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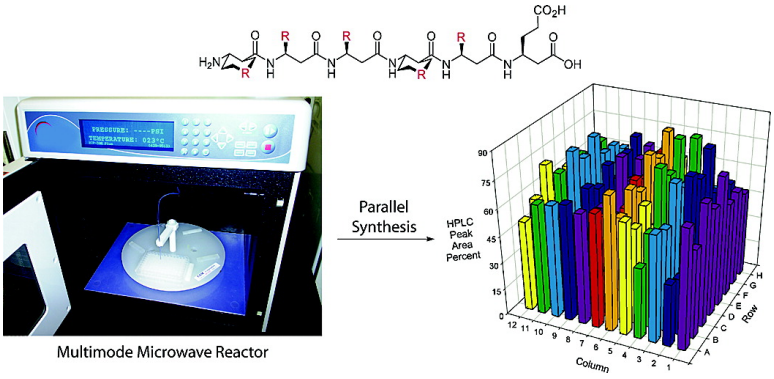

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Microwave-Assisted Parallel Synthesis of a 14-Helical β-Peptide Library

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To facilitate the preparation of β-peptide libraries in parallel, we have adapted reaction conditions for the solid-phase synthesis of 14-helical β-peptides for use in a multimode microwave reactor. The low temperature/pressure requirements of microwave-assisted β-peptide synthesis were found to be compatible with multiwell filter plates composed of polypropylene. Microwave heating of the 96-well plate was sufficiently homogeneous to allow the rapid preparation of a β-peptide library in acceptable purity.

Introduction

Microwave irradiation has been successfully applied to an ever-increasing number of organic reactions with a resulting reduction in synthesis time, improvement in yield, or both.[1] We recently reported that the solid-phase synthesis of β-peptides (oligomers of β-amino acids) could be enhanced by microwave irradiation.[2,3] Although microwave irradiation is attractive for accelerating the discovery of bioactive molecules,[4] harnessing this method of rapid heating for the preparation of combinatorial libraries can be challenging.[5] In parallel synthesis, the reaction mixture components differ from one vessel to the next (in our case, the vessels are wells in a plate). Simultaneous exposure of the entire set of reaction vessels to microwave irradiation, with power control based on the temperature of a single reference vessel, can lead to quite varied synthetic results across the library. Therefore, microwave-assisted reactions are often carried out in an automated sequential manner to allow control of experimental conditions (i.e., temperature).[6] The time-saving aspect of microwave synthesis is diminished by having to irradiate each reaction mixture individually, one after another, even if each sample is irradiated for only a short time. We describe a blend of parallel and sequential microwave irradiation steps in a multimode reactor, which combines the best aspects of both methods, for rapid preparation of a β-peptide library in inexpensive 96-well polypropylene filter plates.

A major problem with microwave-assisted parallel library synthesis in the past has been identifying a suitable reaction vessel.[7] Early reports described both the possibility of and the problems (i.e., inhomogeneous heating and poor mechanical stability at elevated temperatures and pressures) associated with using polypropylene well plates for microwave-assisted synthesis.[8] In response, reaction blocks composed of microwave-absorbent material have been developed for accurate temperature measurement and uniform heating.[9] However, such experimental setups (including a rotating drum for agitation) are expensive and cumbersome to assemble. Furthermore, the glass inserts used with the reaction blocks are fritless, precluding the rapid washing via bottom-filtration that is such an advantageous feature of solid-phase synthesis. Automated liquid handlers capable of washing the solid support are expensive and slow. These drawbacks threaten to negate any time savings achieved by using microwave irradiation, especially during the synthesis of oligomeric molecules that require many sequential reactions.

The experimental conditions that we have developed for the solid-phase synthesis of β-peptides with microwave irradiation employ relatively low temperatures and high-boiling solvents in open vessels.[2,7] Multiwell polypropylene filter plates are sufficiently heat-stable for these conditions, and these plates are inexpensive and allow bottom-filtration of the solid support. We investigated the remaining issues of accurate temperature measurement with small reaction volumes, agitation of the reaction mixtures, and homogeneity of microwave heating throughout the plate in the multimode reactor. We then synthesized a 96-member β-peptide library in parallel, demonstrating the use of inexpensive polypropylene filter plates and microwave irradiation in a multimode reactor as a simple and effective method for the rapid preparation of peptide libraries on solid support in acceptable purities.

The numerous reported biomedical applications of β-peptides[10] justify the combinatorial exploration of this class of "foldamers."[3] The utility of β-peptides stems from the predictable relationship between β-amino acid sequence and folding. β-Peptides have been found to adopt a variety of discrete secondary structures, the most intensively studied of which is the 14-helix (defined by 14-membered ring $N-H_i \rightarrow O{=}C_{i+2}$ hydrogen bonds between backbone amide groups).[3] Seebach et al. discovered that β-peptides composed exclusively of β^3-residues can form the 14-helix,[11] and we have shown that use of β-amino acids with a six-membered ring constraint, such as *trans*-2-aminocyclohexanecarboxylic acid (ACHC) or *trans*-4-aminopiperidine-3-carboxylic acid (APiC), leads to a dramatic enhancement in 14-helix stability relative to β^3-amino acids.[12] Combining cyclic and acyclic

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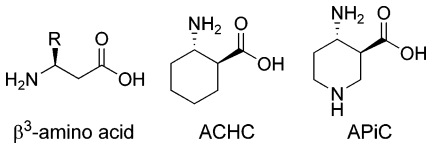
residues allows one to prepare β-peptides that adopt stable shapes and display specific sets of side chains in predictable arrangements. The proteolytic[13] and metabolic[14] stability of β-peptides and the prospect of intracellular delivery[10j] are additional attractions from a biomedical perspective.



Our desire to discover biologically active β-peptides has led us to pursue their combinatorial synthesis. β-Peptides can be synthesized using standard solid-phase methodology developed for α-peptides,[15] but the resulting products are often of low purity, which prevents direct evaluation of their biological properties[16] and has limited prior efforts to the preparation of small sets of β-peptides followed by HPLC purification and screening.[10] Difficulties with both removal of the 9-fluorenylmethoxycarbonyl (Fmoc) protecting group and amide bond formation often arise during the synthesis of 14-helical β-peptides, usually starting with the sixth residue from the C-terminus.[16] These problems were recently resolved by application of microwave irradiation, which both increased the purity of initial β-peptide products and reduced synthesis time by 10-fold,[2] enabling the rapid production of individual β-peptides in sufficient purity that they can be reliably screened without HPLC purification.

We combined microwave-assisted β-peptide synthesis with split-and-mix techniques[17] and recently reported the first one-bead-one-compound β-peptide combinatorial library.[18,19] Exposing the polystyrene macrobeads to multiple cycles of microwave irradiation for each reaction provided the products in good purity and reduced time. This advance has allowed the rapid preparation of large β-peptide libraries (>1000 members; unpublished results). The necessity of high-throughput screening, LC−MS/MS sequencing, and resynthesis for hit validation makes this approach useful for the initial discovery of biologically active compounds but not for subsequent refinement efforts. Lead optimization is best accomplished via smaller, spatially addressable libraries, which allow rapid elucidation of structure−activity relationships (since the identity of all library members is known).[20] If such parallel libraries can be synthesized in sufficient purity, then initial screening can be performed without time-consuming purification of library members. If library members are synthesized on a large enough scale, then purification and validation of compounds identified as active by initial screening can proceed directly, i.e., without resynthesis. Therefore, to increase the throughput of β-peptide preparation and evaluation, we have now expanded microwave-assisted solid-phase β-peptide synthesis methodology to the parallel synthesis of a library in a 96-well polypropylene filter plate.

Results and Discussion

Synthetic Optimization in Multimode Microwave Reactor. To produce a β-peptide combinatorial library in parallel using microwave irradiation, we needed to adapt the solid-phase β-peptide synthesis reaction conditions that we previously developed with a monomode microwave reactor[21] for use in a multimode reactor.[22] β-Peptide **1** was selected for synthetic optimization because this target exemplifies the difficulties of coupling and Fmoc-deprotection in the incorporation of the N-terminal ACHC residue (ACHC1, according to standard peptide numbering).[2,16c] Our previous study showed that manual synthesis produced **1** in only 53% purity (Figure 1 and Figure 2A), even though the penta-β-peptide precursor was 95% pure. Heating the reactions either in a monomode microwave reactor or in an oil bath improved the purity of **1** to 80%. The advantage of microwave irradiation was an overall 10-fold reduction in reaction time, from 1.5 h to 6 min for coupling the β-amino acid and from 15 to 4 min for Fmoc-deprotection.

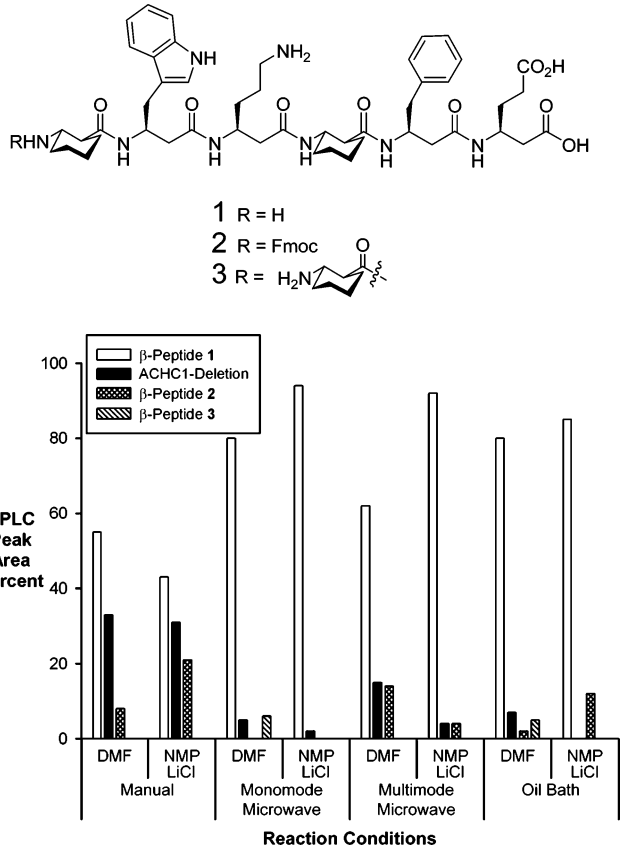


Figure 1. Amount of β-peptide **1** and major impurities (peak area percent, from analytical reversed-phase (RP) HPLC monitored via UV absorbance at 220 nm) resulting from different synthetic conditions. All coupling and deprotection reactions in the synthesis of the hexamer were conducted under the given reaction condition, that is, manual, monomode, or multimode microwave; or oil bath, as described below. The given solvent refers only to the coupling of ACHC1; all other coupling reactions were performed in DMF. ACHC1 was double-coupled and double-deprotected in all cases. Manual: 15-min deprotection, 1.5 h coupling, RT; monomode microwave: 4-min deprotection at 60 °C; all couplings were 6 min at 50 °C in DMF, except for 6 min at 45 °C in 0.8 M LiCl in NMP for ACHC1 where noted. Multimode microwave: 4-min deprotection at 75 °C; all couplings were 6 min at 70 °C in DMF, except for 0.8 M LiCl in NMP for ACHC1 where noted. Oil bath: 15 min deprotection, 1.5 h coupling, 60 °C. Results from the manual, monomode microwave, and oil bath syntheses were reported previously (ref 2).

We previously described the difficulties associated with accurate temperature measurement during microwave irradiation.[2] Target temperatures of 50 °C for amide bond

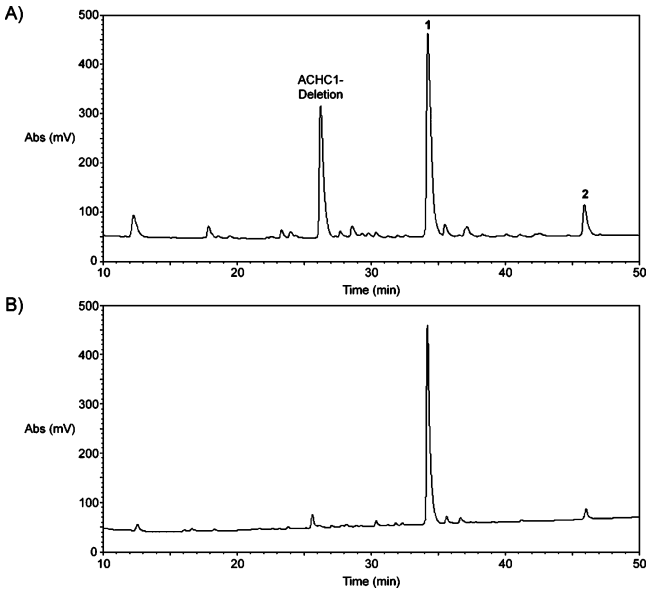


Figure 2. HPLC chromatograms (UV absorbance at 220 nm) of β-peptide **1** prepared under reaction conditions described in Figure 1: (A) manual-DMF and (B) multimode microwave-NMP/LiCl.

formation and 60 °C for Fmoc-removal had given reproducible results (50 W maximum power), but because of our reaction vessel configuration (see Supporting Information) and the limitations of the built-in IR sensor of the monomode microwave reactor,[23] these set temperatures turned out not to be accurate. Direct measurement indicated the final temperature of the reaction mixtures to be 61−64 °C for couplings and 70−75 °C for deprotections. Upon transition to the multimode microwave reactor, we began using a fiber-optic temperature probe, which is directly inserted into the reaction mixture and gives accurate temperature measurements during the course of the reaction. We then synthesized β-peptide **1** with magnetic stirring in the multimode microwave instrument employing 70 °C for coupling and 75 °C for Fmoc-deprotection to reflect our previously optimized conditions (600 W maximum power). However, neither coupling nor Fmoc-deprotection of the N-terminal ACHC went to completion when DMF was used as solvent, and β-peptide **1** was generated in only 62% purity.[24] Performing the coupling of ACHC1 in 1-methyl-2-pyrrolidinone (NMP) containing 0.8 M LiCl gave β-peptide **1** in much improved 92% purity (Figure 2B).[2,25] A 76% yield of β-peptide **1** synthesized under these conditions was quantified by correlation of peak area in analytical RP-HPLC (UV absorbance at 220 nm) to concentration via a calibration curve with an external standard (see Supporting Information).[26]

Microwave-Assisted Synthesis in 96-Well Filter Plate. Having optimized our reaction conditions in the multimode microwave instrument, we prepared small sets of β-peptides in parallel in individual reaction vessels using a 52-position turntable (data not shown);[27] however, our ultimate desire was to transition from using many separate vessels to using a 96-well polypropylene filter plate. We evaluated the homogeneity of microwave heating and its effect on product purity by synthesizing β-peptide **1** in 26 different wells scattered across a plate (Figure 3). Wells not containing resin were filled with fresh DMF before each reaction. The fiber-optic temperature probe was placed in well D6 as a reference

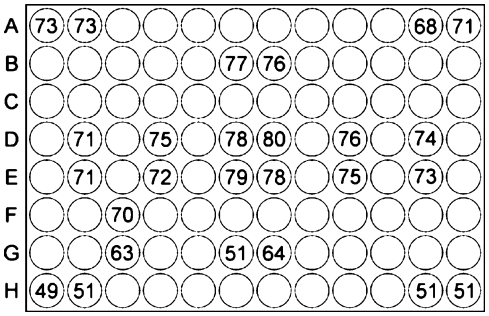


Figure 3. Initial purity of β-peptide **1** (peak area percent from analytical RP-HPLC monitored via UV absorbance at 220 nm) synthesized at various locations within a 96-well plate.

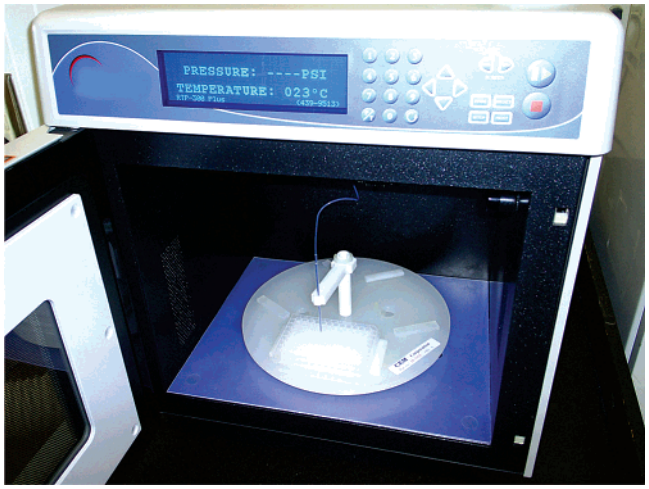


Figure 4. Expermental setup for microwave-assisted solid-phase β-peptide synthesis.

for the entire plate. The plate and temperature probe were held in place by a microtiter plate turntable (Figure 4). We were pleased to observe that the fiber-optic probe could measure the temperature of the small volumes (150 μL per well) associated with a 2.5-μmol-scale synthesis. Washing of the solid support between reaction steps was rapidly accomplished with a vacuum filtration manifold.

β-Peptide **1** was synthesized in an acceptable 69% average purity, but some regions of the plate gave low purities (Figure 3). In particular, the products from rows G and H were synthesized in an average purity of only 54%, significantly lower than the rest of the plate. We believe that this discrepancy resulted from poor agitation rather than uneven heating, since the impurities resulted from deletion of a residue at position 2, 3, 4, or 5; heating problems would have been manifested in the coupling or deprotection of ACHC1. The rows containing lower purity products (rows G and H) were located on the outer edge of the turntable, furthest from the center of the cavity and the magnetic stirrer. The stir bars in these wells were occasionally motionless during the course of the synthesis. This problem was resolved by switching to a smaller stir bar (7 mm in length), which rotates freely within the well, providing good stirring even at the outer edge of the plate. The benefit of this modification was demonstrated through the subsequent synthesis of a β-peptide combinatorial library.

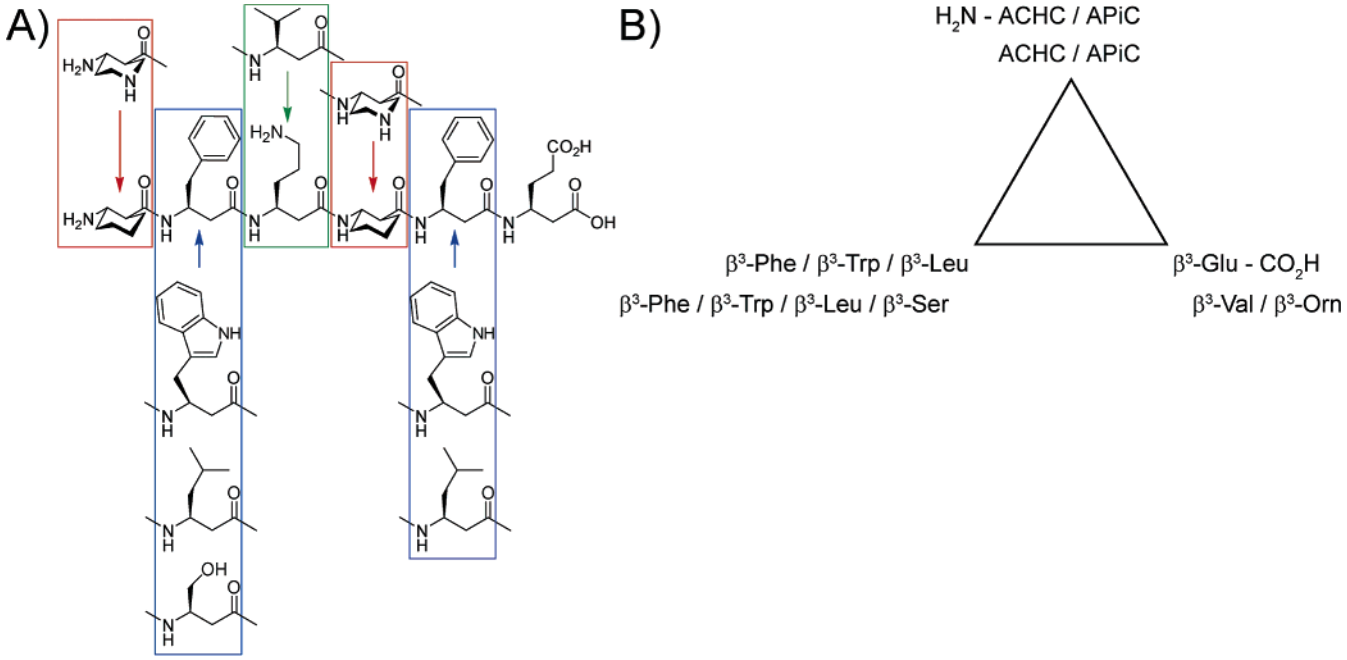


Figure 5. (A) Hexa-β-peptide library ($2 \times 4 \times 2 \times 2 \times 3 = 96$ members). (B) 14-Helical wheel diagram of hexa-β-peptide library.

Parallel Synthesis of a β-Peptide Combinatorial Library. We designed a hexa-β-peptide library based on the sequence of β-peptide **1** (Figure 5). The incorporation of cyclically constrained residues at positions 1 and 4 ensures that the library members will have a high 14-helical propensity.[12] The overall design is amphipathic, displaying a hydrophobic face on 1/3 to 2/3 of the helix, depending upon whether ACHC or APiC is incorporated at positions 1 and 4. Thus, each β-peptide in the folded state should present a hydrophobic face for interaction with biomolecular surfaces while also containing charged groups to promote water solubility. The inclusion of β^3-Val at position 3 and β^3-Ser at position 2 provides variation in the hydrophobic/hydrophilic pattern.

Library synthesis was performed with microwave irradiation using optimized power/temperature settings and a blend of parallel and sequential reactions. Fmoc-β^3-Glu(*t*Bu)-loaded polystyrene Wang resin (100−200 mesh) was distributed in each well of the 96-well filter plate using the method of Lebl et al. with slight modifications.[28] Fmoc-deprotection of all library members was performed simultaneously. However, we found it necessary to couple one β-amino acid at a time (in parallel), because the variable microwave absorption properties of coupling solutions containing different β-amino acids lead to varied reaction temperatures under equivalent microwave irradiation conditions. The N-terminal residues were double-coupled (ACHC in 0.8 M LiCl in NMP, and APiC in DMF) and double-deprotected. At the end of the synthesis, cleavage from the solid support and global side chain deprotection were accomplished for each resin-bound sample by shaking for 2 h at room temperature with TFA/CH_2Cl_2, after which the cleavage solutions were transferred to a solid-bottom polypropylene plate and concentrated using a rotary evaporator. The crude β-peptide product mixtures were each dissolved in DMSO and analyzed by reversed-phase (RP) HPLC (UV absorbance at 220 nm). The major peak in each chromatogram was collected and analyzed by

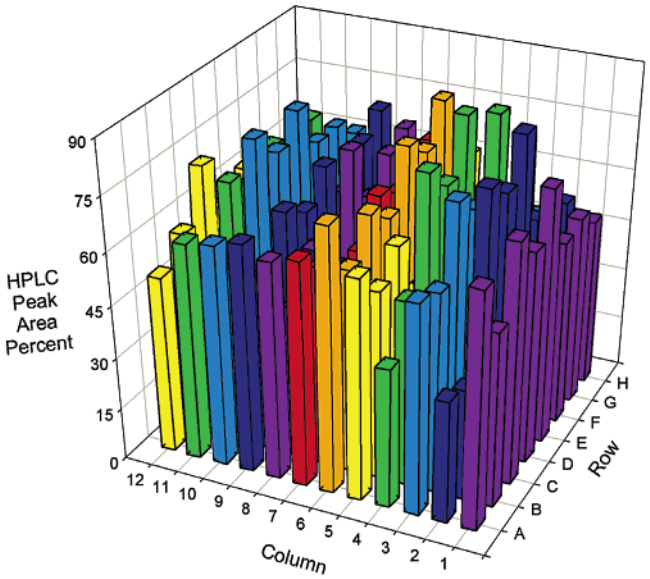


Figure 6. Initial purity of β-peptide products (peak area percent from analytical RP-HPLC monitored via UV absorbance at 220 nm) synthesized in parallel with microwave irradiation in a polypropylene 96-well filter plate. See Figure 9 for complementary presentations of the data.

MALDI-TOF MS. In 97% of the cases (93 of 96), the observed mass for the major HPLC peak corresponded to the expected β-peptide library member. In the other three samples, the second largest peak in the trace was the desired product, with the major peak corresponding to the Fmoc-protected hexa-β-peptide product. The area percent of the peak corresponding to the desired product in each chromatogram was determined by integration (Figure 6), revealing that library members were synthesized in an acceptable 61% average purity (Figure 7).[29]

In an effort to minimize instrument usage during the time-consuming process of product purity assessment, HPLC analysis of compounds from the library (Figures 6 and 7) and samples of β-peptide **1** from the temperature homogene-

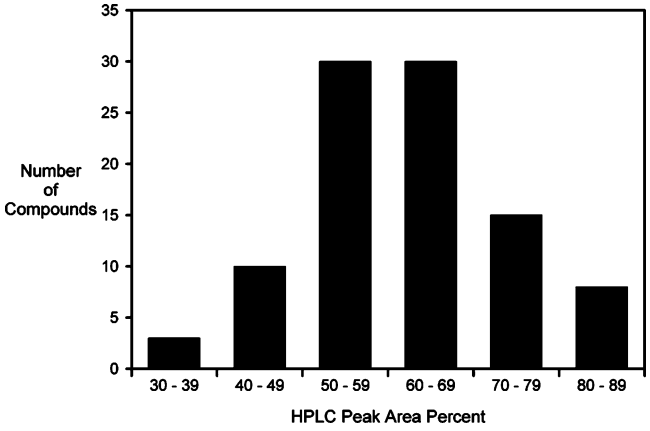


Figure 7. Product purity of hexa-β-peptide library members, determined as the area percent of the major peak in the analytical RP-HPLC chromatogram (UV absorbance at 220 nm).

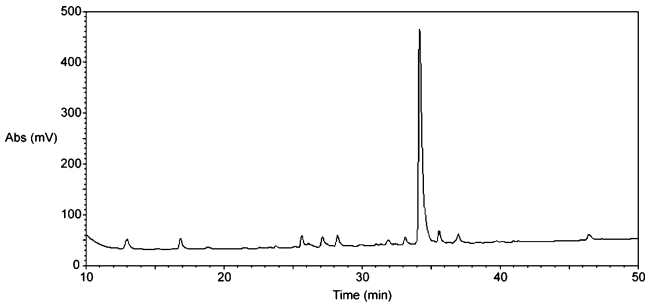


Figure 8. HPLC chromatogram (UV absorbance at 220 nm) of β-peptide **1** prepared as a member of the library and analyzed with the long elution time, from which we calculate an initial purity of 86% (see Supporting Information for the chromatogram obtained with the short elution time that gives rise to a nominal purity of 74% and see text for details).

ity study (Figure 3) was performed with a shorter run time and steeper solvent gradient (10−60% acetonitrile over 25 min instead of 50 min) than we had employed previously for the synthetic optimization (Figures 1 and 2). We were surprised to find that the new elution conditions caused us to underestimate the initial purity of our compounds. β-Peptide **1** was synthesized as a member of the library in well D4 in nominal 74% purity, as determined with the short HPLC elution time, which is comparable to the results obtained in the earlier microwave-assisted parallel synthesis (Figure 3). However, analysis of the same mixture with the longer run time showed that β-peptide **1** was actually produced in 86% purity (Figure 8). Rather than repeat the time-intensive HPLC analysis of each library member with the longer run time, we have chosen to report the average purity (nominally 61%) based on the short run time, although this value probably is artificially low by a significant amount.

We sought to determine whether the variation in product purity was due to uneven heating of the 96-well plate. The three lowest purity members (wells A2, B2, and H12) were located at or near the corners of the plate, but their neighbors were synthesized in higher purities. We averaged the product purities for a number of different regions within the plate (Figure 9). While products from the edges and corners of the plate may have been synthesized in slightly lower purity than products in the center, the differences in average purity were typically <10%. Thus, the variation in product purity

A)

	1	2	3	4	5	6	7	8	9	10	11	12	**Av.**
A	67	35	60	40	63	75	64	62	65	63	62	51	**59**
B	50	32	57	53	54	58	57	44	51	54	51	58	**52**
C	69	81	76	82	61	68	44	55	64	82	69	72	**69**
D	61	75	69	74	43	62	51	45	59	74	64	57	**61**
E	73	86	68	88	58	77	62	73	67	81	70	62	**72**
F	53	58	57	56	52	71	58	55	55	68	49	45	**56**
G	55	61	74	80	67	81	57	63	65	68	69	58	**67**
H	49	53	48	44	52	63	64	66	70	62	55	30	**55**
Av.	**60**	**60**	**64**	**65**	**56**	**69**	**57**	**58**	**62**	**69**	**61**	**54**	**61**

B)

A B	**50**	**57**	**57**
C D E F	**69**	**62**	**66**
G H	**57**	**57**	**57**

C)

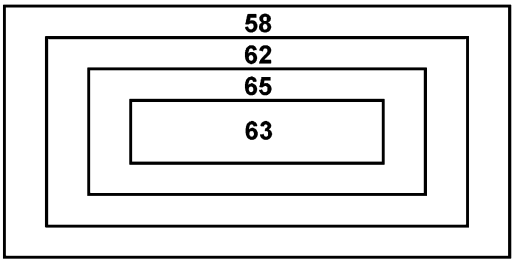


Figure 9. Positional averages of β-peptide product purity: (A) by row and column, (B) by region, and (C) by distance from the center of the plate.

seems to be as much dependent on the sequence as on the location within the plate.

Although product purity was relatively uniform throughout the plate, we wondered whether investigation of the side products would provide additional insight into local differences in reaction temperature. Our previous synthetic optimization of β-peptide **1** had demonstrated that differences of ±10 °C in reaction temperature resulted in different types of impurities.[2,24] Hence, the minor products collected during HPLC analysis of the library were analyzed by mass spectroscopy (Figure 10). We found that the identity of the impurities tended to differ depending on the location of the well. Fmoc-protected side products and penta-β-peptide deletion products were generally identified at the corners and edges of the plate, possibly indicating slightly lower reaction temperatures in these areas. Hepta-β-peptides, resulting from premature Fmoc-deprotection and coupling of a second monomer unit during a single reaction cycle, were typically found closer to the center of the plate, a signal that reaction temperatures may be slightly higher in this region. Without exhaustive identification and quantification of all impurities and improved methods of temperature measurement, however, these speculations must be regarded as tentative.

Conclusion

Microwave irradiation has been used to improve the initial purity of β-peptides and reduce synthesis time. Use of a multimode microwave reactor for solid-phase β-peptide

synthesis has facilitated the preparation of a hexa-β-peptide library using a combination of parallel and sequential irradiation techniques. This library is sufficiently pure for initial screening without HPLC purification, although further improvement in synthetic efficiency would be desirable. The use of inexpensive polypropylene multiwell filter plates for microwave-assisted parallel library solid-phase synthesis is a simple alternative to more complex and expensive equipment for the rapid generation of peptide libraries.

Experimental Section

Microwave-Assisted Parallel β-Peptide Library Synthesis. Fmoc-β^3-Glu(*t*Bu)-loaded PS Wang resin (240 μmol, 375 mg) was swelled with DMF for ~10 min in a polypropylene SPE tube (15 mL, Alltech). The mixture was poured into the center of a 96-well polypropylene filter plate (MultiScreen Solvinert, 0.45 μm hydrophobic PTFE membrane from Millipore). The rest of the wells were filled with DMF. A top box (polypropylene cover from a rack of 0−300-μL Redi-Tip pipet tips from Fisher Scientific) was placed over the plate. While being pressed together, the box and plate were inverted, shaken, and turned right-side-up again, filling each well with an equal volume of the homogeneous resin/DMF mixture. The cover was removed, and the DMF was drained using a vacuum manifold (Millipore) attached to a vacuum pump. The resin was washed (5 × DMF). Deprotection solution (250 μL of 20% piperidine in DMF (v/v)) was added to the resin in each well using a 12-channel multipipet, and a magnetic stir bar (7 mm, VWR) was placed inside each well. The plate was placed on top of an empty solid-bottom polypropylene 96-well plate (250 μL well volume, Greiner) and then slid into a microtiter plate turntable inside the multimode microwave cavity (CEM MARS). [Note: For best results, we now use a 2-mL-deep well polypropylene filter plate with polyethylene frits and long drip spouts in combination with a bottom sealing mat (Artic White) instead of the Millipore filter plate mentioned above.] The fiber-optic temperature probe was positioned in well D6 using the arm attached to the turntable, and the sample was irradiated (600 W maximum power, 75 °C, ramp 2 min, hold 2 min, cool-off 5 min). All microwave irradiation steps were conducted at atmospheric pressure. The plate was removed from the microwave reactor, the resin was washed (5 × DMF), and the drip plate was emptied by shaking. In a separate vial, Fmoc-β^3-hPhe (96.4 mg, 240 μmol) was activated by adding HBTU (480 μL of 0.5 M solution in DMF), DMF (3.52 mL), HOBt (480 μL of 0.5 M solution in DMF), and *i*Pr$_2$EtN (480 μL of 1.0 M solution in DMF). The mixture was vortexed, and 150 μL was added to each of a subset of the wells using a multipipet (Figure 11). The temperature probe was placed in the center of this region of the plate, and the sample was irradiated (600 W maximum power, 70 °C, ramp 2 min, hold 4 min, cool-off 5 min). After washing, Fmoc-β^3-hTrp(Boc) was activated and coupled to resin in a different section of the plate, followed by Fmoc-β^3-hLeu. This constitutes the reaction sequence employed to couple all residues at position 5 (standard peptide numbering, starting from the N-terminus of the full hexa-β-peptide sequence) in the library. The

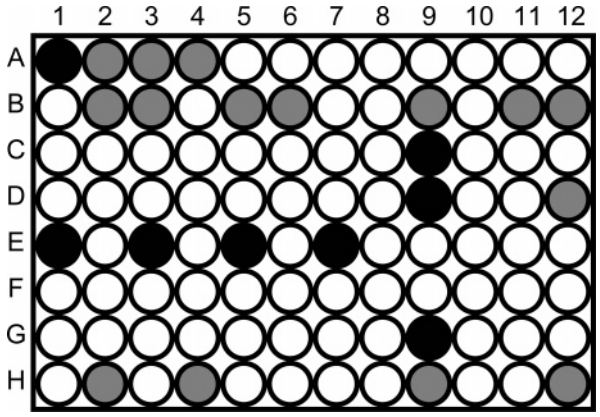


Figure 10. Location of identified impurities from β-peptide library synthesis. Gray = Fmoc-protected and penta-β-peptide deletion products. Black = hepta-β-peptide addition impurities.

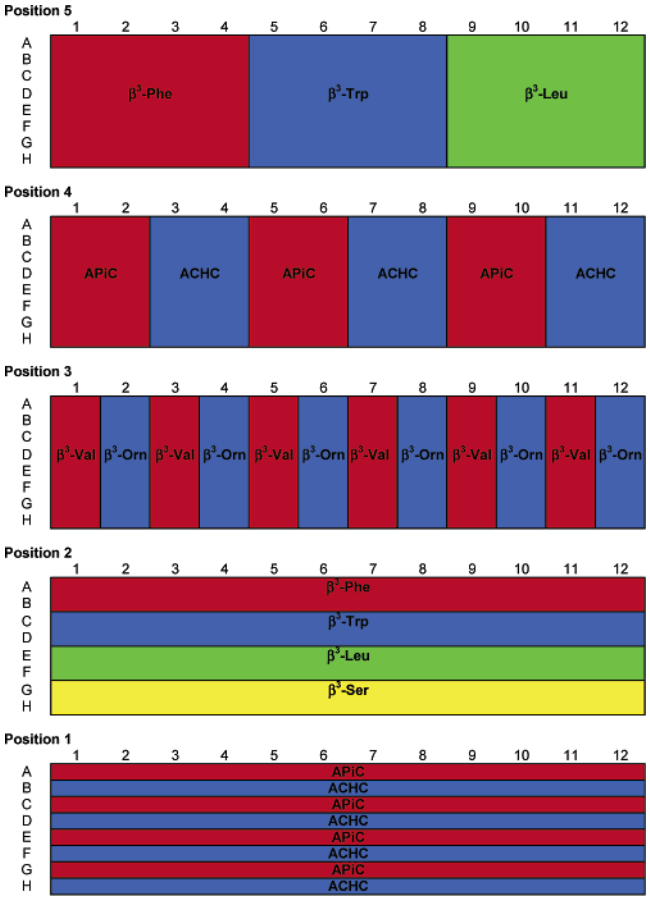


Figure 11. Coupling protocols for stepwise synthesis of spatially defined β-peptide library.

material in all wells was simultaneously Fmoc-deprotected as before. The two different residues at position 4 were coupled sequentially. This stepwise, parallel Fmoc-deprotection/sequential coupling cycle was repeated until the coupling of the residues at position 1. Fmoc-APiC(Boc) at position 1 was double-coupled in DMF. The double-coupling of Fmoc-ACHC at position 1 was performed by activating with solutions of HBTU, HOBt, and *i*Pr$_2$EtN in NMP and adding a solution of LiCl in NMP for a final concentration of 0.8 M LiCl and then adding this solution to the resin. The plate was placed in the microwave reactor and irradiated as before (600 W maximum power, 70 °C, ramp 2 min, hold

4 min, cool-off 5 min). The fiber-optic probe provided accurate temperature measurement, even with the highly microwave-absorbent solvent mixture of 0.8 M LiCl in NMP.[2] The N-terminal residues were then double-deprotected. The resin was washed (5 × DMF, 5 × CH_2Cl_2). Cleavage from the solid support with global side chain deprotection was accomplished by adding triisopropylsilane (10 μL), water (10 μL), trifluoroacetic acid (100 μL), and CH_2Cl_2 (100 μL) to each well. The plate was wrapped tightly in aluminum foil and shaken for 2 h at room temperature on a miniorbital shaker (Lab-Line Instruments). The foil covering was removed, and the cleavage solutions were transferred to a solid-bottom 96-well plate with vacuum filtration and concentrated using a rotary evaporator (SpeedVac with well-plate adapter, Thermo Savant). The crude β-peptide mixtures were dissolved in 250 μL of DMSO. Each sample was analyzed by HPLC (15-μL injection, Shimadzu). The C_4-silica reversed-phase analytical column (5 μm, 4 mm × 250 mm, Vydac) was eluted with a gradient of acetonitrile in water (10−60% or 0−50%, 25 min, 0.1% TFA in each, followed by a 5-min flush with 95% acetonitrile and 5 min of equilibration at the starting concentration) at a flow rate of 1 mL/min. Product purity was determined as peak area percent by integration of the UV absorbance at 220 nm. Integration was performed over the 10−30 min time interval to exclude the large absorbance of DMSO that elutes from 5 to 10 min. The lower threshold of integration was set to exclude peaks with areas <10% of the peak area of the major species. β-Peptide masses were measured by MALDI-TOF-MS (Bruker Reflex II, α-cyano-4-hydroxycinnamic acid matrix).

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Supporting Information Available. Full experimental procedures and characterization of β-peptide library members. This material is available free of charge via the Internet at http://pubs.acs.org.

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