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Bioorganic & Medicinal Chemistry Letters 16 (2006) 3358–3361
Bioorganic & Medicinal Chemistry Letters

A versatile access to new macrocyclic oligoheterocycles (MOH)

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Received 17 March 2006; revised 6 April 2006; accepted 6 April 2006
Available online 5 May 2006

Abstract—An efficient and straightforward methodology for the parallel solid-phase synthesis of a variety of new macrocyclic oligoheterocycles is described. Exhaustive reduction of resin-bound cyclic polyamides using borane generates polyamines. Treatment of separated pairs of amines with a variety of bifunctional reagents provides, following cleavage from the solid support, the desired macrocyclic oligoheterocyclic (MOH) compounds in good yields and purities.

Polyheterocycles have been the subject of intense research interest.[1] The insertion of heterocycles in the macrocyclic template provides additional binding elements for target receptors. Marine organisms are the source of a great variety of biologically active macrocyclic peptides. Many of these are macrocyclic oligoheterocycles and contain considerably modified amino acid building blocks.[2] A large number of oxazole- and/or thiazole-containing natural macrocyclic heterocycles known as *lissoclinum* peptides have been isolated from marine organisms. These compounds were found to exhibit cytotoxic and antineoplastic activities with potential action as metal ion chelating metabolites.[2] Nitrogen-containing ring systems have been widely used as ligands in organometallic chemistry.[3] For example, pyridine and bipyridine have commonly been incorporated into macrocyclic frameworks, affording new ligands that readily complex transition-metal ions.[4] Recently, macrocycle receptors containing a bipyridine moiety as an integral part of a polyamine macrocyclic structure have been reported.[5]

The diverse structure and properties of macrocyclic oligoheterocycles (MOH) render them of particular interest to synthetic and medicinal chemists alike. In this paper, we describe an efficient and straightforward approach for the parallel solid-phase synthesis of a variety of macrocyclic oligoheterocycles from carefully designed resin-bound compounds containing separated pairs of amines.

Starting from *p*-methylbenzhydrylamine (MBHA) resin, a compatible solid support for Boc/Bzl and Fmoc/^{t}Bu solid-phase peptide synthesis (SPPS), the parallel syntheses of macrocyclic polyamines and macrocyclic oligoheterocycles were carried out using the 'teabag' technology[6] employing standard solid-phase peptide synthesis.[7] Exhaustive reduction of amide bonds of the resin-bound proline-containing cyclic peptide **3** with borane in THF[8] generated the corresponding resin-bound macrocyclic polyamines **4** having two tertiary amines and six secondary amines (Scheme 1).

Our approach involves the use of proline (known to induce cyclization)[9], lysine, and glutamic acid as spacers, which upon exhaustive reduction of the amide groups, yielded two pyrrolidines and three pairs of separated secondary amines. Treatment of the resin-bound pyrrolidine-containing macrocyclic polyamine **4** with bifunctional reagents such as thiocarbonyldiimidazole or oxalyldiimidazole led, following cleavage from the solid support, to the corresponding macrocyclic oligoimidazolidinethiones **5** and macrocyclic oligocyclic diketopiperazines **6**, respectively (Scheme 1).[10]

We previously reported that the reduction of amide bonds using the complex BH_3–THF was free of race-

Keywords: Solid-phase synthesis; Macrocyclic oligoheterocycles; Polyamines.
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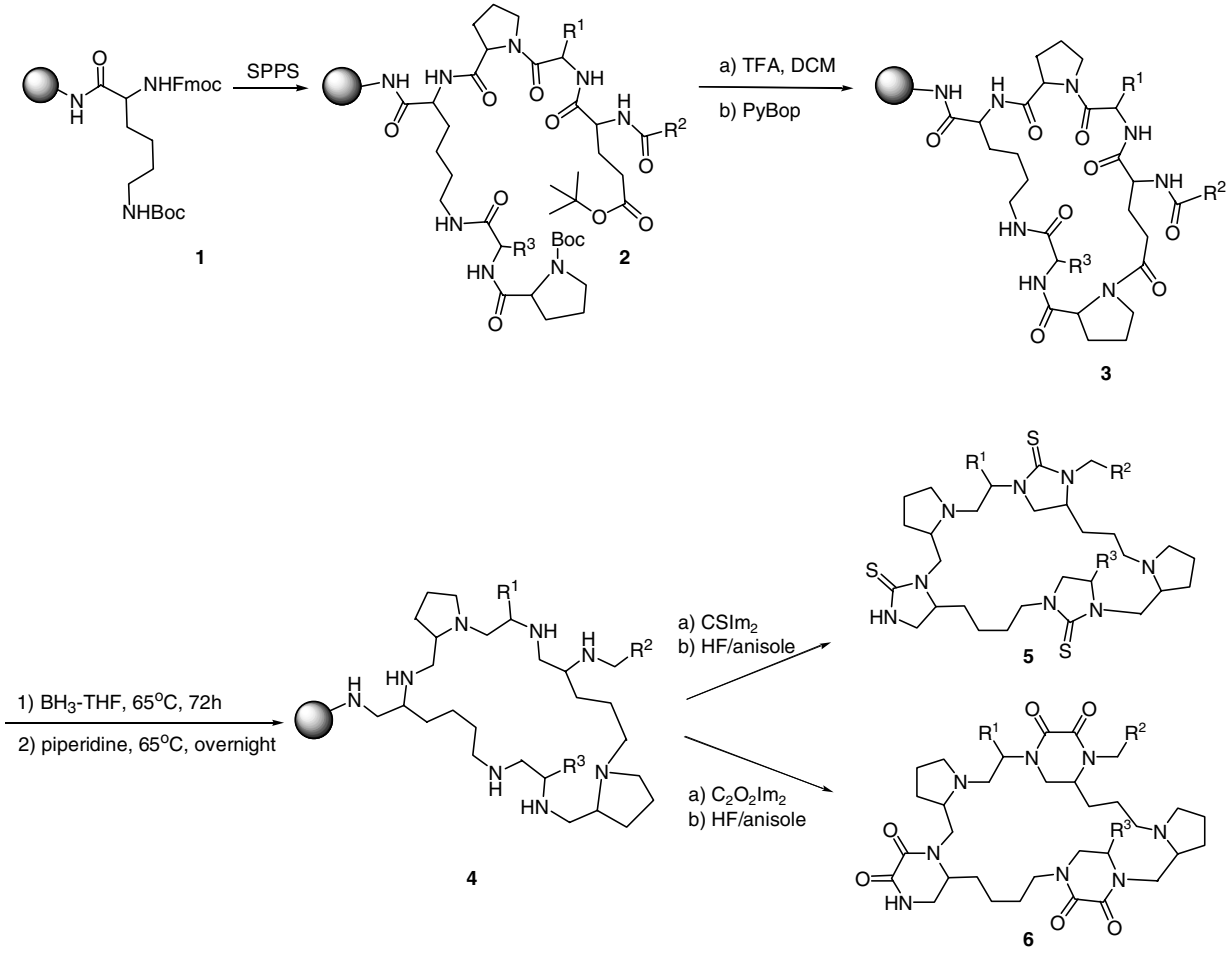
doi:10.1016/j.bmcl.2006.04.039

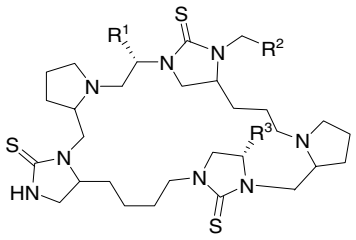


Scheme 1. Formation of the macrocyclic heterocycles from solid-phase bound cyclic polyamine template.

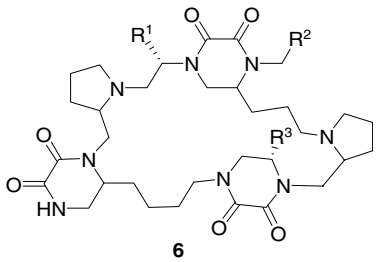
mization by comparing the relative absorbances of different pairs of diastereomers that do not coelute.[8a,b] The same observations were later reported by other groups using different reduction work-up procedures.[8c] We initially examined the feasibility of our approach for the generation of macrocyclic polyamines and their corresponding macrocyclic oligoheterocycles using two representative L-amino acids for R^1 (Ala, Leu), for R^3 (Ala, Phe), and two carboxylic acids (phenylacetic acid and acetic acid) for R^2. Seven individual compounds for each of the macrocyclic polyamines and macrocyclic oligoheterocycles were synthesized (Table 1). Average purities of 50–70% were obtained for all compounds and average crude yields of 80% relative to the initial loading of the resin. Selected representative compounds were characterized by HRMS, NMR and all compounds were characterized by LC–MS. Figure 1 shows the LC–MS spectra of the macrocyclic oligodiketopiperazine obtained from L-leucine, L-alanine, and phenylacetic acid, which is representative of the purities obtained for all cases. The presented approach is not limited to the use of proline, glutamic acid, and lysine as spacers. There are other N-substituted and trifunctionalized amino acids that would also be suitable for providing different designed templates having separated pairs of secondary amines.

Medium- and large-sized oxa- and azaheterocyclic systems are of interest for various applications by virtue of their unique and selective binding properties toward cations, anions, and neutral molecules. Their synthesis has been the subject of many investigations in recent years. An efficient strategy for the synthesis of macrocyclic oligoheterocyclic compounds from resin-bound macrocyclic polyamines having potential biomedical applications was described. Our method allows for wide variations in ring size, heteroatoms, and substitution patterns, and thus facilitates tailor-made syntheses of various macrocyclic oligoheterocyclic systems. Using proline or other building blocks such as oxazolidines, thiazolidines, N-alkylated amino acids and/or piperazines and bifunctional amino acids such as lysine, ornithine, etc., and/or aspartic acid, glutamic acid, etc. as spacers, the strategy presented provides the means for the generation of large numbers of discrete combinatorial libraries of macrocyclic polyamines and macrocyclic oligoheterocyclic compounds. Investigations concerning the complexation properties of the MOH systems are currently in progress.

Table 1. MS and purities of the MOH **5** and **6** derivatives



5



6

Entry	R^1	R^2	R^3	Compound **5** (MW found)	Yield of purified compound **5** (%)	Compound **6** (MW found)	Yield of purified compound **6** (%)
a	–CH_3	–CH_3	–CH_3	(649.2)(MH^+)	42	(685.5)(MH^+)	49
b		–Ph	–CH_3	(767.3)(MH^+)	41	(803.5)(MH^+)	56
c		–CH_3	–CH_3	(691.2)(MH^+)	40	(727.8)(MH^+)	44
d	–CH_3	–Ph	–Ph	(801.2)(MH^+)	39	(837.4)(MH^+)	48
e	–CH_3	–CH_3	–Ph	(725.1)(MH^+)	36	(761.4)(MH^+)	43
f		–Ph	–Ph	(843.2)(MH^+)	42	(879.6)(MH^+)	44
g		–CH_3	–Ph	(767.2)(MH^+)	37	(803.5)(MH^+)	43

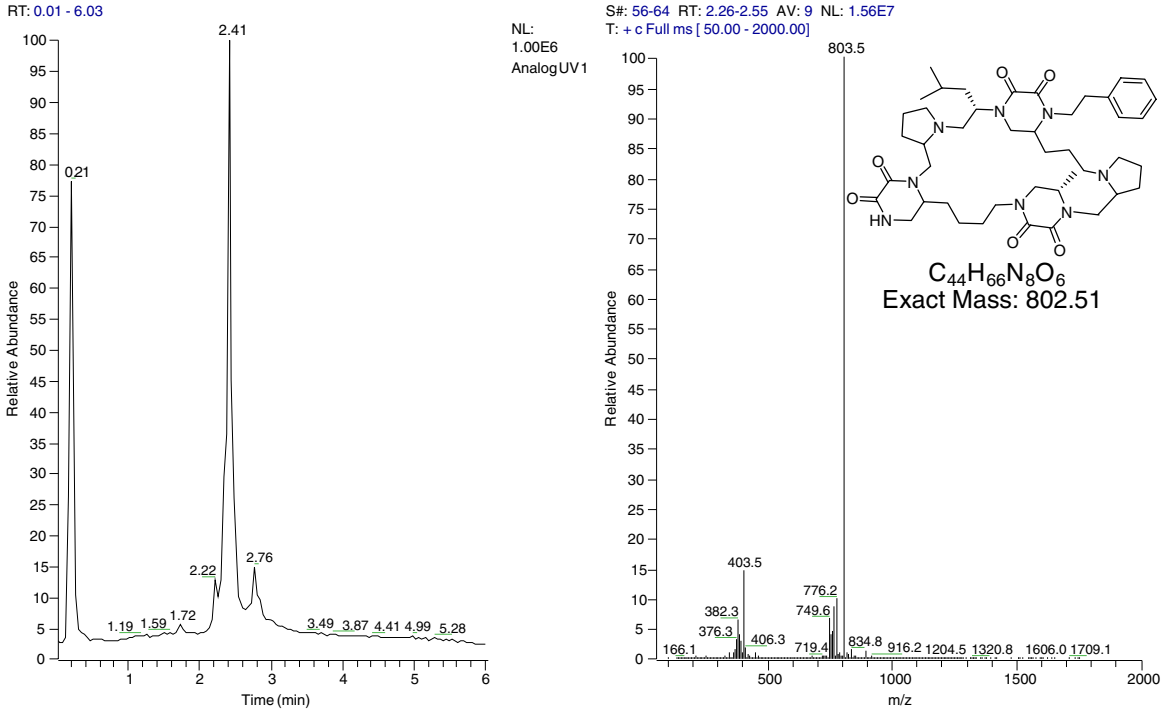


Figure 1. LC–MS of a representative macrocyclic oligodiketopiperazine **6g**.

Acknowledgments

The authors thank Multiple Sclerosis National Research Institute, Diabetes National Group, Alzheimer's and Aging Research Center, Pain Management Research Institute of America, and Osteoporosis and Breast Cancer Research Center for their support.

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10. *Experimental section*: General information. All amino acids, carboxylic acids, and reagents were obtained from commercial suppliers and used without further purification. Solid-phase syntheses were carried out using the 'teabag' method,[6] in which the resin is contained within sealed polypropylene mesh packets. Reactions were carried out in polyethylene bottles. The completeness of amino acid coupling and N-acylation were verified using the ninhydrin (Kaiser) test. General procedure for linear protected peptide synthesis (**2**): Fifty milligrams of *p*-methylbenzyhdrylamine (MBHA) resin (0.1 mequiv/g, 100–200 mesh) was contained within a sealed polypropylene mesh packet. Following neutralization of the amino-resin with 5% diisopropylethylamine (DIEA) in dichloromethane (DCM) followed by washes (2×) with DCM, the Fmoc-Lys(ξ-Boc)-OH (6 equiv, 0.1 M) was coupled in the presence of hydroxybenzotriazole (HOBt) (6 equiv, 0.1 M) and diisopropylcarbodiimide (DIPCDI) (6 equiv, 0.1 M) in anhydrous DMF for 60 min. The Boc group on the N^{ξ} of the lysine was removed with 55% TFA in DCM for 30 min followed by neutralization of the amine. Boc-amino acid (6 equiv, 0.1 M) was coupled to the free N^{ξ} in the presence of hydroxybenzotriazole (HOBt, 6 equiv) and diisopropylcarbodiimide (DIPCDI, 6 equiv) in anhydrous DMF for 60 min. The Boc group was then removed and the amine was neutralized. Boc-proline was coupled using the same conditions described above. The Fmoc group on the N^{α} of the lysine was then removed with 25% piperidine in DMF (2× 10 min) and the resin was washed with DMF (8×). The generated free amine was coupled to Fmoc proline (6 equiv, 0.1 M) in the presence of hydroxybenzotriazole (HOBt, 6 equiv) and diisopropylcarbodiimide (DIPCDI, 6 equiv) in anhydrous DMF for 60 min. Following Fmoc group deprotection with 25% piperidine in DMF (2× 10 min) and Fmoc amino acid coupling in the same conditions as described above, Fmoc was removed and Fmoc-Glu(^{t}Bu)-OH was coupled to the free amine in the same conditions as described above. The Fmoc group was removed and the generated amine was N-acylated with a carboxylic acid (10 equiv) in the presence of DIPCDI (10 equiv) and HOBt (10 equiv) overnight in anhydrous DMF. General procedure for the cyclization of the peptide on the solid support (**3**): The Boc group on the proline and the ^{t}Bu group on the side chain of the glutamic acid were simultaneously removed with a solution of 80% TFA in DCM (1 h). Following washes with DCM (5×) and neutralization, the resin-bound linear polyamides were treated with PyBOP (3 equiv) in anhydrous DMF and DIEA (2 equiv) overnight to undergo intramolecular cyclization. The completeness of the cyclization was monitored by Kaiser test. General procedure for the exhaustive reduction of amide bonds and generation of resin-bound macrocyclic polyamines (**4**): The amide reduction was performed in 50 ml Kimax tubes under nitrogen. The resin packet were treated with 1 M BH_3–THF (40-fold excess over each amide bond). The tubes were heated at 65 °C for 72 h, decanted, washed with THF, and any remaining borane quenched with MeOH. The borane was disproportionated by treatment with piperidine at 65 °C overnight. The resin was then washed with methanol (2×), DMF (6×) and dried. The completeness of the reaction was verified by HF cleavage and analysis by LC–MS of a control set. General procedure for the generation of macrocyclic oligoheterocycles (MOH) (**5** and **6**): Cyclic thiourea and diketopiperazine heterocycles were formed following treatment of the resin-bound polyamines overnight with a 6-fold excess of thiocarbonyldiimidazole (0.05 M) in anhydrous DCM and oxalyldiimidazole (0.05 M) in anhydrous DMF (not soluble in DCM), respectively. Following cleavage from the resin with anhydrous HF in the presence of anisole at 0 °C for 90 min, the desired product was extracted with acetonitrile/water (50:50) and lyophilized. The identity of all compounds were determined by LC–MS and selected representative compounds were characterized by HRMS. Exact mass for **6a** (MH^+) = 685.4367, **6b** (MH^+) = 803.5153, **6e** (MH^+) = 761.4716, **5a** = (MH^+) 649.3871, **5b** (MH^+) = 767.4680, **5e** (MH^+) = 725.4171.