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Intramolecular *Michael-Addition-induced* Z→E Isomerization of *Horner-Emmons* Reaction Products during the Synthesis of the N(14)-C(18) Subunit of Cyclotheonamide A

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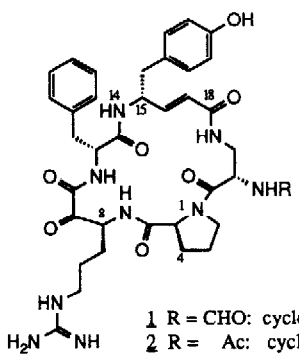
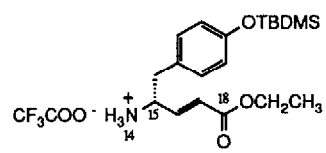
Abstract: The protected N(14) to C(18) amino acid subunit 3 of cyclotheonamide A (1) has been stereoselectively prepared via *Horner-Emmons* reaction followed by a novel intramolecular *Michael-Addition*-induced $Z \rightarrow E$ isomerization of the α,β-unsaturated carboxylic ester 8.

The novel 19-membered cyclic peptides cyclotheonamide A (1) and B (2), recently isolated from a marine sponge of the genus *Theonella*[1], have been shown to possess thrombin-inhibitory activity. The potential usefulness of these compounds as antithrombotic agents and the unique structural features have prompted us to initiate an effort directed towards the synthesis of cyclotheonamide A (1). We wish to report here on the first stereoselective synthesis of the protected N(14) - C(18) amino acid subunit 3 *via* a *Horner-Emmons* reaction followed by a novel $Z \rightarrow E$ isomerization, induced by an intramolecular *Michael-Addition* .



1 R = CHO: cyclotheonamide A
2 R = Ac: cyclotheonamide B



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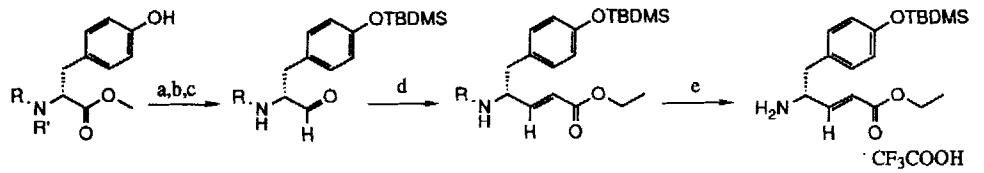
D-Tyrosine derived aldehyde 6, obtained by standard methods[2,3] (91% yield from 4)[4], was converted into the α,β-unsaturated ester 8[5] by reaction with lithio-triethylphosphonoacetate in 65% yield[6]. Subsequent deprotection of the amino group by treatment of 8 with trifluoroacetic acid under non-aequeous conditions led to the γ-amino-ester 3[7] in 55% yield (Scheme 1).



4: R = Boc, R' = H
5: R,R' = $(C_6H_5)_2C$

6: R = Boc
7: R = $(C_6H_5)_2$-CH

8: R = Boc
9: R = $(C_6H_5)_2$-CH

3

Scheme 1 a) TBDMSCl, imidazole, DMF or THF, RT ; b) $LiAlH_4$, THF, 0°C→RT; c) $(COCl)_2$/DMSO, CH_2Cl_2, -78°C→0°C; d) $(EtO)_2(O)P$-CH(Li)COOEt, THF, -78°C; e) TFA, CH_2Cl_2, 0°C→RT

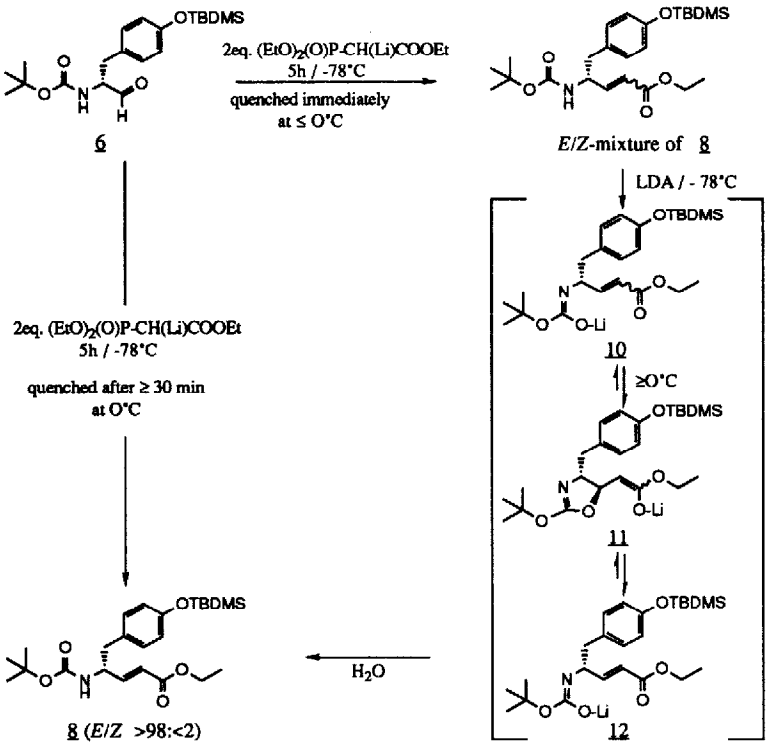
Assuming a stabilized anion during the *Horner-Emmons* reaction[8], rotation around the newly formed C-C single bond is possible. Therefore the initially formed product 8 should be a mixture of *E*- and *Z*-isomers[9,10]. We isolated 8 as a mixture of *E*- and *Z*- isomers (*E*/*Z* = 65:35) by quenching the reaction either at low temperature (-78°C) or immediately after warmup to 0°C. If the reaction was kept for 30 min or longer at 0°C before quenching, only the thermodynamically more stable *E*-isomer was found (see table).

Table. *E/Z-Ratios of 8 and 9 as Function of Temperature and Differently Protected Aldehydes 6 or 7.*

Aldehyde	Reaction time at -78°C	Quenching temp./ Quenching after:	8 or 9 E / Z[a)]
6	0 min	-78°C	65 : 35
6	30 min	-78°C	65 : 35
6	300 min	-78°C	65 : 35
6	≥ 300 min	0°C / immediately	65 : 35
6	≥ 300 min	0°C / after 30 min	>98 : <2
6	≥ 300 min	0°C / after 60 min	>98 : <2
7	≥ 300 min	-78°C	82 : 18
7	≥ 300 min	0°C / immediately	82 : 18
7	≥ 300 min	0°C / after 60 min	82 : 18

a) E/Z-ratios of crude products determined by ^{1}H-NMR (360 MHz)

We assume that the observed isomerization occurs under thermodynamically controlled conditions (≥ 0°C) via an intramolecular *Michael-Addition* (10 → 11) followed by a stereoselective *retro* Michael reaction (11 → 12) to give exclusively the *E*-isomer of 8 after quenching with water (Scheme 2).



Scheme 2

To support our hypothesis, a sample of an isolated *E/Z*-mixture of 8 was treated with 1 equiv. of LDA in THF at -78°C . As expected after warming the reaction mixture to 0°C, isomerization occurred via 10 and 11, and the isolated product 8 was shown to be exclusively the *E*-isomer. In a control experiment, aldehyde 7 (62% yield from 5)[11], lacking the possibility for azaenolate formation, was treated under the same conditions as described for aldehyde 6. As expected, under kinetically controlled conditions (-78°C), an *E/Z* mixture (82/18) of 9[12] was obtained[13,14]. In contrast to aldehyde 6, no isomerization took place after warming the reaction mixture to 0°C (see table). The α,β-unsaturated ester 9 was isolated in 85% yield.

This result supports our hypothesis that in case of the BOC-protected aldehyde 6 isomerization of the initially formed *Horner-Emmons* product 8 occurs under thermodynamically controlled conditions *via* an intramolecular *Michael-Addition* of the azaenolate moiety to the α,β-unsaturated system in 10.

Sample procedure: To a solution of 10.4 mmol triethylphosphonoacetate in 35 ml THF at -78°C a solution of 10.4 mmol butyllithium (1.6M in hexane) is added dropwise. After 10 min at -78°C, a solution of 5 mmol aldehyde in 5 ml THF is added slowly. For reaction time and temperature see table. The reaction is quenched by addition of 20 mmol aqueous sodium sulfate. The aqueous layer is extracted several times with diethyl ether, the combined organic layers are washed with brine, dried over sodium sulfate, filtered and concentrated.

Further purification is done by chromatography on silica gel (MPLC, hexane/ethyl acetate (8:2)), yielding 65-85% product as an oil. *E/Z*- ratios were determined by ^{1}H-NMR spectra (200 or 360 MHz).

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References and Notes:

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5. Spectral and physical data of 8: ^{1}H-NMR (200 MHz,$CDCl_3$): δ 7.01 (2H, d, J = 8.5Hz); 6.89 (1H, dd, J =7.2Hz); 2.81 (2H, m); 1.40 (9H, s); 1.27 (3H, t, J = 7.2Hz); 0.97 (9H, s); 0.18 (6H, s).MS(FAB): 450 $(M+H)^+$. $[\alpha]_{365}$ = -14.35° (c = 0.69, CH_3OH)
   Olefinic protons of *Z*-isomer of 8: ^{1}H-NMR (360 MHz, DMSO): δ 6.14 (1H, dd, J = 11.7, 9.0Hz); 5.72 (1H, dd, J = 11.7, 1.2Hz).
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7. Spectral and physical data of 3: ^{1}H-NMR (360 MHz, $CDCl_3$): δ 7.05 (2H, d, J = 9.0Hz); 6.83 (1H, dd, J = 16.0, 7.2Hz); 6.78 (2H, d, J = 9Hz); 5.92 (1H, d, J = 16.0Hz); 4.12 (2H, q, J = 6.6Hz); 4.02 (1H, m); 3.13 (1H, m); 2.93 (1H, m); 1.24 (3H, t, J = 6.6Hz); 0.97 (9H, s). MS(FAB): 350 $(M+H)^+$. $[\alpha]_D$ = -43.4° (c = 0.60, CH_3OH). M.p.:169.7-170.3°C.
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12. Spectral and physical data of 9: ^{1}H-NMR (360 MHz, $CDCl_3$): 7.26-7.16 (10H, m); 6.95 (2H, d, J = 8.5Hz); 6.82 (1H, dd, J = 16.0, 7.2Hz); 6.75 (2H, d, J = 8.5Hz); 5.84 (1H, dd, J = 16.0, 1.0Hz); 4.77 (1H, s); 4.20 (2H, q, J = 7.8Hz); 3.30 (1H, m); 2.73 (2H, m, J = 3.0Hz); 1.30 (3H, t, J = 7.8Hz); 0.99 (9H, s); 0.20 (6H, s). MS(FAB): 516 $(M+H)^+$. $[\alpha]_D$ = -8.7° (c = 0.90, CH_3OH)
    Olefinic protons of *Z*-isomer of 9: ^{1}H-NMR (360 MHz, $CDCl_3$): δ 6.04-6.02 (1H, dd, J = 12.0, 9.5Hz); 5.79 (1H, m).
13. The different protecting groups cause different steric conditions which might be considered as a reason for different *E/Z*-ratios found for 8 and 9.
14. For an analogous *E*-selective reaction, c.f.: M. T. Reetz, D. Röhrig, *Angew. Chem.*, **1989**, *101*, 1732-1734; *Angew. Chem. Int. Ed. Engl.*, **1989**, *28*, 1706.

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