ORGANIC LETTERS

2004
Vol. 6, No. 10
1681−1683

Highly Efficient Enantiospecific Synthesis of Imidazoline-Containing Amino Acids Using Bis(triphenyl)oxodiphosphonium Trifluoromethanesulfonate

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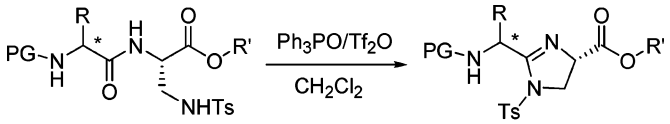
Received March 25, 2004

ABSTRACT



PG = Fmoc or Cbz;
R = *i*-Pr, Bn;
R' = Me, Bn

A highly efficient enantiospecific synthesis of imidazoline-based amino acids is reported from dipeptides composed of a C-terminal β-amino-α-amino acid residue using bis(triphenyl) oxodiphosphonium trifluoromethanesulfonate. These imidazolines were easily converted to imidazoles and incorporated into macrolactam analogues of bistratamide H without loss of stereochemical integrity.

Derivatives of 2-imidazoline and 2-imidazole have attracted substantial interest due to their interesting biological activities.[1] In addition, these heterocycles are useful synthetic intermediates[2] and function as chiral auxiliaries,[3] chiral catalysts,[4] and ligands for asymmetric catalysis.[5] The structures of imidazolines and imidazoles are analogous to those of oxazolines and oxazoles, or thiazolines, and thiazoles, respectively. The latter heterocycles are found in numerous macrolactams isolated from marine sources.[6] Developing new highly enantiospecific methodology for the synthesis of 2-imidazolines and 2-imidazoles will enable the synthesis and biological evaluation of a new class of macrolactam natural product analogues containing these heterocycles, as demonstrated herein. While enantiopure imidazolines have been prepared from 1,2-diamines,[3−5,7] amido alcohols,[4e,8] and other precursors,[9] to the best of our knowledge, the enantio-

(1) (a) Li, H.-Y.; Drummond, S.; DeLucca, I.; Boswell, G. A. *Tetrahedron* **1996**, *52*, 11153. (b) Ueno, M.; Imaizumi, K.; Sugita, T.; Takata, I.; Takeshita, M. *Int. J. Immunopharm.* **1995**, *17*, 597. (c) Rondu, F.; LeBihan, G.; Wang, X.; Lamouri, A.; Touboul, E.; Dive, G.; Bellahsene, B.; Renard, P.; Guardiola-Lemaître, B.; Manéchez, D.; Pénicaud, L.; Ktorza, A.; Godfroid, J.-J. *J. Med. Chem.* **1997**, *40*, 3793. (d) Bousquet, P.; Feldman, J. *Drugs* **1999**, *58*, 799. (e) Schann, S.; Bruban, V.; Pompermayer, K.; Feldman, J.; Pfeiffer, B.; Renard, P.; Scalbert, E.; Bousquet, P.; Ehrhardt, J.-D. *J. Med. Chem.* **2001**, *44*, 1588. (f) Gust, R.; Keilitz, R.; Schmidt, K.; von Rauch, M. *J. Med. Chem.* **2002**, *45*, 3356.

(2) (a) Jones, R. C. F.; Nichols, J. R. *Tetrahedron Lett.* **1990**, *31*, 1771. (b) Jones, R. C. F.; Smallridge, M. J.; Chapleo, C. B. *J. Chem. Soc., Perkin Trans. 1* **1990**, 385. (c) Hayashi, T.; Kishi, E.; Soloshonok, V. A.; Uozumi, Y. *Tetrahedron Lett.* **1996**, *37*, 4969. (d) Lin, Y.-R.; Zhou X.-T.; Dai, L.-X.; Sun, J. *J. Org. Chem.* **1997**, *62*, 1799. (e) Hsiao, Y.; Hegedus, L. S. *J. Org. Chem.* **1997**, *62*, 3585. (f) Jun, M. E.; Huang, A. *Org. Lett.* **2000**, *2*, 2659.

(3) (a) Jones, R. C. F.; Turner, I.; Howard, K. J. *Tetrahedron Lett.* **1993**, *34*, 6329. (b) Jones, R. C. F.; Howard, K. J.; Snaith, J. S. *Tetrahedron Lett.* **1996**, *37*, 1707. (c) Langlois; Y.; Dalko, P. I. *J. Org. Chem.* **1998**, *63*, 8107.

(4) (a) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157. (b) Isobe, T.; Fukuda, K.; Araki, Y.; Ishikawa, T. *Chem. Commun.* **2001**, 243.

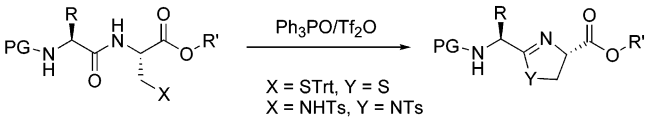
(5) (a) Botteghi, C.; Schionato, A.; Chelucci, G.; Brunner, H.; Kürzinger, A.; Obermann, U. *J. Organomet. Chem.* **1989**, *370*, 17. (b) Morimoto, T.; Tachibana, K.; Achiwa, K. *Synlett* **1997**, 783. (c) Davinport, A. J.; Davies, D. L.; Fawcett, J.; Russell, D. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1500. (d) Menges, F.; Neuburger, M.; Pfaltz, A. *Org. Lett.* **2002**, *4*, 4713.

10.1021/ol049439c CCC: $27.50
Published on Web 04/17/2004

specific synthesis of imidazoline-based amino acids has not been reported from dipeptides composed of a C-terminal β-amino-α-amino acid residue or N-acylated β-amino-α-amino acids. Furthermore, there are very few reports of the synthesis of imidazole-based amino acids.[10]

Recently, we reported biomimetic methodology for the synthesis of thiazolines from N-acylated cysteine substructures using bis(triphenyl) oxodiphosphonium trifluoromethanesulfonate (Scheme 1, X = STrt (trityl), Y = S).[11a]

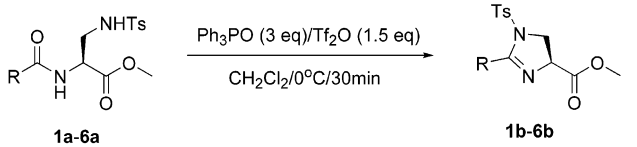
Scheme 1. Heterocycle Formation Mediated by Bis(triphenyl) Oxodiphosphonium Trifluoromethanesulfonate



Thiazolines are formed by nucleophilic attack of the cysteine thiol on the phosphonium-activated amide carbonyl group of the preceding residue, followed by dehydration via phosphine oxide formation. The reaction proceeds in high yield with excellent chemo- and enantiospecificity, without epimerization of the exocyclic stereocenter. Herein, we report a highly efficient enantiospecific synthesis of imidazoline-based amino acids using bis(triphenyl) oxodiphosphonium trifluoromethanesulfonate (Scheme 1, X = NHTs, Y = NTs). The imidazole-based amino acids comprising the macrolactam natural product analogues prepared within are obtained by oxidizing the corresponding imidazolines.

The starting materials for imidazoline formation, N-acylated β-amino-α-amino esters (**1a**−**6a**), and fully protected dipeptides composed of a C-terminal β-amino-α-amino ester residue (**7a**−**13a**), were synthesized either from commercially available *N*-α-Fmoc-*N*-β-4-methyltrityl-l-diaminopropionic acid or L-serine methyl (or benzyl) ester.[12] To examine the scope and limitations of imidazoline formation by the bisphosphonium salt, β-tosylamino-α-acylamino esters (**1a**−**6a**) were subjected to the reaction conditions shown in Table 1. In general, this reaction afforded imidazoline products in high yields with excellent retention of stereochemistry at what was the α-carbon. A decreased enantiomeric excess (86%) was observed only with the 3-CF_3-phenyl-substituted substrate (Table 1, entry 6).

Table 1. Bis-phosphonium Salt-Mediated Synthesis of Imidazolines from β-Tosylamino-α-acylamino Esters



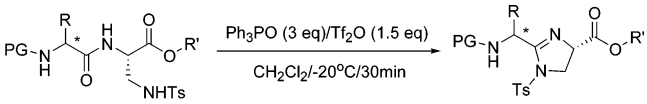
1a-6a 1b-6b

entry	substrates, R	products	yield (%)[a]	ee (%)[b]
1	**1a**, Ph	**1b**	96	97
2[c]	**2a**, Ph	**2b**	95	98
3	**3a**, 4-Me-Ph	**3b**	97	98
4	**4a**, 4-MeO-Ph	**4b**	95	97
5	**5a**, Bn	**5b**	94	99
6[d]	**6a**, 3-CF_3-Ph	**6b**	90	86

[a] Isolated yield. [b] Determined by chiral HPLC. [c] R configuration substrate was used. [d] Starting material exhibited 96% ee.

To apply this method to the synthesis of imidazoline-based amino acids, several α-N-protected dipeptides with tosyl protected β-amino groups were synthesized and evaluated as starting materials (**7a**−**13a**, Table 2).

Table 2. Bis-phosphonium Salt-Mediated Synthesis of Imidazoline-Based Amino Acids from Dipeptides



7a-13a 7b-13b

entry	PG	R (configuration), R′	product	yield (%)[a]	dr[b]	ee (%)[c]
1	**7a**, Cbz	Bn (L), Me	**7b**	71	>99/1	99
2	**8a**, Cbz	Bn (D), Me	**8b**	75	>99/1	98
3	**9a**, Cbz	*i*-Pr (L), Me	**9b**	74	>99/1	>99.5
4	**10a**, Cbz	*i*-Pr (D), Me	**10b**	81	>99/1	99
5	**11a**, Cbz	*i*-Pr (L), Bn	**11b**	74	>99/1	>99.5
6	**12a**, Cbz	*i*-Pr (D), Bn	**12b**	76	>99/1	99
7	**13a**, Fmoc	*i*-Pr (L), Bn	**13b**	88	>99/1	>99.5

[a] Isolated yield. [b] Determined by NMR and chiral HPLC. [c] Determined by chiral HPLC.

In all cases, the corresponding imidazolines were obtained in moderate to very good yields with excellent enantioselectivity observed at both chiral centers. Several imid-

(6) (a) Carmeli, S.; Moore, R. E.; Patterson, G. M. L.; Corbett, T. H.; Valeriote, F. A. *J. Am. Chem. Soc.* **1990**, *112*, 8195. (b) Carmeli, S.; Moore, R. E.; Patterson, G. M. L. *Tetrahedron Lett.* **1991**, *32*, 2593. (c) Boyce, R. J.; Mulqueen, G. C.; Pattenden, G. *Tetrahedron* **1995**, *51*, 7321. (d) Ogino, J.; Moore, R. E.; Patterson, G M. L.; Smith, C. D. *J. Nat. Prod.* **1996**, *59*, 581. (e) Admi, V.; Afek, U.; Carmeli, S. *J. Nat. Prod.* **1996**, *59*, 396. (f) Banker, R.; Carmeli, S. *J. Nat. Prod.* **1998**, *61*, 1248. (g) Ishida, K.; Nakagawa, H.; Murakami, M. *J. Nat. Prod.* **2000**, *63*, 1315. (h) Rudi, A.; Chill, L.; Aknin, M.; Kashman, Y. *J. Nat. Prod.* **2003**, *66*, 575. (i) Degnan, B. M.; Hawkins, C. J.; lavin, M. F.; McCaffrey, E. J.; Parry, D. L.; Watters, D. J. *J. Med. Chem.* **1989**, *32*, 1354. (j) Foster, M. P.; Concepción, G. P.; Caraan, G. B.; Ireland, C. M. *J. Org. Chem.* **1992**, *57*, 6671. (k) Perez, L. J.; Faulkner, D. J. *J. Nat. Prod.* **2003**, *66*, 247. (l) For reviews, see: Davidson, B. S. *Chem. Rev.* **1993**, *93*, 1771. Wipf, P. *Chem. Rev.* **1995**, *95*, 2115.

(7) (a) Mitchell, J. M.; Finney, N. S. *Tetrahedron Lett.* **2000**, *41*, 8431. (b) Sutcliffe, O. B.; Bryce, M. R.; Batsanov, A. S. *J. Organomet. Chem.* **2002**, *656*, 211.

(8) Boland, N. A.; Casey, M.; Hynes, S. J.; Matthews, J. W.; Smyth, M. P. *J. Org. Chem.* **2002**, *67*, 3919.

(9) (a) Hunter, D. H.; Sim, S. K. *Can. J. Chem.* **1972**, *50*, 669. (b) Oi, R.; Sharpless, K. B. *Tetrahedron Lett.* **1991**, *32*, 999. (c) Molina, P.; Díaz, I.; Tárraga, A. *Synett* **1995**, 1031. (d) Hulme, C.; Ma, L.; Romano, J.; Morrissette, M. *Tetrahedron Lett.* **1999**, *40*, 7925. (e) Zhou, X.-T.; Lin Y.-R.; Dai, L.-X.; Sun, J.; Xia, L.-J.; Tang, M.-H. *J. Org. Chem.* **1999**, *64*, 1331. (f) Acharya, A. N.; Ostresh, J. M.; Houghten, R. A. *J. Org. Chem.* **2001**, *66*, 8673. (g) Peddibhotla, S.; Tepe, J. J. *Synthesis* **2003**, 1433.

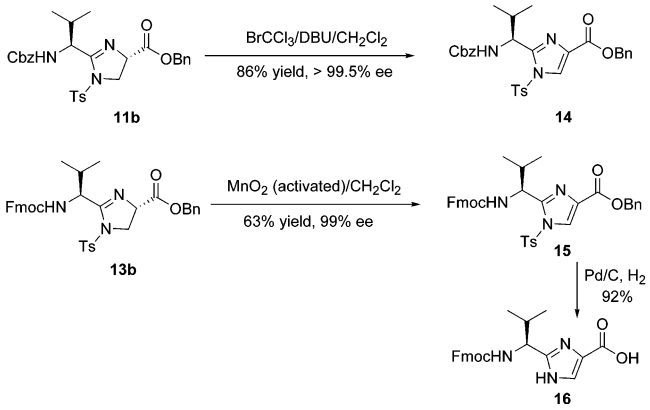
(10) (a) Haberhauer, G.; Rominger, F. *Tetrahedron Lett.* **2002**, *43*, 6335. (b) Haberhauer, G.; Rominger, F. *Eur. J. Org. Chem.* **2003**, 3209.

(11) (a) You, S.-L.; Razavi, H.; Kelly, J. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 83. (b) You, S.-L.; Kelly, J. W. *Chem. Eur. J.* **2004**, *10*, 71. (c) You, S.-L.; Kelly, J. W. *J. Org. Chem.* **2003**, *68*, 9506.

azoline-based amino acids (**8b**−**13b**) revealed two sets of peaks in their NMR spectra. Since only one set of proton signals was observed when the sample was heated to 52 °C, this is likely due to slow epimerization of the nitrogen atom bearing a tosyl group.[12]

As shown in Scheme 2, the Cbz- and Fmoc-protected imidazoline-based amino acids **11b** and **13b** were converted

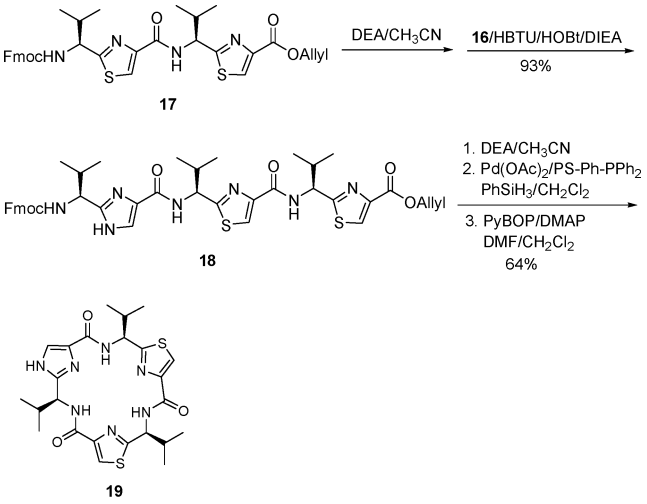
Scheme 2. Synthesis of Imidazole-Based Protected Amino Acids



to imidazoles **14** and **15**, using $BrCCl_3$/DBU (1,8-diazabicyclo-[5.4.0]undec-7-ene)[13] and activated MnO_2,[11b,c] respectively. Both the benzyl and tosyl groups were removed from **15** by hydrogenation affording **16**.

To evaluate the suitability of using these heterocyclic amino acids as building blocks for natural product analogues, imidazole **16** was incorporated into a macrolactam related to bistratamide H as shown in Scheme 3.[6k] Amide **17** (a known compound[11b]) was first treated with diethylamine to liberate the Fmoc group. The resulting free amine of **17** was coupled with dehydration to the carboxyl group of **16** affording diamide **18** in 93% yield (protection of the

Scheme 3. Incorporation of Imidazole-Based Amino Acid **16** into a Macrolactam Analogue of Bistratamide H (**19**)[6k]



imidazole in **16** was not necessary). After removal of the Fmoc and allyl protecting groups from compound **18** using diethylamine and a solid-phase Pd-catalyst, respectively, the final macrolactamization was accomplished using PyBOP and DMAP affording **19** in 64% yield.[11b−c]

In summary, highly efficient enantiospecific syntheses of imidazolines and imidazoline-based amino acids have been achieved using bis(triphenyl) oxodiphosphonium trifluoromethanesulfonate-mediated cyclodehydrations. These imidazolines were easily converted to imidazoles and incorporated into macrolactam analogues of bistratamide H without loss of stereochemical integrity.

Acknowledgment. We gratefully acknowledge NIH Grant GM63212 and the Skaggs Institute for Chemical Biology for generous financial support. We thank Professor Evan T. Powers for helpful discussions.

Supporting Information Available: Experimental details and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049439C

(12) See Supporting Information.

(13) (a) Williams, D. R.; Lowder, P. D.; Gu, Y.; Brooks, D. A. *Tetrahedron Lett.* **1997**, *38*, 331. (b) Downing, S. V.; Aguilar, E.; Meyers, A. I. *J. Org. Chem.* **1999**, *64*, 826.