Solution Phase Combinatorial Chemistry. Discovery of Novel Polyazapyridinophanes with Potent Antibacterial Activity by a Solution Phase Simultaneous Addition of Functionalities Approach

Haoyun An, Lendell L. Cummins, Richard H. Griffey, Ramesh Bharadwaj, Becky D. Haly, Allister S. Fraser, Laura Wilson-Lingardo, Lisa M. Risen, Jacqueline R. Wyatt, and P. Dan Cook*

Contribution from the Department of Medicinal Chemistry, Isis Pharmaceuticals, Inc., 2292 Faraday Avenue, Carlsbad, California 92008

Received December 2, 1996[⊗]

Abstract: Chemical modification of pre-formed asymmetric polyazaphane scaffolds by simultaneous addition of functionality (letters) in solution has been developed for the preparation of tertiary nitrogen-based combinatorial chemistry libraries. This approach has some significant advantages over the more commonly employed solid phase bead splitting/reaction/mixing procedures for the preparation of libraries. Three novel, asymmetric polyazaphanes **32**, **33**, and **37** have been synthesized in high yields by an efficient cyclization of 2,6-bis(bromomethyl)pyridine (**31**) with new orthogonally protected triamines **29**, **30**, and **35**, respectively. Selective deprotection of **32**, **33**, and **37** provided mono-*t*-Boc-protected scaffolds **1**−**3** suitable for solution phase, simultaneous addition of functionalities. Model studies of small libraries of scaffold **2** using CZE analyses indicated that simultaneous addition of 10 benzylic bromide alkylating functionalities would result in libraries containing approximately equimolar amounts of all possible compounds. Sixteen purified tertiary amine libraries **4**−**19** (total complexity of 1600 compounds) were generated by this procedure from scaffold **2**. A "fix-last" combinatorial method was devised to minimize chemical reactions. Several first-round sublibraries of scaffold **2**, containing a mixture of 100 compounds, exhibited potent antimicrobial activities. Twenty single compounds **63**−**82** with uniform functionalities at the combinatorialized sites were synthesized. Some of these pure compounds were more active, while others were less active, compared with the parent mixtures **5** and **10**.

Introduction

Combinatorial chemistry can rapidly generate large numbers of diverse compounds which, when combined with high-throughput screening techniques, provide a very important strategy for generating drug leads as well as for optimizing lead compounds.[1] Initial efforts have focused primarily on chemical libraries of oligomeric materials such as peptides,[2] peptoids,[3] oligocarbamates,[4] vinylogous sulfonyl peptides,[5] carbonucleotides and carbopeptoids,[6] oligoureas,[7] oligonucleotides,[8] and oligosaccharides.[9] More recent efforts are directed to chemical

[⊗] Abstract published in *Advance ACS Abstracts,* April 1, 1997.

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S0002-7863(96)04153-4 CCC: $14.00

libraries of small organic molecules[10] generated by stepwise additions (oligomerizations)[11] or simultaneous addition of reactants (multiple-component condensations, MCCs), utilizing solid phase methods (solid phase organic synthesis, SPOS).[12] Although solution phase combinatorial strategies for the preparation of chemical libraries remains a relatively unexplored area,[13] they may offer significant advantages over solid phase synthesis.[13ef,14]

We have developed an approach to produce combinatorial libraries by chemically modifying pre-formed asymmetric scaffolds by simultaneous addition of functionalities (letters) in solution. The advantages of a solution phase, simultaneous addition of functionalities (SPSAF) approach over the more often employed solid phase, bead splitting/reacting/mixing procedures for the preparation of libraries are several-fold. (1) Solution phase synthesis allows the opportunity for purification and analysis of a combinatorial chemistry process at any reaction steps, if needed. Thus, the high-yielding reactions usually required on solid support are not absolute requirements for reactions in solution. This should allow a broader scope of combinatorial organic synthesis chemistry to be performed. Searching an expanded scope of chemistry increases the possibility of developing reaction conditions which will allow simultaneous addition of functionality (letters).[15] Thus, the usual laborious bead-splitting procedures to prepare equimolar mixtures are avoided. (2) Solution phase syntheses will also allow libraries to be prepared in greater quantities. Sufficient quantities of material that may be derived from solution synthesis will allow testing the libraries in a broader range of assays for many years. This is of particular importance in devising a serial conversion of a library having a specific scaffold (footprint) to one or more additional libraries with very different scaffolds (footprints). (3) The ability to rapidly and continually change the scaffold (footprint) is best accomplished by traditional organic synthesis in solution rather than synthesis on solid supports. As the scaffold has a direct bearing on the structure space searched, the ability to readily change the scaffold is very important. (4) A very significant synthesis advantage will be realized by SPSAF for library synthesis compared to conventional solid phase, bead splitting reaction/mixing procedures. SPSAF for the preparation of chemical libraries may not be as dependent on robotics as are solid support procedures. The chemistry required to prepare libraries by a SPSAF approach consists of the design and synthesis of appropriate scaffolds and subsequent combinatorial reactions.

The selection of scaffolds to combinatorialize in this approach presents a vast number of choices based on known pharmacophores (structure-based libraries) and unknown structures (non-structure-based libraries). Important considerations for selecting scaffolds include (1) ease of synthesis, (2) level of conformational constraint, (3) minimization of the molecular weight of repeating units as well as of the overall molecular weight, (4) asymmetry of scaffolds, (5) number of positions to be combinatorialized, (6) achirality or controlled chirality, (7) selection of a combinatorial position that is orthogonally protected, subsequently deprotected, and fixed last with functionalities (fixed last concept) for an iterative screening process, (8) versatility to readily change the size and shape of the scaffold (footprint), and (9) options for chemical conversion of libraries to libraries.[16] We have identified a number of classes of compounds which "fit" these scaffold selection considerations. In particular, secondary nitrogens in a ring, which on substitution will provide a combinatorialized tertiary nitrogen, seem exquisitely suited for scaffolds in combinatorial chemistry libraries; alkylation and acylations of secondary amines presents a general, simple, and high-yielding combinatorial chemistry.

Rebek and co-workers[13a−d] utilized tetracarboxylic acid chloride substituted xanthene and cubane as scaffolds to prepare amide libraries by simultaneously adding a mixture of amino acids and employed a reverse iterative deconvolution procedure to find active compounds in a relative short time frame. The high symmetry of these scaffolds has considerable impact on the nature of the resulting libraries. The number of distinct compounds (complexity) in the libraries is greatly reduced. For example, because of the two-fold symmetry of the xanthene scaffold, four sites combinatorialized with 19 amino acids should theoretically provide 65 341 distinct compounds assuming similar chemical reactivity of each amino acid. Millions of compounds (4^{19}) would be expected if the scaffold was asymmetric. As the trend is to prepare less complex libraries, this approach appears attractive. However, and surely more important, is the fact that symmetry in the xanthene and, thus, equivalency of the two positions results in distorted libraries. Library compounds possessing any one of the 19 amino acids two, three, or four times are obtained in a lower concentration than the more heterogeneous compounds. McDevitt and Lansbury[13e] employed a 1,3,5-benzenetricarbonyl trichloride scaffold for the preparation of a library of glycotides. In this example three glycosamino acids were added simultaneously

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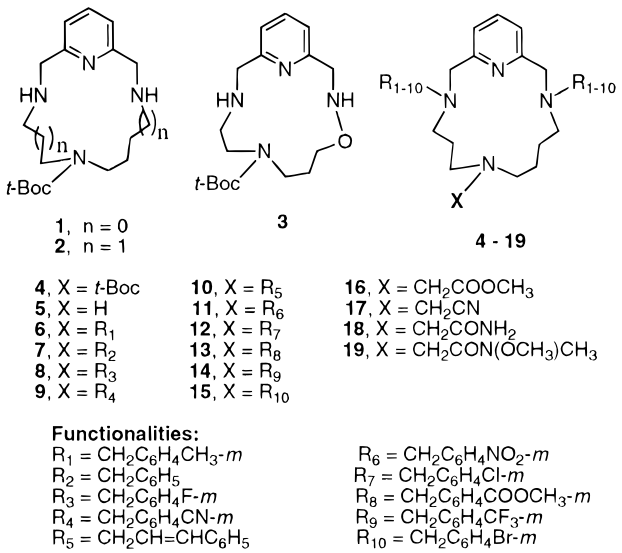

Figure 1. Novel unsymmetric polyazaphane scaffolds **1**−**3** and libraries **4**−**19**.

to provide, without purification, nine out of 10 expected compounds. Again, symmetry of the scaffold reduced the complexity ($3^3 = 27$ to 10) and distorted the library.

In considering the chemical combinatorialization process, we have chosen reactivity and reaction conditions to allow alkylations to go to completion in several hours. This should enhance the likelihood of a near 1:1 ratio of electrophiles (functionalities, letters) to nucleophiles (nucleophilic sites on the scaffolds) which should minimize purification requirements and should tend to minimize differential reactivity of nucleophiles on the scaffold. A set of functionalities will require approximately equal reactivity of each electrophile to provide near-equimolar amounts of individual compounds in the pool. Nucleophilic reaction at one site on the scaffold should not prevent near-equal reactivity at other nucleophilic sites on the scaffold. This conditions is also required in order to provide near-equimolar amounts of individual compounds in the pool. We have employed alkylations in the initial development work. Obviously, other electrophilic reactions, such as acylations, could be utilized as well.

In this paper, we describe the design and synthesis in high yields of three novel, asymmetric polyazaphanes[17] **32**, **33**, and **37** by an efficient cyclization of 2,6-bis(bromomethyl)pyridine (**31**) with novel orthogonally protected triamines **29**, **30**, and **35**, respectively. The key triamine intermediates **29**, **30**, and **35** were prepared from their corresponding mono-*t*-Boc-protected triamines **26**, **27**, and **34**, respectively. Selective deprotection of **32**, **33**, and **37** by thiophenol provided mono-*t*-Boc-protected scaffolds **1**−**3** suitable for solution phase, simultaneous addition of functionalities. In model studies, capillary zone electrophoresis (CZE) and electrospray ionization mass spectrometry (ESI/MS) were utilized to determine product formation in order to assure the relative chemical reactivities of each electrophile with polyazaphane scaffold **2**. These studies indicated that simultaneous addition of 10 benzylic bromide alkylating functionalities results in the libraries containing approximately equimolar amounts of all possible compounds.

(17) Cyclophanes or phanes contain an aromatic nucleus (benzene or arene) and an aliphatic bridge. Heterophanes contain heteroatoms in the aromatic ring, while heteraphanes contain heteroatoms in the bridge. Our compounds include one nitrogen atom in the aromatic ring (pyridine) and three nitrogen atoms in the bridge. They are abbreviated as "polyazaphanes". For the definition of "phanes", also see: Vögtle F. *Cyclophane Chemistry*−*Synthesis, Structures and Reactions;* Vögtle, F., Ed.; Jones, P. R. Translated; John Wiley and Sons, Ltd.: Chichester, U.K., 1993; p 11.

Subsequently, 16 purified tertiary amine libraries **4**−**19** (total complexity of 1600 compounds) (Figure 1) were generated by this procedure from scaffold **2**. Libraries were monitored by TLC, purified by chromatographic techniques, and characterized by ^{1}H NMR and ESI MS spectral data. A "fix-last" combinatorial method was devised to minimize chemical reactions and to allow SAR studies to be performed on the mixtures. Several first-round sublibraries of scaffold **2**, each containing a mixture of 100 compounds, exhibited potent antimicrobial activities. Twenty single compounds from the active sublibraries were synthesized; five of them exhibited potent antimicrobial activities.

Results and Discussion

We elected to examine conformationally constrained, asymmetric polyazaphane scaffolds such as **1**−**3** for our initial development work on a solution phase, simultaneous addition of functionalities (SPSAF) approach. Polyazaphane scaffolds **1**−**3** are relatively small (average molecular weight 336) and have three sites to combinatorialize. These types of scaffolds are non-structure-based, that is, they are not modeled after a known pharmacophore and thus libraries derived from them will allow the search of novel structure space. Biological activities discovered from non-structure-based scaffolds are more likely to result from novel modes of actions rather than activity that may be found from examining known pharmacophores.[18] We believe that, when considering library mixtures and deconvolution processes, the minimization of "suboptimal binders" [19] (low-energy conformers) will facilitate discovery of active compounds. Fewer suboptimal binders are expected from examination of conformationally restricted molecules in a library compared to a library of more flexible molecules in which a composite activity may result from many suboptimal binders.[20]

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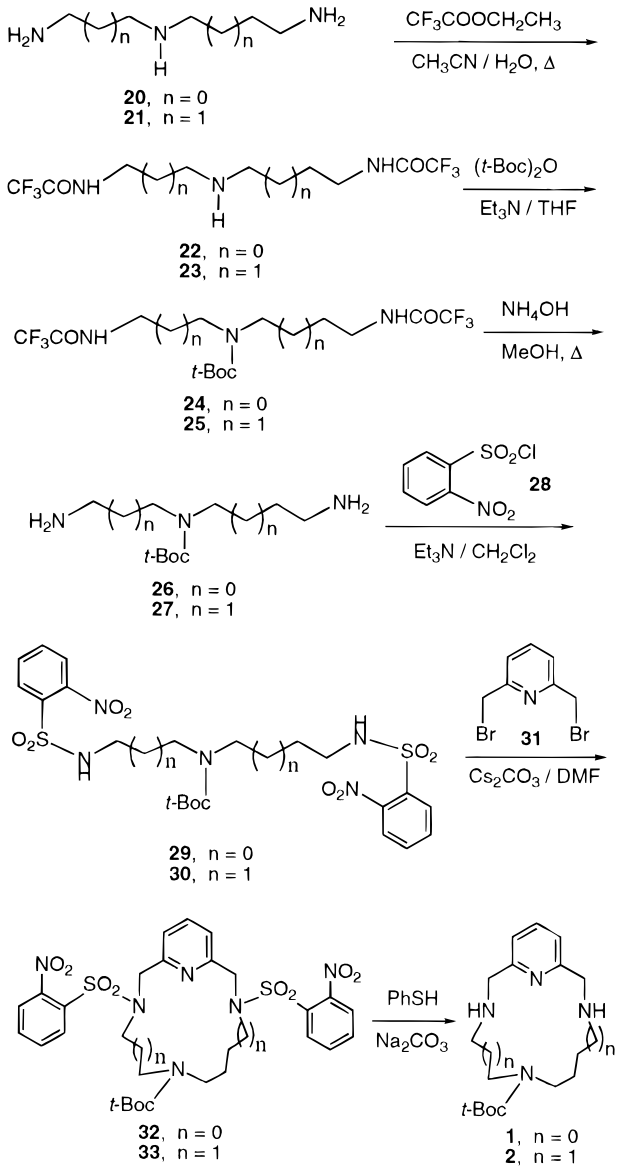
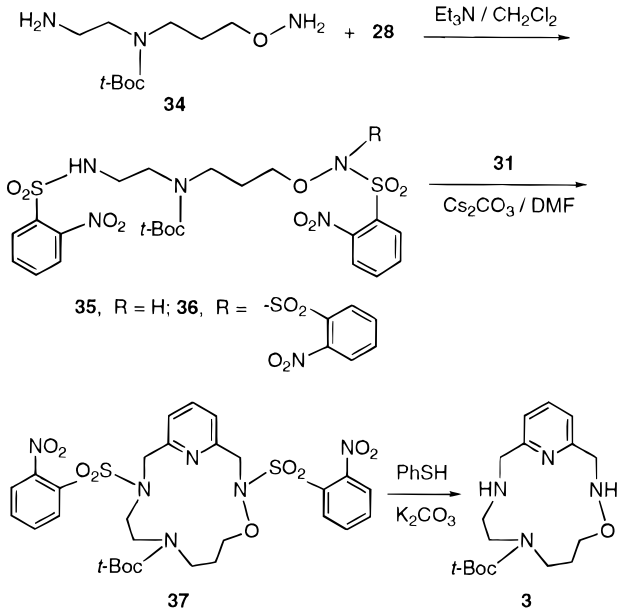
The oxyamine scaffold **3** is of interest because the two "benzyl" secondary amines can be differentiated through their large difference in basicity,[21] and the N−O bond can be hydrolytically cleaved to provide new sublibraries according to the libraries from libraries concept.[16] We were particularly interested in avoiding the bead-splitting processes devised to provide equimolar amounts of each compound in the library.[22] Simultaneous addition of functionalities would circumvent this approach and would facilitate more rapid library production. Also important in the selection of a scaffold is the concept of placing the functionality that differentiates each pool last in the synthetic scheme (fix last concept).[23] This procedure greatly reduces the required chemistry by diverging at the end of a scheme of steps rather than diverging early in the scheme and repeating the same synthetic sequence for each functionality. This is accomplished in the present work by an orthogonal protection protocol allowing the fix-last position to remain blocked during the simultaneous addition of functionalities chemistry.

The scaffolds were synthesized (Schemes 1 and 2) by a novel cyclization of 2,6-bis(bromomethyl)pyridine (**31**) with fully protected triamines **29**, **30**, and **35**. This high-yielding, efficient polyazaphane synthesis is very versatile in that the polyamine synthon can readily be changed to provide a variety of secondary amines and oxyamines in various chain lengths which will afford macrocycles of various ring sizes. A great number of mono- and polycyclic heterocycle platforms are available or could be designed. The cyclization reaction provides orthogonal protection of the benzylamines. This will allow a sequential deprotection−reaction process to combinatorialize **1**−**3** in a single-compound mode, or provide one position available for combinatorialization with the others orthogonally protected for sequential processing (fix first), or provide one of the three positions protected for addition of functionalities simultaneously to prepare mixtures with the other two available positions (fix last). In the later case, the protected position would be liberated

Scheme 1



Scheme 2



(21) *The Determination of Ionization Constants, A Laboratory Mannual*, 3rd ed.; Albert, A., Serjeant, E. P., Eds.; Champman and Hall: New York, 1984; p 151.

(22) Furka, A.; Sebestyen, F.; Asgedom, M.; Dibo, G. *Int. Pept. Protein Res.* **1991**, *37*, 487.

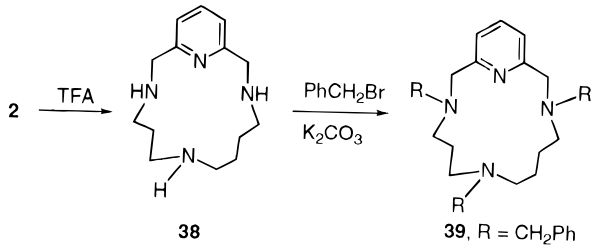
(23) For example, consider a polyazaphane scaffold with four sites to combinatorialize and with one "fixed" or selectively protected site. In the simplest situation (one step for deprotection), 48 reactions are required to completely deconvolute (find the single active compound) for a fix-last process. This consists of (1) a simultaneous addition reaction step using all functional groups, (2) a deprotecting step, (3) a division of the material into 10 pools (assuming 10 functionalities), and (4) reaction of each pool with an individual functionality at the fixed position (the pools are all screened). To do this for four combinatorial sites requires 48 reactions (4 × 12) assuming the scaffold is available as an orthogonally protected species. If the same scaffold is deconvoluted by a fix-first process, 110 reactions are required. This requires (1) a deprotection step of the orthogonally protected scaffold (note to start this approach requires the synthesis of a fully orthogonally protected scaffold), (2) separation into 10 pools, (3) reaction of each pool with each functionality, and (4) repetition of the entire process three times: thus, in total, (4 × 11) reactions (first round) + (3 × 11) reactions (second round) + (2 × 11) reactions (third round) + (1 × 11) reactions (fourth round) = 110 reactions to completely deconvolute by a fix-first process. The number of steps in the fix-first process increases as the number of sites increases relative to the fix-last process (e.g., for 10 functionalities and five sites: fix-first for first round = 55 reactions *vs* 12 for fix-last, and to completely deconvolute is 165 reactions *vs* 60 reactions, and with six sites the first round is 66 *vs* 12 reactions, and 231 *vs* 72 reaction are needed to completely deconvolute). Possibly more important is the likelihood that a high percentage of first-round libraries will not be active in a particular assay, and thus subsequent deconvolution is not required, a potential saving of many reaction steps. In the case of fix-last, a completely orthogonally protected scaffold is not initially required to obtain first-round libraries. In the case of a fix-first process, considerable protection chemistry is required to start the process since completely orthogonally protected scaffold is required and will be of little value if activity is not found in the first round. Furthermore, orthogonally protecting more than three sites can be synthetically challenging.

last and treated individually with the combinatorialization functionalities (fix-last concept) for an iterative deconvolution process. The amine/oxyamine scaffold **3** allows the use of the concept of libraries from libraries[16] in that hydrogenolytic cleavage of the N−O bond of compounds in each sublibrary would linearize polyazaphanes, yielding a series of new sublibraries and greatly change the structure space (footprint) searched.

Various cyclization methods to prepare polyazaphanes have been reported.[24] Typically, N^1,N^ω-bis(amino) compounds protected with Cbz, COOEt, *t*-Boc, Tf, and Ts groups[25] have been employed in a cyclization step to prepare symmetric polyazaphane compounds. Most of these methods require strong basic conditions at elevated temperature and suffer from low yields. Deprotection of the resulting macrocycles are often low-yielding reactions because of the requirements of strong acids or bases or reducing conditions at elevated temperature to remove various blocking groups. These conditions are not compatible with our need to retain one nucleophilic site protected, such as *t*-Boc group, for the fix-last concept and would cleave the N−O bond in polyazaphane **3** as well as other oxyamine-containing polyazaphanes. Therefore, it was necessary to find an efficient cyclization method that also would be compatible with a suitable combination of orthogonal protecting groups. We required a selective deprotection scheme that would yield mono-protected polyazaphane scaffolds for the SPSAF approach. We elected to use the 2-nitrobenzenesulfonyl group[26] for protection of the primary amines of **26**, **27**, and **34**. This process, which begins with a *t*-Boc-protected secondary amine, provides fully protected triamines **29**, **30**, and **35**. Once cyclization has occurred, removal of the sulfonamide protecting group by thiophenol is readily accomplished without affecting the *t*-Boc group. The *t*-Boc group is easily removed as required, and the secondary amine can be fixed with a discriminating functionality at the selected site (fix-last concept) for iterative screening.[23]

Schemes 1 and 2 illustrate the synthesis of fully protected, asymmetric polyazaphane compounds **32**, **33**, and **37** and the corresponding desired mono-protected polyazaphanes scaffolds **1**−**3**. Spermidine (**21**), *N*-(2-aminoethyl)-1,3-propanediamine (**20**), and N^5-(*tert*-butoxycarbonyl)-1,7-diamino-1-oxa-5-azaheptane (**34**)[27] were selected as initial polyamine synthons. They are asymmetric and upon cyclization according to our procedure provide novel, interesting 13-, 14-, and 15-membered polyazaphanes.[17] The mono-*t*-Boc-protected spermidine **27** was prepared from spermidine (**21**) through intermediates **23** and **25** by the reported procedures.[28] Similar procedures were used to prepare mono-*t*-Boc-protected triamine **26** from *N*-(2-aminoethyl)-1,3-propanediamine (**20**) through the corresponding intermediates **22** and **24**. The mono-*t*-Boc-protected triamines **26** and **27** were reacted with 2-nitrobenzenesulfonyl chloride (**28**) in dichloromethane using triethylamine as the base to afford the corresponding triprotected triamines **29** and **30** in 67% and 91% yields, respectively. These key intermediates contain orthogonal protecting groups that can be selectively removed to provide two reactive secondary nitrogen groups for combinatorialization under mild conditions. The combination of *o*-nitrosulfonate and *t*-Boc protecting groups on polyamines and diamines provides a general synthetic approach to a variety of polyazaphane scaffolds suitable for combinatorialization chemistry.

Scheme 3



The 1:1 cyclizations of 2,6-bis(bromomethyl)pyridine (**31**) with orthogonally protected key intermediates **29** and **30** were carried out in DMF at room temperature for 24 h. Cesium carbonate was used as a weak base with the Cs^+ cation serving as a cyclization template. The corresponding macrocyclic compounds **32** and **33** were isolated as white foams in yields of 80% and 73%, respectively. In comparison, the cyclizations of polyamines protected by COOEt, Cbz, or *t*-Boc groups[25] generally provide 20−50% yields. The 2-nitrobenzenesulfonyl protecting groups in **32** and **33** were removed selectively by thiophenol in the presence of K_2CO_3 to give the desired mono-*t*-Boc-protected asymmetric polyazaphane scaffolds **1** and **2** in 94% and 72% yields, respectively. Notable features of this cyclization and deprotection process were the remarkable reaction efficiency, mild reaction conditions, and high yields. This cyclization method and synthetic route should be useful for the syntheses of other types of macrocyclic compounds for combinatorials, molecular recognition, crown ether chemistry, and other areas.

The same route was used for the synthesis of the polyazaphane scaffold **3** containing an N−O bond (Scheme 2). N^5-(*tert*-Butoxycarbonyl)-1,7-diamino-1-oxa-5-azaheptane (**34**)[27] was treated with **28** under the same conditions as for the preparation of **29** and **30**. The desired triprotected triamine product **35** was isolated in 33% yield, and the tetraprotected triamine **36** also was isolated in 45% yield. The reaction conditions have not been optimized for the synthesis of the desired product **35**. The cyclization of **35** with **31** under the same conditions as described above gave the corresponding triprotected polyazaphane compound **37** in 50% yield. The lower yield compared to those of **32** and **33** can be attributed to the different reactivities of two different nitrogenous nucleophiles CH_2NH and ONH in the triamine **35**. Fully protected macrocycle **37** was selectively deprotected by thiophenol in the presence of K_2CO_3, providing the desired polyazaphane scaffold **3** in 97% yield. Novel compounds **26**, **29**, **30**, **32**, **33**, **35**, **37**, and **1**−**3** were characterized by their ^{1}H and ^{13}C NMR data, high-resolution (HR) MS spectroscopic techniques, and combustion analyses. The structure of **36** was confirmed by ^{1}H NMR and ESI MS spectral data. The structure of **2** was further confirmed by the preparation of its derivatives (Scheme 3). Scaffold **2** was treated with trifluoroacetic acid (TFA) to give the corresponding unprotected macrocyclic scaffold **38**. The reaction of **38** with benzyl bromide using K_2CO_3 as the base gave the trisubstituted derivative **39**. Compounds **38** and **39** were characterized by NMR and HRMS spectroscopic techniques. The unprotected scaffold **38** can be used to generate libraries directly, and a reverse iterative deconvolution process similar to Rebek's[13a−c] can be employed. However, the use of

(24) Bradshaw, J. S.; Krakowiak, K. E.; Izatt, R. M. *Aza-Crown Macrocycles;* Taylor, E. C., Ed.; John Wiley and Sons, Inc.: New York, 1993.

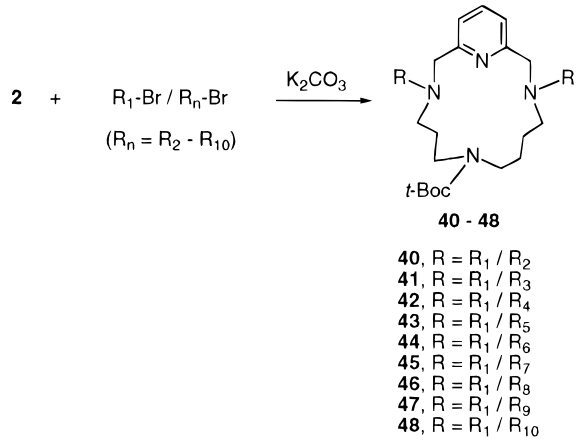
(25) (a) Krakowiak, K. E.; Bradshaw, J. S. *J. Heterocycl. Chem.* **1995**, *32*, 1639. (b) Panetta, V.; Yaouanc, J. J.; Handel, H. *Tetrahedron Lett.* **1992**, *33*, 5505. (c) Pearson, D. P. J.; Leigh, S. J.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1979**, 3113. (d) Hodgkinson, L. C.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1908.

(26) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.

(27) Kung, P. P.; Fraser, A. S.; Guinosso, C. J.; Bharadwaj, R.; Cook, P. D. Unpublished results.

(28) O'Sullivan, M. C.; Dalrymple, D. M. *Tetrahedron Lett.* **1995**, *36*, 3451.

Scheme 4



the corresponding mono-*t*-Boc-protected scaffold **2** as the starting point allows the use of the "fix-last" strategy and a subsequent iterative deconvolution.[23]

For the combinatorialization of scaffolds **1**−**3**, by the simultaneous addition of functionalities (electrophiles), an approximately equal reactivity of each electrophile is required to obtain undistorted libraries. We have selected *meta*-substituted benzylic bromides as an initial class of electrophiles to examine for the SPSAF approach. The differentiating (diversity) groups are located in the *meta* position. These electrophiles are expected to have approximately the same reactivity because different substituents on the *meta* position are expected to have a minimal contribution to the electrophilicity compared with substituents on the *ortho* and *para* positions. The structural diversity demonstrated by *meta*-substituted benzyl moieties would seem limited; however, these type of electrophiles are attractive for initial model studies.

A set of 10 commercially available benzylic bromides R_1−Br, R_2−Br ... R_{10}−Br (see Figure 1 for structural details) were selected as functionalities for simultaneous addition. The two secondary, benzylic nitrogens on scaffold **2** are expected to have approximately the same nucleophilicities. Therefore, the libraries generated by simultaneous reaction of these electrophiles with scaffold **2** are expected to contain all possible compounds in approximately the same amounts. To confirm this hypothesis, we performed model studies by synthesizing several small libraries (Scheme 4) which could be carefully analyzed. An equimolar amount of each electrophile R_1−Br and R_2−Br was reacted simultaneously with scaffold **2** to give library **40** containing four compounds. The electrophile R_1−Br was chosen as the standard and combined separately with each of the other electrophiles R_3−Br, R_4−Br, R_5−Br, R_6−Br, R_7−Br, R_8−Br, R_9−Br, and R_{10}−Br to react with scaffold **2**. In this manner, nine different small libraries, **40**−**48**, containing four compounds each were obtained after chromatographic purification.[29] These pure libraries were confirmed by TLC, ^{1}H NMR, and ESI MS spectral data[30] (see the Experimental Section). Libraries **40**−**48** were all analyzed by capillary zone electrophoresis (CZE) techniques and detected by UV absorption at 214 nm. Figure 2 shows a representative CZE profile of library **45**. The four expected compounds were very well separated with almost the same peak heights. The area percentages of the four peaks are 21.58% (1), 22.87% (2), 26.77% (3), and 28.78% (4), respectively, with a deviation of 7−15%. This relative ratio is appropriate for our biological screening purpose.[31] Other small libraries gave similar CZE profiles. These results indicated that α-bromo-*m*-xylene (R_1−Br) shows approximately the same reactivity as each of the other electrophiles. Therefore, all electrophiles tested should have approximately the same reactivity under our reaction conditions. These data suggest that under these reaction conditions the *meta* position of the benzyl group may be sufficiently isolated from the benzylic reactive site such that a wide variety of more diverse moieties could be placed in the *meta* position with the likelihood of near-equal reactivities.

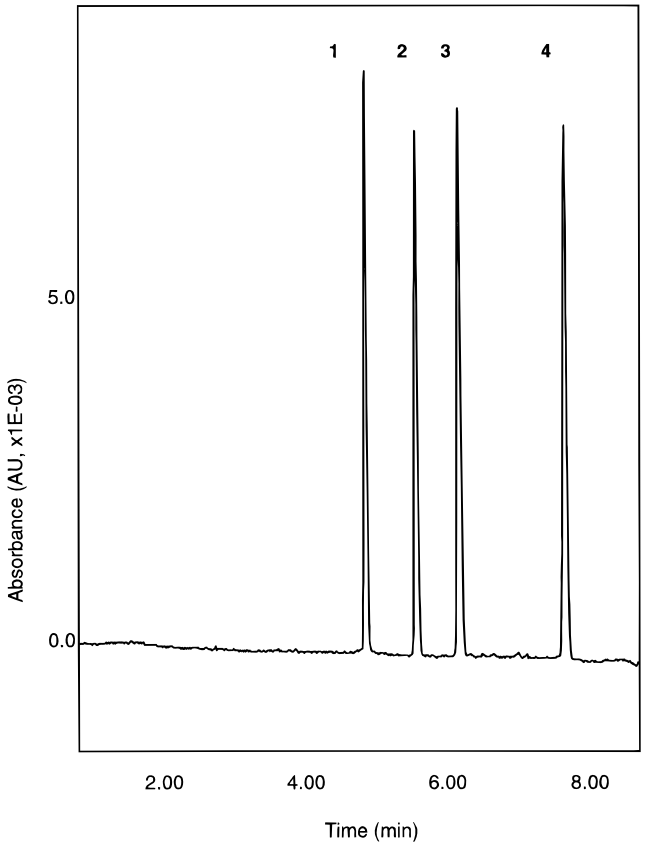


Figure 2. Representative capillary zone electophoresis profile for libraries **45**. CZE conditions: 20 mM ammonium formate buffer containing 0.1% of acetic acid in methanol; detected at 214 nm. Area percentages (peak number): 21.58% (1), 22.87% (2), 26.77% (3), and 28.78% (4) in the deviation of 7−15%. Height percentages (peak number): 26.51% (1), 24.11% (2), 24.98% (3), and 24.38% (4).

To substantiate the above conclusion, model libraries **49**−**52** were prepared by the reaction of scaffold **2** with a set of three, four, and five different electrophiles (Scheme 5) under the same reaction, workup, and purification conditions. Libraries **49**−**52** exhibited acceptable TLC, ^{1}H NMR, and ESI MS spectra (see the Experimental Section). Libraries **49** and **50** were analyzed with CZE, and the nine expected peaks were well-separated. Figure 3 exhibits a CZE profile of library **49**. Area percentages of these peaks deviate 0.2−12% from the expected values. CZE analysis of library **51** (supporting data)

(29) The column loaded with a crude library was eluted with a less polar solvent to remove the excess benzylic bromides and then was eluted with more polar solvents to completely remove the library. All fractions containing library compounds were collected. The preparative thin layer chromatography (PLC) loaded with crude library was developed by selected solvents. The library band, which was generally wider than those of single compounds, was collected to provide pure library without electrophiles and other impurities.

(30) The ^{1}H NMR spectra of libraries show the correct ratio of certain protons. The ESI mass spectra show the peaks ranging from the smallest molecular weight to the largest molecular weight in libraries.

(31) Our current requirement for the libraries is that the molar differences of theoretical amounts and the detected amounts of all compounds in one library are within 20%. The active compounds within this deviation would not be missed using our antibacterial assays.

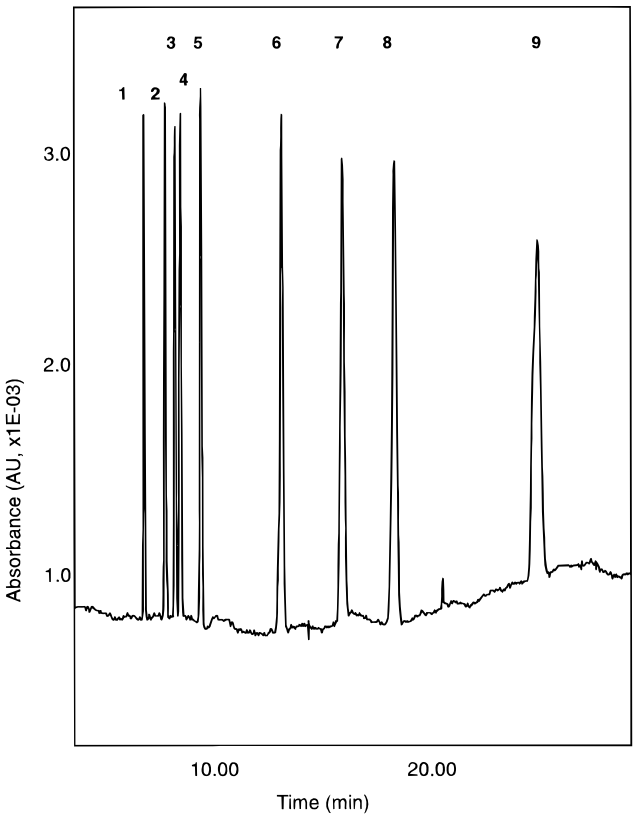
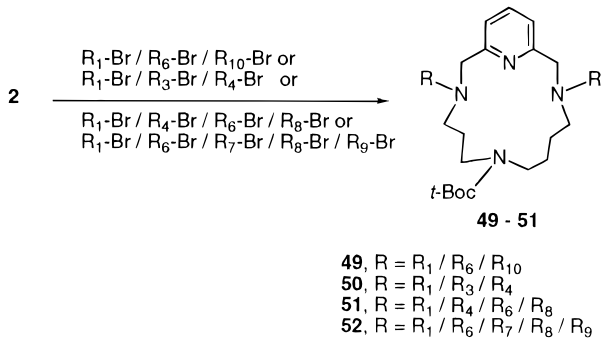


Figure 3. Capillary zone electrophoresis profile of library **49**. CZE conditions: 30 mM ammonium formate buffer containing 0.3% acetic acid in methanol; detected at 214 nm. Area percentages (peak number): 11.08% (1), 11.33% (2), 10.59% (3), 12.19% (4), 11.84% (5), 10.96% (6), 10.94% (7), 11.33% (8), and 9.74% (9) in the deviation of 0.2−12%.

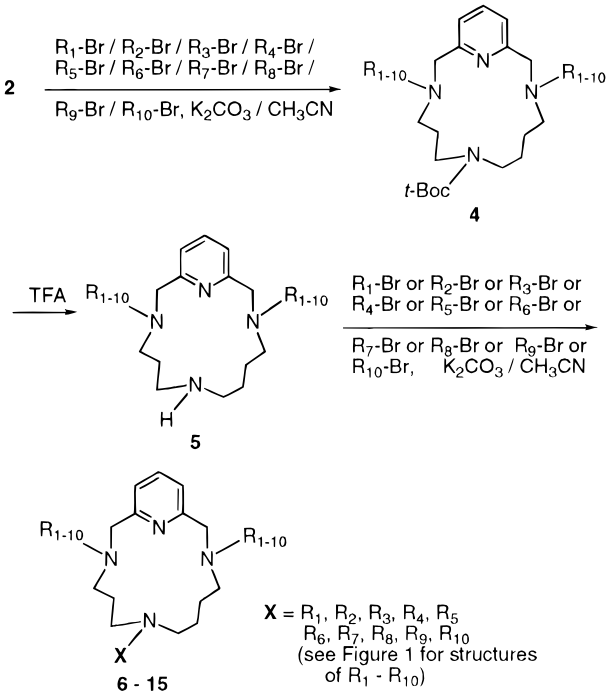
Scheme 5



containing 16 compounds exhibits 12 well-resolved peaks and one broad, later migrating peak representing incomplete separation of four compounds. The CZE analysis of library **52** containing 25 compounds indicated that 20 peaks out of 25 were detected. Five of the 20 peaks represent the incomplete separations of two compounds each (Supporting Information). The above results further indicated that these electrophiles have similar reactivities and that the reactivities of these electrophiles exhibit little influence on the final libraries. Therefore, we were confident that high-quality libraries containing approximately equimolar amounts of all possible compounds would result by simultaneous addition, in solution, of selected functionalities under our reaction conditions.

A mixture containing equimolar amounts of 10 benzylic bromides R_x−Br (x = 1−10, total 2.4 equiv) was added to a stirred mixture of scaffold **2** in acetonitrile using K_2CO_3 as the base (Scheme 6). After an overnight reaction and workup, the

Scheme 6



crude library was purified by flash chromatography on a silica gel column to afford pure library **4** in 94% yield.[32] Combinatorialization of the two different nucleophilic sites on scaffold **2** with 10 functionalities resulted in library **4** containing 100 compounds (10^2 = 100). Library **4** was verified by ^{1}H NMR and ESI MS spectral data.[30] Deprotection of library **4** with TFA gave the corresponding library **5** in 93% yield after chromatographic purification. The secondary amine in intermediate library **5** was reacted sequentially with 10 different functionalities R_x−Br (x = 1−10) under similar conditions as described above for the preparation of library **4**. This afforded 10 different sublibraries **6**−**15** (Scheme 6 and Figure 1) in 60−98% yields after preparative thin layer chromatographic (PLC) purification.[29]

With the key intermediate library **5** containing one reactive site in hand, initial structure activity relationship (SAR) studies were performed on the mixture by introducing several different functionalities at the fixed site (Scheme 7). Adding new functionalities in this manner would "positionally bias" the sublibraries in that the new groups are not combinatorialized at the other positions. The reaction of **5** with methyl α-bromoacetate, bromoacetonitrile, and α-bromoacetamide under similar reaction and purification conditions afforded the corresponding libraries **16**, **17**, and **18**, respectively, in 95−98% yields. The commercially available 2-chloro-*N*-methoxy-*N*-methylacetamide was reacted with **5** at 60−70 °C for 6 h and then at room temperature for 10 h, giving library **19** in 93% yield. The PLC conditions for the purification of libraries **18** and **19** differed from the others because of the more polar functionalities. All libraries described above were prepared in large quantities (200−3000 mg), monitored by TLC, purified by chromatographic techniques, and confirmed by their ^{1}H NMR and ESI MS spectral data. The availability of key intermediate libraries as well as of final sublibraries for broader screening and further reactions is a major advantage of SPSAF process *vs* the usual bead-splitting, solid support synthesis.

(32) The theoretical yield was calculated according to the average molecular weight. The yield was obtained by comparing the amount of isolated library with the theoretical yield.

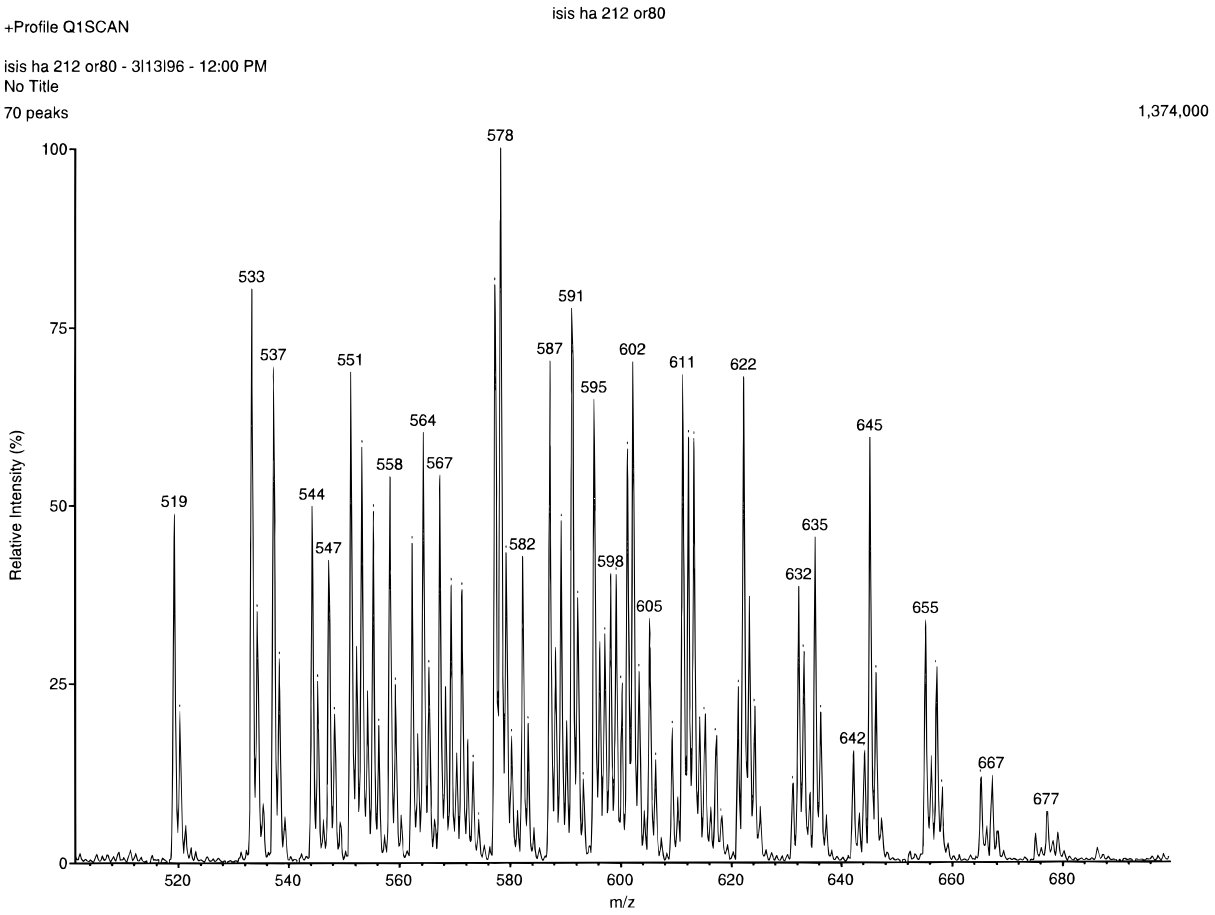
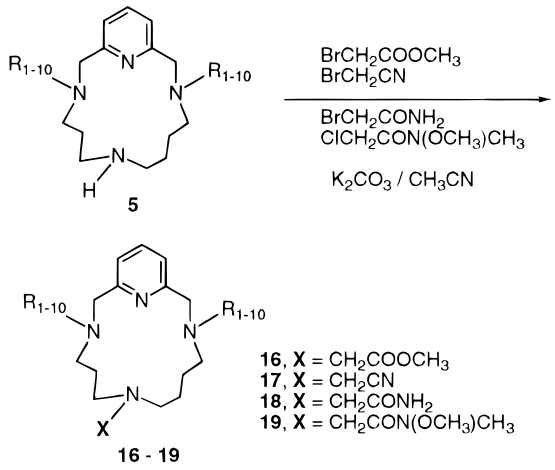


Figure 4. Electrospray ionization mass spectrum of library **7**. Molecular weights range from 518 to 676; 49 distinct peaks[33] corresponding to 100 different compounds.

Scheme 7



The alkylation reactions, performed simultaneously under the described conditions, completely consume the scaffold. Therefore, the possible impurities that may result from these alkylation reactions may be (1) scaffold having an unreacted secondary amine (incomplete alkylations that would provide monoalkylation instead of dialkylation), (2) scaffold having a quaternary nitrogen (overalkylation to yield three or four benzyl substitutions), (3) scaffold with an unreacted secondary amine and a quaternary amine, and (4) benzylic bromides or decomposed benzylic bromides. The initial aqueous extraction would remove the ionic quarternary species and chromatography would remove benzyl species. Mono-, tri-, and tetra-alkylated species were not present in the initial ESI taken before extraction procedures. Obviously, these species were not observed in the ESI taken of the purified libraries. Figure 4 shows the representative electrospray ionization mass spectrum of library **7**. The $(M + H)^+$ peak range 519−677 corresponds to the molecular weight range 518−676 for 100 compounds in library **7**. There were no obvious impurities beyond this range. Forty-nine theoretical molecular weights[33] out of 100 different compounds were all represented by 49 distinct peaks. The simulated electrospray mass spectrum (Figure 5) of library **7** was generated by individually calculating the formula, mass, and isotope distribution for each library member. The masses were tabulated as a seven-point fit to a Gaussian line shape with a 0.15 Da width, and overlapping masses were summed prior to storage in a flat file. A graphical representation of the mass table was inspected visually, and the relative abundance of each functionality was adjusted iteratively to fit the observed mass spectrum. As shown in Figure 5, the mass distribution seen in the computer-simulated spectrum with functionality weights ranging from 0.88 to 1.05 is similar to the observed data in Figure 4.

Initial screening results (Table 1) indicated that sublibraries **5**, **9**, and **10**, containing 100 compounds each, exhibited antimicrobial activities against *E. coli imp*$^-$ and *S. pyogenes* in minimum inhibitory concentration (MIC) in the low micromolar range. Sublibraries **17** and **19** also show activities. Other sublibraries did not show activity at the concentration of 100 μM. The potent activities of sublibraries **5** and **10** prompted us to make 20 single compounds of these libraries. Scaffold **2**

(33) Library **7** has the following 49 theoretically different molecular weights: 518, 532, 536, 543, 544, 546, 550, 552, 554, 557, 558, 561, 562, 563, 566, 568, 569, 570, 576, 577, 578, 581, 586, 588, 589, 590, 594, 597, 600, 601, 602, 604, 608, 610, 611, 612, 614, 620, 621, 622, 623, 631, 634, 641, 644, 654, 655, 664, 676.

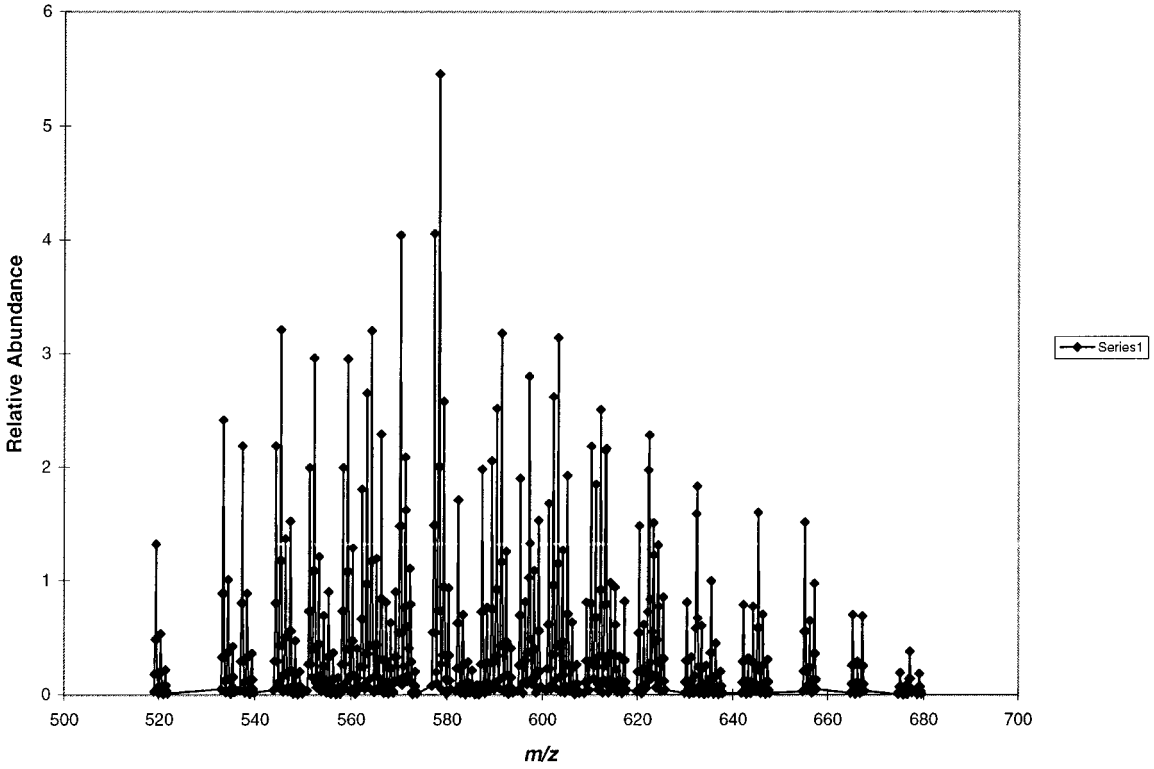


Figure 5. Computer-simulated mass spectrum of library **7**.

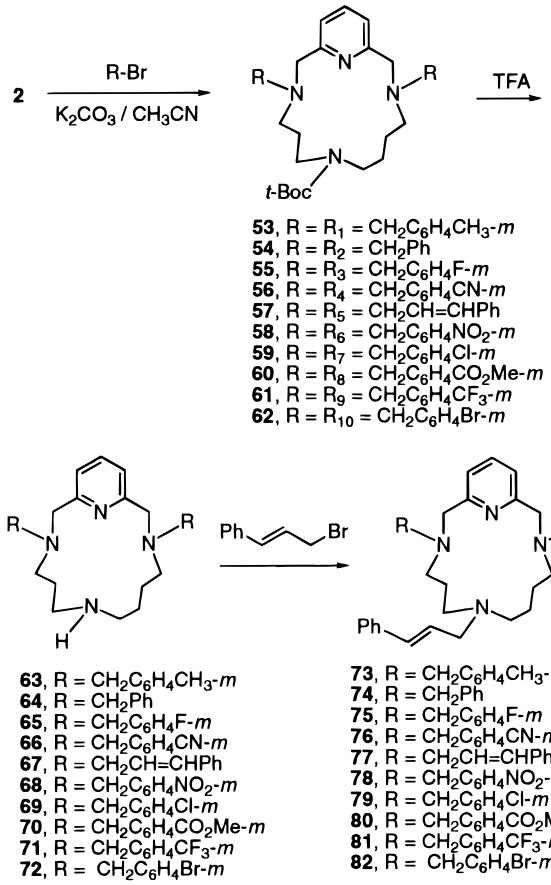
Table 1. Activities of Libraries in Growth Inhibition Assays (MIC, μM)[a]

Library	Complexity	*S. pyogenes*	*E. coli imp*$^-$
4	100	>100	>100
5	100	5−10	10−20
6	100	>100	>100
7	100	>100	>100
8	100	>100	>100
9	100	5−10	5−10
10	100	10−20	<2.5
11	100	>100	>100
12	100	>100	>100
13	100	>100	>100
14	100	>100	>100
15	100	>100	>100
16	100	>100	>100
17	100	10−20	10−20
18	100	>100	>100
19	100	50−100	50−100
2	1	>100	>100
38	1	>100	>100
39	1	>100	>100

[a] The MIC (minimum inhibitory concentration) value is given as a range of library concentration (total concentration of compounds in the libraries). After 24 h, the complete growth was observed at lower bound of the given MIC and no growth was observed at the upper bound.

was reacted with each of the 10 benzylic bromides to give compounds **53**−**62** (Scheme 8). Deprotection of **53**−**62** with TFA afforded products **63**−**72**. Each of the compounds **63**−**72** was reacted with cinnamyl bromide to afford 10 final compounds **73**−**82**. Compounds **63**−**72** and **73**−**82** belong to sublibraries **5** and **10**, respectively. Each of these compounds has the same functionalities in the two combinatorialized positions. Compounds **63**−**82** were screened against *imp*$^-$ and *S. pyogenes*, and the MIC results were listed in Table 2. Six active compounds **69**, **71**−**73**, **77**, and **81** were further tested against *S. aureus*, *E. coli*, *K. pneumoniae*, and *E. faecalis*. Compounds **69**, **71**, and **72** showed low MIC values in most of the assays, while compounds **72**, **76**, and **81** showed high

Scheme 8



selectivity among these assays. Scaffold **2** and compound **38** (Table 1) did not show activity at 100 μM which suggests that some benzylic groups on polyazaphane **38** are essential for activity. Tribenzyl-subsituted compound **39** and a series of other compounds in Table 2 did not show activities. These results suggest that, even though the diversity of substituted benzylic

Table 2. Activities of Compounds **63**−**82** in Growth Inhibition Assays (MIC, μM)[a]

compd no.	*E. coli imp*$^-$	*S. pyogenes*	*S. aureus*	*E. coli*	*K. pneumonie*	*E. faecalis*
63	>20	10−20				
64	>20	>20				
65	>20	>20				
66	>20	>20	>50	>50	>50	>50
67	10−20	5−10				
68	>20	>20				
69	2.5−5	2.5−5	3−6	3−6	6−12	3−6
70	>20	>20				
71	2.5−5	<2.5	3−6	3−6	3−6	1.6−3
72	2.5−5	<2.5	3−6	3−6	6−12	3−6
73	2.5−5	>10	>50	12−25		
74	5−10	5−10				
75	5−10	>20				
76	>20	>20				
77	2.5−5	2.5−5	>50	3−6	3−6	>50
78	>20	>20				
79	>20	>20				
80	10−20	>20				
81	2.5−5	5−10	6−12	12−25	>50	25−50
82	>20	>20				

[a] See footnote *a* to Table 1.

functionalities appears limited, significant discriminating diversity in our antimicrobial assays is provided by substitution of functional groups in the *meta* position of the benzyls. The iterative deconvolution of the active sublibraries is in progress. Further research planned in this area includes the examination of the effect of scaffold ring size on biological activity. Thus, scaffolds **1** and **3**, which are 13- and 15-membered polyazaphanes (scaffold **2** is 14-membered), will be combinatorialized with the same functionality set as described. This should have a significant effect on the size and volume of structural space searched, but interacting functionalities will be the same as in libraries constructed from scaffold **2**.

In conclusion, a highly efficient, versatile synthetic route has been developed for the preparation of polyazaphane scaffolds suitable for solution phase combinatorialization procedures. Three novel asymmetric polyazaphanes scaffolds **1**−**3** were synthesized using this process. A novel solution phase, simultaneous addition of functionalities (SPSAF) process was developed to generate large quantities of libraries containing approximately equimolar amounts of all possible compounds. Sixteen high-quality libraries were prepared from scaffold **2**. The purity of the libraries was confirmed by TLC, CZE, ^{1}H NMR, and ESI/MS spectroscopic techniques. A "fix-last" concept was developed to allow initial SAR studies to be performed on the mixtures. Several of the sublibraries as mixtures of 100 compounds exhibited potent antimicrobial activities. Five single compounds showed promising activities against several assays, and three compounds showed high selectivities in some assays.

Experimental Section

General Methods. Capillary zone electrophoresis (CZE) analyses were performed using a 37 cm fused silica column (50 μm i.d.) and an applied voltage of 30 kV at 25 °C. Columns were flushed with 0.2 M NaOH solution for 1.5 min, then buffered for 2.0 min prior to sample injection. Samples were pressure injected for 3−8 s at 0.5 psi. Compounds **23**, **25**, and **27** were prepared according to the literature procedures.[28] N^5-(*tert*-Butoxycarbonyl)-1,7-diamino-1-oxa-5-azaheptane (**34**) was synthesized according to our procedure.[27] Starting materials and anhydrous DMF, acetonitrile, and THF were purchased from Aldrich and used directly. The bacterial and yeast anti-growth assays were performed in 96-well plate format in 150 μL volume in the presence of library or relevant antibiotic or antifungal controls.[34] Growth was monitored as a function of time by measuring absorbance at 595 nm. The *S. pyogenes* strain was ATCC #14289 and was grown in 1x Todd-Hewitt broth. The *E. coli imp*$^-$ strain was a kind gift of Spencer Bensen and was grown in 1/2x LB.[35] For tier two screening, *S. pyogenes* (ATCC#49399), *S. aureus* (ATCC# 25923), *E. coli* (ATCC# 11775), *K. pneumoniae* (ATCC# 13883), and *E. faecalis* (ATCC# 29212) strains were grown in the standard media. A computer program has been developed to generate simulated mass spectra of combinatorial libraries from input molecular formulas and relative abundances for the scaffold and the functionalities. The nominal molecular mass and isotope distributions ($N + 1$ and $N + 2$ for ^{13}C, ^{15}N, and ^{2}H; all for Cl, Br, and S) are calculated for each library member and converted to a seven-point fit to a Gaussian line shape with a line width specified as input. The program has been written and compiled in C using a Silicon Graphics Crimson computer.

***N*^{1},*N*^{6}-Bis(trifluoroacetyl)-1,6-diamino-3-azahexane (22).** Ethyl trifluoroacetate (16.7 mL, 19.89 g, 0.14 mol, 3.5 equiv) was added to a solution of *N*-(2-aminoethyl)-1,3-propanediamine (**20**) (4.70 g, 40 mmol) in 25 mL of CH_3CN followed by H_2O (0.72 g, 40 mmol, 1 equiv). The resulting reaction mixture was refluxed overnight, and the solvent was evaporated under reduced pressure. The residue was dried under high vacuum to give product **22** as a white solid: mp 131−133 °C, yield 16.8 g (99.4%); silica gel TLC R_f 0.45 (100% EtOH); ^{1}H NMR ($CD_3OD + D_2O$) δ 1.88−2.05 (m, 2 H), 3.08 (t, 2 H, J = 7.6 Hz), 3.23 (t, 2 H, J = 6.0 Hz), 3.40 (t, 2 H, J = 6.8 Hz), 3.63 (t, 2 H, J = 6.0 Hz) (product thus obtained was carried out to the next step without further purification).

***N*^{3}-(*tert*-Butoxycarbonyl)-*N*^{1},*N*^{6}-bis(trifluoroacetyl)-1,6-diamino-3-azahexane (24).** Di-*tert*-butyl dicarbonate (13.2 g, 60 mmol, 1.5 equiv) was added to a cooled solution of **22** (16.8 g, 40 mmol) and Et_3N (10.9 g, 108 mmol, 2.7 equiv) in 140 mL of anhydrous THF. The resulting reaction mixture was stirred at room temperature overnight. Saturated NH_4Cl solution (270 mL) was added, and the resulting mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with brine and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by flash chromatography on a silica gel column (17 × 7 cm). Elution with 100% CH_2Cl_2 and then 20:1 CH_2Cl_2−MeOH afforded product **24** as a white solid: mp 113−114 °C, yield 16.4 g (100%); silica gel TLC R_f 0.37 (50:1 CH_2Cl_2−MeOH); ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 9 H), 1.65−1.88 (m, 2 H), 3.20−3.37 (m, 4 H), 3.40−3.55 (m, 4 H), 7.00 (bs, 1 H), 8.10 (bs, 1 H).

***N*^{3}-(*tert*-Butoxycarbonyl)-1,6-diamino-3-azahexane (26).** Compound **24** (16.4 g, 40 mmol) was treated with a mixture of MeOH−30% NH_4OH (270 mL, 1:2) and refluxed for 20 h. The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography on a silica gel column (25 × 7 cm). Gradient elution with 50:1, 20:1, and then 5:1 MeOH−30% NH_4OH gave product **26** as a colorless oil: yield 6.0 g (69%); silica gel TLC R_f 0.47 (10:1 MeOH−30% NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9 H), 1.54 (bs, 4 H, ex D_2O), 1.56−1.72 (m, 2 H), 2.68 (t, 2 H, J = 6.6 Hz), 2.81 (t, 2 H, J = 6.4 Hz), 3.18−3.35 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 28.22, 31.75, 38.96, 40.43, 44.71, 49.81, 79.32, 155.73; HRMS (FAB) *m/z* 218.186 ($M + 1$)$^+$ ($C_{10}H_{24}N_3O_2$ requires 218.187). Anal. Calcd for $C_{10}H_{23}N_3O_2$: C, 55.27; H, 10.67; N, 19.33. Found: C, 55.39; H, 10.31; N, 18.76.

***N*^{3}-(*tert*-Butoxycarbonyl)-*N*^{1},*N*^{6}-bis(2-nitrobenzenesulfonyl)-1,6-diamino-3-azahexane (29).** A solution of 2-nitrobenzenesulfonyl chloride (**28**) (15.2 g, 68.2 mmol, 2.33 equiv) in 90 mL of CH_2Cl_2 was added dropwise to a stirred solution of **26** (6.35 g, 29.2 mmol) and 24 mL of Et_3N in 90 mL of CH_2Cl_2 at 0 °C. The resulting reaction mixture was allowed to warm to room temperature and further stirred for 1 h. The reaction mixture was diluted with $CHCl_3$ and washed with H_2O and then brine. The organic phase was dried (Na_2SO_4), and the solvent was evaporated under the reduced pressure. The residue was purified by flash chromatography on a silica gel column (20 × 5 cm). Elution with 2:1 and then 1:1 hexanes−EtOAc afforded product **29** as a pale yellow viscous oil: yield 11.5 g (67%); silica gel TLC R_f 0.52 (1:2

(34) National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacterial that Grow Aerobically*, 1993; MCCLS Document M7-A3, Vol. 13, Villanova, PA.

(35) Sampson, B. A.; Misra, R.; Benson, S. A. *Genetics* **1989**, *122*, 491.

hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9 H), 1.56−1.75 (m, 2 H), 2.98−3.10 (m, 2 H), 3.14−3.36 (m, 6 H), 5.60 (bs, 1 H, ex D_2O), 6.20 (bs, 1 H, ex D_2O), 7.66−7.88 (m, 6 H), 8.02−8.13 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 23.25, 40.68, 42.43, 44.18, 45.17, 46.89, 80.64, 125.32, 130.07, 132.94, 133.13, 133.99, 147.85, 156.07; HRMS (FAB) *m/z* 720.039 $(M + Cs)^+$ ($C_{22}H_{29}N_5O_{10}S_2Cs$ requires 720.041). Anal. Calcd for $C_{22}H_{29}N_5O_{10}S_2$: C, 44.97; H, 4.97; N, 11.92. Found: C, 44.78; H, 5.03; N, 11.58.

***N*^{4}-(*tert*-Butoxycarbonyl)-*N*^{1},*N*^{8}-bis(2-nitrobenzenesulfonyl)spermidine (30).** Compound **30** was prepared as above for **29** from 5.32 g (24.0 mmol) of **28**, 2.45 g (10.0 mmol) of *N*^{4}-(*tert*-butoxycarbonyl)-spermidine (**27**)[28] and 8 mL of Et_3N in 60 mL of CH_2Cl_2. The resulting reaction mixture was allowed to warm to room temperature and further stirred for 1 h. Flash chromatographic purification of the crude product gave **30** as a pale yellow viscous oil: yield 5.62 g (91%); silica gel TLC R_f 0.52 (1:2 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 9 H), 1.40−1.52 (m, 4 H), 1.58−1.74 (m, 2 H), 2.98−3.25 (m, 8 H), 5.45 (bs, 1 H, ex D_2O), 6.31 (bs, 1 H, ex D_2O), 7.65−7.85 (m, 6 H), 8.00−8.11 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 25.37, 26.87, 28.35, 40.81, 43.45, 46.39, 79.92, 125.18, 125.33, 130.78, 130.94, 132.77, 132.92, 133.51, 133.79, 148.02, 156.00; HRMS (FAB) *m/z* 748.075 $(M + Cs)^+$ ($C_{24}H_{33}N_5O_{10}S_2Cs$ requires 748.072). Anal. Calcd for $C_{24}H_{33}N_5O_{10}S_2$: C, 46.82; H, 5.40; N, 11.37. Found: C, 46.66; H, 5.40; N, 11.00.

6-(*tert*-Butoxycarbonyl)-3,10-bis(2-nitrobenzenesulfonyl)-3,6,10,-16-tetraazabicyclo[10.3.1]hexadeca-1(16),12,14-triene (32). A mixture of 2.6-bis(bromomethyl)pyridine (**31**) (4.93 g, 18.6 mmol), anhydrous Cs_2CO_3 (24.0 g, 73.6 mmol, 4 equiv), and **29** (10.98 g, 18.6 mmol, 1 equiv) in 500 mL of anhydrous DMF was stirred at room temperature for 24 h. The solvent was evaporated under vacuum, and the residue was dissolved in a mixture of H_2O and $CHCl_3$. The layers were separated, and the aqueous phase was extracted with $CHCl_3$. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on a silica gel column (18 × 5 cm). Elution with 1:1, 1:2, and then 1:4 hexanes−EtOAc gave product **32** as a white foam: yield 10.3 g (80%); silica gel TLC R_f 0.50 (1:4 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9 H), 1.67−1.85 (m, 2 H), 2.60−2.80 (m, 2 H), 3.04−3.15 (m, 2 H), 3.25−3.46 (m, 4 H), 4.55 (s, 4 H), 7.48−7.80 (m, 9 H), 7.96−8.10 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 26.98, 28.34, 45.36, 46.40, 47.07, 49.26, 55.24, 55.65, 79.83, 123.97, 124.25, 124.41, 130.67, 130.92, 131.91, 133.98, 138.64, 148.13, 148.36, 155.06, 155.67; HRMS (FAB) *m/z* 823.086 $(M + Cs)^+$ ($C_{29}H_{34}N_6O_{10}S_2Cs$ requires 823.083). Anal. Calcd for $C_{29}H_{34}N_6O_{10}S_2$: C, 50.42; H, 4.96; N, 12.16. Found: C, 49.95; H, 4.96; N, 12.07.

7-(*tert*-Butoxycarbonyl)-3,12-bis(2-nitrobenzenesulfonyl)-3,7,12,-18-tetraazabicyclo[12.3.1]octadeca-1(18),14,16-triene (33). Macrocyclic compound **33** was synthesized as above for **32** from 1.33 g (5.0 mmol) of **31**, 6.52 g (29 mmol) of anhydrous Cs_2CO_3, and 3.23 g (5.0 mmol) of **30** in 160 mL of anhydrous DMF. Purification of the crude product by flash chromatography gave product **33** as a white foam: yield 2.63 g (73%); silica gel TLC R_f 0.48 (1:4 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.15−1.30 (m, 4 H), 1.36 (s, 9 H), 1.58−1.74 (m, 2 H), 2.98−3.10 (m, 4 H), 3.16−3.40 (m, 4 H), 4.48 (s, 2 H), 4.62 (s, 2 H), 7.43 (d, 2 H, J = 7.6 Hz), 7.61−7.78 (m, 7 H), 7.98−8.10 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 26.14, 26.68, 28.37, 46.72, 47.00, 48.67, 48.84, 53.69, 54.42, 79,60, 122.58, 122.85, 124.27, 130.77, 131.83, 133.77, 138.06, 148.24, 155.67, 156.00, 156.12; HRMS (FAB) *m/z* 851.118 $(M + Cs)^+$ ($C_{31}H_{38}N_6O_{10}S_2Cs$ requires 851.115). Anal. Calcd for $C_{31}H_{38}N_6O_{10}S_2$: C, 51.80; H, 5.33; N, 11.69. Found: C, 51.81; H, 5.48; N, 11.50.

6-(*tert*-Butoxycarbonyl)-3,6,10,16-tetraazabicyclo[10.3.1]hexadeca-1(16),12,14-triene (1). Thiophenol (1.5 mL, 1.60 g, 14.5 mmol, 2.46 equiv) was added to a stirred mixture of fully protected macrocyclic compound **32** (4.15 g, 6.0 mmol) and anhydrous K_2CO_3 (6.63 g, 48 mmol, 8 equiv) in 80 mL of anhydrous DMF. The resulting blue mixture was stirred at room temperature for 2 h, and the color of the reaction mixture gradually changed to yellow. The yellow reaction mixture thus obtained was concentrated under vacuum, and the residue was dissolved in H_2O. The solution was adjusted to pH 13−14 with NaOH solution and was extracted with $CHCl_3$. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on a silica gel column (20 × 3 cm). Elution with 100% MeOH, 100:1 and then 50:1 MeOH−30% NH_4OH, afforded product **1** as a colorless oil: yield 1.81 g (94%); silica gel TLC R_f 0.42 (50:1 MeOH−30% NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 9 H), 1.48−1.65 (m, 2 H), 2.19 (bs, 2 H, ex in D_2O), 2.62 (t, 2 H, J = 6.4 Hz), 2.78 (t, 2 H, J = 6.2 Hz), 3.00 (t, 2 H, J = 6.2 Hz), 3.28 (t, 2 H, J = 6.4 Hz), 3.90 (s, 4 H), 7.04 (t, 2 H, J = 7.0 Hz), 7.56 (t, 1 H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 28.43, 29.89, 46.09, 46.39, 48.31, 48.60, 54.25, 54.67, 79.25, 120.91, 121.31, 137.14, 156.04, 159.95, 160.11; HRMS (FAB) *m/z* 321.230 $(M + H)^+$ ($C_{17}H_{29}N_4O_2$ requires 321.229). Anal. Calcd for $C_{17}H_{28}N_4O_2$: C, 63.72; H, 8.80; N, 17.48. Found: C, 63.24; H, 8.46; N, 17.13.

7-(*tert*-Butoxycarbonyl)-3,7,12,18-tetraazabicyclo[12.3.1]octadeca-1(18),14,16-triene (2). The mono-protected polyazaphane scaffold **2** was synthesized as above for **1** from 1.44 g (2.0 mmol) of **33**, 500 μL (0.53 g, 4.8 mmol) of thiophenol, and 2.21 g (16.0 mmol) of anhydrous K_2CO_3 in 30 mL of anhydrous DMF. The crude product was purified by flash chromatography to afford product **2** as a colorless oil: yield 0.50 g (72%); silica gel TLC R_f 0.44 (50:1 MeOH−30% NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 9 H), 1.42−1.58 (m, 4 H), 1.65−1.80 (m, 2 H), 2.22 (bs, 2 H, ex D_2O), 2.53 (t, 2 H, J = 5.2 Hz), 2.62 (t, 2 H, J = 6.2 Hz), 2.95−3.09 (m, 2 H), 3.21 (t, 2 H, J = 6.2 Hz), 3.85 (s, 4 H), 6.99 (t, 2 H, J = 7.4 Hz), 7.50 (t, 1 H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 24.90, 26.22, 28.45, 29.41, 45.00, 46.16, 46.50, 47.35, 54.10, 54.46, 79.03, 120.81, 121.06, 136.56, 155.57, 159.42; HRMS (FAB) *m/z* 349.261 $(M + H)^+$ ($C_{19}H_{33}N_4O_2$ requires 349.260). Anal. Calcd for $C_{19}H_{32}N_4O_2$: C, 65.49; H, 9.26; N, 16.07. Found: C, 65.61; H, 9.45; N, 15.77.

***N*^{5}-(*tert*-Butoxycarbonyl)-*N*^{1},*N*^{7}-bis(2-nitrobenzenesulfonyl)-1,7-diamino-1-oxa-5-azaheptane (35) and *N*^{5}-(*tert*-Butoxycarbonyl)-*N*^{1},*N*^{1},*N*^{7}-tris(2-nitrobenzenesulfonyl)-1,7-diamino-1-oxa-5-azaheptane (36).** Compound **35** was prepared as above for **29** from 10.64 g (47.0 mmol) of **28**, 4.67 g (20.0 mmol) of **34**,[27] and 16 mL of Et_3N in 140 mL of CH_2Cl_2. Flash chromatographic purification afforded product **35** as a white foam: yield 3.95 g (33%); silica gel TLC R_f 0.62 (1:2 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9 H), 1.72−1.90 (m, 2 H), 3.18−3.41 (m, 6 H), 3.98−4.11 (m, 2 H), 7.68-7.90 (m, 6 H), 8.10−8.25 (m, 2 H); HRMS (FAB) *m/z* 736.035 $(M + Cs)^+$ ($C_{22}H_{29}N_5O_{11}S_2Cs$ requires 736.035). Anal. Calcd for $C_{22}H_{29}N_5O_{11}S_2$: C, 43.78; H, 4.84; N, 11.60. Found: C, 43.69; H, 4.82; N, 11.34.

The tetra-protected triamine **36** also was isolated as a white foam: yield 7.13 g (45%); silica gel TLC R_f 0.49 (1:2 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9 H), 1.75−1.92 (m, 2 H), 3.10−3.42 (m, 6 H), 4.10−4.22 (m, 2 H), 7.68-7.90 (m, 9 H), 8.05−8.25 (m, 3 H); MS (ESI) *m/z* 787 $(M - 1)^+$.

8-(*tert*-Butoxycarbonyl)-3,11-bis(2-nitrobenzenesulfonyl)-4-oxa-3,8,11,17-tetraazabicyclo[11.3.1]heptadeca-1(17),13,15-triene (37). Compound **37** was synthesized as above for **32** from 1.66 g (6.2 mmol) of **31**, 8.20 g (25.0 mmol) of anhydrous Cs_2CO_3, and 3.80 g (6.2 mmol) of **35** in 200 mL of anhydrous DMF. Flash chromatographic purification afforded product **37** as a white foam: yield 2.20 g (50%): silica gel TLC R_f 0.55 (1:4 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.20−1.30 (m, 2 H), 1.38 (s, 9 H), 2.60−3.00 (m, 2 H), 3.16−3.40 (m, 2 H), 3.78−3.95 (m, 2 H), 4.30 (s, 2 H), 4.55 (s, 2 H), 7.50−7.78 (m, 9 H), 7.85−8.10 (m, 2 H); HRMS (FAB) *m/z* 839.078 $(M + Cs)^+$ ($C_{29}H_{34}N_6O_{11}S_2Cs$ requires 839.078). Anal. Calcd for $C_{29}H_{34}N_6O_{11}S_2$: C, 49.28; H, 4.84; N, 11.89. Found: C, 49.27; H, 4.59; N, 11.68.

8-(*tert*-Butoxycarbonyl)-4-oxa-3,8,11,17-tetraazabicyclo[11.3.1]-heptadeca-1(17),13,15-triene (3). Compound **3** was synthesized as above for **1** from 495 mg (0.70 mmol) of **37**, 158 μL (169 mg, 1.53 mmol) of thiophenol, and 0.80 g (5.7 mmol) of anhydrous in 10 mL of anhydrous DMF. Flash chromatographic purification afforded product **3** as a colorless oil: yield 230 mg (97%); silica gel TLC R_f 0.50 (100% MeOH); ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 9 H), 1.45−1.65 (m, 2 H), 2.65 (t, 2 H, J = 6.8 Hz), 2.97 (t, 2 H, J = 7.2 Hz), 3.14 (t, 2 H, J = 6.8 Hz), 3.58 (t, 2 H, J = 6.0 Hz), 3.92 (s, 2 H), 4.05 (s, 2 H), 7.09 (t, 2 H, J = 7.2 Hz), 7.56 (t, 1 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 27.78, 28.43, 43.97, 45.88, 47.32, 54.39, 57.11, 70.57, 79.27, 121.72, 121.87, 137.01, 155.72, 157.88, 159.25; HRMS (FAB) *m/z* 337.224 $(M + H)^+$ ($C_{17}H_{29}N_4O_3$ requires 337.224).

3,7,12,18-Tetraazabicyclo[12,3,1]octadeca-1(18),14,16-triene (38). Trifluoroacetic acid (TFA) (8 mL) was added to a stirred solution of **2** (349 mg, 1.0 mmol) in 3 mL of $CHCl_3$ at 0 °C. The resulting reaction mixture was stirred at room temperature for 4 h. The solvent and excess TFA were evaporated under vacuum. The residue was dissolved in H_2O and adjusted to pH 14 by addition of NaOH solution. The mixture was extracted with $CHCl_3$. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on a silica gel column (11 × 2 cm). Elution with 100% MeOH and then 10:1 MeOH−30% NH_4OH afforded product **38** as a colorless oil: yield 180 mg (73%); silica gel TLC R_f 0.41 (5:1 MeOH-30% NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.24−1.38 (m, 2 H), 1.39−1.58 (m, 4 H), 2.10 (bs, 3 H, ex D_2O), 2.30−2.57 (m, 8 H), 3.64 (s, 2 H), 3.71 (s, 2 H), 6.83 (d, 2 H, J = 7.6 Hz), 7.35 (t, 1 H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 26.76, 27.21, 29.34, 48.16, 48.63, 48.84, 53.99, 55.20, 120.47, 136.32, 159.04, 159.75; HRMS (FAB) *m/z* 249.207 $(M + 1)^+$ ($C_{14}H_{25}N_4$ requires 249.207). Anal. Calcd for $C_{14}H_{24}N_4$: C, 67.70; H, 9.74; N, 22.55. Found: C, 67.02; H, 9.67; N, 22.09.

3,7,12-Tribenzyl-3,7,12,18-tetraazabicyclo[12,3,1]octadeca-1(18),-14,16-triene (39). A mixture of **38** (75 mg, 0.30 mmol), anhydrous K_2CO_3 (0.50 g, 3.6 mmol), and benzyl bromide (120 μL, 169 mg, 0.99 mmol, 3.3 equiv) in anhydrous CH_3CN (5 mL) was stirred at room temperature overnight. The solvent was evaporated, and the residue was dissolved in H_2O−$CHCl_3$. The organic phase was separated off, and the aqueous phase was extracted with $CHCl_3$. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by preparative thin layer chromatography (PLC) on a silica gel plate by using 1:3 hexanes−EtOAc as the developing agent. Product **39** was obtained as a pale yellow oil: yield 60 mg (39%); silica gel TLC R_f 0.52 (1:4 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.18−1.38 (m, 4 H), 1.45−1.62 (m, 2 H), 2.09−2.28 (m, 4 H), 2.47−2.60 (m, 4 H), 3.38 (s, 2 H), 3.62 (s, 2 H), 3.67 (s, 2 H), 3.70 (s, 2 H), 3.75 (s, 2 H), 7.12−7.48 (m, 17 H), 7.60 (t, 1 H, J = 7.6 Hz); HRMS (FAB) *m/z* 519.347 $(M + 1)^+$ ($C_{35}H_{43}N_4$ requires 519.348).

General Procedure for the Preparation of Libraries 40−52 and 4. A solution containing equimolar amounts of selected benzylic bromides (total 2.4 equiv) in anhydrous CH_3CN was added to a stirred mixture of scaffold **2** (1.0 equiv) and anhydrous K_2CO_3 (15 equiv) in CH_3CN. The resulting reaction mixture was stirred at room temperature overnight. The solvent was evaporated and the residue was dissolved in H_2O and $CHCl_3$. The organic phase was separated off, and the aqueous phase was extracted with $CHCl_3$. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on a silica gel column or by preparative thin layer chromatography (PLC) on a silica gel plate to afford desired libraries.

Library 40: colorless oil; yield 115 mg (71%); silica gel TLC R_f 0.47 (3:2 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.38−1.52 (m, 13 H), 1.60−1.80 (m, 2 H), 2.33 (s, 3 H), 2.51−2.68 (m, 4 H), 2.77−3.00 (m, 2 H), 3.02−3.15 (m, 2 H), 3.63 (s, 2 H), 3.68−3.81 (m, 6 H), 6.85−7.60 (m, 12 H); MS (ESI) *m/z* 529, 543, 557 $(M + 1)^+$.

Library 41: colorless oil; yield 117 mg (70%); silica gel TLC R_f 0.48 (3:2 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.35−1.52 (m, 13 H), 1.59−1.78 (m, 2 H), 2.31 (s, 1.5 H), 2.38 (s, 1.5 H), 2.51-2.68 (m, 4 H), 2.74−2.98 (m, 2 H), 3.00−3.14 (m, 2 H), 3.61 (s, 2 H), 3.65−3.70 (m, 6 H), 6.85−7.33 (m, 10 H), 7.52 (t, 1 H, J = 7.6 Hz); MS (ESI) *m/z* 557, 561, 565 $(M + 1)^+$.

Library 4: pale yellow oil; yield 3.40 g (94%); silica gel TLC R_f 0.23−0.78 (1:2 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.30−1.55 (m, 13 H), 1.57−1.80 (m, 2 H), 2.35 (s, 0.15), 2.36 (s, 0.15 H), 2.50-2.70 (m, 4 H), 2.78−2.98 (m, 2 H), 3.00−3.18 (m, 2 H), 3.57−3.88 (m, 8 H), 3.92 (s, 0.3 H), 6.30−6.70 (m, 0.2 H), 6.90−8.50 (m, 11.16 H); MS (ESI) *m/z* 529−687 $(M + 1)^+$.

Preparation of Library 5. Trifluoroacetic acid (TFA) (40 mL) was added to a stirred solution of library **4** (3.37 g, 5.6 mmol) in 8 mL of $CHCl_3$ at 0 °C. The resulting reaction mixture was stirred at room temperature for 4 h. The solvent and excess TFA were evaporated, and the residue was dissolved in 400 mL of $CHCl_3$. The $CHCl_3$ solution was washed with K_2CO_3 solution (200 mL × 2) and brine. After drying (Na_2SO_4) the organic phase was concentrated and the residue was purified by flash chromatography on a silica gel column (12 × 3 cm). Elution with 100% MeOH and then 50:1 and 20:1 MeOH−30% NH_4-OH afforded library **5** as a pale yellow oil: yield 2.62 g (93%); silica gel TLC R_f 0.32−0.53 (20:1 MeOH−30% NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.30−1.75 (m, 6 H), 2.28−2.72 (m, 8.3 H), 3.35−3.82 (m, 8 H), 3.92 (s, 0.3 H), 6.30−6.70 (m, 0.3 H), 6.90−8.50 (m, 11.1 H); MS (ESI) *m/z* 429−587 $(M + 1)^+$.

General Procedure for the Preparation of Libraries 6−19. A selected benzylic bromide or functionality (1.3 equiv) was added to a stirred mixture of library **5** (1.0 equiv) and anhydrous K_2CO_3 (15 equiv) in anhydrous CH_3CN. The resulting reaction mixture was stirred at room temperature overnight. The solvent was evaporated, and the residue was dissolved in H_2O and $CHCl_3$. The organic phase was separated off, and the aqueous phase was extracted with $CHCl_3$. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by preparative thin layer chromatography (PLC) on a silica gel plate to afford the desired libraries.

Library 12: pale yellow oil; yield 106 mg (85%); ^{1}H NMR ($CDCl_3$) δ 1.15−1.40 (m, 4 H), 1.42−1.65 (m, 2 H), 2.05−2.29 (m, 4 H), 2.36 (s, 0.3 H), 2.46−2.63 (m, 4 H), 3.34 (s, 2 H), 3.58−3.86 (m, 8 H), 3.93 (s, 0.3 H), 6.50−8.45 (m, 15.3 H); MS (ESI) *m/z* 553−712 $(M + 1)^+$.

Library 19. Library **19** was prepared according to the general procedure by stirring the reaction mixture at 60−70 °C for 6 h and then at room temperature for 10 h: colorless oil; yield 112 mg (93%); ^{1}H NMR ($CDCl_3$) δ 1.15−1.42 (m, 4 H), 1.43−1.62 (m, 2 H), 2.28−2.65 (m, 8.3 H), 3.11 (s, 3 H), 3.26 (s, 2 H), 3.55−3.84 (m, 11 H), 3.91 (s, 0.3 H), 6.35−8.42 (m, 11.3 H); MS (ESI) *m/z* 530−688 $(M + 1)^+$.

General Procedure for the Preparation of Compounds 53−62. A mixture of benzylic bromide (2.4 equiv), scaffold **2** (1.0 equiv), and anhydrous K_2CO_3 (15 equiv) in anhydrous CH_3CN was stirred at room temperature overnight. The reaction was worked up by the same procedure as for the preparation of libraries **40−52**. Flash chromatographic purification on silica gel column afforded the desired products.

Compound 54: colorless oil; yield 750 mg (97%); silica gel TLC R_f 0.41 (3:2 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.33−1.55 (m, 13 H), 1.57−1.77 (m, 2 H), 2.50−2.68 (m, 4 H), 2.75−2.98 (m, 2 H), 3.00−3.14 (m, 2 H), 3.61 (s, 2 H), 3.69 (s, 2 H), 3.74 (s, 2 H), 3.76 (s, 2 H), 7.03 (d, 1 H, J = 7.4 Hz), 7.12 (d, 1 H, J = 7.4 Hz), 7.19−7.56 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 23.62, 26.27, 28.54, 46.38, 47.22, 51.94, 59.84, 60.44, 60.71, 78.77, 122.23, 122.54, 126.97, 128.23, 129.05, 136.03, 139.66, 139.83, 155.70, 159.12; MS (FAB) *m/z* 529 $(M + H)^+$; HRMS (FAB) *m/z* 661.250 $(M + Cs)^+$ ($C_{33}H_{44}N_4O_2Cs$ requires 661.251).

Compound 55: colorless oil; yield 1.60 g (94%); silica gel TLC R_f 0.69 (3:2 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.30−1.55 (m, 13 H), 1.57−1.76 (m, 2 H), 2.49−2.67 (m, 4 H), 2.72−2.96 (m, 2 H), 3.07 (t, 2 H, J = 6.8 Hz), 3.59 (s, 2 H), 3.68 (s, 2 H), 3.70 (s, 2 H), 3.74 (s, 2 H), 6.86−7.32 (m, 10 H), 7.51 (t, 1 H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 23.69, 26.25, 28.51, 46.34, 47.21, 51.98, 59.24, 59.89, 60.12, 60.51, 78.80, 113.60, 113.96, 115.44, 115.86, 122.18, 122.48, 124.30, 129.50, 129.66, 136.12, 142.75, 142.99, 155.63, 158.93, 159.14, 160.63, 165.51; MS (FAB) *m/z* 697 $(M + Cs)^+$; HRMS (FAB) *m/z* 565.335 $(M + H)^+$ ($C_{33}H_{43}N_4O_2F_2$ requires 565.335).

General Procedure for the Preparation of Compounds 63−72. Compounds **63−72** were prepared from the corresponding compounds **53−62** by the same procedure as for the preparation of library **5**. Flash chromatographic purification provided the desired products.

Compound 63: pale yellow oil; yield 570 mg (96%); silica gel TLC R_f 0.28 (20:1 MeOH−30% NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.37−1.51 (m, 2 H), 1.52−1.75 (m, 4 H), 2.32−2.45 (m, 8 H), 2.52−2.68 (m, 6 H), 3.61 (s, 2 H), 3.64 (s, 2 H), 3.71 (s, 2 H), 3.73 (s, 2 H), 7.03−7.31 (m, 10 H), 7.54 (t, 1 H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 21.52, 23.00, 25.89, 26.77, 47.54, 47.84, 51.45, 52.96, 59.40, 59.63, 60.13, 60.41, 122.57, 126.19, 127.71, 128.14, 129.80, 136.11, 137.75, 139.67, 139.83, 158.67, 159.37; MS (FAB) *m/z* 589 $(M + Cs)^+$; HRMS (FAB) *m/z* 457.332 $(M + H)^+$ ($C_{30}H_{41}N_4$ requires 457.333). Anal. Calcd for $C_{30}H_{40}N_4$: C, 78.90; H, 8.82; N, 12.27. Found: C, 78.68; H, 8.98; N, 12.06.

Compound 64: pale yellow oil; yield 564 mg (93%); silica gel TLC R_f 0.31 (20:1 MeOH−30% NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.35−1.49

(m, 2 H), 1.50−1.75 (m, 4 H), 2.36 (t, 2 H, J = 5.6 Hz), 2.50−2.70 (m, 6 H), 3.59 (s, 2 H), 3.67 (s, 2 H), 3.69 (s, 2 H), 3.74 (s, 2 H), 7.00−7.15 (m, 2 H), 7.20−7.57 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 23.05, 25.85, 26.66, 47.47, 47.72, 51.39, 52.88, 59.44, 59.67, 60.11, 60.38, 122.59, 126.98, 128.27, 129.07, 136.17, 139.72, 139.92, 158.65, 159.36; MS (FAB) *m/z* 561 $(M + Cs)^+$; HRMS (FAB) *m/z* 429.303 $(M + H)^+$ ($C_{28}H_{37}N_4$ requires 429.301). Anal. Calcd for $C_{28}H_{36}N_4$: C, 78.46; H, 8.45; N, 13.07. Found: C, 78.20; H, 8.21; N, 12.82.

General Procedure for the Preparation of Compounds 73−82. A mixture of cinnamyl bromide (1.1 equiv), anhydrous K_2CO_3 (15 equiv), and the corresponding compounds **63**−**72** in anhydrous CH_3-CN was stirred at room temperature for 2−5 h. The same work-up procedure as for the preparation of libraries **6**−**19** was used and was followed by chromatographic purification on a silica gel column to provide the desired product.

Compound 74: colorless oil; yield 124 mg (41%); silica gel TLC R_f 0.45 (5:1 EtOAc−MeOH); ^{1}H NMR ($CDCl_3$) δ 1.24−1.48 (m, 4 H), 1.50−1.67 (m, 2 H), 2.21 (t, 2 H, J = 5.8 Hz), 2.33 (t, 2 H, J = 6.3 Hz), 2.53−2.68 (m, 4 H), 3.10 (d, 2 H, J = 6.3 Hz), 3.68 (s, 4 H), 3.76 (s, 2 H), 3.79 (s, 2 H), 6.09−6.24 (m, 1 H), 6.46 (d, 1 H, J = 16.0 Hz), 7.15−7.61 (m, 18 H); ^{13}C NMR ($CDCl_3$) δ 24.54, 24.76, 24.96, 51.86, 52.42, 52.58, 54.13, 57.06, 60.29, 60.86, 122.48, 126.32, 126.97, 127.23, 128.29, 128.58, 129.11, 131.66, 136.10, 137.47, 140.02, 159.09, 159.35; MS(FAB) *m/z* 545 $(M + H)^+$; HRMS (FAB) *m/z* 677.264 $(M + Cs)^+$ ($C_{37}H_{44}N_4Cs$ requires 677.262). Anal. Calcd for $C_{37}H_{44}N_4$: C, 81.57; H, 8.14; N, 10.28. Found: C, 81.55; H, 8.09; N, 10.13.

Compound 79: colorless oil; yield 362 mg (30%); silica gel TLC R_f 0.55 (5:1 EtOAc−MeOH); ^{1}H NMR ($CDCl_3$) δ 1.25−1.49 (m, 4 H), 1.50−1.69 (m, 2 H), 2.22 (t, 2 H, J = 5.8 Hz), 2.34 (t, 2 H, J = 6.3 Hz), 2.50−2.70 (m, 4 H), 3.09 (d, 2 H, J = 6.3 Hz), 3.66 (s, 2 H), 3.68 (s, 2 H), 3.71 (s, 2 H), 3.73 (s, 2 H), 6.09−6.25 (m, 1 H), 6.46 (d, 1 H, J = 15.8 Hz), 7.12−7.68 (m, 16 H); ^{13}C NMR ($CDCl_3$) δ 24.40, 24.72, 51.72, 52.37, 52.63, 53.94, 57.14, 59.69, 60.09, 60.31, 60.43, 122.50, 126.32, 127.14, 128.38, 128.59, 129.06, 129.55, 131.80, 134.24, 136.25, 137.40, 142.35, 158.87, 158.99; MS (FAB) *m/z* 745 $(M + Cs)^+$; HRMS (FAB) *m/z* 613.284 $(M + H)^+$ ($C_{37}H_{43}N_4Cl_2$ requires 613.286). Anal. Calcd for $C_{37}H_{42}N_4Cl_2$: C, 72.42; H, 6.90; N, 9.13. Found: C, 72.42; H, 6.68; N, 8.99.

Acknowledgment. The authors thank Professor Michael E. Jung and Dr. Thomas W. Bruice for their stimulating scientific discussions. High-resolution (FAB) and electrospray ionization mass spectrometry were provided by The Scripps Research Institute Mass Spectrometry.

Supporting Information Available: Characterization of libraries **42**−**52**, **6**−**11**, and **13**−**18** and compounds **53**, **56**−**62**, **65**−**73**, **75**−**78**, **80**−**82**, capillary zone electrophoresis profiles of libraries **51** and **52**, and NMR spectra of compounds **22**, **24**, **3**, and **39** (21 pages). See any current masthead page for ordering and Internet access instructions.

JA964153R