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Synthetic studies towards the benzophenone precursor for balanol

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Abstract—Synthesis of 4-carboxy-2,6-dimethoxyphenyl 2′-carboxy-6′-methoxyphenyl ketone, an important precursor for balanol's benzophenone portion, has been achieved via a short and efficient route in three steps using *ortho*-lithiation as the key step. In another approach aromatization of 2-(2′-methoxy-6′-methylbenzoyl)-5-methyl-1,3-cyclohexanedione afforded benzophenone precursor 2,6-dimethoxy-4-methylphenyl 2′-methoxy-6′-methylphenyl ketone along with the formation of substituted xanthone.

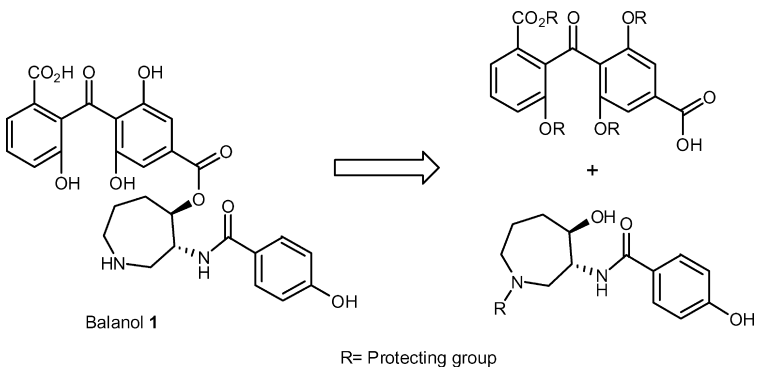
1. Introduction

Balanol (**1**), a novel protein kinase 'C' inhibitor, was isolated in 1993 by Kulanthaivel et al.[1] as an unusual metabolite produced by the fungus *Verticillium balanoides*. Balanol shows remarkable activity against cancer, HIV infection, rheumatoid arthritis, diabetes, central nervous system disorder etc. A wide range of biological activities associated with this compound has attracted researchers to undertake synthesis of balanol and its intermediates.[2]

The synthetic approaches mainly began with disconnection of balanol at its ester linkage to yield the hexahydroazepine and the benzophenone carboxylic acid. The retrosynthesis of balanol is as shown in Scheme 1. Total synthesis of balanol has been achieved by coupling the protected benzophenone domain and hexahydroazepine moiety by esterification using modified Mukaiyama procedure.

The structure–activity relationship studies[3] on balanol (**1**) proved the critical importance of the benzophenone portion for the efficacy of balanol. Any attempted change in this tetra-*ortho*-substituted benzophenone portion resulted in a decrease in its activity. Adams et al.[2c] used benzophenone precursor **2** in the total synthesis of balanol.

The steric hindrance, which makes the synthesis of this tetra-*ortho*-substituted benzophenone difficult, prompted us to undertake its synthesis. Earlier reports on the synthesis of balanol benzophenone precursors are based on the direct utilization of aromatic rings. We envisaged that use of alicyclic systems where the steric hindrance would be less compared to the aromatic systems and later aromatization of these alicyclic systems to the desired benzophenone portion would be a convenient route for the synthesis of this sterically hindered benzophenone portion.



Scheme 1. Retrosynthetic analysis for balanol (**1**).

Keywords: Balanol; Benzophenone; Dicarboxylic acid; Xanthone.
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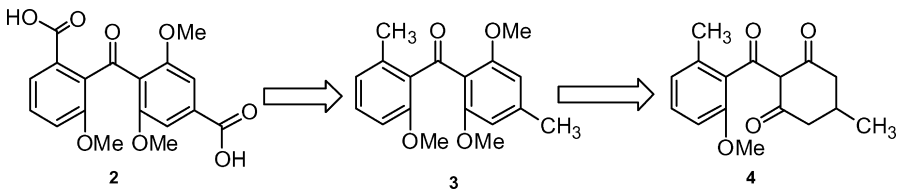


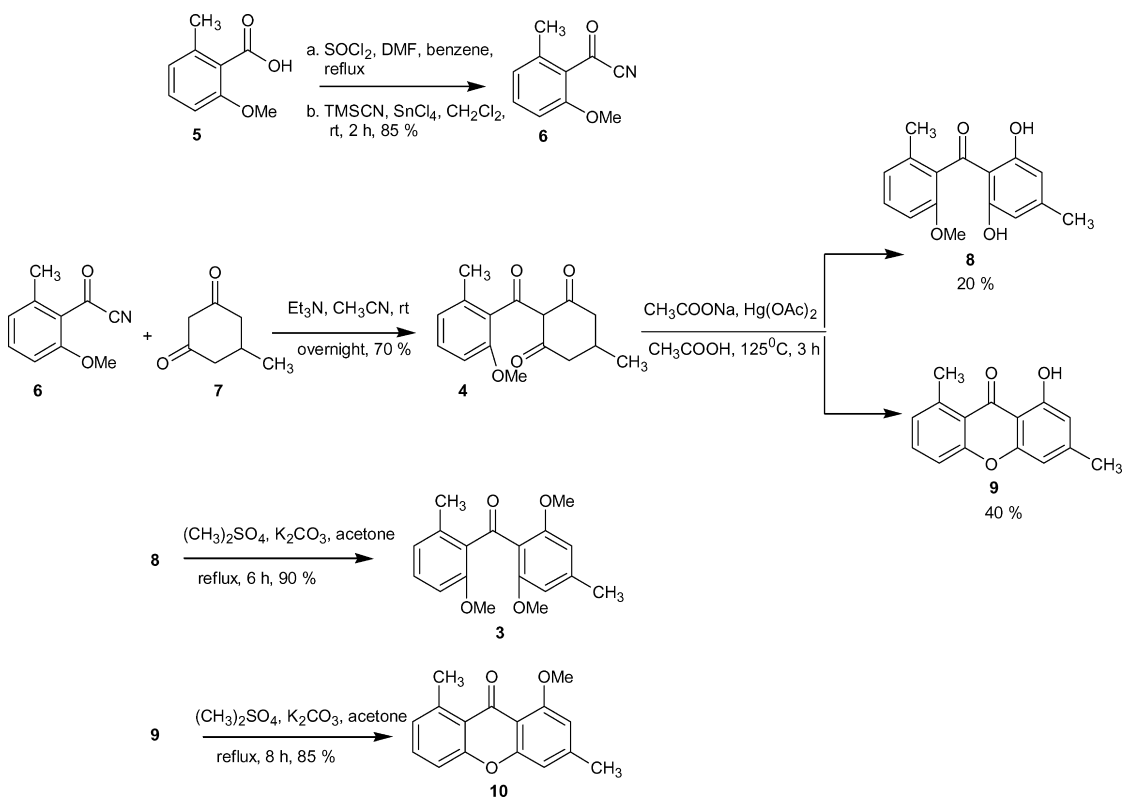
Scheme 2. Retrosynthetic analysis for the synthesis of benzophenone precursor **2**.

Retrosynthetic plan for benzophenone domain **2** (Scheme 2) suggested the triketone **4** as an important intermediate which on aromatization and oxidation would afford benzophenone precursor **3**. Our synthetic route started with synthesis of acyl cyanide **6** from carboxylic acid **5**.[4] Thus carboxylic acid **5** was converted into corresponding acid chloride followed by treatment with trimethylsilyl cyanide in the presence of catalytic stannic chloride to afford the acyl cyanide **6** in 85% yield. The synthesis of triketone **4** was achieved by the treatment of acyl cyanide **6** with 5-methylcyclohexane-1,3-dione (**7**) in presence of triethylamine to give the triketone **4** in 70% yield as shown in Scheme 3.[5,6]

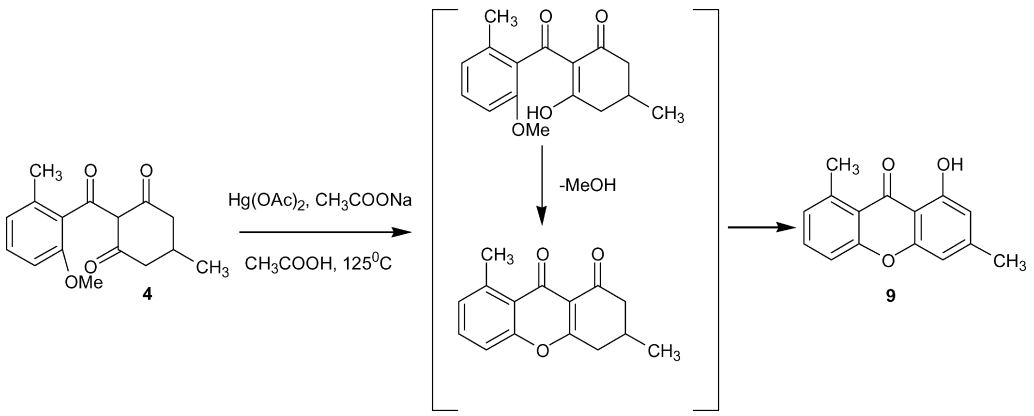
After successful synthesis of triketone **4**, our next aim was to convert compound **4** into the desired benzophenone **3**. Unfortunately the attempted aromatization of the compound **4** using I_2/MeOH,[7] DDQ in benzene or Pd/C failed to give the desired compound **3** and resulted either in the recovery of starting material or a complex reaction mixture. Finally aromatization of compound **4** was achieved using mercuric acetate and sodium acetate in acetic acid under the conditions reported by Oliver et al.[8] for the aromatization of 2-acyl-3-hydroxy-2-cyclohexane-1-ones. Aromatization of the triketone **4** under these conditions resulted in the formation of aromatized product **8** in 20% yield. Formation of compound **8** was confirmed by converting it into the known intermediate **3**, an important benzophenone precursor for balanol. Spectral data for compound **3** were identical to those reported by Adams et al.[2c]

Aromatization of triketone **4** in the presence of mercuric acetate and sodium acetate in acetic acid afforded only 20% of the required product **8** along with formation of xanthone **9**[9] in 40% yield. The ^{1}H NMR spectrum of xanthone **9** exhibited singlets at δ 2.41 and 2.89 for aromatic methyls, singlets at δ 6.55 and 6.65 each integrating for one proton and a singlet at δ 12.86 for chelated –OH group. This xanthone **9** was then methylated using dimethyl sulphate in the presence of potassium carbonate in refluxing acetone to give the corresponding methyl ether **10** whose ^{1}H NMR spectrum showed the presence of only one methoxy group at δ 4.01 confirming the assigned structure of xanthone **9**.

Probable reason for the formation of xanthone would be the loss of methanol during aromatization due to the presence of Lewis acidic mercuric acetate as shown in Scheme 4. Burger



Scheme 3. Synthesis of benzophenone precursor **3**.



Scheme 4. Formation of xanthone **9**.

and Montes[5] reported similar results of dehydration during the synthesis of the antibiotic pyoluteorin.

Thus aromatization of triketone **4** afforded the desired benzophenone **8**, the precursor for balanol, in 20% yield along with the formation of xanthone **9** in 40% yield. Though this reaction yielded the desired intermediate **8** in low yield, the formation of xanthone **9** in this reaction could be explored for the synthesis of substituted xanthones using appropriately substituted triketone **4**.

Low yield for aromatization of triketone **4** to the desired benzophenone **8** in the earlier approach prompted us to explore another route for the synthesis of benzophenone precursor **3** for balanol.

Hollinshead et al.[2b] reported two efficient syntheses of the benzophenone portion of balanol. The key step of this synthesis was the utilization of *ortho*-lithiation reactions to generate a carbinol, which was then oxidized to the benzophenone portion of balanol. We anticipated that coupling of aldehyde **12**, which can be easily prepared from 2,3-dimethylanisole, and commercially available 3,5-dimethoxytoluene under these conditions followed by oxidation would afford the desired benzophenone **2** easily and effectively. Accordingly, 3,5-dimethoxytoluene (**11**) was *ortho*-lithiated[10] using *n*-BuLi in the presence of TMEDA at 0 °C and coupled with the aldehyde **12** to afford alcohol **13** in 70% yield (Scheme 5). Further oxidation of the benzylic alcohol **13** to the desired intermediate **3** was carried out using MnO_2 in dichloromethane at room temperature in 90% yield. This compound showed spectroscopic data in good agreement with those reported by Adams et al.[2c]

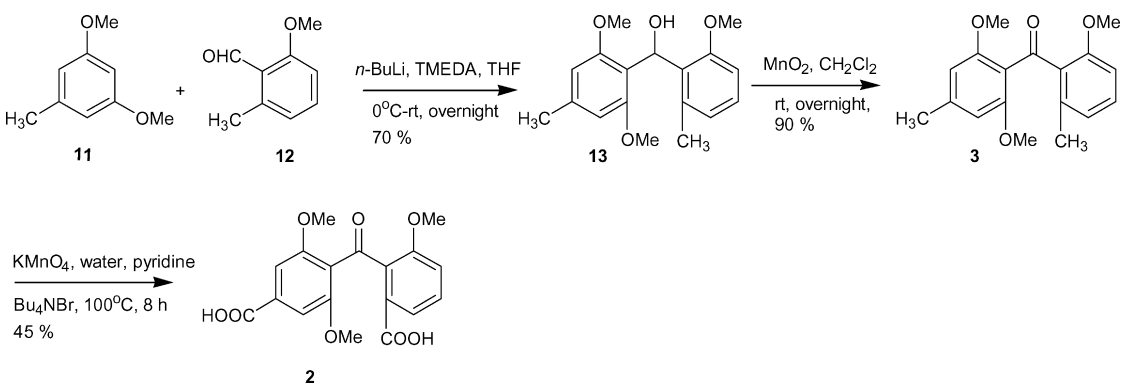
Oxidation of **3** to the dicarboxylic acid **2**, an important precursor for benzophenone portion of balanol (**1**), has been reported by Adams et al.[2c] Thus oxidation of the compound **3** using potassium permanganate and pyridine in the presence of phase transfer catalyst tetrabutylammonium bromide in water afforded the desired benzophenone precursor for balanol **2** in 45% yield.

Thus in conclusion we have achieved synthesis of an important intermediate **2** for balanol's benzophenone portion by using two different approaches. In the first approach we have developed a new method for the synthesis of benzophenone **3** starting with an alicyclic system followed by aromatization to give sterically hindered benzophenone **8** along with formation of xanthone **9**. This method would be useful for the synthesis of substituted xanthones. In another approach, an improved synthesis of dicarboxylic acid **3** has been achieved via a short and efficient route starting from commercially available chemicals in three steps using *ortho*-lithiation as the key step.

2. Experimental

2.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC-200 spectrometer in $CDCl_3$ containing TMS as an internal standard. Infrared spectra (ν_{max} in cm^{-1}) were



Scheme 5. Synthesis of benzophenone precursor **2**.

recorded as either nujol mull or in $CHCl_3$ 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 analyzed by keeping in iodine chamber. Column chromatography was performed on silica gel (60–120 mesh). Petroleum ether refers to the fraction boiling in the range of 60–80 °C.

2.1.1. 2-(2′-Methoxy-6′-methylbenzoyl)-5-methyl-1,3-cyclohexanedione (4). To a stirred solution of 2-methoxy-6-methylbenzoic acid (**5**) (498 mg, 3 mmol) in dry benzene (10 mL), thionyl chloride (0.43 mL, 6 mmol) and a drop of dimethylformamide were added. The resulting mixture was then refluxed for 6 h. After completion of the reaction (checked by paper chromatography), benzene was removed by distillation to leave the acid chloride as a brownish semisolid. IR (neat): 1800 cm^{-1} (acid chloride). Acid chloride obtained above was used for further reaction without purification. To a stirred solution of the acid chloride (554 mg, 3 mmol) and cyanotrimethylsilane (0.48 mL, 3.6 mmol) in dry dichloromethane (5 mL) under nitrogen atmosphere was added stannic chloride (0.2 mL) at room temperature. The stirring was continued for a further 2 h. After the reaction, the mixture was poured into ice-cold water (10 mL) and extracted with dichloromethane. The combined dichloromethane layer was washed with water (20 mL) followed by brine (20 mL) and dried over sodium sulphate. Evaporation of the solvent under reduced pressure afforded crude cyanide **6** as a brown oil (335 mg, 85%). IR ($CHCl_3$): 2150, 1680 cm^{-1}.

Triethylamine (1 mL) was added to a stirred solution of the above acyl cyanide **6** (472 mg, 2.7 mmol) and 5-methyl-cyclohexane-1,3-dione (**7**) (378 mg, 3 mmol) in dry acetonitrile (5 mL) at room temperature and stirring was continued overnight. After completion of the reaction, acetonitrile was evaporated and the mixture was poured into ice-cold 1 N HCl (10 mL). The reaction mixture was then extracted with dichloromethane and the combined organic layer was washed with water (20 mL) followed by brine (20 mL) and dried over sodium sulphate. Evaporation of the solvent and purification by column chromatography over silica gel (eluent 20% ethyl acetate in petroleum ether) afforded the triketone **4** (574 mg, 70%) as a pale yellow thick oil. ^1H NMR ($CDCl_3$, 200 MHz): δ 1.12 (d, J=5.8 Hz, 3H), 2.10–2.88 (m including singlet for benzylic methyl at δ 2.17, 9H), 3.72 (s, 3H, $-OCH_3$), 6.65–6.90 (m, 2H, aromatic), 7.15–7.35 (m, 1H, aromatic). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.25, 21.05, 26.86, 41.09, 46.53, 55.97, 108.50, 114.79, 122.91, 130.04, 135.08, 155.96, 193.56 (C=O), 197.16 (C=O), 199.04 (C=O). Mass (*m*/*z*): 274 (M^+, 5), 259 (M−15, 8), 243 (90), 166 (50), 148 (100). Anal. calcd for $C_{16}H_{18}O_4$: C 70.06, H 6.60; found C 70.00, H 6.61.

2.2. Aromatization of triketone 4

The triketone **4** (274 mg, 1 mmol) was taken in glacial acetic acid (3 mL) in a round bottom flask attached with a short path condenser under argon atmosphere. To this were added mercuric acetate (956 mg, 3 mmol) and sodium acetate (246 mg, 3 mmol). The reaction mixture was heated at 120–125 °C so that the clear liquid turned to a voluminous precipitate that was again redissolved to give a brown coloured liquid with separation of mercury (2–3 h). The mixture was cooled and then 1 N HCl (5 mL) was added and allowed to boil for 30 min. Ethyl acetate was added after cooling and the mixture was filtered through a pad of Celite. The ethyl acetate layer was separated, washed with brine (10 mL), dried over sodium sulphate and concentrated in vacuo. TLC of the reaction mixture indicated the formation of two compounds. Evaporation of the solvent and purification by column chromatography over silica gel (eluent 10–20% ethyl acetate in petroleum ether) afforded the xanthone **9** (96 mg, 40%) and the required compound **8** (55 mg, 20%).

2.2.1. 2,6-Dihydroxy-4-methylphenyl 2′-methoxy-6′-methylphenyl ketone (8). Pale yellow solid, mp 270–273 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 2.22 (s, 3H, Ar-CH_3), 2.25 (s, 3H, Ar-CH_3), 3.76 (s, 3H, −OMe), 6.26 (s, 2H, aromatic), 6.86 (d, J=8 Hz, 1H, aromatic), 6.92 (d, J=8 Hz, 1H, aromatic), 7.36 (t, J=8 Hz, 1H, aromatic). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 18.71, 22.24, 56.02, 108.49, 109.45 (2C), 123.52 (2C), 128.59, 131.57 (2C), 136.02, 149.88 (2C), 155.68, 198.18 (C=O). Mass (*m*/*z*): 272 (M^+).

2.2.2. 1-Hydroxy-3,8-dimethyl-xanthen-9-one (9). Pale yellow solid, mp 146–149 °C (lit.[9] mp 149–151 °C). ^1H NMR ($CDCl_3$, 200 MHz): δ 2.41 (s, 3H, Ar-CH_3), 2.89 (s, 3H, Ar-CH_3), 6.55 (s, 1H, aromatic), 6.65 (s, 1H, aromatic), 7.07 (d, J=8 Hz, 1H, aromatic), 7.25 (d, J=8 Hz, 1H, aromatic), 7.52 (t, J=8 Hz, 1H, aromatic), 12.86 (s, 1H, −OH). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 22.55, 23.30, 106.76, 107.50, 110.99, 115.79, 118.99, 126.67, 134.10, 141.66, 148.13, 155.36, 157.35, 161.61, 183.92 (C=O). Mass (*m*/*z*): 240 (M^+, 100), 222 (12), 211 (30).

2.3. 1-Methoxy-3,8-dimethyl-xanthen-9-one (10)

To the stirred solution of compound **9** (90 mg, 0.37 mmol) and potassium carbonate (76 mg, 0.55 mmol) in dry acetone (2 mL) was added dimethyl sulphate (52 mg, 0.40 mmol). The resulting reaction mixture was refluxed for 8 h. The acetone was then removed under reduced pressure and the residue was diluted with ice-cold water (5 mL) followed by extraction with ethyl acetate. The combined ethyl acetate layer was washed with water (5 mL), brine (5 mL) and dried over sodium sulphate. Evaporation of the solvent afforded the xanthone **10** as a white solid (81 mg, 85%), mp 169–171 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 2.45 (s, 3H, Ar-CH_3), 2.90 (s, 3H, Ar-CH_3), 4.01 (s, 3H, $-OCH_3$), 6.56 (s, 1H, aromatic), 6.81 (s, 1H, aromatic), 7.06 (d, J=7.2 Hz, 1H, aromatic), 7.24 (d, J=7.2 Hz, 1H, aromatic), 7.46 (t, J=7.2 Hz, 1H, aromatic). Mass (*m*/*z*): 254 (M^+, 100), 240 (70).

2.3.1. 2,6-Dimethoxy-4-methylphenyl 2′-methoxy-6′-methylphenyl ketone (3). A mixture of the compound **8** (54 mg, 0.2 mmol) and dimethyl sulphate (0.05 mL, 0.55 mmol) and potassium carbonate (100 mg, 0.72 mmol) in dry acetone (5 mL) was refluxed for 6 h. The acetone was then evaporated under reduced pressure and the residue was diluted with water (5 mL), extracted with ethyl acetate and concentrated to give the benzophenone **3** as a white solid (54 mg, 90%), mp 133–135 °C (lit.[2c] mp 132–133 °C). IR

($CHCl_3$): 1675 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 2.32 (s, 3H, Ar-CH_3), 2.34 (s, 3H, Ar-CH_3), 3.58 (s, 3H, $-OCH_3$), 3.66 (s, 6H, 2× $-OCH_3$), 6.35 (s, 2H, aromatic), 6.68 (d, J=8 Hz, 1H, aromatic), 6.79 (d, J=8 Hz, 1H, aromatic), 7.17 (t, J=8 Hz, 1H, aromatic). Mass (*m/z*): 300 (M^+, 15), 269 (100). Anal. calcd for $C_{18}H_{20}O_4$: C 71.99, H 6.70; found C 72.23, H 6.90.

2.3.2. 1-{(2,6-Dimethoxy-4-methyl)phenyl}hydroxy-methyl-2′-methoxy-6′-methylbenzene (13). *n*-Butyllithium (1.5 mL of a 1.4 M solution in hexane, 2.1 mmol) was added dropwise to a stirred solution of 3,5-dimethoxytoluene (**11**) (304 mg, 2 mmol) and TMEDA (0.31 mL, 2.1 mmol) in anhydrous THF (5 mL) at room temperature under argon atmosphere. The mixture was stirred for 5 h whereupon it was added to a solution of the aldehyde **12** (345 mg, 2.3 mmol) in anhydrous THF (5 mL) at 0 °C. The resulting light yellow solution was stirred at 0 °C for 2 h and at room temperature overnight (the colour changes from light yellow to dark brown). The reaction mixture was then quenched with a saturated solution of ammonium chloride, ice-cold water (5 mL) was added and extracted with ethyl acetate. The ethyl acetate layer was washed with water (10 mL), brine (10 mL) and dried over sodium sulphate. Evaporation of the solvent and purification by column chromatography over silica gel (eluent 15% ethyl acetate in petroleum ether) afforded alcohol **13** (423 mg, 70%) as yellow solid; mp 125–128 °C. IR ($CHCl_3$): 1580, 3450 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 2.30 (s, 3H, Ar-CH_3), 2.32 (s, 3H, Ar-CH_3), 3.75 (s, 6H, 2× $-OCH_3$), 3.78 (s, 3H, $-OCH_3$), 5.80 (d, J=10 Hz, 1H, exchanges with D_2O, $-OH$), 6.37 (s, 2H, aromatic), 6.43 (d, J=8.2 Hz, 1H, aromatic), 6.75 (d, J=8.2 Hz, 1H, aromatic), 7.07 (t, J=8.2 Hz, 1H, aromatic). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 19.96, 22.16, 56.16 (3C), 67.69, 105.99 (2C), 109.96, 117.13, 123.69, 127.36, 131.05, 137.61, 138.41, 158.40, 159.00 (2C). Mass (*m/z*): 302 (M^+, 25), 284 (85), 269 (60), 253 (40), 179 (100). Anal. calcd for $C_{18}H_{22}O_4$: C 71.50, H 7.32; found C 71.58, H 7.24.

2.3.3. 2,6-Dimethoxy-4-methylphenyl 2′-methoxy-6′-methylphenyl ketone (3). Manganese dioxide (1.3 g, 15 mmol) was added in portions to a stirred solution of the alcohol **13** (302 mg, 1 mmol) in anhydrous dichloromethane at room temperature and mixture was stirred overnight. The catalyst was removed by filtration through Celite and the residue was washed with dichloromethane. The filtrate was evaporated to provide the benzophenone **3** (270 mg, 90%) as white crystals; mp 133–135 °C (lit.[2c] 132–133 °C). The spectral data were identical to the product obtained by methylation of compound **8**.

2.3.4. 4-Carboxy-2,6-dimethoxyphenyl 2′-carboxy-6′-methoxyphenyl ketone (2). To a stirred solution of potassium permanganate (284 mg, 1.8 mmol) in water (3 mL) and pyridine (1 mL), a solution of compound **3** (180 mg, 0.6 mmol) in pyridine (2 mL) was added followed by water (1 mL) and a pinch of tetrabutylammonium bromide. The mixture was then heated at 100 °C. After 1 h further quantities of potassium permanganate (in lots of 284 mg, 1.8 mmol) were added at intervals of 1 h until a total of 23.4 equiv. had been added. The reaction mixture was then filtered through Celite. The residue was washed with water (5 mL) and the filtrate was acidified with conc. HCl (5 mL). The aqueous solution was saturated with sodium chloride and extracted with ethyl acetate. The combined extracts were dried over sodium sulphate and evaporated to give dicarboxylic acid **2** as colourless solid (97 mg, 45%); mp 253–255 °C (lit.[2c] 253–256 °C). IR ($CHCl_3$): 1690, 3400 cm^{-1}. ^1H NMR (acetone d_6, 200 MHz): δ 3.76 (s, 3H, $-OCH_3$), 3.82 (s, 6H, 2× $-OCH_3$), 7.33 (d, J=8 Hz, 1H, aromatic), 7.38 (s, 2H, aromatic), 7.50 (d, J=8 Hz, 1H, aromatic), 7.57 (t, J=8 Hz, 1H, aromatic). Mass (*m/z*): 360 (M^+, 10), 342 (8), 315 (25), 299 (30), 285 (90), 209 (98), 195 (100). Anal. calcd for $C_{18}H_{16}O_8$: C 60.01, H 4.47; found C 60.07, H 4.60.

Acknowledgements

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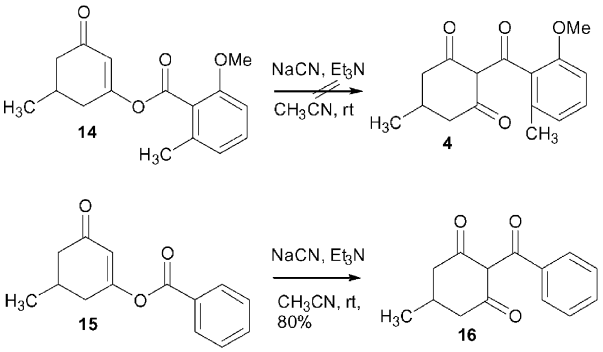
6. The cyanide catalyzed rearrangement of enol ester **14** under conditions reported by Burger and Montes[5] failed to give triketone **4**. However, when unsubstituted benzoate ester **15** was subjected to cyanide catalyzed rearrangement, it afforded triketone **16**



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