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IMPROVED METHODS FOR THE REDUCTIVE ALKYLATION OF METHOXYBENZOIC ACIDS AND ESTERS: APPLICATIONS TO THE SYNTHESIS OF BICYCLIC KETONES

ROBERT J. HAMILTON, LEWIS N. MANDER* and S. PAUL SETHI
Research School of Chemistry, Australian National University, G.P.O. Box 4, Canberra, A.C.T. 2601, Australia

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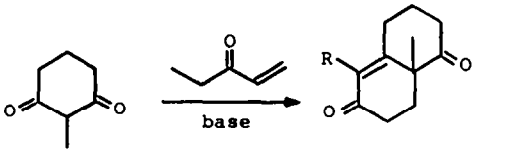
Abstract—A series of methoxybenzoic acids and esters was reduced by metal–ammonia solutions and the resulting 1,4-dihydro products were either alkylated *in situ* or isolated and alkylated subsequently. Three different types of alkyl iodides were employed to introduce the elements of a butanone or pentanone side-chain as a prelude to adding a fused six-membered ring, thereby completing the preparation of several analogues of the Wieland–Miescher ketone **4a** in which the angular substituent was oxygenated.

INTRODUCTION

We recently began a study on the synthesis of bicyclic diketones of general structure **1** with a view to employing them as intermediates for the synthesis of bruceantin **2**[1] (Scheme 1) and other biologically active quassinoids.[2,3] The Wieland–Miescher ketone **4a**[4] and its simple analogue **4b**[5] are readily made by Robinson annulation of 2-methylcyclohexa-1,3-dione **3** (Scheme 2), but the prospect of obtaining compounds of type **1** by an analogous procedure was not sufficiently encouraging as to warrant serious investigation. We therefore embarked upon an investigation into the reductive alkylation of 2,6-dimethoxybenzoic acid **5a** and its methyl ester **5b** as a means of preparing **6a** or **b**, and thence **1a** or **b** (Scheme 3). In this paper we report the successful outcome of this investigation, which has yielded **1a**, **b** and several other useful analogues and derivatives.[6] We also describe a number of cognate activities which provide useful insights into the scope and limitations of the reductive alkylation process, not only for substrates **5a** and **b**, but for methoxybenzoic acid derivatives generally.

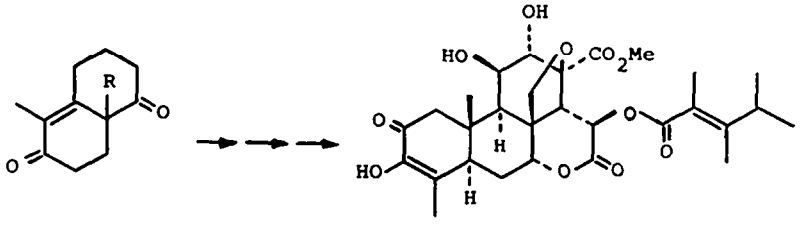
The Birch reductions of methoxybenzoic acids under the standard conditions,[7] which prescribe a moderately large excess of ethanol or methanol, are quite straightforward, although a *para*-methoxyl is invariably hydrogenolyzed. To carry out alkylations of the intermediate enediolate anions, however, it is necessary to minimize the amount of added proton source, and then hydrogenolysis of 2-methoxy substituents can become a serious problem.[8,9] When 2-methoxybenzoic acid itself is reduced by sodium or lithium under "aprotic" conditions, for example, up to 70% hydrogenolysis occurs.[8] The problem is often aggravated by electron-releasing substituents at C(3), C(4) or C(6) while an alkyl or alkoxy group at C(5) minimizes the loss.[10] The molar equivalent of ammonium ion generated by addition of the benzoic acid to the ammonia appears to be the culprit in many cases, since addition of 1 equiv of base may suppress hydrogenolysis completely.[11]

The reductive alkylation of benzoic esters is an excellent alternative, since methoxyl loss is relatively uncommon, solubility is improved, isolation pro-



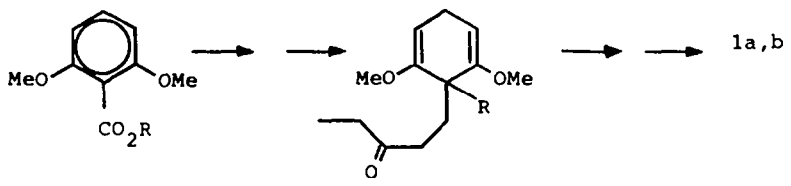
3 4 a R = H b R = Me

Scheme 2.



1 a R = CO_2Me b R = CH_2OR' 2

Scheme 1.



5 a R = H
b R = Me

6 a R = CO_2Me
b R = CH_2OR'

Scheme 3.

cedures are facilitated, and the products are more stable.

Reduction of aromatic esters

Early studies on the reduction of aromatic esters by metal–ammonia systems afforded little, if any, ring-reduced compounds, but rather the products of functional group reduction.[12] Since this was the expected outcome, few systematic attempts to achieve ring-reduction were made until recently, even though some success was obtained with magnesium reductions in 1962.[13]

We were prompted by the seminal work of Narisada and Watanabe on the ring-reduction of aromatic ketones[14] to investigate the application of similar conditions (potassium, liquid ammonia–t-butyl alcohol, −78°) to the reduction of esters, when faced with an intractable reductive alkylation of an intermediate in the total synthesis of gibberellic acid.[15,16]

The outcome was highly successful and independently achieved by Loewenthal (but with sodium metal) on a similar substrate.[17] These studies were followed in our laboratories[11,18] and those of Schultz[19] by a series of studies which demonstrated the generality of the new procedure. We also discovered that sodium and even lithium could be as effective as potassium metal.[11] At about the same time, Rabideau *et al.* developed an alternative protocol, whereby sodium was added to a mixture of substrate and 1.5 molar equiv of water, followed by inverse quenching with ammonium chloride solution. A bulky group attached to C(4), however, was observed to inhibit ring-reduction under these conditions.[20]

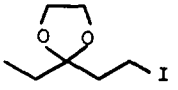
RESULTS AND DISCUSSION

Attempted syntheses of bicyclic diketones **1a** *and* **b**

Before embarking upon the preparation of ester **6a**, an attempt was made to prepare **1a** by the application of conventional annulation methods to the dihydroresorcinol derivative **8**, obtained by hydrolysis of **7** in aqueous acetonitrile–mercury(II) nitrate (Scheme 4), but reaction with ethyl vinyl ketone under a range of conditions afforded only decomposition products, among which methyl 2,6-dihydroxybenzoate was detected. We therefore returned to the original plan of introducing the required pentanone side chain into ester **7** by means of a reductive alkylation process.

Subba Rao *et al.* have shown that acrylic and crotonate esters undergo Michael reactions with the enediolate intermediates from reduction of benzoic acids.[21] No adducts were formed with vinyl ketones, however, and so we did not attempt to treat the anion derived from ester **7** with ethyl vinyl ketone. Instead, we employed the 2-trimethylsilyl analogue,[22] which appeared to be the best of the available synthetic equivalents, but no useful results were obtained.

Alkylation with iodoacetal **9** was examined next,[23] but **7** was recovered along with olefinic acetal **10**.



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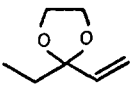
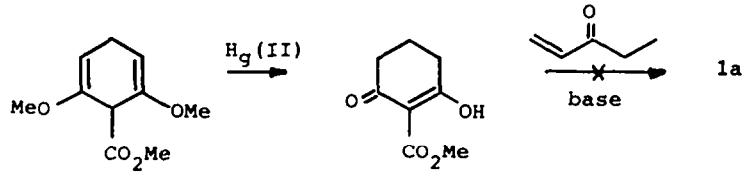


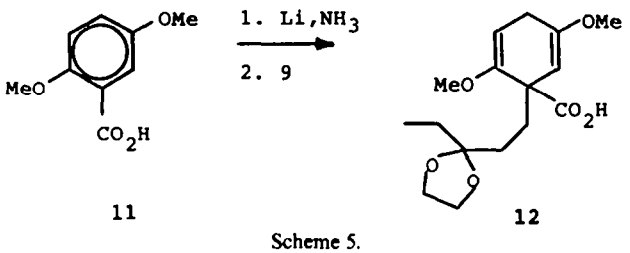
10

Although this proclivity for elimination is fairly characteristic of reagents like **9**, it was possible to use it successfully in the reductive alkylation of 2,5-dimethoxybenzoic acid **11**, affording **12** in 67% yield (Scheme 5). This result was sufficiently encouraging for us to examine the possibility of using an analogue of **9** with only one oxygen-containing substituent with a view to lowering steric hindrance and in the hope that the smaller electron-withdrawing effect would reduce the tendency towards elimination. In the event, reductive alkylation of **5b** with iodides **13a** and **b** under the standard conditions (K, t-BuOH, NH_3, but with



7 8

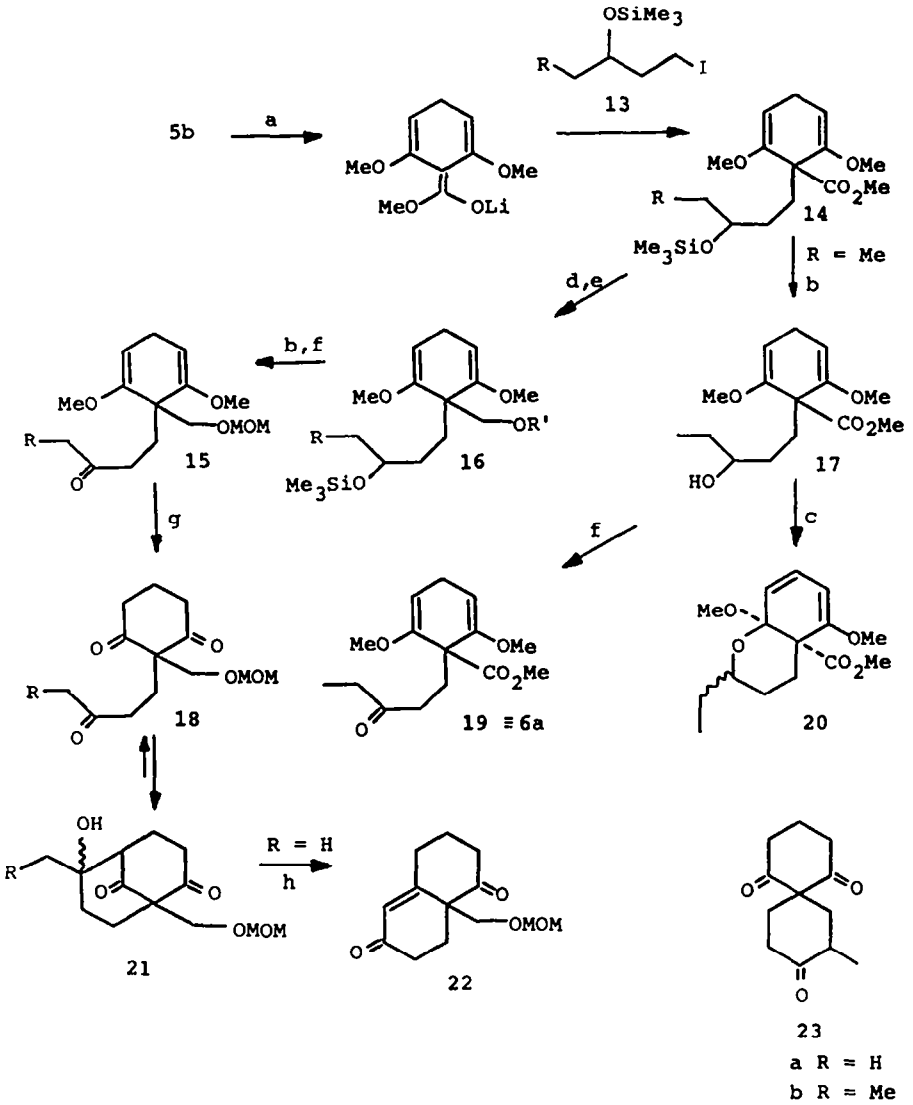
Scheme 4.



11 12

Scheme 5.

added lithium bromide to convert the initial potassium enediolate to the lithium derivative) was exceptionally clean and afforded almost quantitative yields of adducts **14a** and **b**, respectively (Scheme 6). It should be noted that alkylation with simple alkyl halides such as methyl iodide or isopropyl iodide proceeds satisfactorily on the potassium enediolates, but lithium cation exchange is essential with more complex halides. Removal of the trimethylsilyl (TMS) group from **14a** and **b** by fluoride ion was straightforward, but oxidation to the desired ketone **19** (≡ **6a**) was only achieved with difficulty. Chromium(VI)-based re-



Reagents: *a* K,NH_3 *t-BuOH; LiBr.* *b* $KF,MeOH$. *c* $Py_2Cr_2O_7$.
d $LiAlH_4$. *e* $ClCH_2OMe$, iPr_2NEt. *f* *DMSO,DCC.*
g $Hg(NO_3)_2$, $MeCN-H_2O$. *h* *piperidinium benzoate.*

Scheme 6.

agents, for example, led to allylic oxidation, and in one example pyridinium dichromate[24] afforded a product whose spectroscopic properties were consistent with structure **20**. Success was obtained with the Pfitzner–Moffat procedure[25] but attempts to hydrolyse ketone **19** to the parent triketone, or any other useful intermediate, were fruitless. Instead, the ester group in **14a** and **b** was reduced by lithium aluminium hydride and the resulting carbinols **16** (R′ = H) were protected as the methoxymethyl (MOM) ethers.[26] Removal of the TMS group and oxidation as in the preparation of **19** then afforded **15a** and **b**, respectively. Hydrolysis of **15a** by aqueous mercury(II) nitrate[27] furnished a 5:3 mixture of isomeric ketols **21a** with triketone **18a**, whereas only ketol mixture **21b** was obtained from **15b**. All attempts to transform **18b** or **21b** into **1b** (R′ = CH_2OMe) were unsuccessful. The only discreet product (obtained by heating with pyrrolidine) was a trione—formed in 43% yield—to which structure **23** was tentatively assigned. However, a 43% yield of diketone **22** was obtained from **21a** by heating with piperidinium benzoate. Some months after the completion of this phase of the work, Uda and co-workers[28] reported the preparation of **1b** (R^1 = Me, Ac and $CH_2OCH_2CH_2OMe$) by a similar strategy. Our repeated attempts to apply their conditions to the preparation of **1b** (R^1 = MOM) from **18b** were still unsuccessful, however.

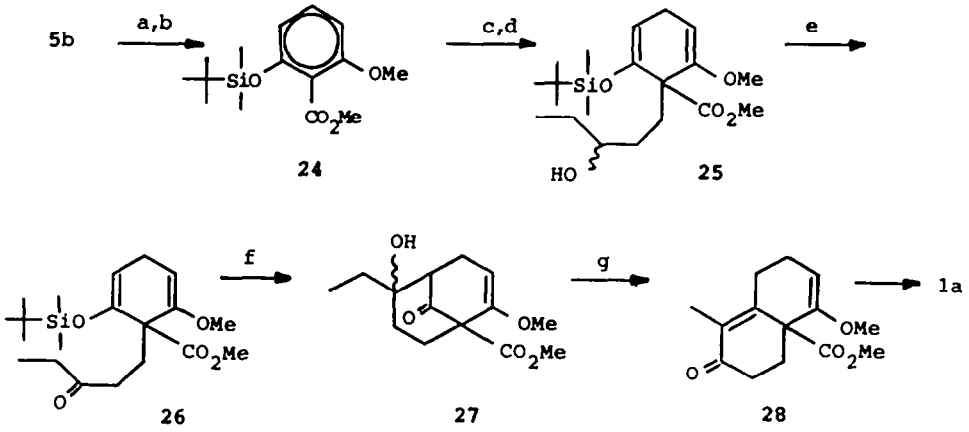
Synthesis of diketone **1a**

The difficulties associated with completing the syntheses of **1a** and **b** were strongly suspected to be closely interlinked with the β-dicarbonyl moiety in the precursor intermediates. We assumed, therefore, that the prospects for a successful completion of the desired annulation would be enhanced if one of the carbonyl groups was masked. Ester **24** was accordingly prepared and subjected to reductive alkylation as outlined in Scheme 7.[29] Each step proceeded in excellent yield up to carbinol **25**, but oxidation of this compound to **26** was barely satisfactory. Nevertheless, removal of the silyl protecting groups smoothly afforded the ketol mixture **27**, which was readily converted by potassium carbonate into **28**. Mercury(III) nitrate catalyzed hydrolysis of the enol ether function in this product then afforded the elusive **1a**.

New synthetic equivalents for vinyl ketones

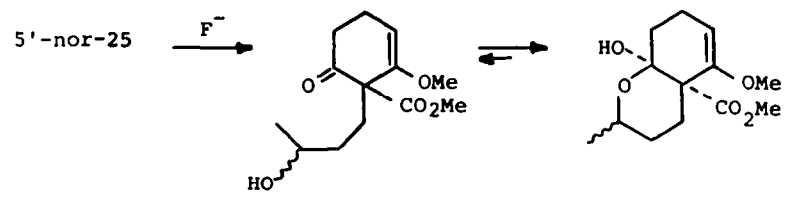
The preceding synthesis of **1a** was on the whole satisfactory, except for the oxidation of the side chain in compound **25**. The dihydroaromatic moiety and the associated enol ether functions place a severe restriction on the range of oxidants which might be used, however. In one attempt to resolve the problem, both silyl groups were removed[30] from the 5′-*nor*-homologue of **25** (Scheme 8) in the hope that keto alcohol **29** might be isolated and oxidized, but the hemiacetal **30** proved (not unexpectedly) to be the major product, and all attempts to achieve a more favourable equilibrium were fruitless.

The quest for effective synthetic equivalents to vinyl ketones is a long standing one, and one which has been pursued with great vigour and ingenuity, especially by Stork and co-workers.[31] However, virtually none of the compounds which have emerged from these programmes appeared to be suitable for the task in hand. In principle, the most promising group of reagents should be allylic halides of general type **31**, but these are characteristically difficult to prepare and handle. They generally give poor yields in alkylation processes because of a strong tendency to undergo E1 elimination.[32] The remarkable nucleophilicity of lithium enolates derived from dihydrobenzoic acids and esters, however, was such that we



Reagents: *a* BCl_3. *b* *t-BuSiMe*$_2$*Cl, imidazole.* *c* K, NH_3, *t-BuOH; LiBr.* *d* **13***b; HOAc.* *e* *DMSO, DCC.* *f* *n-Bu*$_4$*NF, THF.* *g* K_2CO_3, *MeOH.*

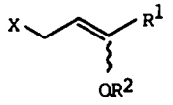
Scheme 7.



29 30

Scheme 8.

were encouraged to believe that they would react satisfactorily with appropriate analogues of **31**.



X = halide

R^1 = alkyl

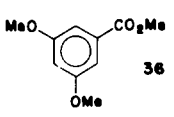
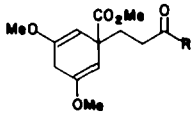
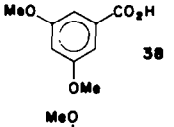
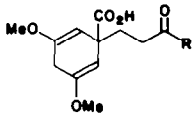
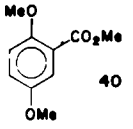
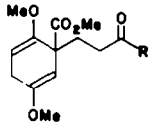
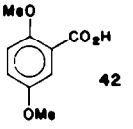
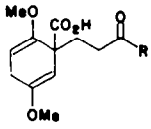
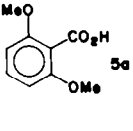
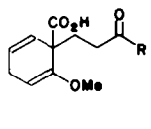
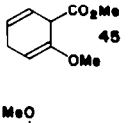
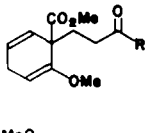
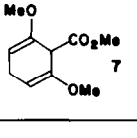
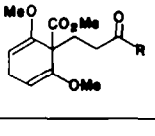
R^2 = alkyl,aryl,acyl,etc

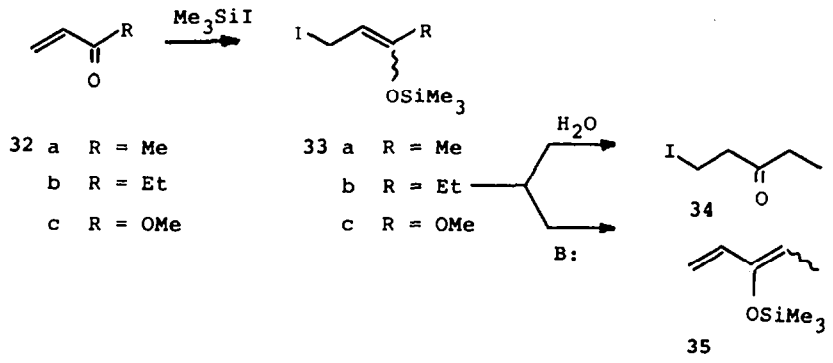
31

Trimethylsilyl iodide had been reported to react, *inter alia*, with vinyl ketone **32b** to form adduct **33b**, from which the β-iodo ketone **34** had been obtained.[33] The enol silyl ether **33b** had not been isolated, but its intermediacy had been confirmed spectroscopically and by the formation of diene **35** after treatment with a mild base (Scheme 9). It appeared that if **33b** and its analogues could be utilized, then they would be ideal candidates for our purpose. In the event, outstanding results were obtained from the reductive alkylation of a wide range of methoxybenzoic acid and ester derivatives with iodides **33a, b** and even iodide **33c** (derived from methyl acrylate); a summary is provided in Table 1.

Reduction of acids **38** and **42** by lithium metal then alkylation with iodides **33a** and **b** gave excellent results

Table 1

ENTRY	ALKYL IODIDE 33	SUBSTRATE	PRODUCT		M.P.	% YIELD
1	R = Me	 36		37a R = Me	50 - 51 °C	84
2	R = Et			37b R = Et	88 - 89 °C	87
3	R = OMe			c R = OMe	71·5 - 72 °C	87
4	R = Me	 38		39 a R = Me	119 - 120 °C	79
5	R = Et			b R = Et	106 - 108 °C	79
6	R = Me	 40		41 a R = Me	68 - 69 °C	79
7	R = Et			b R = Et	71 - 72 °C	83
8	R = Me	 42		43 a R = Me	119 - 120·5°C	82·5
9	R = Et			b R = Et	124 - 125 °C	84
10	R = Me	 5a		44 a R = Me	146 - 146·5°C	74
11	R = Et			b R = Et	134 - 135 °C	68
12	R = Me	 45		46 a R = Me	oil	82
13	R = Et			b R = Et	oil	82
14	R = Me	 7		47 a R = Me	79 - 80·5°C	80
15	R = Et			b R = Et	108 - 109 °C	82



Scheme 9.

(entries 4, 5, 8 and 9). Acid **5a** underwent clean hydrogenolysis of one methoxy group when reduced by sodium and thus adducts **44a** and **b** were obtained (entries 10 and 11). The reductive alkylation of esters **36**, **40** and **5b** under our standard conditions of potassium–ammonia–t-butyl alcohol reduction followed by lithium bromide treatment, and then addition of alkyl iodide gave reasonable quantities of adducts, but superior results were obtained from one of two modified procedures. In the case of esters **36** and **40**, the esters could be reduced directly by lithium instead of potassium metal (entries 1, 2, 3, 6 and 7). For methyl 2-methoxybenzoate and the 2,6-dimethoxy derivative **5b**, however, the use of lithium metal led to 20% methoxyl hydrogenolysis in the former substrate and extensive reduction of the ester group in the latter compound. It was necessary, therefore, to carry out the reduction (K, t-BuOH, NH_3) and alkylation (LDA, THF; iodide **33**) steps separately (entries 12–15), following which excellent yields of **46a**, **b** and **47a**, **b** were obtained.

In all of the alkylations carried out in liquid ammonia, the silyl ether functions were not preserved and the ketones were isolated directly. When the stepwise method was used the enol silyl ethers were obtained, but were promptly converted into the ketones by fluoride treatment, since the silyl ethers decomposed rapidly on exposure to air. Adduct **48**, for example, rapidly reverted to the parent ester **5b** by what we presume to be a radical-initiated chain mechanism (Scheme 10). Dihydroaromatic compounds which can fragment to form stabilized radicals are typically prone to such processes, but compounds like **48** are exceptionally labile.

CONCLUSION

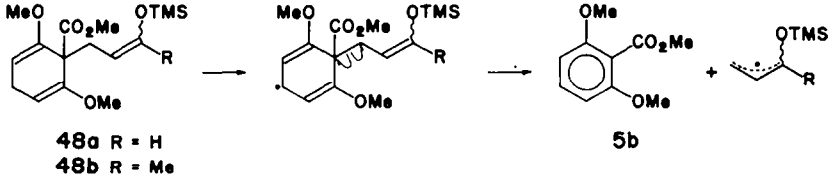
The range of reductive alkylations described in this paper widen the scope of this valuable synthetic process significantly, both in terms of aromatic substrate and electrophile. The experience gained in the preparation of these dihydroaromatic products and their subsequent manipulation should be of considerable value in planning further applications. The demonstration that allylic iodides **33a**, **b** may be used so effectively as operational equivalents to vinyl ketones leads us to the expectation of further important applications to annulation sequences, although the exceptional nucleophilicity of the dihydroaromatic enolate anions is probably difficult to duplicate with other substrates.

EXPERIMENTAL

General directions. M.ps were measured on a Reichert hot stage melting apparatus and are uncorrected. IR spectra were recorded in $CHCl_3$ soln on Jasco IRA-1 and Perkin–Elmer 457 spectrophotometers. NMR spectra were measured in $CDCl_3$ soln relative to TMS (δ 0.000) on Jeol Minimar or FX200 spectrometers operating at 100 and 200 MHz, respectively. Mass spectra were recorded at 70 eV on AEI MS902 and V.G. Micromass 7070F spectrometers. Accurate mass measurements were carried out with heptacosane as a reference compound. TLC was carried out on 2 mm layer Merck Kieselgel HF_{254}. Column chromatography was carried out on Merck Kieselgel, 70–230 mesh. Medium-pressure liquid chromatography was performed on Merck Lobar Li Chroprep Si 60 prepacked columns. Tetrahydrofuran (THF) and Et_2O were distilled from benzophenone–sodium ketyl. Dry NH_3 (100 ml) was distilled into the flame-dried reaction vessel from Na (1.0 g) and $FeCl_3$ (50 mg) after reflux at $-33°$ for 15 min. During workup procedures all aq washes were back-extracted with the appropriate organic solvent. Organic solvent extracts were usually dried over $MgSO_4$. Petroleum ether refers to the fraction with boiling range 40–60°.

Reduction of aromatic carboxylic esters

Procedure A. A soln of ester (0.67 mmol) and dry t-BuOH (74 mg, 1.0 mmol) in dry THF (1.0 ml) and dry NH_3 (20 ml) at $-78°$



Scheme 10.

under N_2 was treated with small chips of K metal (65 mg, 1.6 mg atom) and stirred at this temp for 35 min. The soln was initially pale yellow, but towards the end of the reaction became deep blue. NH_4Cl (0.5 g) was added to give a colourless soln and the mixture reduced to dryness under reduced pressure. The residue was treated with pH 5.5 buffer and extracted twice with Et_2O. After washing with brine and drying (Na_2SO_4), the soln was reduced to a colourless oil.

Reductive alkylation of aromatic carboxylic esters

Procedure B. A soln of ester (5.0 mmol) and t-BuOH (0.37 g, 5.0 mmol) in dry NH_3 (150 ml) and dry THF (10 ml) was cooled to −78° and treated with K (430 mg, 11 mmol) until a persistent blue colour was obtained. This blue colour was then dissipated with 1,3-pentadiene, anhydrous LiBr (0.65 g, 7.5 mmol) was added, and the soln was stirred at −78° for 30 min. Alkyl halide (5.1 mmol) was added and the soln was stirred at −78° for the prescribed time. The NH_3 was then allowed to evaporate overnight and the residue was diluted with pH 5.5 buffer and extracted with Et_2O (2 ×). The combined extracts were washed with brine, dried and evaporated to dryness.

Reductive alkylation of aromatic esters

Procedure C. A soln of aromatic ester (1 mmol) and t-BuOH (74 mg, 1 mmol) in dry THF (5.0 ml) and dry NH_3 (15.0 ml) was cooled to −78° under N_2 and treated with Li (15.0 mg, 2.14 mg atom) until a persistent blue colour was obtained. The soln was allowed to stir at this temp for 20 min and then the blue colour was dissipated with 1,3-pentadiene (10 μl). Alkyl iodide **2** (1.2–1.5 mmol) was added at −78° using a double tipped needle and after the prescribed time, the NH_3 was then allowed to evaporate under a stream of N_2. The residue was diluted with H_2O and extracted with EtOAc (2 × 20 ml), dried (Na_2SO_4), concentrated, and chromatographed on silica gel using ether–hexane (1 : 1) as the eluant.

Reductive alkylation of aromatic acids

Procedure D. Dry NH_3 (15 ml) was added to a soln of carboxylic acid (0.63 mmol) in dry THF (2 ml) under N_2, the resulting suspension of ammonium salt cooled to −78°, and treated with chips of Li metal (~ 2.4 mg atom) until a persistent blue colour was obtained. After 15 min the colour was discharged by the addition of 1,3-pentadiene, alkyl iodide (1.2–1.5 mmol) was added in dry THF (0.6 ml), and stirring continued at −78° for the prescribed time. The NH_3 was removed in a stream of N_2 and the residue dissolved in H_2O. After extraction with Et_2O to remove neutral material, the residue was acidified with pH 5.5 phosphate buffer, and extracted with EtOAc. This extract was washed with brine, dried (Na_2SO_4) and reduced to dryness.

Methyl 2,6-dimethoxy-2,5-cyclohexadiene-1-carboxylate (**7**)

Reduction of methyl 2,6-dimethoxybenzoate, using procedure A, gave ester **7** (quantitative yield) as a yellow oil, which was recrystallized from cold Et_2O–petroleum ether to give white needles (91% overall), m.p. 45.5–46°. IR ν_{max} 1740 (ester), 1695, 1665 (C=C—OCH_3) cm^{-1}. ^{1}H-NMR: δ 4.75 (2H, t, J = 4 Hz, H-3, 5), 3.87–3.70 (1H, m, H-1), 3.62 (3H, s, $CO_2C\underline{H}_3$), 3.44 (6H, s, 2 × $OC\underline{H}_3$), 2.86 (2H, m, H-4). ^{13}C-NMR: δ 171.7 (s, C=O), 150.1 (s, C-2, C-6), 92.9 (dt, J_1 = 156 Hz, J_2 = 4 Hz, C-3, C-5), 54.6 (q, J = 145 Hz, $CO_2\underline{C}H_3$), 52.5 (q, J = 148 Hz, 2 × $O\underline{C}H_3$), 50.0 (d, J = 138 Hz, C-1), 24.5 (t, J = 131 Hz, C-4). MS *m/z* 198 (4%, M^+), 139 (100), 138 (9), 124 (9). (Found: C, 60.51; H, 7.00. Calc for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12%.)

Methyl 6-hydroxy-2-oxo-6-cyclohexene-1-carboxylate (**8**)

Ester **7** (2.00 g, 10 mmol) and mercuric nitrate (1.08 g, 3.3 mmol) were stirred in a soln of H_2O (15 ml) and acetonitrile (70 ml) at room temp for 24 h, under N_2. The solvents were removed *in vacuo* (water bath 40°) and the residue was treated with H_2O and extracted with EtOAc (3 ×). The combined extracts were washed with brine, dried and evaporated to give ester **8** (1.64 g, 90%) as a pale yellow oil. A sample was prepared for analysis by Kugelrohr distillation. IR ν_{max} 2900–2500 (enol OH), 1710 (ester), 1650, 1580 (enol C=C) cm^{-1}. ^{1}H-NMR: δ 14.25 (1H, br s, exch, O<u>H</u>), 3.88 (3H, s, $OC\underline{H}_3$), 2.60 (4H, br t, J = 7 Hz, H-3, H-5), 2.05 (2H, p, J = 7 Hz, H-4). MS *m/z* 170 (66%, M^+), 150 (20), 142 (100), 128 (20), 88 (10), 84 (10). (Found: C, 56.55; H, 5.97. Calc for $C_8H_{10}O_4$: C, 56.47; H, 5.92%.)

3,3-Ethylenedioxy-1-iodopentane (**9**)

1-Chloro-3,3-ethylenedioxypentane (2.0 g, 12 mmol), NaI (9.1 g, 61 mmol), pyridine (400 mg, 5 mmol) and methyl ethyl ketone (75 ml) were heated at reflux under N_2 for 4 days.[34] The solvent was then removed *in vacuo* (water bath 40°) and the residue was diluted with Et_2O. This Et_2O soln was washed with H_2O, 5% w/v $NaHSO_3$ aq, brine, dried and evaporated to yield the iodide **9** (2.9 g, 94%) as an oil. An analytical sample was prepared using PLC. IR ν_{max} (neat) 2960, 2860 (C—H), 1460, 1350, 1330 cm^{-1}. ^{1}H-NMR: δ 3.95 (4H, s, $OC\underline{H}_2C\underline{H}_2O$), 3.17 (2H, t, J = 10 Hz, H-1), 2.26 (2H, t, J = 10 Hz, H-2), 1.65 (2H, q, J = 8 Hz, H-4), 0.93 (3H, t, J = 8 Hz, H-5). MS *m/z* 227 (81%, M^+ − 29), 183 (7), 155 (24), 137 (26), 101 (100). (Found: C, 32.88; H, 5.15; I, 49.78. Calc for $C_7H_{13}IO_2$: C, 32.83; H, 5.12; I, 49.56%.)

1-(3',3'-Ethylenedioxypentyl)-2,5-dimethoxy-2,5-cyclohexadiene-1-carboxylic acid (**12**)

Reductive alkylation by procedure D of 2,5-dimethoxybenzoic acid (114 mg, 0.63 mmol) with iodide **9** (200 mg, 0.78 mmol) for 2 h at −78° gave acid **12** (130 mg, 67%). An analytical sample was prepared by recrystallization from CH_2Cl_2–petroleum ether, m.p. 105–110°. IR ν_{max} 3500–2300 (acid), 1700 (C=O), 1650 (C=C—OCH_3) cm^{-1}. ^{1}H-NMR: δ 8.35 (1H, br s, $CO_2\underline{H}$), 4.80 (1H, t, J = 4 Hz, H-3), 4.38 (1H, s, H-6), 3.92 (4H, s, $OC\underline{H}_2C\underline{H}_2O$), 3.58 (6H, s, 2 × $OC\underline{H}_3$), 2.86 (2H, d, J = 4 Hz, H-4), 2.27–1.20 (6H, m, H-2', 4'), 0.89 (3H, t, J = 8 Hz, H-5'). MS *m/z* 312 (1%, M^+), 238 (8), 268 (23), 152 (94), 152 (67), 101 (100). (Found: C, 61.47; H, 7.91. Calc for $C_{16}H_{24}O_6$: C, 61.52; H, 7.74%.)

1-Iodopentan-3-ol

1-Chloropentan-3-ol[35] (11.0 g, 90 mmol) and NaI (66 g, 440 mmol) were heated at reflux in methyl ethyl ketone (110 ml) under N_2 for 2 days. The mixture was cooled and filtered and the filter cake was washed with hot Me_2CO. The solvents were then removed *in vacuo* and the residue was diluted with H_2O and extracted with Et_2O (3 ×). The combined extracts were washed with sat $NaHSO_3$ aq, brine, dried and evaporated to give 1-iodopentan-3-ol (17.7 g, 92%) as an oil. IR ν_{max} (neat) 3350 (OH) cm^{-1}. ^{1}H-NMR: δ 3.68 (1H, p, J = 7 Hz, H-3), 3.32 (2H, t, J = 7 Hz, H-1), 2.10 (1H, s, exch, OH), 2.08–1.81 (2H, m, H-2), 1.53 (2H, p, J = 8 Hz, H-4), 0.97 (3H, t, J = 8 Hz, H-5). MS *m/z* 214 (100%, M^+), 185 (32), 155 (11), 68 (43), 58 (62). (Found: C, 28.29; H, 5.23; I, 58.93. Calc for $C_5H_{11}IO$: C, 28.06; H, 5.18; I, 59.29%.)

1-Iodo-3-trimethylsiloxypentane (**13b**)

A soln of 1-iodopentanol (14.0 g, 65 mmol), ethyldiisopropylamine (9.2 g, 71 mmol) and trimethylsilyl chloride (7.7 g, 71 mmol) in dry CH_2Cl_2 (200 ml) was stirred at room temp for 30 min. The soln was then washed with pH 5.5 buffer, brine, dried and evaporated to yield a colourless oil which was flash chromatographed over a column of silica (30 × 200 mm) with CH_2Cl_2 as eluant to give **13b** (16.0 g, 86%) as a colourless oil. IR ν_{max} (neat) 2950, 2850 cm^{-1}. ^{1}H-NMR: δ 3.77 (1H, p, J = 6 Hz, H-3), 3.33 (2H, t, J = 6 Hz, H-1), 2.02 (2H, q, J = 6 Hz, H-2), 1.57 (2H, p, J = 8 Hz, H-4), 0.92 (3H, t, J = 8 Hz, H-5), 0.15 (9H, s, $Si(C\underline{H}_3)_3$). MS *m/z* 286 (< 1%, M^+), 271 (66), 257 (100), 243 (38), 185 (21), 131 (90). (Found: C, 33.52; H, 6.61; I, 44.20. Calc for $C_8H_{19}IOSi$: C, 33.57; H, 6.69; I, 44.34%.)

1-Iodo-3-trimethylsiloxybutane (**13a**)

Using the above procedures, 1-chlorobutan-3-ol (15.0 g, 75 mmol) was prepared and converted to the trimethylsilyl ether **13a** (14.7 g, 72%), which was a colourless oil. ^{1}H-NMR: δ 3.87

(1H, p, J = 7 Hz, H-3), 3.20 (2H, t, J = 7 Hz, H-1), 1.92 (2H, q, J = 7 Hz, H-2), 1.12 (3H, d, J = 7 Hz, H-4), 0.08 (9H, s, Si($C\underline{H}_3$)$_3$). MS *m/z* 272 (2%, M^+), 257 (55), 229 (33), 185 (43), 107 (88), 73 (100). (Found: C, 30.76; H, 6.09; I, 46.59. Calc for $C_7H_{17}IOSi$: C, 30.98; H, 6.30; I, 46.62%.)

Methyl 2,6 - *dimethoxy* - 1 - (3' - *trimethylsiloxybutyl*) - 2,5 - *cyclohexadiene* - 1 - *carboxylate* (**14a**)

Methyl 2,6-dimethoxybenzoate **5b** (4.9 g, 25 mmol) was reduced and alkylated at −78° for 3 h with iodide **13a** (7.00 g, 26 mmol) using standard procedure B to give ester **14a** (8.29 g, 97%) as an oil. IR ν_{max} (neat) 1730 (ester), 1690, 1655 (C=C—OCH_3) cm^{-1}. ^{1}H-NMR: δ 4.83 (2H, t, J = 4 Hz, H-3, 5), 3.72–3.63 (1H, m, H-3'), 3.67 (3H, s, $CO_2C\underline{H}_3$), 3.50 (6H, s, 2 × $OC\underline{H}_3$), 2.92 (2H, t, J = 4 Hz, H-4), 2.15–1.90 (2H, m, H-1'), 1.33–1.20 (2H, m, H-2'), 1.14 (3H, d, J = 6 Hz, H-4), 0.08 (9H, s, Si ($C\underline{H}_3$)$_3$). MS *m/z* 242 (2%, M^+), 327 (6), 353 (12), 198 (22), 165 (21), 151 (100). (Found: C, 59.54; H, 8.55. Calc for $C_{17}H_{30}O_5Si$: C, 59.61; H, 8.83%.)

Methyl 2,6 - *dimethoxy* - 1 - (3' - *trimethylsiloxypentyl*) - 2,5 - *cyclohexadiene* - 1 - *carboxylate* (**14b**)

Methyl 2,6-dimethoxybenzoate (9.0 g, 46 mmol) was reduced and alkylated with iodide **13b** (13.4 g, 47 mmol) at −78° for 3 h, using standard procedure B, to give ester **14b** (16.3 g, 100%) as an oil. IR ν_{max} (neat) 1745 (ester), 1695, 1660 (C=C—OCH_3) cm^{-1}. ^{1}H-NMR: δ 4.90 (2H, t, J = 4 Hz, H-3, 5), 3.69 (3H, s, $CO_2C\underline{H}_3$), 3.52 (6H, s, 2 × $OC\underline{H}_3$), 2.90 (2H, t, J = 4 Hz, H-4), 2.17–1.81 (2H, m, H-1'), 1.60–1.04 (4H, m, H-2', 4'), 0.86 (3H, t, J = 8 Hz, H-5'), 0.09 (9H, s, Si ($C\underline{H}_3$)$_3$). MS *m/z* 356 (3%, M^+), 341 (11), 227 (10), 266 (26), 207 (29), 196 (42), 151 (100). (Found: C, 60.51; H, 9.06. Calc for $C_{18}H_{32}O_5Si$: C, 60.64; H, 9.05%.)

Methyl 1 - (3' - *hydroxypentyl*) - 2,6 - *dimethoxy* - 2,5 - *cyclohexadiene* - 1 - *carboxylate* (**17b**)

A soln of ester **14b** (3.00 g, 8 mmol) and KF (2.5 g, 43 mmol) in MeOH (75 ml) and pH 6.8 buffer (45 ml) was stirred at room temp for 17 h. Most of the MeOH was then removed *in vacuo* (water bath 45°) and the residue was extracted with Et_2O (2 ×). The combined Et_2O extracts were washed with brine, dried and evaporated to give the product **17b** (2.40 g, 100%) as a white solid. An analytical sample was prepared by recrystallization of the crude product from Et_2O–petroleum ether (60–80°) to give needles, m.p. 76–77°. IR ν_{max} 3420 (OH), 1740 (ester), 1695, 1660 (C=C—OCH_3) cm^{-1}. ^{1}H-NMR: δ 4.93 (2H, t, J = 4 Hz, H-3, 5), 3.72 (3H, s, $CO_2C\underline{H}_3$), 3.52 (7H, s, 2 × $OC\underline{H}_3$, H-3'), 2.94 (2H, t, J = 4 Hz, H-4), 2.26–2.00 (2H, m, H-1'), 1.71–1.55 (1H, br s, exch, O$\underline{H}$), 1.55–1.12 (4H, m, H-2'), 0.95 (3H, t, J = 8 Hz, H-5'). MS *m/z* 284 (< 1%, M^+), 226 (3), 252 (10), 207 (9), 197 (26), 151 (200). (Found: C, 63.47; H, 8.43. Calc for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51%.)

Methyl 2,6 - *dimethoxy* - 1 - (3' - *oxopentyl*) - 2,5 - *cyclohexadiene* - 1 - *carboxylate* **19** (≡ **6a**)

A soln of alcohol **17b** (1.5 g, 5.3 mmol), dry pyridine (780 mg, 9.9 mmol), trifluoroacetic acid (590 mg, 5.2 mmol) and dry DMSO (12 ml) in dry C_6H_6 (11 ml), under N_2, was treated portionwise with dicyclohexylcarbodiimide (DCC) (3.2 g, 15.5 mmol) over 5 min. The mixture was stirred at room temp for 24 h and then diluted with Et_2O. Precipitated dicyclohexylurea (DCU) was removed by filtration and the Et_2O soln was washed with sat oxalic acid soln. Further DCU precipitated and was removed by filtration. The soln was then washed with sat $NaHCO_3$ aq, brine, dried (Na_2SO_4) and evaporated. The residue was chromatographed (MPLC), with EtOAc (20%)–petroleum ether (80%) as eluant, to give the ketone **6a** (880 mg, 59%), m.p. 106–107°. IR ν_{max} 1740 (ester), 1700 (ketone), 1695, 1660 (C=C—OCH_3) cm^{-1}. ^{1}H-NMR: δ 4.88 (2H, t, J = 4 Hz, H-3, 5), 3.69 (3H, s, $CO_2C\underline{H}_3$), 3.50 (6H, s, 2 × $OC\underline{H}_3$), 2.87 (2H, m, H-4), 2.53–2.00 (6H, e, H-1', 2', 4'), 1.00 (3H, t, J = 8 Hz, H-5'). MS *m/z* 282 (< 1%, M^+), 223 (12), 197 (33), 165 (38), 151 (100). (Found: C, 63.49; H, 7.91. Calc for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85%.)

Methyl - 2 - *ethyl* - 3,4,4a,8a - *tetrahydro* - 5,8a - *dimethoxy* - 2H - 1 - *benzopyran* - 4a - *carboxylate* (**20**)

A soln of **17b** (120 mg, 0.42 mmol) and pyridinium dichromate (273 mg, 0.63 mmol) in dry CH_2Cl_2 (10 ml) was stirred at room temp for 2 days. The mixture was then flash chromatographed over a column of silica (10 × 120 mm) with Et_2O (50%)–petroleum ether (50%) as eluant to give **20** (49 mg, 41%) as an oil. IR ν_{max} 1730 (ester), 1660, 1595 (C=CH—CH=C) cm^{-1}. ^{1}H-NMR: δ 6.16 (1H, dd, J = 6, 10 Hz, H-7), 5.79 (1H, d, J = 10 Hz, H-8), 5.22 (1H, d, J = 6 Hz, H-6), 3.61 (6H, s, $CO_2C\underline{H}_3$, C-8a $OC\underline{H}_3$), 3.65–3.35 (1H, m, H-2), 3.31 (3H, s, C-5 $OC\underline{H}_3$), 2.57–2.01 (2H, m, H-4), 1.74–1.15 (4H, m, H-3 $C\underline{H}_2CH_3$), 0.92 (3H, t, J = 8 Hz, $CH_2C\underline{H}_3$). MS *m/z* 282 (100%, M^+), 251 (46), 223 (30), 195 (42), 165 (32), 151 (50). (Accurate mass: found: 282.1457. Calc for $C_{15}H_{22}O_5$: 282.1468.)

1 - *Hydroxymethyl* - 2,6 - *dimethoxy* - 1 - (3' - *trimethylsiloxypentyl* - 2,5 - *cyclohexadiene* **16b** (R^1 = H)

Ester **14b** (3.00 g, 8.4 mmol) in dry Et_2O (20 ml) was added dropwise over 10 min to a stirred soln of $LiAlH_4$ (450 mg, 12 mmol) in dry Et_2O (120 ml) under N_2. The soln was stirred at room temp for 15 min, then carefully poured into ice-cold pH 5.5 buffer. The Et_2O layer was separated and the aq phase extracted a further 4 times with Et_2O. The combined ethereal extracts were then washed with brine, dried and evaporated to yield **16b** (R^1 = H) (2.68 g, 97%) as a colourless oil. IR ν_{max} (neat) 3450 (OH), 1695, 1660 (C=C—OCH_3) cm^{-1}. ^{1}H-NMR: δ 4.90 (2H, t, J = 4 Hz, H-3, 5), 3.66 (2H, s, $C\underline{H}_2OH$), 3.50 (6H, s, 2 × $OC\underline{H}_3$), 3.50–3.40 (1H, m, H-3'), 2.82 (2H, t, J = 4 Hz, H-4), 1.77 (1H, br s, exch, O$\underline{H}$), 1.72–1.08 (6H, m), 0.82 (3H, t, J = 8 Hz, H-5'), 0.04 (9H, s, Si($C\underline{H}_3$)$_3$). MS *m/z* 298 (13%, $M^+ - 30$), 281 (7), 238 (9), 206 (28), 177 (22), 151 (100). (Found: C, 61.92; H, 9.65. Calc for $C_{17}H_{32}O_4Si$: C, 62.15; H, 9.82%.)

1 - *Hydroxymethyl* - 2,6 - *dimethoxy* - 1 - (3' - *trimethylsiloxybutyl*) - 2,5 - *cyclohexadiene* **16a** (R^1 = H)

Using the previous procedure, **14a** (8.00 g, 23 mmol) was converted to **16a** (7.32 g, 97%), which was a colourless oil. IR ν_{max} (neat) 3440 (OH), 1690, 1650 (C=C—OCH_3) cm^{-1}. ^{1}H-NMR: δ 4.98 (2H, t, J = 4 Hz, H-3, 5), 3.98–3.70 (3H, m, $C\underline{H}_2OH$, H-3'), 3.60 (6H, s, 2 × OCH_3), 2.90 (2H, t, J = 4 Hz, H-4), 1.95–1.25 (5H, m), 1.17 (3H, d, J = 6 Hz, H-4'), 0.08 (9H, s, Si ($C\underline{H}_3$)$_3$). MS *m/z* 267 (1%, $M^+ - 47$), 236 (3), 210 (30), 192 (25), 177 (27), 151 (100). (Found: C, 61.02; H, 9.55. Calc for $C_{16}H_{30}O_4Si$: C, 61.10; H, 9.62%.)

2,6 - *Dimethoxy* - 1 - (*methoxymethyloxymethyl*) - 1 - (3' - *trimethylsiloxypentyl*) - 2,5 - *cyclohexadiene* **16b** (R^1 = CH_2OMe)

A soln of **16b** (R^1 = H) (2.00 g, 6.0 mmol), ethyldiisopropylamine (1.56 g, 12 mmol) and chloromethyl methyl ether (0.93 ml, 12 mmol) in dry CH_2Cl_2 (40 ml) was stirred at room temp, under N_2, for 24 h. The soln was then washed with pH 5.5 buffer (2 ×), H_2O, brine, dried and evaporated to yield **16b** (R^1 = CH_2OMe) as a colourless oil (2.17 g, 95%). IR ν_{max} (neat) 1695, 1660 (C=C—OCH_3) cm^{-1}. ^{1}H-NMR: δ 4.87 (2H, t, J = 4 Hz, H-3, 5), 4.55 (2H, s, $OC\underline{H}_2O$), 3.67 (2H, s, C—$C\underline{H}_2O$), 3.52 (6H, s, 2 × $OC\underline{H}_3$), 3.50–3.36 (1H, m, H-3'), 3.28 (3H, s, $CH_2OC\underline{H}_3$), 2.84 (2H, t, J = 4 Hz, H-4), 1.65–1.10 (6H, m, H-1', 2', 4'), 0.84 (3H, t, J = 8 Hz, C-5'), 0.05 (9H, s, Si($C\underline{H}_3$)$_3$). MS *m/z* 300 (2%, $M^+ - 72$), 296 (4), 224 (37), 206 (30), 177 (45), 151 (100). (Found: C, 61.13; H, 9.63. Calc for $C_{19}H_{36}O_5Si$: C, 61.25; H, 9.74%.)

2,6 - *Dimethoxy* - 1 - (*methoxymethyloxymethyl*) - 1 - (3' - *trimethylsiloxybutyl*) - 2,5 - *cyclohexadiene* **16a** (R^1 = CH_2OMe)

Using the previous procedure, **16a** (R^1 = H) (6.7 g, 21 mmol) was converted to **16a** (R^1 = CH_2OMe) (7.32 g, 96%), which was a colourless oil. IR ν_{max} (neat) 1695, 1660 (C=C—OCH_3) cm^{-1}. ^{1}H-NMR: δ 4.82 (2H, t, J = 4 Hz, H-3, 5), 4.55 (2H, s, $OC\underline{H}_2O$), 3.65 (2H, s, C—$C\underline{H}_2O$), 3.52 (7H, s, 2 × $OC\underline{H}_3$, H-3'), 3.28 (3H, s, $CH_2OC\underline{H}_3$), 2.81 (2H, t, J = 4 Hz, H-4), 1.54–1.14

(4H, e, H-1', 2'), 1.07 (3H, d, J = 6 Hz, H-4'), 0.08 (9H, s, $Si(C\underline{H}_3)_3$). MS *m/z* 268 (4%, $M^+ - 90$), 224 (25), 206 (14), 193 (40), 177 (42), 151 (100). (Found: C, 60.32; H, 9.35. Calc for $C_{18}H_{34}O_5Si$: C, 60.30; H, 9.56%.)

1 - (3' - *Hydroxypentyl*) - 2,6 - *dimethoxy* - 1 - (*methoxymethyloxymethyl*) - 2,5 -*cyclohexadiene*

Trimethylsilyl ether **16b** (R^1 = CH_2OMe) (9.50 g, 25 mmol) was desilylated as for ester **14b** to give the alcohol (7.60 g, 99%) as an oil. IR ν_{max} (neat) 3440 (OH), 1695, 1660 (C=C—OCH_3) cm^{-1}. ^{1}H-NMR: δ 4.88 (2H, t, J = 4 Hz, H-3, 5), 4.52 (2H, s, $OC\underline{H}_2O$), 3.65 (2H, s, C—$C\underline{H}_2O$), 3.54 (6H, s, 2 × $OC\underline{H}_3$), 3.50–3.35 (1H, m, H-3'), 3.27 (s, $CH_2OC\underline{H}_3$), 2.84 (2H, t, J = 4 Hz, H-4), 1.77–1.13 (7H, e), 0.90 (3H, t, J = 8 Hz, H-5'). MS *m/z* 300 (< 1%, M^+), 268 (11), 225 (9), 193 (27), 151 (100). (Found: C, 64.04; H, 9.26. Calc for $C_{16}H_{28}O_5$: C, 63.97; H, 9.40%.)

1 - (3' - *Hydroxybutyl*) - 2,6 - *dimethoxy* - 1 - (*methoxymethyloxymethyl*) - 2,5 - *cyclohexadiene*

Trimethylsilyl ether **16a** (R^1 = CH_2OMe) was desilylated as for ester **14b** to give the alcohol (5.51 g, 98%) as an oil. IR ν_{max} (neat) 3440 (OH), 1695, 1660 (C=C—OCH_3) cm^{-1}. ^{1}H-NMR: δ 4.84 (2H, t, J = 4 Hz, H-3, 5), 4.52 (2H, s, $OC\underline{H}_2O$), 3.77 (1H, m, H-3'), 3.63 (2H, s, C—$C\underline{H}_2O$), 3.53 (6H, s, 2 × $OC\underline{H}_3$), 3.27 (3H, s, $CH_2OC\underline{H}_3$), 2.82 (2H, t, J = 4 Hz, H-4), 1.67 (1H, br s, exch, O$\underline{H}$), 1.58–1.16 (4H, e, H-1', 2'), 1.14 (3H, d, J = 6 Hz, H-4'). MS *m/z* 254 (3%, $M^+ - 32$), 210 (7), 179 (19), 178 (22), 151 (100). (Found: C, 62.78; H, 9.16. Calc for $C_{15}H_{26}O_5$: C, 62.91; H, 9.15%.)

2,6 - *Dimethoxy* - 1 - (*methoxymethyloxymethyl*) - 1 - (3' - *oxopentyl*) - 2,5 - *cyclohexadiene* (**15b**)

The alcohol derived from **16b** (R^1 = CH_2OMe) (1.00 g, 3.3 mmol) was oxidized as for the preparation of **19** to ketone **15b** (643 mg, 65%) (after MPLC), m.p. 43–45°. IR ν_{max} 1700 (ketone), 1690, 1660 (C=C—OCH_3) cm^{-1}. ^{1}H-NMR: δ 4.84 (2H, t, J = 4 Hz, H-3, 5), 4.55 (2H, s, $OC\underline{H}_2O$), 3.70 (2H, s, C—$C\underline{H}_2O$), 3.56 (6H, s, 2 × $OC\underline{H}_3$), 3.31 (3H, s, $CH_2OC\underline{H}_3$), 2.84 (2H, m, H-4), 2.67–2.10 (4H, e, H-2', 4'), 1.90–1.66 (2H, m, H-1'), 1.05 (3H, t, J = 8 Hz, H-5'). MS *m/z* 298 (15%, M^+), 266 (17), 235 (3), 223 (17), 151 (100). (Found: C, 64.36; H, 8.84. Calc for $C_{16}H_{26}O_5$: C, 64.41; H, 8.78%.)

2,6 - *Dimethoxy* - 1 - (*methoxymethyloxymethyl*) - 1 - (3' - *oxobutyl*) - 2,5 - *cyclohexadiene* (**15a**)

The alcohol derived from **16a** (R^1 = CH_2OMe) (1.00 g, 3.5 mmol) was oxidized as for the preparation of **19** to ketone **15a** (590 mg, 59%) (after MPLC), m.p. 57–59°. IR ν_{max} 1700 (ketone), 1695, 1660 (C=C—OCH_3) cm^{-1}. ^{1}H-NMR: δ 4.87 (2H, t, J = 4 Hz, H-3, 5), 4.52 (2H, 2, $OC\underline{H}_2O$), 3.67 (2H, s, C—$C\underline{H}_2O$), 3.52 (6H, s, 2 × $OC\underline{H}_3$), 3.27 (3H, s, $CH_2OC\underline{H}_3$), 2.84 (2H, t, J = 4 Hz, H-4), 2.30 (2H, t, J = 9 Hz, H-2'), 2.09 (3H, s, H-4'), 1.75 (2H, t, J = 9 Hz, H-1'). MS *m/z* 284 (< 1%, M^+), 252 (11), 221 (3), 209 (12), 151 (100). (Found: C, 63.52; H, 8.37. Calc for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51%.)

Hydrolysis of **15b** *to* 1 - (*methoxymethyloxymethyl*) - 1 - (3' - *oxopentyl*) - *cyclohexane* - 2,6 - *dione* (**18b**) *and* exo,endo 6 - *ethyl* - 6 - *hydroxy* - 1 - (*methoxymethyloxymethyl*) - *bicyclo*[3.3.1]*nonane* - 2,9 - *dione* (**21b**)

A soln of **15b** (460 mg, 1.5 mmol) and mercuric nitrate (150 mg, 0.5 mmol) in acetonitrile (21 ml) and H_2O (4.6 ml) was stirred at room temp, under N_2, for 48 h. The solvents were removed *in vacuo* (water bath 40°) and the residue was treated with H_2O and extracted with EtOAc (3 ×). The combined extracts were washed with brine, dried and evaporated to yield the products (390 mg, 93% in total). This mixture was then separated by PLC with Et_2O as eluant. The upper band contained **18b** (150 mg) as an oil. IR ν_{max} (neat) 1700 (ketones) cm^{-1}. ^{1}H-NMR: δ 4.46 (2H, s, $OC\underline{H}_2O$), 3.73 (2H, s, C—$C\underline{H}_2O$), 3.25 (3H, s, $OC\underline{H}_3$), 2.69 (4H, t, J = 8 Hz, H-3, 5), 2.534–2.22 (4H, e, C-2', 4'), 2.03 (4H, t, J = 8 Hz, H-1', 4), 1.03 (3H, t, J = 8 Hz, H-5'). MS *m/z* 270 (< 1%, M^+), 225 (100), 207 (17), 179 (38), 151 (86), 139 (69). (Found: C, 62.06; H, 7.99. Calc for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20%.)

The lower band contained an inseparable mixture of diastereomers **21b**. IR ν_{max} (neat) 3400 (OH), 1700 (ketones) cm^{-1}. ^{1}H-NMR: δ 4.54, 4.52 (2H, ABq, J = 5 Hz, $OC\underline{H}_2O$), 3.92, 3.64 (2H, ABq, J = 10 Hz, C—$C\underline{H}_2O$), 3.33 (3H, s, $OC\underline{H}_3$), 2.90–1.20 (12H, e), 0.95 (3H, t, J = 8 Hz, $CH_2C\underline{H}_3$). MS *m/z* 270 (6%, M^+), 238 (18), 225 (100), 207 (34), 185 (42), 179 (78). (Found: C, 62.48; H, 8.23. Calc for $C_{16}H_{22}O_5$: C, 62.20; H, 8.20%.)

6 - *Hydroxy* - 1 - (*methoxymethyloxymethyl*) - 6 - *methylbicyclo*[3.3.1]*nonane* - 2,9 - *dione* (**21a**)

Ketone **18a** (440 mg, 1.5 mmol) was hydrolysed as above to give the mixture of ketols **21a** (380 mg, 92%). The ^{1}H-NMR spectrum showed two methyl resonances at δ 1.36 and 1.28 which integrated as 72%: 28% respectively, corresponding to the C-6 methyl resonances of the two ketols. The major ketol was obtained by MPLC, using EtOAc (80%)–petroleum ether (20%), to give a pure ketol **18a** (200 mg) (stereochemistry unknown), m.p. 110–112°. IR ν_{max} 3400 (OH), 1700 (ketone) cm^{-1}. ^{1}H-NMR: δ 4.60, 4.52 (2H, ABq, J = 7 Hz, $OC\underline{H}_2O$), 3.87, 3.59 (2H, ABq, J = 10 Hz, C—$C\underline{H}_2O$), 3.36 (3H, s, $OC\underline{H}_3$), 2.88–1.48 (10H, e), 1.36 (3H, s, $C\underline{H}_3$). MS *m/z* 256 (3%, M^+), 233 (10), 224 (10), 221 (100), 193 (45), 166 (45). (Found: C, 60.78; H, 7.98. Calc for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87%.)

3,4,8,8a - *Tetrahydro* - 8a - (*methoxymethyloxymethyl*) - 1,6(2H,7H) - *naphthalenedione* (**22**)

A soln of **21a** (25 mg, 0.098 mmol) and piperidinium benzoate (20 mg, 0.097 mmol) in dry C_6H_6, under N_2, was heated under reflux for 48 h. The mixture was then flash chromatographed over a column of silica (10 × 120 mm), with Et_2O as eluant, to give **22** (10.0 mg, 43%) as a colourless oil. IR ν_{max} 1720 (ketone), 1670, 1620 (enone) cm^{-1}. ^{1}H-NMR: δ 6.90 (1H, s, H-5), 4.67 (2H, s, $OC\underline{H}_2O$), 4.03, 3.85 (2H, Abq, J = 10 Hz, C—$C\underline{H}_2O$), 3.38 (3H, s, $OC\underline{H}_3$), 2.94–1.54 (10H, e). MS *m/z* 238 (9%, M^+), 208 (18), 193 (18), 178 (5), 149 (11), 45 (100). (Accurate mass: found: 238.1206. Calc for $C_{13}H_{18}O_4$: 238.1205.)

7-*Methylspiro*[5.5]*undecan*-1,5,8-*trione* (**23**)

A soln of **18b** (120 mg, 0.44 mmol) and pyrrolidine (50 mg, 0.7 mmol) in dry C_6H_6 (20 ml) was heated at reflux, under N_2, for 4 h. The mixture was then flash chromatographed over a column of silica (10 × 100 mm), with Et_2O as eluant, to give **23** (40 mg, 43%). A sample recrystallized from Et_2O–petroleum ether, m.p. 79–81°. IR ν_{max} 1700 (ketone) cm^{-1}. ^{1}H-NMR: δ 2.94–1.58 (13H, e, 6 × $C\underline{H}_2$, C$\underline{H}$), 1.05 (3H, d, J = 5 Hz, $C\underline{H}_3$). MS *m/z* 208 (21%, M^+), 180 (36), 166 (29), 152 (25), 233 (100). ^{13}C-NMR: δ 211.3 (s, $\underline{C}$=O), 208.9 (s, $\underline{C}$=O), 207.5 ($\underline{C}$=O), 66.3 (s), 40.5 (d), 38.0 (t), 37.4 (t), 30.1 (t), 18.1 (t), 14.4 (q). (Accurate mass: found: 208.1100. Calc for $C_{12}H_{16}O_3$: 208.1099.)

Methyl 2-(t-*butyldimethylsiloxy*)-6-*methoxybenzoate* (**24**)

A soln of methyl 2-hydroxy-6-methoxybenzoate (1.50 g, 8.2 mmol), imidazole (1.40 g, 20.5 mmol) and t-butyldimethylsilyl chloride (1.50 g, 10 mmol) in dry dimethylformamide (DMF) (3 ml) was stirred at room temp for 18 h. The soln was diluted with H_2O, and extracted with EtOAc (2 ×). The combined extracts were washed with brine, dried and evaporated to yield an oil. This oil was recrystallized from cold (−40°) petroleum ether to give **24** (2.24 g, 92%), m.p. 30–32°. IR ν_{max} 1730 (ester) cm^{-1}. ^{1}H-NMR: δ 7.17 (1H, t, J = 7 Hz, H4), 6.50 (2H, d, J = 7 Hz, H-3, 5), 3.89 (3H, s, $CO_2C\underline{H}_3$), 3.80 (3H, s, $OC\underline{H}_3$), 0.97 (9H, s, $SiC(C\underline{H}_3)_3$), 0.22 (6H, s, $Si(C\underline{H}_3)_2$). MS *m/z* 281 (5%, $M^+ - 31$), 265 (10), 239 (100), 224 (4), 209 (5), 194 (3). (Found: C, 60.60; H, 8.32. Calc for $C_{15}H_{24}O_4Si$: C, 60.77; H, 8.16%.)

Methyl 2-(t-*butyldimethylsiloxy*)-1-(3'-*hydroxypentyl*)-6-*methoxy*-2,5-*cyclohexadiene*-1-*carboxylate* (**25**)

Ester **24** (11.0 g, 37.2 mmol) was reduced then alkylated with **13b** (10.9 g, 38 mmol), using procedure B (reduction took 1 h).

After the NH_3 was allowed to evaporate overnight, the remaining THF soln was treated with AcOH (80 ml) and ice (50 g). The soln was stirred at room temp for 30 min and then was diluted with H_2O and extracted with Et_2O (2 ×). The combined extracts were washed with sat $NaHCO_3$ aq, H_2O, then brine. The extract was dried and evaporated to give **25** (12.4 g, 88%) as an oil. IR ν_{max} 3400 (OH), 1750 (ester), 1680, 1660 (C=C—OR) cm^{-1}. ^{1}H-NMR: δ 4.94 (1H, t, J = 5 Hz, H-3), 4.82 (1H, t, J = 5 Hz, H-5), 3.67 (3H, s, $CO_2C\underline{H}_3$), 3.52 (3H, s, $OC\underline{H}_3$), 3.58 (1H, m, H-3'), 2.81 (2H, t, J = 5 Hz, H-4), 2.21–1.10 (7H, e), 0.90 (9H, s, $SiC(C\underline{H}_3)_3$), 0.90 (3H, t, J = 8 Hz, H-5'), 0.19 (3H, s, $SiC\underline{H}_3$), 0.15 (3H, s, $SiC\underline{H}_3$). MS *m/z* 384 (< 1%, M^+), 382 (5), 325 (15), 309 (20), 265 (62), 251 (100), 239 (73). (Found: C, 62.13; H, 7.70. Calc for $C_{20}H_{36}O_5Si$: C, 62.46; H, 7.44%.)

Methyl 2 - (t - *butyldimethylsiloxy*) - 6 - *methoxy* - 1 - (3' - *oxo* - *pentyl*) - 2,5 - *cyclohexadiene* - 1 - *carboxylate* (**26**)

Alcohol **25** (6.14 g, 16 mmol) was oxidized as for **19** to **26** (3.70 g, 60%) (after MPLC), m.p. 30–32°. IR ν_{max} (neat) 1730 (ester), 1700 (ketone), 1680, 1660 (C=C—OR) cm^{-1}. ^{1}H-NMR: δ 4.98 (1H, t, J = 5 Hz, H-3), 4.88 (1H, t, J = 5 Hz, H-5), 3.65 (3H, s, $CO_2C\underline{H}_3$), 3.50 (3H, s, $OC\underline{H}_3$), 2.85 (2H, t, J = 5 Hz, H-4), 2.66–2.18 (6H, e), 1.04 (3H, t, J = 8 Hz, H-5'), 0.87 (9H, s, $SiC(C\underline{H}_3)_3$), 0.18 (3H, s, $SiC\underline{H}_3$), 0.14 (3H, s, $SiC\underline{H}_3$). MS *m/z* 382 (1%, M^+), 315 (21), 313 (18), 298 (29), 265 (95), 251 (63), 239 (100). (Found: C, 62.76; H, 8.81. Calc for $C_{20}H_{34}O_5Si$: C, 62.79; H, 8.96%.)

exo- *and* endo-*Methyl* 6 - *ethyl* - 6 - *hydroxy* - 2 - *methoxy* - 9 - *oxo* - *bicyclo*[3.3.1]*non* - 2 - *ene* - 1 - *carboxylate* (**27**)

A soln of **26** (500 mg, 1.36 mmol) in dry THF (12 ml) at 0° under N_2 was treated with tetra n-butylammonium fluoride (TBAF) (523 mg, 2.0 mmol) and stirred at 0° for 30 min. The soln was then diluted with sat brine and extracted with Et_2O (3 ×). The combined extracts were dried and evaporated to yield a pale yellow oil. MPLC using EtOAc (80%)–petroleum ether (20%) as eluant afforded *exo*-**27** from the early fractions (160 mg), m.p. 137–139°. IR ν_{max} 3430 (OH), 1730 (ester, ketone), 1660 (C=C—OCH_3) cm^{-1}. ^{1}H-NMR: δ 4.95 (1H, m, $W_{1/2}$ = 8 Hz, H-3), 3.78 (3H, s, $CO_2C\underline{H}_3$), 3.56 (3H, s, $OC\underline{H}_3$), 2.74–1.54 (10H, e), 0.91 (3H, t, J = 8 Hz, $CH_2C\underline{H}_3$). MS *m/z* 268 (17%, M^+), 250 (2), 237 (7), 209 (24), 191 (19), 183 (39), 151 (63), 137 (100). (Found: C, 62.89; H, 7.45. Calc for $C_{14}H_{20}O_5$: C, 62.67, H, 7.51%.)

Later fractions gave *endo*-**27** (80 mg, 71% combined yield of both isomers) as an oil. IR ν_{max} 3430 (OH), 1730 (ester, ketone), 1660 (C=C—OCH_3) cm^{-1}. ^{1}H-NMR: δ 5.04 (1H, dd, $J_{3,4\alpha}$ = 5 Hz, $J_{3,4\beta}$ = 2 Hz, H-3), 3.78 (3H, s, $CO_2C\underline{H}_3$), 3.58 (3H, s, $OC\underline{H}_3$), 2.89 (1H, dd, $J_{3,4\alpha}$ = 4 Hz, $J_{4\alpha,4\beta}$ = 16 Hz, H-4α), 2.62–2.40 (2H, m, H-4β, H-5), 2.30–1.41 (7H, e), 0.94 (3H, t, J = 7 Hz, $CH_2C\underline{H}_3$). MS *m/z* 268 (3%, M^+), 250 (11), 222 (49), 207 (14), 194 (27), 163 (100). (Found: C, 62.73; H, 7.72. Calc for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51%.)

The unseparated ketols **27** could be routinely obtained in yields of 90% by flash chromatography.

Methyl 2,3,4,4a,7,8 - *hexahydro* - 5 - *methoxy* - 1 - *methyl* - 2 - *oxo* - *naphthalene* - 4a - *carboxylate* (**28**)

A mixture of **27** (540 mg, 2.1 mmol) and anhyd K_2CO_3 (100 mg, 0.7 mmol) in dry MeOH (10 ml) was stirred at room temp under N_2 for 2 days. The soln was then diluted with H_2O and extracted with Et_2O (3 ×). The combined extracts were washed with brine, dried and evaporated to dryness. Recrystallization from 60–80° petroleum ether gave prisms (405 mg, 75%), m.p. 84–85°. IR ν_{max} 1730 (ester), 1660 (enone C=O, C=C—OCH_3), 1620 (enone C=C) cm^{-1}. ^{1}H-NMR: δ 4.84 (1H, m, H-6), 3.62 (3H, s, $CO_2C\underline{H}_3$), 3.46 (3H, s, $OC\underline{H}_3$), 3.05–2.00 (8H, e), 1.84 (3H, s, $C\underline{H}_3$). ^{13}C-NMR: δ 198.1 (s, C-2), 171.7 (s, $\underline{C}O_2CH_3$), 155.4 (s, C-8a), 153.3 (s, C-5), 131.1 (s, C-1), 95.1 (d, C-6), 55.1 (q, $CO_2\underline{C}H_3$), 52.6 (q, $O\underline{C}H_3$), 51.3 (s, C-4a), 34.4 (t, C-3), 27.0 (t, C-4 or C-8), 22.5 (t, C-4 or C-8), 11.1 (q, $\underline{C}H_3$). MS *m/z* 250 (11%, M^+), 218 (4), 191 (100), 163 (11), 149 (13). (Found: C, 67.07; H, 7.18. Calc for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25%.)

Methyl 2,3,4,4a,5,6,7,8 - *octahydro* - 1 - *methyl* - 2,5 - *dioxo* - *naphthalene* - 4a - *carboxylate* (**1a**)

A soln of **28** (100 mg, 0.40 mmol) and mercuric nitrate (26 mg, 0.08 mmol) in acetonitrile (4.5 ml) and H_2O (1.0 ml) was stirred at room temp under N_2 for 3 days. The soln was diluted with brine and extracted with EtOAc (3 ×). The combined extracts were dried and evaporated. The residue was chromatographed (MPLC), with EtOAc (80%)–petroleum ether (20%) as eluant, to give **1a** (85.6 mg, 91%) as an oil. IR ν_{max} 1730, 1730 (ester, ketone), 1660, 1620 (enone) cm^{-1}. ^{1}H-NMR: δ 3.75 (3H, s, $CO_2C\underline{H}_3$), 2.89–1.92 (10H, e, C-3, 5, 6, 7, 8), 1.81 (3H, s, $C\underline{H}_3$). ^{13}C-NMR: δ 203.4 (s, C-2), 196.9 (s, C-5), 169.8 (s, $\underline{C}O_2CH_3$), 150.6 (s, C-8a), 134.2 (s, C-1), 62.4 (s, C-4a), 53.4 (q, $CO_2\underline{C}H_3$), 38.9 (t, C-6), 33.8 (t, C-3), 28.8 (t, C-4, 7 or 8), 27.1 (t, C-4, 7 or 8), 21.1 (t, C-4, 7 or 8), 11.6 (q, $\underline{C}H_3$). MS *m/z* 236 (44%, M^+), 204 (8), 177 (100), 134 (32). (Found: C, 65.89; H, 7.13. Calc for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83%.)

Methyl 3,4,7,8,4a,8a - *hexahydro* - 8a - *hydroxy* - 5 - *methoxy* - 2 - *methyl* - 2H - 1 - *benzopyran* - 4a - *carboxylate* (**30**)

Treatment of **25** (300 mg, 0.68 mmol) with TBAF, as for **26** gave on chromatography (MPLC) **30** (160 mg, 79%), m.p. 95–97°. IR ν_{max} 3500 (OH), 1710 (ester), 1660 (C=C—OCH_3) cm^{-1}. ^{1}H-NMR: δ 4.97 (1H, m, H-6), 4.10 (1H, m, H-2), 3.87 (3H, s, $CO_2C\underline{H}_3$), 3.56 (3H, s, $OC\underline{H}_3$), 3.30 (1H, s, O$\underline{H}$), 2.50–1.27 (8H, e), 1.12 (3H, d, J = 7 Hz, $C\underline{H}_3$). MS *m/z* 256 (11%, M^+), 238 (13), 224 (34), 197 (34), 179 (100), 151 (47), 137 (66). (Found: C, 60.99; H, 7.98. Calc for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87%.)

Preparation of iodides **33**

Freshly distilled trimethylsilyl iodide (214 μl, 1.5 mmol) was added to a soln of freshly distilled vinyl ketone **32a, b** or methyl acrylate **32c** (1.5 mmol) in dry CH_2Cl_2 (5.0 ml) at −78° under N_2 and stirring continued at −78° for 1 h. This soln was used directly in the alkylation step.

Preparation of the compounds listed in Table 1

Esters **37a–c** and **41a, b** were prepared by procedure C, acids **39a, b** and **43a, b** by procedure D, and acids **44a, b** by procedure D (but with Na metal substituted for Li), and the appropriate iodide **33**. The alkylation phase was complete within a few min at −78°. Ester **45** was prepared by procedure A. Esters **46a, b** and **47a, b** were prepared by the following general procedure: n-BuLi (710 μl, 1.55 M in hexane) was added to a stirred soln of diisopropylamine (154 μl, 1.1 mmol) in THF (2.0 ml) at −78° under N_2. After 30 min a soln of ester **5a** or **45** (1.0 mmol) in THF (2.0 ml) was added, and then stirring continued at −78° for 2 h. A soln of **33** (1.5 mmol) in CH_2Cl_2 at −78° was added using a double tipped needle. After stirring for 10 min, the mixture was poured into cold H_2O (5.0 ml) and the product extracted with EtOAc (2 × 10 ml). The combined organic layers were washed with brine, dried (Na_2SO_4), concentrated and chromatographed on silica gel using 20% Et_2O in hexane as the eluant. The product was desilylated by treatment with TBAF (4 mmol) in THF at 20° for 10 min.

Spectroscopic and analytical data

Compound **37a**. IR ν_{max} 1738 (ester), 1720 (ketone), 1695, 1660 (enol ether) cm^{-1}. ^{1}H-NMR: δ 4.60 (2H, s, H-2, H-6), 3.69 (3H, s, $CO_2C\underline{H}_3$), 3.60 (6H, s, OCH_3), 2.76 (2H, s, H-4), 2.32 (2H, t, J = 7.5 Hz, H-2'), 2.12 (3H, s, H-4'), 2.06 (2H, t, J = 8 Hz, H-1'). MS *m/z* 268 (M^+, 0.2%), 210 (13), 209 (97), 197 (21), 191 (10), 165 (16), 151 (100). (Found: C, 62.69; H, 7.62. Calc for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51%.)

Compound **37b**. IR ν_{max} 1738 (ester), 1720 (ketone), 1695, 1660 (enol ether) cm^{-1}. ^{1}H-NMR: δ 4.60 (2H, s, H-2, H-6), 3.69 (3H, s, $CO_2C\underline{H}_3$), 3.59 (6H, s, OCH_3), 2.75 (2H, s, H-4), 2.38 (2H, q, J = 7.5 Hz, H-4'), 2.29 (2H, t, J = 7.5 Hz, H-2'), 2.07 (2H, t, J = 7.5 Hz, H-1'), 1.03 (3H, t, J = 7.5 Hz, H-5'). MS *m/z* 282

(M^+, 13%), 223 (18), 165 (10), 152 (100), 121 (12). (Found: C, 64.32; H, 8.19. Calc for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85%.)

Compound **37c**. IR ν_{max} 1725 (ester), 1695, 1655 (enol ether) cm^{-1}. ^{1}H-NMR: δ 4.61 (2H, s, H-2, H-6), 3.69 (3H, s, $CO_2\underline{CH}_3$), 3.64 (3H, s, $CO_2\underline{CH}_3$), 3.59 (6H, s, $O\underline{CH}_3$), 2.75 (2H, s, H-4), 2.19 (2H, m, H-2'), 2.09 (2H, m, H-1'). MS *m/z* 285 (M^+ + 1, 2%), 253 (16), 225 (92), 193 (73), 165 (51), 151 (100). (Found: C, 59.01; H, 7.06. Calc for $C_{14}H_{20}O_6$: C, 59.24; H, 7.09%.)

Compound **39a**. IR ν_{max} 3500–2600 (OH), 1710 (carboxyl, ketone), 1695, 1660 (enol ether) cm^{-1}. ^{1}H-NMR: δ 4.59 (2H, s, H-2, H-6), 3.60 (6H, s, CH_3), 2.78 (2H, s, H-4), 2.32 (2H, t, J = 8 Hz, H-2'), 2.12 (3H, s, H-4'), 2.06 (2H, t, J = 8 Hz, H-1'). MS *m/z* 255 (M^- + 1, 2.2%), 209 (54), 183 (39), 177 (11), 165 (10), 152 (100), 151 (86), 139 (33). (Found: C, 61.76; H, 7.20. Calc for $C_{13}H_{18}O_5$: C, 61.41; H, 7.13%.)

Compound **39b**. IR ν_{max} 3500–2600 (OH), 1710 (carboxyl, ketone), 1695, 1660 (enol ether) cm^{-1}. ^{1}H-NMR: δ 4.58 (2H, s, H-2, H-6), 3.59 (6H, s, $O\underline{CH}_3$), 2.78 (2H, s, H-4), 2.80 (2H, q, J = 7.3 Hz, H-4'), 2.32 (2H, t, J = 7.5 Hz, H-2'), 2.07 (2H, t, J = 7.5 Hz, H-1'), 1.03 (3H, t, J = 7.3 Hz, H-5'). MS *m/z* 269 (M^- + 1, 1.3%), 223 (81), 183 (64), 165 (12), 152 (66), 151 (100). (Found: C, 62.13; H, 7.41. Calc for C, 62.67; H, 7.51%.)

Compound **41a**. IR ν_{max} 1730 (ester), 1720 (ketone), 1660 (enol ether) cm^{-1}. ^{1}H-NMR: δ 4.78 (1H, t, J = 4 Hz, H-3), 4.30 (1H, s, H-6), 3.68 (3H, s, CO_2CH_3), 3.53 (6H, s, OCH_3), 2.92, 2.80 (2H, d, ABq, J = 4, 18 Hz, H-4), 2.25 (4H, m, H-1', H-2'), 2.12 (3H, s, H-4'). MS *m/z* 268 (M^+, 21%), 209 (3), 165 (12), 151 (100), 121 (21). (Found: C, 62.73; H, 7.66. Calc for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51%.)

Compound **41b**. IR ν_{max} 1730 (ester), 1718 (ketone), 1660 (enol ether) cm^{-1}. ^{1}H-NMR: δ 4.81 (1H, t, J = 4 Hz, H-3), 4.30 (1H, s, H-6), 3.68 (3H, s, CO_2CH_3), 3.533 (3H, s, OCH_3), 3.528 (3H, s, OCH_3), 2.92, 2.80 (2H, d, ABq, J = 4, 18 Hz, H-4), 2.40 (2H, q, J = 7.3 Hz, H-4'), 2.25 (4H, m, H-1', H-2'), 1.03 (3H, t, J = 7.3 Hz, H-5'). MS *m/z* 282 (M^+, 22%), 223 (38), 165 (16), 152 (100). (Found: C, 64.30; H, 7.90. Calc for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85%.)

Compound **43a**. IR ν_{max} 3500–2500 (OH), 1710 (ketone + carboxyl), 1690, 1660 (enol ether) cm^{-1}. ^{1}H-NMR: δ 4.85 (1H, t, J = 4 Hz, H-3), 4.38 (1H, s, H-6), 3.58 (6H, s, OMe), 2.92, 2.82 (2H, d, ABq, J = 4, 18 Hz, H-4), 2.25 (4H, m, H-1', H-2'), 2.15 (3H, s, H-4'). MS *m/z* 195 (M^+ − 59, 100), 177 (62), 169 (69), 151 (73), 137 (88).

Compound **43b**. IR ν_{max} 3500–2500 (OH), 1708 (ketone + carboxyl), 1690, 1660 (enol ether) cm^{-1}. ^{1}H-NMR: δ 4.82 (1H, t, J = 4 Hz, H-3), 4.37 (1H, s, H-6), 3.56 (3H, s, OCH_3), 3.55 (3H, s, OCH_3), 2.92, 2.80 (2H, d, ABq, J = 4, 18 Hz, H-4), 2.41 (2H, q, J = 7.3 Hz, H-4'), 2.25 (4H, m, H-1', H-2'), 1.03 (3H, t, J = 7.3 Hz, H-5'). MS *m/z* 268 (M^+, 2.9%), 224 (20), 165 (14), 152 (85), 151 (100), 121 (38). (Found: C, 62.58; H, 7.52. Calc for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51%.)

Compound **44a**. IR ν_{max} 3500–2500 (OH), 1708 (ketone + carboxyl), 1685, 1650 (enol ether) cm^{-1}. ^{1}H-NMR: δ 5.96 (1H, dt, J = 10, 4 Hz, H-5), 5.42 (1H, dt, J = 10, 2 Hz, H-6), 4.91 (1H, t, J = 4 Hz, H-3), 3.57 (3H, s, OCH_3), 2.88 (2H, e, H-4), 2.25 (4H, m, H-1', H-2'), 2.12 (3H, s, H-4'). MS *m/z* 224 (M^+, 0.4%), 180 (6), 153 (32), 135 (35), 122 (53), 121 (100). (Found: C, 64.48; H, 7.21. Calc for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19%.)

Compound **44b**. IR ν_{max} 3500–2500 (OH), 1710 (ketone + carboxyl), 1685, 1650 (enol ether) cm^{-1}. ^{1}H-NMR: δ 2.96 (1H, dt, J = 10, 4 Hz, H-5), 5.42 (1H, dt, J = 10, 2 Hz, H-6), 4.91 (1H, t, J = 4 Hz, H-3), 3.55 (3H, s, OCH_3), 2.87 (2H, m, H-4), 2.41 (2H, q, J = 7.3 Hz, H-4'), 2.25 (4H, m, H-1', H-2'), 1.03 (3H, t, J = 7.3 Hz, H-5'). MS *m/z* 194 (M^+ − 44, 9%), 193 (5), 192 (10), 153 (23), 135 (37), 122 (55), 121 (100). (Found: C, 66.08; H, 7.85. Calc for $C_{13}H_{18}O_4$: C, 66.53; H, 7.61%.)

Compound **46a**. IR ν_{max} 1740 (ester), 1715 (ketone), 1660, 1632 (enol ether), 1600 (C=C) cm^{-1}. ^{1}H-NMR: δ 5.93 (1H, dt, J = 10, 4 Hz, H-5), 5.37 (1H, dt, J = 10, 2 Hz, H-6), 4.88 (1H, t, J = 4 Hz, H-3), 3.69 (3H, s, CO_2CH_3), 2.87 (2H, m, H-4), 2.25 (4H, m, H-1', H-2'), 2.12 (3H, s, H-4').

Compound **46b**. IR ν_{max} 1740 (ester), 1715 (ketone), 1660, 1632 (enol ether), 1600 (C=C) cm^{-1}. ^{1}H-NMR: δ 5.93 (1H, dt, J = 10, 4 Hz, H-5), 5.36 (1H, dt, J = 10, 2 Hz, H-6), 4.89 (1H, t, J = 4 Hz, H-3), 3.68 (3H, s, CO_2CH_3), 3.53 (3H, s, OCH_3), 2.85 (2H, e, H-4), 2.40 (2H, q, J = 7.3 Hz, H-4'), 2.20 (4H, m, H-1', H-2'), 1.02 (3H, t, J = 7.3 Hz, H-5').

Compound **47a**. IR ν_{max} 1738 (ester), 1712 (ketone), 1695, 1660 (enol ether) cm^{-1}. ^{1}H-NMR: δ 4.89 (2H, t, J = 3.6 Hz), 3.69 (3H, s, CO_2CH_3), 3.51 (6H, s, OCH_3), 2.88 (2H, m, H-4), 2.30 (2H, m, H-2'), 2.20 (2H, m, H-1'), 2.11 (3H, s, H-4'). MS *m/z* (M^+ − 59, 8%), 197 (24), 165 (31), 151 (100).

Compound **47b** (≡ **19** ≡ **6a**). See earlier preparation.

Methyl E and Z-2,6-dimethoxy-1-(3'-trimethylsiloxy-but-2-enyl)-2,5-cyclohexadiene-1-carboxylate (**48a**). ^{1}H-NMR: δ 4.82 (2H, t, J = 4 Hz), 4.35, 4.18 (1 : 2) (1H, t, J = 67.5 Hz, H-2'), 3.68 (3H, s, CO_2CH_3), 3.51, 3.49 (1 : 2) (6H, s, OCH_3), 2.87 (2H, m, H-4), 2.70 (2H, m, H-1'), 1.68 (3H, overlapping, J = 6.5 Hz, H-4'), 0.17, 0.12 (1 : 2) (3H, s, $Si(CH_3)_3$).

Methyl 2,6-dimethoxy-1-(3'-trimethylsiloxy-pent-2-enyl)-2,5-cyclohexadiene-1-carboxylate (**48b**). ^{1}H-NMR: δ 4.82 (2H, t, J = 4 Hz), 4.18 (1H, t, J = 6.5 Hz, H-2'), 3.68 (3H, s, CO_2CH_3), 3.49 (6H, s, OCH_3), 2.87 (2H, q, J = 4 Hz, H-4), 2.70 (2H, d, J = 6.5 Hz, H-1'), 1.93 (2H, q, J = 7.3 Hz, H-4'), 0.94 (3H, t, J = 7.3 Hz, H-5').

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