and **9b** in excellent yields. In each case, a single isomeric alkene product was generated, and complete regioselectivity was observed for enamine formation and annulation of the unsymmetrical β-diketone **8b** (eq. 1, Table).[12] Hydrogenation of the tetrasubstituted alkene gave a mixture of diastereomers for **9a**, but generated three products upon reduction of **9b**, including partial reduction of the benzylic carbonyl.

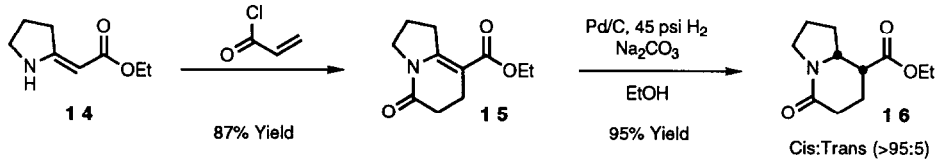
The use of ester EWG substituents also resulted in efficient aza-annulation, but in contrast to the reduction of **9a** and **9b**, hydrogenation of **9c** led to highly *cis* selective product formation (eq. 1, Table).[11,12]

Compound **9d** was formed by a slight modification of this two-step procedure, in which the enamine was formed by the addition of $PhCH_2NH_2$ to $MeO_2CC{\equiv}CCO_2Me$, and then treatment with acryloyl chloride gave **9d**. Diastereoselective formation of **10d** was observed upon subsequent hydrogenation. The reaction of **8e** under identical conditions resulted in a lower yield of **9e**, but hydrogenation still selectively and efficiently produced **10e**. Rationale for the different selectivities observed for **9a** and **9c** was the less favorable enolization of the position α to an ester relative to that of a ketone. The reaction of β-keto esters was also extended to aza-annulation with crotonyl chloride, which produced **12** in 75% yield from **8c** (eq. 2). Hydrogenation of **12** exhibited 75:25 facial selectivity based on the existing stereogenic center.



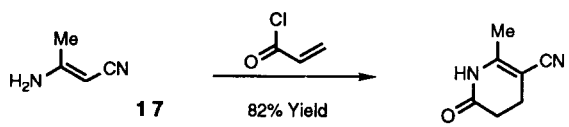
8c 12 13 (2)

Aza-annulation of the cyclic enamino ester **14**, a homolog of proline, produced **15**, the ester of a β-amino acid (eq. 3).[13] The resulting indolizidine product **15** provides some interesting possibilities for amino acid derivatives, and has been used as an intermediate in the synthesis of (±)-tashiromine.[14]



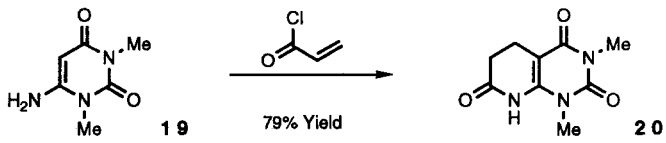
14 15 16 (3)

Turning our attention to the formation of isosteres related to the biologically active pharmaceuticals **2-4**, the condensation/aza-annulation sequence was studied for substrates **8f-i** (eq. 1, Table). The aza-annulation and hydrogenation of **8f** resulted in slightly lower yields than those observed for the esters, but *cis* selectivity in the reduction was high (>95:5). The use of the phosphorous and sulfur[15] electron withdrawing heteroatom substituents gave mixed results. Compound **9g** was efficiently prepared by the two-step convergent process, and hydrogenation led to a 78:22 ratio of diastereomers. For compounds **8h** and **8i**, the sulfone substituent showed a significant effect on the aza-annulation process, with the Ph substituent producing more favorable results. Hydrogenation of **9h** produced an undefined mixture of products, while the reduction of **9i** did not proceed under these conditions. In a related example, the reaction of **17** with acryloyl chloride produced formation of **18** through aza-annulation in good yield, despite the presence of the primary NH_2 enamine (eq. 4). Compound **18** could not be reduced under the standard hydrogenation conditions.



17 18 (4)

An interesting extension of this chemistry, which further demonstrates the utility of this methodology, is aza-annulation with the amino uracil derivative **19** (eq. 5). In this case, aza-annulation efficiently produced the nucleic acid analog **20**.



(5)

In summary, the aza-annulation of stabilized enamino substrates with acryloyl chloride provides an efficient and highly regioselective method for preparing β-amino acid derivatives and peptide isosteres. In some cases, these unsaturated lactams were stereoselectively reduced by catalytic hydrogenation, which was complementary to the *trans* selectivity observed by others for ionic reductions.

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