# The synthesis of substituted tetrahydro-1*H*-xanthen-1-ones and xanthenes†

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A short and an efficient methodology for the synthesis of substituted tetrahydro-1*H*-1-xanthenones and xanthenes is described.

**Keywords:** tetrahydro-1*H*-xanthen-1-ones, xanthenes, balanol, diarylmethanes

Balanol (**1**) is a novel protein kinase C inhibitor produced by the fungus *Verticillium balanoides*. It was originally isolated by Clardy and co-workers in 1993.[1] Its interesting biological activity and structural novelty have stimulated great interest in the synthesis of balanol and its precursors.[2] Moreover the SAR studies on balanol have established the importance of the benzophenone moiety in the efficacy of balanol.[3]

Recently we have reported two independent routes to the synthesis of the sterically congested benzophenone precursor of balanol (Scheme 1).[4] The first route involved synthesis of a triketone and its aromatisation to afford the desired benzophenone portion of balanol, and the second approach relied on the *ortho*-lithiation of 3,5-dimethoxytoluene.

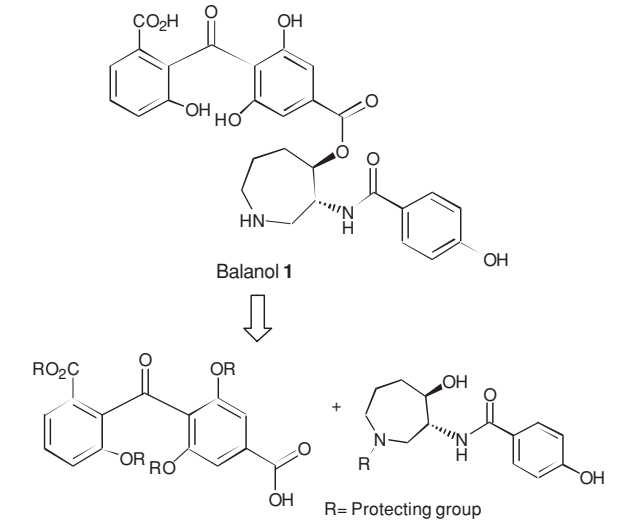
Although we have achieved the synthesis of the sterically hindered benzophenone portion of balanol in 20 % yield, it afforded a xanthone as the major side product. We felt that presence of triketone moieties might be responsible for the difficulties in the aromatisation and that the replacement of the acyl ketone with a methylene functionality would provide an easy access to aromatisation, which could be oxidised at a later stage to give the benzophenone portion of balanol.

Our retrosynthetic plan for the synthesis of the sterically hindered benzophenone domain of balanol using the diarylmethane intermediate **3** is outlined in Scheme 2.

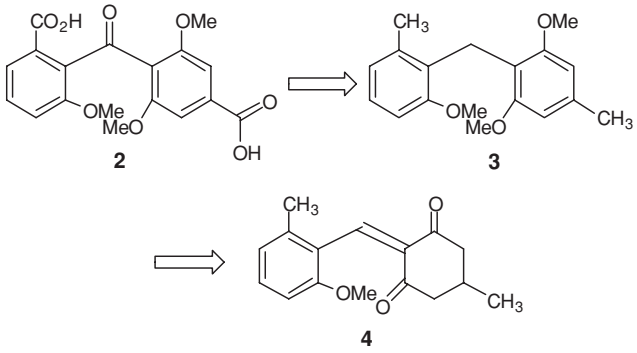
Accordingly, the synthesis of compound **4** commenced with the commercially available 5-methylcyclohexane-1,3-dione and aldehyde **5**[5] by using a Knoevenagel condensation reaction as shown in Scheme 3. Thus 5-methylcyclohexane-1,3-dione was treated with aldehyde **5** in presence of catalytic piperidine in glacial acetic acid at 0 °C and then stirred at room temperature for 6–7 h to afford a reddish coloured solid **4** in 60% yield.

All attempts to aromatise compound **4** under various conditions such as DDQ, $I_2$/MeOH, Pd/C and $Hg(OAc)_2$/$CH_3COONa$ failed to give the desired diarylmethane product. We reasoned that the resistance of compound **4** to aromatisation might be due to the presence of the exocyclic double bond, and so selective reduction of double bond was attempted under hydrogenation conditions using 10% Pd/C, but this resulted in a complex reaction mixture.

Loim *et al.*[6] have reported the reduction of an exocyclic double bond using trifluoroacetic acid and triethylsilane in refluxing carbon tetrachloride. A similar strategy was used for the selective reduction of the exocyclic double bond of compound **4**. Thus, compound **4** in carbon tetrachloride was treated with triethylsilane and trifluoroacetic acid at 50–60 °C to afford a mixture of two compounds, **6** and **7**. Although the desired compound **6,** obtained in 40% yield, showed the expected signals in the $^1$H NMR spectrum, the spectrum was not clean enough, and hence it was subjected to aromatisation with iodine/methanol and characterised as the methyl ether **3** (Scheme 4).




**Scheme 1** Balanol retrosynthetic scheme.




**Scheme 2** Retrosynthetic analysis for the synthesis of benzophenone precursor 2.

The compound **3** was characterised by its spectral data. The $^1$H NMR spectrum of the compound **3** showed the presence of two aromatic methyl groups at δ 2.45 and 2.52, three methoxy groups at δ 3.86 (two groups) and 3.94 (one methoxy group) and the benzylic protons at δ 4.22. Unfortunately, further attempts to oxidise the compound **3** to the desired intermediate **8** under most conditions tried resulted in either a complex mixture or no reaction.

A careful structural analysis of the compound **7**, obtained in 50% yield in the reduction of compound **4**, suggested a cyclised product whose $^1$H NMR showed the disappearance of the olefinic proton at δ 7.90 (exocyclic double bond) and of one of the OMe group singlets (at δ 3.75). Moreover, the $^{13}$C NMR spectrum showed a signal at δ 198, indicating

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† This paper is dedicated to Dr V. H. Deshpande on the occasion of his 63rd birthday.

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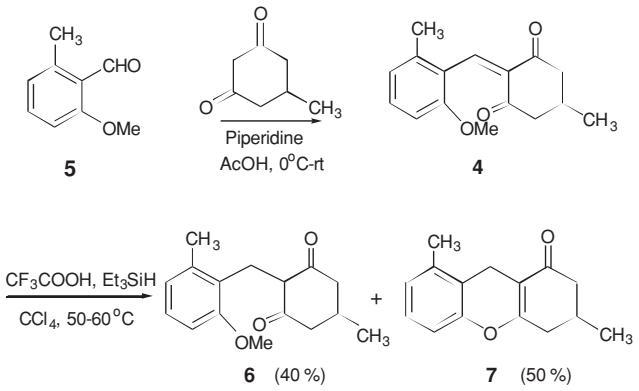
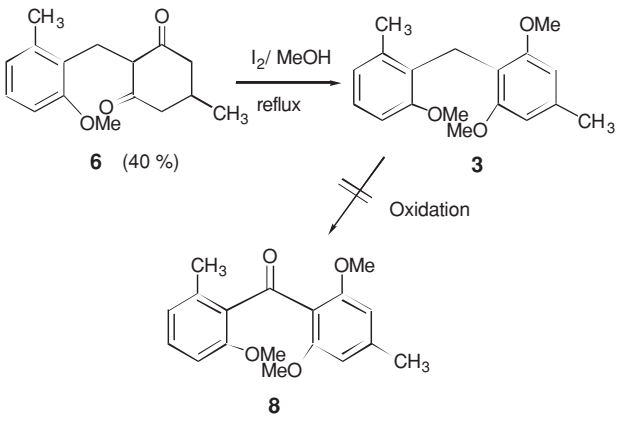



**Scheme 3** Knoevenagel condensation approach.




**Scheme 4** Synthesis of diarylmethane **3**.

the presence of only one carbonyl group. These data are all in good agreement with the assigned cyclised structure **7**. The probable mechanism for the formation of compound **7** is depicted in Scheme 5. The first step would be the reduction of the exocyclic double bond in **4** to afford a 1,3-diketone moiety which exists in mono-enol form. Then loss of methanol due to the highly acidic reaction medium results in the formation of the cyclised product **7**.

Formation of the tetrahydro-1*H*-xanthen-1-one **7** was confirmed by its aromatisation which was carried out with iodine in refluxing methanol to afford the 9*H*-xanthene **9** as a white solid in 75% yield as shown in Scheme 6.

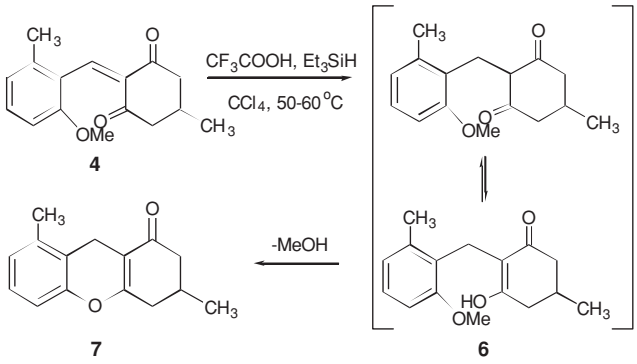
The $^1$H NMR spectrum of xanthene **9** revealed the presence of two aromatic methyl groups which showed as a singlet at δ 2.32, the methoxy group singlet at δ 3.85, and the benzylic protons at δ 3.75. The rest of the protons showed signals in good agreement with the assigned structure.

Xanthene derivatives are important intermediates for many biologically active molecules and possess very interesting biological activities.[7,8] Tetrahydro-1*H*-xanthen-1-ones can be converted into xanthone-derived natural products[9] by simple chemical manipulations, therefore xanthene derivative **9** and the tetrahydro-1*H*-xanthen-1-one **7** obtained in the present study could be of great importance.

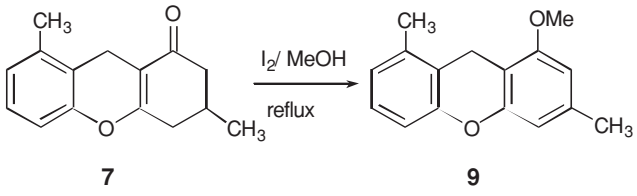
In conclusion, in an attempt to synthesise the benzophenone moiety of balanol, we have developed a new method for the preparation of substituted tetrahydro-1*H*-1-xanthenones and xanthenes.

## Experimental

$^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker AC-200 spectrometer in $CDCl_3$ containing TMS as an internal standard. Infrared spectra were recorded as either nujol mull or in $CHCl_3$




**Scheme 5** Formation of cyclised product 7.




**Scheme 6** Synthesis of xanthene 9.

on Perkin-Elmer Infrared 683 B or 160S FT-IR spectrometer with sodium chloride optics. All solvents and reagents were purified and dried by standard procedures. TLC was carried out on silica gel plates prepared by spreading the slurry in $CCl_4$ and drying at room temperature. The plates were analysed using an iodine chamber. Column chromatography was performed on silica gel (60–120 mesh). Petroleum ether refers to the fraction of boiling range 60–80 °C.

*2-(2′-Methoxy-6′-methylphenylmethylene)-5-methyl-1,3-cyclohexanedione* (**4**): Piperidine (500 mg) was added to a stirred solution of 5-methylcyclohexane-1,3-dione (1.26 g, 0.01 mol) and the aldehyde **5** (1.8 g, 0.012 mol) in glacial acetic acid (3 ml) at 0 °C under nitrogen. The stirring was continued for 30 min, allowing the mixture to warm to room temperature. After completion of the reaction, the mixture was poured into ice-cold water (10 ml) and extracted with chloroform (50 ml × 3). The combined organic layer was washed with brine (20 ml × 3) and dried over sodium sulfate. Evaporation of the solvent under reduced pressure and purification by silica gel column chromatography (eluent 10% ethyl acetate in petroleum ether) yielded compound **4** (1.54 g, 60%) as a reddish solid, m.p. 95–97 °C (petroleum ether/ ethyl acetate). IR ($CHCl_3$): 1721 cm$^{-1}$. $^1$H NMR ($CDCl_3$): δ 1.15 (d, *J* = 5.6 Hz, 3H), 2.25 (s, 3H), 2.10–2.50 (m, 5H), 3.75 (s, 3H, -OMe), 6.72 (d, *J* = 8 Hz, 1H, aromatic), 6.80 (d, *J* = 8 Hz, 1H, aromatic), 7.20 (t, *J* = 8 Hz, 1H, aromatic), 7.90 (s, 1H, olefinic).

*Reduction of compound* **4:** To a stirred solution of the benzylidenedione **4** (2.58 g, 0.01 mol) in anhydrous carbon tetrachloride (20 ml) was added triethylsilane (1.16 g, 0.01 mol) and trifluoroacetic acid (11.4 g, 0.1 mol) at room temperature under argon atmosphere. The reaction mixture was then stirred at 50–60 °C for 3 h. After completion of the reaction, the mixture was poured into ice-cold water (50 ml) and extracted with ethyl acetate (50 ml × 3). The organic layer was washed with water (20 ml × 3) and brine (20 ml × 3) and dried over sodium sulfate. TLC examination of the reaction mixture showed formation of two compounds. Silica gel column chromatographic separation (eluent 10–15% ethyl acetate in petroleum ether) afforded compound **7** in 50% yield and compound **6** in 40% yield as white crystals (characterised after aromatisation).

*3,8-Dimethyl-2,3,4,9-tetrahydro-1H-xanthen-1-one* (**7**): white solid (1.14 g, 50%), m.p. 141–142 °C (petroleum ether/ ethyl acetate). IR ($CHCl_3$): 1680 cm$^{-1}$. $^1$H NMR ($CDCl_3$): δ 1.13 (d, *J* = 5.6 Hz, 3H), 2.07–2.70 (m including singlet for benzylic methyl at δ 2.27, 8H), 3.31 (d, *J* = 14.8 Hz, 1H), 3.43 (d, *J* = 14.8 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 1H, aromatic), 6.92 (d, *J* = 7.8 Hz, 1H, aromatic), 7.07 (t, *J* = 7.8 Hz, 1H, aromatic). $^{13}$C NMR ($CDCl_3$, 50 MHz): δ 18, 20, 22, 28, 35, 45, 109, 114, 119, 126, 128, 138, 150, 165, 198 (C=O). MS: *m/z* 228 ($M^+$, 100), 213 (M-15, 25), 195 (10), 185 (15), 171 (20).

*1,3-Dimethoxy-2-(2′-methoxy-6′-methylbenzyl)-5-methylbenzene* (**3**): The compound **6** (260 mg, 1 mmol) was treated with iodine (254 mg, 2 mmol) in anhydrous methanol (10 ml) under reflux for 6 h.

After completion of the reaction, the methanol was evaporated under reduced pressure, chloroform was added (50 ml) and the chloroform layer was washed with saturated aqueous sodium thiosulfate (20 ml × 3) and water (20 ml × 3). Evaporation of the solvent and column chromatographic purification (eluent 15% ethyl acetate in petroleum ether) of the residue afforded compound **3** (200 mg, 70%) as white crystals: m.p. 108–111 °C (petroleum ether/ ethyl acetate). IR ($CHCl_3$): 1582 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 2.45 (s 3H, Ar–$CH_3$), 2.52 (s, 3H, Ar–$CH_3$), 3.86 (s, 6H, –OMe), 3.94 (s, 3H, OMe), 4.22 (s, 2H, benzylic), 6.54 (s, 2H, aromatic), 6.85–6.97 (m, 2H, aromatic), 7.22 (t, *J* = 7.2 Hz, 1H, aromatic). $^{13}C$ NMR ($CDCl_3$): δ 18, 19, 21, 54, 104, 107, 114, 121, 124, 128, 135, 137, 157, 157. MS: *m/z* 286 ($M^+$, 25), 165 (35), 134 (100). Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.73. Found: C, 75.48; H, 7.68 %.

*1-Methoxy-3, 8-dimethyl-9H-xanthene* (**9**): Compound **7** (228 mg, 1 mmol) was treated with iodine (254 mg, 2 mmol) in refluxing methanol (10 ml) for 8 h. After completion of the reaction, the methanol was removed under reduced pressure and chloroform (50 ml) was added. The chloroform layer was washed with saturated aqueous sodium thiosulfate (20 ml × 3) followed by washing with water (20 ml × 3). Evaporation of the chloroform afforded a yellowish residue which on column chromatography on silica gel (eluent 15–20% ethyl acetate in petroleum ether) yielded compound **9** (180 mg, 75%) as a white solid, m.p. 97–100 °C (petroleum ether / ethyl acetate). IR ($CHCl_3$): 1577 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 2.32 (s, 6H, Ar–$CH_3$), 3.75 (s, 2H, benzylic), 3.85 (s, 3H, OMe), 6.39 (s, 1H, aromatic), 6.50 (s, 1H, aromatic), 6.80–6.95 (m, 2H, aromatic), 7.10 (t, *J* = 7.2 Hz, 1H, aromatic). MS: *m/z* 240 ($M^+$, 50), 239 (80), 225 (70), 209 (100). Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.00; H, 6.75 %.

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