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Total synthesis of ulongamide A, a cyclic depsipeptide isolated from marine cyanobacteria *Lyngbya* sp.

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Abstract—A total synthesis of ulongamide A (**1**), a cytotoxic natural cyclic depsipeptide, was achieved by a convergent route involving coupling of the fragments **7** and **8** to the pentapeptide **24**, and subsequent cyclization thereof after prior removal of the *t*-Boc protecting groups.

1. Introduction

Cyanobacteria, or blue-green marine algae, are of considerable interest because of the impressive number and structural diversity of the metabolites which they produce. A wide variety of biological activities is found amongst these metabolites[1] including extreme toxicity in some instances.[2] Depsipeptides, one class of compounds produced by cyanobacteria, are of potential importance in the therapy of cancer. For example, criptophycin-52, a synthetic analog of criptophycin-1, isolated from *Nostoceae* sp.,[3,4] and dolastatine-10, a modified pentapeptide isolated from a marine cyanobacterium,[5] have been tested as anticancer drugs. In 2002, six new depsipeptides designated as ulongamides A–F, were isolated by Luesch et al.[6] from Palauan collections of the marine cyanobacterium *Lyngbya* sp., and found to possess activity against some types of cancer. Herein, is described the synthesis of ulongamide A (**1**), the first member of this series of compounds.

Luesch et. al.,[6] also showed that ulongamide A (**1**) is a cyclic depsipeptide formally derived from five structural units, four of which are the amino acids **2**, **3**, **5**, and **6**, the fifth being L-lactic acid **4** (Fig. 1). Amino acids **2** and **3** were obtained by N-methylation[7] of L-valine and L-phenylalanine. Compounds **5** and **6** were synthesized in the manner described later in the text.

A convergent strategy was used for the synthesis of **1**. The two starting materials required for this purpose were **7** and **8** (Fig. 2). The depsitripeptide **7** was prepared by sequential coupling of **4**, **5**, and **6**. Dipeptide **8** was likewise obtained from structural units **2** and **3**.

2. Synthesis of depsitripeptide 7

The optically pure benzyl ester **4a** of L-lactic acid was prepared by well known literature methodology.[8,9] The unusual β-amino acid **5** was synthesized using a procedure reported by Kimura et al.,[10] in which the (4*R*,5*S*)-oxazolidinone derivative **9** was N-acylated with propionyl chloride **11**, and the so produced *N*-propionyl derivative **10** (Scheme 1) was subjected to low temperature aldolization with *n*-butanal. The essentially pure (2*R*,3*S*)-aldol **12** thus obtained (78% from **9**), was converted into the azide **13** (43% yield), of inverted configuration, by a Mitsunobu[11] reaction using hydrogen azide. Cleavage of the chiral auxiliary from **13** with alkaline hydrogen peroxide, followed by catalytic reduction of the azido acid **14** provided the β-amino acid **5**, which was transformed into its *t*-Boc derivative **5a**.

The (*S*)-thiazole carboxylic acid **6a** was prepared following the procedure described by Xia and Smith[12] for the (*R*)-enantiomer. To this end, L-alanine (**15**, Scheme 2) was protected as the *t*-Boc derivative **16**, and then

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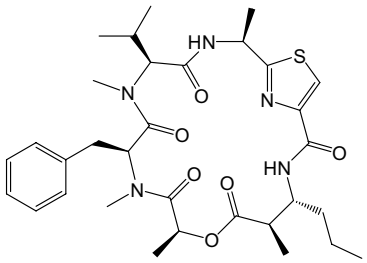
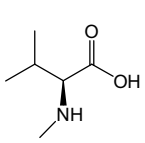


Ulongamide A 1



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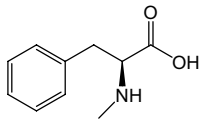

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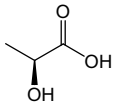

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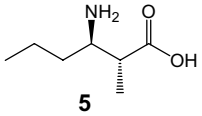

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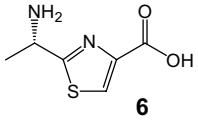

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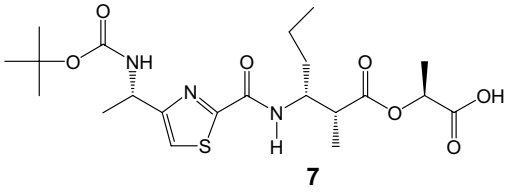
Figure 1. Ulongamide A and its structural components.



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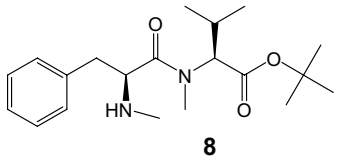

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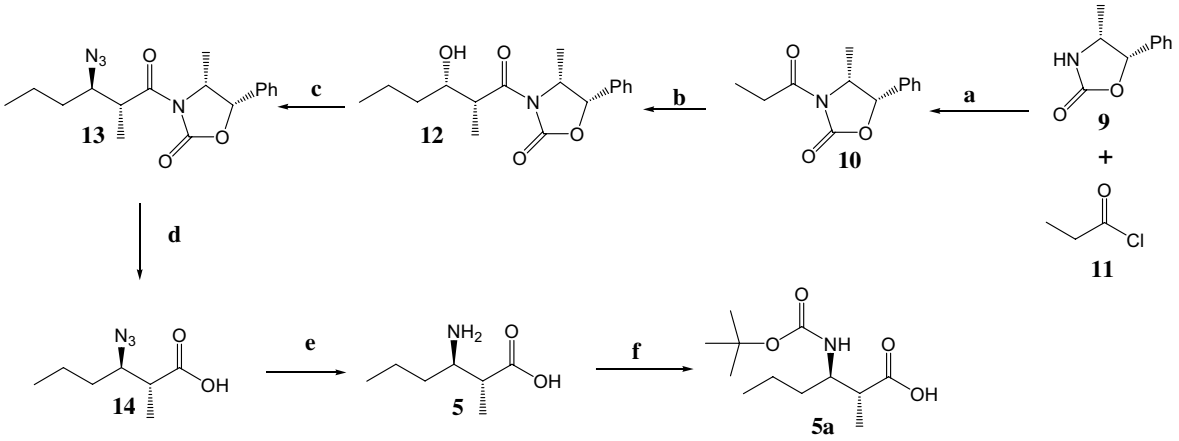
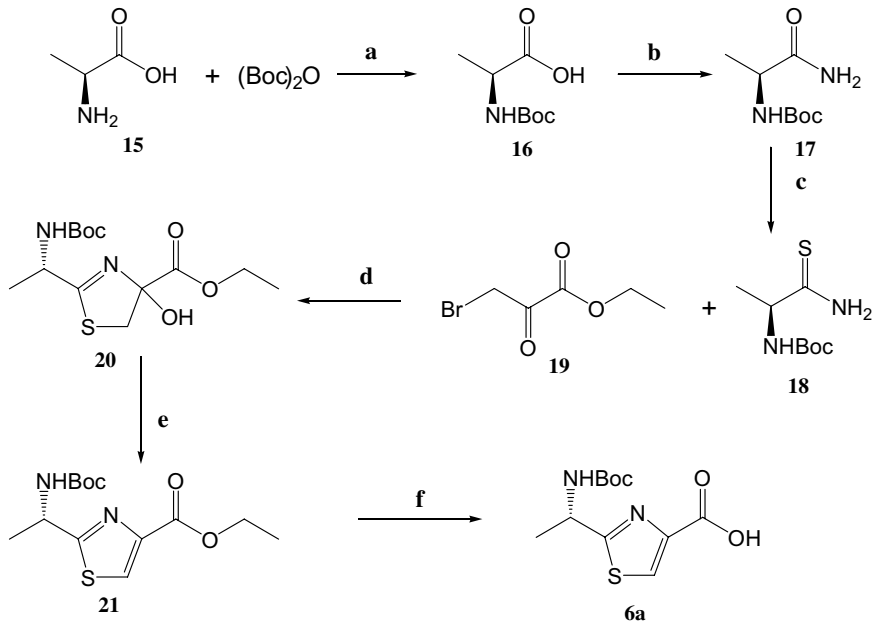
Figure 2. Convergent way.

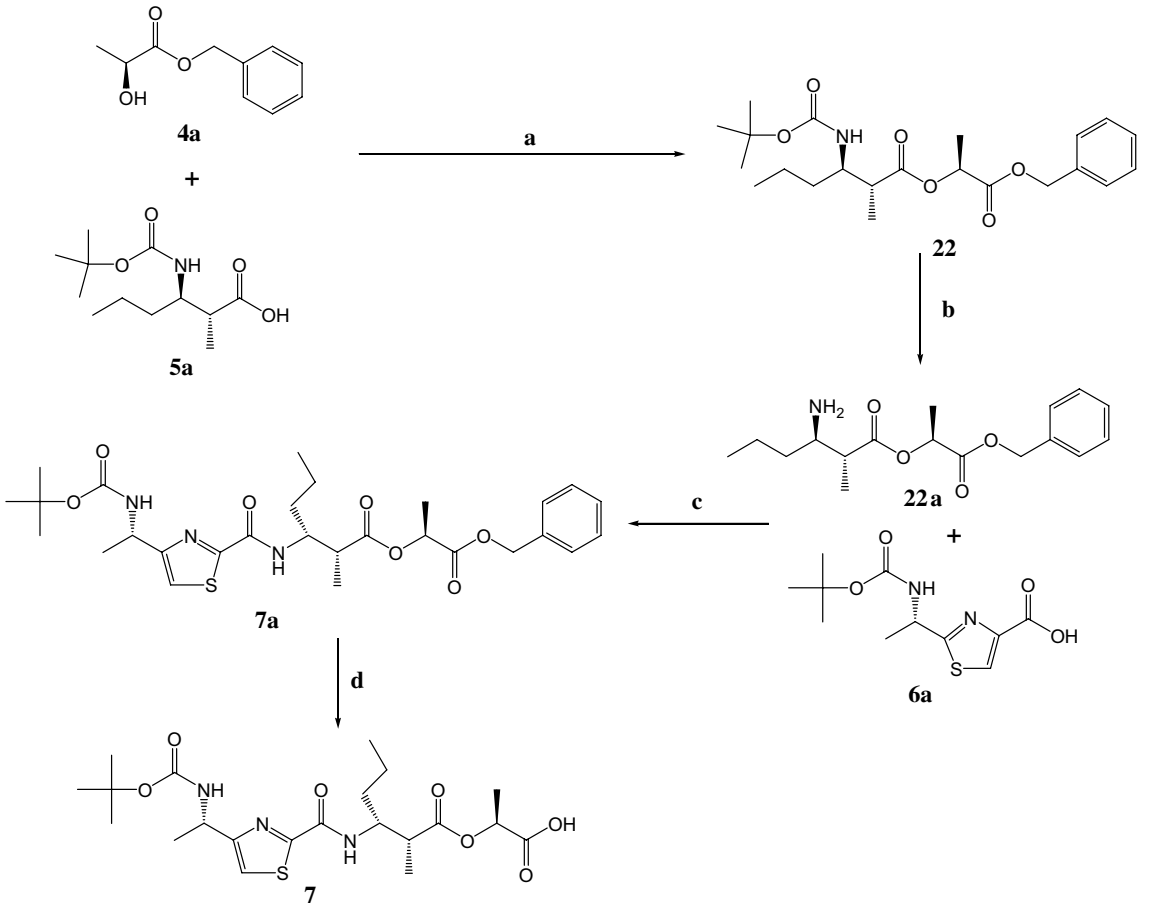


Scheme 1. Synthetic route to **5a**. Reagents and conditions: (a) *n*-BuLi, THF, −78 °C, 93%; (b) 1. DBBT, EDIPA, CH_2Cl_2, 0 °C, 2. *n*-butanal, −78 °C, 84%; (c) DEAD, PPh_3, HN_3, toluene, 43%; (d) H_2O_2, LiOH, H_2O; (e) H_2/Pd–C, methanol, 88%; (f) $(Boc)_2O$, Et_3N, H_2O/*p*-dioxane, 85%.

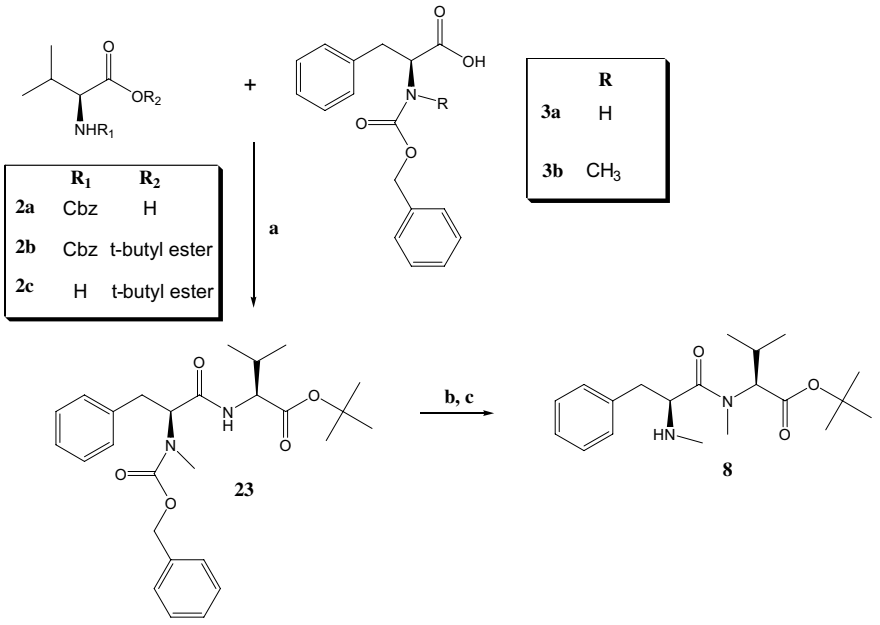
converted into the primary amide **17** by amination of the mixed anhydride derived from ethyl chloroformate. Thionation of **17** with Lawesson's reagent and subsequent reaction of the thioamide **18** with ethyl bromopyruvate **19** generated the hydroxythiazoline **20**, which was converted into the thiazole **21** by treatment with trifluoroacetic anhydride in the presence of 2,6-lutidine. Saponification of **21** with aqueous sodium hydroxide (3 equiv) at room temperature generated the protected amino acid **6a**.



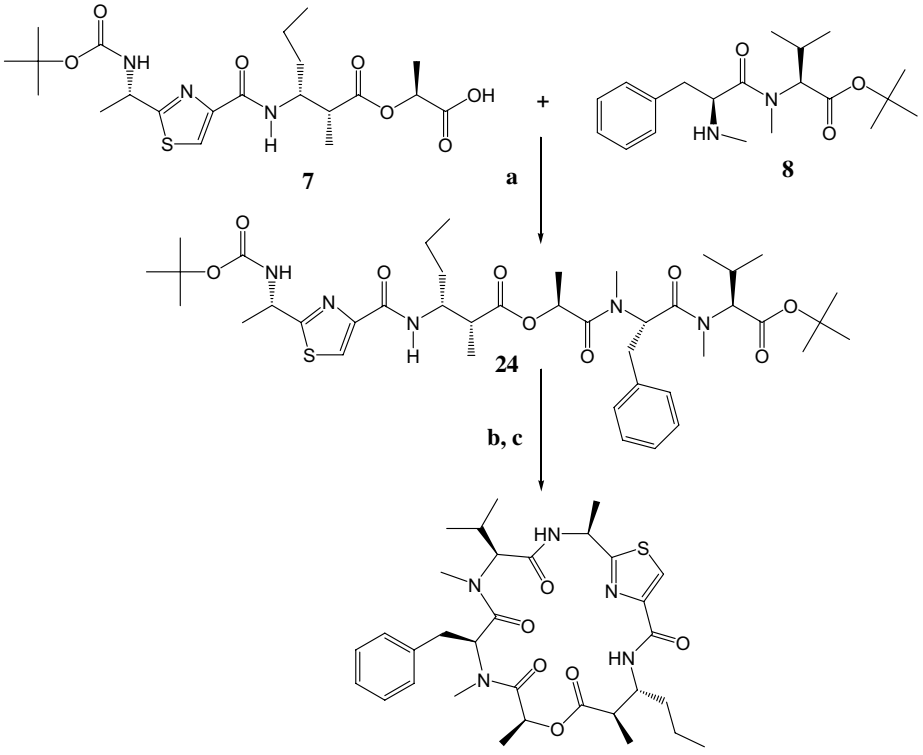
Scheme 2. Synthetic route to **6a**. Reagents and conditions: (a) Et_3N, *p*-dioxane/H_2O (3:1), rt, 16–18 h, 87%; (b) 1. ethyl chloroformate, CH_2Cl_2, −10 °C, 2. NH_3/CH_2Cl_2, 90%; (c) Lawesson's reagent, DME, 16–18 h, 85%; (d) $KHCO_3$, DME, −15 °C; (e) $(CF_3CO)_2O$, lutidine, −15 °C, 77%; (f) $NaOH/H_2O$, 83%.



Scheme 3. Synthetic route to **7**. Reagents and conditions: (a) DCC, DMAP, CH_2Cl_2, 16–18 h, 70%; (b) TFA, CH_2Cl_2, 88%; (c) DCC/HOBt, CH_2Cl_2, 16–18 h, 67%; (d) H_2/Pd–C, 87%.



Scheme 4. Synthetic route to **8**. Reagents and conditions: (a) DCC/HOBt, CH_2Cl_2, 16–18 h, 87%; (b) CH_3I, NaH, THF, 0 °C, 85%; (c) H_2/Pd–C.



Scheme 5. Obtention of ulongamide A. Reagents and conditions: (a) BOP, Et_3N, CH_2Cl_2, 55%; (b) TFA, CH_2Cl_2; (c) BOP, DMF, 80–90 °C, 60%.

With the requisite starting materials in hand, the synthesis of the depsitripeptide **7** was completed by the following sequence of reactions. Coupling of benzyl lactate (**4a**, Scheme 3) with the β-amino acid **5a**, mediated by dicyclohexylcarbodiimide (DCC), provided the bis-protected depsipeptide **22** (70% yield) from which the *t*-Boc group was removed with trifluoroacetic acid, giving the amino compound **22a**. Coupling of **22a** with the thiazole carboxylic acid derivative **6a**, by means of DCC containing hydroxybenzotriazole (HOBt), produced **7a** which on hydrogenolysis generated depsipeptide **7** (58% yield over two steps).

3. Synthesis of dipeptide 8

N-Cbz-L-Phenylalanine **3a** was selectively N-methylated with methyl iodide (sodium hydride) giving **3b** (Scheme 4). Cbz-L-valine **2a** was converted into the *t*-butyl ester **2b** with 2-methylpropene under acidic conditions, and then hydrogenolyzed to L-valine *t*-butyl ester (**2c**).[13] Compounds **2c** and **3b** were then coupled using the DCC–HOBt mixture to afford the dipeptide **23**. Sequential methylation of the valine amido NH of **23** with methyl iodide in the presence of sodium hydride and hydrogenolysis generated dipeptide **8**.

4. Synthesis of depsipentapeptide 24, and cyclization to ulongamide A[14]

The optimum conditions found for the coupling of **7** and **8** utilized BOP in dichloromethane solution. The pentapeptide **24** (55% yield, Scheme 5) so obtained was deprotected with trifluoroacetic acid (TFA), and the crude product, after removal of the TFA in vacuo and dilution with DMF, was cyclized to ulongamide A (**1**, 60% yield) with BOP. The spectral properties[15] of synthetic ulongamide A were fully concordant with those reported[6] for the natural product.

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15. Physical and spectroscopic constants of ulongamide A **1**. White, amorphous solid, mp 85 °C.; $[\alpha]_D^{25}$ +12 (*c* 0.73, MeOH); IR (film) *v*max 3321, 2962, 2934, 2872, 1734, 1672, 1633, 1553, 1522, 1497, 1462, 1271, 1216, 1078, 1048; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.94 (d, 1H, $J = 10.5$), 8.17 (d, 1H, $J = 7.0$), 8.04 (s, 1H), 7.29 (t, 2H), 7.24 (t, 1H), 7.17 (d, 2H), 6.08 (dd, 1H, $J = 9.5, 5.5$), 5.34 (q, 1H, $J = 6.5$), 5.17 (q, 1H, $J = 7.0$), 4.51 (d, 1H, $J = 11$), 4.31 (m, 1H, $J = 10.6, 9.0, 5.0, 2.5$), 3.27 (dd, 1H, $J = 9.5, 15.0$), 3.21 (s, 3H), 3.16 (dd, 1H, $J = 5.5, 15.0$), 2.99 (s, 3H), 2.70 (dq, 1H, $J = 7.0, 2.5$), 2.33 (m, 1H), 1.46 (d, 3H, $J = 6.8$), 1.43 (m, 4H), 1.33 (d, 3H, $J = 6.8$), 1.23 (d, 3H, $J = 7.2$), 0.97 (t, 3H, $J = 7.0$), 0.85 (d, 3H, $J = 6.4$), 0.60 (d, 3H, $J = 7.0$); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 14.5, 16.2, 18.3, 19.3, 19.6, 24.5, 27.3, 29.0, 30.0, 35.4, 35.5, 45.0, 47.7, 50.7, 51.0, 66.4, 67.0, 122.0, 127.0, 128.5, 128.8, 136.0, 149.1, 160.8, 167.9, 169.6, 170.4, 171.9, 172.9; HRFABMS *m*/*z* $[M+H]^+$ 628.3179 (calcd for $C_{32}H_{46}N_5O_6S$, 628.3169).