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Solid Phase Synthesis of a Diketopiperazine Catalyst Containing the Unnatural Amino Acid (*S*)-Norarginine

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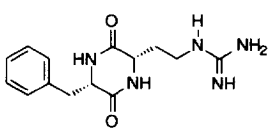
Abstract: A cyclic dipeptide containing the unnatural amino acid (*S*)-norarginine, recently shown to display useful catalytic activity, has been synthesized in good yield and high chemical purity using a solid phase protocol. All reactions in the sequence, including a Hofmann rearrangement and cyclization to diketopiperazine, were performed on the Merrifield polystyrene resin and proceed in high yield. In addition to its improved yield, this new synthesis offers easy access to derivatives and a potential to employ combinatorial strategies to the search for novel catalytic cyclic dipeptides.

The cyclic dipeptide composed of L-phenylalanine and L-norarginine (**1**) has recently been shown in our laboratories to catalyze the enantioselective Strecker synthesis of (*S*)-phenylglycine derivatives from *N*-substituted aldimines and hydrogen cyanide.[1] The original synthesis of **1** involved Curtius rearrangement of the (*S*)-glutamic acid-derived oxazolidinone **2**[2] to a Boc-protected (*S*)-2,4-diaminobutyric acid derivative and later guanylation of the deprotected diketopiperazine **3**. Both steps were found to require long reaction times (3-6 days) and frequently gave low yields. It was expected that by moving to a solid phase, the solubility problems and side reactions that complicated these steps could be circumvented.



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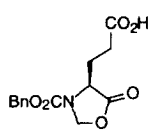

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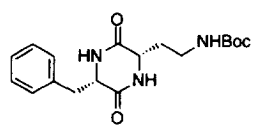
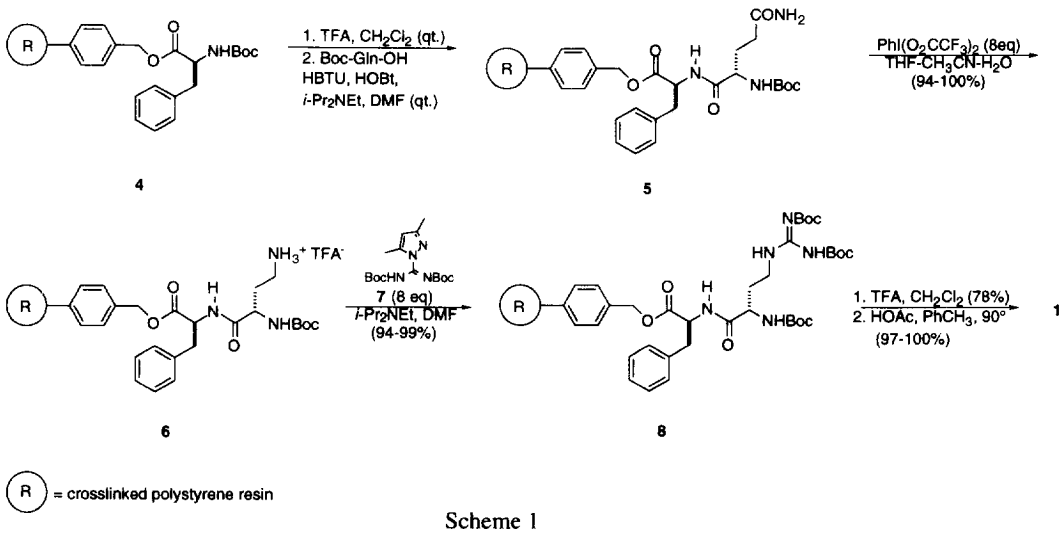


3

The solid phase synthesis relies upon a Hofmann rearrangement of (*S*)-glutamine to obtain the key intermediate (*S*)-2,4-diaminobutyric acid, rather than the Curtius rearrangement of (*S*)-glutamic acid used in the original synthesis. Thus, the Merrifield crosslinked polystyrene resin[3] derivatized with Boc-L-phenylalanine (**4**, Scheme 1) was deprotected and acylated with Boc-L-glutamine, providing the resin-bound dipeptide **5**. It was found that single coupling using HBTU[4] was sufficient for complete acylation, as judged by qualitative ninhydrin test. Hofmann rearrangement of the glutamine residue using bis(trifluroacetoxy)iodobenzene[5] afforded the desired 2,4-diaminobutyric acid-containing dipeptide **6** in near-quantitative yield, based on quantitative ninhydrin test.[6] Previously the insolubility of the diketopiperazine had limited the solvent for guanylation to water, requiring the use of 3,5-dimethylpyrazole-1-carboxamidine nitrate[7] and resulting in low yields; the solid phase synthesis was not affected by such considerations. Consequently, when the original reagent proved unsatisfactory during the revised synthesis, other options were investigated.

To improve the guanylation reaction, the guanidine was synthesized in protected form; this decision was based on the observation that synthesis of acylated guanidines is much more efficient than synthesis of the parent species. To this end, the bis(Boc)-protected guanidine **8** was made using the reagent **7**, prepared by a procedure analogous to that for pyrazole-1-carboxamidine nitrate.[8] The extent of reaction was again estimated, by monitoring the consumption of amine with a quantitative ninhydrin assay, as near quantitative.



Scheme 1

Deprotection of the Boc groups was accomplished using trifluoroacetic acid; the synthesis was completed by refluxing the resin in toluene containing 1.25 M acetic acid. Diketopiperazine formation on the Merrifield resin was extensively studied by Merrifield,[9] resulting in his conclusion that acetic acid in methylene chloride optimally converted resin-bound dipeptides to diketopiperazines. In our case, Merrifield's conditions were ineffective, presumably owing to the lower reaction temperature. Formation of diketopiperazine is accompanied by scission of the peptide-resin ester linkage, thus affording the crude product in solution. Purification by reverse phase HPLC, using previously determined conditions,[1] resulted in **1** being obtained in an overall yield of 54%.

The advantages of the solid phase synthesis are threefold. First, the yields were greatly improved in both of the problematic steps: rearrangement and guanylation. Second, the solubility problems that limited the choice of reagents in solution were no longer a factor, permitting the use of organic-soluble guanylation reagents. Third, purification of the product was greatly simplified by elimination of many of the side-products obtained in the original synthesis. Another, potential benefit of the revised synthesis is its facile adaptation to other systems, permitting either systematic or combinatorial approaches to the synthesis of analogues of **1**. It is anticipated that this latter feature will ease the search for new diketopiperazine catalysts and the study of the mechanism of catalysis by **1**.[10]

References and Notes

1. Iyer, S. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. A. *J. Am. Chem. Soc.* **1996**, *118*, in press.
2. Scholtz, J. M.; Bartlett, P. A. *Synthesis* **1989**, 542-544.
3. Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149-2154.
4. Knorr, R.; Trzeciak, A.; Bannwath, N.; Gillsen, D. *Tetrahedron Lett.* **1989**, *30*, 1927-1930.
5. Loudon, G. M.; Radhakrishnan, A. S.; Almond, M. R.; Blodgett, J. K.; Boutin, R. H. *J. Org. Chem.* **1984**, *49*, 4272-4276.
6. Sarin, V. K.; Kent, S. B. H.; Tam, J. P.; Merrifield, R. B. *Anal. Biochem.* **1981**, *117*, 147-157.
7. Scott, F. L.; O'Donovan, D. G.; Reilly, J. *J. Am. Chem. Soc.* **1953**, *75*, 4053-4054.
8. Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *Tetrahedron Lett.* **1993**, *34*, 3389-3392.
9. Gisin, B. F. ; Merrifield, R. B. *J. Am. Chem. Soc.* **1972**, *94*, 3102-3106.

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