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Chemistry

Dendrimer-supported combinatorial chemistry

(combinatorial chemistry/dendrimer/size exclusion chromatography/solution phase synthesis)

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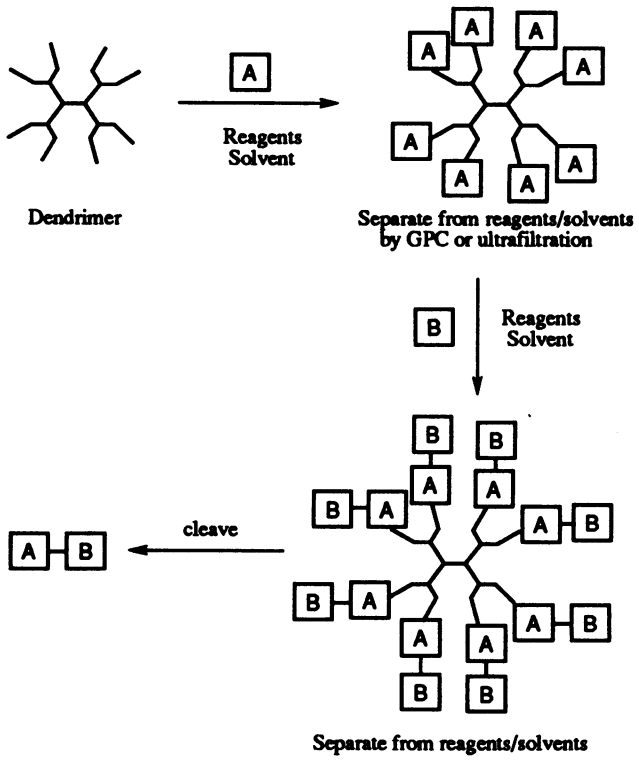
ABSTRACT **A new methodology for the construction of combinatorial libraries is described. The approach, termed dendrimer-supported combinatorial chemistry (DCC), centers on the use of dendrimers as soluble supports. Salient features of DCC include solution phase chemistry, homogeneous purification, routine characterization of intermediates, and high support loadings. To demonstrate the feasibility of DCC, single compounds and a small combinatorial library were prepared via the Fischer indole synthesis. Excellent product yields and purities were obtained, and dendrimer-protected intermediates could be routinely analyzed by ^{1}H and ^{13}C NMR and by mass spectrometry. The results indicate that DCC is a general and efficient strategy for the generation of combinatorial libraries.**

The growing importance of combinatorial chemistry as an integral component of the drug discovery process has spurred remarkable technological and synthetic advances in the field (1). Founded in peptide synthesis (2), solid phase chemistry has emerged as the preeminent method for construction of small molecule combinatorial libraries (3–5). Central to the power of solid phase synthesis is the ease by which reagents and solvents are removed simply by washing. This allows for the purification of resin-bound mixtures of enormous complexity and the use of large reagent excesses to drive reactions to completion. The "infinite dilution" obtained on solid supports can also prevent side reactions that may occur in solution. Despite its advantages, nontrivial liabilities are associated with heterogeneous synthesis. Most notable is the often arduous task of modifying solution phase chemistry to the solid phase, with its potential pitfalls such as poor solvation, differential site accessibility, and incompatibility of the polymer support with reagents or reaction conditions. The process is further hampered by difficulty in routinely monitoring solid phase reactions (6, 7). In an attempt to address these issues, we have explored alternative methods of combinatorial chemistry to facilitate library generation. We describe here a new and general approach toward combinatorial chemistry that combines classical solution phase synthesis with facile homogeneous purification.

The method, which we term dendrimer-supported combinatorial chemistry (DCC), features solution phase synthesis on dendrimer supports. Dendrimers are branching oligomers built generationally from a central core (8–11). Unlike typical polymers, dendrimers are characterized by discrete, controllable molecular architectures. Important for our requirements, low generation dendrimers exist in extended form (12), promoting high reagent accessibility. Outlined schematically in Scheme 1, DCC is conceptually analogous to solid phase combinatorial synthesis, except that reactions are performed in solution and dendrimeric intermediates are separated by size-selective methods such as size exclusion chromatography (SEC) or ultrafiltration. Janda and coworkers (13, 14) have recently described a related approach, termed liquid-phase combinatorial synthesis, in which combinatorial libraries are synthesized on soluble poly(ethylene glycol) supports (13, 14). Precipitation/crystallization of the poly(ethylene glycol) protected molecules from ether allows for removal of reagents and solvents by filtration, thus combining the advantages of solution phase chemistry and the utility of solid phase purification.



Scheme I

We believe that DCC embodies several features well suited to combinatorial chemistry, which derive from the use of dendrimer supports. (i) Solution phase synthesis obviates the need to modify chemistry to the solid phase. (ii) Intermediates may be routinely characterized by a variety of analytical methods, including ^{1}H and ^{13}C NMR, IR, UV, and mass spectrometry. (iii) Because multiple copies of each molecule are synthesized per dendrimer, extremely high loadings may be attained. (4) Size-based purification is general, since it does not rely on other physical differences between support-bound

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Abbreviations footnote: DCC, dendrimer-supported combinatorial chemistry; SEC, size exclusion chromatography; PAMAM, polyamidoamine; HMB, 4-hydroxymethylbezoic acid; DMAP, 4-dimethylaminopyridine; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; DMF, *N,N*-dimethylformamide; HOBt, 1-hydroxybenzotriazole hydrate; PyBOP, benzotriazole-1-yl-oxy-*tris*-pyrrolidino-phosphonium hexafluorophosphate.

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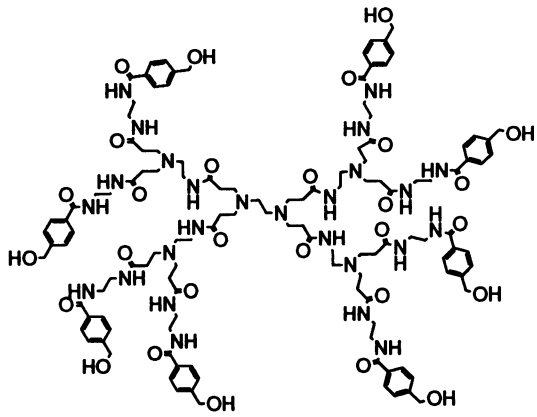
compounds and reagents; large reagent excesses may also be employed. And (v) dendrimers offer a flexible framework that may be engineered to exhibit properties necessary for their desired applications. In this paper we present our efforts to validate the DCC strategy through the preparation of single compounds and a small combinatorial library. We believe the results presented here indicate that solution phase synthesis on dendrimer supports is a general and convenient strategy for the development and implementation of combinatorial chemistry.

Materials and Methods

Unless otherwise noted, all chemicals and reagents were purchased from commercial sources and used without further purification. Starburst polyamidoamine (PAMAM) Dendrimer, Generation 1, was obtained from Aldrich as a 20% solution in MeOH, and the solvent was removed *in vacuo* prior to use. *N,N*-Dimethylformamide (DMF) was dried over 3-Å and 13X sieves. *N,N*-Dimethylacetamide (DMA) was dried over 3-Å sieves. SEC was performed on a 2.5 × 30 cm column using Sephadex LH-20 as the stationary phase and DMF as the eluent (flow rate = 5 ml/min). ^{1}H and ^{13}C NMR were recorded at 500 MHz on a Varian Unity 500 spectrometer. HPLC spectra were obtained on a Hewlett Packard 1090 HPLC, equipped with a reverse-phase 100 × 2.1 mm Hewlett-Packard octadecylsilyl (5 μm) Hypersil column. A linear elution gradient consisting of 9:1 H_2O/MeCN (0.1% trifluoroacetic acid) brought to 100% MeCN (0.1% trifluoroacetic acid) over 17 min, at a flow rate of 0.7 ml/min was employed. Mass spectral data were recorded using a Finnigan MAT TSQ 700 (San Jose, CA) triple-stage quadrupole mass spectrometer. Samples were introduced into the mass spectrometer using an ABI 130 syringe pump HPLC equipped with a Brownlee 2.1 × 30 mm C-4 reverse-phase HPLC column. After injection, samples were eluted directly into the mass spectrometer using a linear gradient of acetonitrile. Spectra were recorded as described elsewhere (15).

Synthesis. PAMAM–HMB (1). To a solution of Starburst PAMAM Dendrimer, Generation 1 (0.1 mmol, 140 mg) dissolved in 4 ml of DMA was added 4-hydroxymethylbenzoic acid (HMB) (1.6 mmol, 214 mg), followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) (1.6 mmol, 307 mg). The reaction was allowed to stir at ambient temperature for 18 h. The dendrimer product was purified by SEC. The eluent was removed by rotary evaporation, and the residue was triturated twice with CH_2Cl_2 and dried under vacuum, affording 240 mg of **1** as a white solid (96% yield). ^{1}H NMR (500 MHz, CD_3OD): δ 7.77 (d, J = 8 Hz, 16H), 7.39 (d, J = 8 Hz, 16H), 4.63 (s, 16H). ^{13}C NMR (500 MHz, DMSO-d_6): δ 172.29, 166.89, 162.86, 146.32, 133.32, 127.57, 126.50, 63.00. MS (ESI): 2503 $[M + H]^+$.

Dendrimer 2. A round bottom flask containing 4.5 ml of DMA was charged with 125 mg (0.05 mmol) of dendrimer **1**, 0.8 mmol (310 mg, 2 equivalents *versus* HMB) of *N*-(9-fluorenyl)methoxycarbonyl (Fmoc)-L-phenylalanine, 0.8 mmol (154 mg, 2 equivalents) of EDC, and 5 mg of 4-dimethylaminopyridine (DMAP). The reaction was allowed to stir for 2.5 h at ambient temperature, after which time an additional equivalent of Fmoc-Phe-OH and EDC were added to the stirring solution. The reaction was allowed to stir for an additional 1.5 h and then was purified by SEC. The combined fractions were concentrated to dryness, and the Fmoc protecting group was removed by treatment with 4 ml of 25% piperidine in DMF for 30 min. The product was purified by SEC and concentrated to dryness, yielding 159 mg of a beige foamy solid (86% overall yield). ^{1}H NMR (500 MHz, 7:1 DMSO-d_6/CD_3OD): δ 7.76 (d, J = 8 Hz, 16H), 7.26 (d, J = 7 Hz, 16H), 7.20 (t, J = 6 Hz, 16 H), 7.16 (unresolved t, 8H), 7.11 (d, J = 6 Hz, 16H), 5.05 (s, 16H), 3.61 (m, 8H). MS (ESI): 3682 $[M + H]^+$.



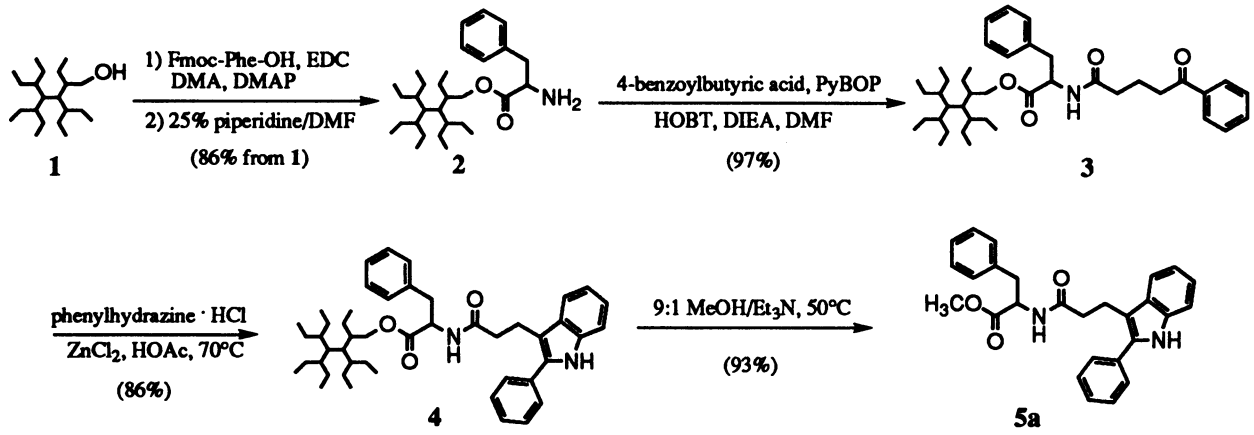
Structure **I**

Dendrimer 3. To a round bottom flask containing supported amino acid **2** (0.03 mmol, 120 mg) dissolved in 4 ml of DMF was added sequentially: 0.5 mmol (99 mg, 2 equivalents) of 4-benzoylbutyric acid, 0.5 mmol (265 mg, 2 equivalents) of benzotriazole-1-yl-oxy-*tris*-pyrrolidino-phosphonium hexafluorophosphate (PyBOP), 0.5 mmol (70 mg, 2 equivalents) of 1-hydroxybenzotriazole hydrate (HOBt), and 1.3 mmol (225 μl, 5 equivalents) of diisopropylethylamine. The reaction was stirred for 3 h at ambient temperature, during which time a white precipitate formed. The reaction mixture was filtered, and the filtrate was purified by SEC. The desired fractions were combined, and the eluent was removed under vacuum, yielding 160 mg of a yellow solid (97% yield). ^{1}H NMR (500 MHz, 7:1 DMSO-d_6/CD_3OD): δ 7.84 (d, J = 6 Hz, 16H), 7.78 (d, J = 7 Hz, 16H), 7.56 (unresolved t, 8H), 7.45 (m, 16H), 7.28 (m, 16H), 7.12 − 7.22 (overlapping m, 32 H), 7.11 (m, 8H), 5.08 (br. s, 16H), 4.54 (m, 8H). MS (ESI): 5075 $[M + H]^+$.

Dendrimer 4. Into a round bottom flask containing **3** (0.008 mmol, 44 mg) was added a 1-ml solution of glacial acetic acid containing 0.5 mmol (72 mg) of phenylhydrazine hydrochloride and 0.5 mmol (68 mg) of zinc chloride. The reaction was heated to 70°C and allowed to mix for 18 h. After cooling to ambient temperature, the reaction mixture was diluted with 1 ml of DMA and purified by SEC. The desired fractions were combined and concentrated to dryness, yielding 42 mg of a yellow solid (86% yield). ^{1}H NMR (500 MHz, 7:1 DMSO-d_6/CD_3OD): δ 7.76 (d, J = 8 Hz, 16H), 7.57 (d, J = 7 Hz, 16H), 7.43 (s), 7.51 (d, J = 7 Hz, 8H), 7.43 (m, 16H), 7.32 (d, J = 7 Hz, 16H), 7.26 (m, 16H), 7.08–7.2 (m, 40H), 7.06 (t, J = 7 Hz, 8H), 6.96 (unresolved t, 8H), 5.06 (br. s, 16H), 4.53–4.56 (m, 8H). MS (ESI): 5659 $[M + H]^+$.

3-Phenyl-2-[3-(2-phenyl-indol-3-yl)-propionylamino]-propionic Acid Methyl Ester (5a). Dendrimer **4** (0.004 mmole, 22 mg) was placed into a round bottom flask along with 2 ml of 9:1 methanol-triethylamine. The suspension was heated to 50°C and allowed to mix for 20 h, during which time the solution became clear. The reaction mixture was concentrated to dryness, and the residue was extracted with 2 × 4 ml of acetonitrile. The insoluble dendrimer was filtered away, and the filtrate evaporated to dryness yielding 12.4 mg of a beige solid (93% yield). ^{1}H NMR (500 MHz, 7:1 DMSO-d_6/CD_3OD): δ 7.59 (d, J = 8 Hz, 2H), 7.53 (d, J = 8 Hz, 1H), 7.46 (t, J = 8 Hz, 2H), 7.34 (d, J = 7 H, 1H), 7.32 (d, J = 7 Hz, 1H), 7.1 − 7.22 (overlapping m, 5H), 7.07 (t, J = 7 Hz, 1H), 6.98 (t, J = 7 Hz, 1H), 4.50 (m, 1H), 3.56 (s, 3H), 2.92–3.00 (overlapping m, 3H), 2.82–2.86 (m, 1H), 2.4–2.45 (m, 2H); MS (ESI): 427.2 $[M + H]^+$.

Combinatorial Library Construction. To each of three samples containing PAMAM–HMB **1** (0.01 mmol, 24 mg) dissolved in 1.5 ml of DMA were added sequentially the



Scheme II

appropriate Fmoc-protected amino acid X_1–X_3 (0.16 mmol), EDC (0.16 mmol, 31 mg), and catalytic DMAP (5 mg). The reactions were stirred at ambient temperature for 4 h, combined and purified by SEC. Solvent was removed by rotary evaporation, and the mixed amino acids were deprotected in 4 ml of 25% piperidine/DMA for 30 min. Purification by SEC and removal of solvent *in vacuo* afforded 83 mg PAMAM–HMB-X_{1-3} as a yellow foam (84% yield from **1** based on average molecular weight of products).

PAMAM–HMB-X_{1-3} was split into three equal pools containing 7.4 μmol (25 mg) of dendrimer in 1.5 ml of DMF. To each pool was added sequentially the appropriate ketoacid Y_1–Y_3 (0.15 mmol), PyBOP (0.15 mmol, 78 mg), HOBt (0.15 mmol, 21 mg), and diisopropylethylamine (0.3 mmol, 52 μl). The reactions were stirred at ambient temperature for 4 h, after which time the ninhydrin test of Kaiser (16) was negative for the three reactions. The crude reaction mixtures were combined and purified by SEC. Removal of solvent *in vacuo* afforded 104 mg of a tan foamy solid (98% yield).

PAMAM–HMB-X_{1-3}-Y_{1-3} was split into three equal pools containing 7.0 μmol (25 mg) of dendrimer in 2.0 ml of 9:1 HOAc/DMA. To each pool was added the appropriate hydrazine hydrochloride Z_1–Z_3 (1.0 mmol) and $ZnCl_2$ (1.0 mmol, 136 mg). The reactions were stirred at 70°C for 20 h. The mixtures were purified separately by SEC and concentrated to dryness *in vacuo*. Results from single compound synthesis indicated that *p*-chlorophenylhydrazine hydrochloride Z_3 would not fully cyclize under the above conditions, so the reaction was repeated on the recovered Z_3-treated dendrimer in glacial acetic acid as described above. Yields: PAMAM–HMB-X_{1-3}-Y_{1-3}-Z_1, 75%; PAMAM–HMB-X_{1-3}-Y_{1-3}-Z_2, 83%; PAMAM–HMB-X_{1-3}-Y_{1-3}-Z_3, 66%.

Each of the three sublibraries was cleaved from the dendrimer support in 3 ml of 9:1 MeOH/Et_3N at 50°C for 18 h. Eluent was removed under vacuum, and the residues were extracted twice with 4 ml of MeCN. Insoluble dendrimer was removed by filtration, and the filtrates were concentrated to dryness, affording the indole sublibraries. Yields: X_{1-3}-Y_{1-3}-Z_1, 90%; X_{1-3}-Y_{1-3}-Z_2, 96%; X_{1-3}-Y_{1-3}-Z_3, 90%.

RESULTS AND DISCUSSION

Synthesis of Single Compounds on Dendrimer Supports. Our initial evaluation of DCC involved preparation of single compounds on Starburst PAMAM Generation 1 (17). Besides being commercially available, PAMAM is highly symmetric, which provides uniform site accessibility and facilitates NMR interpretation, and the eight amine-terminated "arms" may be readily functionalized. We focused our efforts on indole formation via the Fischer indole synthesis (18). Due to the biological and pharmacological significance of indoles, their construction has been actively pursued in our group, and the Fischer indole synthesis has been successfully translated to the solid phase (19). Because strongly acidic conditions are required for cyclization, a base-labile handle was used to anchor compounds onto the dendrimer support. Thus, PAMAM–HMB **1** was prepared by attaching HMB (20) to PAMAM under standard carbodiimide coupling conditions. Purification

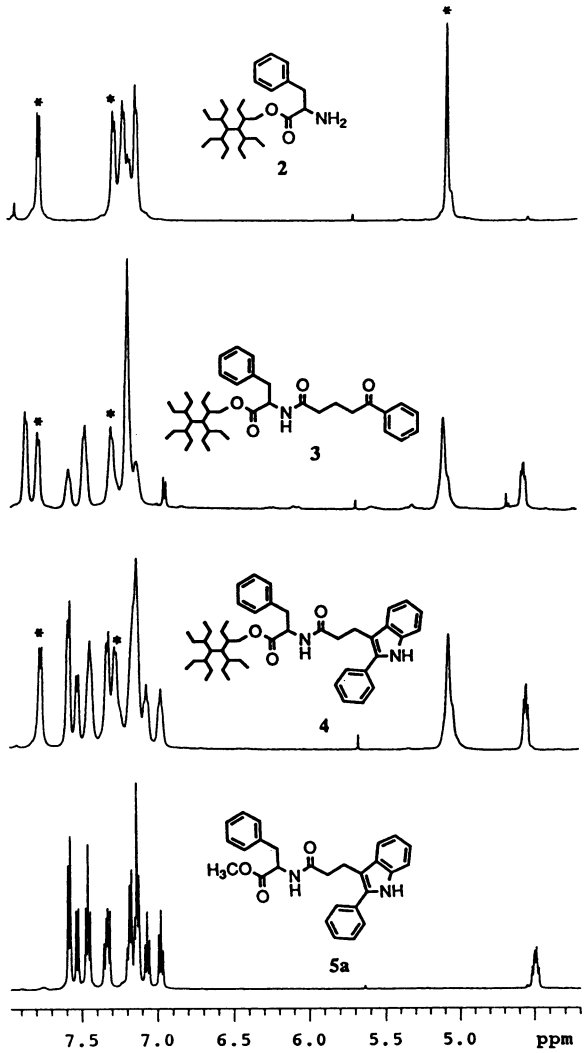


FIG. 1. 1H NMR spectra (500 MHz, 7:1 DMSO-d_6/CD_3OD) comparing dendrimer precursors 2, 3, 4, and indole product 5a. Peaks corresponding to the HMB linker are denoted by an asterisk.

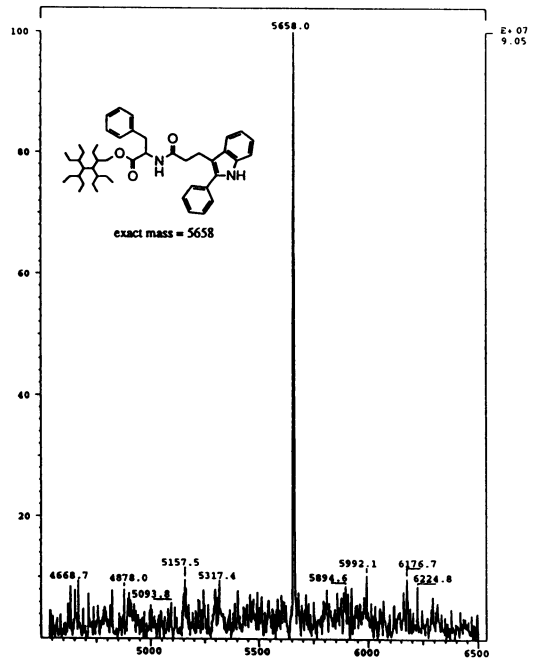


FIG. 2. Electrospray mass spectrum of dendimer-supported indole 4.

of **1** was performed by SEC on Sephadex LH-20, and the dendrimer was characterized by ^1H and ^{13}C NMR and mass spectrometry. Note that each PAMAM–HMB hybrid contains eight cleavable attachment sites for compound synthesis.

Our first attempt at indole construction involved formation of **5a** (Scheme 2) and serves as an illustrative example of our general synthetic approach. The reaction sequence was initiated by loading (Fmoc)-protected L-phenylalanine (16 equivalents *versus* **1**, 2 equivalents *versus* HMB linker) onto **1** using EDC (2 equivalents *versus* HMB) and catalytic DMAP in DMA. Fmoc deprotection in 25% piperidine/DMF afforded **2**. The amine was acylated with 4-benzoylbutyric acid (2.5 equivalents) using PyBOP (2.5 equivalents) and HOBt (2.5 equivalents) in DMF containing Et_3N to give aryl ketone **3**. Cyclization with phenylhydrazine hydrochloride (0.5 M) in glacial acetic acid containing 0.5 M $ZnCl_2$ at 70°C cleanly afforded the dendrimer-supported indole **4**. Cyclizations were also performed in 10–25% DMA/HOAc, although conversions of electron-deficient hydrazines were diminished in

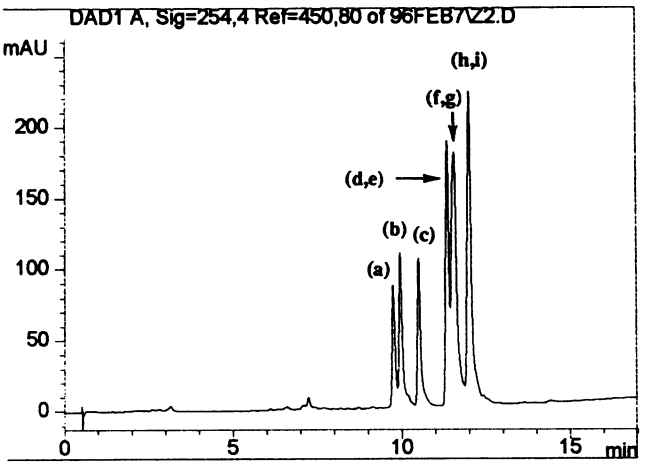
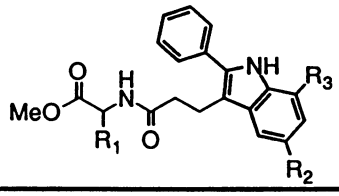


FIG. 3. Reverse-phase HPLC trace (254 nm) of sublibrary Z_2. Peak assignments are as follows: (*a*) $X_1Y_1Z_2$; (*b*) $X_1Y_3Z_2$; (*c*) $X_1Y_2Z_2$; (*d*) $X_2Y_1Z_2$; (*e*) $X_3Y_1Z_2$; (*f*) $X_2Y_3Z_2$; (*g*) $X_3Y_3Z_2$; (*h*) $X_2Y_2Z_2$; (*i*) $X_3Y_2Z_2$.

Table 1. Individually prepared indoles.



	R_1	R_2	R_3	Purity *
5a	$-CH_2Ph$	H	H	99 %
5b	$-CH_2Ph$	*t*-Bu	H	96 %
5c	$-CH_2Ph$	Cl	H	99 %
5d	$-CH_2Ph$	Cl	Cl	84 %
5e	$-CH_2CH(CH_3)_2$	*t*-Bu	H	96 %
5f	$-CH_2CH(CH_3)_2$	Cl	Cl	91 %

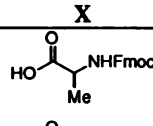
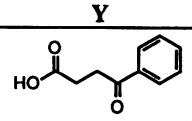
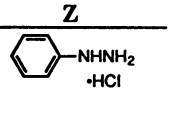
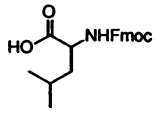
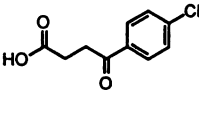
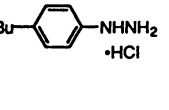
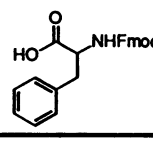
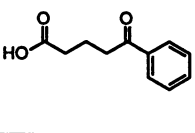
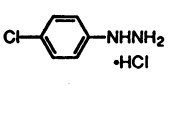
*Determined by reverse-phase HPLC at 254 nm.

mixed solvents, affording significant amounts of starting ketone along with the desired indole (see below).

Cleavage of the indole from the soluble support was achieved using 9:1 MeOH/Et_3N at 50°C, yielding methyl ester **5a** and regenerated **1**. The cleaved product was easily isolated from the dendrimer either by SEC, or by removal of solvent followed by treatment with MeCN and filtration of the insoluble dendrimer. Single products were characterized by HPLC, ^1H NMR, and mass spectrometry. As listed in Table 1, all six individually prepared indoles were obtained in high purity on the first attempt at synthesis. The ^1H NMR spectrum of the cleaved support was essentially unchanged from starting **1**, although the reuse of the recovered dendrimer has not yet been investigated.

All dendrimeric intermediates were purified by SEC on Sephadex LH-20, eluting with DMF; crude reaction mixtures were loaded directly onto the column with no pretreatment, except when filtration of insoluble material was warranted. Purifications were complete within 15 min. Reaction yields averaged greater than 90%, and columns could be reused dozens of times. ^1H NMR spectra of dendritic intermediates were recorded after each step, and in all cases revealed that all reagents and reaction solvents were removed during SEC, even when large excesses were employed. Furthermore, although peak broadening was observed, reactions could be *quantitatively* monitored by NMR. This is illustrated in Fig. 1, which compares ^1H NMR spectra of dendritic precursors **2**, **3**, and **4**, and product indole **5a**. Acylation of **2** to form **3** was confirmed by the large downfield shift of the Phe α-proton from 3.6 to 4.5 ppm and by the appearance of benzoyl protons at 7.84, 7.56, and 7.45 ppm. Conversion to the indole **4** was accompanied by the emergence of two multiplets between 6.9 and 7.1 ppm,

Table 2. Indole library subunits.

	X	Y	Z
1			
2			
3			

which correspond to the indole H-5 and H-6 positions, and by a downfield shift of the β methylene protons from 1.7 to 2.4 ppm (not shown). The *ortho* benzoyl protons also shifted from 7.84 to 7.57 ppm upon cyclization. Indole peak integrations compare extremely well with those derived from the HMB handle (i.e. benzylic protons at 5.1 ppm) and phenylalanine (i.e. α-H at 4.5 ppm), confirming that the heterocycle was formed in high yield. Also evident in Fig. 1 is the strong correlation between the ^{1}H NMR spectra of the dendrimer-supported and cleaved indoles **4** and **5a**, as well as the complete isolation of the final product from the dendrimer.

The dendritic intermediates could also be analyzed using electrospray mass spectrometry. The LC-mass spectrum of **4** is shown in Fig. 2 and exhibits a strong molecular ion peak at 5658. With eight molecular copies synthesized per dendrimer, the presence of a dominant parent peak verifies that the indoles were formed with extremely high efficiency. Strong parent ions were also measured for PAMAM–HMB **1** and indole precursors **2** and **3**. Clearly, the discrete molecular architecture of the dendrimer support was crucial to obtaining mass spectral characterization.

The significance of being able to routinely characterize support-bound intermediates was exemplified in the preparation of **5d**; although cyclization in 25% DMA/HOAc cleanly afforded indoles **5a** and **5b** upon cleavage, reaction with 2,4-dichlorophenylhydrazine hydrochloride under analogous conditions gave mostly starting ketone, as determined from the ^{1}H NMR spectrum of purified dendrimer. The reaction was simply repeated on the recovered dendrimer in glacial acetic acid, this time affording the desired indole **5d** in high purity after methanolysis from the dendrimer support (see Table 1).

Combinatorial Library Construction on Dendrimer Supports. Requisite to combinatorial library construction using the split synthesis approach (21–23) is the ability to cleanly separate mixtures of compounds from reagents and solvents. For DCC to be a general strategy then, dendrimer-bound intermediates must be removed from reagents regardless of the identities of the compounds on the support. Indications from single compound synthesis were favorable, as SEC elution profiles of the different dendrimeric species were extremely similar. To further validate the DCC strategy, a small $3 \times 3 \times 3$ (27 compound) combinatorial library was constructed by split synthesis using chemistry analogous to that presented in Scheme 2. The individual subunits are listed in Table 2.

Library construction was initiated by coupling three equal pools containing **1** with the appropriate Fmoc-protected amino acid X_1–X_3 using EDC/DMAP in DMA. The crude reaction mixtures were combined and purified by SEC, with the dendritic species eluting as a single band. The mixed amino acids were deprotected with 25% piperidine/DMF and purified by SEC. Complete acylation of **1**, and the presence of the three amino acids in approximately equimolar amounts, were confirmed by ^{1}H NMR. The dendrimer-protected amino acids were split into three equal portions and acylated with ketoacids Y_1–Y_3 using PyBOP/HOBt in DMF containing diisopropylethylamine. The reaction mixtures were combined, purified, and split into three equal pools, each ideally containing nine compounds. The pools were reacted with the appropriate arylhydrazine hydrochloride Z_1–Z_3 in 9:1 HOAc/DMA containing $ZnCl_2$ at 70°C, and purified separately, yielding three mixtures containing nominally nine compounds each. The three mixtures were cleaved in 9:1 MeOH/Et_3N at 50°C. Removal of solvent, extraction in MeCN, and filtration of the insoluble dendrimer afforded the three sublibraries addressed in the *z* axis. The HPLC trace of the Z_2 sublibrary is displayed in Fig. 3. All three pools displayed similar HPLC patterns consisting of three smaller peaks followed by three larger peaks, with no significant side products being observed. LC-MS of the library mixtures and retention times of single compounds showed that in all three sublibraries the first three bands corresponded to Ala-modified indoles, while the Leu and Phe derivatives coeluted as three peaks. The generation of library constituents in roughly equimolar amounts and in high purity indicates that dendrimer-supported construction of combinatorial libraries is a viable alternative to solid phase synthesis. Furthermore, we expect that DCC will be well-suited to automation, particularly for library production via the mix and split methodology. Both synthesis and purification steps are performed in solution, and the extremely high loadings capable on dendrimer supports (to obtain the same loading as 100 mg of resin with a typical capacity of 0.23 mmol/g, only seven mg of **1** are required) should greatly facilitate the production of multimilligram quantities of each library constituent, while reducing reaction volumes. The relatively rapid and highly reproducible separation of dendritic intermediates by SEC should also be amenable to parallel synthetic procedures, although purification steps could become rate-limiting in generation of extremely large numbers of single compounds.

Conclusion

Often the most time-consuming aspect of combinatorial library synthesis is not construction of the library itself but rather translation of solution phase chemistry to the solid phase. In addition to synthetic complications that may arise from heterogeneous synthesis, few analytical techniques exist for routine characterization of resin-bound compounds. Even analysis of cleaved intermediates can be ambiguous, since the harsh cleavage solutions that are often required may be detrimental to the molecules of interest. We have presented a new methodology for production of combinatorial libraries that features construction of molecules on dendrimer supports. We believe that the central tenets of DCC—solution phase chemistry and facile purification—coupled with routine and nondestructive characterization of intermediates, will greatly expedite adoption of classical homogeneous reactions to the combinatorial process.

From the results presented herein, we believe it is clear that DCC offers a general strategy by which a wide variety of single compounds and libraries may be created. Furthermore, dendrimer supports present a modular framework that can be custom-tailored to manifest desired properties such as solubility, chemical stability, and loading capacity. We are presently working to expand the range of dendrimer-supported chemistry, including the use of heterogeneous catalysts. We are also pursuing the design of new dendrimer supports and linkers, as well as the development of automated procedures for DCC.

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