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Synthesis of a second-generation pseudopeptide platform

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Abstract

A synthetic pathway is presented to a functionalized pseudopeptide molecular platform for use in supramolecular and solution-phase combinatorial chemistry. The platform contains amino acids with quaternary asymmetric centers, the configurations of which are determined by the method of synthesis.

Keywords: platform; amino acids and derivatives; macrocycles; oxazoles; combinatorial chemistry.

Rigid molecular platforms presenting three functional groups on the same face can serve as core molecules for solution phase combinatorial chemistry as well as templates for synthetic receptors.[1] In the former application, molecular diversity is provided by the well-defined positioning of functionality on a large surface; in the latter application, combinations with rigid spacers give cleft-like structures with convergent functional groups useful for selective molecular recognition.

Earlier, we introduced platform **2** (see Fig. 1) based on the structure of naturally occurring dolastatins (e.g. Dolastatin E (**1**)[3] in Fig. 1) for these purposes.[2] Macrocycle **2** features oxazole rings linked by *trans*-amide bonds. The most favored conformation of **2** features all lone pairs of the oxazole nitrogens and the hydrogens of the secondary amides directed to the center of the macrocycle. This self-satisfying H-bonded pattern largely contributes to the close planarity of the structure. The amino acid residues that connect the heterocycles are all of the same configuration, and the side chains are all presented on the same face of the molecule. However, the electronic environment at the asymmetric centers caused problems with racemization during the synthesis of platform **2**, and decreased the yield of the desired all-*syn* compound. Consequently, the use of platform **2** is limited to non-basic conditions.

This behavior led us to a structure resistant to racemization, with methyl groups replacing the hydrogens at the three asymmetric centers. This modification also allows for the functional groups to be connected directly to the macrocyclic ring where their presentation and orientation are better defined in space. The result is the racemization-free macrocycle **3**.

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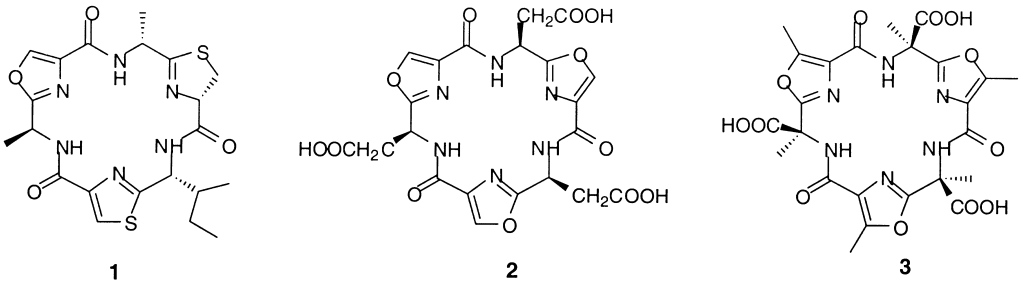
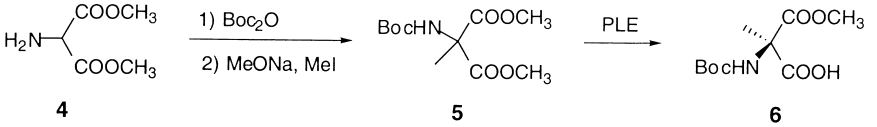


Figure 1. Dolastatin E (**1**), racemization sensitive platform **2** and racemization stable platform **3**

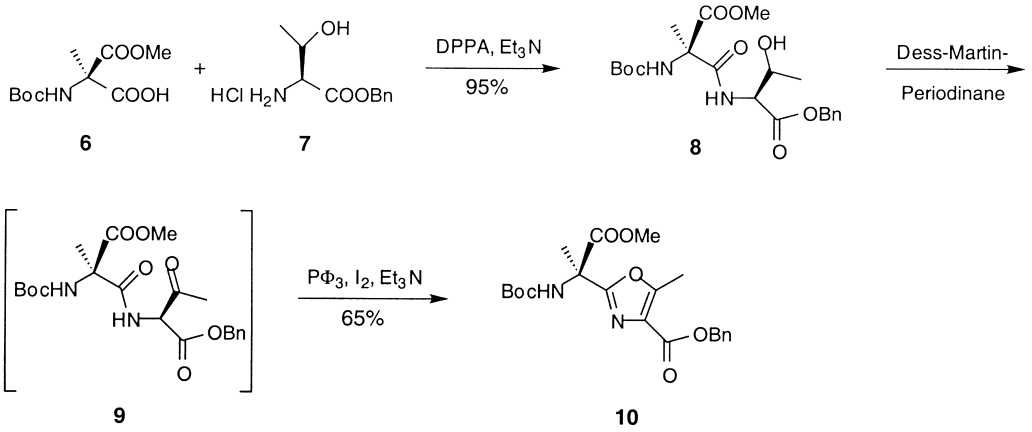
For the synthesis of platform **3** the appropriate amino acids are the natural L-threonine and the synthetic malonic monoester derivative **6** (see Scheme 1).



Scheme 1. Synthetic route to chiral non-natural malonic monoester **6**

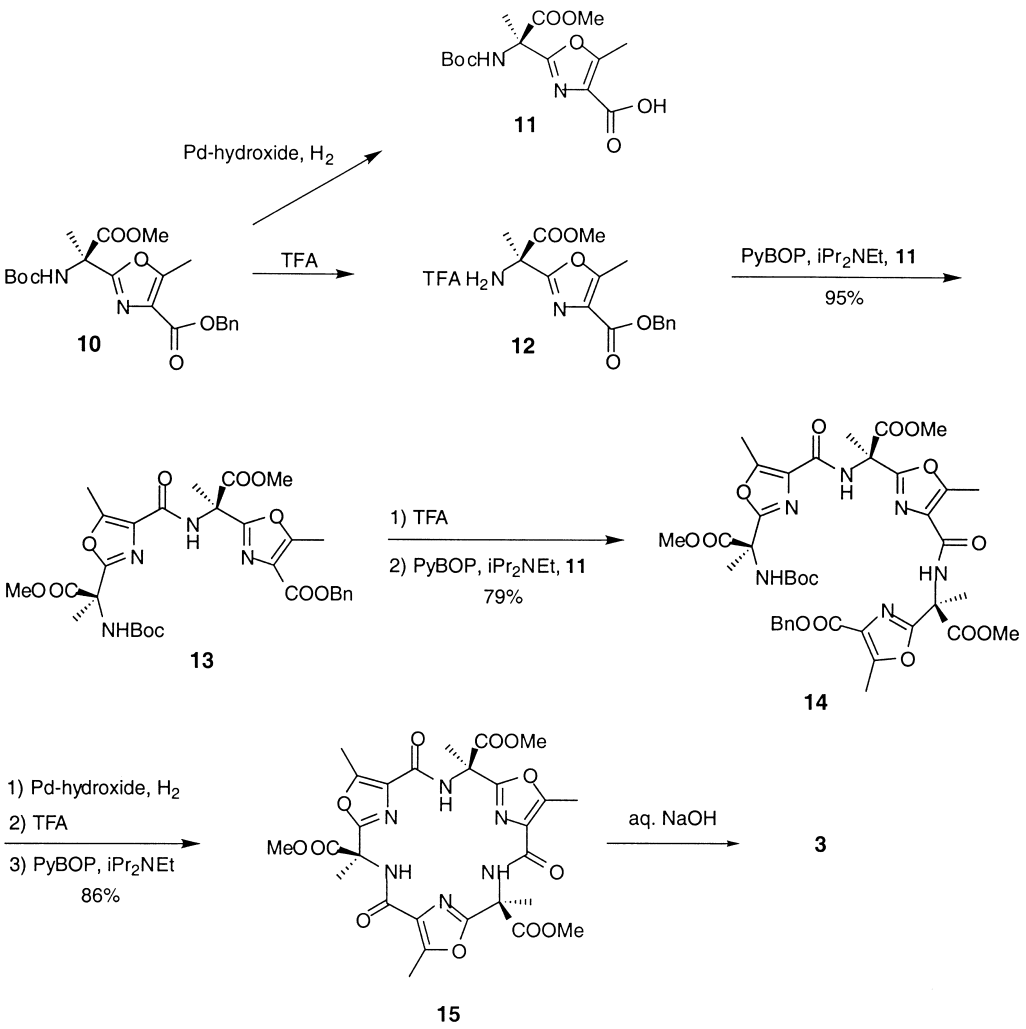
The enantiomerically pure acid **6** is readily available from dimethylamino malonic ester **4** by Boc-protection then alkylation to give compound **5** (Scheme 1). Enzymatic hydrolysis with porcine liver esterase[4]—under optimized conditions using a mixture of CH_3CN and phosphate buffer (pH = 7) as solvent—afforded the enantiomerically pure compound **6**. The preparation can be performed on a 100 g scale.

The synthesis of oxazole building block **10** proceeds from the acid **6** by coupling to H-Thr-OBn (**7**) using diphenylphosphoryl azide (DPPA). The resulting dipeptide **8**[5] is conveniently converted to the corresponding oxazole **10** by sequential treatment with the Dess–Martin periodinane then cyclodehydration with triphenylphosphine in the presence of iodine and triethylamine[6] (Scheme 2). The overall yield of oxazole **10** starting from acid **6** is 60%.



Scheme 2. Synthesis of oxazole building block **10**

The desired platform **3** was synthesized according to Scheme 3. Hydrogenolysis of the Bn ester of **10** with Pearlman's catalyst in a 3:1 mixture of ethanol and acetic acid gave the free acid building block **11**. Acid cleavage of the Boc group of **10** with TFA in CH_2Cl_2 provided the triflouroacetate salt **12**. Coupling to **11** with PyBOP[7] gave oxazole dimer **13** in 95% yield. Cleavage of the Boc group and PyBOP activation were repeated to give protected linear trimer **14**. Deprotection of the carboxyl by hydrogenolysis and removal of the Boc group with TFA in CH_2Cl_2 afforded the linear trimer. The macrolactamization was carried out by PyBOP activation and addition of Hünig's base in DMF, and yielded the triester platform **15** in 86%. The yield for the macrocyclization is much higher than that obtained during the synthesis of **2** and deserves some comment. We can only opine that the extra methyl of the threonine-derived oxazole helps organize—or preorganize—the conformation to the sickle shape appropriate for cyclization and prevents nucleophiles from approaching on a trajectory that leads to intermolecular, rather than intramolecular products. In any case, the protected platform **15** was synthesized on a gram scale



Scheme 3. Stepwise synthesis of triacid platform **3**

and is conveniently transformed into the desired triacid platform **3**[8] by saponification using aqueous NaOH. Fortunately, the triacid platform **3** does not tend to decarboxylation at ambient temperatures; it can be coupled to primary amines leading to the elaboration of combinatorial libraries. Application of **3** in molecular recognition is in progress and will be reported in due course.

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5. General procedure for DPPA activated peptide coupling: To a stirred solution of the *N*-Boc-protected amino acid (1 equiv.), the methyl ester (1.5 equiv.) and *N*,*N*-diisopropylethylamine (1.5 equiv.) in DMF (0.3 M) was added 1.5 equiv. DPPA at 0°C followed by slow addition of 3.8 equiv. *N*,*N*-diisopropylethylamine. Stirring was continued for 20 hours while slowly allowing the reaction mixture to warm to room temperature. The DMF was evaporated, the residue was dissolved in AcOEt and washed with water, saturated $NaHCO_3$ solution, 1 M HCl and brine, then dried over $MgSO_4$ and concentrated in vacuo. Purification was accomplished by chromatography on silica gel with AcOEt:hexane (1:2).
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7. General procedure for PyBOP activated coupling: To a stirred solution of the amino building block (1 equiv.), the acid building block (1 equiv.) and *N*,*N*-diisopropylethylamine (1 equiv.) in DMF (0.06 M) was added 1.2 equiv. PyBOP at room temperature followed by slow addition of 2.8 equiv. *N*,*N*-diisopropylethylamine. Stirring was continued for 24 hours. The workup was as described above.
8. Spectroscopic data for platform **3**: ^{1}H NMR (methanol-d_4): 9.07 (s, 3H), 2.65 (s, 9H), 2.03 (s, 9H). ^{13}C NMR (methanol-d_4): 170.5, 161.9, 161.1, 157.1, 129.7, 60.5, 22.8, 11.7. MALDI–FTMS $[M+Na]^+$: calculated: 611.1344; observed: 611.1342.