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AN APPROACH TOWARD THE TOTAL SYNTHESIS OF CYCLOTHEONAMIDES; PREPARATION OF A C(1) TO N(14) SEGMENT

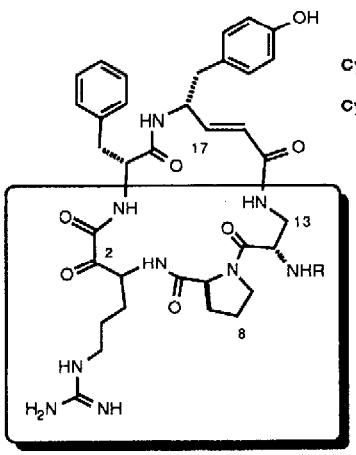
Peter Wipf* and Hong-Yong Kim

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260, U.S.A.

Abstract: The C(1) to N(14) segment of the potent thrombin inhibitor cyclotheonamide A was prepared from L-arginine, L-proline, and L-asparagine. The arginine backbone was extended via a cyanohydrin, and the unusual diaminopropanoic acid residue was obtained from hypervalent iodine oxidation of the asparagine side chain.

Serine proteases are involved in a large number of degradative diseases and malfunctions. Therefore, the development of potent and specific inhibitors of these enzymes has become an area of great interest. The study of the mode of action of mechanism-based inhibitors of serine proteases can provide important models on which the design of new classes of drugs can be based.[1] Cyclotheonamides, recently isolated secondary metabolites from marine sponges of the genus *Theonella*, are potent and selective inhibitors of the serine protease thrombin.[2,3] A long-term goal of our research program is the development of non-peptidic mimetics of biologically important peptides. The cyclotheonamides are particularly well suited as an extension of this study because they combine the relative rigidity of a cyclopentapeptide skeleton with the presence of various already modified, non-proteinogenic amino acids. Lipophilic cyclic peptides offer attractive novel lead structures for selective enzyme inhibition.

The synthetic plan for the total synthesis of cyclotheonamide A is outlined in Scheme I. Besides Pro, D-Phe and 2,3-diaminopropanoic acid (3-aminoalanine, Dpr), the cyclopeptide contains two so far unknown[4] amino acid residues, an α-keto arginine (= Kar)[5] and a vinylogous tyrosine derivative (= D-Vty). This modular synthetic approach will enable the straightforward preparation of analog structures by combination of modified segments with regular ones.



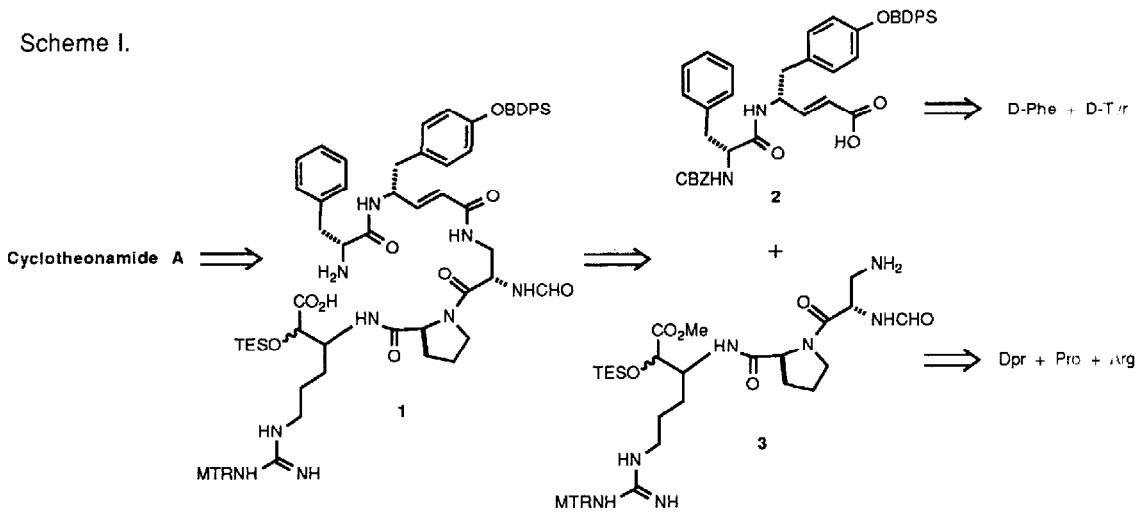
Cyclotheonamide A, R=CHO

Cyclotheonamide B, R=Ac

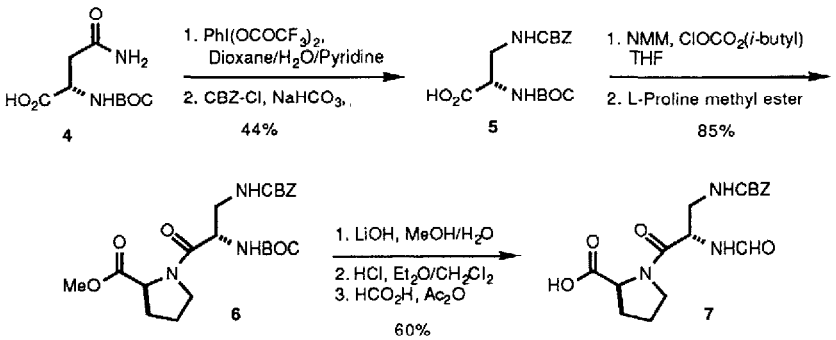
Our attention focused at first on the synthesis of tripeptide segment **3** (Scheme II). Hofmann-type reaction of N-*tert*-butyloxycarbonyl (BOC) protected L-asparagine (**4**) with bis[trifluoroacetoxy]-iodobenzene,[6] followed by acylation with benzylchloroformate (CBZ-Cl), gave bisprotected diaminopropanoic acid **5** in moderate yield.[7,8] Subsequent condensation of the mixed anhydride of acid **5** and isobutylchloroformate with proline methyl ester under Anderson's conditions[9] yielded

dipeptide **6**. Ester hydrolysis was follwed by exchange of BOC with the desired formyl group. Introduction of the formyl group at earlier stages in the synthesis caused problems due to the relatively high hydrophilicity of the formylated species.

Scheme I.



Scheme II.

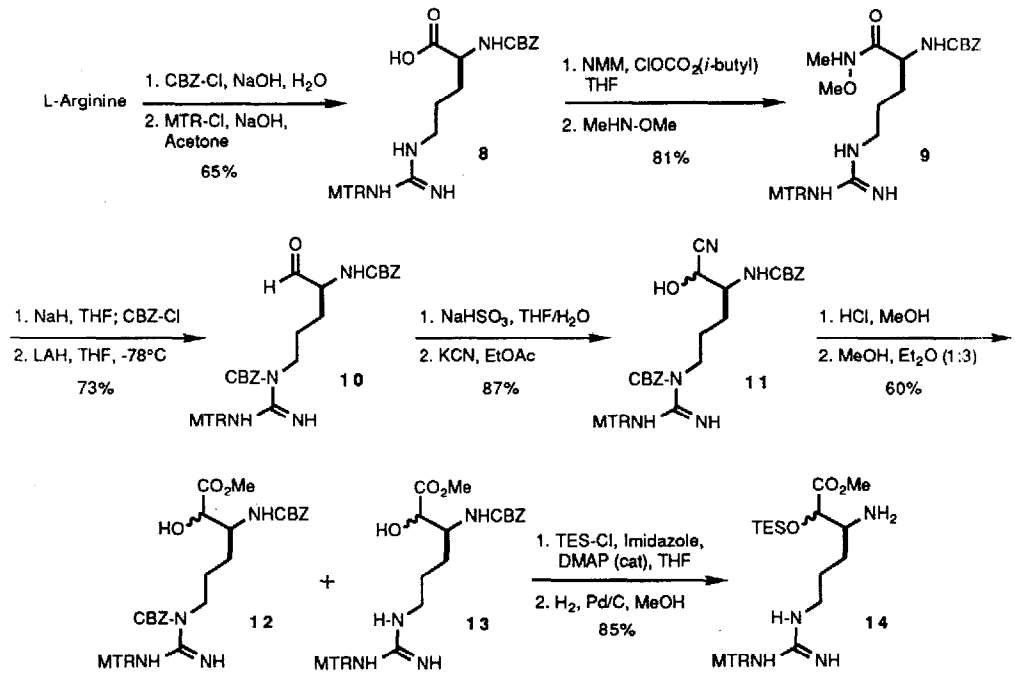


For the preparation of the novel α-keto arginine (Kar) residue in cyclotheonamides,[10] the guanidino function of L-arginine was protected as the 4-methoxy-2,3,6,-trimethylbenzenesulfonyl (MTR)[11] derivative by treatment of N_α-CBZ-Arg-OH with MTR-Cl and aqueous base (Scheme III). Activation of N_α-CBZ-N_ω-MTR-Arg-OH (**8**) with isobutylchloroformate and N-methyl morpholine (NMM) was followed by condensation with N,O-dimethylhydroxylamine. Further protection of the side-chain functionality was necessary at this point, because intramolecular cyclization of the corresponding mono-protected aldehyde **15** to piperidine **16** prevented the planned one carbon chain extension (Scheme IV).[12] The N_α,N_ε-CBZ-N_ω-MTR protected arginine derivative was reduced with lithium aluminum hydride (LAH) to provide amino aldehyde **10**,[13,14,15] which was immediately converted to the corresponding bisulfite adduct without purification. Treatment with potassium cyanide provided cyanohydrin **11** in high overall yield.[16]

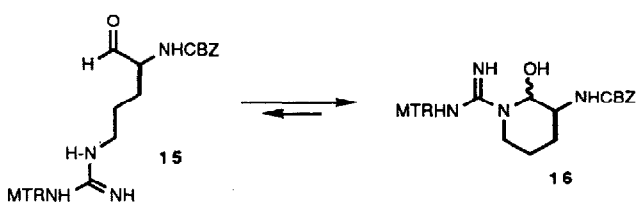
Due to partial N_ε-deprotection, solvolysis with methanolic hydrogen chloride[17] gave a mixture of α-hydroxy esters **12** (major isomers) and **13** (minor isomers). The diastereoselectivity of

this one carbon homologation depended on the reaction conditions and varied from 1 : 1 to better than 3 : 1. Silylation of the secondary alcohol, followed by hydrogenolytic removal of the CBZ groups led to amine **14** in 85% yield. Segment condensation was initiated by conversion of acid **7** into the corresponding mixed anhydride (Scheme V). Addition of amine **14** led to the isolation of tripeptide **17** in 80% yield.

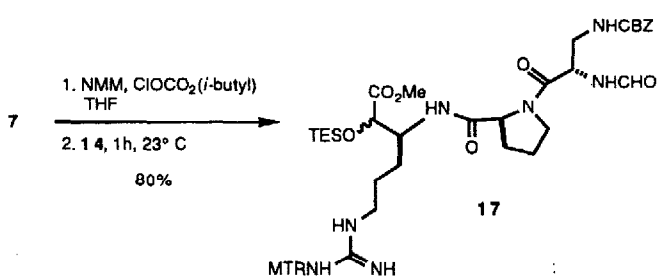
Scheme III.



Scheme IV.



Scheme V.



In summary, the C(1) to N(14) segment of the potent thrombin inhibitor cyclotheonamide A was prepared in good overall yield from readily available starting materials.[18] Key steps include an extension of the arginine backbone via a cyanohydrin, the preparation of the unusual diaminopropanoic acid residue by hypervalent iodine oxidation and the application of mixed anhydrides for the coupling of the subunits. Further progress toward the total synthesis of cyclotheonamides will be reported in due course.

Acknowledgment is made to the donors of The Petroleum Research Fund, administered by the ACS, and to the Central Research Development Fund of the University of Pittsburgh for partial support of this research.

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