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A Sequential Electrochemical Oxidation - Olefin Metathesis Strategy for the Construction of Bicyclic Lactam Based Peptidomimetics

Laura M. Beal and Kevin D. Moeller*

Department of Chemistry, Washington University, St. Louis MO 63130

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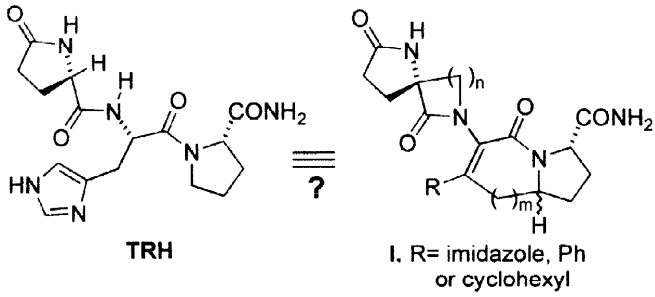
Abstract: A sequential electrochemical amide oxidation - ring closing olefin metathesis sequence has been used to overcome problems associated with the synthesis of seven-membered ring lactam containing bicyclic peptidomimetics. The synthesis of several previously unavailable bicyclic lactam building blocks for constructing constrained thyroliberin analogs is described.

Recently, we found that a conformationally restricted thyroliberin (TRH) analog having two constraints (**I**: n=2, m=1, R=cyclohexyl) was a partial agonist for the TRH endocrine receptor TRH-R.[1,2] This was the first partial agonist found for TRH-R. While the analog did not fully activate TRH-R, it did bind to the receptor more tightly than did the analogous unconstrained analog. Interestingly, neither an analog having a single bridge restricting the pyroglutamate region of TRH (n = 2, m = no bridge)[3], nor an analog having a single bridge restricting the HisPro regions of TRH (n = no bridge, m = 1)[4] showed similar behavior. Both were full agonists. It is tempting to suggest that the loss of agonist behavior observed for the analog containing both bridges resulted from the degree to which this analog was restricted. Can full potency be restored to an analog having both bridges by using larger bridges and systematically adding flexibility back into the analog? While addressing this question initially appears straightforward, the route used to construct the TRH analogs described above is only compatible with the synthesis of fused bicyclic lactam ring skeletons containing six-membered ring lactams (m=1).[5] Therefore, a more versatile synthetic route to the right hand portion of the TRH analogs was needed before any study utilizing alternative ring sizes could be undertaken. We report here a synthetic strategy for constructing constrained TRH building blocks with fused ring skeletons containing both seven- (m=2) and eight-membered (m=3) ring lactam units.

Scheme 1



The constrained building block **2** (Scheme 2) was selected as the initial target for the synthesis of seven-membered ring lactam containing TRH analogs because the chemistry needed for converting building blocks of this

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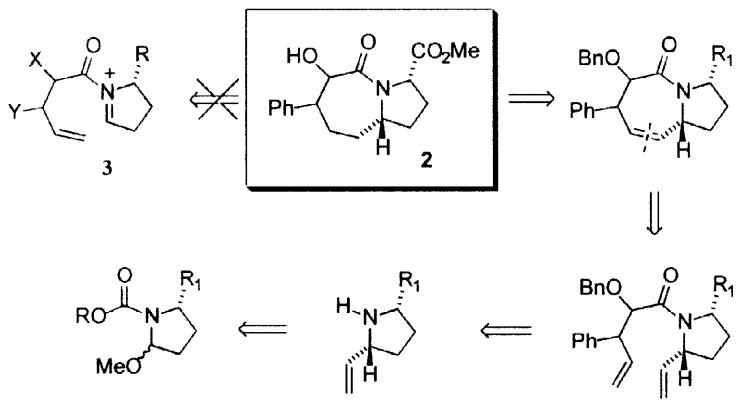
nature into their corresponding TRH analogs is known.[3-5] Initial efforts to make **2** centered on the use of an electrochemical amide oxidation to generate *N*-acyliminium ion **3**. A subsequent cyclization reaction would then complete the synthesis of the lactam ring. This approach failed for two main reasons. First, cyclization reactions having a phenyl (or alkyl) substituent beta to the amide led to rearrangement reactions that generated six-membered ring lactam products and not the desired seven-membered ring lactam.[5] Second, the formation of *N*-acyliminium ion **3** required an anodic oxidation of the corresponding amide.[6] This oxidation reaction could not be done when the carbon alpha to the amide was substituted with an oxygen[5] and was unpredictable when the carbon alpha to the amide was substituted with a nitrogen.[7] For six-membered ring analogs this problem was circumvented by functionalizing the carbon alpha to the amide following the anodic oxidation - cyclization sequence.[3,5] However, in the case of a seven-membered ring lactam attempts to functionalize the carbon alpha to the amide following the cyclization step failed.[8]

Scheme 2

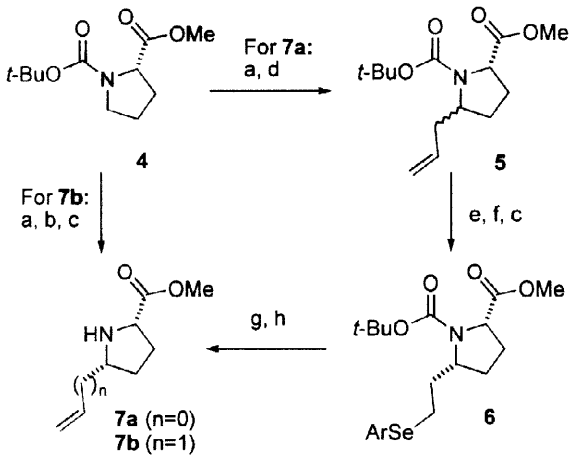


These difficulties prompted us to consider the ring closing olefin metathesis reaction (RCM)[9] based strategy illustrated in Scheme 2. In principle, this route would circumvent the problems encountered above, and allow for the synthesis of bicyclic lactams with the sidechain functionality already in place. A ring closing olefin metathesis reaction would not be subject to problems with cation initiated rearrangement reactions, and an olefin metathesis approach would utilize a vinyl substituted proline derivative and allow for derivatization of the proline ring prior to coupling with the functionalized acid sidechain. In addition, the proposed RCM based route would set the stereochemistry of the bridgehead carbon very early in the synthesis, greatly reducing the impact of a potential mixture at this center. Finally, the RCM route looked to be compatible with the synthesis of bicyclic lactams having both a variety of different ring sizes and a variety of different R groups beta to the lactam carbonyl.

The forward synthesis of the seven- and eight-membered ring lactam building blocks began with the synthesis of the vinyl- and allyl-substituted amino acid starting materials **7a** and **7b** (Scheme 3). While the synthesis of **7a** has been reported,[10] we found it most convenient to make both **7a** and **7b** from the allyl-substituted proline derivative **5**. Compound **5** was synthesized from the methyl ester of proline by first oxidizing the t-Boc protected proline, and then treating the resulting 5-methoxyproline derivative with $BF_3{\cdot}Et_2O$ and allyltrimethyl silane. An approximately 1:1 mixture of cis- and trans-isomers was obtained. For the synthesis of **7a**, the olefin in **5** was cleaved with the use of an ozonolysis reaction followed by a reductive workup to afford the corresponding alcohol. The mixture of isomeric alcohols was converted to the corresponding selenide (**6**) and the cis- and trans-isomers

separated by column chromatography. The selenide was then eliminated with the use of *m*-CPBA and the *t*-Boc group removed with TFA to complete the synthesis of **7a**. For the synthesis of **7b**, $TiCl_4$ was used as the Lewis acid for the allyl addition step in place of $BF_3{\cdot}Et_2O$. Using these conditions, the deprotected allyl substituted amine was generated directly. The cis- and trans-isomers were again separated by chromatography.

Scheme 3

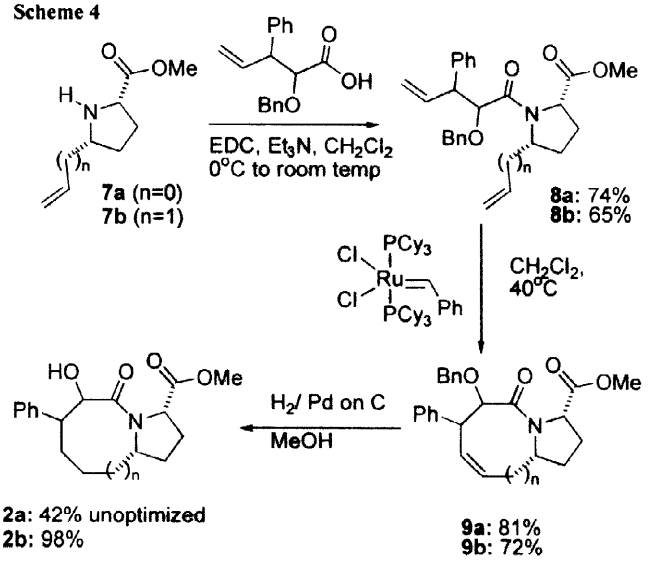


Reagents: a) Carbon anode, Pt cathode, Et_4NOTs, MeOH, 3.0 F/mol, 26.8 mA, 99%. b) $TiCl_4$, CH_2Cl_2, -78°C to room temp, 80%. c) SiO_2 chromatography to separate isomers. d) $BF_3{\cdot}Et_2O$, allylsilane, Et_2O, -40°C to room temp., 77%. e) i. O_3, MeOH, CH_2Cl_2, -78°C; ii. $NaBH_4$, -78°C to room temp., 96%. f) $(n\text{-}Bu)_3P$, $o\text{-}NO_2(C_6H_4)SeCN$, THF, 85%. g) i. MCPBA, CH_2Cl_2, -70°C, 30 min.;ii. Me_2S, Et_3N, -70°C to room temp., 96%. h) TFA, CH_2Cl_2, 65%.

The vinyl- and allyl-substituted proline derivatives **7a** and **7b** were coupled to 2-benzyloxy-3-phenyl-4-pentenoic acid (Scheme 4). In this manner, the olefin metathesis reaction substrates having the desired cis-stereochemistry about the proline ring were obtained.

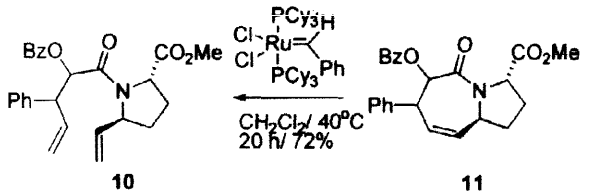
The diene substrates were treated with the Grubb's ruthenium catalyst for the olefin metathesis reaction. In the case of **8a**, two seven-membered ring lactams were obtained in an overall isolated yield of 81%. *For the first time, a fully functionalized seven-membered ring lactam building block was formed!* The isomers resulted from the use of racemic acid in the initial coupling step to form **8a**. It should be noted that the formation of isomeric compounds at this stage of the synthesis was not a problem since the final TRH analogs (**I**) have a double bond in the lactam ring that will remove the isomeric stereocenters. The cyclization of **8b** also proceeded smoothly to form the 8-membered ring lactam products. In this case, a 72% yield of the two stereoisomers was obtained. The syntheses of building blocks **2a** and **2b** were completed by the one step hydrogenation of the double bond formed during the metathesis reaction and removal of the benzyl protecting group.

Scheme 4



For completeness, the bicyclic lactam analog having the S-bridgehead stereochemistry was also synthesized (Scheme 5). In this case, the starting trans vinyl substituted proline needed for making the metathesis substrate could be readily obtained from a stereoselective cuprate addition to the *N*-acyliminium ion derived from the 5-methoxy proline derivative above.[11] As in the earlier examples, the olefin metathesis reaction proceeded smoothly.

Scheme 5



In conclusion, we have found that the combination of an anodic amide oxidation reaction and a ring closing olefin metathesis reaction can provide a convenient route to TRH building blocks that are constrained by either seven- or eight-membered ring lactam groups. The route outlined should provide rapid access to conformationally restricted TRH analogs that will allow for probing the relationship between lactam flexibility and potency at the TRH-R receptor. Work along these lines is currently underway.

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