A New Method for the Oxidation of Alkenes to Enones.[1] An Efficient Synthesis of Δ^5-7-Oxo Steroids

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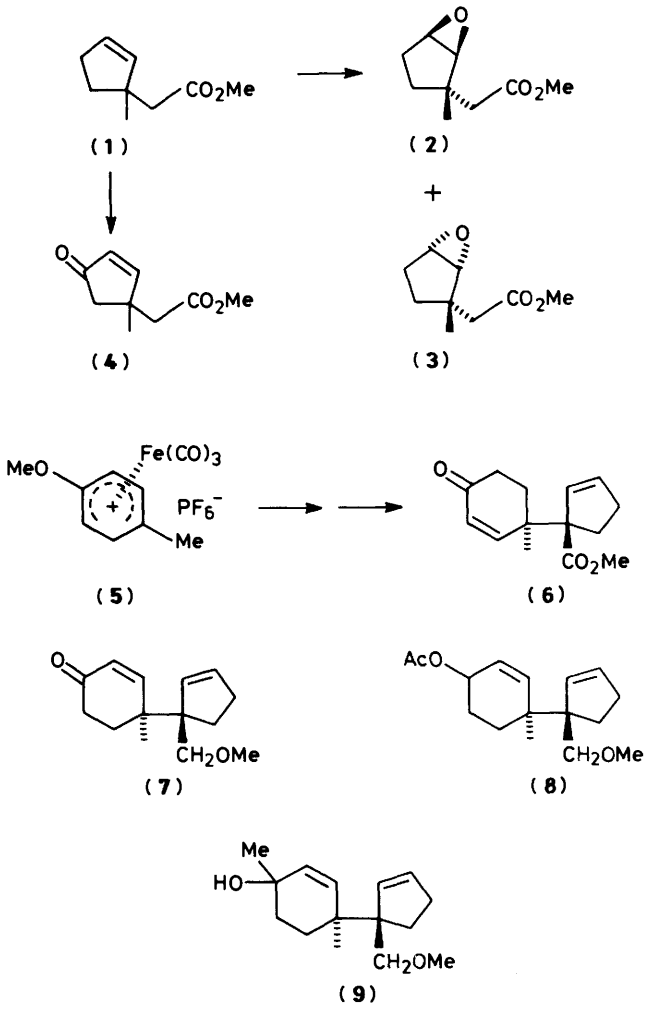
A variety of cycloalkenes were converted into α,β-unsaturated ketones using t-butyl hydroperoxide in the presence of chromium hexacarbonyl catalyst. The scope of the reaction has been partly investigated, and it was found that the allylic oxidation proceeds selectively in the presence of some secondary alcohols. High-yield conversions of steroidal 5,6-enes into the corresponding 5,6-en-7-ones are reported.

Oxidation and reduction of various functional groups represent two of the most important transformations employed by the synthetic organic chemist.[2] There is a continual search for selective methods for effecting such conversions, which allow the manipulation of polyfunctional molecules without recourse to protection–deprotection. Serendipity plays a large part in the discovery of new procedures for such interconversions, and we present here an account of the recent discovery in our laboratory that t-butyl hydroperoxide in the presence of chromium hexacarbonyl catalyst effects allylic oxidation, giving an efficient method for the conversion of alkene into enone which, in some cases, can be carried out in the presence of secondary alcohols. Whilst we have not investigated the full scope of this reaction, the results so far obtained indicate this procedure to be superior to the more traditional methods.

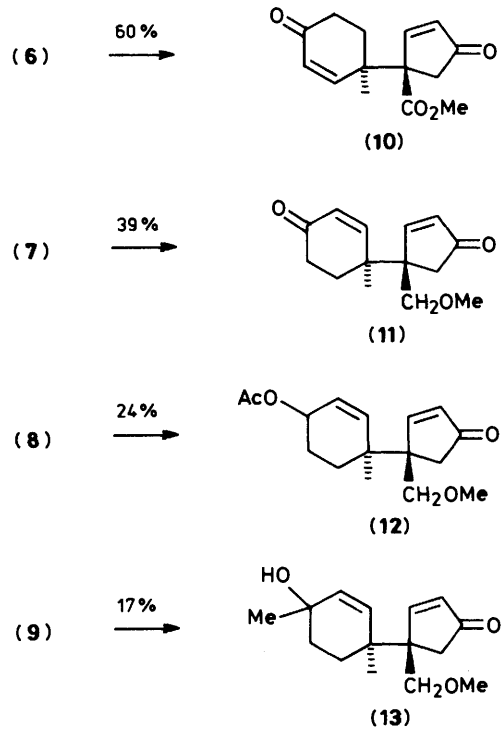
A number of methods are currently available for the conversion of alkene into enone. Several of these, which proceed without double bond migration, are based on the use of chromium trioxide or related high oxidation state chromium species,[3] whilst other methods using singlet oxygen occur with double bond migration.[4] The use of chromium oxide-derived reagents for allylic oxidation has a number of drawbacks. Often the procedure involves the use of a very large excess of reagent and large volumes of solvent, which becomes inconvenient for large-scale reactions. Considerable amounts of tarry chromium residues are produced which are often difficult to filter. Furthermore, alcohol functionalities are oxidized more easily than the allylic methylene group, so that protection–deprotection is required in such cases.

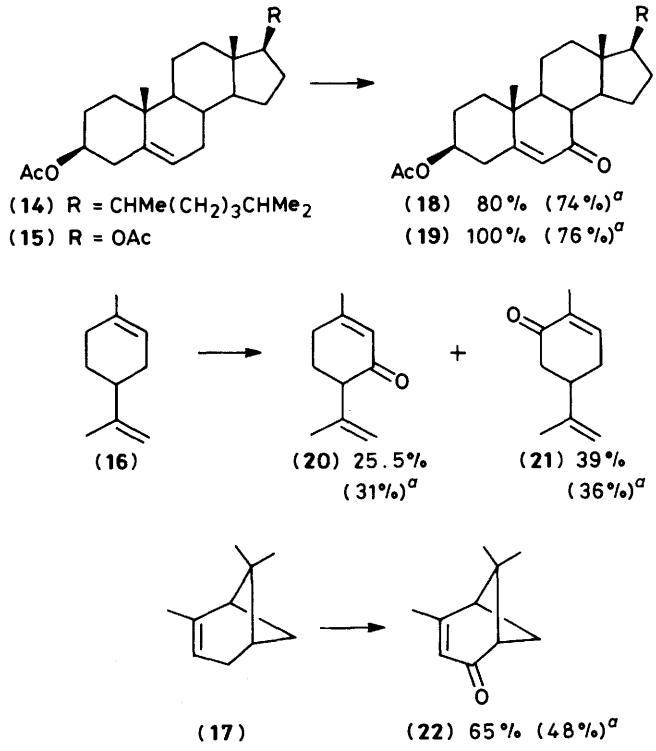


Results and Discussion

During the course of an investigation aimed at the synthesis of trichothecene derivatives,[5] we needed to effect the epoxidation of the cyclopentene derivative (**1**). A number of methods were investigated, including the use of t-butyl hydroperoxide in the presence of molybdenum hexacarbonyl, previously shown to convert alkenes into epoxides.[6] When used in benzene or acetonitrile, the combinations $Mo(CO)_6$–Bu^tOOH or $Mo(CO)_3(CH_3CN)_3$–Bu^tOOH were found to effect the epoxidation of compound (**1**) to give a mixture of the epoxides (**2**) and (**3**), the latter epoxide predominating. Thus, a high degree of stereoselectivity is observed. An authentic sample of compound (**3**) was procured from (**1**) by the following two step sequence: (1) iodolactonization; and (2) treatment with NaOMe. During the course of these studies it was observed that old samples of $Mo(CO)_3(CH_3CN)_3$ catalyst gave poorer epoxidation results, varying amounts of the α,β-unsaturated ketone being produced (n.m.r. spectroscopy).

We turned our attention to the use of chromium hexacarbonyl in these reactions and found that the combination $Cr(CO)_6$–Bu^tOOH–benzene (solvent) led to the predominant formation of the enone (**4**) together with a small amount of the epoxides (**2**) and (**3**). Changing the solvent from benzene to acetonitrile led to the diminished formation of epoxides, and only compound (**4**) was detected in the 200 MHz ^1H n.m.r. spectrum of the crude product. Purification by standard procedures afforded compound (**4**) in 83% yield. It may be noted at this point that the chromium carbonyl may be used in true catalytic amounts, but throughout this study we have employed larger quantities in order to shorten reaction times. The exact nature of the catalyst remains unknown, but the $Cr(CO)_6$ bands in the i.r. spectra are unchanged throughout the reaction.





[a] Data from ref. 3*a*.

Figure. Comparison of Bu^tOOH–$Cr(CO)_6$ oxidations with the best literature methods

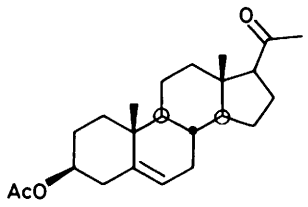
During our studies on trichothecene synthesis we had also converted* the iron complex (**5**) in a few steps into several potential intermediates (**6**)—(**9**), which now required further functionalization of the five-membered ring. Use of Collins reagent or the Salmond procedure[3] on compound (**6**) resulted in very little allylic oxidation, even when a large excess of oxidizing agent was employed for prolonged reaction times. Similarly, selenium dioxide[7] oxidation was unsuccessful, whilst use of *N*-bromosuccinimide gave mixtures of products. However treatment of compound (**6**) with Bu^tOOH–$Cr(CO)_6$ in refluxing acetonitrile led to the bis(enone) (**10**) in 60% yield at 72% conversion. The starting compound was the only other recoverable material. Similarly, the enone (**7**) gave the bis(enone) (**11**), whilst the allylic acetate (**8**) gave compound (**12**), both in poorer yield than from the oxidation of compound (**6**), but better than from the traditional procedures which appear to be more useful when applied to trisubstituted cyclopentenoid systems.[8] (We have not examined the application of our reagent to such compounds; for some useful applications of the oxidation of cyclopentene to cyclopentenone in synthesis see ref. 8.)

The tertiary allylic alcohol (**9**), when treated with the oxidizing system, gave a mixture of products, from which was isolated the enone (**13**) in 17% yield. Whilst this yield is low, it is noteworthy that, to some extent, the tertiary alcohol remains intact, as it is well known that other oxidizing reagents cause oxidative rearrangement of tertiary allylic alcohols.[3] We have not attempted to optimise this conversion by employing different solvents or co-oxidants, or by varying the catalyst.

In order to compare this reaction with similar oxidations using Collins reagent[3a] we examined the oxidation of cholesteryl acetate (**14**), 3,17-bis(acetyloxy)-3β,17β-androst-5-ene (**15**), limonene (**16**), and α-pinene (**17**). The results, together with those reported for the Collins oxidation, are given in the Figure. Use of the chromium carbonyl-catalysed reaction with the steroidal compounds resulted in very high yields of the 7-oxo derivatives (**18**) and (**19**), superior to those obtained using other methods. The oxidation of limonene gave a mixture of isopiperitenone (**20**) and carvone (**21**), similar to the best literature method, whilst the conversion of α-pinene into verbenone (**22**) proceeded in somewhat higher yield.

The results of steroid oxidation are particularly interesting. The 7-oxo derivatives are precursors for the synthesis of B-homoandrostane derivatives, which show interesting biological activity; this is exemplified by B-homodihydrotestosterone which shows androgenic activity equal to, and myotropic activity twice that of testosterone.[9] This particular analogue requires the ketone (**19**) as a precursor. 7-Oxo steroids themselves have been previously investigated as anticortisone agents.[10] Consequently, we examined the oxidation of a further range of steroids using the chromium(0)-catalysed reaction. All of these conversions proceeded in excellent yield. The clean oxidations of 3-(acetyloxy)-3β-pregn-5-en-20-one (**23**) and diosgenin acetate (**24**) indicate that the reaction can be carried out in the presence of relatively sensitive functional groups, and it may be noted in this respect that the reaction mixture is essentially neutral. Previous results on the oxidation of pregnenolone acetate using chromic acid gave compound (**27**) in only 40% yield,[3c] whilst diosgenin acetate reportedly gave (**28**) in 43% yield. The oxidations of stigmasterol acetate (**25**) and limonene show that selectivity can be achieved during the diolefin oxidation. Remarkably, we found that the direct oxidation of stigmasterol (**26**) itself under these conditions cleanly gave 3β-hydroxystigmast-5-en-7-one (**30**) *without oxidation of the secondary alcohol.* Confirmation of this result comes from the fact that the acetylation of compound (**30**) gave (**29**), identical with the product of the oxidation of compound (**25**). The direct oxidation of cholesterol under similar conditions gave a mixture of products containing the corresponding 7-oxo derivative, whose presence was confirmed by acetylation to give the acetate (**18**); however, we did not

* This methodology is based on that described in ref. 5. Full details of the preparation of compounds (**6**)—(**9**) will be given elsewhere.



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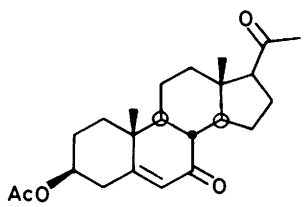

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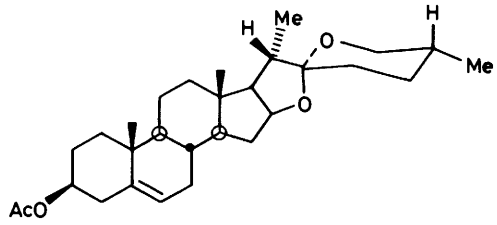

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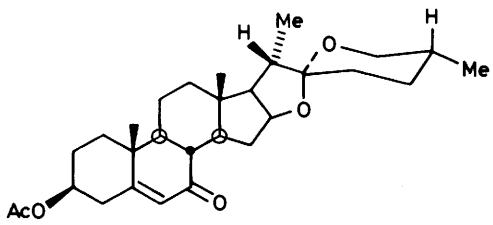

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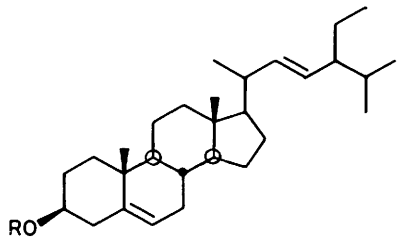
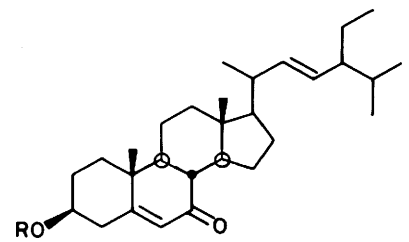
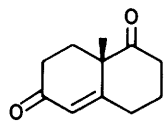


(25) R = Ac
(26) R = H



(29) R = Ac (70%)
(30) R = H (61%)

Ac_2O



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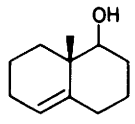

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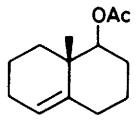

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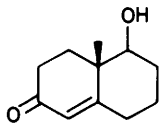

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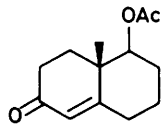

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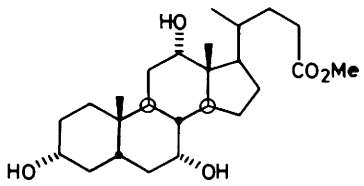

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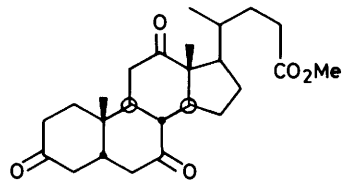

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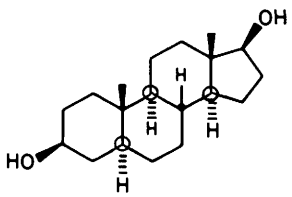

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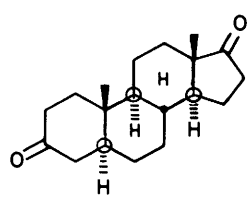

(38)

Reagents: i, $NaBH_4$; ii, $LiAlH_4$, $AlCl_3$

attempt to separate the mixture or study the effect of reaction conditions, nor did we examine the direct allylic oxidation of other hydroxy steroidal 5-ene derivatives.

Oxidation of the octalin derivative (**31**) also proceeded with some selectivity, to give the product (**33**), along with minor products of secondary alcohol oxidation (from i.r. spectra); acetylation of compound (**31**) gave the acetate (**32**). A comparison of the spectral data and t.l.c. results of crude compound (**34**) obtained from (**33**), with those of the pure material obtained by oxidation of the acetate (**32**), indicated that it contained *ca.* 25—30% of saturated ketone impurities; thus, the allylic oxidation is partially selective in this case. We were unable to improve the selectivity by straightforward variation of the reaction conditions.

Although the above experiments indicate *some* potential for the selective conversion of alkenes into enones, the oxidation system nevertheless does oxidize secondary alcohols efficiently in the absence of a double bond. Treatment of methyl cholate (**35**) resulted in the oxidation of all three alcohol groups to give the triketone (**36**), and similarly androstane-3β,17β-diol (**37**) gave androstane-3,17-dione (**38**), both reactions proceeding in high yield.

We have not attempted a detailed mechanistic study of this reaction, but the ability to oxidise allylic methylene in the presence of secondary alcohol groups, despite the fact that these can be oxidised to ketone, is a clear indication that the reaction does not proceed *via* high oxidation state chromium complexes. Further support for this deduction comes from the observations that the reaction mixture in most cases maintains a pale yellow colour throughout, in sharp contrast to the burgundy red colour obtained on mixing a catalytic amount of chromium trioxide with t-butyl hydroperoxide in benzene or acetonitrile. At the end of each reaction, we have been able to recover the chromium hexacarbonyl catalyst almost quantitatively (there are, of course, some mechanical losses). The different course for reactions catalysed by chromium and molybdenum complexes is particularly interesting and prompts us to examine the use of related zero valent metal catalysts.*

In summary, we present the chromium carbonyl-catalysed allylic oxidation described in this paper as an extremely useful method, in terms of both yield and operational simplicity. Further investigations of the reaction conditions will undoubtedly lead to technical improvements, and we expect that this will become the method of choice for the conversion of alkenes into enones in a wide range of organic syntheses.

Experimental

I.r. spectra were recorded with a Perkin-Elmer 1420 instrument, and n.m.r. spectra with Varian EM-360 or XL-200 spectrometers. Mass spectra were kindly provided by Professor H. Andrist, Cleveland State University and by Dr. R. P. Lattimer, the B. F. Goodrich Company, Brecksville, Ohio. M.p.s are uncorrected. All solvents used were freshly distilled under nitrogen as follows: tetrahydrofuran (THF) and benzene from Na–benzophenone; ether from $LiAlH_4$; acetonitrile from CaH_2. Compounds which were characterized by i.r., n.m.r., and mass spectral data only were ascertained to be ≥95% pure by sharp m.p., t.l.c. and/or h.p.l.c. (Gilson 802 instrument) and 200 MHz n.m.r. spectroscopy. Unless otherwise stated, silica gel was generally employed for chromatography. Ether refers to diethyl ether.

Methyl (1-*methylcyclopent-2-enyl*)*acetate* (**1**).—This compound was obtained using the Ireland ester enolate Claisen rearrangement procedure.[11] A solution of lithium di-isopropylamide in THF was prepared by slow addition of n-butyl-lithium (2.5M in hexane; 68.6 ml, 0.171 mol) to a stirred solution of di-isopropylamine (26.4 ml, 0.189 mol) in dry THF (100 ml) at 0 °C under argon (balloon). To this solution, cooled to −78 °C, was added dropwise 3-methylcyclopent-2-enyl acetate (20 g, 0.143 mol) in dry THF (10 ml). The reaction mixture was stirred for 5 min and t-butyldimethylsilyl chloride (25.8 g, 0.171 mol) in dry hexamethylphosphorictriamide (30 ml) and THF (20 ml) was added. The reaction mixture was allowed to warm to room temperature during 1.5 h and diluted with n-pentane (50 ml), washed with water (4 × 50 ml), brine (50 ml), dried ($MgSO_4$) and concentrated on the rotary evaporator. The residue was taken up in benzene (100 ml), dried briefly (K_2CO_3) and gently boiled under reflux overnight (15 h). The solvent was removed, THF (50 ml) was added followed by 1M-tetra-n-butylammonium fluoride (143 ml) in THF (0.143 mol) at room temperature. After 2 h, the mixture was diluted with ether (500 ml) and washed with cold dilute hydrochloric acid (2M; 100 ml). The organic layer was extracted with 2M-sodium hydroxide solution (150 ml) and the aqueous extract was washed with ether (100 ml), acidified to pH 1, and then extracted with ether (3 × 200 ml). The ether extract was washed with water (100 ml) and brine (100 ml), dried ($MgSO_4$) and evaporated. Distillation of the residue afforded pure (1-methylcyclopent-2-enyl)acetic acid, b.p. 92 °C at 3 mmHg, as a pale yellow liquid (13.5 g, 68%); $\nu_{max.}(CHCl_3)$ 3 300—2 500, 1 708, and 950 cm^{-1}; δ (60 MHz; $CDCl_3$) 5.6 (2 H, s), 2.5—1.5 (4 H, m), 2.4 (2 H, s, CH_2CO_2H), and 1.2 (3 H, s); *m/z* [Field Desorption (FD)] 140 (M^+). The carboxylic acid thus obtained (13.5 g, 0.097 mol) and potassium carbonate (20 g, 0.145 mol) were vigorously stirred in acetone (150 ml) under reflux for 0.5 h, after which time dimethyl sulphate (18.3 g, 0.145 mol) was added dropwise. The stirred mixture was heated at reflux for 7 h, and then cooled to room temperature. Aqueous ammonia (50 ml, 50% v/v) was added and the mixture was poured into water (500 ml) and extracted with ether (3 × 150 ml). The combined ether extracts were washed with water, dilute hydrochloric acid, water, and then brine, dried ($MgSO_4$) and concentrated on the rotary evaporator (bath temperature 30 °C). Distillation of the residue afforded the ester (**1**), b.p. 63—64 °C at 11 mmHg as a colourless liquid (13.5 g, 91%); $\nu_{max.}(CHCl_3)$ 1733 cm^{-1}; δ ($CDCl_3$; 60 MHz) 5.5 (2 H, s), 3.5 (3 H, s), 2.4—1.5 (4 H, m), 2.2 (2 H, s, CH_2CO_2Me), 1.0 (3 H, s); *m/z* (FD) 154 (M^+).

Epoxidation of the Methyl Ester (**1**).—(a) Via *iodolactonisation*. This procedure was used to procure an authentic sample of the epoxide (**3**). To a stirred solution of iodine (294 mg, 1.159 mmol) in acetonitrile (7 ml) at 0 °C under argon was added the ester (**1**) (59.5 mg, 0.386 mmol) in acetonitrile (2 ml). The reaction was followed by i.r. spectroscopy and was complete after 5.5 h. The reaction mixture was diluted with ether (50 ml) and washed with saturated aqueous sodium hydrogen carbonate, aqueous sodium thiosulphate, brine, dried ($MgSO_4$), and evaporated to give the crude product as a pale yellow oil consisting mainly of γ-lactone with a small amount of δ-lactone (91 mg, 88%); $\nu_{max.}(CHCl_3)$ 1780 (γ-lactone), and 1 740 cm^{-1} (δ-lactone); δ ($CDCl_3$; 60 MHz) 4.88 (1 H, s), 4.34 (1 H, m), 2.57 (2 H, s), 2.3—1.79 (4 H, m), and 1.57 (3 H, s). This mixture was converted into the epoxide (**3**) as follows. Sodium metal (15.6 mg) was dissolved in methanol (2 ml) at 0 °C under argon. A solution of the above mixture of iodolactones in methanol (2 ml) was added and the mixture was stirred at 0 °C for 5 h. The reaction mixture was neutralized with dilute hydrochloric acid, diluted with ether (25 ml), washed with water, aqueous sodium hydrogen carbonate, and brine, dried ($MgSO_4$) and evaporated to give the product (**3**) as a pale yellow liquid (31.6 mg, 55%); $\nu_{max.}(CHCl_3)$ 1 730, 850 cm^{-1}; δ ($CDCl_3$; 60 MHz) 3.70 (3 H, s,

* Preliminary results using tungsten hexacarbonyl indicate a method for the conversion of alkene into allylic alcohol.

CO_2Me), 3.40 and 3.22 (each 1 H, d, J 3 Hz, epoxide), 2.47 (2 H, s), 2.10—1.70 (2 H, m), 1.29 (2 H, m), and 1.02 (3 H, s); m/z (FD) 170 (M^+).

(b) *Using* Bu^tOOH–$Mo(CO)_6$. To a stirred mixture of molybdenum hexacarbonyl (2.5 mg) and the ester (**1**) (48 mg, 0.314 mmol) in acetonitrile (3 ml) under argon was added t-butyl hydroperoxide (38 μl, 0.38 mmol). The mixture was boiled under reflux for 17 h, cooled to room temperature, and diluted with ether. The solution was washed with aqueous sodium metabisulphite, water, and brine, dried ($MgSO_4$) and evaporated to give the product which was shown to be a 1:4 mixture of the epoxides (**2**) and (**3**) by ^1H n.m.r. spectroscopy (43 mg, 80%). The data for the epoxide (**3**) are given above. Epoxide (**2**) showed the CH_2CO_2Me singlet at δ2.25 and the CH_3 singlet at δ1.20 in the n.m.r. spectrum. These products could not be separated, but the preparation of mixtures containing different ratios (*e.g.*, treatment with *m*-chloroperoxybenzoic acid gives a 1:1.7 mixture) confirmed the assignments.

Methyl (1-*methyl*-4-*oxocyclopent*-2-*enyl*)*acetate* (**4**).—To a solution of the ester (**1**) (100 mg, 0.65 mmol) in MeCN (5 ml) was added chromium hexacarbonyl (0.5 equiv.; 71 mg, 0.32 mmol) and 90% t-butyl hydroperoxide (1.2 equiv.; 80 μl, 0.78 mmol). The mixture was gently refluxed for 18 h and cooled to room temperature, then diluted with ether (100 ml). The ethereal layer was washed with water (10 ml × 3) and brine (10 ml × 2), and dried ($MgSO_4$). The solvent was removed and the residue was chromatographed (preparative t.l.c., 50% ethyl acetate in hexane) to yield the enone as a colourless oil (70 mg, 83%), $\nu_{max.}(CHCl_3)$ 1 735 s (C=O, ester), 1 715sh cm^{-1} (C=O, enone) δ($CDCl_3$) 7.5 (1 H, d, J 6 Hz, C=CH), 6.0 (1 H, d, J 6 Hz, =C–C*H*=CH), 3.7 (3 H, s, OCH_3), 2.5 (2 H, s, CH_2COCH_3), 2.4 [2 H, dd, J_{gem} 18 Hz, C(O)CH_2], and 1.3 (1 H, s, CH_3). m/z (FD) 168 (M^+).

4-(1-*Methyl*-4-*oxocyclohex*-2-*enyl*)-4-*methoxycarbonylcyclopent*-2-*enone* (**10**).—t-Butyl hydroperoxide (85.4 μl, 0.528 mmol) was added to a stirred mixture of compound (**6**) (100 mg, 0.264 mmol) and chromium hexacarbonyl (50 mg, 0.132 mmol) in MeCN (3 ml) under argon. The resulting mixture was then refluxed for 21 h and cooled to room temperature. The reaction mixture was diluted with ether and washed with aqueous sodium metabisulphite, H_2O and brine, and dried ($MgSO_4$). After removal of the solvent under reduced pressure, flash chromatography of the residue (40% ethyl acetate in hexane) gave the starting material (28.3 mg, 28.3%), and the pure bis(enone) ester (**10**) as a pale yellow crystalline solid (45.3 mg, 60% net yield), m.p. 118—119.5 °C; $\nu_{max.}(CHCl_3)$ 1 725, 1 680, and 1 595 cm^{-1}; δ ($CDCl_3$; 60 MHz) 7.73 (1 H, d, J 6 Hz, 3-H), 6.71 (1 H, dd, J 10, 1.5 Hz), 6.27 (1 H, d, J 6 Hz, 2-H), 5.94 (1 H, d, J 10 Hz), 3.79 (3 H, s, CO_2Me), 2.85—2.25 (4 H, m), 2.0—1.65 (2 H, m), and 1.32 (3 H, s); m/z (%) 248 (100), 139 (36), and 108 (75).

4-(1-*Methyl*-4-*oxocyclohex*-2-*enyl*)-4-*methoxymethylcyclopent*-2-*enone* (**11**).—Treatment of compound (**7**) (98.4 mg) as in the preceding experiment, followed by flash chromatography (50% ethyl acetate in hexane) gave recovered starting material (51.9 mg) and the bis(enone) (**11**) (19.1 mg, 39% based on starting material consumed) as a colourless oil; $\nu_{max.}(CHCl_3)$ 1 680, 1 590, 1 460, 1 450, 1 395, 1 110, and 960 cm^{-1}; δ ($CDCl_3$; 200 MHz) 7.54 (1 H, d, J 5.9 Hz, 3-H), 6.94 (1 H, dd, J 10.3, 2.0 Hz), 6.26 (1 H, d, J 5.9 Hz, 2-H), 5.95 (1 H, d, J 10.3 Hz), 3.56 and 3.38 (each 1 H, d, J_{AB} 9.36 Hz, CH_2OMe), 3.31 (3 H, s, OMe), 2.66—2.12 (4 H, m), 2.0 (1 H, m), 1.68 (1 H, m), and 1.23 (3 H, s); m/z (%) [Chemical Ionization (C.I.)] 234 (6), 235 (100, M + 1), 263 (13, M + 29), 275 (7, M + 41), 203 (24), and 109 (23).

4-(4-*Acetoxy*-1-*methylcyclohex*-2-*enyl*)-4-*methoxymethylcyclopent*-2-*enone* (**12**).—Treatment of compound (**8**) (106 mg) as above, followed by flash chromatography (50% ethyl acetate in hexane), gave recovered starting material (20 mg) and the enone (**12**) (19.5 mg, 24% based on starting material consumed) obtained as a colourless oil; $\nu_{max.}(CCl_4)$ 1 725, 1 685, 1 600, 1 465, 1 380, 1 240, 1 120, and 1 040 cm^{-1}; δ ($CDCl_3$; 200 MHz) 7.48 (1 H, d, J 5.8 Hz, 3-H), 6.20 (1 H, d, J 5.8 Hz, 2-H), 5.70 (1 H, d, J 10 Hz), 5.62 (1 H, d, J 10 Hz), 5.22 (1 H, m, C*H*OAc), 3.50 and 3.41 (each 1 H, d, J_{AB} 9 Hz, CH_2OMe), 3.28 (3 H, s, OMe), 2.36 and 2.25 (each 1 H, d, J_{gem} 18 Hz, 5-H_2), 2.06 (3 H, s), 1.76—1.54 (2 H, m), 1.41 (1 H, m), 1.25 (1 H, m), and 1.06 (3 H, s); m/z (%) (C.I.) 2.78 (1.5, M^+), 279 (11, M + 1), 307 (3, M + 29), 319 (1, M + 41), 247 (13), and 220 (100).

4-(4-*Hydroxy*-1,4-*dimethylcyclohex*-2-*enyl*)-4-*methoxycarbonylcyclopent*-2-*enone* (**13**).—Treatment of compound (**9**) (55.2 mg) as above, followed by preparative t.l.c., gave recovered starting material (7.1 mg), the enone (**13**) (9.0 mg) and several other products which were not identified. Compound (**13**) gave $\nu_{max.}(CHCl_3)$ 1 720, 1 685, and 1 595 cm^{-1}; δ ($CDCl_3$; 200 MHz) 7.77 (1 H, d, J 5.8 Hz, enone), 6.21 (1 H, d, J 5.8 Hz, enone), 6.21 (1 H, d, J 5.8 Hz, enone), 5.60 and 5.50 (each 1 H, d, J 9.6 Hz), 3.73 (3 H, s), 2.85 and 2.66 (each 1 H, d, J_{gem} 19.3 Hz, 5-H), 2.12—1.91 (2 H, m), 1.48 (2 H, m), 1.26 (3 H, s), and 1.13 (3 H, s).

3-*Acetoxycholest*-5-*en*-7-*one* (**18**).—Cholesteryl acetate (1 g, 2.33 mmol), $Cr(CO)_6$ (0.5 equiv.; 260 mg, 1.17 mmol) and 90% Bu^tOOH (3 equiv.; 0.7 ml, 7 mmol) were refluxed in MeCN (10 ml) for 15 h. The reaction mixture was cooled to room temperature and diluted with ether (100 ml). The organic layer was washed with H_2O (10 ml × 3) and brine (10 ml × 2) and dried ($MgSO_4$). The solvent was removed and the residue was subjected to flash chromatography (20% ethyl acetate in hexane) to afford the enone (**18**) (820 mg, 80%) as a white solid, m.p. 153—154 °C (lit.,[12] m.p. 155—156 °C); $\nu_{max.}(CHCl_3)$ 1 730, 1 670 cm^{-1}; δ ($CDCl_3$; 60 MHz) δ 5.6 (1 H, br s, olefinic proton), 4.7 [1 H, m, C*H*(OAc)], and 2.6—0.7 (44 H, m).

3,17-*Bis*(*acetyloxy*)-3β,17β-*androst*-5-*ene* (**15**).—3,17-Dihydroxy-3β,17β-androst-5-ene (200 mg, 0.69 mmol) was dissolved in pyridine (0.5 ml), and acetic anhydride (0.6 ml) was added. The mixture was placed in the refrigerator overnight. Water was added, and the product was extracted with ether, washed with dilute hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), and evaporated to give the diacetate (262 mg) as white crystals, m.p. 158—159 °C (lit.,[13] m.p. 158—159 °C). Previous reports give the preparation of the compound in lower yield;[3a] $\nu_{max.}(CHCl_3)$ 1 726 cm^{-1}; δ($CDCl_3$) 0.81 (s, 3 H), 1.03 (s, 3 H), 2.04 (s, 3 H), 2.05 (s, 3 H), 4.61 (m, 1 H), and 5.40 (m, 1 H).

3,17-*Bis*(*acetyloxy*)-3β,17β-*androst*-5-*en*-7-*one* (**19**).—To a solution of 3,17-Bis(acetyloxy)-3β,17β-androst-5-ene (130 mg, 0.35 mmol), in acetonitrile (5 ml) were added t-butyl hydroperoxide (120 μl, 1.20 mmol) and chromium hexacarbonyl (17.6 mg, 0.080 mmol). The mixture was refluxed for 25 h, and then cooled to room temperature. Water (5 ml) was added, the product extracted with ether, dried ($MgSO_4$), and evaporated to give a white solid (144 mg). Residual chromium hexacarbonyl was removed by silica gel chromatography, to give pure compound (**19**) (135 mg, 100%), m.p. 224—225 °C (from MeOH) (lit.[3c] m.p. 224—226 °C); $\nu_{max.}(CHCl_3)$ 1 728, 1 668 cm^{-1}; δ($CDCl_3$) 0.80 (s, 3 H), 1.20 (s, 3 H), 2.03 (s, 6 H), 4.62 (m, 1 H), and 5.71 (s, 1 H); m/z 388 (M^+).

Oxidation of Limonene (**16**).—To a stirred solution of limonene (**16**) (280 mg, 2.18 mmol) in MeCN at room temperature under argon was added the chromium hexacarbonyl (240 mg, 1.09 mmol). Then t-butyl hydroperoxide

(0.44 ml, 4.37 mmol) was added dropwise. The resulting mixture was refluxed for 18 h. The reaction mixture was cooled in an ice-bath, then filtered through a sintered funnel and the precipitate washed with cold benzene. The filtrate was diluted with ether and washed with aqueous sodium metabisulphite, H_2O and brine and dried ($MgSO_4$). The solvent was then removed under reduced pressure. After flash chromatography (20% ethyl acetate in hexane) the starting material (133 mg, 47.7%) was recovered and two enone products, carvone (63 mg, 39% net yield) and isopiperitenone (46.3 mg, 28.5% net yield) were isolated. Carvone was identical with an authentic sample. The n.m.r. spectral data given in the literature [3a] for isopiperitenone is incorrect, and corresponds to that for carvone. Our data is as follows: δ ($CDCl_3$; 200 MHz) 5.90 (1 H, close m), 4.95 (1 H, close m), 4.76 (1 H, close m), 2.95 (1 H, dd, *J* 10, 6 Hz), 2.35 (2 H, m), 2.0 (2 H, m), 1.95 (3 H, s), and 1.75 (3 H, s).

Oxidation of α-Pinene.—To a stirred mixture of α-pinene (277 mg, 2.03 mmol) and chromium hexacarbonyl (224 mg, 1.02 mmol) in MeCN (5 ml) and benzene (0.5 ml) (because α-pinene was not completely soluble in MeCN) under argon was added dropwise t-butyl hydroperoxide (0.61 ml, 6.1 mmol). The resulting mixture was refluxed for 18 h, cooled in an ice-bath, filtered through a sintered funnel and the precipitate (chromium hexacarbonyl) washed with cold benzene. The filtrate was diluted with ether and washed with aqueous sodium metabisulphite, H_2O, and brine, and dried ($MgSO_4$). The solvent was removed under reduced pressure. Flash chromatography (40% ethyl acetate in hexane) afforded verbenone (149 mg, 65% net yield) and the starting material (68 mg, 24%). The i.r. and n.m.r. data of the product enone were identical with the literature.[14]

3-*Acetyloxy*-3β-*pregn*-5-*ene*-7,20-*dione* (**27**).—To a solution of 3-acetyloxy-3β-pregn-5-en-20-one (100 mg, 0.28 mmol) in acetonitrile (5 ml) were added t-butyl hydroperoxide (42 μl, 0.42 mmol) and chromium hexacarbonyl (12.3 mg, 0.056 mmol). The mixture was refluxed for 19 h, and then cooled to room temperature. Water (5 ml) was added, the product was extracted with ether, dried ($MgSO_4$), and evaporated to give a white solid (125 mg). The residual chromium hexacarbonyl was removed by silica gel chromatography, to give the dione (**27**) (102 mg, 98%), m.p. 151—153 °C (lit.,[9a] m.p. 151—153 °C); $\nu_{max.}$($CHCl_3$) 1 724, 1 697, and 1 667 cm^{-1}; δ($CDCl_3$) 5.71 (s, 1 H), 4.70 (m, 1 H), 2.12 (s, 3 H), 2.04 (s, 3 H), and 1.21 (s, 3 H); *m/z* 373 (M^+).

7-*Oxodiosgenin Acetate* (**28**).—Diosgenin (200 mg, 0.48 mmol) was dissolved in pyridine (0.5 ml) and chloroform (0.5 ml), and acetic anhydride (0.6 ml) was added. The mixture was put in the refrigerator overnight. Water was added, and the product extracted with ether, washed with dilute hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and water, dried ($MgSO_4$), and evaporated to give diosgenin acetate (222 mg), m.p. 193—194 °C (lit.,[15] m.p. 187—190 °C); $\nu_{max.}$($CHCl_3$) 1 734 cm^{-1}; δ($CDCl_3$) 0.79 (d, 3 H, *J* 6.6 Hz), 1.04 (s, 3 H), 2.03 (s, 3 H), 2.32 (d, 2 H, *J* 7.2 Hz), 3.42 (m, 2 H), 4.38 (q, 1 H), 4.56 (m, 1 H), and 5.38 (d, 1 H, *J* 6 Hz); *m/z* (%) 456 (M^+).

To a solution of diosgenin acetate (117 mg, 0.26 mmol) in acetonitrile (5 ml) were added t-butyl hydroperoxide (78 μl, 0.78 mmol) and chromium hexacarbonyl (17.3 mg, 0.089 mmol). The mixture was refluxed for 27 h, and then cooled to room temperature. Water (5 ml) was added, the product extracted with ether, dried ($MgSO_4$), and evaporated to give a white solid (130 mg). The residual chromium hexacarbonyl was removed by silica gel chromatography to give pure compound (**28**) (120 mg, 100%), m.p. 196—197 °C (lit.,[16] m.p. 197—198 °C); $\nu_{max.}$ ($CHCl_3$) 1 723, 1 665 cm^{-1}; δ($CDCl_3$) 0.80 (d, 3 H, *J* 5.8 Hz), 0.79 (s, 3 H), 0.99 (d, 3 H, *J* 6.8 Hz), 1.23 (s, 3 H), 2.06 (s, 3 H), 3.44 (m, 1 H), 4.48 (m, 1 H), 4.68 (m, 1 H), and 5.71 (d, 1 H, *J* 1.4 Hz).

3β-*Acetyloxystigmast*-5-*en*-7-*one* (**29**).—Stigmasterol acetate (454 mg, 1 mmol) was treated with $Cr(CO)_6$ (0.25 mmol) and t-butyl hydroperoxide (1.5 mmol) in dry acetonitrile. After being refluxed for 24 h, the reaction mixture was worked up in the usual manner. The residue was chromatographed to give compound (**29**) as a white solid (326 mg, 70%), which was crystallized from methanol as flakes, m.p. 183—185 °C (lit.,[17] m.p. 183—184 °C); $\nu_{max.}$($CHCl_3$) 1 740, 1 670 cm^{-1}, δ ($CDCl_3$; 200 MHz) 5.7 (1 H, d, *J* 1.70 Hz, CH=CO), 4.82—5.18 (2 H, m, 2x vinyl H), 4.71 (1 H, m, C*H*OAc), and 2.05 (3 H, s, $OCOCH_3$).

3β-*Hydroxystigmast*-5-*en*-7-*one* (**30**).—To a solution of stigmasterol (413 mg, 1 mmol) in dry acetonitrile (10 ml), $Cr(CO)_6$ (55 mg, 0.25 mmol) and t-butyl hydroperoxide (135 mg 1.5 mmol) were added. The mixture was refluxed under nitrogen for 24 h, cooled, diluted with water, and extracted with ether. The ether layer was washed with water and dried ($MgSO_4$). The residue after removal of the ether was chromatographed to give compound (**30**) as a white solid (290 mg, 61%). The compound so obtained was crystallized from methanol–light petroleum as needles, m.p. 162 °C (lit.,[17] m.p. 160—162 °C); $\nu_{max.}$($CHCl_3$) 3 360, 1 765 cm^{-1}, δ ($CDCl_3$; 200 MHz) 5.69 (1 H, s, CH=CO), 5.17 and 5.02 (each 1 H, dd, *J* 16, 8 Hz, 2x vinyl H), and 3.62 (1 H, m, C*H*OH).

Conversion of the Alcohol (**30**) *into the Acetate* (**29**).—The above product (**30**) (210 mg) was dissolved in pyridine (1 ml) and treated at 23 °C for 24 h with acetic anhydride (0.5 ml). Work-up in the usual way afforded the acetate which was purified by flash chromatography (0.2 g). Crystallization from methanol gave compound (**29**) as colourless flakes, m.p. 183—184 °C, identical in all respects with the compound obtained by oxidation of stigmasterol acetate.

Oxidation of Compound (**31**).—Compound (**31**) was prepared from the Wieland–Meischer ketone in two steps: (1) $NaBH_4$; (2) $LiAlH_4$, $AlCl_3$.[18] Treatment of this material (166 mg, 1 mmol) with Bu^tOOH (1.2 mmol) and $Cr(CO)_6$ (0.25 mmol) in dry acetonitrile under reflux for 30 h, followed by work-up and chromatography as above gave 4,4a,5,6,7,8-Hexahydro-5-hydroxy-4-methylnaphthalen-2(3*H*)-one (**33**) (100 mg, 60%) as a colourless oil, along with products of oxidation of the secondary alcohol; $\nu_{max.}$(CCl_4) 3 345, 1 670 cm^{-1}; δ ($CDCl_3$); 200 MHz) 5.77 (1 H, d, *J* 1.6 Hz), 3.43 (1 H, dd, *J* 11.18, 4.34 Hz), and 1.21 (3 H, s); *m/z* (FD) 180 (M^+).

Oxidation of Compound (**32**).—Acetylation of compound (**31**), using the standard procedure (Ac_2O, pyridine, 20 °C, overnight) afforded the corresponding acetate (**32**) which was oxidized as follows. The acetate (208 mg, 1 mmol) was treated with Bu^tOOH (1.5 mmol) and $Cr(CO)_6$ (0.25 mmol) in dry acetonitrile (5 ml) at reflux for 30 h. Work-up and chromatography as above gave the pure acetoxy enone (**34**) as a colourless oil (0.15 g, 70%); $\nu_{max.}$($CHCl_3$) 1 735, 1 670, and 1 600 cm^{-1}; δ ($CDCl_3$; 200 MHz) 5.75 (1 H, d, *J* 1.4 Hz), 4.58 (1 H, dd, *J* 11.2, 4.1 Hz, C*H*OAc), 2.38—2.2 (4 H, m), 2.01 (3 H, s), 1.90—1.67 (6 H, m), and 1.21 (3 H, s); *m/z* (FD) 222 (M^+) (Found C, 70.7; H, 8.3. Calc. for $C_{13}H_{18}O_3$: C, 70.3; H, 8.1%). The product (**33**) obtained above was treated with an excess of acetic anhydride in pyridine (16 h; 20 °C), worked up in the usual way and chromatographed to give the product (**34**), having spectroscopic data identical with the compound obtained by oxidation of compound (**32**).

Oxidation of 5α-*Androstane*-3β,17β-*diol giving* 5α-*Androstane*-3,17-*dione* (**38**).—The diol (**37**) (292 mg, 1 mmol) was dissolved in acetonitrile (10 ml) and treated with $Cr(CO)_6$ (0.25 mmol)

and t-butyl hydroperoxide (3 mmol) at reflux for 19 h. Work-up as previously, followed by chromatography afforded 5-androstane-3,17-dione (250 mg, 80%) crystallized from hexane as plates, m.p. 130 °C (lit.,[19] m.p. 132—133 °C); $\nu_{max.}$($CHCl_3$) 1 750, 1 720 cm^{-1}; δ ($CDCl_3$, 200 MHz) 0.864 and 1.02 (each 3 H, s, 2 × CH_3).

Oxidation of Methyl 3,6,12-*Trihydroxycholanate giving Methyl* 3,6,12-*Trioxocholanate* (**36**).—The oxidation was carried out as in the preceding example using Bu^{t}OOH (4 equiv.). After purification by chromatography the trioxo compound (**36**) was obtained (81%), as white plates from hexane, m.p. 181—183 °C (lit.,[20] m.p. 181—182 °C).

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