

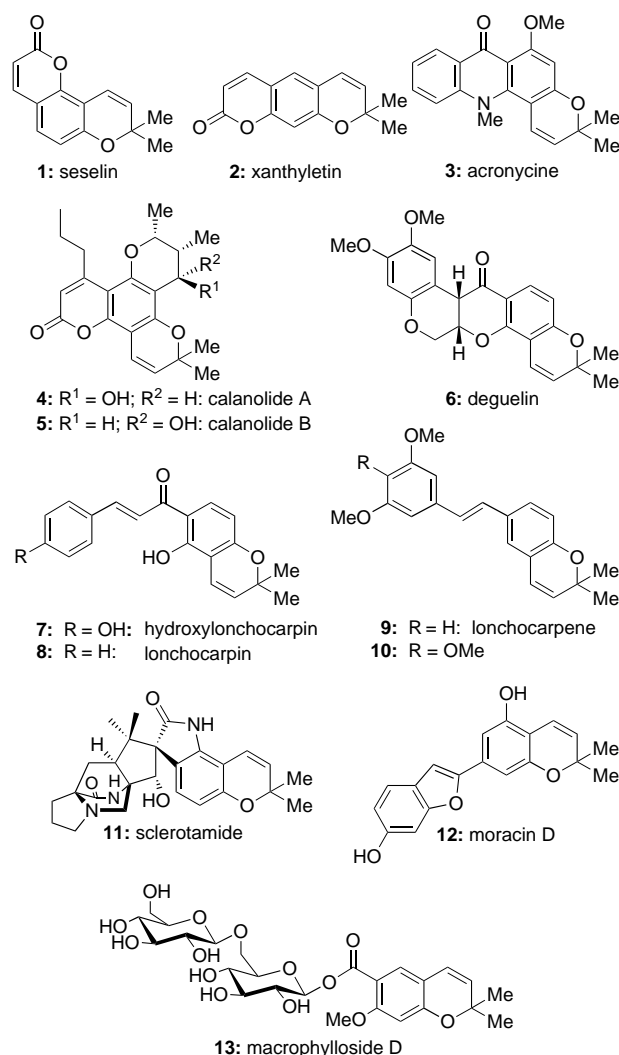
Selenium-Based Solid-Phase Synthesis of Benzopyrans I: Applications to Combinatorial Synthesis of Natural Products**

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Combinatorial chemistry is becoming an increasingly important tool in both chemical biology and drug discovery, and its continued expansion is, to a large extent, contingent upon advances in solid-phase organic synthesis (SPOS) as well as in automation and high-throughput screening (HTS) technologies.^[1] Since the demand for libraries of small organic molecules continues to grow, particularly as a result of recent advances in the fields of chemical genetics, genomics, and proteomics, there is an urgent need to develop more efficient strategies for the high-fidelity solid-phase construction of libraries of natural-product-like and drug-like compounds.^[2] Toward this end our research group has been engaged in the development of novel resins as well as improved linking and release strategies.^[3] Recently, we disclosed^[4] the construction of a polystyrene-based selenenyl bromide resin which encompasses the essential features of both a solid-phase reagent^[5a] and a traceless linker.^[5b-k] We envisaged that such a resin should ideally act as a linker that facilitates bond constructions during the loading operation (that is, acts as a reagent) and then serve as a robust tether through subsequent operations until it is ultimately cleaved in a traceless or functionalizing fashion to effect release of the target. The versatility and efficiency of such a method is readily evident since it reduces the extraneous (noncomplexity building) operations typically associated with the loading of a scaffold and also eliminates the problem of residual functionality in the target structure resulting from the linker.^[6] In this and the following communication^[7] we describe our preliminary efforts toward the application of such a linking strategy for the construction of several polycyclic natural products and other medicinally relevant small organic molecules.

As a forum for demonstrating the utility and efficiency of the proposed seamless linking strategy, we chose to target the 2,2-dimethylbenzopyran moiety which is embedded in numerous natural products including flavanoids, coumarins, rotenoids, stilbenoids, chromene glycosides, and others—several of

which have potential applications in medicine.^[8] For example, **1** (Scheme 1),^[9] **2**,^[9] and **3**^[10] exhibit anticancer activities, whereas **4** and **5** are non-nucleoside, HIV-1-specific, reverse transcriptase inhibitors currently in clinical development.^[11] The cubé resin derived agents **6**, **8**, **9**, and related structures



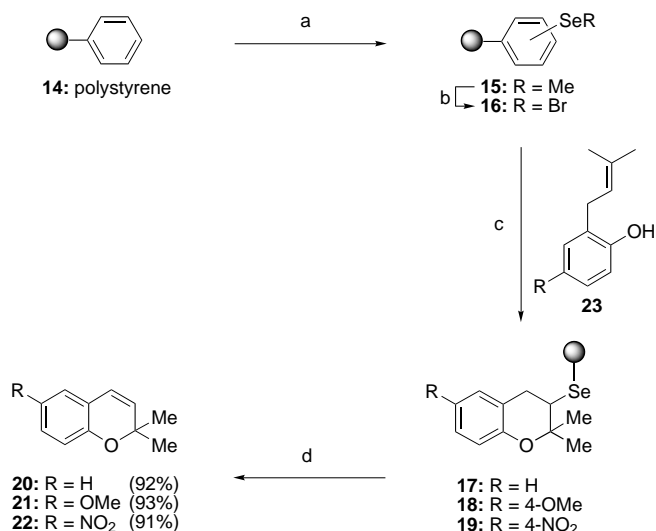
Scheme 1. Representative biologically active natural products containing the 2,2-dimethylbenzopyran moiety.

7 and **10** are under investigation as cancer chemopreventives,^[12] while **11**^[13] and **12**^[14] exhibit insecticidal and antifungal activities, respectively. Furthermore, a growing number of pharmaceutical ligands that incorporate the 2,2-dimethylbenzopyran moiety into their structures have been designed and synthesized (see following paper).^[7] Thus, the development of a practical and reliable method for the solid-phase construction of benzopyrans is of considerable interest and should open the possibility for future combinatorial-based investigations of these as well as other natural and designed molecules.

Initially, we needed to establish the effectiveness of the proposed solid-phase selenium-mediated formation of 2,2-dimethylbenzopyrans,^[15] and we, therefore, undertook a series of preliminary loading and cleavage studies (Scheme 2). As

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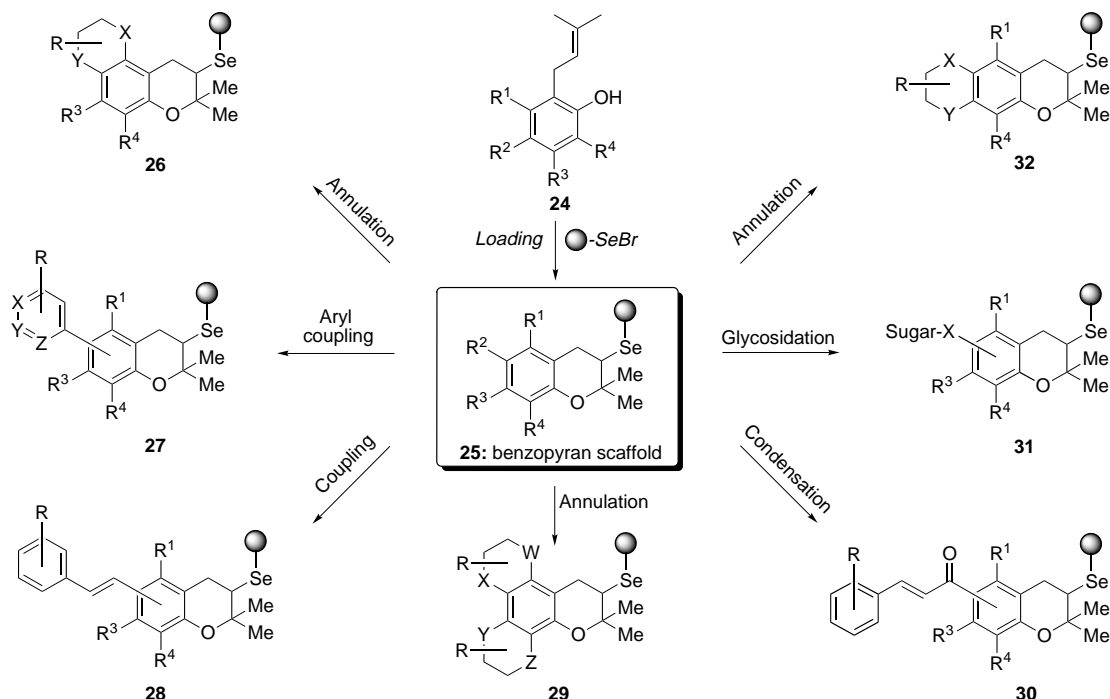


Scheme 2. Preparation of selenium-functionalized resin and preliminary studies on the loading and release of 2,2-dimethylbenzopyrans. a) 1. *n*BuLi (0.6 equiv), polystyrene (1.0 equiv, 1% cross-linked, 100–200 mesh), TMEDA (0.5 equiv), cyclohexane, 65 °C, 4 h; 2. (MeSe)₂ (2.0 mmol g⁻¹ polystyrene), THF, 0 °C, 10 min; b) 1. Br₂ (0.9 equiv), CHCl₃, 0 °C, 30 min; 2. EtOH, 70 °C, 1 h; c) phenol **23** (3.0 equiv), 0–25 °C, 30 min; d) 30% H₂O₂ (10.0 equiv), THF, 25 °C, 30 min. TMEDA = *N,N,N',N'*-tetramethylethylenediamine.

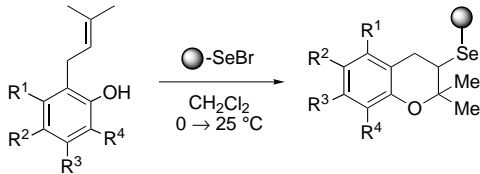
previously reported,^[4] selenenyl bromide resin **16** (Scheme 2) was conveniently prepared from commercial polystyrene (**14**) by lithiation followed by treatment with dimethyl diselenide to give methyl selenide **15**, a conjugate whose subsequent oxidation with bromine gave **16** as a dark red polymer.^[4] Simply stirring resin **16** in CH₂Cl₂ at 0 °C with a threefold excess of various *ortho*-prenylated phenols (**23**) resulted in a

rapid decolorization of the resin (<5 min). These newly loaded resins were then treated with H₂O₂, which resulted in the facile oxidation of the selenide to the corresponding selenoxide. A *syn*-elimination of the selenoxide effected the release of benzopyrans **20–22** in high yield with purities greater than 95%. The high yield and purity of these products suggested that the simultaneous cyclization and loading (cyclo-loading) step proceeded efficiently, regardless of the electronic environment of the phenolic substrate (that is, neutral (**20**), electron rich (**21**), or electron poor (**22**)).

With the effectiveness of the cyclo-loading confirmed, we considered how such technology could be strategically employed for construction of natural products and analogues thereof. The initial loading of various substituted *ortho*-prenylated phenols (**24**) provides functionalized resin-bound benzopyrans (**25**, Scheme 3) for further elaboration towards the skeletons of various 2,2-dimethylbenzopyran-containing natural products. The success of this strategy required not only that the loading step be efficient, but also that it be mild and highly selective so as to tolerate a range of aromatic functionality (R¹–R⁴), preferably without necessitating tedious manipulations of protecting groups. Thus, a series of functionalized *ortho*-prenylated phenols were synthesized and treated with selenenyl bromide resin **16** (Table 1). Encouragingly, the method exhibited broad tolerance toward a wide range of polyfunctionalized aromatic compounds^[16] containing phenols (entries 1–6), methyl ketones (entries 10–12), esters (entries 13, 14), carboxylic acids (entry 15), cyanides (entries 16, 17), nitro groups (entries 18–20), aldehydes (entries 21–26), and halogens (entries 27–35). In all cases the treatment of the resin with a threefold excess of the *ortho*-prenylphenol resulted in nearly quantitative loading and ¹H NMR analysis of the oxidative cleavage products revealed



Scheme 3. Strategy for the construction of resin-bound 2,2-dimethylbenzopyran scaffolds (**25**) and their subsequent solid-phase elaboration to various natural and designed molecular skeletons (**26–32**).

Table 1. Loading of functionalized 2,2-dimethylbenzopyran scaffolds.^[a]


Entry	Substrate preparation ^[b]	R ¹	R ²	R ³	R ⁴	Purity [%] ^[c]
1	B	H	H	H	H	98
2	A	OH	H	H	H	98
3	A	H	OH	H	H	98
4	A	H	H	OH	H	98
5	A	OH	H	OH	H	92
6	A	H	H	OH	OH	98
7	A	H	CH ₂	H	H	98
8	A	H	OMe	OMe	H	98
9	A	OMe	H	H	H	96
10	C	H	Ac	H	H	98
11	A	H	Ac	OH	H	98
12	A	OH	Ac	H	H	98
13	C	H	CO ₂ Me	H	H	92
14	A	H	CO ₂ Me	OH	H	98
15	C	H	CO ₂ H	H	H	96
16	C	H	CN	H	H	98
17	C	H	H	H	CN	98
18	C	H	NO ₂	H	H	98
19	C	H	H	NO ₂	H	94
20	C	H	H	H	NO ₂	96
21	C	H	H	H	CHO	98
22	C	H	CHO	H	H	98
23	A	OH	CHO	H	H	98
24	A	H	CHO	OH	H	88
25	A	OH	CHO	Me	H	98
26	A	Me	CHO	OH	H	98
27	B	Br	H	H	H	98
28	B	H	Br	H	H	98
29	B	H	H	Br	H	98
30	B	H	H	H	Br	91
31	A	H	Br	OH	H	92
32	B	I	H	H	H	94
33	B	H	I	H	H	98
34	B	H	H	I	H	98
35	B	H	H	H	I	98

[a] Loading conditions: selenium bromide resin (1.0 equiv, ca. 1.1 mmol g⁻¹), phenol (3.0 equiv), CH₂Cl₂, 0 → 25 °C, 30 min. [b] Phenolic substrates were prepared in one of three ways: A) Friedel-Crafts alkylation, B) anionic alkylation, or C) aromatic Claisen rearrangement. See reference [16] for representative procedures. [c] Purity was estimated by integration of ¹H NMR signals of crude oxidative cleavage product. Substrate loading was 89–100% in all cases as determined by mass difference of vacuum dried resin. In selected cases the cleavage product was chromatographically purified and the yield after two steps (loading plus cleavage) was determined. These yields ranged from 80–97% (based on an estimated resin functionalization of 1.1 mmol g⁻¹).

the newly constructed benzopyrans to be greater than 95% pure in most cases.

With this collection of functionalized, resin-bound benzopyran platforms in hand, we set out to demonstrate their utility for elaboration toward natural products and combinatorial libraries while concurrently testing the effectiveness of the selenium resin as a robust linker. The first example (Table 2) focused on the construction of several chalcone natural products that are currently being investigated as

potential chemopreventive agents.^[12] The general synthetic procedure (Table 2) involved the condensation of resin-bound benzopyran methyl ketones (**33**) with substituted aldehydes in the presence of NaOMe.^[17] After condensation and in situ elimination to the chalcone framework (**34**), the hydroxyl substituents (R²) were liberated with TsOH · H₂O (for abbreviations of reagents and protecting groups see legends of schemes) and finally the substrates were subjected to oxidative cleavage with H₂O₂. The condensation of pyran scaffold **37** with benzaldehyde, 4-(THPO)-benzaldehyde, or 3-methoxy-4-(THPO)-benzaldehyde followed by deprotection and cleavage led to the natural products **8**, **9**, and **40** in 91, 82, and 57% overall yields, respectively, based on **37**. Similar sequences with scaffolds **38** and **39** resulted in the construction of analogues **41–46** in yields ranging from 54–89%.

A second example of this method is outlined in Table 3 for the radiofrequency encoded split-and-pool synthesis^[18] of the pyranocoumarin anticancer agents^[9] **1**, **2**, and analogues thereof using IRORI microreactor technology.^[19] In a typical experiment^[20] resin-bound benzopyrans possessing an *ortho*-hydroxy aldehyde moiety (**47**) were treated with either a stabilized phosphonium ylide or a β -ketoester to effect olefination through either a Wittig^[21a] or a Knoevenagel^[21b] reaction, respectively, to provide structures of type **48**. These olefins (presumably isomeric mixtures) were thermally equilibrated in situ to the *Z* isomer, which is situated for lactonization with the adjacent phenolic hydroxyl group to give structures of type **49**, oxidative cleavage of which provided pyranocoumarins of type **50**. The natural products **1** and **2** were obtained in yields of 85 and 92%, respectively when scaffolds **51** and **53** were condensed with (carboxymethoxymethylene)triphenylphosphane in *N,N*-diethylaniline at 165 °C for 3 h^[21a] and subsequently cleaved (Table 3). As in the previous example, the parallel treatment of scaffolds **51–54** with (carboxymethoxymethylene)triphenylphosphane, methyl acetoacetate, phenyl acetoacetate, and diethyl malonate under the conditions illustrated in Table 2, followed by oxidative cleavage, led to the production of a small library of angular and linear pyranocoumarins (**55–68**) in yields ranging from 82 to 97%.

In order to further define the versatility of this selenium-linking strategy we undertook the solid-phase synthesis of two additional targets: the prototypical stilbene **72** (Scheme 4) and the hepta-acetate of the natural product macropylloside D (**13**, Scheme 1)^[22] as these are representative examples of the stilbenoid and chromene glycoside classes of benzopyran-containing natural products. Stilbene **72**, a useful model for the natural product **9** (Scheme 1) and the related stilbene **10** (Scheme 1), was constructed from benzopyran **69** (Scheme 4) by a sequence involving a Takai iodoolefination^[23] to afford vinyl iodide **70** (87%)^[24] and subsequent coupling with *n*Bu₃SnPh in the presence of catalytic amounts of [PdCl₂(PPh₃)₂]^[25] to furnish **71** in 65% yield. Resin-bound stilbene **71** was then cleaved under oxidative conditions to give **72** in 42% overall yield from **69**.

Efforts toward the second target, macropylloside hepta-acetate (**81**, Scheme 5), a derivative of a chromene glycoside isolated from *Gentiana macrophylla*,^[22] commenced from benzopyran **73**. Hence, the phenolic hydroxyl group of **73** was

Table 2. Solid-phase parallel synthesis of chalcone natural products and their analogues.^[a]

R ² PhCHO		THPO-	
Scaffold ^[b]			

[a] Reagents and conditions: a) NaOMe (15.0 equiv), R²C₆H₄CHO (10.0 equiv), THF:MeOH (2:1), 25 °C, 72 h, 60–95 %; b) TsOH · H₂O (1.0 equiv), THF:MeOH (10:1), 25 °C, 2 h, 100 %; c) H₂O₂ (10.0 equiv), THF, 25 °C, 30 min, 54–91 % overall yields based on **37**–**39**. [b] See Table 1 for preparation of scaffolds. [c] Yields are of chromatographically pure compounds. All compounds were characterized by ¹H NMR spectroscopy and high resolution mass spectrometry (HR-MS). THP = tetrahydropyranyl, Ts = toluene-4-sulfonyl.

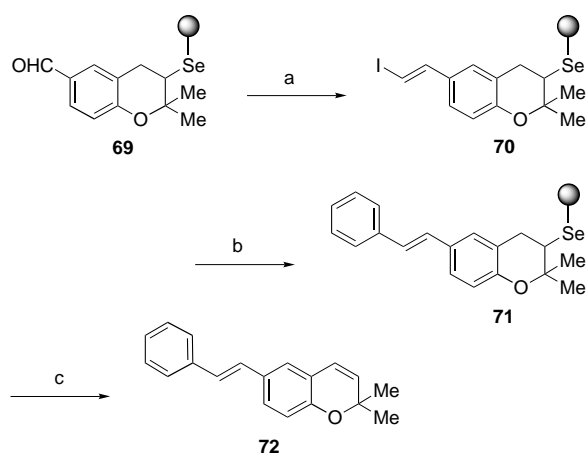
Table 3. Radiofrequency encoded split-and-pool synthesis of the pyranocoumarins seselin (**1**), xanthyletin (**2**), and their analogues (**55**–**68**).^[a]

Reagent	Ph ₃ P=CHCO ₂ Me			
Scaffold ^[b]				

[a] Reagents and conditions: a) Ph₃P=CHCO₂Me (5.0 equiv), PhNEt₂, 165 °C, 3 h, 85–95 %; b) β-ketoester (10.0 equiv), piperidine (0.2 equiv), propionitrile, 95 °C, 2 h, 85–100 %; c) H₂O₂, THF, 25 °C, 30 min, 82–95 % overall yield based on **51**–**54**. [b] See Table 1 for preparation of scaffolds. [c] Yields are of chromatographically pure compounds. All compounds were characterized by ¹H NMR spectroscopy and HR-MS.

first methylated (MeI/NaH, 88 %) ^[24] and the methyl ester of the resulting product **74** then hydrolyzed to reveal the requisite free carboxylic acid **75** ready for the first coupling reaction. In the event, treatment of **75** with trichloroacetimidate **76**^[26] and BF₃ · Et₂O for 12 h at –40 → 0 °C resulted in

smooth coupling to produce β-glycoside **77** (91 %), which underwent selective deprotection upon treatment with HF · py to afford **78** in 89 % yield. The second coupling between resin-bound substrate **78** and trichloroacetimidate **79**^[27] proceeded under similar conditions to afford **80** as a



Scheme 4. Solid-phase synthesis of the prototypical stilbene **72**: a) CrCl_2 (16.0 equiv), CHI_3 (5.0 equiv), THF:dioxane (10:1), 0°C , 3 h, 87%; b) $n\text{Bu}_3\text{SnPh}$ (5.0 equiv), $[\text{PdCl}_2(\text{Ph}_3\text{P})_2]$ (0.1 equiv), DMF, 100°C , 10 h, 65%; c) 30% H_2O_2 (0.1 equiv), THF, 25°C , 30 min, 41% over three steps based on **69**.

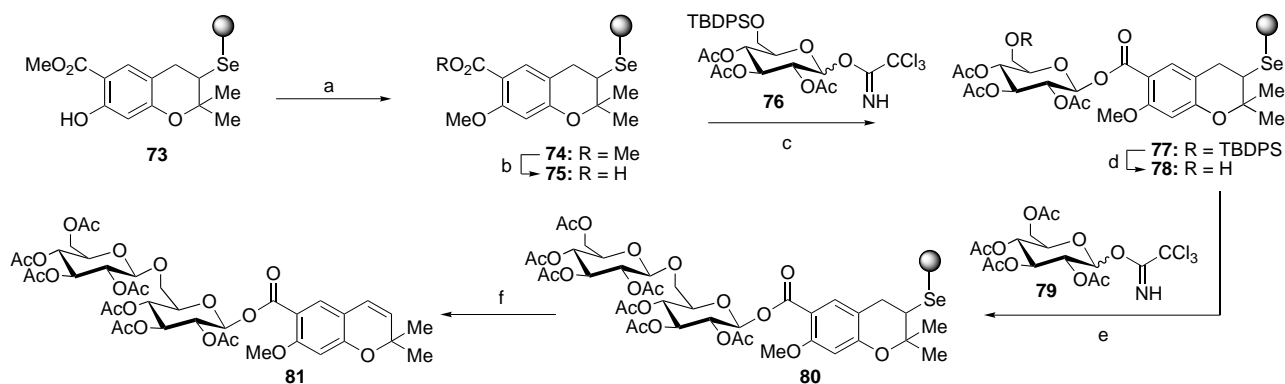
single anomer in 57% yield. Finally, the disaccharide (**80**) was cleaved from the resin to afford hepta-acetylated macrophyllloside (**81**) in 18% yield over six steps based on **73**.

In conclusion, we have described a novel method for the solid-phase construction of 2,2-dimethylbenzopyrans employing a selenium-based linking strategy wherein the loading step constitutes a key ring-forming reaction. Once formed, these resin-bound benzopyrans can be elaborated to a variety of natural products and analogues thereof. Finally, cleavage from the resin is accompanied by introduction of additional functionality in high purity and efficiency. In the following communication^[7] we describe further applications of this strategy, particularly to the construction of various heteroatom-containing small organic molecules of pharmaceutical interest.

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Scheme 5. Solid-phase synthesis of peracetyl macrophyllloside D (**81**): a) NaH (10.0 equiv), MeI (20.0 equiv), DMF, 35°C , 48 h, 88%; b) LiOH (10.0 equiv), THF:H₂O (20:1), 60°C , 12 h, 94%; c) **76** (5.0 equiv), $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (4.0 equiv), 4 Å MS, CH_2Cl_2 , $-40 \rightarrow -0^\circ\text{C}$, 12 h, 91%; d) HF·py (5.0 equiv), THF, $0 \rightarrow 25^\circ\text{C}$, 89%; e) **79** (5.0 equiv), $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (4.0 equiv), 4 Å MS, CH_2Cl_2 , $-40 \rightarrow -10^\circ\text{C}$, 12 h, 57%; f) 30% H_2O_2 (10.0 equiv), THF, 25°C , 30 min, 18% over six steps based on **73**. TBDPS = *tert*-butyldiphenylsilyl.

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Selenium-Based Solid-Phase Synthesis of Benzopyrans II: Applications to Combinatorial Synthesis of Medicinally Relevant Small Organic Molecules**

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In the preceding communication we described a novel selenium-based simultaneous cyclization and loading (cyclo-loading) strategy for the solid-phase combinatorial synthesis of natural products containing the 2,2-dimethylbenzopyran moiety.^[1] Given the vast number and diverse biological activities of these benzopyran natural products, it is reasonable to consider whether this structural motif might be of value in the construction of designed pharmaceutical agents, particularly since natural-product-based mechanistic investigations have revealed that such structures interact with a variety of protein and nucleic acid cellular targets.^[2] Not surprisingly, a search of the patent literature revealed a host of pharmaceutical ligands that contain the 2,2-dimethylbenzopyran skeleton (Scheme 1). Among these are the potassium-channel activators **1** and **2**,^[3] aldosterone biosynthesis inhibitors **3** and **4**,^[4] 5-hydroxytryptamine-3 receptor antagonist **5**,^[5] phosphodiesterase IV inhibitor **6**,^[6] and the ampicillin-derived antibacterial agent **7**.^[7] However, in spite of the potential utility of this substituted benzopyran motif in ligand design, only a limited number of solid-phase methods for its construction has been reported.^[8] Hence we investigated whether our current cyclo-loading approach might be a useful tool in medicinal chemistry for future combinatorial investigations of this class of compounds. Since structures **1–7**, unlike the natural products previously described, are structurally quite diverse and possess a variety of heteroatom functionalities, we sought to effect the solid-phase functionalization of several of the previously described resin-bound benzopyrans^[1] with various heteroatom-based functional groups in order to produce scaffolds embodying their structural features. Herein we describe the synthesis of several representative scaffolds as well as a solid-phase synthesis of androsterone biosynthesis inhibitor **4** (Scheme 1) and a small library of analogues using radiofrequency

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