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NEW ROUTES TO CONFORMATIONALLY RESTRICTED PEPTIDE BUILDING BLOCKS: A CONVENIENT PREPARATION OF BICYCLIC PIPERAZINONE DERIVATIVES

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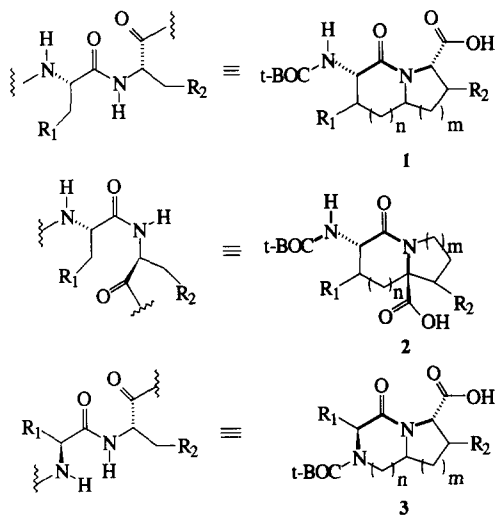
Abstract: A facile route for the synthesis of peptide building blocks that constrain the peptide backbone with a 1,4-diazabicyclo[4.3.0]nonane ring skeleton is reported. The synthesis employed an anodic amide oxidation based approach for generating a functionalized proline derivative, and then utilized the derivative as a general substrate for rapidly assembling the bicyclic ring system.

Over the past several years, we have been working to develop a series of conformationally restricted peptide analogs for probing the relationship between the predicted and actual biological activity of peptide conformations.[1] This work has been exploring the overall utility of analogs that have the peptide backbone "imbedded" into a bicyclic (or polycyclic) carbon framework (Scheme 1).[2] Such an approach allows for preservation and orientation of both the backbone functionality and the amino acid side chains of the peptide. In addition, such an approach offers advantages in terms of the ease with which restricted analogs can be designed from predicted conformations. The design of new, restricted analogs simply involves identifying protons in the desired peptide conformation that are spacially close together and then replacing the protons with an appropriately sized bridge. However, while restricted analogs of this type are simple to design, they are not always simple to construct. For this reason, we have been developing synthetic methods in order to make readily available peptide analogs having the overall structures embodied by compounds **1-3**. To date, our interest in the binding of thyrotropin releasing hormone (TRH) to its endocrine receptor site (TRH-R) has focused much of our attention on peptide analogs of type **1**[3] and type **2**.[4,5]

Scheme 1

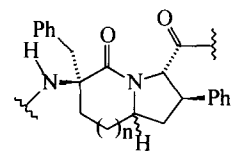


1 2 3

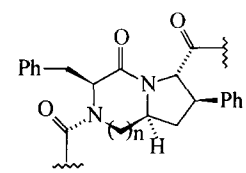
Recently, interest in probing the accuracy of two computer based models for the binding of substance P[6] to its NK1 receptor has led to the design of two new groups of peptide analogs (Scheme 2).[7] These analogs would target the critical Phe[7]-Phe[8] region of substance P. While the structure of **4** appears to be consistent with

the synthetic methodology developed in conjunction with analogs of type **1**, compound **5** would represent an analog of type **3**. In order to study the overall utility of these analogs, we first needed to develop a convenient synthetic route to the functionalized bicyclic ring systems. We report herein an electrochemically based approach for rapidly assembling the novel bicyclic piperazinone ring skeletons (**5**, n = 1).[8]

Scheme 2



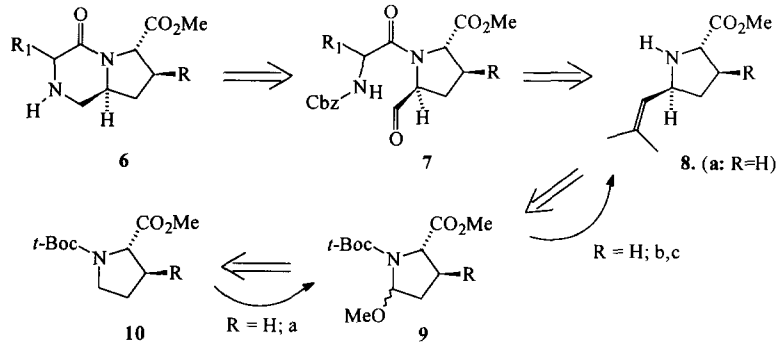
4 (n=0,1)



5 (n=1,2)

The plan for constructing these analogs called for the use of a reductive amination reaction in order to assemble the six-membered ring lactam (Scheme 3). The aldehyde required for this cyclization (**7**) reaction would be derived from a 5-vinyl proline derivative (**8**) that would in turn be generated by electrochemically functionalizing the corresponding proline derivative.[9,10] As a starting point for testing the feasibility of this

Scheme 3

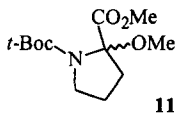


6 **7** **8. (a: R=H)** **10** **9**

R = H; a R = H; b,c

Reagents: (a) Carbon rod anode, Pt wire cathode, undivided cell, 0.03 M Et_4NOTs in MeOH electrolyte solution, constant current of 26.8 mA (3.0 F/mole), 95%; (b) $(CH_3)_2C$ = CHLi, CuBr·Me_2S, BF_3·Et_2O, Et_2O, -78 °C to 0 °C, 89%; c) i. TBDMSOTf, 2,6-lutidene, CH_2Cl_2; ii. *n*-Bu_4NF, H_2O, THF, 0 °C, 68% (over the two steps).

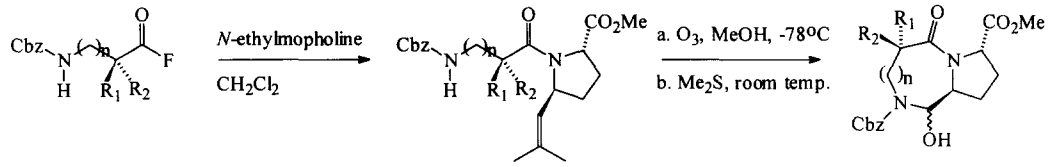
approach, proline methyl ester was selected as the substrate for the electrolysis. As expected, the anodic oxidation proceeded smoothly to form **9**, which was then readily converted into the desired building block **8a**. As an interesting sidenote, it was found that the reaction of the cuprate reagent with the *N*-acyliminium ion derived from **9** could not be allowed to stir for more than 15 minutes before quenching with a 1:1 solution of NH_4OH and saturated NH_4Cl. Longer reaction times led to a decrease in the yield of the 5-vinyl substituted proline and the formation of a proline side product that was methoxylated at the 2-position (**11**). Apparently, kinetic formation of the 5-vinyl substituted proline derivative was reversible under the reaction conditions. Given time, the initial *N*-acyliminium ion isomerized and then trapped methanol at C_2. Due to the electron withdrawing nature of the methyl ester, regeneration of the iminium ion toward C_2 would be expected to be slow, effectively stopping the reaction. The stereochemistry of the vinyl proline derivative was tentatively assigned as trans based on literature precedent.[10] This assignment was confirmed after completing the synthesis of **15a**. At this point, no other isomer could be observed by 300 MHz ^1H NMR.



11

With the 5-vinyl proline derivative **8a** in hand, the desired bicyclic piperazone analogs could be rapidly synthesized in just three steps. Several examples are illustrated below (Scheme 4). In each case, **8a** was coupled to a second amino acid derivative by activating the carboxyl end of the amino acid as the acid fluoride.[11] The

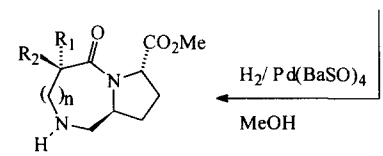
Scheme 4



12a. R_1=H, R_2=CH_3, n=0
12b. R_1=H, R_2=CH_2Ph, n=0
12c. R_1=CH_3, R_2=H, n=0
12d. R_1=H, R_2=H, n=1

13a. 79%
13b. 84%
13c. 75%
13d. 91%

14a. 99%
14b. 98%
14c. 97%
14d. (99%)

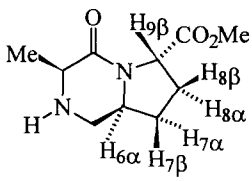


15a. R_1=H, R_2=CH_3, n=0 79%
15b. R_1=H, R_2=CH_2Ph, n=0 62%
15c. R_1=CH_3, R_2=H, n=0 82%
15d. R_1=H, R_2=H, n=1 79%

coupling reactions utilizing the acid fluoride were found to be far superior to alternative routes using either EDC or mixed anhydride based methodologies. Yields using these alternatives were typically in the range of 15-50%. Ozonolysis of the olefin followed by reductive workup led to the aldehyde which immediately cyclized to form the bicyclic ring system. Hydrogenolysis using palladium on barium sulfate then removed both the hydroxy group and the Cbz protecting group and afforded the desired bicyclic peptide mimetics. In the cases forming six-membered rings (**15a-15c**), a small amount (*ca.* 5%) of a minor isomer was formed.

For **15a**, the stereochemistry of the major isomer was assigned with the use of a NOESY experiment. The key crosspeaks used in this assignment are listed in Table 1. The proton and carbon connectivity of **15a** was assigned with the use of an HMBC experiment.[12] As indicated, the stereochemistry of H_6 was assigned relative to the stereochemistry of H_9 by using H_9 to assign the stereochemistry of the protons on C_8 and C_7 and then using the stereochemistry of these centers to establish the stereochemistry of H_6.

Table 1



15a

Signal 1	Signal 2	NOE crosspeak - Volume integral
$H_{9\beta}$	$H_{8\beta}$	0.621
$H_{9\beta}$	$H_{8\alpha}$	0.151
$H_{9\beta}$	$H_{7\beta}$	0.205
$H_{9\beta}$	$H_{7\alpha}$	--
$H_{6\alpha}$	$H_{7\alpha}$	0.816
$H_{6\alpha}$	$H_{7\beta}$	0.386
$H_{6\alpha}$	$H_{8\alpha}$	0.551
$H_{6\alpha}$	$H_{8\beta}$	--

The formation of the bicyclic piperazinone skeleton was compatible with both the use of L- or D-amino acids (**15a** and **15c**), as well as the benzyl substituent (**15b**) needed for the substance P analog synthesis. In addition, the formation of **15d** demonstrated the versatility of the synthetic sequence for generating the

analogous seven-membered ring lactam analogs. In this case, a 2:1 ratio of trans to cis isomers was formed. The stereochemistry of both isomers were assigned with the use of a NOESY experiment in a fashion directly analogous to **15a**.

In conclusion, the synthetic route developed provides a convenient route for rapidily constructing peptide analogs having a bicyclic piperazinone ring skeleton. Efforts to extend this work to the synthesis of substance P analogs having the general structure of **5** are currently underway and will be reported in due course.

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