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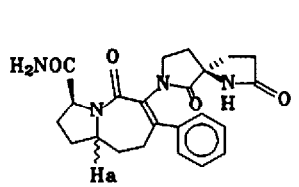
CONFORMATIONALLY CONSTRAINED THYROLIBERIN ANALOGS: A NOVEL ELECTROCHEMICAL ROUTE TO A KEY RIGID PRO-PHE BUILDING BLOCK

Kevin D. Moeller* and Scott L. Rothfus
Department of Chemistry, Washington University, St. Louis, MO 63130

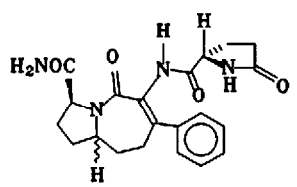
Abstract: An anodic amide oxidation has been employed in the synthesis of a rigid Pro-Phe building block. The key electrochemical step allowed for the functionalization of a proline derivative and led to an annulation procedure for conveniently constructing the bicyclic ring system used to lock the dipeptide building block into a specific conformation.

The active analog approach for modeling the three-dimensional requirements for drug-receptor binding may provide a powerful tool for designing new drug candidates.[1] Unfortunately, attempts to refine the three-dimensional picture obtained can lead to the design of conformationally restricted analogs that have complex structures and are difficult to synthesize for biological testing. One example of such a problem involves the rigid peptide analogs (**I-III**) illustrated in Scheme 1. These analogs were designed by Marshall and coworkers in

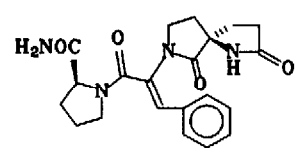
Scheme 1



I Both isomers at Ha are desired.



II



III

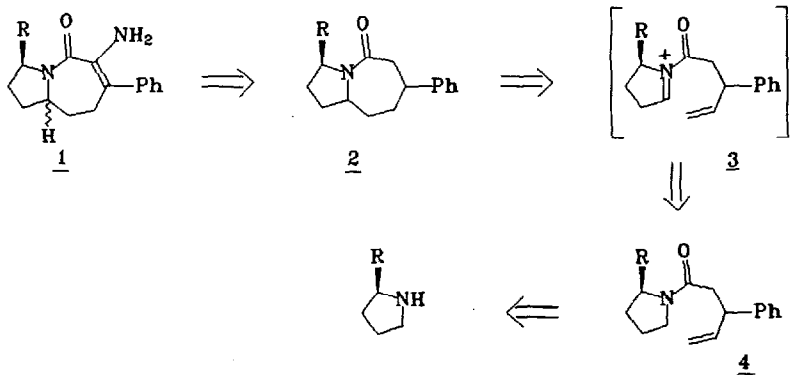
an effort to map the receptor-bound conformation of thyroliberin (TRH).[2] Work on this project stopped when the rigid analogs could not be synthesized.

One of the main problems associated with the synthesis of these analogs involved construction of the seven-membered ring lactam unit used to add rigidity to the left-hand portion of analogs **I** and **II**. Although related five- and six-membered ring lactam rings have been used to fix the conformation of peptide units on numerous occasions,[3] the seven-membered lactam utilized above leads to a 1-aza-2-oxobicyclo[5.3.0]decane ring skeleton that is not common and has only been synthesized on rare occasion.[4,5] Recently we reported that ring systems of this type can be readily prepared using an anodic amide oxidation based procedure for annulating

rings onto amines and amino acid derivatives.[6,7] Herein we report the utility of this method for synthesizing a key Pro-Phe building block (**1**) for use in the synthesis of **I** and **II**.[8]

A retrosynthetic analysis of building block **1** is outlined in Scheme II. In this plan, the key bicyclic ring

Scheme II

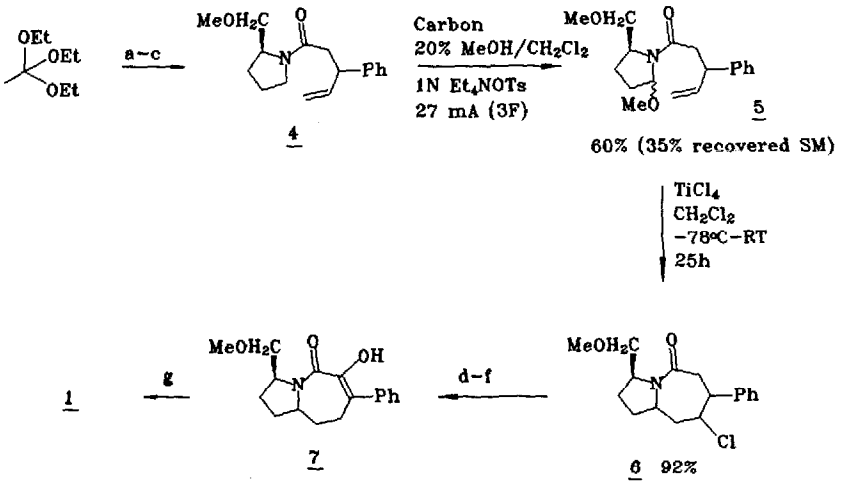


skeleton would arise from synthesis of amide **4** followed by an anodic oxidation reaction in order to form the *N*-acyliminium ion intermediate **3**. Cyclization of an olefin onto *N*-acyliminium ion **3** would then complete the annulation procedure and the synthesis of the desired lactam ring. The plan called for incorporation of the functionality α to the amide following the annulation procedure because oxygen substituents at this position have been shown to interfere with the anodic oxidation of proline derivatives.[9]

The synthesis was completed as illustrated in Scheme III. Amide **4** was prepared from triethyl orthoacetate, cinnamyl alcohol, and (S)-(+)-2-(methoxymethyl)pyrrolidine. This synthesis hinged on the use of an ortho ester Claisen rearrangement.[10] The overall yield of **4** from the orthoester was 63%. The methoxymethyl group was chosen as a protecting group for the proline unit because it was compatible with the electrochemically based annulation procedure, protected the chiral center from racemization, and could be readily cleaved with the use of iodotrimethylsilane.[11]

Amide **4** was oxidized in an undivided cell using constant current conditions, a carbon anode, and a 1 *N* tetraethylammonium tosylate in 20% methanol/ dichloromethane electrolyte solution. A total of 3 faradays of charge was passed. The reaction was run using 12,8 mmol (3.50 g) of amide and led to a 60% yield of the methoxylated amide product (**5**) derived from methanol trapping of the desired *N*-acyliminium ion. In addition, a 35% yield of recovered starting material was obtained. As we have found typical for a number of anodic oxidation reactions, the passage of additional current did not improve the yield of the oxidation reaction, but did decrease the amount of the starting material recovered. A small amount of overoxidized (bismethoxylated) product was observed. Regeneration of the *N*-acyliminium ion and completion of the annulation procedure was accomplished by treatment of the methoxylated amide with titanium tetrachloride in dichloromethane. A 92% isolated yield of the bicyclic amide product was obtained. It should be noted that attempts to directly cyclize the electrochemically generated *N*-acyliminium ions without first trapping with methanol have not been successful.

Scheme III



Reagents: a) cinnamyl alcohol, cat. propionic acid, reflux, 4h. b) KOH, MeOH, reflux, 6h, 82% over two steps. c) i. $(COCl)_2$, cat. DMF, $PhCH_3$, ii. (S)-(+)-2-(methoxymethyl)pyrrolidine, 76%. d) H_2, 5% Pd/C, NaOMe, MeOH, 88%. e) i. LDA, THF, -50 to -40°C, ii. (+)-(2R,8aS)-(camphorsulfonyl)oxaziridine (Davis' reagent), 78%. f) i. NCS, DMS, CH_2Cl_2, -30 to -20°C ii. Et_3N, 76%. g) NH_3, MeOH, 69%.

The synthesis of building block **1** was completed by hydrogenolysis of **6** in order to cleave the carbon-chlorine bond (88%), treatment of the amide with LDA followed by Davis' reagent[12] in order to hydroxylate the carbon α to the amide carbonyl (78%), and oxidation of the resulting alcohol using the Corey-Kim procedure in order to form compound **7** (76%).[13] Finally, the enamine was formed with the use of ammonia in methanol (69%). Building block **1** was isolated as a 1.8:1 mixture of bridgehead diastereomers. At this point, the major isomer has not been identified. Since both isomers are desired for biological testing, the diastereomers will be separated after the completion of TRH analogs **I** and **II**.

In conclusion, it was found that an anodic amide oxidation based strategy for constructing the key Pro-Phe building block **1** was very effective. The synthetic route is nine steps long, leads to a 13% overall yield of **1** (not accounting for the recovered starting material in the amide oxidation), and is capable of producing multigram quantities of the building block. This synthesis serves to illustrate the potential utility of anodic amide oxidations for constructing rigid peptide analogs. Studies aimed at completing the syntheses of **I** and **II** and at using electrochemistry to construct other lactam based rigid peptide building blocks are currently underway.

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References and Notes:

1. For reviews concerning the active analog approach see a) Marshall, G. R.; Barry, C. D.; Bosshard, H. E.; Dammkoehler, R. A.; Dunn, D. A. In *Computer-Assisted Drug Design*, Olson, E. C.; Christoffersen, R. E. Eds.; American Chemical Society, Washington D. C., 1979, pg. 205, b) Marshall, G. R. *Ann. Rev. Pharmacol. Toxicol.* **1987**, *27*, 193, c) Marshall, G. R.; Motoc, I. In *Molecular Graphics and Drug Design*, Burgen, A. S V.; Roberts, G. C. K.; Tute, M. S. Eds.; Elsevier, Amsterdam, 1986, 115.

2. Font, J. Ph.D. Thesis, Washington University in St. Louis, 1986.

3. For examples see a) Rapoport, H.; Wolf, J. P. *J. Org. Chem.* **1989**, *54*, 3164 as well as references 1-8 therein, b) Freidinger, R. M.; Perlow, D. S.; Veber, D. F. *J. Org. Chem.* **1982**, *47*, 104, c) Freidinger, R. M. *J. Org. Chem.* **1985**, *50*, 3631, d) Zydowsky, T. M.; Dellaria Jr., J. F.; Nellans, H. N. *J. Org. Chem.* **1988**, *53*, 5607, e) Kempf, D. J.; Condon, S. L. *J. Org. Chem.* **1990**, *55* 1390, f) Ward, P.; Ewan, G. B.; Jordon, C. C.; Ireland, S. J.; Hagan, R. M.; Brown, J. R. *J. Med. Chem.* **1990**, *33*, 1848, g) Toniolo, C. *Int. J. Peptide Protein Res.* **1990**, *35*, 287.

4. a) Elofson, R. M.; Gadallah, F. F.; Laidler, J. K. *Can. J. Chem.* **1987**, *65*, 2770 and b) Aube, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965.

5. For the successful use of a similar 1-aza-2-oxobicyclo[5.4.0]undecane ring skeleton see Flynn, G. A.; Giroux, E. L.; Dage, R. C. *J. Am. Chem. Soc.* **1987**, *109*, 7914.

6. Moeller, K. D.; Rothfus, S. L.; Wong, P. L. *Tetrahedron* **1991**, *47*, 583.

7. For related electrochemically based annulations see a) Shono, T.; Matsumura, Y.; Tsubata, K. *J. Am. Chem. Soc.* **1981**, *103*, 1172 and b) Moeller, K. D.; Wang, P. W.; Tarazi, S.; Marzabadi, M. R.; Wong, P. L. *J. Org. Chem.* **1991**, *56*, 1058. For reviews of the use of anodic amide oxidations see c) Shono, T. *Tetrahedron* **1984**, *40*, 811, d) Shono, T.; Matsumura, Y.; Tsubata, K. In *Organic Synthesis* vol. 63, Saucy, G. Ed.; Organic Synthesis Inc., 1984, pg. 206 and references therein, and e) Shono, T. In *Topics in Current Chemistry* vol. 148, Steckhan, E. Ed., Springer-Verlag, Berlin Heidelberg New York, 1988, 131.

8. An amide oxidation route has also proven successful for the construction of the spirocyclic unit used to add rigidity to the right-hand portion of analogs **I** and **III**. Unpublished results with Lawrence D. Rutledge.

9. Unpublished results with Scott L. Rothfus.

10. Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

11. a) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761 and b) Eisenbraun, E. J.; Vickery, E. H.; Pahler, L. F. *J. Org Chem.* **1979**, *44*, 4444. These reactions can be used to cleave the methyl ether of methoxymethylpyrrolidine amide derivatives. Unpublished results with Scott L. Rothfus.

12. For an example see Davis, F. A.; Ulatowski, T. G.; Haque, M. S. *J. Org. Chem.* **1987**, *52*, 5288.

13. a) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586, b) For an example using an α-hydroxy lactone see Kraus, G. A.; Fraizer, K. *J. Org. Chem.* **1980**, *45*, 4820.

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