ORGANIC LETTERS

2002
Vol. 4, No. 21
3767−3769

A Novel Synthesis of *N*-Methyl Asparagine, Arginine, Histidine, and Tryptophan

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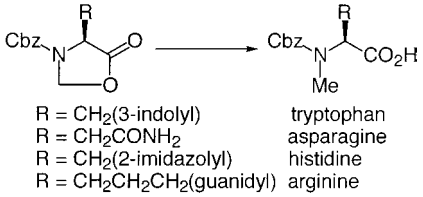
Received August 27, 2002

ABSTRACT



***N*-Methyl amino acid residues in peptides modify several pharmacologically useful parameters, but synthesis of alkylated peptides is hampered by unavailability of *N*-methylated monomers. The syntheses of four *N*-methyl amino acids with basic side chains are presented. The side chains of these basic amino acids needed to be specially protected or constructed. This completes the set of 20 common L-amino acid *N*-methyl derivatives prepared via 5-oxazolidinone intermediates by our group.**

N-Methyl amino acid containing peptides are increasingly recognized as potentially useful therapeutics.[1] *N*-Methylation has been shown to improve pharmacological parameters such as membrane permeability, conformational rigidity, and proteolytic stability.[2]

The ability to construct libraries of compounds including *N*-methyl amino acids is dependent on the ready availability of these building blocks. To date, there has been no method describing the synthesis of the common 20 amino acids in their *N*-methyl form with defined stereochemistry and in high yields by a common route for formation of the *N*-methyl functionality. The majority of syntheses concerning *N*-methyl amino acids focus predominantly on aliphatic amino acids[3] and in some cases the reaction conditions result in racemization.[4] Though the majority of naturally occurring *N*-methyl amino acids in peptides are of the aliphatic type (MePhe, MeAla, MeGly, MeVal, MeIle, MeLeu), there are a number of others that contain basic, acidic, and alcoholic side chains. The syntheses of these *N*-methyl amino acids are often not straightforward or have not been described. The unavailability of these optically active derivatives impedes the synthesis of peptides that possess them.

Herein, we describe the syntheses of the four basic *N*-methyl amino acids tryptophan, asparagine, histidine, and arginine by way of intermediate 5-oxazolidinones. By successfully completing the syntheses of these four *N*-methyl amino acids, using methods similar to those in our previous report,[5] we have exploited the 5-oxazolidinone methodology to the point that it is the first method for preparing the *N*-methyl derivatives of all 20 of the common L-amino acids (Figure 1).

Although the synthetic methods for the four basic *N*-methyl amino acids use a common 5-oxazolidinone-type

(1) Fairlie, D. P. *Curr. Med. Chem.* **1995**, *2*, 654. Angell, Y. M.; Thomas, T. L.; Flentke, G. R.; Rich, D. H. *J. Am. Chem. Soc.* **1995**, *117*, 7279 and references therein.

(2) Cody, W. L.; He, J. X.; Reily, M. D.; Haleen, S. J.; Walker, D. M.; Reyner, E. L.; Stewart, B. H.; Doherty, A. M. *J. Med. Chem.* **1997**, *40*, 2228. Haviv, F.; Fitzpatrick, T. D.; Swenson, R. E.; Nichols, C. J.; Mort, N. A.; Bush, E. U.; Diaz, G.; Bammert, G.; Nguyen, A.; Nellans, H. N.; Hoffman, D. J.; Johnson, E. S.; Greer, J. *J. Med. Chem.* **1993**, *36*, 363. Vitoux, B.; Aubry, A.; Cung, M. T.; Marraud, M. *Int. J. Pept. Protein Res.* **1986**, *27*, 617.

(3) For example: McDermott, J. R.; Benoiton, N. L. *Can. J. Chem.* **1973**, *51*, 2555. O'Donnell, M. J.; Bruder, W. A.; Daugherty, B. W.; Liu, D.; Wojciechowski, K. *Tetrahedron Lett.* **1984**, *25*, 3651. Wisniewski, K.; Kolodziejczyk, A. S. *Tetrahedron Lett.* **1996**, *38*, 483. Dorow, R. L.; Gingrich, D. E. *J. Org. Chem.* **1995**, *60*, 4986.

(4) See references in refs 3 and 5.

(5) Aurelio, L.; Brownlee, R. T. C.; Hughes, A. B.; Sleebs, B. E. *Aust. J. Chem.* **2000**, *53*, 425.

10.1021/ol026799w CCC: $22.00
Published on Web 09/19/2002

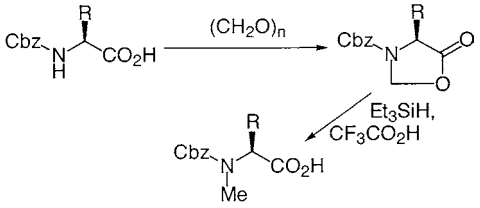
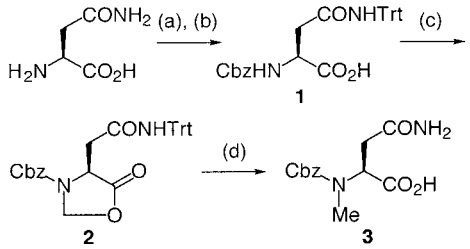


Figure 1. 5-Oxazolidinone strategy for the synthesis of *N*-methyl α-amino acids via reductive cleavage.[5]

intermediate, each of them required a different strategy of protection and/or construction of the side chain that was not compromised by the chemistry required for the generation of the *N*-methyl group.

Asparagine. It has been shown that carbamoylation of the side chain of glutamine allows its conversion to *N*-methyl glutamine.[5] This protection strategy was not possible with asparagine and so an alternative was sought. Tritylation (Trt) of the asparagine amide side chain was achieved under acidic conditions (Scheme 1).[6] Carbamoylation using *N*-(benzyl-

Scheme 1. Synthesis of *N*-Methyl Asparagine **3**[a]



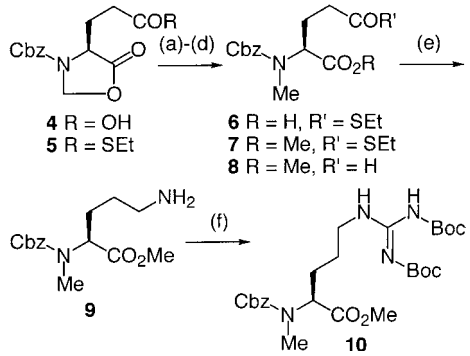
[a] (a) Ph_3COH, H_2SO_4, AcOH, Ac_2O; (b) Et_3N, DMF, $BnOCO_2$-Succ; (c) C_6H_6, $(CH_2O)n$, DMF, CSA, ↑↓, 83%; (d) Et_3SiH, CF_3CO_2H, 75%.

oxycarbonyl-oxy)succinimide ($BnOCO_2$Succ) then gave **1**,[6] and subsequent oxazolidination afforded **2** (83%). The solubility of the asparagine carbamate **1** was not high, and a minimal amount of DMF was included in the reaction protocol to improve substrate solubility and reaction yield. Reductive cleavage of the oxazolidinone **2** gave a 75% yield of the desired *N*-methyl product **3**.[7] In this reaction the *N*-methyl group forms with concomitant removal of the trityl group under the acidic conditions. The low solubility of the *N*-methyl intermediate **3** necessitated workup by concentration of the reaction mixture and column chromatography of the residue rather than the normal aqueous procedure.

Arginine. The reactions depicted in Scheme 2 offer a synthesis of *N*-methyl arginine by direct and less demanding transformations. The oxazolidinone **4** was converted to the thioester **5** (92%) by DCC coupling with ethanethiol.

(6) Sieber, P.; Riniker, B. *Tetrahedron Lett.* **1991**, *32*, 739.
(7) Sokolov, V. V.; Kozhushkov, S. I.; Nikolskaya, S.; Belov, V. N.; Es-Sayed, M.; De Meijere, A. *Eur. J. Org. Chem.* **1998**, 777.

Scheme 2. Synthesis of *N*-Methyl Arginine **10**[a]

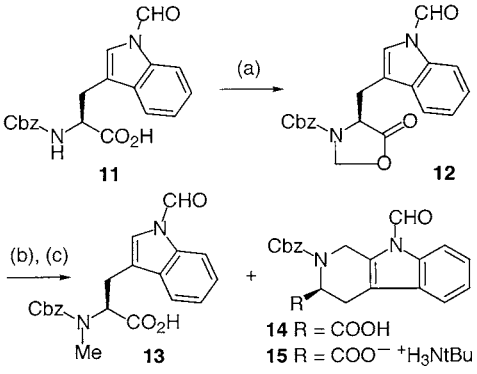


[a] (a) DCC, EtSH, 92%; (b) Et_3SiH, CF_3CO_2H, 87%; (c) CH_2N_2, 100%; (d) Et_3SiH, 10% Pd/C; (e) MeOH, NH_4OAc, $NaCNBH_3$; (f) di-boc-triflylguanidine, DIPEA, 49% from **7**.

Reductive cleavage then proceeded smoothly to give the *N*-methyl amino acid **6** (87%). The carboxylic acid was protected as the methyl ester **7** by diazomethylation,[8] in quantitative yield. The resulting thioester was converted into the aldehyde **8** by treatment with palladium catalyst in the presence of triethylsilane.[9] This material was not purified and reductive amination with ammonium acetate then afforded the *N*-methyl ornithine **9**. Reaction of this with the guanylating reagent di-boc-triflylguanidine gave the desired *N*-methyl arginine **10** in 49% yield from the methyl ester **7**.

Tryptophan. Carbamate protection of tryptophan is an obvious approach to *N*-methyl tryptophan (Abrine), but attempted oxazolidination of the tryptophan carbamate results in decomposition. This is presumably due to side reactions of the indole nitrogen. An electron-withdrawing protecting group was anticipated to solve this problem, and accordingly, *N*-formyl tryptophan[10] was prepared in quantitative yield from L-tryptophan. Carbamoylation then gave the precursor **11** for oxazolidination (Scheme 3). The oxazolidination proceeded in good yield (86%), and **12** was isolated as an oil. The following reductive cleavage did not proceed as planned, and two products were isolated. The minor product

Scheme 3. Synthesis of *N*-Methyl Tryptophan **13**[a]

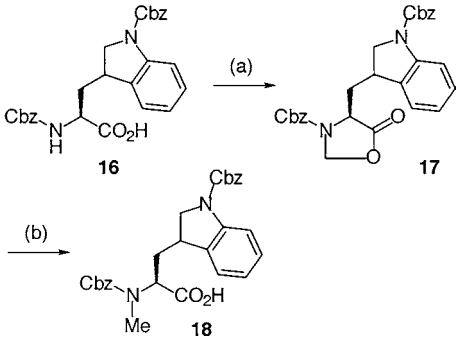


[a] (a) C_6H_6, $(CH_2O)n$, CSA, ↑↓, 86%; (b) Et_3SiH, CF_3CO_2H, **13** 22%, **14** 69%; (c) Et_2O, tBuNH$_2$.

was the expected *N*-methyl tryptophan **13** (22%). The major product was the *β*-carboline **14** (69%), which arises by reaction of the intermediate iminium ion with the indole in an intramolecular electrophilic aromatic substitution. The resulting carboxylic acid **14** was isolated as its *tert*-butylammonium salt **15**.

Dihydrotryptophan. To further substantiate the role of the indole in the intramolecular interception of the iminium intermediate that leads to both **13** and **14**, tryptophan was converted to dihydrotryptophan.[11] This material underwent bis-carbamoylation to give the precursor **16** (Scheme 4).

Scheme 4. Synthesis of the *N*-Methyl Dihydrotryptophan 18[a]

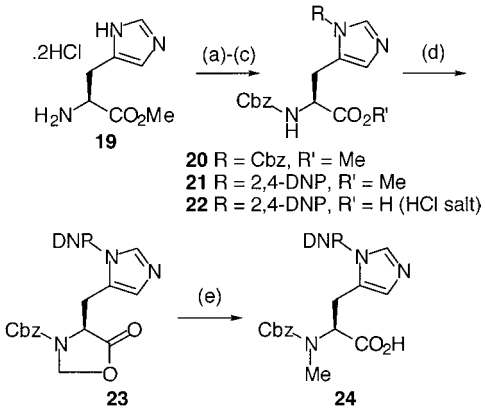


[a] (a) C_6H_6, $(CH_2O)n$, CSA, ⇅, 68%; (b) Et_2SiH, CF_3CO_2H, 83%.

Oxazolidination proceeded smoothly to afford the mixture of diastereoisomers **17**. The key reductive cleavage now proceeded as expected to afford the *N*-methyl dihydrotryptophan **18** in 83% yield.

Histidine. Again, the basic and highly nucleophilic nature of the histidine side chain caused problems in the initial attempts to form *N*-methyl histidine. Selective formation of the α-amino carbamate is also difficult, and so the following sequence (Scheme 5) was adopted. Histidine methyl ester dihydrochloride salt **19** was carbamoylated with 2 equiv of $BnOCO_2Succ$ to give the bis-carbamate **20**. Treatment of this with propylamine effected removal of the imidazole carbamate. The reaction mixture was then evaporated under reduced pressure, and the residue in acetonitrile was treated with 2,4-dinitrofluorobenzene; nucleophilic aromatic substitution afforded the dinitrophenyl imidazole **21**. Treatment of this compound with a mixture of acetic acid and 2 M

Scheme 5. Synthesis of the *N*-Methyl Histidine 24[a]



[a] (a) $BnOCO_2Succ$, Et_3N, CH_3CN, 72%; (b) (i) $PrNH_2$, (ii) Et_3N, CH_3CN, 2,4-dinitrofluorobenzene, 84%; (c) AcOH, 2 M HCl, 3 d, rt, 92%; (d) CH_3CO_2H, Ac_2O, $(CH_2O)n$, CSA 66%; (e) Et_3SiH, CF_3CO_2H, 81%.

hydrochloric acid resulted in hydrolysis of the methyl ester to afford the acid **22**,[12] the precursor for formation of the oxazolidinone. However, standard conditions for its formation could not be used as a result of the insolubility of **22**. This was overcome by dissolving the hydrochloride **22** in acetic acid and acetic anhydride in the presence of camphorsulfonic acid catalyst. Treatment of this mixture with paraformaldehyde afforded the required oxazolidinone **23** in 66% yield. Reductive cleavage then gave the *N*-methyl histidine carbamate **24** with the side chain imidazole still protected with the dinitrophenyl group.

In conclusion, this application of 5-oxazolidinone intermediates to the problematic α-amino acids arginine, histidine, tryptophan, and asparagine for generating *N*-methyl groups has been highly successful. It has generated novel amino acid derivatives for inclusion in wide-ranging target synthesis projects, and further results in these areas will be reported in due course. Elaboration of the chemistry to encompass new conditions for the oxazolidination and reductive cleavage that allows the generation of novel lipoamino acids, esters, peptide coupling chemistry, surfactants, *β*-amino acid derivatives and target syntheses is underway.

Acknowledgment. We thank La Trobe University for the provision of a Post-Graduate scholarship. This research was supported by an Australian Research Council Small Grant.

Supporting Information Available: Experimental procedures and product characterization data for compounds **2**, **3**, **5**−**7**, **10**, **12**, **13**, **15**, **17**, **18**, and **20**−**24**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026799W

(8) De Boer, T. J.; Backer, H. J. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p. 250.
(9) Fukuyama, T.; Liu, G.; Linton, S. D.; Lin, S. C.; Nishino, H. *Tetrahedron Lett.* **1993**, *34*, 2577. Fukuyama, T.; Lin, S. C.; Li. L. *J. Am. Chem. Soc.* **1990**, *112*, 7050.
(10) Previero, A.; Coletti-Previero, M. A.; Cavadore, J.-C. *Biochim. Biophys. Acta* **1967**, *147*, 453.
(11) Daly, J. W.; Mauger, A. B.; Yonemitsu, O.; Antonov, V. K.; Takase, K.; Witkop, B. *Biochemistry* **1967**, *6*, 648.
(12) Siepmann, E.; Zahn, H. *Biochim. Biophys. Acta* **1964**, *82*, 412.