Synthesis and conjugate additions of 2,3,4,9-tetrahydro-1*H*-xanthene-1,9-diones

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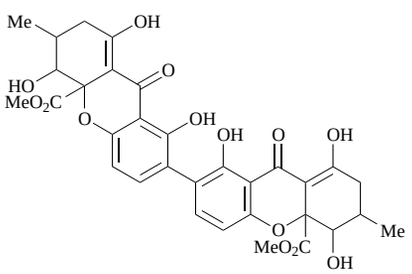
An efficient two step procedure for the synthesis of 2,3,4,9-tetrahydro-1*H*-xanthene-1,9-diones is described. A study of their conjugate additions has shown them to be efficient Michael acceptors. Reaction of 2,3,4,9-tetrahydro-1*H*-xanthene-1,9-dione with tris(methylthio)methyllithium, followed by mercury(II) catalysed methanolysis, gave methyl 1-hydroxy-9-oxo-3,4,4a,9-tetrahydro-2*H*-xanthene-4a-carboxylate, the nucleus of the secalonic acids and other natural products

A number of natural products contain the reduced xanthone unit 3,4,4a,9-tetrahydro-2*H*-xanthen-9-one, of which secalonic acid **1** is typical. First isolated in 1906,[1] seven diastereoisomers have now been isolated from natural sources.[2] This tetrahydroxanthone moiety **2** also features in the lactone ergochrisin,[3] the



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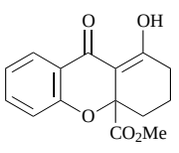

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eumetrin pigments,[4] the beticolin toxins[5] and the antibiotic, xanthoquinodin A1.[6] Previous attempts to obtain compounds of type **2** which relied on the reaction of 7-oxabicyclo-[2.2.1]heptane-2,3-dicarboxylic anhydride with aryllithiums did not proceed as expected.[7] Prior to this, Franck *et al.*[8] prepared a desmethoxycarbonylhemisecalonic acid in low overall yield in a multi-step sequence from a tetrahydroxybenzophenone. More recently,[9] the tetrahydroxanthenedione system has been obtained from the cyclocondensation of 2-acryloyl-2′-hydroxy-acetophenone with 1-pyrrolidinocycloalkenes. We envisaged that compounds of type **2** could be synthesised by conjugate addition to 2,3,4,9-tetrahydro-1*H*-xanthene-1,9-dione **3a**. We now report a facile route to this α,β-unsaturated diketone and related molecules and discuss their behaviour as Michael acceptors.

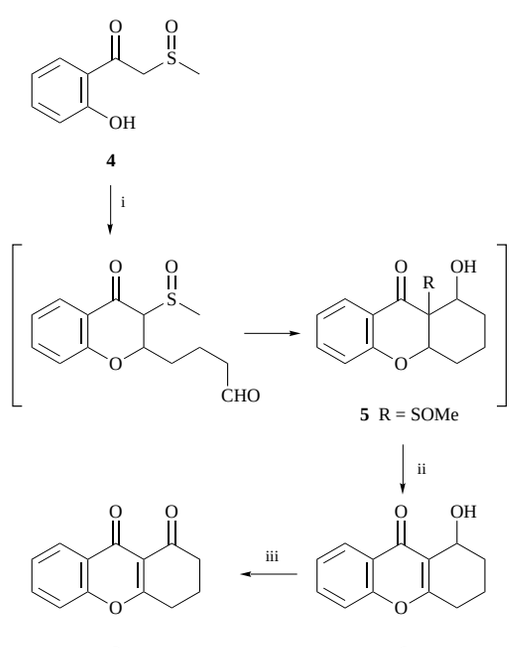
The dione **3a** has been synthesised[10] from the β-keto sulfoxide **4**[11] through condensation with glutaraldehyde and subsequent thermal elimination of methanesulfenic acid from **5**. Oxidation of the reduced xanthone **6** using Jones' reagent completed the sequence (Scheme 1). However, a low overall yield of 7% together with the foul smelling nature of the β-keto sulfoxide prompted a search for an alternative route.

A simple procedure for the preparation of 2-acylcyclohexane-1,3-diones has been described,[12] which is based on the Fries rearrangement[13] of enol esters derived from the acylation of cyclohexane-1,3-dione. Chromones have been prepared by the intramolecular nucleophilic displacement of fluoride from ethyl 2-(2-fluorobenzoyl)-2-acylacetates,[14] and a combination of these two protocols was considered to offer a viable entry to the xanthone **3a**.

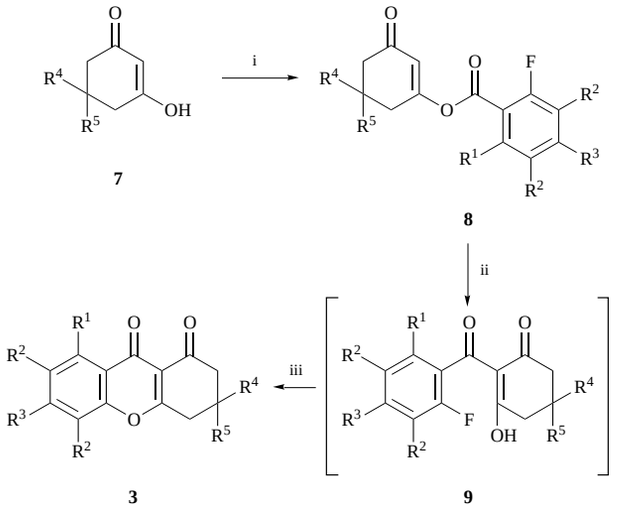
Discussion

Reactions of cyclohexane-1,3-diones **7a**–**f** with 2-fluorobenzoyl chlorides in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) proceeded smoothly at −10 °C in acetonitrile to give the corresponding enol esters **8a**–**f** (Scheme 2). Whilst pyridine has been widely used as solvent and catalyst in acylation reactions, we found DBU to be superior to pyridine giving higher yields (82 to 93%) of purer products. It was essential to employ short reaction times, typically 40 min, and rapid aqueous work-up was necessary in order to minimise hydrolysis of the product. A characteristic alkenyl signal was present at *ca.* 6 ppm in the ^{1}H NMR spectrum of the enol esters **8** and the ester and carbonyl stretching bands occurred around 1740 and 1670 cm^{-1}, respectively.

Attempts to effect the Fries rearrangement of **8a** with two equivalents of aluminium chloride in dichloromethane at 25 °C for 16 h gave a sticky orange solid in moderate yield. The ^{1}H NMR spectrum of this crude material was complex, but suggested the presence of both the Fries product **9a** and cyclised



Scheme 1 *Reagents and conditions*: i, $OHC(CH_2)_3CHO$ (aq.), piperidine, DMF, 50 to 80 °C; ii, 110 to 140 °C, 33%; iii, CrO_3, *conc.* H_2SO_4, H_2O, AcMe, 23%

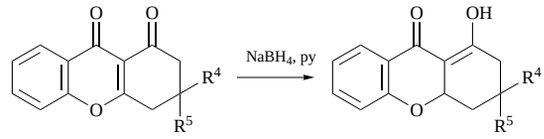


a $R^1 = R^2 = R^3 = R^4 = R^5 = H$
b $R^1 = R^2 = R^3 = R^4 = H, R^5 = Me$
c $R^1 = R^2 = R^3 = H, R^4 = R^5 = Me$
d $R^1 = F, R^2 = R^3 = R^4 = R^5 = H$
e $R^1 = R^2 = H, R^3 = F, R^4 = R^5 = H$
f $R^1 = R^2 = R^3 = F, R^4 = R^5 = H$

Scheme 2 *Reagents and conditions*: i, ArCOCl, DBU, MeCN, −10 °C; ii, $AlCl_3$, DCE, −10 to 25 °C; iii, EtOH, heat

material **3a**. Cyclisation ensued during recrystallisation from ethanol, with the loss of hydrogen fluoride, and pure **3a** was obtained exclusively, although the yield after recrystallisation was only moderate (*ca.* 40%). The insolubility of **3a** in dichloromethane rendered isolation difficult and consequently low recoveries of product were usual, but yields were markedly increased when 1,2-dichloroethane was used as the solvent. A range of substituted derivatives **3b**–**f** was prepared in good to excellent yield (72 to 87%) under these conditions (Scheme 2). Several of these compounds exhibited wide melting ranges, but chromatographic, spectroscopic and analytical data confirm their purity and support the assigned structures. In none of the Fries reactions was any uncyclised product **9** isolated in a pure state, since the elimination of hydrogen fluoride proceeds relatively smoothly under the reaction conditions. The aromatic region of the ^{1}H NMR spectra of the xanthenediones **3a**,**b**,**c** and **e** clearly showed a signal at 8.2 ppm for H-8, typical of a proton *peri* to the carbonyl function in a chromone. The ^{13}C NMR spectra confirmed the presence of the two carbonyl groups which absorbed at *ca.* 193 ppm (C-1) and 178 ppm (C-9). In the IR spectra $\nu_{C=O}$ moved to 1710–1690 and 1645–1630 cm^{-1} for the C-1 and C-9 ketone functions, respectively.

With efficient access to large quantities of the tetrahydroxanthenedione **3a**, its behaviour as a Michael acceptor was investigated. It is known that reduction of acylchromones with sodium borohydride in alcoholic solvents is indiscriminate and leads to complex mixtures of products,[15] and the same proved true for the reduction of **3a** under these conditions when the diketone **10a** could only be obtained in 22% yield. The solvent plays an important role in the reduction of α,β-unsaturated ketones by sodium borohydride and it is reported that in pyridine conjugate reduction is favoured and only the saturated ketones are produced.[16] In like manner, 3-benzoyl-coumarin[17] and -thiocoumarin[18] are converted into the corresponding 3,4-dihydro compounds, but no examples of analogous behaviour of chromones have been reported. We now find that under these conditions, the xanthenedione **3a** is reduced to **10a** in quantitative yield. A similar result was observed with the 3-substituted analogues **3b** and **3c** which were converted in high yield to the corresponding xanthones **10b** and **10c** respectively (Scheme 3). Following conjugate reduction, the aromatic signals in the ^{1}H NMR spectra are comparable with those reported for 3-

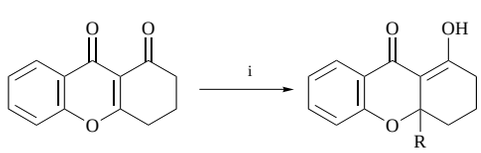


	R^4	R^5	Yield (%)
a	H	H	100
b	H	CH_3	85
c	CH_3	CH_3	78

Scheme 3

acetyl-2-methylchromanone[19] in which the *peri* proton at *ca.* 7.8 ppm is separated from the other signals. A prominent carbonyl stretching band is apparent at *ca.* 1610 cm^{-1} for the diketone; although inspection of the ^{1}H NMR spectra suggests that these compounds are fully enolised, no OH stretching band was seen when their IR spectra were recorded in Nujol. Aromatisation of **10a** to 1-hydroxyxanthone occurred on treatment with *o*-chloranil in refluxing dioxane.

Chromones with an activating group in the 3-position have been converted to the corresponding 2-methylchromanones on treatment with lithium dimethylcuprate(I),[19] and this chemistry was extended to provide a route to unsymmetrical 2,2-dialkylchromanones and -thiochromanones.[20] In marked contrast to the behaviour of simple 3-acylchromones, when **3a** was added to a solution of a homocuprate R_2CuLi, where R = Me, Bu^n or Ph, in THF under conditions reported by Wallace,[19] only mediocre quantities of the corresponding 1,4-adducts **11** were obtained. Employing higher order cuprates derived from copper(I) iodide,[21] the copper(I) bromide–dimethyl sulfide complex[19] and copper(I) cyanide[22] in either THF or diethyl ether led to extensive substrate decomposition and consequently low yields of **11**. Lower order cyanocuprates, RCu(CN)Li, have been used for the regiospecific ring opening of α,β-unsaturated epoxides[23] and recently their addition to α,β-enals and -enones has been accomplished.[24] In similar fashion, the reaction of **3a** with a five-fold excess of lithium methylcyanocuprate(I) in diethyl ether gave an excellent yield of **11a**, without the need for chromatographic purification. THF is known to retard cuprate complex formation[25] and was not a suitable solvent in this work. Similarly, Bu^{n}Cu(CN)Li gave an essentially quanti-



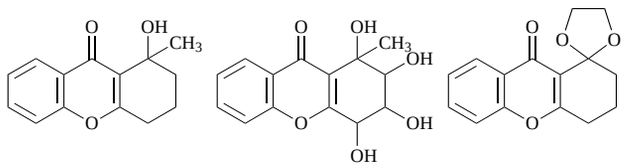
	R	Yield (%)
a	CH_3	93
b	Bu^n	98
c	Bu^s	34
d	Ph	21[a]
e	Et	51
f	4-$CH_3C_6H_4CH_2$	24

Scheme 4 *Reagents and conditions*: i, RCu(CN)Li (5 equiv.), Et_2O, −50 °C or [a] Ph_2CuLi (1.5 equiv.), Et_2O–PhH, −40 to 0 °C

tative yield of **11b** on reaction with xanthenedione **3a**, but reaction with the cyanocuprate derived from *sec*-butyllithium gave a substantially lower yield of **11c**. These results indicate that increasing the steric bulk of the nucleophile hinders the conjugate reaction with substrate **3a**. It is noteworthy that whilst 1,4-addition appeared unfavourable in the latter case, no direct 1,2-attack was observed and unchanged **3a** was recovered at the end of the reaction. Furthermore, no reaction occurred with the *tert*-butylcuprate. Problems were encountered in trying to form the phenylcuprate from copper(I) cyanide and phenyllithium and the alternative reagent Ph_2CuLi was used in this case, but

only a low conversion to the 4a-phenyl derivative **11d** was observed (Scheme 4). The failure of homo and higher order cuprates to add to **3a** is attributed to their greater basicity relative to that of the lower order cyanocuprates. It appears that lower order cyanocuprates offer significant advantages in the conjugate addition reactions of acidic α,β-unsaturated systems which have so far been unappreciated. The ^{1}H NMR spectra of **11a–d** exhibited an aromatic proton pattern similar to that of a chroman-4-one and the appropriate signals appeared for the 4a-substituent. In particular, the 4a-methyl signal for **11a** (1.48 ppm) compared favourably with that for the 4a-methyl group in hemisecalonic acid (1.46 ppm).[8] We were unable to obtain satisfactory elemental analysis for **11c** even though it was chromatographically homogeneous (TLC). However, the similarity of its ^{1}H NMR spectrum with the spectra of **11a–b** and **11d–f** firmly established its constitution.

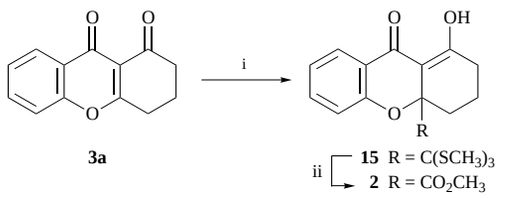
For comparative purposes, the reactivity of **3a** with Grignard reagents was also investigated. Reaction of **3a** with methylmagnesium bromide in diethyl ether gave a mixture of **11a** (40%) and the alcohol **12** (24%). The latter compound arises from direct nucleophilic addition to the substrate. The balance of material was identified as unreacted **3a**, and it is likely that competitive deprotonation of **3a** by the basic Grignard reagent is also a factor in this reaction. The alcohol is interesting because it is structurally similar to the naturally occurring aphloiol **13**,[26] and to the physiologically active compounds



12 **13** **14**

reported by von Strandtmann and co-workers.[10] However, only the 1,4-adducts **11e** and **11f** were isolated when **3a** was reacted with EtCu(CN)MgBr and the cyanocuprate derived from 4-methylbenzylmagnesium bromide, respectively.

The conjugate addition of tris(methylthio)methyllithium, a sulfur stabilised carbanion, to **3a** is of particular interest because it is an ester anion equivalent and would allow the introduction of the 4a-carboxy function found in the secalonic acids and related compounds. The reaction of sulfur stabilised carbanions with α,β-unsaturated ketones generally results in 1,2-addition, but conjugate addition to cyclohexenone has been achieved and the process is favoured by unhindered substrates.[27] Other workers have reported that 1,4-addition results under thermodynamic control, but that kinetic conditions lead to the 1,2-product.[28] Furthermore, the addition of hexamethylphosphoramide (HMPA) to the carbanion prior to addition of the substrate is reported to favour the conjugate reaction.[29] However, no reaction was observed when **3a** was treated with tris(methylthio)methyllithium in a 4:1 mixture of THF and HMPA. Omission of HMPA proved beneficial and the conjugate product **15** was obtained in 20% yield with no evidence for the formation of the 1,2-product. Initial experiments involved addition of the substrate at −80 °C followed by warming to ambient temperature to achieve the thermodynamic conditions reported to favour conjugate reaction. Prolonged reaction at room temperature caused decomposition of both the organolithium reagent and the product; the instability of tris(methylthio)methyllithium has been noted previously.[30] Optimisation of the conjugate addition was achieved by strict temperature control throughout the reaction and maintaining an internal temperature of below −50 °C ensured only limited decomposition of the reagent and increased the yield of the yellow conjugate product to 35%. Incorporation of the $C(SMe)_3$ unit into the product was confirmed by a signal at 2.1 ppm in the ^{1}H NMR spectrum which integrated for 9 protons. In the ^{13}C NMR spectrum, the methylthio groups absorbed at 15.8 ppm and the orthothioester carbon at 89.0 ppm. The signals for C-1 (174.8 ppm) and C-9 (192.0 ppm) are appreciably different from the corresponding absorptions in **11a** (181.6 and 182.4 ppm, respectively). The Hg^{II} catalysed oxidative methanolysis of **15** gave the ester **2** in quantitative yield (Scheme 5). This approach



3a **15** R = $C(SCH_3)_3$ **2** R = CO_2CH_3

Scheme 5 *Reagents and conditions*: i, $LiC(SMe)_3$ (1.1 equiv.), THF, −50 °C, 35%; ii, $HgCl_2$, HgO, MeOH, H_2O, 25 °C, 100%

represents the first successful synthetic route to the secalonic acid half unit. Not surprisingly, the ^{13}C NMR data for **2** correspond closely to the ^{13}C shifts reported for the xanthone subunit of beticolin.[5] In particular, signals for the ester function appear at 52.8 and 172.7 ppm, whilst C-1, C-4a, C-9 and C-9a absorb at 179.5, 85.7, 185.1 and 104.6 ppm, respectively. There was evidence in the ^{1}H and ^{13}C NMR spectra of a trace of an impurity in the product, but this did not show in either the elemental analysis or chromatographically. However, the sample softened at 123 °C before melting at 126–129 °C.

It was thought that the modest yield of the adduct **15** could be attributed to the acidic nature of the C-4 proton in **3a**, and therefore the major pathway was deprotonation by $LiC(SMe)_3$. For this reason it was decided to decrease the acidity of **3a** by temporarily removing one of the ketone functions. Of the two carbonyls in 3-acylchromones, the exocyclic carbonyl group can be selectively protected as the ketal,[31] and **3a** should react in a similar fashion. Although a variety of conditions exist for ketalisation, the particularly mild conditions developed by Chan *et al.*[32] seemed appropriate for this reactive substrate. Reaction of **3a** with ethylene glycol and trimethylchlorosilane in 1,2-dichloroethane at reflux gave the mono-ketal **14** in excellent yield. However, the reaction of **14** with tris(methylthio)-methyllithium was unsuccessful and only unchanged starting material was recovered. Evidently, removal of one of the carbonyl functions in **3a** not only decreases the acidity of the C-4 position but also deactivates the ring towards conjugate addition.

Experimental

Reactions requiring anhydrous conditions were performed using oven-dried glassware and conducted under nitrogen. Anhydrous solvents were prepared according to published procedures[33] and stored over activated 4 Å molecular sieves. Melting points are uncorrected. IR spectra were recorded on a Mattson Galaxy 3000 FT-IR spectrometer. NMR spectra were recorded on a Bruker WM250 instrument for $CDCl_3$ solutions; coupling constants *J* are given in Hz. Distillations were performed using a bulb-to-bulb (Kügelrohr) apparatus (Büchi GKR-50 glass tube oven) and all boiling points quoted relate to the oven temperature at which distillation commenced. Flash chromatography was performed on silica gel (Sorbsil C60, MPD 60 Å, 40–60 μm) according to the published procedure.[34]

General method for the preparation of 3-oxocyclohex-1-enyl benzoates 8

To a stirred suspension of the appropriate cyclohexane-1,3-dione (85 mmol) in dry acetonitrile (100 cm^3) was added a solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (102 mmol) in acetonitrile (20 cm^3) in one portion. Dissolution of the dione was almost instantaneous. The resulting brown solution was cooled to −10 °C and then treated dropwise with an equimolar

quantity of the aroyl chloride (85 mmol) in acetonitrile (40 cm^3), maintaining the temperature below 0 °C. Within minutes after completion of this addition the reaction was judged complete from TLC inspection. Dilution with ethyl acetate (200 cm^3), washing with saturated aqueous sodium chloride (2 × 200 cm^3), 2 M hydrochloric acid (2 × 200 cm^3) and finally with saturated aqueous sodium hydrogen carbonate (2 × 200 cm^3), followed by evaporation of the dried organic extracts (Na_2SO_4) provided the crude product. Distillation under reduced pressure gave the ester in an analytically pure state. The following compounds were prepared by this protocol.

3-Oxocyclohex-1-enyl 2-fluorobenzoate 8a. From 2-fluorobenzoyl chloride and cyclohexane-1,3-dione as colourless needles (88%) after crystallisation from ethyl acetate and hexane, mp 58–60 °C; ν_{max}(Nujol)/cm^{-1} 1738, 1667 and 1611; δ_H 2.16 (2H, m, H-5′), 2.48 (2H, dt, *J* 1.2, 6.8, H-4′), 2.69 (2H, dt, *J* 1.2, 6.8, H-6′), 6.06 (1H, t, *J* 1.2, H-2′), 7.24 (2H, m, Ar-H), 7.61 (1H, m, Ar-H), 8.00 (1H, m, Ar-H) (Found: C, 66.6; H, 4.7. $C_{13}H_{11}FO_3$ requires C, 66.7; H, 4.7%).

5-Methyl-3-oxocyclohex-1-enyl 2-fluorobenzoate 8b. From 2-fluorobenzoyl chloride and 5-methylcyclohexane-1,3-dione as a colourless oil (86%), bp 165 °C at 0.04 mbar;† ν_{max}(Nujol)/cm^{-1} 1746, 1670 and 1612; δ_H 1.09 (3H, d, *J* 6.1, Me), 2.12 (1H, m, H-5′), 2.52 (4H, m, H-4′, H-6′), 5.99 (1H, s, H-2′), 7.16 (2H, m, Ar-H), 7.58 (1H, m, Ar-H), 7.93 (1H, m, Ar-H) (Found: C, 67.9; H, 5.5; F, 7.6. $C_{14}H_{13}FO_3$ requires C, 67.7; H, 5.3; F, 7.6%).

5,5-Dimethyl-3-oxocyclohex-1-enyl 2-fluorobenzoate 8c. From 2-fluorobenzoyl chloride and 5,5-dimethylcyclohexane-1,3-dione as a colourless oil (93%), bp 165 °C at 0.04 mbar, which crystallised on standing, mp 40–43 °C; ν_{max}(Nujol)/cm^{-1} 1737, 1667 and 1612; δ_H 1.15 (6H, s, Me), 2.32 (2H, s, H-6′), 2.55 (2H, s, H-4′), 6.05 (1H, s, H-2′), 7.20 (2H, m, Ar-H), 7.59 (1H, m, Ar-H), 8.00 (1H, m, Ar-H) (Found: C, 68.7; H, 5.9; F, 7.4. $C_{15}H_{15}FO_3$ requires C, 68.7; H, 5.87; F, 7.2%).

3-Oxocyclohex-1-enyl 2,6-difluorobenzoate 8d. From 2,6-difluorobenzoyl chloride and cyclohexane-1,3-dione as a colourless oil (82%), bp 155 °C at 0.04 mbar which crystallised on standing, mp 36–40 °C; ν_{max}(Nujol)/cm^{-1} 1750, 1680 and 1610; δ_H 2.12 (2H, m, H-5′), 2.44 (2H, t, *J* 6.7, H-6′), 2.67 (2H, dt, *J* 1.0, 6.7, H-4′), 6.05 (1H, apparent s, H-2′), 7.00 (2H, m, Ar-H), 7.49 (1H, m, Ar-H) (Found: C, 61.8; H, 3.9; F, 15.3. $C_{13}H_{10}F_2O_3$ requires C, 61.9; H, 4.0; F, 15.1%).

3-Oxocyclohex-1-enyl 2,4-difluorobenzoate 8e. From 2,4-difluorobenzoyl chloride and cyclohexane-1,3-dione as a colourless oil (82%), bp 150 °C at 0.04 mbar; ν_{max}(Nujol)/cm^{-1} 1750, 1680 and 1613; δ_H 2.10 (2H, m, H-5′), 2.44 (2H, t, *J* 6.7, H-6′), 2.65 (2H, t, *J* 6.7, H-4′), 6.01 (1H, s, H-2′), 6.94 (2H, m, Ar-H), 8.01 (1H, m, Ar-H) (Found: C, 61.8; H, 3.9; F, 15.1. $C_{13}H_{10}F_2O_3$ requires C, 61.9; H, 4.0; F, 15.1%).

3-Oxocyclohex-1-enyl 2,3,4,5,6-pentafluorobenzoate 8f. From 2,3,4,5,6-pentafluorobenzoyl chloride and cyclohexane-1,3-dione as a colourless oil (91%), bp 160 °C at 0.04 mbar; ν_{max}(CCl_4)/cm^{-1} 1739, 1650 and 1604; δ_H 2.10 (2H, m, H-5′), 2.45 (2H, t, *J* 6.5, H-6′), 2.62 (2H, dt, *J* 1.0, 6.5, H-4′), 6.01 (1H, s, H-2′). Satisfactory elemental analysis could not be obtained for this compound; its constitution was verified by conversion to **3f**.

General method for the preparation of 2,3,4,9-tetrahydro-1*H*-xanthene-1,9-diones 3

A stirred suspension of aluminium chloride (40 mmol) in dry 1,2-dichloroethane (100 cm^3) at −8 °C (ice–ethanol) was treated dropwise with a solution of the appropriate ester **8** (19.8 mmol) in 1,2-dichloroethane (40 cm^3). During the addition the aluminium chloride dissolved giving a pale brown solution. After stirring at this temperature for 1 h, the mixture was kept at room temperature until the reaction was adjudged complete by TLC. The mixture was poured into 2 M hydrochloric acid (100 cm^3), water (100 cm^3) and ice (*ca.* 200 g) and then extracted with chloroform (3 × 80 cm^3). Evaporation of the dried organic extracts (Na_2SO_4) provided the crude product as a red–brown oil or solid. Recrystallisation provided the pure product. The following compounds were obtained by this procedure.

2,3,4,9-Tetrahydro-1*H*-xanthene-1,9-dione 3a. From ester **8a** as colourless needles (75%) after recrystallisation from ethyl acetate, mp 170–200 °C (decomp.); ν_{max}(Nujol)/cm^{-1} 1693, 1634 and 1615; δ_H 2.18 (2H, m, H-3), 2.60 (2H, t, *J* 6, H-2), 3.00 (2H, t, *J* 6, H-4), 7.40 (2H, m, Ar-H), 7.65 (1H, m, Ar-H), 8.23 (1H, dd, *J* 1.7, 7.8, H-8) (Found: C, 72.9; H, 4.6. $C_{13}H_{10}O_3$ requires C, 72.9; H, 4.7%).

2,3,4,9-Tetrahydro-3-methyl-1*H*-xanthene-1,9-dione 3b. From ester **8b** as colourless needles (72%) after crystallisation from ethanol and ethyl acetate, mp 158 °C; ν_{max}(Nujol)/cm^{-1} 1692, 1633 and 1613; δ_H 1.50 (3H, d, *J* 7.0, Me), 1.80–3.20 (5H, m, H-2, H-3, H-4), 7.40 (2H, m, Ar-H), 7.66 (1H, m, Ar-H), 8.22 (1H, dd, *J* 1.7, 7.8, H-8) (Found: C, 74.0; H, 5.3. $C_{14}H_{12}O_3$ requires C, 73.7; H, 5.3%).

2,3,4,9-Tetrahydro-3,3-dimethyl-1*H*-xanthene-1,9-dione 3c. From ester **8c** as colourless needles (82%) after crystallisation from ethyl acetate and hexane, mp 135.5–136 °C; ν_{max}(Nujol)/cm^{-1} 1691 and 1630; δ_H 1.16 (6H, s, 2 × Me), 2.46 (2H, s, H-2), 2.85 (2H, s, H-4), 7.38 (2H, m, Ar-H), 7.64 (1H, m, Ar-H), 8.21 (1H, dd, *J* 1.7, 7.8, H-8) (Found: C, 74.5; H, 5.8. $C_{15}H_{14}O_3$ requires C, 74.4; H, 5.8%).

8-Fluoro-2,3,4,9-tetrahydro-1*H*-xanthene-1,9-dione 3d. From ester **8d** as pale brown needles (74%) after recrystallisation from ethanol, mp 217.5–218 °C (decomp.); ν_{max}(Nujol)/cm^{-1} 1707, 1645 and 1622; δ_H 2.16 (2H, m, H-3), 2.59 (2H, t, *J* 6.5, H-2), 2.96 (2H, t, *J* 6.5, H-4), 7.03 (1H, m, Ar-H), 7.20 (1H, m, Ar-H), 7.57 (1H, m, Ar-H) (Found: C, 67.1; H, 3.8; F, 8.1. $C_{13}H_9FO_3$ requires C, 67.2; H, 3.9; F, 8.2%).

6-Fluoro-2,3,4,9-tetrahydro-1*H*-xanthene-1,9-dione 3e. From ester **8e** as colourless needles (86%) after recrystallisation from ethyl acetate and hexane, mp 151–171 °C (decomp.); ν_{max}(Nujol)/cm^{-1} 1704, 1639 and 1613; δ_H 2.17 (2H, m, H-3), 2.59 (2H, t, *J* 6.5, H-2), 2.99 (2H, t, *J* 6.5, H-4), 7.10 (2H, m, Ar-H), 8.21 (1H, m, Ar-H) (Found: C, 66.9; H, 3.8; F, 8.3. $C_{13}H_9FO_3$ requires C, 67.2; H, 3.9; F, 8.2%).

5,6,7,8-Tetrafluoro-2,3,4,9-tetrahydro-1*H*-xanthene-1,9-dione 3f. From ester **8f** as colourless plates (87%) after recrystallisation from ethyl acetate, mp 180–210 °C (decomp.); ν_{max}(Nujol)/cm^{-1} 1704, 1642 and 1585; δ_H 2.17 (2H, m, H-3), 2.55 (2H, t, *J* 6.5, H-2), 3.02 (2H, t, *J* 6.5, H-4) (Found: C, 54.6; H, 2.0; F, 26.6. $C_{13}H_6F_4O_3$ requires C, 54.6; H, 2.1; F, 26.6%).

General method for the preparation of 3,4,4a,9-tetrahydro-1-hydroxy-2*H*-xanthen-9-ones 10

A stirred suspension of the xanthenedione **3** (56 mmol) in anhydrous pyridine (150 cm^3) was treated with sodium borohydride (56 mmol) in portions. The suspension dissolved and the resulting dark solution was stirred at room temperature for 3 h. After pouring onto ice (*ca.* 200 g) and 2 M hydrochloric acid (200 cm^3), the mixture was extracted with ethyl acetate (3 × 100 cm^3). The combined organic extracts were washed with 2 M hydrochloric acid (4 × 200 cm^3) and brine (200 cm^3). After drying (Na_2SO_4), evaporation of the solvent provided the crude product. The following compounds were prepared according to this method.

3,4,4a,9-Tetrahydro-1-hydroxy-2*H*-xanthen-9-one 10a. From chromone **3a** as pale yellow crystals (100%) after sublimation, mp 71.5–73.5 °C; ν_{max}(Nujol)/cm^{-1} 1608; δ_H 1.96 (3H, m, H-3, H-4), 2.39 (3H, m, H-2, H-4), 5.05 (1H, m, H-4a), 6.91 (1H, m, Ar-H), 7.03 (1H, m, Ar-H), 7.42 (1H, m, Ar-H), 7.84 (1H, dd, *J* 1.7, 7.8, H-8), 14.97 (1H, s, OH) (Found: C, 72.1; H, 5.5. $C_{13}H_{12}O_3$ requires C, 72.2; H, 5.6%).

3,4,4a,9-Tetrahydro-1-hydroxy-3-methyl-2*H*-xanthen-9-one 10b. From chromone **3b** as a yellow solid (85%), distilled at 130 °C at 0.04 mbar, mp 49–63 °C; ν_{max}(Nujol)/cm^{-1} 1609; δ_H

† 1 bar = 10^5 Pa.

1.10 (3H, m, Me), 1.64 (1H, m, H-4), 2.19 (4H, m, H-2, H-3, H-4), 5.06 (1H, m, H-4a), 6.95 (1H, m, Ar-H), 7.03 (1H, m, Ar-H), 7.42 (1H, m, Ar-H), 7.86 (1H, m, H-8), 14.55–14.95 (1H, br s, OH) (Found: C, 73.0; H, 6.0. $C_{14}H_{14}O_3$ requires C, 73.0; H, 6.1%).

3,4,4a,9-Tetrahydro-1-hydroxy-3,3-dimethyl-2*H*-xanthene-9-one 10c. From chromone **3c** as orange prisms (78%) after crystallisation from ethyl acetate and hexane, mp 92.5–93.5 °C; ν_{max}(Nujol)/cm^{-1} 1606; δ_H 0.99 (3H, s, Me), 1.12 (3H, s, Me), 1.79 (1H, dd, *J* 10.2, 12.3, H-4), 2.06 (1H, m, H-4), 2.16 (1H, dd, *J* 1.4, 18.5, H-2), 2.38 (1H, dd, *J* 1.4, 18.5, H-2), 5.06 (1H, m, H-4a), 6.92 (1H, m, Ar-H), 7.04 (1H, m, Ar-H), 7.43 (1H, m, Ar-H), 7.86 (1H, dd, *J* 1.8, 7.8, H-8), 14.86 (1H, s, OH) (Found: C, 73.8; H, 6.6. $C_{15}H_{16}O_3$ requires C, 73.8; H, 6.6%).

1-Hydroxy-9*H*-xanthen-9-one

A mixture of 3,4,4a,9-tetrahydro-1-hydroxy-2*H*-xanthen-9-one **10a** (0.5 g), *o*-chloranil (1.14 g) and 1,4-dioxane (40 cm^3) was refluxed for 5 h. The residue remaining after filtration and evaporation of the cooled filtrate was eluted from silica with ethyl acetate–hexane (1:9) and recrystallised from hexane to give the title compound (77%), mp 148.5–149 °C as a yellow solid (lit.,[35] mp 148–149 °C).

General method for the preparation of 4a-substituted 3,4,4a,9-tetrahydro-1-hydroxy-2*H*-xanthen-9-ones 11

To a stirred suspension of copper(I) cyanide (116.7 mmol) in dry diethyl ether (150 cm^3) at −50 °C was added a solution of the alkyllithium (116.8 mmol), maintaining the temperature below −25 °C at all times. Towards the end of the addition the copper(I) cyanide dissolved. The homogeneous solution of the cuprate was cooled to −70 °C and stirred for 30 min. The chromone **3a** (5.0 g, 23.35 mmol) was added in portions *via* a powder funnel. An initial red colouration was apparent. The mixture was stirred below −50 °C until the reaction was complete. The resulting mixture was poured into water (300 cm^3) and hydrochloric acid (50 cm^3), and filtered through Celite. The filter cake was washed with ethyl acetate (2 × 100 cm^3) and the organic layer was separated. After drying (Na_2SO_4), removal of the solvent gave the conjugate addition product. The following compounds were prepared in this way.

3,4,4a,9-Tetrahydro-1-hydroxy-4a-methyl-2*H*-xanthen-9-one 11a. From chromone **3a** and lithium methylcyanocuprate(I) as golden yellow crystals (93%) after crystallisation from light petroleum (bp 40–60 °C), mp 91–93.5 °C; ν_{max}(Nujol)/cm^{-1} 1607; δ_H 1.48 (3H, s, Me), 1.83 (1H, m, H-3), 2.04 (3H, m, H-3, H-4), 2.47 (2H, m, H-2), 6.88 (1H, m, Ar-H), 7.00 (1H, m, Ar-H), 7.42 (1H, m, Ar-H), 7.85 (1H, dd, *J* 1.3, 7.8, H-8), 15.27 (1H, s, OH) (Found: C, 72.9; H, 6.1. $C_{14}H_{14}O_3$ requires C, 73.0; H, 6.1%).

4a-Butyl-3,4,4a,9-tetrahydro-1-hydroxy-2*H*-xanthen-9-one 11b. From chromone **3a** and lithium *n*-butylcyanocuprate(I) as a pale yellow solid (98%) after distillation at 160 °C at 0.04 mbar, mp 66–68 °C; ν_{max}(Nujol)/cm^{-1} 1607; δ_H 0.79 (3H, t, *J* 7.1, Me), 1.23 (4H, m, H-2′, H-3′), 1.60 (2H, m, H-3), 1.89 (3H, m, H-1′, H-4), 2.30 (1H, m, H-4), 2.43 (2H, m, H-2), 6.87 (1H, m, Ar-H), 6.98 (1H, m, Ar-H), 7.40 (1H, m, Ar-H), 7.84 (1H, dd, *J* 1.3, 7.7, H-8), 15.34 (1H, s, OH) (Found: C, 75.1; H, 7.4. $C_{17}H_{20}O_3$ requires C, 75.0; H, 7.4%).

4a-(Butan-2-yl)-3,4,4a,9-tetrahydro-1-hydroxy-2*H*-xanthen-9-one 11c. From chromone **3a** and lithium *sec*-butylcyanocuprate(I) as a yellow–brown oil (34%) after column chromatography (ethyl acetate–hexane, 1:9) and distillation at 160 °C at 0.04 mbar as a yellow oil; ν_{max}(Nujol)/cm^{-1} 1607; δ_H 0.82 (6H, m, 2 × Me), 1.00 (1H, m, H-3′), 1.30 (1H, m, H-3′), 1.84 (3H, m, H-2′, H-3), 2.02 (2H, m, H-4), 2.32 (2H, m, H-2), 6.87 (1H, m, Ar-H), 6.98 (1H, m, Ar-H), 7.41 (1H, m, Ar-H), 7.84 (1H, m, H-8), 14.99 (1H, br s, OH).

3,4,4a,9-Tetrahydro-1-hydroxy-4a-phenyl-2*H*-xanthen-9-one 11d. A 2.0 M solution of phenyllithium in 25% diethyl ether–benzene (21.0 cm^3, 42 mmol) was added to a stirred suspension of copper(I) iodide (4.01 g, 21 mmol) in dry diethyl ether (100 cm^3) at −5 °C under nitrogen, keeping the internal temperature below 0 °C. The resulting dark solution was stirred below 0 °C for 15 min, cooled to −80 °C and treated with **3a** (3.0 g, 14 mmol) in portions *via* a powder funnel. After stirring below −40 °C for 100 min, the reaction mixture was allowed to warm to 0 °C and then stirred at 0 °C for a further 6 h. The usual work-up gave a sticky brown solid. Purification by column chromatography (ethyl acetate–hexane, 1:9) and recrystallisation from light petroleum (bp < 40 °C) gave the title compound **11d** as golden yellow crystals (0.86 g, 21%), mp 140–143 °C; ν_{max}(Nujol)/cm^{-1} 3401, 1648 and 1606; δ_H 1.34 (1H, m, H-3), 1.67 (1H, m, H-3), 2.26 (2H, m, H-4), 2.46 (2H, m, H-2), 6.79 (1H, m, Ar-H), 6.88 (1H, m, Ar-H), 7.20 (4H, m, Ar-H), 7.39 (2H, m, Ar-H), 7.70 (1H, dd, *J* 1.7, 7.8, H-8), 15.56 (1H, s, OH) (Found: C, 78.1; H, 5.5. $C_{19}H_{16}O_3$ requires C, 78.1; H, 5.5%).

4a-Ethyl-3,4,4a,9-tetrahydro-1-hydroxy-2*H*-xanthen-9-one 11e. From chromone **3a** and magnesium ethylcyanocuprate(I) bromide as yellow crystals (51%) after elution from silica with ethyl acetate–hexane (1:9) and crystallisation from diethyl ether, mp 70–80 °C; ν_{max}(Nujol)/cm^{-1} 1607; δ_H 0.85 (3H, t, *J* 7.3, Me), 1.57 (1H, m, CH_2Me), 1.71 (1H, m, H-3), 1.89 (2H, m, H-3, H-4), 2.05 (1H, m, CH_2Me), 2.30 (1H, m, H-4), 2.46 (2H, m, H-2), 6.89 (1H, m, Ar-H), 7.00 (1H, m, Ar-H), 7.41 (1H, m, Ar-H), 7.83 (1H, dd, *J* 1.7, 7.8, H-8), 15.30 (1H, s, OH) (Found: C, 73.9; H, 6.5. $C_{15}H_{16}O_3$ requires C, 73.8; H, 6.6%).

3,4,4a,9-Tetrahydro-1-hydroxy-4a-(4-methylbenzyl)-2*H*-xanthen-9-one 11f. From chromone **3a** and magnesium (4-methylbenzyl)cyanocuprate(I) bromide as colourless prisms (24%) after elution from silica with ethyl acetate–hexane (1:9) and crystallisation from ethyl acetate–hexane, mp 121–123 °C; ν_{max}(Nujol)/cm^{-1} 1606; δ_H 1.90 (3H, m, H-3, H-4), 2.10 (1H, m, H-4), 2.33 (3H, s, Me), 2.49 (2H, m, H-2), 2.79 (1H, d, *J* 14.7, CH_2Ar), 3.35 (1H, d, *J* 14.7, CH_2Ar), 6.96 (3H, m, Ar-H), 7.06 (3H, m, Ar-H), 7.51 (1H, m, Ar-H), 7.90 (1H, dd, *J* 1.7, 7.8, H-8), 15.48 (1H, s, OH) (Found: C, 78.8; H, 6.5. $C_{21}H_{20}O_3$ requires C, 78.7; H, 6.3%).

2,3,4,9-Tetrahydro-1-hydroxy-1-methyl-1*H*-xanthen-9-one 12

A solution of methylmagnesium bromide in diethyl ether (15.0 mmol) was added dropwise to a stirred suspension of **3a** (1.5 g, 7.01 mmol) in dry diethyl ether (80 cm^3) at −18 °C. Gradual dissolution of the substrate occurred giving an orange–red solution. After stirring for 30 min, the mixture was poured onto ice (*ca.* 50 g) and 1 M hydrochloric acid (100 cm^3), and extracted with ethyl acetate (2 × 100 cm^3). The combined organic extracts were washed with aqueous ammonium chloride (2 × 200 cm^3), dried (Na_2SO_4) and evaporated to yield an orange–yellow oil. Column chromatography (ethyl acetate–hexane, 1:5) gave the 1,4-adduct **11a** followed by the title compound **12**, obtained as a yellow solid (0.64 g, 40%) and a yellow oil (0.38 g, 24%) respectively. The latter solidified and was crystallised from ethyl acetate and hexane as yellow–brown crystals, mp 75–77 °C; ν_{max}(Nujol)/cm^{-1} 3531, 3483, 3417, 1626 and 1600; δ_H 1.64 (3H, s, Me), 1.95 (4H, m, H-2, H-3), 2.73 (2H, m, H-4), 5.39 (1H, s, OH), 7.37 (2H, m, Ar-H), 7.63 (1H, m, Ar-H), 8.16 (1H, dd, *J* 1.4, 8.4, H-8) (Found: M$^+$, 230.093 99. $C_{14}H_{12}O_3$ requires *M*, 230.094 29).

3,4,4a,9-Tetrahydro-1-hydroxy-4a-[tris(methylthio)methyl]-2*H*-xanthen-9-one 15

A 2.3 M solution of *n*-butyllithium in hexane (3.1 cm^3, 7.71 mmol) was added dropwise to a stirred solution of tris(methylthio)methane (1.03 ml, 7.71 mmol) in dry tetrahydrofuran (50 cm^3) at −60 °C over 30 min, maintaining the internal temperature below −55 °C. After stirring below −60 °C for 50 min, the mixture was treated with **3a** (1.50 g, 7.01 mmol) in portions *via* a powder funnel. The resulting red solution was stirred below

−70 °C for 12 h, poured carefully onto water (200 cm^3) and ice (*ca.* 100 g) and extracted with ethyl acetate (3 × 100 cm^3). The solvent was removed from the dried (Na_2SO_4) organic extracts to give a yellow–brown oil. Purification by column chromatography (ethyl acetate–hexane, 1:9) and recrystallisation from ethyl acetate and hexane yielded yellow crystals (0.90 g, 35%), mp 97–99 °C; ν_{max}(Nujol)/cm^{-1} 1607; δ_H 1.77 (1H, m, H-3), 2.13 (1H, m, H-3), 2.15 [9H, s, $(SMe)_3$], 2.48 (2H, m, H-4), 2.61 (1H, m, H-2), 2.90 (1H, m, H-2), 6.79 (1H, m, Ar-H), 7.00 (1H, m, Ar-H), 7.41 (1H, m, Ar-H), 7.81 (1H, dd, *J* 1.6, 7.8, H-8), 15.12 (1H, s, OH); δ_C 15.8, 19.7, 32.8, 36.6, 84.4, 89.0, 103.2, 115.7, 119.2, 120.9, 125.1, 134.7, 158.1, 174.8 and 192.0 (Found: C, 55.3; H, 5.4; S, 25.9. $C_{17}H_{20}S_3O_3$ requires C, 55.4; H, 5.5; S, 26.1%).

Methyl 3,4,4a,9-tetrahydro-1-hydroxy-9-oxo-2*H*-xanthene-4a-carboxylate 2

A solution of **15** (0.51 g, 1.38 mmol), mercuric chloride (1.53 g, 5.62 mmol) and mercuric oxide (0.50 g, 2.33 mmol) in methanol–water (34 cm^3, 12:1) was stirred at room temperature for 6 h. The resulting white suspension was filtered through Celite, and the residue was washed with dichloromethane (2 × 70 cm^3). The filtrate was diluted with water (100 cm^3), extracted with dichloromethane (2 × 500 cm^3), the combined organic extracts were washed with 60% aqueous ammonium acetate (2 × 50 cm^3), followed by saturated aqueous ammonium chloride (2 × 50 cm^3). The solvent was removed *in vacuo* from the dried (Na_2SO_4) organic extracts to give the title compound **2** (0.38 g, 100%). Recrystallisation from ethyl acetate and hexane yielded very pale red–brown crystals, mp 123–129 °C; ν_{max}(Nujol)/cm^{-1} 1744, 1682 and 1605; δ_H 1.90 (2H, m, H-3), 2.17 (1H, m, H-4), 2.46 (3H, m, H-2, H-4), 3.62 (3H, s, OMe), 7.04 (2H, m, Ar-H), 7.43 (1H, m, Ar-H), 7.81 (1H, dd, *J* 1.6, 7.6, H-8), 15.31 (1H, s, OH); δ_C 17.4, 30.4, 33.1, 52.8, 85.7, 104.6, 117.6, 120.5, 122.3, 126.5, 135.3, 158.5, 172.7, 179.5 and 185.1 (Found: C, 65.7; H, 5.1. $C_{15}H_{14}O_5$ requires C, 65.7; H, 5.1%).

Spiro[[1,3]dioxolane-2,1′-(2′,3′,4′,9′-tetrahydro-1′*H*-xanthen)]-9-one 14

Chlorotrimethylsilane (14.4 cm^3, 46.75 mmol) was added in one portion to a stirred solution of **3a** (10.0 g, 46.7 mmol) and ethylene glycol (3.60 g, 58.0 mmol) in dry 1,2-dichloroethane (150 cm^3) under an argon atmosphere and the mixture was heated to reflux. After 100 h, a wine-red solution was obtained. The mixture was cooled to room temperature, diluted with chloroform (400 cm^3) and washed with 5% aqueous sodium hydrogen carbonate (2 × 200 cm^3). Evaporation of the dried (Na_2SO_4) organic phase provided an orange–brown oil. Purification by passage through a short path of silica (ethyl acetate–hexane, 1:1) and recrystallisation from ethyl acetate and hexane gave the title compound **14** as colourless crystals (10.86 g, 90%), mp 93–97.5 °C; ν_{max}(Nujol)/cm^{-1} 1752, 1673, 1642 and 1595; δ_H 1.83 (4H, m, H-2, H-3), 2.59 (2H, m, H-4), 3.96–4.39 [4H, m, $(CH_2)_2$], 7.23 (2H, m, Ar-H), 7.47 (1H, m, Ar-H), 8.05 (1H, dd, *J* 1.9, 7.8, H-8) (Found: C, 70.0; H, 5.5. $C_{15}H_{14}O_4$ requires C, 69.8; H, 5.5%).

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