ORGANIC LETTERS

2000
Vol. 2, No. 14
2037−2040

A Second-Generation Synthesis of Polypyrrolinone Nonpeptidomimetics: Prelude to the Synthesis of Polypyrrolinones on Solid Support

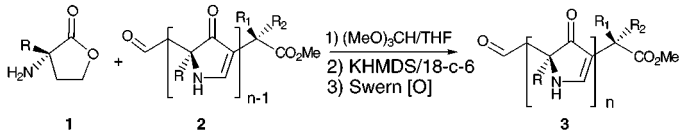
Amos B. Smith, III,* Hu Liu, and Ralph Hirschmann*

Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104

smithab@sas.upenn.edu

Received April 11, 2000

ABSTRACT



1 2 3

A second-generation asymmetric synthesis of polypyrrolinones (3) has been achieved exploiting scalemic α-aminolactones (1) as building blocks. Imine formation between an appropriate lactone (1) and aldehyde (2), followed in turn by pyrrolinone ring construction promoted by KHMDS in the presence of 18-crown-6 and modified Swern oxidation furnished pyrrolinone aldehyde 3. This iterative, efficient three-step protocol paves the way for the synthesis of polypyrrolinones on solid support.

In 1992 we reported the design and synthesis of nonpeptide peptidomimetics based on the 3,5,5-trisubstituted pyrrolin-4-one ring system.[1] Depending on the structure, these polypyrrolinones, which are stable to both strong acid and proteases, can adopt diverse conformations including those analogous to β-strands,[1a,d] β-turns, and helices.[1i] Exploiting the β-strand structural motif, we designed and synthesized several potent, bioavailable inhibitors of the HIV-1 aspartic acid protease[1c,f,h] which exhibited improved membrane transport properties[2] relative to their peptidal counterparts. The improved transport was attributed to the presence of intramolecular hydrogen bonds between adjacent pyrrolinone rings (NH and CO), which led to a reduction in desolvation energy upon membrane transport.[1c,3] We have also successfully employed a bispyrrolinone in the construction of a pyrrolinone−peptide hybrid ligand, which bound the Class II MHC protein HLA-DR1 in an extended β-strand-like conformation with potency similar to that of the native peptide.[4] Taken together, these results suggest that the polypyrrolinone scaffold holds considerable promise for the design of a wide variety of peptidomimetics.

The cornerstone of our initial iterative polypyrrolinone syntheses entailed imine formation followed by metalloimine

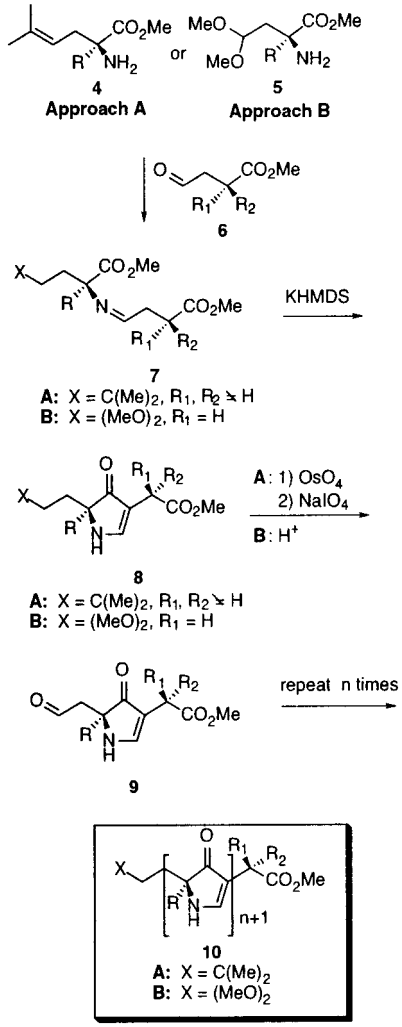
(1) (a) Smith, A. B., III; Keenan, T. P.; Holcomb, R. C.; Sprengeler, P. A.; Guzman, M. C.; Wood, J. L.; Carroll, P. J.; Hirschmann, R. *J. Am. Chem. Soc.* **1992**, *114*, 10672. (b) Smith, A. B., III; Holcomb, R. C.; Guzman, M. C.; Keenan, T. P.; Sprengeler, P. A.; Hirschmann, R. *Tetrahedron Lett.* **1993**, *34*, 63. (c) Smith, A. B., III; Hirschmann, R.; Pasternak, A.; Akaishi, R.; Guzman, M. C.; Jones, D. R.; Keenan, T. P.; Sprengeler, P. A.; Darke, P. L.; Emini, E. A.; Holloway, M. K.; Schleif, W. A. *J. Med. Chem.* **1994**, *37*, 215. (d) Smith, A. B., III; Guzman, M. C.; Sprengeler, P. A.; Keenan, T. P.; Holcomb, R. C.; Wood, J. L.; Carroll, P. J.; Hirschmann, R. *J. Am. Chem. Soc.* **1994**, *116*, 9947. (e) Smith, A. B., III; Akaishi, R.; Jones, D. R.; Keenan, T. P.; Guzman, M. C.; Holcomb, R. C.; Sprengeler, P. A.; Wood, J. L.; Hirschmann, R.; Holloway, M. K. *Biopolymers (Peptide Science)* **1995**, *37*, 29. (f) Smith, A. B., III; Hirschmann, R.; Pasternak, A.; Guzman, M. C.; Yokoyama, A.; Sprengeler, P. A.; Darke, P. L.; Emini, E. A.; Schleif, W. A. *J. Am. Chem. Soc.* **1995**, *117*, 11113. (g) Smith, A. B., III; Benowitz, A. B.; Favor, D. A.; Sprengeler, P. A.; Hirschmann, R. *Tetrahedron Lett.* **1997**, *38*, 3809. (h) Smith, A. B., III; Hirschmann, R.; Pasternak, A.; Yao, W.; Sprengeler, P. A.; Holloway, M. K.; Kuo, L. C.; Chen, Z.; Darke, P. L.; Schleif, W. A. *J. Med. Chem.* **1997**, *40*, 2440. (i) Smith, A. B., III; Favor, D. A.; Sprengeler, P. A.; Guzman, M. C.; Carroll, P. J.; Furst, G. T.; Hirschmann, R. *Bioorg. Med. Chem.* **1999**, 9.

(2) Thompson, W. J.; Fitzgerald, P. M. D.; Holloway, M. K.; Emini, E. A.; Darke, P. L.; McKeever, B. M.; Schleif, W. A.; Quintero, J. C.; Zugay, J. A.; Tucker, T. J.; Schwering, J. E.; Homnick, C. F.; Nunberg, J.; Springer, J. P.; Huff, J. R. *J. Med. Chem.* **1992**, *35*, 1685.

(3) Hirschmann, R.; Smith, A. B., III; Sprengeler, P. A. In *New Perspectives in Drug Design*; Dean, P. M., Jolles, G., Newton, C. G., Eds.; Academic: London, 1995; pp 1−14.

10.1021/ol0059293 CCC: $19.00
Published on Web 06/09/2000

Scheme 1

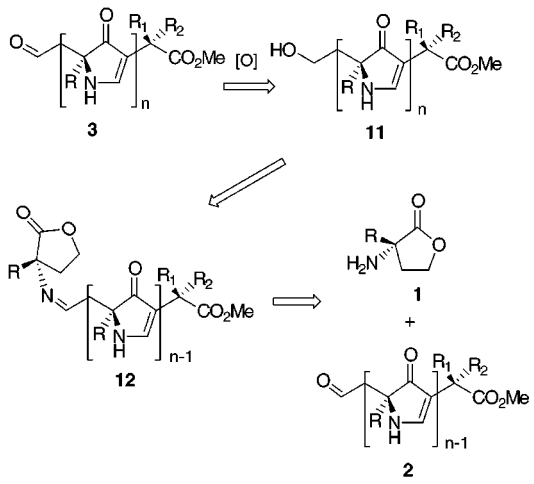


cyclization to generate the pyrrolinone ring (Scheme 1).[1d,4b] Depending on the nature of group X in pyrrolinone **8**, either a two-step oxidation [(a) OsO_4/NMO;[5] (b) $NaIO_4$; Approach A] or strong acid hydrolysis (Approach B) was employed[4,6] to unmask the aldehyde moiety to permit iteration of the reaction sequence. Studies directed toward the synthesis of polypyrrolinones on solid support,[7] however, revealed that neither approach was suitable, due to the incompatibilities of the OsO_4 and the strong acid procedures with the solid support and pyrrolinone functionality.[8]

In this Letter, we report the development of a more efficient, three-step iterative synthesis of polypyrrolinones. Application of this second-generation protocol to the synthesis of polypyrrolinones on solid support, as disclosed in the accompanying Letter,[7] paves the way for the generation of a wide variety of libraries based on the pyrrolinone structural motif.

For a second-generation strategy, we envisioned that pyrrolinone aldehyde **3** (Scheme 2) would be accessible by

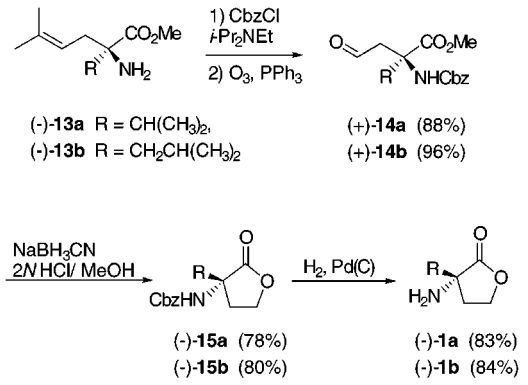
Scheme 2



oxidation of the hydroxyl group in pyrrolinone **11**. Disconnection of **11** then leads to iminolactone **12**, prepared from lactone **1** and aldehyde **2**. Iteration of this three-step sequence with a variety of α-aminolactones should lead to diverse polypyrrolinones.

To explore this scenario, we prepared α-aminolactones (−)-**1** from amino ester (−)-**13**,[1d] already available in our laboratory (Scheme 3).[9] Four steps were required; protection

Scheme 3



of the amino group with benzyl chloroformate followed by ozonolysis furnished amino aldehydes (+)-**14** in >88% yield

(4) (a) Smith, A. B., III; Benowitz, A. B.; Guzman, M. C.; Sprengeler, P. A.; Hirschmann, R.; Schweiger, E. J.; Bolin, D. R.; Nagy, Z.; Campbell, R. M.; Cox, D. C.; Olson, G. L. *J. Am. Chem. Soc.* **1998**, *120*, 12704. (b) Smith, A. B., III; Benowitz, A. B.; Sprengeler, P. A.; Barbosa, J.; Guzman, M. C.; Hirschmann, R.; Schweiger, E. J.; Bolin, D. R.; Nagy, Z.; Campbell, R. M.; Cox, D. C.; Olson, G. L. *J. Am. Chem. Soc.* **1999**, *121*, 9286.

(5) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973.

(6) Approach B was designed specifically for the construction of pyrrolinones not fully substituted on the carbon adjacent to the unsaturation in the pyrrolinone ring [e.g., **8** (R_1 = H)].[4b]

(7) Smith, A. B., III; Liu, H.; Okumura, H.; Favor, D. A.; Hirschmann, R. *Org. Lett.* **2000**, *2*, 2041−2044.

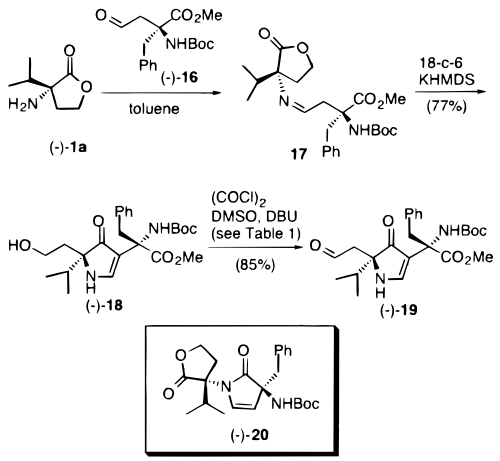
(8) To access the bispyrrolinone aldehyde [e.g., **3** (*n* = 2)], 4 N HCl and heating are required.

(9) Studies to develop a general asymmetric synthesis of α-aminolactones (**1**) will be reported in due course.

(two steps).[10] Reduction with sodium cyanoborohydride[11] (2 N HCl/methanol) proceeded with concomitant cyclization to furnish Cbz-protected aminolactones (−)-**15**; hydrogenation then gave the desired α-aminolactones (−)-**1**, which could be used without purification.

Polypyrrolinone construction entailed condensation of (−)-**1a** (Scheme 4) with Boc-protected amino aldehyde (−)-**16**

Scheme 4



to furnish an unstable imine (**17**), which was directly treated with excess KHMDS (8 equiv) in the presence of 18-crown-6 (8 equiv); the resulting red solution was stirred for 2 h at 0 °C and 3 h at rt and then treated with 5% aqueous $NaHSO_4$ to furnish hydroxypyrrolinone (−)-**18** in 77% yield (two steps). In the absence of 18-crown-6, the yield of (−)-**18** was only 55%. Interestingly, other amide bases, such as LDA, LTMP, and LiHMDS, led to unsaturated lactam (−)-**20** as a major side product (ca. 40%).[12] Presumably (−)-**20** derives via addition of the metalloimine nitrogen to the carbomethoxy group. When KHMDS/18-crown-6 was employed, lactam (−)-**20** was formed in less than 5%.

Swern oxidation of (−)-**18** employing DBU as base[13] then furnished aldehyde (−)-**19**[1d] (Scheme 4) in 85% yield (Table 1). Other oxidants including the Dess−Martin periodinane[14]

Table 1. Oxidation of (−)-**18** to (−)-**19**

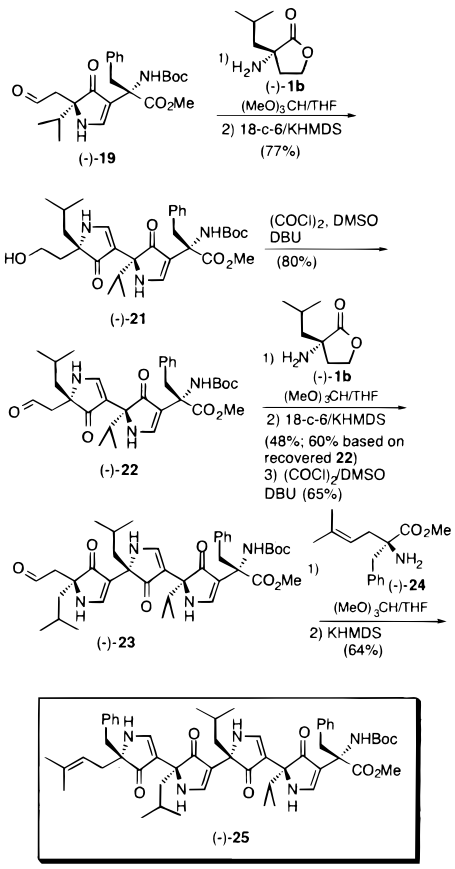
entry	conditions	(−)-**19**, % yield[a]
1	Dess−Martin	26
2	Dess−Martin, pyr	39
3	SO_3/pyr, DMSO/Et_3N (4:1)	25
4	SO_3/pyr, DMSO, *i*-Pr_2NEt	decomposition
5	$(COCl)_2$, DMSO, Et_3N	46
6	$(COCl)_2$, DMSO, *i*-Pr_2NEt	87[b]
7	$(COCl)_2$, DMSO, DBU	85

[a] Isolated yield. [b] Product contains impurity.

and the Parikh−Doering sulfur trioxide−pyridine complex[15] afforded (−)-**19** in lower yield (0−39%). For the Swern oxidation, the choice of base proved crucial (Table 1, entries 5−7); best results were obtained with DBU and Hunig's base (ca. >85% yield). However, the product derived using Hunig's base contained impurities difficult to separate by chromatography.

To secure the viability of the polypyrrolinone synthesis employing α-aminolactones, we selected known tetrapyrrolinone (−)-**25**[1d] as our next target (Scheme 5). Two

Scheme 5



iterations of the aforementioned three-step protocol (e.g., imine formation, metalloimine cyclization, and Swern oxidation) furnished trispyrrolinone aldehyde (−)-**23**[1d] in 19% overall yield for the six steps. Significantly improved yields were obtained when imine formation was carried out at rt for 12 h with a 1:1 (v/v) mixture of trimethyl orthoformate[16] and THF.[17] Trispyrrolinone aldehyde (−)-**23** was then capped

(10) The structure assigned to each new compound is in accord with its infrared, 500 MHz ^1H NMR, and 125 MHz ^{13}C NMR spectra, as well as appropriate parent ion identification by high-resolution mass spectrometry.

(11) (a) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897. (b) Koft, E. R. *Tetrahedron* **1987**, *43*, 5775.

(12) The structure of (−)-**20** was confirmed by single-crystal X-ray analysis; we thank Dr. P. Carroll, University of Pennsylvania.

(13) Boger, D. L.; Jacobson, I. C. *J. Org. Chem.* **1991**, *56*, 2115.

(14) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(15) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

(16) (a) Look, G. C.; Murphy, M. M.; Campbell, D. A.; Gallop, M. A. *Tetrahedron Lett.* **1995**, *36*, 2937. (b) Ruhland, B.; Bhandari, A.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 253.

with aminoester (−)-**24**[1d] derived from phenylalanine to furnish tetrapyrrolinone (−)-**25** (64% yield), identical in all aspects [500 MHz ^{1}H, 125 MHz ^{13}C, IR, MS] with an authentic sample.[1d]

In summary, a second-generation iterative synthesis of polypyrrolinones employing scalemic α-aminolactones has been developed. Importantly, the new protocol is efficient, requires only three steps per iteration, and avoids the use of either OsO_4 or strong acid, both found to be incompatible with solid-support synthesis. In the accompanying Letter, we disclose an extension of this method to the synthesis of polypyrrolinones on solid support.

(17) This new protocol represents a departure from our standard imine formation conditions (azeotropic water removal with benzene or toluene).[1d]

Acknowledgment. Financial support was provided by the National Institutes of Health (Institute of General Medical Science) through Grant GM-41821. We also thank Drs. G. Furst, P. Carroll, and Mr. J. Dykins, Directors of the University of Pennsylvania Spectroscopic Facilities, for assistance in obtaining NMR spectra, X-ray crystal structures, and high-resolution mass spectra, respectively.

Supporting Information Available: Spectroscopic and analytical data for **14**, **15**, **1**, **18**−**23**, and **25**, as well as representative experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0059293