An Efficient and Short Degradation of the Cholic Acid Side Chain: A New Method for the Preparation and Dehydrogenation of 4,5-Dihydro-oxazoles

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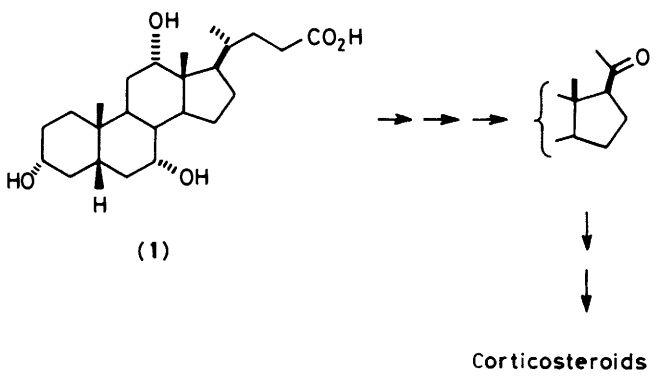
11-Oxolithocholic acid (**2**) and other unhindered aliphatic carboxylic acids undergo an efficient, boric acid mediated, condensation with 2-amino-2-methylpropan-1-ol (**3**) to give the corresponding 4,5-dihydro-oxazoles. The latter can be dehydrogenated in high yield to the α,β-unsaturated derivatives (*e.g.* **18**) with benzeneseleninic acid or anhydride. Acylation with trichloroacetyl chloride in the case of (**18**) followed by ozonolysis and saponification furnishes the 20-oxopregnane derivative (**21**) in over 80% overall yield. The side chain can also be cleaved in one step by benzeneseleninic acid albeit in relatively low yield [10—40% from (**4**) or (**5**)].

In spite of important progress in microbiology, the synthesis of corticosteroids starting with cholic acid from ox bile still remains the method of choice.[1] The ready availability of cholic acid (**1**) and its functionalised C ring make it especially suited as a precursor for corticosteroids. A key sequence in the synthesis is the degradation of the side chain to a pregnane derivative (Scheme 1). The original lengthy Barbier-Wieland degradation



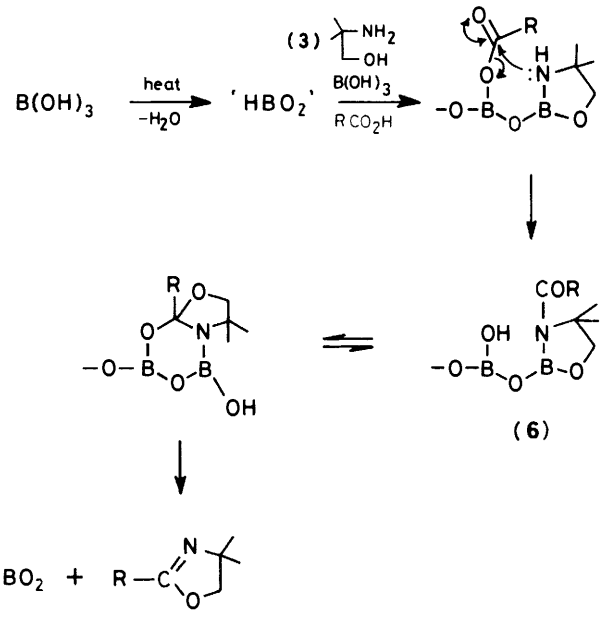
(**1**)

Scheme 1.

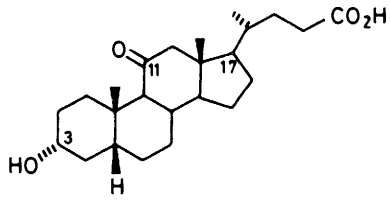
was replaced by the more efficient Meystre-Miescher method, now the basis of the industrial process.[2] Several recent methods have also been reported[3] that either give lower overall yield or involve a photochemical step which could not be employed in an industrial synthesis. We now report a highly efficient and concise degradation of the side chain to the 20-ketone using the versatile chemistry of dihydro-oxazoles.[4]

We first required a cheap and direct synthesis of dihydro-oxazoles[4] from carboxylic acids. Simple heating of 11-oxolithocholic acid (**2**) (generously provided by Roussel-Uclaf) with the amino alcohol (**3**) was not successful. A catalyst was needed to induce the formation of the intermediate amide and the subsequent ring closure. Boric acid appeared to be an ideal candidate. On moderate heating it loses a molecule of water to give HBO_2 which could react with the carboxylic acid and the amino alcohol to give an intermediate of structure (**6**) (or other variants).* The amine is thus well placed to interact with the now close and activated carbonyl to afford the amide. Further similar catalysis could induce the final cyclisation to the oxazoline (**4**) (Scheme 2).

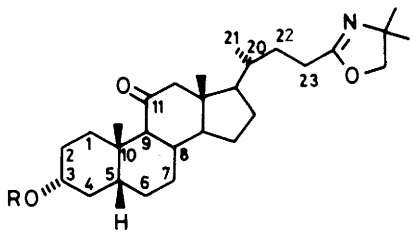
* A similar template mechanism has been postulated for tin mediated esterification.[5]



Scheme 2.



(**2**)

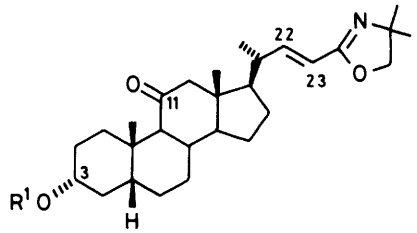


(**4**) R = H
(**5**) R = Ac

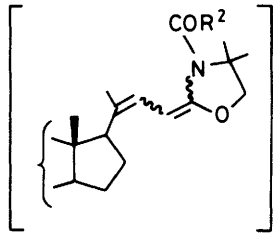
Table 1.

RCO_2H	Yield of
(2)	(4) 96%
(7) R = $(Me)_2CHCH_2$	(8) 44%
(9) R = Ph_2CHCH_2	(10) 93%
(11) R = $Me(CH_2)_{14}$	(12) 97%
(13) R = $CH_2 = CH(CH_2)_8$	(14) 90%
(15) R = Cyclohexyl	(16) 82%
(17) R = *p*-$MeOC_6H_4$	No reaction

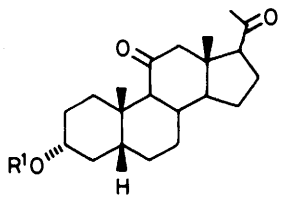
When a mixture of the acid (**2**), 2-amino-2-methylpropan-1-ol (**3**) and boric acid was heated in xylene, a smooth reaction occurred and the crystalline dihydro-oxazole (**5**) was formed in 95% yield. This reaction appears to be general for relatively unhindered aliphatic and alicyclic acids (Table 1). It cannot be applied to aromatic acids. Boric acid had been used before in the preparation of *N*-acyl indoles[6] but its use in the synthesis of dihydro-oxazoles does not seem to have been reported.



(**18**) $R^1 = H$
(**19**) $R^1 = Ac$



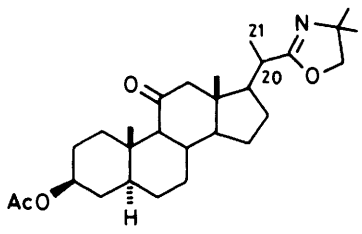
(**20**) R^2 = Ac, ClCO, CCl_3CO



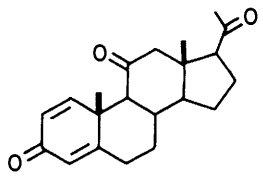
(**21**) $R^1 = H$
(**22**) $R^2 = Ac$

After acetylation of the free 3α-hydroxy group [(**5**), 100%], the next step was to introduce unsaturation at position 22. To this end we used the activating effect of the dihydro-oxazole ring to place a halogen at position 23, followed by dehydrohalogenation. This sequence was only moderately successful however and overall yields of (**19**) were relatively low.

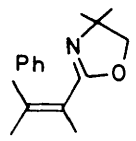
Considering that the dihydro-oxazole function is an analogue of a ketone and that its tautomer is the analogue of an enol, we have developed a more expedient and efficient process for making α,β unsaturated dihydro-oxazoles. This new method involves the use of benzeneseleninic acid or anhydride, reagents which gave excellent results in the dehydrogenation of steroidal ketones.[7] Thus, heating the dihydro-oxazole (**5**) with $PhSeO_2H$ (or its anhydride) in benzene for 5 min produced the desired unsaturated compound (**19**) in 80% yield. When pyridine was used as solvent, the reaction was slower but the yield of (**19**) was practically quantitative. Moreover, under these conditions, protection of the 3α-hydroxy group was not necessary. The dihydro-



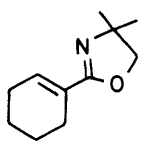
(**23**)
(**24**) $\Delta^{20,21}$



(**28**)



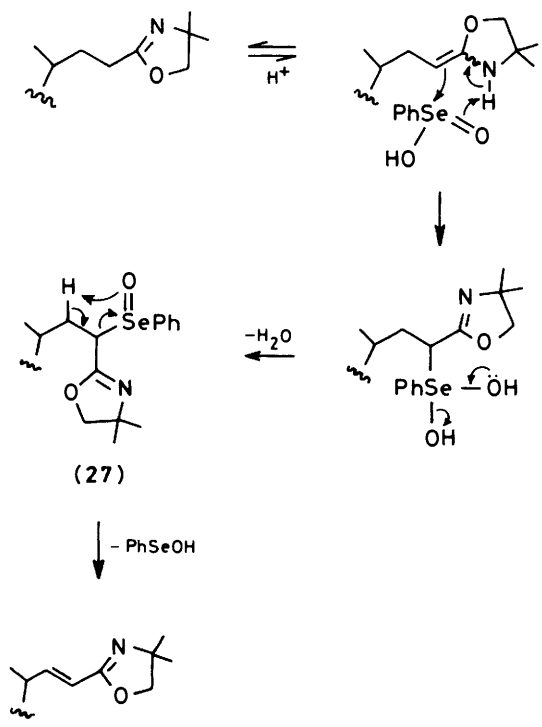
(**25**)



(**26**)

oxazole (**4**) could be directly and cleanly dehydrogenated to (**18**) (100%).

We have used this system to dehydrogenate a variety of dihydro-oxazoles (Table 2). The generality appears to be limited only by the tolerance of other functional groups towards benzeneseleninic acid or anhydride. A likely mechanism is shown in Scheme 3. Acid catalysed tautomerism followed by an ene reaction and loss of a molecule of water gave the selenoxide (**27**). Thermal elimination of benzeneseleninic acid introduces the desired double bond.



Scheme 3.

To complete the degradation of the cholic acid side chain, it was necessary to shift the unsaturation of the 20,22 position by acylation at the nitrogen to give (**20**). A simple ozonolysis would then yield the 20-keto steroid (**22**). Acetylation with acetyl chloride–triethylamine in boiling toluene and ozonolysis of the

Table 2.

	Yield of
(4)	(18) 100%
(5)	(19) 100%
(23)	(24) 81%
(10)	(25) 85%
(16)	(26) 92%

* When geometrical isomerisation is possible, the double bond is in the *E* configuration.

crude reaction product gave the ketone (**22**) in only moderate yield (*ca.* 40%). The acetylation step was not very clean. With the more reactive phosgene as the acylation reagent, the reaction occurred smoothly at room temperature. Ozonolysis offorded the desired ketone (**22**) in 90—95% yield. Thus the degradation of the side chain was completed in practically three steps in an overall yield of *ca.* 90%.

To circumvent the high cost of benzeneseleninic acid involved in large scale manipulations, we established conditions for the degradation allowing for the recovery of diphenyl diselenide and without isolation of the various intermediates.

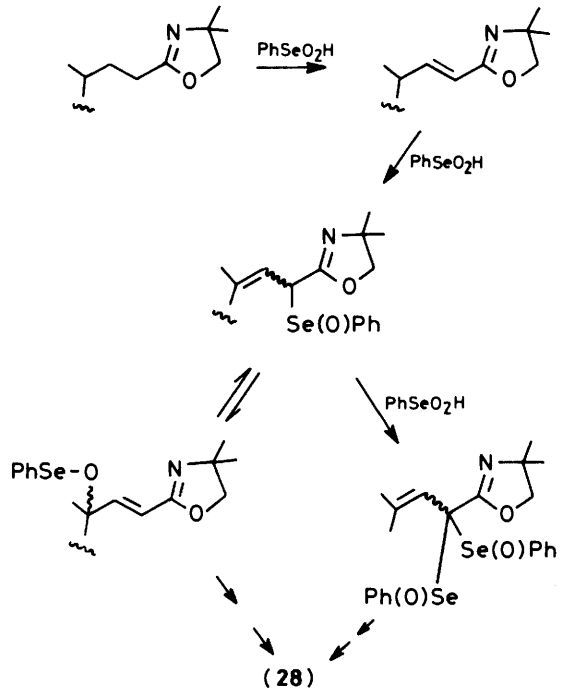
Thus heating the dihydro-oxazole (**4**) with benzeneseleninic acid in dichloromethane–pyridine followed by treatment with aqueous sodium dithionite and drying of the organic layer by filtration through potassium carbonate, gave a dry solution of the α,β unsaturated dihydro-oxazole (**18**) and diphenyl diselenide in dichloromethane–pyridine. This was cooled to 0 °C and treated with trichloroacetyl chloride which displaced the double bond and esterified the free 3α-OH group [(**20**); $R^1 = R^2 = CCl_3CO$]. An aqueous solution of potassium carbonate was added, followed by ozonolysis, reduction of the ozonides with dimethyl sulphide and saponification with sodium hydroxide in methanol. The ozone not only cleaved the side chain but also oxidised the diphenyl diselenide to benzeneseleninic anhydride. In the saponification step, this was transformed into sodium benzeneseleninate and remained in the aqueous phase. The organic phase contained the 20-oxo steroid (**21**) which could be isolated in 80% overall yield by chromatography. For large scale work, this can be replaced by a simple filtration on silica and crystallisation. The aqueous phase treated with sodium dithionite and extracted with dichloromethane gave the diphenyl diselenide in 94% yield. Diphenyl diselenide can be oxidised into benzeneseleninic acid in almost quantitative yield by aqueous hydrogen peroxide.

This process for the degradation of the cholic acid side chain is clearly both highly efficient and economical and can certainly be further optimised.

In the course of our study, we found that the cleavage of the side chain can be effected in one step by simply heating the dihydro-oxazole (**5**) with benzeneseleninic acid or anhydride in benzene in the presence of iodoxybenzene. This latter reagent serves to oxidise the diphenyl diselenide present back to benzeneseleninic anhydride.[7] The yield of 20-ketone (**22**) is 35—40%. This yield could not be further improved, partly because the ketone itself is not very stable to the reaction conditions.

The mechanism for this transformation is not yet clear. Some possibilities are depicted in Scheme 4.

If the same reaction is performed on the dihydro-oxazole (**4**), compound (**28**), possessing the important dienone moiety in ring A is produced in a single step. Although the yield is low (10—15%), the number of steps involved is quite impressive (at least 14!).



Scheme 4.

Experimental

M.p.'s were measured on a Kofler hot plate and are uncorrected. N.m.r. spectra were run in deuteriochloroform with tetramethylsilane as internal standard. Optical rotations are for chloroform solutions.

2-(3β-*Hydroxy*-11-*oxo*-24-*norcholan*-23-*yl*)-4,4-*dimethyl*-4,5-*dihydro-oxazole*. (**4**).—A mixture of 11-oxo-lithocholic acid (**2**) (12.9 g), amino alcohol (**3**) (4 g) and boric acid (0.8 g) was heated in refluxing xylene (240 ml) with azeotropic removal of water for *ca.* 45 h. The solvent was removed under reduced pressure and the residue dissolved in hot methanol (60 ml). 5% Aqueous potassium carbonate (250 ml) was added and the mixture boiled for 1 h, cooled, and the white solid filtered off and dried. It consisted of practically pure dihydro-oxazole (**4**) (14 g, 96%), m.p. 163—165 °C (ethyl acetate); $[\alpha]_D$ +47° (*c*, 0.5); $\nu_{max.}$(Nujol) 3 300, 1 703, and 1 660 cm^{-1}; δ_H* 3.80 (2 H, s, 5′-H), 3.50 (1 H, br, 3-H), 1.20 (6 H, s, 4′-Me), 1.10 and 0.60 (6 H, 2 × s, 10 and 13-Me) (Found: C, 75.55; H, 10.1; N, 3.15. $C_{28}H_{45}NO_3$ requires C, 75.80; H, 10.22; N, 3.16%).

2-(2-*Methylpropyl*)-4,4-*dimethyl*-4,5-*dihydro-oxazole* (**8**).—A mixture of isovaleric acid (22 g), 2-amino-2-methylpropanol (25.4 g) and boric acid (2.4 g) was heated in refluxing xylene with azeotropic removal of water for 4 days. The xylene was distilled and the distillate filtered through silica. The silica was washed with hexane to remove the xylene and then with ether to elute the dihydro-oxazole (**8**). Evaporation of the ether and distillation gave 6.13 g of (**8**). Distillation of the residue from the reaction mixture afforded a further 8.57 g of product. Total yield 14.7 g (44%); b.p. 50 °C[8] (Kugelrohr; oven temperature) at 10 mmHg; $\nu_{max.}$(neat) 1 660 cm^{-1}; δ_H 3.95 (2 H, s) and 1.35 (6 H, s).

2-(2,2-*Diphenylethyl*)-4,4-*dimethyl*-4,5-*dihydro-oxazole* (**10**).—In a similar way the *title compound* (**10**) was prepared from 3,3-diphenylpropionic acid (11.3 g), 2-amino-2-methyl-

* Throughout, the primed positions refer to the oxazole ring.

propanol (7.1 g) and boric acid (1.26 g) in xylene (250 ml); yield 13 g (93%), m.p. 87 °C (ether); $\nu_{max.}$ 1 660 cm^{-1}; δ_H 7.51 (10 H, s), 4.63 (1 H, t, *J* 4.5 Hz), 3.84 (2 H, s), 3.07 (2 H, d, *J* 4.5 Hz), 1.06 (6 H, s) (Found: C, 81.7; H, 7.6; N, 5.0. $C_{19}H_{21}NO$ requires C, 81.51; H, 7.77; N, 4.98%).

2-*Pentadecyl*-4,4-*dimethyl*-4,5-*dihydro-oxazole* (**12**).—A mixture of palmitic acid (3 g), the amino alcohol (**3**) (2.3 g), and boric acid (0.4 g) were heated in refluxing xylene (150 ml) for 65 h. The xylene was removed under reduced pressure and the residue distilled (Kugelrohr, 220 °C, 4 mmHg) to give the *title compound* as a colourless liquid (3.52 g, 97%); $\nu_{max.}$ 1 660 cm^{-1}; δ_H 4.17 (2 H, s) (Found: C, 77.8; H, 12.75; N, 4.8. $C_{20}H_{39}NO$ requires C, 77.55; H, 12.69; N, 4.52%).

2-(*Dec*-9-*enyl*)-4,4-*dimethyl*-4,5-*dihydro-oxazole* (**14**).—In a similar fashion, the *title compound* (**14**) (13.9 g, 90%) was obtained from undec-10-enoic acid (12 g), 2-amino-2-methylpropanol (9.5 g), and boric acid (1.6 g) in xylene (300 ml), b.p. (Kugelrohr oven temperature) 170 °C at 5 mmHg; $\nu_{max.}$(neat) 1 660 cm^{-1}; δ_H 5.8 (1 H, m), 5.0 (2 H, m), 3.87 (2 H, s), 2.20 (4 H, m), 1.27 (6 H, s), 1.23 (12 H, br s) (Found: C, 75.9; H, 11.45; N, 5.85. $C_{15}H_{27}NO$ requires C, 75.89; H, 11.47; N, 5.90%).

2-*Cyclohexyl*-4,4-*dimethyl*-4,5-*dihydro-oxazole* (**16**).—This compound was prepared as described above from cyclohexanecarboxylic acid (10.3 g), 2-amino-2-methylpropanol (15 g), and boric acid (0.4 g) in xylene (250 ml) as a colourless liquid (11.9 g, 82%), b.p. (Kugelrohr) 150 °C at 5 mmHg (lit.,[9] b.p. 95—97 °C (14 mmHg); $\nu_{max.}$(neat) 1 660 cm^{-1}.

2-(3β-*Acetoxy*-11-*oxo*-5α-*pregnan*-20-*yl*)-4,4-*dimethyl*-4,5-*dihydro-oxazole* (**23**).—To a mixture of 3β-acetoxy-11-oxo-5α-pregnane-20-carboxylic acid (1.0 g) and dimethylformamide (3 drops) in dry benzene (10 ml) was added dropwise oxalyl chloride (0.5 ml). When the evolution of hydrogen chloride had ceased the excess of oxalyl chloride was distilled off and the cooled reaction mixture was added to a solution of 2-amino-2-methylpropanol (**3**) (0.7 g) in benzene (5 ml). The reaction mixture was stirred at room temperature for 30 min, and then 5% aqueous potassium carbonate (30 ml) was added. The benzene was distilled off and the white solid thus obtained was filtered off and dried. Without further purification, it was dissolved in dry dichloromethane (5 ml), cooled to 0 °C, and treated with thionyl chloride (0.4 ml) in dichloromethane (2 ml). After 45 min at 0 °C, the solution was shaken with 5% potassium carbonate and the organic phase was separated and dried. Evaporation and crystallisation of the residue from methanol gave the pure *dihydro-oxazole* (**23**) (0.86 g, 76%), m.p. 168—169 °C $[\alpha]_D$ = +16° (*c*, 0.85); $\nu_{max.}$(Nujol) 1 735, 1 705, and 1 660 cm^{-1}; δ_H 4.83 (1 H, br), 3.94 (2 H, br s), 2.22 (2 H, br s), 2.05 (3 H, s), 1.30 and 1.27 (6 H, 2 × s), and 1.06 and 0.69 (6 H, 2 × s) (Found: C, 73.35; H, 9.4; N, 3.0. $C_{28}H_{43}NO_4$ requires C, 73.48; H, 9.47; N, 3.06%).

2-(3β-*Acetoxy*-11-*oxo*-5α-*pregn*-20-*yl*-)-4,4-*dimethyl*-4,5-*dihydro-oxazole* (**24**).—A mixture of the dihydro-oxazole (**23**) (162 mg), benzeneseleninic acid (90 mg), and pyridine (1 ml) in dry benzene (10 ml) was heated to reflux under nitrogen for 6 h with azeotropic removal of water. The solvents were removed under reduced pressure and the residue chromatographed on silica (ethyl acetate–hexane, 1:2) to give the pure *alkene* (**24**) (131 mg, 81%), m.p. 144—145 °C (methanol); $[\alpha]_D$ = +6° (*c*, 1.2); $\nu_{max.}$ (dichloromethane) 1 735, 1 700, 1 645, and 1 600 cm^{-1}; δ_H 6.20 (1 H, s), 5.56 (1 H, s), 4.78 (1 H, br), 4.03 (2 H, s), 1.32 and 1.29 (6 H, 2 × s), and 1.04 and 0.50 (6 H, 2 × s) (Found: C, 73.25; H, 9.2; N, 3.3. $C_{28}H_{41}NO$ requires C, 73.80; H, 9.07; N, 3.07%).

2-(2,2-*Diphenylvinyl*)-4,4-*dimethyl*-4,5-*dihydro-oxazole* (**25**).—A mixture of the dihydro-oxazole (**10**) (450 mg) and benzeneseleninic acid (440 mg) was heated in refluxing benzene (10 ml) under a nitrogen atmosphere for 2 h with azeotropic removal of water. Evaporation of the solvent followed by chromatography of the residue on silica (ethyl acetate–hexane 3:7) gave the *alkene* (**25**) as white crystals (455 mg, 85%), m.p. 84—85 °C (ethyl acetate); $\nu_{max.}$(Nujol) 1 640 and 1 590 cm^{-1}; δ_H 7.53 (10 H, br s), 6.65 (1 H, s), 3.81 (2 H, s), and 1.27 (6 H, s) (Found: C, 82.25; H, 7.0; N, 5.1. $C_{19}H_{19}NO$ requires C, 82.27; H, 6.90; N, 5.05%).

2-*Cyclohex*-1-*enyl*-4,4-*dimethyl*-4,5-*dihydro-oxazole* (**26**).—A mixture of the dihydro-oxazole (**16**) (320 mg), benzeneseleninic acid (412 mg), and pyridine (0.1 ml) was heated in refluxing benzene (10 ml) for 1 h under an inert atmosphere with azeotropic elimination of water. The solution was filtered through a silica column with first hexane and then with ether as eluants to give the title compound as a colourless liquid (231 mg, 92%); $\nu_{max.}$(neat) 1 660 and 1 600 cm^{-1}; δ_H 6.80 (1 H, m), 4.00 (2 H, s), 2.30 (4 H, m), 1.67 (4 H, m), and 1.30 (6 H, s).

2-(3α-*Hydroxy*-11-*oxo*-24-*norchol*-22-*en*-23-*yl*)-4,4-*dimethyl*-4,5-*dihydro-oxazole* (**18**).—A solution of the dihydro-oxazole (**4**) (106 mg) in dry tetrahydrofuran (5 ml) and pyridine (1 ml) was heated to 60 °C. Benzeneseleninic acid (190 mg) was added and the mixture kept at 60 °C for 1 h after which it was cooled to room temperature and treated with 33% hydrogen peroxide (2 ml). After vigorous stirring for 20 min, 5% potassium carbonate was added followed by extraction with dichloromethane. The organic phase was washed with water, dried (K_2CO_3), and evaporated. The residue was adsorbed on a short silica column and eluted with ethyl acetate to give the *title compound* as a white crystalline solid (106 mg, *ca.* 100%), m.p. 203—205 °C (ether); $[\alpha]_D$ +37° (*c*, 0.6); $\nu_{max.}$(Nujol) 1 690, 1 665, and 1 601 cm^{-1}; δ_H 6.60 and 6.30 (1 H, dd, *J* 9 and 16 Hz), 5.85 (1 H, d, *J* 16 Hz), 3.65 (1 H, br), 1.31 (6 H, s), and 1.18 and 0.67 (6 H, 2 × s) (Found: C, 76.0; H, 10.05; N, 3.3. $C_{28}H_{43}NO_3$ requires C, 76.15; H, 9.81; N, 3.17%).

2-(3β-*Acetoxy*-11-*oxo*-24-*norchol*-22-*en*-23-*yl*)-4,4-*dimethyl*-4,5-*dihydro-oxazole* (**19**).—A mixture of the dihydro-oxazole (**4**) (2.5 g), *N*,*N*-dimethylaminopyridine (200 mg) and acetic anhydride (5 ml) in dichloromethane (10 ml) was kept at room temperature for 1 h. The excess of acetic anhydride was removed by shaking with aqueous potassium carbonate. The organic layer was dried and filtered through a silica plug to give, after evaporation, the dihydro-oxazole (**5**) (2.72 g, 100%). This was used without further purification in the next step.

A solution of (**5**) (155 mg) and benzeneseleninic anhydride (225 mg) in dry pyridine (5 ml) was heated to 60 °C for 6 h. The mixture was then poured into 5% aqueous potassium carbonate and extracted with dichloromethane. The organic phase was washed with water, dried, and evaporated and the residue purified by chromatography on silica using first dichloromethane–hexane (1:1; to remove diphenyl diselenide) and then ether as eluant to give the dihydro-oxazole (**19**) (155 mg, 100%) as a white crystalline solid, m.p. 158—163 °C (ether); $[\alpha]_D$ +49° (*c*, 0.5); $\nu_{max.}$(dichloromethane) 1 720, 1 700, 1 670, and 1 605 cm^{-1}; δ_H 6.35 and 6.20 (1 H, dd, *J* 15 and 7 Hz), 5.70 (1 H, d, *J* 15 Hz), 4.60 (1 H, br), 3.82 (2 H, s), 1.25 (6 H, s), and 1.17 and 0.65 (6 H, 2 × s) (Found: C, 74.25; H, 9.5; N, 3.15. $C_{30}H_{45}NO_4$ requires C, 74.50; H, 9.38; N, 2.90%).

3α-*Acetoxy*-5β-*pregnane*-11,20-*dione* (**22**).—To a solution of the dihydro-oxazole (**19**) (86 mg) in toluene (dry, 4 ml) and triethylamine (0.5 ml) was added a solution of phosgene (*ca.* 75 mg) in toluene (0.4 ml). The mixture was kept at room temper-

ature for 30 min, filtered, and the toluene removed under reduced pressure. The residue was dissolved in dichloromethane (5 ml) and a stream of ozone passed into the cooled (0 °C) solution until the intermediate [(**20**) (R^2 = COCl)] had been consumed. An excess of dimethyl sulphide was added and the solution was filtered through an alumina plug to give an oil which slowly crystallised (61 mg, 90%), m.p. and mixed m.p. 130—133 °C $[\alpha]_D$ +125° (*c*, 1.3) (lit.,[10] m.p. 129—130 °C $[\alpha]_D$ 130°).

3α-*Hydroxy*-5β-*pregnane*-11,20-*dione* (**21**).—A solution of the oxazoline (**4**) (365 mg) and benzeneseleninic acid (457 mg) in dichloromethane (10 ml) and pyridine (1 ml) was heated to reflux for 6 h. The excess of benzeneseleninic acid was reduced with sodium dithionite (455 mg) dissolved in the mimimum of water. The reaction mixture was then filtered through a short column packed with a layer each of potassium carbonate and sodium dithionite. To the filtered and cooled (0 °C) yellow solution was then added dropwise trichloroacetyl chloride (0.5 ml). The mixture was kept at 0 °C for 4 h, diluted with dichloromethane (10 ml), and treated with potassium carbonate (1.7 g) in the minimum of water. After being stirred for a few minutes, the resulting mixture was ozonolysed for 20 min at 0 °C (complete discoloration). Dimethyl sulphide (2 ml) was added and the solvents were evaporated under reduced pressure. The residue was taken up in methanol (20 ml), treated with 30% sodium hydroxide (0.5 ml) and, after 20 min at room temperature, extracted with dichloromethane; the organic layer was washed repeatedly with water. The combined aqueous washings were neutralised with hydrochloric acid and treated with an excess of sodium dithionite to give after extractive work-up practically pure diphenyl diselenide (377 mg, 94%).

The organic layer was dried, evaporated, and the residue purified on a short silica column (ethyl acetate–hexane 9:1) to give the dione (**21**) (219 mg, 80%), m.p. 174—176 °C (ethyl acetate) (lit.,[10] m.p. 174—174.5 °C) $[\alpha]_D$ +109° (*c*, 1); $\nu_{max.}$(Nujol) 3 250 and 1 690 cm^{-1}; δ_H 2.16 (3 H, s) and 1.18 and 0.58 (6 H, 2 × s).

3α-*Acetoxy*-5β-*pregnane*-11,20-*dione* (**22**).—A mixture of the dihydro-oxazole (**5**) (232 mg), benzeneseleninic acid (28 mg), iodoxybenzene (594 mg), and benzene (10 ml) was heated to reflux for 8 h. The solvent was removed under reduced pressure and the residue purified by chromatography on silica (ethyl acetate–hexane 1:1) to give dione (**22**) (72 mg, *ca.* 40%) identical with authentic material.

Pregna-1,4-*diene*-3,11,20-*trione* (**28**).—A mixture of diphenyl diselenide (62 mg) and iodoxybenzene (1.4 g) in refluxing toluene (30 ml) was heated until the yellow colour had disappeared. The dihydro-oxazole (**4**) (440 mg) was added and heating resumed for 6—7 h. Filtration, evaporation, and careful chromatography on silica of the residue (dichloromethane–ether gradient) gave the dienone as a yellow oil which slowly crystallised (40 mg, *ca.* 12%), identical with authentic material m.p. and mixed m.p. 163—168 °C.[7]

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