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Synthetic Studies of a Constrained Ring Didemnin Analog

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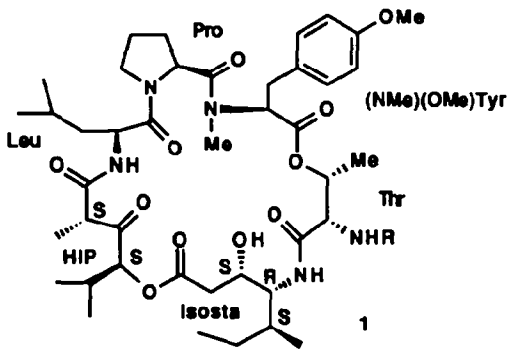
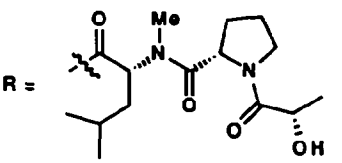
Abstract: An asymmetric Diels-Alder reaction in the presence of 3.0 M lithium perchlorate-diethyl ether was used to generate the initial stereochemistry for a cyclohexane amino acid (3), a key intermediate in the preparation of a fused ring didemnin analog. This constrained ring macrocycle should provide insight into the binding site conformation of the bioactive species.





R = H·HCl macrocycle, 1b

The didemnin class (**1**) of biologically active cyclodepsipeptides, isolated from a marine tunicate,[1] has shown considerable antitumor, antiviral, and immunosuppressive activity. To date, the proposed structural features essential for activity (the side chains attached to the amino group of threonine, the isostatine hydroxyl group, and the tyrosine unit) are based for the most part on conjecture.[2] Although the bioactivity of the most potent member, didemnin B (**1a**), has been attributed to its side chain,[3] few other structural features have been examined. Therefore, investigations were undertaken to synthesize a modified macrocycle which tethers the isostatine unit to the macrocycle *via* a cyclohexane ring, to provide a more rigid and structurally stable conformation, a fused ring system (**2**, **Scheme 1**). It has been reported that some peptide-like compounds in which (3S,4S)-4-amino-3-hydroxy-6-methylheptanoic acid (statine) was replaced with (3S,4S)-4-amino-3-hydroxy-5-cyclohexylpentanoic acid exhibited improved bioactivity as antihypertensive agents.[4-6] Such changes could alter the biological activity of the molecules and help to determine binding site/conformation as well as the importance of the isostatine hydroxyl group in active compounds.

A molecular modeling study[7] of a series of cyclohexyl analogs (**2**) was conducted, and their structures were compared to that of didemnin B in order to generate the correct stereochemistry needed for the ring subunit. The minimized molecular modeling structure of **1a** was originally generated from the X-ray

coordinates provided by Hossain and coworkers.[2] The best overlay was obtained with a cyclohexyl ring in which all three contiguous stereogenic centers have the S configuration (**Figure 1**). The stereogenic center α to the nitrogen is of the R configuration in didemnin B; however, after further investigation, the axial N on the cyclohexyl ring with the S configuration afforded the closest superimposed overlay. A retrosynthetic analysis similar to our synthetic approach to the macrocycle[8] was undertaken so that the same methodology could be employed once the cyclohexyl amino acid (**3**) was synthesized. This unit would then be esterified with the α-(α-hydroxyisovalery)propionyl unit (HIP, **4**) and then coupled with the tetrapeptide (**5**, **Scheme 1**).

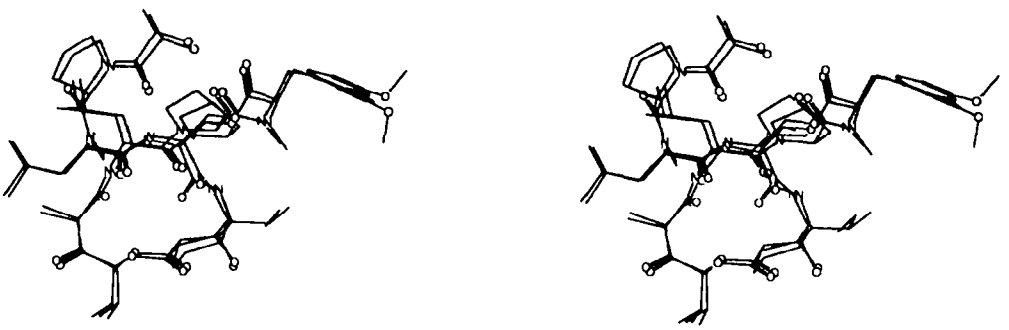
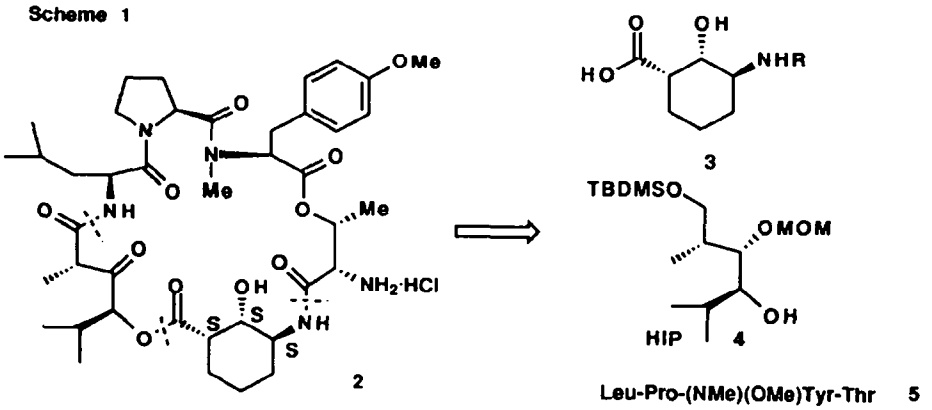


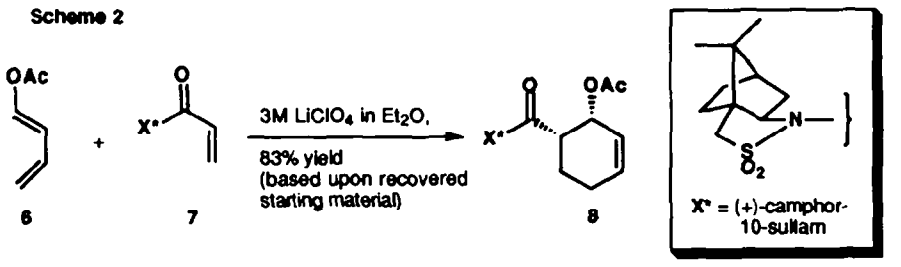
Figure 1. Molecular Modeling Overlay of **2** with **1a** in Stereoview.

Scheme 1



The synthesis of this deceptively simple cyclohexyl amino acid was then undertaken (**Scheme 2**). The initial stereochemistry for this substructure was obtained by an asymmetric Diels-Alder reaction using the Oppolzer camphorsultam directing group.[9-13] The diene (**6**) was obtained in 57% yield from crotonaldehyde in refluxing Ac_2O under basic conditions (68:32 E:Z ratio). Only the E isomer reacts in the Diels-Alder reaction.[14] Oppolzer's camphorsultam was coupled with acryloyl chloride to generate the dienophile (**7**). The diene and the dienophile were first refluxed in toluene to give a modest 3:1 diastereoselectivity. Early attempts with different Lewis acids such as $TiCl_4$ and $EtAlCl_2$ resulted in poor yields presumably because of the low reactivity of the diene. The best conditions for the Diels-Alder reaction required lithium perchlorate, as reported

by Grieco.[15,16] This reaction afforded an 83% yield of the major diastereomer and 5% of another diastereomer which could be chromatographically separated (based upon 25% recovered dienophile starting material). These conditions yielded a 5-fold increase in selectivity (3:1 to 17:1). At this point, two of the three stereogenic centers were set. The relative and absolute stereochemistries of this Diels-Alder product were confirmed by single crystal X-ray analysis (**Figure 2**).[17]



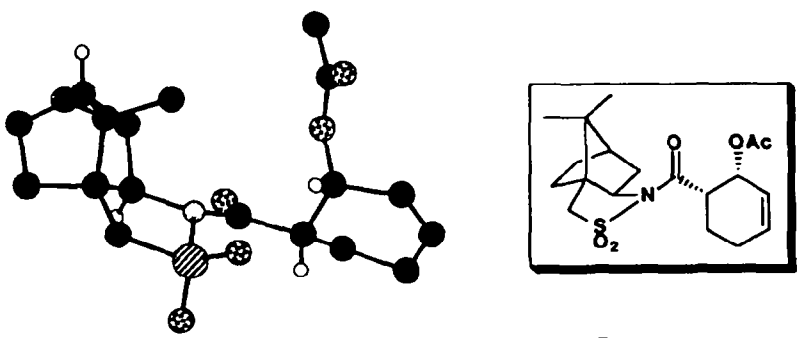


Figure 2. Diels-Alder product (**8**) X-ray ORTEP

The third stereogenic center was formed by an iodolactonization of the methoxy acid **9** resulting from camphorsultam hydrolysis followed by protection of the intermediate secondary alcohol as a methyl ether (**Scheme 3**). Iodolactonization afforded **10**. The iodine was removed with Bu_3SnH, and the resulting lactone (**11**) was opened with methoxide. A 70% yield of compound **12** was obtained with about 25% of a β-ester epimer (determined by NMR) resulting from the basic conditions.[18] Introduction of the amino function as a diastereomeric mixture (**13**, 1:1 ratio) was effected by oxidizing the hydroxyl group to a ketone, followed by reductive amination with benzylamine and triacetoxyborohydride.[19,20] Although this approach destroys the third stereogenic center, the diastereomeric mixture will be separated at a later stage such as after esterification with the HIP unit (**4**). The diastereomeric esters will be used to make two new analogs for testing.

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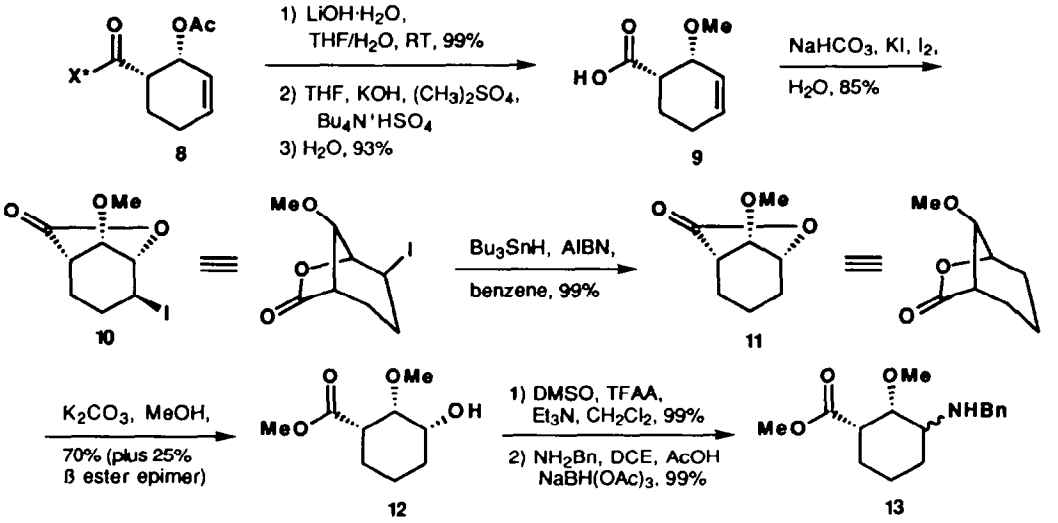
Scheme 3



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7 Calculations were performed using MacroModel v3.1X on a Silicon Graphics Iris 4D/320S computer. Minimizations were generated using PRCG followed by FMNR with MM2 force field to obtain an overlay RMS of 0.070.

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17 Compound 7 crystallizes in the monoclinic space group $P2_1$ (systematic absences 0k0: k=odd) with cell dimensions of a=9.217(2), b=7.499(1), c=14.287(3) Å, ß=104.35(2)°, V=956.6(6) Å^3, z=2 and d_{calc}=1.324g/cm^3. A total of 1876 reflections were measured, of which 1663 unique reflections with $F^2>3\sigma(F^2)$. All atoms were located and refinement converged to R_1=0.064 and R_2=0.088.

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