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Synthesis of Polypyrrolinones on Solid Support

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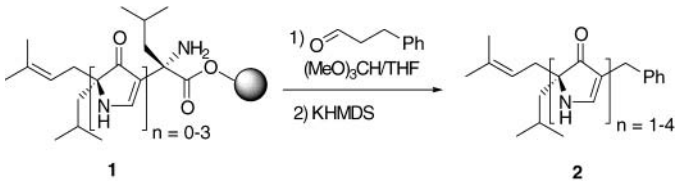
ABSTRACT



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An efficient, three-step iterative synthesis of polypyrrolinones has been achieved on solid support, setting the stage for the construction of a wide variety of libraries based on the pyrrolinone scaffold. Central to the approach is an effective end-game sequence featuring pyrrolinone ring construction with traceless release from the solid support.

Recent observations in our laboratory[1] suggest that the polypyrrolinone structural motif, designed initially to mimic peptide and protein β-strand/β-sheet structural motifs,[1a,d] may in fact represent a privileged nonpeptide scaffold, able to mimic not only the extended β-strand/β-sheet conformation but also other diverse conformations including those analogous to β-turn and helices.[1j] This unexpected diversity, if accessible in a controlled fashion, would expand the scope of the polypyrrolinone scaffold for the development of low-molecular-weight ligands for a variety of biologically important targets. The previously developed iterative solution-phase syntheses of polypyrrolinones,[1a,d,k] however, were not suitable for the rapid preparation of large numbers of polypyrrolinone congeners. We therefore became interested in developing an iterative, solid-phase synthetic strategy,[2] conceptually not unlike the Merrifield peptide synthesis,[3] leading eventually to library syntheses. Herein we disclose an efficient, three-step iterative synthesis of polypyrrolinones on solid support.

Known monopyrrolinone (−)-**7**[1d] and bispyrrolinone (−)-**11**[1d] were selected as initial targets for solid-support synthesis (Scheme 1). At the outset, we explored our solution-phase chemistry,[1] with the clear intent of devising a traceless linker

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(2) (a) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (b) Fruchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17. (c) Czarnik, A. W., Ellman, J. A., Eds. Combinatorial Chemistry Special Issue. *Acc. Chem. Res.* **1996**, *29*, 112. (d) Bunin, B. A. In *The Combinatorial Index*; Academic Press: London, 1998.

(3) Merrifield, R. B. *J. Am. Chem. Soc.* **1963**, *85*, 2149.

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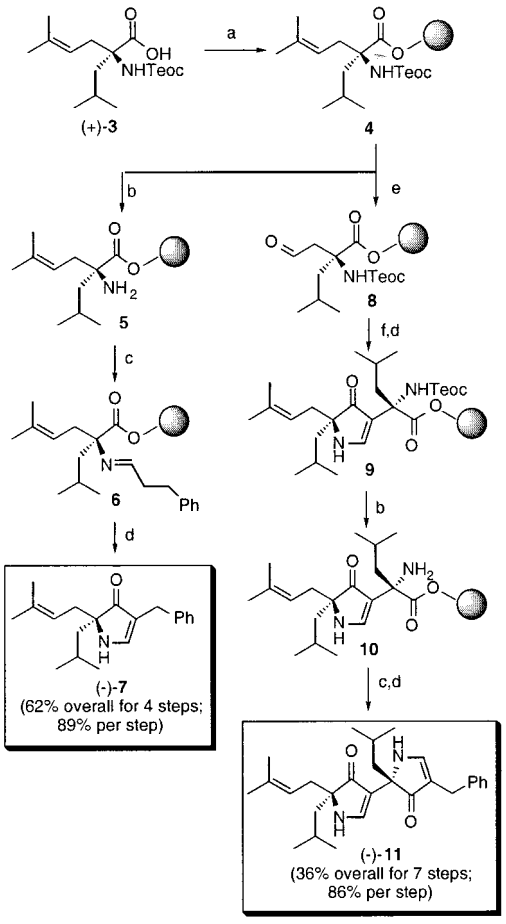
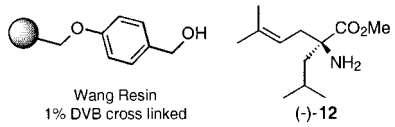
Scheme 1



(a) Wang resin, DEAD, PPh_3; (b) TBAF; (c) $PhCH_2CH_2CHO$, $(MeO)_3CH$/THF, 2 treatments; (d) KHMDS; (e) O_3, PPh_3; (f) (-)-**12**, $(MeO)_3CH$/THF, 2 treatments.

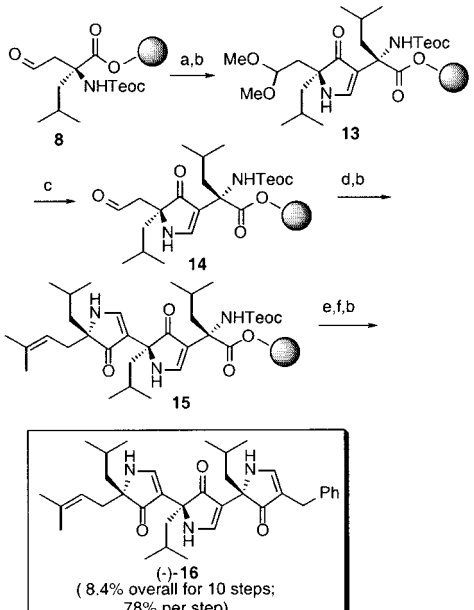


strategy[4] to detach the polypyrrolinone from the resin. Toward this end, the Teoc-protected amino acid (+)-**3**[5] (1.1 equiv) was attached to Wang resin via Mitsunobu reaction[6] to provide resin-bound amino ester **4**. Removal of the Teoc protecting group (TBAF) afforded amino ester **5** bound to the resin, which was condensed with hydrocinnamaldehyde ($PhCH_2CH_2CHO$) exploiting trimethyl orthoformate in THF to drive imine formation to completion.[7] Reacting imine **6** with KHMDS (10 equiv) led via metalloimine not only to cyclization of the pyrrolinone ring but also to traceless release from the resin; chromatography furnished known monopyrrolinone (−)-**7**[1d] in 62% yield (four steps; average yield/step 89%).

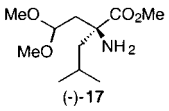
For bispyrrolinone (−)-**11**,[1d] ozonolysis[8] of resin-bound amino ester **4** furnished aldehyde **8**. Imine formation with amino ester (−)-**12**,[1d] followed by KHMDS-promoted metalloimine cyclization, gave monopyrrolinone **9**. Removal of the Teoc group (TBAF), followed in turn by imine formation with hydrocinnamaldehyde and metalloimine formation with KHMDS, again led to cyclization and release from the resin to furnish known bispyrrolinone (−)-**11**[1d] in 36% isolated yield for the seven steps (average yield/step 86%).

Having successfully constructed mono- and bispyrrolinones (−)-**7** and (−)-**11**, we turned to trispyrrolinone (−)-**16** as our next target (Scheme 2). Union of resin-bound amino aldehyde **8** with amino ester (−)-**17**[1k] via imine formation (two cycles), followed by metalloimine cyclization (KHMDS), furnished monopyrrolinone **13**. Release of the aldehyde functionality with acid (TsOH/40 °C) provided resin-bound pyrrolinone **14**, which was then converted to

Scheme 2

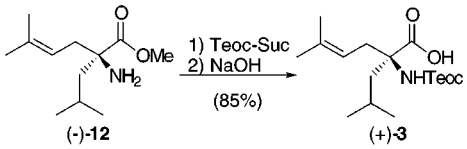


(a) (-)-**17**, $(MeO)_3CH$/THF, 2 treatments; (b) KHMDS; (c)TsOH, 40 °C; (d) (-)-**12**, $(MeO)_3CH$/THF, 2 treatments; (e) TBAF; (f) $PhCH_2CH_2CHO$, $(MeO)_3CH$/THF, 2 treatments.



(4) Plunkett, M. J.; Ellman, J. A. *J. Org. Chem.* **1995**, *60*, 6006.

(5) Teoc-protected amino acid (+)-**3** was prepared as following from the corresponding free methyl amino ester (−)-**12**:



(6) (a) Krchnak, V.; Flegelova, Z.; Weichsel, A. S.; Lebl, M. *Tetrahedron Lett.* **1995**, *36*, 6193. (b) Rano, T. A.; Chapman, K. T. *Tetrahedron Lett.* **1995**, *36*, 3789.

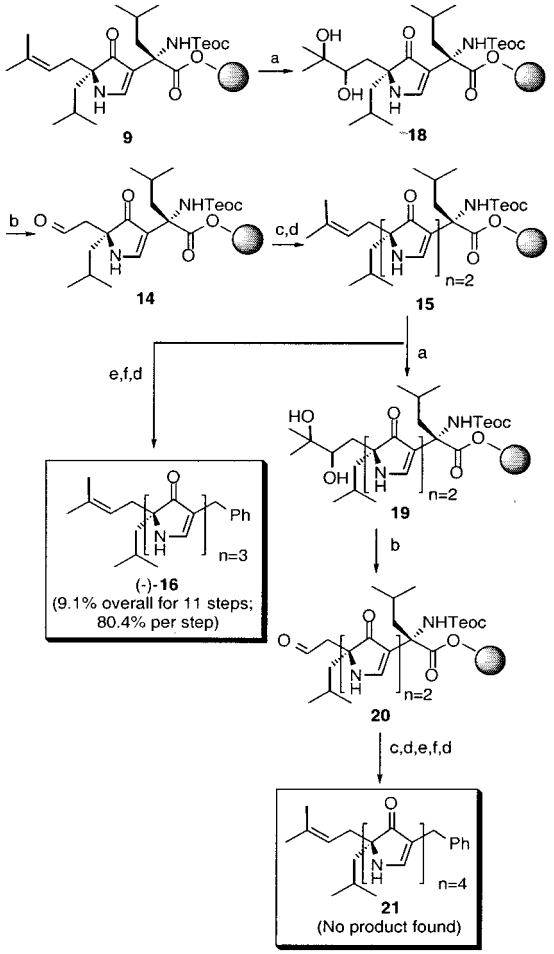
(7) (a) Look, G. C.; Murphy, M. M.; Campbell, D. A.; Gallop, M. A. *Tetrahedron Lett.* **1995**, *36*, 2937. (b) Ruhland, B.; Bhandari, A.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 253.

(8) Panek, J. S.; Zhu, B. *J. Am. Chem. Soc.* **1997**, *119*, 12022.

bispyrrolinone **15** via iteration of the above sequence, again employing amino ester (−)-**12**. Isolation of trispyrrolinone (−)-**16** was then achieved after Teoc removal (TBAF) and what has now become our standard end-game resin release protocol: imine formation with hydrocinnamaldehyde and metalloimine cyclization. The isolated yield of (−)-**16**[9] was 8.4% (10 steps; average yield/step 78%). Although continuation of this iterative process was highly tempting, we recognized that each iteration required increasingly more vigorous acidic conditions to effect hydrolysis of the dimethyl acetal.

To circumvent the need for acid-promoted liberation of the aldehyde functionality, we turned to a pyrrolinone system carrying a terminal prenyl substitutent [e.g., **9**]. As demonstrated in our solution syntheses of polypyrrolinones, the requisite aldehyde functionality for iterative pyrrolinone ring construction can be liberated via a two-step oxidation sequence (Scheme 3).[1d] Toward this end, treatment of resin-

Scheme 3



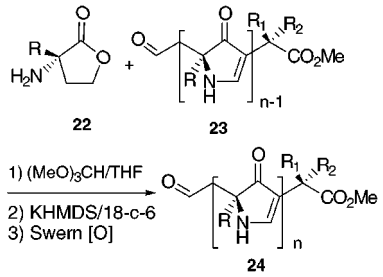
(a) OsO_4, NMO; (b) $NaIO_4$; (c) (-)-**12**, $(MeO)_3CH$/THF, 2 treatments; (d) KHMDS; (e) TBAF; (f) $PhCH_2CH_2CHO$, $(MeO)_3CH$/THF, 2 treatments.

bound pyrrolinone **9** with a catalytic amount of OsO_4 in the presence of NMO furnished diol **18**.[10] Interestingly, this transformation was marked by a reversible (vide infra) color change of the resin from golden brown to dark purple. We speculate that the dark color results from a residual osmium-containing species derived from the resin. The infrared spectrum of **18** also indicated partial oxidation of the polystyrene resin. The diol was next oxidized with $NaIO_4$ to give aldehyde **14**, which was removed from the resin, again employing hydrocinnamaldehyde; trispyrrolinone (−)-**16** was isolated in a 9.1% overall yield (11 steps). Interestingly, the color of the resin slowly returned to golden brown during this reaction sequence.

Although the two-step oxidation protocol permitted the solid-support construction of trispyrrolinone (−)-**16**, the sequence failed during the next iteration. In this case, the resin remained black through out the sequence. Attempts to remove residual osmium species by washing **19** with DMSO solutions saturated with ligands known to complex with osmium, such as KCN,[11] KSCN, and NH_3, failed to return the resin color to golden brown.[12]

Recognizing the difficulties associated with both strong acid hydrolysis and $OsO_4/NaIO_4$ oxidations, we developed the aminolactone-based strategy reported in the preceding Letter.[13] This sequence features imine formation using α-aminolactone building blocks, followed by metalloimine cyclization and Swern oxidation (Scheme 4).

Scheme 4



To explore this strategy on solid support, we selected tetrapyrrolinone (−)-**21** as our target. Toward this end, imine formation between resin-bound aminoaldehyde **8** with aminolactone (−)-**26** followed by cyclization promoted by KHMDS in the presence of 18-crown-6 furnished hydroxy pyrrolinone **25** bound to the resin (Scheme 5). Subsequent Swern oxidation[14] resulted in aldehyde **14**. Repetition of the pyrrolinone ring formation sequence first with amino ester

(9) 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.

(10) de Bont, D. B. A.; Moree, W. J.; Liskamp, R. M. J. *Bioorg. Med. Chem.* **1996**, *4*, 667.

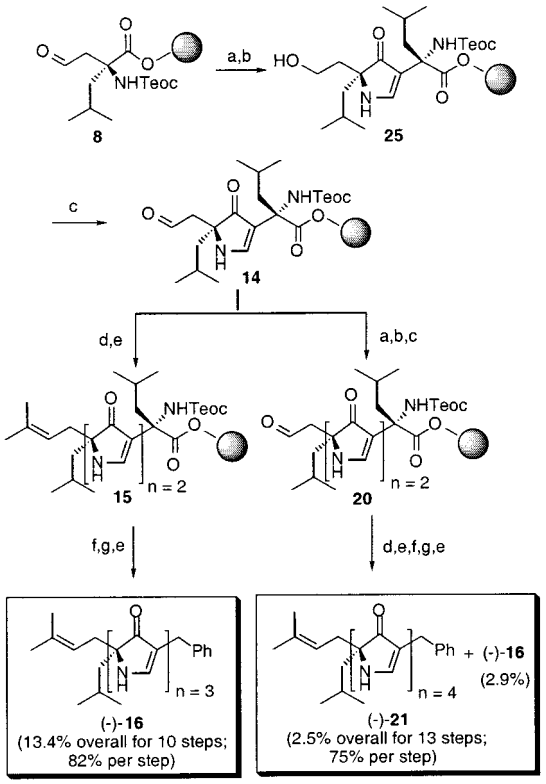
(11) Due to the high toxicity of DMSO solutions of KCN, extreme caution should be taken.

(12) Greenwood, N. N.; Earnshaw, A. In *Chemistry of The Elements*; Pergamon Press: Cambridge, 1984.

(13) Smith, A. B., III; Liu, H.; Hirschmann, R. *Org. Lett.* **2000**, *2*, 2037−2040.

(14) (a) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651. (b) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

Scheme 5



(a) (-)-**26**, $(MeO)_3CH$/THF, 2 treatments; (b) KHMDS/18-c-6; (c) $(COCl)_2$/DMSO, DBU; -78 °C; (d) (-)-**12**, $(MeO)_3CH$/THF, 2 treatments; (e) KHMDS; (f) i) CsF/DMF, ii) TBAF; (g) $PhCH_2CH_2CHO$, $(MeO)_3CH$/THF, 2 treatments.

(-)-**26**

(−)-**12** and then with hydrocinnamaldehyde provided trispyrrolinone (−)-**16** in 13.4% isolated yield (10 steps; average yield/step 82%). It is noteworthy that this yield is higher than both those obtained from the dimethyl acetal (8.4%) and the $OsO_4/NaIO_4$ oxidation (9.1%) protocols (Schemes 2 and 3, respectively). Moreover, the aminolactone approach could be extended to tetrapyrrolinone (−)-**21**. Thus, beginning with resin-bound aldehyde **14**, three-step iterations respectively with (−)-**26**, (−)-**12**, and hydrocinnamaldehyde provided after chromatography tetrapyrrolinone (−)-**21** in 2.5% overall yield (13 steps), along with a 2.9% yield of trispyrrolinone (−)-**16**. Formation of (−)-**16** derives, we believe, via incomplete reactions of **14** to **20**.

In summary, a three-step iterative solid-support synthesis of polypyrrolinones has been developed. Current efforts are directed toward the further development of this protocol, as well as the design and synthesis of a variety of pyrrolinone libraries; progress with this venture will be reported in due course.

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Supporting Information Available: Spectroscopic and analytical data for (+)-**3**, **4**−**9**, **14**, **25**, (−)-**16**, and (−)-**21**, as well as experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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