Radical-mediated cyclisation of δ-aryl-β-dicarbonyl compounds to β-tetralones [3,4-dihydronaphthalen-2(1*H*)-ones]

Joanne F. Jamie and Rodney W. Rickards*

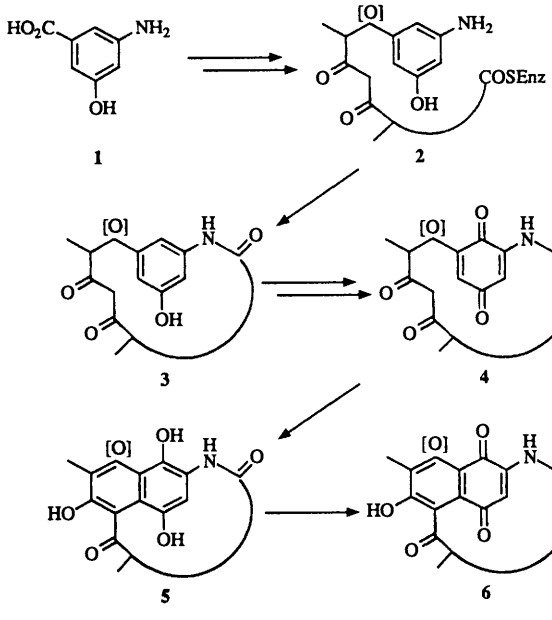
Research School of Chemistry, Australian National University, Canberra, ACT 0200, Australia

δ-Aryl-β-dicarbonyl compounds carrying electron-releasing groups in the aromatic ring undergo efficient radical-mediated oxidative cyclisation to β-tetralones in the presence of four equivalents of manganese(III) acetate in acetic acid. Secondary oxidation invariably results in acetoxylation at the benzylic α-position of the initially-formed β-tetralones. Use of the oxidant cerium(IV) ammonium nitrate in methanol affords the corresponding α-methoxylated β-tetralones. The α-acetoxy-α-acyl-β-tetralones, but not their α-acetoxy-α-alkoxycarbonyl analogues, are aromatised in high yield on treatment with alkaline silica gel, providing an effective synthetic entry to appropriately substituted β-naphthols. The possible involvement of such radical-mediated intramolecular annulations of δ-aryl β-diketone intermediates in the biosynthetic formation of the second carbocyclic ring of the naphthalenoid ansamycin antibiotics is discussed in relation to the previously proposed Michael addition mechanism.

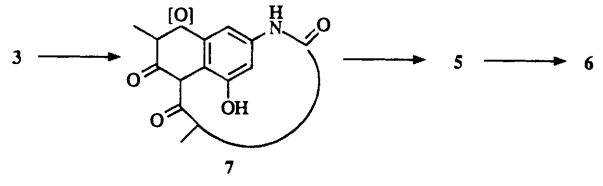
The macrocyclic lactam antibiotics of the ansamycin group display a broad spectrum of biological activity, various representatives being effective against bacteria, fungi, viruses, protozoa and some cancers.[1] Rifampicin, a semisynthetic derivative of the natural antibiotic rifamycin SV, is widely used in the chemotherapy of the mycobacterial infections tuberculosis and leprosy. The biosynthesis of these antibiotics in producing bacteria of the genera *Streptomyces* and *Nocardia* has been studied extensively,[2] and stems from the key biosynthetic precursor 3-amino-5-hydroxybenzoic acid (AHB) **1**.[3,4] This unusual non-protein amino acid initiates the enzymic formation of the polyketide skeleton, which is extended by the sequential addition of propionate and acetate units, with appropriate adjustment of functionality (Scheme 1).[5] Upon completion of the skeleton **2**, the terminal carboxy group acylates the amino function of the initiating AHB unit to form the characteristic lactam system **3**. While this process leads directly to ansamycins of the benzenoid **3** (and benzoquinonoid **4**) subgroup, those of the naphthalenoid (and naphthoquinonoid) subgroup raise the problem as to how their second carbocyclic ring is formed.

All known ansamycins of the naphthalenoid subgroup carry oxygen functionality at the position *para* to the original phenolic hydroxy group of AHB. Accordingly, we have suggested that their biosynthesis proceeds by oxidation of a phenolic lactam (**3**, Scheme 1) to a benzoquinonoid intermediate **4**.[5] Michael addition of an unreduced β-dicarbonyl system, already appropriately sited in the ansa chain, then closes the second carbocyclic ring. The resulting naphthoquinols **5**, or their naphthoquinonoid oxidation products **6**, would then carry nuclear substituents typical of the ansamycin antibiotics. Biomimetic synthesis has provided circumstantial evidence for such a biosynthetic pathway.[5,6]

The present work investigates an alternative to this Michael addition pathway from benzenoid ansamycins to their naphthalenoid counterparts (Scheme 2). This alternative involves



Scheme 1 Proposed biosynthetic route to naphthalenoid ansamycins *via* Michael addition



Scheme 2 An alternative biosynthetic route to naphthalenoid ansamycins *via* radical cyclisation

radical-mediated cyclisation of the β-dicarbonyl system present in the ansa bridge onto the phenolic ring of the lactam **3**, to form the second carbocyclic ring of the tetralone intermediate **7**. Oxidation *para* to the original phenolic hydroxy group of AHB would then follow, rather than precede, carbocyclic ring closure, to yield the appropriately substituted naphthalenoid **5** and naphthoquinonoid **6** ansamycins.

Prior to commencement of the present work, the only examples of the intramolecular addition of β-dicarbonyl radicals to aromatic rings were those reported by Kende and coworkers.[7] Oxidation with alkaline potassium hexacyanoferrate(III) or hexachloroiridate of phenols carrying carbon chains terminated by enolisable carbocyclic or heterocyclic β-diketones gave five- and six-membered annulation products, generally in moderate to good yields. Acyclic β-diketones were not studied by these authors, however, while acyclic β-keto esters and malonates failed to cyclise.[7b] In contrast, olefinic

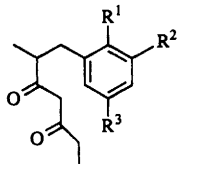
β-keto esters,[8,9] olefinic malonates[10] and several olefinic β-diketones[8c,9] had been cyclised effectively with the one-electron oxidant manganese(III) triacetate. We therefore examined the application of this reagent to the oxidative cyclisation of aromatic β-dicarbonyl systems, as a biomimetic model for the crucial cyclisation of the phenolic lactam **3** to the tetralone **7** in the alternative biosynthetic route to naphthalenoid ansamycins (Scheme 2). During the course of this study, other authors have described the use of manganese(III) acetate for the oxidative cyclisation of acyclic β-keto esters[11] and malonates,[12] and two carbocyclic β-diketones,[13] directly onto aromatic rings. Cerium(IV) and iron(III) salts have also been reported for this purpose with β-keto esters[11] and malonates,[14] respectively.

Results and discussion

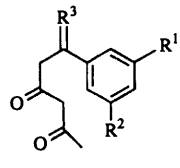
Synthesis of the δ-aryl-β-dicarbonyl compounds

The δ-aryl β-diketones **8**, **9** and **11**–**13** and the δ-aryl-β-keto ester **16** were synthesised in good to excellent yields by alkylation of the dilithio-enolates of heptane-3,5-dione, pentane-2,4-dione, and ethyl acetoacetate with the appropriately substituted benzyl bromides. Hydrogenolysis of the benzyl ether **9** afforded the phenolic β-diketone **10**. The δ-hydroxy-δ-aryl β-diketone **14** and its β,δ-triketone analogue **15** were prepared in high yields by aldol and Claisen reactions, respectively, with the dilithio-enolate of pentane-2,4-dione. NMR Spectroscopy indicated that the diketones **8**–**14** and the triketone **15** all existed predominantly in H-bonded enolic forms, in contrast to the non-enolised *keto* ester **16**.

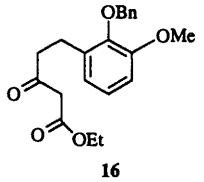
The required 2-benzyloxy-3-methoxy-, 3,5-dimethoxy- and 3,5-dibenzyloxy-benzyl bromides **17**, **18** and **19** were in turn prepared efficiently from the readily available *o*-vanillin, 3,5-dimethoxybenzaldehyde and 3,5-dihydroxybenzoic acid, *via* bromination of the respective benzyl alcohols. Although bromination of 2-benzyloxy-3-methoxybenzyl alcohol could be effected satisfactorily with *N*-bromosuccinimide in the presence of dimethyl sulfide,[15] the same reagents caused selective ring bromination with the more electrophilic 3,5-dibenzyloxybenzyl alcohol. Thus one equivalent of the reagents gave 2-bromo-3,5-dibenzyloxybenzyl alcohol **21** in 81% yield, while two equivalents gave 2-bromo-3,5-dibenzyloxybenzyl bromide **22** in 66% yield. The use of carbon tetrabromide in the presence of triphenylphosphine, however, afforded the desired 3,5-dibenzyloxybenzyl bromide **19** in 92% yield. 3-Acetylamino-5-benzyloxybenzyl bromide **20** was synthesised from methyl 3-amino-5-hydroxybenzoate[16] *via* selective benzylation of the phenolate anion.[6]



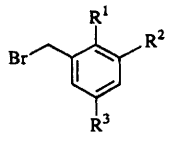
	R^1	R^2	R^3
8	H	H	H
9	OBn	OMe	H
10	OH	OMe	H
11	H	OBn	OBn
12	H	NHAc	OBn



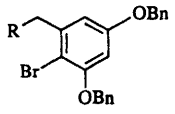
	R^1	R^2	R^3
13	OMe	OMe	H_2
14	OMe	OMe	H, OH
15	OBn	OBn	=O



16



	R^1	R^2	R^3
17	OBn	OMe	H
18	H	OMe	OMe
19	H	OBn	OBn
20	H	NHAc	OBn



21 R = OH
22 R = Br

Oxidative cyclisation of the δ-aryl-β-dicarbonyl compounds

The δ-aryl-β-dicarbonyl compounds **8**–**16** were treated under standardised conditions with 4.2 equiv. of anhydrous manganese(III) acetate in acetic acid at room temperature for 22 h under argon. The yields of the resulting β-tetralones, and of β-naphthols when formed, are shown in Table 1. In all cases the tetralones isolated were acetoxylated at the benzylic position. This results from secondary oxidation of the initially-formed enolisable tetralones by the excess of manganese(III) acetate, and subsequent reaction with the solvent. Similar benzylic oxidations have been observed by Citterio and co-workers during cyclisation of β-keto esters onto aromatic rings.[11] The naphthols arise by elimination of acetic acid from these tetralones.

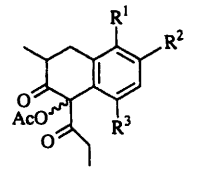
The δ-phenyl β-diketone **8**, the aryl ring of which bears no other substituents, failed to react under the standard conditions. The reaction was still substantially incomplete after the same time at 60 °C, but coupled gas chromatography–mass spectrometry (GC–MS) indicated the presence of small amounts of the two diastereomeric tetralones **23** (*ca.* 9%), the naphthol **32** (*ca.* 6%) and 2-methyl-3-phenylpropanoic acid (5%), together with starting diketone (46%) and much uncharacterisable material. The naphthol probably arises in this case by thermal aromatisation of the acetoxylated tetralones during the oxidation reaction. The unreactivity of this diketone **8** is in accord with the work of Aidhen and Narasimhan on carbocyclic β-diketones,[13] and of Citterio and co-workers on acyclic β-keto esters[11] and malonates,[12] who showed that manganese(III)-mediated cyclisation is greatly facilitated by the presence of electron-releasing groups on the aromatic ring, especially when *meta* to the dicarbonyl substituent. With δ-aryl β-diketones in particular, the cyclisation process is effective only when the ring is sufficiently electron-rich, in agreement with the electrophilic nature of the radical. When this is not the case, alternative oxidation and oligomerisation processes dominate.

The remaining δ-aryl-β-dicarbonyl compounds **9**–**16** all carry two electron-releasing groups on the aromatic ring, at least one and sometimes both of which are *meta* to the dicarbonyl substituent. All these substrates under the standard oxidation conditions gave good (66%) to excellent (93%) yields of cyclisation products, except for the phenolic β-diketone **10** and the β,δ-triketone **15**, from which no cyclisation products could be isolated.

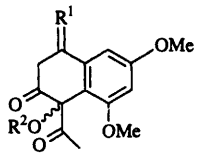
Table 1 Radical mediated cyclisation of δ-aryl-β-dicarbonyl compounds **8**–**16**[a]

Substrate	Tetralone	Yield (%)	Naphthol	Yield (%)
8	**23**	0 (9)[b]	**32**[c]	0 (6)[b]
9	**24**	56	**33**[d]	11
10	**25**	0	—	0
11	**26**	93	**34**	0
12	**27**	93	**35**	0
13	**28**	71	—	0
14	**29**	95	—	0
15[e]	—	—	**38**	0
16	**36**	81	**41**	0

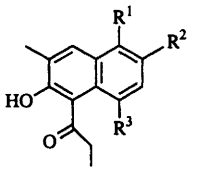
[a] Standardised reaction conditions at room temperature. [b] The same reaction conditions, but at 60 °C. [c] Probably formed thermally during the reaction. [d] Probably formed during gravity chromatography. [e] The initial cyclisation product would be the naphthol tautomer **38**.



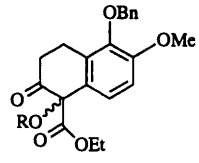
	R^1	R^2	R^3
23	H	H	H
24	OBn	OMe	H
25	OH	OMe	H
26	H	OBn	OBn
27	H	NHAc	OBn



	R^1	R^2
28	H_2	Ac
29	H, OH	Ac
30	H_2	Me
31	H_2	H



	R^1	R^2	R^3
32	H	H	H
33	OBn	OMe	H
34	H	OBn	OBn
35	H	NHAc	OBn



36 R = Ac
37 R = H

The 2,3-dialkoxyphenyl diketone **9** yielded the diastereomeric tetralones **24** and the aromatised naphthol **33** in 56% and 11% yield, respectively, together with 21% recovery of starting material. Aromatisation in this case may have occurred through extended contact with silica gel during gravity chromatography, since the use of dry flash chromatography in subsequent reactions appeared to avoid such products. Repetition of the reaction with 2.2 equiv. of hydrated manganese(III) acetate[17] under air, not argon, afforded 3-(2-benzyloxy-3-methoxyphenyl)-2-methylpropanoic acid in 83% yield. This acid probably arises from interception of the initially-formed β-dicarbonyl radical by molecular oxygen and decomposition of the resulting hydroperoxide,[18] and its structure was confirmed by synthesis from propanoic acid.

The β-keto ester **16**, carrying the same 2,3-dialkoxyphenyl substituent as the β-diketone **9**, cyclised smoothly under standard conditions to the acetoxylated tetralone **36** in 81% yield. In contrast to the diketone, however, the keto ester when reacted with 2.2 equiv. of hydrated manganese(III) acetate in air gave some tetralone (14%), together with the corresponding oxidative cleavage product 3-(2-benzyloxy-3-methoxyphenyl)propanoic acid (50%).

The 2-hydroxy-3-methoxyphenyl diketone **10** corresponding to the dialkoxyphenyl diketone **9** gave intractable material under the standard oxidation conditions, while some starting material (7%) only was isolated on halving the quantity of oxidant. The tetralones **25** could not be detected. Manganese(III) acetate is known to oxidise phenols to phenoxyl radicals, resulting in oligomerisation and polymerisation,[17,19] and we are unaware of any successful cyclisations of phenolic β-dicarbonyl compounds with this reagent.

High yields of the acetoxylated tetralones **26–28** resulted from oxidation of the 3,5-disubstituted phenyl β-diketones **11–13** under standard conditions, regardless of the extent of methyl substitution around the diketone, the nature of the aryl ether substituents, or the replacement of an ether group by an acetamide (*cf.* Table 1). As expected for electrophilic substitution of an acetamide, cyclisation onto the asymmetrically substituted phenyl ring of the diketone **12** occurred regiospecifically *para* to the acetamide function, affording the tetralones **27** in 93% yield. Oxidative cyclisation to the tetralones **29** was also unaffected by the presence of the benzylic alcohol function in the substrate **14**.

In contrast, however, the δ-aryl β,δ-triketone **15** yielded uncharacterisable material together with trace amounts of 3,5-dibenzyloxyacetophenone and 3,5-dibenzyloxybenzoic acid. These fragments presumably arise from oxidative cleavage[18] at the β- and δ-carbonyl groups, the former with decarboxylation of the resulting β-keto acid. Cyclisation in this case would yield an initial tetralone which, without acetoxylation, would tautomerise rapidly to the dihydroxynaphthalene **38**. Since such a naphthol would be expected to oxidise readily in the presence of the excess of manganese(III) acetate,[17,19,20] the reaction was repeated using 2.2 rather than 4.2 equiv. of oxidant, but with the same result. Consequently, it is unclear whether the failure of this reaction is due to the presence of an alternative diketone site for radical formation, to electronic deactivation of the aryl ring, or to oxidative decomposition of the initial cyclisation product.

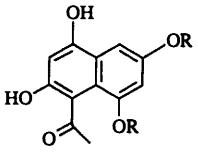
During the course of this work, Citterio and co-workers reported cerium(IV) ammonium nitrate to be more efficient than manganese(III) acetate for the oxidative cyclisation of δ-aryl-β-keto esters, giving moderate yields of tetralones under milder conditions without the need for a correctly *meta*-positioned electron releasing group on the aromatic ring.[11] The 3,5-dimethoxyphenyl diketone **13** was therefore subjected to oxidation with the cerium(IV) reagent in methanol, for comparison with the manganese(III) process above. Provided that the crude reaction extract was washed with aqueous sodium hydrogen carbonate before concentration, in order to remove traces of the nitric acid produced in the reaction, the methoxylated tetralone **30** could be obtained in 80% yield. If the washing step was omitted, varying yields of this tetralone **30** (26–41%) and its hydroxylated analogue **31** (17–36%) were obtained, and in lower total yield (*ca.* 60%). The methoxylated tetralone **30**, like the acetoxylated tetralones from the manganese(III) reactions, arises from secondary oxidation at the benzylic position of the initially-formed enolisable tetralone.[11] When concentrated from solution containing a trace of nitric acid, it was partially converted into the hydroxylated tetralone **31** and decomposed further on standing.

Structure and aromatisation of the tetralones

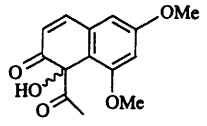
The tetralones containing two stereogenic centres, **23**, **24**, **26**, **27** and **29**, were formed as mixtures of two diastereomers in approximately 1 : 1 ratio as measured by ^{1}H NMR spectroscopy (or GC–MS for the tetralones **23**), except for the acetamidotetralones **27** where the diastereomer ratio was 1.3 : 1. Separation of these mixtures was not attempted, except in the cases of the 6,8-dibenzyloxytetralones **26** and the hydroxytetralones **29** where dry flash chromatography afforded individual diastereomers. The structures of all tetralones were confirmed by spectroscopic and analytical data. Where benzyl ether groups were present in the 5 or 8 positions of the tetralones, their benzyloxy methylene protons invariably showed diastereotopic NMR behaviour, resulting either from restricted rotation or the presence of a stereogenic centre in the adjacent hydroaromatic ring. Thus the 6,8-dibenzyloxytetralone diastereomers **26** each showed two distinct benzyloxy methylene systems, one a two-proton singlet, the second an AB system with J *ca.* 11 Hz. This characteristic NMR feature confirmed the two tetralones formed on oxidative cyclisation of the diketone **12** as the expected 6-acetamido-8-benzyloxy diastereomers **27**, rather than the alternative 8-acetamido-6-benzyloxy regioisomers.

The acetoxylated tetralones tended to aromatise to the corresponding naphthols during extended chromatography on silica gel, as mentioned earlier for the tetralones **24**. Initial attempts to separate the diastereomeric 6,8-dibenzyloxytetralones **26**, by gravity chromatography on neutral silica gel, resulted in complete conversion into the naphthol **34**. The use of silica gel buffered at pH 4 or 10, or Florisil, also caused substantial aromatisation. For preparation of the naphthol itself, it was convenient to stir the crude product mixture from oxidative cyclisation of the 3,5-dibenzyloxyphenyl β-diketone **11** with

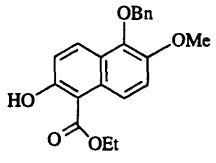
silica gel buffered at pH 10 in dichloromethane. This afforded the naphthol **34** in 68% overall yield. Similar treatment of the acetoxylated tetralones **24** and **27** gave the naphthols **33** and **35** in 81 and 80% yields. In contrast, the attempted elimination with basic silica gel of acetic acid from the hydroxytetralones **29**, in order to obtain the dihydroxynaphthalene **39**, resulted only in dehydration and hydrolysis to the naphthalenone **40** in 77% yield. The acetoxylated tetralone ester **36** partially aromatised to the naphthol **41** (20%) under these conditions, but hydrolysis of the acetate to form the hydroxylated tetralone **37** in 75% yield was favoured. Citterio and co-workers have aromatised differently substituted tetralone esters by adsorption on silica gel and heating in refluxing benzene.[11]



38 R = Bn
39 R = Me



40



41

Conclusions

The present work establishes an efficient radical-mediated oxidative cyclisation of δ-aryl-β-dicarbonyl compounds to β-tetralones. The annulation process promoted by manganese(III) acetate in acetic acid requires the presence of electron-releasing groups on the aromatic ring. The cyclisation is invariably followed by secondary oxidation and attack by solvent at the benzylic α-position of the initially-formed β-tetralones. The resulting α-acetoxy-α-acyl-β-tetralones, but not their α-alkoxycarbonyl analogues, can be readily aromatised to β-naphthols. The two-stage sequence constitutes an effective synthetic entry to appropriately substituted naphthols.

This cyclisation of δ-aryl β-diketones to β-tetralones (excluding the subsequent acetoxylation) also suggests the viability of a radical-mediated mechanism for the possible biosynthetic conversion of ansamycin antibiotics of the benzenoid group into those of the naphthalenoid group (Scheme 2). In particular, the model cyclisation in high yield of the diketone **12** to the tetralone **27** parallels closely the hypothetical biosynthetic cyclisation of the macrocyclic lactam **3** to the tetralone **7**. The model and natural systems carry similar relevant functionality, apart from the question of the undefined oxidation level at the benzylic position of the lactam **3**. The radical-mediated cyclisation is clearly viable with a methylene or secondary alcohol group at this site, as shown by the diketones **8**–**13** and **14**, respectively. Either functionality in the lactam intermediate **3** could lead to the 8-deoxy naphthalenoid ansamycins, although the former is biosynthetically less likely. Naphthalenoid ansamycins carrying an 8-hydroxy group, however, are known to be derived from intermediates that retain carboxyl oxygen of the primary precursor AHB (**1**), presumably at the carbonyl oxidation level.[4] We have been unable to demonstrate radical-mediated cyclisation in a model δ-aryl β,δ-triketone of this type (**15**), and would therefore have to invoke specific enzyme control of the process in this case. This limitation, together with the fact that all naphthalenoid ansamycins known to date have oxygen introduced at the 1-position, leads us to favour biosynthetic annulation by the previously proposed Michael addition route (Scheme 1).

Experimental

General procedures

Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. Ultraviolet and visible spectra were recorded on Hewlett-Packard 8450A or Varian DMS 90 spectrophotometers, infrared spectra on Perkin-Elmer 683 or 1800 (FT) spectrophotometers. NMR Spectra were recorded on JEOL JNM FX 200, Varian XL 200E, Varian Gemini 300, and Varian VXR-500 spectrometers. All NMR spectra unless otherwise indicated were recorded in $CDCl_3$ which had been left over potassium carbonate to remove acid and water, using tetramethylsilane or the solvent signal ($CHCl_3$ δ 7.26) as internal reference. Coupling constants (J) are given in Hz. Electron impact and chemical ionisation (CI, NH_3) mass spectra were recorded on a VG Micromass 7070F spectrometer. The molecular ion (M^+), if present, and peaks with intensity greater than 20% of the base peak are reported, unless additional data are pertinent. High resolution mass spectra (HRMS) were obtained from an AEI MS 902 instrument. Gas liquid chromatography–mass spectroscopy (GC–MS) was performed on a Hewlett-Packard 5890 gas chromatograph with a 12 m × 0.2 mm HP-1 capillary column coupled to a Hewlett-Packard 5970 mass spectrometer employing electron impact ionisation. Microanalyses were carried out by the Australian National University Microanalytical Service.

Where necessary, solvents and reagents were purified and dried according to the procedures of Perrin and Armarego.[21] Most organic solvents were distilled before use. Petroleum spirit refers to the fraction with bp 40–60 °C. Manganese(III) acetate dihydrate was obtained from Aldrich, cerium(IV) ammonium nitrate from Ajax Chemicals (AR grade). Anhydrous manganese(III) acetate and cerium(IV) ammonium nitrate were prepared by drying over P_2O_5, *in vacuo*, for at least 24 h. The molarity of solutions of butyllithium in hexane was determined by titration against 2,5-dimethoxybenzyl alcohol according to the method of Winkle and co-workers.[22] All organic extracts were dried over anhydrous magnesium sulfate, unless otherwise indicated, and solvents removed *in vacuo* on a rotary evaporator.

Gravity and flash chromatography[23] were carried out using 230–400 mesh silica gel. Dry flash chromatography[24] was performed using Merck 60 PF_{254} (7747) or 60 HF_{254} (7739) silica gel. For thin layer chromatography, 0.25 mm Merck silica gel 60 F_{254} plates were used for analytical purposes and 0.5 mm or 1 mm for preparative work. Thin layer chromatograms were visualised under UV light, or by spraying with 13% vanillin in sulfuric acid, followed by heating at 200 °C.

Acid-washed silica gel was prepared by stirring a slurry of silica gel (100 g, 230–240 mesh) and hydrochloric acid (0.1 M, 500 ml) for 30 min. The silica gel was collected by filtration, washed with water until the filtrate was at the required pH, and then activated by heating at 105–110 °C for 16 h. Base-washed silica gel was prepared by stirring silica gel (100 g, 230–240 mesh) with aqueous ammonia (25%, 500 ml) for 30 min, followed by treatment as above.

Preparation of dilithio-enolates

Dilithio-enolates (10.0 mmol) were prepared by the fairly rapid dropwise addition of the dicarbonyl compounds (10.0 mmol) to vigorously stirred solutions of lithium diisopropylamide (21.0 mmol) or lithium 2,2,6,6-tetramethylpiperidide (21.0 mmol) (prepared at 0 °C from equimolar quantities of butyllithium and diisopropylamine or 2,2,6,6-tetramethylpiperidine) in dry THF (30–40 ml) at 0 °C. The colourless solutions were maintained at that temperature for 45 min before use.

2-Methyl-1-phenylheptane-3,5-dione 8

Benzyl bromide (1.0 g, 5.8 mmol) in dry tetrahydrofuran (THF) (20 ml) was added to a solution of dilithioheptane-3,5-dione (6.0 mmol) in THF (15 ml) (prepared from lithium diisopropylamide and heptane-3,5-dione) under argon at −20 °C. The solution was then equilibrated to room temperature and stirred for 1 h. Work-up as for the diketone **9** afforded an orange oil, which was purified by flash chromatography (hexane–dichloromethane, 1:1) to give *2-methyl-1-phenylheptane-3,5-dione* **8** (1.0 g, 80%) as a pale yellow oil (Found: C, 77.2; H, 8.4. Calc. for $C_{14}H_{18}O_2$: C, 77.0; H, 8.3%); ν_{max}(film)/cm^{-1} 2970, 1610, 1455, 695; δ_H(200 MHz) 7.34–7.10 (m, 5 H, Ph), 5.40 (s, 0.9 H, 4-H of the enolic form), 3.44 (s, 0.2 H, 4-H_2 of the keto form), 3.11–2.90 (m, 1 H, 1-H), 2.72–2.50 (m, 2 H, 1-H and 2-H), 2.27 (q, *J* 7.6, 2 H, CH_2CH$_3$), 1.20–1.05 (m, 6 H, 2-CH$_3$ and CH$_2$CH_3 in keto and enolic forms); δ_C(50.3 MHz) (enolic form) 196.5 (s, CO), 196.2 (s, CO), 139.5 (s, ArC-1), 128.9 (d, 2 × ArCH), 128.2 (d, 2 × ArCH), 126.1 (d, ArC-4), 97.5 (d, C-4), 43.7 (d, C-2), 39.5 (t, C-1), 31.1 (t, C-6), 16.6 (q, 2-CH$_3$), 9.0 (q, C-7); *m/z* 218 (M$^+$, 6%), 99 (CH$_3$CH$_2$CO-CH$_2$CO$^+$, 100), 91 (C$_7$H$_7^+$, 81), 57 (CH$_3$CH$_2$CO$^+$, 31).

1-(2-Benzyloxy-3-methoxyphenyl)-2-methylheptane-3,5-dione 9

The benzyl bromide **17** (0.20 g, 0.65 mmol) in dry THF (4 ml) was added dropwise to a solution of dilithioheptane-3,5-dione (0.80 mmol) in THF (4 ml) (prepared from lithium diisopropylamide and heptane-3,5-dione) at −30 °C under argon. The solution was then allowed to equilibrate to room temperature, and after 1 h was quenched with 20% aqueous sodium dihydrogen orthophosphate and extracted with ethyl acetate. The extracts were washed with saturated aqueous ammonium chloride, dried (Na_2SO_4) and concentrated to provide a yellow oil. Flash chromatography of the oil (pentane–dichloromethane, 1:1) yielded 1-*(2-benzyloxy-3-methoxyphenyl)-2-methylheptane-3,5-dione* **9** (0.21 g, 91%) as a pale yellow viscous oil (Found: C, 74.5; H, 7.2. Calc. for $C_{22}H_{26}O_4$: C, 74.5; H, 7.4%); ν_{max}(film)/cm^{-1} 1710, 1600, 1585, 1478, 1460, 1273, 1082, 750; δ_H(200 MHz) 15.50 (br s, 0.9 H, OH), 7.60–7.30 (m, 5 H, OCH$_2$*Ph*), 7.05–6.70 (m, 3 H, Ar 4-H, Ar 5-H and Ar 6-H), 5.32 (s, 0.9 H, 4-H of the enolic form), 5.03 (s, 2 H, OCH_2Ph), 3.90 (s, 3 H, OCH$_3$), 3.36 (d, *J* 2.2, 0.2 H, 4-H_2 of the keto form), 3.05–2.90 (m, 1 H, 1-H), 2.75–2.60 (m, 2 H, 1-H and 2-H), 2.24 (q, *J* 7.6, 2 H, CH_2CH$_3$), 1.08 (t, *J* 7.6, 3 H, CH$_2$CH_3), 1.06 (d, *J* 6.8, 3 H, 2-CH$_3$); δ_C(50.1 MHz) (enolic form) 197.0 (s, CO), 195.5 (s, CO), 152.7 (s, ArC-3 or ArC-2), 146.8 (s, ArC-2 or ArC-3), 138.0 (s, Ph), 133.7 (s, ArC-1), 128.3 (d, Ph), 128.2 (d, Ph), 128.0 (d, Ph), 123.7 (d, ArC-5 or ArC-6), 122.8 (d, ArC-6 or ArC-5), 110.8 (d, ArC-4), 97.6 (d, C-4), 74.5 (t, OCH$_2$), 55.7 (q, OCH$_3$), 42.7 (d, C-2), 34.7 (t, C-1), 31.5 (t, C-6), 16.9 (q, 2-CH$_3$), 9.6 (q, C-7); *m/z* 354 (M$^+$, 2%), 99 (CH$_3$CH$_2$COCH$_2$CO$^+$, 36), 91 (C$_7$H$_7^+$, 100), 57 (CH$_3$CH$_2$CO$^+$, 62).

1-(2-Hydroxy-3-methoxyphenyl)-2-methylheptane-3,5-dione 10

The diketone **9** (50 mg, 0.14 mmol) in ethanol (10 ml) was hydrogenated over 10% palladium on charcoal (20 mg) until 1 mol equiv. had been absorbed. The catalyst was removed by vacuum filtration through a small plug of acid-washed silica gel and the filtrate was evaporated to dryness. The crude product was purified by gravity chromatography (acid-washed silica gel; increasing polarity from pentane to dichloromethane) to give 1-*(2-hydroxy-3-methoxyphenyl)-2-methylheptane-3,5-dione* **10** (26 mg, 70%) as a pale yellow oil (Found: C, 68.3; H, 7.9. Calc. for $C_{15}H_{20}O_4$: C, 68.2; H, 7.6%); ν_{max}(film)/cm^{-1} 3450, 2975, 2940, 1595, 1480, 1270, 1080; δ_H(200 MHz) 6.77–6.59 (m, 3 H, Ar 4-H, Ar 5-H and Ar 6-H), 5.82 (br s, 1 H, OH), 5.47 (s, 0.85 H, 4-H of the enolic form), 3.87 (s, 3 H, OCH$_3$), 3.55 (s, 0.30 H, 4-H_2 of the keto form), 3.0 (m, 1 H, 1-H), 2.80–2.60 (m, 2 H, 1-H and 2-H), 2.28 (q, *J* 7.6, 2 H, CH_2CH$_3$), 1.15–0.90 (m, 6 H, 2-CH$_3$ and CH$_2$CH_3 in keto and enolic forms; δ_C(50.3 MHz) (enolic form) 197.6 (s, CO), 195.5 (s, CO), 146.3 (s, ArC-3 or ArC-2), 143.7 (s, ArC-2 or ArC-3), 125.5 (s, ArC-1), 123.1 (d, ArCH), 119.1 (d, ArCH), 108.7 (d, ArCH), 97.6 (d, C-4), 55.9 (q, OCH$_3$), 42.3 (d, C-2), 34.0 (t, C-1), 31.4 (t, C-6), 17.2 (q, 2-CH$_3$), 9.6 (q, C-7); *m/z* 264 (M$^+$, 23%), 192 (M$^+$ − CH$_3$CH$_2$COHCH$_2$, 30), 164 (52), 137 (ArCH$_2^+$, 100), 99 (CH$_3$CH$_2$COCH$_2$CO$^+$, 57), 57 (CH$_3$CH$_2$CO$^+$, 48).

1-(3,5-Dibenzyloxyphenyl)-2-methylheptane-3,5-dione 11

The benzyl bromide **18** (0.61 g, 1.6 mmol) in dry THF (10 ml) was added dropwise to dilithioheptane-3,5-dione (2.0 mmol) in THF (10 ml) (prepared from lithium diisopropylamide and heptane-3,5-dione) at −20 °C under argon. The mixture after equilibration to room temperature was stirred for 1 h. Work-up as for the diketone **9** gave a yellow oil, which was purified by flash chromatography (petroleum spirit–dichloromethane, 1:1) to provide 1-*(3,5-dibenzyloxyphenyl)-2-methylheptane-3,5-dione* **11** (0.30 g, 44%) as a colourless oil (Found: C, 78.1; H 7.2. Calc. for $C_{28}H_{30}O_4$: C, 78.1; H, 7.0%); ν_{max}(film)/cm^{-1} 1600, 1455, 1150, 695; δ_H(300 MHz) 7.50–7.30 (m, 10 H, 2 × OCH$_2$*Ph*), 6.46 (d, *J* 2.2, 1 H, Ar 4-H), 6.40 (d, *J* 2.2, 2 H, Ar 2-H and Ar 6-H), 5.46 (s, 0.85 H, 4-H of the enolic form), 4.97 (s, 4 H, 2 × OCH_2Ph), 3.40 (s, 0.30 H, 4-H_2 of the keto form), 3.00–2.84 (m, 1 H, 1-H), 2.61–2.50 (m, 2 H, 1-H and 2-H), 2.27 (q, *J* 7.6, 2 H, CH_2CH$_3$), 1.15–1.00 (m, 6 H, 2-CH$_3$ and CH$_2$CH_3 in keto and enolic forms); δ_C(50.3 MHz) (enolic form) 196.5 (s, CO), 195.9 (s, CO), 159.8 (s, ArC-3 and ArC-5), 141.9 (s, ArC-1), 136.8 (s, Ph), 128.5 (d, Ph), 127.9 (d, Ph), 127.5 (d, Ph), 108.2 (d, ArC-2 and ArC-6), 99.9 (d, ArC-4), 97.6 (d, C-4), 69.9 (t, 2 × OCH$_2$), 43.9 (d, C-2), 40.1 (t, C-1), 31.5 (t, C-6), 17.1 (q, 2-CH$_3$), 9.6 (q, C-7); *m/z* 430 (M$^+$, 7%), 91 (C$_7$H$_7^+$, 100).

1-(3-Acetylamino-5-benzyloxyphenyl)-2-methylheptane-3,5-dione 12

The diketone **12** was synthesised by the method of Day.[5,6] The benzyl bromide **20** (660 mg, 2.0 mmol), prepared from methyl 3-amino-5-hydroxybenzoate,[16] was added in dry THF (12 ml) to a stirred solution of lithium 2,2,6,6-tetramethylpiperidide [2.0 mmol, prepared at 0 °C from equimolar quantities of butyllithium and 2,2,6,6-tetramethylpiperidine in THF (6 ml) at 0 °C] at −10 °C under argon. After 5 min, the solution containing the ionised bromide was added, *via* Teflon tubing, to dilithioheptane-3,5-dione (0.8 mmol) in THF (4 ml) (prepared from lithium 2,2,6,6-tetramethylpiperidide and heptane-3,5-dione) at −20 °C. The mixture was allowed to warm to room temperature and after 1 h, the yellow solution was worked up in the manner described for the diketone **9**. Gravity chromatography (increasing polarity from dichloromethane to dichloromethane–ethyl acetate, 2:1) of the crude product provided 1-*(3-acetylamino-5-benzyloxyphenyl)-2-methylheptane-3,5-dione* **12** (540 mg, 72%) as a colourless oil. IR and ^{1}H NMR data were in agreement with those reported by Day;[6] δ_C(50.3 MHz) (enolic form) 196.3 (s, CO), 196.1 (s, CO), 168.3 (s, *C*OCH$_3$), 159.2 (s, ArC-5), 141.8 (s, ArC-3), 138.9 (s, Ph or ArC-1), 136.8 (s, ArC-1 or Ph), 128.5 (d, Ph), 127.9 (d, Ph), 127.5 (d, Ph), 112.7 (d, ArCH), 111.8 (d, ArCH), 104.2 (d, ArCH), 97.7 (d, C-4), 70.0 (t, OCH$_2$), 44.0 (d, C-2), 39.9 (t, C-1), 31.6 (t, C-6), 24.7 (q, COCH$_3$), 17.3 (q, 2-CH$_3$), 9.6 (q, C-7); *m/z* 381 (M$^+$, 1%), 91 (C$_7$H$_7^+$, 100).

6-(3,5-Dimethoxyphenyl)hexane-2,4-dione 13

The benzyl bromide **18** (500 mg, 2.15 mmol) in dry THF (6 ml) was added to a solution of dilithiopentane-2,4-dione (2.35 mmol) in THF (prepared from lithium 2,2,6,6-tetramethylpiperidide and pentane-2,4-dione) at −20 °C under argon. The solution was then allowed to equilibrate to room temperature and after 1 h, the yellow solution was worked up as for the diketone **9**. The crude product was subjected to flash chromatography (acid-washed silica gel; hexane–ethyl acetate, 2:1) to give 6-*(3,5-dimethoxyphenyl)hexane-2,4-dione* **13** (500 mg, 92%)

as a colourless oil (Found: C, 66.9; H, 7.5. Calc. for $C_{14}H_{18}O_4$: C, 67.2; H, 7.3%); δ_H(300 MHz) 15.50 (br s, 0.9 H, OH), 6.37 (d, *J* 2.2, 2 H, Ar 2-H and Ar 6-H), 6.34 (t , *J* 2.2, 1 H, Ar 4-H), 5.51 (s, 0.9 H, 3-H of the enolic form), 3.79 (s, 6 H, 2 × OCH_3), 3.58 (s, 0.2 H, 3-H_2 of the keto form), 2.88 (t, *J* 7.4, 2 H, CH_2), 2.60 (t, *J* 7.4, 2 H, CH_2), 2.23 (s, *ca.* 0.3 H, $COCH_3$ of the keto form), 2.06 (s, *ca.* 2.7 H, $COCH_3$ of the enolic form); δ_C(75.5 MHz) 193.3 (CO), 190.9 (CO), 160.8 (ArC-3 and ArC-5), 143.1 (ArC-1), 106.3 (ArC-2 and ArC-6), 100.0 (ArC-4 or C-3), 99.1 (C-3 or ArC-4), 55.3 (2 × OCH_3), 39.8 (CH_2), 31.7 (CH_2), 24.8 ($COCH_3$); *m/z* 250 (M^+, 16%), 165 ($M^+ - CH_3COCH_2CO$, 100), 85 ($CH_3COCH_2CO^+$, 33).

6-(3,5-Dimethoxyphenyl)-6-hydroxyhexane-2,4-dione 14

3,5-Dimethoxybenzaldehyde (600 mg, 3.6 mmol) in dry THF (18 ml) was added dropwise to dilithiopentane-2,4-dione (5.2 mmol) in THF (16 ml) (prepared from lithium 2,2,6,6-tetramethylpiperidide and pentane-2,4-dione) at −30 °C, under argon. The mixture was allowed to warm to room temperature and was stirred for 1 h. Work-up as for the diketone **9** gave an oil, which was purified by dry flash chromatography (hexane–ethyl acetate, 1:1) to yield 6-(3,5-*dimethoxyphenyl*)-6-*hydroxyhexane*-2,4-*dione* **14** (870 mg, 91%) as a pale yellow viscous oil (Found: C, 63.5; H, 7.1. Calc. for $C_{14}H_{18}O_5$: C, 63.2; H, 6.8%); ν_{max}(film)/cm^{-1} 3440, 1723, 1598, 1463, 1430, 1357, 1297, 1205, 1157, 1062; δ_H(300 MHz) 15.30 (br s, 0.8 H, OH), 6.52 (d, *J* 2.2, 1.6 H, Ar 2-H and Ar 6-H of the enolic form), 6.50 (d, *J* 2.3, 0.4 H, Ar 2-H and Ar 6-H of the keto form), 6.39 (t, *J* 2.3, 0.2 H, Ar 4-H of the keto form), 6.37 (t, *J* 2.2, 0.8 H, Ar 4-H of the enolic form), 5.52 (s, 0.8 H, 3-H of the enolic form), 5.16 (dd, *J* 11.1, 3.3, 0.2 H, 6-H of the keto form), 5.10 (dd, *J* 8.0, 4.4, 0.8 H, 6-H of the enolic form), 3.79 (s, 1.2 H, 2 × OCH_3 of the keto form), 3.78 (s, 4.8 H, 2 × OCH_3 of the enolic form), 3.61 (s, 0.4 H, 3-H_2 of the keto form), 3.25 (br s, 1 H, OH), 2.98–2.44 (m, 2 H, 5-H_2, keto and enolic forms), 2.23 (s, 0.6 H, $COCH_3$ of the keto form), 2.05 (s, 2.4 H, $COCH_3$ of the enolic form); δ_C(75.5 MHz) (enolic form) 194.3 (CO), 189.2 (CO), 160.9 (ArC-3 and ArC-5), 145.6 (ArC-1), 103.4 (ArC-2 and ArC-6), 101.0 (ArC-4 or C-3), 99.6 (C-3 or ArC-4), 70.9 (C-6), 55.3 (2 × OCH_3), 47.7 (C-5), 24.1 (C-1); *m/z* 266 (M^+, 15%), 181 ($M^+ - CH_3COCH_2CO$, 24), 166 (57), 139 (100), 124 (21), 100 ($CH_3COCH_2COCH_3^+$, 39), 85 ($CH_3COCH_2CO^+$, 94).

1-(3,5-Dibenzyloxyphenyl)hexane-1,3,5-trione 15

Benzyl 3,5-dibenzyloxybenzoate (800 mg, 1.9 mmol) in dry THF (10 ml) was slowly added to a solution of dilithiopentane-2,4-dione (6.7 mmol) in THF (40 ml) (prepared from lithium 2,2,6,6-tetramethylpiperidide and pentane-2,4-dione) at 0 °C under argon. The solution was then allowed to equilibrate to room temperature. After 1 h, work-up as for the diketone **9**, followed by flash chromatography (hexane–diethyl ether, 1:3), afforded 1-(3,5-*dibenzyloxyphenyl*)*hexane*-1,3,5-*trione* **15** (590 mg, 76%), mp 80–83 °C (as yellow crystals from diethyl ether, lit.,[6] 81–84 °C), with ^{1}H NMR data identical to those reported by Day;[6] ν_{max}(KBr)/cm^{-1} 3427, 1739, 1707, 1605, 1583, 1169; *m/z* 416 (M^+, 0.2%), 91 ($C_7H_7^+$, 100).

Ethyl 5-(2-benzyloxy-3-methoxyphenyl)-3-oxopentanoate 16

Butyllithium (1.5 ml, 1.6 M in hexane, 2.4 mmol) was added dropwise to a solution of diisopropylamine (0.32 ml, 2.3 mmol) in dry THF (5 ml) at 0 °C under argon. To this pale yellow solution was added dropwise ethyl acetoacetate (0.14 ml, 1.1 mmol). The resulting dark yellow solution was stirred at 0 °C for 20 min, before benzyl bromide **17** (0.34 g, 1.1 mmol) in THF (5 ml) was slowly added. Stirring was continued at 0 °C for 45 min. The orange solution was quenched with a mixture of hydrochloric acid (0.2 ml, 36%), water (0.5 ml) and diethyl ether (1.5 ml). The two layers were separated and the aqueous phase further extracted with diethyl ether. The organic layers were combined, washed with water until neutral, dried and concentrated to provide a pale yellow oil. Chromatography of the oil (acid-washed silica gel; petroleum spirit–dichloromethane, 1:1) gave *ethyl* 5-(2-*benzyloxy*-3-*methoxyphenyl*)-3-*oxopentanoate* **16** (0.23 g, 60%) as white crystals, mp 45–46 °C (Found: C, 70.7; H, 7.0. Calc. for $C_{21}H_{24}O_5$: C, 70.8; H, 6.8%); ν_{max}(melt)/cm^{-1} 1745, 1718, 1480, 1270, 1080, 755, 700; δ_H(200 MHz) 7.47–7.34 (m, 5 H, OCH_2Ph), 7.10–6.74 (m, 3 H, Ar 4-H, Ar 5-H and Ar 6-H), 5.03 (s, 2 H, OCH_2Ph), 4.15 (q, *J* 7.2, 2 H, OCH_2CH_3), 3.88 (s, 3 H, OCH_3), 3.33 (s, 2 H, 2-H_2), 2.91–2.68 (m, 4 H, 4-H_2, 5-H_2, 2nd order), 1.24 (t, *J* 7.2, 3 H, OCH_2CH_3); δ_C(50.3 MHz) 202.1 (s, C-3), 167.0 (s, C-1), 152.7 (s, ArC-3 or ArC-2), 145.7 (s, ArC-2 or ArC-3), 137.7 (s, Ph), 134.5 (s, ArC-1), 128.3 (d, Ph), 128.1 (d, Ph), 127.9 (d, Ph), 124.0 (d, ArC-6 or ArC-5), 121.8 (d, ArC-5 or ArC-6), 110.6 (d, ArC-4), 74.5 (t, OCH_2Ph), 61.2 (t, OCH_2CH_3), 55.6 (q, OCH_3), 49.0 (t, C-2), 43.5 (t, C-4), 24.3 (t, C-5), 14.0 (q, OCH_2CH_3); *m/z* 356 (M^+, 0.4%), 91 ($C_7H_7^+$, 100).

2-Benzyloxy-3-methoxybenzyl bromide 17

2-Benzyloxy-3-methoxybenzaldehyde was prepared (94%) from 2-hydroxy-3-methoxybenzaldehyde, and was converted (86%) into 2-benzyloxy-3-methoxybenzyl alcohol by modification of literature methods.[25,26] The alcohol was brominated by the method of Barton *et al.*[15] Dimethyl sulfide (0.6 ml, 8.2 mmol) in dry dichloromethane (2 ml) was added dropwise to an ice-cold suspension of *N*-bromosuccinimide (1.4 g, 7.9 mmol) in dichloromethane (20 ml) under nitrogen. The mixture was cooled to −30 °C and stirred for 30 min. The benzyl alcohol (0.8 g, 3.3 mmol) in dichloromethane (4 ml) was slowly added to the cooled mixture, which was then warmed to room temperature and stirred for 4 h. The orange solution was quenched with brine (25 ml), extracted with diethyl ether, and the extracts dried and evaporated to give a viscous oil. Flash chromatography (pentane–dichloromethane, 2:1) afforded 2-*benzyloxy*-3-*methoxybenzyl bromide* **17** (0.64 g, 64%) as white crystals, mp 43–44 °C (Found: C, 58.6; H, 4.9; Br, 26.0. Calc. for $C_{15}H_{15}BrO_2$: C, 58.6; H, 4.9; Br, 26.0%); ν_{max}(melt)/cm^{-1} 1480, 1275, 1230, 1085, 1070, 750, 697; δ_H(200 MHz) 7.53–7.30 (m, 5 H, OCH_2Ph), 7.10–6.86 (m, 3 H, 4-H, 5-H and 6-H), 5.21 (s, 2 H, OCH_2Ph), 4.56 (s, 2 H, CH_2Br), 3.92 (s, 3 H, OCH_3); δ_C(50.3 MHz) 152.8 (s, C-3 or C-2), 146.0 (s, C-2 or C-3), 137.5 (s, Ph), 132.0 (s, C-1), 128.3 (d, Ph), 128.2 (d, Ph), 127.9 (d, Ph), 124.2 (d, C-5 or C-6), 122.5 (d, C-6 or C-5), 112.9 (d, C-4), 74.5 (t, OCH_2), 55.7 (q, OCH_3), 28.3 (t, CH_2Br); *m/z* 308 (M^+, 0.4%), 306 (M^+, 0.4), 227 (M^+ − Br, 3), 136 ($M^+ - PhCH_2Br$, 56), 91 ($C_7H_7^+$, 100), 65 (43).

3,5-Dimethoxybenzyl bromide 18

3,5-Dimethoxybenzyl alcohol was prepared (98%) by reduction of the aldehyde with sodium borohydride in ethanol, and had mp and spectral data in agreement with the literature.[27] Bromination was effected by the method of Kuchar *et al.*[28] Phosphorus tribromide (1 ml, 10.5 mmol) was added dropwise to an ice-cold mixture of the alcohol (3.6 g, 21.5 mmol) and dry pyridine (150 ml, 1.85 mmol) in anhydrous diethyl ether (30 ml) under argon. After 1 h, the reaction mixture was quenched with ice. The organic layer was separated, and the aqueous layer extracted with diethyl ether. The organic layers were combined, washed with saturated aqueous sodium hydrogen carbonate and water, dried and evaporated, to provide 3,5-*dimethoxybenzyl bromide* **18** (4.4 g, 88%) as white crystals, mp 71–72 °C (lit.,[29] 71–72 °C), with ^{1}H NMR data in agreement with that of Appleton and co-workers;[30] δ_C(75.5 MHz) 160.8 (C-3 and C-5), 139.6 (C-1), 106.8 (C-2 and C-6), 100.4 (C-4), 55.2 (2 × OCH_3), 33.5 (CH_2Br); *m/z* 232 (M^+, 8%), 230 (M^+, 8), 151 (M^+ − Br, 100).

3,5-Dibenzyloxybenzyl bromide 19

3,5-Dibenzyloxybenzyl alcohol was prepared from 3,5-dihydroxybenzoic acid by the route of Anand and Ranjan.[31]

The alcohol (3.1 g, 9.7 mmol) in acetonitrile (30 ml) was treated with carbon tetrabromide (3.7 g, 11.2 mmol) and triphenylphosphine (2.9 g, 11.1 mmol), under argon. After 1 h, the acetonitrile was removed under vacuum and the residue gravity chromatographed (pentane–dichloromethane, 1 : 1) to give 3,5-*dibenzyloxybenzyl bromide* **19** (3.4 g, 92%) as white crystals, mp 95–96 °C (lit.,[32] 94 °C); ν_{max}(KBr)/cm^{-1} 1596, 1343, 1298, 1167, 1157, 1049, 692; δ_H(200 MHz) 7.50–7.30 (m, 10 H, 2 × OCH$_2$*Ph*), 6.64 (d, *J* 2.2, 2 H, 2-H and 6-H), 6.55 (d, *J* 2.2, 1 H, 4-H), 5.01 (s, 4 H, 2 × OC*H*$_2$Ph), 4.39 (s, 2 H, CH$_2$Br); δ_C(50.3 MHz) 160.0 (s, C-3 and C-5), 139.7 (s, C-1), 136.5 (s, Ph), 128.6 (d, Ph), 128.0 (d, Ph), 127.5 (d, Ph), 108.0 (d, C-2 and C-6), 102.1 (d, C-4), 70.0 (t, 2 × OCH$_2$), 33.6 (t, CH$_2$Br); *m/z* 384 (M$^+$, 7%), 382 (M$^+$, 6), 91 ($C_7H_7^+$, 100).

2-Bromo-3,5-dibenzyloxybenzyl alcohol 21

N-Bromosuccinimide (0.06 g, 0.34 mmol) in dry dichloromethane (2 ml) was cooled to 0 °C under argon and dimethyl sulfide (40 ml, 0.54 mmol) in dichloromethane (0.5 ml) was added dropwise, after the method of Barton *et al.*[15] After addition, the yellow mixture was cooled to −30 °C and stirred at that temperature for 30 min. 3,5-Dibenzyloxybenzyl alcohol (0.10 g, 0.31 mmol) in dichloromethane (0.5 ml) was slowly added to the cooled suspension. After 15 min at −30 °C, the orange solution was worked up as above. Preparative TLC (dichloromethane) provided 2-*bromo*-3,5-*dibenzyloxybenzyl alcohol* **21** (0.10 g, 81%) as white crystals, mp 112–113 °C (lit.,[33] 108–110 °C), with ^{1}H NMR data identical to that of Sinhababu and Borchardt;[33] ν_{max}(Nujol)/cm^{-1} 3320, 1585, 1170, 735, 695; δ_C(50.1 MHz) 158.9 (s, C-3 or C-5), 155.6 (s, C-5 or C-3), 141.8 (s, C-1), 136.5 (s, Ph), 136.4 (s, Ph), 128.5 (d, Ph), 128.0 (d, Ph), 127.9 (d, Ph), 127.5 (d, Ph), 126.9 (d, Ph), 106.2 (d, C-4 or C-6), 101.2 (d, C-6 or C-4), 70.8 (t, O*C*H$_2$Ph), 70.3 (t, O*C*H$_2$Ph), 65.1 (t, CH$_2$OH); *m/z* 400 (M$^+$, 1%), 398 (M$^+$, 1), 91 ($C_7H_7^+$, 100).

2-Bromo-3,5-dibenzyloxybenzyl bromide 22

Dimethyl sulfide (0.2 ml, 2.7 mmol) in dry dichloromethane (1 ml) was added to an ice-cold suspension of *N*-bromosuccinimide (0.45 g, 2.5 mmol) in dichloromethane (8 ml) under argon, after the method of Barton *et al.*[15] The yellow mixture was cooled to −30 °C and maintained for 30 min at that temperature before the dropwise addition of 3,5-dibenzyloxybenzyl alcohol (0.52 g, 1.6 mmol) in dichloromethane (4 ml). The mixture was then allowed to equilibrate to room temperature and stirring was continued for 4 h. Brine was added to the orange solution and the organic material was extracted with diethyl ether. The extracts were dried, evaporated, and the resulting crude solid gravity chromatographed (pentane–dichloromethane, 3 : 1) to afford 2-*bromo*-3,5-*dibenzyloxybenzyl bromide* **22** (0.49 g, 66%) as white crystals, mp 82–83 °C (lit.,[34] 77–78 °C), with ^{1}H NMR data identical to that of Elix and Ferguson;[34] ν_{max}(Nujol)/cm^{-1} 1600, 1580, 1335, 1175, 735, 695; δ_C(50.1 MHz), 158.7 (s, C-3 or C-5), 156.2 (s, C-5 or C-3), 138.6 (s, C-1), 136.2 (s, Ph), 136.1 (s, Ph), 128.6 (d, Ph), 128.2 (d, Ph), 127.9 (d, Ph), 127.5 (d, Ph), 126.9 (d, Ph), 108.7 (d, C-4 or C-6), 105.9 (s, C-2), 102.2 (d, C-6 or C-4), 71.0 (t, OCH$_2$), 70.4 (t, OCH$_2$), 33.8 (t, CH$_2$Br); *m/z* 464 (M$^+$, 0.6%), 462 (M$^+$, 1.2), 460 (M$^+$, 0.6), 383 (M$^+$ − Br, 0.5), 381 (M$^+$ − Br, 0.5), 91 ($C_7H_7^+$, 100).

Oxidation of 2-methyl-1-phenylheptane-3,5-dione 8 with manganese(III) acetate

The diketone **8** (50 mg, 0.23 mmol) in acetic acid (1.6 ml) was treated with manganese(III) acetate (0.97 mmol) as for the diketone **9**, but at 60 °C. The crude reaction product was subjected to dry flash chromatography (increasing polarity from hexane–dichloromethane, 1 : 1, to dichloromethane) to give, in order of elution, recovered diketone (18 mg, 36%), a fraction containing the diketone (5 mg, 10%) contaminated with the naphthalenone **23** (*ca.* 9% by GC–MS) and the naphthol **32** (*ca.* 4% by GC–MS), 3-methyl-1-propionyl-2-naphthol **32** (1 mg, 2%), 2-methyl-3-phenylpropanoic acid (2 mg, 5%) and 26 mg of uncharacterisable material. GC–MS of the second fraction showed 1-*acetoxy*-3,4-*dihydro*-3-*methyl*-1-*propionylnaphthalen*-2(1H)-*one* **23** as two separated diastereomers (1 : 1) with similar spectra, *m/z* 274 (M$^+$, 1%), 218 (M$^+$ − CH$_3$CHCO, 28), 176 (M$^+$ − CH$_3$CHCO − CH$_2$CO, 100), 161 (22), and 3-*methyl*-1-*propionyl*-2-*naphthol* **32**, *m/z* 214 (M$^+$, 20%), 185 (M$^+$ − CH$_3$CH$_2$, 100). 2-*Methyl*-3-*phenylpropanoic acid* (Found: C, 73.1; H, 7.5. Calc. for $C_{10}H_{12}O_2$: C, 73.2; H, 7.4%); ν_{max}(film)/cm^{-1} 3400–2500, 1705, 695; δ_H(200 MHz) 7.33–7.15 (m, 5 H, Ph), 3.15–3.0 (m, 1 H, 2-H or 3-H), 2.80–2.50 (m, 2 H, 3-H and 2-H or 3-H$_2$), 1.18 (d, *J* 6.6, 3 H, CH$_3$); δ_C(50.3 MHz) 182.4 (s, CO), 139.0 (s, ArC-1), 129.0 (d, Ph), 128.4 (d, Ph), 126.4 (d, Ph), 41.3 (d, C-2), 39.3 (t, C-3), 16.5 (CH$_3$); *m/z* 164 (M$^+$, 21%), 91 ($C_7H_7^+$, 100), 65 (24).

Cyclisation of 1-(2-benzyloxy-3-methoxyphenyl)-2-methylheptane-3,5-dione 9

The diketone **9** (47 mg, 0.13 mmol) in dry degassed acetic acid (1 ml) was added in one portion to anhydrous manganese(III) acetate (0.56 mmol) under argon. After 22 h, the brown reaction mixture was quenched with brine and extracted with chloroform. The extracts were dried and evaporated. Gravity chromatography (acid-washed silica gel; hexane–dichloromethane, 1 : 2) of the brown oil afforded 5-*benzyloxy*-6-*methoxy*-3-*methyl*-1-*propionyl*-2-*naphthol* **33** (5 mg, 11%) as pale yellow crystals, mp 72–74 °C (Found: C, 75.2; H, 6.6. Calc. for $C_{22}H_{22}O_4$: C, 75.4; H, 6.3%); ν_{max}(KBr)/cm^{-1} 3800, 1611, 1570, 1422, 1341, 1280, 1237, 1206, 1194, 1175, 1113, 965, 806, 750, 705; δ_H(300 MHz) 13.5 (s, 1 H, OH), 8.08 (s, 1 H, 4-H), 7.75 (d, *J* 9.5, 1 H, 7-H or 8-H), 7.57–7.29 (m, 6 H, OCH$_2$*Ph* and 8-H or 7-H), 5.18 (s, 2 H, OC*H*$_2$Ph), 4.01 (s, 3 H, OCH$_3$), 3.19 (q, *J* 7.3, 2 H, C*H*$_2$CH$_3$), 2.36 (s, 3 H, 3-CH$_3$), 1.33 (t, *J* 7.3, 3 H, CH$_2$C*H*$_3$); δ_C(75.5 MHz) 208.8 (s, CO), 162.2 (s), 147.3 (s), 142.8 (s), 137.6 (s, Ph), 129.8 (d), 129.1 (s), 128.6 (d, Ph), 128.5 (d, Ph), 128.3 (d, Ph), 126.3 (s), 124.4 (s), 120.6 (d), 115.3 (d), 114.3 (s), 75.6 (t, OCH$_2$), 56.7 (q, OCH$_3$), 37.0 (t, *C*H$_2$CH$_3$), 16.6 (q, 3-CH$_3$), 9.5 (q, CH$_2$*C*H$_3$); *m/z* 350 (M$^+$, 11%), 294 (M$^+$ − COCHCH$_3$, 9), 259 (M$^+$ − CH$_2$Ph, 58), 91 ($C_7H_7^+$, 100), 65 (23), 57 (CH$_3$CH$_2$CO$^+$, 65).

Further elution gave starting material (10 mg, 21% recovery) and the two diastereomeric 1-*acetoxy*-5-*benzyloxy*-3,4-*dihydro*-6-*methoxy*-3-*methyl*-1-*propionylnaphthalen*-2(1H)-*ones* **24** (1.1 : 1) (30 mg, 56%) as a pale yellow solid (Found: C, 70.4; H, 6.5. Calc. for $C_{24}H_{26}O_6$: C, 70.2; H, 6.4%); ν_{max}(CH$_2$Cl$_2$)/cm^{-1} 2985, 2940, 1755, 1733, 1715, 1490, 1440, 1370, 1280, 1230, 1080, 700; δ_H(300 MHz) 7.50–7.34 (m, 5 H, OCH$_2$*Ph*), 7.02 (d, *J* 8.6, 7-H or 8-H), 6.86 (d, *J* 8.6, 8-H or 7-H), 6.83 (d, *J* 8.6, 7-H or 8-H), 6.76 (d, *J* 8.6, 8-H or 7-H), 5.04 (d, *J ca.* 11, OC*H*$_2$Ph, part of AB system), 5.02 (d, *J ca.* 11, OC*H*$_2$Ph, part of AB system superimposed on part of AB system at δ 5.04), 5.00 (d, *J ca.* 11, OC*H*$_2$Ph, part of AB system superimposed on part of AB system at δ 5.02), 4.97 (d, *J ca.*11, OC*H*$_2$Ph, part of AB system), 3.89 (s, OCH$_3$), 3.87 (s, OCH$_3$), 3.35–2.30 (m, 5 H, C*H*$_2$CH$_3$, 4-H$_2$ and 3-H), 2.23 (s, COCH$_3$), 2.12 (s, COCH$_3$), 1.20 (d, *J* 6.6, 3-CH$_3$), 1.11 (d, *J* 6.4, 3-CH$_3$), 1.04 (t, *J* 7.2, CH$_2$C*H*$_3$), 0.92 (t, *J* 7.2, CH$_2$C*H*$_3$); δ_C(75.5 MHz) 208.2 (CO), 206.2 (CO), 205.8 (CO), 203.5 (CO), 169.1 (O*C*OCH$_3$), 168.6 (O*C*OCH$_3$), 153.1 (C-5 or C-6), 152.9 (C-5 or C-6), 144.7, 144.3, 137.7 (Ph), 137.4 (Ph), 133.1, 132.0, 129.6, 128.8 (Ph), 128.6 (Ph), 128.5 (Ph), 128.4, 128.2, 126.3, 122.4 (C-7 or C-8), 119.6 (C-7 or C-8), 111.4 (C-8 or C-7), 111.0 (C-8 or C-7), 89.6 (C-1), 87.2 (C-1), 74.9 (OCH$_2$), 74.6 (OCH$_2$), 55.7 (OCH$_3$), 41.9, 39.4, 32.1, 30.5, 27.9, 20.7 (OCO*C*H$_3$), 14.5 (3-CH$_3$), 14.4 (3-CH$_3$), 7.1 (CH$_2$*C*H$_3$), 6.9 (CH$_2$*C*H$_3$); *m/z* 410 (M$^+$, 2%), 354 (M$^+$ − COCHCH$_3$, 25), 312 (M$^+$ − COCHCH$_3$ − CH$_2$CO, 37), 91 ($C_7H_7^+$, 100).

Oxidation of 1-(2-benzyloxy-3-methoxyphenyl)-2-methylheptane-3,5-dione 9 with manganese(III) acetate

The diketone **9** (5.0 mg, 0.014 mmol), manganese(III) acetate

dihydrate (8 mg, 0.03 mmol) and glacial acetic acid (0.1 ml) were stirred for 22 h in a stoppered flask. The brown suspension was poured into brine, extracted with ethyl acetate, dried and concentrated to provide a dark brown oil. Gravity chromatography (acid-washed silica gel; dichloromethane–ethyl acetate, *10:1*) afforded 3-(2-benzyloxy-3-methoxyphenyl)-2-methylpropanoic acid (3.5 mg, 83%) as a colourless oil, identical with material prepared by synthesis.

3-(2-Benzyloxy-3-methoxyphenyl)-2-methylpropanoic acid

The acid was prepared by the method of Pfeffer and co-workers.[35,36] Butyllithium (1.5 ml, 1.6 M in hexane, 2.4 mmol) was added dropwise to a stirred solution of diisopropylamine (0.34 ml, 2.4 mmol) in dry THF (2 ml), at −20 °C under nitrogen. After 15 min, propanoic acid (820 ml, 1.1 mmol) was slowly added. The milky white mixture was kept at −20 °C for 15 min then warmed to 5 °C. Hexamethylphosphoramide (HMPA) (0.5 ml, 2.5 mmol) was added to the mixture, which became homogeneous within 5 min. The pale yellow solution was maintained at 5 °C for an additional 15 min, then cooled to 0 °C and the benzyl bromide **17** (0.34 g, 1.1 mmol) in THF (1 ml) was added in one portion. The reaction temperature rose to 10 °C. After stirring for 4 h at room temperature, the pale yellow mixture was cooled to 0 °C and acidified with hydrochloric acid (10%). The aqueous layer was separated and extracted with petroleum spirit. The combined organic layers were washed with dilute hydrochloric acid (10%), water and brine, then dried and evaporated to provide a yellow oil. Purification by flash chromatography (acid-washed silica gel; pentane–dichloromethane, 1:1) afforded 3-(2-*benzyloxy*-3-*methoxyphenyl*)-2-*methylpropanoic acid* (0.20 g, 61%) as a viscous colourless oil (Found: C, 71.9; H, 6.4. Calc. for $C_{18}H_{20}O_4$: C, 72.0; H, 6.7%); ν_{max}(film)/cm^{-1} 3500–2400, 1705, 1600, 1480, 1275, 1085, 750, 700; δ_H(200 MHz) 9.90 (br s, 1 H, OH), 7.50–7.28 (m, 5 H, OCH_2Ph), 7.05–6.77 (m, 3 H, Ar 4-H, Ar 5-H and Ar 6-H), 5.05 (s, 2 H, OCH_2Ph), 3.90 (s, 3 H, OCH_3), 3.10–2.94 (m, 1 H, 3-H), 2.93–2.75 (m, 1 H, 2-H), 2.70–2.60 (m, 1 H, 3-H), 1.11 (d, *J* 7.0, 3 H, 2-CH_3); δ_C(50.3 MHz) 182.3 (s, CO), 152.7 (s, ArC-3 or ArC-2), 146.2 (s, ArC-2 or ArC-3), 137.9 (s, Ph), 133.3 (s, ArC-1), 128.3 (d, Ph), 128.0 (d, Ph), 127.0 (d, Ph), 123.8 (d, ArC-5 or ArC-6), 122.6 (d, ArC-6 or ArC-5), 110.9 (d, ArC-4), 74.5 (t, OCH_2), 55.7 (q, OCH_3), 39.9 (d, C-2), 33.9 (d, C-3), 16.6 (q, 2-CH_3); *m/z* 300 (M^+, 6%), 91 ($C_7H_7^+$, 100).

Oxidation of 1-(2-hydroxy-3-methoxyphenyl)-2-methylheptane-3,5-dione 10 with manganese(III) acetate

The phenol **10** (27 mg, 0.10 mmol) in dry degassed acetic acid (0.7 ml) was added to anhydrous manganese(III) acetate (0.21 mmol) under argon. After 22 h, the initially orange–red mixture had faded to pale orange. Work-up as for the cyclisation of the diketone **9** provided a brown viscous oil which upon gravity chromatography (acid-washed silica gel; increasing polarity from dichloromethane to ethyl acetate) afforded starting material (2 mg, 7% recovery) together with an intractable tar (24 mg).

1-Acetoxy-6,8-dibenzyloxy-3,4-dihydro-3-methyl-1-propionylnaphthalen-2(1*H*)-ones 26

The diketone **11** (100 mg, 0.23 mmol) in acetic acid (1.7 ml) was treated with manganese(III) acetate (0.96 mmol) as for the diketone **9**. Purification of the brown solid product by dry flash chromatography (dichloromethane) afforded the diastereomeric 1-*acetoxy*-6,8-*dibenzyloxy*-3,4-*dihydro*-3-*methyl*-1-*propionylnaphthalen*-2(1H)-*ones* **26**. The first diastereomer (45 mg, 40%) eluted as pale yellow crystals, mp 52–54 °C (Found: C, 74.1; H, 6.5. Calc. for $C_{30}H_{30}O_6$: C, 74.1; H, 6.2%); ν_{max}(KBr)/cm^{-1} 1743, 1729, 1713, 1606, 1245, 1159; δ_H(300 MHz) 7.41–7.33 (m, 10 H, 2 × OCH_2Ph), 6.44 (d, *J* 2.2, 1 H, 5-H or 7-H), 6.41 (d, *J* 2.2, 1 H, 7-H or 5-H), 5.02 (s, 2 H, 6-OCH_2Ph), 4.96 (d, *J* 11.0, 1 H, 8-OCH_2Ph, part of AB system), 4.85 (d, *J* 11.0, 1 H, 8-OCH_2Ph, part of AB system), 3.22 (dd, *J ca.* 12, *ca.* 12, 1 H, 4-H pseudo-axial), 3.04–2.88 (m, 2 H, 4-H pseudo-equatorial, 3-H pseudo-axial, 2nd order), 2.64 (q, *J* 7.1, 2 H, CH_2CH_3), 2.07 (s, 3 H, $COCH_3$), 1.16 (d, *J* 6.1, 3-CH_3), 0.71 (t, *J* 7.1, CH_2CH_3); δ_C(75.5 MHz), 206.6 (s, CO), 203.5 (s, CO), 169.1 (s, $COCH_3$), 160.5 (s, C-6 or C-8), 157.2 (s, C-8 or C-6), 142.2 (s, C-4a or C-8a), 136.8 (s, Ph), 136.1 (s, Ph), 128.8 (d, Ph), 128.7 (d, Ph), 128.6 (d, Ph), 128.3 (d, Ph), 128.2 (d, Ph), 127.8 (d, Ph), 118.3 (s, C-8a or C-4a), 104.7 (d, C-5), 98.8 (d, C-7), 88.2 (s, C-1), 70.5 (t, OCH_2), 70.1 (t, OCH_2), 42.7 (d, C-3), 37.6 (t, CH_2CH_3), 31.3 (t, C-4), 20.6 (q, $COCH_3$), 13.4 (q, 3-CH_3), 6.4 (q, CH_2CH_3); *m/z* 486 (M^+, 0.5%), 430 ($M^+ - COCHCH_3$, 1), 387 ($M^+ - COCHCH_3 - COCH_3$, 1), 91 ($C_7H_7^+$, 100).

The second diastereomer (60 mg, 53%) eluted contaminated with 8% of the first as a pale yellow solid (Found: C, 73.9; H, 6.5. Calc. for $C_{30}H_{30}O_6$: C, 74.1; H, 6.2%); ν_{max}(KBr)/cm^{-1} 1739, 1706, 1605; δ_H(300 MHz) 7.45–7.30 (m, 10 H, 2 × OCH_2Ph), 6.48 (d, *J* 2.2, 1 H, 5-H or 7-H), 6.45 (d, *J* 2.2, 1 H, 7-H or 5-H), 5.04 (s, 2 H, 6-OCH_2Ph), 4.97 (d, *J* 11.1, 1 H, 8-OCH_2Ph, part of AB system), 4.88 (d, *J* 11.1, 1 H, 8-OCH_2Ph, part of AB system), 3.59 (dd, *J* 15.5, 5.6, 1 H, 4-H pseudo-axial), 3.02 (m, 1 H, 3-H pseudo-equatorial), 2.75 (dd, *J* 15.5, 4.2, 1 H, 4-H pseudo-equatorial), 2.75–2.54 (2 × dq superimposed, *J ca.* 13, *ca.* 7.3 for both protons, 2 H, CH_2CH_3, diastereotopic), 2.04 (s, 3 H, $COCH_3$), 1.20 (d, *J* 7.3, 3 H, 3-CH_3), 0.75 (t, *J* 7.1, 3 H, CH_2CH_3); δ_C(75.5 MHz) 206.7 (s, CO), 206.5 (s, CO), 169.6 (s, $COCH_3$), 160.8 (s, C-6 or C-8), 157.8 (s, C-8 or C-6), 140.5 (s, C-4a or C-8a), 136.7 (s, Ph), 136.1 (s, Ph), 128.9 (d, Ph), 128.8 (d, Ph), 128.5 (d, Ph), 128.4 (d, Ph), 128.1 (d, Ph), 127.8 (d, Ph), 116.4 (s, C-8a or C-4a), 106.1 (d, C-5), 99.0 (d, C-7), 85.4 (s, C-1), 70.6 (t, OCH_2), 70.1 (t, OCH_2), 44.0 (d, C-3), 36.9 (t, CH_2CH_3), 32.1 (t, C-4), 20.4 (q, $COCH_3$), 16.1 (q, 3-CH_3), 6.6 (q, CH_2CH_3); *m/z* 486 (M^+, 0.4%), 430 ($M^+ - COCHCH_3$, 1), 387 ($M^+ - COCHCH_3 - COCH_3$, 1), 91 ($C_7H_7^+$, 100).

1-Acetoxy-6-acetylamino-8-benzyloxy-3,4-dihydro-3-methyl-1-propionylnaphthalen-2(1*H*)-ones 27

The diketone **12** (420 mg, 1.1 mmol) in acetic acid (8 ml) was treated with manganese(III) acetate (4.6 mmol) as for the diketone **9**. Purification of the crude product by dry flash chromatography (dichloromethane–ethyl acetate, 2:1) yielded, as a white solid, 1-*acetoxy*-6-*acetylamino*-8-*benzyloxy*-3,4-*dihydro*-3-*methyl*-1-*propionylnaphthalen*-2(1H)-*one* **27** (450 mg, 93%) as a mixture of diastereomers (1.3:1) (Found: C, 68.6; H, 6.5; N, 3.0. Calc. for $C_{25}H_{27}NO_6$: C, 68.6; H, 6.2; N, 3.2%); ν_{max}(KBr)/cm^{-1} 2935, 1732, 1713, 1659, 1611, 1420, 1272, 1251; δ_H(300 MHz) (2 diastereomers, 1.3:1) 7.60 (br s, 1 H, NH), 7.45–7.33 (m, 5 H, OCH_2Ph), 6.72 (br s, 1 H, 5-H or 7-H), 6.62 (br s, 1 H, 7-H or 5-H), 5.00 (d, *J* 11.1, *ca.* 0.6 H, OCH_2Ph of major isomer, part of AB system), 4.99 (d, *J* 10.9, *ca.* 0.4 H, OCH_2Ph of minor isomer, part of AB system), 4.89 (d, *J* 11.1, *ca.* 0.6 H, OCH_2Ph of major isomer, part of AB system), 4.86 (d, *J* 10.9, *ca.* 0.6 H, OCH_2Ph of minor isomer, part of AB system), 3.53 (dd, *J* 15.5, 5.5, *ca.* 0.6 H, 4-H pseudo-axial of major isomer), 3.17 (dd, *J ca.* 13.5, *ca.* 13.5, *ca.* 0.4 H, 4-H pseudo-axial of minor isomer), 3.02–2.92 (m, *ca.* 0.6 H, 3-H pseudo-equatorial of major isomer), 2.90–2.56 (m, *ca.* 3.4 H, 3-H pseudo-axial of minor isomer, 4-H pseudo-equatorial and CH_2CH_3), 2.12 (s, *ca.* 1.8 H, $NCOCH_3$ of major isomer), 2.11 (s, *ca.* 1.2 H, $NCOCH_3$ of minor isomer), 2.06 (s, *ca.* 1.2 H, $OCOCH_3$ of minor isomer), 2.01 (s, *ca.* 1.8 H, $OCOCH_3$ of major isomer), 1.17 (d, *J* 7.5, *ca.* 1.8 H, 3-CH_3 of major isomer), 1.14 (d, *J* 6.3, *ca.* 1.2 H, 3-CH_3 of minor isomer), 0.74 (t, *J* 7.1, *ca.* 1.8 H, CH_2CH_3 of major isomer), 0.71 (t, *J* 7.1, *ca.* 1.2 H, CH_2CH_3 of minor isomer); δ_C(75.5 MHz) (2 diastereomers, 1.3:1) 206.6 (CO), 206.5 (CO), 206.3 (CO), 203.3 (CO), 169.5 ($OCOCH_3$, major isomer), 169.1 ($OCOCH_3$, minor isomer), 169.0 ($NCOCH_3$), 157.2 (C-8, major isomer), 156.6 (C-8, minor isomer), 141.5, 140.1, 139.9,

136.0, 128.7 (Ph), 128.6 (Ph), 128.5 (Ph), 128.4 (Ph), 128.2 (Ph), 121.0, 119.0, 111.7 (C-5 or C-7, major isomer), 110.3 (C-5 or C-7, minor isomer), 102.3 (C-7 or C-5, major isomer), 102.2 (C-7 or C-5, minor isomer), 88.0 (C-1, major isomer), 85.1 (C-1, minor isomer), 70.6 (OCH_2), 43.8 (C-3, major isomer), 42.6 (C-3, minor isomer), 37.1 (CH_2CH_3, minor isomer), 36.4 (CH_2CH_3, major isomer), 32.0 (C-4, major isomer), 31.3 (C-4, minor isomer), 24.4 ($NCOCH_3$), 20.5 ($OCOCH_3$, minor isomer), 20.3 ($OCOCH_3$, major isomer), 16.0 ($3\text{-}CH_3$, major isomer), 13.3 ($3\text{-}CH_3$, minor isomer), 6.5 (CH_2CH_3, minor isomer), 6.3 (CH_2CH_3, major isomer); *m/z* 437 (M^+, 0.4%), 91 ($C_7H_7^+$, 100), 43 (CH_3CO^+, 23).

1-Acetoxy-1-acetyl-3,4-dihydro-6,8-dimethoxynaphthalen-2(1*H*)-one 28

The diketone **13** (40 mg, 0.16 mmol) in acetic acid (1.1 ml) was treated with manganese(III) acetate (0.67 mmol) as for the diketone **9**. Dry flash chromatography (hexane–ethyl acetate, 3:1) of the crude product afforded, in order of elution, recovered diketone (3 mg, 7%) and 1-*acetoxy*-1-*acetyl*-3,4-*dihydro*-6,8-*dimethoxynaphthalen*-2(1H)-*one* **28** (35 mg, 71%) as white crystals, mp 150–152 °C (Found: C, 63.0; H, 6.2. Calc. for $C_{16}H_{18}O_6$: C, 62.1; H, 5.9%); ν_{max}(KBr)/cm^{-1} 1716, 1607, 1250, 1216, 1157; δ_H(300 MHz) 6.33 (d, *J ca.* 2, 1 H, 5-H or 7-H), 6.31 (d, *J ca.* 2, 1 H, 7-H or 5-H), 3.80 (s, 3H, OCH_3), 3.73 (s, 3 H, OCH_3), 3.52–3.27 (m, 1 H, 3-H or 4-H), 3.00–2.70 (m, 3 H, CH_2 and CH), 2.50 (s, 3 H, $COCH_3$), 2.08 (s, 3 H, $OCOCH_3$); δ_C(75.5 MHz) 204.2 (CO), 201.9 (CO), 168.9 ($OCOCH_3$), 161.1 (C-6 or C-8), 158.2 (C-8 or C-6), 142.0 (C-4a or C-8a), 117.8 (C-8a or C-4a), 104.0 (C-5 or C-7), 97.7 (C-7 or C-5), 87.1 (C-1), 55.6 (OCH_3), 55.3 (OCH_3), 39.4 (C-3 or C-4), 29.4 (C-4 or C-3), 26.5 ($COCH_3$), 20.8 ($OCOCH_3$); *m/z* 306 (M^+, 4%), 264 ($M^+ - CH_2CO$, 23), 222 ($M^+ - CH_2CO - CH_2CO$, 66), 221 ($M^+ - CH_2CO - CH_3CO$, 100), 193 (221 − CO, 38).

1-Acetoxy-1-acetyl-3,4-dihydro-4-hydroxy-6,8-dimethoxynaphthalen-2(1*H*)-ones 29

The diketone **14** (200 mg, 0.75 mmol) in acetic acid (5.4 ml) was treated with manganese(III) acetate (3.2 mmol) as for the diketone **9**. The product was purified by dry flash chromatography (hexane–ethyl acetate, 1:1) to give the two diastereomeric 1-*acetoxy*-1-*acetyl*-3,4-*dihydro*-4-*hydroxy*-6,8-*dimethoxynaphthalen*-2(1H)-*ones* **29** (1:1) (220 mg, 95%) as a yellow solid. Further dry flash chromatography (hexane–ethyl acetate, 1:1) of the mixture (60 mg) afforded a faster eluting diastereomer (24 mg) as a cream solid (Found: C, 59.9; H, 5.7. Calc. for $C_{16}H_{18}O_7$: C, 59.6; H, 5.6%); ν_{max}(KBr)/cm^{-1} 3500, 1729, 1711, 1253, 1157; δ_H(300 MHz) 6.60 (d, *J* 2.3, 1 H, 5-H or 7-H), 6.42 (d, *J* 2.3, 1 H, 7-H or 5-H), 4.99 (ddd, *J* 12.0, 4.2, 2.7, 1 H, 4-H pseudo-equatorial), 4.48 (d, *J* 12.0, 1 H, OH), 3.85 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 3.20 (dd, *J* 14.6, 4.2, 1 H, 3-H pseudo-axial), 3.03 (dd, *J* 14.6, 2.7, 1 H, 3-H pseudo-equatorial), 2.50 (s, 3 H, $COCH_3$), 2.15 (s, 3 H, $OCOCH_3$); δ_C(75.5 MHz) 202.6 (CO), 199.4 (CO), 169.7 ($OCOCH_3$), 161.9 (C-6 or C-8), 157.8 (C-8 or C-6), 141.3 (C-4a or C-8a), 116.8 (C-8a or C-4a), 104.9 (C-5 or C-7), 99.8 (C-7 or C-5), 88.2 (C-1), 70.9 (C-4), 55.7 (OCH_3), 55.5 (OCH_3), 47.3 (C-3), 26.2 ($COCH_3$), 21.1 ($OCOCH_3$); *m/z* 322 (M^+, 6%), 280 ($M^+ - CH_2CO$, 32), 238 ($M^+ - CH_2CO - CH_2CO$, 70), 237 ($M^+ - CH_2CO - CH_3CO$, 100), 220 (42), 191 (43), 167 (22), followed by a slower eluting diastereomer (19 mg) as a pale yellow solid (Found: M^+, 322.1053. Calc. for $C_{16}H_{18}O_7$: *M*, 322.1053); δ_H(300 MHz) 6.87 (d, *J* 2.2, 1 H, 5-H or 7-H), 6.38 (d, *J* 2.2, 1 H, 7-H or 5-H), 5.25 (m, 1 H, 4-H pseudo-axial), 4.95 (1 H, br s, OH), 3.84 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 3.10 (dd, *J* 13.7, 4.7, 1 H, 3-H pseudo-equatorial), 2.89 (dd, *J* 13.7, 11.0, 1 H, 3-H pseudo-axial), 2.51 (s, 3 H, $COCH_3$), 2.07 (s, 3 H, $OCOCH_3$); δ_C(75.5 MHz) 204.2 (CO), 199.5 (CO), 169.2 ($OCOCH_3$), 161.5 (C-6 or C-8), 157.7 (C-8 or C-6), 145.6 (C-4a or C-8a), 115.5 (C-8a or C-4a), 100.7 (C-5 or C-7), 99.0 (C-7 or C-5), 87.1 (C-1), 67.5 (C-4), 55.4 (OCH_3), 55.3 (OCH_3), 49.5 (C-3), 26.6 ($COCH_3$), 20.6 ($OCOCH_3$); *m/z* 322 (M^+, 4%), 280 ($M^+ - CH_2CO$, 32), 238 ($M^+ - CH_2CO - CH_2CO$, 100), 237 ($M^+ - CH_2CO - CH_3CO$, 62), 220 (95), 205 (33), 191 (38).

1-Acetyl-3,4-dihydro-1,6,8-trimethoxynaphthalen-2(1*H*)-one 30 and 1-acetyl-3,4-dihydro-1-hydroxy-6,8-dimethoxynaphthalen-2(1*H*)-one 31

(a) Anhydrous cerium(IV) ammonium nitrate (590 mg, 1.1 mmol) in dry degassed methanol (1.2 ml) was slowly added to the diketone **13** (65 mg, 0.26 mmol) in methanol (0.6 ml) at 0 °C under argon. After 5 min, the pale orange solution was diluted with ethyl acetate (100 ml) and washed sequentially with water (10 ml), 10% aqueous sodium hydrogen carbonate (10 ml), and water until the aqueous layer was neutral. Dry flash chromatography (hexane–ethyl acetate, 2:1) of the pale yellow oil obtained on drying and concentration of the organic layer afforded 1-*acetyl*-3,4-*dihydro*-1,6,8-*trimethoxynaphthalen*-2(1H)-*one* **30** (58 mg, 80%), mp 128–129 °C, as white crystals from ethyl acetate–hexane (Found: C, 64.8; H, 6.7. Calc. for $C_{15}H_{18}O_5$: C, 64.7; H, 6.5%); ν_{max}(KBr)/cm^{-1} 1730, 1707, 1611, 1585, 1349, 1322, 1201, 1148, 1128, 1093; δ_H(300 MHz) 6.37 (d, *J* 2.3, 1 H, 5-H or 7-H), 6.35 (d, *J* 2.3, 7-H or 5-H), 3.83 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 3.10–2.95 (m, 3 H, CH_2 and CH), 2.99 (s, 3 H, OCH_3), 2.70–2.63 (m, 1 H, 3-H or 4-H), 2.41 (s, 3 H, $COCH_3$); δ_C(75.5 MHz) 207.0 (CO), 206.0 (CO), 161.1 (C-6 or C-8), 159.1 (C-8 or C-6), 141.8 (C-4a or C-8a), 117.5 (C-8a or C-4a), 104.0 (C-5 or C-7), 98.0 (C-7 or C-5), 91.1 (C-1), 55.8 (OCH_3), 55.4 (OCH_3), 52.4 (OCH_3), 39.4 (C-3 or C-4), 29.4 (C-4 or C-3), 25.8 ($COCH_3$); *m/z* 278 (M^+, 0.2%), 236 ($M^+ - CH_2CO$, 31), 235 ($M^+ - CH_3CO$, 100), 207 ($M^+ - CH_3CO - CO$, 49).

(b) Anhydrous cerium(IV) ammonium nitrate (990 mg, 1.8 mmol) in dry degassed methanol (2 ml) was added dropwise to the diketone **13** (110 mg, 0.44 mmol) in methanol (1 ml) at 0 °C under argon. After 5 min, the pale orange solution was diluted with diethyl ether (3 ml) and subjected to successive dry flash chromatography (hexane–ethyl acetate, 2:1) to give 1-*acetyl*-3,4-*dihydro*-1,6,8-*trimethoxynaphthalen*-2(1H)-*one* **30** (32 mg, 40%) and 1-*acetyl*-3,4-*dihydro*-1-*hydroxy*-6,8-*dimethoxynaphthalen*-2(1H)-*one* **31** (42 mg, 36%) as a pale yellow oil (Found: M^+, 221.0806. Calc. for $C_{12}H_{13}O_4$: *M*, 221.0814); ν_{max}(film)/cm^{-1} 3440, 2940, 2840, 1720, 1600, 1460, 1350, 1205, 1150, 835; δ_H(300 MHz) 6.35 (d, *J* 2.3, 1 H, 5-H or 7-H), 6.33 (d, *J* 2.3, 7-H or 5-H), 4.89 (s, 1 H, OH), 3.80 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 3.20–3.10 (m, 2 H), 2.95–2.88 (m, 2 H), 2.18 (s, 3 H, $COCH_3$); δ_C(75.5 MHz) 206.9 (CO), 206.8 (CO), 161.1 (C-6 or C-8), 158.9 (C-8 or C-6), 139.1 (C-4a or C-8a), 118.6 (C-8a or C-4a), 104.3 (C-5 or C-7), 97.8 (C-7 or C-5), 82.7 (C-1), 55.6 (OCH_3), 55.4 (OCH_3), 36.7 (C-3 or C-4), 30.5 (C-4 or C-3), 25.2 ($COCH_3$); *m/z* 264 (M^+, 0.2%), 222 ($M^+ - CH_2CO$, 26), 221 ($M^+ - CH_3CO$, 100), 193 ($M^+ - CH_3CO - CO$, 58).

Oxidation of 1-(3,5-dibenzyloxyphenyl)hexane-1,3,5-trione 15 with manganese(III) acetate

The triketone **15** (150 mg, 0.36 mmol) was treated with manganese(III) acetate (0.78 mmol) in acetic acid (2.6 ml) as for the diketone **9**. The pale yellow mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed twice with saturated aqueous sodium hydrogen carbonate, dried and evaporated. The crude residue on preparative TLC (hexane–ethyl acetate, 2:1) provided 3,5-dibenzyloxyacetophenone (4 mg, *ca.* 3%); δ_H(300 MHz) 7.50–7.34 (m, 10 H, 2 × OCH_2Ph), 7.20 (d, *J* 2.2, 2 H, 2-H and 6-H), 6.82 (t, *J* 2.2, 1 H, 4-H), 5.08 (s, 4 H, 2 × OCH_2Ph), 2.56 (s, 3 H, CH_3), in agreement with the partial data published by Vu and co-workers[37]; *m/z* 332 (M^+, 3%), 91 ($C_7H_7^+$, 100), and a mixture (95 mg) that could not be separated by further preparative TLC or

column chromatography. The basic washings from work-up were acidified with hydrochloric acid (5%), extracted with ethyl acetate, dried and concentrated to afford 3,5-dibenzyloxybenzoic acid (5 mg, *ca.* 4%) as white needles, mp 215–217 °C (lit.,[38] 214–216 °C); ν_{max}(KBr)/cm^{-1} 3420 (br), 1692, 1596, 1302, 1167, 695; δ_H[$CDCl_3$ + $(CD_3)_2SO$, 300 MHz] *ca.* 8.3 (br s, 1 H, OH), 7.45–7.25 (m, 12 H, OCH_2*Ph*, 2-H and 6-H), 6.85 (t, *J* 2.4, 1 H, 4-H), 5.09 (s, 4 H, 2 × OCH_2Ph); δ_C[$CDCl_3$ + $(CD_3)_2SO$, 75.5 MHz] 168.2 (CO), 159.6 (C-3 and C-5), 136.4 (2 × Ph), 132.8 (C-1), 128.5 (Ph), 127.9 (Ph), 127.4 (Ph), 108.4 (C-2 and C-6), 107.1 (C-4), 70.1 (2 × OCH_2); *m/z* 334 (M^+, 1%), 91 ($C_7H_7^+$, 100).

Ethyl 1-acetoxy-5-benzyloxy-1,2,3,4-tetrahydro-6-methoxy-2-oxonaphthalene-1-carboxylate 36

The β-keto ester **16** (150 mg, 0.42 mmol) in acetic acid (3 ml) was treated with manganese(III) acetate (1.8 mmol) as for the diketone **9**. Dry flash chromatography (hexane–ethyl acetate, 3:1) of the crude product gave recovered ester (12 mg, 8%), followed by *ethyl 1-acetoxy-5-benzyloxy-1,2,3,4-tetrahydro-6-methoxy-2-oxonaphthalene-1-carboxylate* **36** (140 mg, 81%) as cream crystals, mp 108–109 °C (Found: C, 67.0; H, 6.2. Calc. for $C_{23}H_{24}O_7$: C, 67.0; H, 5.9%); ν_{max}($CHCl_3$)/cm^{-1} 1750, 1495, 1440, 1285, 1240, 1217, 1080; δ_H(200 MHz) 7.44–7.30 (m, 5 H, OCH_2*Ph*), 7.19 (d, *J* 8.7, 1 H, 7-H or 8-H), 6.88 (d, *J* 8.7, 1 H, 8-H or 7-H), 5.06 (d, *J* 11.1, 1 H, OCH_2Ph, part of AB system), 4.96 (d, *J* 11.1, 1 H, OCH_2Ph, part of AB system), 4.25–4.00 (m, 2 H, OCH_2CH_3, diastereotopic), 3.90 (s, 3 H, OCH_3), 3.31–2.49 (m, 4 H, 3-H_2, 4-H_2, 2nd order), 2.17 (s, 3 H, $COCH_3$), 1.16 (t, *J* 7.2, OCH_2CH_3); δ_C(50.3 MHz) 202.3 (s, C-2), 169.0 (s, CO), 166.3 (s, CO), 152.8 (s, C-6 or C-5), 144.2 (s, C-5 or C-6), 137.4 (s, Ph), 131.7 (s, C-4a or C-8a), 128.4 (d, Ph), 128.3 (d, Ph), 128.2 (d, Ph), 126.6 (s, C-8a or C-4a), 121.6 (d, C-7 or C-8), 111.2 (d, C-8 or C-7), 81.6 (s, C-1), 74.7 (t, OCH_2Ph), 62.5 (t, OCH_2CH_3), 55.8 (q, OCH_3), 36.5 (t, C-3 or C-4), 21.5 (t, C-3 or C-4), 20.8 (q, $COCH_3$), 13.8 (q, OCH_2CH_3); *m/z* 412 (M^+, 1%), 91 ($C_7H_7^+$, 100).

Oxidation of ethyl 5-(2-benzyloxy-3-methoxyphenyl)-3-oxopentanoate 16 with manganese(III) acetate

The β-keto ester **16** (50 mg, 0.14 mmol), manganese(III) acetate dihydrate (80 mg, 0.30 mmol) and glacial acetic acid (1 ml) were stirred for 22 h in a stoppered flask. The brown suspension was poured into brine and extracted with ethyl acetate. Gravity chromatography (acid-washed silica gel; increasing polarity from petroleum spirit–dichloromethane, 1:1, to dichloromethane) of the dried, evaporated extracts provided ethyl 1-acetoxy-5-benzyloxy-1,2,3,4-tetrahydro-6-methoxy-2-oxonaphthalene-1-carboxylate **36** (7 mg, 14%), followed by *3-(2-benzyloxy-3-methoxyphenyl)propanoic acid* (20 mg, 50%) as a colourless oil (Found: M^+, 286.1205. Calc. for $C_{17}H_{18}O_4$: *M*, 286.1205); ν_{max}(film)/cm^{-1} 3500–2400, 1710, 1475, 1270, 1215, 1080, 750, 700; δ_H(200 MHz) 7.50–7.30 (m, 5 H, OCH_2*Ph*), 7.05–6.70 (m, 3 H, Ar 4-H, Ar 5-H and Ar 6-H), 5.04 (s, 2 H, OCH_2Ph), 3.89 (s, 3 H, OCH_3), 2.95 (m, 2 H, CH_2, 2nd order), 2.60 (m, 2 H, CH_2, 2nd order); δ_C(50.1 MHz) 178.2 (CO), 152.9 (ArC-3 or ArC-2), 146.1 (ArC-2 or ArC-3), 137.9 (Ph), 134.3 (ArC-1), 128.4 (Ph), 128.1 (Ph), 127.9 (Ph), 124.0 (ArC-5 or ArC-6), 121.8 (ArC-6 or ArC-5), 111.1 (ArC-4), 74.6 (OCH_2), 55.8 (OCH_3), 34.4 (C-2), 25.5 (C-3); *m/z* 286 (M^+, 6%), 92 (21), 91 ($C_7H_7^+$, 100), 65 (23).

5-Benzyloxy-6-methoxy-3-methyl-1-propionyl-2-naphthol 33

To the tetralone **24** (29 mg, 0.07 mmol) in dichloromethane (1 ml) was added silica gel (0.5 g, pH 10). After 16 h, the slurry was filtered, the solid washed with ethyl acetate, and the combined filtrates evaporated to dryness to give a pale yellow viscous oil. Gravity chromatography (silica gel, pH 10; dichloromethane–petroleum spirit, 1:1) afforded *5-benzyloxy-6-methoxy-3-methyl-1-propionyl-2-naphthol* **33** (20 mg, 81%) identical with material obtained earlier.

6,8-Dibenzyloxy-3-methyl-1-propionyl-2-naphthol 34

The diketone **11** (200 mg, 0.46 mmol) in acetic acid (3.3 ml) was treated with manganese(III) acetate (2.0 mmol) as for the diketone **9**. The crude product was stirred with silica gel (10 g, pH 10) in dichloromethane (15 ml) for 19 h. The mixture was filtered and the solid washed with ethyl acetate. The combined filtrates were evaporated, and the residue in dichloromethane filtered through a small plug of silica gel (pH 10) to provide *6,8-dibenzyloxy-3-methyl-1-propionyl-2-naphthol* **34** (133 mg, 68% based on the diketone **11**) as pale yellow crystals, mp 36–38 °C (Found: C, 79.2; H, 6.4. Calc. for $C_{28}H_{26}O_4$: C, 78.9; H, 6.1%); ν_{max}(melt)/cm^{-1} 3450, 1690, 1625, 1605, 1505, 1400, 1255, 1160, 695; δ_H(300 MHz) 8.85 (s, 1 H, OH), 7.49–7.34 (m, 11 H, 2 × OCH_2*Ph* and 4-H), 6.79 (d, *J* 2.2, 1 H, 5-H or 7-H), 6.73 (d, *J* 2.2, 7-H or 5-H), 5.13 (s, 2 H, OCH_2Ph), 5.11 (s, 2 H, OCH_2Ph), 2.75–2.55 (m, 2 H, CH_2CH_3, diastereotopic), 2.36 (s, 3 H, 3-CH_3), 0.86 (t, *J* 7.3, CH_2CH_3); δ_C(75.5 MHz) 210.9 (s, CO), 156.2 (s, ArCO), 154.4 (s, ArCO), 152.2 (s, ArCO), 137.0 (s, Ph), 136.1 (s, Ph), 131.7 (d, C-4), 130.4 (s), 128.8 (d, Ph), 128.4 (d, Ph), 128.3 (d, Ph), 127.9 (d, Ph), 127.8 (d, Ph), 117.7 (s), 116.5 (s), 101.2 (d, C-5 or C-7), 100.7 (d, C-7 or C-5), 71.5 (t, OCH_2), 70.2 (t, OCH_2), 37.9 (t, CH_2CH_3), 16.4 (d, 3-CH_3), 8.8 (q, CH_2CH_3); *m/z* 426 (M^+, 2%), 91 ($C_7H_7^+$, 100).

6-Acetylamino-8-benzyloxy-3-methyl-1-propionyl-2-naphthol 35

The tetralone **27** (260 mg, 0.6 mmol) in dichloromethane (20 ml) was treated with silica gel (5 g, pH 10) as for the tetralone **24**. Filtration of the crude product in ethyl acetate through a small column of silica gel (pH 10) gave, on concentration of the eluent, *6-acetylamino-8-benzyloxy-3-methyl-1-propionyl-2-naphthol* **35** (180 mg, 80%) as pale yellow crystals, mp 93–95 °C (Found: C, 73.0; H, 6.3; N, 3.5. Calc. for $C_{23}H_{23}NO_4$: C, 73.2; H, 6.1; N, 3.7%); ν_{max}(KBr)/cm^{-1} 3403, 3304, 2934, 1691, 1665, 1615, 1586, 1551, 1502, 1457, 1413, 1376, 1333, 1286, 1260, 1171, 1092, 697; δ_H(300 MHz) 8.9 (br s, 1 H, NH), 7.80 (br s, 1 H, OH), 7.45–7.30 (m, 8 H, OCH_2*Ph*, 4-H, 5-H and 7-H), 5.04 (s, 2 H, OCH_2Ph), 2.60 (m, 2 H, CH_2CH_3, diastereotopic), 2.32 (s, 3 H, 3-CH_3), 2.20 (s, 3 H, $NCOCH_3$), 0.82 (t, *J* 7.3, 3 H, CH_2CH_3); δ_C(75.5 MHz) 211.0 (s, $COCH_2CH_3$), 169.1 (s, $NCOCH_3$), 153.6 (s, C-2 or C-8), 153.0 (s, C-8 or C-2), 135.9 (s, Ph or C-6), 134.6 (s, C-6 or Ph), 132.0 (d, C-4), 129.8 (s), 128.9 (s), 128.7 (d, Ph), 128.4 (d, Ph), 127.8 (d, Ph), 119.2 (s, C-3), 116.3 (s), 109.8 (d, C-5), 102.6 (d, C-7), 71.4 (t, OCH_2), 37.9 (t, CH_2CH_3), 24.4 (q, $NCOCH_3$), 16.3 (q, 3-CH_3), 8.6 (q, CH_2CH_3); *m/z* 377 (M^+, 7%), 91 ($C_7H_7^+$, 100), 43 (CH_3CO^+, 61).

Ethyl 5-benzyloxy-1,2,3,4-tetrahydro-1-hydroxy-6-methoxy-2-oxonaphthalene-1-carboxylate 37 and ethyl 5-benzyloxy-2-hydroxy-6-methoxynaphthalene-1-carboxylate 41

The ester **36** (12 mg, 0.03 mmol) in dichloromethane (2 ml) was treated with silica gel (1 g, pH 10) as for the tetralone **24**. Gravity chromatography (silica gel, pH 10; increasing polarity from dichloromethane to dichloromethane–ethyl acetate, 4:1) of the crude material provided *ethyl 5-benzyloxy-2-hydroxy-6-methoxynaphthalene-1-carboxylate* **41** (2 mg, 20%) (Found: M^+, 352.1310. Calc. for $C_{21}H_{20}O_5$: *M*, 352.1310); δ_H(300 MHz) 12.30 (s, 1 H, OH), 8.58 (d, *J* 9.3, 1 H, 3-H or 4-H), 8.28 (d, *J* 9.3, 1 H, 4-H or 3-H), 7.56–7.36 (m, 6 H, OCH_2*Ph* and 7-H or 8-H), 7.12 (d, *J* 9.3, 1 H, 8-H or 7-H), 5.17 (s, 2 H, OCH_2Ph), 4.60 (q, *J* 7.1, 2 H, OCH_2CH_3), 4.02 (s, 3 H, OCH_3), 1.56 (t, *J* 7.1, 3 H, OCH_2CH_3); δ_C(75.5 MHz) 172.7 (CO), 163.6 (ArCO), 147.1 (ArCO), 142.8 (ArCO), 137.7 (Ph), 130.4 (ArCH), 128.7 (Ph), 128.5 (Ph), 128.3 (Ph), 127.4 (ArC), 125.8 (ArC), 124.9 (ArC), 121.7 (ArCH), 119.8 (ArCH), 116.8 (ArCH), 75.5 (OCH_2Ph), 61.8 (OCH_2CH_3), 56.7 (OCH_3), 14.1 (OCH_2CH_3); *m/z* 352 (M^+, 7%), 261 ($M^+ - CH_2Ph$), 215 (30), 91 ($C_7H_7^+$, 100).

Further elution gave *ethyl 5-benzyloxy-1,2,3,4-tetrahydro-1-hydroxy-6-methoxy-2-oxonaphthalene-1-carboxylate* **37** (8 mg,

75%) as a colourless oil (Found: M^+, 370.1416. Calc. for $C_{21}H_{22}O_6$: *M*, 370.1416); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3460, 1740, 1720, 1490, 1440, 1280, 1250, 1215, 1080; δ_H(300 MHz) 7.43–7.25 (m, 6 H, OCH_2*Ph* and 7-H or 8-H), 6.97 (d, *J* 8.7, 1 H, 8-H or 7-H), 5.06 (d, *J* 11.2, 1 H, OCH_2Ph, part of AB system), 5.01 (d, *J* 11.2, 1 H, OCH_2Ph, part of AB system), 4.50 (s, 1 H, OH), 4.16 (q, *J* 7.1, 2 H, OCH_2CH_3), 3.94 (s, 3 H, OCH_3), 3.23–3.15 (m, 1 H, CH_2), 2.93–2.82 (m, 2 H, CH_2), 2.41–2.27 (m, 1 H, CH_2), 1.22 (t, *J* 7.1, OCH_2CH_3); δ_C(75.5 MHz) 207.7 (s, CO), 169.8 (s, CO), 153.0 (s, C-6 or C-5), 144.0 (s, C-5 or C-6), 137.5 (s, Ph), 131.0 (s, C-4a or C-8a), 128.8 (d, Ph), 128.6 (d, Ph), 128.4 (d, Ph), 127.7 (s, C-8a or C-4a), 122.4 (d, C-7 or C-8), 111.4 (d, C-8 or C-7), 79.2 (s, C-1), 74.8 (t, OCH_2Ph), 62.5 (t, OCH_2CH_3), 55.7 (q, OCH_3), 34.1 (t, C-3), 20.6 (t, C-4), 13.7 (q, OCH_2CH_3); *m/z* 370 (M^+, 1%), 297 ($M^+ - CH_3CH_2OCO$, 9), 91 ($C_7H_7^+$, 100).

1-Acetyl-1-hydroxy-6,8-dimethoxynaphthalen-2(1*H*)-one 40

The tetralone **29** (80 mg, 0.25 mmol) in dichloromethane (8 ml) was treated with silica gel (2 g, pH 10) as for the tetralone **24**. Dry flash chromatography (hexane–ethyl acetate 1:1) of the crude produce gave 1-*acetyl*-1-*hydroxy*-6,8-*dimethoxynaphthalen*-2(1H)-*one* **40** (50 mg, 77%) as a viscous orange oil (Found: M^+, 262.0841. Calc. for $C_{14}H_{14}O_5$: *M*, 262.0841); ν_{max}(film)/cm^{-1} 3390, 1760, 1623, 1371, 1213, 1198, 1160; δ_H(300 MHz) 9.25 (s, 1 H, OH), 7.17 (d, *J* 8.8, 1 H, 3-H or 4-H), 7.12 (d, *J* 8.8, 1 H, 4-H or 3-H), 6.69 (d, *J* 2.1, 1 H, 5-H or 7-H), 6.47 (d, *J* 2.1, 1 H, 7-H or 5-H), 4.00 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 2.37 (s, 3 H, $COCH_3$); δ_C(75.5 MHz) 169.5 (CO), 157.5 (C-6 or C-8), 157.1 (C-8 or C-6), 145.0 (CO), 135.2 (C-4a or C-8a), 132.0 (C-8a or C-4a), 123.2 (C-3 or C-4), 117.7 (C-4 or C-3), 111.3 (C-1), 99.3 (C-5 or C-7), 98.2 (C-7 or C-5), 56.2 (OCH_3), 55.3 (OCH_3), 20.7 ($COCH_3$); *m/z* 262 (M^+, 12%), 220 ($M^+ - CH_2CO$, 100), 205 (56), 177 (32).

Acknowledgements

The work described was carried out during the tenure of an Australian Postgraduate Research Award and a Kodak Scholarship (J. F. J.).

References

1 For reviews see: M. Brufani, *Top. Antibiot. Chem.*, 1977, **1**, 91; W. Wehrli, *Top. Curr. Chem.*, 1977, **72**, 21; K. L. Rinehart, Jr. and L. S. Shield, *Fortschr. Chem. Org. Naturst.*, 1976, **33**, 231.

2 For biosynthetic reviews see: O. Ghisalba, *Chimia*, 1985, **39**, 79; O. Ghisalba, J. A. L. Auden, T. Schupp and J. Nüesch, in *Biotechnology of Industrial Antibiotics*, ed. E. J. Vandamme, Marcel Dekker, New York, 1984, p. 281; G. Lancini, in *Biochemistry and Genetic Regulation of Commercially Important Antibiotics*, ed. L. C. Vining, Addison-Wesley, London, 1983, p. 231; G. Lancini and M. Grandi, in *Antibiotics. Vol. IV. Biosynthesis*, ed. J. W. Corcoran, Springer-Verlag, Berlin, 1981, p. 12.

3 J. J. Kibby, I. A. McDonald and R. W. Rickards, *J. Chem. Soc, Chem. Commun.*, 1980, 768; O. Ghisalba, H. Fuhrer, W. J. Richter and S. Moss, *J. Antibiot.*, 1981, **34**, 58; O. Ghisalba and J. Nüesch, *J. Antibiot.*, 1981, **34**, 64; K. Hatano, S. I. Akiyama, M. Asai and R. W. Rickards, *J. Antibiot.*, 1982, **35**, 1415; K. L. Rinehart, Jr., M. Potgieter, W. Jin, C. J. Pearce, D. A. Wright, J. L. C. Wright, J. A. Walter and A. G. McInnes, in *Trends in Antibiotic Research. Genetics, Biosynthesis, Actions, and New Substances*, ed. H. Umezawa, A. L. Demain, T. Hata and C. R. Hutchinson, Japan Antibiotics Research Association, Tokyo, 1982, p. 171; T. S. Wu, J. Duncan, S. W. Tsao, C. J. Chang, P. J. Keller and H. G. Floss, *J. Nat. Prod.*, 1987, **50**, 108; H. G. Floss and J. M. Beale, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 146.

4 M. G. Anderson, D. Monypenny, R. W. Rickards and J. M. Rothschild, *J. Chem. Soc., Chem. Commun.*, 1989, 311.

5 R. W. Rickards, in *Studies in Natural Products Chemistry. Vol. 9*, ed. Atta-ur-Rahman, Elsevier Science Publishers B.V., Amsterdam, 1991, p. 431; *Proceedings of the Fifth Asian Symposium on Medicinal Plants and Spices*, ed. B. H. Han, D. S. Han, Y. N. Han and W. S. Woo, Seoul, 1984, p. 615.

6 A. I. Day, Ph.D. Thesis, Australian National University, Canberra, 1983.

7 (*a*) A. S. Kende, F. H. Ebetino and T. Ohta, *Tetrahedron Lett.*, 1985, **26**, 3063; (*b*) A. S. Kende, K. Koch and C. A. Smith, *J. Am. Chem. Soc.*, 1988, **110**, 2210.

8 (*a*) B. B. Snider, R. Mohan and S. A. Kates, *J. Org. Chem.*, 1985, **50**, 3659; (*b*) B. B. Snider, R. Mohan and S. A. Kates, *Tetrahedron Lett.*, 1987, **28**, 841; (*c*) R. Mohan, S. A. Kates, M. A. Dombroski and B. B. Snider, *Tetrahedron Lett.*, 1987, **28**, 845; (*d*) B. B. Snider and M. A. Dombroski, *J. Org. Chem.*, 1987, **52**, 5487; (*e*) B. B. Snider, J. J. Patricia and S. A. Kates, *J. Org. Chem.*, 1988, **53**, 2137; (*f*) J. E. Merritt, M. Sasson, S. A. Kates and B. B. Snider, *Tetrahedron Lett.*, 1988, **29**, 5209.

9 J. R. Peterson, R. S. Egler, D. B. Horsley and T. J. Winter, *Tetrahedron Lett.*, 1987, **28**, 6109.

10 E. J. Corey and M.-C. Kang, *J. Am. Chem. Soc.*, 1984, **106**, 5384.

11 A. Citterio, L. Pesce, R. Sebastiano and R. Santi, *Synthesis*, 1990, 142.

12 A. Citterio, D. Fancelli, C. Finzi, L. Pesce and R. Santi, *J. Org. Chem.*, 1989, **54**, 2713.

13 I. S. Aidhen and N. S. Narasimham, *Tetrahedron Lett.*, 1989, **30**, 5323; *Indian J. Chem, Sect. B*, 1993, **32**, 222.

14 A. Citterio, A. Cerati, R. Sebastiano, C. Finzi and R. Santi, *Tetrahedron Lett.*, 1989, **30**, 1289.

15 D. H. R. Barton, R. D. Bracho, A. A. L. Gunatilaka and D. A. Widdowson, *J. Chem. Soc., Perkin Trans. 1*, 1975, 579.

16 A. M. Becker, R. W. Rickards and R. F. C. Brown, *Tetrahedron*, 1983, **39**, 4189.

17 W. J. de Klein, in *Organic Syntheses by Oxidation with Metal Compounds*, ed. W. J. Mijs and C. R. H. I. de Jonge, Plenum Press, New York, 1986, p. 261, and references cited therein.

18 V. Karnojitzky, *Russ. Chem. Rev. (Engl. Transl.)*, 1981, **50**, 888.

19 R. van Helden and E. C. Kooyman, *Rec. Trav. Chim. Pays-Bas*, 1961, **80**, 57.

20 B. B. Snider and J. J. Patricia, *J. Org. Chem.*, 1989, **54**, 38.

21 D. D. Perrin and W. L. F. Armarego, *Purification of Laboratory Chemicals*, 3rd Edn, Pergamon Press, Oxford, 1988.

22 M. R. Winkle, J. M. Lansinger and R. C. Ronald, *J. Chem. Soc., Chem. Commun.*, 1980, 87.

23 W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

24 *Practical Organic Chemistry: A Student Handbook of Techniques*, ed. J. T. Sharp, I. Gosney and A. G. Rowley, Chapman and Hall, London, 1989, p. 160.

25 D. D. Weller, E. P. Stirchak and D. L. Weller, *J. Org. Chem.*, 1983, **48**, 4597.

26 A. M. Choudhury, *J. Chem. Soc., Perkin Trans. 1*, 1974, 132.

27 D. D. Ridley, E. Ritchie and W. C. Taylor, *Aust. J. Chem.*, 1968, **21**, 2979.

28 M. Kuchar, B. Brunová, V. Rejholec, Z. Roubal and O. Nemecek, *Collect. Czech. Chem. Commun.*, 1976, **41**, 633.

29 R. Huisgen, G. Seidl and I. Wimmer, *Liebigs Ann. Chem.*, 1964, **677**, 21.

30 D. C. Appleton, B. Brocklehurst, J. McKenna, J. M. McKenna, S. Thackeray and A. R. Walley, *J. Chem. Soc., Perkin Trans. 2*, 1980, 87.

31 R. C. Anand and H. Ranjan, *Bull. Chem. Soc. Jpn*, 1983, **56**, 1889.

32 B. Lal, P. Singh, A. P. Bhaduri and K. Kar, *Indian J. Chem.*, 1975, **13**, 898.

33 A. K. Sinhababu and R. T. Borchardt, *J. Org. Chem.*, 1983, **48**, 2356.

34 J. A. Elix and B. A. Ferguson, *Aust. J. Chem.*, 1978, **31**, 1041.

35 P. E. Pfeffer and L. S. Silbert, *J. Org. Chem.*, 1970, **35**, 262.

36 P. E. Pfeffer, L. S. Silbert and J. M. Chirinko, Jr., *J. Org. Chem.*, 1972, **37**, 451.

37 B. Vu, G. Mezey-Vandor and M. Nogradi, *Liebigs Ann. Chem.*, 1984, 734.

38 N. Katagiri, J. Nakano and T. Kato, *J. Chem. Soc., Perkin Trans. 1*, 1981, 2710.

Paper 6/03211G
Received 8th *May* 1996
Accepted 4th *July* 1996