Pergamon

Tetrahedron Letters 40 (1999) 7939–7943

TETRAHEDRON
LETTERS

The synthesis of bicyclic lactam based His-Pro building blocks: the effect of substituent polarity on an intramolecular bond migration

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Received 14 July 1999; revised 24 August 1999; accepted 25 August 1999

Abstract

A strategy for constructing bicyclic lactam amino acid building blocks with imidazole sidechains is reported. The synthetic route described utilizes an electrochemical amide oxidation to functionalize a proline derivative, and then a sequential cyclization–rearrangement strategy to construct a substituted six-membered ring lactam. Alternatively, the seven-membered ring lactams were obtained without rearrangement when electron withdrawing groups were present beta to the amide carbonyl. © 1999 Elsevier Science Ltd. All rights reserved.

We have been working to develop new synthetic chemistry in support of efforts to experimentally probe the relationship between the predicted and actual biological activity of peptide conformations.[1] Much of this work has focused on the synthesis and biological testing of conformationally constrained analogs of the hypothalamic tripeptide thyroliberin (TRH/*p*-GluHisProNH$_2$).[2,3] For example, a family of constrained TRH analogs having the overall structure of **1a** has been synthesized and tested for its ability to bind and activate the TRH endocrine receptor TRH-R.[4,5] In this work, the central histidine unit of TRH was replaced with a cyclohexylalanine moiety. This change was made in order to simplify the synthesis of the analogs until the effectiveness of the added bridges could be determined. Having established that the bridges in **1a** still allow for binding to TRH-R, we have initiated efforts to synthesize more potent analogs that contain the central histidine unit found in the natural hormone **1b**. We report herein the synthesis of the imidazole containing building blocks **2b** needed for these efforts.

The plan for constructing analogs **1b** called for an approach closely related to the one used to synthesize analogs **1a** (Scheme 1). In these earlier syntheses, a cyclization–rearrangement reaction sequence was used to transform the methoxylated amide **5a** into the bicyclic lactam building block **2a**.[1a,5a,6] Once in hand, building block **2a** was readily converted into the desired TRH analogs. Along these lines, we envisioned the synthesis of analogs **1b** as proceeding through the analogous building block **2b**, which would in turn be made from methoxylated amide **5b**. In the case of **5b**, the cyclization–rearrangement

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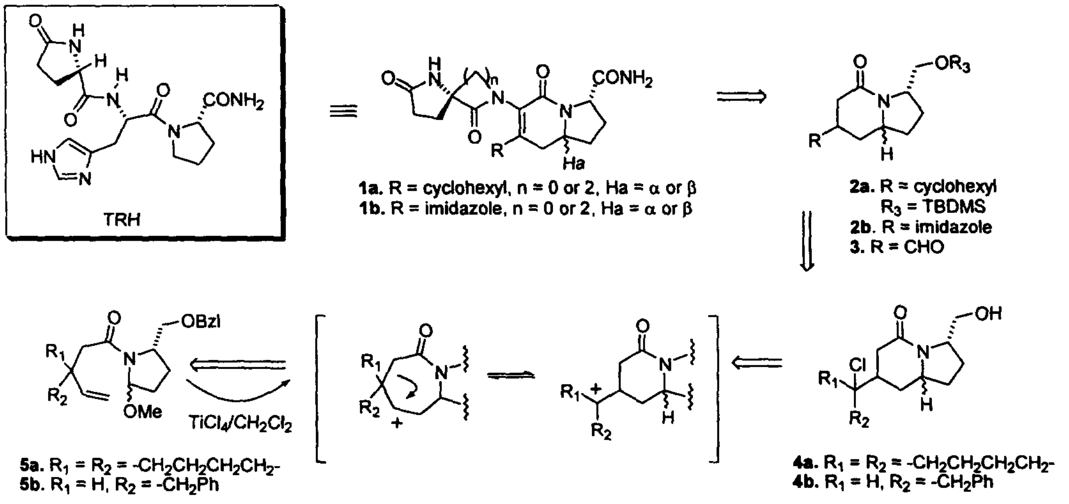
PII: S0040-4039(99)01652-4

sequence was expected to afford **4b**. Elimination of the chloride, cleavage of the resulting olefin, and conversion of the aldehyde into an imidazole ring[7] would then complete the synthesis of **2b**. While such an approach would not control the stereochemistry of the lactam ring, the double bond in **1b** and the need for testing both bridgehead isomers of **1b** meant that a more involved stereocontrolled synthesis was not necessary.

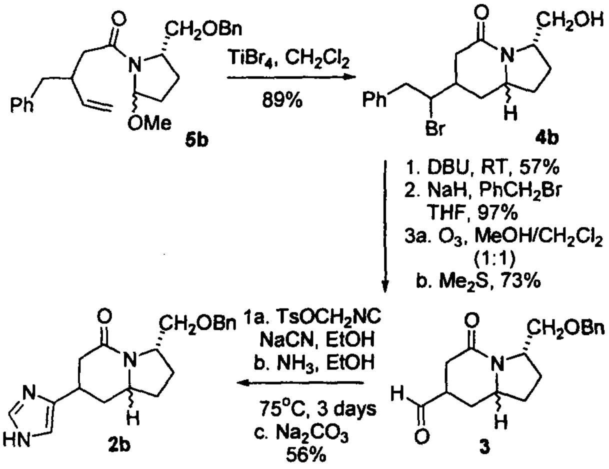


Scheme 1.

In practice, the methoxylated amide was readily available using the same chemistry used to make **5a**.[5] The titanium tetrabromide initiated cyclization of **5b** led to an 89% isolated yield of the desired six-membered ring lactam product **4b** (Scheme 2). As in earlier cyclization reactions,[1a,6,8] the presence of the six-membered ring lactam was established with the use of an HMQC experiment to determine proton/carbon correlations and a combination of COSY and HMBC experiments to assign the complete connectivity of the molecule. Titanium tetrabromide was used as the Lewis acid in order to provide a better leaving group for the subsequent elimination reaction. Elimination of the bromide in **4b** with DBU, protection of the primary alcohol as a benzyl ether, and cleavage of the resulting styrene led to the formation of aldehyde **3**. The aldehyde was then converted to the imidazole ring (**2b**) as initially planned in a 56% isolated yield. In this sequence, the use of the benzyl ether was used in place of the TBDMS group used in **2a** because of its compatibility with the conditions needed for forming the imidazole ring.

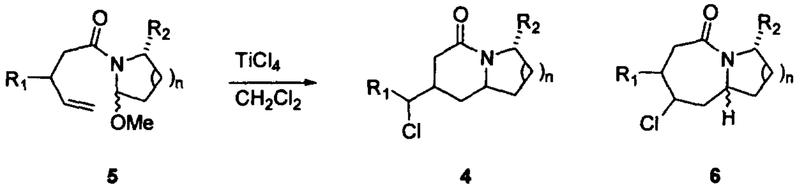
Suprisingly, a closely related approach to **2b** starting from the methoxylated amide **5c** (Table 1) was not successful. With **5c**, the cyclization reaction did not lead to the subsequent rearrangement and did not form the desired six-membered ring lactam product. Instead, the seven-membered ring lactam **6c** was obtained in an 85% isolated yield. The presence of the seven-membered ring was established by assigning the complete connectivity of the molecule with the use of HMQC, COSY, and HMBC experiments. The formation of the seven-membered ring lactam from **5c** was in direct contrast to the previously studied cyclization of substrate **5d**. In this case, the presence of a methyl substituent beta to the amide had led to an 82% isolated yield of the six-membered ring product **4d**.[1a,6]

Two theories are proposed to explain this difference. First, the CH_2OAc substituent utilized in substrate **5c** was inductively electron-withdrawing. As such, the CH_2OAc group would destabilize the cationic intermediate **8** formed from the rearrangement relative to the initially formed **7** (Fig. 1). Second, it was possible that the presence of the acetate group stabilized the seven-membered ring intermediate



Scheme 2.

Table 1



Substrate	R_1	R_2	n	Yield 4^a	Yield 6^a
5c	CH_2OAc	CH_2OBzl	1	--	85% (R_2=CH_2OH)
5d[b]	CH_3	CH_2OBzl	1	82% (R_2=CH_2OH)	--
5e	4-$NO_2C_6H_4$	CH_2OBzl	1	--	61% (R_2=CH_2OH)
5f[b]	Ph	CH_2OBzl	1	90% (R_2=CH_2OH)	--
5g[c]	CH_3	H	2	60%	--
5h[c]	CH_2OAc	H	2	--	75%
5i[c]	4-$NO_2C_6H_4$	H	2	--	63%

a. The yields are for isolated product.

b. Reference 1a

c. The yields for these cases are for two steps; the anodic oxidation to form **9** and then the cyclization.

by electron donation from the carbonyl to form **9**. Of course, a combination of both effects could be important.

In order to investigate if the inductive effect associated with the electron-withdrawing group would prevent the rearrangement reaction in the absence of a neighboring group effect, the *p*-nitrophenyl substituted substrate **5e** was synthesized and treated with titanium tetrachloride. The corresponding phenyl substituted substrate **5f** had previously been shown to afford the six-membered ring lactam obtained from cyclization and rearrangement.[1a,6] In the case of **5e**, the seven-membered ring lactam

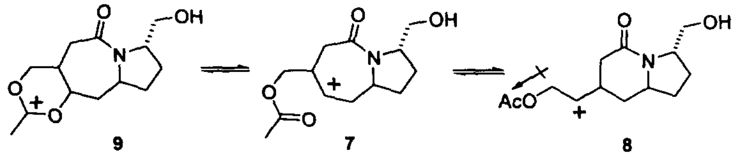
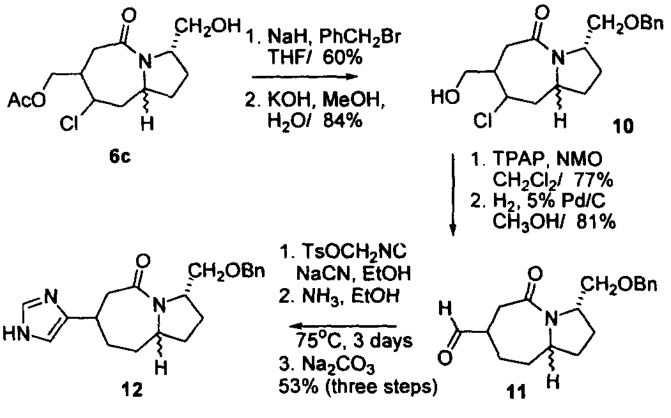


Figure 1.

6e was obtained in a 61% isolated yield. No six-membered ring product was observed. Clearly, the neighboring group effect was not needed in order to prevent the rearrangement reaction.

The observations made using the five-membered ring amine-derived substrates also proved true for substrates derived from a six-membered ring amine (**5g**–**5i**). As observed in earlier peptidomimetic syntheses using pipecolic acid derivatives,[9] the *N*-α-methoxyalkylamides derived using a six-membered ring amine were not as stable as their five-membered ring counterparts. For this reason, problems with the lability of the six-membered ring derivatives were avoided by carrying the crude methoxylated amides directly into the titanium chloride catalyzed cyclization. The yields given in Table 1 for the reactions originating from **5g**–**5i** are reported for the two-step anodic oxidation–$TiCl_4$ initiated cyclization reaction.

The observation that an electron withdrawing group beta to the amide carbonyl allowed for the formation of seven-membered ring lactams suggested that the overall approach might also prove useful for synthesizing TRH building blocks having a bicyclic[5.3.0]decane ring skeleton. To this end, the cyclized product **6c** was converted into building block **12** (Scheme 3). This synthesis involved protection of the primary alcohol in **6c** followed by cleavage of the acetate group. The subsequent oxidation of the primary alcohol led to a spontaneous elimination of the chloride group. Hydrogenation of the resulting double bond afforded aldehyde **11**, which was then converted into the desired imidazole ring.



Scheme 3.

In conclusion, the anodic oxidation–cyclization strategy initially utilized to make conformationally constrained cyclohexylAla^2-TRH derivatives can be readily modified to allow for the synthesis of the imidazole containing building blocks needed for synthesizing constrained analogs of the natural hormone. Building blocks with both six- and seven-membered ring lactam constraints were made. The synthesis of the constrained TRH analogs from the building blocks is currently underway and will be reported in due course.

Acknowledgements

We thank the National Institutes of Health (R01 GM53240) for their generous support of this work. We also gratefully acknowledge the Washington University High Resolution NMR facility, partially supported by NIH grants RR02004, RR05018, and RR07155, and the Washington University Mass Spectrometry Resource Center, partially supported by NIHRR00954, for their assistance.

References

1. For selected examples, see: (a) Li, W.; Hanau, C. E.; d'Avignon, A.; Moeller, K. D. *J. Org. Chem.* **1995**, *60*, 8155. (b) Fobian, Y. M.; d'Avignon, D. A.; Moeller, K. D. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 315. (c) Rutledge, L. D.; Perlman, J. H.; Gershengorn, M. C.; Marshall, G. R.; Moeller, K. D. *J. Med. Chem.* **1996**, *39*, 1571. (e) Fobian, Y. M.; Moeller, K. D. *Methods in Molecular Medicine*; Kazmierski, W. M., Ed. Peptidomimetics Protocols. Humana Press Inc.: Totowa, NJ, 1998; Vol. 23, p. 259. (f) Beal, L. M.; Moeller, K. D. *Tetrahedron Lett.* **1998**, *39* 4639. (g) Tong, Y.; Fobian, Y. M.; Wu, M.; Boyd, N. D.; Moeller, K. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1679.
2. For reviews on the biology of TRH, see: *Thyrotropin-Releasing Hormone: Biomedical Significance*; Metcalf Olson, G. L.; Cheung, H. C.; Voss, M. E.; Hill, D. E.; Kahn, M.; Madison, V. S.; Cook, C. M.; Sepinwall, J., Eds.; Proceedings of the Biotech USA 89 Meeting 1989; San Francisco, October 1989.
3. For alternative approaches to understanding TRH/TRH-R binding, see: (a) Hinkle, P. M.; Woroch, E. L.; Tashjian, G. H. *J. Biol. Chem.* **1974**, *249*, 3085. (b) Goren, H. J.; Bauce, L. G.; Vale, W. *Mol. Pharmacol.* **1977**, *13*, 606. (c) Kamiya, K.; Takamoto, M.; Wada, Y.; Fujino, M.; Nishikawa, M. *J. Chem. Soc., Chem. Commun.* **1980**, 438. (d) Sharif, N. A.; To, Z.; Whiting, R. L. *Biochem. Biophys. Res. Commun.* **1989**, *161*, 1306. (e) Vonhof, S.; Feuerstein, G. Z.; Cohen, L. A.; Labroo, V. M. *Eur. J. Pharmacol.* **1990**, *180*, 1.
4. For a description of the active analog approach used to design the analogs **1a** and **1b**, see: (a) Marshall, G. R.; Gorin, F. A.; Moore, M. L. In *Annual Reports in Medicinal Chemistry*; Clarke, F. H., Ed.; Academic: New York, 1978; Vol. 13, p. 227. (b) Font, J. Ph.D. Thesis, Washington University, St. Louis, MO, 1986. (c) For an alternative application of these models to the construction of TRH mimetics, see: Olson, G. L.; Cheung, H. C.; Chiang, E.; Madison, V. S.; Sepinwall, J.; Vincent, G. P.; Winokur, A.; Gary, K. A. *J. Med. Chem.* **1995**, *38*, 2866.
5. For partially constrained analogs, see: (a) Li, W.; Moeller, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 10106. (b) Laakkonen, L.; Li, W.; Perlman, J. H.; Guarnieri, F.; Osman, R.; Moeller, K. D.; Gershengorn, M. C. *Mol. Pharmacol.* **1996**, *49*, 1092. For fully constrained analogs, see: Chu, W.; Perlman, J. H.; Gershengorn, M. C.; Moeller, K. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3093.
6. Moeller, K. D.; Hanau, C. E.; d'Avignon, A. *Tetrahedron Lett.* **1994**, *35*, 835.
7. Horne, D. A.; Yakushijin, K.; Büchi, G. *Heterocycles* **1994**, *39*, 139.
8. (a) d'Avignon, D. A.; Hanau, C. E.; Fobian, Y. M.; Moeller, K. D. *Coordination Chem.* **1994**, *32*, 135. (b) Kao, J.; Li, W.; Moeller, K. D. *Magn. Reson. Chem.* **1997**, *35*, 267.
9. Wong, P. L.; Moeller, K. D. *J. Am. Chem. Soc.* **1993**, *115*, 11434.