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A Novel Synthesis of 2,3-Disubstituted Benzopyran-4-ones and Application to the Solid Phase

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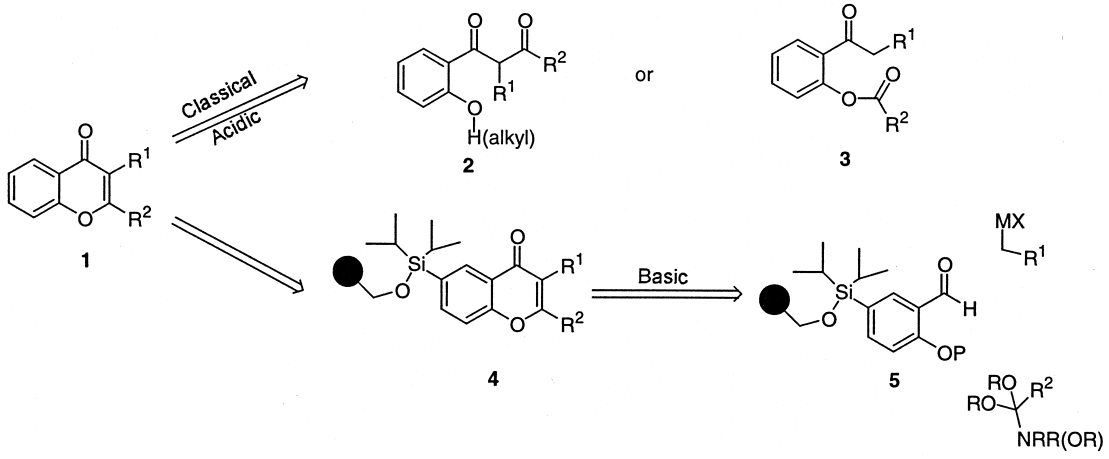
Abstract—The development of a novel synthesis of 2,3-disubstituted benzopyran-4-ones and application to the solid phase are reported. Following model studies using benzyl alcohol as a surrogate for polystyrene hydroxymethyl resin, we utilized our previously established traceless diisopropylsilyloxy linker methodology to synthesize a small library of target benzopyranones in generally high yield and purity.

Substituted benzopyranones encompass an important class of pharmacophores that possess a wide range of interesting biological activities.[1] Although there are several publications on the synthesis of 2,3-disubstituted benzopyran-4-ones in the solution phase,[2] there have been no reports on their synthesis on the solid phase apart from the synthesis of large libraries of the related dihydrobenzopyran template.[3] Thus, our objective was to develop solution-phase methodology that would be readily amenable to solid-phase application.

In doing so, we wished also to demonstrate a broader utility of our previously established traceless diisopropylsilyloxy linker[4a] that is closely related to earlier reported silicon linker methodologies.[4a–d]

Classically, 2,3-disubstituted benzopyranones **1** are synthesized by intramolecular condensation of compound **2**,[2e] which is usually obtained by Baker–Venkataraman rearrangement of compound **3** or via Claisen ester condensation (Scheme 1). Most approaches require harsh acidic conditions for the final condensation step. In our initial work, we carried out model studies to access solid-supported benzopyranone **4** utilizing similar chemistry to build up the pyranone ring. Since our diisopropylsilyloxy linker is sensitive to acidic conditions, we resorted to the



Scheme 1.

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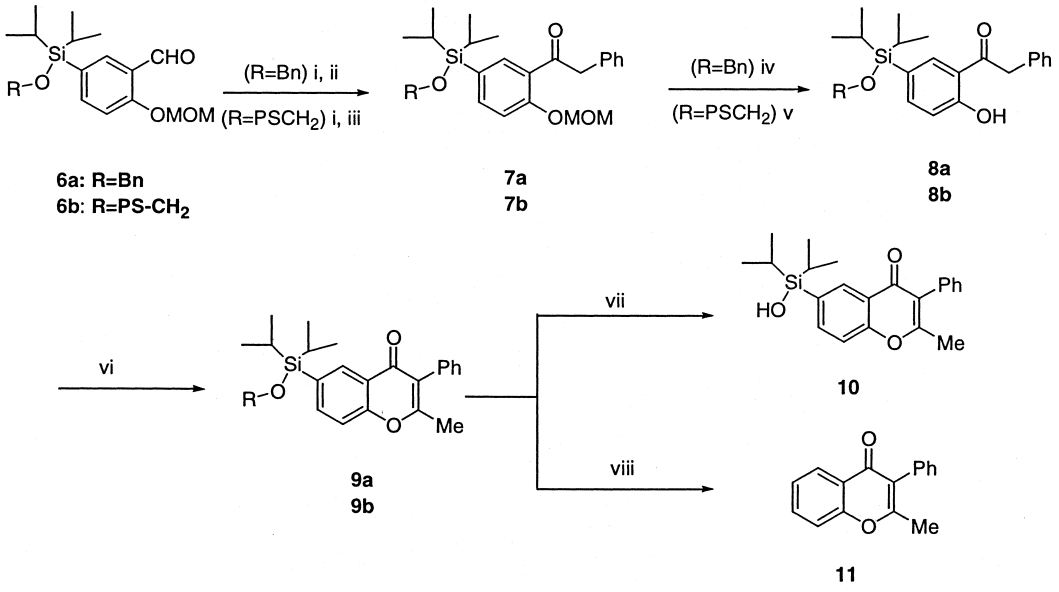


Scheme 2. Reagents and conditions: (i) BnMgCl, THF, 4 h; (ii) Swern; iii) IBX, DMSO/THF; (iv) 6% TFA, DCM, 0°C; (v) 4% TFA, DCM, 0°C; (vi) *N*,*N*-dimethylacetamide dimethyl acetal, THF, 40°C, 6 h; (vii) 0.01 M TBAF, THF, 1 h; (viii) saturated CsF, DMF, 60°C, 16 h or 0.2 M TBAF, THF/DMF (1:4), 45°C, 30 min.

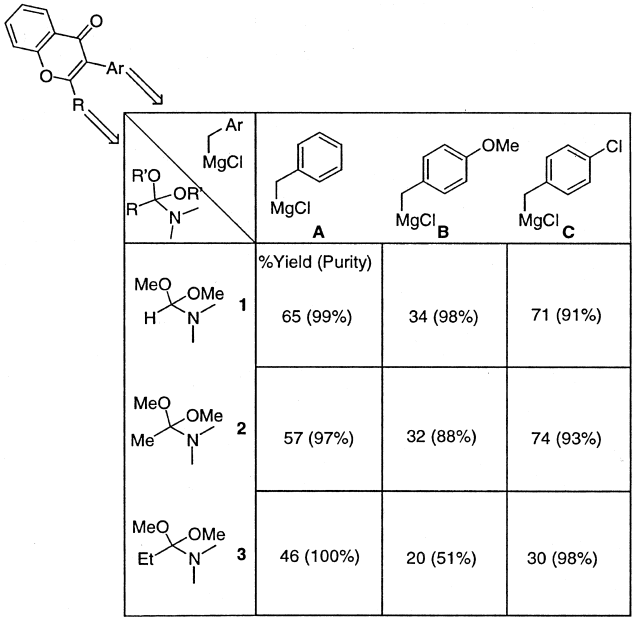
relatively less common condensation under basic conditions (typically piperidine in refluxing pyridine for several hours). Preliminary work showed that these conditions on polystyrene support led to poor swelling properties and gave products of low purity. We therefore set as our goal to develop a short, high yielding synthesis that would avoid some of the extreme conditions previously utilized, and furthermore would be amenable to solid-phase combinatorial library generation.

Retrosynthetically, 2,3-disubstituted benzopyran-4-ones **1** can be thought of as being derived from salicyl aldehydes **5** (Scheme 1). The R^1 substituents can be introduced by various organometallic reagents, and the R^2 substituents should be derivable from orthoesters or amide acetals.

To determine the feasibility of this strategy for solid-phase synthesis, we first carried out solution model studies in which benzyl alcohol was used as a surrogate for hydroxymethyl polystyrene resin. Our initial target was **11** with R^1=Ph and R^2=Me (Scheme 2). Addition of benzylmagnesium chloride to the aldehyde **6a**[4a] followed by Swern oxidation gave the ketone **7a**. Removal of the MOM protecting group in the presence of the silyloxy linker was accomplished by treatment of **7a** with 6% TFA in dichloromethane at 0°C. Reaction of the resulting phenol **8a** with trimethylorthoformate or *N*,*N*-dimethylformamide dimethyl acetal yielded the benzopyranone **9a**. Selective cleavage of the silicon–oxygen bond (to get the silanol **10**) or the silicon–carbon bond (to obtain the benzopyranone **11**) was achieved by fluoride ion under appropriate reaction conditions.

The solution-phase conditions were then applied to the solid-phase (Scheme 2). Encapsulation of the resin-bound aldehyde **6b**[4a] in IRORI MacroKan™ reactors, followed by treatment with the benzyl Grignard reagent gave the corresponding alcohol. For library synthesis, the Grignard reagents that were not commercially available were synthesized by reacting magnesium anthracene with substituted benzyl halides in THF.[5] The benzylic alcohol was oxidized with IBX[6] (1-hydroxy-1,2-benziodoxol-3(1*H*)-one) in DMSO/THF to the corresponding ketone **7b**, which was then treated with 4% TFA in dichloromethane to selectively remove the MOM group in the presence of the silyloxy linker. The resin-bound silicon–oxygen bond in MOM ether **7b** was considerably more sensitive to TFA than the corresponding solution-phase analog **7a**. The phenol **8b** was treated with the amide acetal in THF to give the resin-bound benzopyranone **9b**. For library synthesis, amide acetals that were not commercially available were synthesized by

Table 1. (yields based on starting hydroxymethyl polystyrene; purity based on HPLC after filtration through alumina)



treatment of *N*,*N*-dimethyl amides with trimethyloxonium tetrafluoroborate followed by sodium methoxide.[7] Treatment of resin **9b** with CsF or 0.2 M TBAF in DMF gave the target benzopyranone **11**, whereas 0.01 M tetrabutylammonium fluoride in THF yielded the silanol **10**. The resin reactions were followed by TLC and mass spectrometry on the silanols obtained by treatment of a small portion of the resin-bound intermediates with 1.0 M tetrabutylammonium fluoride in THF. One set of resin-bound compounds **6b**–**9b** was characterized by gel-phase ^{13}C NMR spectroscopy. Library benzopyranones were characterized by ^{1}H and ^{13}C NMR spectroscopy, chemical ionization mass spectrometry and HPLC. A representative array is shown in Table 1.

In summary we have designed a short, efficient synthesis of 2,3-disubstituted benzopyran-4-ones and have applied this to the solid phase. We have also demonstrated further versatility of our previously reported solid-supported diisopropylsilyloxy traceless linker. We are extending this methodology to the synthesis of other fused heterocyclic templates, and will report on this work in future disclosures.

Experimental

Materials and methods

Standard reagents were obtained from commercial suppliers and used without further purification. Column chromatography was carried out using E. Merck 60 (230–400 mesh) silica gel. Thin layer chromatography was performed using Merck 60 F254 0.25 μm silica gel plates. ^{1}H and ^{13}C NMR spectra were obtained on a Varian Unity 400 MHz spectrometer at 400 and 101 MHz, respectively. Spectra were obtained in $CDCl_3$ with TMS as the internal standard and are reported in ppm. Chemical ionization mass spectra (CIMS) were recorded on a Fisons Trio 2A instrument with 1% ammonia in methane as the reagent gas. Atmospheric pressure chemical ionization mass spectra (APCIMS) were recorded using a VG Trio 2000 mass spectrometer in a matrix of MeOH/CH_3CN/DMSO. Following normal work-up procedures, organic extracts were dried over anhydrous Na_2SO_4 prior to concentration. A single lot of hydroxymethyl polystyrene resin (Bachem California, Catalog #D-2105, Lot #ZN996, 1% cross-linked, 100–200 mesh) was used for all solid-phase synthesis. Library synthesis was carried out in IRORI MacroKans™. Abbreviations used: TFA=trifluoroacetic acid; TBAF= tetrabutylammonium fluoride; DCM=dichloromethane.

5-[Bis(1-methylethyl)(phenylmethoxy)silyl]-2-(methoxymethoxy)benzaldehyde (6a). Aldehyde **6a** was synthesized according to the procedure reported earlier by our group[4a] and recrystallized from hexanes to give a colorless crystalline solid. mp 52.5–53.0°C; HRMS *m*/*z* calcd: 387.1991 (MH^+), found: 387.1996.

1-[5-[Bis(1-methylethyl)(phenylmethoxy)silyl]-2-(methoxymethoxy)phenyl]-2-phenylethanone (7a). To a solution of benzylmagnesium chloride (2.0 M in THF, 10.3 mL, 20.6 mmol) at 0°C was added a solution of aldehyde **6a**[4a] (4.0 g, 10.3 mmol) in THF (20 mL). The mixture was gradually warmed to 25°C and stirred for 4 h. The mixture was carefully quenched with H_2O and extracted with ether. The ether phase was washed with H_2O (2×) and then with brine, dried and concentrated to give crude alcohol intermediate as a pale yellow gum. Purification by column chromatography (20:1 to 10:1 hexanes/EtOAc) gave 1-[5-[bis(1-methylethyl)(phenylmethoxy)-silyl]-2-(methoxymethoxy)phenyl]-2-phenylethanol (4.04 g, 82%) as a colorless viscous liquid. ^{1}H NMR δ 7.47–7.35 (m, 6H), 7.29–7.11 (m, 7H), 5.24–5.14 (m, 3H), 4.86 (s, 2H), 3.51 (s, 3H), 3.14 (dd, *J*=13.4, 5.4 Hz, 1H), 3.02 (dd, *J*=13.4, 5.8 Hz, 1H), 2.53 (d, *J*=5.6 Hz, 1H), 1.32 (m, 2H), 1.09 (d, *J*=7.3 Hz, 6H), 1.03 (m, 6H); ^{13}C NMR: δ 155.3, 141.4, 138.5, 135.3, 133.5, 131.3, 129.5, 128.3, 128.2, 126.9, 126.5, 126.3, 125.9, 113.1, 94.3, 71.8, 65.4, 56.3, 44.3, 17.7, 17.6, 17.4, 12.3. A solution of DMSO (1.42 mL, 20.05 mmol) in DCM (10 mL) was added dropwise to a solution oxalyl chloride (2.0 M in DCM, 5.01 mL, 10.03 mmol) precooled to −78°C. The mixture was stirred for 2 min at −78°C and then treated by slow addition of a solution of the above alcohol (4.0 g, 8.35 mmol) in 50 mL DCM. The mixture was stirred for 15 min at −78°C, treated with triethylamine (5.8 mL, 41.78 mmol) and allowed to gradually warm to 25°C. The mixture was diluted with DCM (200 mL) and washed with H_2O (3×100 mL) followed by saturated aqueous NH_4Cl (1×100 mL). The organic layer was dried and concentrated to leave a residue that was chromatographed (20:1 hexanes/EtOAc) to give **7a** (3.6 g, 90%) as a colorless viscous liquid. ^{1}H NMR δ 7.82 (d, *J*=1.4 Hz, 1H), 7.65 (dd, *J*=8.4, 1.5 Hz, 1H), 7.41–7.19 (m, 12H), 5.29 (s, 2H), 4.88 (s, 2H), 4.30 (s, 2H), 3.50 (s, 3H), 1.35 (sep, *J*=7.5 Hz, 2H), 1.09 (d, *J*=7.3 Hz, 6H), 1.03 (d, *J*=7.5 Hz, 6H); ^{13}C NMR δ 200.5, 156.9, 141.1, 139.8, 136.6, 135.1, 129.7, 128.5, 128.4, 128.3, 127.0, 126.9, 126.7, 125.9, 114.1, 94.3, 65.5, 56.6, 50.2, 17.5, 17.4, 12.2; CIMS *m*/*z*: 477 (MH^+, 39%); HRMS *m*/*z* calcd: 477.2461(MH^+), found: 477.2466.

1-[5-[Bis(1-methylethyl)(phenylmethoxy)silyl]-2-(hydroxy)phenyl]-2-phenylethanone (8a). To a vigorously stirred solution of **7a** (1.0 g, 2.1 mmol) in DCM (15 mL) at 0°C was added TFA (0.75 mL, 9.7 mmol). The mixture was stirred at 0°C for 1 h, diluted with DCM, and washed with H_2O (3×) and then brine. The organic phase was dried and concentrated to an oil that was chromatographed (40:1 hexanes/EtOAc) to give **8a** (0.85 g, 94%) as a pale brown liquid. ^{1}H NMR δ 12.32 (s, 1H), 8.02 (d, *J*=1.4 Hz, 1H), 7.61 (dd, *J*=8.2, 1.4 Hz, 1H), 7.44–7.15 (m, 11H), 6.99 (d, *J*=8.4 Hz, 1H), 4.89 (s, 2H), 4.08 (s, 2H), 1.33 (sep, *J*=7.5 Hz, 2H), 1.09 (d, *J*=7.5 Hz, 6H), 1.02 (d, *J*=7.5 Hz, 6H); ^{13}C NMR δ 204.4, 163.9, 142.3, 141.1, 137.7, 134.0, 129.3, 128.7, 128.4, 127.2, 127.1, 125.9, 123.5, 118.9, 118.2, 65.5, 45.3, 17.5, 17.3, 12.1; CIMS *m*/*z*: 433 (MH^+, 100%).

6-[Bis(1-methylethyl)(phenylmethoxy)silyl]-2-methyl-3-phenyl-4*H*-1-benzopyran-4-one (9a). To a solution of **8a** (0.08 g, 0.18 mmol) in THF (5.0 mL) was added *N*,*N*-dimethylacetamide dimethyl acetal (0.25 mL, 1.5 mmol) and the mixture was stirred at 40°C for 6 h. After cooling, the mixture was diluted with ether, washed with H_2O and then saturated aqueous ammonium chloride. The organic phase was dried and concentrated to a residue that was

chromatographed (20:1 to 10:1 hexanes/EtOAc) to provide **9a** (0.072 g, 85%) as a colorless gum. ^{1}H NMR δ 8.47 (d, J=1.4 Hz, 1H), 7.88 (dd, J=8.2, 1.4 Hz, 1H), 7.46–7.26 (m, 11H), 4.93 (s, 2H), 2.33 (s, 3H), 1.42 (sep, J=7.5 Hz, 2H), 1.11 (d, J=7.5 Hz, 6H), 1.05 (d, J=7.5 Hz, 6H); ^{13}C NMR δ 176.8, 163.2, 156.9, 140.9, 139.3, 133.2, 132.9, 131.2, 130.4, 128.4, 128.3, 127.8, 127.1, 126.0, 124.1, 122.8, 117.0, 65.6, 19.6, 17.5, 17.3, 12.2; CIMS *m/z* 457 (MH^+, 100%).

6-[Hydroxybis(1-methylethyl)silyl]-2-methyl-3-phenyl-4*H*-1-benzopyran-4-one (10). To a solution of benzopyranone **9a** (46 mg, 0.1 mmol) in THF (15 mL) was added TBAF (1.0 M solution in THF, 0.15 mL, 0.15 mmol), and the mixture was stirred for 1 h at 25°C. The mixture was diluted with H_2O, and extracted with ether. The combined ether layers were dried, filtered through a plug of silica gel and concentrated to give silanol 10 (32 mg, 89%) as a colorless oil. CIMS *m/z* (rel int) 367 (MH^+, 100%).

2-Methyl-3-phenyl-4*H*-1-benzopyran-4-one[8] **(11**; **A2 of Table 1)**. To a solution of **9a** (0.05 g, 0.11 mmol) in DMF (1 mL) was added TBAF (0.25 mL, 1.0 M solution in THF, 0.25 mmol) and the mixture was stirred at 45°C for 0.5 h. The mixture was cooled, diluted with H_2O, and extracted with ether (2×). The combined ether layers were washed with H_2O, brine, and dried. Concentration provided a residue that was chromatographed (20:1 to 10:1 hexanes/EtOAc) to obtain **11** (0.02 g, 84%) as a colorless solid. mp 138.0–138.5°C; ^{1}H NMR δ 8.20 (d, J=7.8 Hz, 1H), 7.62 (t, J=8.0 Hz, 1H), 7.42–7.22 (m, 7H), 2.29 (s, 3H); ^{13}C NMR δ 176.8, 163.2, 155.9, 133.3, 133.1, 130.4, 128.4, 127.7, 126.3, 124.8, 123.7, 123.5, 117.6, 19.5; CIMS *m/z* (rel int) 237 (MH^+, 100); HRMS *m/z* calcd: 237.0915 (MH^+), found: 237.0915.

1-[5-[Bis(1-methylethyl)(polystyrylmethoxy)silyl]-2-(methoxymethoxy)phenyl]-2-phenylethanone (7b). To resin-bound aldehyde **6b**[4a] (0.7 mmol/g) in five MacroKans™ (5×0.250 g) was added anhydrous THF (50 mL). The suspension was stirred under N_2 for 5 min and then the THF was decanted. To the resin was added anhydrous THF (50 mL) followed by benzylmagnesium chloride (2.0 M in THF, 2.5 mL, 5.0 mmol) providing ~0.1 M final concentration. The mixture was stirred vigorously for 15 min, and the THF solution was decanted. This cycle of Grignard reagent treatment was repeated and the resulting yellow colored resin was quenched with H_2O and then washed successively with saturated aqueous ammonium chloride (3×50 mL), H_2O (4×50 mL), isopropanol (3×50 mL) and THF (3×50 mL) to leave an off-white resin. The resin was dried under vacuum at 25°C overnight to give the intermediate resin-bound alcohol (0.264 g/can). ^{13}C NMR δ 155.2, 94.2, 71.8, 65.4, 56.3, 44.3, 17.5, 12.2. To a suspension of the resin-bound alcohol (4×0.264 g) in THF (25 mL) was added a solution of IBX (2.0 g, 7.1 mmol) in DMSO (25 mL). The mixture was stirred for 1 h at 25°C. The solution was decanted and the treatment was repeated. The resin was washed successively with DMSO (3×50 mL), THF (3×50 mL) and DCM (3×50 mL), and then dried under vacuum at 25°C overnight to give **7b** (0.264 g/can). The ^{13}C NMR absorption of the starting material at δ 71.8 disappeared, indicating the complete consumption of starting alcohol. ^{13}C NMR δ 94.4, 65.5, 56.5, 50.3, 17.5, 12.2.

1-[5-[Bis(1-methylethyl)(polystyrylmethoxy)silyl]-2-(hydroxy)phenyl]-2-phenylethanone (8b). To a vigorously stirred suspension of resin-bound ketone **7b** (3×0.264 g) in DCM (50 mL) at 0°C was gradually added TFA (2.0 mL) along the inner walls of the flask. The mixture was stirred at 0°C for 1 h. The solution was decanted and the resin was washed successively with DCM (3×50 mL) and THF (3×50 mL). The resin was dried under vacuum at 25°C overnight to give **8b** (0.254 g/can). ^{13}C NMR δ 209.5, 164.0, 145.7, 142.4, 137.7, 134.1, 128.1, 118.3, 65.5, 45.4, 17.5, 12.2.

6-[Bis(1-methylethyl)(polystyrylmethoxy)silyl]-2-methyl-3-phenyl-4*H*-1-benzopyran-4-one (9b). To a suspension of resin-bound phenol **8b** (2 × 0.254 g) in THF (10 mL) was added *N*,*N*-dimethylacetamide dimethyl acetal (0.5 mL, 3.0 mmol). The mixture was heated at 40°C for 6 h. The mixture was cooled and the resin was washed with THF (6×30 mL) and then dried under vacuum at 25°C overnight to give **9b** (0.256 g/can). ^{13}C NMR δ 65.3, 19.6, 17.5, 12.3.

2-Methyl-3-phenyl-4*H*-1-benzopyran-4-one (11; A2 of Table 1) by cleavage of resin-bound 9b. To a suspension of **9b** (0.256 g) in DMF (8.0 mL) was added TBAF (1.0 M solution in THF, 2.0 mL). The mixture was stirred at 45°C for 30 min, cooled to 25°C, diluted with H_2O, and extracted with ether. The combined ether layers were washed with H_2O (3×) and brine, dried, and evaporated to a concentrated solution that was filtered through a plug of alumina to give **11** (26 mg, 65% overall yield from **6b**). The spectral data were identical to those given above.

General procedure for preparation of a library of benzopyranones (Table 1). IRORI MacroKans™ were marked by hand (using a needle) with a unique alphanumeric code, and then loaded with resin-bound aldehyde **6b**[4a] (0.15 g/can). The cans were subjected to the same sequence of reactions as described in Scheme 2.

General procedure for cleavage of resin-bound benzopyranones with CsF. The MacroKans™ containing the resin-bound benzopyranones were placed in vials and to each of these was added a saturated solution of CsF in anhydrous DMF (10 mL). The vials were capped and heated at 60°C on a shaker at 150 rpm for 16 h. The vials were cooled to 25°C, diluted with H_2O (20 mL) and extracted into ether (20 mL). (Alternatively, the DMF can be evaporated over a stream of N_2 overnight, and the residue taken up in ether.) The ether layer was washed with H_2O (2×), brine, and dried. The ether layer was filtered through a short plug of alumina to give the benzopyranones in the yields and purity shown in Table 1.

Analytical data

3-Phenyl-4*H*-1-benzopyran-4-one[8,9] **(A1).** ^{1}H NMR δ 8.29 (dd, J=8.1, 0.7 Hz, 1H), 7.99 (s, 1H), 7.66 (t, J=7.0 Hz, 1H), 7.55–7.34 (m, 7H); ^{13}C NMR δ 176.2, 156.2, 153.0,

133.6, 131.8, 128.9, 128.5, 128.2, 126.4, 125.4, 125.2, 124.6, 118.0; CIMS *m*/*z* (rel int) 223 (MH^+, 100).

3-(4-Methoxyphenyl)-4*H*-1-benzopyran-4-one[8,9] (B1). ^{1}H NMR δ 8.28 (d, J=8.0 Hz, 1H), 7.96 (s, 1H), 7.63 (dt, J=8.5, 1.2 Hz, 1H), 7.49–7.37 (m, 3H), 6.94 (d, J=8.7 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR δ 176.4, 159.6, 156.2, 152.4, 133.5, 130.1, 126.4, 125.1, 125.0, 124.5, 124.1, 118.0, 114.0, 55.3; CIMS *m*/*z* (rel int) 253 (MH^+, 100).

3-(4-Chlorophenyl)-4*H*-1-benzopyran-4-one[9] (C1). ^{1}H NMR δ 8.23 (d, J=8.1 Hz, 1H), 7.95 (s, 1H), 7.63 (t, J=7.3 Hz, 1H), 7.51–7.33 (m, 6H); ^{13}C NMR δ 175.9, 156.2, 153.0, 134.2, 133.8, 130.3, 130.2, 128.7, 126.4, 125.4, 124.5, 124.3, 118.1; CIMS *m*/*z* (rel int) 257 (MH^+, 100).

3-(4-Methoxyphenyl)-2-methyl-4*H*-1-benzopyran-4-one (B2). ^{1}H NMR δ 8.19 (dd, J=7.8, 1.2 Hz, 1H), 7.61 (dt, J=7.3, 1.7 Hz, 1H), 7.45–7.32 (m, 2H), 7.18 (d, J=8.8 Hz, 2H), 6.94 (d, J=8.8 Hz, 2H); ^{13}C NMR δ 176.9, 159.1, 135.5, 133.2, 131.5, 126.3, 124.7, 117.6, 115.5, 113.9, 55.3, 19.5; CIMS *m*/*z* (rel int) 267 (MH^+, 100).

3-(4-Chlorophenyl)-2-methyl-4*H*-1-benzopyran-4-one (C2). ^{1}H NMR δ 8.18 (dd, J=8.1, 1.2 Hz, 1H), 7.63 (m, 1H), 7.42–7.33 (m, 4H), 7.22–7.19 (m, 2H), 2.29 (s, 3H); ^{13}C NMR δ 176.5, 167.3, 156.0, 133.3, 133.1, 130.3, 128.4, 127.7, 126.3, 124.8, 123.2, 123.1, 117.6, 26.2; CIMS *m*/*z* (rel int) 271 (MH^+, 100).

3-(4-Chlorophenyl)-2-ethyl-4*H*-1-benzopyran-4-one (C3). ^{1}H NMR δ 8.19 (d, J=8.1 Hz, 1H), 7.64 (t, J=8.3 Hz, 1H), 7.44–7.34 (m, 4H), 7.22–7.17 (m, 2H), 2.55 (q, J=7.6 Hz, 2H), 1.23 (t, J=7.6 Hz, 3H); ^{13}C NMR δ 176.8, 167.4, 156.0, 133.8, 133.5, 131.7, 131.5, 128.7, 126.2, 124.9, 123.3, 117.7, 26.1, 11.9; CIMS *m*/*z* (rel int) 285 (MH^+, 100).

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6. Caution! IBX has been reported to detonate upon heavy impact and heating over 200°C. In our hands some batches of IBX exploded at its melting point, while most other batches decomposed with browning: (a) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019. (b) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272.

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