# HALOGENATED 2*H*-1-BENZOPYRANS: SYNTHESES AND REACTIVITY TOWARD ALUMINIUM, MAGNESIUM, AND LITHIUM ORGANOMETALLICS

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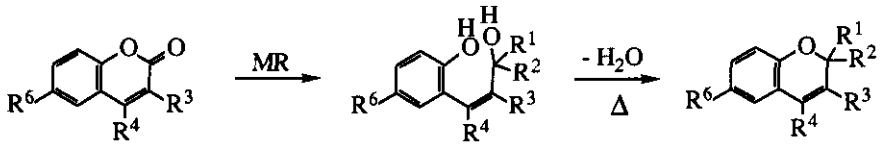
Abstract- 3-, 4-, or 6-Halo-2*H*-1-benzopyrans are prepared by reacting the halogenated coumarins with lithium, magnesium or aluminium organometallics, and further thermal cyclization of the resulting o-hydroxycinnamyl alcohols. The method is not applicable for 3-halo-2*H*-1-benzopyrans with no-substituents on C-2. The 3-, or 4-halo-2*H*-1-benzopyrans derivatives give non-metallated products when the species obtained are subjected to metal-halogen interchange with butyllithium, whereas the 6-bromo derivatives afford 6-lithium-2*H*-1-benzopyrans.

The literature shows different methods to obtain halogenated 2*H*-1-benzopyrans, either from halogenated non-cyclic substrates,[1-5] or from preformed heterocycles.[6-12] We have been exploring the possibilities of the classic method, which is depicted in Scheme 1: the coumarins (**1-4**) are treated with organometallics, and the resulting diols (**5**) are subjected to further cyclization.

The first step of Scheme 1 has been already described in previous articles.[13,14] This work is focussed on the cyclization step, which has been carried out as for other non-halogenated compounds,[15] i.e. dehydration in refluxing toluene, xylene, or mesitylene in the presence of silica gel. The degree of substitution and the position of the halogen are the decisive factors on the yield obtained. (Table 1)




**1-4** **5** **6**

**1** $R^3 = R^4 = H$, $R^6 = Br$
**2** $R^3 = R^6 = H$, $R^4 = Cl$
**3** $R^4 = R^6 = H$, $R^3 = Br$
**4** $R^4 = R^6 = H$, $R^3 = Cl$

Scheme 1

Table 1

Cyclization of 2-(3-hydroxy-1-propenyl)phenols (**5**) to 2*H*-1-benzopyrans (**6**).

| Starting Compd | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^6$ | Solvent (reflux) | Time (h) | Products (%) |
|---|---|---|---|---|---|---|---|---|
| **5a** | Me | Me | H | H | Br | Xylene | 1 | **6a** (55) |
| **5b** | Me | Me | H | Cl | H | Toluene | 1 | **6b** (76) |
| **5c** | Et | Et | H | Cl | H | Toluene | 1 | **6c** (70) |
| **5d** | Pr | Pr | H | Cl | H | Toluene | 1 | **6d** (66) |
| **5e** | Bu | Bu | H | Cl | H | Toluene | 1 | **6e** (72) |
| **5f** | H | H | Br | H | H | Mesitylene | 3 | **6f** (0) |
| **5g** | Me | H | Br | H | H | Xylene | 3 | **6g** (36) |
| **5h** | Et | H | Br | H | H | Xylene | 3 | **6h** (40) |
| **5i** | Bu | H | Br | H | H | Xylene | 3 | **6i** (42) |
| **5j** | Me | Me | Br | H | H | Xylene | 1.5 | **6j** (60) |
| **5k** | Et | Et | Br | H | H | Xylene | 1.5 | **6k** (57) |
| **5l** | Bu | Bu | Br | H | H | Xylene | 1.5 | **6l** (56) |
| **5m** | H | H | Cl | H | H | Mesitylene | 3 | **6m** (0) |
| **5n** | Me | H | Cl | H | H | Xylene | 6 | **6n** (38) |
| **5o** | Bu | H | Cl | H | H | Xylene | 6 | **6o** (53) |
| **5p** | Me | Me | Cl | H | H | Xylene | 3 | **6p** (87) |
| **5q** | Et | Et | Cl | H | H | Xylene | 4 | **6q** (71) |

When a bromine atom is attached to the carbocycle, the process reaches similar yields to those obtained for cyclizations of non-halogenated *o*-hydroxycinnamyl alcohols (**5**), such as 55% for 6-bromo-2,2-dimethyl-2*H*-1-benzopyran (**6a**). Instead, 66-76% yields are obtained for 4-chloro-2,2-dialkyl-2*H*-1-benzopyrans (**6b-e**). This increase may be interpreted considering the presence of a substituent attached to C-4, since we have previously demonstrated that cyclizations are easier when a 4-substituted heterocycle is obtained.[15]

The series 3-halogenated **6f-q** was subjected to a complete study, as both the degree of substitution on C-2 (primary, secondary and tertiary alcohols) and the nature of the halogen ($R^3$ = Cl or Br) were systematically changed. Some parallelism with the alkyl analogues is observed,[15] although the yields are usually lower. The process is accomplished easily and the results are more satisfactory for chloro derivatives and for more substituted C-2. Instead, for primary alcohols ($R^1 = R^2 = H$; $R^3$ = halogen), the reaction needs energetic conditions (refluxing mesitylene), and gives a mixture of products where the solvent is incorporated to the molecule, as shown by nmr and mass spectra.

A one-pot synthetic procedure from the halogenated coumarin (**1-4**), without isolating **5** (Table 2) is advantageous. This method only presents limitations when a deficient control of the first step gives rise to non-halogenated benzopyrans as by-products, which make difficult the ulterior chromatographic separation.

The benzopyrans (**6a**) ($R^1 = R^2 = Me$, $R^3 = R^4 = H$, $R^6 = Br$), (**6b**) ($R^1 = R^2 = Me$, $R^3 = R^6 = H$, $R^4 = Cl$), and (**6j**) ($R^1 = R^2 = Me$, $R^4 = R^6 = H$, $R^3 = Br$) were chosen among them as representative examples to study their reactivity toward organometallics. Our previous work showed that 2*H*-1-benzopyrans are fairly stable toward organolithium reagents, but undergo an opening process with addition and isomerization of the C=C bond with alkylaluminium and organomagnesium reagents.[16,17] Thus, two different possibilities may be predicted for the halogenated heterocycles: (a) metal-halogen interchange (for LiR) and subsequent reactivity of the metallated species, and (b) transformations due to the proper reactivity of the heterocycle.

When 6-bromo-2,2-dimethyl-2*H*-1-benzopyran (**6a**) is treated with butyllithium in ether at room temperature, a clean metal-halogen interchange is observed, and no other competitive processes such as opening of the heterocycle, alkylation or dimerization are detected.[18,19] The lithium derivative (**7**) allows the introduction of different substituents in C-6 (Scheme 2, Table 3), providing a versatile method to obtain 6-functionalized benzopyrans from 6-halogenated coumarins.

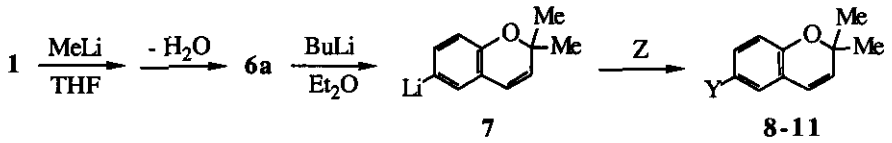
Table 2

Conditions for the formation of the intermediates 2-(3-hydroxy-1-propenyl)phenols (**5**) in the one-pot syntheses of 2*H*-1-benzopyrans (**6**) from coumarins (**1-4**).

| Start. Compd | MR | Ratio[a] | Solv. | Temp. (°C) | Time (h) | Product (%) |
|---|---|---|---|---|---|---|
| **1** | MeLi | 1/2 | THF | -10 | 1 | **6a** (60) |
| **2** | MeMgI | 1/6 | THF | 0 | 2 | **6b** (70) |
| **2** | EtMgBr | 1/5 | THF | 0 | 1 | **6c** (65) |
| **2** | PrMgBr | 1/5 | THF | 0 | 1 | **6d** (61) |
| **2** | BuMgBr | 1/5 | THF | 0 | 1 | **6e** (70) |
| **3** | $Al^{i}Bu_3$ | 1/4 | Toluene | 0 | 10 | **6f** (0) |
| **3** | DIBAL-H/MeMgI | 1/1; 1/2 | Toluene/$Et_2O$ | -40-0 | 0.75 | **6g** (36) |
| **3** | DIBAL-H/EtMgBr | 1/1; 1/2 | Toluene/$Et_2O$ | -40-0 | 0.75 | **6h** (40) |
| **3** | $Al^{n}Bu_3$ | 1/4 | Toluene | 0 | 10 | **6i** (42) |
| **3** | MeMgI | 1/4 | Toluene | 0 | 3 | **6j** (60) |
| **3** | EtMgI | 1/4 | Toluene | 0 | 3 | **6k** (56) |
| **3** | BuMgI | 1/4 | Toluene | 0 | 3 | **6l** (56) |
| **4** | DIBAL-H | 1/6 | Toluene | 0 | 10 | **6m** (0) |
| **4** | DIBAL-H/MeMgI | 1/1; 1/2 | Toluene/$Et_2O$ | -40-0 | 0.75 | **6n** (36) |
| **4** | $Al^{n}Bu_3$ | 1/4 | Toluene | 0 | 10 | **6o** (51) |
| **4** | MeMgI | 1/4 | Toluene/$Et_2O$ | 0 | 0.5 | **6p** (60) |
| **4** | EtMgBr | 1/4 | Toluene | 0 | 0.5 | **6q** (55) |

[a]Ratio: Starting compound/MR. More information about the intermediates (**5**) and their reaction conditions and hydrolysis may be found on references 10 and 11.

Instead, 4-chloro-2,2-dimethyl-2*H*-1-benzopyran (**6b**) gives 4-butyl-2,2-dimethyl-2*H*-1-benzopyran (**13**) after reaction with butyllithium, probably by a coupling process through the metallated species (**12**) (Scheme 3).[18,19] Unfortunately, this reaction was not extensive to other organolithium reagents, such as methyllithium which did not react.



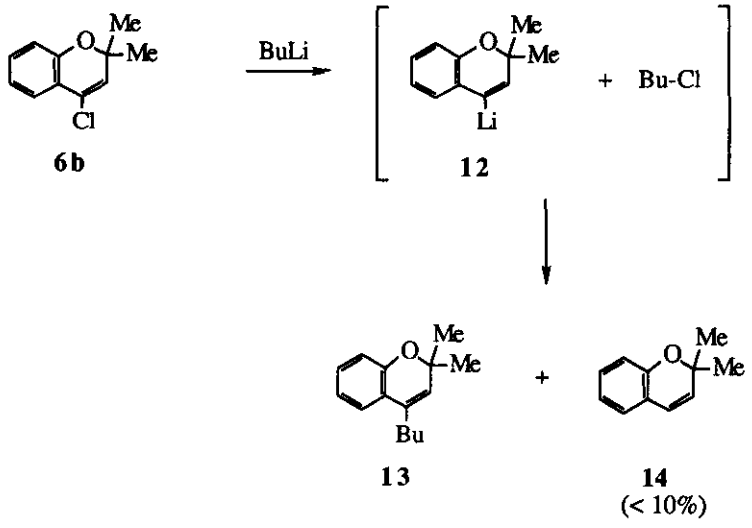

Scheme 2

Table 3

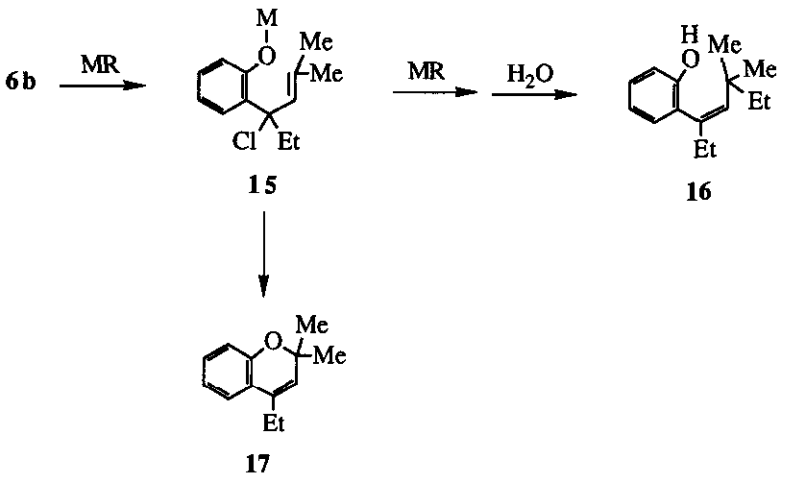
Captions to Scheme2

| Z | 7/Z Ratio | Time (m) | Temp.(°C) | Y | Prod. (%) |
|---|---|---|---|---|---|
| $CO_2$ | * | 30 | * | $-CO_2H$ | **8** (80) |
| $ClCONMe_2$ | 1/3 | 180 | -70 → -30 | $-CONMe_2$ | **9** (82) |
| $HCONMe_2$ | 1/4 | 30 | -70 → -30 | -COH | **10** (96) |
| $ClSiMe_3$ | 1/4 | 15 | -20 | $-SiMe_3$ | **11** (92) |

*Excess of solid $CO_2$.




Scheme 3




Scheme 4

Table 4

Captions to Scheme 4

| MR | **6b**/MR Ratio | Solvent | Temp.(°C) | Time(h) | % **16**[a] | % **17**[a] |
|---|---|---|---|---|---|---|
| $AlEt_3$ | 1/4 | Toluene | 20 | 6 | 30 | 50 |
| $AlEt_3$ | 1/2 | Toluene | 20 | 12 | 28 | 49 |
| $AlEt_3$ | 1/1 | Toluene | 20 | 24 | < 10[b] | < 10[b] |
| $AlEt_3$[c] | 1/3 | Toluene | 25 | 3 | 25 | 30 |
| EtMgBr | 1/3 | Ether | 20 | 24 | -[d] | -[d] |
| EtMgBr | 1/3 | Toluene | 110 | 12 | -[e] | -[e] |

[a] Estimated by $^1H$ nmr of the crude product

[b] Untransformed product: > 50%

[c] Uv irradiated (refs. 16 and 17)

[d] Untransformed product: > 80%

[e] Decomposition observed.

On the other hand, the reaction of **6b** with triethylalumminum or ethylmagnesium bromide yields *Z*-*o*-(3,3-dimethyl-1-ethylpent-1-enyl)phenol (**16**) (15-50%) and 2,2-dimethyl-4-ethyl-2*H*-1-benzopyran (**17**) (25-55%)

(Table 4). A possible path for the formation of these two compounds is depicted on Scheme 4. The alkylation with opening of the heterocycle and olefinic isomerization would afford a reactive halogenated derivative (**15**). This could undergo a further alkylation and allylic isomerization to give **16**, whose configuration was established by an $^1$H nmr NOE experiment. The formation of **17** could follow an alternative path to that of **13** (Scheme 3), that is, cyclization of either the intermediate (**15**), or its hydrolysis product. All the attempts to trap the intermediate (**15**) or to improve the ratio of the benzopyran (**17**) were unsuccessful.

The reactions of 3-bromo-2*H*-1-benzopyrans (**6j**) with lithium, magnesium or aluminium organometallics were cumbersome, giving always black residues even at low temperatures, and thus no attempts to isolate products have been carried out.

## EXPERIMENTAL

The mp was measured on a Leit Laborlux D microscope with a heating device and is uncorrected. The bps correspond to the oven temperature in a Kugelrohr Büchi GKR-51. Nmr spectra were recorded on Bruker AC80 and AC300 spectrometers, and chemical shifts are given downfield from $SiMe_4$ as internal standard. Mass spectra were measured on a Hewlwett-Packard 5988A mass spectrometer.

Starting 6-bromocoumarin,[20] 4-chlorocoumarin,[21] 3-bromocoumarin,[22] 3-chlorocoumarin,[23] and o-hydroxycinnamyl alcohols (**5**)[13,14] were prepared as previously described.

Cyclization of **5** to 2*H*-1-benzopyrans (**6**). General procedure. A mixture of 5 mmol of the substrate, 4 g of silica gel (Merck, Kiesegel-60) recently activated at 120°C, and 20 ml of toluene, xylene, or mesitylene was refluxed for 1-4 h (see Table 1). The reflux should be equipped with either a Dean-stark trap or a Soxhlet extractor charged with 3Å molecular sieves. The process was monitored by tlc silica gel ($CH_2Cl_2$/$Et_2O$, 20/1). The hot mixture was filtered and the silica gel was washed with hot ethyl acetate (2 x 10 ml). The filtrate was concentrated, and the resulting oil was chromatographed on silica gel-hexane.

One-pot syntheses of **6** from **1-4**. Four representative examples are collected here. Strict control of the conditions are required in the reactions between halocoumarins and organometallics, as has been previously reported.[13,14]

*Synthesis of 6-bromo-2,2-dimethyl-2H-1-benzopyran* (**6a**). MeLi (7.3 ml of a 1.5 M of $Et_2O$ solution, 11 mmol) was added dropwise to a magnetically stirred solution of **1** (1.12 g, 5 mmol) in THF (100 ml) at -10°C.

Table 5

Physical, Spectroscopic, and analytical data for the compounds described.

| Compd | bp (°C)/torr or mp (°C) | $^1$H Nmr ($CDCl_3$, TMS) (J in Hz) | Formula | Ms (m/z) | Analyses: Found (Calcd) C% | H% |
|---|---|---|---|---|---|---|
| **6a** | 85-90/0.5 | 1.39(s, 6H), 5.60(d, 1H, J=9.8), 6.21(d, 1H, J=9.8), 6.50-7.30(m, 3H) | $C_{11}H_{11}OBr$ | 240($M^+$+2, 27), 238($M^+$, 28), 223(100) | 55.31 (55.26)) | 4.52 (4.64) |
| **6b** | 98-100/1.5 | 1.44(s, 6H), 5.71(s, 1H), 6.70-7.51(m, 4H) | $C_{11}H_{11}OCl$ | 196($M^+$+2, 3), 194($M^+$, 10), 170(100) | 67.75 (67.87) | 5.72 (5.70) |
| **6c** | 100-105/1.5 | 0.93(t, 6H, J=7), 1.56-1.86(m, 4H), 5.62(s, 1H), 6.70-7.46(m, 4H) | $C_{13}H_{15}OCl$ | 224($M^+$+2, 1), 222($M^+$, 3), 193(100) | 70.41 (70.11) | 6.85 (6.79) |
| **6d** | 105-110/0.9 | 0.80-1.31(m, 6H), 1.37-1.79(m, 8H), 5.64(s, 1H), 6.68-7.46(m, 4H) | $C_{15}H_{19}OCl$ | 252($M^+$+2, 5), 250($M^+$, 15), 207(100) | 71.79 (71.85) | 7.56 (7.64) |
| **6e** | 135-139/2 | 0.73-1.05(m, 6H), 1.05-1.94(m, 12H), 5.63(s, 1H), 6.67-7.45(m, 4H) | $C_{17}H_{23}OCl$ | 280($M^+$+2, 1), 278($M^+$, 3), 221(100) | 73.10 (73.23) | 8.49 (8.31) |
| **6g** | 70-75/0.7 | 1.61(d, 3H, J=6.5), 5.14(qd, 1H, J=6.5 and 0.6), 6.79(d, 1H, J=0.6), 6.90-7.37(m, 4H) | $C_{10}H_9OBr$ | 226($M^+$+2, 13), 224($M^+$, 14), 115(100) | 53.28 (53.36) | 3.95 (4.03) |
| **6h** | 110-115/2.1 | 1.17(t, 3H, J=7.3), 3.68(m, 2H), 4.94(td, 1H, J=6.0 and 0.4), 6.81(br s, 1H), 6.89-7.35(m, 4H) | $C_{11}H_{11}OBr$ | 240($M^+$+2, 10), 238($M^+$, 11), 209(100) | 55.01 (55.26) | 4.56 (4.64) |
| **6i** | 105-110/1 | 0.88(t, 3H, J=6.1), 1.41(m, 4H), 1.74(m, 2H), 4.84 (ddd, 1H, J=5.5, 5.4 and 0.5), 6.68(d, 1H, J=0.5), 6.72-7.22(m, 4H) | $C_{13}H_{15}OBr$ | 268($M^+$+2, 8), 266($M^+$, 9), 209(100) | 58.20 (58.44) | 5.71 (5.66) |
| **6j** | 80-85/0.9 | 1.63(s, 6H), 6.75(s, 1H), 6.82-7.32(m, 4H) | $C_{11}H_{11}OBr$ | 240($M^+$+2, 17), 238($M^+$, 18), 225(100) | 55.40 (55.26) | 4.51 (4.64) |
| **6k** | 130/3 | 0.99(t, 6H, J=7.3), 1.50-2.10(m, 4H), 6.74(s, 1H), 6.70-7.50(m, 4H) | $C_{13}H_{15}OBr$ | 268($M^+$+2, 42), 266($M^+$, 43), 237(100) | 58.32 (58.44) | 5.52 (5.66) |
| **6l** | 140-145/0.5 | 0.86(t, 6H, J=6.1), 1.10-2.10(m, 12H), 6.72(s, 1H), 6.73-7.25(m, 4H) | $C_{17}H_{23}OBr$ | 324($M^+$+2, 6), 322($M^+$, 6), 265(100) | 63.41 (63.16) | 7.02 (7.17) |

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|---|---|---|---|---|---|---|
| **6n** | 80-85/1.5 | 1.47(d, 3H, J=6.5), 4.96(q, 1H, J=6.5), 6.50(s, 1H), 6.80-7.30(m, 4H) | $C_{10}H_9OCl$ | 182($M^+$+2, 6), 180($M^+$, 23), 165(100) | 66.38 (66.49) | 4.95 (5.02) |
| **6o** | 95-100/1.5 | 0.89(t, 3H, J=7.2), 1.45(m, 4H), 1.80(m, 2H), 4.77 (dd, 1H, J=8.3 and 3.9), 6.50(s, 1H), 6.80-7.25(m, 4H) | $C_{13}H_{15}OCl$ | 224($M^+$+2, 12), 222($M^+$, 42), 165(100) | 69.89 (70.11) | 6.83 (6.79) |
| **6p** | 80-85/1 | 1.53(s, 6H), 6.44(s, 1H), 6.70-7.20(m, 4H) | $C_{11}H_{11}OCl$ | 196($M^+$+2, 6), 194($M^+$, 19), 179(100) | 67.48 (67.87) | 5.90 (5.70) |
| **6q** | 100-105/1 | 0.99(t, 6H, J=7.4), 1.74(m, 2H), 1.93(m, 2H), 6.56 (s, 1H), 6.70-7.20(m, 4H) | $C_{13}H_{15}OCl$ | 224($M^+$+2, 3), 222($M^+$, 8), 193(100) | 70.23 (70.11) | 6.90 (6.79) |
| **8**[a] | 160 | 1.41(s, 6H), 5.80(d, 1H, J=9.8), 6.50(d, 1H, J=9.8), 6.75-7.95(m, 3H), 8.00(s, 1H) | $C_{12}H_{12}O_3$ | 204($M^+$, 17), 189(100) | 70.37 (70.58) | 5.72 (5.92) |
| **9**[b] | 90-95/0.5 | 1.24(s, 6H), 2.84(s, 6H), 5.45(d, 1H, J=9.8), 6.13(d, 1H, J=9.8), 6.50-7.05(m, 3H) | $C_{14}H_{17}NO_2$ | 231($M^+$, 20), 216(100) | 72.49 (72.70) | 7.60 (7.41) |
| **10** | 123-125/2 | 1.23(s, 6H), 5.45(d, 1H, J=10), 6.12(d, 1H, J=10), 6.50-7.50(m, 3H), 9.59(s, 1H) | $C_{12}H_{12}O_2$ | 188($M^+$, 14), 173(100) | 76.32 (76.57) | 6.23 (6.43) |
| **11** | 55-60/0.3 | 0.46(s, 9H), 1.61(s, 6H), 5.71(d, 1H, J=9.8), 6.50(d, 1H, J=9.8), 6.93-7.52(m, 3H) | $C_{14}H_{20}OSi$ | 234($M^+$+2, 1), 233($M^+$+1, 2), 232($M^+$, 10), 217(100) | 72.18 (72.36) | 8.90 (8.67) |
| **13** | 140-145/1.5 | 0.93(t, 3H, J=7.3), 1.39(s, 6H), 1.40(m, 2H), 1.42(m, 2H), 2.35(t, 2H, J=6.8), 5.38(s, 1H), 6.70-7.22(m, 4H) | $C_{15}H_{20}O$ | 217($M^+$+1, 1), 216($M^+$, 9), 201(100) | 83.10 (83.29) | 9.11 (9.32) |
| **14** | 84-85/1.5 | 1.42(s, 6H), 5.71(d, 1H, J=9.8), 6.29(d, 1H, J=9.8), 6.70-7.22(m, 4H) | $C_{11}H_{12}O$ | 160($M^+$, 18), 145(100) | 82.29 (82.47) | 7.65 (7.55) |
| **16** | 106-110/3 | 0.75(s, 3H), 0.81(t, 3H, J=7.4), 0.83(s, 3H), 0.98(t, 3H, J=7.4), 1.26(q, 2H, J=7.4), 2.20(m, 2H), 5.05 (br s, 1H, OH), 5.60(t, 1H, J=1.2), 6.70-7.30(m, 4H) | $C_{15}H_{22}O$ | 218($M^+$, 29), 147(100) | 82.69 (82.52) | 10.01(10.16) |
| **17** | 110-115/3 | 1.14(t, 3H, J=7.1), 1.39(s, 6H), 2.38(qd, 2H, J=7.1 and 1.4), 5.37(t, 1H, J=1.4), 6.60-7.36(m, 4H) | $C_{13}H_{16}O$ | 188($M^+$, 10), 173(100) | 83.05 (82.94) | 8.70 (8.57) |

[a] $^1H$ nmr in DMSO-$d_6$.

[b] N%: Found 5.96; Calcd (6.06).

The reaction finished after 1 h, as shown by tlc, and then the solution was poured into ice-water and acidified with 2N HCl. The organic layer was separated, washed with saturated aqueous $NaHCO_3$, and dried ($MgSO_4$). The solvent was evaporated, and the remaining oil was refluxed with 20 ml of xylene and 4 g of silica gel for 1 h. Work-up as detailed in the General Procedure yielded 0.71 g (60%) of **6a** as a pale-yellow oil; bp 85-90°C/0.5 mmHg (lit.,[4] 116°C/5 mmHg).

*Synthesis of 4-chloro-2,2-dimethyl-2H-1-benzopyran* (**6b**).[14] A freshly prepared solution of MeMgI (15 mmol in 30 ml of $Et_2O$) was added dropwise to a magnetically stirred solution of **2** (0.90 g, 5 mmol) in THF (200 ml) at 0°C. The reaction finished after 1 h, and then the solution was hydrolyzed with cold saturated $NH_4Cl$, and quickly separated, dried ($MgSO_4$), and concentrated *in vacuo*. The remaining oil was refluxed with 20 ml of toluene and 4 g of silica gel for 1 h. Work-up as detailed in the General Procedure yielded 0.68 g (70%) of **6b** as a yellow oil; bp 98-100°C/1.5 mmHg.

*Synthesis of 3-bromo-2,2-dimethyl-2H-1-benzopyran* (**6j**). A freshly prepared solution of MeMgI (20 mmol in the smallest volume of $Et_2O$, ca. 2 ml) was added dropwise to a magnetically stirred solution of **3** (1.12 g, 5 mmol) in toluene (100 ml) at 0°C. After 3 h the reaction had finished, then work-up as for **6a** yielded 0.71 g (60%) of **6j** as a pale-yellow oil; bp 80-85°C/0.9 mmHg.

*Reaction of 3-chlorocoumarin with DIBAL-H/MeMgI. Synthesis of 3-chloro-2-methyl-2H-1-benzopyran* (**6n**). A 1 M solution of DIBAL-H in hexane (2.3 ml, 2.3 mmol) was added dropwise to a magnetically stirred solution of **4** (0.40 g, 2.2 mmol) in toluene (50 ml) at -40°C. The temperature was allowed to rise to 0°C for 15 min, then a solution containing 4.4 mmol of MeMgI in $Et_2O$ was syringed into the reaction mixture, and it was stirred for 30 min at 0°C. Further hydrolysis and work-up as above yielded 0.14 g (36%) of **6n** as a pale-yellow oil; bp 80-85°C/1.5 mmHg.

Bromine-lithium exchange.[18] Synthesis of 2,2-dimethyl-6-lithio-2*H*-1-benzopyran (**7**). BuLi (2.6 ml of a 1.6 M solution in hexanes, 4.2 mmol) was added dropwise for a period of 10 min to a magnetically stirred solution of **6a** (0.5 g, 2.1 mmol) in $Et_2O$ (30 ml) at room temperature. The solution was protected from sunlight, stirred for an additional hour, and used *in situ* without further purification. The interchange is higher than 95% as revealed by the examination of an $^1H$ nmr spectrum of 2,2-dimethyl-2*H*-1-benzopyran (**14**)[14,26] from an hydrolyzed sample.

Synthesis of 2,2-dimethyl-2*H*-1-benzopyran-6-carboxylic acid (**8**). An excess of solid $CO_2$ was added to a solution of 2,2-dimethyl-6-lithio-2*H*-1-benzopyran (**7**) (2.1 mmol), synthesized as above. After 30 min of

stirring at room temperature, the mixture was hydrolyzed with ice and extracted three times with a 5% aqueous solution of NaOH. The aqueous layer was acidified with 2N HCl, and the carboxylic acid was extracted twice with $Et_2O$. Washing the extract with water, drying the solution ($MgSO_4$), and evaporation *in vacuo* gave a solid, which was recrystallized from $Et_2O$, yielding 0.34 g (80%) of **8** as a white solid; mp 160°C (lit.,[24] 158.5-160°C).

Synthesis of 2,2,*N*,*N*-tetramethyl-2*H*-1-benzopyran-6-carboxamide (**9**). Dimethylcarbamoyl chloride (0.58 ml, 6.3 mmol) was added dropwise for a period of 10 min to a magnetically stirred solution of **7** (2.1 mmol) in $Et_2O$ (30 ml) at -70°C. The temperature was allowed to rise to -30°C with stirring for 3 h, and 50 ml of an aqueous solution containing 5 g of KOH (86.12 mmol) was then added with vigorous stirring. The organic layer was separated, and the aqueous solution was extracted with $Et_2O$ (2 x 20 ml). Washing with water, drying ($MgSO_4$) the solution, and concentration of the solution gave a residue, which was distilled *in vacuo* in a rotatory furnace, yielding 0.39 g (81%) of **9** as a yellow oil; bp 90-95°C/0.5 mmHg (150-155°C/0.9 mmHg).

Synthesis of 2,2-dimethyl-2*H*-1-benzopyran-6-carboxaldehyde (**10**). *N*,*N*-Dimethylformamide (0.65 ml, 8.4 mmol) was added dropwise to a magnetically stirred solution of **7** (2.1 mmol) in $Et_2O$ (30 ml) at -80°C. The temperature was allowed to rise to -40°C, and the solution was hydrolyzed with 2N HCl with vigorous stirring. The organic layer was separated, washed with an aqueous saturated solution of $NaHCO_3$, and dried ($MgSO_4$). Concentration of the solution yielded 0.37 g (95%) of highly pure **10** as a colorless oil; bp 123-125°C/2 mmHg (lit.,[25] 160-170/3 mmHg).

Synthesis of 2,2-dimethyl-6-trimethylsilyl-2*H*-1-benzopyran (**11**). $Me_3SiCl$ (1.07 ml, 8.4 mmol) was added dropwise to a magnetically stirred solution of **7** (2.1 mmol) in $Et_2O$ (30 ml) at -20°C. The temperature was allowed to rise to -5°C for 15 min, and then the solution was hydrolyzed with 5N HCl with vigorous stirring. The organic layer was separated, and the aqueous solution was extracted with $Et_2O$ (2 x 20 ml). Washing with an aqueous saturated solution of $NaHCO_3$, drying the solution ($MgSO_4$), and concentration of the solution gave a residue, which was distilled *in vacuo*, yielding 0.45 g (92%) of **11** as a colorless oil; bp 55-60°C/0.3 mmHg.

4-Butyl-2,2-dimethyl-2*H*-1-benzopyran (**13**). A similar procedure to that described for **7**, but starting from 4-chloro-2,2-dimethyl-2*H*-1-benzopyran (**6b**) (0.40 g, 2 mmol), and further hydrolysis, concentration *in vacuo*, and chromatography (silica gel-hexane) yielded 0.21 g (48%) of **13** as a colorless oil; bp 140-145/1.5 mmHg. Mass and $^1H$ nmr spectra of the crude mixture revealed the presence of 2,2-dimethyl-2*H*-1-benzopyran (**14**)[26] in a ratio lower than 10%.

Reaction of 4-chloro-2,2-dimethyl-2*H*-1-benzopyran (**6b**) with triethylaluminium. A solution of **6b** (0.40 g, 2.0 mmol) in toluene (10 ml) was added to a solution of $AlEt_3$ (1.10 ml, 8 mmol) in toluene (50 ml), and the mixture was stirred for 6 h at room temperature. The solution was then poured into ice-water and acidified with 2N HCl until the aluminium hydroxide formed just dissolved. The organic layer was separated, washed with water, dried ($MgSO_4$), and the solvent was removed *in vacuo*. The residue was chromatographed in a silica gel column, using hexane/toluene (5/1) as eluant, yielding 0.07 g (15%) of *Z-o*-(3,3-dimethyl-1-ethylpent-1-enyl)phenol (**16**) as a colorless oil (bp 106-110/3 mmHg), and 0.08 g (20%) of 2,2-dimethyl-4-ethyl-2*H*-1-benzopyran (**17**) as a colorless oil (bp 110-115/3 mmHg).

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