

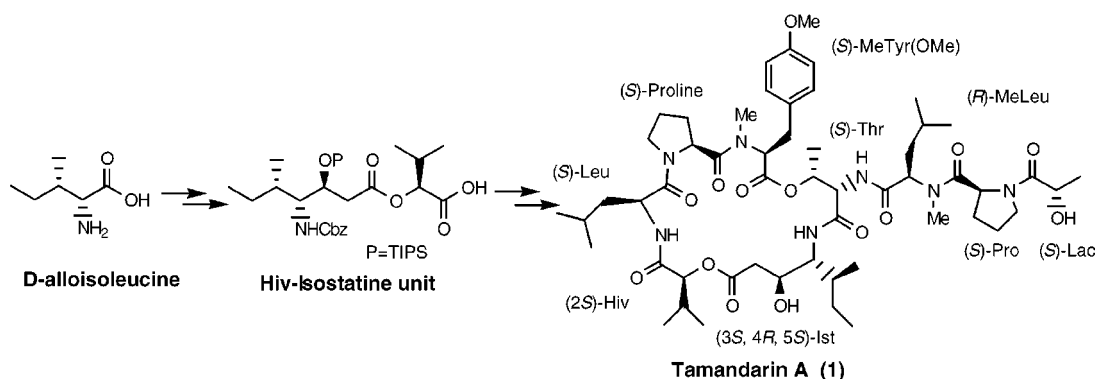
# The First Total Synthesis of (–)-Tamandarin A

Bo Liang, Padma Portonovo, Matthew D. Vera, Dong Xiao, and Madeleine M. Joullie\*

Department of Chemistry, University of Pennsylvania,  
Philadelphia, Pennsylvania 19104-6323  
mjoullie@sas.upenn.edu

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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<sub>50</sub> 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).

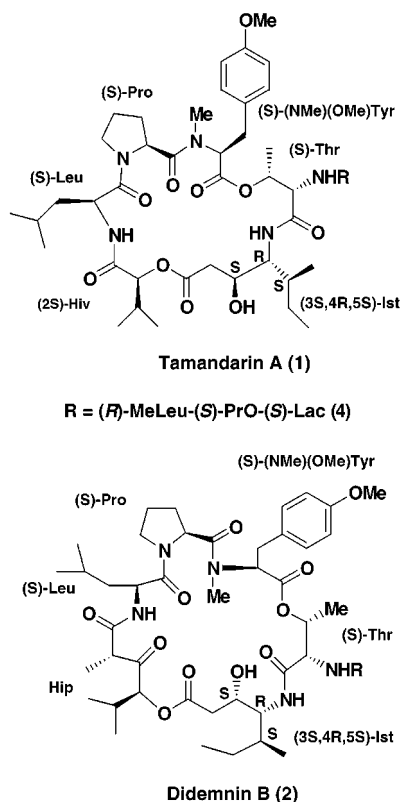
Tamandarin A (1), a newly isolated natural product similar in structure to didemnin B (2), was shown to be somewhat more active in vitro than 2 against pancreatic carcinoma with an ED<sub>50</sub> value of 1.5–2 ng/mL. We report here the first total synthesis of 1. The key steps include a practical stereoselective 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).<sup>1</sup> The structure of 1 is similar to that of didemnin B (2), a potent antiviral, immunosuppressive, and antitumor agent.<sup>2</sup> The macrocyclic core of tamandarin A contains the simpler  $\alpha$ -hydroxyisovaleryl (Hiv) isostatine unit, rather than the more complex  $\alpha$ -( $\alpha$ -hydroxyisovaleryl)-propionyl (Hip) isostatine subunit of didemnin B. The

remainder of the tamandarin A structure is identical to that of didemnin B.

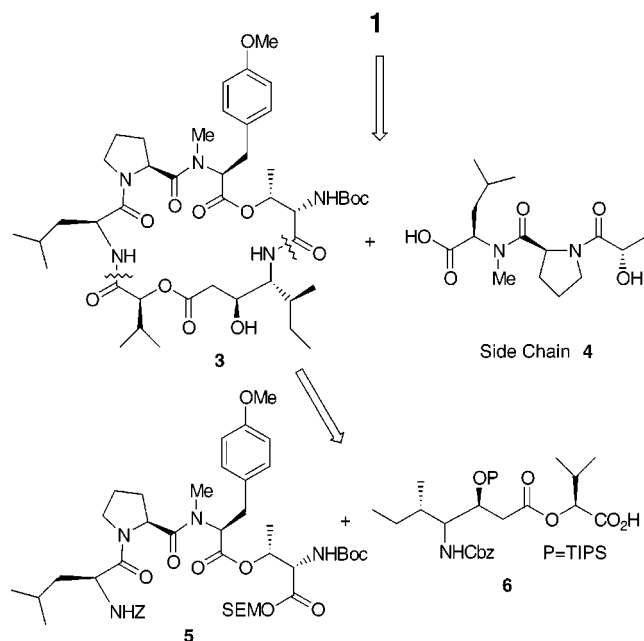
Beyond the structural homology, 1 seems to exhibit much of the same biological activity as 2. It retains similar levels of in vitro antitumor activity in clonogenic assays (1–2 ng/mL) as well as protein biosynthesis inhibition properties.<sup>1</sup> The limited supply of 1 from its natural source has 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.<sup>3</sup>

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

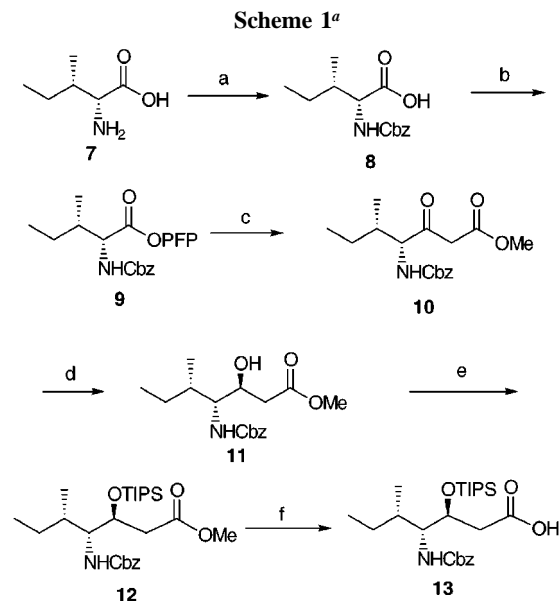
The retrosynthetic analysis of **1** is shown in Figure 2. The macrocyclic core of the target molecule is disconnected into two fragments, the tetrapeptide portion **5** and the Hiv-



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

isostatine unit **6**. Compound **5** is an advanced intermediate used in our previous synthesis of **2**.<sup>2d</sup>

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*)-



<sup>a</sup> Reagents and conditions: (a) Cbz-succinimide, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt (99%); (b) pentafluorophenol, EDAC·HCl, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt; (c) LiCH<sub>2</sub>CO<sub>2</sub>Me, THF, -78 °C (80% two steps); (d) KBH<sub>4</sub>, MeOH, -30 to 0 °C; de 91% (99%); (e) TIPSOtF, 2,6-lutidine, CH<sub>2</sub>Cl<sub>2</sub>, rt (94%); (f) 1 M NaOH, MeOH: THF:H<sub>2</sub>O (1:1:1), 0 °C to rt (95%).

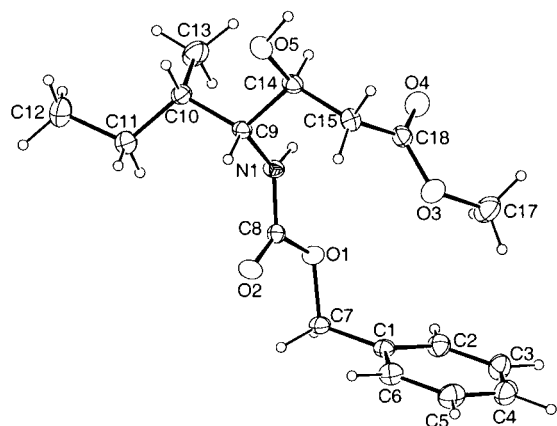
isostatine portion **13** can be prepared from the noncoded α-amino acid D-alloisoleucine (**7**) on a multigram scale, which we accomplished in four steps from commercially available (*S*)-2-methylbutanol.<sup>4</sup> The amino function of **7** was protected as its benzyloxycarbonyl (Cbz) derivative **8**. Activation of the carboxylic functionality of **8** as its pentafluorophenyl ester,<sup>2f,5</sup> followed by condensation with the lithium enolate of the methyl acetate, gave the β-ketoester **10**.<sup>6</sup> Stereoselective reduction of **10** with KBH<sub>4</sub> gave **11** as

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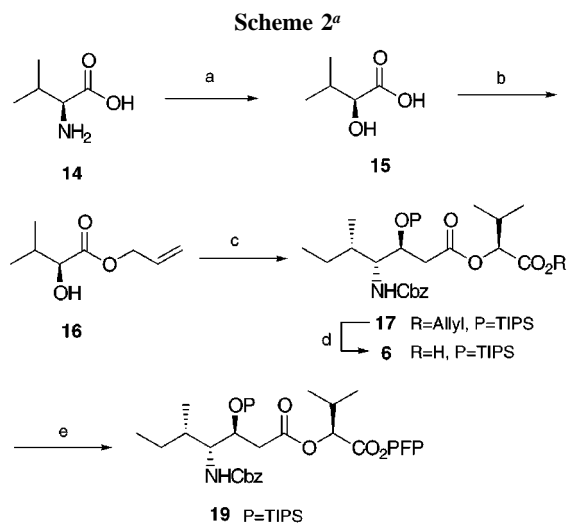
an 11:1 diastereomeric mixture.<sup>7</sup> Crystallization of **11** afforded the diastereomerically pure product, whose stereochemistry was determined by the NMR coupling constants of the corresponding 2,2-dimethyloxazolidine<sup>7</sup> and further confirmed by X-ray crystallography (Figure 3).



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

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

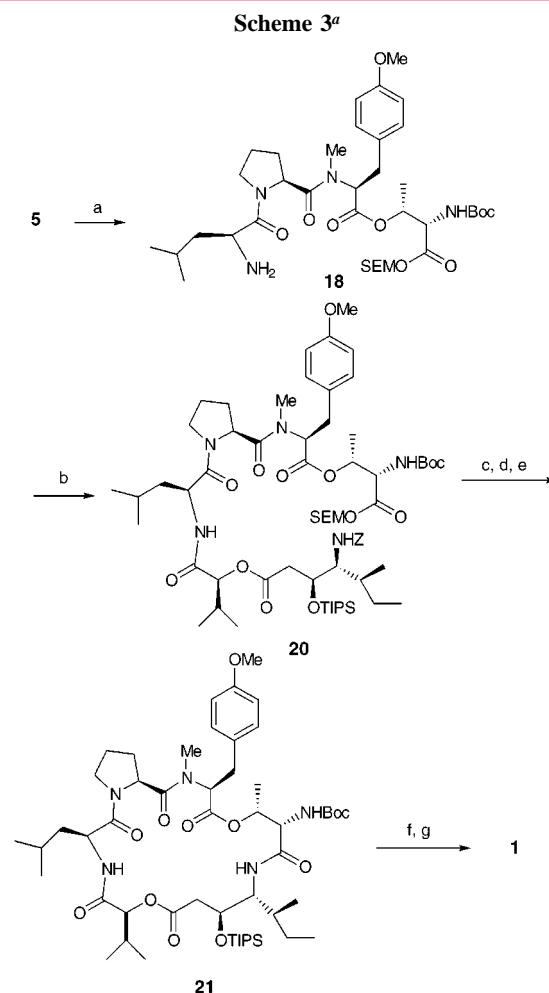
The Hiv (**15**) obtained from L-valine<sup>2d</sup> was protected as its allyl ester (**16**, Scheme 2); the coupling of **16** with the



<sup>a</sup> Reagents and conditions: (a) 1 N H<sub>2</sub>SO<sub>4</sub>, NaNO<sub>2</sub>, 0 °C to rt (78%); (b) allyl bromide, DMF, K<sub>2</sub>CO<sub>3</sub>, Bu<sub>4</sub>NI, rt (96%); (c) **13**, DCC, DMAP, 0 °C to rt (65%); (d) Pd(PPh<sub>3</sub>)<sub>4</sub>, morpholine, THF, rt; (e) PFPOH, EDAC·HCl, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt (83% two steps overall).

isostatine unit (**13**) using DCC and DMAP afforded **17**. Removal of the allyl group of **17** using Pd(PPh<sub>3</sub>)<sub>4</sub> gave acid **6** in quantitative yield.<sup>8</sup>

Hydrogenolysis of the Cbz group of the fully protected tetrapeptide **5** gave free amine **18** (Scheme 3). Coupling of



<sup>a</sup> (a) H<sub>2</sub>, Pd/C, EtOAc/MeOH (98%); (b) **19**, DIEA, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt (96%); (c) MgBr<sub>2</sub>·Et<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, -15 to 0 °C; (d) H<sub>2</sub>, 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<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt (56% two steps overall).

amine **18** with acid **6** using PyBrOP<sup>9</sup> or HATU<sup>10</sup> 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<sup>11</sup> with MgBr<sub>2</sub>·Et<sub>2</sub>O was selective in the presence of the Boc, TIPS, Cbz, and ester functionalities, as we had demonstrated previously.<sup>12</sup> 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**.<sup>2d</sup> 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,<sup>13</sup> to afford tamandarin A {[α]<sub>D</sub><sup>20</sup> -43.93 (*c* 1.05, CHCl<sub>3</sub>)}, identical with the natural product (IR, <sup>1</sup>H and <sup>13</sup>C spectra).

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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