



Natural Products Analogs as Scaffolds for Supramolecular and Combinatorial Chemistry

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Abstract: A new class of analogs of natural products useful for supramolecular and combinatorial chemistry is presented. Starting from the structure of natural dolastatins, we have designed and synthesized a series of amino acid-based unnatural rigid platforms having multiple functional groups pointing in the same direction. The stereochemistry of the final product is entirely determined by the chirality of the constituent amino acids. © 1998 Elsevier Science Ltd. All rights reserved.

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Rigid structures that present multiple functional groups in the same direction are much admired in molecular recognition research. Calixarenes,¹ resorcinarenes,² Kemp's triacid³ and tetraaryl porphyrins⁴ are but a few examples, and it appears to make no difference to their success that these molecules were originally intended for other applications. We have looked to natural products for such structures and introduce here a platform based on the general class of dolastatins.

Dolastatin E⁵ **1** features relatively flat heterocycles linked by conventional *trans* amide bonds. These amides are arranged in such a way that the pattern of alternating hydrogen bond donor and acceptor sites lining the interior of the macrocycle are self-satisfying: any other conformation introduces destabilizing secondary interactions⁶ in this pattern. Accordingly, the molecule is expected to be rigid. If the amino acid residues that link the serine- or cysteine-derived heterocycles are all of the same configuration, then the side chains will all be presented on the same face of the structure. This is summarized in the minimalist formulation of **2** (Figure 1) and results in platforms that offer many of the attributes of the others listed above. Modeling of the symmetric platform **2a** using MacroModel⁷ and the Amber⁸ and MM2⁹ force fields showed that the platform is indeed rigid, with the three acidic substituents protruding as shown.

As the synthesis of several dolastatins and congeners has been accomplished,^{10–14} simple modifications of those methods were sufficient for the synthesis of **2**. The only significant choices involved orthogonal protective groups that provide “addresses” on the skeleton. If symmetry is desirable, then the synthesis is simplified. The pattern of hydrogen donors mentioned above are self-organizing toward cyclization and a mere oligomerization of a simple subunit can lead to the product. If each side chain is different, the synthesis becomes correspondingly more complex.

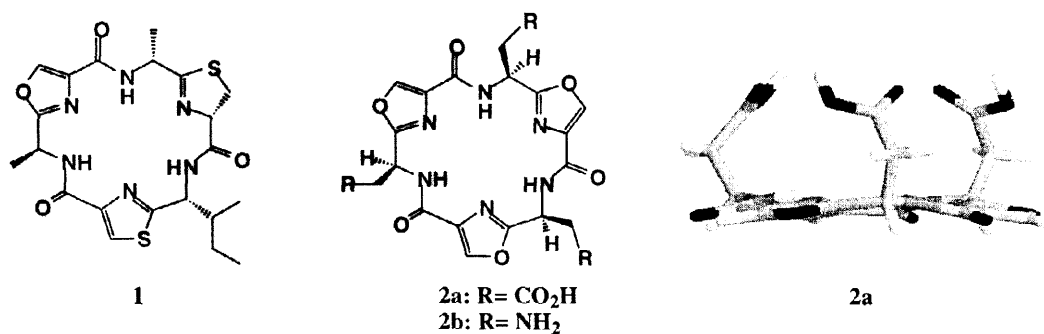
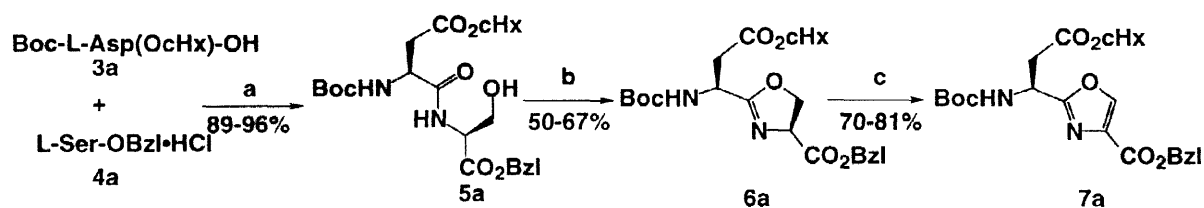


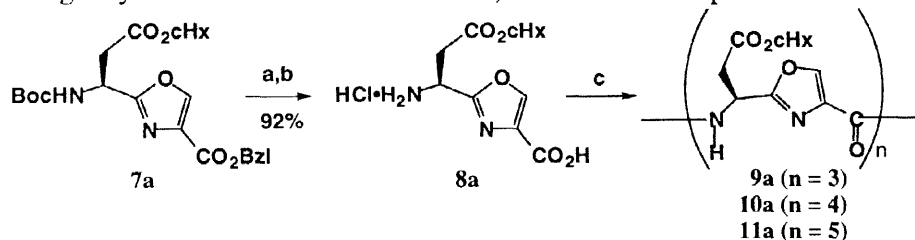
Figure 1. Dolastatin E (1), new symmetric platforms (2a,b), and Amber* minimized structure of 2a.

The synthesis of platform **2a** starts with the coupling of N-L-Asp(OcHx)-OH **3a** and L-serine benzyl ester **4a** using diphenylphosphoryl azide (DPPA) to give the dipeptide **5a**, which can conveniently be converted to the corresponding oxazoline **6a** upon treatment with the Burgess reagent.¹⁵ The oxazoline can then be treated with DBU and BrCCl₃ in CH₂Cl₂ to afford oxazole **7a**.¹⁶



Scheme 1. (a) DPPA, Et₃N, DMF, 0°C. (b) Burgess Reagent, THF, 70°C. (c) DBU, BrCCl₃, CH₂Cl₂, 0°C-rt.

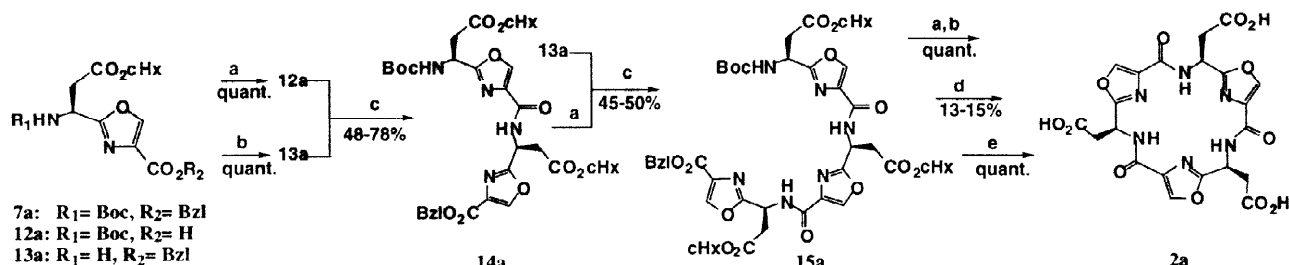
A macrocyclization on the oxazole hydrochloride **8a** was first attempted. Oxazole **7a** was deprotected by hydrogenolysis in THF to give the free acid, and removal of the BOC group via TFA in CH₂Cl₂ was followed by treatment with HCl in dioxane/diethyl ether to provide the subunit oxazole as the tractable hydrochloride **8a**. The unprotected oxazole was then treated with HBTU and Et₃N in DMF (scheme 2), but a complex mixture of oligomers containing only small amounts of the trimer **9a**, tetramer **10a** and pentamer **11a** was recovered.



Scheme 2. (a) H₂, Pd/C, THF, rt. (b) TFA, CH₂Cl₂, HCl in dioxane/diethyl ether, rt. (c) HBTU, DMF, 0°C-rt.

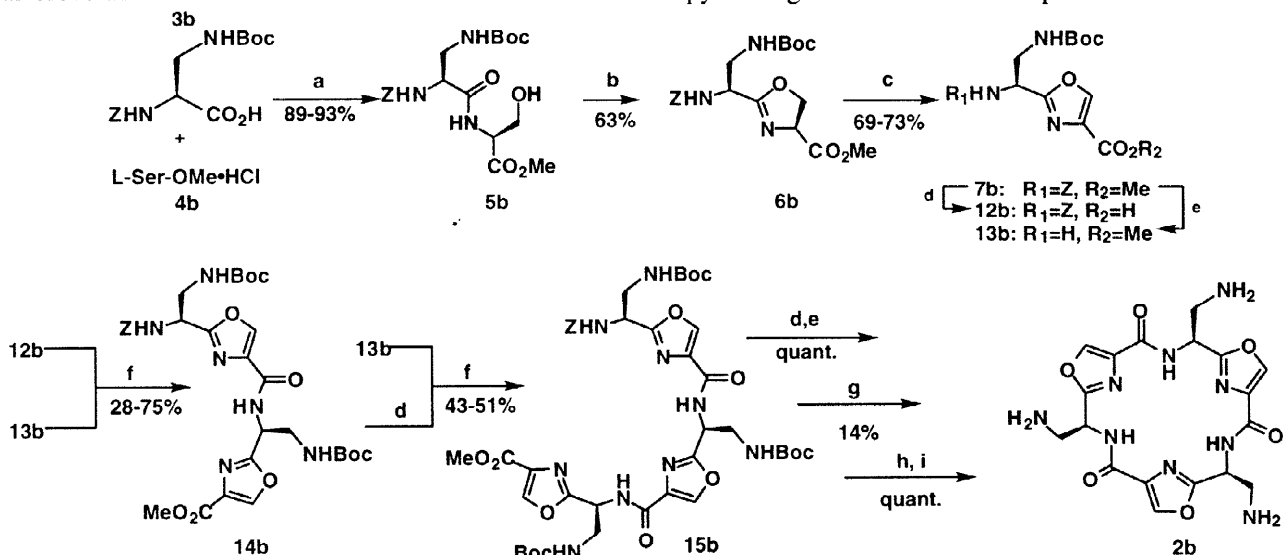
A less direct procedure, but one that followed the well-trodden paths of peptide synthesis proved more successful. Compound **7a** was iteratively deprotected and coupled to itself using isobutyl chloroformate (Scheme 3) to yield the protected trimer **15a**. Deprotection as before gave the free linear trimer and the

cyclization was accomplished with HATU in DMF yielding **9a** in 13–15% yield.^{17, 18} The three cyclohexyl esters were hydrolysed uneventfully by aq. NaOH in MeOH to give **2a**.



Scheme 3. (a) H_2 , Pd/C, THF, rt. (b) TFA, CH_2Cl_2 , rt. (c) isobutyl chloroformate, NMM, CH_2Cl_2 , 0°C–rt. (d) HATU, DMF, 0°C–rt. (e) NaOH, H_2O , MeOH.

Platform **2b** was synthesized according to Scheme 4. The β -aminoalanine **3b** was prepared according to known procedures.¹⁹ The only difference from the synthesis of platform **2a** regards the deprotection steps of the amino and carboxyl termini. The benzyloxycarbonyl group (Z) was used as the protecting group of the α - NH_2 and a Boc group was used to protect the β -amino functionality. The carboxyl terminus was protected as a methyl ester. Coupling of acid **12b** and amine **13b** via the mixed anhydride showed a wide variability in yield. The *N*-Boc protected platform **9b** was purified by HPLC. Deprotection of the Boc groups by TFA/ CH_2Cl_2 (1:2) afforded the trifluoroacetate salt of **2b**. Final treatment with pyridine gave the free triamine platform **2b**.



Scheme 4. (a) DPPA, Et_3N , DMF, 0°C. (b) Burgess Reagent, THF, 70°C. (c) DBU, BrCCl_3 , CH_2Cl_2 , 0°C–rt. (d) aq. NaOH, MeOH, rt. (e) H_2 , Pd/C, THF, rt. (f) isobutyl chloroformate, NMM, CH_2Cl_2 , 0°C–rt. (g) HATU, DMF, 0°C–rt. (h) TFA– CH_2Cl_2 7:10. (i) Pyridine.

Applications of platforms **2a,b** in supramolecular chemistry are ongoing in our laboratories. In the meantime we note that **2a,b** have potential in the combinatorial field, especially as new core molecules, for use in either solid phase or solution phase synthesis.²⁰ The preparation of the platforms with three different addresses for library deconvolution will be reported in due course.²¹

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- Conditions for the macrocyclization: Linear trimer (0.151 mmol) in 10ml of anhydrous dimethylformamide was added to a stirred solution of *O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (0.453 mmol) and 2,4,6 collidine (0.483 mmol) in 125ml of anhydrous dimethylformamide via syringe pump over a period of two days. Solvent was then evaporated *in vacuo* and the residue was taken up in 20ml of 1N hydrochloric acid and 100ml of ethyl acetate. Aqueous layer was extracted two more times with ethyl acetate (2x50ml) and the combined organic layers were washed with brine (2x10ml), dried with anhydrous magnesium sulfate and evaporated *in vacuo*. Pure **9a** was obtained by column chromatography (chloroform/methanol 95:5).
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- All novel compounds were characterized by NMR spectroscopy and high resolution mass spectroscopy (LRMS ESI-MS for **2a,b**). Spectroscopic data for **2a**: ¹H-NMR (DMSO-*d*₆) δ 8.87 (s, 3H), 8.46 (d, ³J=1Hz, 3H), 5.42 (m, 3H), 3.05 (m, 6H). ESI-MS: [M-H]⁺: expected 545; found 545. Spectroscopic data for **2b**: ¹H-NMR (pyridine-*d*₅) δ 9.22 (d, ³J=1Hz, 3H), 8.98 (s, 3H), 6.08 (m, 3H), 4.28, 3.93 (dd, AB system, 6H). ESI-MS: [M-H]⁺: expected 460; found 460.