Organoiron Complexes in Organic Synthesis. Part 23.[1] New Strategies for Steroid and Aphidicolane Synthesis

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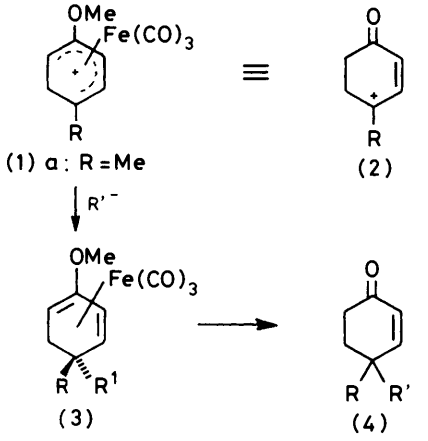
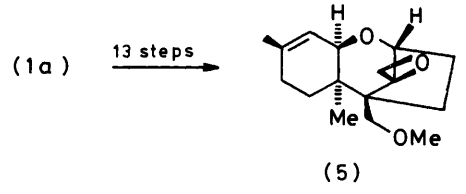
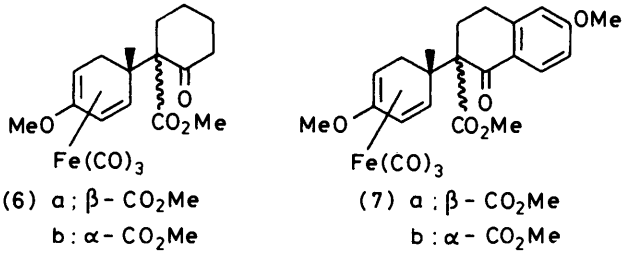
Methodology allowing the application of tricarbonyl(4-methoxy-1-methylcyclohexadienylium)iron hexafluorophosphate(1a) as a ring A synthon for the construction of D-homoaromatic steroid derivatives is described, *via* its regiospecific reaction with the potassium enolate of methyl 6-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate. A model study is presented towards the conversion of (1a) into the tetracyclic diterpene aphidicolin (12), in which the complex is converted in 12 steps to the spirotricyclic compound (46).

PREVIOUS work [2-4] has exemplified the application of tricarbonyl-cyclohexadienyliron complexes of structure (1) as synthetic equivalents of the cyclohexenone γ-cation







(2), in particular our recent application [3] of (1a) to the synthesis of the trichothecene derivative (5). Herein we report model studies aimed at an entry into the steroid and aphidicolane skeleta, based on our previously reported conversion [4] of (1a) in a single step to complexes (6) and (7).

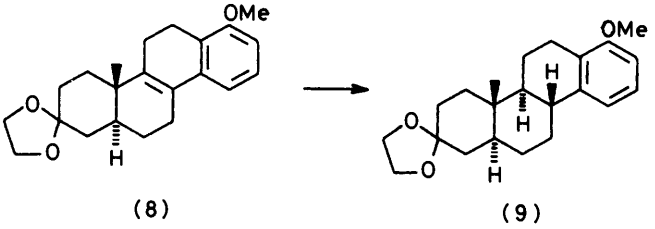
Total synthesis of steroids has enjoyed much attention over the years. Pertinent to our work are the classical syntheses by W. S. Johnson's group,[5] in which an intermediate such as (8) is converted into (9), having the correct stereochemistry at C-8 and C-9. More recently many new approaches to steroid synthesis have been reported, using intramolecular cycloaddition reactions of *o*-quinodimethane derivatives,[6] and various other methods.[7] Also of relevance to our study is Kametani's recently reported conversion of the intermediate (10) into (11), with appropriate C-8,9 stereochemistry,[8] and the development of suitable methodology for elaboration of the aromatic ring to the appropriate steroidal D-ring.[9] Our aim was, therefore, to effect conversion of the diastereoisomers (7) into intermediates related to (10), *i.e.*, possessing a C-8,9 double bond.

Aphidicolin (12) [10] and the related stemodinane [11] derivatives (13) are members of a class of diterpenes having an unusual tetracyclic framework. These compounds show interesting biological properties, including antiviral and antitumour activity,[10,11] and have been the subject of much recent synthetic effort. Total syntheses of aphidicolin [12] and stemodinane derivatives [13] have recently been achieved by a number of groups, and a number of approaches to the same molecules have been reported.[14] Of particular relevance to the work described herein is the Corey aphidicolin synthesis, employing a tricyclic intermediate (14) having C-8 ketone functionality (aphidicolin numbering) which was utilised to introduce the single carbon destined to complete the five-membered C ring. We therefore set out to examine the conversion of complexes (6) into a similar tricyclic system, using a route which would allow the ester group of (6) to become the desired C-8 ketone functionality.

RESULTS AND DISCUSSION

We first describe two approaches we have taken for the elaboration of the intermediates (7) to D-homoaromatic steroid systems. Whilst we have been able to separate the diastereoisomers of this complex by fractional crystallisation, we decided to use the mixture for the subsequent three steps since we anticipated that a

mixture would be regenerated during demethoxycarbonylation of a single isomer at the later stage. Thus, the mixture was treated with anhydrous trimethylamine *N*-oxide [15] to remove the $Fe(CO)_3$ group, and the resulting mixture of diastereoisomeric dienol ethers was converted into the cyclohexenone derivatives (15) under



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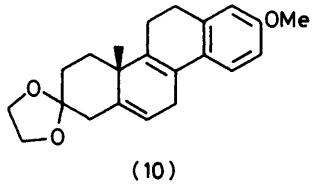

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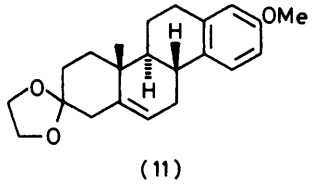

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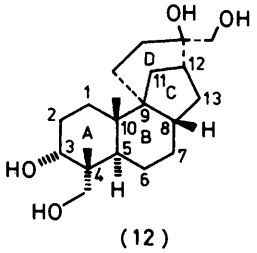

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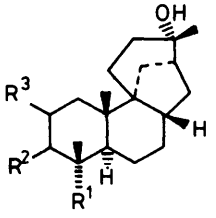

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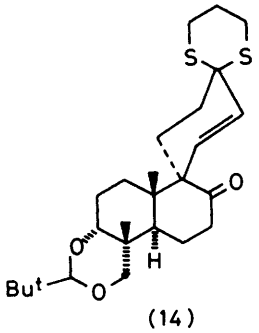
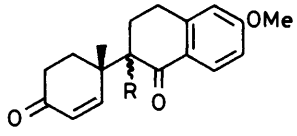


(14)

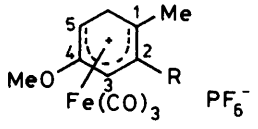
standard conditions. Demethoxycarbonylation [16] afforded the anticipated mixture of diastereoisomeric enones (16), which were easily separated by flash chromatography.[17] Thus, we were able to produce crystalline single isomers in good yield, whose subsequent elaboration could be examined. At this stage we were unable to assign unambiguously the structures of the separate isomers, but the subsequent reactions demonstrated that the lower-melting, less-polar isomer possessed the 9α-stereochemistry (steroid numbering), *i.e.* that corresponding to the correct steroid system, whilst the other isomer possessed the incorrect 9β-stereochemistry. At this point we were faced with the task of introducing a two- or three-carbon fragment onto the A ring which would serve to become ring B by cyclisation onto the tetralone carbonyl functionality. Whilst it might be argued that the most expedient way to achieve this would be to include a suitable side chain in the original dienylium complex, using for example a complex such as (17), there were two reasons why we decided



(15) R = CO_2Me

(16) a ; R = β-H

b ; R = α-H



(17) R = $CH_2CH_2CO_2Me$

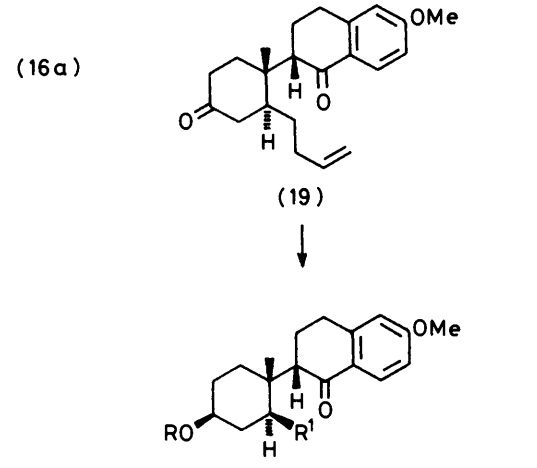
(18) R = Me

to avoid this approach. One was the fact that suitable aromatic precursors are not readily available and the conventional synthesis, for example, of 3-bromo-4-methylanisole involves an inefficient multistep sequence,[18] whilst the second reason was our observation [19] that the related dienyl complex (18) reacts with cyclic keto ester enolates entirely at the unsubstituted dienyl terminus C-5. Consequently, we decided that the only path available to us was the manipulation of enones (16).

The most obvious way of introducing the appropriate ring fragment into (16) was by a conjugate addition of a suitable organocuprate.

Reaction of the incorrect 9β-epimer (16a) with but-4-enylmagnesium bromide in the presence of cuprous bromide and tri-n-butylphosphine occurred smoothly to give the desired ketone (19) which was found to be fairly unstable and was reduced to the alcohol (20) within 48 h of its isolation (Scheme 1). We have assumed that the conjugate addition takes place from the less hindered face of the cyclohexenone,[20] giving the stereochemistry shown for (19). A minor amount of ketone was also observed which was presumed to arise from cuprate addition to the α-face of the enone, but which was not fully characterised. The 3β-stereochemistry (steroid numbering) for the

alcohol was assigned on the expectation that sodium borohydride reduction of the 3-oxo-group occurs, as in the steroid series, and in similar conformationally anchored cyclohexanones, along the axial vector.[21]



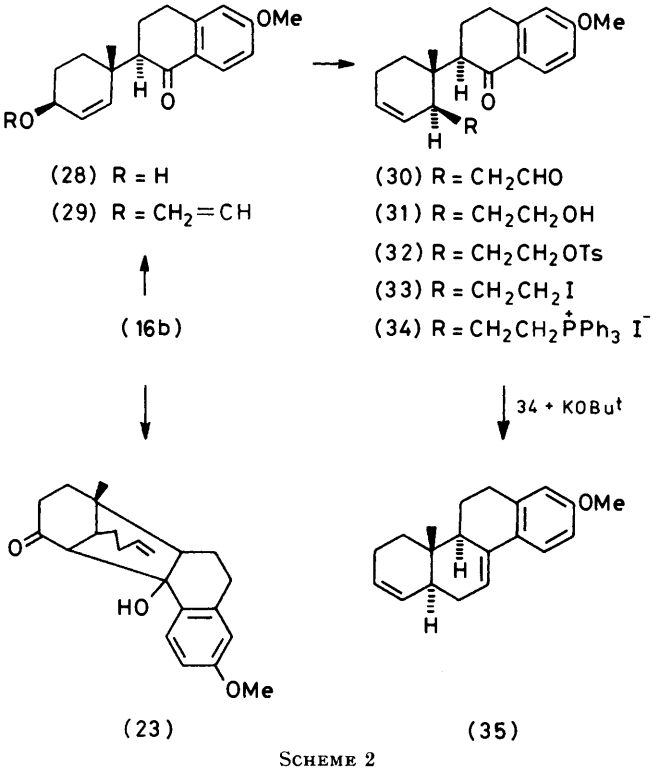
SCHEME 1

Interestingly, the correct 9α-epimer (16b) did not undergo satisfactory cuprate addition. The major product from this reaction showed the presence in the i.r. spectrum of a saturated ketone group, at 1 710 cm^{-1} but complete loss of the tetralone carbonyl group, whilst the presence of an OH group was indicated by absorptions at 3 600 and 3 400 cm^{-1}, and the butenyl group by a peak at 1 640 cm^{-1}. By comparison of the known behaviour of similar enones observed in our laboratory [22] (see later) we assigned structure (23) to this compound arising from spontaneous cyclisation of the enolate generated during cuprate addition, but full characterisation was impeded by its apparent tendency to undergo dehydration. This observation was useful in assigning the stereochemistries of the enones (16), as follows. Dreiding models indicate that alignment of the tetralone carbonyl group with the intermediate cuprate-derived enolate in such a way as to lead to cyclisation, results in severe interactions between the ring A methylene groups and the aromatic D-ring in epimer (16a), whilst there is no such overlap between A- and D-rings of (16b). Thus, cyclisation of (16a) is expected to be a high-energy process, owing to severe steric interactions, whilst (16b) experiences no such problems. With the alcohol (20) in hand we decided to investigate the construction of an appropriate D-homoaromatic steroid. Direct ozonolysis of (20) gave only low yields of aldehyde, but protection of (20) as the methoxymethyl ether (21), followed by ozonolysis, afforded the aldehyde (22) in good yield, whose aldol cyclisation could now be examined.

Treatment of the aldehyde (22) with sodium methoxide in methanol resulted in smooth conversion into the cyclised aldehyde (24), with very little (<5%) epimerisation at C-9. Decarbonylation of this compound with chlorotris(triphenylphosphine)rhodium, to give (25), proved to be exceptionally difficult, requiring a large excess of the reagent and prolonged heating for effective conversion. On the other hand, treatment of (22) with potassium t-butoxide in anhydrous tetrahydrofuran at reflux temperature, followed by careful quenching at lower temperature, afforded (24) and the corresponding β,γ-unsaturated aldehyde (26), separable by chromatography. It is well-known that treatment of α,β-unsaturated ketones and aldehydes under these conditions effects their deconjugation,[23] though we have not attempted to effect conversion of (24) into (26). In contrast to the conjugated aldehyde, the latter compound underwent smooth decarbonylation with Wilkinson's catalyst to give (27), in which the incorrect stereochemistry at C-9 has been lost, thereby achieving our initial objective. The resemblance between (27) and the intermediates (9) and (11) used by Johnson and Kametani is sufficiently close to enable us to see that steroid total synthesis can be achieved using the complex (1a) as a ring A synthon.

Our inability to utilise the 9-α-epimer (16b) was, however, cause for concern, since we wished to be able to utilize both compounds in a single sequence. Consequently, we have examined alternative methodology for introducing the B-ring fragment which does not involve generation of enolates of the 3-oxo-group (steroid numbering) and which therefore avoids the problems encountered with the cuprate addition. Borohydride reduction of (16b) occurred selectively at the cyclohexenone carbonyl group to give the allylic alcohol (28) as the major product (Scheme 2), assigned the 3β-stereochemistry (steroid numbering) by analogy with the reduction of steroidal ketones, as above. A minor amount of epimeric alcohol was produced which could be separ-

ated by chromatography. The allylic alcohol (28) was converted into the vinyl ether (29) under standard conditions, and this material underwent smooth Claisen rearrangement in refluxing decalin to give the aldehyde (30) in good overall yield, thereby introducing an appropriate ring B fragment with the correct (trans A/B) stereochemistry. All that remained was to effect cyclisation of the terminal carbon atom of this moiety onto the

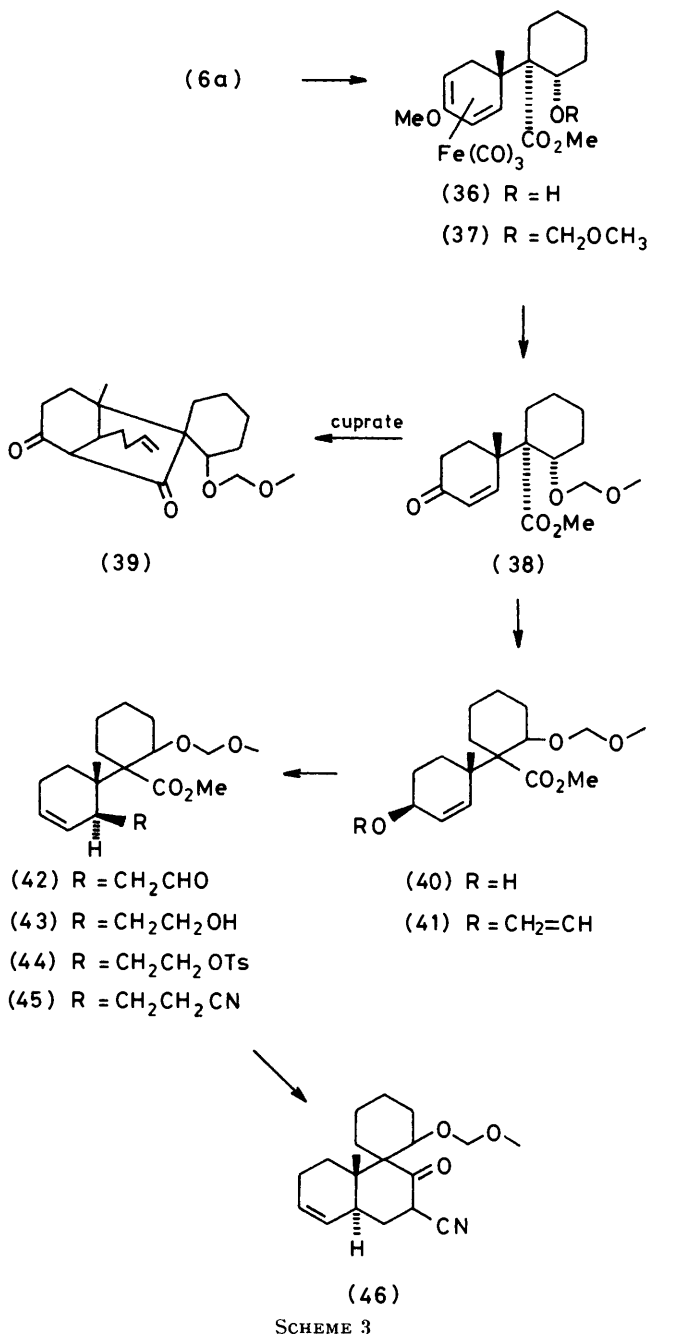


SCHEME 2

tetralone carbonyl group, and for this we chose to investigate an intramolecular Wittig reaction, which has recently been employed for the construction of five-,[24] six-,[25] and large-[26] membered rings.

The conversion of the aldehyde (30) into the required phosphonium derivative was achieved using a conventional sequence : reduction to the primary alcohol (31), followed by sequential conversion into the tosylate (32), iodide (33), and thence to the triphenylphosphonium salt (34), obtained as a white moisture-sensitive solid, insoluble in hydrocarbon solvents. Treatment of (34) with potassium-t-butoxide resulted in ring closure to give the D-homoaromatic steroid derivative (35), possessing the correct stereochemistry at C-9.

Whilst the n.m.r. signals of the 19-methyl group cannot be taken as definitive of the stereochemistry of the A/B and B/C ring junctions in these compounds, owing to fairly wide variations in literature values and the unavailability of appropriate reference compounds, there is some support for our stereochemical assignments of products (26), (27) and (35). Thus, the D-homoaromatic steroid derivatives prepared by Kametani *et al.* having *trans* A/B stereochemistry usually show the 19-methyl



SCHEME 3

group at *ca.* δ 0.7—1.0, whilst the corresponding *cis* A/B compounds show this group at *ca.* δ 1.2 p.p.m. Our compounds (26), (27), and (35) give n.m.r. absorptions at δ 0.90, 1.06, and 0.86, respectively, supporting the assignment of the *trans* A/B ring junction.

We have also ascertained that the epimeric enone intermediate (16a) can be successfully applied in the Claisen rearrangement sequence but we have not investigated the complete series of transformations described for (16b). The formation of compound (35) again establishes a strategy for steroid total synthesis using the complex (1a), since transformation of a 3,4-double bond,

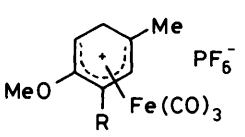
via the α-epoxide, to give both 3α-hydroxy and 3α,4β-diol derivatives, has already been established.[27] Our future work in this area will examine the use of a C/D ring nucleophile which is more closely related to the steroidal ring system, and this avoids lengthy elaboration of the homoaromatic D ring. The present study serves to establish two approaches to the construction of the B ring, essential for the planning of effective total syntheses.

Having derived suitable methodology for the steroid approaches, we turned our attention to a possible strategy for the synthesis of aphidicolane-related compounds. For these purposes the single diastereoisomer (6a) was chosen as a suitable model substrate, since this was readily available from our previous work.[4] Reduction with sodium borohydride furnished the alcohol (36), previously characterised,[28] which was protected as the methoxymethyl ether (37) in the usual way.

Removal of the $Fe(CO_3)$ group, followed by mild acid hydrolysis afforded the enone derivative (38) which now required the introduction of a suitable ring B fragment. Again, addition of cuprate reagents was accompanied by cyclisation of the intermediate enolate (for both diastereoisomeric enones, in fact) to give the useless tricyclic compound (39) as the major product.[22] Since we were unable to overcome this problem, our attention was turned to the application of a Claisen rearrangement for achieving the desired transformation. To this end, the enone (38) was reduced with sodium borohydride to the allylic alcohol (40), which was converted into the corresponding vinyl ether (41) as above (Scheme 3). This compound underwent rearrangement in refluxing decalin to give moderate yields of the aldehyde (42). Since we required to effect a Dieckman cyclisation onto the ester group with the formation of a six-membered B ring, it is clear that a homologation step was necessary. Reduction of the aldehyde (42) with sodium borohydride gave the alcohol (43) which was converted into the tosylate (44) and thence to the nitrile (45). The latter compound contained small amounts of an impurity (t.l.c.) which was shown in the subsequent step to be cyclised material, so that the nitrile was not further purified. Treatment of the crude (45) with sodium hydride in refluxing tetrahydrofuran afforded, after chromatographic purification, the desired cyclised compound (46) as a white crystalline solid.

These experiments, undertaken as a model study, serve to establish a method of construction of the A, B, and D rings of aphidicolane derivatives. Clearly, the intermediate (45) is quite far removed from the final objective, and further functionalisation of both the A and D rings is necessary for further progress. Since this would require a number of steps for its completion, we have instead diverted our attention to the synthesis of complexes of general structure (46), and their reactions with keto-ester nucleophiles of structure (47). Successful application of these compounds, coupled with the above method for ring B construction, is expected to furnish a more convergent route to the aphidicolin and stemodinane ring systems.

We have established successful methods for the conversion of tricarbonylcyclohexadienyliumiron salts into both steroids and precursors for aphidicolin synthesis. These approaches to natural product synthesis are



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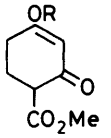

(47)

interesting in the light of the recent synthesis by Birch *et al.* of the complex (1a) in optically active form.[29] Thus it can be seen that there is now a potential for asymmetric synthesis of a range of interesting and important natural products.

EXPERIMENTAL

I.r. spectra were recorded with a Perkin-Elmer 577, mass spectra with A.E.I. MS12 (organometallics) or MS30 (organic compounds) and ^1H n.m.r. spectra with Varian EM360 (60 MHz), EM390 (90 MHz), or Bruker WH 400 (400 MHz) instruments. M.p.s are uncorrected. All chromatographic operations with iron complexes were conducted under an atmosphere of nitrogen. Solvents were freshly distilled under nitrogen as follows: tetrahydrofuran (THF) from sodium–benzophenone; dichloromethane and toluene from calcium hydride; diethyl ether from lithium aluminium hydride.

Methyl 2-(1-Methyl-4-oxocyclohex-2-enyl)-6-methoxy-1,2,3,-4-tetrahydronaphthalene-2-carboxylate (15).—The complexes (7) (11.2 g) were heated at 50—60 °C with anhydrous trimethylamine *N*-oxide (22.5 g) in benzene (270 ml) for 3.5 h. The cooled reaction mixture was filtered through Celite and the residues and filter cake were washed with ethyl acetate. The organic extracts were washed with water, dried ($MgSO_4$), and evaporated to yield crude dienol ether which was immediately dissolved in methanol (250 ml) and stirred at room temperature whilst a solution of oxalic acid (14 g) in water (80 ml) was added. Stirring was continued for 40 min after which time the mixture was added to water (700 ml) and neutralised with saturated aqueous sodium hydrogencarbonate. Extraction with ethyl acetate in the usual way afforded the crude tetralones (15). Whilst these could be separated by t.l.c. no attempt was made to obtain the individual diastereoisomers. Minor impurities were removed by column chromatography to give a white crystalline mixture of the diastereoisomers (15), analytically pure, $\nu_{max.}$ ($CHCl_3$) 1 730, 1 675, and 1 602 cm^{-1}; δ($CDCl_3$) 7.95 (1 H, dd, *J* 10, 2.5 Hz, enone), 7.5—6.5 (3 H, complex due to diastereoisomers), 5.85 (1 H, d, *J* 10 Hz), 3.79 (3 H, s), 3.63 and 3.60 (3 H, 2 × s), 2.9—2.0 (8 H, m), and 1.42 and 1.33 (3 H, 2 × s); *m/z* (%) 342 (5), 234 (100), 219 (5), 202 (50), and 148 (75) (Found: C, 70.15; H, 6.6. Calc. for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48%).

2-(1-Methyl-4-oxocyclohex-2-enyl)-6-methoxy-3,4-dihydronaphthalen-1(2H)-one (16).—The mixture of diastereoisomeric oxo-esters (15) (5.45 g) was dissolved in dry hexamethylphosphoramide (HMPA) (50 ml) under an argon atmosphere and tetramethylammonium acetate (8.0 g) was added. The stirred mixture was heated at 100 °C for 6.5 h when examination of the i.r. spectrum indicated the reaction to be complete. The cooled mixture was poured into water

(250 ml) and the product thoroughly extracted with ether. The ether extracts were washed with water, dilute hydrochloric acid, water, and aqueous sodium hydrogencarbonate and then dried ($MgSO_4$) and evaporated to give the crude product. Filtration of an ethyl acetate solution of this material through alumina afforded the mixture of diastereoisomers (16) as a colourless syrup (3.9 g, 87%) showing only trace impurities on t.l.c. Chromatography on silica gel using first 30%, then 40% ethyl acetate in light petroleum (b.p. 30—40 °C) gave two major fractions. The faster-running band afforded the '9α-epimer' (16b) as a white crystalline solid, m.p. 75—77 °C (2.4 g, 46%), $\nu_{max.}$ ($CHCl_3$) 1 676 and 1 603 cm^{-1}; δ($CDCl_3$) 7.90 (1 H, d, *J* 8.6 Hz), 7.26 (1 H, d, *J* 10.3 Hz), 6.75 (1 H, dd, *J* 8.6, 2.5 Hz), 6.62 (1 H, d, *J* 2.5 Hz), 5.83 (1 H, d, *J* 10.3 Hz), 3.80 (3 H, s), 3.0—1.9 (9 H), and 1.30 (3 H, s); *m/z* (%) 284 (10), 269 (1), 227 (10), 211 (8), 195 (5), and 176 (100) (Found: C, 76.1; H, 7.1. Calc. for $C_{18}H_{20}O_3$: C, 76.3; H, 7.09%). The slower band afforded the 9β-epimer (16a) as a white crystalline solid, m.p. 115.5—116.5 °C (1.9 g, 31%; combined yield 77%); $\nu_{max.}$ ($CHCl_3$) 1 675 and 1 605 cm^{-1}; δ($CDCl_3$) 7.87 (1 H, d, *J* 8.6 Hz), 6.91 (1 H, dd, *J* 10.2, 1.6 Hz, enone), 6.75 (1 H, dd, *J* 8.6, 2.5 Hz), 6.63 (1 H, d, *J* 2.5 Hz), 5.84 (1 H, d, *J* 10.2 Hz), 3.79 (3 H, s), 3.0—1.7 (9 H), and 1.23 (3 H, s) (Found: C, 75.6; H, 6.95%; *M*, 284 Calc. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09%; *M*, 284).

2-(2-*But*-3-*enyl*-1-*methyl*-4-*oxocyclohexyl*)-6-*methoxy*-3,4-*dihydronaphthalen*-1(2H)-*one* (19).—But-4-enylmagnesium bromide was prepared in dry THF under argon in the usual way from but-4-enyl bromide (350 mg) and magnesium (50 mg). To a stirred suspension of cuprous bromide (100 mg) in THF (1 ml) was added sufficient freshly distilled tri-n-butylphosphine in order to dissolve completely the bromide. The solution was cooled to −20 °C and the above Grignard reagent was added dropwise (syringe). The mixture was further cooled to −40 °C and the enone (16a) (140 mg) in THF (1.5 ml) was added dropwise (syringe).

Stirring was continued at this temperature until reaction was complete as judged by t.l.c. (4—5 h) after which the mixture was poured into saturated aqueous ammonium chloride; it was then stirred for 10 min and the product extracted in the usual way with ether. The crude product was purified by preparative t.l.c. (silica gel–ether) which separated it from a minor amount of epimeric material, to give the ketone (19) as a colourless oil (131 mg, 79%), $\nu_{max.}$ ($CHCl_3$) 3 080 (=CH_2), 1 715, 1 680, 1 642, 1 603, and 910 cm^{-1}; δ($CDCl_3$) 7.81 (1 H, d, *J* 8.6 Hz), 6.70 (1 H, dd, *J* 8.6, 2.0 Hz), 6.53 (1 H, s, br), 5.65 (1 H, m), 4.95 (1 H, d, *J* 8 Hz), 4.80 (1 H, s, br), 3.80 (3 H, s), 3.1—1.6 (16 H), and 1.10 (3 H, s); *m/z* (%) 340 (0.1), 322 (5), and 176 (100) (Found: C, 77.20; H, 8.51; Calc. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29%).

2-(2-*But*-3-*enyl*-4β-*hydroxy*-1-*methylcyclohexyl*)-6-*methoxy*-3,4-*dihydronaphthalen*-1(2H)-*one* (20).—The ketone (19) (240 mg) was dissolved in methanol (2.5 ml) and cooled to 0 °C. Sodium borohydride (40 mg) was added and the mixture was stirred for 30 min. Aqueous work-up and ether extraction in the usual way, followed by preparative t.l.c. afforded the alcohol (20) as a colourless syrup (178 mg, 72%), $\nu_{max.}$ ($CHCl_3$) 3 610, 3 500, 3 070, 1 670, 1 642, 1 603 and 910 cm^{-1}; δ($CDCl_3$) 7.93 (1 H, d, *J* 8.5 Hz), 6.83 (1 H, dd, *J* 8.5, 2.5 Hz), 6.67 (1 H, d, *J* 2.5 Hz), 5.8 (1 H, m), 5.03 (1 H, d, br, *J* 10 Hz), 4.88 (1 H, s, br), 3.85 (3 H, s), 3.75 (1 H, m), 3.1—1.2 (16 H, and 1 H exch. D_2O), and 0.97 (3 H, s); *m/z* (%) 342 (1), 324 (2), and 176 (100) (Found: C, 77.5; H, 8.6. Calc. for $C_{22}H_{30}O_3$: C, 77.16; H, 8.33%).

2-(2-*But*-3-*enyl*-4β-*methoxymethoxy*-1-*methylcyclohexyl*)-6-*methoxy*-3,4-*dihydronaphthalen*-1(2H)-*one* (21).—To a solution of the alcohol (20) (466 mg) in dry dichloromethane (10 ml) was added di-isopropylethylamine (2.5 ml) and chloromethyl methyl ether (1.9 ml). The solution was heated to reflux under nitrogen for 8 h, cooled, and diluted with water (10 ml). After being stirred for 10 min, the mixture was diluted with dichloromethane (10 ml) and the aqueous phase discarded; the organic phase was washed with water, dried, and evaporated to yield the ether (21), essentially pure (495 mg, 94%), $\nu_{max.}$ (CCl_4) 3 080, 1 680, 1 642, 1 603, and 905 cm^{-1}; δ($CDCl_3$) 7.85 (1 H, d, *J* 8.5 Hz), 6.70 (1 H, dd, *J* 8.5, 2.5 Hz), 6.58 (1 H, d, *J* 2.5 Hz), 5.7 (1 H, m), 5.0 (1 H, d, *J* 8 Hz), 4.73 (1 H, s, br), 4.60 (2 H, s), 3.77 (3 H, s), 3.7 (1 H, m), 3.32 (3 H, s), 3.1—1.2 (16 H), and 0.96 (3 H, s); *m/z* (%) 386 (0.5), 325 (25), and 176 (100) (Found: *M*, 386.2449; Calc. for $C_{24}H_{34}O_4$: *M*, 386.2457).

2-(2-*Formylethyl*-4β-*methoxymethoxy*-1-*methylcyclohexyl*)-6-*methoxy*-3,4-*dihydronaphthalen*-1(2H)-*one* (22).—The tetralone (21) (50 mg) was dissolved in dichloromethane (2 ml), containing a small amount of methanol (*ca.* 0.1 ml), and cooled to −78 °C. Ozone was passed through the solution at this temperature, until t.l.c. examination showed complete reaction. An excess of dimethyl sulphide was added and the mixture was warmed to room temperature and allowed to stand overnight. Removal of solvent, followed by preparative t.l.c. afforded the aldehyde (22) as a colourless oil (43 mg, 85%), $\nu_{max.}$ (CCl_4) 2 708, 1 728, 1 680, and 1 603 cm^{-1}; δ($CDCl_3$) 9.80 (1 H, s), 7.91 (1 H, dd, *J* 9, 2 Hz), 6.80 (1 H, dd, *J* 9, 2.5 Hz), 6.67 (1 H, m), 4.66 (2 H, s), 3.85 (3 H, s), 3.6 (1 H, m), 3.36 (3 H, s), 3.1—1.1 (16H), and 0.97 (3 H, s); *m/z* (%) 388 (2), 327 (20), and 176 (100) (Found: *M*, 388.2241. Calc for $C_{23}H_{32}O_5$: *M*, 388.2250).

Aldol Cyclisations of the Aldehyde (22).—(a) *Using* NaOMe. The aldehyde (22) (100 mg) was dissolved in methanol (5 ml) containing sodium methoxide (35 mg), and the solution was heated under reflux for 8 h. Aqueous work-up and ether extraction in the usual way, followed by preparative t.l.c. afforded the cyclised aldehyde (24) (78 mg, 82%) as a colourless oil, containing a minor amount of epimeric material shown by an aldehyde signal at δ 9.67 in the n.m.r. spectrum (*ca.* 5%); $\nu_{max.}$ (CCl_4) 1 663 and 1 602 cm^{-1}; δ($CDCl_3$) 9.85 (1 H, s), 7.05 (1 H, d, *J* 9 Hz), 6.72 (2 H, m), 4.67 (2 H, s), 3.81 (3 H, s), 3.5 (1 H, m), 3.38 (3 H, s), 3.0 (2 H, m), 2.5—1.2 (12 H), and 0.93 (3 H, s); *m/z* (%) 342 (100, *M* − CO), 327 (20), 295 (8), 281 (12), 265 (45), and 239 (10) (Found: C, 74.9; H, 8.53%; *M* − CO, 342.2194. Calc. for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16%; *M* − CO, 342.2194).

(b) *Using* $KOBu^t$. The aldehyde (22) (32 mg) was dissolved in dry THF (3 ml), and freshly sublimed potassium t-butoxide (20 mg) was added. The mixture was heated under reflux for 3 h, cooled, poured into ice-cold water, and extracted with ether in the usual way. Preparative t.l.c. afforded the above conjugated aldehyde (24) (9.5 mg, 32%), and the faster-running oily non-conjugated aldehyde (26) as a mixture of C-7 epimers (11.4 mg, 38%), together with some unchanged starting material (6 mg, 20%). Variation in work-up procedure, *e.g.* quenching with dilute acetic acid, or change in reaction times, gave no improvement in the ratio of (24) and (25); spectral data for (25): $\nu_{max.}$ (CCl_4) 1 725 and 1 603 cm^{-1}; δ($CDCl_3$) 9.69 (d, *J* 2.0 Hz) and 9.15 (d, *J* 3.5 Hz, epimeric CHO), 6.97 (1 H, d, *J* 9 Hz), 6.66 (2 H, m), 4.63 and 4.60 (2 H, 2 × s, OCH_2O, epimers), 3.75 (3 H, s), 3.5 (2 H, m), 3.35 (3 H, s), 2.65 (2 H, m), 2.3—1.2 (13 H), and 1.23 (3 H, s); M^+, 370.

17-*Methoxy*-3β-*methoxymethoxy*-9β-D-*homo*-18-*norandrosta*-7,13,15,17-*tetraene* (25).—The aldehyde (24) (6 mg) was dissolved in toluene (2 ml) under argon, and freshly prepared chlorotris(triphenylphosphine)rhodium(I) (Wilkinson's catalyst, 20 mg, 3 equiv.) was added. The mixture was heated under reflux for 10 h, solvent was removed under reduced pressure, and the residue subjected to preparative t.l.c., to yield the product (25) (3.0 mg, 56%) as a colourless oil, $\nu_{max.}$ (CCl_4) 1 603vw cm^{-1}; δ($CDCl_3$) (400 MHz) 7.24 (1 H, d, *J* 9 Hz), 6.65 (1 H, d, *J* 9 Hz), 6.56 (1 H, s, br), 5.79 (1 H, d, *J* 7 Hz), 4.67 (2 H, s), 3.75 (3 H, s), 3.65, (1 H, m), 3.33 (3 H, s), 2.90 (2 H, m), 2.1—1.0 (14 H), 0.90 (3 H, s); *m/z* (%) 342 (95), 327 (5), 281 (8), 265 (30), and 249 (25) (Found: *M*, 342.2196. Calc. for $C_{22}H_{30}O_3$: *M* 342.2195).

17-*Methoxy*-3β-*methoxymethoxy*-D-*homo*-18-*norandrosta*-8,13,15,17-*tetraene* (27).—The aldehyde (26) (8.0 mg) was dissolved in dry toluene under argon atmosphere. Wilkinson's catalyst (12 mg) was added and the mixture was heated under reflux for 2.5 h, and then worked up as above, to afford the tetracyclic derivative (27) (5.7 mg, 77%) as an oil, $\nu_{max.}$ (CCl_4) 1 602w cm^{-1}; δ($CDCl_3$) (400 MHz) 7.13 (1 H, d, *J* 9 Hz), 6.72 (1 H, d, *J* 9 Hz), 6.66 (1 H, s, br), 4.70 (2 H, narrow ABq, OCH_2O diastereotopic), 3.79 (3 H, s), 3.55 (1 H, m), 3.37 (3 H, s), 2.75—1.4 (15 H), and 1.06 (3 H, s); *m/z* (%) 342 (90), 327 (35), 295 (15), 281 (2), and 265 (100) (Found: *M*, 342.2195. Calc. for $C_{22}H_{30}O_3$: *M*, 342.2195).

2-(4β-*Hydroxy*-1-*methylcyclohex*-2-*enyl*)-6-*methoxy*-3,4-*dihydronaphthalen*-1(2H)-*one* (28).—The ketone (16b) (284 mg) was stirred in methanol (3 ml) at 0 °C whilst sodium borohydride (50 mg) was added. The mixture was stirred for 30 min, and then worked up in the usual way; the product was purified by preparative t.l.c. to afford the single epimeric alcohol (28) as a colourless oil which would not be crystallised (255 mg, 89%). A minor amount of epimeric material was separated but not further characterised, $\nu_{max.}$ ($CHCl_3$) 3 610, 3 500, 1 745w (aromatic overtone), 1 680, and 1 602 cm^{-1}; δ($CDCl_3$) 7.90 (1 H, d, *J* 8.5 Hz), 6.74 (1 H, dd, *J* 8.5, 2.5 Hz), 6.60 (1 H, d, *J* 2.5 Hz), 5.77 (1 H, dd, *J* 10.4 Hz), 5.60 (1 H, d, *J* 10 Hz), 4.12 (1 H, m), 3.80 (3 H, s), 2.87 (2 H, m), 2.5—1.5 (9 H and 1 H exch D_2O), and 1.27 (3 H, s) (Found: C, 75.2; H, 7.9%; *M*, 286.1562. Calc. for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74%; *M*, 286.1569).

2-(1-*Methyl*-4β-*vinyloxycyclohex*-2-*enyl*)-6-*methoxy*-3,4-*dihydronaphthalen*-1(2H)-*one*.—The alcohol (28) (180 mg) was dissolved in ethyl vinyl ether (5 ml) and vinyl acetate (108 mg) and mercuric acetate (400 mg) were added. The mixture was heated to reflux under argon, cooled, and evaporated under reduced pressure; the residue was subjected to preparative t.l.c. to afford the sensitive ether (29) (175 mg, 89%) as a colourless oil, $\nu_{max.}$ (CCl_4) 3 130w, 17 45w, 1 680, 1 640, and 1 602 cm^{-1}; δ($CDCl_3$) 7.80 (1 H, d, *J* 8.5 Hz), 6.66 (1 H, dd, *J* 8.5, 2.5 Hz), 6.50 (1 H, d, *J* 2.5 Hz), 6.22 (1 H, dd, *J* 14, 7 Hz), 5.75 (1 H, d, J_{AB} 10 Hz), 5.55 (1 H, d, J_{AB} 10 Hz), 4.16 (1 H, m), 4.12 (1 H, dd, *J* 14, 1.7 Hz), 3.86 (1 H, dd, *J* 7, 1.7 Hz), 3.74 (3 H, s), 2.8 (2 H, m), 2.4—1.4 (7 H), and 1.23 (3 H, s); *m/z* (%) 269 (65, *M* − C_2H_3O), 268 (25), 253 (40), 227 (5), 177 (100), and 176 (90).

2-[2-*Formylmethyl*-1-*methylcyclohex*-3-*enyl*]-6-*methoxy*-3,4-*dihydronaphthalen*-1-(2H)-*one* (30).—The ether (29) (400 mg) was heated under reflux in decalin (20 ml) for 5 h. The excess of decalin was removed under high vacuum and the residue was subjected to preparative t.l.c., to afford the aldehyde (30) as an oil (276 mg, 69%), $\nu_{max.}$ (CCl_4) 2 720, 1 730s, 1 680, and 1 602 cm^{-1}; δ($CDCl_3$) 9.9 (1 H, t, *J* 2.5 Hz), 7.92 (1 H, d, *J* 9 Hz), 6.77 (1 H dd, *J* 9, 2.5 Hz), 6.62 (1 H, d, *J* 2.5 Hz), 5.95 (1 H, m), 5.6 (1 H, m), 3.80 (3 H, s), 2.9 (2 H, m), 2.6—1.2 (10H), and 1.02 (3 H, s); *m/z* (%) 312 (20), 279 (8), 253 (8), 207 (45), and 176 (100) (Found: *M*, 312.1727. Calc. for $C_{20}H_{24}O_3$: *M*, 312.1725).

2-[2-(2-*Hydroxyethyl*)-1-*methylcyclohex*-3-*enyl*]-6-*methoxy*-3,4-*dihydronaphthalen*-1(2H)-*one* (31).—The aldehyde (30) (275 mg) was dissolved in 1 : 1 methanol–dioxan (5 ml) and stirred at 0 °C whilst sodium borohydride (100 mg) was added. The mixture was stirred for 3 h and worked up in the usual way to afford the alcohol (31) as a colourless oil, purified by preparative t.l.c. (200 mg, 73%), $\nu_{max.}$ (CCl_4) 3 630, 3 500, 1 677, and 1 660sh, 1 603 cm^{-1}; δ($CDCl_3$) 7.90 (1 H, d, *J* 8.5 Hz), 6.75 (1 H, dd, *J* 8.5, 2.5 Hz), 6.60 (1 H, d, *J* 2.5 Hz), 5.60 (2 H, s, br,), 3.80 (3 H, s), 3.73 (2 H, t, *J* 3.5 Hz), 2.93 (2 H, dd, *J* 7, 4 Hz), 2.67 (1 H, dd, *J* 12, 4.5 Hz), 2.3—1.3 (9 H), 1.70 (1 H, s, br, exch. D_2O), and 1.06 (3 H, s) (Found: C, 76.15; H, 8.55%; *M*, 314. Calc. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34%; *M*, 314).

2-[1-*Methyl*-2-(2-p-*tolylsulphonyloxyethyl*)*cyclohex*-3-*enyl*]-6-*methoxy*-3,4-*dihydronaphthalen*-1(2H)-*one* (32).—The alcohol (31) (160 mg) was treated with toluene-*p*-sulphonyl chloride (120 mg) in dry pyridine (5 ml) at 0 °C overnight. The mixture was then treated with water (0.1 ml) at 0 °C for 0.5 h and poured into ice-cold dilute hydrochloric acid. Ether extraction, followed by washing with water and aqueous sodium hydrogencarbonate, drying ($MgSO_4$), and evaporation afforded the oily tosylate, purified by preparative t.l.c. (220 mg, 92%), $\nu_{max.}$ (CCl_4) 1 680, 1 603, 1 370, and 1 172 cm^{-1}; δ($CDCl_3$) 7.81 (1 H, d, *J* 8.5 Hz), 7.76 (2 H, d, *J* 8.0 Hz), 7.28 (2 H, d, *J* 8.0 Hz), 6.69 (1 H, dd, *J* 8.5, 2.5 Hz), 6.54 (1 H, d, *J* 2.5 Hz), 5.62 (1 H, d, J_{AB} 10.5 Hz), 5.40 (1 H, dd, *J* 10.5, 3 Hz), 4.10 (2 H, t, *J* 6 Hz), 3.77 (3 H, s), 2.9 (2 H, m), 2.52 (1 H, dd, *J* 12, 3 Hz), 2.42 (3 H, s), 2.3—1.2 (9 H), and 1.00 (3 H, s); *m/z* (%) 468 (2) and 296 (100) (Found: *M*, 478.1978. Calc. for $C_{27}H_{32}O_5S$: *M*, 468.1970).

2-[2-(2-*Iodoethyl*)-1-*methylcyclohex*-3-*enyl*]-6-*methoxy* 3,4-*dihydronaphthalen*-1(2H)-*one* (33).—The tosylate (32) (150 mg) was heated under reflux for 6 h in dry acetone (3 ml) with sodium iodide (100 mg). The mixture was diluted with ether (50 ml) and the resulting solution was washed with water (3 × 15 ml) and dried ($MgSO_4$). Removal of ether, followed by preparative t.l.c. afforded the iodide (33) as a colourless oil which darkened with time (235 mg, 90%), $\nu_{max.}$ (CCl_4) 1 680 and 1 602 cm^{-1}; δ($CDCl_3$) 7.90 (1 H, d, *J* 8.5 Hz), 6.73 (1 H, dd, *J* 8.5, 2.5 Hz), 6.60 (1 H, d, *J* 2.5 Hz), 5.6 (2 H, m), 3.79 (3 H, s), 3.3 (2 H, m), 2.9 (2 H, m), 2.61 (1 H, dd, *J* 12, 4 Hz), 2.4—1.4 (9 H), and 1.03 (3 H, s); *m/z* (%) 424 (40), 406 (10), 391 (5), 381 (10), 370 (8), 297 (45), and 296 (100) (Found: *M*, 424.0891. Calc. for $C_{20}H_{25}IO_2$: *M*, 424.0899).

17-*Methoxy*-D-*homo*-18-*norandrosta*-3,7,13,15,17-*pentaene* (35).—The iodide (33) (220 mg) and triphenylphosphine (137 mg) were stirred in dry xylene under argon at 100 °C for 24 h, to give a white precipitate. The temperature of the mixture was raised to 125 °C for 2 h and then cooled to room temperature. The white precipitate was filtered off, washed rapidly with dry ether, and dried *in vacuo* (yield 90 mg).

Removal of solvent from the liquors, followed by chromatography gave unchanged iodide (33) (130 mg, 59%), which could be recycled. The yield of phosphonium salt (34), based on reacted iodide was 62%. Use of extended reaction times and larger excess of triphenylphosphine

gave no significant improvement. The phosphonium salt thus obtained was suspended in dry THF (5 ml), freshly sublimed potassium t-butoxide (25 mg) was added, and the mixture was heated to reflux under argon atmosphere until no further change occurred on t.l.c. examination (6—8 h). The solvent was removed and the residue was subjected to preparative t.l.c. to afford the cyclised product (35) obtained as a colourless oil (19 mg, 52%), $\nu_{max.}$ (CCl_4) 1 610 cm^{-1}; $\delta(CDCl_3)$ 7.13 (1 H, d, J 8.5 Hz), 6.51 (1 H, dd, J 8.5, 2.5 Hz), 6.41 (1 H, d, J 2.5 Hz), 5.77 (1 H, d, br, J 6 Hz), 5.57 (1 H, d, J_{AB} 10.5 Hz), 5.30 (1 H, d, J_{AB} 10.5 Hz), 3.69 (3 H, s), 2.83 (2 H, m), 2.3—1.2 (10H), and 0.86 (3 H, s); m/z (%) 280 (65), 265 (7), 186 (65), and 174 (100) (Found: C, 86.0; H, 8.25%; M, 280.1820. Calc. for $C_{20}H_{24}O$: C, 85.67; H, 8.63%; M, 280.1827).

Tricarbonyl{1—4-η-}[5-(1-*methoxycarbonyl*-2-*methoxymethoxycyclohexyl*)-2-*methoxy*-5-*methylcyclohexa*-1,3-*diene*]-*iron* (37).—To a solution of the hydroxy-ester complex (36) (1.45 g) in dichloromethane (45 ml), was added di-isopropylethylamine (2.4 ml) and chloromethyl methyl ether (2.2 ml). The mixture was heated at reflux temperature under nitrogen atmosphere for 8 h. Water (5 ml) was added to the cooled mixture and this was stirred for 10 min. The organic layer was separated, washed with water, dried (K_2CO_3), and evaporated to give the crude ether (37) as a yellow oil (1.6 g, 100%) which was used without further purification, $\nu_{max.}$ ($CHCl_3$) 2 050, 1 970, 1 730, and 1 490 cm^{-1}; $\delta(CDCl_3)$ 4.97 (1 H, dd, J 7, 2 Hz), 4.79 and 4.62 (2 H, ABq, J 7 Hz), 3.77 (3 H, s), 3.75 (1 H, m, obscured), 3.62 (3 H, s), 3.42 (3 H, s), 3.25 (1 H, d, J 7 Hz), 3.20, (1 H, m), 2.55 (1 H, dd, J_{gem} 15, $J_{5,6}$ 3 Hz), 2.3—0.9 (9 H), and 1.2 (3 H, s).

Methyl 2-*Methoxymethoxy*-(1-*methyl*-4-*oxocyclohex*-2-*enyl*)-*cyclohexanecarboxylate* (38).—The above complex (37) (1.6 g) was treated with anhydrous trimethylamine N-oxide (4 g) in refluxing benzene (50 ml) for 4 h. The cooled mixture was filtered through Celite and the filtrate and washings were washed with 10% brine, dried (Na_2CO_3), and evaporated to give the disengaged ligand (1.1 g, 98%). This material was stirred in methanol at 0 °C whilst a solution of oxalic acid (2.7 g) in water (15 ml) was added. Stirring was continued for 1 h, after which the mixture was poured into aqueous sodium hydrogencarbonate (220 ml); the product was extracted in the usual way with ether. Purification by column chromatography on silica gel (55 g) using ether–light petroleum (1 : 1) afforded the pure enone (38) as a white crystalline compound, m.p. 69.5—71 °C (0.76 g, 79% from complex), $\nu_{max.}$ ($CHCl_3$) 1 730, 1 710, and 1 675 cm^{-1}; $\delta(CDCl_3)$ 7.38 (1 H, dd, J 10, 2 Hz), 5.85 (1 H, d, J 10 Hz), 4.78 and 4.63 (2 H, ABq, J 7 Hz), 3.77 (3 H, s), 3.65 (1 H, dd, obscured, J 11, 4 Hz, axial CHO), 3.40 (3 H, s), 2.66—1.1 (12 H), and 1.32 (3 H, s), m/z (%) 310 (5), 266 (10), and 140 (100) (Found: C, 65.8; H, 8.35. Calc. for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44%).

Methyl 1-(4-*Hydroxy*-1-*methylcyclohex*-2-*enyl*)-2-*methoxymethoxycyclohexanecarboxylate* (40).—The enone (39) (573 mg) was dissolved in methanol (30 ml) and cooled to 0 °C. Sodium borohydride (42 mg) was added and the mixture was stirred for 0.5 h, after which time it was poured into ethyl acetate (100 ml). The organic layer was washed with 10% brine (2 × 100 ml) and water (2 × 50 ml), and then dried and evaporated to yield the alcohol (40) which was purified by preparative t.l.c. (540 mg, 94%), $\nu_{max.}$ ($CHCl_3$) 3 608, 3 500, and 1 725 cm^{-1}; $\delta(CDCl_3)$ 5.86 (1 H, d, br, J_{AB} 11 Hz), 5.60 (1 H, d, br, J_{AB} 11 Hz), 4.6 (2 H, close ABq, OCH_2O, diastereotopic), 3.67 (3 H, s), 3.34 (3 H, s), 2.5—1.1 (13 H, 1 H exch. D_2O), and 1.1 (3 H, s) (Found: C, 65.85; H, 9.25; M, 312. Calc. for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03%, M, 312).

Methyl 2-*Methoxymethoxy*-1-(1-*methyl*-4-*vinyloxycyclohex*-2-*enyl*)*cyclohexanecarboxylate* (41).—The alcohol (40) was converted into the vinyl ether as described above for compound (29) (yield 82%), $\nu_{max.}$ (CCl_4) 3 105, 1 735, 1 715, 1 680, 1 610 cm^{-1}; $\delta(CCl_4)$ 6.23 (1 H, dd, J 14.7 Hz), 5.85 (1 H, d, br, J_{AB} 11 Hz), 5.57 (1 H, d, br, J_{AB} 11 Hz), 4.58 (2 H, close ABq, OCH_2O diastereotopic), 4.2 (1 H, m), 4.13 (1 H, dd, J 14, 1.5 Hz), 3.90 (1 H, dd, J 7, 1.5 Hz), 3.64 (3 H, s), 3.43 (1 H, dd, J 10.5, 4 Hz), 3.33 (3 H, s), 2.3—1.1 (12 H), and 1.11 (3 H, s); m/z (%) 295 (12, $M - C_2H_3O$), 263 (1), 249 (1), 233 (1), 203 (8), 141 (20), 140 (8), 121 (30), 119 (95), and 117 (100) (Found: $M - C_2H_3O$, 295.1908. Calc. for $C_{17}H_{27}O_4$: 295.1908).

Methyl 2-*Methoxymethoxy*-1-(1-*methyl*-2-*formylmethylcyclohex*-3-*enyl*)*cyclohexanecarboxylate* (42).—The allyl vinyl ether (41) was subjected to Claisen rearrangement in refluxing decalin as described above for the preparation of compound (30) (yield: 68% at 70% conversion); $\nu_{max.}$ (CCl_4) 2 720 and 1 730 cm^{-1}; $\delta(CCl_4)$ 9.73 (1 H, close m), 5.56 (1 H, d, br, J_{AB} 11 Hz), 5.27 (1 H, d, br, J_{AB} 11 Hz), 4.70 and 4.56 (2 H, ABq, J_{AB} 7 Hz, OCH_2O diastereotopic), 3.60 (3 H, s), 3.55 (1 H, obscured), 3.33 (3 H, s), 2.67 (1 H, ddd, J 15, 4, 1.5 Hz), 2.4—1.1 (14 H), and 0.95 (3 H, s) (Found: C, 67.85; H, 8.65%; M, 338.2083. Calc. for $C_{19}H_{40}O_5$: C, 67.43; H, 8.94%; M, 338.2093).

Methyl 1-[2-(2-*Hydroxyethyl*)-1-*methylcyclohex*-3-*enyl*]-2-*methoxymethoxycyclohexanecarboxylate* (43).—The aldehyde (42) (140 mg) was reduced with sodium borohydride as described for the preparation of the alcohol (31), to afford the crude alcohol (43) as a colourless oil which was not further purified (130 mg, 93%); $\nu_{max.}$ (CCl_4) 3 500br, 1 740, and 1 720 cm^{-1}; $\delta(CDCl_3)$ 5.47 (2 H, m), 4.68 (2 H, ABq), 3.63 (3 H, s), 3.60 (3 H, m, obscured), 3.36 (3 H, s), 2.5—1.0 (15 H, and 1 H exch. D_2O), 1.04 (3 H, s); m/z 340 (M^+).

Methyl 2-*Methoxymethoxy*-1-[1-*methyl*-2-(2-p-*tolylsulphonyloxyethyl*)*cyclohex*-3-*enyl*]*cyclohexanecarboxylate* (44).—The crude alcohol (43) (120 mg) was treated with *p*-toluenesulphonyl chloride–pyridine as described above for tosylate (32). The product was purified by preparative t.l.c. to give the tosylate (44) obtained as a colourless oil (130 mg, 75%), $\nu_{max.}$ (CCl_4) 1 745, 1 720, 1 603, 1 375, and 1 182 cm^{-1}; $\delta(CDCl_3)$ 7.67 (2 H, d, J 8 Hz), 7.20 (2 H, d, J 8 Hz), 5.49 (1 H, d, br, J_{AB} 10 Hz), 5.18 (1 H, d, br, J_{AB} 10 Hz), 4.55 (2 H, close ABq), 4.02 (2 H, t, J 7 Hz), 3.55 (3 H, s), 3.5 (1 H, obscured), 3.30 (3 H, s), 2.95 (1 H, d, br), 2.41 (3 H, s), 2.4—1.1 (14 H), and 0.98 (3 H, s) (Found: C, 63.55; H, 7.35%; M, 494. Calc. for $C_{24}H_{38}O_7S$: C, 63.14; H, 7.74%; M, 494).

Methyl 1-[2-(2-*Cyanoethyl*)-1-*methylcyclohex*-3-*enyl*]-2-*methoxymethoxycyclohexanecarboxylate* (45).—The tosylate (44) (40 mg) was dissolved in hexamethylphosphoramide (1 ml) and sodium cyanide (10 mg) was added. The stirred mixture was heated under argon at 65—70 °C for 2 h. The cooled mixture was poured into water and the product was extracted in the usual way with ether. Examination of the crude product showed no residual tosylate, but the presence of a small amount (5—10%) of cyclised material, so the compound was not further purified (yield, 20 mg, 71%), $\nu_{max.}$ (CCl_4) 2 260, 1 740, 1 720, and 1 660w cm^{-1}; $\delta(CDCl_3)$ 5.50 (2 H, close ABq, br), 4.68 (2 H, close ABq), 3.60 (3 H, s), 3.55 (1 H, obscured), 3.37 (3 H, s), 2.97 (1 H, d, br, J 10 Hz), 2.6—1.1 (16 H), and 1.06 (3 H, s).

Dieckman Cyclisation of the Nitrile (45).—The above crude

product (45) (20 mg) was heated at reflux under argon in dry THF with sodium hydride (5 mg) for 11 h. The stirred mixture was cooled to 0 °C and methanol (0.1 ml) followed by dilute acetic acid (0.5 ml) were added. Aqueous work-up and ether extraction, followed by preparative t.l.c. afforded the tricyclic cyanoketone (46) as a white crystalline solid, m.p. 147—149 °C (9 mg, 50%), $\nu_{max.}$ ($CHCl_3$) 2 265, 1 727, and 1 655w cm^{-1}; δ($CDCl_3$) 5 70 (1 H, dm, J_{AB} 10 Hz), 5.24 (1 H, dd, J 10, 2.5 Hz), 4.71 and 4.58 (2 H, ABq, 3.65 (2 H, m), 3.37 (3 H, s), 2.9 (1 H, d, br, J 15 Hz), 2.4—1.2 (14 H), and 1.03 (3 H, s); *m/z* (%) 317 (80), 285 (40), and 262 (100) (Found: C, 71.8; H, 8.5; *M*, 317.1987. Calc. for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57%; *M*, 317.1991).

We are grateful to the Royal Society and SERC for generous financial support of our work, and to the University of Cambridge for laboratory facilities.

[2/240 *Received*, 9*th February*, 1982]

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