Reaction of 4-Hydroxycoumarin Derivatives with Activated Dimethyl Sulphoxide†

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The Swern reaction of 3-alkyl-4-hydroxycoumarins affords in high yield α-chloro-α-alkyl-*o*-hydroxyacetophenone derivatives, resulting from the halogenodecarbonylation of the pyranone ring. On a model compound, other activators of DMSO‡ (TFAA,‡ P_4O_{10}, DCC,‡ SO_3–pyridine) gave mixtures of methylthiomethyl derivatives, accompanied by a dimeric product in the case of P_4O_{10}. The formation of the halogenated acetophenones and the dimeric product can be rationalized assuming the initial formation of a chromandionyl sulphonium salt, followed by nucleophilic displacement by the chloride counterion or by the unchanged 4-hydroxycoumarin. The resulting 3,3-disubstituted chromandiones are then hydrolytically decarboxylated during the aqueous work-up.

In the course of studies on the haemorrhagic toxins from *Ferula communis* L.,[1–3] we needed to oxidize the isomeric ω-hydroxyferulenols (**1a**) and (**2a**) to their corresponding aldehydes. Activated MnO_2 or $BaMnO_4$ gave a complex mixture of products, whereas the reaction with $Cr^{(VI)}$-based reagents (PCC, PDC, Jones) was not stereospecific, affording the same *E*-unsaturated aldehyde from both isomers.[3] Variable amounts of pyrano[3,2-*c*]coumarin derivatives, resulting from the oxidative cyclization of the 3-allyl-4-hydroxycoumarin moiety, were also formed under these conditions.[2] Complete stereochemical integrity was observed when (**1a**) and (**2a**) were oxidized according to the Swern protocol (oxalyl chloride–DMSO‡).[4] However, the 4-hydroxycoumarin nucleus was also attacked, resulting in the unexpected formation of the α-chloro α-(12-oxo)dodecatrienyl acetophenones (**1b**) (60% yield) and (**2b**) (65% yield) from (**1a**) and (**2a**), respectively. Ferulenol (**3a**),[1] the isomeric ω-acetoxyferulenols (**4a**) and (**5a**)[3] and *O*(7)-methylammoresinol (**6a**)[5] were also smoothly converted by the Swern reagent into the corresponding chloroacetophenones [(**3b**), (**4b**), (**5b**), and (**6b**), respectively].

4-Hydroxycoumarin derivatives have been reported to react with activated (Ac_2O) DMSO, but only under relatively drastic conditions (heating at 150 °C for several hours), to give mainly dimeric products derived from dicoumarol.[6,7] The reaction of (**1a**)—(**6a**) with activated DMSO at the low temperatures (< 60 °C) used for the Swern oxidation is thus surprising, and led us to investigate the general behaviour of 4-hydroxycoumarins towards DMSO activated with various electrophiles. All reactions were carried out according to the standard procedures for the oxidation of alcohols to carbonyl compounds (room or low temperatures).[8] 4-Hydroxy-3-methylcoumarin (**7**), easily available from methyl salicylate,[9] was chosen as a model compound, and quantitatively converted into the chloropropiophenone (**10a**) by the Swern reagent.

As outlined in Table 1, the activation of DMSO with electrophiles other than oxalyl chloride and phosphorus pentaoxide led to mixtures of the methylthiomethyl derivatives (**11**) and (**12**). With phosphorus pentaoxide as electrophile,[10] besides (**11**) and (**12**), the dimeric compound (**10b**) was also formed. The *O*-methylthiomethyl derivative (**12**) was not stable, and spontaneously isomerized to the *C*-methylthiomethyl derivative (**11**) both in solution and in the solid state, possibly *via* 1,3-sigmatropic rearrangement of the oxygen-carbon bond of the thioacetal carbon. However, this process is slow, requiring months for completion (see Experimental section), and thus does not play any role in the product distribution of the reaction of (**7**) with activated DMSO. Under the conditions reported in ref. 8, reaction of (**7**) with Ac_2O-activated DMSO gave the corresponding acetate (47% yield).

Table 1. Reaction of (**7**) with activated DMSO

Activator	Product(s) (yield %)
Oxalyl chloride	(**10a**) (95)
P_4O_{10}	(**10b**) (23) + (**11**) (2) + (**12**) (6)
SO_3–pyridine	(**11**) (6) + (**12**) (2)
TFAA	(**11**) (23) + (**12**) (4)
DCC	(**11**) (23) + (**12**) (2)

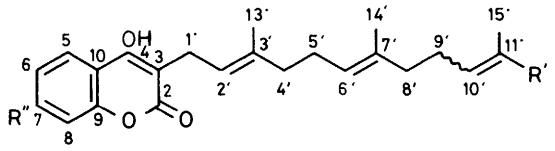
The results presented in Table 1 can be rationalized as follows: the methylthiomethyl derivatives might derive from the reaction of (**7**), an ambident nucleophile, with the methylenesulphonium cation $(CH_2{=}SCH_3)^+$ resulting from the Pummerer rearrangement of activated DMSO,[8] whereas the formation of the acetophenone derivatives when oxalyl chloride or P_4O_{10} are used to activate DMSO presumably involves the initial formation of the sulphonium ion (**8**). The latter might then undergo nucleophilic displacement by the chloride counterion or unreacted -4-hydroxy-3-methyl-coumarin to give the chromandione derivatives (**9a, b**) bearing an electron withdrawing group at C-3. Compounds of this type react very fast with nucleophiles,§ and might then be hydrolytically decarboxylated during the aqueous work-up of the reaction, resulting in the formation of (**10a**) and (**10b**). The fact that the dimeric product (**10b**) was not formed at all when oxalyl chloride was used to activate DMSO implies that the reaction of (**8**) with chloride is much faster than its reaction with 4-hydroxy-3-methylcoumarin. A reaction of this type presumably takes place only when a poorly nucleophilic counterion such as phosphate is present.

The mechanism depicted in the Scheme was substantiated by the following facts: (i) 3-chloro-3-methylchromandione (**9a**),[9]

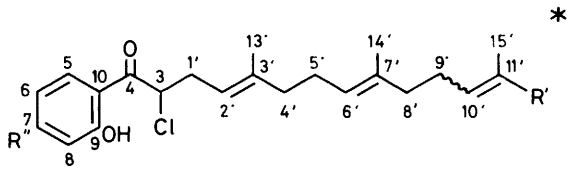
† Presented in part by G. A. at Bononiachem, Bologna, 12th October 1988.

‡ DMSO = dimethyl sulphoxide, TFAA = trifluoroacetic anhydride, DCC = dicyclohexylcarbodi-imide, NCS = *N*-chlorosuccinimide.

§ The half-life of (**9a**) in 0.6 M Hepes buffer in 1 : 1 dioxane–D_2O has been estimated to be *ca.* 3 min at 35 °C.[9]

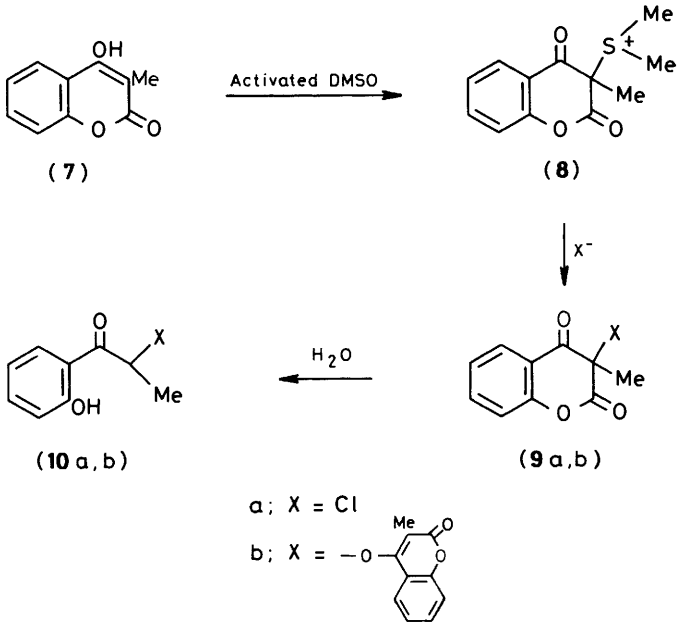


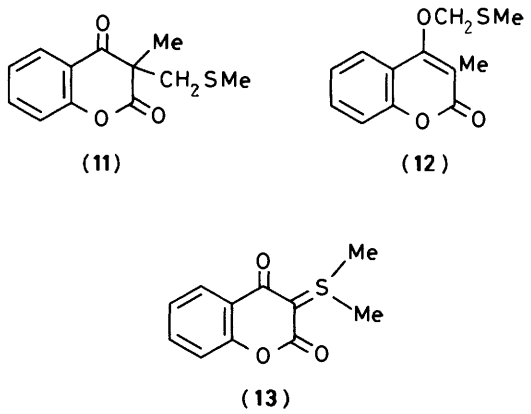
	R′	Δ^{10}	R″
(1a)	CH_2OH	*Z*	H
(2a)	CH_2OH	*E*	H
(3a)	H	—	H
(4a)	CH_2OAc	*Z*	H
(5a)	CH_2OAc	*E*	H
(6a)	H	—	OMe



	R′	Δ^{10}	R″
(1b)	CHO	*Z*	H
(2b)	CHO	*E*	H
(3b)	H		H
(4b)	CH_2OAc	*Z*	H
(5b)	CH_2OAc	*E*	H
(6b)	H		OMe

* Non-systematic numbering system shown (see Table 2)





Scheme. Possible mechanism for the formation of (**10a**) and (**10b**) upon treatment of (7) with oxalyl chloride- or P_4O_{10}-activated DMSO

postulated as an intermediate during the Swern reaction of (7), could be converted into (**10a**), the product of the Swern reaction, by simple treatment with triethylamine and water, *i.e.* under the conditions of the work-up of the Swern reaction; (ii) the Swern reaction of ferulenol (**3a**) and *O*(7)-methylammoresinol (**6a**) did not give any product halogenated on the isoprenoid side-chain, even though the terminal dimethylallyl group is a good scavenger of positive halogen species. The involvement of a negative chlorine species in the formation of (**10a**) from (7) was further confirmed by the isolation of (**10a**) from the treatment of (7) with the Corey-Kim reagent [*N*-chlorosuccinimide (NCS) –dimethyl sulphide].[11] The latter is used for the conversion of allylic and benzylic alcohols into chlorides *via* a displacement mechanism, and thus chloride anions are necessarily present. The mechanism of the reaction of (7) with the Swern and the Corey-Kim reagents is presumably the same (formation of a sulphonium ion, nucleophilic displacement, and then hydrolytic decarboxylation).* With regard to the reaction with the Corey-Kim reagent, the behaviour of (7) is different from that of 2-methyl-1,3-dicarbonyl compounds, that, probably for steric reasons,[12] do not form sulphonium salts under these conditions.[12] This different behaviour might be related to the different stereochemistry of the enol form of 1,3-dicarbonyl compounds and of 4-hydroxycoumarin (*Z*-enol *vs.* *E*-enol respectively).

Active methylene compounds have been reported to react with activated DMSO to give stabilized sulphonium ylides,[13] and 4-hydroxycoumarin itself, formally the enol form of a β-ketolactone, has been reported to be converted into the chromone ylide (**13**) upon simple heating with DMSO.[6] When 4-hydroxycoumarin was instead treated with the Swern reagent, no isolable product could be obtained from the reaction mixture. Other 4-hydroxycoumarins unsubstituted at C-3 (4,7-dihydroxy- and 4-hydroxy-7-methoxy-coumarin) behaved in a similar way, proving that an alkyl group at C-3 is necessary for the success of the reaction. *O*(7)-Methylammoresinol (**6a**), which bears an activating methoxy group on the benzenoid ring of the coumarin nucleus, was converted into the corresponding halogenated ketone (**6b**) with no attack at the benzenoid ring. However, when a phenolic hydroxy group was present on the benzenoid ring, the reaction failed, since 4-hydroxy-3-methylcoumarins bearing an extra hydroxy at C-5, C-6, or C-7 all gave complex mixtures of products.†

* As suggested by one referee, we carried out control experiments treating (7) with oxalyl chloride and P_4O_{10} in the absence of DMSO, and with NCS in the absence of dimethyl sulphide. No reaction took place with oxalyl chloride and P_4O_{10}, whereas with the electrophilic chlorinating agent NCS, (**10a**) was formed, as observed in the presence of dimethylsulphide. 'Electrophilic' and 'nucleophilic' chlorination could be distinguished using ferulenol (**3a**) as a probe. With NCS alone, (**3a**) was completely degraded, probably on account of halogenation of the isoprenoid olefinic chain. In the presence of dimethyl sulphide, a mixture of the chloroacetophenone (**3b**) and unchanged (**3a**) (*ca.* 1:4) was obtained instead.

† Phenols have been reported to undergo a selective *ortho*-methylthiomethylation with activated ($SOCl_2$) DMSO.[14]

Table 2. ^{1}H N.m.r. data (270 MHz, $CDCl_3$, $SiMe_4$ as internal standard, 25 °C)*

	Chemical shifts δ/p.p.m. (*J*/Hz)					
	(1b)	**(2b)**	**(3b)**	**(4b)**	**(5b)**	**(6b)**
3-H	5.12 t (7.2)	5.12 t (7.2)	5.12 t (7.3)	5.12 t (7.3)	5.11 t (7.2)	5.04 t (7.3)
5-H	7.80 br d (7.9)	7.79 br d (7.9)	7.79 br d (7.9)	7.79 br d (7.9)	7.79 br d (7.9)	7.68 br d (9.1)
6-H	6.92 br t (7.9)	6.94 br t (7.9)	6.94 br t (7.9)	6.94 br t (7.9)	6.94 br t (7.9)	6.48 br d (9.1)
7-H	7.52 br t (7.9)	7.52 br t (7.9)	7.52 br t (7.9)	7.52 br t (7.9)	7.52 br t (7.9)	6.48 br d (9.1)
8-H	7.02 br d (7.9)	7.03 br d (7.9)	7.03 br t (7.9)	7.03 br d (7.9)	7.02 br d (7.9)	6.46 br s
$1'_a$-H	2.87 m	2.87 m	2.88 m	2.87 m	2.88 m	2.83 m
$1'_b$-H	2.76 m	2.74 m	2.73 m	2.76 m	2.73 m	2.75 m
2′-H	5.16 br t (7.4)	5.14 br t (7.4)	5.16 br t (7.4)	5.15 br t (7.4)	5.14 br t (7.4)	5.15 br t (7.4)
6′-H	5.06 br t (7.4)	5.09 br t (7.4)	5.08 br t (7.4)	5.06 br t (7.4)	5.05 br t (7.0)	5.10 br t (7.4)
$9'_{a,b}$-H	2.61 q (7.5)	2.41 q (7.5)	*a*	*a*	*a*	*a*
10′-H	6.46 br t (7.5)	6.43 br t (7.5)	5.04 br t (7.5)	5.35 br t (7.3)	5.41 br t (7.6)	5.10 br t (7.4)
12′-H	1.77 br s	9.37 s	1.67 br s[b]	1.74 br s	4.43 s	1.69 br s[b]
13′-H	1.66 br s[b]	1.65 br s[b]	1.66 br s[b]	1.67 br s[b]	1.66 br s[b]	1.67 br s[b]
14′-H	1.58 br s[b]	1.59 br s[b]	1.59 br s[b]	1.56 br s[b]	1.56 br s	1.58 br s[c]
15′-H	10.10 s	1.73 br s	1.56 br s[b]	4.57 s	1.64 br s[b]	1.60 br s[c]
OH	11.90 s	11.89 s	11.91 s	11.94 s	11.90 s	12.43 s
OAc				2.06 s	2.06 s	
OMe						3.86 s

[a] Signals could not be assigned due to overlapping. [b] Signals in same column are interchangeable. [c] Signals are interchangeable. * Non-systematic numbering is used for compounds **(1b)**—**(6b)** to facilitate comparison with the corresponding natural products;[1–3] see structure for details.

Table 3. ^{13}C N.m.r. data (67.5 MHz, 25 °C, $CDCl_3$, $SiMe_4$ as int. standard). Assignments are based upon multiplicity and chemical shift considerations, as well as comparison with literature data[1–3]

	Chemical shift δ/p.p.m.			
	(1b)	**(2b)**	**(3b)**	**(4b)**
C(3)	56.01 d	55.98 d	56.06 d	56.04 d
C(4)	198.89 s	198.81 s	198.96 s	198.96 s
C(5)	129.99 d	129.89 d	129.99 d	130.00 d
C(6)	119.19 d	119.01 d	119.15 d	119.16 d
C(7)	137.22 d	137.01 d	137.19 d	137.19 d
C(8)	118.93 d	118.85 d	118.92 d	118.91 d
C(9)	163.53 s	163.47 s	162.42 s	163.52 s
C(10)	117.31 s	117.30 s	117.33 s	117.32 s
C(1′)	32.40 t	32.37 t	32.44 t	32.42 t
C(2′)	118.85 d	117.27 d	118.03 d	118.08 d
C(3′)	139.98 s	139.85 s	140.24 s	140.15 s
C(4′)	39.49 t[a]	39.44 t[a]	39.65 t[a]	39.61 t[a]
C(5′)	26.21 t	26.18 t	26.73 t	26.28 t
C(6′)	125.43 d	124.99 d	123.71 d	124.42 d
C(7′)	133.40 s	133.60 s	135.70 s	134.60 s
C(8′)	39.25 t[a]	37.84 t[a]	39.67 t[a]	39.52 t[a]
C(9′)	25.15 t	27.33 t	26.33 t	26.88 t
C(10′)	149.18 d	154.16 d	123.71 d	130.51 d
C(11′)	136.07 s	139.28 s	131.27 s	129.70 s
C(12′)	16.41 q	195.01 s	25.71 q	21.42 q
C(13′)	15.98 q[b]	16.32 q[b]	17.68 q[b]	15.97 q[b]
C(14′)	16.41 q[b]	15.81 q[b]	16.44 q[b]	16.43 q[b]
C(15′)	191.19 s	9.16 q	16.00 q	63.22 t
OAc				171.17 s
				20.96 q

[a,b] Signals are interchangeable.

The formation of halogenated products during the Swern oxidation of alcohols has been attributed to the presence of positive halogen species in the medium.[15] Our results show that chlorine can be introduced under these conditions also as an anion, and a similar mechanism might also account for the formation of halogenated products when carbonyl compounds which exist largely as the enol tautomer are formed during the oxidative reaction.*

The use of the Swern reagent represents a mild and chemoselective method for the conversion of 4-hydroxycoumarins into α-chloroα-alkyl-*o*-hydroxyacetophenones, which are compounds of pharmacological interest[16] as well as intermediates for the synthesis of benzofuranones.[17] The reaction might be of synthetic relevance since the alternative methods for the synthesis of these compounds are either incompatible with the presence of double bonds (*e.g.* use of SO_2Cl_2 or molecular chlorine on 4-hydroxycoumarins followed by decarboxylation),[18] or require drastic conditions which often lead to mixtures of products (*e.g.* Houben-Hoesch or Fries rearrangement of α-halogenophenyl esters,[19a,b] or treatment of phenol with α-chloronitriles in the presence of BF_3 and $AlCl_3$[18c]). The limitations of the Swern method are the availability of suitable precursors and the failure of the reaction when hydroxy groups are present on the coumarin benzenoid ring.

Experimental

M.p.s were determined on a Büchi SMP 20 apparatus and are uncorrected. Electron impact mass spectra were taken on a Varian Mat CH7A apparatus; chemical ionization mass spectra were taken on a VG EQ 70/70 apparatus. U.v. spectra were taken on a Beckman DB-GT spectrophotometer. I.r. spectra were recorded on a Perkin-Elmer model 237 spectrophotometer. ^{1}H and ^{13}C N.m.r. spectra were obtained on a JEOL GX 270/89 spectrometer (270 and 67.5 MHz respectively). Si gel 60 (70—230 mesh) (Merck) was used for column chromatography. A Waters microporasyl column (80 × 3 cm) was used for prep. h.p.l.c., using a Waters differential refractometer R 401. Dry dichloromethane, DMSO, and triethylamine were distilled from calcium hydride, under reduced pressure (water pump) in the case of DMSO. The temperature of solid CO_2–acetone baths is consistently indicated as −78 °C, room temperature (20—26 °C) as 25 °C.

To compare more easily the experimental spectral data for compounds **(1b)**—**(6b)** with those of their corresponding natural products,[1–3] the numbering of the coumarin precursors

* For the formation of halogenated products during the Swern oxidation of β-hydroxy carbonyl compounds, see refs. 10 and 15.

is maintained also in the acetophenone derivatives. ^1H and ^{13}C N.m.r. data are given in Tables 2 and 3.

Reaction of 4-*Hydroxycoumarins* (**1a**)—(**6a**) *and* (**7**) *with the Swern Reagent*.—The reaction with (**1a**) is reported as representative; to a cooled (−60 °C) solution of oxalyl chloride (256 µl, 392 mg, 2.93 mmol, 2.80 equiv.) in dry dichloromethane (6.4 ml), dry DMSO (416 µl, 458 mg, 5.87 mmol, 5.6 equiv.) was added dropwise, and the reaction mixture was stirred for 10 min at −60 °C. A solution of (**1a**) (400 mg, 1.05 mmol) in dichloromethane–DMSO (2.4 ml) was then added dropwise, resulting in the formation of a white precipitate. The reaction was stirred for 45 min at −60 °C, dry triethylamine (1.162 g, 11.5 mmol, 10.9 equiv.) was then added, and after stirring for 15 min at −60 °C, the solution was allowed to warm to 25 °C over 1 h. A bulky yellowish precipitate was formed. Brine (*ca.* 15 ml) was added and the mixture was transferred into a separatory funnel and extracted with dichloromethane. The organic phase was washed with brine, dried ($MgSO_4$) and evaporated. The residue, when analyzed by t.l.c. (hexane–EtOAc, 8:2), showed only one u.v. active spot (R_f 0.34). After column chromatography (10 g silica gel, hexane–EtOAc, 9:1, as eluant), (**1b**) (245 mg, 60%) was obtained as a colourless oil. The reaction of (**2a**)—(**6a**) and (**7**) with the Swern reagent was carried out in the same way, but only 1.4 equiv. of oxalyl chloride were used for compounds (**3a**)—(**6a**) and (**7**), which lacked sidechain hydroxy groups. Reaction of (**1a**) and (**2a**) with 1.2 equiv. of Swern reagent gave a mixture of products and unchanged starting material. Compounds (**2b**)—(**6b**) and (**10a**)[19a] were obtained from (**2a**)—(**6a**) and (**7**) in yields of 65, 72, 58, 63, 62, and 95%, respectively.

(2Z,6E,10E)-13-*Chloro*-14-(2-*hydroxyphenyl*)-2,6,10-*trimethyl*-14-*oxo*-*tetradeca*-2,6,10-*trienal* (**1b**), colourless oil, $\lambda_{max.}$(EtOH) 326 and 258; $\nu_{max.}$ 1 675, 1 645, 1 620, 1 580, 1 450, 1 310, 1 250, and 1 165 cm^{-1}; *m/z* (c.i., isobutane) 391 ($C_{23}H_{29}{}^{37}ClO_3 + H)^+$ ($M^+ + H$, 30%), 389 ($C_{23}H_{29}{}^{35}ClO_3 + H)^+$ ($M^+ + H$, 45), 187 (90), and 121(100).

(2E,6E,10E)-13-*Chloro*-14-(2-*hydroxyphenyl*)-2,6,10-*trimethyl*-14-*oxo*-*tetradeca*-2,6,10-*trienal* (**2b**), colourless oil, $\lambda_{max.}$(EtOH) 326 and 258 nm; $\nu_{max.}$(liquid film) 1 690, 1 645, 1 620, 1 580, 1 450, 1 310, 1 260, and 1 165 cm^{-1}; *m/z* (c.i., isobutane) 391 ($C_{23}H_{29}{}^{37}ClO_3 + H)^+$ ($M^+ + H$, 25%), 389 ($C_{23}H_{29}{}^{37}ClO_3 + H)^+$ ($M^+ + H$, 38), 187 (90), and 121 (100).

(4E,8E)-2-*Chloro*-1-(2-*hydroxyphenyl*)5,9-*dimethyltetradeca*-4,8,12-*trien*-1-*one* (**3b**), colourless oil, $\lambda_{max.}$(EtOH) 325 and 258 nm; $\nu_{max.}$(liquid film) 1 650, 1 620, 1 580, 1 490, 1 455, 1 310, and 1 165 cm^{-1}; *m/z* (e.i., 70 eV) 376 ($C_{23}H_{31}{}^{37}ClO_2)^+$ (M^+, 1%), 374 ($C_{23}H_{31}{}^{35}ClO_2)^+$ (M^+, 1), 339 ($M^{-35}Cl$, 2), and 121 ($C_7H_5O_2{}^+$, 100).

(4E,8E,12Z)-14-*Acetoxy*-2-*chloro*-1-(2-*hydroxyphenyl*)-5,9,13-*trimethyltetradeca*-4,8,12-*trien*-1-*one* (**4b**), colourless oil, $\lambda_{max.}$(EtOH) 326 and 260 nm; $\nu_{max.}$(liquid film) 1 740, 1 645, 1 618, 1 580, 1 490, 1 450, 1 240, and 1 160 cm^{-1}; *m/z* (e.i., 70 eV) 434 ($C_{25}H_{33}{}^{37}ClO_4$) (M^+, <1%), 432 ($C_{25}H_{33}{}^{35}ClO_4$) (M^+, <1), 396 ($M^+ - HCl$, 2), and 121 ($C_7H_5O_2{}^+$, 100).

(4E,8E,12E)-14-*Acetoxy*-2-*chloro*-1-(2-*hydroxyphenyl*)-5,9,13-*trimethyltetradeca*-4,8,12-*trien*-1-*one* (**5b**), colourless oil, $\lambda_{max.}$(EtOH) 326 and 258 nm; $\nu_{max.}$(liquid film) 1 740, 1 635, 1 620, 1 580, 1 450, 1 250, 1 165, and 760 cm^{-1}; *m/z* (e.i., 70 eV) 434 ($C_{25}H_{33}{}^{37}ClO_4$) (M^+, <1%), 432 ($C_{25}H_{33}{}^{35}O_4$) (M^+, <1), and 121 ($C_7H_5O_2{}^+$, 100).

(4E,8E)-3-*Chloro*-1-(2-*hydroxy*-4-*methoxyphenyl*)-5,9-*dimethyltetradeca*-4,8,12-*trien*-1-*one* (**6b**), colourless oil, $\nu_{max.}$ (liquid film) 1 630, 1 580, 1 510, 1 445, 1 375, 1 260, and 1 210 cm^{-1}; *m/z* (e.i., 70 eV) 406 ($C_{24}H_{33}{}^{37}ClO_3$) (M^+, <1%), 404 ($C_{24}H_{33}{}^{35}ClO_3$) (M^+, <1), 369 ($M^+ - Cl$, 17), 335 (10), and 151 $(C_8H_7O_3)^+$.

Reaction of (**7**) *with* P_4O_{10}-*Activated DMSO*.—To a cooled (0 °C) suspension of P_4O_{10} (483 mg, 3.41 mmol) in dry dichloromethane (8.5 ml), DMSO (242 µl, 3.41 mmol, 2 equiv.) and (**7**) (300 mg, 1.70 mmol) were added. The reaction mixture was allowed to warm to 25 °C, and stirred for 4 h until t.l.c. analysis showed complete disappearance of the starting material [$CHCl_3$–acetone, 6:1; R_f of (**7**) = 0.25]. The solution was then cooled to 0 °C and triethylamine was added (831 µl, 603 mg, 5.45 mmol). After stirring for 30 min at 0 °C, water was added, followed by dilute HCl, and the mixture was extracted with chloroform, washed with brine, and dried ($MgSO_4$). The organic phase was evaporated and the crude reaction mixture was separated by column chromatography (10 g silica gel, hexane–EtOAc, 8:2, as eluant) to give a mixture of (**10b**), (**11**), and (**12**) (196 mg). Crystallization from hexane gave (**10b**) (127 mg, 23%). The mother liquors were separated by h.p.l.c. (hexane–EtOAc, 8:2) to give (**11**) (8 mg, 2%) and (**12**) (24 mg, 6%). No unchanged (**7**) was present in the reaction mixture (t.l.c. and ^1H n.m.r. analysis).

3-*Methyl*-4-[2-(2-*hydroxyphenyl*)-1-*methyl*-2-*oxoethoxy*]-2H-*benzo*[b]*pyran*-2-*one* (**10b**), colourless crystals (from hexane), m.p. 119—123 °C, $\lambda_{max.}$(EtOH) 329, 309, 282, and 273 nm; $\nu_{max.}$(KBr disc) 1 700, 1 630, 1 610, 1 455, 1 100, 1 080, 926, and 750 cm^{-1}; *m/z* (e.i., 70 eV) 324 ($C_{19}H_{16}O_5)^-$ (M^+, 20%), 176 (70), 150 (45), and 121 ($C_7H_5O_2{}^+$, 100); δ_H($CDCl_3$, 270 MHz, $SiMe_4$ as ref.) 11.95 (1 H, s, OH), 7.85 (1 H, br d, *J* 7.3 Hz), 7.57 (1 H, br d, *J* 8.3 Hz), *ca.* 7.40 (4 H, m), 7.06 (1 H, br d, *J* 8.3 Hz), 6.93 (1 H, br t, *J* 7.3 Hz), 5.82 (1 H, q, *J* 6.8 Hz), 2.20 (3 H, s), and 1.78 (3 H, d, *J* 6.8 Hz).

3-*Methyl*-3-*methylthiomethyl*-3,4-*dihydro*-2H-*benzo*[b]-*pyran*-2,4-*dione* (**11**), colourless crystals (from hexane–ether), m.p. 75—78 °C, $\lambda_{max.}$(EtOH) 308 and 254 nm; $\nu_{max.}$(KBr disc) 1 770, 1 680, 1 610, 1 465, 1 320, and 1 225 cm^{-1}; *m/z* (e.i., 70 eV) 236 ($C_{12}H_{12}O_3S)^+$ (M^+, 80%), 221 (18), 189 (55), 161 (32), 121 (43), 115 (50), and 69 (100); δ_H($CDCl_3$, 270 MHz, $SiMe_4$ as ref.) 7.97 (1 H, br d, *J* 7.8 Hz), 7.69 (1 H, br t, *J* 7.8 Hz), 7.30 (1 H, br t, *J* 7.8 Hz), 7.24 (1 H, br d, *J* 7.8 Hz), 3.29 (1 H, d, *J* 13.6 Hz), 3.12 (1 H, d, *J* 13.6 Hz), 2.11 (3 H, s), and 1.58 (3 H, s).

3-*Methyl*-4-*methylthiomethoxy*-2H-*benzo*[b]*pyran*-2-*one* (**12**), colourless crystals (from hexane–ether), m.p. 72—76 °C, $\lambda_{max.}$(EtOH) 310 and 270 nm; $\nu_{max.}$(KBr disc) 1 700, 1 630, 1 610, 1 450, 1 325, 1 100, 1 080, 925, and 760 cm^{-1}; *m/z* (e.i., 70 eV) 236 ($C_{12}H_{12}O_3S$) (M^+, 100%), 189 (38), 121 (73), 115 (81), 92 (74), and 77 (74); δ_H($CDCl_3$, 270 MHz, $SiMe_4$ as ref.) 7.73 (1 H, br d, *J* 7.8 Hz), 7.50 (1 H, br t, *J* 7.8 Hz), *ca.* 7.28 (2 H, m), 5.29 (2 H, s), 2.34 (3 H, s), and 2.20 (3 H, s). At fridge temperature (**12**) slowly rearranged to (**11**). A sample dissolved in $CDCl_3$ and left in solution at 25 °C, was regularly analyzed by ^1H n.m.r. spectroscopy; after *ca.* 2 months, 50% isomerization had taken place. T.l.c. analysis of a sample used for m.p. determination showed that some isomerization had also taken place during the melting process.

Reaction of (**7**) *with* SO_3–*Pyridine-activated DMSO*.—To a solution of (**7**) (200 mg, 1.13 mmol) in DMSO (3.7 ml, 4.0 g, 51 mmol), triethylamine (2.65 ml, 1.93 g, 19 mmol) and SO_3–pyridine (1.152 g, 7.38 mmol, 6.5 equiv.) were added, and the solution was stirred under nitrogen for 10 days. The reaction mixture was then diluted with water, acidified (NH_4Cl), and extracted with dichloromethane. The residue obtained from evaporation of the organic phase was chromatographed on a silica gel column (10 silica, hexane–EtOAc, 8:2, as eluant) to give (**11**) (24 mg, 6%), and (**12**) (8 mg, 2%). Elution with hexane–EtOAc, 1:9, gave unchanged (**7**) (81 mg) (conversion = 60%).

Reaction of (**7**) *with Trifluoroacetic Anhydride-activated DMSO*.—To a cooled (−78 °C) solution of DMSO (242 µl, 266 mg, 3.41 mmol, 2 equiv.) in dry dichloromethane (5 ml) was added dropwise a solution of trifluoroacetic anhydride (360 µl,

535 mg, 2.55 mmol, 1.5 equiv.) in dry dichloromethane (2 ml) under nitrogen atmosphere. After stirring for 10 min at −60 °C, (**7**) (300 mg, 1.70 mmol) was added and the solution was stirred for a further 30 min at −60 °C. Triethylamine was then added and the solution was stirred for 10 min at − 60°C and then allowed to warm to 25 °C, diluted with water, acidified (NH_4Cl) and extracted with dichloromethane. The residue obtained from evaporation of the organic phase was chromatographed on silica gel, as described for the reaction of (**7**) with SO_3–pyridine-activated DMSO, to give (**11**) (92 mg, 23%) and (**12**) (16 mg, 4%), along with unchanged (**7**) (45 mg) (conversion = 85%).

Reaction of (**7**) *with Dicyclohexylcarbodi-imide-activated DMSO.*—To a solution of (**7**) (400 mg, 2.27 mmol) in DMSO (2 ml), benzene (2 ml), and pyridine (252 μl, 4.54 mmol, 2 equiv.), was added trifluoroacetic acid (171 ml, 254 mg, 2.27 mmol, 1 equiv.) followed by dicyclohexylcarbodi-imide (1 397 g, 6.78 mmol, 3 equiv.). A thick precipitate was formed almost instantaneously, and the reaction was stirred for 6 h at 25 °C. Diethyl ether (10 ml) and oxalic acid (1.478 g) in methanol (10 ml) were then added. After the mixture had been stirred for an additional 30 min at 25 °C, water (20 ml) was added, and dicyclohexylurea was separated from the reaction mixture by filtration. The filtrate was transferred to a separatory funnel, diluted with water, extracted with dichloromethane, and the combined organic extracts were dried and evaporated. The residue was purified by column chromatography, as described for the reaction of (**7**) with SO_3–pyridine-activated DMSO to give (**11**) (123 mg, 23%) and (**12**) (10.7 mg, 2%). No unchanged (**7**) was present in the reaction mixture (t.l.c. analysis).

Reaction of (**7**) *with Dimethylsulphide–*N*-Chlorosuccinimide.*—To a cooled (−78 °C) suspension of *N*-chlorosuccinimide (NCS) (1.144 g, 8.60 mmol, 5.0 equiv.) in dry dichloromethane (3 ml) was added dropwise dimethylsulphide (3.0 ml, 40.9 mmol, 24 equiv.), and the solution was stirred for 1 h at −78 °C under nitrogen. A solution of (**7**) (300 mg, 1.70 mmol) and DMSO (300 μl) in dry dichloromethane (2 ml) was then added dropwise. After the mixture had been stirred for 1 h at −78 °C, triethylamine (3.77 ml, 27.06 mmol, 15.88 equiv) was added. The solution was stirred for a further hour at −78 °C, then allowed to warm to 25 °C, diluted with saturated aqueous NH_4Cl, and extracted with CH_2Cl_2. The organic phase was washed with brine and evaporated. The residue was purified by column chromatography (10 g silica gel, hexane–EtOAc, 8:2) to give (**10a**) (204 mg, 65%).

Reaction of (**10a**) *with Triethylamine–Water.*—A sample of (**10a**) (100 mg) was suspended in dichloromethane (5 ml), and then triethylamine (1 ml) and water (0.5 ml) were added, resulting in the instantaneous formation of a yellow solution. After further dilution with water and extraction with dichloromethane (**11a**) (92 mg) was obtained.

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