Pergamon

Tetrahedron Letters, Vol. 37, No. 13, pp. 2261-2264, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00270-5

A New Synthesis of Cyclotheonamide B via Guanidination of Ornithine

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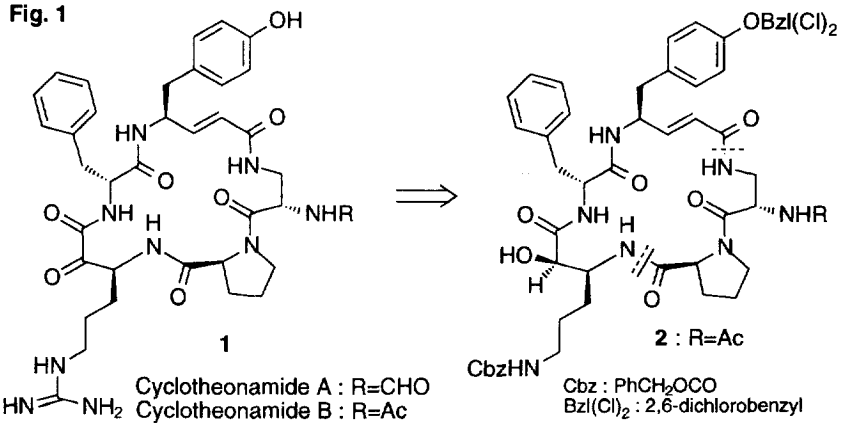
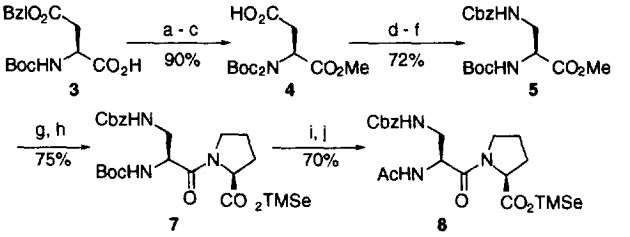
Abstract: A macrocyclic thrombin inhibitor, cyclotheonamide B (**1**, R=Ac) was synthesized via a new approach: guanidination of the ornithine-containing macrocyclic peptide (**2**). In comparison of various coupling reagents, pentafluorophenyl diphenylphosphinate (FDPP) gave the macrocyclic peptide (**2**) in good yield, and the configuration of the amino acid residue has been revealed to be important for the macrolactamization.

Cyclotheonamides (**1**, A: R=CHO; B: R=Ac) isolated from a marine sponge *Theonella* strongly inhibit various proteinases, particularly thrombin, and are the first macrocyclic thrombin inhibitors having two novel amino acid residues: a vinylogous tyrosine and α-keto homolog of arginine (Fig. 1).[1] Their structural uniqueness as well as their inhibitory activities have prompted us[2] and other groups to study these compounds.[3-5] In the synthesis of arginine-containing peptides, a side reaction (the ornithine formation) is often encountered.[6,7] Arylsulfonyl protection of the guanidino function in arginine has proved useful to prevent the ornithine formation. However, side reactions with some amino acid residues are unavoidable during deprotection of peptides with strongly acidolytic conditions.[6,8] The possibility of preparing arginine-containing peptides by guanidination of the δ-amino groups of the appropriate ornithine-containing precursors has long been recognized.[9] Such a strategy is attractive for its potential to eliminate the many problems associated with the use of conventionally protected arginine starting materials in peptide synthesis.[10] We report here a new approach for the synthesis of cyclotheonamide B (**1**, R=Ac) via the guanidination of the ornithine-containing macrocyclic peptide (**2**).[3d]

Fig. 1



N-Bis-(*tert*-butyloxycarbonyl(Boc))aspartic acid α-methyl ester (**4**), prepared from N^{α}-Boc-aspartic acid β-benzyl ester (**3**), underwent the modified Curtius reaction with diphenyl phosphorazidate (DPPA, $(C_6H_5O)_2P(O)N_3$)[11] to give N^{α}-Boc-N^{β}-Cbz-*L*-diaminopropanoic acid methyl ester (**5**)[12] after deprotection and protection at the α-amino group. Deprotection at the α-caboxyl function followed by condensation with the p-toluenesulfonate salt of *L*-proline trimethylsilylethyl(TMSe) ester (**6**) by use of diethyl phosphorocyanidate (DEPC, $(C_2H_5O)_2P(O)CN$) afforded the dipeptide (**7**). The required dipeptide fragment (**8**) was conveniently prepared by deprotection of the Boc group and subsequent acetylation (Scheme 1).



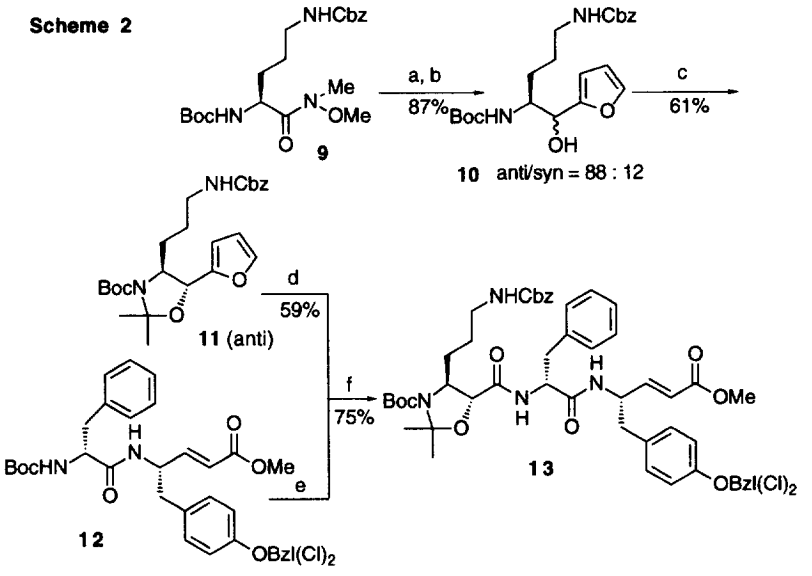
Scheme 1 Boc : Bu^{t}OCO; TMSe : $Me_3SiCH_2CH_2$

a) MeI, $KHCO_3$, DMF, 0°C, 3 h, r.t., 4 h. b) Boc_2O, 4-dimethylaminopyridine, MeCN, r.t., 5.5 h. c) H_2, 5% Pd-C, MeOH, r.t., 45 min. d) DPPA, Et_3N, benzene, r.t., 45 min, reflux, 45 min; then benzyl alcohol, reflux, 17 h. e) 4N HCl-dioxane, 0°C, 1.5 h. f) Boc_2O, Et_3N, CH_2Cl_2, r.t., overnight. g) LiOH, THF-H_2O (3:1), 0°C, 2 h. h) *L*-ProOTMSe·HOTs (**6**), DEPC, N-methylmorpholine, DMF, 0°C, overnight. i) CF_3CO_2H-CH_2Cl_2 (1:1), 0°C, 2 h. j) Ac_2O, Et_3N, CH_2Cl_2, 0°C, 2 h, r.t., overnight.

For the synthesis of the tripeptide fragment (**13**) containing the ornithine derivative (Scheme 2), a precursor of the α-keto homolog of arginine, the Weinreb amide of N^{α}-Boc-N^{δ}-Cbz-ornithine (**9**) was condensed with furyllithium, followed by reduction to afford a mixture of the β-amino alcohols (**10**, anti/syn 88:12). A kinetic resolution occurred during protection of the β-amino alcohols (**10**), and the anti-oxazolidine isomer (**11**) was obtained as a single isomer. The conversion of the furyl group of **11** to a carboxylate group was accomplished by RuO_4 oxidation.[13] The coupling of the resulting acid with the dipeptide derived from **12** which was prepared according to our previous procedure[2] produced the ornithine-containing tripeptide (**13**).

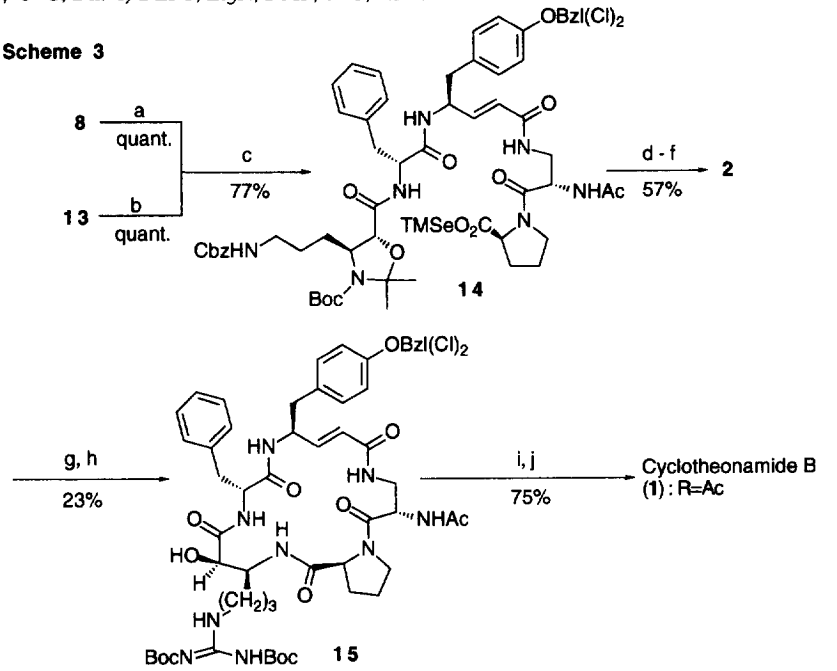
Deprotection of the dipeptide (**8**) at the N^{β}-position and the tripeptide (**13**) at the C-terminal, respectively, and subsequent coupling by use of DEPC gave the linear pentapeptide (**14**). Then, tetrabutylammonium fluoride and trifluoroacetic acid were used for the deprotection of the pentapeptide (**14**) at the C- and N-terminals, respectively. In the early stage of our work, we obtained the best result (42% yield) by using WSCI-HOBt for the cyclization of the analog of **14** in which vinylogous *L*-tyrosine was replaced by vinylogous *D*-tyrosine.[14] However, the macrocyclic peptide (**2**) was produced in low yield (16%) under the same cyclization conditions. The other coupling reagents (DPPA[15] and DEPC[15a,b]) also gave **2** in low yield (8% and 12%, respectively) even after extended reaction time (3.5 days). Moreover, the activated ester (pentafluorophenyl ester)[3a,15b] similarly resulted in 8% yield of **2**. Surprisingly, however, the cyclization of **14** proceeded in higher yield (43%) by using pentafluorophenyl diphenylphosphinate (FDPP, $(C_6H_5)_2P(O)OC_6F_5$)[16] for a shorter reaction time (4.5 h), and the optimum cyclization conditions (Scheme 3) gave **2** in 57% yield.[2,17] The cyclization seems to be enhanced by the appropriate conformation of the linear peptide in solution and the efficiency of the coupling reagents.[18] The cyclic peptide (**2**) was treated with 31% HBr-HOAc and subsequent guanidination with *N,N'*-di-(*tert*-butoxycarbonyl)thiourea[19] gave the arginine-containing macrocyclic peptide (**15**, R=Bzl(Cl)$_2$). To our knowledge, this is the first example of selective deprotection of a Cbz group and benzyl type ether group with 31% HBr-HOAc.[20] Finally, oxidation of the α-hydroxy group with Dess-Martin periodinane, followed by *O,N*-deprotection, produced cyclotheonamide B (**1**, R=Ac) in 75% yield.[21]

Scheme 2



a) Furyllithium, THF, -78°C, 35 min. b) K-selectride, THF, -78°C, 30 min. c) 2,2-Dimethoxypropane, pyridine·*p*-TsOH, CH_2Cl_2, r.t., 60 h. d) $NaIO_4$, $RuCl_3$ (cat.), MeCN-EtOAc-H_2O (2:2:3), r.t., 1.5 h. e) 4 N HCl-dioxane, 0° C, 2 h. f) DEPC, Et_3N, DMF, 0 °C, 4.5 h.

Scheme 3



a) H_2, 5% Pd-C, MeOH, r.t., 45 min. b) LiOH, THF-H_2O (3:1), 0°C, 20 min, r.t., 4 h. c) DEPC (1.5 eq), Pr^i_2NEt (2.0 eq), DMF, 0°C, overnight. d) Bu_4NF, THF, 0°C, 3 h, r.t., 2 h. e) TsOH·H_2O (7 eq), CH_2Cl_2, r.t., 15 h. f) FDPP, Pr^i_2NEt, DMF, r.t.,14 h. g) 31% HBr-HOAc, r.t., 25 min. h) *N,N'*-Di-(*tert*-butoxycarbonyl)thiourea, $HgCl_2$, Et_3N, DMF, 0°C, 10 min, r.t., 0.5 h. i) Dess-Martin periodinane, MeCN-CH_2Cl_2 (1:2), 55°C, 7 h. j) CF_3CO_2H-thioanisole, r.t., 13 h, then HPLC purification.

This work will again show the superiority of FDPP for the macrolactamization[2,16,17] and the strategy adopted here can be applied to syntheses of other arginine-containing compounds.

Acknowledgements: This work was financially supported in part by the Ministry of Education, Science, Sports, and Culture, Japan. J. D. is grateful to the Japan Society for the Promotion of Science for a post-graduate fellowship.

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20. The product by Bzl($Cl)_2$-deprotection was also obtained in a 1.3:1 ratio of Bzl($Cl)_2$-protected and deprotected products. Fortunately, the Bzl($Cl)_2$-deprotected product can be converted to cyclotheonamide B (**1**, R=Ac) by selective silylation of the phenol group of the macrocyclic peptide (**14**, R=H), which is similar to the note 44a in ref 3c. Shorter treatment times with 31% HBr-HOAc can enhance the ratios of Bzl($Cl)_2$-protected and deprotected products, but the chemical yield of the protected macrocyclic peptide (**15**, R=Bzl($Cl)_2$) is not improved.
21. Cyclotheonamide B (**1**, R=Ac) is identical to the authetic sample by HPLC, 500 MHz ^{1}H-NMR, and FAB-MS comparisons.

(*Received in Japan* 8 *January* 1996; *revised* 5 *February* 1996; *accepted* 8 *February* 1996)