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# Synthesis and peptide coupling of protected 2-pyrrolylalanine

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ABSTRACT

2-Pyrrolylalanine has been synthesized in two protected forms and applied in the solution-phase synthesis of a dipeptide. (2*S*)-*N*-(Boc)-*N*′-(phenylsulfonyl)- and (2*S*)-*N*,*N*′-bis-(phenylsulfonyl)-3-(2-pyrrolyl)alanines (**7** and **9**) were obtained, respectively, in 14% and 13% overall yields and six and seven steps from oxazolidine β-methyl ester **1**, which was derived from L-aspartic acid. Homoallylic ketone **2** was obtained from a copper-catalyzed cascade addition of vinylmagnesium bromide to **1** and converted into pyrrolylalanines **7** and **9** by a sequence featuring subsequent olefin oxidation and Paal-Knorr condensation. Protected pyrrolylalanine **9** was then introduced into a dipeptide.



## 1. Introduction

Practical methods for the synthesis of structurally complex amino acid derivatives are of fundamental importance, due to the widespread use of these building blocks in peptides, proteins, and other related compounds of interest in the physical and life sciences.[1] For example, amino acids containing side chains possessing a five member heterocyclic ring are components of naturally occurring peptides, marine organism, natural products,[2] peptidomimetics,[3] macromolecular scafolds,[4] and building blocks in combinatorial synthesis.[5]

Histidine surrogates possessing thienyl, furyl, triazolyl, tetrazolyl, thiazolyl, imidazolyl, and pyrazolyl rings, all have been used to study the importance of hydrogen bond acceptor and donator properties of the imidazole side chain in peptides.[6] On the other hand, few syntheses of pyrrolylalanine analogs have been reported, for the most part giving racemic product.[7–9] To the best of our knowledge,[7–13] there has been only one application of pyrrolylalanine in peptide chemistry, in which racemic amino acid **17d** (R = H, R′ = Cbz, R″ = Boc) was introduced into a TRH (pGlu-His-Pro-NHMe) analog to investigate the role of histidine for activity (Fig. 1).[7b]

In the context of our investigations of biologically active peptides bearing histidine residues,[14,15] we became interested in the synthesis of enantiopure (2*S*)-2-pyrrolylalanine and its suitable protection for peptide synthesis. In this light, we appreciated the seminal research of Professor Wasserman featuring the application of vicinal tricarbonyl precursors for the preparation of various pyrrole products, in particular the synthesis of enantiopure (2*S*)-3-(2-carboxy-3-oxo-5-pyrrolyl)alanine analog **15** (Fig. 1).[10] Like Wasserman, we perceived aspartic acid as an ideal enantiopure starting material for the construction of the heterocyclic amino acid. We report now the use of aspartate derivative **1** in routes to pyrrolylalanine featuring our copper-catalyzed cascade addition of vinyl magnesium bromide to this β-amino ester.[16] In addition, sulfonamide protection has been examined for the preparation of a pyrrolylalaninyl-proline dipeptide model for studying the influence of the pyrrole moiety on prolyl amide isomer population.

## 2. Results and discussion

Following our strategy for the preparation of *N*-(Boc)-3-(6-methylpyridazinyl)alanine,[17] 2-pyrrolylalanine was pursued by a route starting from oxazolidine β-methyl ester **1**, which was readily prepared in four steps and in 47% yield from L-aspartic acid as chiral educt.[17] The Cu-catalyzed cascade addition of excess vinylmagnesium bromide to methyl ester **1** in THF at −45 °C gave γ,δ-unsaturated ketone **2** in 63% yield (Scheme 1). Oxidation of olefin **2** using a mixture of $OsO_4$, $NaIO_4$, and 2,6-lutidine in dioxane/water gave γ-ketoaldehyde **3** in 95% yield.[18] Pyrrole **4** was isolated in 72% yield from the Paal-Knorr[19] condensation of γ-ketoaldehyde **3** with ammonium formate in acetonitrile containing a mixture of NaOAc/AcOH (1:1, 1 equiv w/w) at 65 °C.

In considering the oxidation of the primary alcohol to the carboxylic acid, concern arose over the potential for competitive pyrrole oxidation and degradation.[20] In earlier experience making bipyrrole and prodigiosin analogs,[21] sulfonamide protection of the ring nitrogen prevented oxidation of electron rich pyrroles during double bond oxidations.[22] *N*′-(Phenysulfonyl)pyrrole **5** was thus prepared on the treatment of pyrrole **4** with *t*-BuOK, 18-crown-6 ether and phenylsulfonyl chloride in THF in 80% yield.

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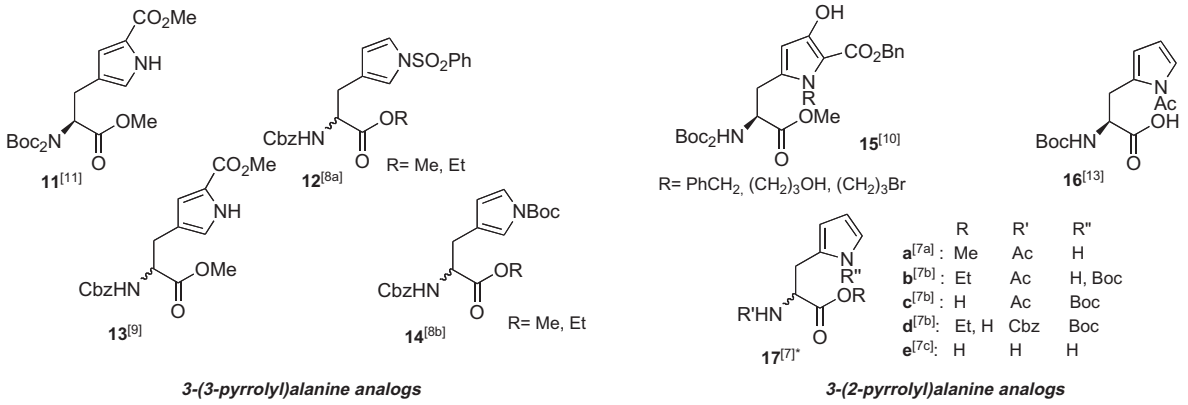
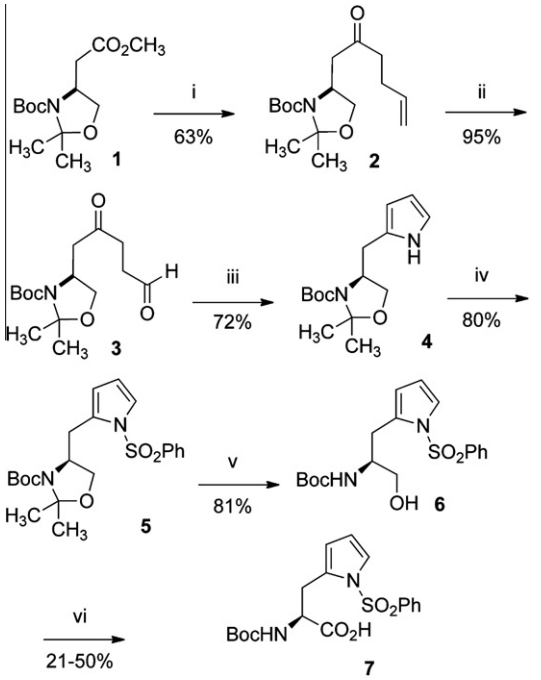


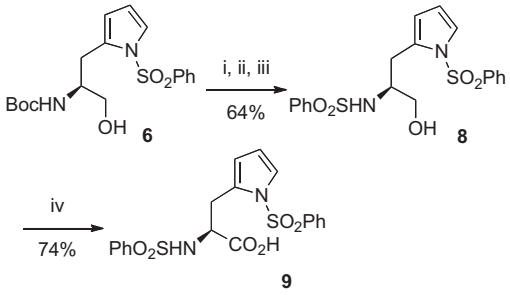

**Figure 1.** Protected pyrrolylalanine analogs. *__17e__ was not isolated.




**Scheme 1.** Synthesis of *N*-(Boc)-*N*′-(phenylsulfonyl)-3-(2-pyrrolyl)alanine **7**. Reagents and conditions: (i) vinylmagnesium bromide, CuCN, THF, −45 °C; (ii) cat $OsO_4$, $NaIO_4$, 2,6-lutidine, dioxane/$H_2O$; (iii) $NH_4CO_2H$, AcOH/NaOAc, MeCN, 65 °C; (iv) *t*-BuOK, 18-c-6, $PhSO_2Cl$, THF, 0 °C; (v) 80% AcOH aq, 50 °C, overnight; (vi) TEMPO, $NaClO_2$, NaOCl, sodium phosphate buffer, MeCN, 35 °C, overnight.

Oxazolidine **5** was then ring opened using 80% aqueous acetic acid at 50 °C overnight to afford *N*-(Boc)amino alcohol **6** in 81% yield. (2*S*)-*N*-(Boc)-*N*′-(phenylsulfonyl)-3-(2-pyrrolyl)alanine **7** was finally obtained by oxidation using TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) free radical, sodium chlorite, and sodium hypochlorite in a sodium-phosphate-buffered acetonitrile solution, albeit in low yields (21–50%, Scheme 1).[17,23]

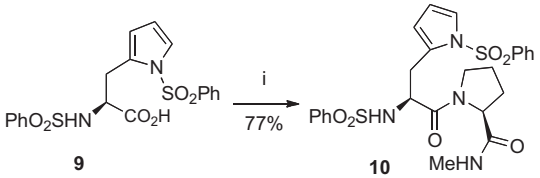
Low yields in the oxidation of primary alcohol **6** to carboxylate **7** inspired a change in the α-amino protecting group from Boc to benzenesulfonyl. Treatment of carbamate **6** with 25% trifluoroacetic acid (TFA) in dichloromethane, followed by N-sulfonylation of the resulting amine with phenylsulfonyl chloride and $Na_2CO_3$ in dioxane/water provided (2*S*)-*N*,*N*′-bis-(phenylsulfonyl)-3-(2-pyrrolyl)alaninol **8** in 64% overall yield (Scheme 2). An attempt to oxidize alcohol **8** using $O_2$ in the presence of Pt in a mixture of $H_2O$/2-propanol/AcOEt[24] gave only recovered starting material, and decomposition occurred using $NaIO_4$ in the presence of $RuCl_3$




**Scheme 2.** Synthesis of *N*,*N*′-bis-(phenylsulfonyl)-3-(2-pyrrolyl)alanine **9**. Reagents and conditions: (i) TFA/DCM; (ii) 0.1 N HCl; (iii) $Na_2CO_3$, $PhSO_2Cl$; dioxane/$H_2O$; (iv) TEMPO, $NaClO_2$, NaOCl, sodium phosphate buffer, MeCN, 35 °C, overnight.

in $CCl_4$/MeCN/$H_2O$.[25] Employing the TEMPO oxidation conditions described above, (2*S*)-*N*,*N*′-bis-(phenylsulfonyl)-3-(2-pyrrolyl)alanine **9** was obtained in 74% yield from alcohol **8**.

With the interest of studying the influence of the aromatic density of the pyrrole moiety on the prolyl amide isomer population, 2-pyrrolylalanine **9** was next introduced into a dipeptide model and the relative populations of prolyl *cis*- and *trans*-amide isomer were measured by proton NMR spectroscopy. 2-Pyrrolylalanine **9** was coupled to proline *N*′-methylamide hydrochloride using TBTU, HOBt, and DIEA in acetonitrile to give *N*,*N*′-bis-(phenylsulfonyl)-3-(2-pyrrolyl)alaninyl-proline *N*′-methylamide **10** in 77% yield (Scheme 3). The prolyl major *trans*- and minor *cis*-amide isomers were assigned by NMR spectroscopy in chloroform on the basis of their characteristic nuclear overhauser effects between the α-proton of the 3-pyrrolylalanine residue and, respectively, the δ-protons and the α-proton of the proline residue in the NOESY spectrum. A 13:87 ratio of amide *cis*- and *trans*-isomers N-terminal to proline **10** was measured by integration of the isomeric quadruplets for the 2-pyrrolylalanine α-proton in the NMR spectrum in chloroform. The effect of the phenysulfonyl electron withdrawing




**Scheme 3.** Synthesis of *N*,*N*′-bis-(phenylsulfonyl)-3-(2-pyrrolyl)alaninyl-proline *N*′-methylamide **10**. Reagents and conditions: (i) ProNHMe·HCl, TBTU, HOBt, DIEA, 0 °C, MeCN, overnight.

group on the pyrrolylalanine residue may reduce the amide *cis*-isomer population relative to π-enriched arylalanine analogs.[17,26–33]

Sulfonamide protection gave access to the desired pyrrolylalanine target **9**, which could be coupled to the N-terminal of a peptide; however, attempts (TBAF in THF, $SmI_2$ in DMPU/THF, and Mg in MeOH) were unsuccessful in removing the sulfonyl groups from dipeptide **10**. Alternative protection, such as the pyridine-2-sulfonyl group, which has been reported to be cleaved under milder conditions (Mg/MeOH or $SmI_2$/DMPU/THF)[34,35] is currently being explored to enhance the utility of 2-pyrrolylalanine in peptide chemistry and will be described in future.

In conclusion, methodology has been developed for the synthesis of protected 2-pyrrolylalanine from aspartic acid. Protection of 2-pyrrolylalanine with sulfonyl groups has allowed insertion of this unnatural amino acid into a dipeptide model. Considering 2-pyrrolylalanine as an asparagine and histidine mimic, opportunity exists for employing this surrogate for studying structure–function relationships in peptide science and medicinal chemistry.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.089.

## References and notes

1. (a)*Synthesis of Peptides and Peptidomimetics: Houben-Weyl Methods in Organic Chemistry*; Goodman, M., Felix, A., Morodwe, L., Toniolo, C., Eds.; Thieme: Stuttgart, D, 2001; (b)*Peptidomimetics Protocols*; Kazmierski, W. M., Ed.; Humana Press: Toyota, NJ, USA, 1999.
2. Somogyi, L.; Haberhauer, G.; Rebek, J., Jr. *Tetrahedron* **2001**, *57*, 1699–1708.
3. (a) Falorni, M.; Giacomelli, G.; Porcheddu, A.; Dettori, G. *Eur. J. Org. Chem.* **2000**, 3217–3222; (b) Plant, A.; Stieber, F.; Scherkenbeck, J.; Losel, P.; Dyker, H. *Org. Lett.* **2001**, *3*, 3427–3430; (c) Chakraborty, T. K.; Mohan, B. K.; Kumar, S. K.; Kunwar, A. C. *Tetrahedron Lett.* **2002**, *43*, 2589–2592.
4. Mann, E.; Kessler, H. *Org. Lett.* **2003**, *5*, 4567–4570.
5. (a) Perrotta, E.; Altamura, M.; Barani, T.; Bindi, S.; Giannotti, D.; Harmat, N. J. S.; Nannicini, R.; Maggi, A. *J. Comb. Chem.* **2001**, *3*, 453–460; (b) Lewis, J. G.; Bartlett, P. A. *J. Comb. Chem.* **2003**, *5*, 278–284; (c) Edwards, A. A.; Ichihara, O.; Murfin, S.; Wilkes, R.; Whittaker, M.; Watkin, D. J.; Fleet, G. W. J. *J. Comb. Chem.* **2004**, *6*, 230–238.
6. (a) Heyl, D. L.; Dandabathula, M.; Kurtz, K. R.; Mousigian, C. *J. Med. Chem.* **1995**, *38*, 1242–1246; (b) Hsieh, K.-h.; Jorgensen, E. C. *J. Med. Chem.* **1979**, *22*, 1199–1205; (c) Ikeda, Y.; Kawahara, S.-i.; Taki, M.; Kuno, A.; Hasegawa, T.; Taira, K. *Protein Eng.* **2003**, *16*, 699–706.
7. (a) de la Hoz, A.; Díaz-Ortiz, A.; Gómez, M. V.; Mayoral, J. A.; Moreno, A.; Sánchez-Migallón, A. A.; Vásquez, E. *Tetrahedron* **2002**, *57*, 5421–5428; (b) Bladon, C. M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1151–1158; (c) Herz, W.; Dittmer, K.; Cristol, S. J. *J. Am. Chem. Soc.* **1948**, *70*, 504–507.
8. (a) Rousseau, J.-F.; Dodd, R. H. *J. Org. Chem.* **1998**, *63*, 2731–2737; (b) Beecher, J. E.; Tirrell, D. A. *Tetrahedron Lett.* **1998**, *39*, 3927–3930.
9. Yamano, K.; Shirahama, H. *Tetrahedron* **1992**, *48*, 1457–1464.
10. (a) Wasserman, H. H.; Long, Y. O.; Zhang, R.; Parr, J. *Heterocycles* **2002**, *58*, 393–403; (b) Wasserman, H. H.; Long, Y. O.; Zhang, R.; Parr, J. *Tetrahedron Lett.* **2002**, *43*, 3351–3353.
11. Adamczyk, M.; Johnson, D. D.; Reddy, R. E. *Tetrahedron: Asymmetry* **2000**, *11*, 3063–3068.
12. Masquelin, T.; Broger, E.; Müller, K.; Schmid, R.; Obrecht, D. *Helv. Chim. Acta* **1994**, *77*, 1395–1411.
13. Sarkar, K.; Singha, S. K.; Chattopadhyay, S. K. *Tetrahedron: Asymmetry* **2009**, *20*, 1719–1721.
14. Sabatino, D.; Proulx, C.; Klocek, S.; Bourguet, C. B.; Boeglin, D.; Ong, H.; Lubell, W. D. *Org. Lett.* **2009**, *11*, 3650–3653.
15. Goupil, E.; Tassy, D.; Bourguet, C.; Quiniou, C.; Wisehart, V.; Petrin, D.; Le Gouill, C.; Devost, D.; Zingg, H. H.; Bouvier, M.; Saragovi, H. U.; Chemtob, S.; Lubell, W. D.; Claing, A.; Hebert, T. E.; Laporte, S. A. *J. Biol. Chem.* **2010**, *285*, 25624–25636.
16. (a) Hansford, K. A.; Dettwiler, J. E.; Lubell, W. D. *Org. Lett.* **2003**, *5*, 4887–4890; (b) Dettwiler, J. E.; Lubell, W. D. *Can. J. Chem.* **2004**, *82*, 318–324.
17. Dörr, A. A.; Lubell, W. D. *Biopolymers* **2007**, *88*, 290–299.
18. Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. *Org. Lett.* **2004**, *6*, 3217–3219.
19. (a) Hansford, K. A.; Zanzavora, V.; Dorr, A. A.; Lubell, W. D. *J. Comb. Chem.* **2004**, *6*, 893–898; (b) Dorr, A. A.; Lubell, W. D. *Can. J. Chem.* **2007**, *85*, 1006–1017.
20. Joule, J. A.; Mills, J. K. *Heterocyclic Chemistry*, 4th ed.; Springer: New York, 2000. p 246.
21. (a) Tshibaka, T.; Roche, I. U.; Dufresne, S.; Lubell, W. D.; Skene, W. G. *J. Org. Chem.* **2009**, *74*, 9497–9500; (b) Jolicoeur, B.; Lubell, W. D. *Can. J. Chem.* **2008**, *86*, 213–218; (c) Jolicoeur, B.; Lubell, W. D. *Org. Lett.* **2006**, *8*, 6107–6110.
22. Jolicoeur, B.; Chapman, E. E.; Thompson, A.; Lubell, W. D. *Tetrahedron* **2006**, *62*, 11531–11563.
23. (a) Dettwiler, J. E.; Lubell, W. D. *J. Org. Chem.* **2003**, *68*, 177–179; (b) Zhao, M.; Li, J.; Mano, E.; Song, Z.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *J. Org. Chem.* **1999**, *64*, 2564–2566.
24. (a) Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1988**, *53*, 2367–2371; (b) Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1989**, *54*, 1866–1875.
25. Carlsen, P. H. J.; Katsuki, K.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936–3938.
26. MacArthur, M. W.; Thornton, J. M. *J. Mol. Biol.* **1991**, *218*, 397–412.
27. We have defined the term prolyl amide as 'a tertiary amide composed of the pyrrolidine nitrogen of the prolyl residue and the carbonyl of the N-terminal residue'. Halab, L.; Lubell, W. D. *J. Am. Chem. Soc.* **2002**, *124*, 2474–2484.
28. (a) Hetzel, R.; Wüthrich, K. *Biopolymers* **1979**, *18*, 2589–2606; (b) Grathwohl, C.; Wüthrich, K. *Biopolymers* **1976**, *15*, 2043–2057.
29. (a) Yao, J.; Brüschweiler, R.; Dyson, H. J.; Wright, P. E. *J. Mol. Biol.* **1994**, *116*, 12051–12052; (b) Yao, J.; Dyson, H. J.; Wright, P. E. *J. Mol. Biol.* **1994**, *243*, 754–766; (c) Yao, J.; Feher, V. A.; Espejo, B. F.; Reymond, M. T.; Wright, P. E.; Dyson, H. J. *J. Mol. Biol.* **1994**, *243*, 736–753; (d) Dyson, H. J.; Rance, M.; Houghten, R. A.; Lerner, R. A.; Wright, P. E. *J. Mol. Biol.* **1988**, *201*, 161–200.
30. Wu, W.-J.; Raleigh, D. P. *Biopolymers* **1998**, *45*, 381–394.
31. Stewart, D. E.; Sarkar, A.; Wampler, J. E. *J. Mol. Biol.* **1990**, *214*, 253–260.
32. (a) Stimson, E. R.; Montelione, G. T.; Meinwald, Y. C.; Rudolph, R. K. E.; Scheraga, H. A. *Biochemistry* **1982**, *21*, 5252–5262; (b) Juy, M.; Lam-Thanh, H.; Linter, K.; Fermandjian, S. *Int. J. Peptide Protein Res.* **1983**, *22*, 437–449.
33. Thomas, K. M.; Naduthambi, D.; Zondlo, N. J. *J. Am. Chem. Soc.* **2005**, *128*, 2216–2217.
34. Goulaic-Dubois, C.; Guggisberg, A.; Hesse, M. *J. Org. Chem.* **1995**, *60*, 5969–5972.
35. Han, H.; Bae, I.; Yoo, E. J.; Lee, J.; Do, Y.; Chang, S. *Org. Lett.* **2004**, *6*, 4109–4112.