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# Passerini Reaction−Amine Deprotection−Acyl Migration Peptide Assembly: Efficient Formal Synthesis of Cyclotheonamide C

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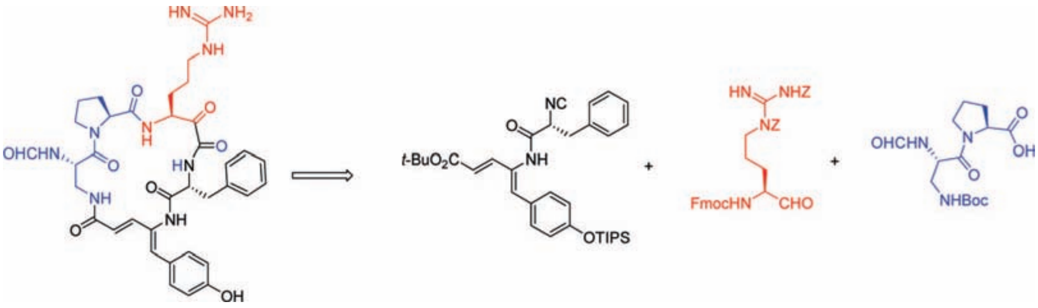
## ABSTRACT



**A short, convergent, formal total synthesis of cyclotheonamide C is described. The key linear pentapeptide intermediate is assembled at the same time as the elaboration of the α-hydroxyhomoarginine (H-hArg) residue via a three-component Passerini reaction−amine deprotection−*O,N*-acyl migration strategy.**

α-Hydroxyhomoamino acids (H-hXaa) and their oxidized counterparts α-ketohomoamino acids (K-hXaa) are present in natural products[1] and in synthetic, biologically active compounds, notably taxane anticancer agents[2] and protease inhibitors.[3] The α-ketohomoarginine (K-hArg) residue is a structural feature of each of the cyclotheonamides (Cts), a family of cyclic pentapeptides isolated from the marine sponges *Theonella swinhoei* and *Theonella ircinia*.[4] The Cts are potent inhibitors of serine proteases such as thrombin ($IC_{50} = 2.9{-}200$ nM),[4] and the highly electrophilic K-hArg plays a key role in the covalent attachment of Cts to the

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enzyme active site.[5] Due to their biological activity and their challenging molecular structure, the Ct family has attracted the attention of a number of research groups, and several total syntheses of CtA and/or CtB have been described.[6] In each case, the K-hArg feature was revealed in a late-stage oxidation of an α-hydroxyhomoarginine (H-hArg) residue which had been incorporated into a cyclic pentapeptide. As a result, the several-step preparation of an appropriately protected H-hArg residue was required upstream. A different approach was adopted by Wasserman in his total synthesis of CtE$_2$ and CtE$_3$ whereby the K-hArg feature was generated sooner in the synthetic sequence through use of α-ketocyanophosphorane amino acid intermediates.[7] We recently adapted this elegant approach for a total synthesis of CtC (**1**; Figure 1), revealing some limitations on the way.[8] Taking CtC as a representative target within the family, we have sought to develop convergent synthetic strategies which feature *simultaneous* peptide assembly and creation of the H-hArg (or K-hArg) residue; adopting this concept, we recently described the first total synthesis of CtC.[9]

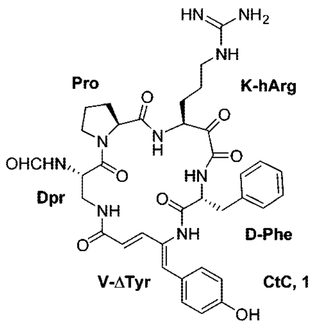
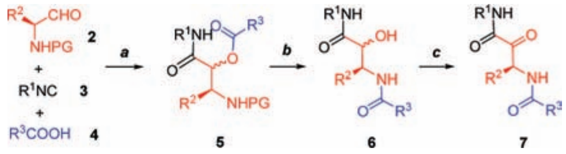


**Figure 1.** Molecular structure of cyclotheonamide C (CtC).

The Passerini three-component reaction (P-3CR)[10] has emerged as a powerful tool for establishing molecular complexity in a single step with optimal atom economy.[11] A potentially useful synthetic extension is the Passerini reaction−amine deprotection−acyl migration (PADAM) sequence, first conceived as a tool for combinatorial synthesis of peptidomimetics[12,13] (Scheme 1). This process involves reaction of an aldehyde **2**, an isonitrile **3**, and a carboxylic acid **4** to give the P-3CR α-acyloxyamide product **5**, whose *N*-terminal is then deprotected to induce *O*,*N*-migration of the acyl fragment to provide a H-hXaa-containing peptide **6**. Optional subsequent oxidation leads to the corresponding K-hXaa-peptide **7**. To date, only one application has been described in natural product synthesis, that of eurystatin A.[14,15] The use of this approach for the synthesis of cyclotheonamide-type fragments was at one stage considered, although no cyclic peptide assembly was ventured.[16]

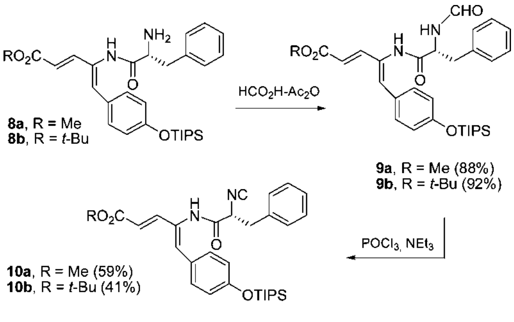
**Scheme 1.** PADAM Sequence[a]



[a] Key: (a) P-3CR; (b) amine deprotection, followed by *O*,*N*-acyl migration. Optionally, this sequence can be followed by an oxidation (c).

We reasoned that, with judicious choice of appropriately protected amino acid and peptide fragments, a PADAM strategy could be applied to the construction of complex linear pentapeptides and provide a concise access to CtC. The two dipeptide isonitriles **10a** and **10b** were obtained by formylation of the known[9,17] parent amines **8** followed by dehydration of the resulting formamides **9** (Scheme 2).

**Scheme 2.** Synthesis of Isonitriles **10a** and **10b**



The sensitive dehydration step was examined using several systems (Burgess' salt; triphosgene−NEt$_3$; POCl$_3$−NEt$_3$)[18]

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(13) An interesting related process involving acylcyanides in place of aldehydes has been described: Oaksmith, J. M.; Peters, U.; Ganem, B. *J. Am. Chem. Soc.* **2004**, *126*, 13606.

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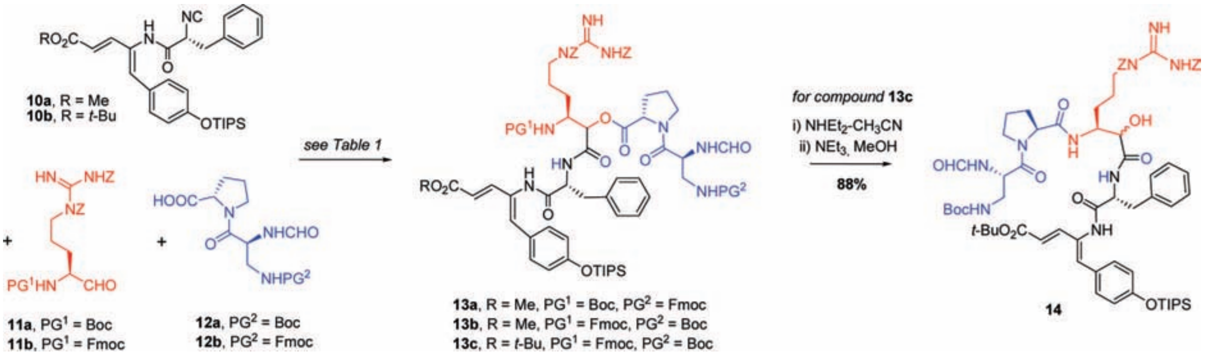
**Scheme 3.** Optimization of the P-3CR and Elaboration of Pentapeptide **14** Using the PADAM Sequence



to minimize degradation and racemization. The latter set of conditions gave the best results, allowing the isolation of the pure isonitriles in 52% and 38% yields for the two steps, respectively, without racemization.[19] The two amino aldehyde components **11a** and **11b**[9,20] and the two dipeptide acids **12a** and **12b**[8,21] (shown in Scheme 3) were obtained using previously reported methods.

With the appropriate reagents in hand, we focused our attention on the PADAM sequence, beginning with the study of the P-3CR construction of α-acyloxyamides **13** (Table 1). Bearing in mind that subsequent selective deprotection of the amine of the H-hArg residue was required in order to allow for the *O*,*N*-migration step of the PADAM sequence, the P-3CR involving isonitrile **10a** and the orthogonally protected duo Boc-amino aldehyde **11a** and Fmoc-dipeptide acid **12b** was tested first. Unfortunately, the desired pentadepsipeptide **13a** was never formed; only starting materials were recovered from reactions conducted under typical P-3CR conditions (Table 1, entry 1). This problem could be overcome by simple inversion of the protecting group ensemble. The P-3CR between Fmoc-amino aldehyde **11b** and Boc-dipeptide acid **12a** furnished the desired pentadepsipeptide **13b** in 57% yield (entry 2).[22] It was noteworthy that the excess of aldehyde and/or acid partner did not improve the reaction (entry 3). While the isolation of **13b** was a significant achievement, in that it demonstrated that P-3CR assembly of pentadepsipeptides was possible, we desired a protecting group suite which would allow a subsequent one-step *N*/*C*-termini deprotection protocol for macrocyclization. This objective was achieved by preparing the pentadepsipeptide **13c** from isonitrile **10b**, Fmoc-amino aldehyde **11b**, and Boc-dipeptide acid **12a** in an acceptable 44% yield (entry 4).[22] Use of a purified isonitrile **10b** sample proved to be vital, since the employment of crude dipeptide drastically decreased the yield of **13c** (entry 5).

**Table 1.** P-3CR Preparation of Depsipeptides **13** in Scheme 3[a]

| entry | **10**[b] | **11** (equiv) | **12** (equiv) | product | yield (%) |
|---|---|---|---|---|---|
| 1 | **10a** | **11a** (1.2) | **12b** (1.2) | **13a** | 0 |
| 2 | **10a** | **11b** (1.2) | **12a** (1.2) | **13b** | 57 |
| 3 | **10a** | **11b** (2.3) | **12a** (2.3) | **13b** | 53 |
| 4 | **10b** | **11b** (1.2) | **12a** (1.2) | **13c** | 44 |
| 5 | **10b**[c] | **11b** (1.2) | **12a** (1.2) | **13c** | 13 |

[a] Standard conditions: 0.02 M solution of **10**, $CH_2Cl_2$ + trace of DMF, rt, 3−6 days. [b] 1 equiv of isonitrile was used in each case. [c] Crude material was used.

Selective Fmoc deprotection of the pentadepsipeptide **13c** using diethylamine at 0 °C followed by *O*,*N*-dipeptide migration induced by treatment with triethylamine at room temperature provided the key linear pentapeptide **14** in 88% yield (Scheme 3). The transacylation step might conceivably have taken place during the Fmoc deprotection step, but to ensure its completion, the crude deprotected material was subjected to the reported transacylation conditions.[12,16,23] In this way, we successfully created the H-hArg feature within a complex linear pentapeptide, which represents the most elaborate use of the PADAM strategy to date.

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(15) The *O*,*N*-acyl migration in an *O*-acyl isopeptide has been exploited for the synthesis of an amyloid β-peptide, see: Skwarczynski, M.; Kiso, Y. *Curr. Med. Chem.* **2007**, *14*, 2813, and references cited therein.

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(19) In related work (unpublished), racemization occurred during the preparation of the ester isonitrile from enantiomerically pure L-*N*-formyl-Phe-OMe in our hands; for similar problems, see: Bon, R. S.; Hong, C.; Bouma, M. J.; Schmitz, R. F.; De Kanter, F. J. J.; Lutz, M.; Spek, A. L.; Orru, R. V. A. *Org. Lett.* **2003**, *5*, 3759. We therefore verified that no such problems arose for amide isonitriles, such as **10a** and **10b**, using a known model amide isonitrile. See the Supporting Information for details.

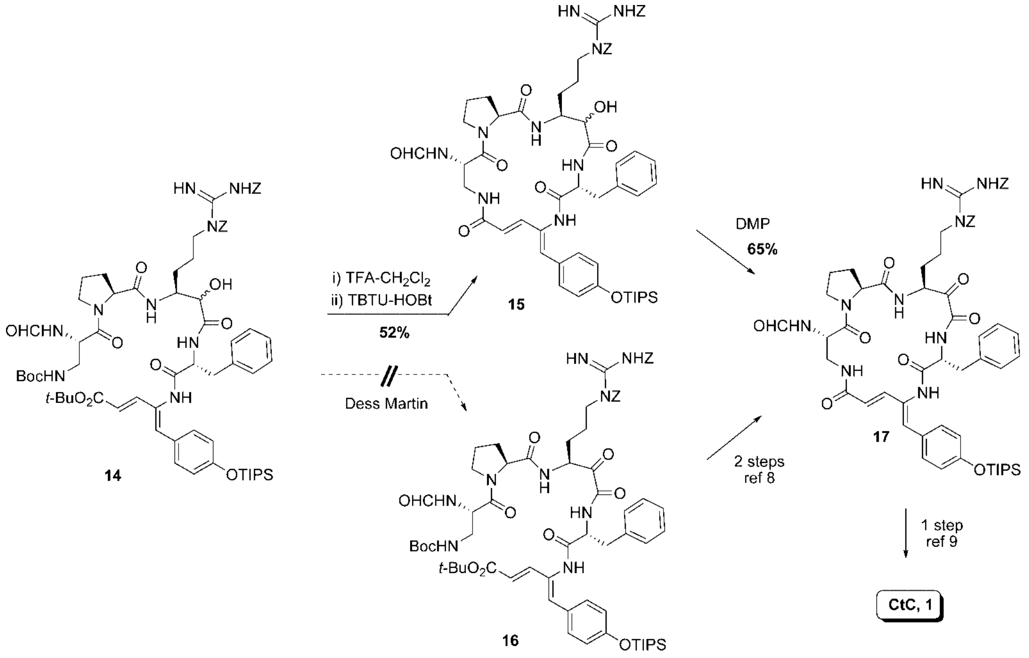
(20) Review: Gryko, D.; Chalko, J.; Jurczak, J. *Chirality* **2003**, *15*, 514.

(21) Waki, M.; Kitajima, Y.; Izumiya, N. *Synthesis* **1981**, 266.

(22) The P-3CR is sometimes diastereoselective; however, in our case, it was difficult to estimate dr values for depsipeptides **13b** (no clear component separation on NMR or HPLC analyses) and **13c**, although for the latter an estimated dr of ∼2:1 can be deduced from $^1$H NMR spectral analysis. Subsequent analysis of product **15**, derived from **13c**, confirmed that the dr was low (vide infra). For an enantioselective catalytic P-3CR and leading references on diastereoselective P-3CR, see: Wang, S.-X.; Wang, M.-X.; Wang, D.-X.; Zhu, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 388.

(23) This transformation proved to be difficult to monitor by TLC (identical $R_f$ values) and $^1$H NMR (presence of diastereoisomers and rotamers).

**Scheme 4.** Formal Synthesis of Cyclotheonamide C from the PADAM Pentapeptide **14**



The acquisition of pentapeptide **14** offered an opportunity to establish the importance of the order of events en route to the advanced cyclic peptide **17**, a known one-step precursor of CtC.[9] Simultaneous *N*/*C* termini deprotection of pentapeptide **14** was achieved using trifluoroacetic acid, and macrocyclization was achieved using TBTU/HOBt to provide the cyclic pentapeptide **15** in 52% yield (Scheme 4). Comparison of analytical data of **15** with those previously obtained by us for this compound[9] indicated a 65:35 mixture of two diastereomers (see the Supporting Information for details), undoubtedly the result of limited diastereoselectivity in the P-3CR formation of **13c**. This was of no consequence for the achievement of our objectives, however, since the stereogenic center in question becomes an sp$^2$ carbon in the target molecule. Indeed, oxidation of the H-hArg residue of **15** with DMP gave the CtC precursor **17** as a single stereoisomer with spectral and physical data identical to those previously described.[8,9] Significantly, the alternative transformation of linear H-hArg pentapeptide **14** into **17** failed (Scheme 3): attempted oxidation of **14** using DMP provided none of the desired compound **16**, a two-step precursor of **17**.[8] In conditions which had been successful for the conversion of **15** into **17**, starting material **14** was recovered unreacted while under more drastic conditions (excess oxidizing agent; longer reaction times) degradation was observed.

In conclusion, in this original approach to the synthesis of CtC, we have demonstrated the unprecedented utility of the PADAM strategy for the successful assembly of a complex pentapeptide intermediate from simple precursors and the simultaneous creation of a masked K-hArg moiety within it. This third (formal) total synthesis of CtC underlines the value of retaining a masked K-hArg as long as possible in the synthetic sequence and is the most convergent to date.

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**Supporting Information Available:** Full experimental procedures, characterization data, and copies of NMR spectra for all significant products; details of model compound study to confirm no racemization. This material is available free of charge via the Internet at http://pubs.acs.org.

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