Natural Product-like Combinatorial Libraries Based on Privileged Structures. 1. General Principles and Solid-Phase Synthesis of Benzopyrans

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Abstract: Herein we report a novel strategy for the design and construction of natural and natural product-like libraries based on the principle of *privileged structures*, a term originally introduced to describe structural motifs capable of interacting with a variety of unrelated molecular targets. The identification of such privileged structures in natural products is discussed, and subsequently the 2,2-dimethylbenzopyran moiety is selected as an inaugural template for the construction of natural product-like libraries via this strategy. Initially, a novel solid-phase synthesis of the benzopyran motif is developed employing a unique cycloloading strategy that relies on the use of a new, polystyrene-based selenenyl bromide resin. Once the loading, elaboration, and cleavage of these benzopyrans was established, this new solid-phase method was then thoroughly validated through the construction of six focused combinatorial libraries designed around natural and designed molecules of recent biological interest.

Introduction

Natural products play important roles in both drug discovery and chemical biology. In fact, many approved therapeutics as well as drug candidates are derived from natural sources.[1] Additionally, natural products have been extensively used to elucidate complex cellular mechanisms, including signal transduction and cell cycle regulation leading to the identification of important targets for therapeutic intervention.[2] As a result of recent advances in biology, there is now an increased demand for new natural product-like small molecules. Specifically, the fields of genomics and proteomics promise the rapid identification of large numbers of gene products for which small molecule modulators will be of both biological and medicinal interest.[3] Moreover, the combination of cell biology and high throughput technology has led to the development of various cellular assays in which small molecule libraries can be used to efficiently identify and help study previously unknown macromolecular targets.[4]

Despite the increased need for new natural products, their isolation and structure elucidation still remain a highly labor-intensive process.[5] As an alternative, chemists are now enlisting the tools of solid-phase combinatorial synthesis to construct libraries of natural product analogues and natural product-like compounds.[6] Many of these libraries attempt to emulate the structural characteristics observed in natural products but, at the same time, provide more rapid access to larger collections of products that possess greater diversity and incorporate optimized physical and pharmacological properties into their structures. A number of different strategies have emerged for making these libraries with the earliest efforts focused on the immobilization of complex natural product skeletons (usually derived from either semisynthesis or total synthesis) onto solid support to be used as scaffolds which are derivatized and cleaved to provide focused libraries. Examples of this approach include the construction of small libraries based upon the natural products yohimbine,[7] paclitaxel,[8] sarcodictyins,[9] and vancomycin.[10] In a related approach, the convergent total synthesis of several natural products has been achieved on solid support, and the use of multicomponent building block pools in these

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syntheses has resulted in the production of libraries as demonstrated for the prostaglandins,[11] epothilones,[12] muscones,[13] (*S*)-zearalenone,[14] and HPE.[15] To achieve the construction of larger (nontarget directed) libraries, Schreiber et al. has described several diversity-oriented solid-phase synthetic strategies used to create libraries of complex structures for screening in various chemical genetic applications.[16] More recently, a solid-phase combinatorial construction of carpanone-like libraries using a biosynthesis inspired reaction sequence was reported by Shair.[17] Finally, while not a chemical strategy per se, various genetic recombination techniques have been used to re-engineer microorganisms to synthesize "unnatural" natural products, especially in the area of polyketide biosynthesis.[18]

We now introduce a strategy for the construction of natural product-like libraries using the concept of *privileged structures*, a term first proposed by Evans et al. to describe select structural types (originally benzodiazepines and benzazepines) that bind to multiple, unrelated classes of protein receptors as high affinity ligands.[19] These privileged structures are typically rigid, polycyclic heteroatomic systems capable of orienting varied substituent patterns in a well-defined three-dimensional space.[20] The tendencies of derivatives of these privileged structures to exhibit binding affinity toward various receptors and enzymes has made them attractive scaffolds for discovery libraries, particularly in cases when there is only limited structural information available about the target.[19] The utility of this approach is readily evident by the numerous libraries which are designed and constructed on such scaffolds.[21,22]

Given the success of privileged structures in medicinal chemistry, we envisioned a similar application of this concept to the construction of natural product-like libraries, especially since the principal use of such libraries is to discover ligands for either unknown or recently discovered biological targets. We were particularly intrigued by the possibility that using scaffolds of natural origin, which presumably have undergone evolutionary selection over time, might confer favorable bioactivities and bioavailabilities to library members. Thus, we sought to identify privileged structural subunits found in biologically active natural products and use them as templates for the construction of libraries. Our generalized strategy is outlined in Figure 1. Accordingly, after identification of a motif, a suitable solid-phase methodology would be developed for the efficient loading, functionalization, and cleavage of compounds based on the structure of interest. The preliminary testing and refinement of this method is proposed to be accomplished through the solid-phase synthesis of various natural products and small demonstration libraries of analogues. It was reasoned that using focused libraries as a synthetic testing ground for the solid-phase chemistry will have a 3-fold advantage in that it (a) requires the testing of a wide variety of reactions in situations where the cleavage products could be carefully analyzed to determine reaction reliability, (b) would provide access to libraries focused around several natural products of current biological interest, thereby facilitating structure activity studies of these molecules, and (c) should create a collection of several hundred unique compounds that can be added to the larger, anticipated libraries to enhance overall diversity. Completion of these smaller libraries is expected to provide a basis set of solid-phase reactions amenable to the template of interest, and from this pool it would be possible to select several reaction sequences useful for the construction of a larger, more diverse natural product-like library. This latter effort might also require additional reaction validation as well as an appropriate high throughput encoding strategy such that cleavage of the members of this large library would result in a collection of spatially distinct compounds in a suitable format for biological screening as suggested in Figure 1.

To demonstrate these principles, in this and the following articles, we detail the construction of a 10 000-membered natural product-like library based on the 2,2-dimethylbenzopyran template, a structural motif found in numerous natural products. In this paper, we outline our rationale for selecting the benzopyran as a privileged structure and then describe the

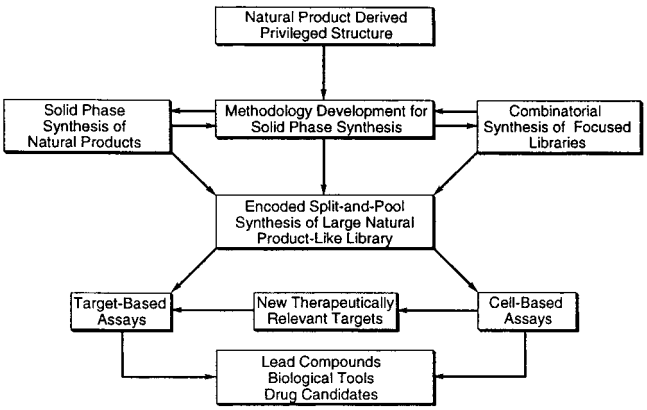

Figure 1. Overall strategy for the design, synthesis, and application of natural product-like combinatorial libraries based upon privileged structures.

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development of solid-phase chemistry for its construction through a unique cycloloading strategy.[23] The versatility and reliability of this cycloloading strategy is subsequently refined through the solid-phase synthesis of six small combinatorial libraries and various other natural and designed benzopyran-type molecules of recent medicinal interest. The following paper describes the application of this chemistry to the construction of a 10 000-membered natural product-like library paying particular attention to diversity assessment, quality control, use of a new encoding technology, and biological applications.[24] The final paper of this series describes a practical parallel solution phase approach for the diversity enhancement of these benzopyran libraries through the introduction of additional functionality on the pyran ring of the template.[25]

Results and Discussion

Selection of the Benzopyran as a Privileged Structure. From the outset, we were aware that ultimate success of these efforts was contingent on the proper choice of a privileged natural product motif to be used as a library template. In deliberating, we required a structure that was found as a subunit in a large number of natural products with diverse biological activities, and this template needed to accommodate the installation of a maximum degree of diversity via solid-phase split-and-pool synthesis. Furthermore, the scaffold should contain one or more rigid ring systems such that substituents would be presented to potential binding targets in a well-defined fashion. Finally, we required that the template be sufficiently lipophilic to ensure good cell membrane penetration, and that the majority of final library members be of less than 500 molecular weight.[26]

A search of chemical abstracts revealed the 2,2-dimethyl-2*H*-benzopyran moiety to be present in more than 4000 compounds including natural products and designed structures.[27] The relatively high incidence of this benzopyran unit (and its derivatives, vide infra) in natural products is partially attributable to the numerous prenylation and cyclization reactions in many polyketide biosynthesis pathways. Representative members of these natural products are illustrated in Figure 2 along with their reported biological activities. Examining the characteristics of compounds **1**−**44** (Figure 2) reveals their diverse structural properties, and more importantly, their wide ranging biological actions, suggesting that derivatives of this benzopyran motif may be capable of interacting with a variety of cellular targets. In addition, the fact that many of the structures are active in cell-based assays suggested that derivatives of the benzopyran unit remain sufficiently lipophilic to cross cell membranes, a key feature of any biologically relevant small molecule library.[26] These generalizations were corroborated by the fact that a variety of designed pharmaceutical ligands containing the motif have recently been disclosed, including compounds **40**−**44** (Figure 2); furthermore, a topographical analysis of structures of known therapeutics identified the benzopyran moiety as a preferential framework for drug design.[28] A final, more subtle, advantage to the use of the 2,2-dimethylbenzopyran template is that the olefin of the pyran ring constitutes a latent site of diversity. In other words, while this olefin will not be modified in the primary library, one could envision a range of subsequent modifications that could be used to either increase library diversity or enhance the properties of a particular lead structure. Such pyran olefins are readily modified by hydrogenation, epoxidation, dihydroxylation, and aminohydroxylation giving rise to a large number of biologically active structures,[27] prominent examples of which include the ATP-dependent potassium channel activator cromakalim[70] (**45**, Figure 3), the anti-HIV agent suksdorfin[71] (**46**, Figure 3), and the antineoplastic natural product β-lapachone[72] (**47**). The molecular diversity implementations of these modi-

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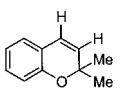
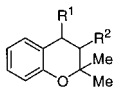


[Structure **1**]



[Structure **2**]

(i.e. hydrogenated, hydroxylated, aminohydroxylated, etc.) revealed an additional 8000 structures. For the diversity implications of this second search criteria, see the final paper of this series.[25]

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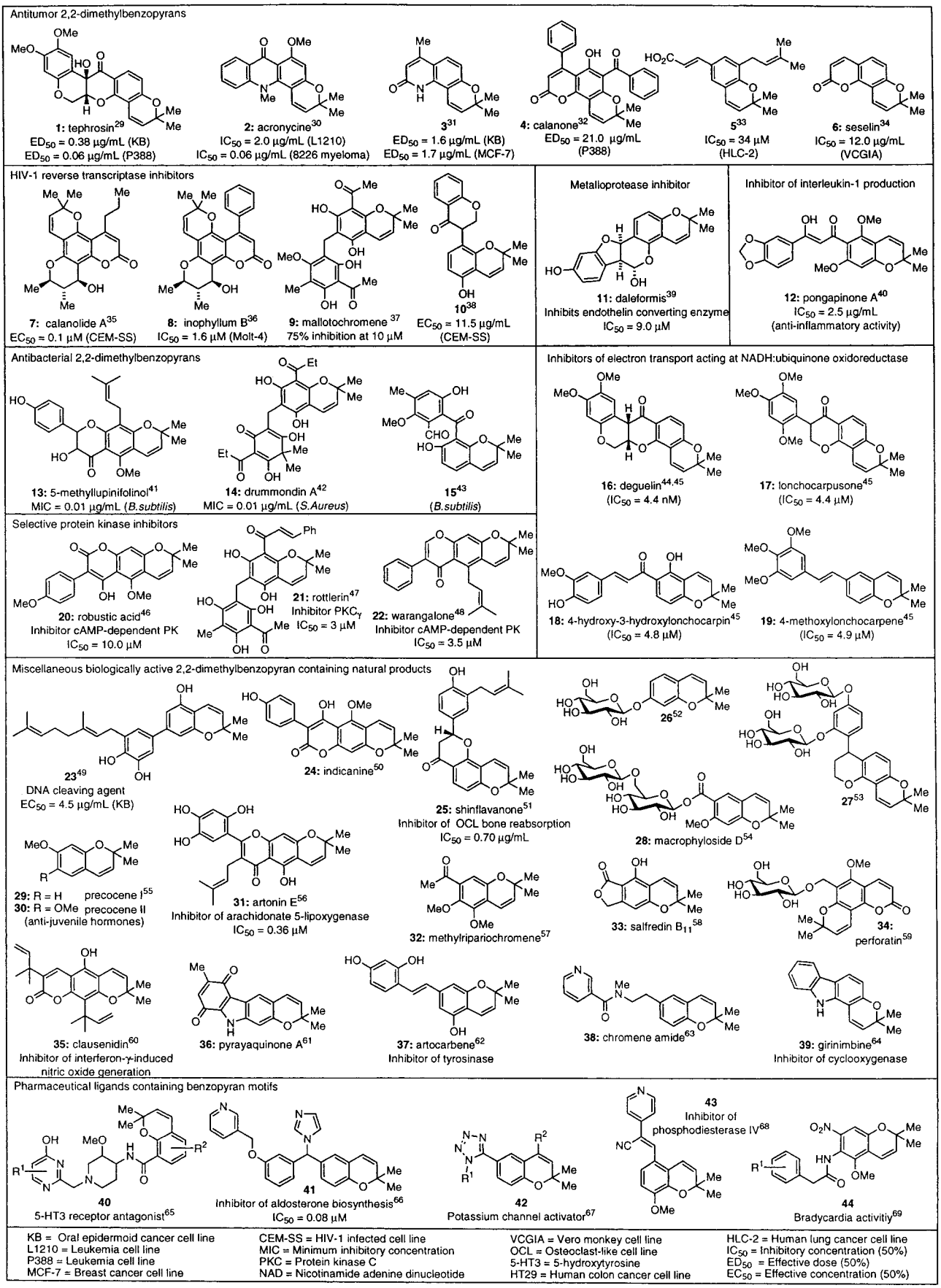


Figure 2. Selected examples of benzopyran containing natural products and pharmaceutical ligands along with reported biological activities.

fications and a unique parallel solution-phase strategy for introducing them into the current benzopyran libraries are discussed in the third paper of this series.[25]

Development of Solid-Phase Chemistry. When considering a solid-phase method to load, derivatize, and cleave the benzopyran motif, we were particularly interested in developing

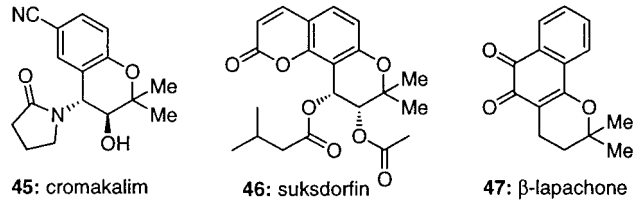
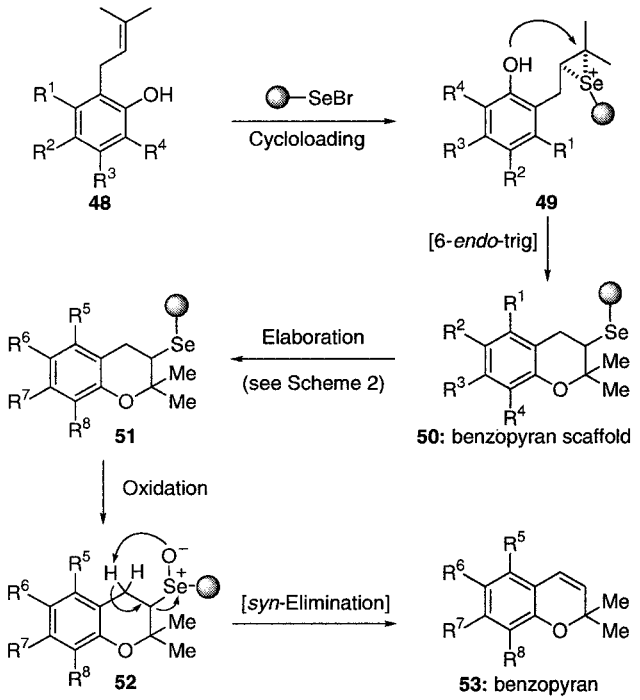


Figure 3. Selected examples of biologically active benzopyrans in which the pyran olefin has been modified.

a strategy whereby the loading and/or cleavage step(s) would contribute to the complexity of the target structure.[73] The versatility and efficiency of such a method is readily evident as it reduces the extraneous (noncomplexity building) operations typically associated with the loading/cleaving operations of a scaffold and also eliminates the issue of residual functionality in the target structure resulting from the linker. Well-suited to this application was a polystyrene-based selenenyl bromide resin recently developed in our laboratories[74a] which is capable of loading substrates through electrophilic cyclization reactions.[75] Thus, one could envision (as outlined in Scheme 1) the loading of an *o*-prenylated phenol (**48**, Scheme 1) through a precedented[76] 6-*endo*-trig cyclization to give resin-bound benzopyrans (**50**) linked to the resin through a selenoether. Such resin-bound scaffolds could then be elaborated (see Scheme 2) to a variety of natural and designed structures using the functionality of the aromatic ring. Such elaborations may include, but are not limited to, annulations, condensations, aryl/vinyl couplings, glycosidations, and organometallic additions as illustrated in Scheme 2. Subsequently, the desired benzopyran derivative can be released from solid support by oxidation of the selenide to the corresponding selenoxide which undergoes spontaneous *syn*-elimination at 25 °C. Besides its efficiency and chemical robustness (see Table 2), linking of the pyran ring offers the added advantage that all four positions of the aromatic ring (i.e. $R^1-R,^4$ structure **50** of Scheme 1) remain available for instal-

Scheme 1. Proposed Solid-Phase Loading, Elaboration, and Cleavage of 2,2-Dimethylbenzopyran.[a]



[a] *o*-Prenylated phenols (**48**) are immobilized through cycloloading with a polystyrene-based selenenyl bromide resin to give resin-bound benzopyran scaffolds (**50**) which can be elaborated and subsequently cleaved *via* oxidation and spontaneous *syn*-elimination of the selenium tether.

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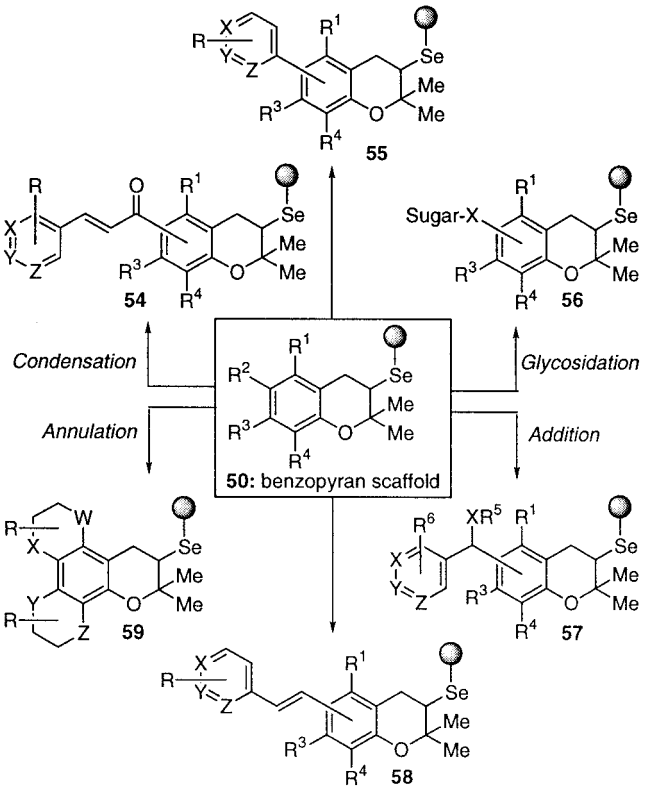
Scheme 2. Potential Reaction Pathways Leading to Structurally Diverse Derivatives of Resin-Bound Benzopyrans

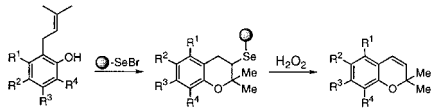


lation of diversity elements. This contrasts, for example, with the use of a more traditional linking strategy whereby the tether would likely be attached directly to the aromatic ring through either a phenol or aniline group. The disadvantage of the latter approach is that it (a) would remove a position of diversity on the aromatic ring (since one position is committed to the linker) and (b) would constrain all products to possessing either a phenolic or an amino group at that position.

In practice, the requisite selenenyl bromide resin (**64**, Scheme 3) was prepared[74a] from commercial polystyrene (1% DVB cross-linked, 100−200 mesh) via standard lithiation[77] followed by treatment with dimethyl diselenide to give methyl selenide **62**, a conjugate whose oxidation with bromine in $CHCl_3$ afforded ionic species **63**. Upon heating in ethanol, **63** fragmented providing desired selenenyl bromide resin **64** as a dark red polymer with swelling properties similar to typical cross-linked polystyrene. To date, well over a kilogram of this resin has been prepared in our laboratories with loadings ranging from 0.5 to 1.75 mmol/g (as controlled by the stoichiometry of the dimethyl diselenide reagent). After some experimentation, it was determined that a functionalization of 1.1 mmol/g was best suited for most synthetic applications and was thus employed for all further studies.

As shown in Table 1, a large number of *o*-prenylated phenols were prepared (see Supporting Information) and subsequently tested in the described cycloloading reaction. In a typical loading experiment, a suspension of selenenyl bromide resin **64** in CH_2Cl_2 at 25 °C was treated with a solution containing 2.0 equiv of *o*-prenylated phenol. Rapid resin decolorization was typically observed in under 5 min, presumably signifying consumption of the selenenyl bromide functionality. After 20 min, the resin was filtered, washed, and dried under vacuum. The success of each loading was determined by cleaving the reaction product via oxidation of the phenylseleno group to the corresponding selenoxide (H_2O_2, THF, 25 °C, 20 min) followed by *syn*-elimination and concomitant release of the product. Typically, a dilute solution of methyl sulfide in THF was then added to the reaction vessel to quench any remaining oxidant and the resulting solution was concentrated in vacuo.[78] All cleavage products were then analyzed by ^{1}H NMR spectroscopy and mass spectrometry (MS) to determine estimated purity. Loading proceeded smoothly in all cases except for phenols **76**, **99**, and **100 (**Table 1).[79] While the number of scaffolds prepared and tested considerably exceeds the actual number required for construction of most libraries, we sought to demonstrate, by these studies, the generality of this loading strategy and its

Table 1. Loading and Cleavage of 2,2-Dimethylbenzopyrans[a]



entry	phenol	prep[b]	R^1	R^2	R^3	R^4	purity[c] (%)
1	**65**	A	OH	H	H	H	95
2	**66**	A	H	OH	H	H	95
3	**67**	A	H	H	OH	H	95
4	**68**	A	OH	H	OH	H	95
5	**69**	A	H	H	OH	OH	95
6	**70**	A	H	H	H	OMe	95
7	**71**	A	OMe	H	OMe	H	95
8	**72**	A	OMe	H	H	H	95
9	**73**	C	H	Ac	H	H	95
10	**74**	A	H	Ac	OH	H	95
11	**75**	D	OH	Ac	H	H	95
12	**76**	C	H	H	H	Ac	- - -
13	**77**	C	H	CO_2Me	H	H	95
14	**78**	A	H	CO_2Me	OH	H	95
15	**79**	D	OH	CO_2Me	H	OH	95
16	**80**	C	H	CO_2Me	H	OMe	95
17	**81**	C	H	CO_2H	H	H	95
18	**82**	C	CN	H	H	H	95
19	**83**	C	H	CN	H	H	95
20	**84**	C	H	CN	H	OMe	95
21	**85**	C	H	H	CN	H	95
22	**86**	C	H	H	H	CN	95
23	**87**	C	H	NO_2	H	H	95
24	**88**	C	H	H	NO_2	Me	95
25	**89**	C	H	CHO	H	H	95
26	**90**	D	OH	CHO	H	H	95
27	**91**	A	H	CHO	OH	H	95
28	**92**	D	OMe	CHO	OH	H	95
29	**93**	A	Me	CHO	OH	H	95
30	**94**	A	H	CHO	OH	OMe	95
31	**95**	C	H	CHO	H	OMe	95
32	**96**	C	H	CHO	H	OEt	95
33	**97**	C	OMe	CHO	H	H	95
34	**98**	C	H	H	CHO	OMe	95
35	**99**	C	H	OMe	H	CHO	- - -
36	**100**	C	CHO	H	H	OMe	- - -
37	**101**	B	Br	H	H	H	90
38	**102**	B	H	Br	H	H	90
39	**103**	B	H	H	Br	H	95
40	**104**	B	H	H	H	Br	95
41	**105**	B	H	Br	OH	H	95
42	**106**	B	H	Me	H	Br	95
43	**107**	B	Br	H	H	OMe	95
44	**108**	B	I	H	H	H	95
45	**109**	B	H	I	H	H	95
46	**110**	B	H	H	I	H	95
47	**111**	B	H	H	H	I	95

[a] Loading conditions: 1.0 equiv of selenenyl bromide resin (1.1 mmol/g), 2.0 equiv of phenol, CH_2Cl_2, 0 → 25 °C, 20 min. [b] See Supporting Information for Methods A−D used in the preparation of phenolic substrates [c] Purity was estimated by integration of ^{1}H NMR signals of crude oxidative cleavage product.

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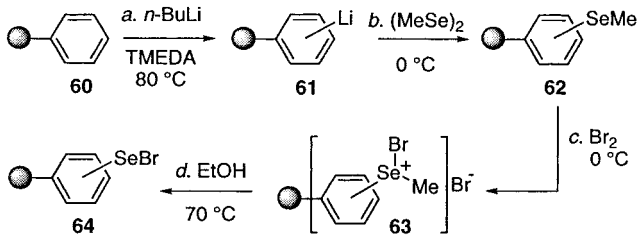
Scheme 3. Preparation of Selenium Functionalized Resin (**64**)[a]



[a](a) 0.6 equiv of *n*-BuLi, 1.0 equiv of polystyrene (1% cross-linked, 100-200 mesh), 0.5 equiv of TMEDA, cyclohexane, 65 °C, 4 h; (b) $(MeSe)_2$ (1.0 mmol/g polystyrene), THF, 0 °C, 20 min; (c) 1.0 equiv of Br_2, $CHCl_3$, 0 °C, 20 min; (d) EtOH, 75 °C, 2 h. TMEDA = N,N,N',N'-tetramethylethylenediamine.

tolerance to almost all aromatic functionality (R^1-R^4) without necessitating any nonproductive protecting group manipulations. Moreover, ready access to an array of scaffolds facilitated our reaction development studies, and it convincingly illustrates how this selenium-based linking strategy comprises a powerful tool for future combinatorial chemistry investigations of almost any natural product of the 2,2-dimethylbenzopyran family.

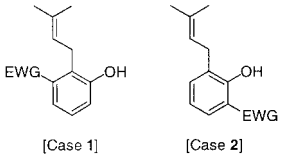
Solid-Phase Synthesis of Benzopyran Natural Products and Focused Libraries Thereof. With a large set of functionalized, resin-bound benzopyran platforms in hand, we were positioned to begin testing reaction pathways leading to various structural types of interest. At the same time, we were also interested in evaluating the stability of the selenium tether under a variety of chemical and physical conditions. In the context of these efforts, we targeted several benzopyran-containing products, including chalcones, pyranocoumarins, chromene glycosides, stilbenoids, polycyclic steroid biosynthesis inhibitors, *N*-heterocycles, and pyranoflavones.

The first of these libraries centered on a family of benzopyran-containing chalcones with important biological activities. Specifically, lonchocarpin (**131**, Scheme 4), 4-hydroxylonchocarpin (**134**), and 4-hydroxy-3-methoxylonchocarpin (**18**), all isolated from Cubé resin, have been shown to interrupt mitochondrial electron transport by inhibition of NADH:ubiquinone oxidoreductase (Complex I).[45] Interestingly, it has recently been shown that inhibition of NADH:ubiquinone oxidoreductase correlates strongly with reduction in the activity of an ornithine decarboxylase (ODC), an enzyme involved in the biosynthesis of polyamine growth factors.[80] Since ODC activity is unregulated in various cancer cells, blocking its activity holds promising chemotherapeutic and chemopreventive possibilities.[81] Separately, the bis-benzopyran-containing paratocarpin A (**148**, Scheme 4) has been reported to inhibit tumor invasion activity in the MCF-7/6 breast cancer cell line.[82] In light of these intriguing activities, we targeted these four natural products (**18**, **131**, **134**, and **148**) and their analogues as illustrated in Scheme 4. Hence, benzopyrans (**112**) bearing a methyl ketone substituent were condensed with various benzaldehydes (**119**−**126**) to produce, presumably, the β-hydroxy ketone adducts which were prone to spontaneous elimination to give resin-bound chalcones **113**.[83] Chalcones containing a THP protected phenol were treated with TsOH to reveal the free phenol, and subsequently, all products were cleaved from the resin by treatment with hydrogen peroxide in THF. As shown, application of this reaction sequence to scaffolds **116**−**118** and aldehydes **119**−**129** resulted in the formation of lonchocarpin (**131**), 4-hydroxylonchocarpin (**134**), 4-hydroxy-3-methoxylonchocarpin (**18**), and paratocarpin A (**148**) in 91, 82, 57, and 85% overall yields, respectively, along with 22 analogues in yields ranging from 25 to 90%.

The second natural product-based library is outlined in Scheme 5, which demonstrates the construction of linear and angular pyranocoumarins similar to the natural products xanthyletin (**207**, Figure 4), xanthoxyletin (**208**, Figure 4), and seselin (**6**, Figure 4). These three coumarins and their derivatives have been the focus of numerous biological investigations and they are reported to exhibit cytotoxic, anti-viral, and anti-platelet aggregation activities among others.[34,84] As illustrated, four major reaction pathways were developed to facilitate the split-and-pool combinatorial construction of these and other coumarin-type structures. Individual library members were identified by radiofrequency encoding using IRORI tags and MacroKan technologies.[85−87] All four reaction pathways commenced from resin-bound benzopyrans (**155**, Scheme 5) possessing an *o*-hydroxy aldehyde functionality. Treatment of these scaffolds with aryl, alkyl, or alkoxy β-ketoesters (**173**−**177** and **180**−**186**) in the presence of piperidine (EtCN, 95 °C) resulted in Knoevanagel condensation and concomitant transesterification to provide lactones of type **156** or **157**, respectively.[88] Moreover, treatment of scaffold **155** with substituted phenyl acetic acids (**187**−**190**) in the presence of DCC and 4-DMAP at 180 °C in DMSO resulted in the formation of 2-aryl

(78) Quenching with methyl sulfide proved most practical when cleaving large numbers of compounds simultaneously since the reagent can be conveniently added as a THF solution to all reaction vessels. After 10 min the resin can be removed and the filtrate concentrated directly to provide the desired benzopyran cleavage product. Given the volatility of methyl sulfide, any excess was removed during evaporation leaving only the desired cleavage product and a trace amount of DMSO (produced by oxidation of Me_2S). This residual DMSO is inconsequential since most samples are directly dissolved in DMSO for biological screening. As described in the following paper, it is this facile cleaving operation which greatly facilitated the use of automation in synthesizing the 10 000-membered library.[25] Incidentally, for individual cleavages of larger amounts of resin, one can also employ a standard aqueous workup using sodium sulfite to quench the residual oxidant (see Experimental Procedures in the Supporting Information for the details of both protocols).

(79) While loading failures were rare, they occurred for two specific substituent patterns, namely when electron-withdrawing groups [EWG] were situated either adjacent to the prenyl group [Case **1**] or adjacent to the phenolic group participating in the cyclization reaction [Case **2**]. In these cases, the desired scaffolds typically were loaded with the EWG masked.



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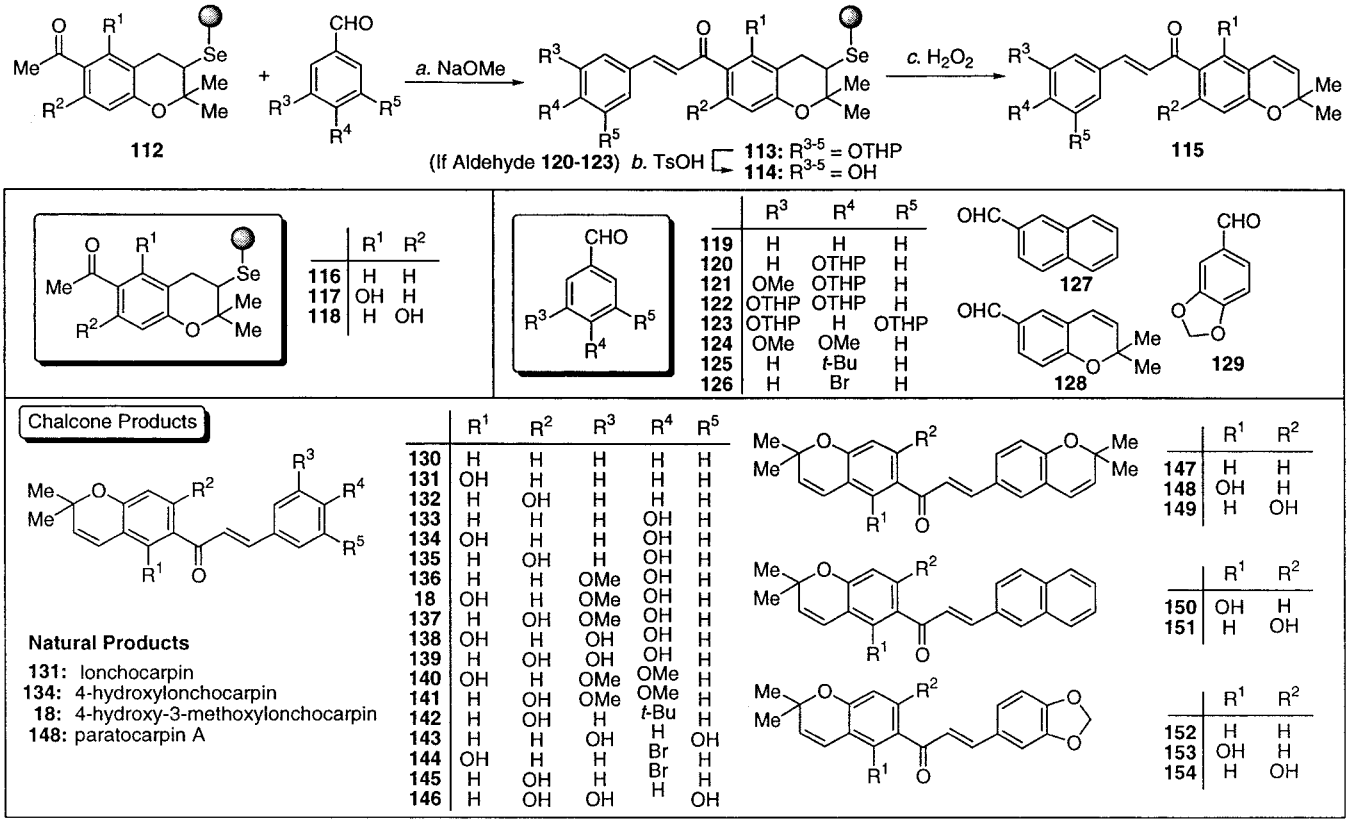
(86) A full discussion of the IRORI encoding and sorting technologies employed in these libraries is provided in the following paper.[25]

(87) 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).

Scheme 4. Parallel Solid-Phase Synthesis of Chalcone Natural Products (**18**, **131**, **134**, and **148**) and Analogues Thereof[a,b]



[a](a) 10.0 equiv of $R^{3\text{-}5}C_6H_4CHO$, 10.0 equiv of NaOMe, THF:MeOH (2:1), 25 °C, 72 h; (b) 2.0 equiv of $TsOH \cdot H_2O$, THF:MeOH (9:1), 25 °C, 1 h; (c) 6.0 equiv of H_2O_2, THF, 25 °C, 20 min. [b]Compounds obtained in less than 95% purity after cleavage were purified by chromatography. All products were characterized by ^{1}H-NMR and HRMS (See Supporting Information for data).

coumarins[89] of type **159**, while condensation of scaffold **155** with stabilized Wittig reagents (**171** and **172**) at 165 °C in *N*,*N*-diethylaniline afforded coumarins of type **160**.[90] At this stage, structures containing no further functionality were cleaved under standard conditions to provide benzopyrans of type **162**−**165**. In one of the two remaining cases, the protected phenol of **156** was liberated (TsOH) and alkylated with halides R^3X (**178** and **179**) before being oxidatively cleaved. In the other case, structures of type **157** containing an alkyl ester moiety were hydrolyzed [LiOH, THF:H_2O (20:1), 50 °C, 12 h] to provide the free acid **161**. Unfortunately, all attempts to effect coupling of this carboxylic acid (**161**) with either alcohols or amines were hampered by poor conversion, and as such the free acid itself was simply cleaved. Selected application of these reaction pathways to scaffolds **166**−**170** using the illustrated building blocks resulted in the construction of a 37-membered coumarin library, as shown in Figure 4, which included the natural products seselin (**6**), xanthyletin (**207**), and xanthoxyletin (**208**).

The third library was constructed based on a chromene glycoside (**245**, Scheme 6) isolated from *Ageratum conyzoides*.[52] Our interest in achieving the synthesis of carbohydrate-containing structures stems from the propensity of sugars to improve the solubility and cellular targeting of small organic molecules, thereby making them attractive combinatorial building blocks.[91] Hence, the trichloroacetimidates of three sugars, D-glucose (**231**), D-xylose (**235**), and L-rhamnose (**239**), were prepared by a three-step procedure consisting of peracetylation (Ac_2O, Et_3N, 4-DMAP), removal of the anomeric acetate (*n*-$BuNH_2$, THF, 25 °C), and formation of the trichloroacetimidates (Cl_3CCN, DBU, 0 °C) to afford **234**, **238**, and **242**, respectively, as illustrated in Scheme 7.[92] Using IRORI radiofrequency tagging and MacroKans, three phenol-containing scaffolds (**243**, **244**, and **251**) were simultaneously coupled with each sugar. These couplings were accomplished by treatment of a suspension of the phenolic scaffolds, trichloroacetimidates, and 4 Å molecular sieves with $BF_3 \cdot Et_2O$ at −40 °C and allowing the reactions to warm to 0 °C over 12 h. The resulting resin-bound chromene glycosides were then deprotected (**228** → **229**) [NaOMe, THF:MeOH (5:1), 24 h] and cleaved under standard oxidative conditions. Analysis of the cleavage products by ^{1}H NMR spectroscopy demonstrated that the couplings proceeded with complete stereoselectivity for the β-glycosides in all cases typically with purities of better than 90%. Encouraged by the facility and selectivity of these glycosidations, we next targeted a more complex carbohydrate containing benzopyran, namely macrophylloside heptaacetate (**263**, Scheme 7), the parent of which is a chromene glycoside isolated from *Gentiana macrophylla*.[54] Hence, the phenol of **255** was first methylated (MeI, NaH, DMF, 35 °C, 88%) and the methyl ester of the resulting product (**256**) was hydrolyzed to reveal the requisite free

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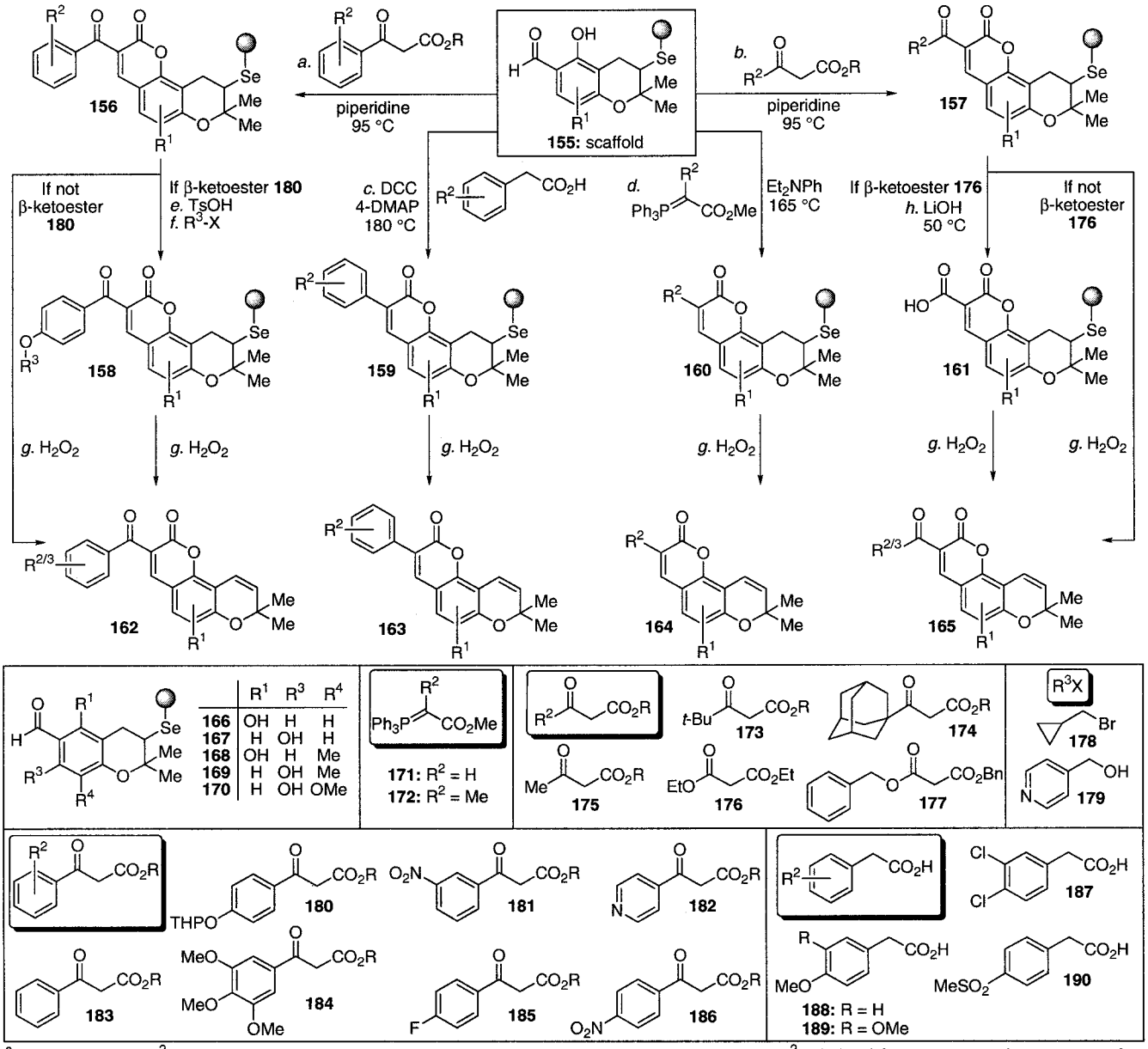
Scheme 5. Radiofrequency Encoded Split-and-Pool Synthesis of Linear and Angular Pyranocoumarins[a−c]



	R1	R3	R4
166	OH	H	H
167	H	OH	H
168	OH	H	Me
169	H	OH	Me
170	H	OH	OMe

[a](a) 10.0 equiv of $R^2C_6H_4C(O)CH_2CO_2R$, 5.0 equiv of piperidine, EtCN, 95 °C, 2 h; (b) 10.0 equiv of $R^2C(O)CH_2CO_2R$, 5.0 equiv of piperidine, EtCN, 95 °C, 2 h; (c) 5.0 equiv of $R^2C_6H_4CH_2CO_2H$, 5.0 equiv of DCC, 1.0 equiv of 4-DMAP, DMSO, 180 °C, 48 h; (d) 5.0 equiv of $Ph_3P{=}C(R^2)CO_2Me$, Et_2NPh, 165 °C, 2 h; (e) 2.0 equiv of $TsOH{\bullet}H_2O$, THF:MeOH (9:1), 25 °C, 1 h; (f) For R^3-X = **178**: 10.0 equiv of **178**, 15.0 equiv of K_2CO_3, DMF, 80 °C, 12 h; For R^3-X = **179**: 10.0 equiv of **179**, 10.0 equiv of PPh_3, 15.0 equiv of DEAD, CH_2Cl_2, 25 °C, 24 h; (g) 6.0 equiv of H_2O_2, THF, 25 °C, 20 min; (h) 5.0 equiv of $LiOH{\bullet}H_2O$, THF:H_2O (20:1), 50 °C, 12 h. [b]Compounds obtained in less than 95% purity after cleavage were purified by chromatography. All products were characterized by ^{1}H-NMR and HRMS (see Supporting Information for data). [c]See Figure 4 for structures of coumarin products.

carboxylic acid **257** ready for the first coupling reaction. In the event, treatment of carboxylic acid **257** and trichloroacetimidate **258**[93] with $BF_3{\cdot}Et_2O$ at −40 °C and then warming to 0 °C over 12 h resulted in smooth coupling to produce *β*-glycoside **259** (91%), which underwent selective deprotection upon treatment with HF·py to afford **260** in 89% yield. The second coupling between resin-bound substrate **260** and trichloroacetimidate **261** (prepared as shown in Scheme 6) proceeded under similar conditions affording **262** in 57% yield as a single anomer. Finally, the disaccharide was cleaved from the resin to afford heptaacetylated macrophylloside (**263**) in 18% isolated yield over six steps based on **255**.

As a fourth combinatorial application of this linking strategy, we undertook the synthesis of a recently reported aldosterone biosynthesis inhibitor[66] (**41**, Scheme 8) and various analogues of it, again using radiofrequency encoded split-and-pool techniques. The synthesis commenced with a halogen−metal exchange[94] of resin-bound aryl bromide **264** by treatment with excess *n*-BuLi at −78 °C and warming to 0 °C, after which time it was cooled to −78 °C and various aldehydes (**271**−**275**) were added. The reaction mixture was then warmed to 25 °C and stirred for 12 h (99% yield for the case of aldehyde **271**). The resulting benzhydrols (**266**) were then subjected to a standard Mitsunobu reaction (DEAD, Ph_3P, THF, 25 °C) with various imidazole derivatives (**276**−**280**) (85% yield for the case

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(94) Ding, C. Z. *Synth. Commun.* **1996**, *26*, 4267−4273.

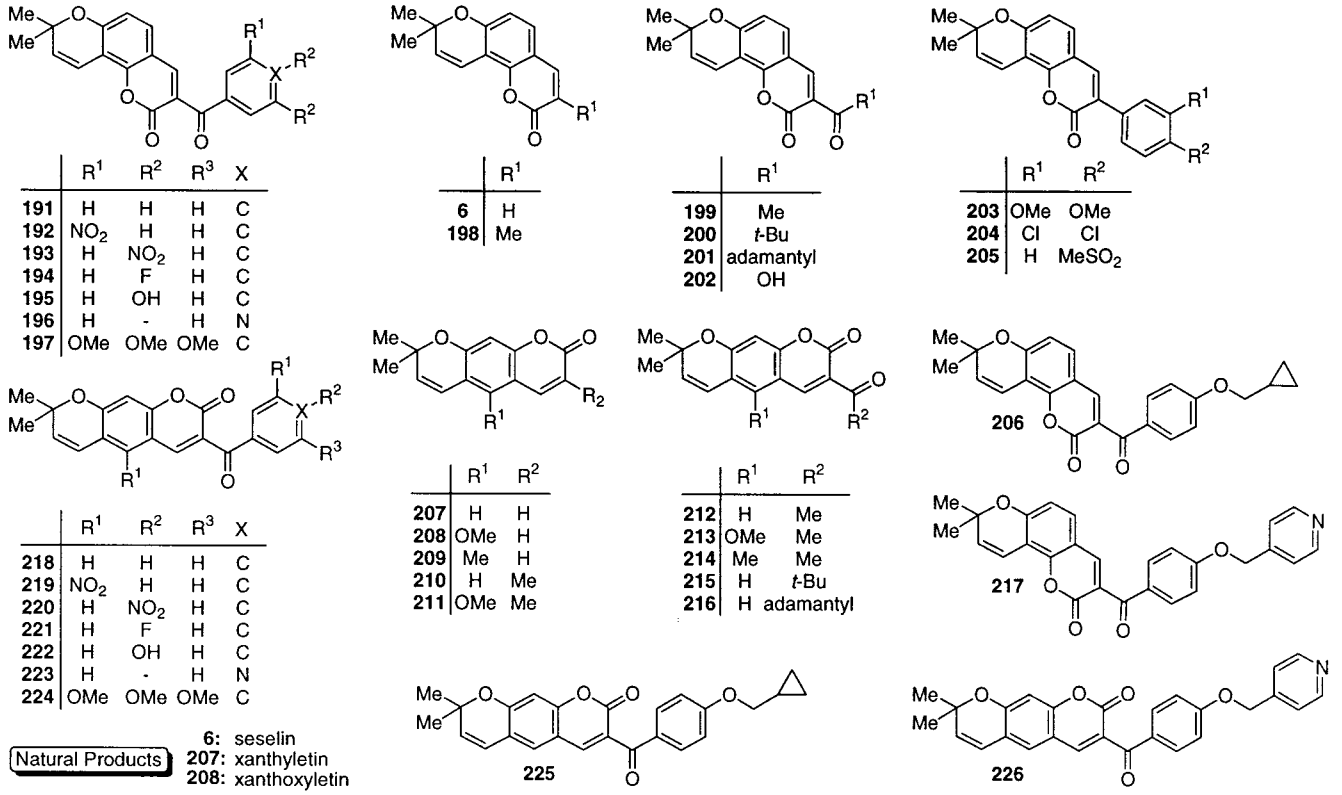

Figure 4. Linear and angular pyranocoumarin natural products (**6**, **207**, and **208**) and analogues generated from Scheme 5.

of aldehyde **272**, amine **276**).[66] At this juncture, those structures derived from aldehydes other than **272** were oxidatively cleaved to provide structures of type **268**, whereas those derived from aldehyde **272** were deprotected (TsOH, THF:MeOH (9:1), 25 °C) to reveal a phenolic group at the C-3 position (100% yield for the case of aldehyde **272** and amine **276**). The liberated phenol was then reacted with one of two benzyl alcohols (**281** or **282**) under Mitsunobu conditions, to furnish derivatives of type **269** which were cleaved to afford the previously reported compound (**41**, 75% overall yield based on **264**) and various structural analogues.

In a fifth library, we targeted a recently disclosed phosphodiesterase IV inhibitor (**43**, Figure 1 and Scheme 9) with a unique cyano-stilbenoid structure.[68] As outlined along the top of Scheme 9, these structures can be readily accessed by condensation of a resin-bound benzaldehyde with a substituted phenylacetonitrile. Unfortunately, the required aldehyde to synthesize phosphodiesterase inhibitor **43** failed to load as previously described.[79] We circumvented this difficulty through loading of the corresponding aryl bromide (**303**) followed by conversion to the desired aldehyde **304** through a halogen metal exchange[94] and quenching with DMF in 99% yield. Newly constructed scaffold **304** along with scaffolds **305** and **306** were then condensed with three heterocyclic phenylacetonitriles (**300**−**302**) in a parallel fashion, and the resulting stilbenoids were cleaved to afford the previously reported phosphodiesterase IV inhibitor **43** (72% overall yield**)** as well as several structural analogues.

In our sixth and final library, we continued to address the issue of installing *N*-heterocyclic functionality onto the benzopyran template. Specifically, we were interested in the synthesis of tetrazole structures similar to those found in potassium channel activator **42** (Figure 2).[67] Such tetrazoles are readily constructed from the corresponding aryl nitriles. Hence, a series of five nitrile-containing scaffolds (**320**−**324**, Scheme 10) were prepared and encoded for split-and-pool synthesis. Initially, all compounds were pooled and condensed with azidotrimethyltin (toluene, 100 °C, 12 h) to provide the corresponding stannylated tetrazoles.[95] The secondary nitrogens of these tetrazoles were liberated by washing with aqueous trifluoroacetic acid (TFA) and subsequently alkylated with various alkyl halides (**325**−**330**).[96] Finally, the resin-bound tetrazoles were cleaved under oxidative conditions to afford a series of substituted tetrazoles (**331**−**366**, Scheme 10).

To further evaluate the versatility of this selenium linking strategy and our ability to access other benzopyran-containing structures of interest, we undertook the solid-phase target-directed synthesis of several molecules as outlined in Scheme 11. In the first example, bromobenzopyran **264** was converted to the corresponding tri-*n*-butylstannane **367** through a halogen−metal exchange followed by quenching with *n*-Bu_3SnCl.[94] Tri-*n*-butylstannane **367** was then reacted with several aryl iodides under palladium(0)-catalyzed coupling conditions[97] to afford structures **368** and **369** which were subsequently cleaved to give compounds **370** (90%) and **371** (85%). Interestingly, while these electron-deficient aryl iodides coupled quite effectively, attempts to employ either unsubstituted or electron-rich aryl iodides resulted in low yields of the desired coupling products.

A second example focused on the construction of benzofuran **376** (Scheme 11) through a Sonogashira/Castro-Stevens bis-coupling strategy.[98] In the first event, aryl iodide **372** was coupled to (trimethylsilyl)acetylene in the presence of $PdCl_2$ at 50 °C.[99] The resulting alkyne was then deprotected with

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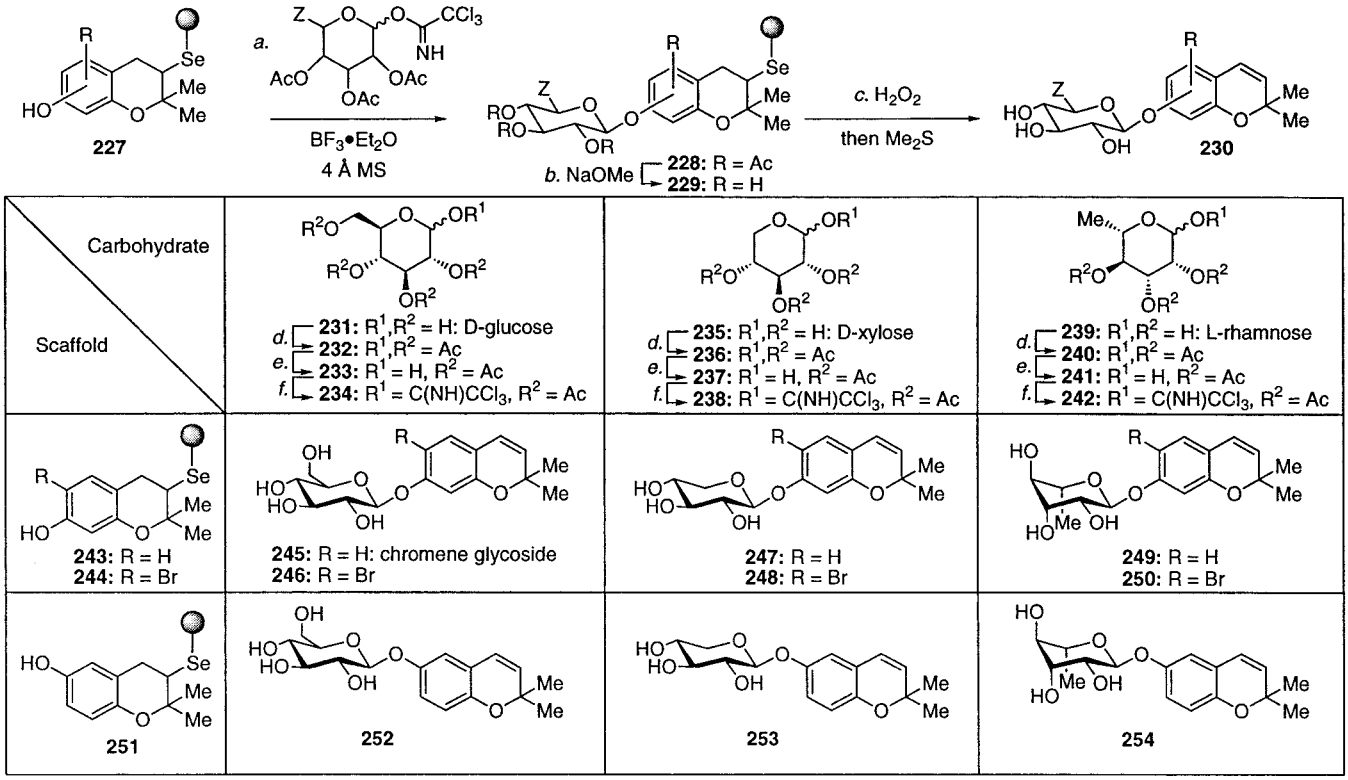
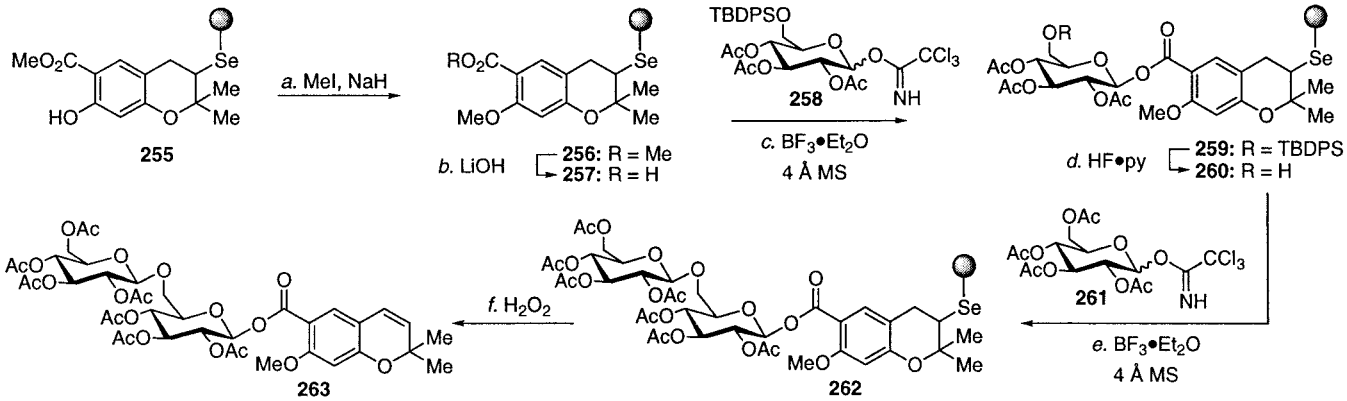
Scheme 6. Radiofrequency Encoded Split-and-Pool Synthesis of Chromene Glycoside Isolated from *Ageratum conyzoides* (**245**) and Analogues Thereof[a,b]



[a](a) 5.0 equiv of trichloroacetimidate, 4.0 equiv of $BF_3•Et_2O$, 4 Å MS, CH_2Cl_2, -40 → 0 °C , 12 h; (b) 10.0 equiv of NaOMe, THF:MeOH (5:1), 25 °C, 24 h; (c) 6.0 equiv of H_2O_2, THF, 25 °C, 30 min; (d) 7.0 equiv of Ac_2O, 10.0 equiv of Et_3N, 0.1 equiv of 4-DMAP, CH_2Cl_2, 0 → 25 °C, 5 h; (e) 1.5 equiv of *n*-$BuNH_2$, THF, 25 °C, 8 h; (f) 15.0 equiv of Cl_3CCN, 0.1 equiv of DBU, CH_2Cl_2, 0 °C, 30 min. [b]All glycoside products were obtained in greater than 90% purity upon cleavage and were characterized by ^{1}H-NMR and HRMS (see Supporting Information for data). DBU = 1,8-diazabicylo[5.4.0]undec-7-ene. 4-DMAP = 4-(dimethylamino)pyridine.

Scheme 7. Solid-Phase Synthesis of Peracetyl Macrophylloside D (**263**)[a]



[a] (a) 10.0 equiv of NaH, 20.0 equiv of MeI, DMF, 35 °C, 48 h, 88%; (b) 10.0 equiv of LiOH, THF:H_2O (10:1), 60 °C, 12 h, 94%; (c) 5.0 equiv of **258**, 4.0 equiv of $BF_3•Et_2O$, 4 Å MS, CH_2Cl_2, -40 → 0 °C, 12 h, 91%; (d) 5.0 equiv of HF•py, THF, 0 → 25 °C, 89%; (e) 5.0 equiv of **261**, 4.0 equiv of $BF_3•Et_2O$, 4 Å MS, CH_2Cl_2, -40 → -10 °C, 12 h, 57%; (f) 6.0 equiv of H_2O_2, THF, 25 °C, 20 min, 18% over six steps based on **255**. TBDPS = *t*-butyldiphenylsilyl.

TBAFand subsequently coupled to 2-iodophenol under Pd-$(OAc)_2(Ph_3P)_2$ catalysis.[100] Finally, the coupling product was cleaved under oxidative conditions to provide furan **376** in 52% yield over four steps based on **372**.

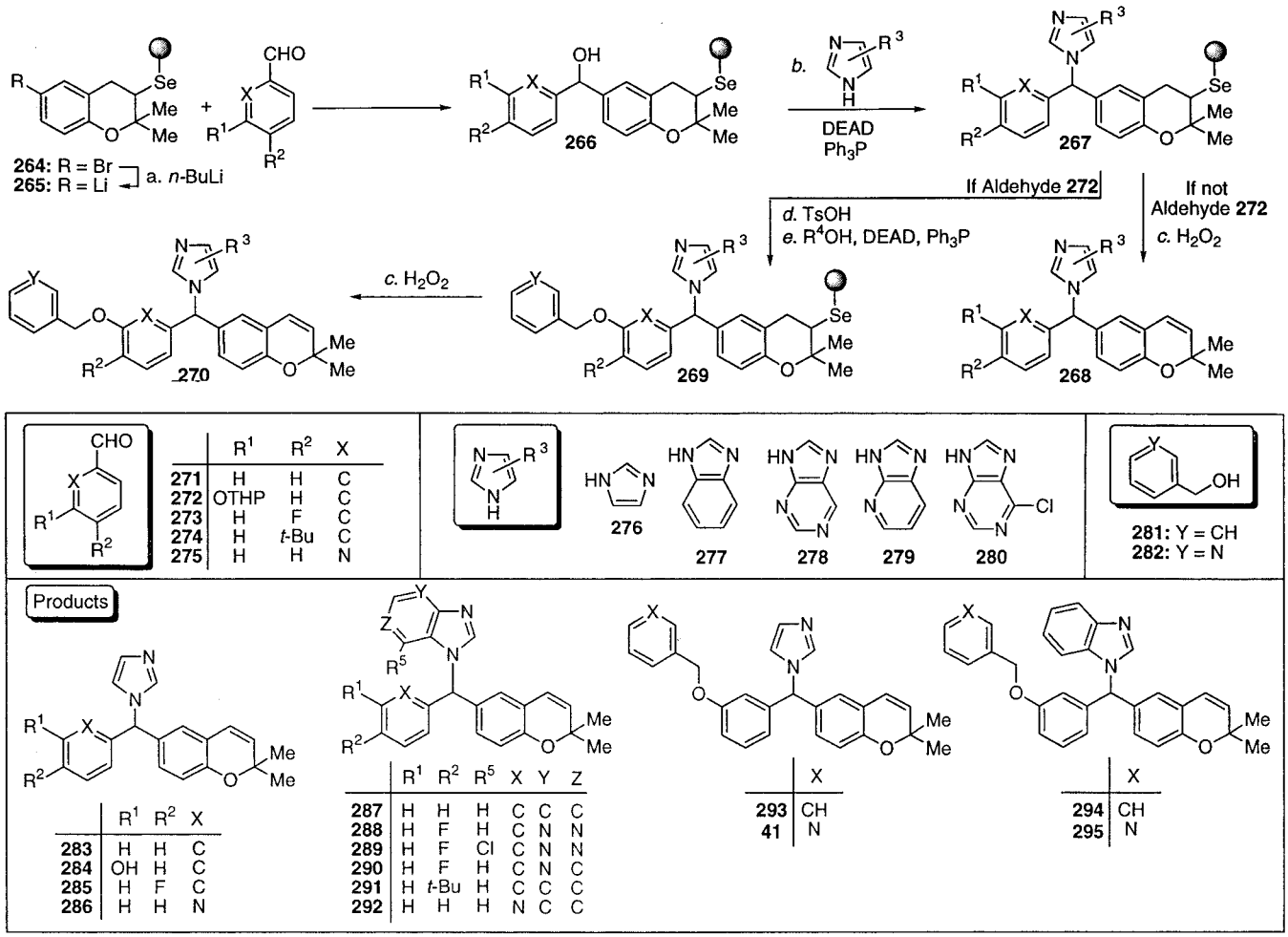
In the third example, acetophenone **116** (Scheme 11) was converted to pyrazole **380** by initial conversion to the corresponding β-dicarbonyl system via enolate formation with LHMDS followed by quenching with benzoyl cyanide to afford **377** in 87% yield. Condensation of **377** with hydrazine hydrate in the presence of a catalytic amount of acetic acid gave resin-bound pyrazole **378** in 87% yield.[101] This pyrazole was then alkylated with MeI to furnish **379** and cleaved to give pyrazole **380** in 58% overall yield based on **116**.[102]

(99) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467−4470.

(100) Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313−3315.

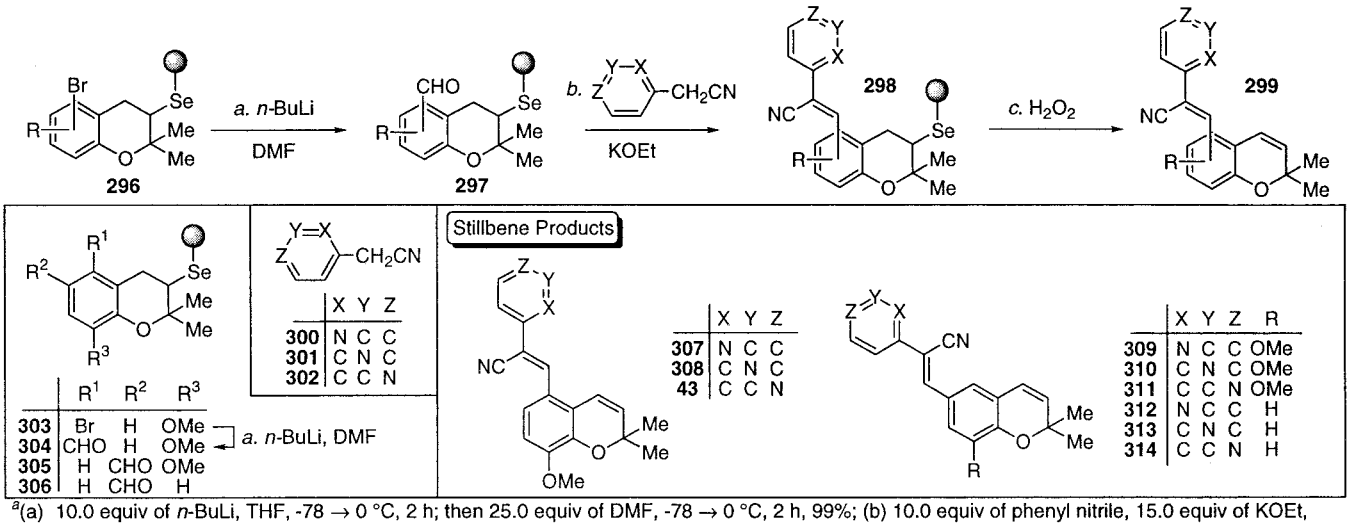
(101) Siddiqui, A. U.; Rao, U. M.; Srinivas, M.; Siddiqui, A. H. *Org. Proc. Proc. Int.* **1992**, *24*, 355−358.

Scheme 8. Synthesis of Aldosterone Biosynthesis Inhibitor **41** and Selected Analogues Thereof[a]



[a](a) 10.0 equiv of *n*-BuLi, THF, -78 → 0 °C, 2 h; then 20.0 equiv of aldehyde, -78 → 25 °C, 12 h; (b) 15.0 equiv of amine, 15.0 equiv of DEAD, 10.0 equiv of Ph_3P, THF, 25 °C, 48 h; (c) 6.0 equiv of H_2O_2, THF, 25 °C, 20 min; (d) 2.0 equiv of $TsOH \cdot H_2O$, THF:MeOH (10:1), 25 °C, 1 h; (e) 10.0 equiv of benzyl alcohol, 15.0 equiv of DEAD, 10.0 equiv of Ph_3P, THF, 25 °C, 48 h. [b]All products were chromatographically purified and characterized by ^{1}H-NMR and HRMS (see Supporting Information for data).

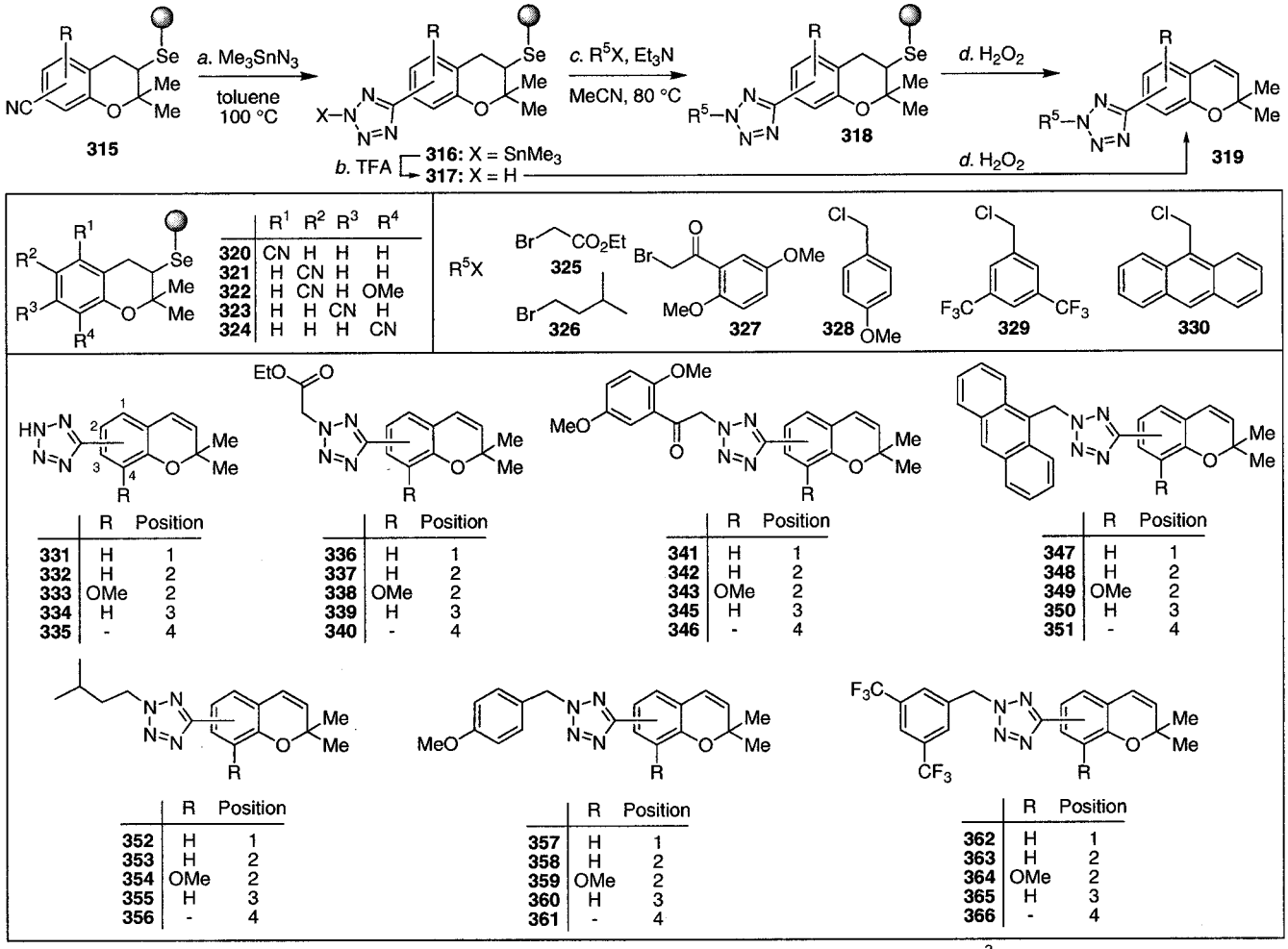
Scheme 9. Solid-Phase Parallel Synthesis of Phosphodiesterase Inhibitor **43** and Analogues Thereof[a,b]



[a](a) 10.0 equiv of *n*-BuLi, THF, -78 → 0 °C, 2 h; then 25.0 equiv of DMF, -78 → 0 °C, 2 h, 99%; (b) 10.0 equiv of phenyl nitrile, 15.0 equiv of KOEt, THF:EtOH (4:1), 25 °C, 3 h; (c) 6.0 equiv of H_2O_2, THF, 25 °C, 20 min. [b]All products were obtained in greater than 90% purity upon cleavage and were characterized by ^{1}H-NMR and HRMS (see Supporting Information for data).

A fourth example involved conversion of benzoic acid **381** into oxazole **384** (Scheme 11). Hence, alkylation of **381** was effected by treatment with α-bromo acetophenone and DBU in DMF at 80 °C to afford **382** in quantitative yield. Heterocycle formation was accomplished by treatment of **382** with acetamide and $BF_3 \cdot Et_2O$ in xylenes at 140 °C to give **383** (55% yield)

Scheme 10. Radiofrequency Encoded Split-and-Pool Synthesis of the Substituted Tetrazole Library[a]



[a](a) 5.0 equiv of Me_3SnN_3, toluene, 100 °C, 12 h; (b) 1.0 equiv TFA, THF:H_2O (50:1), 25 °C, 2 h; (c) 10.0 equiv of R^2X, 15.0 equiv of Et_3N, MeCN, 80 °C, 12 h; (d) 6.0 equiv of H_2O_2, THF, 25 °C, 20 min. [b]Compounds obtained in less than 90% purity after cleavage were purified by chromatography. In cases of less than 90% purity, the contaminant was typically a small amount of an isomeric product (i.e. alkylation at the 1-position rather than the 2-position of the tetrazole). All products were characterized by ^{1}H-NMR and HRMS (See Supporting Information for data). TFA = trifluoroacetic acid.

Table 2. Reaction Conditions Under Which Selenium Tether Is Stable[a]

temperature	from −78 to 195 °C
Lewis acids	$SnCl_4$, BF_3·OEt_2, $ZnCl_2$, $SnCl_2$
Brönsted acids	HCl, AcOH, TFA (aq), TsOH, PPTS
organometallics	RMgX, RLi, R_2CuLi, Wittig
reducing agents	$NaBH_4$, $NaCNBH_3$, BH_3·THF, DIBAL, $LiBH_4$, $LiAl(O\text{-}tBu)_3H$, $SnCl_2$·$2H_2O$
bases	LDA, LHMDS, NaHMDS, NaH, K_2CO_3, Cs_2CO_3, pyridine, piperidine, *i*-Pr_2NEt, Et_3N, LiOH (aq), NaOH (aq), NaOMe, KOEt, KO*t*-Bu
electrophiles	R−X, RC(O)X, $[RC(O)]_2O$, RCHO
miscellaneous	Pd reagents, DCC, $SOCl_2$, $COCl_2$, DEAD, Ph_3P, TBAF, HF·py, Cl_2Cy_2Ru=CHPh
solvents	CH_2Cl_2, THF, DMF, C_6H_6, MeC_6H_5, DMSO, *N*,*N*-diethylaniline, mesitylene, MeCN, EtCN

[a] During the current and related synthetic studies in these laboratories, the above listed reagents and conditions were found to be compatible with the selenoether linking strategy.

which was cleaved to afford oxazole **384** in 42% yield over three steps based on **381**.[103]

Pyranoflavone **387** (Scheme 11) was constructed next from methyl ketone **117** by condensation with 4-(*t*-Bu)-benzaldehyde (same conditions as in Scheme 4) to give chalcone **385**, which was subsequently treated with elemental iodine in DMSO at 180 °C for 30 min and then cleaved to afford flavone **387** in 27% overall yield from **117**.[104] In a final example, the previously synthesized seselin (**6**) was reconstructed in an attempt to test the stability of the linking approach to the highly practical Grubbs olefin metathesis reaction. Hence, aldehyde scaffold **166** (Scheme 11) was transformed to styrene **388** by treatment with Ph_3P=CH_2 in 100% yield. The phenolic group of **388** was then acylated with acryloyl chloride to provide **389** which was treated with Cl_2Cy_2Ru=CHPh to effect the ring closing metathesis reaction.[105] Finally, coumarin **390** was cleaved to provide seselin (**6**) in 77% overall yield from **166**.

Conclusion

In conclusion, we have described the rational selection of a benzopyran-based privileged structure for use in the construction of natural product-like libraries and the development of general strategies for its construction and diversification. A novel cycloloading protocol has been developed for the efficient

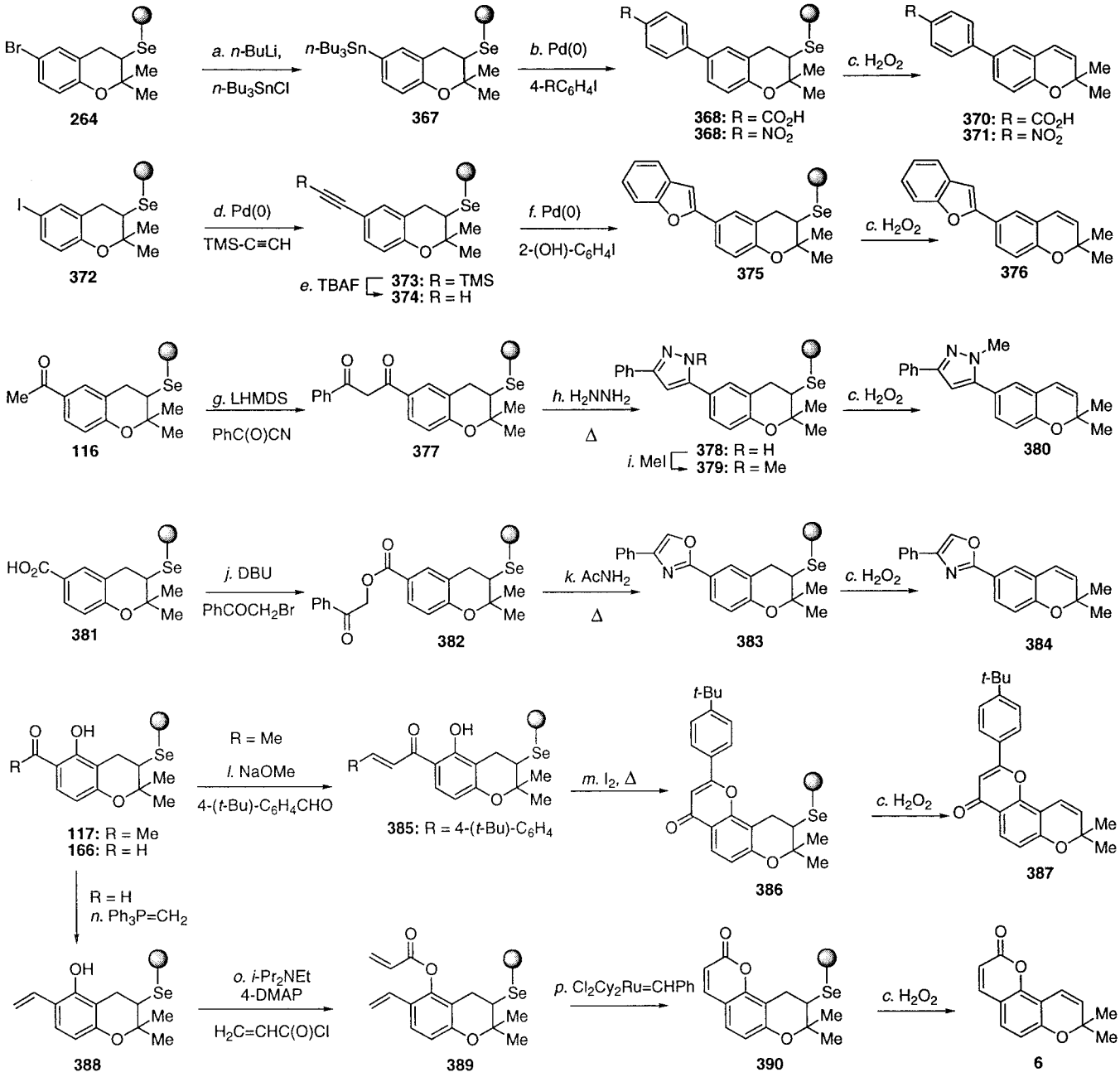
(102) Inspection of ^{1}H NMR spectrum of **373** after cleavage revealed that the product was a 1:1 mixture of regioisomers.

(103) Huang, W.; Pei, J.; Chen, B.; Pei, W.; Ye, X. *Tetrahedron* **1996**, *52*, 10131−10136.

(104) Tan, W.; Li, W.-D.; Huang, C.; Li, X.; Xing, Y. *Synth. Commun.* **1999**, *29*, 3369−3377.

(105) Nicolaou, K. C.; Rodríguez, R. M.; Mitchell, H. J.; van Delft, F. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 1874−1876.

Scheme 11. Synthesis of Miscellaneous Benzopyran Containing Structures[a]



[a](a) 10.0 equiv of *n*-BuLi, THF, -78 °C, 2 h; then 15.0 equiv of *n*-Bu_3SnCl, -78 → 0 °C, 1 h, 100%; (b) 0.05 equiv of Pd_2dba_3, 0.05 equiv of P(2-furyl)$_3$, 5.0 equiv of 1-iodo-4-nitrobenzene, DMF, 100 °C, 12 h, 85%; (c) 6.0 equiv of H_2O_2, THF, 25 °C, 20 min; (d) 10.0 equiv of (trimethylsilyl)acetylene, 0.5 equiv of $PdCl_2$, 0.5 equiv of CuI, DMF:Et_3N (5:1), 50 °C, 12 h, 90%; (e) 5.0 equiv of TBAF, DMF, 25 °C, 12 h, 87%; (f) 2.0 equiv of 2-iodophenol, 0.5 equiv $Pd(OAc)_2(PPh_3)_2$, 0.5 equiv of CuI, DMF:Et_3N (5:1), 80 °C, 24 h, 69%; (g) 3.0 equiv of LHMDS, 5.0 equiv of benzoyl cyanide, THF, -78 → 0 °C, 1 h, 88%; (h) 10.0 equiv of $H_4N_2 \bullet H_2O$, 0.05 equiv of AcOH,THF:MeOH (2:1), 65 °C, 3 h, 87%; (i) 10.0 equiv of MeI, 5.0 equiv of NaH, THF, 40 °C, 12 h; (j) 10.0 equiv of α-bromoacetophenone, 20.0 equiv of DBU, DMF, 80 °C, 12 h, 100%; (k) 10.0 equiv of acetamide, 1.0 equiv of $BF_3 \bullet Et_2O$, xylenes, 140 °C, 48 h, 55%; (l) 15.0 equiv *t*-Bu-benzaldehyde, 10.0 equiv of NaOMe, THF:MeOH (3:1), 25 °C, 48 h, 62%; (m) 10.0 equiv of I_2, DMSO, 180 °C, 2 h, 45%; (n) 10.0 equiv of $CH_2=PPh_3$, THF, 0 → 25 °C, 15 h, 100%; (o) 20.0 equiv of acryloyl chloride, 20.0 equiv EtN(*i*-Pr)$_2$, 1.0 equiv of 4-DMAP, CH_2Cl_2, 25 °C, 2.5 h, 85%; (p) 0.3 equiv of $Cl_2Cy_2Ru=CHPh$, CH_2Cl_2, 40 °C, 24 h. LHMDS = lithium bis(trimethylsilyl)amide. TBAF = tetrabutylammonium fluoride.

loading, elaboration, and cleavage of this general template. The fidelity of the devised method was validated under various reaction conditions through the parallel and split-and-pool synthesis of several small organic molecule libraries. As shown in Table 2, these synthetic efforts have confirmed the robustness of our selenoether tether under a range of reaction conditions, as required for the successful synthesis of diverse natural product-like libraries. In fact, it is arguable whether other conventional linkers could withstand this array of reaction conditions, and yet still be cleaved under such facile conditions as those employed in the present case.[106] In the following paper, we describe the application of the chemistry and principles developed in this phase of the program to the construction of a

(106) For a recent review of linkers, see: Guiller, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091−2157.

10 000-membered library of biologically relevant, natural product-like compounds.[24]

Acknowledgment. Financial support for this work was provided by The Skaggs Institute for Chemical Biology and National Institutes of Health (U.S.A.), fellowships from the Department of Defense (to J.P.), the American Chemical Society Division of Medicinal Chemistry (sponsored by Parke-Davis, Hoescht Marion Roussel, Abbott, Wyeth Ayerst, and Bristol Myers Squibb) (to J.P.), and the Ministerio de Educacion y Cultura, Spain (to S.B.), and grants from Amgen, Bayer AG, Boehringer-Ingelheim, Glaxo, Hoffmann-La Roche, DuPont, Merck, Novartis, Pfizer, and Schering Plough.

Supporting Information Available: Experimental procedures for resin and library preparation, tabulated ^{1}H NMR and MS 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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