Total Syntheses and Biological Investigations of Tamandarins A and B and Tamandarin A Analogs

Bo Liang, David J. Richard, Padma S. Portonovo, and Madeleine M. Joullié*

Contribution from the Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323

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Abstract: Tamandarins A (**1**) and B (**2**), two natural products similar in structure to didemnin B (**3**), were recently isolated from a Brazilian marine ascidian of the family Didemnidae. The cytotoxicity of **1** was reported to be somewhat more potent in vitro than that of **3** against various human cancer cell lines. The present account describes the first total syntheses of **1** and **2**, and the syntheses of tamandarin A side chain analogues. The cytotoxicity data for these compounds show that the side chain modifications exhibit a parallel effect for both didemnins and tamandarins. This observation supports tamandarins' role as didemnins' mimic.

Introduction

Tamandarins A and B (**1** and **2**) are two naturally occurring cytotoxic cyclic depsipeptides recently isolated from a Brazilian ascidian of the family Didemnidae.[1] The structures of **1** and **2** are similar to that of didemnin B (**3**), a potent antiviral immunosuppressant and antitumor agent.[2−8] The macrocyclic cores of tamandarin A (**1**) and tamandarin B (**2**) contain the α-hydroxyisovaleryl (Hiv) isostatine unit and α-hydroxyisovaleryl (Hiv) norstatine unit, respectively, rather than the more complex α-(α-hydroxyisovaleryl)propionyl (Hip) isostatine moiety of didemnin B (Figure 1).

Beyond its structural homology, **1** was reported to exhibit much of the same biological activity as **3**.[1] Tamandarin A retains similar levels of in vitro antitumor activity in clonogenic assays (1 to 2 ng/mL) as well as protein biosynthesis inhibition properties.[1] However, no data were reported for tamandarin B (**2**) due to the isolation of an insufficient quantity of this minor metabolite.[1] The limited supply of **1** and **2** from their natural source has prevented their full biological characterization. In particular, it was not established whether tamandarin A is a fully competent mimic of didemnin B in vitro and in vivo, and screening for antiviral and immunosuppressive activities has not been reported. A viable synthetic route to tamandarins A and B would make these investigations possible. We reported the first total synthesis of **1** in a recent communication.[9] The same synthetic strategy was applied successfully to the syntheses of **2**[10] and tamandarin A analogues.[11] With this highly efficient approach in hand, analogue preparation and screening have been greatly 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.[12−17] We present here an efficient, convergent synthetic strategy, which provides access to both **1** and **2**, as well as their analogues. The synthetic tamandarin A analogues, **4**, **5**, and **6**, have shown parallel potencies to those of the side chain didemnin congeners **7**, **8**, and **9**. With dehydrodidemnin B (Aplidine) (**7**) reentering clinical trials,[18] the discovery of potent tamandarin analogues may redefine lead compounds in clinical trials.[11]

Results and Discussion

Total Syntheses of Tamandarins A (1) and B (2). Due to the importance of side chain structure for the biological activity of didemnins, a synthetic scheme which involves addition of the side chain to the macrocycle as the final step was necessary for facilitating analogue preparation. The retrosynthetic analysis of **1** and **2** is shown in Figure 2. The macrocyclic cores of the target molecules are further disconnected into two fragments, the tetrapeptide portion **13** and the Hiv-isostatine unit **14** or Hiv-

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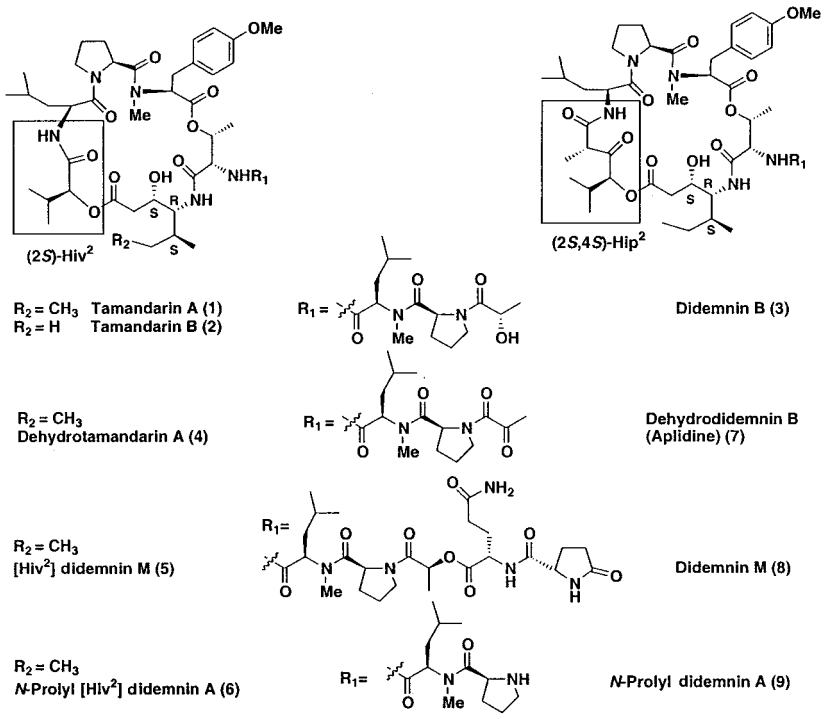


Figure 1. Structures of didemnins, tamandarins, and analogues.

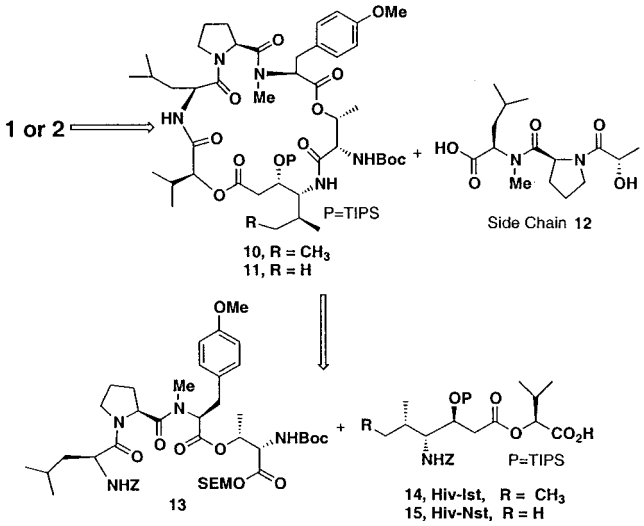
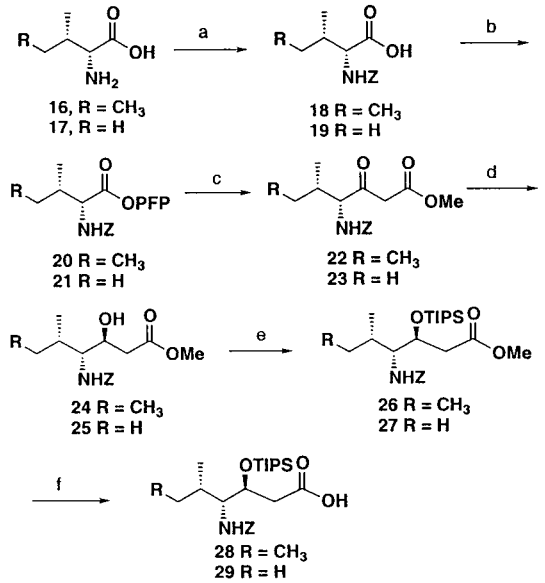


Figure 2. Retrosynthesis of tamandarins A (**1**) and B (**2**).

norstatine unit **15**. Compound **13** is an advanced intermediate used in our previous synthesis of **3**.[5]

The syntheses began with the lower portions of the macrocycle (Figure 2), (2*S*)-Hiv-isostatine unit (Hiv-Ist) **14** or (2*S*)-Hiv-norstatine unit (Hiv-Nst) **15**. The (3*S*,4*R*,5*S*)-isostatine portion **28** may be prepared from the noncoded α-amino acid, D-alloisoleucine (**16**), which was prepared in four steps from affordable and commercially available (*S*)-2-methyl butanol on a multigram scale.[19] D-Valine was employed as the starting material for the synthesis of the analogous norstatine acid **29** (Scheme 1). The amino functions of **16** and **17** were protected as benzyloxycarbonyl (Z) derivatives **18** and **19**. Activation of the carboxylic functionalities of the resulting compounds (**18** and **19**) by formation of their PFP esters (**20** and **21**),[7,20] followed by condensation with the lithium enolate of methyl

Scheme 1[a]



[a] Reagents and conditions. **16** to **28**: (a) Z-succinimide, Et_3N, CH_2Cl_2, 0 °C to room temperature (99%); (b) PFPOH, EDAC•HCl, DMAP, CH_2Cl_2, 0 °C to room temperature; (c) $LiCH_2CO_2Me$, THF, −78 °C (80% two steps); (d) KBH_4, MeOH, −30 to 0 °C (99%); (e) TIPSOTf, 2,6-lutidine, CH_2Cl_2, room temperature (94%); (f) 1 M NaOH, MeOH:THF:H_2O (1:1:1), 0 °C to room temperature (95%). **17** to **29**: (a) Z-Cl, saturated $NaHCO_3$, 0 °C to room temperature (93%); (b) PFPOH, EDAC·HCl, DMAP, CH_2Cl_2, 0 °C to room temperature (95%); (c) $LiCH_2CO_2Me$, THF, −78 °C (83%); (d) KBH_4, MeOH, −30 to 0 °C (77%); (e) TIPSOTf, 2,6-lutidine, CH_2Cl_2, room temperature (82%); (f) 1 M NaOH, MeOH:THF:H_2O (1:1:1), 0 °C to room temperature (81%).

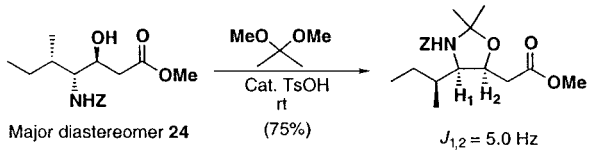
acetate, afforded the β-ketoesters **22** and **23**, respectively.[21] The stereoselective reduction with KBH_4 gave a diastereomeric mixture (11:1),[22] which provided the diastereomerically pure

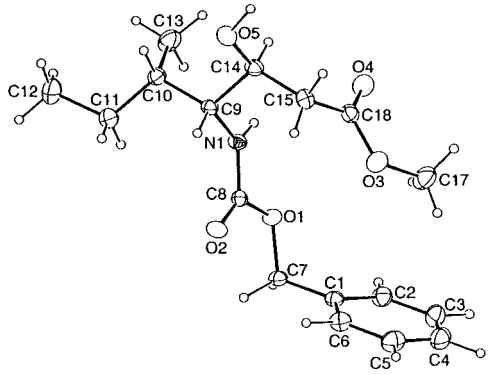
(19) Portonovo, P.; Liang, B.; Joullié, M. M. *Tetrahedron: Asymmetry* **1999**, *10*, 1451−1455.

(20) Schmidt, U.; Kroner, M.; Griesser, H. *Synthesis* **1989**, 832−835.

(21) Harris, B. D.; Bhat, K. L.; Joullié, M. M. *Tetrahedron Lett.* **1987**, *28*, 2837−2840.

Scheme 2





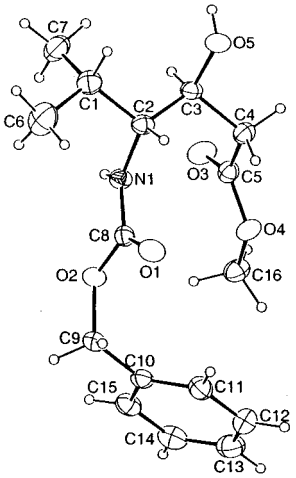


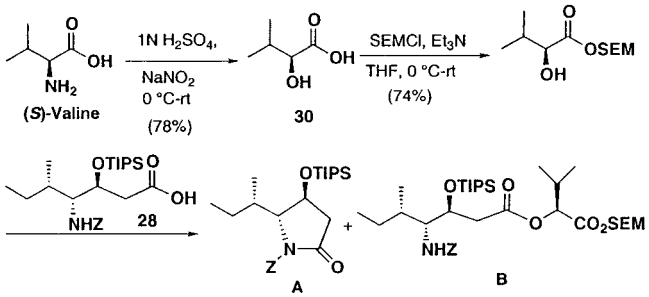
Figure 3. ORTEP drawings of compounds **24** (top) and **25** (bottom).

products **24** and **25** by recrystallization in ether/hexane. This reducing agent was found to provide superior diastereoselectivity in comparison to other reagents which were investigated. The reduction of **22** with KBH_4 at room temperature gave an 80% de in 8 min. By lowering the temperature to −30 to 0 °C, the de was 91% after 15 min. $NaBH_4$ gave an 85% de in 15 min at a temperature of −78 °C. The stereochemistry of the major stereoisomer (**24**) was determined by the NMR coupling constant of the corresponding 2,2-dimethyl oxazolidine ($J_{1,2}$ = 5 Hz),[22] (Scheme 2) and further confirmed by X-ray analysis. The X-ray structures of **24** and **25** are shown in Figure 3. Conversion of the secondary hydroxyl groups to their TIPS ethers, followed by hydrolysis of the methyl esters, produced acids **28** and **29**.

Elaboration of the isostatine acid was accomplished by coupling with the SEM ester of hydroxyisovaline using various coupling conditions (Scheme 3). Unfortunately, utilization of this substrate resulted in the formation of the lactamized product **A** as the major compound instead of the desired linear compound **B**. However, use of the allyl protecting group provided esters **32** and **33** in good yield by treatment with DCC/DMAP and EDAC•HCl/DMAP, respectively (Scheme 4). Removal of the

(22) Harris, B. D.; Joullié, M. M. *Tetrahedron* **1988**, *44*, 3489−3500.

Scheme 3



conditions	A%	B%
DCC, DMAP, toluene 0 °C-rt	40	10
IPCF, DMAP, Et_3N 0 °C	45	15

allyl ester with tetrakis(triphenylphosphine)palladium(0) afforded the acids **14** and **15** in quantitative yield.[23]

With the lower fragments of **1** and **2** in hand, formation of the macrocyclic linear precursor was the next challenge. Tetrapeptide **13** was synthesized in multigram scale utilizing our previous synthetic strategy (Scheme 4).[5] Hydrogenolysis of **13** provided the free amine **34**, which when coupled with the acid (**32**) using PyBrOP[24] or HATU[25−29] afforded the linear precursor (**35**) in poor yield. However, reaction of the activated PFP ester (**37**) provided the protected linear precursor **35** in 96% yield (Scheme 5). In like manner, the linear precursor (**36**) of tamandarin B (**2**) was also synthesized by the analogous reaction in good yield. Selective cleavage of the SEM ester in the presence of Boc, TIPS, and Z protecting groups was achieved with $MgBr_2 \cdot Et_2O$ as previously reported.[30,31] The resulting acids were converted to their free secondary amines by hydrogenolysis. Macrocyclization with HATU then afforded the fully protected macrocycles (**39** and **40**).

The tamandarin macrocycle salts were obtained by treatment with hydrogen chloride (gas) in ethyl acetate, which successfully removed both Boc and TIPS protecting groups. The synthesis of the side chain **12** was accomplished by using the modified strategy developed in our previous synthesis of **3**.[5,32] The X-ray of the advanced intermediate L-Lac-L-Pro-*N*-Methyl-D-Leu methyl ester (**41**) is shown in Figure 4. The tamandarin A macrocycle salt was coupled with this side chain by using BOP[33] to afford tamandarin A, which possessed spectral properties in agreement with those of the natural product (IR, ^1H, and ^{13}C spectra). Although BOP was the reagent of choice in all previous investigations,[5,34−36] the analogous reaction with the tamandarin

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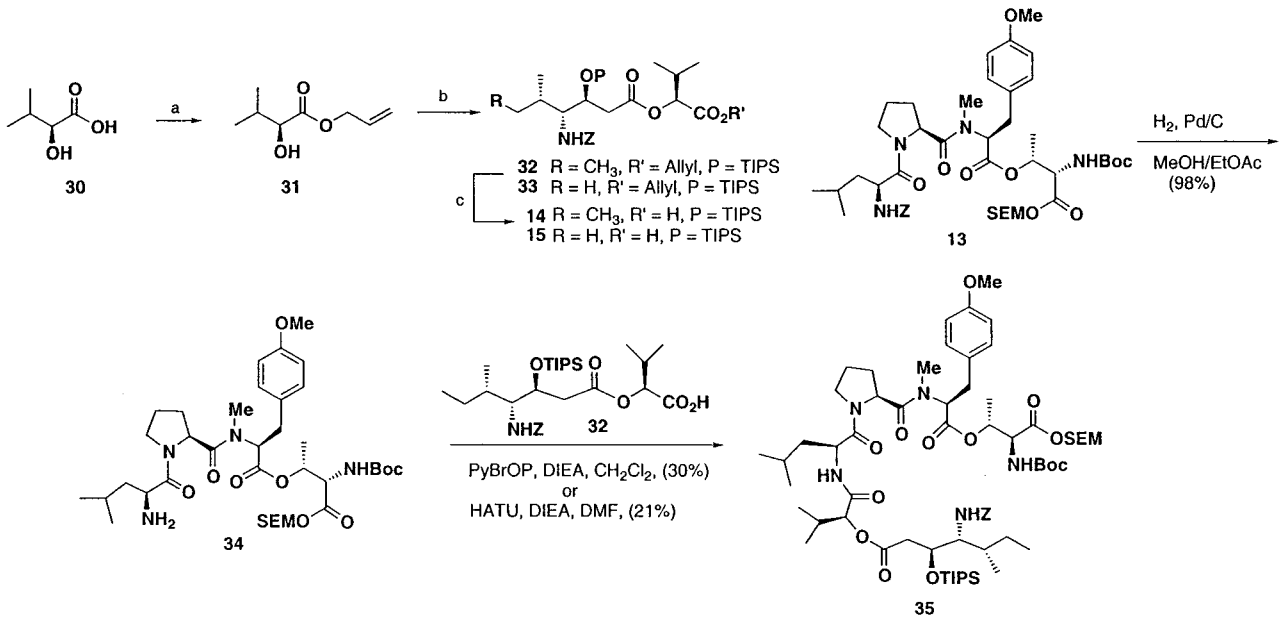
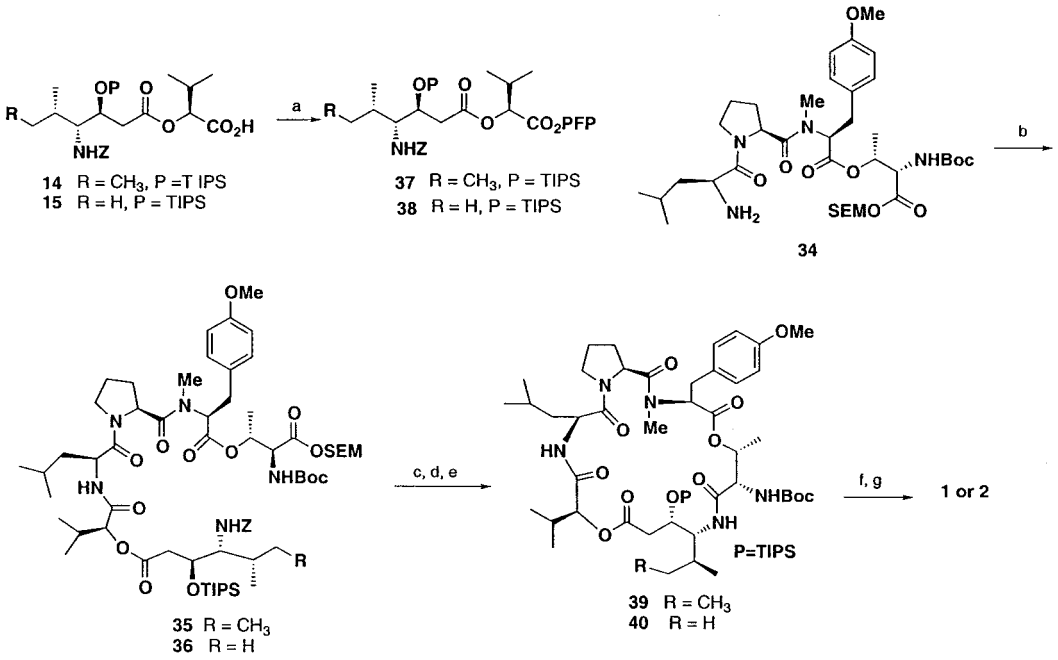
Scheme 4[a]



[a] Reagents and conditions: (a) allyl bromide, DMF, K_2CO_3, Bu_4NI, room temperature (96%). **31** to **14**: (b) **28**, DCC, DMAP, 0 °C to room temperature (65%); (c) $Pd(PPh_3)_4$, morpholine, THF, room temperature. **31** to **15**: (b) **29**, EDAC·HCl, DMAP, CH_2Cl_2, 0 °C to room temperature (60%); (c) $Pd(PPh_3)_4$, morpholine, THF, room temperature.

Scheme 5[a]



[a] Reagents and conditions. Synthesis of **1**: (a) PFPOH, EDAC·HCl, DMAP, CH_2Cl_2 (83% 2 steps overall from allyl deprotection); (b) **37**, DIEA, DMAP, CH_2Cl_2, 0 °C to room temperature (96%); (c) $MgBr_2$·Et_2O, CH_2Cl_2, −15 to 0 °C; (d) H_2, Pd/C, EtOAc/MeOH (1:1), room temperature; (e) HATU, DMF, DIEA, room temperature (63% 3 steps overall); (f) HCl(g), EtOAc, −30 to 0 °C; (g) **12**, BOP, NMM, CH_2Cl_2, 0 °C to room temperature (56% 2 steps overall). Synthesis of **2**: (a) PFPOTf, Pyr., CH_2Cl_2 (64% 2 steps overall from allyl deprotection); (b) **38**, DIEA, DMAP, CH_2Cl_2, 0 °C to room temperature (79%); (c) $MgBr_2$·Et_2O, CH_2Cl_2, −15 to 0 °C; (d) H_2, Pd/C, EtOAc/MeOH (1:1), room temperature; (e) HATU, DMF, DIEA, room temperature (23% 3 steps overall); (f) HCl(g), EtOAc, −30 to 0 °C; (g) **12**, DEPBT, DIEA, CH_2Cl_2, 0 °C to room temperature (85% 2 steps overall).

B macrocycle provided the final product only in 20% yield. The yield of this coupling was dramatically improved by use of the newly reported coupling reagent 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-one (DEPBT).[37]

Tamandarin A Analogues: Design and Syntheses

Though the complete SAR profile and mechanism(s) of action of didemnins are still evolving, it is believed that the side chains are important in determining biological activities as illustrated in Table 1.[4] Didemnin A is the simplest member of the family, having only *N*-methyl-D-leucine as its side chain. Didemnin B

(35) Pfizenmayer, A. J.; Ramanjulu, J.; Vera, M. D.; Ding, X.; Xiao, D.; Chen, W.-C.; Joullié, M. M.; Tandon, D.; Toogood, P. L. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3653−3656.

(36) Pfizenmayer, A. J.; Ramanjulu, J.; Vera, M. D.; Ding, X.; Xiao, D.; Chen, W.-C.; Joullié, M. M. *Tetrahedon* **1999**, *55*, 313−334.

(37) Li, H.; Jiang, X.; Ye, Y.-h.; Fan, C.; Romoff, T.; Goodman, M. *Org. Lett.* **1999**, *1*, 91−93.

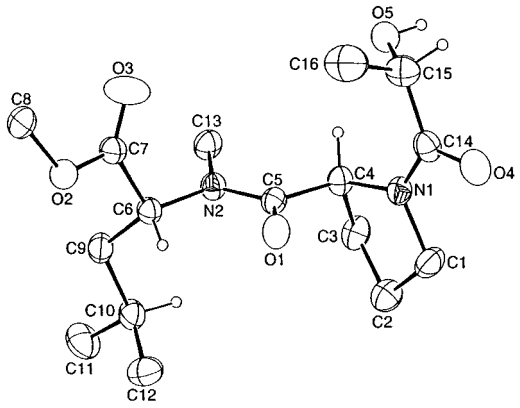


Figure 4. ORTEP drawing of L-Lac-L-Pro-*N*-Methyl-D-Leu methyl ester **41**.

Table 1. The Importance of the Side Chain for the Biological Activities of Didemnins[a]

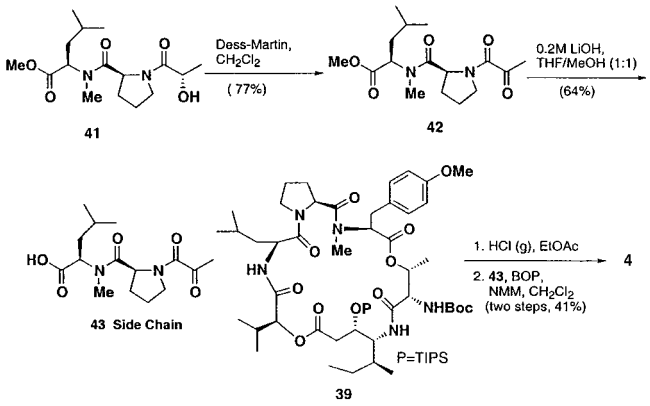
Compound name	Immunosuppressive Activity IC_{50} in MLR assay	Cytotoxic Activity IC_{50} against P388 cells
didemnin A	0.98 nM	11 nm
didemnin B (**3**)	0.42 nM	1.8 nM
dehydrodidemnin B (Aplidine) (**7**)	0.38 nM	0.18 nM
didemnin M (**8**)	0.00076 nM	1.5 nM

[a] IC_{50} concentration at 50% inhibition.

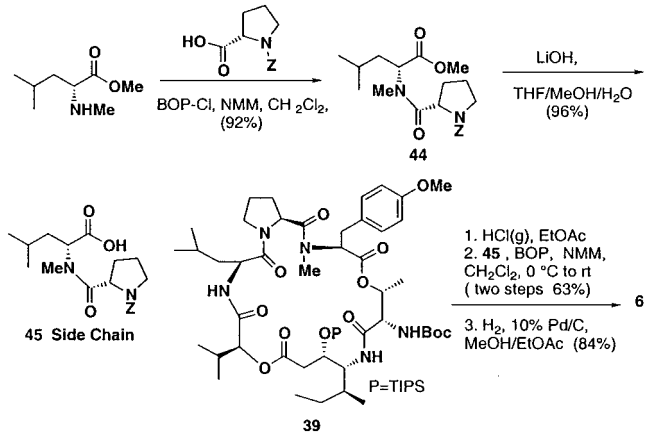
(**3**), the first marine natural product that entered Phase I and II clinical trials, has been the lead didemnin compound over the past 20 years of didemnin research. Dehydrodidemnin B (Aplidine) (**7**), which contains a pyruvyl residue instead of the lactyl group of **3,** exhibited a 10-fold increase in cytotoxicity. Furthermore, the cardiotoxicity which caused didemnin B to be discontinued in clinical trials was not observed with this compound.[18] For this reason, dehydrodidemnin B was believed to have clinical potential and was introduced by PharmaMar into Phase I clinical trials in January, 1999.[18] Didemnin M (**8**), which has an elongated side chain relative to didemnin B, has shown exceptional immunosuppressive activity with 0.76 pM IC_{50} in the mixed lymphocyte reaction assay.[4] *N*-Prolyldidemnin A (**9**),[7,34] which lacks the lactyl group present in **3**, has been synthesized as a didemnin analogue and shown cytotoxicity comparable to didemnin B.

Tamandarin A (**1**) has been reported to exhibit cytotoxic and protein biosynthesis inhibition properties comparable to those of didemnin B,[1] suggesting that the macrocyclic Hip subunit may not be required for bioactivity. However, the immunosuppressive activity of tamandarin-type congeners has not been examined. Our current research effort is focused on determining the effects of side chain structural changes on this property. To investigate the consequences of the Hip-to-Hiv modification present in tamandarin-type congeners for the varied biological effects exerted by this family of natural products, analogue synthesis was undertaken. With the synthesis of [Hiv^2]didemnin M (**5**) recently reported,[32] we now disclose the syntheses of dehydrotamandarin A (**4**) and *N*-prolyl [Hiv^2]didemnin A (**6**). These analogues, which have not been isolated as natural products, contain the simplified tamandarin macrocycle and the same side chains which are present in dehydrodidemnin B (**7**), didemnin M (**8**), and *N*-prolyldidemnin A (**9**), respectively. Biological testing of these compounds, and comparison to the results provided by their didemnin counterparts, will establish the relevance of both the Hiv^2 residue and the effect of side chain variations on the biological activities.

Scheme 6



Scheme 7



With the A tamandarin macrocycle **39** in hand, the synthesis of dehydrotamandarin A (**4**) was straightforward (Scheme 6). Dess-Martin oxidation of the secondary alcohol **41** provided the diketone compound **42** and saponification of the methyl ester afforded the free acid side chain **43**. The synthetic tamandarin A analogue **4** was synthesized employing the BOP mediated coupling strategy described above.

The synthesis of *N*-prolyl [Hiv^2] didemnin A (**6**) is shown in Scheme 7. The coupling of *N*-methyl D-leucine methyl ester and *N*-Z-proline with BOP-Cl provided the dipeptide **44** in high yield, which was subjected to saponification to afford the carboxylic acid **45**. The two-step deprotection of the fully protected tamandarin A macrocycle **39**, followed by coupling with the side chain **45**, gave the desired product. Removal of the Z protecting group present on the proline residue afforded the synthetic tamandarin A analogue **6**.

Biological Investigations of the Natural Products and Synthetic Analogues

Tamandarin B (**2**) and the synthetic tamandarin A analogues **4**, **5**, and **6** were tested by the National Cancer Institute against various cell lines in vitro.[38] A representative sample of cytotoxic activity data, derived from 48 h of continuous drug exposure of at least five concentrations at 10-fold dilutions, is shown in Table 2.

The cytotoxicity data show that tamandarin B (**2**) is more active than didemnin B (**3**), dehydrotamandarin A (**4**) exhibits over a 10-fold potency increase, and both [Hiv^2] didemnin M (**5**) and *N*-prolyl [Hiv^2] didemnin A (**6**) possess comparable cytotoxicity, though examination of the immunosuppressive

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Table 2. NCI-60 Mean Data from the NCI-60 Tumor Cell Screen[a]

Compound	Growth Inhibition (GI_{50})	50% Cell Kill (LC_{50})
didemnin B (**3**)	13 nM	3.8 μM
tamandarin B (**2**)	2.3 nM	1.4 μM
dehydrotamandarin A (**4**)	1 nM	2.7 μM
[Hiv^2] didemnin M (**5**)	4 nM	7.6 μM
N-prolyl [Hiv^2] didemnin A (**6**)	16 nM	10.2 μM

[a] Preliminary results from the NCI-60 tumor cell screen. Concentrations for 50% growth inhibition (GI_{50}) and 50% cell kill (LC_{50}) are based upon the mean-graph midpoint across all cell lines.

activity of **5** is still in progress. The side chain modifications of tamandarin A provide strong evidence that tamandarins do mimic the biological activities of the didemnins. To target the localization properties of these compounds, coumarin-labeled fluorescent didemnins[39] and tamandarins[11,40] have been synthesized. The two probes were shown to share the same localization pattern in predators (fish) and to behave similarly. These results further indicate that tamandarin A (**1**) is a competent mimic of didemnin B (**3**).

(39) Portonovo, P.; Ding, X.; Leonard, M. S.; Joullié, M. M. *Tetrahedron* **2000**, *56*, 3687−3690.

(40) Joullié, M. M.; Leonard, M. S.; Portonovo, P.; Liang, B.; Ding, X.; La Clair, J. J. **2001**, manuscript in preparation.

Conclusion

We have completed the first total syntheses of the tamandarin natural products, as well as some of their synthetic analogues. Biological studies indicate that tamandarin A is a competent mimic of didemnin B. These investigations should greatly enhance the still-unfolding research on the mechanism(s) of action of the family of didemnidae ascidian metabolites.

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Supporting Information Available: All experimental procedures, X-ray data of compounds **24**, **25**, and **41**, and copies of IR, ^1H, and ^{13}C NMR spectra of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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