Solution Phase Combinatorial Chemistry. Synthesis of Novel Linear Pyridinopolyamine Libraries with Potent Antibacterial Activity

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Novel linear pyridinopolyamine derivatives **1**−**3**, **7**, and **8** have been synthesized as scaffolds for combinatorial drug discovery. The mono-*t*-Boc- and monotosyl-protected linear scaffolds **1** and **2** were obtained by a Schiff base type cyclization of 2,6-pyridinedicarboxaldehyde (**24**) with monoprotected triamines **22** and **23** using Ni^{2+} as a metal template, followed by reductive cleavage and decomplexation in a one-pot procedure. The unprotected linear scaffold **3** was obtained by treating **1** with TFA. Scaffold **1** was also synthesized from the orthogonally protected pyridinopolyamine **7** which was constructed from 2,6-bis(bromomethyl)pyridine (**29**) in four steps. Selective deprotection of the key intermediate **7** afforded **8**, which was further selectively deprotected to give scaffold **1**. A combinatorial chemistry strategy involving solution phase simultaneous addition of functionalities (SPSAF) is described. Thirteen high-purity tertiary amine libraries (**9**−**21**) (total 1638 compounds) were synthesized by the SPSAF and fix last methodologies from linear polyamine scaffolds **1** and **2**. All libraries were examined by TLC, purified by chromatographic techniques, and characterized by ^{1}H NMR and ESI MS spectral data. A fix last methodology was utilized to minimize chemical reactions and perform SAR studies directly on libraries. Several first-round sublibraries of scaffold **1**, containing 126 compounds each, exhibited potent antibacterial activity with MICs of 1−12 μM against *Streptococcus pyogenes* and *Escherichia coli imp*$^-$.

Introduction

Combinatorial chemistry has received considerable attention as a potential tool for drug discovery and lead optimization.[1,2] Initial combinatorial libraries have been composed of a variety of oligomeric materials such as peptides,[3] nucleotides,[4] saccharides,[5] ureas,[6] peptoids,[7] and carbamates[8] obtained from solid phase synthesis. However, since oligomeric materials generally have unfavorable pharmacokinetic properties as therapeutic agents, more recent efforts have focused on the generation of chemical libraries of small organic molecules.[9−11] Along with this new direction, a variety of solid support synthesis techniques have evolved.[11,12] Interestingly, solution phase combinatorial methodologies, relative to solid support procedures, have not been widely

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explored.[13−15] Furthermore, combinatorial chemistry research has primarily focused on polypeptide backbones and known pharmacophores.[16−19] In contrast to these approaches, we have elected to not base our combinatorial libraries on known structures or pharmacophores but to search novel structure space with a variety of scaffolds which provide various shapes (footprints). Also, we believe solution phase procedures offer significant advantages over solid phase methods[20] and we have recently described a new solution phase simultaneous addition of functionalities (SPSAF) combinatorial strategy for the preparation of chemical libraries.[21,22] By this approach, a series of high-purity libraries were generated from unsymmetrical, novel polyazaphane scaffolds. One of these polyazaphanes was prepared containing an oxyamine (N−O) moiety in the polyamine portion of the polyazaphane which provides a cleavable linkage for generating libraries from libraries.

In the present work, we have elected to isolate the linear unsubstituted scaffold that would be generated from the polyazaphane by a libraries from libraries approach and combinatorialize it directly according to the SPSAF approach. This required the design and synthesis of linear pyridinopolyamines scaffolds **1**−**3** (Figure 1). After model studies based on the synthesis of small libraries which could be carefully analyzed, 13 high-purity linear tertiary amine libraries (**9**−**21**) (Figure 1, Schemes 5 and 6) were synthesized from scaffolds **1** and **2** by the SPSAF approach. Initial antibacterial screening results of the first-round sublibraries are also disclosed.

Results and Discussion

The monoprotected triamines **22** and **23**[23] were cyclized with 2,6-pyridinedicarboxaldehyde (**24**) by using Ni^{2+} cation as a metal template (Scheme 1). The cyclic nickel complexes **25** were directly reduced by $NaBH_4$ without isolation. In this process, the Schiff base double bonds were reduced along with reductive cleavage of the N−O bond in the macrocyclic complexes to give complexes **26**. Direct decomplexation of **26** with NaCN followed by NaOH treatment gave desired linear pyridinopolyamine products **1** and **2** in 26% and 21% yields, respectively. The linear structures of product **1** and **2** were established by ^1H and ^{13}C NMR and HR(FAB) MS spectral data, and combustion analyses. In order to characterize scaffolds **1** and **2**, various derivatives were prepared (Schemes 1 and 2). Treatment of *t*-Boc-protected scaffold **1** with trifluoroacetic acid (TFA) gave the corresponding completely deprotected scaffold **3**. Compound **3** was reacted with benzyl bromide under weak carbonate basic condi-

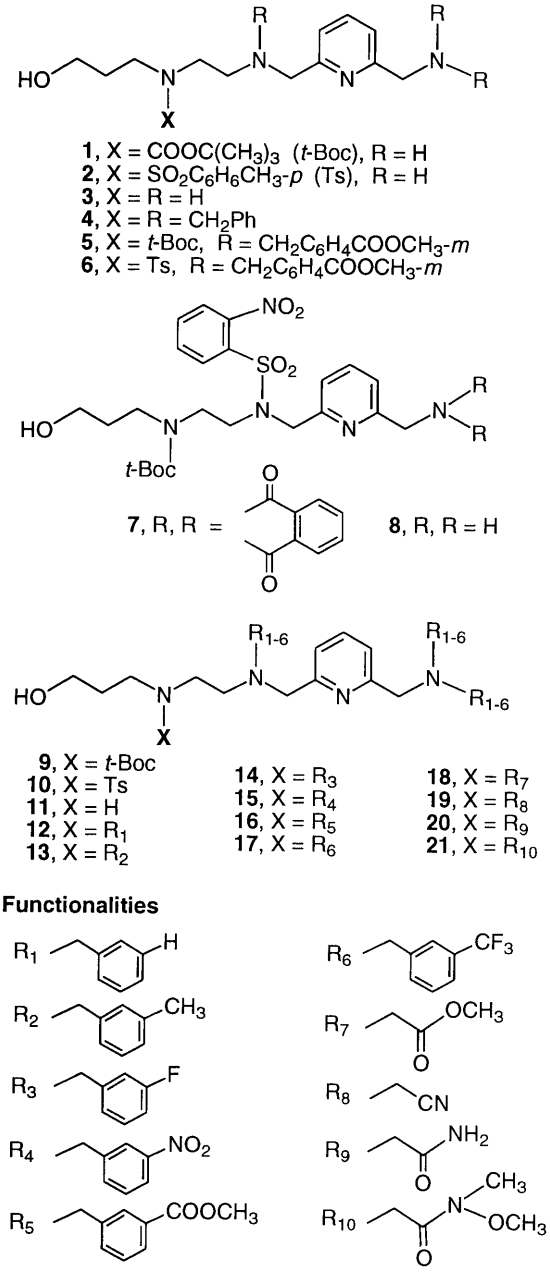

Figure 1. New linear pyridinopolyamine derivatives and libraries.

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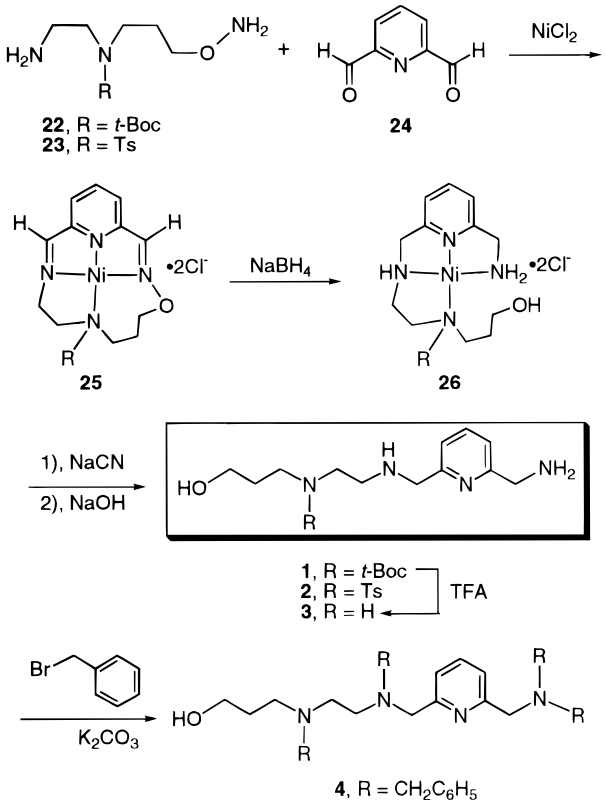
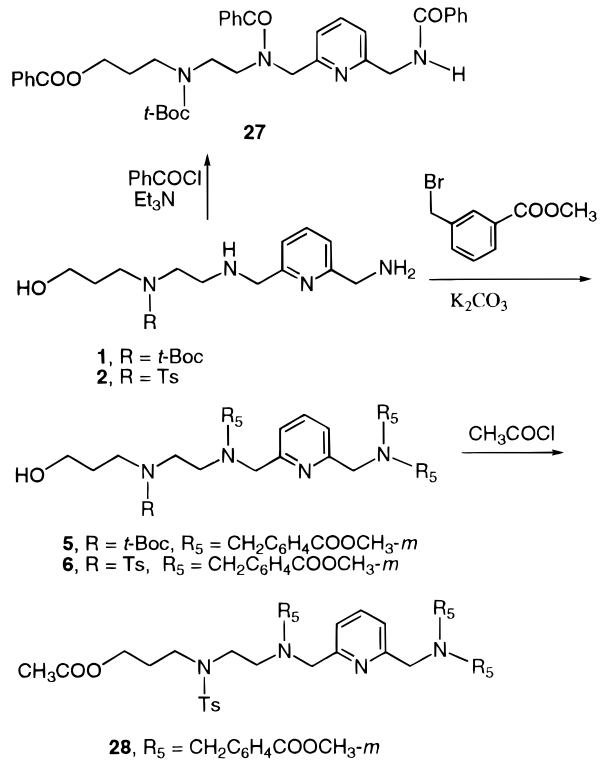
Scheme 1

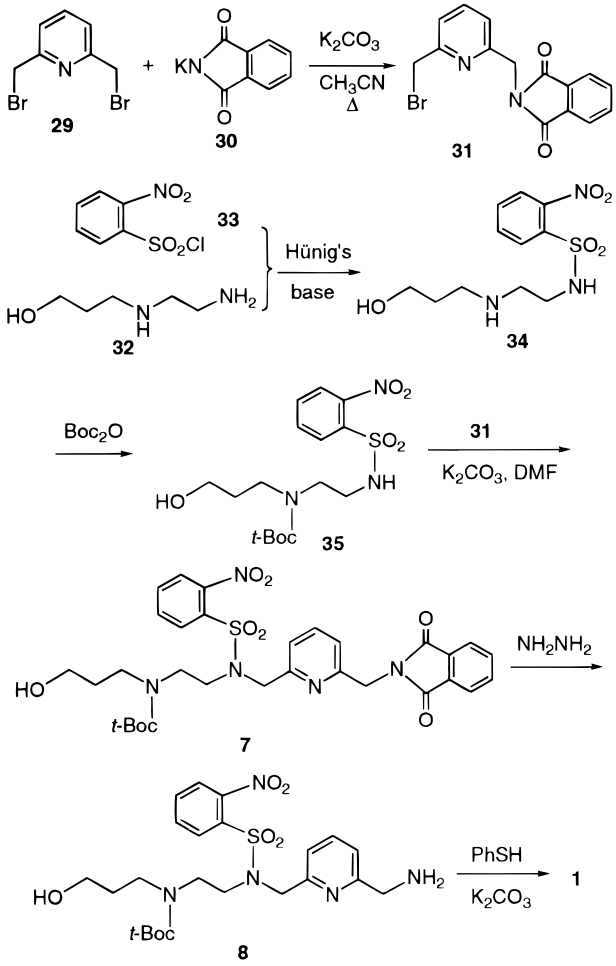


Scheme 2



tion to give the tetrabenzylated derivative **4**. When compound **1** was treated with excess benzoyl chloride in the presence of Et_3N, the corresponding tetrabenzoylated product **27** was obtained (Scheme 2). When compound **1** was reacted with 1.98 equiv of methyl 3-(bromomethyl)benzoate, the trialkylated product **5** and dialkylated product were isolated. The trialkylated product **6** was also obtained by the reaction of **2** with methyl 3-(bromomethyl)benzoate. Compound **6** was further treated with an excess amount of acetyl chloride. The hydroxyl group of **6** was the only reactive site left and reacted with acetyl chloride to give the corresponding ester **28**. Derivatives **3**−**6**, **27**, and **28** were all characterized by NMR and HRMS spectroscopic techniques. The structures of these derivatives further confirmed the linear structure of compounds **1** and **2**. If the N−O bond in complexes **25** was not cleaved, the corresponding macrocyclic compounds would be produced after decomplexation instead of the linear compounds **1** and **2**. The corresponding macrocyclic compound of linear compound **1** was synthesized by another method.[21,22] The linear compound **1** showed completely different ^1H and ^{13}C NMR spectral and chromatographic properties from those of the corresponding macrocyclic compound.[22]

Scheme 3



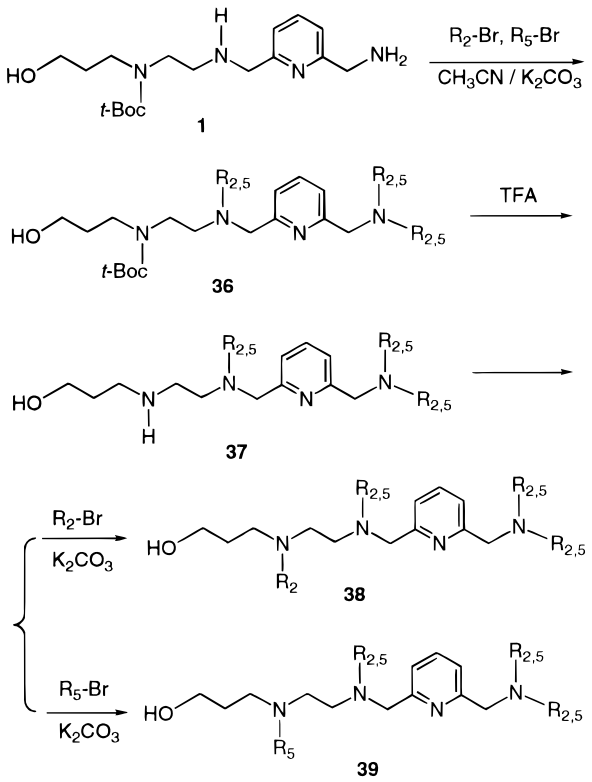
This one-pot procedure for the synthesis of scaffold **1** (Scheme 1) is convenient; however, starting material **22** is difficult to prepare.[23] In order to fully utilize pyridinopolyamine **1** for expanded combinatorial library studies and for subsequent iterative deconvolutions, we have designed another synthetic route (Scheme 3) which provided scaffold **1** through the orthogonally protected compound **7**. The reaction of 2,6-bis(bromomethyl)pyridine (**29**) with 1.1 equiv of potassium phthalimide (**30**) using K_2CO_3 as the base gave 2-(bromomethyl)-6-(phthalimidomethyl)pyridine (**31**). Treatment of *N*-(3-hydroxypropyl)ethylene diamine (**32**) with 1.0 equiv of 2-nitrobenzenesulfonyl chloride (**33**) in the presence of diisopropylethylamine afforded the desired monoprotected product **34** in a 57% yield. Compound **34** was

treated with di-*tert*-butyl dicarbonate to give diprotected product **35** in a 93% yield. Sulfonamide **35** was alkylated with bromide **31** at rt under weak carbonate basic condition. The orthogonally protected product **7** was obtained in an 88% yield. This key intermediate (**7**) contains three different protecting groups, each of which can be selectively removed under mild conditions without affecting the other two. Compound **7** was selectively deprotected with hydrazine, providing the corresponding diprotected product **8**. Further selective deprotection of compound **8** with thiophenol[24] in the presence of K_2CO_3 gave the scaffold **1**. Monoprotected compound **1** obtained by this route shows the same chromatographic and spectroscopic properties as those of compound **1** synthesized by the previous route (Scheme 1). New compounds **31**, **34**, **35**, **7**, and **8** were all characterized by ^1H and ^{13}C NMR and HRMS spectroscopies.

The unprotected parent scaffold **3** can be used as the scaffold to make libraries directly; however, we elected to use monoprotected derivatives **1** and **2** as scaffolds in a fix last combinatorial methodology which allows iterative deconvolution. Six different benzyl bromide derivatives (see Figure 1 for structural details) have been determined by capillary electrophoresis techniques to be desirable functionalities (electrophiles) to add in a simultaneous manner.[22]

Model studies with two functionalities (Scheme 4) were first carried out in order to find appropriate reaction, workup, and chromatographic conditions for each library preparation step. Electrophiles R_2Br ($BrCH_2C_6H_4CH_3$-*m*) and R_5Br ($BrCH_2C_6H_4COOCH_3$-*m*) were chosen as initial functionalities for model studies because the quality of these libraries could readily be assessed by ^1H NMR due to the distinct methyl groups. In addition, these differential electron-donating and -withdrawing functional groups would represent the range of influences of other groups. A equal molar mixture of R_2Br and R_5Br (total 4 equiv) was added to a stirred mixture of scaffold **1** and anhydrous K_2CO_3 in CH_3CN (Scheme 4). After overnight reaction and general workup, the crude reaction mixture was purified by flash chromatography[25] on a silica gel column to give pure library **36** in a 93% yield.[26] Library **36** containing six compounds[27] with four different molecular weights was confirmed by ^1H NMR and ESI MS spectral data.[28] The ^1H NMR spectrum of library **36** showed the right ratio for different protons in the library and 1:1 ratio for CH_3 and $COOCH_3$ protons. ESI MS spectrum showed all four peaks with expected masses $[M + H]^+$ and four $[M + Na]^+$ peaks representing the sodium contamination. The $[M + Na]^+$ peaks generally

Scheme 4



were not present in other libraries. The sodium contamination, probably introduced during the workup, did not influence the purity of libraries. Deprotection of library **36** with TFA afforded intermediate library **37** which showed the expected four peaks in the MS spectrum. Library **37** was divided into two parts which were treated with two selected electrophiles R_2Br and R_5Br using K_2CO_3 as the base to give final libraries **38** and **39**, respectively, after chromatographic purification. Libraries **38** and **39** were all confirmed by ^1H NMR and ESI MS spectra.

After successful preparation of model libraries from scaffold **1** and selected functionalities, six functionalities were used to prepare larger libraries (Scheme 5). A solution containing equal molar amounts of six benzylic bromides R_xBr ($x = 1-6$, 1.0 mmol each for a total of 6.0 mmol, 3.6 equiv) in CH_3CN was added to the reaction mixture containing scaffold **1** and K_2CO_3. After overnight reaction and aqueous workup, library **9** was obtained in a 76% yield[26] following flash chromatographic purification. Combinatorialization of the three nitrogenous reactive sites of scaffold **1** with six different functionalities results in a library containing 126 different compounds instead of 216 (6^3) compounds because of the C_2 symmetry of the primary amine.[27] Library **9** was verified by ^1H NMR and ESI MS in which all peaks fall in a range between the smallest molecular weight and the largest molecular weight (see Experimental Section). Library **10** was similarly obtained in a 71% yield. Because the *t*-Boc protecting group in library **9** is easily removed compared to the tosyl group in library **10**, the *t*-Boc-protected intermediate library **9** was used for further preparation of other sublibraries. Library **9** was treated with TFA to afford the corresponding library **11** in a 95% yield. This key intermediate library **11** with the last reactive site was reacted with 1.5 equiv of benzyl bromide (R_1Br) to give the final library **12** in a 70% yield after preparative thin layer chromatographic (TLC) purification.[25] Final

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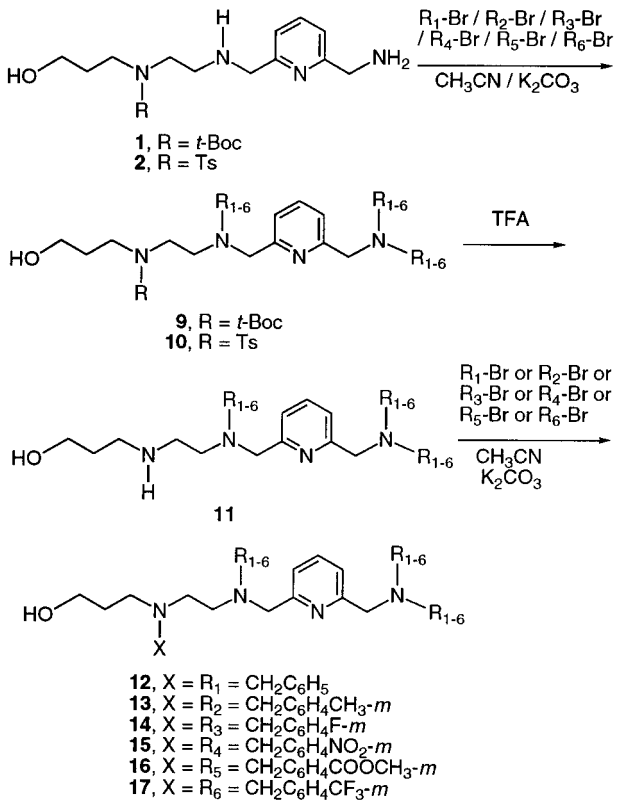
(25) The column loaded with crude library was eluted with a less polar solvent to remove the excess benzyl bromide derivatives and then eluted with more polar solvents to completely remove the library. All fractions containing library compounds were collected. The preparative thin layer chromatography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

(26) 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.

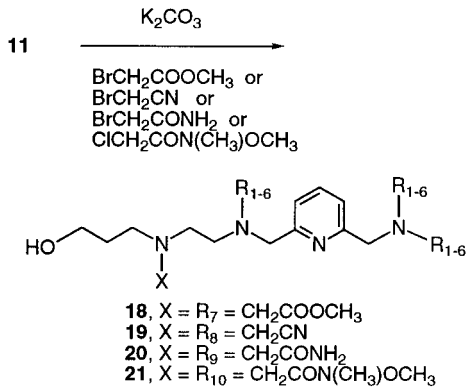
(27) A scaffold with *n* unsymmetric sites was combinatorialized with *m* functionalities to give a library containing m^n compounds. A scaffold with *n* sites and one C_2 symmetric element was combinatorialized with *m* functionalities to give a library containing $[m^{n-1}(m + 1)]/2$ compounds.

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

Scheme 5



Scheme 6



libraries **13**−**17** were prepared under similar conditions by parallel reactions of the intermediate library **11** with five other functionalities R_xBr ($x = 2-6$). These libraries differ by the functionality on the last fixed position as required in our iterative deconvolution process. The ESI mass spectrum of library **15** shows all 52 distinct peaks out of 126 compounds in the range from the smallest molecular weight 643 to the largest molecular weight 847. Computer simulation[22] of library **15** exhibits almost the same mass spectrum (Supporting Information).

To introduce new functionalities and increase the diversity of libraries, the intermediate library **11** having the last position available was further reacted with methyl α-bromoacetate (R_7Br), bromoacetonitrile (R_8Br), and α-bromoacetamide (R_9Br) under similar conditions to afford the corresponding libraries **18**, **19**, and **20**, respectively (Scheme 6). Library **11** was reacted with commercially available 2-chloro-*N*-methoxy-*N*-methylacetamide ($R_{10}Cl$) at 50−60 °C for 24 h to give the library **21**. More polar developing agents were used for preparative TLC purification of libraries **20** and **21** due to the increased polarity of the libraries. All libraries described above were monitored by TLC, purified by chromatographic techniques,[25] and verified by ^{1}H NMR and ESI MS spectra.[28] The fix last combinatorial methodology allows SAR studies to be performed directly on libraries and thus further increases the diversity. The functionalities placed in the fixed position are "positionally biased" in that they are not combinatorialized throughout the other positions.

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

library	complexity	*S. Pyogenes*	*E. coli imp*$^-$	*C. albicans*
9	126	>100	>100	
10	126	>100	>100	
11	126	1−5	1−5	5−25
12	126	1−5	1−5	5−25
13	126	>100	>100	
14	126	>100	>100	
15	126	>100	>100	
16	126	>100	>100	
17	126	>100	>100	
18	126	>100	>100	
19	126	5−12	5−25	25−50
20	126	12−25	5−25	>100
21	126	5−12	5−25	25−50
2	1	>100	>100	
3	1	>100	>100	
4	1	5−25	5−25	1−5

[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, complete growth was observed at lower bound of the given MIC and no growth was observed at the upper bound. Ampicillin and tetracycline were used as antibacterial references for *S. pyogenes* and *E. coli imp*$^-$. Amphotericin B was used as antifungal reference for *C. albicans*.

Table 1 shows the antibacterial activity of libraries **9**−**21** and single compounds **2**−**4** in growth inhibition assays. The activity was expressed by minimum inhibitory concentration (MIC) in μM. All samples were screened against *Streptococcus pyogenes* and *Escherichia coli imp*$^-$ bacterial antigrowth assays. The highest concentration tested was 100 μM. At this concentration libraries **9**, **10**, and **13**−**18** and compounds **2** and **3** did not exhibit inhibition. Libraries **11** and **12** showed strong inhibition against *S. pyogenes* and *E. coli imp*$^-$ with MIC of 1−5 μM. Libraries **19**−**21** and tetrabenzyl-substituted compound **4** were inhibitory against the bacteria with MICs of 5−12 to 12−25 μM. Results from the *Candida albicans* assay indicated that library **20** is more specific against bacteria than other active libraries. Strong inhibition of compound **4** against *C. albicans* indicated its potent antifungal activity. These results indicated that two of nine original libraries (**9**−**17**) and three of four extended libraries (**18**−**21**) show potential antibacterial activity against *S. pyogenes* and *E. coli imp*$^-$ with MICs in the micromolar range. Even though only one set of functionalities was described in this paper to illustrate the SPSAF and fix last methodologies, various other functionalities can easily be introduced to generate other diverse libraries. A significant advantage of this approach is that large quantities of libraries are readily prepared which provide material for other assays and for the conversion of one library into another library. Further studies on the preparation of new libraries based on this linear scaffold, biological screening for various assays, and iterative deconvolution of active libraries will be reported in due course.

In conclusion, we have synthesized novel linear pyridinopolyamine derivatives **1** and **2** by the cycliczation of monoprotected triamines **22** and **23** with 2,6-pyridinedicarboxaldehyde (**24**) followed by reductive cleavage and decomplexation in a one-pot procedure. Scaffold **1** was also synthesized by another route through orthogonally protected key intermediates **7** and **8**. Intermediate **7** with three different protecting groups can be used for the preparation of various combinatorial libraries and for the deconvolution of active libraries to find lead compounds. Scaffold **1** can be used to make various libraries with different types of functionalities by different reactions. Solution phase simultaneous addition of functionalities (SPSAF) combinatorial approach was extensively utilized to generate 13 libraries with high purity from the linear scaffold. The quality of libraries was judged by TLC and ^{1}H NMR and ESI MS spectroscopic techniques. Large quantities of libraries are available for future screening. A fix last combinatorial methodology was used to make more diverse libraries, perform SAR studies directly on libraries, and more effectively find active libraries. The methodologies we described here can be used to generate various other combinatorial libraries for drug discovery. Libraries **11**, **12**, and **19**−**21** show potent antimicrobial activity against *S. pyogenes* and *E. coli imp*$^-$ in MICs of low μM ranges.

Experimental Section

Proton and carbon NMR spectra were recorded at 199.975 MHz unless otherwise indicated. N^5-(*tert*-Butoxycarbonyl)-1,7-diamino-1-oxa-5-azaheptane (**22**)[23] and N^5-tosyl-1,7-diamino-1-oxa-5-azaheptane (**23**)[23,29] were prepared according to our documented procedure. Other starting materials were purchased from Aldrich and TCI America Chemical Companies. The bacterial and yeast antigrowth assays were performed in 96-well plate format in 150 μL volume in the presence of library or relevant antibiotic or antifungal controls.[30] 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 1× Todd-Hewitt broth. The *E. coli imp*$^-$ strain was a kind gift of Spencer Bensen and was grown in 1/2× LB.[31] The *C. albicans* was ATCC #10231 and was grown in YM media.

3-[[2-[[[6-(Aminomethyl)-2-pyridinyl]methyl]amino]-ethyl](*tert*-butoxycarbonyl)amino]-1-propanol (1). A solution of **22**[23] (2.50 g, 10.7 mmol) in 15 mL of EtOH was added to a stirred solution of $NiCl_2 \cdot 6H_2O$ (2.55 g, 10.7 mmol) in 60 mL of EtOH−H_2O (1:1). 2,6-Pyridinedicarboxaldehyde (**24**) (1.45 g, 10.7 mmol) was added to the above blue solution followed by glacial AcOH (1.0 mL). The resulting deep blue solution was stirred at rt for 2 h and then at 80 °C for 6 h. The solution was cooled to 0 °C, and then $NaBH_4$ (2.0 g, 52.0 mmol) was added in portions. The reaction mixture was stirred at rt overnight and at 80 °C for 2 h. The cooled reaction mixture was concentrated under reduced pressure to remove EtOH. The reaction mixture was diluted with 30 mL of H_2O, and NaCN (4.9 g, 100 mmol) was added. The resulting mixture was stirred at 80 °C for 1 h. The cooled reaction mixture was basified to pH 13−14 with aqueous NaOH and then extracted with $CHCl_3$. The combined organic phase was washed with brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography on a silica gel column. Elution with 100% MeOH and then 100:1 MeOH−30% NH_4OH gave 0.94 g (26%) of product **1** as a pale yellow oil: silica gel TLC R_f 0.40 (30:1 MeOH−30% NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 9H), 1.50−1.65 (m, 2H), 2.50 (br, 1H, ex D_2O), 2.77 (t, 2H, J = 6.2 Hz), 3.10−3.28 (m, 4H), 3.35−3.48 (m, 2H), 3.83 (s, 2H), 3.88 (s, 2H), 7.08 (d, 2H, J = 7.5 Hz), 7.54 (t, 1H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 28.4, 31.0, 43.8, 47.7, 48.0, 54.9, 58.7, 79.9, 119.4, 120.2, 136.9, 156.5, 159.0, 161.4; MS (EI) m/z 338 (M)$^+$; MS (CI$^+$ and FAB$^+$) m/z 339 (M + 1)$^+$; MS (CI$^-$) m/z 337 (M − 1)$^-$; HRMS (EI) m/z 338.231 (M)$^+$ ($C_{17}H_{30}N_4O_3$ requires 338.231). Anal. Calcd for $C_{17}H_{30}N_4O_3$: C, 60.33; H, 8.93. Found: C, 60.75; H, 8.86.

3-[[2-[[[6-(Aminomethyl)-2-pyridinyl]methyl]amino]-ethyl](tosyl)amino]-1-propanol (2). Pyridinopolyamine **2** was prepared as above for **1** from **23**[23,29] (1.0 g, 3.8 mmol), 10 mL of EtOH, $NiCl_2 \cdot 6H_2O$ (0.88 g, 3.7 mmol), **24** (0.5 g, 3.7 mmol), and 30 mL of EtOH−H_2O (1:1). Chromatographic purification of the crude product gave 0.30 g (21%) of product **2** as a pale yellow oil: silica gel TLC R_f 0.42 (30:1 MeOH−30% NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.65−1.80 (m, 2H), 2.36 (s, 3H), 2.77 (t, 2H, J = 6.0 Hz), 3.05−3.20 (m, 4H), 3.55 (t, 2H, J = 5.7 Hz), 3.79 (s, 2H), 3.86 (s, 2H), 7.05 (d, 2H, J = 7.6 Hz), 7.21 (d, 2H, J = 8.0 Hz), 7.51 (t, 1H, J = 7.6 Hz), 7.61 (d, 2H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 21.5, 31.9, 46.7, 47.4, 48.1, 49.5, 54.5, 58.5, 119.7, 120.5, 127.3, 129.7, 135.7, 137.1, 143.4, 158.6, 161.0; HRMS (FAB) m/z 393.197 (M + 1)$^+$ ($C_{19}H_{29}N_4SO_3$ requires 393.196). Anal. Calcd for $C_{19}H_{28}N_4O_3S$: C, 58.14; H, 7.19. Found: C, 58.08; H, 6.97.

3-[[2-[[[6-(Aminomethyl)-2-pyridinyl]methyl]amino]-ethyl]amino]-1-propanol (3). CF_3COOH (5 mL) was added dropwise to a stirred solution of **1** (190 mg, 0.56 mmol) in 2 mL of CH_2Cl_2 at 0 °C. The resulting reaction mixture was stirred at rt for 4 h. The solvent was evaporated, and the residue was purified by flash chromatography on a silica gel column. Elution with 100% MeOH and then 10:1 MeOH−30% NH_4OH afforded 75 mg (56%) of the title compound **3** as a colorless oil: silica gel TLC R_f 0.40 (5:1 MeOH−30% NH_4OH); ^{1}H NMR ($CDCl_3$) δ 1.57−1.72 (m, 2H), 2.57 (br, 5H), 2.65−2.88 (m, 6H), 3.69 (t, 2H, J = 5.6 Hz), 3.81 (s, 2H), 3.88 (s, 2H), 7.07 (dd, 2H, J = 7.6, 2.8 Hz), 7.53 (t, 1H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 31.3, 47.7, 48.8, 49.0, 49.4, 55.0, 63.2, 119.4, 120.3, 136.9, 159.22, 161.4; HRMS (FAB) m/z 239.187 (M + 1)$^+$ ($C_{12}H_{23}N_4O$ requires 239.187).

3-[[2-[Benzyl[[6-[[dibenzylamino]methyl]-2-pyridinyl]methyl]amino]ethyl]benzylamino]-1-propanol (4). A mixture of **3** (37 mg, 0.155 mmol), anhydrous K_2CO_3 (0.20 g, 1.4 mmol), and benzyl bromide (78 μL, 112 mg, 0.66 mmol, 4.25 equiv) in 5 mL of anhydrous CH_3CN and 2 mL of anhydrous DMF was stirred at rt overnight. The solvent was evaporated under vacuum, and the residue was dissolved in H_2O and $CHCl_3$. The layers were separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic phase was washed with brine and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by preparative thin layer chromatography (PLC) on a silica gel plate using 15:1 EtOAc−MeOH as the developing agent affording 46 mg (51%) of the title compound **4** as a pale yellow oil: silica gel TLC R_f 0.43 (20:1 EtOAc−MeOH); ^{1}H NMR ($CDCl_3$) δ 1.56−1.75 (m, 2H), 2.50−2.75 (m, 6H), 3.45−3.85 (m, 14H), 7.12−7.70 (m, 23H); HRMS (FAB) m/z 599.377 (M + 1)$^+$ ($C_{40}H_{47}N_4O$ requires 599.375).

3-[[2-[Benzoyl[[6-[(benzoylamino)methyl]-2-pyridinyl]methyl]amino]ethyl](*tert*-butoxycarbonyl)amino]-1-propyl Benzoate (27). Benzoyl chloride (0.5 mL, 0.71 g, 4.2 mmol) was added dropwise at rt to a stirred solution of **1** (40 mg, 0.11 mmol) in 5 mL of $CHCl_3$ containing 0.5 mL of Et_3N. After being stirred at rt for 1 h, the reaction mixture was diluted with $CHCl_3$. The solution was washed with aqueous $NaHCO_3$ and brine. The dried (Na_2SO_4) $CHCl_3$ solution was concentrated under reduced pressure, and the residue was purified by flash chromatography on a silica gel column. Elution with 1:1 hexanes−EtOAc and then 100% EtOAc afforded 60 mg (78%) of the tribenzoylated derivative **27** as a pale yellow oil: silica gel TLC R_f 0.30 (1:2 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 9H), 1.70 (m, 2H), 3.20−3.70 (m, 6H), 4.25−4.38 (m, 2H), 4.74 (s, 2H), 4.77 (s, 2H), 7.00−8.10 (m, 18H); MS (ESI) m/z 651 (M + 1)$^+$, 673 (M + Na)$^+$.

(29) An, H.; Guinosso, C. J.; Fraser, A. S.; Cook, P. D. *J. Heterocyc. Chem.* Submitted.

(30) 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.

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

Preparation of Compound 5. Compound **5** was prepared as above for **4** from **1** (100 mg, 0.29 mmol), K_2CO_3 (170 mg, 1.23 mmol), and methyl 3-(bromomethyl)benzoate (135 mg, 0.59 mmol, 1.98 equiv) in 17 mL of CH_3CN. The crude product was purified by flash chromatography on a silica gel column. Elution with 1:1 hexanes−EtOAc and then 100% EtOAc afforded 90 mg (39%) of tribenzylated product **5** as a colorless oil: silica gel TLC R_f 0.52 (100% EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 9H), 1.40−1.60 (m, 2H), 2.56−2.68 (m, 2H), 3.15−3.35 (m, 4H), 3.38−3.54 (m, 2H), 3.58−3.78 (m, 10H), 3.88, 3.89 (s, 9H), 7.30−7.48 (m, 4H), 7.50−7.70 (m, 4H), 7.83−8.07 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 28.2, 30.5, 43.1, 45.0, 52.1, 57.9, 58.2, 58.7, 59.7, 60.4, 80.0, 121.0, 128.4, 129.7, 129.9, 130.2, 133.3, 137.1, 139.5, 139.7, 156.7, 158.7, 158.9, 167.1; MS (ESI) m/z 783 $(M + 1)^+$.

The column was further eluted with 10:1 and then 5:1 EtOAc−MeOH, giving 80 mg (42%) of the dibenzylated product as pale yellow oil: silica gel TLC R_f 0.42 (5:1 EtOAc−MeOH); ^{1}H NMR ($CDCl_3$) δ 1.28 (s, 9H), 1.45−1.60 (m, 2H), 2.64 (t, 2H, J = 6.5 Hz), 2.88 (br, 1H, NH), 3.15−3.32 (m, 4H), 3.38−3.50 (m, 2H), 3.70 (s, 2H), 3.76 (s, 2H), 3.80−3.95 (m, 10H), 7.08−7.18 (m, 1H), 7.27−7.42 (m, 3H), 7.46−7.68 (m, 3H), 7.83−8.05 (m, 4H); MS (ESI) m/z 635 $(M + 1)^+$.

3-[[2-[3-(Methoxycarbonyl)benzyl[[6-[[bis[(3-methoxycarbonyl)benzyl]amino]methyl]-2-pyridinyl]methyl]amino]ethyl]tosylamino]-1-propanol (6). Derivative **6** was prepared as above for **5** from **2** (130 mg, 0.33 mmol), methyl 3-(bromomethyl)benzoate (137 mg, 0.6 mmol), and K_2CO_3 (0.20 g, 1.4 mmol) in 8 mL of CH_3CN. Chromatographic purification afforded 110 mg (49%) of trisubstituted product **6** as a colorless oil: silica gel TLC R_f 0.37 (1:2 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.48−1.60 (m, 2H), 2.35 (s, 3H), 2.60−2.76 (m, 2H), 3.07−3.25 (m, 4H), 3.48−3.60 (m, 2H), 3.64 (s, 4H), 3.67 (s, 2H), 3.71 (s, 2H), 3.75 (s, 2H), 3.90, 3.91 (ss, 9H), 7.14−7.70 (m, 13H), 7.84−8.08 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 21.5, 31.3, 45.6, 46.8, 52.1, 52.8, 57.9, 58.7, 59.7, 60.3, 121.1, 121.4, 127.0, 128.4, 129.7, 130.0, 130.2, 133.4. 133.5, 136.8, 137.1, 139.5, 143.2, 158.3, 158.9, 167.1; MS (ESI) m/z 837 $(M + 1)^+$; HRMS (FAB) m/z 837.356 $(M + 1)^+$ ($C_{46}H_{52}N_4SO_9$ requires 837.353).

3-[[2-[[3-(Methoxycarbonyl)benzyl][[6-[[bis[(3-methoxycarbonyl)benzyl]amino]methyl]-2-pyridinyl]methyl]amino]ethyl]tosylamino]-1-propyl Acetate (28). Acetyl chloride (0.5 mL) was added dropwise to a stirred solution of **6** (40 mg, 47 μmol) and Et_3N (0.5 mL) in 5 mL of $CHCl_3$. The resulting reaction mixture was stirred at rt for 1 h and diluted with $CHCl_3$ (50 mL). The $CHCl_3$ solution was washed three times with aqueous $NaHCO_3$ and once with brine. The dried (Na_2SO_4) organic phase was concentrated under reduced pressure, and the residue was purified by flash chromatography on a silica gel column. Elution with 2:1 hexanes−EtOAc and then 100% EtOAc afforded 40 mg (95%) of acetate product **28** as a pale yellow oil: silica gel TLC R_f 0.42 (1:1 hexanes−ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 1.55−1.70 (m, 2H), 1.94 (s, 2H), 2.37 (s, 3H), 2.60−2.73 (m, 2H), 2.99−3.10 (m, 2H), 3.13−3.25 (m, 2H), 3.25−3.40 (m, 2H), 3.64 (s, 4H), 3.67(s, 2H), 3.71 (s, 2H), 3.76 (s, 2H), 3.90, 3.91 (ss, 9H), 7.20 (d, 2H, J = 8.3 Hz), 7.30−7.70 (m, 9H), 7.85−8.10 (m, 6H); MS (FAB) m/z 879 $(M + H)^+$; HRMS (FAB) m/z 1011.258 $(M + Cs)^+$ ($C_{48}H_{54}N_4SO_{10}Cs$ requires 1011.261).

2-(Bromomethyl)-6-(phthalimidomethyl)pyridine (31). A mixture of 2,6-bis(bromomethyl)pyridine (**29**) (10.0 g, 37.7 mmol), potassium phthalimide (**30**) (7.69 g, 41.5 mmol, 1.1 equiv), and anhydrous K_2CO_3 (15.6 g, 113.2 mmol, 3.0 equiv) in 480 mL of anhydrous CH_3CN was heated at reflux for 24 h. The solvent was evaporated, and the residue was dissolved in 400 mL of H_2O. The mixture was extracted with CH_2Cl_2 (2 × 400 mL). The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column. Elution with 7:3 and then 4:6 hexanes−EtOAc gave 4.82 g (39%) of product **31** as white crystals: mp 137−138 °C; silica gel TLC R_f 0.52 (4:6 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.47 (s, 2H), 5.00 (s, 2H), 7.14 (d, 1H, J = 7.6 Hz), 7.34 (d, 1H, J = 7.6 Hz), 7.64 (t, 1H, J = 7.6 Hz), 7.74−7.77 (m, 2H), 7.89−7.91 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 33.7, 42.8, 120.3, 122.2, 123.5, 132.2, 134.1, 137.7, 155.2, 156.6, 168.1; HRMS (FAB) m/z 331.007 $(M + 1)^+$ ($C_{15}H_{12}N_2O_2Br$ requires 331.008). Anal. Calcd for $C_{15}H_{11}N_2O_2Br$: C, 54.40; H, 3.35; N, 8.46. Found: C, 54.29; H, 3.33; N, 8.23.

3-[[2-[(2-Nitrobenzenesulfonyl)amino]ethyl]amino]-1-propanol (34). A solution of 2-nitrobenzenesulfonyl chloride (**33**) (46.9 g, 211 mmol, 1.0 equiv) in 500 mL of CH_2Cl_2 was added to a stirred solution of *N*-(3-hydroxypropyl)ethylenediamine (**32**) (25.0 g, 211 mmol) and diisopropylethylamine (36.9 mL, 211 mmol) in 450 mL of CH_2Cl_2 at 0 °C by means of a double-ended needle under an Ar atmosphere over a period of 0.5 h. The resulting reaction mixture was stirred at 0 °C for 1 h, quenched with H_2O (400 mL), and extracted with CH_2Cl_2 (7 × 400 mL). The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residual oil was purified by flash chromatography on a silica gel column. Elution with 100% EtOAc and then 3:7 EtOAc−MeOH afforded 36.78 g (57%) of the monoprotected product **34** as a colorless oil: silica gel TLC R_f 0.47 (100:1 MeOH−30% NH_4OH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.66−1.71 (m, 2H), 2.78−2.81 (m, 4H), 3.20 (t, 2H, J = 5.6 Hz), 3.69 (br, 3H, ex D_2O), 3.75 (t, 2H, J = 5.6 Hz), 7.73−7.77 (m, 2H), 7.84−7.86 (m, 1H), 8.12−8.15 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 31.0, 42.9, 48.3, 48.4, 62.9, 125.3, 131.0, 132.7, 133.4, 133.6, 148.0; HRMS (FAB) m/z 304.096 $(M + 1)^+$ ($C_{11}H_{18}N_3O_5S$ requires 304.096).

3-[[2-[(2-Nitrobenzenesulfonyl)amino]ethyl](*tert*-butoxycarbonyl)amino]-1-propanol (35). A solution of di-*tert*-butyl dicarbonate (26.6 g, 122 mmol) in anhydrous THF (200 mL) was added to a stirred solution of **34** (36.8 g, 121 mmol) and Et_3N (34.0 mL, 244 mmol) in 200 mL of anhydrous THF at 0 °C for 20 min. The resulting reaction mixture was stirred at rt for 24 h and concentrated under reduced pressure. The residue was treated with saturated $NaHCO_3$ (300 mL), and the mixture was extracted with CH_2Cl_2 (2 × 600 mL). The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column. Elution with 6:4 and then 1:4 hexanes−EtOAc afforded 45.6 g (93%) of compound **35** as a colorless oil which solidified upon standing: mp 79−80 °C; silica gel TLC R_f 0.33 (1:4 hexanes−EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45 (s, 9 H), 1.60−1.78 (m, 2H), 3.21−3.40 (m, 6H), 3.45−3.70 (m, 2H), 5.85 (br, 1H), 7.74−7.89 (m, 3H), 8.08−8.15 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.2, 30.6, 42.3, 44.0, 47.0, 58.4, 80.8, 125.2, 130.7, 132.7, 133.6, 147.9, 156.4; HRMS (FAB) m/z 536.046 $(M + Cs)^+$ ($C_{16}H_{25}N_3O_7SCs$ requires 536.045). Anal. Calcd for $C_{16}H_{25}N_3O_7S$: C, 47.63; H, 6.25; N, 10.41. Found: C, 47.84; H, 6.40; N, 10.21.

3-[[2-[(2-Nitrobenzenesulfonyl)[[6-(phthalimidomethyl)-2-pyridinyl]methyl]amino]ethyl](*tert*-butoxycarbonyl)amino]-1-propanol (7). A mixture of **35** (16.4 g, 40.8 mmol), **31** (14.9 g, 45.0 mmol, 1.1 equiv), and anhydrous K_2CO_3 (39.5 g, 285 mmol) in 100 mL of anhydrous DMF was stirred at rt under an Ar atmosphere for 24 h. The solvent was evaporated under reduced pressure. The residue was dissolved in H_2O (200 mL), and the mixture was extracted with CH_2Cl_2 (2 × 200 mL). 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. Elution with 6:1 hexanes−EtOAc and then 100% EtOAc afforded 23.5 g (88%) of the orthogonally protected product **7** as a white foam: silica gel TLC R_f 0.42 (100% EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38 (s, 9H), 1.54−1.57 (m, 2H), 3.16−3.18 (m, 4H), 3.43−3.47 (m, 4H), 3.62 (br, 1H, ex D_2O), 4.59 (s, 2H), 4.89 (s, 2H), 7.17−7.23 (m, 3H), 7.56−7.64 (m, 4H), 7.75−7.78 (m, 2H), 7.87−7.89 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 28.2, 30.3, 42.5, 42.7, 45.1, 46.5, 52.8, 58.1, 80.6, 120.3, 121.2, 123.4, 124.0, 125.2, 128.1, 128.9, 130.4, 131.6, 132.0, 133.3, 133.4, 134.2, 137.6, 147.8, 155.0, 154.5, 156.4, 167.9; HRMS (FAB) m/z 786.122 $(M + Cs)^+$ ($C_{31}H_{35}N_5O_9SCs$ requires 786.121).

3-[[2-[(2-Nitrobenzenesulfonyl)[[6-(aminomethyl)-2-pyridinyl]methyl]amino]ethyl](*tert*-butoxycarbonyl)amino]-1-propanol (8). A solution of **7** (9.94 g, 15.2 mmol) in 100 mL of CH_2Cl_2 under an Ar atmosphere was cooled to 0 °C, and hydrazine (3.50 mL, 65.8 mmol, 4.3 equiv) was added slowly. The resulting reaction mixture was stirred at rt for

24 h and then treated with H_2O (200 mL). The mixture was extracted with CH_2Cl_2 (2 × 200 mL). 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. Elution with 9:1 and then 1:4 EtOAc−MeOH afforded 6.13 g (77%) of diprotected product **8** as a pale yellow thick oil: silica gel TLC R_f 0.45 (100:1 MeOH−30% NH_4OH); ^1H NMR (DMSO-d_6, D_2O, 400 MHz) δ 1.31 (s, 9H), 1.41−1.55 (m, 2H), 2.93−3.05 (m, 2H), 3.23−3.30 (m, 2H), 3.31−3.33 (m, 2H), 3.39−3.43 (m, 2H), 3.62 (s, 2H), 4.63 (s, 2H), 7.09−7.11 (d, 1H, J = 7.6 Hz), 7.28−7.30 (d, 1H, J = 7.6 Hz), 7.65−7.69 (t, 1H, J = 7.6 Hz), 7.74−7.76 (m, 1H), 7.84−7.86 (m, 1H), 7.92−7.95 (m, 1H), 7.95−8.02 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 27.9, 31.0, 44.1, 45.1, 46.3, 47.1, 52.4, 58.3, 78.8, 119.8, 119.9, 124.2, 130.0, 132.3, 134.3, 137.3, 147.5, 154.3, 154.5, 162.6; HRMS (FAB) m/z 656.116 $(M + Cs)^+$ ($C_{23}H_{33}N_5O_7SCs$ requires 656.115). Anal. Calcd for $C_{23}H_{33}N_5O_7S$: C, 52.76; H, 6.35. Found: C, 52.41; H, 6.16.

3-[[2-[[[6-(Aminomethyl)-2-pyridinyl]methyl]amino]-ethyl](*tert*-butoxycarbonyl)amino]-1-propanol (1). Thiophenol (185 μL, 199 mg, 1.8 mmol) was added to a stirred mixture of **8** (0.53 g, 1.0 mmol) and anhydrous K_2CO_3 (1.0 g, 7.2 mmol) in anhydrous DMF (20 mL). The resulting reaction mixture was stirred at rt for 3 h and concentrated under vacuum to remove the solvent. The residue was dissolved in a mixture of H_2O and $CHCl_3$, and the pH was adjusted to 13−14. The organic phase was separated, and the aqueous phase was extracted with $CHCl_3$. The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography on a silica gel column. Elution with 100% MeOH and then 50:1 MeOH−30% NH_4OH afforded 250 mg (74%) of the title compound **1** as a pale yellow oil. The compound **1** obtained by this procedure (Scheme 3) shows identical chromatographic and spectroscopic properties to those of the same compound synthesized by another route (Scheme 1).

Preparation of Library 36. A solution of α-bromo-*m*-xylene (0.494 g, 2.66 mmol, 2 equiv) and methyl 3-(bromomethyl)benzoate (0.61 g, 2.66 mmol, 2 equiv) in 25 mL of anhydrous CH_3CN was added dropwise at rt to a stirred mixture of **1** (0.45 g, 1.33 mmol) and anhydrous K_2CO_3 (2.67 g, 19.3 mmol) in 40 mL of anhydrous CH_3CN. The resulting reaction mixture was stirred at rt overnight. After the solvent was evaporated, the residue was dissolved in H_2O and $CHCl_3$. The layers were separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic phase 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. Elution with 10:1 hexanes−EtOAc and then 100% EtOAc afforded 0.88 g (93%) of the intermediate library **36** as a pale yellow oil: silica gel TLC R_f 0.31, 0.42, 0.54 and 0.62 (1:2 hexanes−EtOAc); ^1H NMR ($CDCl_3$) δ 1.26 (s, 9H), 1.40−1.60 (m, 2H), 2.32 (s, 2.25H), 2.34 (s, 2.25H), 2.57−2.68 (m, 2H), 3.15−3.35 (m, 4H), 3.40−3.52 (m, 2H), 3.55−3.78 (m, 10H), 3.91 (s, 2.25H), 3.92 (s, 2.25H), 6.98−7.08 (m, 2H), 7.10−7.24 (m, 4H), 7.30−7.72 (m, 6H), 7.85-8.10 (m, 3H); MS (ESI) m/z 651, 695, 739, 783 $(M + H)^+$; 673, 717, 761, 805 $(M + Na)^+$.

Preparation of Library 37. CF_3COOH (8 mL) was added to a flask containing library **36** (0.75 g, 1.04 mmol) at 0 °C. The resulting solution was stirred at rt for 3 h. TFA was evaporated under reduced pressure, and the residue was dissolved in 200 mL of chloroform. The solution was washed three times with a saturated K_2CO_3 solution and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by flash chromatography on a silica gel column. Elution with 100% methanol and then 100:1 MeOH−30% NH_4OH afforded 0.50 g (78%) of library **37** as a pale yellow oil: silica gel TLC R_f 0.43 (100:1 MeOH−30% NH_4OH); ^1H NMR ($CDCl_3$) δ 1.52−1.67 (m, 2H), 2.32 (s, 2.25H), 2.34 (s, 2.25H), 2.56−2.68 (m, 6H), 3.54−3.78 (m, 12H), 3.90 (s, 2.25H), 3.92 (s, 2.25H), 6.98−7.23 (m, 6H), 7.27−7.70 (m, 6H), 7.86−8.09 (m, 3H); MS (ESI) m/z 551, 595, 639, 683 $(M + 1)^+$.

General Procedure for the Preparation of Libraries 38, 39, and 12−21. A mixture of selected benzylic bromide (1.4 equiv), library **37** or **11** (1.0 equiv), and K_2CO_3 (15 equiv) in anhydrous CH_3CN was stirred at rt for 23 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in H_2O−$CHCl_3$. The layers were separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic phase was dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by preparative thin layer chromatography (PLC) affording the desired library.

Library 38: colorless oil, yield 160 mg (53%), silica gel TLC R_f 0.36−0.54 (20:1 EtOAc−MeOH); ^1H NMR ($CDCl_3$) δ 1.55−1.70 (m, 2H), 2.25 (s, 2.25H), 2.30 (s, 2.25H), 2.34 (s, 3H), 2.47−2.68 (m, 6H), 3.38−3.74 (m, 14H), 3.89 (s, 2.25H), 3.92 (s, 2.25H), 6.91−7.25 (m, 10H), 7.28−7.68 (m, 6H), 7.84−8.10 (m, 3H); MS (ESI) m/z 655, 699, 743, 787 $(M + 1)^+$; 677, 721, 765, 809 $(M + Na)^+$.

Library 39: pale yellow oil, yield 0.25 g (88%), silica gel TLC R_f 0.40−0.58 (20:1 EtOAc−MeOH); ^1H NMR ($CDCl_3$) δ 1.55−1.70 (m, 2H), 2.29 (s, 2.25H), 2.33 (s, 2.25H), 2.47−2.68 (m, 6H), 3.44−3.72 (m, 14H), 3.88 (s, 3H), 3.89 (s, 2.25H), 3.91 (s, 2.25H), 6.97−7.22 (m, 7H), 7.28−7.68 (m, 7H), 7.78−8.08 (m, 5H); MS (ESI) m/z 699, 743, 787, 831 $(M + 1)^+$; 721, 765, 809, 853 $(M + Na)^+$.

Library 9. This library was prepared as above for **36** from **1** (560 mg, 1.65 mmol), anhydrous K_2CO_3 (3.5 g, 25.0 mmol), and a solution of benzyl bromide (123 μL, 171 mg, 1.0 mmol), 3-fluorobenzyl bromide (124 μL, 189 mg, 1.0 mmol), α-bromo-*m*-xylene (141 μL, 185 mg, 1.0 mmol), methyl 3-(bromomethyl)benzoate (229 mg, 1.0 mmol), 3-nitrobenzyl bromide (216 mg, 1.0 mmol) and α′-bromo-α,α,α-trifluoro-*m*-xylene (155 μL, 239 mg, 1.0 mmol) in 90 mL of anhydrous CH_3CN. Library **9** was obtained as a pale yellow oil: yield 0.89 g (76%); silica gel TLC R_f 0.30−0.70 (1:2 hexanes−EtOAc); ^1H NMR ($CDCl_3$) δ 1.27 (s, 9H), 1.40−1.70 (m, 2H), 2.32 (s, 0.75H), 2.34 (s, 0.75H), 2.47−2.72 (m, 2H), 3.15−3.35 (m, 4H), 3.38−3.52 (m, 2H), 3.54−3.80 (m, 12H), 3.91 (s, 0.75H), 3.92 (s, 0.75H), 6.90−8.32 (m, 15.2H); MS (ESI) m/z 609−813 $(M + 1)^+$.

Library 10. This library was prepared as above for **9** from six benzylic bromides (0.2 mmol each), **2** (130 mg, 0.33 mmol), and anhydrous K_2CO_3 (0.80 g, 5.7 mmol) in 20 mL of anhydrous CH_3CN. Library **10** was obtained as a pale yellow oil: yield 180 mg (71%); silica gel TLC R_f 0.30−0.70 (1:4 hexanes−EtOAc); ^1H NMR ($CDCl_3$) δ 1.27 (s, 9H), 1.41−1.62 (m, 2H), 2.32 (s, 0.75H), 2.34 (s, 0.75H), 2.38 (s, 3H), 2.58−2.80 (m, 2H), 3.04−3.28 (m, 4H), 3.50−3.85 (m, 12H), 3.91 (s, 0.75H), 3.92 (s, 0.75H), 6.85−8.30 (m, 19.2H); MS (ESI) m/z 663−867 $(M + 1)^+$.

Library 11. This library was synthesized as above for library **37** from 0.77 g (1.08 mmol) of library **9** and 8 mL of TFA. Library **11** was obtained as a pale yellow oil: yield 0.63 g (95%); silica gel TLC R_f 0.36−0.50 (100:1 MeOH−30% NH_4OH); ^1H NMR ($CDCl_3$) δ 1.49−1.68 (m, 2H), 2.32 (s, 0.75H), 2.34 (s, 0.75H), 2.53−2.76 (m, 6H), 3.50−3.80 (m, 14H), 3.90 (s, 0.75H), 3.92 (s, 0.75H), 6.85−8.30 (m, 15.2H); MS (ESI) m/z 509−713 $(M + 1)^+$.

Library 12: colorless oil, yield 71 mg (70%), silica gel TLC R_f 0.30−0.45 (20:1 EtOAc−MeOH); ^1H NMR ($CDCl_3$) δ 1.60−1.76 (m, 2H), 2.31 (s, 0.75H), 2.33 (s, 0.75H), 2.48−2.73 (m, 6H), 3.42−3.80 (m, 14H), 3.89 (s, 0.75H), 3.91 (s, 0.75H), 6.85−8.30 (m, 20.2H); MS (ESI) m/z 656−860 $(M + 1)^+$.

Library 13: pale yellow oil, yield 55 mg (78%), silica gel TLC R_f 0.25−0.50 (20:1 EtOAc−MeOH); ^1H NMR ($CDCl_3$) δ 1.55−1.72 (m, 2H), 2.25 (s, 3H), 2.30 (s, 0.75H), 2.34 (s, 0.75H), 2.49−2.70 (m, 6H), 3.45 (s, 2H), 3.49−3.78 (m, 14H), 3.89 (s, 0.75H), 3.92(s, 0.75H), 6.85−8.30 (m, 19.2H); MS (ESI) m/z 613−817 $(M + 1)^+$.

Library 14: colorless oil, yield 45 mg (45%), silica gel TLC R_f 0.43−0.60 (40:1 EtOAc−MeOH); ^1H NMR ($CDCl_3$) δ 1.55−1.75 (m, 2H), 2.32 (s, 0.75H), 2.34 (s, 0.75H), 2.47−2.75 (m, 6H), 3.40−3.80 (m, 14H), 3.90 (s, 0.75H), 3.92 (s, 0.75H), 6.80−8.30 (m, 19.2H); MS (ESI) m/z 616−820 $(M + 1)^+$.

Library 15: pale yellow oil, yield 45 mg (41%), silica gel TLC R_f 0.47−0.68 (50:1 EtOAc−MeOH); ^1H NMR ($CDCl_3$) δ 1.55−1.74 (m, 2H), 2.31 (s, 0.75H), 2.33 (s, 0.75H), 2.48−2.72 (m, 6H), 3.45−3.80 (m, 14H), 3.90 (s, 0.75H), 3.92 (s, 0.75H), 6.80−8.30 (m, 19.2H); MS (ESI) m/z 643−847 $(M + 1)^+$.

Library 16: colorless oil, yield 60 mg (49%), silica gel TLC R_f 0.37−0.57 (40:1 EtOAc−MeOH); ^1H NMR ($CDCl_3$) δ 1.57−

1.75 (m, 2H), 2.31 (s, 0.75H), 2.33 (s, 0.75H), 2.48−2.73 (m, 6H), 3.42−3.80 (m, 14H), 3.89 (s, 3.75H), 3.91 (s, 0.75H), 6.85−8.30 (m, 19.2H); MS (ESI) m/z 656−860 $(M + 1)^+$.

Library 17: pale yellow oil, yield 75 mg (71%), silica gel TLC R_f 0.55−0.73 (50:1 EtOAc−MeOH); ^{1}H NMR ($CDCl_3$) δ 1.47−1.78 (m, 2H), 2.32 (s, 0.75H), 2.34 (s, 0.75H), 2.48−2.85 (m, 6H), 3.45−3.80 (m, 14H), 3.90 (s, 0.75H), 3.92 (s, 0.75H), 6.80−8.30 (m, 19.2H); MS (ESI) m/z 666−870 $(M + 1)^+$.

Library 18: pale yellow oil, yield 45 mg (65%), silica gel TLC R_f 0.39−0.56 (20:1 EtOAc−MeOH); ^{1}H NMR ($CDCl_3$) δ 1.50−1.68 (m, 2H), 2.31 (s, 0.75H), 2.34 (s, 0.75H), 2.56−2.80 (m, 6H), 3.25 (s, 2H), 3.52−3.80 (m, 17H), 3.90 (s, 0.75H), 3.92 (s, 0.75H), 6.85−8.30 (m, 15.2H); MS (ESI) m/z 581−785 $(M + 1)^+$.

Library 19: pale yellow oil, yield 37 mg (58%), silica gel TLC R_f 0.48−0.69 (40:1 EtOAc−MeOH); ^{1}H NMR ($CDCl_3$) δ 1.57−1.74 (m, 2H), 2.30 (s, 0.75H), 2.34 (s, 0.75H), 2.56−2.80 (m, 6H), 3.38−3.82 (m, 16H), 3.91 (s, 0.75H), 3.93 (s, 0.75H), 6.85−8.30 (m, 15.2H); MS (ESI) m/z 548−752 $(M + 1)^+$.

Library 20: pale yellow thick oil, yield 35 mg (53%), silica gel TLC R_f 0.35−0.60 (3:1 EtOAc−MeOH); ^{1}H NMR ($CDCl_3$) δ 1.50−1.70 (m, 2H), 2.30 (s, 0.75H), 2.34 (s, 0.75H), 2.42−2.70 (m, 6H), 3.04 (s, 2H), 3.52−3.85 (m, 14H), 3.90 (s, 0.75H), 3.92 (s, 0.75H), 5.38−5.68 (bs, 2H), 6.85−8.32 (m, 15.2H); MS (ESI) m/z 566−770 $(M + 1)^+$.

Library 21. This library was prepared according to general procedure by stirring the reaction mixture at 50−60 °C for 24 h and obtained as a pale yellow oil: yield 42 mg (59%); silica gel TLC R_f 0.15−0.46 (2:1 EtOAc−MeOH); ^{1}H NMR ($CDCl_3$) δ 1.50−1.76 (m, 2H), 2.30 (s, 0.75H), 2.34 (s, 0.75H), 2.55−2.82 (m, 6H), 3.09 (s, 3H), 3.37 (s, 2H), 3.48−3.80 (m, 17H), 3.90 (s, 0.75H), 3.92 (s, 0.75H), 6.85-8.32 (m, 15.2H); MS (ESI) m/z 610−814 $(M + 1)^+$.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **1**−**8**, **23**, and **34**; ^{1}H NMR spectrum, electrospray MS, computer-simulated MS, and theorectical molecular masses of library **15** (28 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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