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Design and synthesis of hydrophobic, bulky χ^2-constrained phenylalanine and naphthylalanine derivatives

Wei Wang, Junyi Zhang, Chiyi Xiong and Victor J. Hruby*

Department of Chemistry, University of Arizona, Tucson, AZ 85721, USA

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Abstract—A series of novel hydrophobic, bulky χ^2-constrained phenylalanine and naphthylalanine derivatives were designed and synthesized. Asymmetric hydrogenations of α-enamides using Burk's DuPHOS-based Rh(I) catalysts generated high enantiomerically pure α-amino acid derivatives, which subsequently underwent Suzuki cross couplings with boronic acid derivatives to afford these aromatic substituted amino acids in high yields and with high enantioselectivity.

The backbone conformations of peptides and proteins such as α-helix, β-sheet, β-turn, and so forth provide critical templates for the three-dimensional structures when interacting with their receptors/acceptors, whereas the overall shape and intrinsic stereoelectronic properties of the peptides and proteins important for molecule recognition, signal transduction, enzymatic specificity, immunomodulation, and other biological effects depend on arrangement of the side chain groups of amino acid residues in three dimensional χ space (their χ^1, χ^2, etc. torsional angles). The side chain conformation can be controlled by introducing an alkyl/aryl group at the β-position or on the aromatic rings of aromatic amino acid residues. These kinds of modifications do not perturb the backbone conformation significantly, and still allow the peptide backbone and side chain some degree of flexibility, which often is necessary and even crucial for peptide and peptidomimetic activity. In the past, our group has designed and synthesized many novel χ-constrained amino acids, mainly focusing on introducing alkyl groups at the β-position of amino acids.[1–3] We have demonstrated

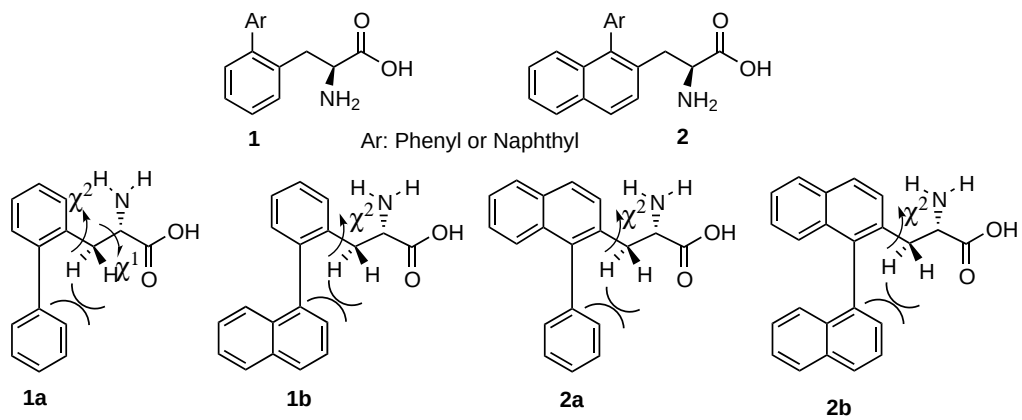

Figure 1. Structures of *o*-substituted-aryl phenylalanines and naphthylalanines.

Keywords: asymmetric hydrogenation; DuPHOS; constrained amino acids; phenylalanine; naphthylalanine.
* Corresponding author. Tel.: (520) 621-6332; fax: (520) 621-8407; e-mail: hruby@u.arizona.edu

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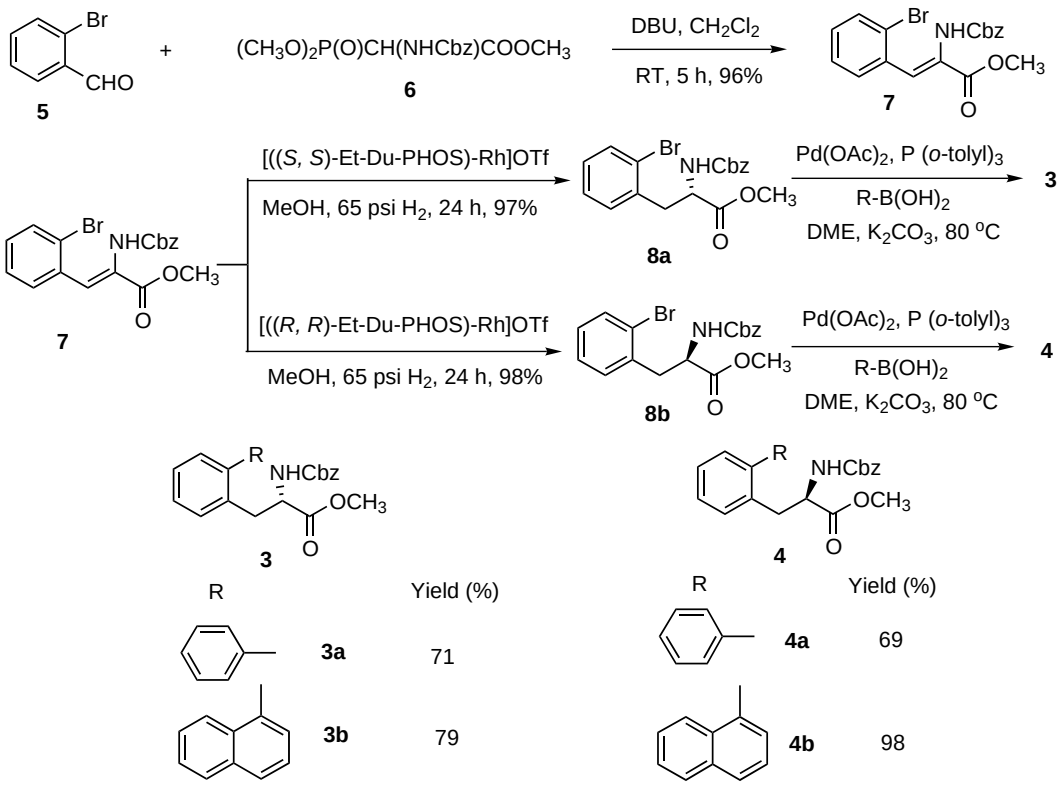
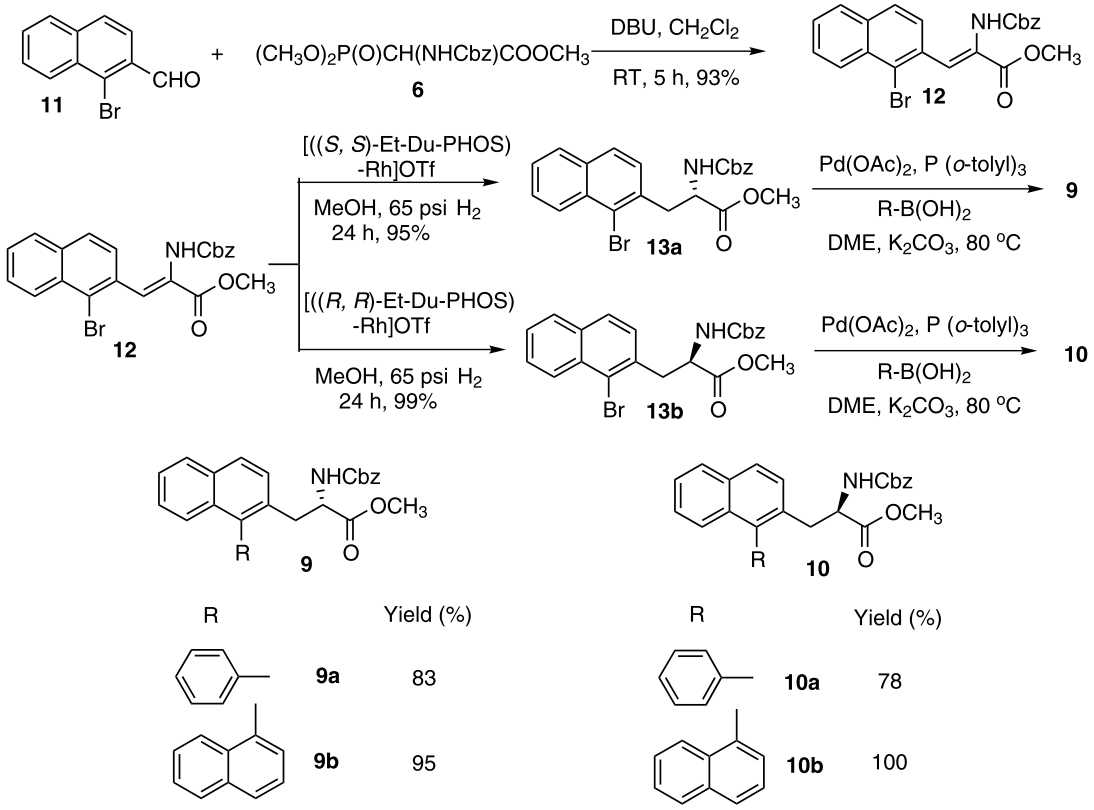
that the incorporation of these unnatural amino acids into biologically active peptides and peptidomimetics can enhance the potency and selectivity significantly.[2–6] However, introducing an alkyl or aryl group on the aromatic ring of an aromatic amino acid residue, particularly in the *ortho* position which can significantly restrict its conformation in χ^2 space, has been much less explored.[2,7–9] The χ^2 torsional angle can be efficiently restricted by the interaction between the aryl moiety and the β-hydrogens of amino side chain in the *o*-substituted phenylalanine and naphthylalanine derivatives **1** and **2** (Fig. 1).

In our α-melanocyte stimulating hormone (MSH) project, we have found that Phe (preferably D-Phe) plays a critical role in activity and selectivity.[4,10] For example, the substitution of D-Phe in MT-II with D-Nal (naphthylalanine) (2′) led to a potent and selective antagonist ligand, SHU-9119, for melanocortin receptor (MCR) 4.[11] To further improve activity and selectivity and understand the relationship of peptide ligands and their receptors, we have proposed to use χ^2-constrained, hydrophobic and bulky aromatic-substituted phenylalanines **1** and naphthylalanines **2** to substitute D-Phe in MT-II or D-Nal (2′) in SHU-9119. In addition, these amino acids can provide a large lipophilic surface for binding to receptors, and for crossing membrane barriers (e.g. blood brain barriers (BBB) and intestinal mucosa), which provides an opportunity to address three issues simultaneously. Herein we would like to report an efficient approach to the asymmetric synthesis of these unusual amino acids. The general strategy involves the asymmetric hydrogenation of α-enamides to generate functional α-amino acids in high optical purity which serve as common intermediates from which a variety aromatic substituted amino acid derivatives may be readily obtained through Suzuki-type cross couplings (Schemes 1 and 2). Recently we used a similar method to synthesize novel 5-aryl tryptophan derivatives.[12]

The synthesis of the *o*-aryl substituted phenylalanines **3** and **4** started from commercially available 2-bromobenzylaldehyde **5** (Scheme 1). The Horner–Emmons olefination of aldehyde **5** with phosphonate $(MeO)_2$-P(O)CH(NHCbz)COOMe **6** gave the dehydroamino acid derivative **7** with *Z*-configuration as a major product (Z/E>95/5) in 96% yield.[13] Compound **6** was synthesized in three steps following literature procedures.[14] The amino group in **7** was protected by Cbz (benzyloxycarbonyl), which can be readily removed by Pd catalyzed hydrogenation to give a free amine, which can be reprotected as N^{α}-Boc (*tert*-butoxycarbonyl) or N^{α}-Fmoc (9-fluorenylmethoxycarbonyl)) for the solid-phase peptide synthesis. The dehydroamino ester **7** underwent asymmetric hydrogenations to give α-amino acid derivatives. We chose 1,2-bis ((2*S*,5*S*)/(2*R*,5*R*)-2,5-diethylphospholano)benzene (cyclooctadiene) rhodium(I) trifluoromethane sulfonate ((*S*,*S*)/(*R*,*R*) [Et-DuPHOS-Rh] OTf) as catalysts for the asymmetric hydrogenations since they give almost exclusively single enatiomer (>97% ee) in high yields (>96%).[15,16] These catalysts show high efficiency (at a ratio of catalyst to substrate up to 1/2500)[16] and are commercially avail-



Scheme 1. Synthesis of *o*-substituted phenylalanine derivatives.



Scheme 2. Synthesis of *o*-substituted naphthylalanine derivatives.

able.[17] Furthermore, both *Z* and *E* dehydroamino acids using this type of catalysts gave one single isomer.[16] In this case, we separated the two isomers by column chromatography. The isolated (*Z*)-dehydroamino acid ester **7** was used for asymmetric hydrogenations with a higher ee than that of (*E*) isomer. The (*S*,*S*) catalyst afforded the amino acid derivative **8a** with an absolute *S* configuration, based on the selectivity of the (*S*,*S*)-Et-DuPHOS ligand, in high yield and high ee (>96%).[16] The (*R*) amino acid **8b** was also obtained using (*R*,*R*)-Et-DuPHOS as the ligand in high yield and high ee as well. *o*-Bromophenylalanines **8a**,**b** were subjected to Suzuki cross couplings with phenyl and naphthyl boronic acids to give amino acid derivatives **3** and **4** in 69–98% yields. We have tried several Suzuki cross coupling reaction conditions and found the following reaction conditions to give the best yields without any racemization: 5 mol% $Pd(OAc)_2$ and 10 mol% tri(*o*-tolyl)phosphine as the catalyst, 1.5 equiv boronic acid and 2.0 equiv Na_2CO_3 in a mixture of ethylene glycol dimethyl ether (DME) and H_2O at 80°C. A longer reaction time (12 h) was required for the formation of the sterically hindered products. The enantiomeric purity was determined by chiral HPLC analysis and no racemizations were observed during the cross couplings.[18]

Using a similar strategy, we synthesized *o*-aromatic substituted naphthylalanine derivatives **9** and **10** (Scheme 2). The isolated (*Z*) α-enamide **12** was obtained as the major product by condensation of 1-bromo-2-naphthylaldehyde **11** with **6** in the presence of DBU in CH_2Cl_2 in 93% yield. Asymmetric hydrogenation of α-enamide **12** in the presence of 5 mol% catalyst, Rh(I)-(*S*,*S*)-Et-DuPHOS or Rh(I)-(*R*,*R*)-Et-DuPHOS, 65 psi of H_2, 24 h in methanol gave (*S*) or (*R*) N^{α}-Cbz-*o*-bromonaphthylalanine methyl esters **13a**,**b** in 95–99% yield and >98% ee, respectively.[19] The *o*-bromonaphthylalanines **13a**,**b** were reacted with phenyl and naphthyl boronic acids through Suzuki cross coupling reactions to give final compounds **9** and **10**. We employed the same coupling reaction conditions as used before in good yields for the phenylboronic acid-based reactions. An incomplete reaction was observed for the coupling with naphthylboronic acid. However, using 5 mol% $Pd(PPh_3)_4$ instead of $Pd(OAc)_2$ and P(*o*-tolyl)$_3$, 1.5 equiv. boronic acid, 2.0 equiv. Na_2CO_3, in benzene–water, 80°C, for 36 h afforded a complete reaction in high yields (>95%).

Interestingly in these *o*-substituted phenylalanines and naphthylalanines, we found that two diasteromers were obtained for **3b**, **4b**, **9b**, and **10b**. ^{1}H NMR showed two groups of proton signals. About 1:1 and 1:2 ratios of diastereomers in **3b** and **4b** and in **9b** and **10b** were observed, respectively, during the Suzuki couplings based on the integrations of ^{1}H NMR. Although they are diastereomers, they could not be separated by silica gel chromatography. Their structures are presumably assigned as shown (**4b** and **10b** not shown) in Fig. 2. Because of the interaction between the large naphthyl moiety and the β-hydrogens of amino side chain, the naphthyl group in **3b** and **9b** were away from the two β-hydrogens of amino side chain to reduce steric hin-

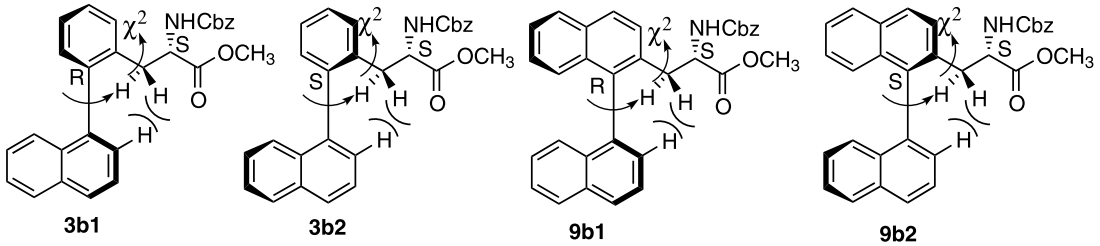


Figure 2.

drance. The detailed conformation studies of these amino acids currently are being investigated via X-ray crystal structures, NMR, and computer modeling and calculations. It is also realized that these conformationally constrained amino acids bearing fluorophores will be very useful in structure–activity studies of peptides and receptors.

An efficient method has been developed for the synthesis of novel aromatic-substituted χ^2-constrained phenylalanine and naphthylalanine derivatives. These amino acids were synthesized through asymmetric hydrogenations using Burk's DuPHOS-based catalysts with high e.e. (>96%), followed by Suzuki crossing couplings also in high yields. The method can be easily scaled up for the synthesis of a large amount of these amino acids. The incorporation of the amino acids into biologically active α-MSH peptides and peptidomimetics, biological evaluation, and structure–biological activity relationship study of the peptides and peptidomimetics are currently under extensive investigation.

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References

1. Hruby, V. J. *Life Sci.* **1982**, *31*, 189–199.
2. Hruby, V. J.; Li, G.; Haskell-Luevano, C.; Shenderovich, M. *Biopolym. (Pept. Sci.)* **1997**, *43*, 219–266.
3. Hruby, V. J.; Shenderovich, M.; Liao, S.; Porreca, F.; Yamamura, H. I. In *Rational Molecular Design in Drug Research*, *Alfred Benzon Symposium No*. 42; Liljefors, T.; Jorgensen, F. S.; Krogsgaard-Larsen, P., Eds.; Munksgaard Intl. Publ. Ltd: Copenhagen, 1998; pp. 51–62.
4. Hruby, V. J.; Balse, P. M. *Curr. Med. Chem.* **2000**, *7*, 945–970.
5. Liao, S.; Lin, J.; Shenderovich, M. D.; Han, Y.; Hosohata, K.; Davis, P.; Qiu, W.; Porreca, F.; Yamamura, H. I.; Hruby, V. J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 3049–3052.
6. Liao, S.; Shenderovich, M. D.; Zhang, Z.; Maletinska, L.; Slaninova, J.; Hruby, V. J. *J. Am. Chem. Soc.* **1998**, *120*, 7393–7394.
7. Tang, X. J.; Soloshonok, V. A.; Hruby, V. J. *Tetrahedron: Asymmetry* **2000**, *11*, 2917–2925.
8. Jiao, D.; Russell, K. C.; Hruby, V. J. *Tetrahedron* **1993**, *49*, 3511–3520.
9. Qian, X.; Russell, K. C.; Boteju, L. W.; Hruby, V. J. *Tetrahedron* **1995**, *51*, 1033–1054.
10. Hruby, V. J.; Han, G. In *The Melanocortin Receptors*; Cone, R. D., Ed.; Humana Press: Totowa, NJ, 2000; pp. 239–261.
11. Hruby, V. J.; Lu, D.; Sharma, S. D.; Castrucci, A.; de, L.; Kesterson, R. A.; Al-Obeidi, F. A.; Hadley, M. E.; Cone, R. D. *J. Med. Chem.* **1995**, *38*, 3454–3461.
12. Wang, W.; Xiong, C. Y.; Yang, J. Q.; Hruby, V. J. *Tetrahedron Lett.* **2001**, *42*, 7717–7719.
13. Schmidt, U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A.; Mangold, R.; Meyer, R.; Riedl, B. *Synthesis* **1992**, 487–490.
14. Schmidt, U.; Lieberknecht, A.; Wild, J. *Syn. Commun.* **1984**, 53–60.
15. Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363–372.
16. Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Soc. Chem.* **1993**, *115*, 10125–10138.
17. Strem Chemicals, Inc., 7 Mulliken Way, Dexter Industrial Park, Newburyport, MA 01950–9899, USA.
18. Chiralcel OD column (0.46×25 cm), hexanes/isopropanol (90/10) at a flow rate of 1.5 mL/min. Essentially one single peak was obtained in each case of **3a**-(*S*) and **4a**-(*R*). The retention time: **3a**-(*S*): 8.1 min, **4a**-(*R*): 11.3 min.
19. Use the same column and conditions as described in Ref 18. Essentially one single peak was observed in each case of **13a**-(*S*) and **13b**-(*R*). The retention time: **13a**-(*S*): 15.0 min, **13b**-(*R*): 18.6 min.