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The First Total Synthesis of (−)-Tamandarin A

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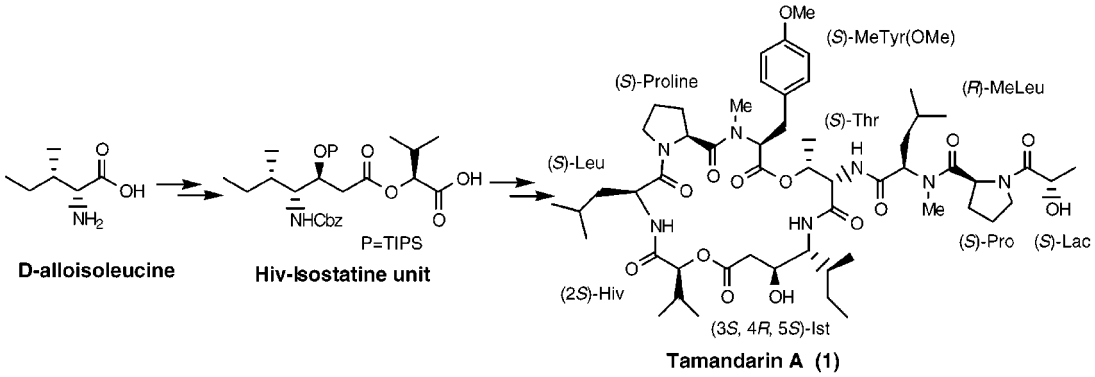
ABSTRACT



Tamandarin A (1), a newly isolated natural product similar in structure to didemnin B (2), was shown to be somewhat more active in vitro than 2 against pancreatic carcinoma with an ED_{50} value 1.5 to 2 ng/mL. We report here the first total synthesis of 1. The key steps include a practical stereoselective synthesis of the Hiv-isostatine unit, high-yielding linear precursor formation, a successful macrocyclization, and coupling of the macrocycle with the side chain to afford tamandarin A (1).

Tamandarin A (**1**), a mewly isolated natural product similar in structure to didemnin B (**2**), was shown to be somewhat more active in vitro than **2** against pancreatic carcinoma with an ED_{50} value of 1.5−2 ng/mL. We report here the first total synthesis of **1**. The key steps include a practical stereoselective synthesis of the Hiv-isostatine unit, high-yielding linear precursor formation, a successful macrocyclization, and coupling of the macrocycle with the side chain to afford tamandarin A (**1**).

Tamandarin A (**1**) is a cyclic depsipeptide recently isolated from an unidentified Brazilian ascidian of the family Didemnidae (Figure 1).[1] The structure of **1** is similar to that of didemnin B (**2**), a potent antiviral, immunosuppressive, and antitumor agent.[2] The macrocyclic core of tamandarin A contains the simpler α-hydroxyisovaleryl (Hiv) isostatine unit, rather than the more complex α-(α-hydroxyisovaleryl)-propionyl (Hip) isostatine subunit of didemnin B. The remainder of the tamandarin A structure is identical to that of didemnin B.

Beyond the structural homology, **1** seems to exhibit much of the same biological activity as **2**. It retains similar levels of in vitro antitumor activity in clonogenic assays (1−2 ng/mL) as well as protein biosynthesis inhibition properties.[1] The limited supply of **1** from its natural source has prevented its full biological characterization. In particular, it has not been established whether tamandarin A is a fully competent mimic of didemnin B in vitro and in vivo, and screening for antiviral and immunosuppressive activity has not been reported. A viable synthetic route to tamandarin A will allow such an investigation to proceed. Since tamandarin A is considerably easier than other didemnins to access synthetically, the process of analogue preparation and screening should be accelerated. Such analogues could enhance the still-unfolding research directed at untangling the molecular mechanism(s) by which didemnins and related compounds exert their multifaceted cytotoxic and cytostatic effects.[3]

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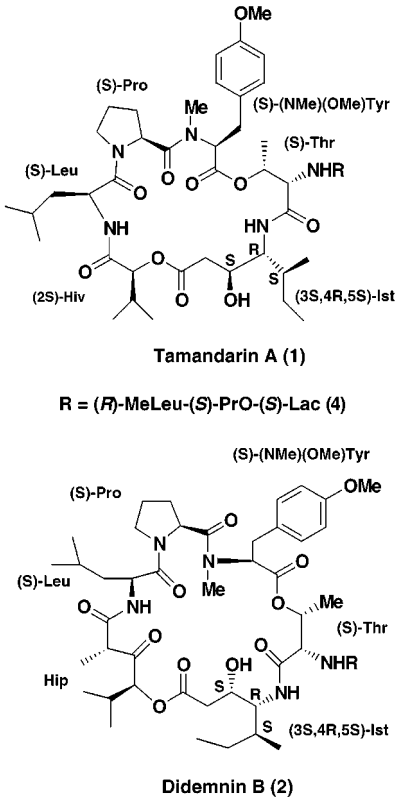


Figure 1. Structures of tamandarin A (**1**) and didemnin B (**2**).

The retrosynthetic analysis of **1** is shown in Figure 2. The macrocyclic core of the target molecule is disconnected into two fragments, the tetrapeptide portion **5** and the Hiv-isostatine unit **6**. Compound **5** is an advanced intermediate used in our previous synthesis of **2**.[2d]

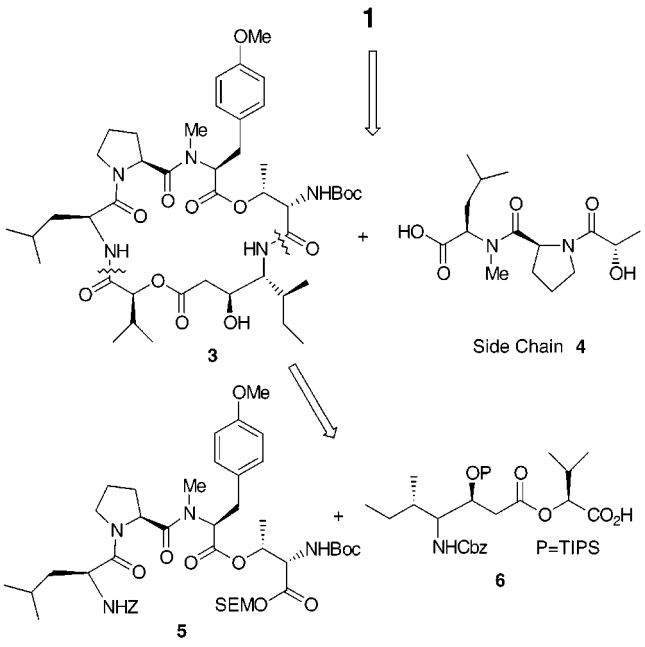
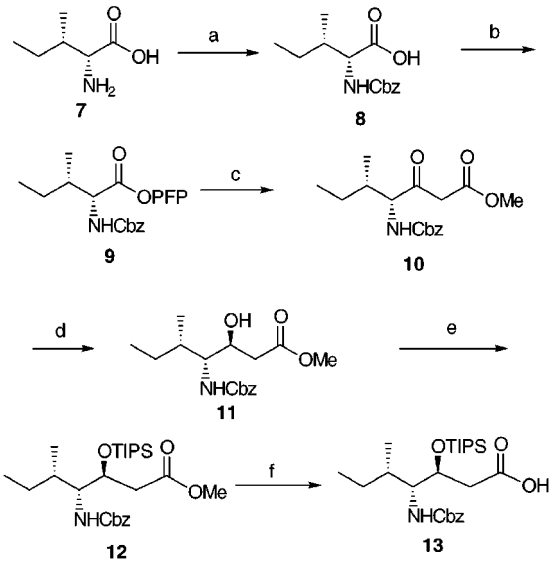


Figure 2. Retrosynthesis of tamandarin A (**1**).

The synthesis of the target molecule (**1**) begins with the (2*S*)-Hiv-isostatine unit **6** (Scheme 1). The (3*S*,4*R*,5*S*)-isostatine portion **13** can be prepared from the noncoded α-amino acid D-alloisoleucine (**7**) on a multigram scale, which we accomplished in four steps from commercially available (*S*)-2-methylbutanol.[4] The amino function of **7** was protected as its benzyloxycarbonyl (Cbz) derivative **8**. Activation of the carboxylic functionality of **8** as its pentafluorophenol ester,[2f,5] followed by condensation with the lithium enolate of the methyl acetate, gave the *β*-ketoester **10**.[6] Stereoselective reduction of **10** with KBH_4 gave **11** as

Scheme 1[a]



[a] Reagents and conditions: (a) Cbz-succinimide, Et_3N, CH_2Cl_2, 0 °C to rt (99%); (b) pentafluorophenol, EDAC·HCl, DMAP, CH_2Cl_2, 0 °C to rt; (c) $LiCH_2CO_2Me$, THF, −78 °C (80% two steps); (d) KBH_4, MeOH, −30 to 0 °C; de 91% (99%); (e) TIPSOTf, 2,6-lutidine, CH_2Cl_2, rt (94%); (f) 1 M NaOH, MeOH:THF:H_2O (1:1:1), 0 °C to rt (95%).

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(3) (a) Crews, C. M.; Collins, J. L.; Lane, W. S.; Snapper, M. L.; Schreiber, S. L. *J. Biol. Chem.* **1994**, *269*, 15411−15414. (b) Crews, C. M.; Lane, W. S.; Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 4316−4319. (c) Meng, L.; Sin, N.; M., C. C. *Biochemistry* **1998**, *37*, 10488−10492. (d) SirDeshpande, B. V.; Toogood, P. L. *Biochemistry* **1995**, *34*, 9177−9184.

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an 11:1 diastereomeric mixture.[7] Crystallization of **11** afforded the diastereomerically pure product, whose stereochemistry was determined by the NMR coupling constants of the corresponding 2,2-dimethyloxazolidine[7] and further confirmed by X-ray crystallography (Figure 3).

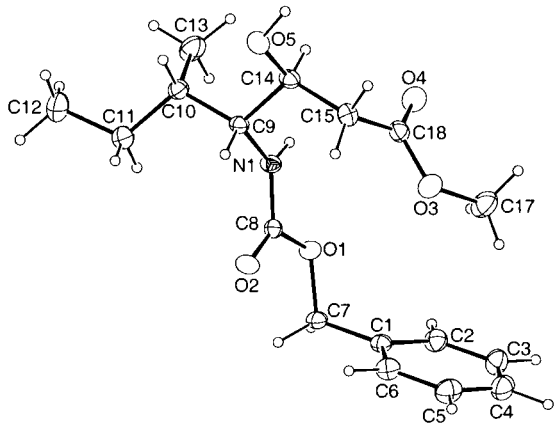
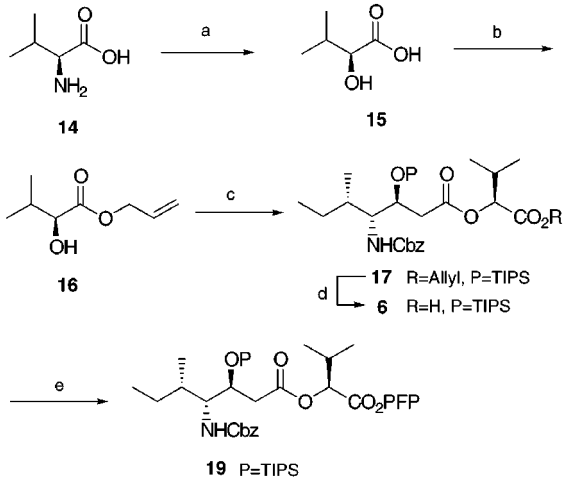


Figure 3. ORTEP drawing of compound **11**.

Protection of the secondary hydroxyl group of **11** as the TIPS ether afforded a separable mixure of diastereomeric methyl esters. Purification by chromatography and hydrolysis with 1 N NaOH solution gave the acid **13**.

The Hiv (**15**) obtained from L-valine[2d] was protected as its allyl ester (**16**, Scheme 2); the coupling of **16** with the isostatine unit (**13**) using DCC and DMAP afforded **17**. Removal of the allyl group of **17** using $Pd(PPh_3)_4$ gave acid **6** in quantitative yield.[8]

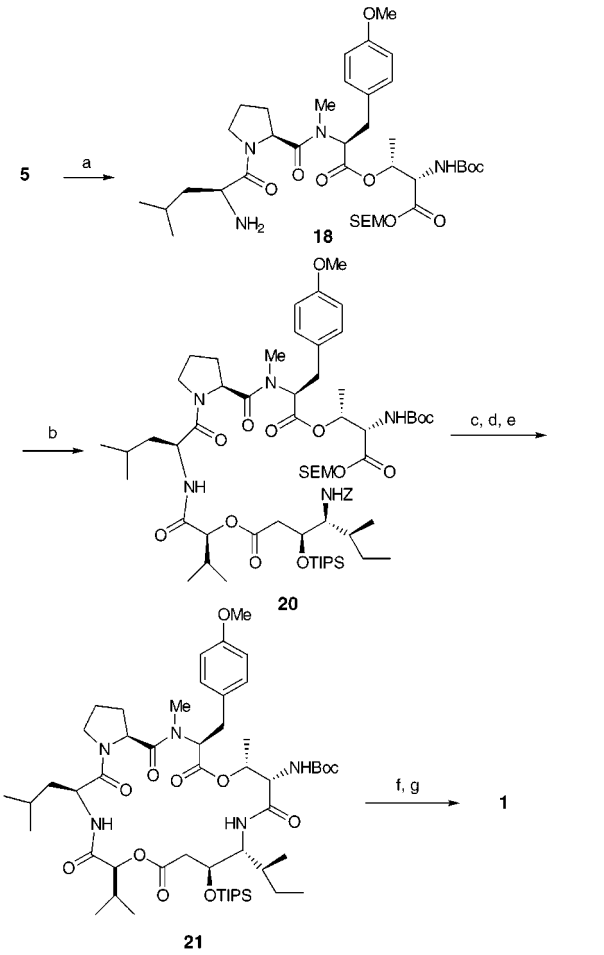
Scheme 2[a]



[a] Reagents and conditions: (a) 1 N H_2SO_4, $NaNO_2$, 0 °C to rt (78%); (b) allyl bromide, DMF, K_2CO_3, Bu_4NI, rt (96%); (c) **13**, DCC, DMAP, 0 °C to rt (65%); (d) $Pd(PPh_3)_4$, morpholine, THF, rt; (e) PFPOH, EDAC·HCl, DMAP, CH_2Cl_2, 0 °C to rt (83% two steps overall).

Hydrogenolysis of the Cbz group of the fully protected tetrapeptide **5** gave free amine **18** (Scheme 3). Coupling of amine **18** with acid **6** using PyBrOP[9] or HATU[10] afforded the linear precursor of **1** (**20**) in poor yield. However, the coupling of the activated PFP ester **19** of acid **6** and amine **18** provided the protected linear precursor **20** in 96% yield. Mild cleavage of the SEM ester[11] with $MgBr_2$·Et_2O was selective in the presence of the Boc, TIPS, Cbz, and ester functionalities, as we had demonstrated previously.[12] The resulting acid was subjected to hydrogenolysis. Macrocyclization using HATU afforded product **21** in good yield. The synthesis of the side chain was accomplished using the modified strategy developed in our previous synthesis of **2**.[2d] Hydrogen chloride (gas) in ethyl acetate successfully cleaved both Boc and TIPS protecting groups on the macrocycle **21** to yield a product, which was coupled to side chain **4** using BOP,[13] to afford tamandarin A {$[\alpha]^{20}_D$ −43.93 (*c* 1.05, $CHCl_3$)}, identical with the natural product (IR, ^1H and ^{13}C spectra).

Scheme 3[a]



[a] (a) H_2, Pd/C, EtOAc/MeOH (98%); (b) **19**, DIEA, DMAP, CH_2Cl_2, 0 °C to rt (96%); (c) $MgBr_2$·Et_2O, CH_2Cl_2, −15 to 0 °C; (d) H_2, Pd/C, EtOAc/MeOH (1:1), rt; (e) HATU, DMF, DIEA, rt (63% three steps overall); (f) HCl(g), EtOAc, −30 to 0 °C; (g) **4**, BOP, NMM, CH_2Cl_2, 0 °C to rt (56% two steps overall).

In conclusion, we have achieved the first total synthesis of (−)-tamandarin A (**1**) in 15 steps from D-alloisoleucine, in 12.8% overall yield and 87.2% average yield per step. This efficient synthetic route to tamandarins is anticipated to accelerate SAR and mechanistic studies of this interesting natural product.

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Supporting Information Available: Experimental procedures, characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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