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Stereoselective Synthesis of Novel Dipeptide β-Turn Mimetics Targeting Melanocortin Peptide Receptors

Junyi Zhang, Chiyi Xiong, Jinfa Ying, Wei Wang,[†] and Victor J. Hruby*

Department of Chemistry, University of Arizona, 1306 East University Boulevard, Tucson, Arizona 85721

hruby@u.arizona.edu

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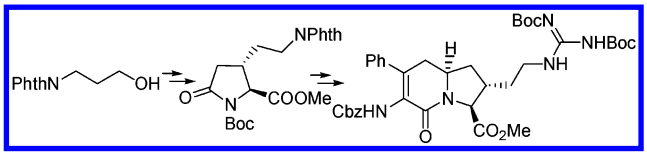
ABSTRACT

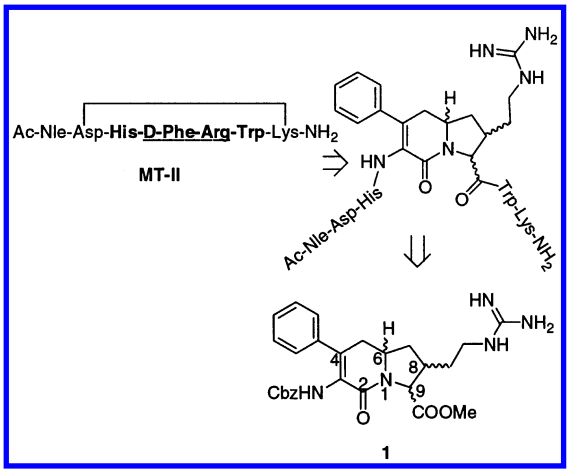


The novel dipeptide β-turn mimetic, 4,8-disubstituted azabicyclo[4.3.0]nonane amino acid ester (15), has been synthesized to serve as a peptide mimetic of the dipeptide Phe-Arg, which contains two important pharmacophore elements in melanotropin peptides. Introduction of side-chain functionality at C-8 was achieved by using β-functionalized pyroglutamate (8) as a synthetic precursor. The side chain at C-4 was introduced by bromination of dehydroamino acid intermediate (10) followed by Suzuki cross-coupling.

As part of our ongoing program for the design of novel melanotropin peptide mimetics, we have identified the core bioactive sequence of melanotropin peptides as His-(D/L)-Phe-Arg-Trp[1] and found a β-turn structural feature which includes the Phe and Arg residues.[2] Based on these findings, we have initiated a program to examine the structure−activity relationship of melanocyte stimulating hormone (MSH) peptides by replacing the dipeptide Phe-Arg with β-turn dipeptide mimetics, such as azabicyclo[4.3.0]nonane amino acids **1** (Scheme 1).

In our efforts to implement this plan, we need to develop a flexible synthetic approach to dipeptide mimetics such as

Scheme 1. Melanotropin Peptide Mimetic Dipeptide Analogues



1 (Scheme 1). Some successful methodologies have been reported for the synthesis of indolizidinone amino acids.[3] However, to the best of our knowledge, little success has been reported in the synthesis of indolizidinone amino acids with appropriate side-chain functionalities which correspond to the side chains of natural amino acids.[4] Many studies have

* To whom correspondence should be addressed. Phone: (520) 621-6332. Fax: (520) 621-8407.

[†] Genomics Institute of the Novartis Research Foundation, 10675 John Jay Hopkins Drive, San Diego, CA 92121.

(1) (a) Hruby, V. J.; Wilkes, B. C.; Hadley, M. E.; Al-Obeidi, F.; Sawyer, T. K.; Staples, D. J.; DeVaux, A. E.; Dym, O.; Castrucci, A. M. L.; Hintz, M. F.; Riehm, J. P.; Rao, K. R. *J. Med. Chem.* **1987**, *30*, 2126. (b) Haskell-Luevano, C.; Miwa, H.; Dickinson, C.; Hruby, V. J.; Yamada, T.; Gantz, I. *Biochem. Biophys. Res. Commun.* **1994**, *204* (3), 1137. (c) Haskell-Luevano, C.; Toth, K.; Boteju, L.; Job, C.; Castrucci, A. M. L.; Hadley, M. E.; Hruby, V. J. *J. Med. Chem.* **1997**, *40*, 2740.

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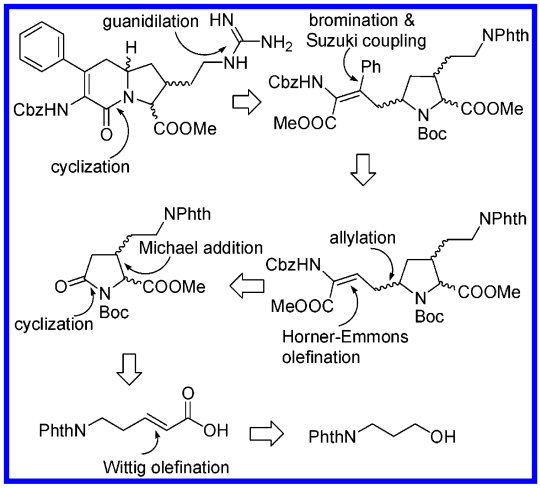
shown that amino acid side-chain moieties are involved directly in interactions between peptide ligands and receptors/acceptors that are critical for the biological activities and receptor selectivities.[5] Herein, we would like to report the first synthesis of indolizidinone amino acid ester with appropriate amino acid side-chain functionalities at both C4 and C8 positions.

The retrosynthetic analysis of the target mimetic **1** is described in Scheme 2. The bicyclic lactam system could be

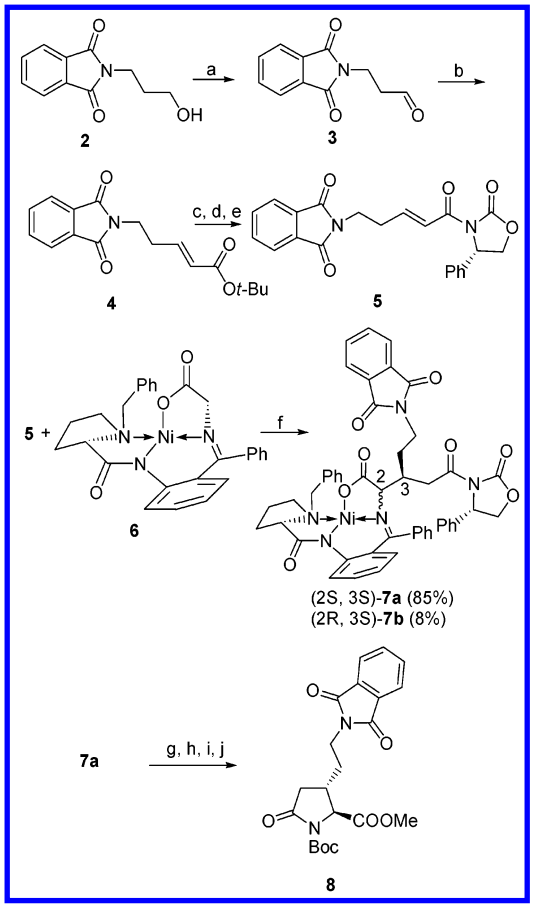
Scheme 2. Retrosynthetic Analysis of Dipeptide Mimetic **1**



approached from a dehydroamino acid intermediate. The functional group at C-4 was introduced by bromination of the dehydroamino acid intermediate followed by Suzuki coupling. Stereoselectively introducing allyl groups at the C-5 position of β-functionalized pyroglutamates and appropriate elaboration could afford dehydroamino acid intermediates. The novel β-functionalized pyroglutamic acid was prepared from readily available compounds by Ni(II) complex chemistry.

As illustrated in Scheme 2, the proposed approach would include diverse reactions. Therefore, it was important to identify the proper protecting group for the amino group in the starting material which would later be functionalized in the final step. This protecting group should be sufficiently robust to survive the projected reactions, and also should be orthogonal to other functionalities and be labile enough to be removed in the final step. Furthermore, based on our earlier studies, it seems likely that a mono protected nitrogen would interfere with the aldehyde intermediate.[6] All of these requirements prompted us to choose the phthalimide group to doubly protect the amine group. Our first synthetic target was the novel pyroglutamic acid derivative with the desired functionality at the β-position. The synthesis started from readily available *N*-(3-hydroxypropyl) phthalimide **2** (Scheme 3). Aldehyde **3** was prepared in good yield by PCC oxidation

Scheme 3. Synthesis of β-Functionalized Pyroglutamate **8**[a]



[a] Reagents: (a) oxalyl chloride, DMSO, TEA, CH_2Cl_2, 86%; (b) *t*-$BuOCOCH_2PPh_3Br$, NaOH, TEA, CH_2Cl_2, H_2O, 95%; (c) TFA (50% in CH_2Cl_2); (d) *t*-BuCOCl, TEA, THF, −78 °C; (e) (*S*)-4-phenyl-2-oxazolidinone, *n*-BuLi, THF, −78 °C, 89%; (f) DBU (15 mol %), DMF, rt; (g) 3 N HCl, MeOH; (h) NH_4OH; (i) $SOCl_2$, MeOH; (j) $(Boc)_2O$, DMAP, acetonitrile, 54%.

of alcohol **2** following the literature procedure.[7] However, when the reaction was performed on a large scale, the reduced chromium byproduct made workup difficult. Thus, we employed the Swern oxidation as a good alternative synthetic method to prepare **3** on a large scale. Wittig olefination of aldehyde **3** with (*tert*-butoxycarbonylmethyl)-triphenylphosphonium bromide in the presence of NaOH and triethylamine in a two-phase system of dichloromethane/H_2O gave the (*E*)-5-*N*-phthalimido-α,β-unsaturated *tert*-butyl ester **4** in excellent yield. The *tert*-butyl protecting group was removed by treatment with 50% TFA in dichloromethane,

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and *S*-4-phenyl-2-oxazolidinone was coupled to deprotected **4** as the chiral auxiliary for asymmetric functionalization of the β-position in the next step. Michael acceptor **5** underwent asymmetric Michael addition with the Ni(II) complex **6**[8] to give a mixture of (2*S*,3*S*)-**7a** and (2*R*,3*S*)-**7b**. Our previous studies have shown that the addition reaction with Ni(II) complex **6** will provide excellent stereoselectivities (>95%) in the preparation of β *aryl*- or alkyl-substituted pyroglutamic acid derivatives.[9] In this case, however, treatment of **5** with DBU and Ni(II) complex **6** at room temperature did not afford such excellent stereoselectivity. Two critical reaction conditions, reaction time and temperature, were investigated in order to optimize stereoselectivity and yield. The reaction at room temperature for 5 min provided moderate selectivity and excellent yields. More reaction time was expected to improve the selectivity for the more thermodynamically stable product. However, prolonged reaction time did not make much difference in stereoselectivity and resulted in lower yield due to decomposition of the product. At low temperature, the reaction proceeded extremely slowly and resulted in no reaction at −40 °C or very low yields at 0 °C. However, when the reaction was run from 0 °C to room temperature in 30 min, greatly improved stereoselectivities (**7a**/**7b** = 10:1) and yields (93%) were obtained.

Hydrolysis of the Ni(II) complex **7a** followed by cyclization under basic conditions afforded the corresponding β-functionalized pyroglutamic acid (Scheme 3). Attempts to purify the amino acid by Dowex ion-exchange resin column were not successful probably due to a contamination of the uncyclized product. Instead the crude amino acid was protected directly to give the N^{α}-Boc pyroglutamate **8** which was purified by flash column chromatography. The configuration was confirmed by X-ray crystallographic analysis (Figure 1). The lactam moiety of pyroglutamate usually could

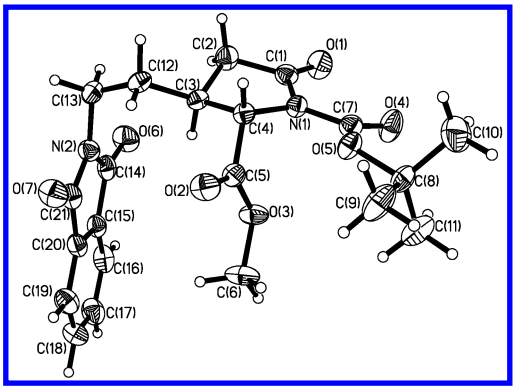
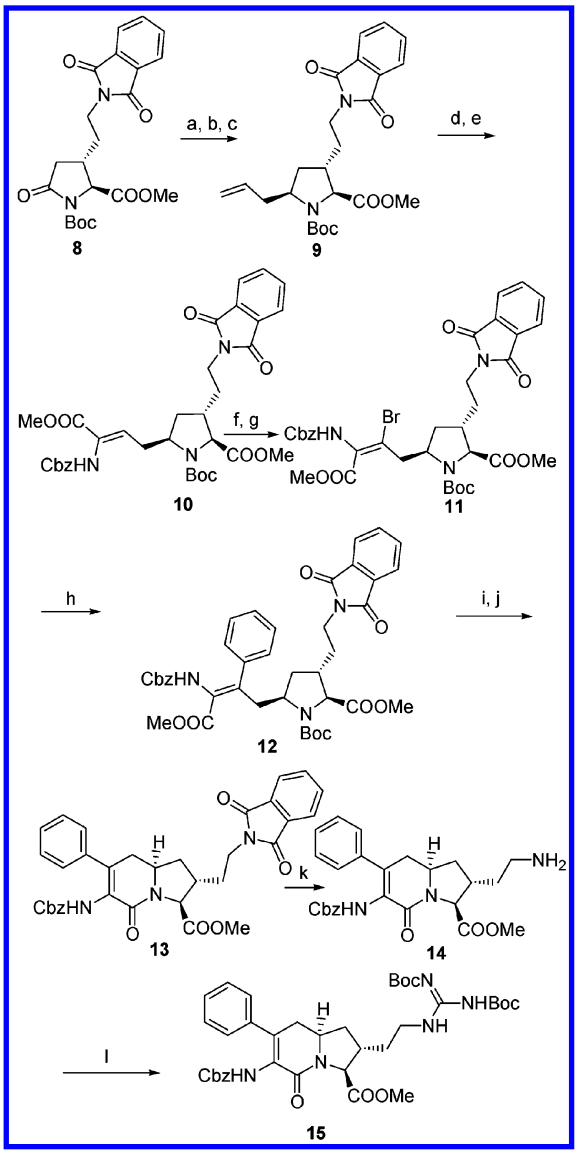


Figure 1. X-ray structure of compound **8**.

be reduced selectively by Super-Hydride ($LiBEt_3H$).[10] However, in agreement with a previous report,[11] the treatment of **8** with Super-Hydride ($LiBEt_3H$) also resulted in the reduction of the phthalimide protecting group. Therefore, we chose to use DIBAL-H which the phthalimide group is stable to. The reduction by DIBAL-H followed by treatment with methanol in the presence of a catalytic amount of *p*-TsOH

Scheme 4. Synthesis of 4,8-Disubstituted Indolizidinone Amino Acid Ester **15**[a]



[a] Reagents: (a) DIBAL-H, THF, −78 °C; (b) Ts-OH, MeOH; (c) $BF_3{\cdot}Et_2O$, $Me_3SiCH_2CH{=}CH_2$, Et_2O, −40 °C, 64%; (d) OsO_4, $NaIO_4$, THF/H_2O; (e) DBU, $(MeO)_2P(O)CH(NHCbz)COOCH_3$, CH_2Cl_2, rt, 79%; (f) NBS, $CHCl_3$; (g) DABCO, $CHCl_3$, 78%; (h) $PhB(OH)_2$, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, Na_2CO_3, DME, 80 °C; (i) 20% TFA, CH_2Cl_2, rt; (j) $CHCl_3$, rt, 24 h, 61%; (k) NH_2NH_2, EtOH, CH_3Cl; (l) *N*,*N*′-bis(*tert*-butoxycarbonyl)-*N*″-triflylguanidine, TEA, CH_2Cl_2, 83%.

afforded the methoxy aminal which was directly subjected to allyltrimethylsilane and boron trifluoride in ether without further purification. As a result of a neighboring group participation of the methyl ester[3d] and the steric effect of the β-substituent, the allylsilane addition to the *N*-acylimin-

(8) Chiral Ni(II) complex (*S*)-**6** was prepared according to a literature procedure; see: Belokon, Y. N.; Bulychev, A. G.; Vitt, S. V.; Struchkov, Y. T.; Batsanov, A. S.; Timofeeva, T. V.; Tsyryapkin, V. A.; Ryzhov, M. G.; Lysova, L. A.; Bakhmutov, V. I.; Belikov, V. M. *J. Am. Chem. Soc.* **1985**, *107*, 4252.

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ium intermediate gave exclusively the trans product **9** related to the β-substituent (Scheme 4). The optically pure intermediate **9** underwent osmylation and subsequent oxidation with $NaIO_4$ to afford the aldehyde intermediate. The dehydroamino acid ester **10** was obtained via the Horner−Emmons olefination of the aldehyde intermediate (Scheme 4).

With the dehydroamino acid ester **10** in hand, we treated it with *N*-bromosuccinimide (NBS) in chloroform to produce the α-bromo imines (Scheme 4). Upon treatment with an amine base, the α-bromo imine intermediates underwent tautomerization to afford the (*Z*)-β-bromo-α,β-dehydroamino acid **11**. We have observed that using DABCO instead of TEA and DBU in the tautomerization step results in the *Z* isomers exclusively.[12] Coleman and Carpenter[13] have suggested that DABCO-induced isomerization can interconvert the kinetically formed *E*-vinyl bromide to the thermodynamically favored *Z* isomer through a Michael addition−elimination reaction sequence. Suzuki coupling of **11** with phenyl boronic acid introduced the phenyl side-chain at the β position of dehydroamino acid. The crude product of Suzuki coupling **12** was deprotected and then cyclized to furnish **13** in good yield (Scheme 4). Deprotection of the phthalimide protecting group in **13** was accomplished by treatment with hydrazine at room temperature for 24 h. Workup and purification of free amine **14** after the deprotection gave poor yields. Thus, the crude free amine **14** was directly guanidinated to give **15** (Scheme 4), using the commercially available guanidinating reagent, *N*,*N*′-Bis(*tert*-butoxycarbonyl)-*N*″-triflylguanidine. Although an initial attempt using DMAP as base failed, the guanidinating reaction with triethylamine afforded **15** in good yield. The configuration of **15** was confirmed by NOE (Table 1).

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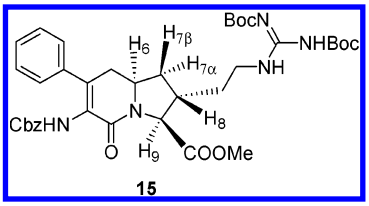
Table 1. NOE Data of **15**



15

protons		NOE
H_8	$H_{7\alpha}$	0.80
H_8	$H_{7\beta}$	1.46
H_6	$H_{7\alpha}$	1.05
H_6	$H_{7\beta}$	0.66
H_6	H_8	n.o.[a]
H_6	H_9	0.20

[a] NOE not observed.

In conclusion, we have developed an efficient approach to the synthesis of dipeptide β-turn mimetics **1** which can serve as mimetics of the dipeptide Phe-Arg in our α-MSH program. The synthesis of other diastereomers of the β-turn mimetics **1**, the incorporation of them into melanotropin peptides, and the study of their structure−activity relationships are under investigation.

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

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