

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

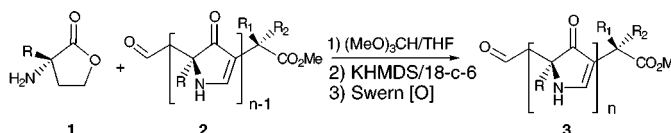
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## ABSTRACT



A second-generation asymmetric synthesis of polypyrrolinones (**3**) has been achieved exploiting scalemic  $\alpha$ -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.<sup>1</sup> Depending on the structure, these polypyrrolinones, which are stable to both strong acid and proteases, can adopt diverse conformations including those analogous to  $\beta$ -strands,<sup>1a,d</sup>  $\beta$ -turns, and helices.<sup>1i</sup> Exploiting

the  $\beta$ -strand structural motif, we designed and synthesized several potent, bioavailable inhibitors of the HIV-1 aspartic acid protease<sup>1c,f,h</sup> which exhibited improved membrane transport properties<sup>2</sup> 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.<sup>1c,3</sup> 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  $\beta$ -strand-like conformation with potency similar to that of the native peptide.<sup>4</sup> Taken together, these results suggest that the polypyrrolinone scaffold holds considerable promise for the design of a wide variety of peptidomimetics.

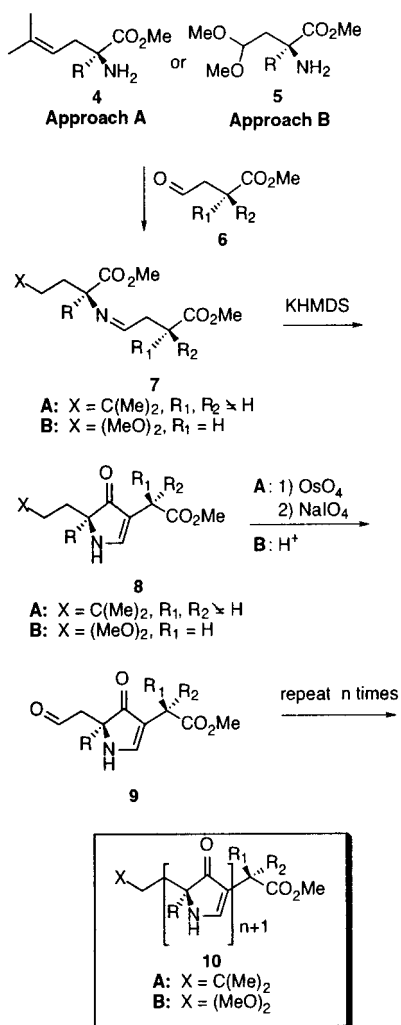
The cornerstone of our initial iterative polypyrrolinone syntheses entailed imine formation followed by metalloimine

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(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.

Scheme 1



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

(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<sub>1</sub> = H)].<sup>4b</sup>

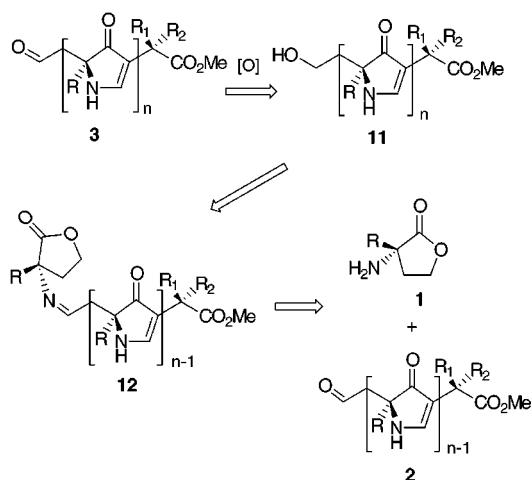
(7) Smith, A. B., III; Liu, H.; Okumura, H.; Favor, D. A.; Hirschmann, R. *Org. Lett.* **2000**, *2*, 2041–2044.

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

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,<sup>7</sup> 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

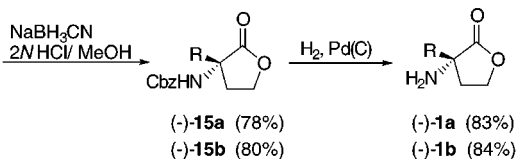
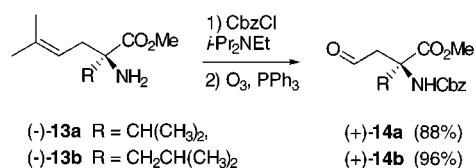
Scheme 2



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**,<sup>1d</sup> already available in our laboratory (Scheme 3).<sup>9</sup> Four steps were required; protection

Scheme 3

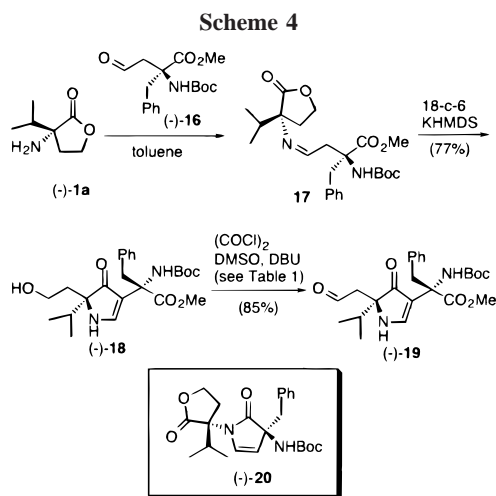


of the amino group with benzyl chloroformate followed by ozonolysis furnished amino aldehydes (+)-**14** in >88% yield

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

(two steps).<sup>10</sup> Reduction with sodium cyanoborohydride<sup>11</sup> (2 N HCl/methanol) proceeded with concomitant cyclization to furnish Cbz-protected aminolactones (–)-**15**; hydrogenation then gave the desired  $\alpha$ -aminolactones (–)-**1**, which could be used without purification.

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



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<sub>4</sub> 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%).<sup>12</sup> 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<sup>13</sup> then furnished aldehyde (–)-**19**<sup>1d</sup> (Scheme 4) in 85% yield (Table 1). Other oxidants including the Dess–Martin periodinane<sup>14</sup>

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

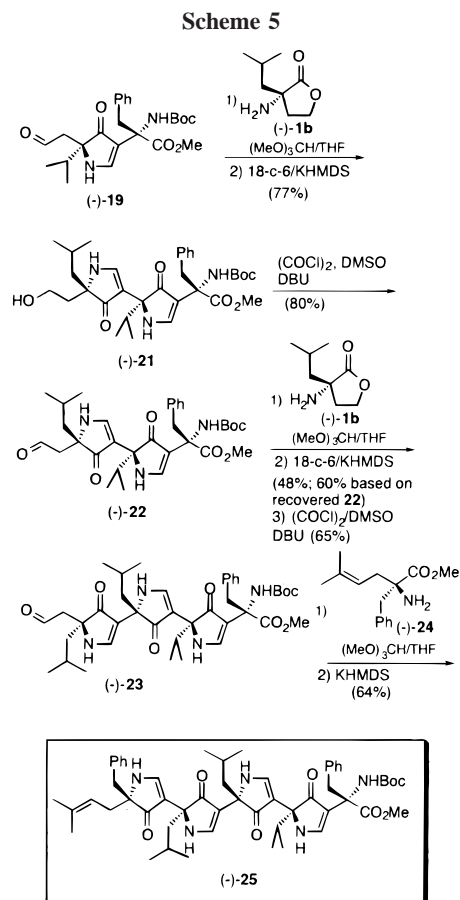
entry	conditions	(–)- <b>19</b> , % yield <sup>a</sup>
1	Dess–Martin	26
2	Dess–Martin, pyr	39
3	SO <sub>3</sub> /pyr, DMSO/Et <sub>3</sub> N (4:1)	25
4	SO <sub>3</sub> /pyr, DMSO, <i>i</i> -Pr <sub>2</sub> NEt	decomposition
5	(COCl) <sub>2</sub> , DMSO, Et <sub>3</sub> N	46
6	(COCl) <sub>2</sub> , DMSO, <i>i</i> -Pr <sub>2</sub> NEt	87 <sup>b</sup>
7	(COCl) <sub>2</sub> , DMSO, DBU	85

<sup>a</sup> Isolated yield. <sup>b</sup> Product contains impurity.

and the Parikh–Doering sulfur trioxide–pyridine complex<sup>15</sup> 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  $\alpha$ -aminolactones, we selected known tetrapyrrolinone (–)-**25**<sup>1d</sup> as our next target (Scheme 5). Two



iterations of the aforementioned three-step protocol (e.g., imine formation, metalloimine cyclization, and Swern oxidation) furnished trispyrrolinone aldehyde (–)-**23**<sup>1d</sup> 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<sup>16</sup> and THF.<sup>17</sup> Trispyrrolinone aldehyde (–)-**23** was then capped

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

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

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

In summary, a second-generation iterative synthesis of polypyrrolinones employing scalemic  $\alpha$ -aminolactones has been developed. Importantly, the new protocol is efficient, requires only three steps per iteration, and avoids the use of either OsO<sub>4</sub> 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.

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

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**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>.

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