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Stereoselective Synthesis of Dipeptide β-Turn Mimetics: 7-Benzyl and 8-Phenyl Substituted Azabicyclo[4.3.0]nonane Amino Acid Esters†

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A stereoselective method has been developed for the synthesis of 7- and 8-substituted dipeptide β-turn mimetic azabicyclo[4.3.0]nonane amino acid esters. The allyl groups were introduced in high diastereoselectivity, controlled by 3-phenyl or 4-benzyl groups in pyroglutamic acid derivatives **3** or **9**, respectively. The precursors, dehydroamino acids **7** and **13** derived from **5** or **11**, underwent asymmetric hydrogenations with Burk's DuPHOS Rh(I)-based catalysts to furnish α-amino acid derivatives in high stereoselectivity. The resulting amino acids **8** and **14** were converted to the β-turn mimetics 6,5-bicyclic lactams **1a**−**d** in high yields.

Introduction

In the recent past, there has been an increasing interest in the development of rigid dipeptide β-turn mimetics to try to mimic or induce β-turn secondary structural features of peptides and proteins that are thought to play important roles in molecular recognition and biological activity.[1−3] A great deal of effort has focused on the design and synthesis of small constrained mimetics of reverse-turn structures to provide a better understanding of the molecular basis of peptide and protein interactions. Several peptide mimetic systems have been proposed to mimic different types of reverse-turns.[1] Azabicyclo[*X*.*Y*.0]alkane amino acids are particularly attractive because of their ability to serve as conformationally fixed surrogates of peptide turn secondary structures (Figure 1).[1b] The growing use of these dipeptide surrogates in the investigation of structure−activity relationships of various biologically peptides has created a demand for new methodology for synthesizing these peptide mimetics. Several procedures have been developed for the synthesis of such bicyclic lactams.[1,2] In these approaches, one particularly effective and versatile route, developed by Lubell and co-workers, has been employed for the preparation of enantiopure indolizidinone-type bicyclic lactam systems.[1,3]

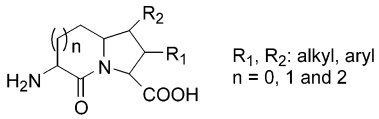

FIGURE 1. Azabicyclo[*X*.*Y*.0]alkane amino acids.

Although quite a few successes have been reported in obtaining mimetics which can force or stabilize β-turns, little success has been reported in incorporating mimetics for the active site of peptide hormone or neurotransmitter receptors because of the lack of appropriately positioned side chain groups. In the event of molecular recognition, the backbone conformations of peptides and proteins provide critical templates for the three-dimensional structures when interacting with their receptors/acceptors. However, the overall shape and intrinsic stereoelectronic properties of the peptides and proteins important for molecule recognition, signal transduction, enzymatic specificity, immunomodulation, and other

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(2) For recent examples for the synthesis of β-turn mimetics, see: (a) Manzoni, L.; Belvisi, L.; Scolastico, C. *Synlett* **2000**, 1287−1288. (b) Manzoni, L.; Colombo, M.; May, E.; Scolastico, C. *Tetrahedron* **2001**, *57*, 249−255. (c) Beal, L. M.; Liu, B.; Chu, W.; Moeller, K. D. *Tetrahedron* **2000**, *56*, 10113−10125. (d) Angioini, M.; Araneo, S.; Belvisi, L.; Cesarotti, E.; Checchia, A.; Crippa, L.; Manzoni, L.; Scolastico, C. *Eur. J. Org. Chem.* **2000**, 2571−2581. (e) Angiolini, M.; Araneo, S.; Belvisi, L.; Cesarotti, E.; Checchia, A.; Crippa, L.; Manzoni, L.; Scolastico, C. *Eur. J. Org. Chem.* **2000**, 2571−2581. (f) Hanessian, S.; McNaughton-Smith, G. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1567−1572. (g) Hanessian, S.; Ronan, B.; Laoui, A. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1397−1400. (h) Kim, H.-O.; Nakanishi, H.; Lee, M. S.; Kahn, M. *Org. Lett.* **2000**, *2*, 301−302. (i) Boatman, P. D.; Ogbu, C. O.; Eguchi, M.; Kim, H. O.; Nakanishi, H.; Cao, B.; Shea, J. P.; Kahn, M. *J. Med. Chem.* **1999**, *42*, 1367−1375.

(3) For recent development of the synthesis of β-turn mimetics with side chain functionalities by Lubell and co-workers, see: (a) Gosselin, F.; Lubell, W. D. *J. Org. Chem.* **1998**, *63*, 7463−7471. (b) Gosselin, F.; Lubell, W. D. *J. Org. Chem.* **2000**, *65*, 2163−2171. (c) Polyak, F.; Lubell, W. D. *J. Org. Chem.* **1998**, *63*, 5937−5949. (d) Polyak, F.; Lubell, W. D. *J. Org. Chem.* **2001**, *66*, 1171−1180. (e) Feng, Z.; Lubell, W. D. *J. Org. Chem.* **2001**, *66*, 1181−1185.

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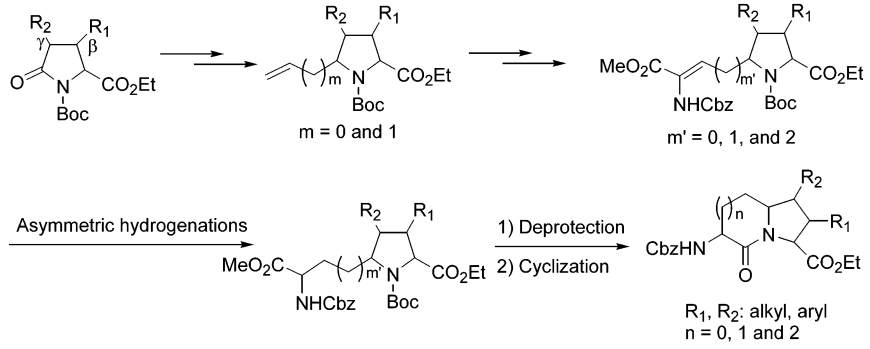
SCHEME 1. General Approach for the Synthesis of Azabicyclo[*X.Y.*0]alkane Amino Acids



biological effects usually depend on the arrangement of the side chain groups of amino acid residues in three-dimensional space. The side chain moieties involved directly in the binding are critical for biological activity and selectivity for receptors/acceptors or subtype receptors and ligands. Their 3D architecture (topography) and stereoelectronic properties provide the critical complementary shape and chemical properties that favor efficient molecular recognition.

To mimic the backbone *and* side chain conformations of β-turns, a synthetic strategy requires stereocontrolled introduction of side chain functionalities. Furthermore, the synthesis of such β-turn mimetics should be easily accessible from readily available or prepared starting materials. To fulfill the criteria, recently we have developed two efficient methods to construct dipeptide β-turn mimetics in high stereoselectivity.[4] Our continuing efforts in this area are directed toward the development of efficient methods for the synthesis of other β-turn mimetics with appendages of side chain functionalities. Herein, we would like to report an approach for introducing alkyl and aryl side chains onto the azabicyclo[*X.Y.*0]-alkane amino acids in a highly stereocontrolled manner (Scheme 1). The strategy involves starting from easily synthesized and optically pure β- or γ-substituted pyroglutamic acid derivatives.[5,6] Stereoselectively introducing allyl groups at the C_5 position of β- or γ-substituted pyroglutamic acid derivatives and the elaboration of them can afford dehydroamino acids, which can undergo asymmetric hydrogenations followed by deprotection and lactam cyclization to furnish substituted 6/5 fused bicyclic β-turn mimetics (Scheme 1). In this study, benzyl and phenyl groups are successfully introduced at positions 7 and 8 in high diastereoselectivity (Schemes 2 and 3). The synthesis of 7-benzyl analogues has been reported by Lubell and co-workers using a Claisen condensation/reductive amination/lactam cyclization method. However, to the best of our knowledge, the 8-phenyl substituted analogues, which can mimic dipeptide Ala−Phe, have not been reported in the literature. The hydrophobic benzyl and phenyl groups are very attractive because they could improve peptide−receptor affinity by interacting with hydrophobic pockets of receptors.

Results and Discussion

Synthesis of 7-Benzyl Azabicyclo[4.3.0]nonane Amino Acid Derivatives 1a,b. The synthesis of 7-benzyl azabicyclo[4.3.0]nonane amino acid derivatives **1a**,**b** is illustrated in Scheme 2, starting from pyroglutamic ethyl ester **2**. Ethyl (2*S*,4*R*)-1-Boc (*tert*-butoxycarbonyl)-4-benzylpyroglutamate (**3**) was prepared by a modification of literature procedures.[6] A related literature procedure only gave a moderate yield (~59%).[7] However, longer reaction times gave a higher yield (up to 76%) without sacrificing stereoselectivity. Only one diastereomer was formed with a *4S* configuration, as observed in the literature. Selective reduction of the lactam moiety of **3** with Super-Hydride ($LiBEt_3H$) in THF at −78 °C and subsequent reaction of the resulting hemiaminal in methanol in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) gave the corresponding aminal **4** as two isomers in 93% yield. The crude product **4** was pure enough for the next step reaction without further purification. When **4** was treated with $BF_3{\cdot}OEt_2$ and allyltrimethylsilane at −40 °C, following a literature procedure,[8] only about 20% of the desired product **5** was obtained with the rest of the decomposed products.[8] However, when the reaction temperature was lowered to −78 °C, the reaction yield was significantly improved to 76%. The allylsilane addition to the *N*-acyliminium derived from **4** gave exclusively *trans* product related to the 4-benzyl group. The outcome is consistent with what was observed in the 3-phenyl pyroglumatic ester by Moeller and co-workers.[8] The nucleophile attacked the *N*-acyliminium ion from the *si*-face of the molecule because the *re*-face was blocked by the benzyl group (Figure 2). The ethyl ester group has little effect on the addition. The observed stereochemistry is opposite to that of R·Cu-complex addition to the *N*-acyliminium to give

(4) For more recent methods from our laboratory, see: (a) Wang, W.; Xiong, C.-Y.; Hruby, V. J. *Tetrahedron Lett.* **2001**, *42*, 3159−3161. (b) Qiu, W.; Gu, X.; Soloshonok, V. A.; Carducci, M. D.; Hruby, V. J. *Tetrahedron Lett.* **2001**, *42*, 145−148.

(5) For a recent review regarding the synthesis of pyroglutamic acid derivatives, see: Najera, C.; Yus, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2245−2303.

(6) For methods developed in our laboratory for the synthesis of β-substituted pyroglutamic acid and proline derivatives, see: (a) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Tetrahedron Lett.* **2001**, *41*, 135−139. (b) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 2172−2175. (c) Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Van Meervelt, L.; Yamazaki, T. *J. Org. Chem.* **2000**, *65*, 6688−6696. (d) Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Van Meervelt, L. *Tetrahedron* **1999**, *55*, 12045−12058. (e) Soloshonok, V. A.; Cai, C.; Hruby, V. J.; Van Meervelt, L.; Mischenko, N. *Tetrahedron* **1999**, *55*, 12031−12044. (f) Soloshonok, V. A.; Cai, C.; Hruby, V. J. *Tetrahedron: Asymmetry* **1999**, *10*, 4265−4269.

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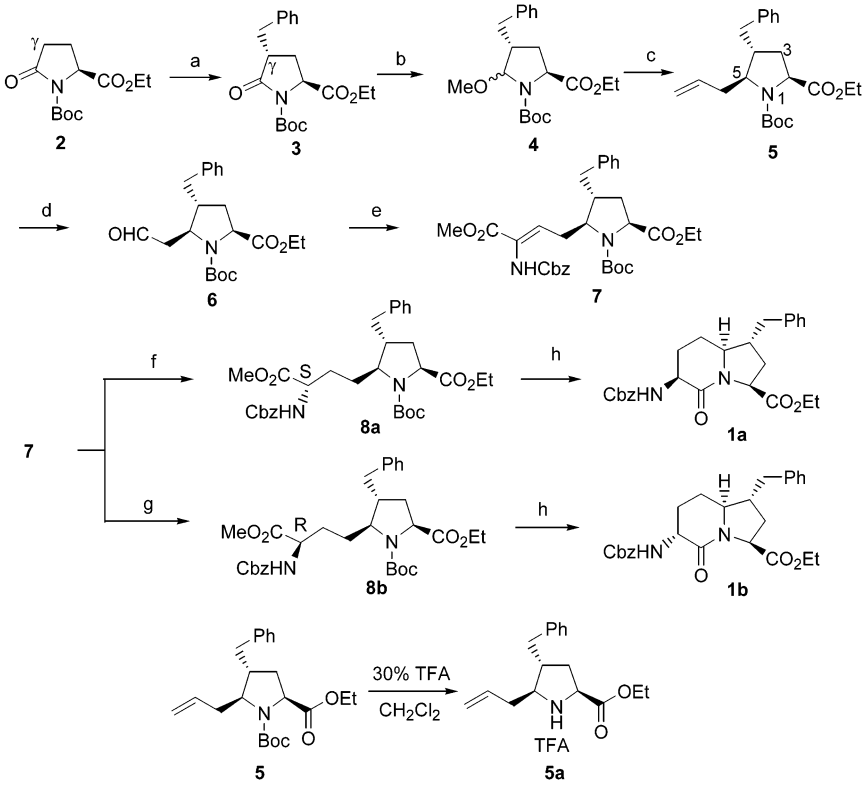
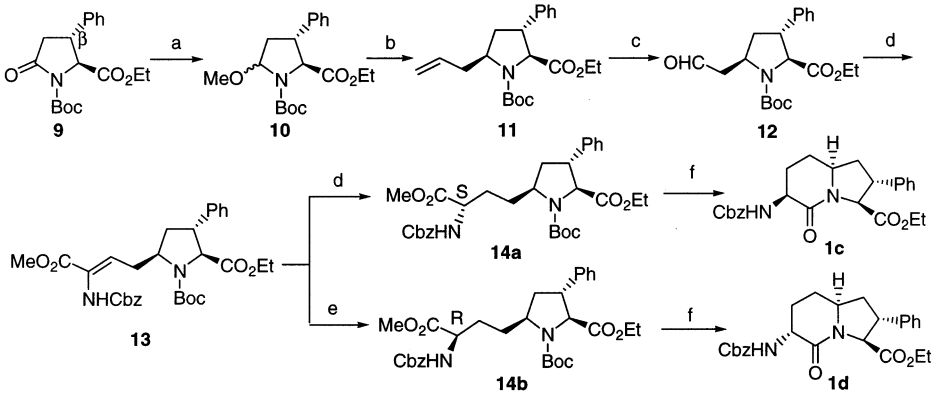
(8) Tong, Y.; Fobian, Y. M.; Wu, M.; Boyd, N. D.; Moeller, K. D. *J. Org. Chem.* **2000**, 2484−2493.

SCHEME 2. Synthesis of 7-Benzyl Azabicyclo[4.3.0]nonane Amino Acid Derivatives[a]



[a] (a) LiHMDS, BnBr, THF, −78 °C, 76%. (b) (i) Super-Hydride, THF, −78 °C; (ii) *p*TsOH (cat.), MeOH, two steps (93%). (c) BF_3—OEt_2, $Me_3SiCH_2CH{=}CH_2$, 76%. (d) O_3, then Me_2S, 5 d, 63%. (e) $(MeO)_2P(O)CH(NHCbz)COOCH_3$, DBU, CH_2Cl_2, rt, 4 h, 100%. (f) Rh(I)(COD)-(*S*,*S*)-Et-DuPHOS, H_2 (75 psi), 24 h, MeOH, 95%. (g) Rh(I)(COD)-(*R*,*R*)-Et-DuPHOS, H_2 (75 psi), 24 h, MeOH, 96%. (h) (i) 30% TFA, CH_2Cl_2, 2 h; (ii) TEA, CH_2Cl_2, 5 days, 76−83%.

SCHEME 3. Synthesis of 8-Phenyl Azabicyclo[4.3.0]nonane Amino Acid Derivatives[a]



[a] (a) (i) $LiBEt_3H$, THF, −78 °C; (ii) *p*-TsOH (cat.), MeOH, rt, overnight. (b) $CH_2{=}CHCH_2Si(CH_3)_3$, BF_3—Et_2O, −40 °C, 3 steps (74%). (c) O_3, CH_2Cl_2, −78 °C, then Me_2S, rt, 5 d, 81%. (d) $(MeO)_2P(O)CH(NHCbz)COOCH_3$, DBU, CH_2Cl_2, rt, 6 h, 90%. (d) Rh(I)(COD)-(*S*,*S*)-Et-DuPHOS, H_2 (70 psi), 24 h, MeOH, 100%. (e) Rh(I)(COD)-(*R*,*R*)-Et-DuPHOS, H_2 (70 psi), 24 h, MeOH, 100%. (f) (i) 30% TFA, CH_2Cl_2, rt, 1 h; (ii) TEA, CH_2Cl_2, 6 d, 83−87%.

cis products related to the 4-benzyl group reported in the literature (Figure 2).[9] However, in the latter case, the ester group played a dominant role in the control of stereochemistry through formation of a Cu(I) complex to block the *β*-face, whereas the 4-benzyl group had little effect on the allyl addition (Figure 2).[9] Because of rotamers (*cis* and *trans*) in the proline derivative **5**, complicating the ^1H NMR, the Boc group was removed to give **5a** with a "clean" ^1H NMR to allow us to determine the stereochemistry of the allyl group (Scheme 2). The stereochemistry of the resulting allyl addition product was assigned as the *S* configuration in **5a** by NOE experiments that showed 1.4%, 1.5%, and 1.1% enhancement in H_a, H_b, and H_d, respectively, by irradiation of H_c (Figure 3). No NOE effect on H_e was observed by irradiation of the same H_c. The stereochemistry at C_5 of the proline derivative position was further confirmed by NOE experiments of the final product **1a** (Figure 3).

(9) Collado, I.; Ezquerra, J.; Pedregal, C. *J. Org. Chem.* **1995**, *60*, 5011−5015.

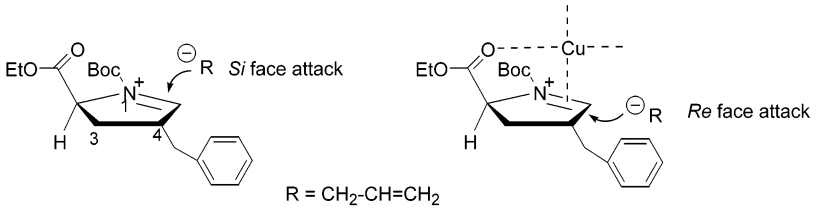


FIGURE 2.

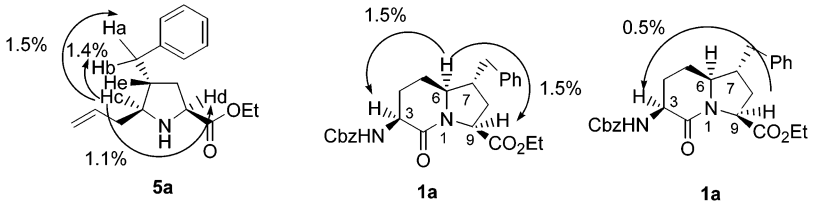


FIGURE 3.

With the optically pure intermediate **5** in hand, we elaborated it to give the final products **1a**,**b** in high yields and high stereoselectivity. Ozololysis, followed by Me_2S reduction of the double bond in compound **5**, afforded aldehyde **6** in 63% yield. The key intermediate, dehydroamino acid **7**, was obtained with the (*Z*) isomer as the major product via the Horner−Emmons olefination of aldehyde **6** in a quantitative yield.[10] A mixture of the two (*Z*) and (*E*) isomers was used for the asymmetric hydrogenations without separation. The resulting dehydroamino ester **7** underwent asymmetric hydrogenations to give the α-amino acid derivatives in high diastereoselectivity. The Burk's catalysts [Rh(I) (COD) (*S*,*S*)-Et-DuPHOS or (*R*,*R*)-Et-DuPHOS]OTf were employed as the catalyst in high yields (>95%) and high diastereoselectivity (>96% ee).[11] We tried to determine the diastereoselectivity of asymmetric hydrogenations using ^{1}H NMR. Unfortunately, the two existing rotamers in **8** complicated their evaluation. However, only one diastereomer was observed on the basis of TLC analysis. At this point, we did not make a further effort to determine diastereoselectivity. However, only one diastereomer, **1a** or **1b**, was obtained from the amino acid ester **8a** or **8b**, respectively, after cleavage of the N^{α}-Boc group and cyclization. It should be noted that Scolastico and coworkers employed Rh(I) Prophos or (+)/(−)BitianP catalysts for asymmetric hydrogenations with similar dehydroamino acid derivative substrates to have achieved good diastereoselectivities (72−80% de).[1e] However, we have successfully used Burk's catalysts to synthesize many novel amino acids and dipeptide β-turn mimetics in high enantioselectivity and/or diastereoselectivity under low to medium hydrogen pressure and, hence, have used them here.[4a,12] The new absolute configurations were assigned as *S* in **8a** and *R* in **8b** on the basis of the selectivity of the (*S*,*S*)-Et-DuPHOS and (*R*,*R*)-Et-DuPHOS ligands, respectively.[13] The formation of the new chiral centers in **8a**,**b** was well controlled by asymmetric hydrogenations. Compounds **8a**,**b** were converted to the final products **1a**,**b** in two steps. Deprotection of the N^{α}-Boc group by TFA was followed by intramolecular lactamization in the presence of TEA in CH_2Cl_2 to afford **1a**,**b** in 76−83% yields. It took a long time to complete the lactamization reaction, which was monitored by TLC, at room temperature because of the steric hindrance of the secondary amine. It was found that the reaction rates were similar despite the different configurations in **8a** and **8b**. Increasing the reaction temperature should facilitate lactamization.[2e] The stereochemistry at position 6 of (*S*)-configuration in **1a** was further verified by NOE experiments. Strong NOE effects (∼1.5%) were observed at H_3 and H_9 via irradiation of H_6. Furthermore, the irradiation of H_9 generated a 0.5% NOE effect for H_3. In addition, the optical rotation of (3*S*,6*S*,7*S*,9*S*)-2-oxo-3-*N*-(Boc)amino-7-benzyl-1-azabicyclo[4.3.0]nonane-9-carboxylic acid ($[\alpha]_D^{23}$ −6.0 (*c* 1.2, $CHCl_3$)) derived from **1a** is similar to that of the compound synthesized by Lubell and co-workers ($[\alpha]_D^{20}$ −5.9 (*c* 2.0, $CHCl_3$)).[3c]

Synthesis of 8-Phenyl Azabicyclo[4.3.0]nonane Amino Acid Derivatives 1c,d. Using a similar strategy, we also synthesized novel 8-phenyl substituted β-turn mimetics **1c**,**d** (Scheme 3). The starting material β-phenyl pyroglutamic ester **9** was efficiently prepared using our highly stereocontrolled Michael addition method.[6] Recently, we have developed an efficient route for asymmetric synthesis of a variety of β-substituted pyroglutamic acids and proline derivatives.[6] The key step was the asymmetric Michael addition, which was well controlled by two chiral auxiliaries, for example, the proline-based chiral Ni(II) complex and the Evans chiral auxiliary in high diastereoselectivity (>98% de).[6] The same proce-

(10) For the synthesis of the intermediate phosphate and dehydroamino acids, see: Schmidt, U.; Griesser, H.; Leitenberger, V.; Lieberknecht, A.; Mangold, R.; Meyer, R.; Riedl, B. *Synthesis* **1992**, 487−490.

(11) For recent reviews regarding the applications of DuPHOS-based catalysts in asymmetric hydrogenations, see: (a) Burk, M. J.; Gross, M. F.; Harper, T. G. P.; Kalberg, C. S.; Lee, J. R.; Martinez, J. P. *Pure Appl. Chem.* **1996**, *68*, 37−44. (b) Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363−372.

(12) We and others have used the DuPHOS-based catalysts for the synthesis of novel amino acids. See: (a) Hiebl, J.; Kollmann, H.; Rovenszky, F.; Winkler, K. *J. Org. Chem.* **1999**, *64*, 1947−1952. (b) Wang, W.; Xiong, C. Y.; Yang, J. Q.; Hruby, V. J. *Tetrahedron Lett.* **2001**, *42*, 7717−7719. (c) Wang, W.; Zhang, J.; Xiong, C.; Hruby, V. J. *Tetrahedron Lett.* **2002**, *43*, 2137−2140. (d) Wang, W.; Xiong, C.; Yang, J.; Hruby, V. J. *Synthesis* **2002**, 94−98. (e) Wang, W.; Xiong, C.; Zhang, J.; Hruby, V. J. *Tetrahedron* **2002**, *58*, 3101−3110.

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dures were employed to convert lactam **9** into the intermediate aminal **10** in two steps by selective reduction of lactam **9** to a hemiaminal, followed by reaction with methanol in the presence of a catalytic amount of *p*-TsOH. Interestingly, it was found that when **10** was treated with $BF_3{\cdot}Et_2O$ at −40 °C and allyltrimethylsilane, a good yield (over 74%) was observed with formation of exclusively the *trans* product related to the 3-phenyl group. In this case, the 3-phenyl group controlled the stereochemistry of an allylsilane addition to the *N*-acyliminium derived from **10**, as was observed in **5** for the 4-benzyl group and by Moeller and co-workers.[8] The aldehyde **12** was obtained by ozololysis, followed by Me_2S reduction of the double bond in **11** in 81% yield. Then the product was reacted with the phosphonate $(MeO)_2P(O)CH(NHCbz)COOMe$ in the presence of DBU to give dehydroamino ester **13** in 90% yield with a 13/1 ratio of (*Z*)/(*E*). Asymmetric hydrogenations of **13** in the presence of [(COD)(*S*,*S*)-Et-DuPHOS Rh(I)]OTf or [(COD)(*R*,*R*)-Et-DuPHOS Rh(I)]OTf afforded amino acids (*S*)-**14a** and (*R*)-**14b**, respectively, in quantitative yields and high diastereoselectivity. Again, only one isomer was obtained on the basis of TLC analysis. The final β-turn mimetic products **1c,d** were obtained as one isomer in each case in two steps, deprotection and lactamization, in high yields. Again, a long reaction time was required for the lactamization reactions. The conformation effect in (*S*)-**14a** and (*R*)-**14b** had little influence on the lactamization. The results were consistent with what we observed for (*S*)-**8a** and (*R*)-**8b**.

Conclusion

We have developed an efficient approach to the synthesis of stereocontrolled side chain appended azabicyclo-[4.3.0]nonane amino acids in high diastereoselectivity. In this approach, the allyl group was stereoselectively introduced at the C_5 position, controlled by a 4-benzyl or 3-phenyl group rather than by the ethyl ester group. Asymmetric hydrogenations using Burk's Rh(I)-based catalysts with the chiral ligand (*S*,*S*)- or (*R*,*R*)-Et-DuPHOS generated (*S*) and (*R*) α-amino acids, respectively, in high stereoselectivity and high yields. This method could be further exploited for the synthesis of other diastereomers starting from different substituted pyroglutamic acid derivatives to give 7/5 azabicyclo[*X*.*Y*.0] amino acids (Scheme 1).[2e] The synthesis of such β-turn mimetics using this approach and the incorporation of these molecules into biologically active peptides and the study of structure−activity relationships are under investigation.

Experimental Section

General. ^1H and ^{13}C NMR were performed on 300, 500, or 600 MHz spectrometers using TMS and $CDCl_3$ as internal standards. High-resolution mass spectra (HRMS) were recorded on an instrument in the University of Arizona Mass Spectroscopy Laboratory. Optical rotations were measured on a polarimeter. Melting points (mp) are uncorrected and were obtained in open capillaries. Commercially available starting materials and reagents were of ACS grade or better and used as received. THF was distilled from Na and benzophenone, and methylene chloride (CH_2Cl_2) was distilled from CaH_2; HPLC grade methanol was used for hydrogenations. Column chromatography was performed using silica gel (230−400 mesh). Thin-layer chromatography (TLC) was performed on 13 181 silica gel-based sheets with a fluorescent indicator. Unless otherwise stated, yields refer to isolated yields of products of greater than 95% purity, as estimated by ^1H and ^{13}C NMR spectroscopy. All new compounds were characterized by ^1H, ^{13}C, and HRMS or elemental analysis.

Ethyl (2*S*,4*S*)-1-(*tert*-Butoxycarbonyl)-4-benzyl Pyroglutamate (3). To a solution of pyroglutamic ester **2** (7.4 g, 28.76 mmol) in THF (180 mL) at −78 °C was added a 1.0 M solution of LiHMDS (31.64 mL, 31.64 mmol) under argon atmosphere. After the solution was stirred for 1.5 h at −78 °C, benzyl bromide (4.1 mL, 34.51 mmol) in THF (45 mL) was added into the reaction mixture and the stirring was continued for 5 h at this temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl (225 mL) at −78 °C and then was extracted with ether (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtrated, and evaporated to dryness under reduced pressure. The crude product was purified by flash silica gel chromatography, eluting with ethyl acetate/hexanes (1/5 then 1/4) to give a white solid (5.78 g, 76%). Mp 99−101 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.16−7.32 (m, 5H), 4.46 (dd, 1H, J_1 = 3.0 Hz, J_2 = 8.4 Hz), 4.18 (q, 2H, J = 7.2 Hz), 3.29 (dd, 1H, J_1 = 4.2 Hz, J_2 = 13.8 Hz), 2.87−2.98 (m, 1H), 2.66 (dd, 1H, J_1 = 9.3 Hz, J_2 = 13.8 Hz), 1.95−2.09 (m, 2H), 1.50 (s, 9H), 1.25 (t, 3H, J = 7.2 Hz).

(4*S*)-*N*$^{\alpha}$-*tert*-Butoxycarbonyl-4-benzyl-5-methoxy-L-proline Ethyl Ester (4). To a solution of **3** (5040 mg, 14.52 mmol) in THF (120 mL) was added Super-Hydride (1.0 M in THF, 17.5 mL) at −78 °C under an Ar atmosphere. After the mixture was stirred for 35 min at the same temperature, it was quenched with saturated $NaHCO_3$ (50 mL) and warmed to 0 °C (∼30 min). To the above mixture was added 140 drops of a 30% H_2O_2 aqueous solution at 0 °C, and the solution was stirred at 0 °C for 30 min. After removal of THF under reduced pressure, the remaining aqueous solution was extracted with diethyl ether (3 × 70 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a colorless oil. To the above obtained oily residue in MeOH (80 mL) was added p-TsOH·H_2O (276 mg, 1.45 mmol), and the mixture was stirred at room temperature overnight under Ar atmosphere. After the mixture was quenched with saturated $NaHCO_3$ (15 mL) and the methanol was removed, the remaining mixture was extracted with diethyl ether (3 × 70 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give crude **4** as a colorless oil (4900 mg, 93%). The crude product was used for the next step reaction without further purification. ^1H NMR (500 MHz, $CDCl_3$) δ 7.32−7.12 (m, 5H), 5.11 (s, 0.2H), 5.08 (d, 0.4H, J = 5.0 Hz), 4.92 (d, 0.4H, J = 2.5 Hz), 4.48 (t, 0.4H, J = 9.0 Hz), 4.34−4.08 (m, 3.6H), 3.44 (s, 0.75H), 3.41 (s, 1.5H), 3.35 (s, 0.75H), 2.85 (dd, 0.5H, J_1 = 8.0 Hz, J_2 = 13.5 Hz), 2.66−2.38 (m, 2.5H), 2.26−2.06 (m, 1.5H), 1.85 (m, 0.5H), 1.51 (s, 2.25H), 1.46 (s, 4.5H), 1.40 (s, 2.25H), 1.19−1.30 (m, 3H); HRMS (FAB) calcd for $C_{20}H_{30}NO_5$ (M + H) 364.2124, found 364.2123.

(4*S*,5*S*)-*N*$^{\alpha}$-*tert*-Butoxycarbonyl-5-allyl-4-benzyl-L-proline Ethyl Ester (5). To a solution of crude **4** (3180 mg, 8.76 mmol) in Et_2O (20 mL) were added allyltrimethylsilane (6.3 mL, 39.42 mmol) and $BF_3{\cdot}Et_2O$ (1.1 mL, 9.02 mmol) at −78 °C under an Ar atmosphere. After 3 h at the same temperature, the cold bath was removed and the reaction mixture was warmed to room temperature (∼30 min). The reaction mixture was diluted with Et_2O (50 mL), quenched with $NaHCO_3$ (25 mL), and then extracted with diethyl ether (2 × 60 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude product as a slightly yellow oil. The pure product **5** was obtained as a colorless oil after flash column chromatography (silica gel, 50 g, 200−400 mesh, hexanes/ethyl acetate 8:1) (2472 mg, 76%). $[\alpha]^{22}_D$ +17.3 (*c* 1.00, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32−7.15 (m, 5H), 5.78 (m, 1H), 5.04 (d, 1H, J = 17.7 Hz),

5.03 (d, 1H, J = 10.2 Hz), 4.38 (t, 0.4H, J = 8.1 Hz), 4.25 (t, 0.6H, J = 8.1 Hz), 4.17 (q, 2H, J = 6.9 Hz), 3.77 (m, 0.6H), 3.63 (m, 0.4H), 2.78−2.63 (m, 1.6H), 2.54−2.44 (m, 1.4H), 2.36−2.24 (m, 2H), 1.98 (dd, 2H, J_1 = 5.4 Hz, J_2 = 8.4 Hz), 1.48 (s, 3.6H), 1.43 (s, 5.4H), 1.26 (t, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 173.2, 154.7, 153.9, 139.8, 135.5, 129.2, 128.7, 126.5, 117.1, 80.2, 63.09, 63.05, 61.13, 61.10, 59.1, 58.8, 43.9, 42.7, 39.7, 39.0, 38.3, 33.2, 32.6, 28.6, 28.5, 14.4, 14.3. HRMS (FAB): calcd for $C_{22}H_{32}NO_4$ (M + H), 374.2331; found, 374.2325.

(4*S*,5*S*)-5-Allyl-4-benzyl-L-proline Ethyl Ester (5a). A solution of **5** (900 mg, 2.41 mmol) in a mixture of CH_2Cl_2 (8 mL) and TFA (3 mL) was stirred at room temperature under Ar overnight. Evaporation of solvents gave the product as an oil (930 mg, 100%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.26 (m, 3H), 7.16−7.14 (m, 2H), 5.76 (m, 1H), 5.32 (d, 1H, J = 14.7 Hz), 5.31 (d, 1H, J = 11.1 Hz), 4.56 (m, 1H), 4.36−4.18 (m, 2H), 3.64 (m, 1H), 2.88 (dd, 1H, J_1 = 4.8 Hz, J_2 = 13.5 Hz), 2.66 (dd, 1H, J_1 = 7.5 Hz, J_2 = 13.5 Hz), 2.56−2.35 (m, 3H), 2.31−2.19 (m, 3H), 1.28 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 138.1, 131.0, 129.1, 128.8, 127.2, 121.8, 64.1, 64.0, 58.0, 43.7, 37.8, 35.5, 34.9, 14.0. HRMS (FAB): calcd for $C_{17}H_{24}NO_2$ (M + H), 274.1807; found, 274.1806.

(4*S*,5*S*)-*N*$^\alpha$-*tert*-Butoxycarbonyl-4-benzyl-5-[(2-oxoethyl)]-L-proline Ethyl Ester (6). Through a solution of **5** (2472 mg, 8.76 mmol) in CH_2Cl_2 (35 mL) at −78 °C was bubbled O_3 until the solution turned purple. After an additional 15 min, Ar was passed through the reaction mixture until the solution became colorless. To the above solution was added Me_2S (15 mL, 198.8 mmol), and the mixture was stirred at room temperature under Ar atmosphere for 5 d. After removal of solvent under reduced pressure, the residue was purified by flash column chromatography (silica gel, 32 g, 200−400 mesh, hexanes/ethyl acetate 6:1) to give pure product **6** as a colorless oil (1500 mg, 63%). $[\alpha]^{22}_D$ −22.4 (c 1.50, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (brs, 1H), 7.30−7.15 (m, 5H), 4.42 (t, 0.33H, J = 7.5 Hz), 4.27 (t, 0.67H, J = 7.5 Hz), 4.19−4.07 (m, 3H), 2.99−2.77 (m, 2H), 2.59−2.54 (m, 2H), 2.28 (m, 1H), 2.04−1.93 (m, 2H), 1.46 (s, 3H), 1.41 (s, 6H), 1.26 (t, 3H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.2, 173.2, 173.1, 153.8, 139.2, 129.1, 128.8, 126.8, 126.7, 81.3, 80.7, 61.4, 61.3, 59.1, 58.7, 58.5, 49.1, 48.3, 46.0, 44.8, 39.24, 39.19, 33.3, 32.6, 28.5, 28.4, 14.4, 14.3. HRMS (FAB): calcd for $C_{21}H_{30}NO_5$ (M + H), 376.2124; found, 376.2111.

(4*S*,5*S*)-*N*$^\alpha$-*tert*-Butoxycarbonyl-5-[(*Z*)-3-benzoxycarbonylamino-3-methoxycarbonylallyl]-4-benzyl-L-proline Ethyl Ester (7). To a solution of $(MeO)_2P(O)CH(NHCbz)CO_2Me$ (1388 mg, 4.19 mmol) in CH_2Cl_2 (5 mL) at room temperature was added DBU (0.58 mL, 4.19 mmol) slowly. After ∼10 min, a solution of **6** (1310 mg, 3.49 mmol) in CH_2Cl_2 (5 mL) was added into the above mixture and the resulting mixture was stirred for 4 h at room temperature under an Ar atmosphere. The solvent was removed under reduced pressure, and the residue was dissolved in EtOAc (120 mL). The solution was washed with 1 N HCl (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated to give an oil. The crude product was purified by flash column chromatography (silica gel, 50 g, 200−400 mesh, hexanes/ethyl acetate/CH_2Cl_2 5:1:1 then 4:1:1) to give **7** as a clear oil (2020 mg, 100%). $[\alpha]^{22}_D$ +34.1 (c 1.16, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (brs, 1H), 7.39−7.23 (m, 8H), 7.14−7.11 (m, 2H), 6.56 (t, 1H, J = 7.5 Hz), 5.18−5.10 (m, 2H), 4.39 (t, 0.6H, J = 8.5 Hz), 4.24−4.16 (m, 2.4H), 3.85 (m, 1H), 3.75 (s, 1.2H), 3.72 (s, 1.8H), 2.70 (dd, 0.6H, J_1 = 7.0 Hz, J_2 = 14.0 Hz), 2.62−2.46 (m, 3.4H), 2.25 (m, 1H), 2.08−2.01 (m, 2H), 1.41 (s, 3.6H), 1.38 (s, 5.4H), 1.25 (t, 3H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 174.0, 165.3, 155.1, 154.9, 154.2, 139.3, 136.6, 133.4, 132.5, 129.1, 128.8, 128.7, 128.6, 128.5, 128.3, 128.2, 128.1, 126.8, 126.7, 126.5, 80.8, 67.5, 67.1, 62.4, 62.0, 61.8, 61.5, 59.1, 58.8, 52.3, 45.8, 44.5, 39.4, 34.5, 33.6, 33.5, 32.7, 28.3, 14.4, 14.3. HRMS (FAB): calcd for $C_{32}H_{41}N_2O_8$ (M + H), 581.2863; found, 581.2863.

(4*S*,5*S*)-*N*$^\alpha$-*tert*-Butoxycarbonyl-5-[(3*S*)-3-benzoxycarbonylamino-3-methoxycarbonylpropyl]-4-benzyl-L-proline Ethyl Ester (8a). A hydrogenation bottle was charged with **7** (630 mg, 1.1 mmol) in degassed methanol (15 mL, HPLC grade) and then was purged with argon for about 15 min, followed by adding [(*S*,*S*)-(COD)-Et-DuPHOS Rh(I)]OTf (1.56 mg, 0.0022 mmol). After five vacuum/hydrogen cycles, the reaction bottle was pressurized to an initial pressure of 75 psi. The reaction proceeded for 24 h. After evaporation of solvent, the crude product was purified by flash column chromatography, eluting with ethyl acetate/hexanes/methylene chloride (1:6:1) to afford an oil (600 mg, 95%). $[\alpha]^{23}_D$ −6.7 (c 0.76, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34−7.21 (m, 8H), 7.13−7.10 (m, 2H), 5.54 (d, 0.4H, J = 6.6 Hz), 5.46 (d, 0.6H, J = 6.6 Hz), 5.09 (dd, 2H, J_1 = 12.6 Hz, J_2 = 27.6 Hz), 4.41 (t, 0.8H, J = 8.4 Hz), 4.30−4.24 (m, 1.2 H), 4.19−4.11 (m, 2H), 3.77 (m, 1H), 3.71 (brs, 2H), 3.66 (m, 1H), 2.66−2.45 (m, 2H), 2.18 (m, 1H), 2.03−1.90 (m, 3H), 1.77−1.55 (m, 3H), 1.46 (s, 3.6H), 1.41 (s, 5.4H), 1.22 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 173.4, 173.1, 173.0, 156.2, 154.8, 154.2, 139.5, 139.4, 136.6, 136.5, 129.0, 128.6, 128.5, 128.4, 128.22, 128.15, 128.0, 126.5, 80.3, 80.2, 66.9, 66.8, 62.5, 62.2, 61.2, 61.1, 58.6, 58.1, 54.1, 54.0, 52.4, 45.2, 44.2, 39.4, 33.1, 32.5, 30.6, 30.4, 29.1, 28.7, 28.5, 28.4, 14.3, 14.2. HRMS (FAB): calcd for $C_{32}H_{43}N_2O_8$ (M + H), 583.3019; found, 583.3020.

(4*S*,5*S*)-*N*$^\alpha$-*tert*-Butoxycarbonyl-5-[(3*R*)-3-benzoxycarbonylamino-3-methoxycarbonylpropyl]-4-benzyl-L-proline Ethyl Ester (8b). In a manner similar to the preparation of **8a,** using [(*R*,*R*)-(COD)Et-DuPHOS Rh(I)]OTf as a catalyst gave **8b** in 96% yield. $[\alpha]^{22}_D$ −13.3 (c 1.64, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.12 (m, 8H), 7.13−7.11 (m, 2H), 5.77 (d, 0.4H, J = 7.5 Hz), 5.47 (d, 0.6H, J = 7.5 Hz), 5.10 (s, 2H), 4.43−4.39 (t, 0.8H, J = 8.5 Hz), 4.24−4.32 (m, 1.2H), 4.15−4.09 (m, 2H), 3.79 (m, 1H), 3.72 (s, 0.8H), 3.71 (s, 1.2H), 3.62 (m, 1H), 2.68−2.45 (m, 2H), 2.19 (m, 1H), 2.03−1.89 (m, 3H), 1.76−1.54 (m, 3H), 1.45 (s, 3.6H), 1.42 (s, 5.4H), 1.29−1.20 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 173.4, 173.0, 172.9, 156.3, 156.1, 154.9, 154.4, 139.6, 139.5, 136.6, 136.5, 129.1, 128.7, 128.6, 128.5, 128.3, 128.2, 126.6, 80.4, 67.0, 66.9, 62.7, 62.5, 61.3, 61.2, 58.9, 58.4, 54.3, 53.9, 52.4, 45.2, 44.3, 39.5, 33.1, 32.7, 30.3, 29.1, 28.6, 28.4, 14.4, 14.3. HRMS (FAB): calcd for $C_{32}H_{43}N_2O_8$ (M + H), 583.3019; found, 583.3023.

(3*S*,6*S*,7*S*,9*S*)-Ethyl 2-Oxo-3-*N*$^\alpha$-(benzoxycarbonyl)amino-7-benzyl-1-azabicyclo[4.3.0]nonane-9-carboxylate (1a). To a solution of **8a** (320 mg, 0.55 mmol) in CH_2Cl_2 (7.0 mL) was added TFA (3.0 mL) dropwise at room temperature under Ar atmosphere, and the mixture was stirred for 2 h. After removal of the solvent and TFA under reduced pressure, the residue was dissolved in CH_2Cl_2 (50 mL), followed by addition of TEA (0.38 mL, 2.75 mmol). The resulting reaction mixture was stirred at room temperature under Ar for 5 d. Evaporation of solvent gave an oil, which was dissolved in ethyl acetate (80 mL) and then was washed with 1 N HCl aqueous solution (15 mL) and brine (15 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated to give a colorless oil, which was purified by flash column chromatography (silica gel, 18 g, 200−400 mesh, EtOAc/hexane 1:4 then 1:2) to give a pure product (187 mg, 76%). $[\alpha]^{22}_D$ −7.9 (c 1.70, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.12 (m, 10H), 5.83 (d, 1H, J = 5.5 Hz), 5.10 (s, 2H), 4.47 (d, 1H, J = 9.0 Hz), 4.18−4.09 (m, 3H), 3.36 (m, 1H), 2.74 (dd, 1H, J_1 = 6.5 Hz, J_2 = 13.5 Hz), 2.68 (dd, 1H, J_1 = 8.0 Hz, J_2 = 13.5 Hz), 2.41 (m, 1H), 2.07 (dd, 1H, J_1 = 6.0 Hz, J_2 = 13.0 Hz), 1.94 (m, 1H), 1.76 (m, 1H), 1.56−1.64 (m, 3H), 1.23 (t, 3H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 168.9, 156.2, 138.9, 136.5, 128.9, 128.7, 128.6, 128.1, 128.0, 126.7, 66.8, 61.5, 61.0, 57.9, 50.5, 47.2, 38.4, 35.2, 27.0, 26.0, 14.1. HRMS (FAB): calcd for $C_{26}H_{31}N_2O_5$ (M + H), 451.2233; found, 451.2235.

(3*R*,6*S*,7*S*,9*S*)-Ethyl 2-Oxo-3-*N*$^\alpha$-(benzoxycarbonyl)-amino-7-benzyl-1-azabicyclo[4.3.0]nonane-9-carboxylate (1b). In a manner similar to the preparation of **1a**,

compound **8b** was treated with TEA in CH_2Cl_2 to give **1b** in 83% yield. $[\alpha]^{22}_D$ −36.1 (*c* 1.80, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.12 (m, 10H), 5.67 (d, 1H, *J* = 4.5 Hz), 5.07 (dd, 2H, J_1 = 12.0 Hz, J_2 = 25.0 Hz), 4.39 (m, 1H), 4.11 (m, 2H), 3.96 (m, 1H), 3.29 (m, 1H), 2.79 (m, 1H), 2.50 (m, 1H), 2.40 (m, 1H), 2.25 (m, 1H), 1.98−1.78 (m, 4H), 1.56 (m, 1H), 1.21 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 168.2, 156.5, 138.9, 136.5, 128.9, 128.7, 128.6, 128.1 (2C), 126.6, 66.9, 64.8, 61.3, 57.6, 52.5, 45.4, 37.4, 34.6, 28.3, 26.9, 14.2. HRMS (FAB): calcd for $C_{26}H_{31}N_2O_5$ (M + H), 451.2233; found, 451.2237.

(3*R*)-*N*$^\alpha$-*tert*-Butoxycarbonyl-5-methoxy-3-phenyl-L-proline Ethyl Ester (10). To a solution of **9** (560 mg, 1.68 mmol) in THF (15 mL) was added Super-Hydride (1.0 M in THF, 2.02 mL) at −78 °C under Ar atmosphere. After the mixture was stirred for 35 min at −78 °C, it was quenched with saturated $NaHCO_3$ (3.5 mL) and warmed to 0 °C (∼30 min). Then, to the above mixture was added 10 drops of 30% H_2O_2 aqueous solution at 0 °C, and the resulting mixture was stirred at 0 °C for another 30 min. The reaction mixture was extracted with diethyl ether (3 × 5 mL) after removing the THF under reduced pressure. The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated under vacuum to give a colorless oil. To the above obtained oil in MeOH (3.5 mL) was added *p*-TsOH·H_2O (32 mg, 0.17 mmol), and the mixture was stirred at room temperature overnight under Ar atmosphere. After the mixture was quenched with saturated $NaHCO_3$ (3.5 mL) and the solvent was removed, the reaction mixture was extracted with diethyl ether (3 × 12 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under vacuum to give crude **10** as a colorless oil (528 mg, 90%). HRMS (FAB): calcd for $C_{18}H_{24}NO_4$ (M − MeO), 318.1705; found, 318.1708.

(3*R*,5*S*)-*N*$^\alpha$-*tert*-Butoxycarbonyl-5-allyl-3-phenyl-L-proline Ethyl Ester (11). To a solution of crude **10** (420 mg, 1.20 mmol) in Et_2O (5 mL) were added allyltrimethylsilane (0.861 mL, 5.42 mmol) and BF_3·Et_2O (0.15 mL, 1.24 mmol) at −40 °C under Ar atmosphere. Then, the cold bath was removed and the reaction mixture was stirred for 30 min. After the reaction mixture was diluted with Et_2O (4 mL) and quenched with $NaHCO_3$ (4 mL), it was extracted with diethyl ether (3 × 6 mL). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated under vacuum to give the crude product as a slightly yellow oil. Purification of the crude product by flash column chromatography (silica gel, 15 g, 200−400 mesh, hexane/diethyl ether 1:1) gave pure product **11** as a colorless thick oil (350 mg, 82%, and 74% overall yield from **9**). $[\alpha]^{24}_D$ +62.0 (*c* 1.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.23 (m, 5H), 5.92−5.79 (m, 1H), 5.13 (d, 1H, *J* = 17.0 Hz), 5.07 (d, 1H, *J* = 10.2 Hz), 4.34−4.00 (m, 4H), 3.51 (q, 1H, *J* = 9.0 Hz), 2.82−2.67 (m, 1H), 2.40−2.30 (m, 1H), 2.18−2.13 (m, 2H), 1.49 (s, 3H), 1.41 (s, 6H), 1.19 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 154.2, 153.6, 140.2, 139.9, 135.5, 128.9, 127.5, 117.4, 80.5, 80.4, 77.4, 67.1, 66.5, 61.2, 61.1, 58.1, 57.9, 48.2, 47.3, 39.3, 38.6, 38.2, 28.6, 28.5, 14.4, 14.3. HRMS (FAB): calcd for $C_{21}H_{30}NO_4$ (M + H), 360.2175; found, 360.2170.

(3*R*,5*S*)-*N*$^\alpha$-*tert*-Butoxycarbonyl-3-phenyl-5-(2-oxoethyl)-L-proline Ethyl Ester (12). A solution of **11** (373 mg, 1.04 mmol) in CH_2Cl_2 (10 mL) at −78 °C was bubbled with O_3 until the solution turned purple. Then, after an additional 15 min, Ar was passed through the reaction mixture to get rid of excess O_3. To the above obtained solution was added Me_2S (4.60 mL, 62.3 mmol), and the mixture was stirred at room temperature under Ar atmosphere for 5 d. After removal of the solvent under reduced pressure, flash column chromatography (silica gel, 13 g, 200−400 mesh, hexane/diethyl ether 1:1) of the crude product gave pure **12** as a colorless oil (304 mg, 81%). $[\alpha]^{24}_D$ +54.5 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.86 (brs, 1H), 7.35−7.22 (m, 5H), 4.57−4.46 (m, 1H), 4.39 (d, 0.33H, *J* = 7.5 Hz), 4.24 (d, 0.67H, *J* = 7.5 Hz), 4.21−4.10 (m, 2H), 3.49 (t, 0.33H, *J* = 7.5 Hz), 3.46 (t, 0.67H, *J* = 7.5 Hz), 3.25 (dd, 0.67H, J_1 = 4.2 Hz, J_2 = 17.1 Hz), 3.13 (dd, 0.33H, J_1 = 4.5 Hz, J_2 = 16.8 Hz), 2.82−2.69 (m, 1H), 2.45−2.33 (m, 1H), 2.13−2.05 (m, 1H), 1.48 (s, 3H), 1.41 (s, 6H), 1.21 (t, 2H, *J* = 7.2 Hz), 1.18 (t, 1H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 172.8, 172.7, 153.6, 153.4, 139.7, 129.0, 127.6, 127.5, 127.3, 81.2, 81.0, 77.4, 66.7, 66.2, 61.4, 61.3, 53.2, 49.4, 48.7, 48.1, 47.3, 39.7, 38.4, 30.0, 28.5, 28.4, 14.4, 14.3. HRMS (FAB): calcd for $C_{20}H_{28}NO_5$ (M + 1), 362.1967; found, 362.1975.

(3*R*,5*S*)-*N*$^\alpha$-*tert*-Butoxycarbonyl-5-[(*Z*)-3-benzoxycarbonylamino-3-methoxycarbonylallyl]-3-phenyl-L-proline Ethyl Ester (13). To a solution of $(MeO)_2P(O)CH(NHCbz)CO_2Me$ (300 mg, 0.830 mmol) in CH_2Cl_2 (3 mL) at room temperature was added DBU (0.137 mL, 1.00 mmol) slowly, and after 10 min, to the solution was added a solution of **12** in CH_2Cl_2 (3 mL). The mixture was stirred for 6 h at room temperature under Ar atmosphere. After removal of the solvent under reduced pressure, the reaction mixture was dissolved in EtOAc (35 mL), washed with 1 N HCl (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give a solid. The crude product was purified by flash column chromatography (silica gel, 15 g, 200−400 mesh, hexane/diethyl ether 1:1) to give 395 mg of the (*Z*) isomer and 30 mg of the (*E*) isomer (90% overall yield, *Z*/*E* 13:1). $[\alpha]^{26}_D$ +66.5 (*c* 0.85, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 0.4H), 7.60 (s, 0.6H), 7.39−7.22 (m, 10H), 6.67 (dd, 1H, J_1 = 7.2 Hz, J_2 = 9.0 Hz), 5.24−5.11 (m, 2H), 4.34 (d, 0.4H, *J* = 9.6 Hz), 4.30−4.21 (m, 2H), 4.17 (d, 0.6H, *J* = 9.3 Hz), 4.11−4.03 (m, 1H), 3.73 (brs, 3H), 3.59−3.48 (m, 1H), 2.88−2.75 (m, 1H), 2.49−2.23 (m, 2H), 2.08 (d, 0.6H, *J* = 6.3 Hz), 2.05 (d, 0.4H, *J* = 6.3 Hz), 1.41 (s, 3.6H), 1.36 (s, 5.4H), 1.14 (t, 1.8H, *J* = 7.2 Hz), 1.11 (t, 1.2H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 173.7, 165.4, 155.1, 155.0, 154.3, 153.9, 139.4, 139.1, 136.6, 133.5, 132.7, 128.9, 128.8, 128.7, 128.6, 128.3, 128.1, 128.0, 127.7, 127.6, 127.5, 127.4, 81.0, 80.9, 77.4, 75.3, 67.1, 67.0, 66.7, 61.7, 61.5, 57.4, 57.2, 48.7, 47.8, 40.3, 38.6, 34.8, 34.3, 28.3, 28.2, 14.3, 14.2. HRMS (FAB): calcd for $C_{31}H_{39}N_2O_8$ (M + H), 567.2706; found, 567.2707.

(3*R*,5*S*)-*N*$^\alpha$-*tert*-Butoxycarbonyl-4-phenyl-5-[(3*S*)-3-benzoxycarbonylamino-3-methoxycarbonylpropyl]-L-proline Ethyl Ester (14a). To a solution of **13** (140 mg, 0.247 mmol) in degassed MeOH (10 mL, HPLC grade) at room temperature was added Rh(I)(COD)(*S*,*S*)-Et-DuPHOS (0.4 mg, 0.0005 mmol, 0.2 mol %). After five cycles of vacuum/H_2, the reaction was pressed at an initial H_2 pressure of 75 psi at room temperature. After 24 h, the solvent was removed under reduced pressure and the residue was passed through a short silica gel column (200−400 mesh, 12 g), eluting with EtOAc/hexane (1:1) to remove the catalyst. The product was pure enough for the next step reaction as a colorless oil (143 mg, 100%). $[\alpha]^{23}_D$ +31.8 (*c* 0.56, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.21 (m, 10H), 5.87 (d, 0.6H, *J* = 7.8 Hz), 5.53 (d, 0.4H, *J* = 7.5 Hz), 5.12 (s, 2H), 4.43−4.33 (m, 1H), 4.20−3.97 (m, 4H), 3.75 (s, 1H), 3.73 (s, 2H), 3.52−3.43 (m, 1H), 2.25−2.14 (m, 1H), 2.05−1.82 (m, 4H), 1.62−1.54 (m, 1H), 1.45 (s, 3.6H), 1.40 (s, 5.4H), 1.17 (t, 1.8H, *J* = 7.2 Hz), 1.14 (t, 1.2H, *J* = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 172.7, 156.1, 153.8, 139.9, 139.6, 136.4, 136.2, 128.7, 128.4, 128.0, 127.9, 127.3, 127.2, 80.4, 66.8, 66.1, 60.9, 60.3, 57.8, 57.5, 54.2, 53.7, 52.2, 48.1, 47.2, 39.2, 38.3, 31.0, 30.4, 29.3, 28.7, 28.3, 14.1. HRMS (FAB): calcd for $C_{31}H_{41}N_2O_8$ (M + H), 569.2863; found, 569.2858.

(3*R*,5*S*)-*N*$^\alpha$-*tert*-Butoxycarbonyl-4-phenyl-5-[(3*R*)-3-benzoxycarbonylamino-3-methoxycarbonylpropyl]-L-proline Ethyl Ester (14b). To a solution of **13** (110 mg, 0.194 mmol) in degassed MeOH (8 mL, HPLC grade) at room temperature was added Rh(I)(COD)-(*R*,*R*)-Et-DuPHOS (0.3 mg, 0.0004 mmol, 0.2 mol %). After five cycles of vacuum/H_2, the reaction was pressed at an initial H_2 pressure of 75 psi at room temperature. After 24 h, the solvent was removed under reduced pressure and the residue was passed through a short silica gel column (200−400 mesh, 10 g), eluting with EtOAc/

hexane (1:1) to remove the catalyst. The product was pure enough for the next reaction step as a colorless oil (110 mg, 100%). $[\alpha]^{22}_D$ +39.7 (*c* 1.10, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.22 (m, 10H), 5.59 (d, 0.6H, J = 7.5 Hz), 5.51 (d, 0.4H, J = 7.5 Hz), 5.12 (m, 2H), 4.40−4.36 (m, 1H), 4.20−4.02 (m, 4H), 3.75 (s, 3H), 3.51−3.44 (m, 1H), 2.23−2.17 (m, 1H), 2.03−1.79 (m, 4H), 1.64−1.58 (m, 1H), 1.47 (s, 3.6H), 1.40 (s, 5.4H), 1.16 (t, 1.8H, J = 7.0 Hz), 1.13 (t, 1.2H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 173.1, 156.3, 154.3, 153.9, 140.3, 140.0, 136.6, 128.9, 128.6, 128.1, 127.5, 127.4, 80.5, 77.4, 75.3, 67.0, 66.9, 66.2, 61.1, 57.8, 57.6, 54.1, 54.0, 52.5, 48.3, 47.5, 39.7, 38.5, 30.9, 29.8, 29.6, 29.3, 28.5, 28.4, 14.4. HRMS (FAB): calcd for $C_{31}H_{41}N_2O_8$ (M + H), 569.2863; found, 569.2852.

(3*S*,6*S*,8*R*,9*S*)-Ethyl 2-Oxo-3-*N*-(benzoxycarbonyl)amino-7-benzyl-1-azabicyclo[4.3.0]nonane-9-carboxylate (1c). To a solution of **14a** (120 mg, 0.211 mmol) in CH_2Cl_2 (3.5 mL) was added TFA (1.5 mL) dropwise at room temperature under Ar atmosphere, and the mixture was stirred for 1 h. After removal of the solvent and TFA, a slightly yellow oil was obtained. To a solution of the residue in CH_2Cl_2 (30 mL) was added Et_3N (0.210 mL, 1.48 mmol), and the reaction mixture was stirred at room temperature under Ar atmosphere for 6 d. After removal of the solvent under reduced pressure, the residue was dissolved in EtOAc (20 mL), and the solution was washed with 1 N HCl (2 × 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated to give a colorless oil, which was purified by flash column chromatography (silica gel, 35 g, 200−400 mesh, EtOAc/hexane 1:4) to give a pure product (80 mg, 87%). $[\alpha]^{23}_D$ +111.7 (*c* 1.16, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.19 (m, 10H), 5.57 (brs, 1H), 5.11 (m, 2H), 4.72 (s, 1H), 4.29−4.15 (m, 2H), 4.13−4.04 (m, 1H), 3.86−3.75 (m, 1H), 3.51 (d, 1H, J = 7.5 Hz), 2.53−2.48 (m, 1H), 2.24−2.13 (m, 1H), 2.08−2.00 (m, 2H), 1.94−1.66 (m, 2H), 1.27 (t, 3H, J = 7.5 Hz); ^{13}C NMR (75MHz, $CDCl_3$) δ 171.2, 168.3, 156.4, 142.1, 136.3, 128.8, 128.4, 127.9 (two overlapped peaks, 127.89 and 127.93), 127.0, 126.6, 66.7, 64.2, 61.4, 54.8, 52.4, 45.8, 39.0, 28.6, 27.6, 14.1. HRMS (FAB): calcd for $C_{25}H_{29}N_2O_5$ (M + H), 437.2076; found, 437.2086.

(3*R*,6*S*,8*R*,9*S*)-Ethyl 2-Oxo-3-*N*-(benzoxycarbonyl)amino-7-benzyl-1-azabicyclo[4.3.0]nonane-9-carboxylate (1d). To a solution of **14b** (50 mg, 0.088 mmol) in CH_2Cl_2 (3.5 mL) was added TFA (1.5 mL) dropwise at room temperature under an Ar atmosphere, and the mixture was stirred for 1 h. After removal of the solvent and TFA, a slightly yellow oil was obtained. To a solution of the residue in CH_2Cl_2 (15 mL) was added Et_3N (0.086 mL, 0.62 mmol), and the reaction mixture was stirred at room temperature under an Ar atmosphere for 6 d. After removal of solvent under reduced pressure, the residue was dissolved in EtOAc (10 mL), and the solution was washed with 1 N HCl (2 × 5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated to give a colorless oil (40 mg), which was purified by flash column chromatography (silica gel, 15 g, 200−400 mesh, EtOAc/hexane 1:4) to give a pure product (36 mg, 83%). $[\alpha]^{23}_D$ +117.0 (*c* 0.52, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.15 (m, 10H), 5.87 (d, 1H, J = 6.4 Hz), 5.12 (s, 2H), 4.70 (s, 1H), 4.33−4.19 (m, 3H), 3.87−3.84 (m, 1H), 3.58 (d, 1H, J = 7.2 Hz), 2.59−2.49 (m, 1H), 2.30−2.04 (m, 3H), 1.86−1.66 (m, 2H), 1.29 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 168.9, 156.1, 141.7, 136.4, 128.9, 128.4, 128.0, 127.9, 127.2, 126.3, 66.7, 64.2, 61.6, 54.7, 50.4, 46.6, 39.5, 27.0, 26.7, 14.1. HRMS (FAB): calcd for $C_{25}H_{29}N_2O_5$ (M + H), 437.2076; found, 437.2072.

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Supporting Information Available: ^1H NMR spectra of **1a**−**d**, **3**, **5**, **5a**, **6**, **7**, **8a**,**b**, **11**, **12**, **13**, and **14a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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