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3,8-Diazabicyclo[3.2.1]octan-2-one Peptide Mimetics: Synthesis of a Conformationally Restricted Inhibitor of Farnesyltransferase†

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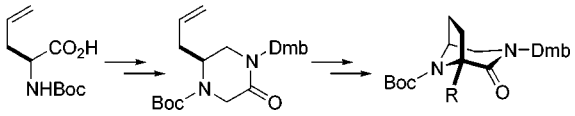
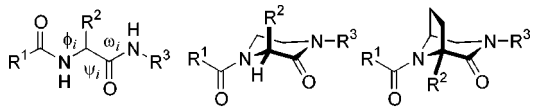
ABSTRACT



A new synthesis of the 3,8-diazabicyclo[3.2.1]octan-2-one framework is described. Transannular enolate alkylation of piperazinone derivatives provides a flexible route to highly constrained bicyclic peptidomimetic synthons with substitution at the Cα position. The chemistry was used to produce a conformationally constrained farnesyltransferase inhibitor, which aided the elucidation of enzyme-bound conformation.

The manipulation of amino acid conformation is an important strategy in the chemical investigation of biological systems. Conformationally constrained amino acid segments have been important tools for drug design in support of understanding and optimizing interactions between ligands and macromolecules.[1] Methods of affixing desired dihedral angles within the backbone of a peptide segment are numerous,[1a−c] and many employ the Freidinger strategy of incorporating ring-induced constraints.[2]



1 **2** **3**

Piperazinones **2** function as peptidomimetics wherein the N_i and N_{i-1} positions of an amino acid backbone fragment **1** are linked by an ethylene unit. This ring constraint results in restriction of the ϕ_i, ψ_i, and ω_i torsion angles.[3] Amino group acylation induces an A(1,3)-strain-enforced pseudoaxial position of the Cα side chain (R^2) substituent, further restricting the conformation.[4] A more rigid variant of **2** with better defined structure is achieved by the incorporation of a transannular bridge. Thus, the 3,8-diazabicyclo[3.2.1]octan-2-one compound **3** is a piperazinone−proline hybrid in which the side chain (R^2) substituent is forced to occupy a pseudoequatorial position with respect to the piperazinone ring by virtue of the diaxially disposed ethano bridge. Since chair−chair interconversion is prevented, the peptide backbone torsion angles are severely constrained. While methods

† Dedicated to Professor David A. Evans on the occasion of his 60th birthday.

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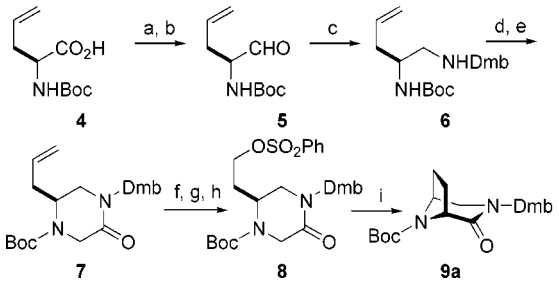
exist for the construction of the unsubstituted scaffold (**3**, R^2 = H) from pyroglutamate derivatives,[5] most of these syntheses have provided racemic material,[5b−f] and none features the incorporation of a Cα side chain substituent. In this report we describe a versatile synthetic approach to **3** that enables facile substitution at the Cα position. We also discuss the synthesis and biological characterization of a novel 3,8-diazabicyclo-[3.2.1]octan-2-one farnesyltransferase inhibitor that provides insight into the enzyme-bound conformation of related flexible inhibitors (vide infra).

The synthesis is based on the preparation of an appropriately substituted piperazinone[3,6] followed by a pivotal transannular alkylation reaction[7] to install the [3.2.1] bicyclic ring system (Scheme 1). Boc-(*S*)-allylglycine **4** was converted to the corresponding aldehyde **5**[8] and then used to reductively alkylate 2,4-dimethoxybenzylamine to give **6**. Chloroacetylation and base-promoted cyclization provided the 5-allyl-2-piperazinone **7**. Refunctionalization of the olefin in **7** was accomplished by oxidative cleavage, aldehyde reduction, and conversion to the benzenesulfonate **8**. Finally, after treatment of **8** with LiHMDS in THF at −78 °C and warming the reaction to 0 °C, an intramolecular enolate alkylation occurred to afford the bicyclic framework **9a** in 86% yield.[9,10]

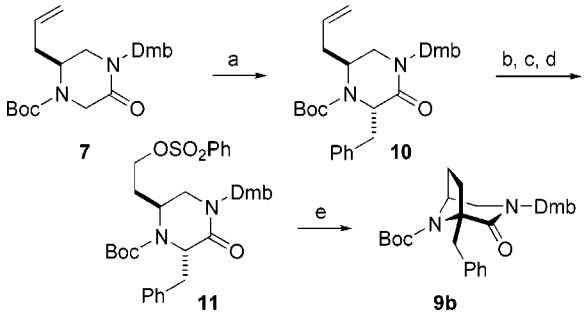
Scheme 1[a]



[a] Reagents and conditions: (Dmb = 2,4-dimethoxybenzyl) (a) MeO(Me)NH·HCl, EDC, HOBt, DMF, 0 °C, 24 h, 67%. (b) $LiAlH_4$, Et_2O, −50 → 5 °C, 3 h, 85%. (c) 2,4-(MeO)BnNH$_2$, $Na(AcO)_3BH$, 4 Å MS, $ClCH_2CH_2Cl$, 16 h, 90%. (d) $ClCH_2COCl$, $NaHCO_3$, EtOAc−H_2O, 0 °C, 30 min, 93%. (e) Cs_2CO_3, DMF, 65 °C, 16 h, 75%. (f) OsO_4, NMO, *t*-BuOH, THF, H_2O, 7 h; $NaIO_4$, $NaHCO_3$, 1.5 h, 96% (g) $NaBH_4$, EtOH, 0 °C → rt, 1 h, 92%. (h) $PhSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C → rt, 1 h, 83%. (i) LiHMDS, THF, −78 → 0 °C, 40 min, 86%.

An amino acid Cα side chain substituent was easily introduced into the bicyclic framework from the piperazinone intermediate **7**, providing a method for the preparation of a constrained phenylalanine isostere.[11] Thus, alkylation of **7** with benzyl bromide (Scheme 2) provided the *trans*-disubstituted compound **10** (diastereoselectivity ≥ 95:5). Smooth conversion as before to the benzenesulfonate **11**, followed by cyclization with strong base (LDA, THF, −78 to 0 °C),[12] afforded the constrained bicyclic analogue **9b**.

Scheme 2[a]



[a] Reagents and conditions: (a) LiHMDS, THF, −78 °C; BnBr, −78 °C, 3.5 h, 74% borsm. (b) OsO_4, NMO, *t*-BuOH, THF, H_2O, 2.5 h; $NaIO_4$, $NaHCO_3$, 2 h. (c) $NaBH_4$, EtOH, 0 °C, 20 min, 70% two steps. (d) $PhSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C, 1 h, 90%. (e) LDA, THF, −78 → 0 °C, 2 h, 63%.

The intermediate **9a**, prepared above, was used to synthesize a conformationally restricted inhibitor of farnesyltransferase (FTase). FTase is an important posttranslational processing enzyme that prenylates proteins and enables the participation of some in signal transduction during cell proliferation.[13] Inhibitors of this enzyme (FTI) are promising antitumor agents, and several are currently being evaluated in human clinical trials.[14] During our investigations of peptidomimetic 1-aryl-2-piperazinone FTIs (e.g., **12**, Figure

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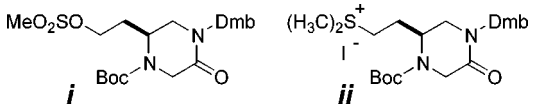
(9) Compound **9a** was subjected to Boc-deprotection (HCl, EtOAc, 0 °C), conversion to the (+)- and (−)-10-camphorsulfonamides (10-camphorsulfonyl chloride, Et_3N, DMF), and HPLC analysis to confirm ≥ 97% enantiomer purity.

(10) Transannular alkylation of the methanesulfonate ***i*** under the same conditions provided an 8:1 mixture of **9a** and the alcohol derived from cleavage of the methanesulfonyl group. Attempts to cyclize the sulfonium salt ***ii*** derived from L-methionine were unsuccessful.



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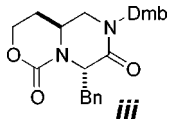
(12) Attempted cyclization using LiHMDS (THF, −78 to 0 °C, 5 h) gave only recovered **11**. The use of KHMDS under the same conditions resulted in gradual conversion to the dihydrooxazinone ***iii***.



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1),[15] we discovered that they adopt a folded conformation when bound to the enzyme and that a macrocyclic constraint (e.g., **13**) enhances potency by stabilizing the bound conformation.[16] The importance of the carbonyl group position for FTase inhibitory activity was also established.[17] We sought to further elucidate enzyme-bound conformations of these compounds with respect to the position of the carbonyl group. In principle, this could be accomplished by constraining the conformational flexibility of the piperazinone ring and inhibiting the positional mobility of the carbonyl group. On the basis of these considerations, a 3,8-diazabicyclo-[3.2.1]octan-2-one analogue of the macrocycle **13** was selected as a target for synthesis.

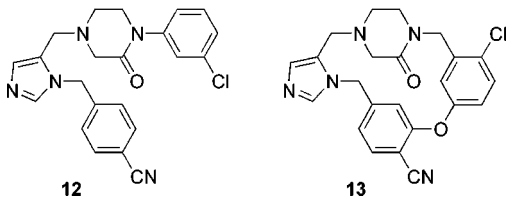
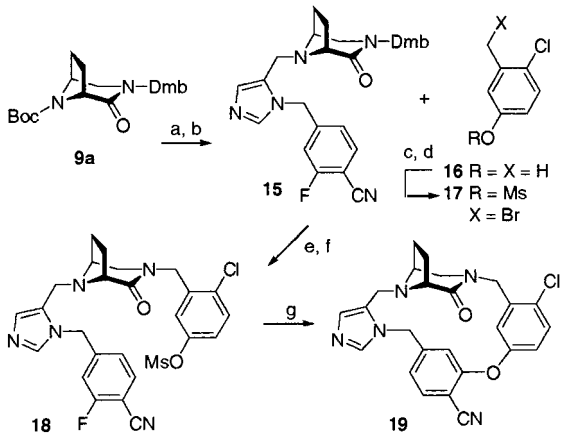


Figure 1. Piperazinone farnesyltransferase inhibitors **12** and **13**.

The intermediate **9a** was deprotected and reductively alkylated with 1-(3-fluoro-4-cyanobenzyl)imidazole-5-carboxaldehyde (**14**)[16] to provide amine **15** (Scheme 3). The 2,4-dimethoxybenzyl amide protecting group, normally sensitive to treatment with TFA,[18] required prolonged exposure to triflic acid and triethylsilane in a solubilizing dichloromethane−acetonitrile mixture to effect deprotection. The robustness of this protecting group is likely due to protonation of the piperazinone amino group in **15**, which impedes protonation of the nearby amide. Alkylation of the bridged piperazinone with bromide **17** gave **18**, which was subjected to a tandem base-promoted methanesulfonate group deprotection and S_NAr cyclization to provide the cyclophane **19**.[19]

Scheme 3[a]



[a] Reagents and conditions: (a) HCl, EtOAc, 0 °C, 0.5 h, 100%. (b) 1-(3-fluoro-4-cyanobenzyl)imidazole-5-carboxaldehyde (**14**), $Na(AcO)_3BH$, 4 Å MS, DCE, 24 h, 56%. (c) MsCl, Et_3N, CH_2Cl_2, 30 min. (d) NBS, AIBN, CCl_4, 80 °C, 14 h, 70%, two steps. (e) TfOH, Et_3SiH, CH_2Cl_2−CH_3CN, 14 d, 69% based on 75% conv. (f) NaH, DMF, **17**, 0 °C, 1 h, 55%. (g) Cs_2CO_3, DMSO, 80 °C, 5 h, 34%.

The calculated lowest-energy structure of **19** reveals the anticipated conformation with the ethylene bridge projecting to the exterior of the macrocyclic ring (Figure 2, gray).[20]

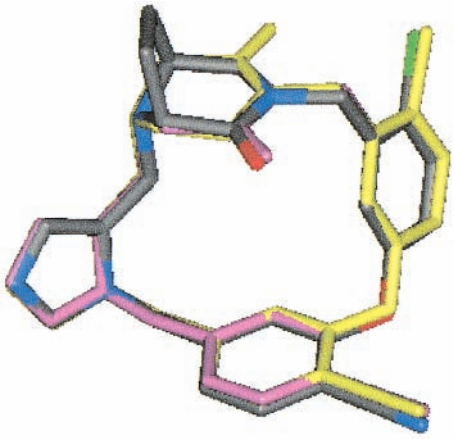


Figure 2. Superposition of the calculated lowest energy conformations of **19** (gray) and **13** (pink), and a conformation of **13** with the carbonyl group projecting back (yellow).

Variable temperature ^1H NMR studies revealed differential line broadening below 0 °C, with two sets of resonances at −50 °C (∼5:1 ratio), indicating slow conformational exchange. NOE data obtained at room temperature are consistent with a mixture of available species, most likely

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(20) (a) Molecular modeling: Conformations were generated using metric matrix distance geometry algorithm JG (S. Kearsley, Merck & Co., Inc., unpublished). The structures were subjected to energy minimization within Macromodel (ref 20b) using the MMFF force field. (b) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

derived from mobility of the imidazole, cyanophenyl, and chlorophenyl rings relative to the 3,8-diazabicyclo[3.2.1]-octan-2-one ring.[21] Compound **13**, in its lowest energy state (Figure 2, pink),[20] adopts the same conformation as does **19**. The corresponding orientation of **13** with the carbonyl group projected in the opposite direction[22] is only 2.63 kcal/mol higher in energy (Figure 2, yellow). In comparison, a conformation of **19** with the alternative rearward orientation of the carbonyl group (not shown) is 39.2 kcal/mol higher in energy than the ground state, since it requires that the ethylene bridge reside in the congested interior of the macrocycle.

Compound **19** was assayed for inhibition of FTase-catalyzed incorporation of [^{3}H]-farnesylpyrophosphate into recombinant Ras-CVIM[23] and was found to be more potent than the parent unbridged compound **13** (IC_{50} **19** = 0.13 nM, IC_{50} **13** = 0.7 nM). Taken with the conformational analyses described above, this result suggests that the FTase-bound conformation of **13** is one in which the carbonyl group is projected in a forward orientation (*S*-configuration of the piperazinone plane), as in the constrained compound **19**. This, in conjunction with earlier results,[16] implies that 1-aryl-2-piperazinone FTIs (e.g., **12**) adopt a similar enzyme-bound conformation as well.

In summary, a new method for the synthesis of the 3,8-diazabicyclo[3.2.1]octan-2-one framework enables access to Cα-substituted derivatives as constrained peptide mimetics. A bicyclic-constrained analogue of a piperazinone farnesyltransferase inhibitor was prepared and was useful for the elucidation of enzyme-bound conformation.

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Supporting Information Available: Experimental procedures and characterization for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) This interpretation is supported by computational analyses (ref 20), which revealed only moderate energy increases for the following conformational perturbations relative to lowest energy **19** (cf. Figure 2): front-to-back rotations of the imidazole, cyanophenyl rings and back-to-front rotation of the chlorophenyl ring (1.66 kcal/mol); axial−equatorial isomerization (2.94 kcal/mol).

(22) An alternative conformation of **13** with the carbonyl projected in the opposite direction relative to **19** is the enantiomer of lowest energy **13**.

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