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An efficient synthesis of the tamandarin B macrocycle

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ABSTRACT

A reliable, high yielding cyclization protocol for the macrocycle of tamandarin B is presented. This strategy will facilitate the synthesis of side chain analogs.

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1. Introduction

Since their discovery by Rinehart and co-workers the didemnins[1] have been of great interest to the synthetic and medicinal chemistry communities. Didemnin B (**1**) was the first marine natural product to reach phase II clinical trials (Fig. 1).[2] Didemnin B and other related analogs have stimulated many total syntheses to date.[3–7] Tamandarins A (**2**) and B (**3**) were reported by Vervoort and Fenical in 2000 and found to possess a very similar structure to that of the didemnins (Fig. 1).[8] The main structural difference is that the didemnins possess a 23-membered ring containing a more complex α(α-isovalerylpropionyl) (Hip) residue while the tamandarins possess a 21-membered ring containing a simpler hydroxyisovaleric (Hiv) acid residue. Macrolactamization at the Pro[4]-*N*,*O*-Me$_2$-Tyr[5] junction has so far provided the highest yields for the didemnins[6,9] and tamandarin macrocyclic analogs.[10,11] A reliable, high yielding cyclization protocol for tamandarin B would make the macrocycle more available and facilitate the synthesis of side chain analogs.

2. Results

The retrosynthetic analysis (Scheme 1) shows the desired cyclization at the Pro[4]-*N*,*O*-Me$_2$-Tyr[5] junction. In the previous synthesis, cyclization occurred at the Thr-Nst position.[12,13] The new linear precursor (**5**) may be divided into three fragments; *N*,*O*-Me$_2$-Tyr-Thr (**6**), carboxylic acid (**7**), and Pro-Leu-Hiv (**8**) unit.

The synthesis commenced with the formation of the Pro-Leu-Hiv fragment **8** (Scheme 2). Proline benzyl ester (**9**) was coupled to Boc-Leu with diethyl cyanophosphonate (DEPC) to yield amide **10** in good yield.[6] The Boc group was removed and the resulting salt was coupled to hydroxyisovaleric acid (**11**) using BOP (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate) to yield the desired alcohol **8**.

The norstatine fragment was synthesized next (Scheme 3). Boc-D-valine (**12**) was activated as its pentafluorophenyl ester (**14**) and condensed with the lithium enolate of methyl acetate to yield β-ketoester **15**. The ketone was reduced using potassium borohydride to provide alcohol **16**. The resulting alcohol was protected as its TBS ether and the methyl ester was hydrolyzed to yield desired acid **7**.[10]

The last fragment to be synthesized was the *N*,*O*-Me$_2$-Tyr-Thr fragment **6** (Scheme 4). Tyrosine derivative **18** was made by known procedures.[4] A carbodiimide-mediated esterification with alcohol **19** resulted in the desired product (**20**). Removal of the methyl ester with trimethyltin hydroxide resulted in acid **6** in excellent yield.[14]

The reaction of acid **7** and alcohol **8** with EDCI (*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride), DCC (dicyclohexyl carbodiimide), or isopropenyl chloroformate did not result in a high yield of **21** (Scheme 5). As in the first generation synthesis, lactam formation from the activated acid was the major product (**22**) of these reactions.[13]

In order to decrease the nucleophilicity of the carbamate nitrogen, oxazolidine **23** was synthesized from alcohol **16** (Scheme 6). Methyl ester **23** was then hydrolyzed to acid **24** which was then subjected to the reaction conditions.

Oxazolidine acid **24** successfully prevented lactam formation and provided the desired product **25** in 94% yield (Scheme 7). This

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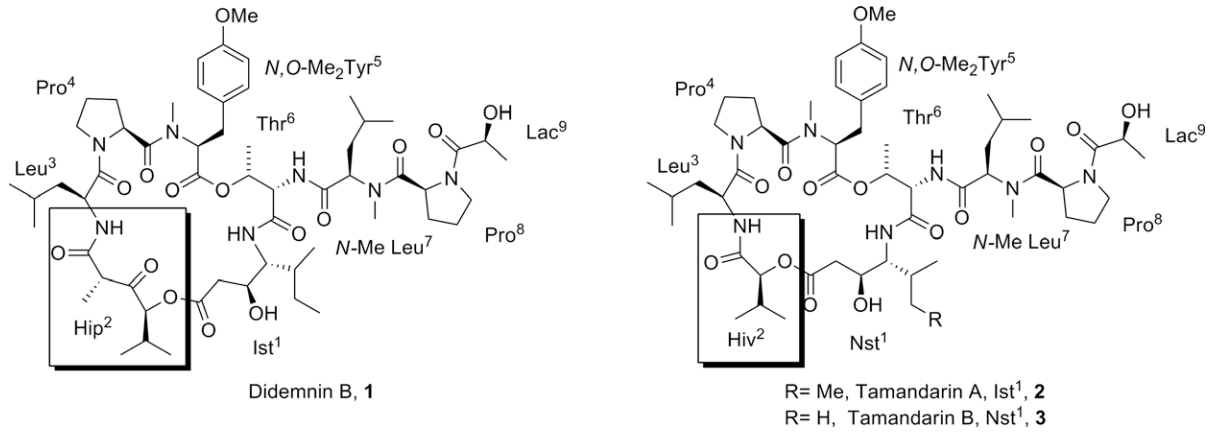
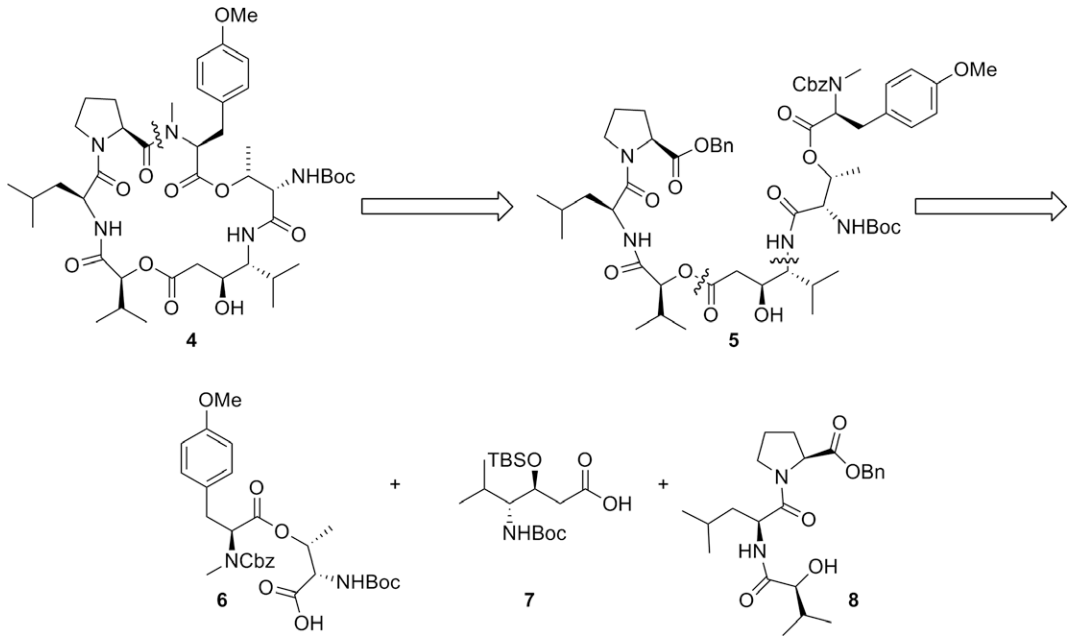
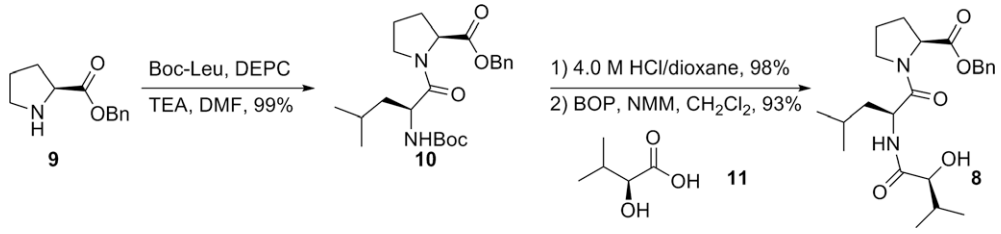


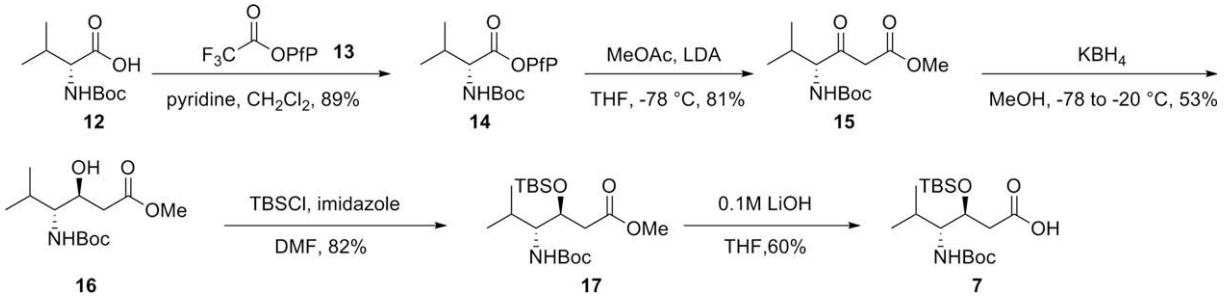
Figure 1. Structures of didemnin B (**1**) and tamandarins A (**2**) and B (**3**).



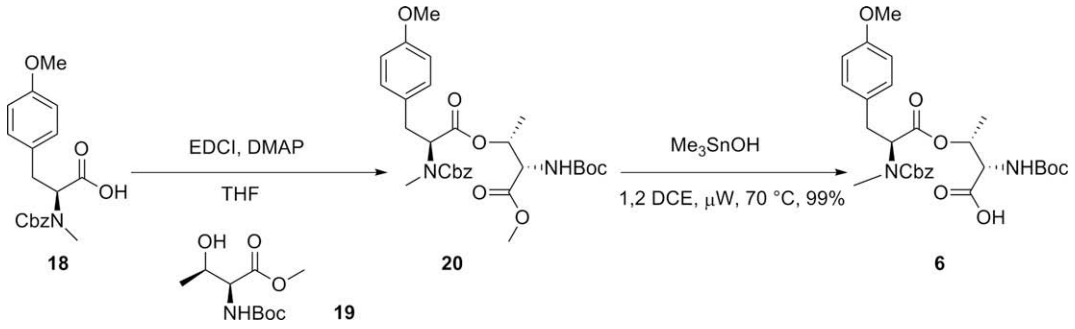
Scheme 1. Retrosynthetic analysis.



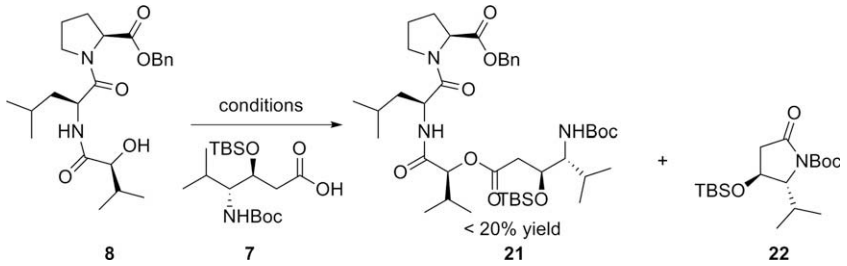
Scheme 2. Synthesis of alcohol **8**.



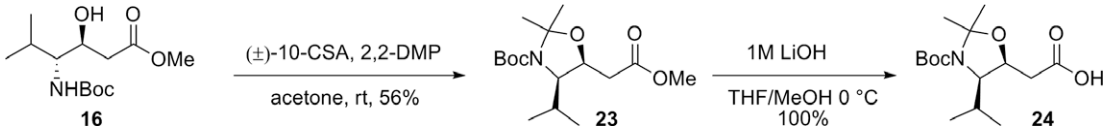
Scheme 3. Synthesis of acid **7**.



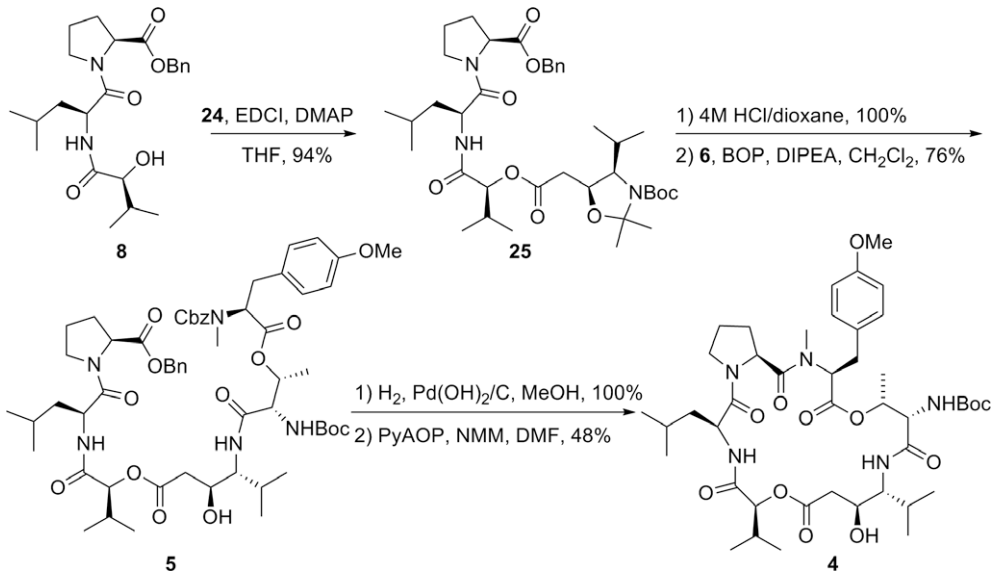
Scheme 4. Synthesis of acid **6**.



Scheme 5. Failed reaction conditions.



Scheme 6. Synthesis of oxazolidine acid **24**.



Scheme 7. Linear precursor formation and cyclization.

change in the protecting group prevented the undesired side reaction and improved the overall yield significantly. After removal of the Boc group and oxazolidine fragmentation under acidic conditions, the resulting salt was coupled to acid **6** to form the protected linear precursor **5**. The terminal protecting groups were then removed under hydrogenolysis conditions to afford the linear precursor. Cyclization with PyAOP ((7-azabenzotriazol-1-yloxy) tripyrrolidinophosphonium hexafluorophosphate) led to the desired macrocycle (**4**) in good yield.

3. Conclusion

The tamandarin B macrocycle has been made using a second generation strategy by cyclization at the Pro^4-*N*,*O*-Me$_2$-Tyr^5 junc-

tion. This macrocycle synthesis is highly convergent and provides useful quantities for analog synthesis.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.091.

References and notes

1. Rinehart, K. L., Jr.; Gloer, J. B.; Cook, J. C., Jr.; Mizsak, S. A.; Scahill, T. A. *J. Am. Chem. Soc.* **1981**, *103*, 1857–1859.
2. Vera, M. D.; Joullié, M. M. *Med. Res. Rev*. **2002**, *22*, 102–145.
3. Rinehart, K. L., Jr.; Kishore, V.; Nagarajan, S.; Lake, R. J.; Gloer, J. B.; Bozich, F. A.; Li, K. M.; Maleczka, R. E., Jr.; Todsen, W. L.; Munro, M. H. G.; Sullins, D. W.; Sakai, R. *J. Am. Chem. Soc.* **1987**, *109*, 6846–6848.
4. Li, W.-R.; Ewing, W. R.; Harris, B. D.; Joullié, M. M. *J. Am. Chem. Soc.* **1990**, *112*, 7659–7672.
5. Jouin, P.; Poncet, J.; Dufour, M.-N.; Pantaloni, A.; Castro, B. *J. Org. Chem.* **1989**, *54*, 617–627.
6. Hamada, Y.; Kondo, Y.; Shibata, M.; Shioiri, T. *J. Am. Chem. Soc.* **1989**, *111*, 669–673.
7. Schmidt, U.; Kroner, M.; Griesser, H. *Tetrahedron Lett.* **1988**, *29*, 3057–3060. 4407–4408.
8. Vervoort, H.; Fenical, W.; De A. Epifanio, R. *J. Org. Chem.* **2000**, *65*, 782–792.
9. Jou, G.; Gonzales, I.; Albericio, F.; Lloyd-Williams, P.; Giralt, E. *J. Org. Chem.* **1997**, *62*, 354–366.
10. Adrio, J.; Cuevas, C.; Manzanares, I.; Joullié, M. M. *Org. Lett.* **2006**, *8*, 511–514.
11. Adrio, J.; Cuevas, C.; Manzanares, I.; Joullié, M. M. *J. Org. Chem.* **2007**, *72*, 5129–5138.
12. Joullié, M. M.; Portonovo, P.; Liang, B.; Richard, D. J. *Tetrahedron Lett.* **2000**, *41*, 9373–9376.
13. Liang, B.; Richard, D. J.; Portonovo, P.; Joullié, M. M. *J. Am. Chem. Soc.* **2001**, *123*, 4469–4474.
14. Nicolaou, K. C.; Estrada, A. A.; Zak, M.; Lee, S. H.; Safina, B. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 1378–1382.