Communication

Synthetic Studies of a Didemnin B Analog Based on a 2,3-Diamino Sugar Scaffolding

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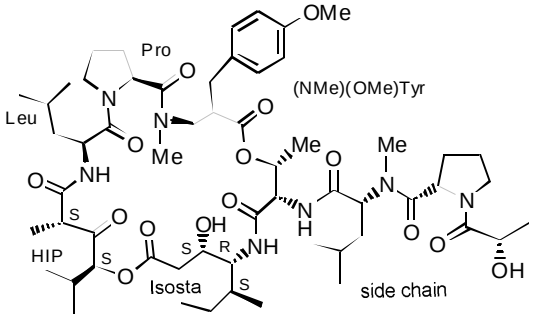
Reductive amination, amidation using BOP [(1H-1,2,3-benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate] and esterification *via* DCC (dicyclohexylcarbodiimide) were the key synthetic steps to generate an advanced intermediate in the preparation of a didemnin B analog based on a sugar scaffolding (**2**). This analog should provide insight into the bioactive conformation of didemnin B.

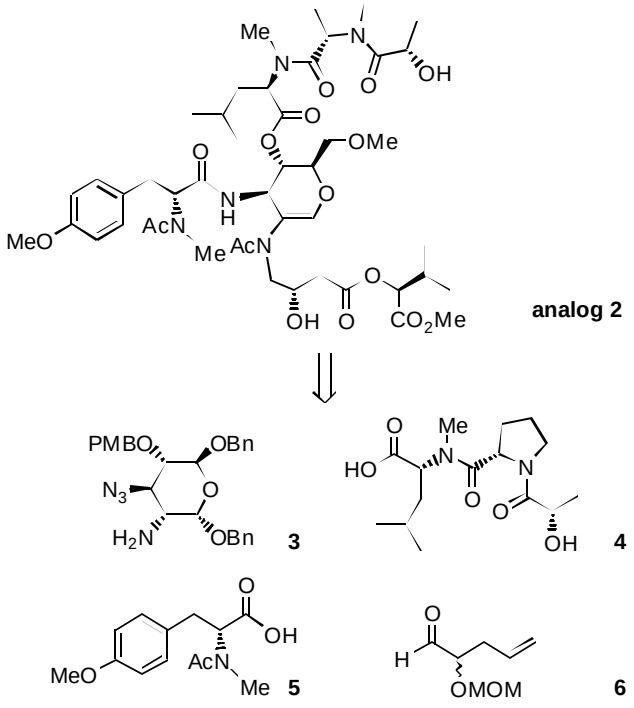
Didemnin B (**1**), a novel cyclodepsipeptide, was isolated in 1981 from a marine tunicate of the family *Didemnidae*.[1] This natural product was found to display a wide spectrum of biological activity including antitumor, antiviral and immunosuppressive activities. The proposed active sites for the bioactivity based on the X-ray analysis and solution conformation studies are the side chain attached to the amino group of threonine, the hydroxyl group of isostatine, and the tyrosine unit.[2,3] However, preliminary structure activity relationships suggest that the side chain is the most essential feature of the three.[4]



Didemnin B, 1

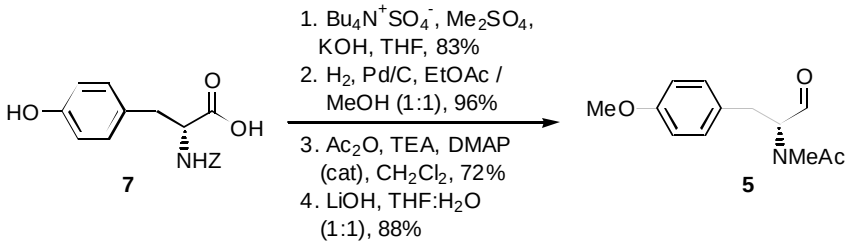
A molecular modeling study was initiated to find a suitable template which would maintain the spacial relationship of the three active sites.[5] The minimized molecular modeling structure of didemnin B (**1**) was originally generated from the X-ray coordinates provided by Hossain and coworkers.[2] The best overlay of the structures was obtained with all three structural features in presumed bioactive conformation when 2,3-diamino glycal was used as the template (Fig. 1). The retrosynthetic analysis of an analog **2** (Scheme I) provided benzyl 2-amino-3-azido-4-*O*-*p*-methoxybenzyl-6-*O*-benzyl-2,3-dideoxy-α-D-glucopyranoside (**3**) and the three side chains (**4**, **5**, **6**). We envisioned the introduction of the unsaturation in the sugar ring after the incorporation of the side chains.

Scheme I

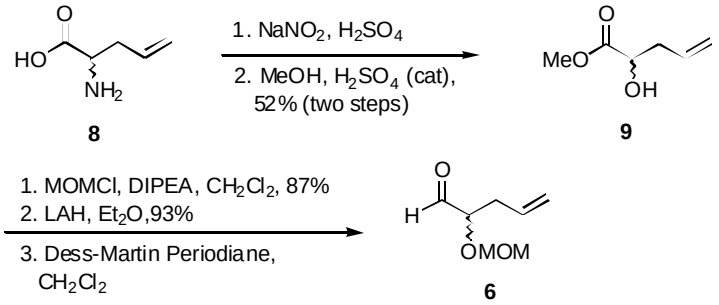


The synthesis of the 2-amino-3-azido sugar (**3**) and didemnin B side chain (**4**) was reported earlier.[6] The preparation of the side chain **5** began with protected L-tyrosine (Scheme II). Phase transfer reaction with dimethyl sulfate gave a permethylated compound which was immediately deprotected and acylated under standard conditions. Hydro-

Scheme II



Scheme III



ly sis of the methyl es ter gave com pound **5** in 88% yield. 2-Amino pentenoic acid (**8**) was used to syn the size the side chain **6** (Scheme III). Con ver sion to the α-hydroxy acid followed by methanolysis gave the methyl es ter **9**. The hydroxyl was pro tected as a MOM ether. Re duc tion of the methyl es ter fol lowed by ox i da tion gave the al de hyde **6**, which was used in the next step with out pu ri fi ca tion.

In cor po ra tion of the first side chain was ef fected by reductive amination of al de hyde **6** with com pound **3** us ing sodium triacetoxyborohydride[7,8] and the re sult ing amine was im me di ately pro tected as its ac e tate (Scheme IV). Chemoselective re duc tion of the azide with H_2S(g) fol lowed by the cou pling of acid **5** us ing BOP and the re moval of *p*-methoxy benzyl group un der ox i da tive con di tions gave com pound **11**.[9,10]

DCC cou pling of the re sult ing sec ond ary al co hol with *N*-methyl-Boc-D-leucine, fol lowed by dihydroxylation of the ter mi nal alkene gave the diol **12**. Periodate cleav age of compound **12** gen er ated an al de hyde which was fur ther ox i dized to the cor re spond ing carboxylic acid un der Masamune's conditions.[11] The resulting acid was esterified with methyl (*S*)-2-hydroxy-3-methylbutanoate[12] un der DCC con di tions. Re moval of Boc and MOM groups was ac com plished in one step using trifluoroacetic acid. The final coupling with L-lactyl-L-proline[12] was achieved un der BOP con di tions to pro vide com pound **13** in 81% yield. Cur rently, we are looking into ways of in tro duc ing unsaturation in the sugar ring and in the pro cess of test ing the bi o log i cal ac tiv ity of compound **13**.

The solid state struc ture of didemnin B clearly shows that the dimethyltyrosine res i due and the isostatine hydroxyl group pro trude out ward from the in te rior of the macrocycle,[2] lead ing to spec u la tion that they may be in volved in re cep tor bind ing. How ever, our pre lim i nary work on the struc ture-activity re la tion ships of the didemnins has re sulted in an incon gru ent and con tra dic tory pic ture. There fore, we hope to learn whether the im por tance of the isostatine re gion is related to stereochemistry or conformational ef fects by checking the bi o log i cal ac tiv i ties of com pound **13** and an a log **2** since they are only a lit tle dif fer ent in the sugar ring. Com pari son of the bi o log i cal ac tiv i ties of com pound **13** and an a log **2**

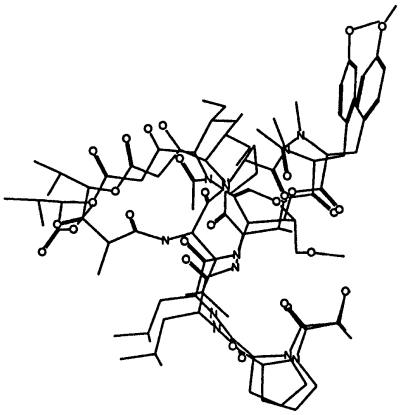
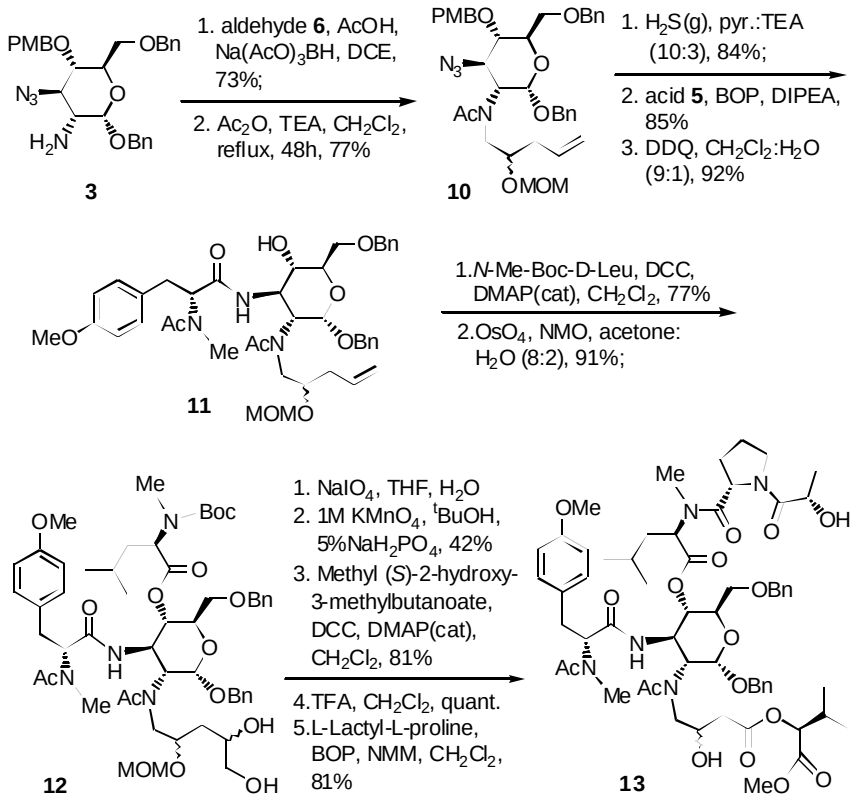


Fig. 1. Molecular mod el ing over lay of didemnin B (**1**) with an a log **2**.

Scheme IV



may prove valuable in the design of a second generation of drugs based on these conformational and biological studies. Although we obtained a diastereomeric mixture of compound **13**, the diastereomers will be separated at a later stage to make two new analogs with different chirality at the isostatine region for biological testing. After having obtained sufficient structure-conformation-activity data, different templates could be built on the non-critical part of the molecule without affecting the affinity, transport, and activity properties of the didemnins.

ACKNOWLEDGMENTS

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Key Words

Didemnin B; Sugar scaffolding; Bioactive conformation; Molecular modeling; Cyclodepsipeptide.

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10. Spec tro scopic data for com pound **11**: R_f 0.13 (40% ac e-tone/hex ane); $[\alpha]_D^{25}$ +73.28° (*c* 1.25, $CHCl_3$); IR (neat) 3304 (br), 2930 (br), 1625 (s), 1513 (s), 1454 (w), 1248 (w), 1034 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.05 (s, 3H), 2.06 (s, 3H), 2.70-2.90 (m, 4H), 2.75 and 2.79 (s, 3H, ro ta tional iso mers), 3.20-3.28 (br s, 1H), 3.28 (s, 3H), 3.75 (s, 3H, 3.73, 3.72, ro ta tional iso mers), 3.61-3.95 (m, 4H), 4.11-4.14 (m, 1H), 4.44-4.99 (m, 12H), 5.03-5.04 (m, 1H), 5.43-5.44 (m, 1H), 5.61-5.80 (m, 1H), 6.66-6.76 (m, 1H), 6.80-6.81 and 7.01-7.06 (m, 4H), 7.25-7.38 (m, 10H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 21.7, 22.9, 37.2, 38.2, 38.5, 39.0 47.2, 51.1, 54.1, 55.7, 56.8, 68.2, 69.3, 69.9, 73.9, and 74.7 (diastereomers), 96.1, 99.4 and 101.6 (diastereomers), 117.9, 118.1, 127.5, 127.8, 128.0, 128.2, 128.5, 129.0, 129.2, 129.4, 129.5, 129.6, 129.8, 132.9, 133.2, 133.4, 134.6, 136.3, 137.9, 158.4, 171.5, 171.9, 172.0, 172.6; HRMS calcd for $C_{42}H_{55}N_3O_{10}Na$: *m/z* 784.3785, found 784.3763.
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