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Synthetic Studies of Tamandarin B Side Chain Analogues

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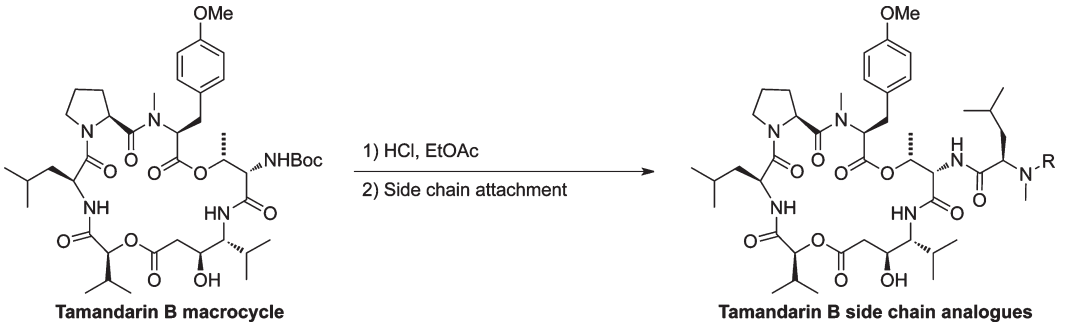

The syntheses of three tamandarin B analogues are described. The goal of these studies was to prepare material to determine their relative therapeutic index and to gain an oversight as to their potential for clinical applications.

Introduction

The discovery of the didemnin family of marine depsipeptides (Figure 1) represented an exciting and intriguing chapter in natural product chemistry.[1] The unusual structure of the macrocycle[2] and the impressive in vivo biological activity of the congeners[3] have led to many studies by research groups from all over the world.[4] Clinical studies of a second-generation didemnin, dehydrodidemnin B (aplidine), continue to stimulate active research in medicinal chemistry.[5]

Congeners having norstatine instead of isostatine in the macrocycle were also isolated (Figure 1). These natural products may be viewed as having an isopropyl side chain attached to residue 1 instead of a *sec*-butyl group and were found to retain the same biological properties. Nordidemnin B (**4**) was shown to be equipotent with didemnin B (**3**) against L1210 cells indicating for the first time that a minor modification in the alkyl side chain of Ist[1] was tolerated.[6]

In 2000, Vervoort and Fenical reported the isolation of two novel cytotoxic cyclic depsipeptides from a Brazilian marine ascidian of the family Didemnidae.[7] They named the major metabolite tamandarin A (**1**) and the corresponding minor metabolite tamandarin B (**2**). Interpretation of FABMS data and extensive 2D NMR studies supported the structures of these new metabolites. Acid and alkaline hydrolysis allowed the assignment of the absolute configurations of the various amino acid components. Tamandarins A and B are structurally similar to didemnin B (**3**)[8,9] and nordidemnin B (**4**),[10] differing from these natural products only in the macrocylic core. While the didemnins possess a 23-membered macrocycle containing an α-(α-hydroxyisovaleryl)propionic acid (Hip^2) unit, the tamandarins contain

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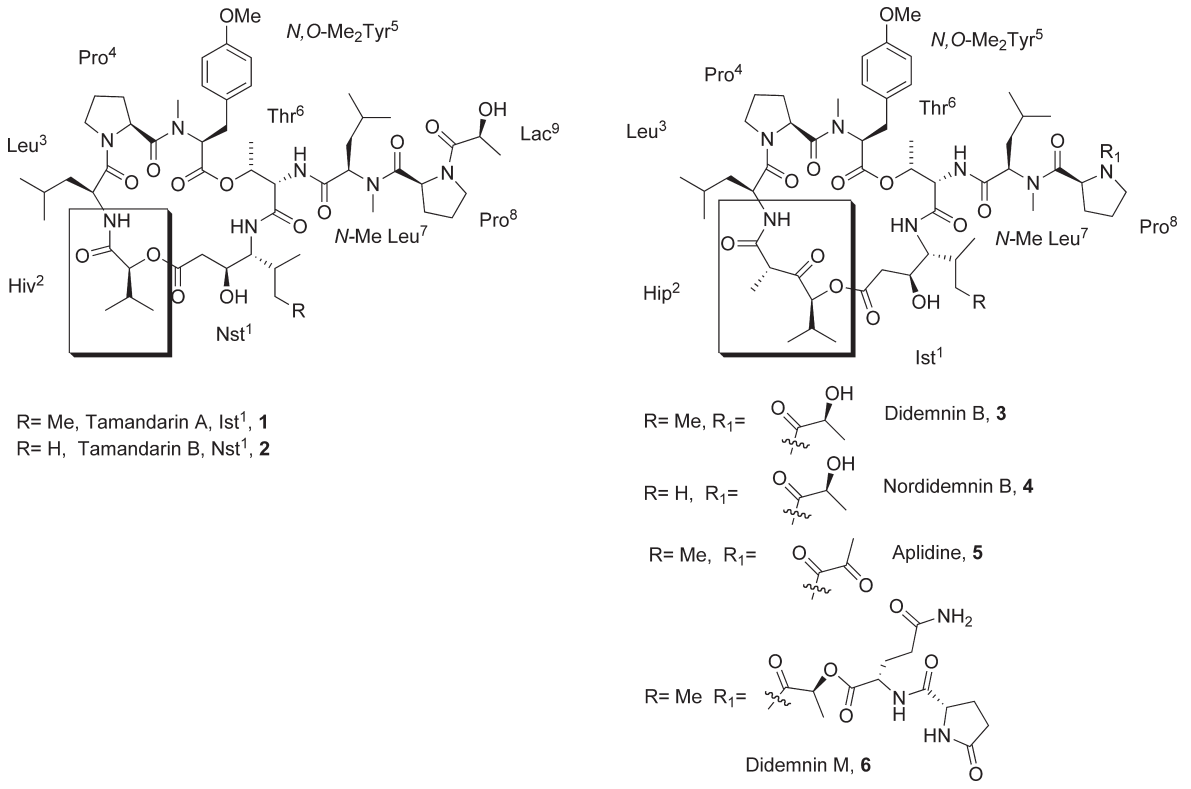

FIGURE 1. Structures of tamandarins A (**1**) and B (**2**) and didemnin B (**3**), nordidemnin B (**4**), aplidine (**5**), and didemnin M (**6**).

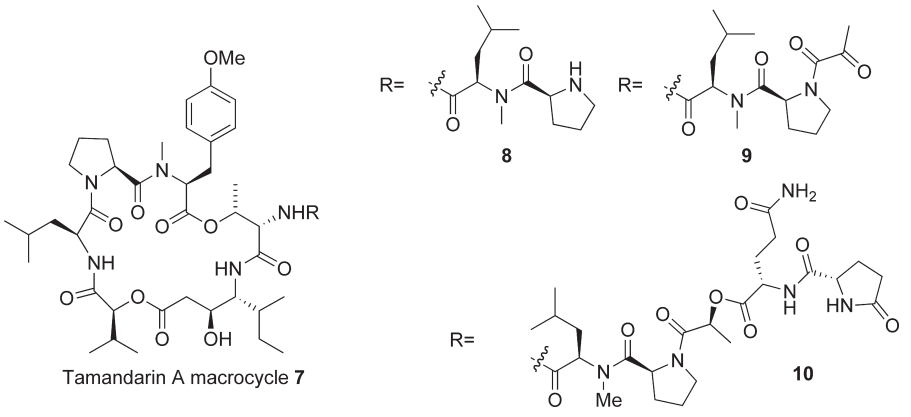

FIGURE 2. Structures of tamandarin A side chain analogues (**8**, **9**, and **10**).

the simpler hydroxyisovaleric acid (Hiv[2]) unit and as such, consist of a 21-membered macrocycle. Tamandarin A (**1**) contains an isostatine (Ist[1]) moiety while tamandarin B (**2**) contains a norstatine (Nst[1]) residue (Figure 1).

The initial structural studies of the solution conformation of **1** indicated that the lack of the chiral propionic unit resulted in only minor conformational differences.[7] The backbone configuration of **1** is stabilized by the same three hydrogen bonds present in **3**: Ist[1] NH-Leu[3] CO, Leu[3] NH-MeLeu[7] CO, and Lac[9] CO-Thr[6] NH, providing the same "bent figure eight" shape of the cyclic peptide ring with the side chain folding back over the cyclic portion of the molecule.[2] Tamandarin B (**2**)[7] and nordidemnin B (**4**)[11] are the only congeners that have a norstatine instead of an isostastine unit in the macrocycle. The first total synthesis of **1** was reported by Joullié and co-workers in 1999,[12] followed by that of **2** in 2000.[13]

To further explore not only the biological activity profile of **1** and **2** but also the possibility that the tamandarins could serve as mimics of the didemnins, a series of tamandarin A analogues with modifications in the side chain region were prepared and exhibited impressive biological activity.[14,15] These new compounds contained the tamandarin A macrocycle

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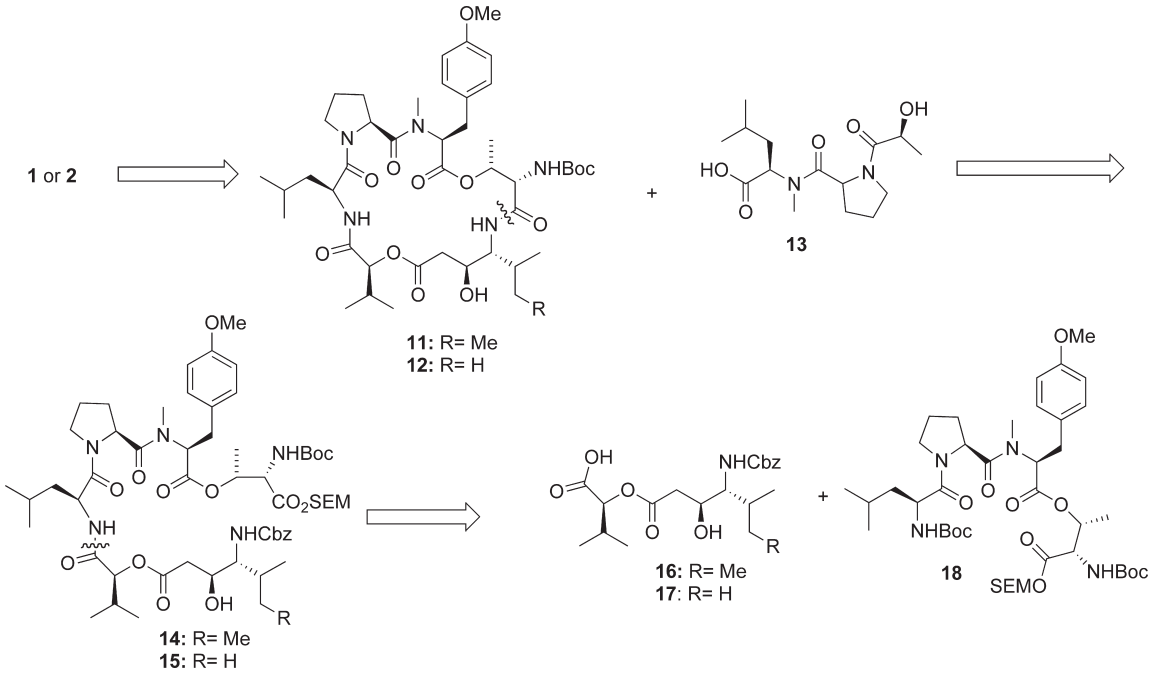
SCHEME 1. Original Retrosynthetic Approach to Tamandarins A (1) and B (2)



with some of the same side chains found in naturally occurring didemnins (Figure 2).[16]

Several analogues of tamandarin B involving modifications in the macrocycle were also prepared and evaluated for anticancer activity providing further insight into the structure–activity relationships of the tamandarins.[17] On the basis of these promising results, we decided to continue these studies by preparing novel tamandarin B analogues with the most active side chains found in the didemnins.

Though the SAR profile and mechanism(s) of action[18–20] of these marine metabolites are still evolving, it is well established that the biological activities of didemnins are strongly dependent upon the structure of the side chain peptide residues.[4] The importance of the *N*-Me-D-Leu[7] residue has been extensively investigated.[21–23] Changes including shortening of the leucine alkyl chain, removal of the *N*-Me group, or replacing D-leucine for L-leucine all caused a significant decrease in the cytotoxic activity. Interestingly, the two nordidemin epimers were equipotent as protein synthesis inhibitors and provided early evidence for separate mechanisms mediating the cytotoxicity and the protein synthesis inhibition.[24] The change in biological activity observed with the tamandarin A analogues in comparison with the natural product (**1**) mirrored the behavior of the analogous didemnin analogues in comparison with the parent structure didemnin B (**3**). These results indicated that tamandarins may share the same molecular targets and mechanism of action as the didemnins. A more definitive study using fluorescence microscopy and synthetic fluorescent didemnin and tamandarin analogues produced more data supporting the theory of a common mechanism of action for these two families of compounds.[25]

Our current research efforts are focused on determining the effects of side chain structural changes on the biological activity of tamandarin B (**2**). To this end, we selected three side chains that exhibited improved or selective biological activity when attached to the didemnin macrocycle.[3] Two of these side chains are shown in Figure 2. A side chain, a $\psi[CH_2NH]$ surrogate, was designed in our laboratory to investigate the importance of the prolyl amide in didemnins and appeared to maintain the biological activity while decreasing toxicity.[16] Side chain **9** is the side chain of aplidine, now in clinical testing.[5] Analogues **21** and **22** could therefore produce compounds of therapeutic value. Side chain **10** present in didemnin M[3,26] was chosen for testing the immunosuppressant activity of **20**. According to recent unpublished results, **20** is believed to be one of the most potent immunosuppressive agents known. It is currently under investigation.

Although synthetic studies of didemnins and tamandarins are known, synthetic approaches to their structures still present challenging problems. The ability to selectively couple the side chain to the macrocycle as a final step was the strategy behind our original retrosynthetic approach

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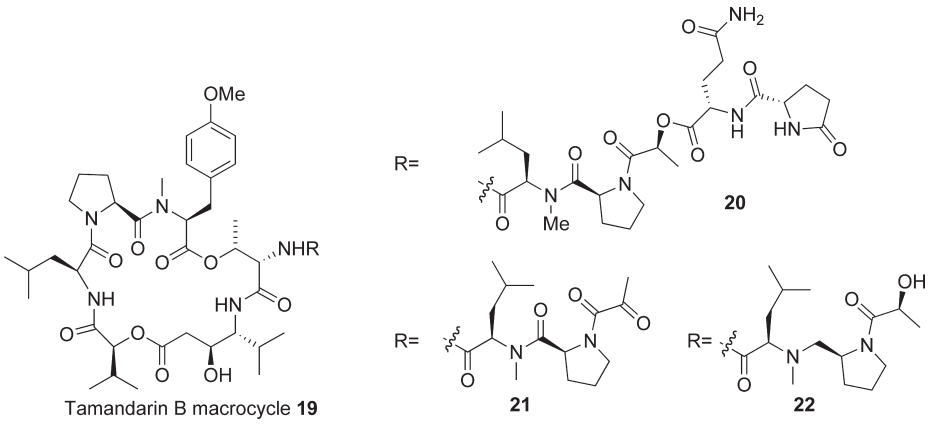
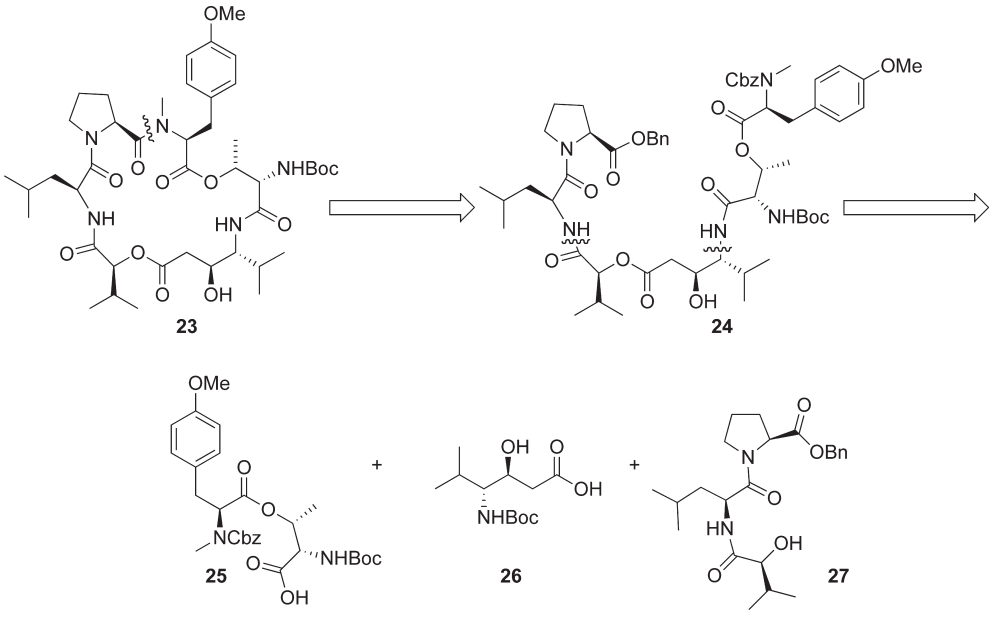


FIGURE 3. Structures of tamandarin B side chain analogues **20**, **21**, and **22**.

SCHEME 2. Revised Retrosynthetic Approach to the Tamandarin B Macrocycle (23)



as it would facilitate future side chain analogue production (Scheme 1).

Results and Discussion

Naturally occurring tamandarin B (**2**) was reported to possess more potent antitumor activity than didemnin B.[16] In an effort to further explore the structure−activity relationship of **2** as well as the relationship between the tamandarins and the didemnins, we now report the preparation of three tamandarin B side chain analogues (Figure 3). The selected side chains are those found in the naturally occurring aplidine (dehydrodidemnin B)[3,27] and didemnin M.[3] The third side chain is a novel didemnin B analogue,[16] a ψ[CH_2NH]amide bond surrogate between *N*-Me-D-Leu[7] and Pro[8] that exhibited enhanced activity in the NCI-60 tumor cell screen.

To efficiently prepare these side chain tamandarin B analogues, an improved synthetic route to the tamandarin B macrocyle (**19**) was needed. The approach used by Joullié and co-workers to prepare tamandarin B analogues modified in the macrocycle afforded a much improved yield in comparison to the original syntheses of **1** and **2** and therefore was adapted to prepare the tamandarin B macrocycle (**19**).[28] The revised retrosynthetic approach is shown in Scheme 2. Rather than closing the macrocycle at the Nst^1-Thr^6 position, the new approach selected the Pro^4-*N*,*O*-Me_2Tyr^5 junction as the site of macrolactamization. Several didemnin syntheses also have used this site very successfully.[29,30] With a reliable, higher yielding route to the macrocycle,[31] our focus shifted to prepare a variety of side chains which could be coupled to the tamandarin B scaffold and subsequently screened for biological activity.

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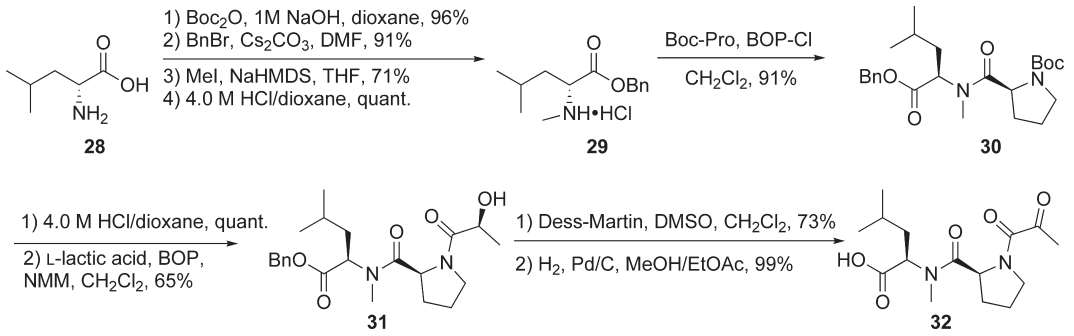
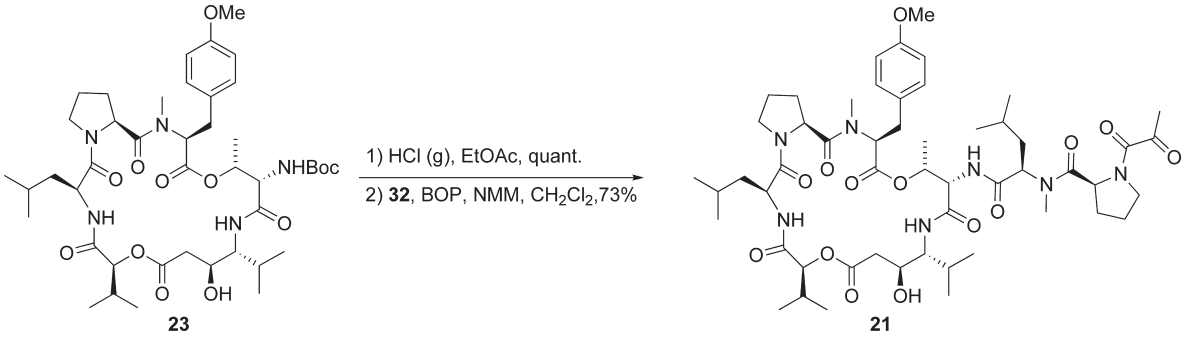
(31) Lassen, K. M.; Lee, J.; Joullié, M. M. *Tetrahedron Lett.* **2010**, *51*, 1635.

SCHEME 3. Synthesis of Aplidine Side Chain 32



SCHEME 4. Installation of the Aplidine Side Chain 32



Synthesis of Dehydrotamandarin B. Dehydrodidemnin B (aplidine)[3,32,33] features the same macrocyclic core structure as didemnin B, with the point of differentiation lying in the side chain. Aplidine features a pyruvyl group at position 9 whereas didemnin B possesses a lactyl group. Aplidine was found to be approximately 10 times as active as didemnin B against L1210 murine leukemia cells and P388 murine leukemia. Aplidine is also strikingly active against two more difficult cancers, B16 melanoma and Lewis lung. Additionally, an increased life span was observed with leukemia, melanoma, and ovarian cancer, and a reduction in tumor size observed with nonsmall cell lung, breast, prostate, and gastric tumors. Researchers were impressed by the enhanced antitumor activity and the reduced toxicity, in particular the lack of cardiac toxicity, which had been an issue with didemnin B clinical trials.[3,32,33] Aplidine was in phase II clinical trials for renal, head and neck, pancreas, lung (NSCLC), and colorectal cancer.[5,34−37] Aplidin is used clinically in anticancer treatments in combination with Gemcitabine or Carboplatin. In addition to its cytotoxicity activity it also exhibits strong antiangiogenic activity that supports its use in multiple myeloma. It appears to be well tolerated in vivo.

In an effort to examine the influence of the pyruvyl group on the biological activity of tamandarin B, the synthesis of dehydrotamandarin B (**21**) was undertaken.

The first step in the synthesis was Boc protection of D-leucine followed by benzyl ester formation (Scheme 3).[38] Treatment of the Boc protected amine with NaHMDS and methyl iodide resulted in *N*-methylation in good yield (**29**). Removal of the Boc group afforded the hydrochloride salt **29** in quantitative yield. This salt was then coupled to Boc-Pro with BOPCl in high yield (**30**). Removal of the Boc group and coupling to L-lactic acid with BOP provided alcohol **31**. Oxidation followed by benzyl group removal under hydrogenolysis conditions led to the fully functionalized side chain (**32**). The synthesis of this side chain is similar to our previously published route. The only minor difference is the Me-D-Leu acid portion is protected as a benzyl ester instead of a methyl ester. This minor change allows intermediate **31** to be used as a common intermediate in the synthesis of **20** without protecting group manipulation (Scheme 3).[14] The synthesis of the novel analogue (−)-dehydrotamandarin B was completed by the BOP- mediated coupling between acid **32** and the amine salt of macrocycle **23** in 73% yield (Scheme 4). This coupling was significantly better than previous efforts on the tamandarin A macrocycle which proceeded in 43% yield.[14]

Synthesis of Tamandarin M. The isolation of didemnin M, along with six other didemnins, was reported in 1995 by Rinehart and co-workers.[26] Didemnin M had previously been reported by another group, but named didemnin H.[39]

(32) Lobo, C. G.; GarciaPozo, S. G.; deCastro, I. N.; Alonso, F. J. *Anticancer Res*. **1997**, *17*, 333.
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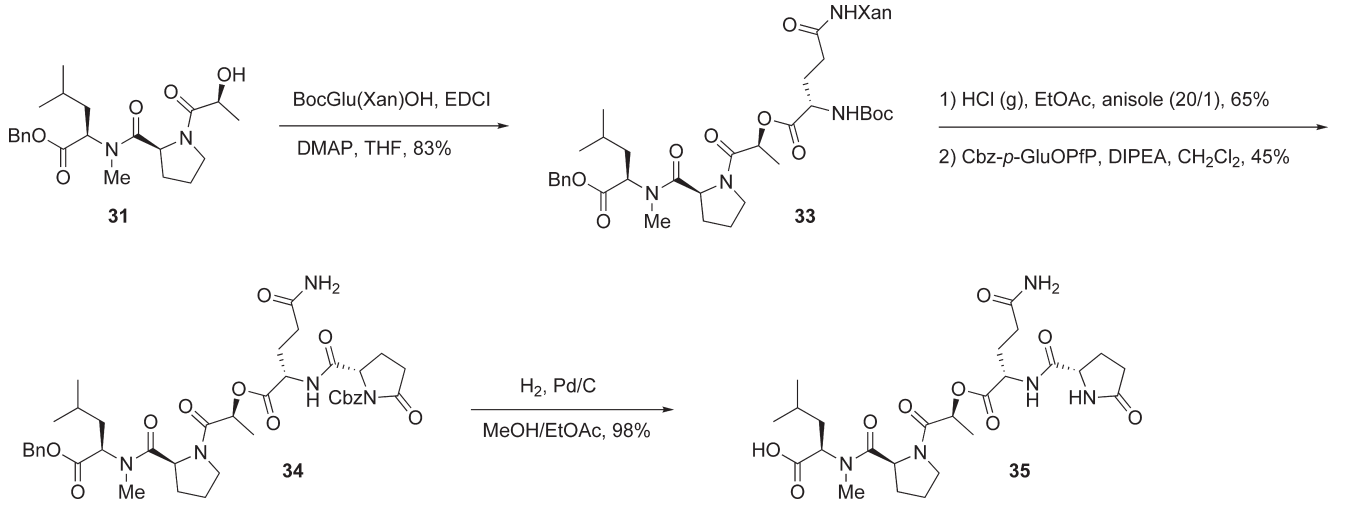
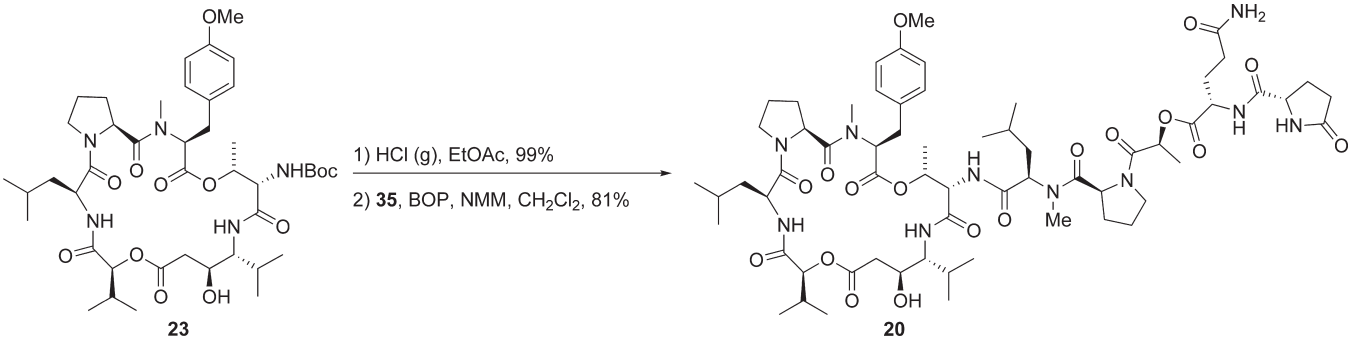
(38) Dutton, F. E.; Lee, B. H.; Johnson, S. S.; Coscarelli, E. M.; Lee, P. H. *J. Med. Chem*. **2003**, *46*, 2057.

SCHEME 5. Synthesis of Tamandarin Side Chain M (35)



SCHEME 6. Installation of the Tamandarin M Side Chain (35)



In an extensive study of the biological properties of several didemnin congeners, Rinehart and co-workers reported that didemnin M showed the strongest inhibition of the immune response, with an IC_{50} value in the picomolar range in a two-way mixed lymphocyte response (MLR) assay.[3] In an effort to further explore the structure−activity relationships of the tamandarins, we sought to prepare a hybrid analogue, tamandarin M (**20**). The synthesis of the tamandarin M side chain began with **31**, an intermediate in the synthesis of the aplidine side chain (Scheme 3). Esterification of **31** with BocGlu(Xan)OH using EDCI led to compound **33** (Scheme 5). Simultaneous removal of the Boc and xanthyl group with HCl gas led to the corresponding salt, which was condensed with the pentafluorophenyl ester of Cbz-*p*GluOPfP to yield **34**. The remaining protecting groups were removed under hydrogenolysis conditions to yield side chain **35**. This second-generation synthesis of this side chain is shorter than its original synthesis. Compound **31** was where the first- and second-generation synthesis converged. The original synthesis takes eight steps and six of these are protection/deprotection steps. In this more efficient second-generation synthesis compound **31** is made in seven steps, but only four reactions are protections/deprotections. Also no protecting groups need to be exchanged in this second-generation synthesis. In the original synthesis compound **31** is first formed as a methyl ester and has to be converted to a benzyl ester through a hydrolysis/reprotection sequence.[15]

The preparation of **20** was achieved via the coupling of the amine salt of the tamandarin B macrocycle (**23**) and fragment **35**, using BOP to afford the final product in 81% yield (Scheme 6). This yield was significantly increased with the tamandarin B macrocycle. Coupling of this side chain to the tamandarin A macrocycle only proceeded in 32% yield.[15]

Synthesis of ψ[CH_2NH] Amide Surrogate Analogue. In an effort to explore the structure−activity relationship of the tamandarins, in particular, the influence of the side chain portion, and perhaps improve the biological potency of these compounds, a side chain with an amide bond surrogate, previously tested in the didemnins,[16] was prepared. In this analogue (**22**), the amide bond between the leucine and proline residues of the side chain was reduced. Commercially available *N*-Boc-L-proline (**36**) was converted to aldehyde **37** with use of a known reduction/oxidation sequence.[40] Reductive amination of **36** with the free amine of salt **29** led to **38**.[41] Removal of the Boc protecting group, followed by coupling to L-lactic acid provided the protected side chain **39** in 61% yield over two steps. Benzyl group removal afforded side chain acid **40** (Scheme 7).[42] This synthesis is one step

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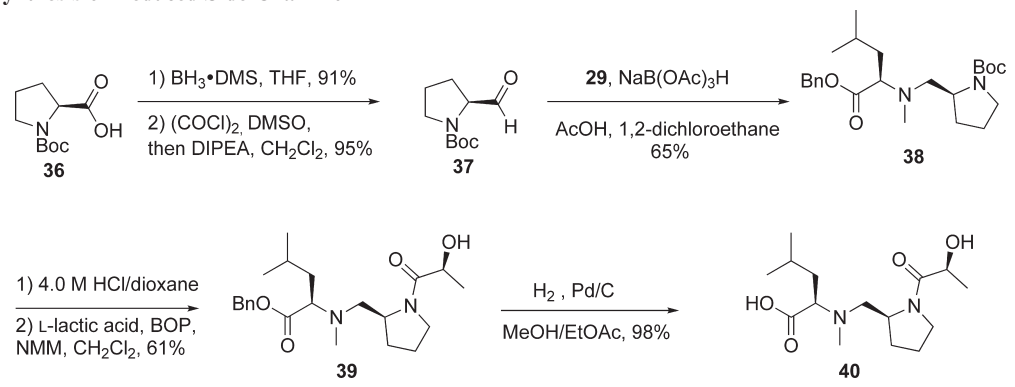
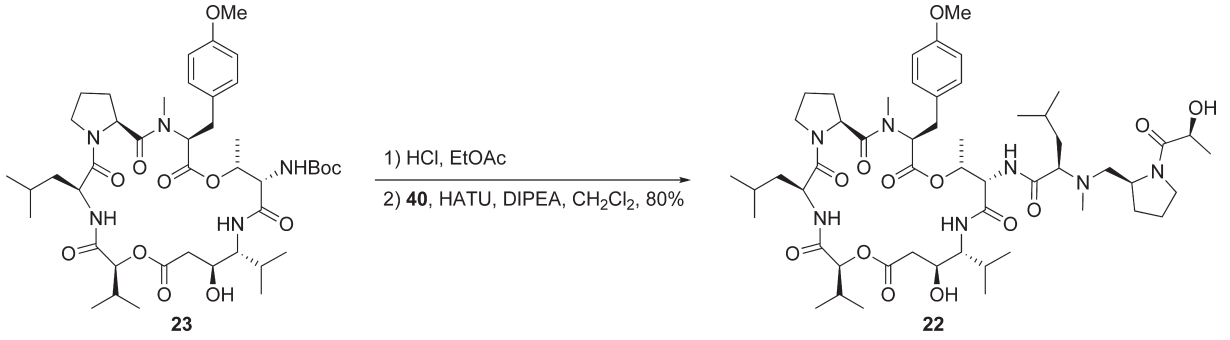
(42) Ding, A. X. Ph.D. Thesis, University of Pennsylvania, **2000**.

SCHEME 7. Synthesis of Reduced Side Chain 40



SCHEME 8. Installation of the ψ[CH_2NH] Amide Surrogate Side Chain 40



shorter than our previous synthesis and uses amine salt **29**, which is a common intermediate in the synthesis of the two previously discussed side chains.[16] Finally, coupling side chain **40** to the macrocyclic salt led to the desired compound (**22**) in 80% yield (Scheme 8). This coupling yield is higher than the previous example of coupling this side chain to the didemnin B macrocycle (72%).[16]

Biological Activity. The three analogues were submitted to the NCI for screening in the NCI-60 tumor cell screen. Tamandarin M (**20**) delivered remarkable activity with GI_{50} values for all cell lines that were $\leq$10 nM while maintaining TGI values that were less than 200 nM in 50 of the cell lines and LC_{50} values that were greater than 1 μM in 45 of the cell lines examined. Dehydrotamandarin B (**21**) had GI_{50} values that were $\leq$10 nM in 23 of the 60 cell lines with TGI values that were less than 700 nM in 29 of the cell lines and LC_{50} values of greater than 1 μM in 55 of the cell lines. Amide surrogate (**22**) had 28 GI_{50} values below 10 nM, 44 TGI values below 700 nM, and 48 LC_{50} values greater than 1 μM. Of these three analogues tamandarin M (**20**) has the most potent activity across the cell lines tested.

Conclusion

In view of the promising bioactivity of some of the members of the tamandarin family, we have been actively investigating their synthetic routes, many of which have proven challenging and have required extensive experimentation. Three novel tamandarin B side chain analogues (**20**, **21**, and **22**) have been prepared by using an alternate synthesis of the tamandarin B macrocycle. Two of the compounds (**20** and **21**) contain side chains found in naturally occurring didemnin compounds with enhanced bioactivity. All three analogues were tested at the National Cancer Institute against various cell lines in vitro and all new compounds exhibited promising bioactivity. The immunosuppressant activity of **20** is under investigation and appears to be more potent than that of didemnin M.

Experimental Section

General Methods. All reactions were carried out under an argon atmosphere. Tetrahydrofuran was distilled over sodium benzophenone, and dichloromethane, methanol, and 1,2-dichloroethane were distilled over calcium hydride prior to use. Column chromatography was conducted with silica gel 60 (240−400 mesh) and solvent systems are listed under individual experiments. Analytical thin-layer chromatography (TLC) was performed on silica gel (60F-254) plates (0.25 mm). Plates were visualized using ceric ammonium molybdate, or ninhydrin. Proton and carbon magnetic resonance spectra were recorded on a 500 MHz spectrometer at 500 and 125 MHz, respectively.

General Procedure for Removal of Benzyl and Cbz Groups. The desired substrate was dissolved in a 1:1 mixture of anhydrous MeOH/EtOAc (0.1 M). To this solution was added 10% Pd/C (10 wt %). The reaction vessel was evacuated and purged with hydrogen gas. The reaction was monitored by TLC and was filtered through a pad of Celite when complete. Removal of solvent under reduced pressure provided the product, which was used without further purification.

Procedure for the Preparation of Tamandarin B Macrocyclic Salt. Macrocycle **23** (14 mg, 0.017 mmol) was dissolved in EtOAc (4 mL) and cooled to −30 °C. HCl gas was bubbled over this solution while keeping the temperature at −30 °C for 10 min. The flow of HCl gas was stopped and stirring continued at −30 °C for an additional 30 min. The temperature was raised to 0 °C for 1 h. At this point TLC showed that the starting material had been consumed. The solvent was removed

under reduced pressure to yield the macrocyclic salt (13 mg, quantitative) as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (m, 18H), 1.19−1.52 (m, 5H), 1.66 (s, 2H), 1.80 (s, 2H), 1.92−2.15 (m, 5H), 2.25 (m, 2H), 2.37 (m, 1H), 2.65 (s, 3H), 2.99 (m, 1H), 3.16−3.36 (m, 2H), 3.43−3.66 (m, 2H), 3.78 (s, 3H), 3.96−4.06 (m, 2H), 4.53−4.76 (m, 2H), 4.83 (d, J = 4.16 Hz, 1H), 5.46 (s, 1H), 6.82 (m, 1H), 7.05 (m, 2H), 7.53 (s, 1H), 7.92−8.42 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.6, 17.8, 18.7, 20.6, 23.4, 24.9, 28.2, 30.2, 33.7, 37.6, 40.4, 47.0, 49.8, 55.3, 57.8, 59.3, 66.4, 67.4, 69.4, 80.2, 114.0, 129.5, 130.3, 158.6, 166.2, 168.7, 170.6, 171.1, 172.2, 175.1; IR (neat, cm^{-1}) 3333, 2956, 2925, 2873, 1739, 1636, 1512, 1246; HRMS (ESI) m/z calcd for $C_{38}H_{60}N_5O_{10}$ $(M - Cl)^+$ 746.4340, found 746.4342; $[\alpha]^{19}_D$ −83.03 (c 0.67, CH_2Cl_2).

Boc-D-leucine Benzyl Ester. D-Leucine (5 g, 38.1 mmol) was suspended in 1 M NaOH (76 mL) and dioxane (23 mL) and the mixture was cooled to 0 °C. To this solution was added Boc anhydride (9.15 g, 41.9 mmol) in dioxane (30 mL). The reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with water (100 mL) and extracted with hexanes (3 × 100 mL). The remaining aqueous layer was acidified with solid citric acid and extracted with ethyl acetate (3 × 100 mL). The organic extracts were washed with water (50 mL) and brine (50 mL) and dried over $MgSO_4$. Filtration and concentration under reduced pressure led to the product as a clear oil (8.51 g, 97%) that was used directly in the next step. The Boc protected product (8.51 g, 36.8 mmol) was dissolved in anhydrous DMF (75 mL) and cooled to 0 °C. To this solution was added cesium carbonate (12.0 g, 36.8 mmol) and the reaction was allowed to stir for 20 min. Benzyl bromide (4.37 mL, 36.8 mmol) was added to the reaction mixture via syringe and the mixture was allowed to warm to room temperature and stirred overnight. Water (300 mL) was added to the reaction and was then extracted with hexanes (3 × 150 mL). The combined organic extracts were washed with water and brine and dried over $MgSO_4$. Concentration under reduced pressure led to the product as a clear oil (10.76 g, 91%): R_f 0.41 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (d, J = 4.10 Hz, 3H), 0.93 (d, J = 4.10 Hz), 1.46 (s, 9H), 1.49 (m, 1H), 1.65 (m, 2H), 4.49 (s, 1H), 4.89 (s, 1H), 5.16 (q, J = 13.4 Hz, 2H), 7.32 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 22.8, 24.8, 28.3, 41.7, 52.1, 66.9, 79.8, 128.1, 128.3, 128.5, 135.7, 155.5, 173.5; IR (neat, cm^{-1}) 3365, 2958, 1718, 1508, 1366, 1251, 1164; HRMS (ESI) m/z calcd for $C_{18}H_{27}NO_4Na$ $(M + Na)^+$ 344.1838, found 344.1850; $[\alpha]^{23}_D$ 32.56 (c 1.12, MeOH).

***N*-Me-*N*-Boc-D-leucine Benzyl Ester.** *N*-Boc-leucine benzyl ester (3.61 g, 11.2 mmol) was dissolved in anhydrous THF (56 mL) and cooled to 0 °C. Methyl iodide (3.54 mL, 56.2 mmol) was added to this solution followed by 1 M NaHMDS (16.8 mL, 16.8 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by addition of saturated ammonium chloride (50 mL). The reaction mixture was extracted with diethyl ether (2 × 50 mL). The combined organic phases were washed with 10% HCl (30 mL), saturated $NaHCO_3$ (30 mL), and brine (30 mL), and dried over $MgSO_4$. The solvent was evaporated to yield the crude product as a brown oil. The oil was purified by column chromatography (2→4% EtOAc/hexanes) to yield the product as a clear oil (2.76 g, 73%): R_f 0.40 (10% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92 (d, J = 6.55 Hz, 3H), 0.94 (d, J = 5.83 Hz, 3H), 1.43 (s, 9H), 1.56 (m, 1H), 1.68 (m, 2H), 2.79 (m, 3H), 4.6−4.8 (m, 1H), 5.15 (m, 2H), 7.33 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 23.7, 24.6, 28.2, 32.4, 37.4, 56.0, 57.2, 66.5, 80.1, 127.3, 128.2, 128.5, 135.7, 155.4, 156.2, 172.26; IR (neat, cm^{-1}) 2958, 1740, 1702, 1455, 1391, 1367, 1323, 1156, 970; HRMS (ESI) m/z calcd for $C_{19}H_{29}NO_4Na$ $(M + Na)^+$ 358.1995, found 358.1990; $[\alpha]^{25}_D$ 23.96 (c 1.0, MeOH).

***N*-Boc-proline-*N*-Me-D-leucine Benzyl Ester (30).** *N*-Me-*N*-Boc-D-leucine benzyl ester (4.66 g, 13.9 mmol) was dissolved in 4.0 M HCl in dioxane (20 mL) at room temperature. The reaction was complete after 2 h. The solvent was evaporated to yield *N*-Me-D-leucine benzyl ester hydrochloride (**29**), (3.78 g, quantitative) as a white solid, which was used without further purification. Boc-proline (2.99 g, 13.9 mmol) was dissolved in anhydrous CH_2Cl_2 (46 mL) and cooled to −15 °C. To this solution was added BOP-Cl (3.72 g, 14.6 mmol) and NMM (1. 64 mL, 14.8 mmol). The resulting mixture was stirred for 30 min, then **29** (3.78 g, 13.9 mmol) and NMM (5 mL, 45.9 mmol) were added. The reaction was allowed to warm to room temperature and stirred for 24 h. The mixture was diluted with EtOAc (100 mL), washed with 10% HCl (30 mL), saturated $NaHCO_3$ (30 mL), and brine (30 mL), dried over $MgSO_4$, and filtered. After solvent evaporation the crude product was purified by column chromatography (10→20% acetone/hexanes) to yield the product (4.75 g, 92%) as a white solid: R_f 0.5 (30% acetone/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (m, 6H) 1.40 (m, 9H), 1.63 (s, 1H), 1.70−1.78 (m, 1H), 1.79−2.20 (m, 3H), 3.02 (m, 3H), 3.37−3.48 (m, 1H), 3.53−3.69 (m, 1H), 4.60 (dd, J = 8.59, 3.39 Hz), 5.14 (m, 2H), 7.32 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 23.3, 25.1, 28.2, 30.4, 31.7, 32.6, 37.8, 46.4, 55.2, 57.1, 66.7, 79.5, 128.1, 128.5, 135.6, 153.9, 171.6, 173.3; IR (neat, cm^{-1}) 2958, 2931, 2872, 1741, 1699, 1661, 1396, 1169; HRMS (ESI) m/z calcd for $C_{24}H_{36}N_2O_5Na$ $(M + Na)^+$ 455.2522, found 455.2515; $[\alpha]^{26}_D$ −1.54 (c 1.0, CH_2Cl_2).

L-Lactyl-L-prolyl-*N*-methyl-D-leucine Benzyl Ester (31). Benzyl ester **30** (300 mg, 0.69 mmol) was dissolved in 4.0 M HCl in dioxane (3 mL) and the mixture was allowed to stir at room temperature for 2 h. The solvent was removed and the resulting salt was redissolved in anhydrous CH_2Cl_2 (3 mL) and cooled to 0 °C. To this solution was added L-lactic acid (52 μL, 0.69 mmol), BOP (0.368 g, 0.83 mmol), and NMM (0.31 mL, 2.78 mmol). The mixture was allowed to warm to room temperature and stirred overnight. The reaction was diluted with CH_2Cl_2 (25 mL) and washed with 10% HCl (10 mL), saturated $NaHCO_3$ (10 mL), and brine (10 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (25% acetone/hexanes) to yield the product (0.172 g, 61%) as a clear oil: R_f 0.48 (50% acetone/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.78−1.01 (m, 6H), 1.33 (m, 6H), 1.43 (m, 2H), 1.74 (m, 2H), 1.91 (m, 2H), 2.09 (m, 2H), 3.01 (s, 3H), 3.52 (t, J = 6.75 Hz, 2H), 4.29 (q, J = 5.98 Hz, 1H), 5.15 (m, 3H), 7.31 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.4, 21.3, 23.1, 24.8, 28.3, 32.1, 37.4, 46.5, 55.6, 568, 65.5, 66.6, 128.0, 128.4, 128.6, 135.6, 171.1, 172.1, 173.2; IR (neat, cm^{-1}) 3415, 2957, 2873, 1739, 1651, 1456, 1129, 843; HRMS (ESI) m/z calcd for $C_{22}H_{32}N_2O_5Na$ $(M + Na)^+$ 427.2209, found 427.2194; $[\alpha]^{26}_D$ −14.07 (c 0.76, $CHCl_3$).

Pyruvyl-prolyl-*N*-methyl-D-leucine Benzyl Ester (32). Lactyl-prolyl-*N*-methyl-D-leucine benzyl ester (120 mg, 0.296 mmol) was dissolved in anhydrous CH_2Cl_2 (1.00 mL) and dimethyl sulfoxide (0.30 mL). To this solution was added Dess−Martin periodinane (629 mg, 1.48 mmol). The reaction was allowed to stir for 24 h at which time it was quenched with 5% $Na_2S_2O_3$ (5 mL) and diluted with Et_2O (25 mL). The organic layer was separated and washed with saturated $NaHCO_3$ (5 mL) and water (5 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography (20% acetone/hexanes) to yield the product (87 mg, 73%) as a yellow oil: R_f 0.27 (30% acetone/hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.91 (m, 6H), 1.43 (m, 1H), 1.60−1.90 (m, 6H), 2.20−2.45 (m, 3H), 2.81−3.10 (m, 3H), 3.52−3.92 (m, 2H), 4.92 (m, 1H), 5.04−5.22 (m, 3H), 7.36 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.2, 22.3, 23.3, 24.9, 26.1, 31.1, 32.1 37.2, 47.5, 57.8, 58.5, 66.9, 128.1, 128.3, 128.5, 136.5, 163.6, 170.9 172.6, 198.7; IR (neat, cm^{-1}) 3460, 2958, 2873, 1739, 1715, 1652, 1455, 1206; HRMS (ESI) m/z calcd for $C_{22}H_{30}N_2O_5Na$ $(M + Na)^+$ 425.2052, found 425.2040; $[\alpha]^{21}_D$ −2.58 (c 0.96, $CHCl_3$).

Dehydrotamandarin B (21). The tamandarin B macrocyclic salt (8.0 mg, 0.010 mmol) was dissolved in anhydrous CH_2Cl_2 (1 mL) and cooled to 0 °C. To this solution was added side chain **32** (5.0 mg, 0.015 mmol), BOP (7.0 mg, 0.15 mmol), and NMM (4.5 μL, 0.041 mmol). The reaction was allowed to warm to room temperature and stirred overnight. The reaction was quenched with brine (4 mL) and the mixture was extracted with EtOAc (3 × 10 mL). The organic phase was washed with 10% HCl (5 mL), 5% $NaHCO_3$ aq (5 mL), and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated to yield the crude product. The product was purified by reverse phase HPLC (10% MeOH/H_2O→100% MeOH gradient over 40 min) to yield the product (8 mg, 73%) as a white solid: R_f 0.26 (30% acetone/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.78−1.07 (m, 24H), 1.25 (m, 10H), 1.40 (t, J = 7.49 Hz, 3H), 1.45 (m, 1H), 1.61 (m, 5H), 1.72−2.28 (m, 10H), 2.43−2.50 (m, 1H), 2.53−2.62 (m, 3H), 3.03−3.12 (m, 3H), 3.13−3.20 (m, 1H), 3.55−3.74 (m, 3H), 3.79 (s, 3H), 3.81−3.89 (m, 1H), 3.91−4.04 (m,1H), 4.28−4.40 (m, 1H), 4.63 (m, 1H), 4.89 (t, J = 10.17 Hz, 1H), 5.05 (d, J = 4.49 Hz, 1H), 5.16−5.27 (m, 1H), 5.28−5.36 (m, 1H), 6.84 (m, 2H), 7.08 (d, J = 7.91 Hz, 2H), 7.42−7.56 (m, 1H), 7.72−7.85 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 16.6, 17.0, 17.4, 18.9, 20.4, 20.8, 21.4, 22.7, 23.5, 23.8, 24.9, 26.3, 27.1, 28.0, 29.4, 29.7, 30.0, 30.6, 31.2, 34.0, 35.8, 38.7, 39.2, 46.7, 48.7, 48.8, 54.7, 55.2, 56.9, 57.3, 58.3, 58.9, 66.0, 70.9, 78.7, 114.1, 129.8, 130.3, 158.6, 161.3, 168.6, 169.6, 170.4, 170.5, 171.7, 172.2, 172.9, 173.9, 201.11; IR (cm^{-1}) 3340, 2957, 2926, 2871, 1741, 1662, 1636, 1514, 1457, 1170, 1078; HRMS (ESI) m/z calcd for $C_{53}H_{81}N_7O_{14}Na$ $(M + Na)^+$ 1062.5739, found 1062.5760; $[\alpha]^{17}_D$ −18.68 (c 0.2, CH_2Cl_2).

***N*^{2}-Boc-*N*^{5}-xanthyl-glutaminyl-*O*-L-lactyl-L-prolyl-*N*-methyl-D-leucine Benzyl Ester (33).** L-Lactyl-L-prolyl-*N*-methyl-D-leucine benzyl ester (2.24 g, 5.5 mmol) was dissolved in anhydrous THF (30 mL) and the solution was cooled to 0 °C. To this was added N^2-Boc-N^5-glutamine (3.07 g, 7.2 mmol), followed by EDCI (1.48 g, 7.7 mmol) and DMAP (1.34 g, 11 mmol). The reaction was allowed to warm to room temperature and stirred overnight. EtOAc (50 mL) was added and the solution was washed sequentially with 10% HCl (25 mL), saturated $NaHCO_3$ (25 mL), and brine (25 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography (15→20% acetone/hexanes) to yield the product (3.70 g, 83%) as a white solid: R_f 0.54 (50% acetone/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.73 (t, J = 6.63 Hz, 2H), 0.80 (d, J = 6.50 Hz, 2H), 0.86 (d, J = 6.65 Hz, 3H), 0.97 (dd, J = 16.2, 6.53 Hz, 1H), 1.35 (d, J = 5.85 Hz, 3H), 1.43 (s, 9H), 1.60−1.69 (m, 2H), 1.78−1.88 (m, 2H), 1.88−2.20 (m, 3H), 2.22−2.42 (m, 2H), 2.70 (m, 3H), 2.89−2.98 (m, 1H), 3.43−3.69 (m, 2H), 3.72 (t, J = 6.25 Hz, 2H), 4.31−4.64 (m, 1H), 4.91 (m, 2H), 5.11 (m, 2H), 6.50 (m, 1H), 7.00−7.12 (m, 4H), 7.18−7.37 (m, 7H), 7.39−7.51 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.4, 14.1, 16.0, 21.3, 22.5, 23.1, 24.9, 25.3, 28.3, 29.0, 31.5, 32.0, 34.6, 36.0, 37.3, 43.5, 46.7, 55.8, 56.7, 66.3, 116.2, 121.2, 123.3, 123.5, 127.9, 128.4, 128.8, 129.4, 135.7, 151.1, 168.6, 170.1, 171.9, 172.1; IR (neat, cm^{-1}) 3305, 2959, 1743, 1712, 1652, 1481, 1456, 1258; HRMS (ESI) m/z calcd for $C_{45}H_{57}N_4O_{10}$ $(M + H^+)$ 813.4075, found 813.4078; $[\alpha]^{24}_D$ −27.24 (c 0.89, $CHCl_3$).

Protected Tamandarin M Side Chain (34). N^2-Boc-N^5-xanthyl-glutaminyl-*O*-L-lactyl-L-prolyl-*N*-methyl-D-leucine benzyl ester (407 mg, 0.50 mmol) was dissolved in EtOAc (4.75 mL) and anisole (0.25 mL) and the mixture was cooled to −20 °C. Gaseous HCl was added over a 5 min period in which the reaction color went from yellow to red. The reaction was stirred at −20 °C for 1 h and at 0 °C for 1 h. Argon was then bubbled through the solution as it was allowed to warm to room temperature. The solvent was evaporated and the remaining residue was triturated with diethyl ether (10 mL) to produce a white solid, which was removed by filtration. The remaining ether solution was evaporated and triturated again to produce a second crop of the hydrochloride salt. The product was isolated as a white solid (0.182 g, 64%) that was used in the next step without further purification. The HCl salt (0.182 g, 32 mmol) was dissolved in anhydrous dichloromethane (1.4 mL) and the solution was cooled to 0 °C. To this solution was added *N*-Cbz-pGlu-OPfP (0.140 g, 32 mmol) and DIPEA (225 μL, 1.28 mmol). The mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with brine (3 mL) and diluted with CH_2Cl_2 (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were washed with 10% HCl (5 mL), 5% $NaHCO_3$ aq (5 mL), and brine (5 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated to yield the crude product, which was purified by column chromatography (1−5% MeOH/CH_2Cl_2) to yield the product (77 mg, 31%) as a white solid: R_f 0.41 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.86 (d, J = 6.52 Hz, 3H), 0.91 (d, J = 6.67 Hz, 3H), 1.38 (m, 1H), 1.44−1.57 (m, 3H), 1.69−1.79 (m, 3H), 1.93−2.33 (m, 9H), 2.35−2.47 (m, 2H), 2.68 (t, J = 9.87 Hz, 1H), 2.71 (t, J = 9.97 Hz, 1H), 2.99 (s, 3H), 3.57 (q, J = 7.68 Hz, 1H), 3.70 (q, J = 7.75 Hz, 1H), 4.46−4.60 (m, 2H), 4.86 (dd, J = 8.40, 4.76 Hz, 1H), 5.05−5.28 (m, 4H), 5.42 (m, 1H), 6.93 (s, 1H), 7.24−7.39 (m, 10H), 7.51 (d, J = 6.55 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.8, 21.1, 22.2, 23.2, 24.9, 25.1, 27.1, 28.3, 31.1, 31.3, 31.6, 37.4, 46.7, 51.9, 55.0, 57.2, 59.5, 66.8, 68.2, 69.2, 127.9, 128.2, 128.5, 128.6, 135.1, 135.5, 151.3, 168.6, 170.7, 171.1, 171.5, 171.9, 173.5, 175.6; IR (neat, cm^{-1}) 3432, 3328, 3214, 2951, 1791, 1742, 1661, 1452, 1304, 1189; HRMS (ESI) m/z calcd for $C_{40}H_{51}N_5O_{11}Na$ $(M + Na)^+$ 800.3483, found 800.3495; $[\alpha]^{27}_D$ −57.03 (c 0.77, $CHCl_3$).

Tamandarin M (20). The tamandarin B macrocyclic salt (10.0 mg, 0.013 mmol) was dissolved in anhydrous CH_2Cl_2 (1 mL) and the solution was cooled to 0 °C. To this solution was added side chain **35** (11.0 mg, 0.019 mmol), BOP (9.0 mg, 0.019 mmol), and NMM (6.0 μL, 0.051 mmol). The reaction was allowed to warm to room temperature and stirred overnight. The reaction was quenched with brine (4 mL) and the resulting mixture was extracted with EtOAc (3 × 10 mL). The organic phase was washed with 10% HCl (5 mL), 5% $NaHCO_3$ aq (5 mL), and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated to yield the crude product. The product was purified by reverse phase HPLC (10% MeOH/H_2O→100% MeOH gradient over 40 min) to yield the product (13 mg, 81%) as a white solid. R_f 0.21 (50% EtOAc/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.76−1.05 (m, 24H), 1.15−1.32 (m, 10H), 1.36−1.42 (m, 5H), 1.46 (d, J = 7.07 Hz, 2H), 1.52−1.66 (m, 3H), 1.72 (m, 2H), 1.89 (m, 2H), 1.96−2.31 (m, 9H), 2.34−2.46 (m, 2H), 2.54 (s, 3H), 2.61 (m, 1H), 2.92 (m, 1H), 2.97 (s, 2H), 3.06−3.16 (m, 2H), 3.32 (dd, J = 14.16, 3.95 Hz, 1H), 3.53−3.74 (m, 4H), 3.77 (s, 3H), 3.87 (m, 2H), 4.15 (t, J = 4.16 Hz, 1H), 4.49 (m, 2H), 4.57 (dd, J = 7.73, 4.68 Hz, 1H), 4.74 (t, J = 7.05 Hz, 1H), 4.87 (m, 1H), 4.91 (d, J = 5.05 Hz, 1H), 5.01 (m, 1H), 5.11 (q, J = 6.70 Hz, 1H), 5.25 (dd, J = 9.45, 6.00 Hz, 1H), 5.94 (s, 1H), 6.81 (d, J = 8.30 Hz, 2H), 7.05 (d, J = 8.35 Hz, 2H), 7.75 (d, J = 9.40 Hz, 1H), 7.80 (d, J = 9.80 Hz, 1H), 8.52 (d, J = 6.35 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 15.9, 16.1, 16.9, 17.9, 18.8, 20.3, 20.9, 21.4, 22.7, 23.6, 23.7, 24.6, 24.9, 25.7, 27.2, 27.9, 28.8, 29.3, 29.7, 30.2, 31.1, 31.8, 31.9, 34.0, 26.1, 38.6, 39.2, 39.5, 46.8, 47.1, 48.3, 51.8, 53.8, 54.3, 55.3, 56.3, 56.6, 56.8, 57.0, 58.4, 66.1, 68.7, 69.5, 71.2, 79.4, 114.1, 129.8, 130.4, 158.6, 168.8, 169.4, 169.5, 170.5, 170.8, 171.1, 171.3, 172.6, 173.3, 173.5, 176.5, 178.8; IR (cm^{-1}) 3337, 2958, 1928, 2873, 1741, 1662, 1636, 1514, 1456, 1248; HRMS (ESI) m/z calcd for $C_{63}H_{96}N_{10}O_{18}Na$ $(M + Na)^{2-}$ 1303.6802, found 1303.6832; $[\alpha]^{17}_D$ −35.49 (c 0.65 CH_2Cl_2).

***N*-Boc-Prolinal (37).** This compound was prepared according procedures by Reed. The product matched reported spectral and physical characteristics.[40]

***N*-Boc-Pro-ψ(NHCH$_2$)-*N*-Methyl-leucine Benzyl Ester (38).** Boc-prolinal (430 mg, 2.15 mmol) and *N*-methyl-leucine benzyl ester (508 mg, 2.15 mmol) were dissolved in anhydrous 1,2-dichloroethane (5 mL). The reaction was cooled to 0 °C and acetic acid (0.5 mL) was added then the solution was stirred for 20 min. Sodium triacetoxyborohydride (637 mg, 3.01 mmol) was added to the reaction and the mixture was allowed to warm to room temperature and to stir for 3 h. The reaction was quenched with saturated NH_4Cl and diluted with CH_2Cl_2 (15 mL). The organic layer was washed with 10% HCl (10 mL), 5% $NaHCO_3$ aq (10 mL), and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to yield the crude product. The crude product was purified by column chromatography (10→20% EtOAc/hexanes) to afford the product (580 mg, 65%) as a yellow oil: R_f 0.68 (30% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (m, 6H), 1.42 (s, 9H), 1.56 (m, 1H), 1.68 (m, 1H), 1.80 (m, 4H), 2.30 (m, 4H), 2.51−2.80 (m, 1H), 3.31 (m, 3H), 3.70−3.95 (m, 1H), 5.13 (m, 2H), 7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.4, 22.9, 24.7, 28.5, 36.8, 39.2, 40.3, 46.1, 55.9, 66.1, 79.1, 128.2, 128.3, 128.5, 136.0, 154.4, 172.8; IR (neat, cm^{-1}) 2958, 2873, 1731, 1694, 1456, 1394, 1171; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{38}N_2O_4Na$ $(M+Na)^+$ 441.2730, found 441.2741; $[\alpha]^{22}_D$ 10.7 (*c* 0.8 $CHCl_3$).

L-Lactyl-Pro-ψ(NHCH$_2$)-*N*-methyl-D-leucine Benzyl Ester (39). *N*-Boc-Pro-ψ(NHCH$_2$)-*N*-methyl-leucine benzyl ester (0.128 g, 0.316 mmol) was dissolved in 4.0 M HCl in dioxane (5 mL). The reaction was stirred for 2 h and the solvent was evaporated to yield the hydrochloride salt in quantitative yield. The resulting salt (0.122 g, 0.316 mmol) was dissolved in anhydrous CH_2Cl_2 (2 mL) and cooled to 0 °C. To this solution was added L-lactic acid (25 μL, 0.332 mmol), BOP (0.154 g, 0.348 mmol), and NMM (173 μL, 1.58 mmol). The reaction was allowed to warm to room temperature and stirred overnight. The reaction was diluted with EtOAc (20 mL) and washed with 10% HCl (10 mL), 5% $NaHCO_3$ aq (10 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to yield the crude product. The crude product was purified by column chromatography (20→50% EtOAc/hexanes) to yield the product (75 mg, 61%) as a yellow oil: R_f 0.30 (50% EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83−0.92 (m, 6H), 1.29 (d, J = 6.55 Hz, 3H), 1.38−1.70 (m, 4H), 1.76−2.01 (m, 4H), 2.28−2.48 (m, 5H), 2.64−2.87 (m, 1H), 3.24−3.50 (m, 3H), 4.06−4.40 (m, 1H), 5.12 (d, J = 4.75 Hz, 2H), 7.33 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.3, 20.9, 22.3, 22.7, 23.4, 23.9, 24.8, 27.7, 29.6, 37.4, 38.4, 46.0, 56.6, 65.4, 66.0, 128.1, 128.3, 128.4, 135.8, 172.5, 173.6; IR (neat, cm^{-1}) 3426, 2957, 2925, 2863, 1731, 1639, 1452, 1127; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{35}N_2O_4$ $(M+H)^+$ 391.2597, found 391.2585; $[\alpha]^{19}_D$ −1.55 (*c* 0.58, $CHCl_3$).

ψ[CH$_2$NH] Amide Surrogate (22). The tamandarin B macrocyclic salt (15.0 mg, 0.019 mmol) was dissolved in anhydrous CH_2Cl_2 (1 mL) and cooled to 0 °C. To this solution was added side chain **39** (12 mg, 0.038 mmol), HATU (12 mg, 0.031 mmol), and DIPEA (14 μL, 0.077 mmol). The reaction was allowed to warm to room temperature and stirred overnight. The reaction was diluted with EtOAc (15 mL) and washed with 10% HCl (5 mL), 5% $NaHCO_3$ aq (5 mL), and brine (5 mL), dried over Na_2SO_4, filtered, and concentrated to yield the product (15 mg, 83%) as a white solid. R_f 0.46 (10% MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.0−1.05 (m, 24H), 1.19 (m, 1H), 1.25 (t, J = 7.09 Hz, 3H), 1.29−1.39 (m, 5H), 1.40−1.52 (m, 3H), 1.57−1.81 (m, 5H), 1.82−2.05 (m, 3H), 2.07−2.18 (m, 3H), 2.33 (d, J = 10.00 Hz, 3H), 2.41 (m, 1H), 2.53 (s, 2H), 2.77 (s, 3H), 2.89 (m, 1H), 3.12 (m, 2H), 3.28−3.50 (m, 3H), 3.52−3.71 (m, 3H), 3.76 (s, 3H), 3.94 (m, 1H), 4.26 (m, 2H), 4.56 (m, 2H), 4.84 (d, J = 6.05 Hz, 2H), 5.01 (m, 1H), 6.80 (d, J = 8.15 Hz, 2H), 7.05 (d, J = 7.95 Hz, 2H), 7.62 (d, J = 9.15 Hz, 1H), 7.68 (d, J = 8.34 Hz, 1H), 7.77 (d, J = 8.53 Hz, 1H), 8.00 (t, J = 8.90 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.5, 16.5, 18.1, 18.5, 20.3, 20.8, 21.1, 22.0, 22.6, 23.0, 23.5, 24.4, 24.9, 25.1 25.6, 27.6, 28.0, 30.3, 34.1, 36.0, 36.7, 38.6, 45.8, 46.4, 46.8, 48.3, 54.5, 56.4, 57.1, 57.2, 58.9, 63.6, 64.6, 65.1, 65.4, 65.8, 68.8, 69.3, 71.3, 79.3, 114.0, 129.8, 130.4, 158.6, 165.8, 168.8, 169.8, 170.3, 171.2, 172.5, 172.9, 173.2; IR (cm^{-1}) 3339, 2956, 2920, 2868, 1742, 1661, 1654, 1633, 1511, 1094; HRMS (ESI) *m*/*z* calcd for $C_{53}H_{86}N_7O_{13}$ $(M+H)^+$ 1028.6284, found 1028.6300; $[\alpha]^{18}_D$ −65.55 (*c* 0.34, CH_2Cl_2).

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra are provided for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.