Functionalisation of Saturated Hydrocarbons. Part 13.[1] Further Studies on the Gif Oxidation of Cholestane Derivatives

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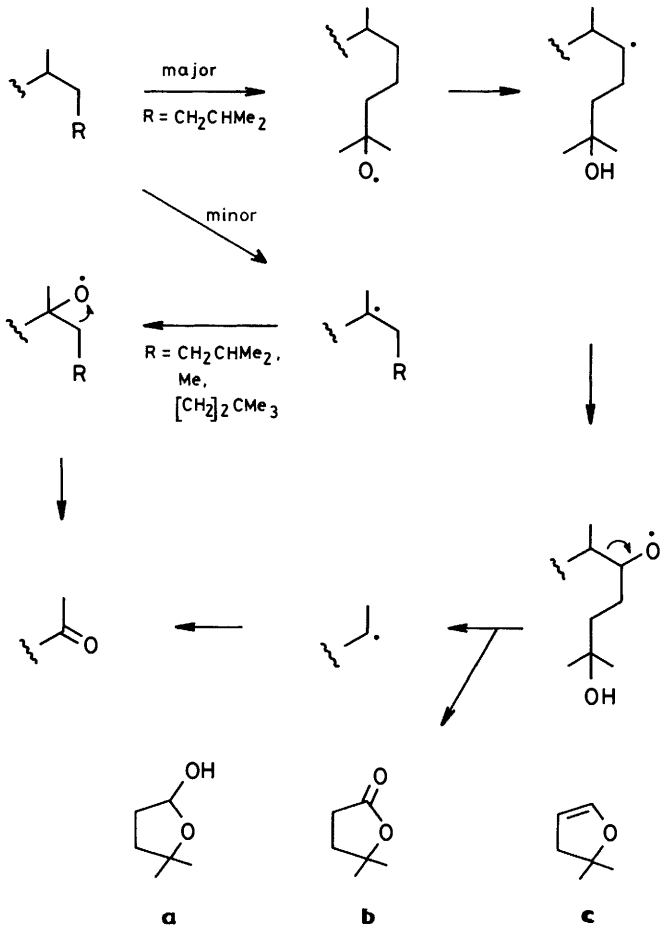
The oxidation of cholest-4-en-3-one by the Gif^{IV} system to give progesterone has been studied over the temperature range −40 to +80 °C. The optimum temperature is ~ +20 °C. Below 0 °C the yield of progesterone diminishes and the formation of a new compound, 25-hydroxycholest-4-en-3-one, is observed. The latter has been synthesised from lithocholic acid.

An unexpected major product of the oxidation was A-nor-5β-cholestan-3-one, identified by comparison with an authentic sample.

In previous papers[2–5] we reported on the oxidation of a variety of cholestane derivatives by the Gif system. As a rule, the major oxygenated products that we isolated were the corresponding 20-ketones which result from the industrially important side-chain cleavage. The other oxygenated products were ketones simply derived from the formal replacement of a methylene group by a carbonyl, as usually observed in the Gif system.[6] With the aid of suitably chosen substrates, we demonstrated that the partition between side-chain cleavage and oxidation of the steroidal nucleus depends on the substitution pattern of the A (or A,B) ring. Electron-withdrawing substituents seem to favour the former reaction. For example, 3β,5a,6β-triacetoxycholestane[4] afforded the 20-ketone as the major product (4.7%), followed by the 15- (2.8%), the 16- (2.1%), and the 24-ketone (2.1%). Careful examination of the volatile fraction by g.c.–m.s. showed that the rest of the side-chain is recovered as a mixture of furan derivatives **a**—**c**. This observation led us to propose a plausible mechanism to account for the side-chain cleavage (Scheme 1). In brief, the key intermediate was postulated to be a 25-alkoxyl radical (probably arising from a C-25 carbon-centred radical). This alkoxyl radical would abstract a hydrogen atom at the 22 position through a six-membered transition state, thus generating a new carbon radical. The latter is trapped by oxygen to give in turn an alkoxyl radical. Cleavage of the 20–22 C–C bond affords the tetrahydrofuran (THF) derivative **a** and the C-20 carbon radical which finally evolves to the 20-ketone. To test this hypothesis, we prepared and oxidised 25-methylcholesta-1,4-dien-3-one together with a shortened side-chain derivative, 24-norchola-1,4-dien-3-one. In each case, the amount of the 20-ketone was ~25% of the quantity isolated in the oxidation of cholesta-1,4-dien-3-one. We then concluded that a minor pathway in which a C-20 tertiary carbon radical is initially formed still operates and accounts for the formation of the pregna-1,4-dien-3-one[2] (Scheme 1). In this paper, we describe new results which add credit to our previous mechanistic proposal, and we report an unprecedented A-ring contraction from a conjugated enone.



Scheme 1.

Results and Discussion

The Gif system has been studied extensively in our laboratory.[6,7] In its most elaborate form (Gif^{IV} system),[6] this consists of an iron cluster $Fe_3O(OAc)_6Pyr_{3.5}$ as catalyst, a pyridine–acetic acid mixture as solvent, zinc powder as reductant, and air as the oxidant. Most of the parameters have been examined in detail, except the effect of varying the temperature (usually the oxidations were carried out at 20—25 °C). However, it was already shown that at 0 °C oxidation of adamantane still occurred at an appreciable rate.[6] As the postulated mechanism (Scheme 1) involves unimolecular and bimolecular steps, one could expect that a decrease in temperature would preferentially slow down the unimolecular processes, and thus modify the nature and/or the distribution of the oxidised products.

Table. Oxidation of cholest-4-en-3-one (**1**) at different temperatures

Cholestenone (**1**) + Zn + AcOH + $Fe_3O(OAc)_6Pyr_{3.5}$ $\xrightarrow[5.5h,\ T\,°C]{Pyr/H_2O/O_2}$

3 30 60 0.02 mmol of reagents

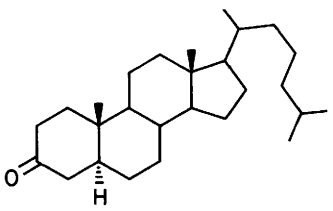
T/°C	Zn[a] (%)	(**1**)[b] (%)	20-one (**3**)[c] (%)	25-ol (**2**)[d] (%)	(**3**)/(**2**)
80	n.d.	81	2.7	0	*f*
60	n.d.	72	4.3	0	*f*
40	n.d.	55	4.5	0	*f*
20	n.d.	56	5.0	0	*f*
20[e]	n.d.	53	4.3	0	*f*
0[e]	0	54	4.3	0.7	6.7
−15[e]	2	80	3.3	3.75	0.72
−25[e]	16	81	1.0	5.5	0.18
−30[e]	81	81	0	6.8	0
−40[e]	95	95	n.d.	n.d.	n.d.

[a] Zn recovered after 5.5 h; n.d. = not determined. [b] Unchanged cholestenone (**1**). [c] Yield of 20-ketone (**3**) calculated from consumed cholestenone (**1**). [d] Yield of 25-alcohol (**2**) calculated from consumed cholestenone (**1**). [e] Experiment in the absence of water. [f] Infinity [no (**2**) formed].

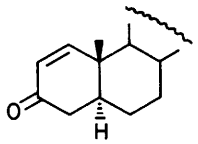
We selected cholest-4-en-3-one (**1**) to study the effect of the temperature on the side-chain cleavage by the Gif system. This substrate had already been examined and was shown to produce relatively high quantities of progesterone.[3] Oxidation of compound (**1**) was performed at temperatures ranging from −40 to +80 °C (Table). The reaction mixtures obtained after oxidation were extracted and carefully analysed by column chromatography followed by h.p.l.c. (see Experimental section). Three fractions were recovered after column chromatography: (i) the less polar fraction (A) contains an hitherto unidentified product (4.5% based on substrate consumed), the structure of which will be discussed below; (ii) the medium fraction (B) is unchanged starting material; (iii) the polar fraction (C) consists of the oxidation products, the 20-ketone being the major compound, as shown by quantitative h.p.l.c. determination and comparison with an authentic sample of progesterone (**3**). Cursory examination of the Table shows that above 40 °C the total oxidation and the amount of 20-ketone tend to decrease. When the temperature is lowered the same figure is observed. At −40 °C the reaction becomes very slow. However, the decrease in the amount of 20-ketone is counterbalanced by the appearance of a new compound. The latter was isolated by h.p.l.c. from an oxidation mixture formed at −25 °C. Spectral data (i.r., n.m.r., m.s.) are closely related to those of the starting material (**1**) and strongly suggest that the parent 25-H is replaced by a hydroxy group. In order to confirm the structure (**2**) for this product, we undertook to correlate this compound with an authentic specimen of 25-hydroxycholest-4-en-3-one.

The target molecule was synthesised from lithocholic acid (**4**) which possesses both a hydroxy group at C-3, presumably suitable for introduction of an enone, and a carbon group at C-24 permitting the elaboration of the desired 25-hydroxycholestane side-chain. For the construction of the side-chain, we, of course, followed a route very similar to that recently published by our group,[8] in connection with a short and efficient synthesis of the 25-hydroxyvitamin D_3 side-chain. Lithocholic acid was converted into the corresponding acetate (**5**) by conventional acetylation [acetic anhydride, pyridine, *N*,*N*-dimethylaminopyridine (DMAP)]. The carboxy group was transformed to the acid chloride (**6**) [oxalyl chloride, trace of dimethylformamide (DMF)], which was treated with *N*-hydroxypyridine-2-thione sodium salt to afford the mixed anhydride (**7**). The latter was photolysed *in situ*, in the presence of 2-nitropropene and camphorsulphonic acid, to give the nitro derivative (**8**) by a radical chain reaction.[9] Conversion into the ketone (**9**) was achieved by treatment with an aqueous solution of $TiCl_3$, followed by acetylation as partial deacetylation occurred under the acidic reaction conditions. The overall yield of ketone (**9**) from lithocholic acid was 59%. The acetoxy ketone (**9**) was then transformed into the diol (**10**) by reaction with methylmagnesium iodide (yield 73%). Oxidation with pyridinium dichromate (PDC) afforded the corresponding 3-keto steroid (**11**). The question was then: how to dehydrogenate selectively the compound (**11**) to the desired enone (**2**)?

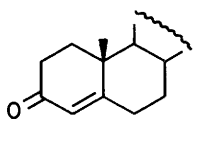
Many methods have been elaborated to dehydrogenate ketones to enones.[10,11] One of the most useful consists in elimination of a transient selenoxide produced *in situ* by reaction of benzeneseleninic anhydride (BSA) with the ketone (or the corresponding alcohol).[11] We selected the ketone (**12**), easily obtained from lithocholic acid (**4**), as a suitable model. Upon treatment with BSA (0.5 mol equiv.; refluxing THF; 48 h), the ketone (**12**) afforded a modest yield of the desired enone (**13**) (36%), accompanied by the isomeric 1-enone (**14**) (20%), the doubly dehydrogenated compound (**15**) (13%), and the starting material (**12**) (13%). Addition of camphorsulphonic acid (1 mol equiv.) permitted us to lower the temperature and to improve the yield in compound (**13**) (20 °C, 4 h: 52%; 5 °C, 24 h: 54%). We sought to improve the reaction by using a system catalytic towards selenium, based on the presence of a co-oxidant. Preliminary experiments involving catalytic amounts of diphenyl diselenide and stoicheiometric quantities of a co-oxidant (oxone, $NaClO_2$, pyridine *N*-oxide, *m*-chloroperbenzoic acid, hydrogen peroxide, dichlorodicyanobenzoquinone, tetracyanobenzoquinone) failed to give appreciable amounts of the enone (**13**). However, t-butyl hydroperoxide and especially *m*-iodylbenzoic acid afforded satisfactory results. When the oxidation of compound (**12**) was attempted in THF in the presence of 2 mol equiv. of *m*-iodylbenzoic acid and 0.1 mol equiv. of $(PhSe)_2$ at 20 °C for 24 h (or under reflux for 35 min), the enone (**13**) was the major product (62%), accompanied by



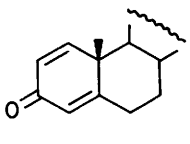
(**16**)



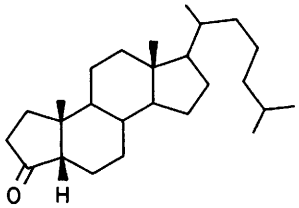
(**17**)



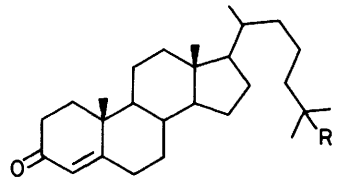
(**1**)



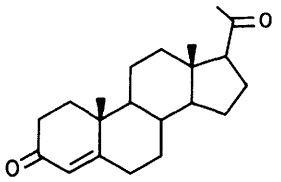
(**18**)



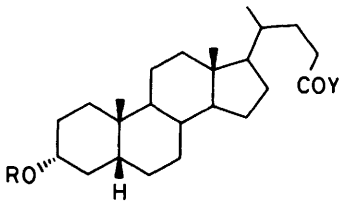
(**19**)



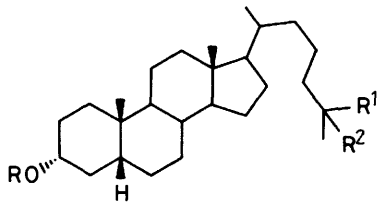
(1) R = H
(2) R = OH



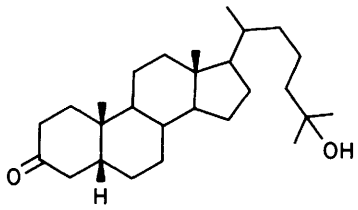
(3)



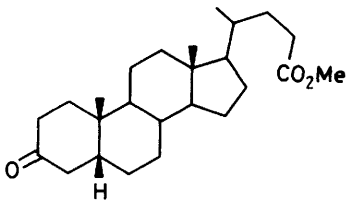
(4) R = H, Y = OH
(5) R = Ac, Y = OH
(6) R = Ac, Y = Cl
(7) R = Ac, Y = ON



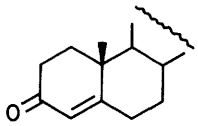
(8) R = Ac, R^1 = NO_2, R^2 = SPyr
(9) R = Ac, R^1R^2 = O
(10) R = H, R^1 = OH, R^2 = Me



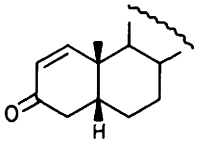
(11)



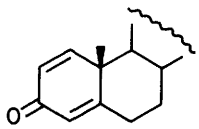
(12)



(13)

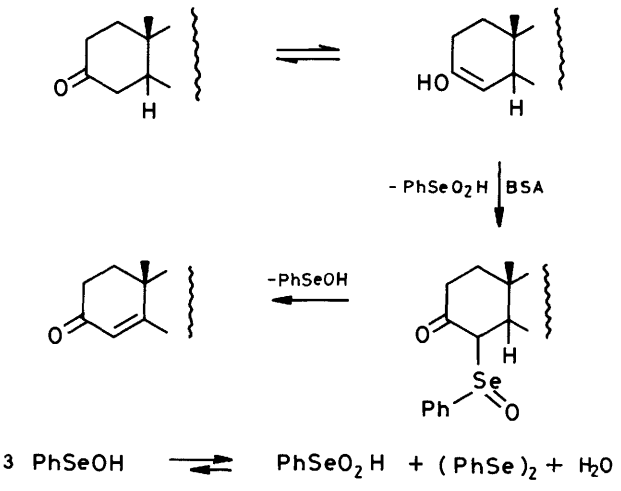


(14)



(15)

minor amounts of compounds (**14**) (10%) and (**15**) (< 10%). Under identical conditions, cholestan-3-one (**16**) gave a mixture of cholest-1-en-3-one (**17**) (70%), cholest-4-en-3-one (**1**) (8.5%), and cholesta-1,4-dien-3-one (**18**) (< 2%). Thus, the regioselectivity of the dehydrogenation strictly follows the well established dependence of the enolisation site on the nature of the A/B ring junction.[12] These results fully corroborate the mechanism postulated previously,[11] in which the enol was thought to be the reactive species (Scheme 2). The positive role

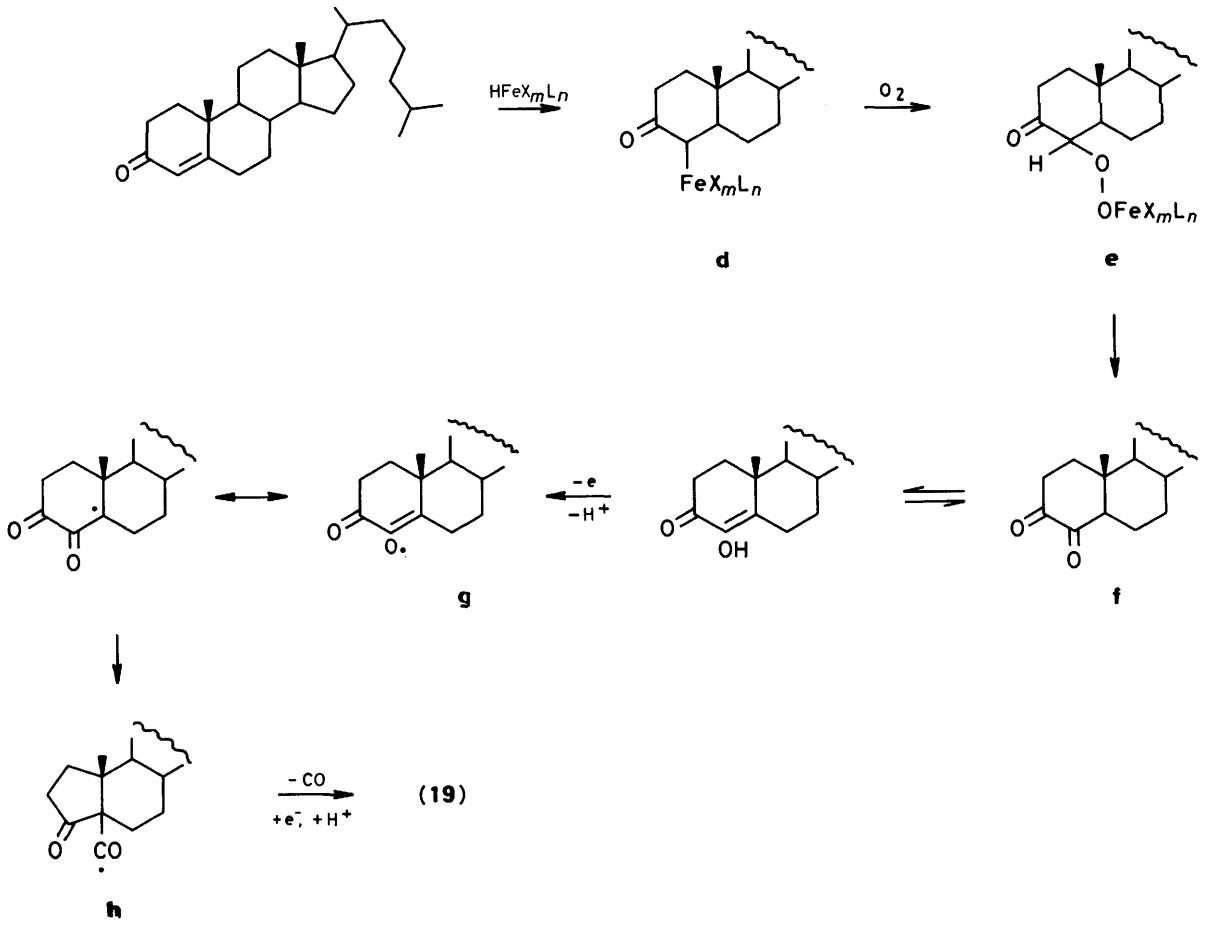


Scheme 2.

of the added camphorsulphonic acid could be: (i) to enhance the rate of the enolisation and (ii) to give rise to a more reactive mixed anhydride $PhSe(O)OSO_3R$ (BSA, insoluble in THF, smoothly dissolved on addition of camphorsulphonic acid).

Oxidation of compound (**11**) by the above system (catalytic amount of diphenyl diselenide, *m*-iodylbenzoic acid, THF) afforded 25-hydroxycholest-4-en-3-one (**2**) in 69% yield. Physical (m.p., $[\alpha]_D$) and spectral (n.m.r., m.s., i.r.) data of the latter are identical with those of the product isolated from the Gif oxidation at −25 °C of cholest-4-en-3-one (**1**) (see above). Interestingly enough, 25-hydroxycholest-4-en-3-one (**2**) failed to give an appreciable amount of progesterone (**3**) on oxidation by the Gif system according to the 'standard' procedure. This probably reflects the inability of the 25-hydroxy group to generate the corresponding alkoxyl radical under these conditions.

The structure of the non-polar compound isolated in the fraction A (*vide supra*) was deduced from spectral data: the ^1H n.m.r. (400 MHz) spectrum displayed signals for five methyl groups, four of which have the same chemical shifts as in the cholestenone (**1**); the i.r. spectrum showed an absorption at 1 745 cm^{-1}; and the mass spectrum indicated a molecular weight of 372 which could correspond to a $C_{26}H_{44}O$ formula. On this basis, A-norcholestan-2-one and A-norcholestan-3-one are plausible structures, the configuration at C-5 being uncertain. The positive Cotton effect and the observed m.p. (76—77 °C) agree only with the structure (**19**). This was definitely confirmed by direct comparison (t.l.c.; 400 MHz ^1H n.m.r.; m.s.) with an authentic sample of A-nor-5β-cholestan-3-one (A-norcoprostanone) kindly supplied by Prof. G. Ourisson.



Scheme 3.

In a preceding part of this series,[13] we have already described the intriguing behaviour of olefins towards the Gif system. As to the formation of compound (**19**), we tentatively propose the mechanism outlined in Scheme 3. The initial step would be the addition of an Fe–H species across the double bond which affords the intermediate alkyliron derivative **d**. Such an addition was postulated to occur in the selective reduction of conjugated enones with $Fe(CO)_5$–NaOH *under an inert atmosphere.*[14] Under air, the alkyliron intermediate **d** would insert a molecule of oxygen to give **e** which evolves into the diosphenol **f**. One-electron oxidation of the latter would lead to the radical **g**, prone to rearrange into an A-ring-contracted intermediate **h**. Finally, decarbonylation and reduction of **h** affords the A-norcholestanone (**19**). Of course, further experiments would be needed to give precise information on the mechanism and to extend the scope of the reaction.

In this paper, we have furnished new evidence which strongly supports the mechanism postulated initially for the cholesterol side-chain degradation by the Gif system. Recently, Groves *et al.* published very interesting results concerning the hydroxylation of cholesterol at C-25 [and selective epoxidation of 24,25-didehydrocholesterol] by means of tailor-made porphyrins included in a synthetic biomembrane.[15] Their system also probably involves a C-25 radical intermediate (if we assume that the P_{450} mechanism is operating). However, the neighbourhood and the conformational flexibility are quite different in such an organised system: the reaction stops at the 25-hydroxy level, all the more because this product is tightly bound to the metal centre.

Experimental

M.p.s were determined with a Reichert Thermovar hot-stage apparatus and are uncorrected. ^1H N.m.r. spectra were obtained for solutions in deuteriochloroform and a 400 MHz Bruker WM 400 instrument was generally used. Optical rotations were measured with a Perkin-Elmer 141 polarimeter for chloroform solutions. I.r. spectra were recorded with a Perkin-Elmer 297 i.r. spectrophotometer. Mass spectra were performed with a Riber R 1010 machine. H.p.l.c. was performed with a Waters Associates Liquid Chromatograph equipped with a Lambda-max 480 LC spectrophotometer u.v. detector and a Jobin Yvon Iota Differential Refractometer. Preparative normal-phase Ultrasphere-SiO_2 and reverse-phase Ultrasphere ODS, 5μM, 10 mm × 25 cm columns and SDS Purex grade solvents were used in h.p.l.c. work. T.l.c. was carried out on T.L.C. Ready-foils F1500/LS 254 and column chromatography was with Merck Silica Gel 60. Circular dichroism spectra were recorded on a Jobin Yvon Autodichrograph Mark V.

Oxidation of Steroids.—The general procedure is illustrated by the oxidation of cholest-4-en-3-one (**1**). Cholest-4-ene-3-one (**1**) (1.154 g, 3 mmol), zinc powder (1.96 g, 30 mmol), iron cluster[7] (15 mg, 2×10^{-2} mmol), pyridine (45 ml), water (3 ml, when specified), and acetic acid (3.5 ml, 60 mmol) in a conical flask (150 ml) were stirred under the static pressure of an oxygen-filled balloon at the indicated temperature for 5.5 h. The following mixtures were used as cooling-baths: 0 °C, ice–water; −15, −20, and −25 °C, $(CH_2OH)_2$–solid CO_2; −30 °C, CCl_4–solid CO_2; −40 °C, MeCN–solid CO_2; the temperature of the

bath was verified every 15 min, and adjusted, if necessary, by addition of solid CO_2. The unchanged zinc was allowed to settle and was collected. The supernatant was cooled in an ice-bath and acidified with 25% (v/v) sulphuric acid (*ca.* 85 ml), until pH 2. Water (200 ml) was added and the mixture was extracted with ether (4 × 200 ml). The organic layer was successively washed with 0.5M sulphuric acid (100 ml), saturated aq. sodium hydrogen carbonate (2 × 1000 ml), and brine, and was dried over Na_2SO_4. The solvent was evaporated off under reduced pressure to yield the crude oxidation mixture. This residue was chromatographed on silica gel (50 g) and afforded four fractions: fraction A (34 mg; pentane–ether, 9:1); fraction B (670 mg, 58%; starting material (**1**); pentane–ether, 8:2); fraction C (198 mg; pentane–ether, 1:1); and fraction D (124 mg; ether). The latter consisted of numerous polar products, each in very small amounts. Purification of fraction A by h.p.l.c. (normal phase; hexane–isopropyl alcohol, 9:1) gave A-nor-5β-cholestan-3-one (**19**) (22 mg, 2.0%), m.p. 76—77 °C (from MeOH) (lit.,[16] 73.5—74.5 °C); $[\alpha]_D^{20}$ +129° (lit.,[16] +105°); $\nu_{max.}(CCl_4)$ 1 745 cm^{-1}; δ(400 MHz) 0.67 (3 H, s), 0.86 (6 H, d, *J* 2 Hz), 0.90 (3 H, d, *J* 6.5 Hz), and 1.15 (3 H, s); *m/z* 372 (M^+), 233, 217 (100%), and 97; C.D. $\Delta\Sigma_{306}$ +2.7 (MeOH) (lit.,[17] positive Cotton effect by o.r.d.). Fraction C was purified by normal-phase h.p.l.c. (hexane–ethyl acetate, 8:2), and afforded progesterone (**3**) (25 mg, 2.7%), identified on comparison with an authentic specimen.

Isolation of 25-*Hydroxycholest*-4-*en*-3-*one* (**2**) *and Quantitative Determination of the* 20-*One*:25-OH *Ratio*.—The crude oxidation mixture isolated from the experiment at −25 °C was treated as above. Fraction C was submitted to h.p.l.c. (normal phase, hexane–ethyl acetate, 75:25; then reverse phase, acetonitrile) and afforded the 25-hydroxycholestenone (**2**) (11 mg), m.p. 146—150 °C (from MeOH) (lit.,[18] 149—150 °C); $[\alpha]_D^{23}$ +76° (*c* 0.037) (lit.,[18] +96°, *c* 0.6; lit.,[19] +88.4°, *c* 2.0); $\nu_{max.}(CHCl_3)$ 3 610, 3 450, 1 660, and 1 620 cm^{-1}; δ(400 MHz; [$^2H_5$]pyridine) 0.67 (3 H, s), 1.01 (3 H, d, *J* 6 Hz), 1.03 (3 H, s), 1.46 (6 H, s), 5.06 (1 H), and 5.89 (1 H, s); δ(400 MHz; $CDCl_3$) 0.71 (3 H, s), 0.93 (3 H, d, *J* 6 Hz), 1.18 (3 H, s), 1.21 (6 H, s), and 5.73 (1 H, s); *m/z* 400 (M^+), 382 (100%), 269, 245, and 229. These physical and spectral data are identical to those obtained from an authentic sample (*vide infra*). The determination of the ratio (**3**):(**2**) in other experiments was carried out by carefully weighing the fraction C of each run and analysing an aliquot by h.p.l.c. (see above). Comparison with calibration curves established with authentic samples of compounds (**2**) and (**3**) afforded the yields of these compounds present in the reaction mixture.

Blank Experiments Related to the Formation of A-*Nor*-5β-*cholestan*-3-*one* (**19**; 5β-H).—When cholestenone (**1**) was treated as in the standard procedure but under argon, fraction A weighed only 2 mg and for the same reaction but in the absence of iron catalyst, fraction A was obtained only in 1 mg yield. The cholestenone (**1**) was purified by h.p.l.c. and submitted to oxidation under conditions identical with those described above. The same isolation and purification procedures as above afforded the title compound in comparable amounts (16 mg, 1.45%). This rules out the hypothesis that compound (**20**) was present in the starting material, or that an impurity in the latter could be responsible for the formation of compound (**20**).

25-*Oxo*-27-*nor*-5β-*cholestan*-3α-*yl Acetate* (**9**).—A suspension of lithocholic acid (**4**) in a mixture of acetic anhydride (20 ml) and pyridine (20 ml) containing DMAP (200 mg) was refluxed for 3 h. Water (40 ml) was then slowly added, and the mixture was allowed to cool to room temperature. The white solid was collected by filtration, washed copiously with water, then with cold acetone (a few ml), and finally dried *in vacuo* at 50 °C. The crude acetate (**5**) (10.29 g, 93%) was used without purification in the next step.

Oxalyl chloride (0.25 ml, 2.9 mmol) was added to a solution of the above acetate (**5**) (837 mg, 2 mmol) in anhydrous benzene (10 ml) containing DMF (1 drop). After 18 h at room temperature, the solvent was distilled off under reduced pressure. The residue was then taken up in dry dichloromethane (10 ml) and the resulting solution was added, under argon and in the dark, to an ice-cooled suspension of the sodium salt of *N*-hydroxypyridine-2-thione (358 mg, 2.4 mmol, dried azeotropically with toluene) in dichloromethane (10 ml). When the formation of the mixed anhydride was complete (1.5 h as judged by t.l.c.), a solution of dry camphorsulphonic acid (929 mg, 4 mmol) in dichloromethane (10 ml), and 2-nitropropene[20] (610 mg, 7 mmol) were successively added. The reaction mixture was then irradiated (tungsten lamp, 300 W) for 15 min at 0 °C. The solvent and the excess of 2-nitropropene were removed under reduced pressure. To the resulting residue, dissolved in THF (20 ml), was added a 15% commercial aqueous solution of $TiCl_3$ (21 g). After being stirred for 15 h the mixture was treated with the same quantity of aqueous $TiCl_3$ and stirred for a further 5 h. The mixture was then poured into water (100 ml) and extracted with ether. The extract was washed successively with saturated aq. sodium hydrogen carbonate (3 × 100 ml) and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The resulting oil was taken up in dichloromethane and treated with acetic anhydride (1 ml) in the presence of few crystals of DMAP. After 18 h at room temperature the reaction mixture was poured into saturated aq. sodium hydrogen carbonate and extracted with dichloromethane. Usual work-up afforded a light yellow oil, which was purified by silica gel column chromatography (eluant hexane–ether, 9:1) to give *keto acetate* (**9**) (540 mg, 63%), m.p. 118—119 °C (from acetone); $[\alpha]_D^{18}$ 44.9° (*c* 2.3); $\nu_{max.}(CHCl_3)$ 1 720 and 1 715 cm^{-1}; δ(400 MHz; $CDCl_3$) 0.64 (3 H, s), 0.92 (6 H, m), 2.03 (3 H, s), 2.14 (3 H, s), 2.39 (2 H, m), and 4.69 (1 H, m); *m/z* 370 (M^+ − AcOH, 100), 355 (15), 257 (35), 230 (38), and 215 (77%) (Found: C, 78.2; H, 10.9. $C_{18}H_{46}O_3$ requires C, 78.08; H, 10.77%).

5β-*Cholestane*-3α,25-*diol* (**10**).—To a solution of the ketone (**9**) (360 mg, 2 mmol) in a mixture of ether (36 ml) and THF (4 ml) at 0 °C was added dropwise, under argon, an ethereal solution of methylmagnesium iodide (20 mmol, prepared from iodomethane and magnesium). The reaction mixture was allowed to warm to room temperature and was stirred overnight. After the mixture had been cooled to 0 °C, water (5 ml), 1M hydrochloric acid (40 ml), and ether (40 ml) were successively added. The aqueous layer was extracted with ether (2 × 100 ml) and the combined extracts were washed successively with saturated aq. sodium hydrogen carbonate (50 ml) and saturated aq. sodium thiosulphate (50 ml), then dried over Na_2SO_4, and finally concentrated under reduced pressure. The resulting white solid was submitted to column chromatography (eluant dichloromethane–ethyl acetate, 7:3) and afforded the *title compound* (**10**) (509 mg, 63%), m.p. 183 °C (from AcOEt); $[\alpha]_D^{23}$ +28° (*c* 0.21); δ(200 MHz; $CDCl_3$) 0.64 (3 H, s), 0.92 (6 H, d + 2), 1.21 (6 H, s), and 3.45 (1 H, m); *m/z* 386 ($M^{+\bullet}$ − H_2O, 100), 371 (38), 368 (24), and 353 (12%) (Found: C, 79.8; H, 11.7. $C_{27}H_{48}O_2$ requires C, 80.13; H, 11.96%).

25-*Hydroxy*-5β-*cholestan*-3-*one* (**11**).—PDC[21] (2.1 g, 5.6 mmol) was added, at room temperature, to a solution of the diol (**10**) (450 mg, 1.11 mmol) in a mixture of DMF (36 ml) and pyridine (4 ml). The reaction mixture was stirred for 2.5 h at room temperature, then poured into water (250 ml). The aqueous layer was extracted with ether (3 × 100 ml) and the

extracts were washed successively with 0.5M sulphuric acid (30 ml), saturated aq. sodium hydrogen carbonate (30 ml), and brine (30 ml), dried over Na_2SO_4, and finally evaporated under reduced pressure. The crude residue was chromatographed on a silica gel column (eluant hexane–ether, 1:1), and afforded the *title compound* (**11**) (399 mg, 89%), m.p. 102—104 °C (from hexane); $[\alpha]_D^{20}$ +34.7° (*c* 1.68); $\nu_{max.}(CHCl_3)$ 3 600, 3 450, and 1 705 cm^{-1}; δ(200 MHz; $CDCl_3$) 0.68 (3 H, s), 0.92 (3 H, d, *J* 6 Hz), 1.02 (3 H, s), 1.21 (6 H, s), and 2.76 (1 H, t, *J* 15 Hz); *m/z* (384 ($M^+ - H_2O$, 22), 369 (5), 273 (5), 271 (7), and 59 (100%) (Found: C, 80.6; H, 11.7. $C_{27}H_{46}O_2$ requires C, 80.83; H, 11.52).

25-*Hydroxycholest*-4-*en*-3-*one* (**2**).—A mixture of diphenyl diselenide (16 mg, 0.10 mmol), camphorsulphonic acid (120 mg, 0.49 mmol), and m-iodylbenzoic acid (290 mg, 0.98 mmol) in THF (1 ml) was refluxed for 15 min. A solution of the keto alcohol (**11**) (197 mg, 0.98 mmol) in THF (3 ml) was then added and the mixture was refluxed for another 30 min. After having cooled to room temperature, the mixture was poured into saturated aq. sodium hydrogen carbonate (10 ml) and extracted with ether (3 × 10 ml). Usual work-up afforded a crude residue, which was purified by preparative layer chromatography (hexane–ether, 4:6). The major product was the title compound (**2**) (135 mg, 69%), m.p. 148—150 °C (from MeOH) (lit.,[18] 149—150 °C); $[\alpha]_D^{20}$ +86.7° (*c* 0.475) (lit.,[18] +96°, *c* 0.6; +88.4°, *c* 2.0); $\nu_{max.}(CHCl_3)$ 1 660 and 1 620 cm^{-1}; δ(400 MHz; $CDCl_3$) 0.71 (3 H, s), 0.93 (3 H, d, *J* 6 Hz), 1.18 (3 H, s), 1.21 (6 H, s), and 5.73 (1 H, s); *m/z* 385 (46), 382 ($M^+ - 18$, 100), 367 (45), 340 (43), 298 (46), 297 (46), 269 (38), 229 (20), and 124 (27%).

Methyl 3-*Oxo*-5β-*cholan*-24-*oate* (**12**).—This compound was prepared by chromic oxidation[22] of methyl lithocholate.[23]

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