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Ligong Chen, Zhengshuang Xu, Tao Ye *et al.*

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Bohua Long,[ab] Shoubin Tang,[c] Ligong Chen,*[a] Shiwei Qu,[c] Bo Chen,[c] Junyang Liu,[c] Anita R. Maguire,[d] Zhuo Wang,[e] Yuqing Liu,[e] Hui Zhang,[c] Zhengshuang Xu*[c] and Tao Ye*[bce]

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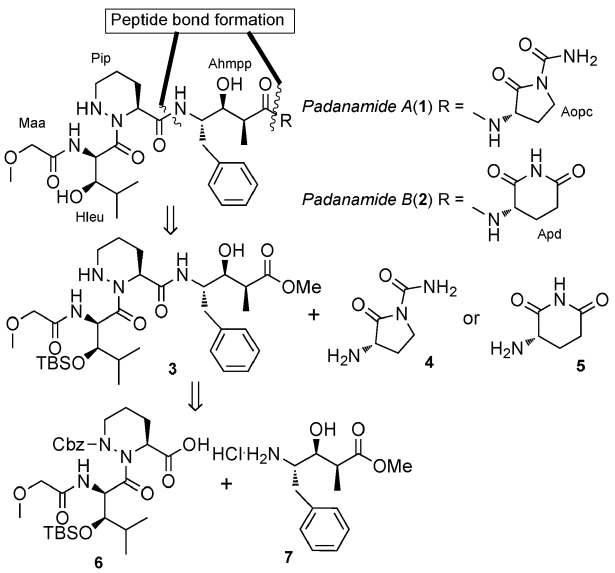
The first total syntheses of padanamides A and B have been achieved, unambiguously confirming their structures.

Many of the marine sediment-derived natural products[1] possess unique structural features rarely or never found among the compounds isolated from the terrestrial sources. It is thus not surprising that their molecular modes of action are sometimes also unique, prompting their investigation as potential targets for total synthesis and drug development. The vast majority of secondary metabolites, especially peptides, are derived from *Streptomyces* sp. obtained from a marine sediment.[2] We have been interested for some time in marine peptides and view their synthesis as a key route to structural modification and subsequent activity control.[3] Here we report our efforts in the total synthesis of two highly modified linear tetrapeptides, padanamides A and B (Scheme 1).

Padanamides A and B were isolated from laboratory cultures of a *Streptomyces* sp. obtained from marine sediment collected near the passage Padana Nahua in Papua New Guinea.[4] The gross chemical structures of padanamides A and B were established using spectral techniques. Their absolute configurations were elucidated by a combination of spectroscopic, chemical degradation and single-crystal X-ray diffraction analyses. Padanamide B was cytotoxic to Jurkat cells, while padanamide A was suspected to inhibit cysteine and methionine biosynthesis.

Our synthetic approach for padanamides A and B is outlined in Scheme 1. Padanamides A and B contain the same tripeptide unit (**3**) and differ only in the last residue at the C-termini. Consequently, a synthetic approach including the late-stage incorporation of either (*S*)-3-amino-2-oxopyrrolidine-1-carboxamide (Aopc) (**4**) or (*S*)-3-aminopiperidine-2,6-dione (Apd) (**5**) at the C-termini would potentially access both **1** and **2**. We envisaged that the key intermediate **3** would arise from the assembly of acid **6** and amino alcohol **7**.



Scheme 1 Retrosynthetic analysis of padanamides A (**1**) and B (**2**).

The synthesis of key intermediate **3** commenced with the preparation of 2*R*,3*R*-3-hydroxyleucine. Initial experiments for the conversion of azidoester **9**[5] to its corresponding acid **11** included protection of the secondary alcohol of **9** as its TBS ether followed by saponification of the ethyl ester with lithium hydroxide, which led to extensively epimerization at the azide group-bearing center. Gratifyingly, reversing the order of the protection and hydrolysis sequence proved to be more successful. Thus, treatment of azidoester **9** with lithium hydroxide afforded carboxylic acid **10**, which was then converted into the corresponding silyl ether **11** in 72% overall yield by reaction with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) in the presence of 2,6-lutidine. No epimerization was observed in any of

[a] *School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, China. E-mail: lgchen@tju.edu.cn*
[b] *The Hong Kong Polytechnic University Shenzhen Research Institute, Shenzhen, China*
[c] *Laboratory of Chemical Genomics, Peking University Shenzhen Graduate School, Xili, Nanshan District, Shenzhen, 518055, China. E-mail: xuzs@pkusz.edu.cn*
[d] *Department of Chemistry and School of Pharmacy, Analytical and Biological Chemistry Research Facility, University College Cork, Cork, Ireland. E-mail: a.maguire@ucc.ie; Tel: +353-21-4902125*
[e] *Department of Applied Biology & Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong, China. E-mail: bctaoye@inet.polyu.edu.hk; Tel: +852 34008722*

† Electronic supplementary information (ESI) available: Full details of experimental procedures for compounds **1–7**, **10–12**, **14–15**, **17–19**, **21**, **24**, **26–28**, **30–31** and NMR spectra of compounds **1–7**, **10–12**, **14**, **17–19**, **21**, **27–28** and **30**. See DOI: 10.1039/c3cc00178d

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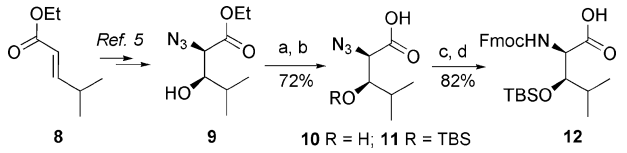


Scheme 2 (a) LiOH, THF–MeOH–H_2O, 0 °C; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (c) H_2, Pd/C, MeOH, rt; (d) Fmoc–Cl, $NaHCO_3$, THF–H_2O, rt.

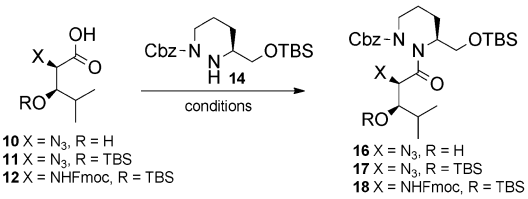
these two transformations. Reduction of the azide group of **11** followed by protection of the resulting amine with Fmoc–Cl produced acid **12** in 82% overall yield (Scheme 2).

The synthesis of protected piperazic alcohol **14** began with the enantiomerically pure (*S*)-tetrahydropyridazine **13**,[6] a known building block available from proline-catalyzed asymmetric α-hydrazination of 5-bromopentanal, protection of alcohol with TBS–Cl and subsequent NaH-promoted cyclization. Two Cbz protecting groups in **13** were removed under catalytic hydrogenation with 5% Pd–C to give the corresponding cyclic hydrazine. The sterically less-hindered nitrogen atom of the resulting cyclic hydrazine was then reprotected *in situ* with CbzCl to provide **14** in 86% yield. (*S*)-Tetrahydropyridazine **13** is also easily converted into the corresponding piperazic ester **15**. Thus, removal of the TBS protecting group in **13** resulted in an alcohol, which was converted into the corresponding carboxylic acid *via* a TEMPO/$NaClO/NaClO_2$ promoted oxidation process.[7] After conversion of the carboxylic acid to its methyl ester, it was then elaborated to piperazic ester **15** in 64% overall yield using an identical strategy as described for **14** (Scheme 3). Literature precedent[8] suggested that *N*-2 acylation of a piperazic-acid-derivative is a challenging task due to the unusually poor nucleophilicity of the piperazic ester. In order to take advantage of the higher reactivity of the piperazic alcohol, we decided to employ **14** as the N-terminal coupling partner for the synthesis of segment **6**.

With 3-hydroxyleucine-derived acids **10–12** and piperazic alcohol **14** in hand, the coupling reactions were investigated. Unfortunately, all attempts to effect condensation of acid **10** with piperazic alcohol **14** under the influence of coupling reagents (such as HATU (entry 1) and PyBOP (entry 2)) or *via* a mixed anhydride (entry 3) did not succeed. The reactions led only to decomposition of the starting material. Gratifyingly, silver cyanide-mediated coupling[9] of **14** with acid chlorides derived from either **11** or **12** proceeded smoothly, delivering dipeptides **17** and **18** in 85% and 80% yield, respectively (Scheme 4).

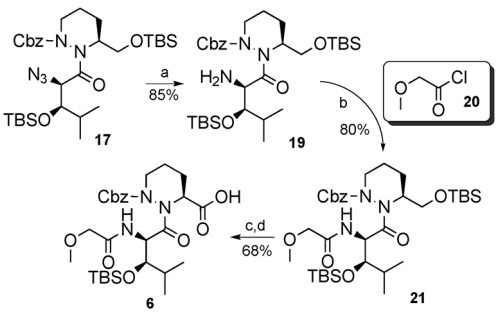
The Staudinger reduction of azide **17** with PPh_3 in THF–H_2O was followed by a condensation of the resulting amine with acid chloride **20** to afford tripeptide **21** in 68% overall yield for the two steps. Selective removal of the primary TBS group of **21** with CSA/MeOH followed by oxidation of the resulting hydroxyl group with $NaIO_4$ in the presence of catalytic amounts of $RuCl_3$ furnished carboxylic acid **6** in 68% yield over the two steps (Scheme 5).

Methyl ester of Ahmpp (**7**) was prepared from the known aldol adduct **24** (ref. 10) through a diastereoselective *syn* aldol addition of



Entry	Hleu	Conditions	yield and product
1	**10**	HATU, HOAt, DIPEA, DMF, rt, overnight	no desired product (**16**)
2	**10**	PyBOP, DIPEA, DMF, rt, overnight	no desired product (**16**)
3	**10**	$ClCO_2{}^tBu$, NMM, THF, -10 °C, 0.5h; then **14**, rt, overnight	no desired product (**16**)
4	**11**	1. $(COCl)_2$, DMF (cat.), CH_2Cl_2, 0 °C 2. **14**, AgCN, Toluene, 80 °C, 1h	85% (**17**)
5	**12**	1. $(COCl)_2$, DMF (cat.), CH_2Cl_2, 0 °C 2. **14**, AgCN, Toluene, 80 °C, 1h	80% (**18**)

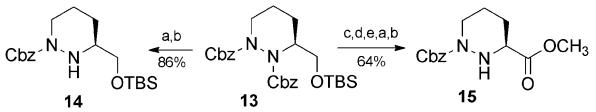
Scheme 4 Attempted synthesis of dipeptide fragment. HATU: 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HOAT: 1-hydroxy-7-azabenzotriazole; PyBOP: benzotriazol-1-yl-oxytripyrrolidino-phosphonium hexafluorophosphate.



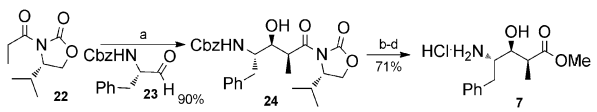
Scheme 5 (a) PPh_3, THF–H_2O, reflux; (b) Et_3N, CH_2Cl_2, 0 °C–rt; (c) CSA, MeOH–CH_2Cl_2; (d) $NaIO_4$, $RuCl_3$, acetone–H_2O.

the boron (*Z*)-enolate derived from (*S*)-4-isopropyl-3-propionyl-2-oxazolidinone (**22**) with *N*-Cbz-L-phenyl-alaninal **23**.[11] Hydrolysis of the chiral auxiliary of **24** with LiOH–H_2O_2 followed by esterification of the resulting adduct with MeI, and Cbz hydrogenolysis, produced **7** in 71% yield over three steps (Scheme 6). Condensation of acid **6** with amine **7** *via* the mixed carbamic–carbonic anhydride gave rise to **25** in 86% yield. Unexpectedly, attempted hydrogenolysis of the Cbz protecting group in **25** under a variety of reaction conditions resulted in decomposition of the starting material. We then elected to cleave off the Cbz protecting group in **6** prior to coupling with amine **7**. Gratifyingly, this revised approach produced the tripeptide unit **3** in 72% yield over two steps (Scheme 7).

With the key intermediate **3** in hand, we next turned our attention to the synthesis of (*S*)-3-amino-2-oxopyrrolidine-1-carboxamide (Aopc) (**4**) or (*S*)-3-aminopiperidine-2,6-dione (Apd) (**5**). Thus, treatment of the known lactam **27** with sodium hydride and



Scheme 3 (a) H_2, Pd/C; (b) Cbz–Cl, Et_3N, MeOH; (c) TBAF, THF; (d) TEMPO, $NaClO/NaClO_2$; (e) $SOCl_2$, MeOH, −20 °C.



Scheme 6 (a) Bu_2BOTf, $^iPr_2NEt$, CH_2C1_2, 0 °C; then **23**, −78 to 25 °C; (b) LiOH, H_2O_2, THF–H_2O; (c) $NaHCO_3$, MeI, DMF; (d) H_2, Pd/C, MeOH, 1 N HCl (aq.).

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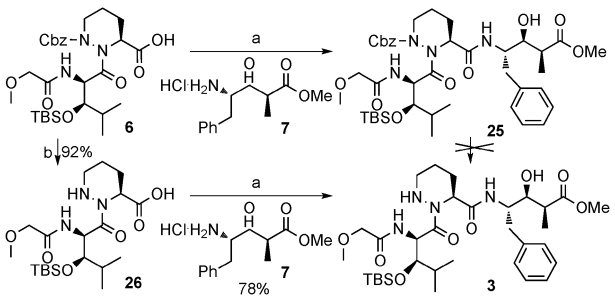
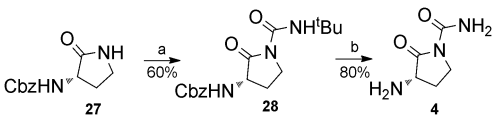
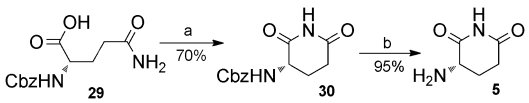


Scheme 7 (a) $ClCO_2{}^tBu$, NMM, THF; then **7**, −20 °C–rt; (b) H_2, Pd/C, MeOH.



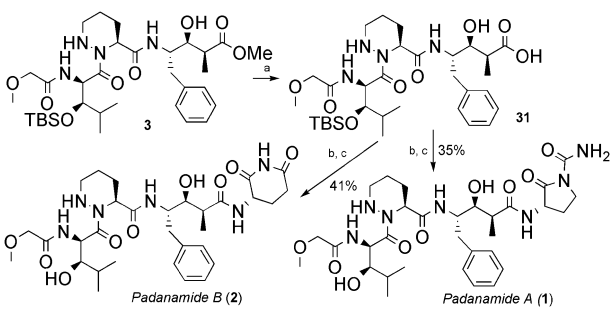
Scheme 8 (a) NaH, *tert*-butylisocyanate, THF, 0 °C; (b) TFA, anisole, Δ 16 h.



Scheme 9 (a) DCC, HOSu, THF–DMF, −78 °C–rt; then $CHCl_3$, Δ 3 h; (b) H_2, Pd/C (10%), MeOH, rt, 2 h.

tert-butylisocyanate in THF afforded urea **28** in 60% yield. Acidic cleavage of both the *tert*-butyl and Cbz groups in **28** gave rise to the required intermediate **4** in 80% yield (Scheme 8). (*S*)-*N*-Cbz-α-aminoimide **5** was obtained in 67% yield in a two-step sequence including a DCC-mediated intramolecular cyclization of *N*-Cbz-L-glutamine leading to adduct **30**, and subsequent hydrogenolytic removal of the carboxybenzyl group (Scheme 9).

At this juncture, the time had arrived to assemble the key intermediate **3** with Aopc (**4**) or Apd (**5**) leading to padanamides A and B, respectively. Thus, saponification of the methyl ester of **3** followed by coupling with (*S*)-3-amino-2-oxopyrrolidine-1-carboxamide (Aopc) (**4**) and cleavage of TBS ether provided padanamide A **1** in 35% yield over three steps. Under identical conditions, padanamide B was obtained in 45% overall yield from the condensation of **3** and **5** (Scheme 10). The spectral data for synthetic **1** and **2** (^1H, ^{13}C NMR and HMRS) were identical with those published for the natural products, and the optical rotation of our products ($[\alpha]_D^{25}$ −11.4, *c* 0.2, MeOH, for padanamide A; $[\alpha]_D^{25}$ −20.7, *c* 0.2, MeOH, for padanamide B) corresponded well with the literature value (lit. $[\alpha]_D^{25}$ −10.7, *c* 5.2, MeOH, for padanamide A; $[\alpha]_D^{25}$ −21.5, *c* 7.3, MeOH, for padanamide B), which led us to conclude that synthetic **1** and **2** were of the same absolute stereochemistry as natural padanamides A and B.



Scheme 10 (a) LiOH, THF–MeOH–H_2O; (b) BOPCl, **4** or **5**, HOAT, NMM, THF, 0 °C–rt, 18 h; (c) 40% HF, MeCN, 0 °C, 3 h. BOPCl: bis(2-oxo-3-oxazolidinyl)phosphinic chloride.

In summary, we have accomplished the total synthesis of padanamides A and B from the known azidoester **9** in 7.1 and 8.3% overall yield, respectively, with the longest linear sequence of 12 steps. This synthesis confirmed the structures of padanamides A and B. The extension of this chemistry toward the synthesis of padanamide analogues for further biological evaluation is underway and will be reported in due course.

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