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Total Synthesis of (-)-Bistatramide C

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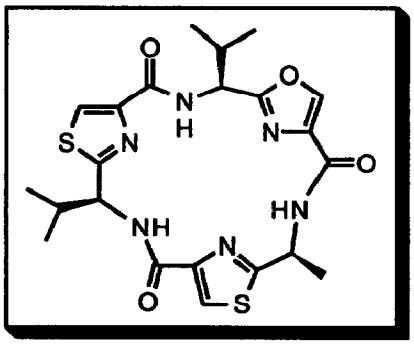
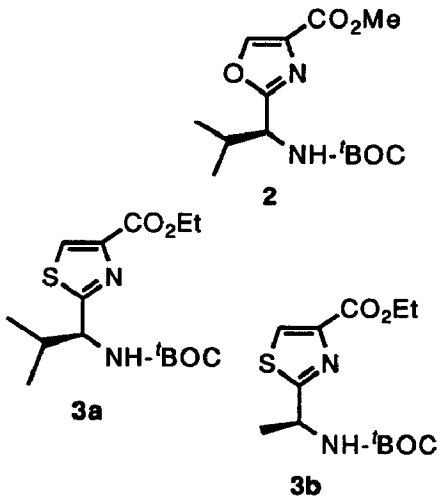
Abstract: *The total synthesis of macrocyclic hexapeptide Bistatramide C is reported from enantiomerically pure oxazole and thiazole amino acids.*

A wide range of naturally occurring compounds containing thiazole and/or oxazole rings in their structures has been known for many years. However, it has been mainly during the last decade when a growing number of those oxazole/thiazole containing natural products have been isolated from marine organisms.[1]

We have directed our efforts toward the synthesis of several of these natural products as have several other groups.[2] We now wish to report the total synthesis of our first target, Bistatramide C **1**, a macrocyclic hexapeptide recently isolated from *Lissoclinum bistratum*.[3] One oxazole **2**, and two thiazole (**3a**, **3b**) derived amino acids, seen by simple disconnection at the amide bonds, become suitable precursors to the target.



1
Bistatramide C



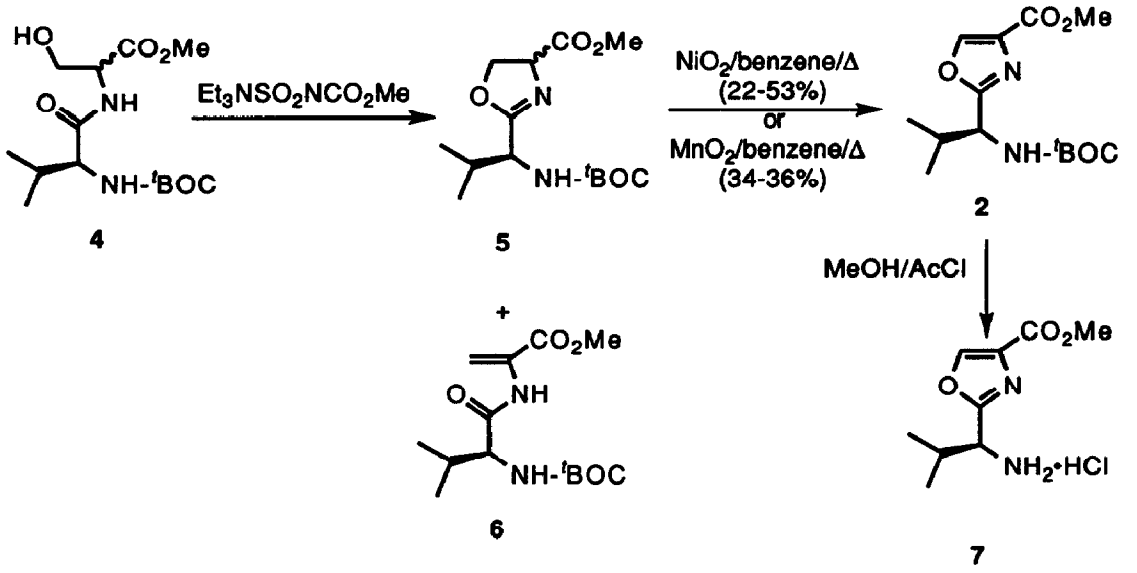
2

3a

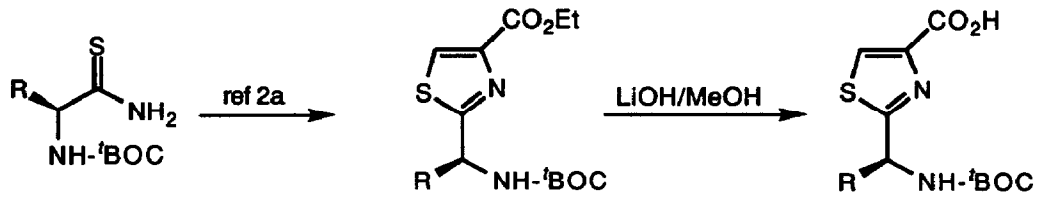
3b

Synthesis of the requisite oxazole **2** was accomplished by first treating the valine-serine derived dipeptide **4** with Burgess Reagent[4] in THF to give the oxazoline **5** in 60-78 % yield.[5] A small amount (5-8%) of dehydration product **6** was also obtained. Attempts at preparing oxazoline **5** by direct coupling of *t*-BOC-*N*-valine with serine methyl ester, using Vorbruggen's

conditions,[6] resulted in only a 22% yield of **5** while enamide **6** was obtained as the major product (47%). Oxidation of oxazoline **5** to the desired oxazole **2** was performed either with NiO_2/benzene[7] or MnO_2/benzene and proceeded with moderate yields as shown. Removal of the *t*-BOC group with acetyl chloride in methanol[8] gave the requisite amino oxazole **7** in quantitative yield.



Thiazole derived aminoesters **3a, 3b** were prepared by the recently improved[2a] modified Hantzsch reaction which led to enantiomerically pure materials. Basic hydrolysis, using LiOH in aqueous methanol gave the free acids **8a, 8b** in good to excellent yields. Both thiazoles were properly equipped to be utilized in the cyclo-coupling required to reach **1**.



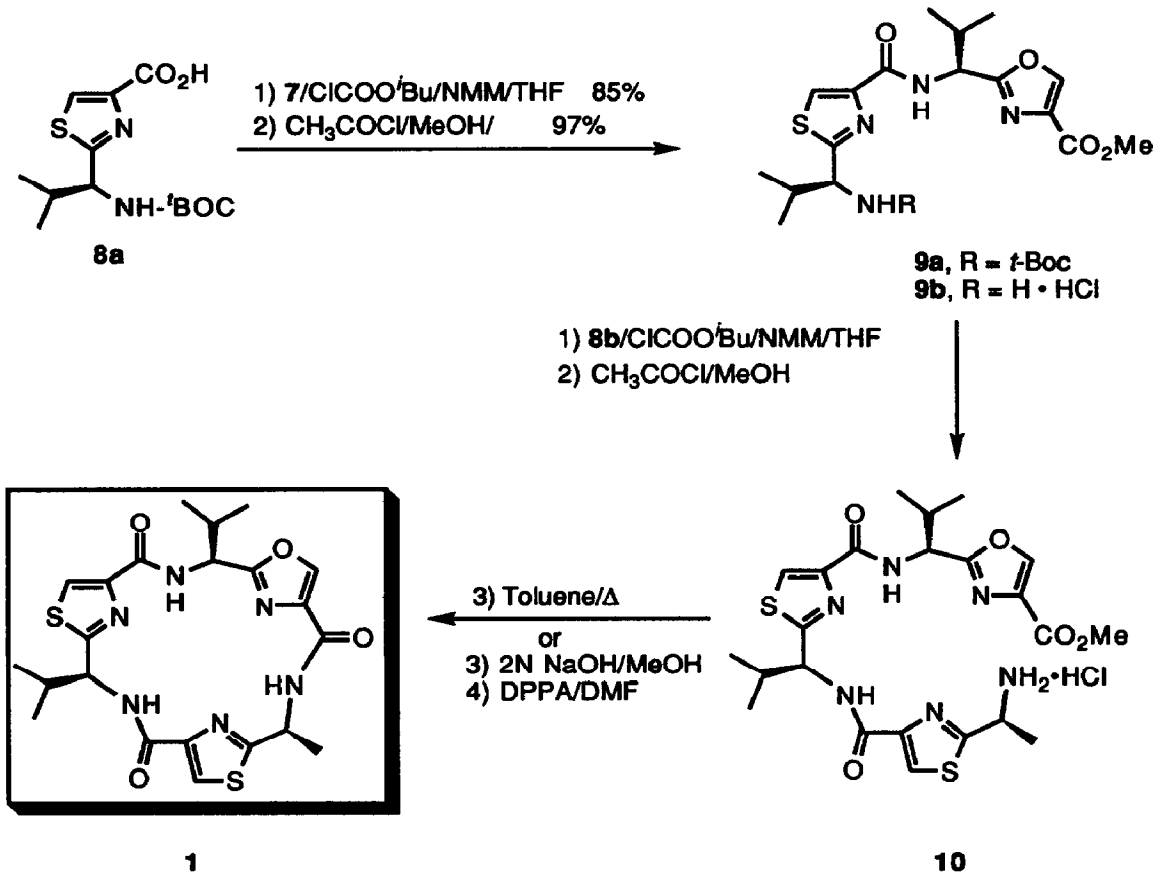
3a, R = ^{i}Pr 84%
3b, R = Me 96%

8a, R = ^{i}Pr 99%
8b, R = Me 73%

The coupling of oxazole **7** and thiazoles **8a** and **8b** was accomplished using mixed anhydride methodology. Thus, treatment of **8a** with isobutyl chloroformate, in the presence of *N*-

methylmorpholine (NMM), followed by addition of oxazole **7** gave *t*-BOC-*L*-(Val)-Oxz-*L*-(Val)-Thz-OMe **9a** in 85% yield. Deprotection of the amine was achieved almost quantitatively with acetyl chloride-methanol to give *L*-(Val)-Oxz-*L*-(Val)-Thz-OMe, **9b.**

Similarly, coupling of **9b** and thiazole **8b,** followed by amine deprotection, yielded the hexapeptidic ester **10.** Final closure of **10** was carried out by refluxing crude **10** in toluene for two days to give the bistatramide C **1** in 15-43% overall yield from **9.** The yields, however, were quite variable so another method to cyclize **10** was sought.



Ester **10** was hydrolyzed with 2N methanolic NaOH, and the resulting carboxylate was treated with diphenylphosphorylazide (DPPA)[9] in DMF. The resulting acyl azide was allowed to stand and after 2 days at room temperature **1** was obtained in 17% overall yield from **9a.** Thus, the yield obtained for **1** was ~70% for each of the five steps from **9a** to **1.**

The spectroscopic data for synthetic material **1** were found to be identical to those reported for the isolated natural product by comparison of the spectra. Optical rotations, on the other hand, obtained for two different spectroscopically pure synthetic samples of **1** were $[\alpha]_D = -104°$ (c 0.44,

$CHCl_3$) and $[\alpha]_D = -90°$ (c 0.30, $CHCl_3$). The reported rotation[3] for the isolated natural product is $[\alpha]_D = -65°$ (c 0.42, $CHCl_3$).[10] The NMR data of the synthetic material matched completely with the spectrum of an authentic sample of **1** which supports the reported structure and purity of the product.

Further studies to reach other members of this class of cyclic polypeptides are in progress.

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10. The isolation of **1** (ref. 3) was accomplished to provide 3.2 mg of natural material and this could account for the discrepancy noted for the specific rotation (Dr. T. Foderaro, University of Utah, private communication).

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