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A Synthetic Route for the Generation of C-7 Substituted Azepinones

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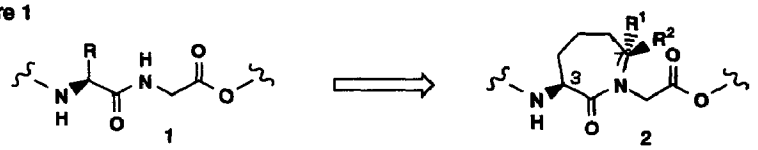
Abstract: A versatile method for the synthesis of 3-amino azepinones possessing alkyl substitution at the C-7 position is described. Compounds of this type may be viewed as conformationally restricted dipeptide surrogates.

The incorporation of conformationally restricted peptidomimetic surrogates in bioactive molecules represents an important field of study in the design and synthesis of medicinal compounds.[1] Such modifications have the potential to enhance the potency, metabolic stability and bioavailability of various peptide based inhibitors and receptor agonist/antagonists. One of the simpler replacements for dipeptide **1** (Figure 1) may be represented by lactam **2** in which conformational restriction is effected via covalent linkage of the R group with the glycine amide nitrogen.

As part of our efforts to generate novel protease inhibitors for the treatment of congestive heart failure and hypertension, our attention has been directed towards the utilization of ε-lactams of the type **2**. Critical to our studies was the ability to ascertain the effects of various alkyl substituents at the C-7 position of the azepinone ring (where both R^1 and $R^2 \neq H$) with respect to biological activity. Alkyl groups at this position could enhance binding of the molecule through hydrophobic interaction with the enzyme. Substitution may also introduce another degree of conformational restriction to the molecule.

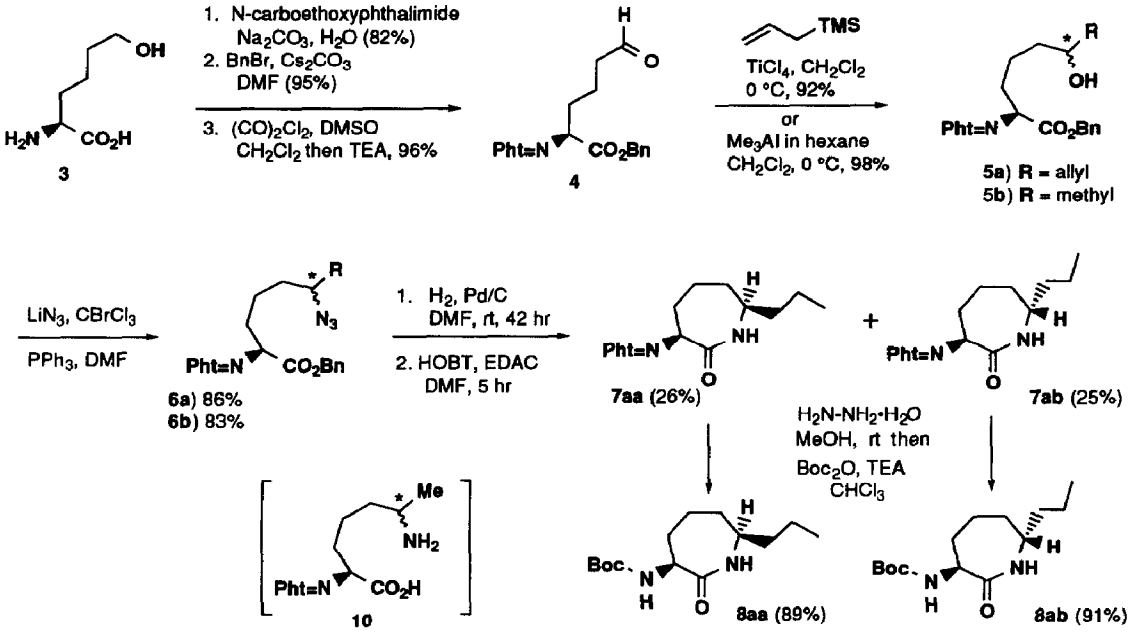
Figure 1



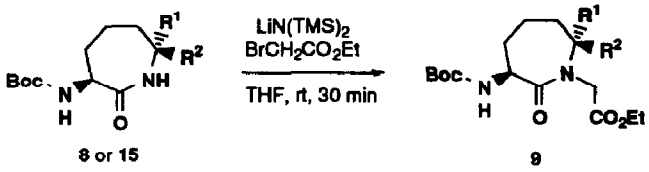
A variety of syntheses for the generation of 3-amino-γ- and δ-lactams have been reported.[2] Literature methods for the synthesis of substituted 3-amino-ε-lactams **2** are either stereorandom[3] at both chiral centers, providing mixtures of racemic compounds, or are unable to provide access to both stereoisomers at C-7.[4] Access to both isomers is necessary in order to determine the effect of stereochemistry at the C-7 position on biological activity. These limitations of known methodologies provided the impetus to develop a new and general method for the synthesis of C-7 substituted azepinones **2**.

L-ε-Hydroxynorleucine[5] proved to be an excellent starting material, possessing both the desired S stereochemistry and the six carbons necessary for construction of the basic azepinone ring (Scheme 1). Phthalimido protection of **3** followed by benzylation of the acid functionality afforded the intermediate alcohol which was subsequently oxidized to the corresponding aldehyde **4**.[6] Treatment of **4** with allytrimethylsilane under $TiCl_4$ catalysis[7] or with Me_3Al in hexane[8] provided the allyl and methyl adducts **5a** and **5b** respectively in excellent yields. As expected, the products were obtained as a 1:1 mixture of diastereomers. The requisite nitrogen functionality was introduced by conversion of alcohols **5a** and **5b** to their corresponding azides.[9] Treatment of **6a** with H_2 over Pd/C in DMF[10] effected hydrogenolysis of the benzyl ester as well as reduction of both the allyl group and the azide functionality. Filtration followed by addition of water soluble carbodiimide and HOBT provided a 1:1 mixture of azepinones **7aa** and **7ab** which were readily separable by flash chromatography.[11] Stereochemical assignment of these isomers was based on single crystal x-ray analysis of isomer **7ab**. Attempts to alkylate the sterically congested lactam nitrogen of either **7aa** or **7ab** with ethyl haloacetate under standard conditions[12] resulted in the formation of partially epimerized desired product in low yield. The propensity of the C-3 center to racemize made it necessary to replace the base sensitive phthalimido group with the hardier Boc group.

Scheme 1



Thus, hydrazinolysis of either **7aa** or **7ab** followed by carbamate formation with Boc_2O gave the corresponding lactams **8aa** and **8ab** in good yield. Rapid alkylation of **8** was best effected using $LiN(TMS)_2$ as base (Equation 1). Under these conditions,[13] **9a** and **9b** were obtained in good yield without epimerization at the C-3 center. No products due to alkylation of the Boc group were observed.



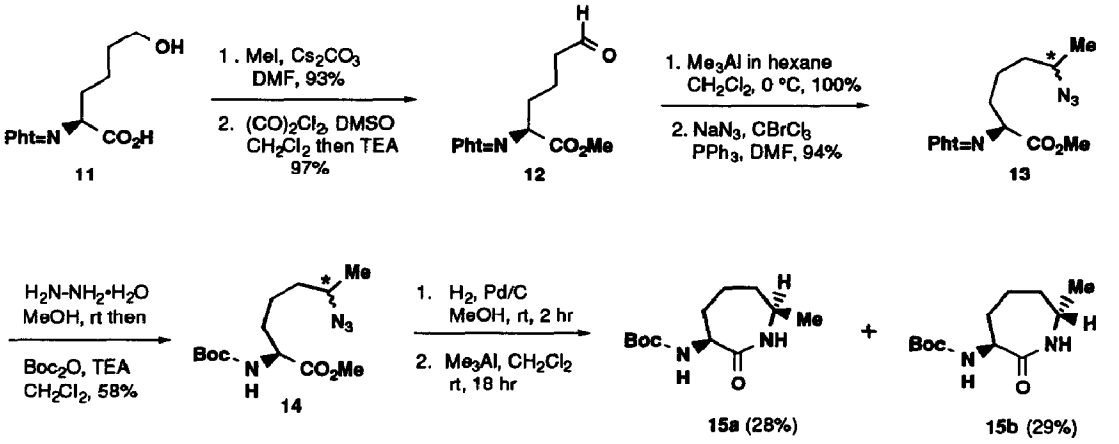
	R¹	R²	% yield
9a	propyl	H	83
9b	H	propyl	87
9c	methyl	H	100
9d	H	methyl	85

(Eq. 1)

Synthesis of the methyl substituted azepinones followed a slightly different route. Reduction of **6b** (Scheme 1) under the previously described conditions afforded intermediate amino acid **10**. In contrast to the propyl substituted case, we were unable to effect intramolecular cyclization of **10** in synthetically useful yields. The reason for this change in reactivity is unclear but necessitated development of the route depicted in Scheme 2.

Similar to the conversion of **3** to **6b**, N-phthaloyl-L-ε-hydroxynorleucine (**11**) was methylated then subjected to Swern oxidation to give aldehyde **12**. Subsequent treatment with Me_3Al followed by $NaN_3/CBrCl_3/PPh_3$ in DMF provided a 1:1 mixture of diastereomeric azides **13** in 85% overall yield from **11**. At this point the phthalimido group was removed and replaced with Boc. Hydrogenation of **14** provided the corresponding amine which, upon treatment with 2.0 equivalents Me_3Al in CH_2Cl_2,[14] afforded the readily separable lactams **15a** and **15b** in 57% yield.[11] Stereochemical assignment of the isomers was based on single crystal x-ray analysis of isomer **15b**. Alkylation of the lactam nitrogen of **15a** and **15b** proceeded smoothly (Equation 1) to afford **9c** and **9d** respectively in good yield and homochiral form.

Scheme 2



It is expected that this newly developed methodology can be applied towards the synthesis of other C-7 substituted azepinones simply by the appropriate choice of aldehyde and organometallic reagent (for R^1 or R^2). In addition, diastereoselective coupling of organometallic reagents[15] with aldehydes **4** or **12** has the potential to afford the corresponding secondary alcohols, and eventually the desired lactams, in high overall selectivity.

Conversion of lactams **9** to their corresponding amines or acids can readily be effected by treatment with either HCl in dioxane or aqueous NaOH in EtOH respectively. Utilization of these intermediates for the synthesis of metalloprotease inhibitors will be the subject of a future disclosure.

Acknowledgment: Appreciation is expressed to Ms. Mary Malley for performing the crystallographic analysis on compounds **7ab** and **15b**.

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10. The use of methanol as solvent in the hydrogenation of **6a** or **6b** gives poor yields of the corresponding amino acids.
11. For compound **7aa**: mp = 155-160 °C, $[\alpha]_D$ = +55.7° (c = 0.7, $CHCl_3$), TLC R_f 0.48 (75/25-EtOAc/hexanes on SiO_2); for compound **7ab**: mp = 148-150 °C, $[\alpha]_D$ = -5.7° (c = 0.4, $CHCl_3$), TLC R_f 0.38 (75/25-EtOAc/hexanes on SiO_2); for compound **15a**: mp = 108-109 °C, $[\alpha]_D$ = +18.1° (c = 0.27, CH_2Cl_2), TLC R_f 0.39 (1/1-EtOAc/hexanes on SiO_2); for compound **15b**: mp = 137-138 °C, $[\alpha]_D$ = -2.8° (c = 0.82, CH_2Cl_2), TLC R_f 0.23 (1/1-EtOAc/hexanes on SiO_2)
12. A variety of bases (NaOH, NaH, t-BuOK), alkylating agents (ethyl bromoacetate, ethyl chloroacetate) and solvents (THF, DMF, t-BuOH) were tried.
13. In a typical reaction, a solution of the Boc lactam (2 mmol) in dry THF (20 mL) at room temperature is treated with $LiN(TMS)_2$ (1.0 M in THF, 2.6 mL) followed by ethyl bromoacetate (450 μL, 4 mmol). After 30 minutes, the mixture is quenched with saturated NH_4Cl and extracted with EtOAc. The organic extract is washed with brine, dried (Na_2SO_4), filtered and evaporated. Flash chromatography on silica gel affords the desired product.
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