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Total synthesis of cyclotheonamides E_2 and E_3: application of cyano ylide methodology

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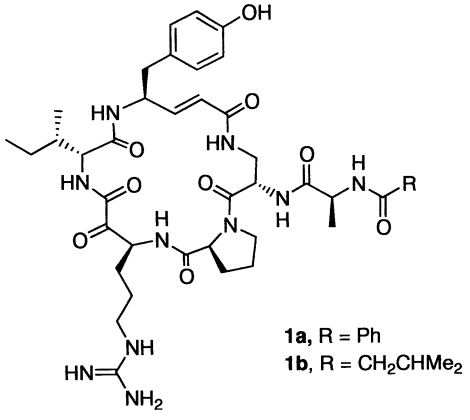
Abstract—A total synthesis of cyclotheonamides E_2 and E_3 is reported. A key step in the synthesis involves the formation of the α-keto amide linkage by application of the cyano ylide activation of a carboxyl group as developed in our earlier syntheses of cyclic peptides in the family of protease inhibitors.

The cyclotheonamides (A, B, C, D, E), recently isolated from marine sources, are a family of cyclic pentapeptides which show notable activity as inhibitors of serine proteases.[1,2] Because of their biological properties and unusual structural features, considerable attention has been given to the study of the mode of enzyme inhibition and synthesis of these macrocyclic α-keto lactams. Total syntheses of cyclotheonamides A and B have been reported[2] by Schreiber, Maryanoff, Wipf, Ottenheijm and Shioiri.



1a, R = Ph
1b, R = CH_2CHMe_2

Adding to the interest in this area has been the recent isolation of two new members of the family, cyclotheonamides E_2 (**1a**) and E_3 (**1b**),[1b] which contain most of the elements of cyclotheonamides A and B, except for the presence of a D-alloisoleucine residue in the place of D-phenylalanine, and side chains containing benzoylalanine and isovalerylalanine residues. A unique functional unit in all cyclotheonamides is associated with the extra carbonyl α to the amide linkage in the arginine residue. It has been suggested that this active carbonyl group is involved in the deactivation of a protease by serving as an enzyme transition state analogue.[2b] It is also noteworthy that the cyclotheonamides have structural features similar to those of the immunosuppressants bearing α-keto amide functions such as FK-506 and rapamycin.[3]

We now report the first synthesis of cyclotheonamides E_2 and E_3. In this work, the cyano ylide methodology is employed in activating the arginine carboxyl group for amide bond formation, with the concomitant introduction of a carbonyl group α to the amide group.[4] A number of the steps in our synthesis make use of protecting groups in common with the procedures published in the early synthetic work. However, our strategy has unique features which should be of considerable value in future syntheses of compounds in this family. In particular, the formation of the relatively robust α-keto amide at an early stage of the synthesis avoids problems in earlier syntheses associated with α-hydroxy precursors generated en route to the α-keto amide residue. It precludes the necessity for carrying a mixture of diastereomers through subsequent steps in the synthesis, as well as the protection of the hydroxyl group needed to avoid the possibility of competing intramolecular lactone formation. Overall, the simplicity of forming the α-keto amide residue using the cyano ylide activation procedure avoids the extra steps needed to generate, protect, deprotect and oxidize an alcohol intermediate to the α-keto function.[5,6]

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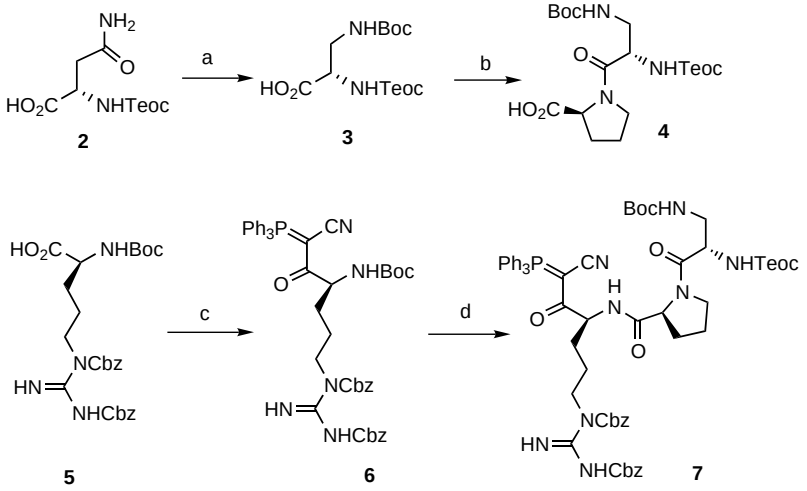
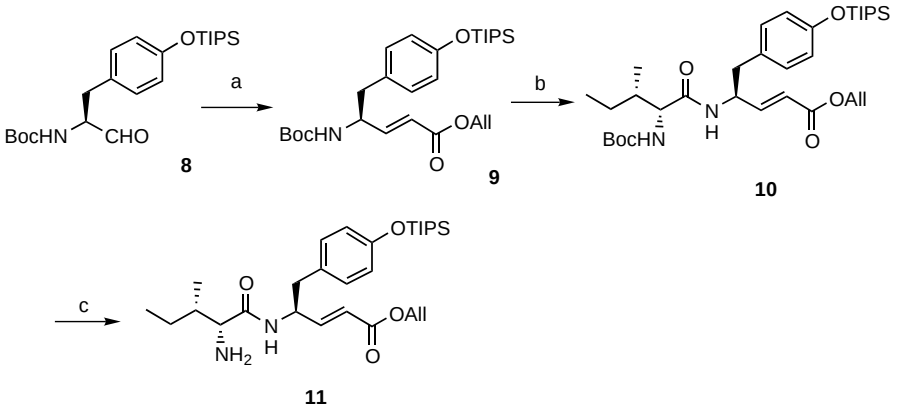
Our synthesis began with the formation of the tripeptide from arginine, proline and diaminopropionic acid (Scheme 1). The latter acid, formed by a Curtius-type degradation of Teoc-aspargine (**2**)[7] using bis(trifluoroacetyl) iodobenzene (TIB), was then converted to the *N*-Boc derivative **3**. The acid **3** was then coupled (EDCl) with proline benzyl ester to form the protected dipeptide which, on hydrogenation (Pd–C), yielded **4**. In a separate pathway, the ylide **6** was prepared from arginine having a Boc-protected amino group, and a doubly Cbz-protected guanidino residue (**5**).[8] Reaction of **5** with (triphenylphosphoranylidine)acetonitrile yielded the acyl cyano ylide **6** (86%).[4a] TFA removal of the Boc group from **6** then yielded the free amine for coupling with **4** (EDCI, HOBt) to form the tripeptide **7** (78%).

To continue the synthesis, L-Boc-tyrosine methyl ester was converted to the TIPS derivative,[9] and then reduced with DIBALH to the aldehyde **8**. A Wittig reaction of **8** with allyl (triphenylphosphoranylidine)-acetate (Scheme 2) yielded the allyl-protected α,β-unsaturated ester **9** which, on treatment with TFA and coupling (EDCl, HOBt, Et_3N) with D-Boc-alloisoleucine gave the dipeptide **10** containing a vinylogous tyrosine. Removal of the Boc group yielded **11** for reaction in the next stage with **7**.

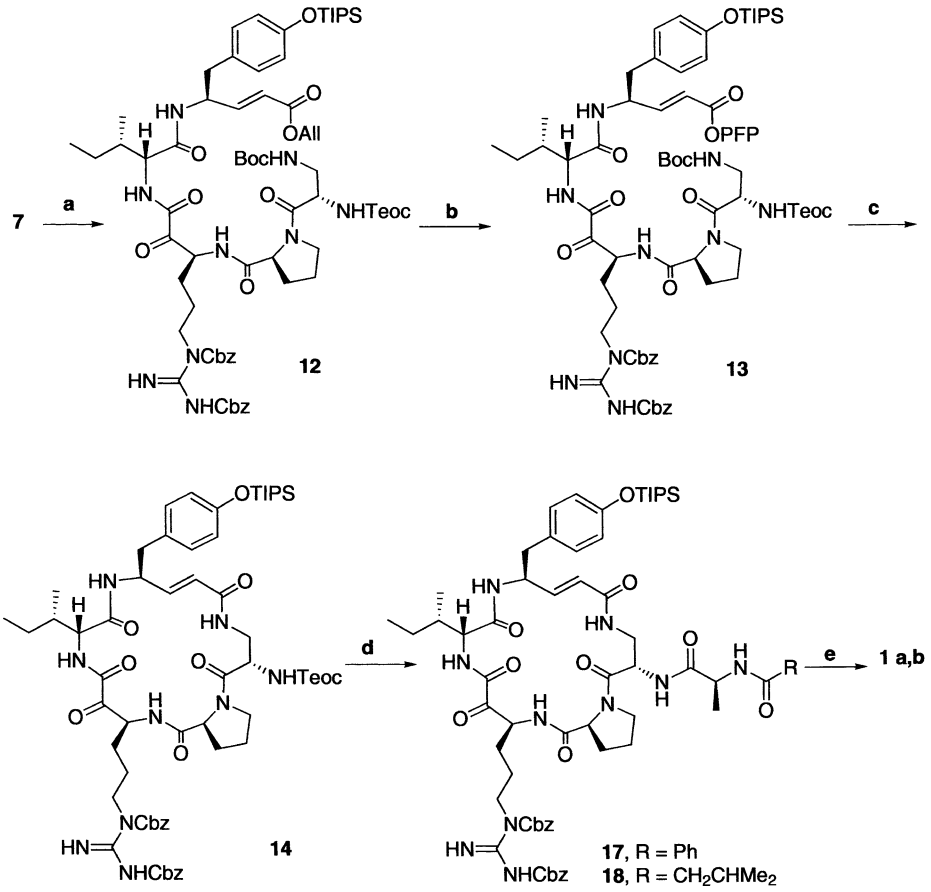
Tripeptide (**7**) was now ozonized to generate the strongly electrophilic α,β-diketonitrile intermediate, not isolable, which formed an amide bond with **11** to yield the pentapeptide **12** (75%) (Scheme 3). At this point in the synthesis, we found it expedient to change the allyl protecting group to a pentafluoro phenoxy group for enhanced activation of the ester. This was readily accomplished, first by the use of Pd^0 to regenerate the carboxyl group (86%)[10] and then DCC-promoted coupling with pentafluorophenol (PFPOH) yielding **13** (88%).[11] For the ring closure of **13** to **14**, we first selectively cleaved the Boc group with HCl in Et_2O–CH_2Cl_2 in the presence of the acid-labile Teoc group[12] and we then carried out lactam formation with DMAP, $NaHCO_3$ (61%). The removal of the Teoc protecting group to yield **17** and **18** took place with TFA, permitting the installation of side chains (EDCl, HOBt) with *N*-benzoylalanine (**15**) to yield **17** and isovaleryalanine (**16**), forming **18**.



Scheme 1. *Reagents and conditions*: (a) TIB, Py; then Boc_2O, NaOH, 77%; (b) EDCI, HOBt, Pro-OBn, 88%; then Pd–C, H_2, 100%; (c) EDCI, DMAP, Ph_3P=CHCN, 86%; (d) TFA; then EDCI, HOBt, **4**, 78%.



Scheme 2. *Reagents and conditions*: (a) Ph_3P=$CHCO_2$All, 90%; (b) TFA; then EDCI, HOBt, Et_3N, D-Boc-alle, 85%; (c) TFA; then aq. $NaHCO_3$, 100%.



Scheme 3. *Reagents and conditions*: (a) O_3; then **11**, 75%; (b) $Pd(PPh_3)_4$, $PhSiH_3$, 86%; then DCC, PFP-OH, 88%; (c) (1) HCl in Et_2O–CH_2Cl_2; then DMAP, $NaHCO_3$, 61%; (d) TFA; then aq. $NaHCO_3$, (2) EDCI, HOBt, **15** or **16**, 83–85%; (e) HF·Py, 70–72%.

The Cbz and TIPS protecting groups in **17** and **18** were then removed smoothly with HF·Py, yielding synthetic cyclotheonamides E_2 (**1a**) and E_3 (**1b**), which were fully characterized by HRMS, ^1H and ^{13}C NMR. The NMR spectra of **1a** and **1b** were identical in all significant respects with the corresponding spectra of the natural materials, kindly sent to us by Professors Fusetani and Nakao.

Supporting information available. Spectroscopic and analytical data as well as experimental procedures for compounds **1**–**18**. See any current masthead page for ordering and Internet access information.

Acknowledgements

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References

1. (a) Nakao, Y.; Oku, N.; Matsunaga, S.; Fusetani, N. *J. Nat. Prod.* **1998**, *61*, 667–670; (b) Fusetani, N.; Matsunaga, S.; Matsumoto, H.; Takebayashi, H. *J. Am. Chem. Soc.* **1990**, *112*, 7053–7056.
2. (a) Hagihara, M.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 6570–6571; (b) Maryanoff, B. E.; Greco, M. N.; Zhang, H.-C.; Andrade-Gordon, P.; Kauffman, J. A.; Nicolaou, K. C.; Liu, A.; Brungs, P. H. *J. Am. Chem. Soc.* **1995**, *117*, 1225–1239; (c) Wipf, P.; Kim, H. *J. Org. Chem.* **1993**, *58*, 5592–5594; (d) Bastiaans, H. M. M.; Van der Baan, J.; Ottenheijm, H. C. J. *J. Org. Chem.* **1997**, *62*, 3880–3889; (e) Deng, J.; Hamada, Y.; Shioiri, T.; Matsunaga, S.; Fusetani, N. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1729–1731.
3. Schreiber, S. L.; Crabtree, G. R. *Immunol. Today* **1992**, *13*, 136–142.
4. (a) Wasserman, H. H.; Ho, W.-B. *J. Org. Chem.* **1994**, *59*, 4364–4366; (b) Wasserman, H. H.; Petersen, A. K. *Tetrahedron Lett.* **1997**, *38*, 953–956; (c) Wasserman, H. H.; Petersen, A. K. *J. Org. Chem.* **1997**, *62*, 8972–8973.
5. Matsuura, S.; Niu, C.-H.; Cohen, J. S. *Chem. Commun.* **1976**, 451–452.
6. An additional difference between our synthesis and earlier work lies in the final macrolactamization site. In contrast to the other synthetic routes, the ring closure in

our sequence took place between the NH terminus of the diaminopropionic acid residue and the carboxyl group of the α,β-vinylogous tyrosine. Di-Cbz protection of the guanidine residue provided excellent protection throughout the sequence and permitted easy removal at the last stage with HF·Py and anisole (70–72%).[5] As outlined, all steps were accomplished in good to excellent yields.

7. Waki, M.; Kitajima, Y.; Izumiya, N. *Synthesis* **1981**, 266–268.
8. Jetten, M.; Peters, C. A. M.; van Nispen, J. W. F. M.; Ottenheijm, H. C. J. *Tetrahedron Lett*. **1991**, *32*, 6025–6028.
9. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc*. **1972**, *94*, 6190–6191.
10. Dessolin, M.; Guillerez, M.-G.; Thieriet, N.; Guibe, F.; Loffet, A. *Tetrahedron Lett*. **1995**, *36*, 5741–5744.
11. Schmidt, U.; Lieberknecht, A.; Griesser, H.; Talbiersky, J. *J. Org. Chem*. **1982**, *47*, 3261–3264.
12. Carpino, L. A.; Tsao, J.-H. *Chem. Commun*. **1978**, 358–359.