Natural Product-like Combinatorial Libraries Based on Privileged Structures. 3. The "Libraries from Libraries" Principle for Diversity Enhancement of Benzopyran Libraries

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Abstract: As described in the preceding two papers, our interest in the construction of natural and natural product-like libraries for chemical biology studies led to the development of a new solid-phase cycloloading strategy for the construction of substituted benzopyrans. Herein, we report a parallel solution-phase method that facilitates the enhancement of both the size and diversity of these non-oligomeric benzopyran libraries using the "libraries from libraries" principle. We examine the rationale behind the use of this tandem strategy to construct discrete small molecule libraries, and describe the development of a polymer-assisted solution-phase (PASP) methodology necessary to effect the required transformations. Once developed, this chemistry is applied to two demonstration libraries.

Introduction

Combinatorial chemistry has become an increasingly important tool for the rapid construction of small molecule libraries for use in drug discovery and chemical biology.[1] The balanced design of these libraries typically requires a careful compromise between size, diversity, complexity, and purity.[2] Many times, achieving an effective balance of these elements requires the development of novel solid-phase and parallel solution-phase synthetic tools, and, in certain cases, it even requires the coupling of multiple combinatorial techniques. As described in the preceding papers, our interest in the construction of natural product-like libraries for chemical biology studies led to the development of a new solid-phase cycloloading strategy for the construction of substituted benzopyrans.[3,4] Herein, we report a parallel solution-phase method that facilitates the enhancement of both the size and diversity of these nonoligomeric small molecule libraries using the "libraries from libraries" principle originally introduced by Houghten et al. for the chemical transformation of peptide-based libraries.[5] We will begin by examining the rationale behind the use of this tandem strategy to construct discrete small molecule libraries. Subsequently, the development of the requisite polymer-assisted solution-phase methodology (PASP)[6] and its application to two demonstration libraries will be discussed.

Results and Discussion

Rationale and Design for Solution-Phase Diversity Enhancement. As illustrated in Scheme 1, our previous solid-phase synthetic efforts provided rapid access to substituted benzopyrans using a cycloloading/elaboration/oxidative cleavage sequence which enabled construction of a 10 000-membered discovery library as well as several smaller focused libraries.[3,4] The motivation for constructing libraries on this particular template stemmed from the fact that the benzopyran ring system (**5**, Figure 1) is found in over 4 000 natural and designed products which exhibit a wide range of biological activities. As these studies progressed, it became increasingly evident that there were at least an additional 8 000 natural and designed benzopyrans that contained modifications of the pyran olefin (i.e. structure **6**, Figure 1).[7] Interestingly, in some cases these derivatized ring systems (**6**, Figure 1) exhibited biological properties not shared by their olefinic counterparts while in

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(1) For reviews, see: (a) Ellingboe, J. W. *Curr. Opin. Drug Discovery Dev.* **1999**, *2*, 350−357. (b) Lee, M. S.; Nakanishi, H.; Kan, M. *Curr. Opin. Drug Discovery Dev.* **1999**, *2*, 332−341. (c) Watson, *Angew. Chem., Int. Ed.* **1999**, *38*, 1903−1908. (d) Schreiber, S. L. *Bioorg. Med. Chem.* **1998**, *6*, 1127−1152.

(2) For reviews, see: (a) Bunib, B. A.; Dener, J. M.; Livingston, D. A. *Annu. Rep. Med. Chem.* **1999**, *34*, 267−286. (b) Baldwin, J. J. *Comb. Chem. Mol. Diversity Drug Discovery* **1998**, 181−188. (c) Oliver, S. F.; Abell, C. *Curr. Opin. Chem. Biol.* **1999**, *3*, 299−306. (d) Ellingboe, J. W. *Med. Chem. Res.* **1998**, *8*, 181−186.

(3) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939−9953.

(4) Nicolaou, K. C.; Pfefferkorn, J. A.; Mitchell, H. J.; Roecker A. J.; Barluenga, S.; Cao, G.-Q.; Affleck, R. L.; Lillig, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 9954−9967.

(5) (a) Ostrech, J. M.; Husar, G. M.; Blondelle, S. E.; Dörner, B.; Weber, P. A.; Houghten, R. A. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 11138−11142. (b) Nefzi, A.; Ostrech, J. M.; Meyer, J.-P.; Houghten, R. A. *Tetrahedron Lett.* **1997**, *38*, 931−934. (c) Ostrech, J. M.; Schoner, C. C.; Hamashin, V. T.; Nefzi, A.; Meyer, J.-P.; Houghten, R. A. *J. Org. Chem.* **1998**, *63*, 8622−8623. (d) Cuervo, J. H.; Weitl, F.; Ostrech, J. M.; Hamashin, V. T.; Hannah, A. L.; Houghten, R. A. In *Peptides 94: Proceedings of the 23rd European Peptide Symposium*; Maria, H. L. S., Ed.; ESCOM: Leiden, 1995; pp 465−466. Ostrech, J. M.; Blondelle, S. E.; Dörner, B.; Houghten, R. A. In *Combinatorial Chemistry;* Methods in Enzymology, Vol. 267; Abelson, J. N., Ed.; Academic Press: San Diego, 1996; pp 220−234.

(6) For a review including other "mixed-technology" (i.e. combined solid-phase and solution-phase) studies, see: Flynn, D. L.; Devraj, R. V.; Parlow, J. J. *Curr. Opin. Drug Discovery Dev.* **1998**, *1*, 41−50.

10.1021/ja0020355 CCC: $19.00
Published on Web 09/30/2000

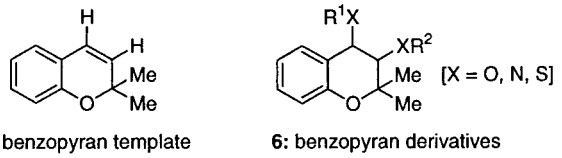
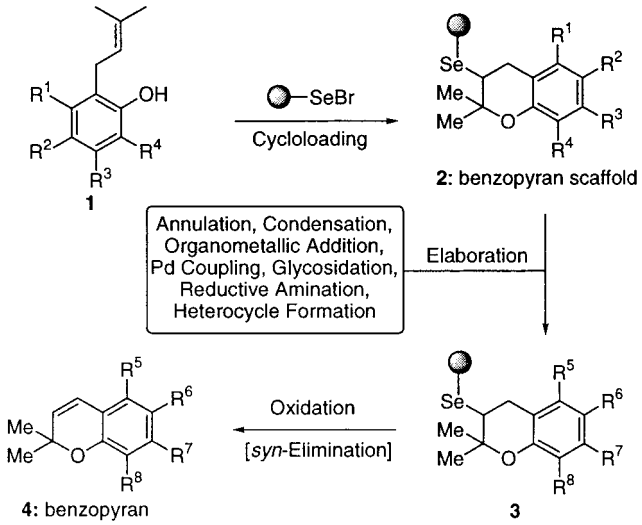


Figure 1. General structures of olefinic (**5**) and derivatized (**6**) versions of the benzopyran skeleton.

other cases such modifications enhanced the activity and/or bioavailability of the parent molecule. Representative examples of these modified benzopyrans are shown in Figure 2 and include synthetic pharmaceutical ligands (**7**−**11**), natural products (**12**−**14**), and synthetic analogues of olefin-containing natural products (**15** and **16**). Cromakalin[8] (**7**) and symakalin[9] (**8**) are potent activators of ATP-dependent potassium channels, while SB-204269[10] (**9**) was recently disclosed as a new antimigraine lead compound with a novel site of action. 4-Benzylpiperazinobenzopyran **10** has been shown to modulate multidrug resistance activity, whereas benzopyran **11** was reported as a highly selective inhibitor of phosphodiesterase IV.[11,12] The natural product β-lapachone (**12**) exhibits a broad range of antineoplastic activities,[13] while (+)-khellactone (**13**) and its numerous derivatives are known to have various

Scheme 1. Recently Reported Solid-Phase Strategy for Loading, Elaboration, and Cleavage of 2,2-Dimethylbenzopyrans[a]



[a] *o*-Prenylated phenols (**1**) are immobilized through cycloloading with a polystyrene-based selenenyl bromide resin to give resin-bound benzopyran scaffolds (**2**) which can be elaborated and subsequently cleaved *via* oxidation and spontaneous *syn*-elimination of the selenium tether.

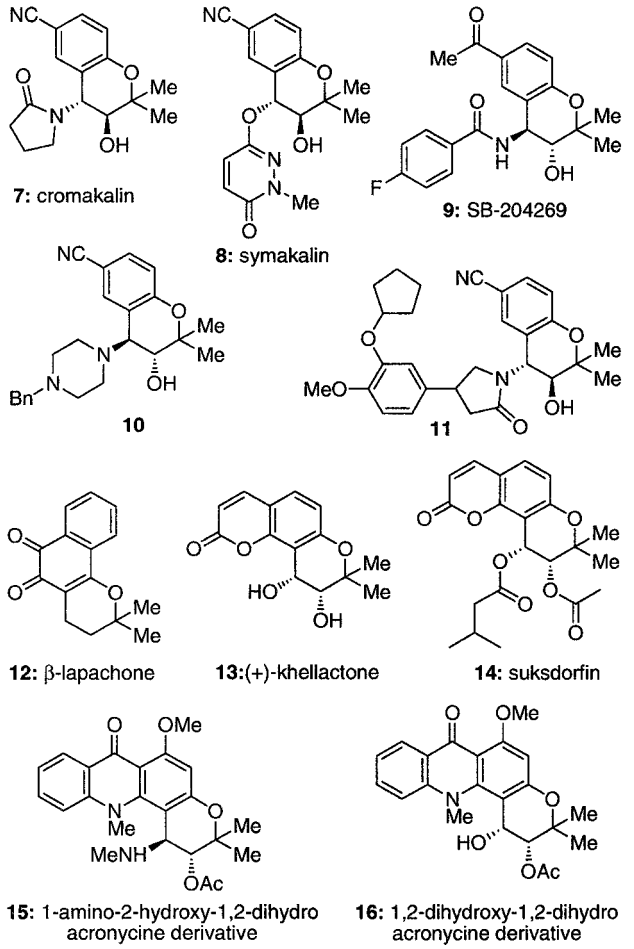


Figure 2. Selected examples of natural or designed biologically active benzopyrans in which the pyran olefin has been modified.

cytotoxic and antiviral activities.[14] One of the most studied (+)-khellactone derivatives, suksdorfin (**14**), is a potent anti-HIV agent acting through an unknown mechanism of action.[15] Compounds **15** and **16** are the 1-amino-2-acetoxy and 1-hydroxy-2-acetoxy synthetic analogues of the naturally occurring anticancer agent acronycine, and they exhibit improved cytotoxity profiles as compared to the parent natural product.[16]

The collection of structures in Figure 2 along with the additional 8 000 related structures uncovered by a search of chemical abstracts offered convincing evidence that the pyran olefin contained in our previous libraries represented a valuable site of latent diversity.[3,4] It was envisioned that modification of this position in copies of the original split-and-pool library would enhance both size and diversity while concomitantly increasing the pharmacological potential of library members. Such a "libraries from libraries" principle was originally introduced by

(7) The chemical abstracts search was performed using SciFinder. During the search for benzopyran ring system **6** (Figure 1) care was taken to exclude compounds which possessed the *Pmc* (2,2,5,7,8-pentamethylchroman-6-sulfonyl) peptide protecting group since such structures do not represent true derivatives of the benzopyran template.

(8) Ashwood, V. A.; Buckingham, R. E.; Cassidy, F.; Evans, J. M.; Faruk, E. A.; Hamilton, T. C.; Nash, D. J.; Stemp, G.; Willcocks, K. *J. Med. Chem.* **1986**, *29*, 2194−2201.

(9) Bergmann, R.; Eiermann, V.; Gericke, R. *J. Med. Chem.* **1990**, *33*, 2759−2767.

(10) Chan, W. N.; Evans, J. M.; Hadley, M. S.; Herdon, H. J.; Jerman, J. C.; Parsons, A. A.; Read, S. J.; Stean, T. O.; Thompson, M.; Upton, N. *Biorg. Med. Chem. Lett.* **1999**, *9*, 285−290.

(11) Hiessböck, R.; Wolf, C.; Richter, E.; Hitzler, M.; Chiba, P.; Kratzel, M.; Ecker, G. *J. Med. Chem.* **1999**, *42*, 1921−1926.

(12) Pinto, I. L.; Buckle, D. R.; Readshaw, S. A.; Smith, D. G. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1743−1746.

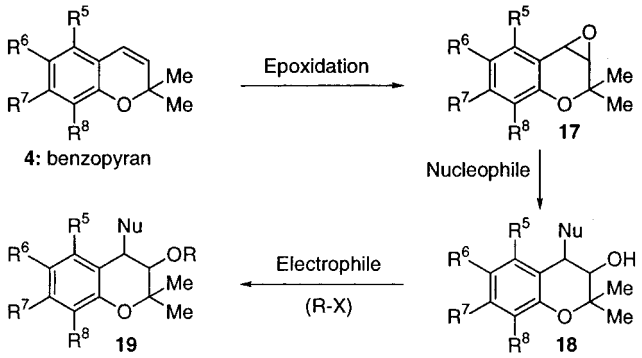
(13) (a) Wuerzberger, S. M.; Pink, J. J.; Planchon, S. M.; Byers, K. L.; Bornmann, W. G.; Boothman, D. A. *Cancer Res.* **1998**, *58*, 1876−1885. (b) Li, C. J.; Li, Y.-Z.; Ventura Pinto, A.; Pardee, A. B. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 13369−13374.

(14) (a) Lemmich, J.; Pedersen, P. A.; Nielsen, B. E. *Tetrahedron Lett.* **1969**, 3365−3366. (b) For examples of (+)-khellactone derivatives, see: Xie, L.; Takeuchi, Y.; Cosentino, M.; Lee, K.-H. *J. Med. Chem.* **1999**, *42*, 2662−2672, and references therein.

(15) Lee, T. T−Y.; Kashiwada, Y.; Huang, L.; Snider, J.; Cosentino, M.; Lee, K.-H. *Bioorg. Med. Chem.* **1994**, *2*, 1051−1056.

(16) (a) Elomri, A.; Mitaku, S.; Michel, S.; Skaltsounis, A.-L.; Tillequin, F.; Koch, M.; Pierré, A.; Guilbaud, N.; Léonce, S.; Kraus-Berthier, L.; Rolland, Y.; Atassi, G. *J. Med. Chem.* **1996**, *39*, 4762−4766. (b) Magiatis, P.; Mitaku, S.; Skaltsounis, A.-L.; Tillequin, F.; Koch, M.; Pierré, A.; Atassi, G. *Chem. Pharm. Bull.* **1999**, *47*, 611−614.

Scheme 2. Standard Method for Elaboration of Benzopyran Olefins



Houghten in 1994 when he described a strategy whereby a primary peptide library was constructed and then used, in essence, as the starting material for further chemical transformations, resulting in a second combinatorial library with enhanced properties.[5] Houghten's work focused on peptide-based libraries which were constructed and subsequently peralkylated, exhaustively reduced, and/or transformed into various heterocycles.[5] Given the success of these efforts, we anticipated that a similar strategy might be employed with nonoligomeric small organic molecules such as the current benzopyrans which represent a desirable class of potential ligands and drug candidates. It seemed intuitive that enhancing the size (and presumably the diversity) of a library through the introduction of additional sites of diversity is a superior strategy as compared to simply creating an equally large library by using a greater number of building blocks to vary fewer overall sites of diversity.[17] Hence, we deliberated on potential methods to effect such transformations on these small molecule libraries. It was obvious that since the pyran olefin was generated during cleavage from the solid support, these changes could most likely not be introduced via our solid-phase methodology; consequently, we required a solution-phase method whereupon one could use copies of the split-and-pool library as starting points for new libraries.

A brief search of the literature revealed that one of the most established routes for derivatizing the olefinic site of benzopyran rings was through epoxidation as outlined in Scheme 2.[18] As shown, pyran **4** is converted to the corresponding epoxide **17** which is reacted with nucleophiles giving rise to alcohol **18**. This secondary alcohol can then be reacted with electrophiles to provide derivatized benzopyran **19**. It was envisaged that this same technique might be applied in parallel to libraries as outlined in Figure 3, whereby the compounds of the original pyran library, cleaved from solid support directly into 96-well microtiter plates, could be diluted and partitioned into multiple plates, thereby creating copies of the primary library. To each of the reaction wells would then be added a suitable epoxidizing agent to effect, in parallel, the transformation of each benzopyran to its corresponding epoxide. These epoxides could then be opened with various nucleophiles (one nucleophile for each copy of the library being used) and the resulting alcohols could also be further derivatized with electrophilic reagents if necessary. The overall effect of this strategy would be to multiply the size of the primary library and, at the same time, possibly enrich its physical and pharmacological properties.

Development of Parallel Solution-Phase Methods. While conceptually attractive, the implementation of such a proposal was contingent upon several key factors, including the following: (a) definition of a suitable method for the simultaneous epoxidation of diverse substrates in microtiter plates with no byproducts; (b) definition of suitable methods for opening of these epoxides with various nucleophiles (i.e. alcohols, amines, thiols, etc) wherein any excess or unreacted reagent could be readily scavenged; (c) definition of suitable methods for electrophilic derivatization of the products resulting from the epoxide opening such that any excess or unreacted reagent could be easily scavenged; and (d) development of suitable experimental techniques for transfer of starting materials and reagents, evaporation of solvents, sequestering of excess reagents, and characterization of final compounds. These challenges and their practical solutions will be discussed consecutively, culminating in the application of the developed techniques to the derivatization of two representative benzopyran libraries generated by the previously described solid-phase methods. Through the latter two studies, we will demonstrate the continuity (solid phase → solution phase) and generality of the described chemistry.

The first task required finding an efficient method to epoxidize the benzopyran olefins found in the original library. A critical aspect of this step required that the reagent be sufficiently general so that substrates with diverse electronic and steric environments could be epoxidized under similar reaction conditions, since one could imagine that a given microtiter plate would contain a heterogeneous mixture of compounds in its wells. Moreover, since the epoxidation reagent and its byproducts had to be easily removed from the epoxides after the reaction, it was apparent that either a solid supported epoxidizing reagent or a volatile solution phase oxidant would be the reagent of choice.

A search of the literature revealed multiple examples where organometallic epoxidation catalysts (typically chiral salen manganese complexes) have been immobilized on solid supports and used for the epoxidation of various olefinic substrates.[19] Very recently, Song et al. described such a system containing a polymer-bound (pyrrolidine salen)manganese(III) complex which, in the presence of a co-oxidant, could epoxidize benzopyran ring systems in high yield and good enantiopurities.[19a] A slight limitation of this and other related methods, however, is that the catalytic complex typically cannot be recycled and that one must also employ a stoichiometric co-oxidant (i.e. *m*-CPBA, NMO, NaOCl, or PPNO) in the reaction mixture.[19] Thus, while the potential of such polymer-bound reagents in the current study was significant, we decided (for demonstration purposes) to pursue a nonchiral solution-phase epoxidation method at least in the initial phases. This decision simplified the chemistry. Furthermore, once the complete protocol was

(17) For an insightful review of library diversity, see: Kauvar, L. M.; Laborde, E. *Curr. Opin. Drug Discovery Dev.* **1998**, *1*, 66−70 and references therein.

(18) For a representative example, see: Rovnyak, G. C.; Ahmed, S. Z.; Ding, C. Z.; Dzwonczyk, S.; Ferra, F. N.; Humphyreys, W. G.; Grover, G. J.; Santafianos, D.; Aywal, K. S.; Baird, A. J.; McLaughlin, L. G.; Normandin, D. E.; Sleph, P. G.; Traeger, S. C. *J. Med. Chem.* **1997**, *40*, 24−34 and references therein.

(19) (a) Song, C. E.; Roh, E. J.; Yu, B. M.; Hi, D. Y.; Kim, S. C.; Lee, K.-J. *Chem. Commun.* **2000**, 615−616. (b) Kim, G.-J.; Shin, J.-H. *Tetrahedron Lett.* **1999**, *40*, 6827−6830. (c) Angelino, M. D.; Laibinis, P. E. *Macromolecules* **1998**, *31*, 7581−7587. Pozzi, G.; Cinato, F.; Montanari, F.; Quici, S. *Chem. Commun.* **1998**, 877−878. (d) Janssen, K. B. M.; Laquiere, I.; Dehaen, W.; Parton, R. F.; Vankelecom, I. F. J.; Jacobs, P. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3481−3487. (e) Vankelecom, I. F. J.; Tas, D.; Parton, R. F.; de Vyver, V. V.; Jacobs, P. A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1346−1348. (f) Sabater, M. J.; Corma, A.; Domenech, A.; Fornés, V.; García, H. *Chem. Commun.* **1997**, 1285−1286. (g) Minutolo, F.; Pini, D.; Salvadori, P. *Tetrahedron Lett.* **1996**, *37*, 3375−3378. (h) Minutolo, F.; Pini, D.; Petri, A.; Salvadori, P. *Tetrahedron: Asymmetry* **1996**, *7*, 2293−2302. (i) De, B. B.; Lohray, B. B.; Sivaram, S.; Dhal, P. K. *Tetrahedron: Asymmetry* **1995**, *6*, 2105−2108. (j) De, B. B.; Lohray, B. B.; Dhal, P. K. *Tetrahedron Lett.* **1993**, *34*, 2371−2374.

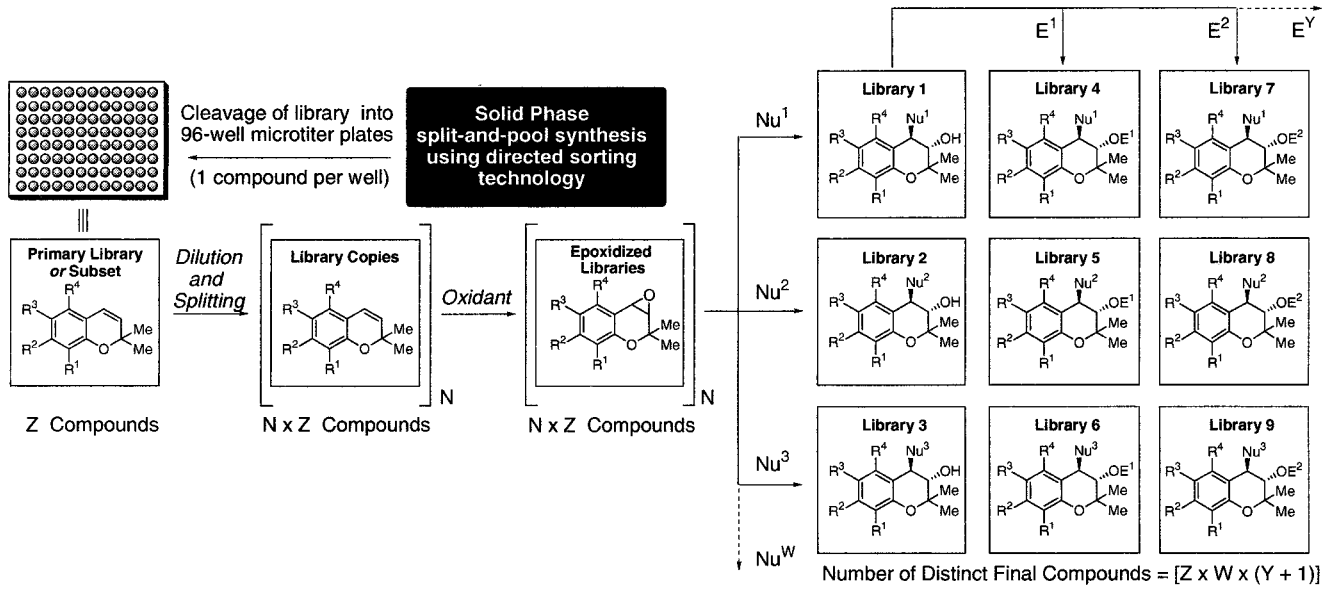


Figure 3. Proposed application of "libraries from libraries" concept to enhance the size and diversity of benzopyran libraries. A benzopyran library is initially constructed using solid-phase split-and-pool synthesis, and it is formatted into 96-well microtiter plates upon cleavage with one compound per well. The compounds in these wells are then dissolved in solvent and partitioned among *N* microtiter plates. All compounds can then either be retained as final compounds or reacted with suitable electrophiles (E^1 through E^y).

established, other methods of epoxidation (both chiral or nonchiral) could easily be incorporated to suit the needs of the particular library at hand.

The search for a volatile solution-phase epoxidizing agent focused on the dioxirane family [DMDO (dimethyl dioxirane) and MTMDO (methyl[trifluromethyl]dioxirane)] of oxidants.[20] Encouragingly, Messeguer et al. reported epoxidation of a series of sensitive precocenes with DMDO at low temperatures.[21] Hence, we proceeded to test this reagent with a variety of benzopyran substrates from the libraries generated by the previous solid-phase studies. As shown in Table 1, these representative substrates possessed a varied array of substituents. In a typical case, the benzopyran in acetone at 0 °C was treated with a solution of freshly prepared DMDO[22] for 1 h and the reaction mixture was then concentrated under vacuum and analyzed by ^{1}H NMR spectroscopy. In all cases except entry 9 (Table 1), nearly complete conversion to the corresponding epoxide was observed. The more reactive MTMDO was also examined and found to effect similar conversions; however, the volatility of this reagent proved detrimental to its use in parallel synthesis, and accordingly, DMDO became the reagent of choice for all subsequent studies. One concern, particularly in light of reports by Messeguer et al. from the precocene series,[21] was the hydrolytic stability of the resulting benzopyran epoxides. Product stability was particularly important since an unavoidable consequence of performing a large number of epoxidations in parallel was that removal of excess reagents and solvent from the microtiter plates would likely require more time than would be expected for evaporation of a single reaction vessel by conventional techniques. Indeed, while we found most of these epoxides to be quite stable for several hours at 25 °C, we did observe small amounts (<10%) of hydrolysis products after a few hours, presumably via opening of the epoxide moiety by residual water from the reagent and/or solvent. It was, however, found that this undesirable hydrolysis could be substantially suppressed if the stock solution of DMDO in acetone was redistilled a second time onto 4 Å molecular sieves.[22] In addition, evaporation of excess reagent and solvent at 0 °C rather than 25 °C also reduced the amount of diol observed. Using both of these techniques in conjunction, hydrolysis of the epoxides was significantly reduced such that, on average, little or no diol was observed in the first 4 h after the epoxides were formed, thereby allowing a suitable time frame for multiple parallel elaborations.

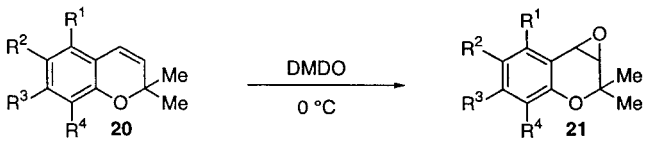
The second experimental consideration required the determination of a reliable method to open these epoxides with a variety of nucleophiles. Two requirements of this reaction were (a) high conversion in a reasonable time frame (<72 h) and (b) the ability to remove any unreacted reagent either through evaporation or sequestering with a solid-phase resin (vide infra). To begin our studies, we prepared a significant quantity of epoxide **22** (Table 2) via the previous oxidation procedure. This epoxide was then reacted with various oxygen, nitrogen, and sulfur nucleophiles as illustrated in Table 2. In a typical experiment the epoxide (**22**, Table 2) was treated with the nucleophile at 25 °C in a suitable solvent. After the indicated time period, the reaction mixture was concentrated under vacuum and analyzed by ^{1}H NMR spectroscopy. The experiments of entries 1−3 revealed that alkyl alcohols in the presence of catalytic amounts of Amberlyst-15 [H^+] resin resulted in complete conversion to the corresponding 1-alkoxy-2-hydroxybenzopyrans in ≤30 min. Opening of the epoxide with 4-nitro- and 4-methoxyphenols (entries 4 and 5) resulted in 77 and 88% conversions, respectively, after 24 h. Screening of several thiols (entries 7−9) revealed that such openings worked best with the thiol as solvent in the presence of a catalytic amount of Amberlyst-15 [H^+] resin (100% conversion over 24 h, entry 8). Last, a series of amines (entries 10−25) were screened, including alkylamines, anilines, and heterocyclic amines. As illustrated in Table 2, most of these amines exhibited substantial conversion after 72 h. Notable disappointments included no conversion for 2-pyrrolidinone (entry 25) and low conversion

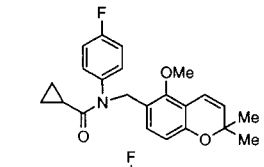
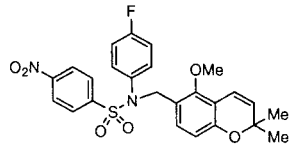
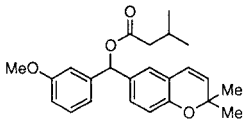
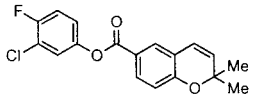
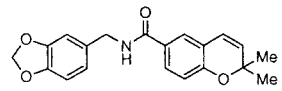
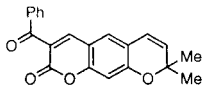
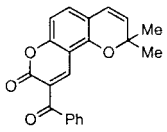
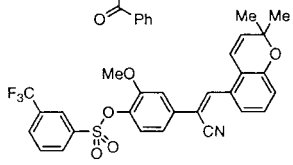
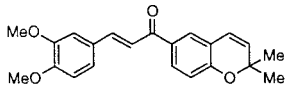
(20) For a previous example of dioxirane-based epoxidations in parallel solution-phase combinatorial chemistry, see: Bolli, M. H.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2243−2246.

(21) Bujons, J.; Camps, F.; Messeguer, A. *Tetrahedron Lett.* **1990**, *31*, 5235−5236. Also, see: Reisch, J.; Top, M. *Pharmzie*, **1991**, *46*, 745.

(22) Stock solutions of DMDO in acetone were prepared as previsouly described, see: Adam, W.; Chan, Y.-Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem.* **1987**, *52*, 2800−2803.

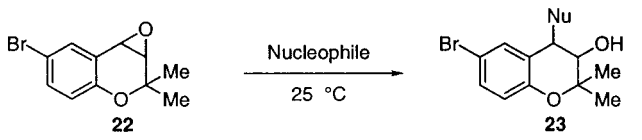
Table 1. Epoxidation of Selected Benzopyran-Containing Structures[a]



Entry	Substrate[b]	Time (h)	Conversion (%)[c]
1		1	84
2		1	95
3		1	100
4		1	99
5		1	100
6		1	81
7		1	100
8		1	100
9		4	50

[a]Reaction conditions: 4.0 equiv of DMDO, acetone, 0 °C. [b]See Reference 3 for preparation of substrates. [c] Conversion estimated by ^{1}H-NMR of crude reaction mixture. DMDO = dimethyldioxirane.

Table 2. Opening of Epoxide (**22**) with Various Nucleophiles[a]



Entry	Nucleophile[a]	Time (h)	Solvent	Catalyst[b]	Conversion (%)[c]
1	MeOH	0.5	MeOH	Am	100
2	EtOH	0.5	EtOH	Am	100
3	iPrOH	0.5	isopropanol	Am	100
4	4-NO_2phenol	24	CH_2Cl_2	Am	77
5	4-methoxyphenol	24	CH_2Cl_2	Am	84
6	AcOH[d]	0.5	CH_2Cl_2	Am	100
7	EtSH	72	CH_2Cl_2	-	50
8	EtSH[e]	24	EtSH	Am	100
9	iPrOH	72	CH_2Cl_2	-	50
10	NH_4OH	72	CH_2Cl_2	-	76
11	$MeNH_2$	48	CH_2Cl_2	-	100
12	*n*-butylamine[f]	72	CH_2Cl_2	-	62
13	3-ethoxy-*n*-propyl amine	72	CH_2Cl_2	-	72
14	isopropyl amine	72	CH_2Cl_2	-	17
15	cyclobutylamine	72	CH_2Cl_2	-	98
16	4-methylcyclohexylamine	72	CH_2Cl_2	-	50
17	aniline	72	CH_2Cl_2	-	90
18	4-fluoro-aniline	72	CH_2Cl_2	-	65
19	benzylamine	72	CH_2Cl_2	-	86
20	pyrrolidine	48	CH_2Cl_2	-	100
21	piperidiine	48	CH_2Cl_2	-	97
22	morpholine	72	CH_2Cl_2	-	84
23	5-aminotetrazole	72	CH_2Cl_2	-	58
24	imidazole	72	CH_2Cl_2	-	45
25	2-pyrrolidinone	72	CH_2Cl_2	-	0

[a]3.0 equiv of nucleophile was used unless otherwise noted. [b]Am = Amberlyst-15 [H^+] resin. [c]Conversion estimated by ^{1}H-NMR of crude reaction mixture. [d]Product was a mixture of esters. [e]EtSH was used as the solvent. [f]When 1:1 CH_2Cl_2:*n*-butylamine was used, 100% conversion was attained after 72 h.

for isopropylamine, imidazole, and 5-aminotetrazole (entries 14, 23, and 24, respectively).

As discussed above, an important experimental complication was that any excess or unreacted nucleophiles had to be removed or scavenged from the reaction wells before the compounds could be either screened or further derivatized.[23] In general, while the alcohols and thiols were all volatile such that any excess reagent was readily removed by evaporation under vacuum, the phenols were an exception and since they only displayed intermediate conversions in the previous test it was decided to exclude them from the present studies.[24] In contrast, however, many of the nonvolatile amines exhibited excellent reactivities and their unique structures would significantly enhance the diversity of the library; consequently, we required a method whereby the excess amine reagents could be effectively sequestered. This was readily accomplished, as demonstrated in Scheme 3, through the use of a polymer-bound isocyanate[25] as a scavenging agent. In the case shown, epoxide **22** was treated with the nonvolatile reagent morpholine (3.0 equiv) in CH_2Cl_2 for 72 h, after which time 4.0 equiv of polymer-bound methyl isocyanate[25,26] was added and the reaction vessel was agitated for 1 h. Removal of the resin and concentration afforded amino alcohol **24** in 100% yield with no evidence of residual morpholine.

The third experimental consideration was the development of various techniques whereby the products of the epoxide openings might be derivatized with electrophilic reagents. As outlined in Scheme 3, we briefly explored two general types of reactions. Initially, we considered acetylation of the resulting secondary alcohol, using amino alcohol **25** as a representative example. Hence, alcohol **25** was treated with Ac_2O (5.0 equiv) and polymer-bound 4-(*N*-benzyl-*N*-methylamino)pyridine[27] in CH_2Cl_2 and agitated for 24 h at 25 °C. The excess acylating agent was then scavenged by addition of polymer-bound tris-

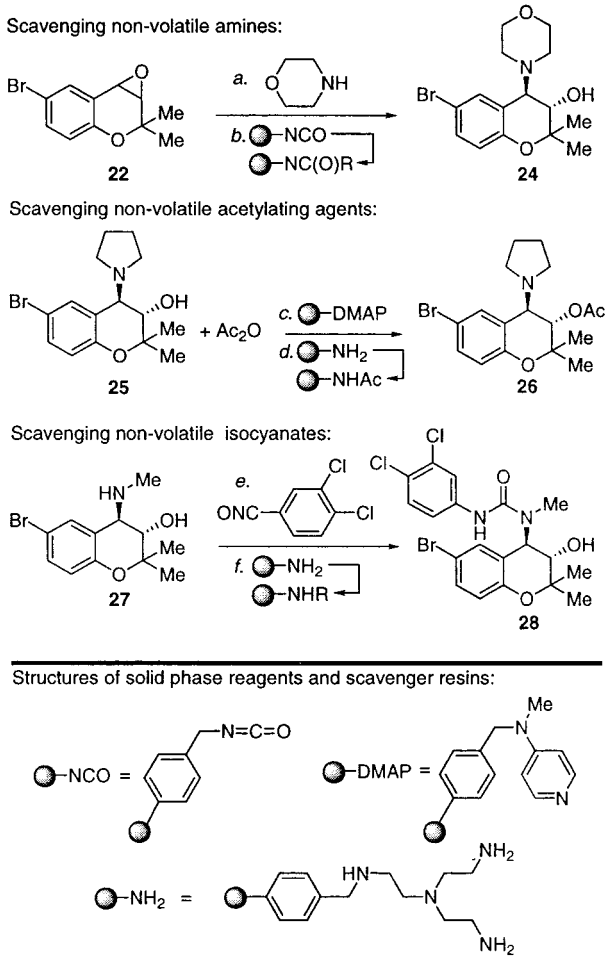
(23) For a review, see: Parlow, J.; Devraj, R. V.; South, M. S. *Curr. Opin. Chem. Biol.* **1999**, *3*, 320−336.

(24) It is noteable that several methods have been described for sequestering excess phenolic reagents. Therefore if desired, these types of nucleophiles could indeed be used in the current protocol. For examples, see: (a) Parlow, J. J. *Tetrahedron Lett.* **1996**, *37*, 5257−5260. (b) Xu, W.; Mohan, R.; Morrissey, M. M. *Tetrahedron Lett.* **1997**, *38*, 7337−7340.

(25) (a) Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. *Tetrahedron Lett.* **1996**, *37*, 7193−7196. (b) Kaldor, S. W.; Fritz, J. E.; Tang, J.; McKinney, E. R. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 3041−3044.

(26) Booth, J. R.; Hodges, J. C. *J. Am. Chem. Soc.* **1997**, *119*, 4882−4886.

Scheme 3. General Methods for the Use of Solid-Phase Reagents and Scavenger Resins for the Synthesis of Benzopyran Derivatives[a,b]



[a](a) 3.0 equiv of morpholine, CH_2Cl_2, 25 °C, 72 h; (b) 4.0 equiv of polymer-bound methylisocyanate (1.0 mmol/g), CH_2Cl_2, 25 °C, 1 h, 100%; (c) 5.0 equiv of Ac_2O, 3.0 equiv of polymer-bound 4-(*N*-benzyl-*N*-methylamino)-pyridine (2.0 mmol/g), CH_2Cl_2, 25 °C, 12 h, 90%; (d) 6.0 equiv of polymer-bound tris(2-aminoethyl)amine (4.5 mmol/g), CH_2Cl_2, 25 °C, 1 h, 100%; (e) 2.0 equiv of 3,4-dichlorophenylisocyanate, 25 °C, 1 h; (f) 3.0 equiv of polymer-bound tris(2-aminoethyl)amine (4.5 mmol/g), CH_2Cl_2, 25 °C, 1 h, 100%. [b]Yields are reported as conversion estimated by integration of ^{1}H-NMR signals.

(2-aminoethyl)amine[26] followed by agitation for an additional 1 h. Removal of the resins by filtration and subsequent concentration afforded 1-amino-2-acetoxybenzopyran **26** in 100% overall yield and >95% purity. In a second example, a secondary amine, introduced during epoxide opening with a primary amine, was derivatized by reaction with a representative isocyanate. Hence, 1-amino-2-hydroxybenzopyran **27** in CH_2Cl_2 at 25 °C was treated with 3,4-dichlorophenyl isocyanate. After 1 h, polymer-bound tris(2-aminoethyl)amine[26] was added to scavenge residual isocyanate reagent and the reaction vessel was agitated for an additional 1 h. Removal of the resin by filtration and concentration afforded urea **28** in 100% overall yield and in >95% purity.

With the various reaction pathways established, a final consideration before applying the developed strategy to the diversity enhancement of two representative benzopyran libraries was given to determining the appropriate experimental format. Even though the two demonstration libraries to be described are relatively small (50- and 120-membered), attention was paid to developing an experimental protocol that would accommodate the eventual construction of significantly larger libraries and be compatible with most currently available automated synthesis and liquid handling systems.[28] Hence, all reactions were conducted in Whatman MultiChem 96-well microtiter plates and filtrations were performed with Whatman Unifilter polypropylene fritted microtiter plates. The 96-well format was nicely suited to this method since the previously described automated cleavage from solid support formatted the compounds in 96-well plates. All dilutions and reagent additions were performed via multichannel pipets, while evaporation of solvents and volatile reagents from plates was accomplished either with a 96-channel argon manifold or a vacuum chamber. Finally, reaction agitation was carried out with orbital shakers, and low-temperature reactions were performed in a temperature-controlled room.

Diversity Enhancement of Pyranocoumarin and Sulfonamide Libraries. To provide a context for evaluating the practicality and generality of this proposed parallel solution-phase chemistry, the synthesis of two demonstration libraries was undertaken. In the first example, a 10-membered pyranocoumarin library was constructed by solid-phase chemistry and then derivatized to a series of 1,2-dihydroxy-, 1-alkoxy-2-hydroxy- and 1-alkoxy-2-acetoxybenzopyrans, all of which are structurally similar to several reported cytotoxic antineoplastic agents.[29] Thus, as shown in Scheme 4, the starting pyranocoumarin olefin library was constructed as described in the preceding paper.[3] Briefly, scaffolds of type **29** were condensed with several β-keto esters and Wittig reagents in a split-and-pool fashion using IRORI MacroKans and radio frequency encoding[30] to afford structures of type **30** which were cleaved individually to provide a 10-membered pyranocoumarin library. This 10-membered library was then diluted, transferred to a microtiter plate, and partitioned into five copies (i.e. a total of 50 wells were occupied).[31] At 0 °C, a ca. 0.1 M solution of DMDO in acetone was added to each of the 50 wells and the plate was agitated for 1 h. The excess DMDO and reaction solvent were then evaporated at 0 °C using a positive argon pressure over a 15 min interval. To the individual rows of the plate, each containing a discrete copy of the original 10-membered library, was then added an alcohol R^3OH (i.e. H_2O, MeOH, EtOH (2 rows), or *i*-PrOH) along with a catalytic amount of Amberlyst-15 [H^+] resin and the plate was agitated at 25 °C for 1 h to effect opening of these epoxides to the alkoxy alcohol of type **33**. The resin was then removed by filtration and the resulting solutions (in wells) were concentrated and dried under vacuum. To demonstrate the feasibility of a subsequent electrophilic reaction, the compounds in one of the ethanol-treated rows were then acetylated. In the event, the starting

(27) Purchased from Aldrich Chemical Co. (Milwaukee, WI).

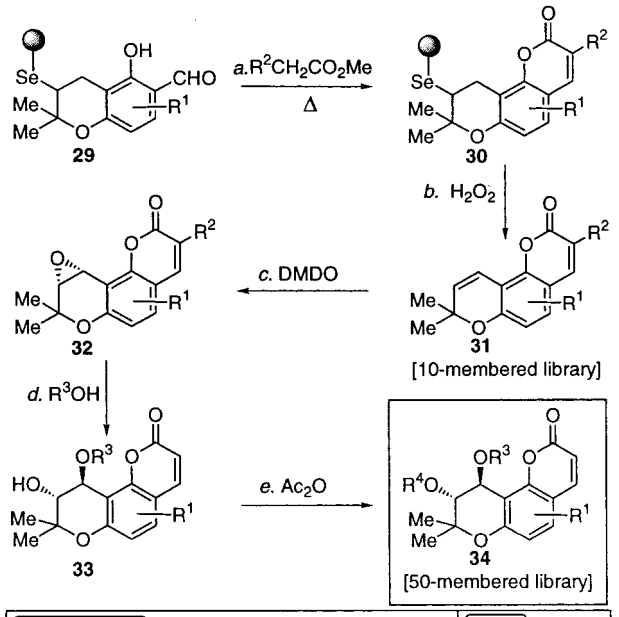
(28) For a review of relevant automation technologies, see: Bondy, S. S. *Curr. Opin. Drug Discovery Dev.* **1998**, *1*, 116−119.

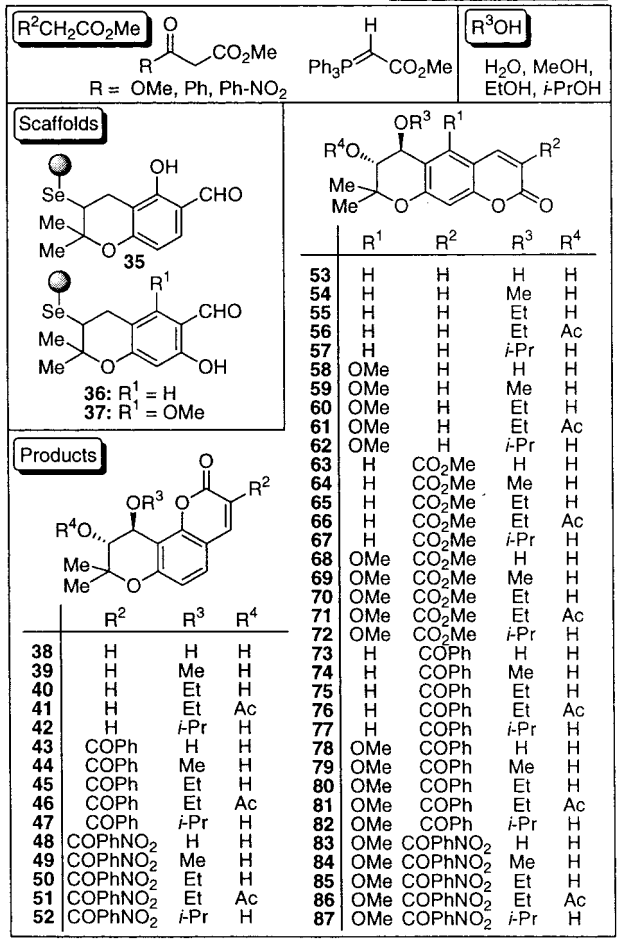
(29) (a) Duh, C.-Y.; Wang, S.-K.; Wu, Y.-C. *Phytochemistry* **1991**, *30*, 2812−2814. (b) Duh, C.-Y.; Wang, S.-K.; Wu, Y.-C. *Phytochemistry* **1992**, *31*, 1829−1830. (c) Magiatis, P.; Melliou, E.; Skaltsounis, A.-L.; Mitaku, S.; Léonce, S.; Renard, P.; Pierré, A.; Atassi, G. *J. Nat. Prod.* **1998**, *61*, 982−986.

(30) (a) Nicolaou, K. C.; Xiao, X.-Y.; Parandoosh, Z.; Senyei, A.; Nova, M. P. *Angew. Chem., Int. Ed. Engl.* **1995**, *107*, 2476−2479. (b) Moran, E. J.; Sarshar, S.; Cargill, J. F.; Shahbaz, M. J. M.; Lio, A.; Mjalli, A. M. M.; Armstrong, R. W. *J. Am. Chem. Soc.* **1995**, *117*, 10787−10788. We thank Mr. Rick Brown of Discovery Partners International (DPI) for a generous gift of IRORI MacroKans (K.C.N. is an advisor of DPI).

(31) For these method development experiments, 3.0 mg of compound was distributed to each well of the microtiter plate to facilitate ^{1}H NMR analysis of the final products; however, significantly smaller quantities (i.e. <0.1 mg/per well) could be employed once the protocol is validated.

Scheme 4. Solid-Phase Synthesis and Solution-Phase Amplification of Pyranocoumarin Library[a,b]





	R²	R³	R⁴
38	H	H	H
39	H	Me	H
40	H	Et	H
41	H	Et	Ac
42	H	*i*-Pr	H
43	COPh	H	H
44	COPh	Me	H
45	COPh	Et	H
46	COPh	Et	Ac
47	COPh	*i*-Pr	H
48	$COPhNO_2$	H	H
49	$COPhNO_2$	Me	H
50	$COPhNO_2$	Et	H
51	$COPhNO_2$	Et	Ac
52	$COPhNO_2$	*i*-Pr	H

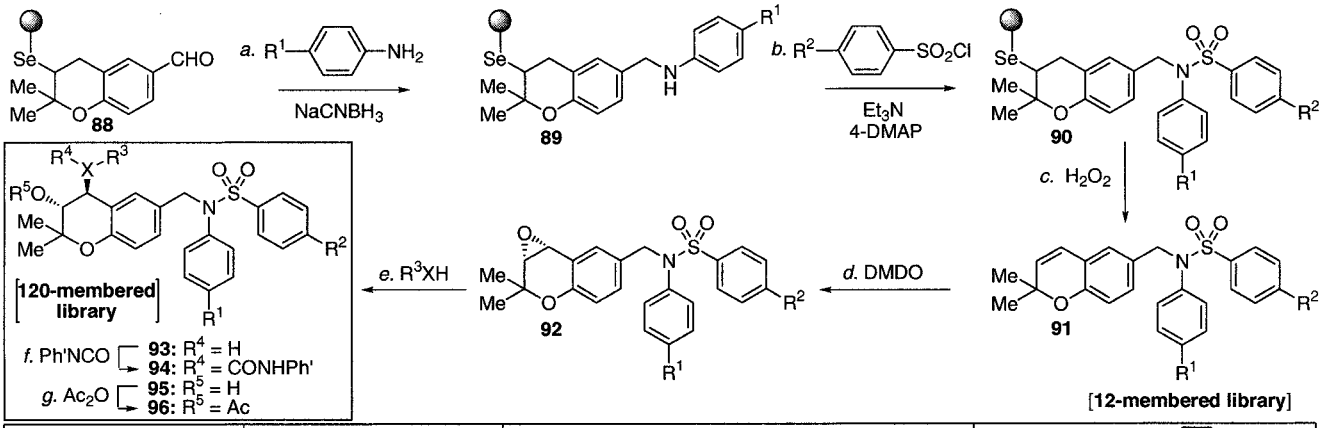
	R¹	R²	R³	R⁴
53	H	H	H	H
54	H	H	Me	H
55	H	H	Et	H
56	H	H	Et	Ac
57	H	H	*i*-Pr	H
58	OMe	H	H	H
59	OMe	H	Me	H
60	OMe	H	Et	H
61	OMe	H	Et	Ac
62	OMe	H	*i*-Pr	H
63	H	CO_2Me	H	H
64	H	CO_2Me	Me	H
65	H	CO_2Me	Et	H
66	H	CO_2Me	Et	Ac
67	H	CO_2Me	*i*-Pr	H
68	OMe	CO_2Me	H	H
69	OMe	CO_2Me	Me	H
70	OMe	CO_2Me	Et	H
71	OMe	CO_2Me	Et	Ac
72	OMe	CO_2Me	*i*-Pr	H
73	H	COPh	H	H
74	H	COPh	Me	H
75	H	COPh	Et	H
76	H	COPh	Et	Ac
77	H	COPh	*i*-Pr	H
78	OMe	COPh	H	H
79	OMe	COPh	Me	H
80	OMe	COPh	Et	H
81	OMe	COPh	Et	Ac
82	OMe	COPh	*i*-Pr	H
83	OMe	$COPhNO_2$	H	H
84	OMe	$COPhNO_2$	Me	H
85	OMe	$COPhNO_2$	Et	H
86	OMe	$COPhNO_2$	Et	Ac
87	OMe	$COPhNO_2$	*i*-Pr	H

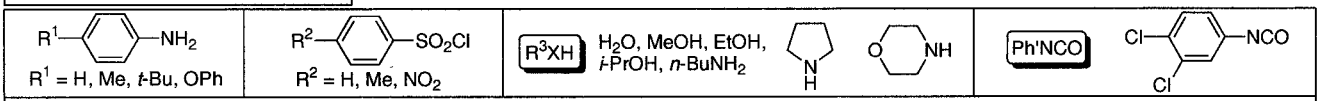
[a](a) For β-ketoester: 10.0 equiv of β-ketoester, 1.0 equiv of piperidine, EtCN, 95 °C, 2 h; For Wittig: 5.0 equiv of $Ph_3P=C(R^2)CO_2Me$, Et_2NPh, 165°C, 2 h; (b) 6.0 equiv of H_2O_2, THF, 25 °C, 20 min; (c) 4.0 equiv of DMDO, acetone, 0 °C, 1 h; (d) 0.2 equiv of Amberlyst-15 [H^+] resin, R^3OH, 25 °C, 30 min; (e) 5.0 equiv of Ac_2O, 3.0 equiv of polymer-bound 4-(*N*-benzyl-*N*-methylamino)-pyridine (2.0 mmol/g), CH_2Cl_2, 25 °C, 12 h; then 6.0 equiv of polymer-bound tris(2-aminoethyl)amine. [b]All products were characterized by ESMS and selected products by ^{1}H-NMR (see Supporting Information for data).

1-ethoxy-2-hydroxybenzopyrans were dissolved in CH_2Cl_2 and treated with Ac_2O in the presence of polymer-bound 4-(*N*-benzyl-*N*-methylamino)pyridine[26] at 25 °C for 12 h at which point polymer-bound tris(2-aminoethyl)amine[25] was added to scavenge the remaining Ac_2O. The resins were then removed by filtration and the filtrates were concentrated to provide the expected 1-ethoxy-2-acetoxypyranocoumarin series (**41**, **46**, **51**, **56**, **61**, **66**, **71**, **76**, **81**, and **86**). With the chemistry now complete, the final 50-compound library (**38**−**87**, Scheme 4) was analyzed to determine compound integrity and purity. All 50 compounds were analyzed by ESMS with 41/50 confirmed hits. In addition, 11 randomly selected compounds were analyzed by ^{1}H NMR spectroscopy and found to be of high purity (>85%), with water typically being the only observed contaminant (see Supporting Information for ESMS data and representative spectra). Notably, the majority of the 9/50 compounds for which the parent mass peak was not found contained an aromatic nitro group, and NMR analysis of several indicated that the desired product was in fact present suggesting that these compounds may simply be fragmenting to a considerable extent during mass spectrscopy.

A second combinatorial application of this methodology is outlined in Scheme 5 for the solid-phase synthesis and solution-phase multiplication of a benzopyran-based sulfonamide library. The initial 12-membered, olefin-containing library was synthesized in a directed split-and-pool fashion using IRORI Macro-Kans and radio frequency encoding,[30] as described in the previous paper.[3,4] Briefly, aldehyde scaffold **88** underwent a reductive amination in the presence of substituted anilines and sodium cyanoborohydride to afford resin-bound secondary amines of type **89** which were then reacted with substituted benzenesulfonyl chlorides to afford sulfonamides of type **90**. Oxidative cleavage of these sulfonamides resulted in a 12-membered library (structures of type **91**) which was diluted with CH_2Cl_2 and partitioned out into 10 copies for a total of 120 compounds each in individual wells.[31] To these 120 reaction wells in parallel was added a solution of DMDO in acetone at 0 °C. After agitation for 1 h at 0 °C, the excess reagent and solvent were removed by positive argon pressure followed by evaporation under vacuum. To the resulting epoxides was then added a series of nucleophiles as follows: (a) five copies were reacted with hydroxyl-containing nucleophiles [H_2O, MeOH, EtOH (×2), and *i*-PrOH] in the presence of a catalytic amount of Amberlyst-15 [H^+] resin, and (b) five copies were reacted with amines [*n*-$BuNH_2$ (×2), pyrrolidine (×2), morpholine]. After 1 h at 25 °C, the alcoholic openings were complete and the Amberlyst-15 [H^+] resin was removed by filtration and the resulting filtrates were concentrated. One of the duplicate ethanol copies was then acetylated as described above to provide the corresponding 1-ethoxy-2-acetoxybenzopyran series (**100**, **110**, **120**, **130**, **140**, **150**, **160**, **170**, **180**, **190**, **200**, and **210**). The amine openings proceeded at 25 °C for 24 h, after which time the reaction wells containing volatile amines (i.e. *n*-$BuNH_2$ and pyrrolidine) were concentrated while to the morpholine-containing wells (nonvolatile) were added polymer-bound methyl isocyanate[25,26] (see Scheme 3) to scavenge the excess amine. Subsequent filtration and concentration then afforded the desired amino alcohols.[32] To further evaluate the potential of this strategy for the use of electrophilic reagents to elaborate these amino alcohol products, experiments with both acetic anhydride and a phenyl isocyanate were conducted. In the first event, one of the two copies of the pyrrolidine-opened benzopyrans was acetylated in CH_2Cl_2 by treatment with Ac_2O in the presence of polymer-bound 4-(*N*-benzyl-*N*-methylamino)pyridine[27] at 25

Scheme 5. Solid-Phase and Solution-Phase Synthesis of Benzopyran-Based Sulfonamide Library[a,b]





	R^3X	R^5		R^3X	R^4	R^5
97	HO	H	**102**	*n*-BuN	H	H
98	MeO	H	**103**	*n*-BuN	CONPh'	H
99	EtO	H	**104**	pyrrolidine		H
100	EtO	Ac	**105**	pyrrolidine		Ac
101	*i*-PrO	H	**106**	morpholine		H

	R^3X	R^5		R^3X	R^4	R^5
107	HO	H	**112**	*n*-BuN	H	H
108	MeO	H	**113**	*n*-BuN	CONPh'	H
109	EtO	H	**114**	pyrrolidine		H
110	EtO	Ac	**115**	pyrrolidine		Ac
111	*i*-PrO	H	**116**	morpholine		H

	R^3X	R^5		R^3X	R^4	R^5
117	HO	H	**122**	*n*-BuN	H	H
118	MeO	H	**123**	*n*-BuN	CONPh'	H
119	EtO	H	**124**	pyrrolidine		H
120	EtO	Ac	**125**	pyrrolidine		Ac
121	*i*-PrO	H	**126**	morpholine		H

	R^3X	R^5		R^3X	R^4	R^5
127	HO	H	**132**	*n*-BuN	H	H
128	MeO	H	**133**	*n*-BuN	CONPh'	H
129	EtO	H	**134**	pyrrolidine		H
130	EtO	Ac	**135**	pyrrolidine		Ac
131	*i*-PrO	H	**136**	morpholine		H

	R^3X	R^5		R^3X	R^4	R^5
137	HO	H	**142**	*n*-BuN	H	H
138	MeO	H	**143**	*n*-BuN	CONPh'	H
139	EtO	H	**144**	pyrrolidine		H
140	EtO	Ac	**145**	pyrrolidine		Ac
141	*i*-PrO	H	**146**	morpholine		H

	R^3X	R^5		R^3X	R^4	R^5
147	HO	H	**152**	*n*-BuN	H	H
148	MeO	H	**153**	*n*-BuN	CONPh'	H
149	EtO	H	**154**	pyrrolidine		H
150	EtO	Ac	**155**	pyrrolidine		Ac
151	*i*-PrO	H	**156**	morpholine		H

	R^3X	R^5		R^3X	R^4	R^5
157	HO	H	**162**	*n*-BuN	H	H
158	MeO	H	**163**	*n*-BuN	CONPh'	H
159	EtO	H	**164**	pyrrolidine		H
160	EtO	Ac	**165**	pyrrolidine		Ac
161	*i*-PrO	H	**166**	morpholine		H

	R^3X	R^5		R^3X	R^4	R^5
167	HO	H	**172**	*n*-BuN	H	H
168	MeO	H	**173**	*n*-BuN	CONPh'	H
169	EtO	H	**174**	pyrrolidine		H
170	EtO	Ac	**175**	pyrrolidine		Ac
171	*i*-PrO	H	**176**	morpholine		H

	R^3X	R^5		R^3X	R^4	R^5
177	HO	H	**182**	*n*-BuN	H	H
178	MeO	H	**183**	*n*-BuN	CONPh'	H
179	EtO	H	**184**	pyrrolidine		H
180	EtO	Ac	**185**	pyrrolidine		Ac
181	*i*-PrO	H	**186**	morpholine		H

	R^3X	R^5		R^3X	R^4	R^5
187	HO	H	**192**	*n*-BuN	H	H
188	MeO	H	**193**	*n*-BuN	CONPh'	H
189	EtO	H	**194**	pyrrolidine		H
190	EtO	Ac	**195**	pyrrolidine		Ac
191	*i*-PrO	H	**196**	morpholine		H

	R^3X	R^5		R^3X	R^4	R^5
197	HO	H	**202**	*n*-BuN	H	H
198	MeO	H	**203**	*n*-BuN	CONPh'	H
199	EtO	H	**204**	pyrrolidine		H
200	EtO	Ac	**205**	pyrrolidine		Ac
201	*i*-PrO	H	**206**	morpholine		H

	R^3X	R^5		R^3X	R^4	R^5
207	HO	H	**212**	*n*-BuN	H	H
208	MeO	H	**213**	*n*-BuN	CONPh'	H
209	EtO	H	**214**	pyrrolidine		H
210	EtO	Ac	**215**	pyrrolidine		Ac
211	*i*-PrO	H	**216**	morpholine		H

[a](a) 10.0 equiv of aniline, THF, 65 °C, 4 h; then 15.0 equiv $NaCNBH_3$, THF, 65 °C, 6 h; (b) 10.0 equiv of sulfonyl chloride, 20.0 equiv of Et_3N, 1.0 equiv of 4-DMAP, CH_2Cl_2, 25 °C, 12 h; (c) 6.0 equiv of H_2O_2, THF, 25 °C, 30 min; (d) 4.0 equiv of DMDO, acetone, 0 °C, 1 h; (e) For alcohols: 0.2 equiv of Amberlyst-15 [H^+] resin, R^3OH, 25 °C, 1 h; For amines: 12.0 equiv of R^3NH, CH_2Cl_2, 25 °C, 24 h; (f-g) See Scheme 3. [b]All products were characterized by ESMS and selected products by ^{1}H-NMR (see Supporting Information for data).

°C for 24 h, after which time polymer-bound tris(2-aminoethyl)-amine[26] was added to scavenge the remaining Ac_2O. Subsequent filtration then afforded the desired 1-amino-2-acetoxybenzopyrans (**105**, **115**, **125**, **135**, **145**, **155**, **165**, **175**, **185**, **195**, **205**, and **215**). In a second example, one of the two *n*-$BuNH_2$-opened benzopyrans was reacted with 3,4-dichlorophenylisocyanate in CH_2Cl_2 at 25 °C for 2 h to afford the corresponding ureas (**103**, **113**, **123**, **133**, **143**, **153**, **163**, **173**, **183**, **193**, **203**, and **213**). The residual isocyanate reagent was then scavenged by addition of polymer-bound tris(2-aminoethyl)amine.[26] Upon completion of the library, members were evaluated for structural integrity and relative purity. As before, all compounds were analyzed by ESMS with 120/120 confirmed hits. A sample of 24 randomly selected compounds were also analyzed by ^{1}H NMR spectroscopy and found to be at least 80% pure in most cases, with many greater than 90% pure. This attests to the overall fidelity of both the solid- and solution-phase chemistry over the 6 or 7 steps required to synthesize these compounds (see Supporting Information for ESMS data and representative spectra).

Conclusion

In this paper we described a unique protocol whereby solution-phase combinatorial chemistry can be applied to enhance the size and properties of benzopyran libaries generated through solid-phase split-and-pool techniques. This work represents an application of Houghten's "libraries from libraries" strategy[5] to a nonoligomeric primary library; moreover, given the substantial literature precedent surrounding the types of modifications employed, it is anticipated that these transformations might significantly enhance the potential biological utility of these natural product-like libraries.

In conclusion, in this series of papers we have demonstrated the design, synthesis, and amplification of a biologically relevant small organic molecule library based upon a naturally occurring "privileged" structure. The combinatorial methods developed combined both solid- and solution-phase synthetic strategies, delivering over 10 000 natural and natural product-like compounds. Concomitantly, this work facilitated the development of a new solid-phase resin as well as a novel cycloloading-based linking strategy. It is anticipated that this current work in conjunction with an ongoing search for new reactions, technologies, and molecular diversity will contribute to the growing need for small molecule libraries to be used in screening against the many biological targets soon to be revealed by the deciphering of the human genome.

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Supporting Information Available: Experimental procedures for library preparation, tabulated ESMS data for all library members, and representative ^{1}H NMR spectra of crude cleavage products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(32) During preliminary test reactions using *n*-$BuNH_2$ or pyrrolidine with CH_2Cl_2 as solvent, a significant quantity of an unknown impurity was leached out of the chemically resistant microtiter plates (see Supporting Information for the ^{1}H NMR spectrum of impurity). It was found that this problem could be either minimized by pretreatment of the plates followed by washing or eliminated by insertion of Pyrex test tubes (6 × 50 mm, Corning product number 9820-6) into the round-bottom wells prior to addition of substrates and reagents. This latter method was employed whenever these two reagents were used.