75. Fe(II)-Induced Fragmentation Reaction of γ-Hydroperoxy-α,β-enones

Part 1

Synthesis of 13(14→8)-*abeo*-Steroids

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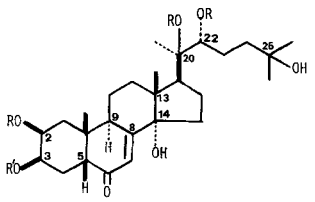
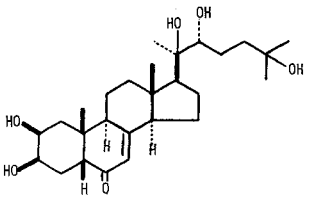
(6.II.87)

Some steroidal analogues embodying the hitherto unknown 13(14→8)-*abeo* skeleton have been synthesized by Fe(II)-induced rearrangement (tandem β-fission/reductive alkylation) of 14α-hydroperoxy-7-en-6-ones. The configurational assignment was made by thorough analysis of NMR spectra; the structure of one of the products was unambiguously assessed by X-ray single-crystal analysis.

Introduction. – Recently, we have briefly reported [1] that irradiation of the insect-moulting hormone 20-hydroxyecdysone (= crustecdysone; **1**) [2] in H_2O through *Pyrex* yielded, in addition to the reduction products **2** and **3** containing intact steroidal framework, the unprecedented ketone **4** and the cyclobutanol **5**. Our attention was focused on



1 R = R' = H
6 R = R' = Me_2C



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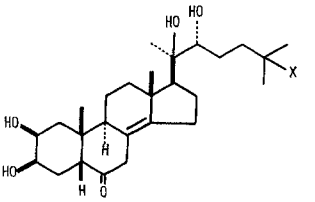

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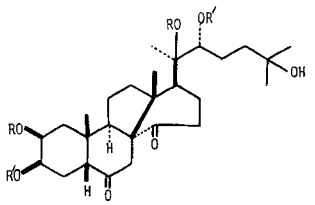
7 X = H



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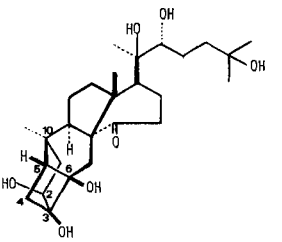
12 R = R' = Me_2C



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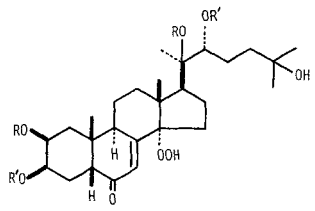
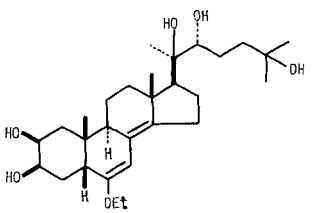


8 R = R' = H
10 R = R' = Me_2C



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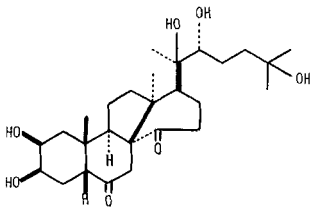

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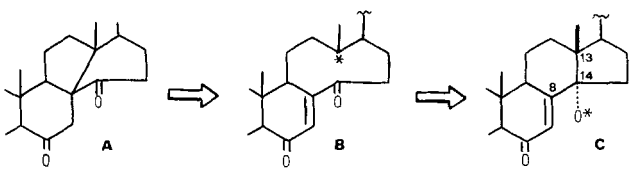
the mechanism of formation of **4** in which a contraction-expansion of skeleton (*i.e.*, 6/5→5/6 ring transformation) had occurred. This presumably could be accommodated within a reaction scheme which involves the 1,4-H transfer to form a 14α-oxyl radical, followed by its β-fission and fast transannular rebonding to **4**. Finally, it is likely that **5** is the result of a secondary photochemical reaction of **4** involving a conventional *Norrish* Type II process. Structural assignments **4** and **5**, although plausible, have to be regarded as tentative in the absence of any more compelling evidence. The independent synthesis of **4** and that of some analogues embodying the 13(14→8)-*abeo*-ergostane skeleton (= 8, 13-*cyclo*-13,14-*seco*-ergostane) were subsequently achieved for the purpose of structure confirmation.

Results and Discussion. – From the retrosynthetic perspective *(Scheme)*, we envisioned construction of the 13(14→8)-*abeo* system **A** *via* retroconjugated addition of a nucleophilic centre (starred position) to the 9-membered enone **B**. In turn, the latter might be generated by stereoelectronically allowed fragmentation (ionic and/or radical) of a γ-oxygenated enone **C**.

Scheme



(* = • or ⊖)

To examine the feasibility of this strategy, we first explored the tandem *retro*-aldol/*Michael* addition procedure (vinylogous α-hydroxy-ketone rearrangement). This ionic mechanism had ample precedent in the chemistry of the *Galbulimima* alkaloids [3]. Accordingly, when **1** was treated with a variety of bases under several sets of homogeneous or heterogeneous conditions, only varying ratios of recovered starting material and minor side products were obtained. Nor was any success to be found starting from 2,3:20,22-diacetonide derivative **6** [4] under similar conditions[1]).

This failure suggested the need for a modified synthetic approach, and we turned our attention to the 14α-oxyl radical **C**(* = •) as a potential precursor of **A**. It is well known

[1]) An attempt to effect the rearrangement of **1** to **4** under acidic conditions resulted uniformly in extensive decomposition.

that cyclopentyloxyl and higher cycloalkyloxyl radicals suffer either H-transfer (intra- and/or intermolecular) or β-fission [5]. As stated by *Beckwith* and coworkers [6], β-fission is favoured when the bond concerned lies close to the plane of an adjacent semi-occupied orbital (*trans*-antiperiplanar relationship). In our system **C**(* = •), where a strong conformational preference is recognizable, the direction of ring opening would conform to this guideline. Inspection of a model of the most stable conformation of a 14α-oxyl radical **C**(* = •) reveales that the above mentioned relationship exists only for the C(13)–C(14) bond. If these stereoelectronic hypotheses are correct, we should expect, therefore, that a nucleophilic radical at C(13) would be trapped rapidly by the enedione system leading ultimately to the target ketone of type **A**. In the event, one would anticipate that the involvement of a *tert*-alkyl radical (increased energy of the SOMO; see **B**(* = •)) and the presence of an electron-withdrawing substituent at both C-atoms of the enedione double bond (lowered energy of the LUMO of C=C) would synergistically enhance the rate of transannular radical addition [7]. The mechanism of this reaction presumably would parallel that observed in Fe(II)-induced fragmentation of ascaridole [8].

Reagent systems that have been used successfully in generation of alkoxyl radicals are generally based on homolysis of an O–X bond [9] such as the $Pb(OAc)_4$ oxidation of alcohols, the $Pb(OAc)_4/I_2$ reaction, the photolysis of nitrites (*Barton* reaction), and the reduction of *tert*-alkyl hydroperoxides with metal complexes. Although the hydroperoxide for our purposes was not immediately available, we favoured the last procedure because of the tolerance of diverse functional groups towards its conditions and the expected sensitivity of the product.

A variety of methods for introducing the hydroperoxy function into the angular 14α-position and starting from either **3** or 20-hydroxyecdysone **1** itself were explored. *Nakanishi et al.* [10] first reported that **7** (an analogue of **3**) could serve as precursor of the corresponding 14α-hydroperoxy-enone; the latter compound was generated as intermediate in a dye-sensitized photooxygenation process. In line with this precedent, a solution of **3** in pyridine was irradiated under O_2 in the presence of hematoporyrin as a sensitizer at r.t. However, the yields of hydroperoxide **8** were low (20–35%) and the conversion incomplete. More favourable results were obtained by autooxidation of 6-ethoxy-6,8(14)-dienepentol **9**. The latter was available in nearly quantitative yield by azeotropical removal of H_2O from a carefully degassed EtOH soln. of **3** in the presence of tetrafluoroboric acid as a catalyst.

The structure of **9** was indicated by the UV spectrum (251 nm) and confirmed by the IR (1650 and 1625 cm^{-1}) and fast atom bombardment mass spectrum (FAB-MS, positive-ion mode) with $(M + H)^+$ at m/z 493. In addition, the presence of a heteroannular dienol ether was indicated by the ^{1}H-NMR signal at 5.28 ppm (*s*) for H–C(7) and by 4 low-field ^{13}C-NMR signals at 95.5 (*d*), 123.6 (*s*), 141.2 (*s*), and 159.1 (*s*) ppm for C(7), C(14), C(8), and C(6), respectively.

It is well known that many dienol ethers undergo ready autooxidation [11]; compound **9** was exceptionally prone to this reaction. Thus, when a solution of **9** in MeOH containing catalytic amount of oxalic acid was placed in an air-filled flask and set aside at r.t. in the dark for 6 h, a mixture of the requisite **8** (57%) and 20-hydroxyecdysone **1** (9%) was isolated.

For preparative purposes and in order to improve the yield of **8**, we have developed a direct method of hydroperoxidation starting from **1** itself. It has been reported that

α,β-unsaturated ketones having a leaving group at the γ-position normally undergo reductive elimination on reaction with metals in NH_3 [12]. Accordingly, exposure of **6** [4][2]) to Li in liq. NH_3/THF gave, after slow evaporation *without rigorous exclusion of* O_2 and aqueous workup, the 14α-hydroperoxide as 2,3:20,22-diacetonide **10** in 82% yield. Deprotection proceeded under remarkably mild conditions. Thus, exposure of **10** to THF/0.5N aq. HCl 2:1 at r.t. for 6 h smoothly afforded the hydroperoxide **8** as a crystalline compound in nearly quantitative yield.

Hydroperoxide **8** was surprisingly stable and could be stored at room temperature, in the dark, without appreciable decomposition for several months[3]). Elemental analysis ($C_{27}H_{44}O_8$) and iodometric titration supported the presence of one hydroperoxy group. While EI-MS failed to detect $M^{+\cdot}$ of **8** owing to fragmentation, the FAB-MS (Xe, glycerol matrix) permitted the detection of the quasi-molecular ion $(M + H)^+$ at m/z 497. Configurational assignment to **8** was originally inferred from its spectral data and later substantiated chemically. Methyl signals in the ^{1}H-NMR ((D$_5$)pyridine) of **8** (Me(19), 1.07; Me(18), 1.20; Me(26) and Me(27), 1.36 ppm) occur at nearly the same positions as the corresponding signals in **1**. Conversely, a diagnostic difference in the ^{13}C-NMR was found for C(14) whose *s* (SFORD) absorbs *ca.* 11 ppm further downfield in **8** than in **1** [13].

Chemoselective reduction of **8** with Me_2S (CH_2Cl_2, r.t.) provided **1** in quantitative yield. The formation of **8** implied the oxygenation (through a free-radical chain mechanism [14]) of a dienolate anion which likely resulted from elimination of alkoxide at C(14) [12]. The stereochemical outcome could be the result of steric-approach control in attack of dioxygen ($^3O_2$) from the α-face (*i.e. anti* to the angular Me groups).

With the hydroperoxide **8** in hand in reasonable quantities, we next turned our attention to the preparation of the target ketone **4**. The interaction of *tert*-alkyl hydroperoxides with Fe(II) salts provided an unambiguous method for the generation of alkoxyl radicals [15]. In accord with our original expectations, the addition of an acidic solution (pH 3) of $FeSO_4 \cdot 7H_2O$ to **8** in THF/H_2O at r.t. led to virtually instantaneous formation of a mixture of **4** (85%) and **1** (5%) as the sole products[4]). The spectral (IR, ^{1}H- and ^{13}C-NMR) features of **4** were superimposable upon those of the product isolated from photoirradiation of **1**. In particular, the ^{13}C-NMR spectra showed that formation of the 13(14→8)-*abeo* skeleton from **8** had proceeded with exceptionally good stereochemical control producing uniquely one of the 4 possible diastereoisomers.

Inasmuch as ketone **4** is the *Michael*-type adduct derived from **1**, it should be possible, in principle, to effect a reversal of the addition under suitable conditions. Indeed, treatment of **4** with NaOH/MeOH (reflux, 2.5 h) led to **1** in 89% isolated yield.

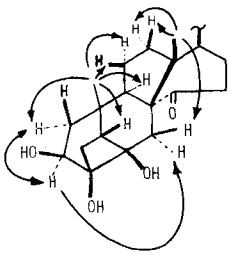


Fig. 1. *Diagnostic NOE interactions in* **5**

[2]) Protection of the diol functions in **1** was necessary to enhance the solubility in liq. NH_3/THF.

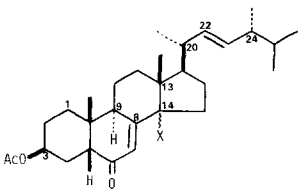
[3]) Occasionally, **8** was isolated in low (< 5%) and erratic yields from the photolysis of **1** in H_2O or H-donating alcohols, although great care was taken to remove the residual O_2 from the Ar purge.

[4]) Alternative attempts to convert **8** to **4** either thermally (neat, 160°) or photolytically (high-pressure Hg lamp) were unsuccessful giving noticeably lower yields (15–40%).

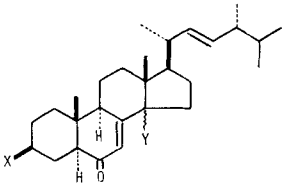
The likelihood of the assumptions for structure **4** was further supported by ring closure of **4** to the cyclobutanol **5** (65%) on quartz-filtered irradiation of an EtOH solution of **4**. Spectral data and chromatographic behaviour of **5** were identical with those of the most polar photoproduct obtained from **1** in H_2O. The structure of **5** was based on ^{1}H-NMR (600 MHz) spectra and extensive NOE experiments (see NOE connectivity pattern in *Fig. 1*). The clean photoinduced conversion of **4** to **5** indicated that H_α–C(3) of **4** is ideally juxtaposed[5]) to be abstracted by the n,π^*-excited carbonyl group at C(6) (*Norrish* type II process) [16b], and only diastereoisomer **4** meets all the above requirements.

Structure **11** was considered as a plausible alternative for the target ketone, but this possibility was discounted on spectral evidence in favor of **4** as NOE experiments on the 2,3:20,22-diacetonide derivative **12** disclosed a *'syn'* relationship of H_β–C(7) and Me(18). In order to unambiguously settle the stereochemical problem posed by the formation of **4**, we planned an X-ray analysis, but no X-ray-quality crystals of either **4** or simple derivatives could be obtained.

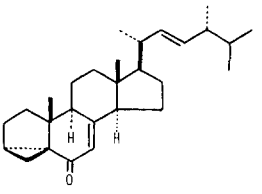
For the purpose of obtaining material suitable for crystal-structure determination and in order to test the applicability of our procedure, our attention was next turned to **13** and **14** as a possible source of the 14α-hydroperoxides **15** and **16**, respectively, bearing the essential configurational features of **8**. The first problem arose during initial attempts to generate **13** and **14** as products from 3α,5α-*cyclo*-ergosta-7,22-dien-6-one (**17**) [17]. Acid-catalyzed cyclopropane ring-opening in $AcOH/H_2SO_4$ produced, after standard acetylation, the requisite **13** and **14** only in 10 and 26% yield, respectively. TLC indicated the presence of two other close-moving side products. Analysis of their ^{1}H-NMR [18] and



13 X = α-H
15 X = α-OOH
18 X = β-H
21 X = α-OH



14 X = OAc, Y = α-H
16 X = OAc, Y = α-OOH
19 X = OAc, Y = β-H
23 X = OH, Y = α-OOH
25 X = OH, Y = α-OH



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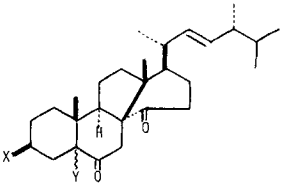
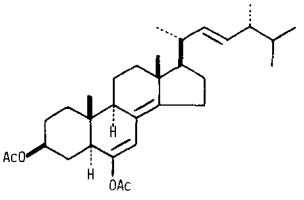


20 X = OAc, Y = β-H
24 X = OH, Y = α-H
26 X = OAc, Y = α-H



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[5]) This favourable condition is an O···H distance smaller than the sum of the *van der Waals* radii of these two atoms with the H–C(3) bond in the plane of C(6) = O. For a closely related example, see [16a].

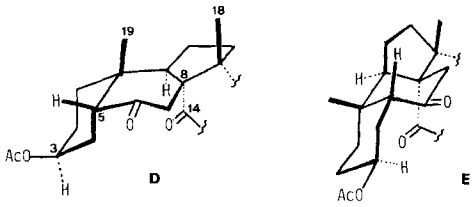
^{13}C-NMR spectra [19] enabled unambiguous assignments to be made and suggested structures **18** and **19** (36 and 14% yield, resp.). The formation of all four isomers **13**, **14**, **18**, and **19** suggested that equilibrium may have occurred under the reaction conditions. The observed stereoisomerization at C(5) and C(14) was supported by experiments in which each of the pure isomers was treated to give the mixture **13/14/18/19**. Crystallization of the crude mixture from MeOH afforded the mixture **13/18**, but pure **13**, **14**, **18**, and **19** could be obtained by careful chromatography. Although the mixture **13/18** was stable in the solid state, it easily suffered aerial oxidation in solution.

Bubbling air through a solution of **13/18** in 0.01M $HClO_4$ in EtOAc for 6 h at r.t. gave rise to a stereoisomerically homogeneous hydroperoxy-enone. On the assumption that hydroperoxidation of the proper heteroannular enolic form of **13/18** would occur from the less hindered face, this product was formulated as **15**.

The ^{1}H-NMR spectrum ($CDCl_3$) of **15** showed 2 diagnostic *s* (3 H) at 0.74 and 0.98 ppm due to Me(18) and Me(19), respectively, and the olefinic H–C(7) resonating at 5.8 ppm which displayed allylic coupling to H_α–C(9). Also, as expected, the molecular formula of **15** ($C_{30}H_{46}O_5$) established by FAB-MS (*m/z* 487 for $(M + H)^+$) differed by 2 O-atoms from that of **13** and **18**.

When **15** was exposed to acidic $FeSO_4$ solution, we found that it reacted nearly as well as **8** to give ketone **20** and 14α-hydroxyenone **21** in a 9:1 ratio. The latter was shown to be identical with that obtained by either deoxygenation (Me_2S, CH_2Cl_2, r.t.) of **15** or allylic oxidation (SeO_2, dioxane, 70°) of enone **13**.

The EI-MS of the major compound **20** exhibited a molecular ion at *m/z* 470 ($C_{30}H_{46}O_4$) whilst the IR spectrum ($CHCl_3$) showed key absorptions at 1740 (C=O, ester) and 1710 (saturated cyclohexanone). The ^{1}H-NMR spectrum ($CDCl_3$, 300 MHz) of **20** displayed Me signals at 0.73 and 1.13 ppm as *s*, and at 0.77, 0.80, 0.86, and 1.11 as *d* (J = 7.0), which could be assigned to Me(18), Me(19), and to Me(26), Me(27), Me(28), and Me(21), respectively.



Furthermore, as previously reported for **4** and **12**, an examination of *Dreiding* models of **20** revealed that a 'steroid' *cis*-fused A–B conformation **D** (*i.e.*, H_α–C(3) equatorially oriented) suffers a severe non-bonding interaction between angular Me groups. The alternative conformation **E** in which H_α–C(3) is axial, would be, therefore, the preferred conformation for **20**. This assumption was supported by the ^{1}H-NMR data, the H_α–C(3) at 4.78 ppm exhibiting typical *trans*-diaxial and axial-equatorial couplings (J = 12.0 and 5.7, resp.) to the 2 H–C(2) and 2 H–C(4).

Disappointingly, any attempts to verify the structure of **20** by single-crystal X-ray analysis were precluded due to twinning of the thin crystals obtained.

With the 5α-anones **14/19**, recovered from the above mother liquors it was decided to produce the 14α-hydroperoxide **16** and to investigate its Fe(II)-induced rearrangement in order to gain an insight into the detailed geometry of the target ketone. Initial attempts to convert **14/19** into **16** were complicated by the formation of by-products, but the preparation was subsequently accomplished when the 5α-dienol acetate **22** prepared according to [20] from **14/19** was used as starting material. Thus, autooxidation of **22** in MeOH/H_2O

10:1 in the presence of K_2CO_3 for 3 h at r.t. furnished, with concomitant hydrolysis, the crystalline hydroperoxide **23** in 67% yield. The configuration at C(14) was assigned by comparison of the ^{1}H-NMR data of **23** with the ones of **15**. The most striking difference was the value of the chemical shift of Me(19) (0.82 in **23** *vs.* 0.98 ppm in **15**) while the remaining Me signals and H–C(7) of **23**, occurred at nearly the same positions as the corresponding signals in **15**.

Not surprisingly, the reaction of **23** with $FeSO_4$, run as previously described for **8** and **15**, produced an easily separated mixture of the expected ketone **24** (79%) and 14α-hydroxy-enone **25** (12%) as diastereoisomerically homogeneous compounds. The latter compound was identical with an authentic sample prepared by deoxygenation (KI, AcOH, r.t.) of **23**. The structure of **24** was assigned from its spectroscopic properties.

In particular, the IR of **24** revealed a new band at 1710 cm^{-1} and the EI-MS a molecular ion at *m/z* 428. The ^{1}H-NMR (300 MHz, $CDCl_3$) showed the presence of 4 *d* (each J = 7.0 and 3 H) at 0.79 and 0.81 (Me(26)/Me(27)), 0.89 (Me(28)), and 1.05 ppm (Me(21)), a *dd* (J = 12.0, 3.8) at 2.06 ppm (H_{ax}–C(5)), and an *AB* system (J = 17.8) at 2.29 and 2.47 ppm (2 H–C(7)). We presumed that **24** has the same configuration as ketone **20** except at C(5). This was sustained by the ^{1}H-NMR data of **24** indicating an axial orientation of H_α–C(3) (3.57 ppm, *tt*, J = 11.0, 4.4; *cf.* above).

The chemical behaviour of **24** under basic conditions mirrored that of **4** affording in good yield the 14α-hydroxy-enone **25**. Finally, the structure and configuration of **24** was unambiguously established by a single-crystal X-ray analysis of its 3-acetate **26** (see below), matching the assignments proposed herein for C(8) (*R*) and C(13) (*R*) of **4** and **20**.

The configuration of **4**, **20**, and **24** requires that the overall reaction is a stereospecific process proceeding with retention of configuration at the stationary terminus C(13) of the migrating bond and complete π-face selectivity (due to the conformational constraint) in the subsequent transannular radical addition. The fact that only one ketone was isolated after the Fe(II)-induced rearrangement of the corresponding hydroperoxide, in compliance with the failure to intercept a C-radical at C(13) by addition of Cu(II) salts [21] and the lack of long-range functionalization products [22] suggest that a concerted mechanism is operative.

X-Ray Data of 26. – The results of the X-ray studies on **26** are illustrated in *Figs. 2* and *3* which show the thermal-ellipsoid plot, drawn by means of the ORTEP program [23], of the tetracyclic portion and side chain, respectively. The heavier atom coordinates are reported in *Table 1*. Selected bond lengths, bond angles, and selected torsion angles are given in *Tables 2*, *3*, and *4*, respectively.

Crystal data for **26** confirm the unprecedented 13(14→8)-*abeo* backbone, in which rings B, C, and D share the centre C(8) and rings C and D become a five- and six-membered ring, respectively. The junction of rings A and B is *trans* as expected, the C(19)–C(10)–C(5)–H torsion angle being −175°. The configuration at C(13) is maintained intact on migration of the bond C(13)–C(14) from C(14) to C(8), and this process confers to the newly formed chiral centre C(8) the (*R*) configuration. As a consequence, the groups Me(18) and Me(19) could be considered as synclinal [24], with a torsion angle C(19)–C(10)–C(13)–C(18) of 58.8°. The side chain is affected by disorder, the C(25)-to-C(28) moiety being distributed over two different orientations.

Referring to the treatment of *Duax et al.* [25], the asymmetry parameters and the corresponding ring conformations are summarized as shown in *Table 5*.

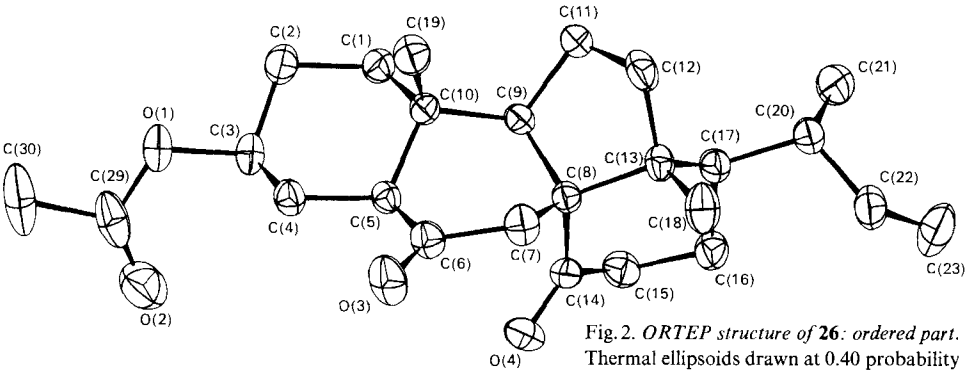


Fig. 2. *ORTEP structure of* **26***: ordered part.* Thermal ellipsoids drawn at 0.40 probability level, with the atom-numbering scheme.

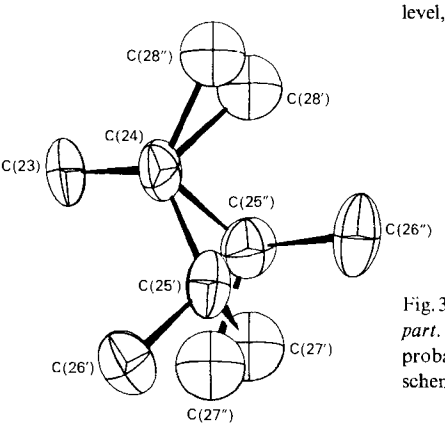


Fig. 3. *ORTEP structure of* **26***: disordered part.* Thermal ellipsoids drawn at 0.30 probability level, with the atom-numbering scheme.

Table 1. *Heavy-Atom Coordinates ($\times 10^4$) and their Standard Deviations*

	x	*y*	*z*		*x*	*y*	*z*
C(1)	9033(4)	2392(3)	5783(2)	C(20)	10252(4)	2645(4)	1849(2)
C(2)	8450(5)	2105(4)	6591(2)	C(21)	11600(5)	3688(6)	1930(2)
C(3)	6423(5)	2056(3)	6502(2)	C(22)	9154(5)	2598(4)	1031(2)
C(4)	5640(4)	1130(3)	5901(2)	C(23)	9202(7)	3361(6)	452(2)
C(5)	6260(4)	1384(3)	5101(2)	C(24)	8102(6)	3269(4)	–364(2)
C(6)	5526(4)	467(3)	4487(2)	C(25')	6496(6)	4194(5)	–522(4)
C(7)	6390(4)	446(3)	3734(2)	C(26')	5000(8)	4030(9)	28(5)
C(8)	7389(3)	1614(3)	3579(2)	C(27')	7162(9)	5547(6)	–410(7)
C(9)	8753(3)	1991(3)	4328(2)	C(28')	9372(8)	3301(9)	–1021(4)
C(10)	8326(3)	1474(3)	5133(2)	C(25'')	7873(8)	4619(5)	–661(4)
C(11)	10654(4)	1698(4)	4121(2)	C(26'')	7061(9)	4610(9)	–1556(4)
C(12)	10341(5)	939(4)	3366(2)	C(27'')	6309(9)	5163(9)	–247(6)
C(13)	8629(4)	1442(3)	2897(2)	C(28'')	9329(9)	2662(9)	–928(5)
C(14)	5972(3)	2601(3)	3381(2)	C(29)	4273(6)	2066(4)	7419(3)
C(15)	6535(4)	3780(3)	3040(2)	C(30)	4059(8)	1652(6)	8257(3)
C(16)	7430(4)	3485(3)	2313(2)	O(1)	5949(3)	1743(3)	7286(1)
C(17)	9080(4)	2692(3)	2540(2)	O(2)	3169(4)	2569(4)	6950(2)
C(18)	7842(6)	566(4)	2261(2)	O(3)	4358(4)	–252(3)	4593(2)
C(19)	9170(5)	209(4)	5327(2)	O(4)	4439(3)	2447(3)	3480(2)

Table 2. *Bond Lengths* (Å)[a]. E.s.d. in parentheses.

C(1)–C(2)	1.537(5)	C(9)–C(11)	1.550(4)	C(17)–C(20)	1.565(4)
C(2)–C(3)	1.510(5)	C(11)–C(12)	1.528(5)	C(20)–C(21)	1.522(7)
C(3)–C(4)	1.507(5)	C(12)–C(13)	1.523(4)	C(20)–C(22)	1.525(5)
C(4)–C(5)	1.528(4)	C(8)–C(13)	1.596(4)	C(22)–C(23)	1.301(6)
C(5)–C(6)	1.503(4)	C(8)–C(14)	1.525(4)	C(23)–C(24)	1.524(6)
C(6)–C(7)	1.518(5)	C(14)–C(15)	1.504(5)	C(3)–O(1)	1.472(4)
C(7)–C(8)	1.527(5)	C(15)–C(16)	1.525(5)	O(1)–C(29)	1.357(5)
C(8)–C(9)	1.583(4)	C(16)–C(17)	1.521(4)	C(29)–C(30)	1.531(7)
C(9)–C(10)	1.560(4)	C(13)–C(17)	1.558(5)	C(29)–O(2)	1.206(6)
C(1)–C(10)	1.541(4)	C(13)–C(18)	1.511(5)	C(6)–O(3)	1.212(4)
C(5)–C(10)	1.548(4)	C(10)–C(19)	1.544(5)	C(14)–O(4)	1.198(3)

[a]) Bond distances involving disordered atoms range between 1.568 and 1.572 Å (average e.s.d. 0.009 Å).

Table 3. *Bond Angles* (°). E.s.d. in parentheses.

C(1)–C(2)–C(3)	108.8(3)	C(15)–C(16)–C(17)	110.4(2)
C(2)–C(3)–C(4)	112.8(3)	C(16)–C(17)–C(13)	113.0(2)
C(3)–C(4)–C(5)	110.4(3)	C(17)–C(13)–C(8)	111.2(2)
C(4)–C(5)–C(6)	112.0(3)	C(17)–C(13)–C(12)	108.2(2)
C(5)–C(6)–C(7)	116.3(3)	C(18)–C(13)–C(8)	113.0(3)
C(6)–C(7)–C(8)	114.2(3)	C(18)–C(13)–C(12)	111.5(3)
C(7)–C(8)–C(9)	111.0(2)	C(18)–C(13)–C(17)	111.3(2)
C(8)–C(9)–C(10)	115.5(2)	O(4)–C(14)–C(8)	121.6(3)
C(9)–C(10)–C(1)	107.8(2)	O(4)–C(14)–C(15)	120.2(3)
C(10)–C(1)–C(2)	113.7(3)	C(13)–C(17)–C(20)	116.2(3)
C(4)–C(5)–C(10)	113.9(2)	C(16)–C(17)–C(20)	110.4(3)
C(6)–C(5)–C(10)	109.8(2)	C(17)–C(20)–C(21)	110.0(3)
C(1)–C(10)–C(5)	108.2(2)	C(17)–C(20)–C(22)	113.7(3)
C(9)–C(10)–C(5)	108.5(2)	C(21)–C(20)–C(22)	112.3(3)
C(19)–C(10)–C(1)	110.0(2)	C(20)–C(22)–C(23)	127.5(4)
C(19)–C(10)–C(5)	109.3(3)	C(22)–C(23)–C(24)	125.9(5)
C(19)–C(10)–C(9)	112.9(3)	C(23)–C(24)–C(25′)	115.0(4)
O(1)–C(3)–C(2)	106.3(2)	C(24)–C(25′)–C(26′)	114.7(5)
O(1)–C(3)–C(4)	110.0(3)	C(24)–C(25′)–C(27′)	111.4(4)
O(3)–C(6)–C(5)	122.5(3)	C(26′)–C(25′)–C(27′)	106.1(6)
O(3)–C(6)–C(7)	121.2(3)	C(23)–C(24)–C(28′)	110.3(4)
C(8)–C(9)–C(11)	106.0(2)	C(25′)–C(24)–C(28′)	112.9(5)
C(10)–C(9)–C(11)	115.5(2)	C(23)–C(24)–C(25″)	104.8(4)
C(9)–C(11)–C(12)	105.4(2)	C(24)–C(25″)–C(26″)	108.7(5)
C(11)–C(12)–C(13)	105.5(3)	C(24)–C(25″)–C(27″)	105.6(5)
C(12)–C(13)–C(8)	101.2(2)	C(26″)–C(25″)–C(27″)	103.1(6)
C(13)–C(8)–C(9)	104.1(2)	C(23)–C(24)–C(28″)	107.4(4)
C(7)–C(8)–C(13)	112.1(2)	C(25″)–C(24)–C(28″)	104.5(5)
C(7)–C(8)–C(14)	106.9(2)	C(3)–O(1)–C(29)	115.8(3)
C(13)–C(8)–C(14)	112.4(2)	O(1)–C(29)–C(30)	107.2(4)
C(9)–C(8)–C(14)	110.4(2)	O(1)–C(29)–O(2)	125.3(4)
C(8)–C(14)–C(15)	118.2(2)	C(30)–C(29)–O(2)	127.4(5)
C(14)–C(15)–C(16)	108.1(3)		

Table 4. *Selected Torsion Angles* (°). E.s.d. in parentheses.

C(1)–C(2)–C(3)–C(4)	57.7(4)	C(8)–C(9)–C(11)–C(12)	–11.5(3)
C(2)–C(3)–C(4)–C(5)	–56.6(4)	C(9)–C(11)–C(12)–C(13)	34.7(4)
C(3)–C(4)–C(5)–C(10)	53.9(4)	C(11)–C(12)–C(13)–C(8)	–42.8(3)
C(4)–C(5)–C(10)–C(1)	–51.9(3)	C(12)–C(13)–C(8)–C(9)	34.4(3)
C(5)–C(10)–C(1)–C(2)	53.9(4)	C(13)–C(8)–C(9)–C(11)	–14.2(4)
C(10)–C(1)–C(2)–C(3)	–57.2(4)	C(8)–C(14)–C(15)–C(16)	54.2(4)
C(5)–C(6)–C(7)–C(8)	–20.4(4)	C(14)–C(15)–C(16)–C(17)	–60.6(4)
C(6)–C(7)–C(8)–C(9)	51.2(4)	C(15)–C(16)–C(17)–C(13)	61.5(4)
C(7)–C(8)–C(9)–C(10)	–22.8(4)	C(16)–C(17)–C(13)–C(8)	–49.4(4)
C(8)–C(9)–C(10)–C(5)	–33.2(3)	C(17)–C(13)–C(8)–C(14)	39.2(4)
C(9)–C(10)–C(5)–C(6)	65.0(3)	C(13)–C(8)–C(14)–C(15)	–44.3(4)
C(10)–C(5)–C(6)–C(7)	–38.5(4)		

Table 5. *Asymmetry Parameters and Ring Conformations for* **26** *According to* [25]

Ring	Ref. atom(s)	Parameter	Deg.	Conformation
A	C(2)	ΔC_s	2.0	chair
B	C(5)–C(10)	ΔC_2	4.1	distorted half chair
C	C(9)	ΔC_2	1.9	half chair
D	C(8)	ΔC_s	4.1	distorted chair

The average of absolute values of torsion angles for ring A (55.2°) compares well with the results obtained in two independent gas-electron-diffraction studies of cyclohexane, 54.6 ± 0.5° and 55.2 ± 0.5° [26]. The internal strain of the molecule around C(8) is noticed by some very long bond lengths, particularly C(8)–C(9) (1.583 Å) and C(8)–C(13) (1.596 Å). The abnormal length of the C(8)–C(13) bond accounts for its facile breaking in **24** to afford the 14α-hydroxy-enone **25** *via* a *retro-Michael*/aldol reaction under base conditions. Another pair of long bond lengths is noteworthy, C(13)–C(17) (1.558 Å) and C(17)–C(20) (1.565 Å). These lengths, however, can offer some relief to the very short 1,5 intramolecular distance C(18)···C(22) (3.305 Å). Two of the shortest C–C bond length are C(2)–C(3) (1.510 Å) and C(3)–C(4) (1.507 Å), as a normal feature for steroids bearing an ester or OH group at C(3) [27].

The bond C(22)=C(23) appears to be very short (1.301 Å); however, this distance changes to 1.327 Å when corrected for riding motion [28]. Correspondingly, on correction, the adjacent bond lengths C(20)–C(22) and C(23)–C(24) are increased by only 0.002 and 0.007 Å, respectively. In the disordered side chain *(Fig. 3)*, the rather long values found for the bond lengths (see refinement) actually refer to CH_3–C lengths. Within each of the two orientations of the chain, the bond angles (which were in no way tied during the refinement) show substantially normal values ranging from 103 to 115°.

Table 6. *Intermolecular Contacts in the Crystal of* **26**

Atom in *x, y, z*	To atom	In position	Distance (Å)
C(4)	C(15)	$1-x, -1/2+y, 1-z$	3.66
C(15)	C(29)	$1-x, 1/2+y, 1-z$	3.72
C(16)	C(30)	$1-x, 1/2+y, 1-z$	3.74
C(25′)	C(30)	$x, y, -1+z$	3.80
C(26″)	C(29)	$x, y, -1+z$	3.78

Most intermolecular distances are in the normal range. There are, however, some contacts shorter by 0.2 Å or more than the sum of involved *van der Waals* radii (CH_2 and CH_3 2.0, O 1.4, H 1.2 Å) [29] (see *Table 6*).

Geometrical calculations were mostly performed using the program PARST [30]. A preliminary account of structural results has been given [31].

Conclusions. – Although the fragmentation of hydroperoxides has been extensively investigated from a mechanistic standpoint, the only significant synthetic applications reported in [32] involve Fe(II)/Cu(II)-induced reaction of α-alkoxy hydroperoxides. We have developed a new and potentially useful approach to 13(14→8)-*abeo*-steroids not readily accessible by conventional methods, based on a tandem fragmentation/reductive alkylation of 14-hydroperoxy-7-en-6-ones. This procedure has allowed the successful application to other γ-hydroperoxy-enones, and results of these studies will be reported in due course.

Experimental Part

1. *General.* TLC and prep. TLC: plates from *Merck;* eluent *A* = $CHCl_3$/MeOH/H_2O 75:24:1, *B* = CH_2Cl_2/MeOH 81:19, *C* = hexane/AcOEt 2:1; detection by fluorescence quenching (254 or 360 nm) or by spraying with vanillin/H_2SO_4 in EtOH and heating. Flash chromatography (FC) [33]: silica gel *60* (0.040–0.063 mm). M.p.: uncorrected; *Büchi* apparatus. $[\alpha]_D$: *Perkin-Elmer,* model *241.* UV/VIS spectra (λ_{max} (log ε)): *Perkin-Elmer.* IR spectra: *Perkin-Elmer 681.* ^{1}H-NMR spectra: *Bruker WP-80* (80 MHz), *Varian XL-200* (200 MHz), *Bruker CPX-300* (300 MHz); 600-MHz spectra and related NOEDS experiments were recorded at Carnegie-Mellon University, Pittsburg, on the NMR spectrometer assembled there; TMS as internal reference (= 0 ppm); coupling constants (*J*) in Hz. ^{13}C-NMR spectra (25.2 MHz): *Varian XL-100*; TMS as internal reference (= 0 ppm); multiplicities from off-resonance decoupled spectrum. HR-MS, EI-MS, and FAB-MS (positive-ion mode): *VG 70-7OEO-HF.*

2. *Irradiation of (20*R,*22*R*)-2β,3β,14,20,22,25-Hexahydroxy-5β-cholest-7-en-6-one* (**1**) *in H_2O.* A soln. of **1** (960 mg, 2.0 mmol) in H_2O (2000 ml) was irradiated in an immersion apparatus with *Pyrex*-filtered light (λ > 290 nm) from a *HPK* 125-W medium-pressure Hg lamp. Ar was bubbled through the soln. 0.5 h prior to irradiation as well as during the reaction. After 12 h (TLC (*A*): traces of **1**, 4 photoproducts), the solvent was evaporated and the residue flash-chromatographed (5 × 100 cm silica-gel column, eluent *B*) giving successively **2**–**5**.

*(20*R,*22*R*)-2β,3β,20,22,25-Pentahydroxy-5β-cholest-7-en-6-one* (**2**): 139 mg (15%) of colourless foam. R_f (*A*) 0.43. UV (MeOH): 247 (4.13). IR (KBr): 3425 (OH), 1665 (C=O). ^{1}H-NMR (200 MHz, (D_5)pyridine): 0.97 (*s*, CH_3(18), CH_3(19)); 1.48, 1.51 (2*s*, CH_3(26), CH_3(27)); 1.56 (*s*, CH_3(21)); 2.88 (*ddd*, *J* = 11.0, 5.2, 2.5, H–C(9)); 3.88 (*dd*, *J* = 10.0, 2.2, H–C(22)); 4.29 (br. *dt*, *J* = 11.0, 3.5, H–C(2)); 4.47 (br. *m*, $w_{1/2}$ = 7, H–C(3)); 5.86 (*t*, *J* = 2.5, H–C(7)). ^{13}C-NMR ((D_5)pyridine): 37.2 (C(1)); 67.4 (C(2)); 67.4 (C(3)); 32.1 (C(4)); 50.5 (C(5)); 202.0 (C(6)); 121.2 (C(7)); 163.8 (C(8)); 35.2 (C(9)); 37.6 (C(10)); 21.6 (C(11)); 39.2 (C(12)); 43.4 (C(13)); 57.1 (C(14)); 20.6 (C(15)); 32.5 (C(16)); 55.2 (C(17)); 13.7 (C(18)); 23.9 (C(19)); 76.0 (C(20)); 20.6 (C(21)); 76.8 (C(22)); 26.6 (C(23)); 41.7 (C(24)); 68.8 (C(25)); 29.2 (C(26)); 29.2 (C(27)). FAB-MS: 465 ($(M + H)^+$).

*(20*R,*22*R*)-2β,3β,20,22,25-Pentahydroxy-5β-cholest-8(14)-en-6-one* (**3**): 325 mg (35%) of colourless needles. M.p. 174° (dec., H_2O). R_f (*A*) 0.40. IR ($CHCl_3$): 1695 (C=O). ^{1}H-NMR (200 MHz, (D_5)pyridine): 0.80 (*s*, CH_3(19)); 0.93 (*s*, CH_3(18)); 1.34, 1.36 (2*s*, CH_3(26), CH_3(27)); 1.39 (*s*, CH_3(21)); 2.60 (br. *d*, *J* = 14.0, H_α–C(7)); 3.01 (br. *d*, *J* = 14.0, H_β–C(7)); 3.86 (br. *t*, *J* = 4.7, H–C(22)); 4.17 (br. *dt*, *J* = 11.0, 3.5, H–C(2)); 4.59 (*m*, $w_{1/2}$ = 7, H–C(3)). ^{13}C-NMR ((D_6)DMSO): *inter alia* 66.8 (C(2)); 66.5 (C(3)); 202.4 (C(6)); 122.8 (C(8)); 150.6 (C(14)); 18.6 (C(18)); 24.5 (C(19)); 75.4 (C(20)); 21.3 (C(21)); 75.4 (C(22)); 26.0 (C(23)); 40.7 (C(24)); 68.7 (C(25)); 28.9, 29.6 (C(26), C(27)); 3 *d* at 54.1, 56.2, 56.9; 7 *t* at 19.7, 21.5, 25.4, 31.6, 32.6, 35.7, 36.8. FAB-MS: 465 ($(M + H)^+$).

*(8*R,*20*R,*22*R*)-2β,3β,20,22,25-Pentahydroxy-8,13-*cyclo-*13,14-*seco-*5β-cholestane-6,14-dione* (**4**): 221 mg (23%) of amorphous glass. R_f (*A*) 0.39. IR (KBr): 3440 (OH), 1715 (C=O). ^{1}H-NMR (200 MHz, (D_5)pyridine): 1.18 (*s*, CH_3(19)); 1.44 (*s*, CH_3(26), CH_3(27)); 1.54 (*s*, CH_3(21), CH_3(18)); 3.17 (*d*, *J* = 16.0, *AB* of *ABX*, H–C(7));

4.06 (br. *d*, *J* = 9.0, H–C(22)); 4.17 (*ddd*, each *J* ≈ 3.5, H–C(2)); 4.26 (br. *dt*, *J* = 10.0, 3.5, H–C(3)). ^{13}C-NMR ((D$_5$)pyridine): *inter alia* 69.5 (C(2)); 67.5 (C(3)); 50.1 (C(5)); 210.3 (C(6)); 65.4 (C(8)); 46.6 (C(9)); 39.0 (C(10)); 57.9 (C(13)); 215.5 (C(14)); 49.8 (C(17)); 17.6 (C(18)); 27.8 (C(19)); 77.2 (C(20)); 22.1 (C(21)); 76.2 (C(22)); 42.1 (C(24)); 69.5 (C(25)); 30.2 (C(26)); 29.9 (C(27)); 8 *t* at 39.1, 28.0, 41.1, 36.0, 40.2, 25.9, 25.9, 26.9. FAB-MS: 481 ((*M* + H)$^+$).

*(20*R,*22*R*)-2β,3β,6β,20,22,25-Hexahydroxy-3,6:8,13-bis(*cyclo*)-13,14-*seco*-5β-cholestan-14-one* (**5**): 176 mg (18%) of amorphous glass. R_f (*A*) 0.33. IR (KBr): 3420 (OH), 1698 (C=O). ^{1}H-NMR (600 MHz, (D$_5$)pyridine): 1.010 (*s*, CH$_3$(19)); 1.330, 1.340 (2 br. *s*, CH$_3$(26), CH$_3$(27)); 1.350 (*s*, CH$_3$(18)); 1.480 (br. *s*, CH$_3$(21)); *ca.* 1.7 (*m*, H$_\alpha$–C(11)); 1.869 (br. *dd*, *J* = 15.1, 6.3, H$_\alpha$–C(1)); 1.896 (*d*, *J* = 15.6, H$_\beta$–C(7)); *ca.* 1.9 (*m*, H$_\alpha$–C(12)); *ca.* 2.0 (*m*, H$_\beta$–C(11)); 2.108 (*dd*, *J* = 15.1, 8.4, H$_\alpha$–C(1)); *ca.* 2.15 (*m*, H$_\beta$–C(12)); 2.186 (*d*, *J* = 7.0, H–C(5)); *ca.* 2.29 (*m*, H$_\beta$–C(16)); *ca.* 2.3 (*m*, H–C(17)); 2.411 (*d*, *J* = 9.1, H$_\beta$–C(4)); *ca.* 2.42 (*m*, H$_\alpha$–C(16)); *ca.* 2.47 (*m*, H$_\beta$–C(15)); 2.603 (*ddd*, *J* = 9.1, 7.0, 1.8, H$_\alpha$–C(4)); 2.916 (*d*, *J* = 15.6, H$_\alpha$–C(7)); 3.099 (*t*, *J* = 9.4, H–C(9)); 4.502 (*ddd*, *J* = 9.1, 7.0, 1.8, H–C(2)). ^{13}C-NMR ((D$_5$)pyridine): 38.2 (C(1)); 69.9 (C(2)); 79.3 (C(3)); 29.6 (C(4)); 47.3 (C(5)); 78.8 (C(6)); 42.9 (C(7)); 63.6 (C(8)); 39.2 (C(9)); 36.3 (C(10)); 29.0 (C(11)); 37.9 (C(12)); 58.7 (C(13)); 214.0 (C(14)); 25.8 (C(15)); 26.3 (C(16)); 49.9 (C(17)); 16.8 (C(18)); 27.6 (C(19)); 76.9 (C(20)); 21.7 (C(21)); 75.8 (C(22)); 27.6 (C(23)); 41.9 (C(24)); 69.2 (C(25)); 29.6 (C(26)); 29.9 (C(27)). FAB-MS: 481 ((*M* + H)$^+$).

3. *(20*R,*22*R*)-6-Ethoxy-5β-cholesta-6,8(14)-diene-2β,3β,20,22,25-pentol* (**9**). A soln. of **3** (250 mg, 0.54 mmol) in dry EtOH (100 ml) containing 60% aq. HBF$_4$ soln. (1 ml) was refluxed under N$_2$ using a *Dean-Stark* trap (filled with 3 Å molecular sieves) for 3.5 h (TLC (A): complete conversion into a less polar compound of R_f 0.50). The solvent was evaporated, the residue partitioned between CHCl$_3$ and 5% NaHCO$_3$ soln., and the combined org. extract washed with brine, dried, and evaporated to give crude **9** as an amorphous foam (95%). A small portion of the sample was purified by prep. TLC (*A*) to give an anal. sample as a colourless glass. UV (MeOH): 251 (4.09). IR (nujol): 1650, 1625 (C=C). ^{1}H-NMR (100 MHz, (D$_5$)pyridine): 0.90 (*s*, CH$_3$(19)); 1.21 (*t*, *J* = 7.0, C*H*$_3$CH$_2$O); 1.35 (br. *s*, CH$_3$(18), CH$_3$(26), CH$_3$(27)); 1.46 (*s*, CH$_3$(21)); 3.74 (*q*, *J* = 7.0, CH$_3$C*H*$_2$O); 3.81 (br. *d*, *J* = 10.0, H–C(22)); 4.02 (br. *d*, *J* = 11.0, H–C(2)); 4.30 (*m*, $w_{1/2}$ = 7, H–C(3)); 5.28 (*s*, H–C(7)). ^{13}C-NMR ((D$_5$)pyridine): 38.5 (C(1)); 69.5 (C(2)); 76.9 (C(3)); 35.3 (C(4)); 42.2 (C(5)); 159.1 (C(6)); 95.5 (C(7)); 141.1 (C(8)); 35.8 (C(9)); 37.4 (C(10)); 22.7 (C(11)); 37.6 (C(12)); 44.6 (C(13)); 123.6 (C(14)); 25.1 (C(15)); 20.3 (C(16)); 50.6 (C(17)); 21.3 (C(18)); 23.5 (C(19)); 76.5 (C(20)); 21.7 (C(21)); 77.2 (C(22)); 27.2 (C(23)); 42.4 (C(24)); 69.5 (C(25)); 29.8 (C(26)); 30.3 (C(27)); 62.3 (CH$_3$*C*H$_2$O); 14.7 (*C*H$_3$CH$_2$O). FAB-MS: 493 ((*M* + H)$^+$).

4. *Acid-Catalyzed Autooxidation of* **9** *to* **8**. Enol ether **9** (210 mg, 0.42 mmol) in MeOH (50 ml) and 0.61M aq. oxalic acid soln. (1 ml) was placed in an air-filled flask (100 ml) and set aside at r.t. in the dark for 6 h. The solvent was evaporated, the residue partioned between CHCl$_3$ and 5% NaHCO$_3$ soln., the aq. layer extracted twice with CHCl$_3$, and the combined extract evaporated. Separation of the residue by FC (*B*) gave **8** (120 mg, 57%) and **1** (19 mg, 9%).

*(20*R,*22*R*)-14-Hydroperoxy-2β,3β,20,22,25-pentahydroxy-5β-cholest-7-en-6-one* (**8**): M.p. 158° (dec., AcOEt. R_f (*A*) 0.37 (purple spot with *N*,*N*-dimethyl-*p*-phenylendiammonium hydrochloride spray [34]). UV (MeOH): 243. IR (CHCl$_3$): 1667 (C=O). ^{1}H-NMR (80 MHz, (D$_5$)pyridine): 1.07 (*s*, CH$_3$(19)); 1.21 (*s*, CH$_3$(18)); 1.36 (2*s*, CH$_3$(26), CH$_3$(27)); 1.47 (*s*, CH$_3$(21)); 4.16 (*m*, $w_{1/2}$ = 18, H–C(2)); 4.22 (*m*, $w_{1/2}$ = 8, H–C(3)); 6.25 (*d*, *J* = 2.5, H–C(7)). ^{13}C-NMR ((D$_5$)pyridine): *inter alia* 66.7 (C(2)); 66.7 (C(3)); 49.4 (C(5)); 202.0 (C(6)); 124.4 (C(7)); 161.1 (C(8)); 94.8 (C(14)); 48.4 (C(17)); 76.6 (C(20)); 76.9 (C(21)); 68.8 (C(25)). FAB-MS: 497 ((*M* + H)$^+$).

5. *(20*R,*22*R*)-14-Hydroperoxy-25-hydroxy-2β,3β:20,22-bis[(1-methylethylidene)dioxy]-5β-cholest-7-en-6-one* (**10**) *from* **6**. To a soln. of **6** (500 mg, 0.89 mmol) [4] in anh. THF (5 ml) and anh. NH$_3$ (40 ml) was added Li in wires under mechanical stirring (15 g, 2.14 mol). After 15 min stirring, the dry ice/acetone-filled condenser was replaced by a water-jacketed condenser and the NH$_3$ evaporated within 1 h using a steam bath. The mixture was poured into sat. aq. NH$_4$Cl soln., extracted with Et$_2$O, and worked up as usual, and the colourless residue (550 mg) purified by FC (EtOAc): **10** (420 mg, 82%) as an amorphous solid. R_f (AcOEt): 0.40. UV (MeOH): 242. IR (CHCl$_3$): 1670 (C=O). ^{1}H-NMR (80 MHz, CDCl$_3$): 0.84 (*s*, CH$_3$(18)); 1.00 (*s*, CH$_3$(19)); 1.24 (3*s*, CH$_3$(21), CH$_3$(26), CH$_3$(27)); 1.34 (*s*, (CH$_3$)$_2$C); 1.42, 1.50 (2*s*, (CH$_3$)$_2$C); 2.78 (br. *t*, *J* = 7.2, H–C(9)); 3.67 (br. *d*, *J* = 6.8, H–C(22)); 4.12 (*m*, $w_{1/2}$ = 18, H–C(2)); 4.28 (*m*, $w_{1/2}$ = 8, H–C(3)); 5.82 (br. *d*, *J* = 2.5, H–C(7)). FAB-MS: 577 ((*M* + H)$^+$).

6. *Hydrolysis of* **10** *to* **8**. To a soln. of 100 ml of THF/0.5N HCl 2:1 under N$_2$ was added **10** (350 mg, 0.625 mmol) and stirred at r.t. for 6 h. The mixture was diluted with CHCl$_3$, washed with 5% NaHCO$_3$ soln. and brine. Drying and evaporation gave pure **8** (286 mg, 95%), identical in all spectroscopic properties with the sample prepared from **9**.

7. *Base-Induced Conversion of* **4** *into* **1**. A soln. of **4** (36 mg, 0.075 mmol) in MeOH (15 ml) was refluxed under Ar in the presence of 2M NaOH (1.25 ml) until the reaction was completed (2.5 h). The mixture was partitioned

between EtOAc and 0.5N H_2SO_4. The dried org. layer was evaporated and the residue fractioned by prep. TLC (*A*) to afford **1** (32 mg, 89%).

8. *Acid-Catalyzed Hydrolysis of 3α,5α-* cyclo-*Ergosta-7,22-dien-6-one* (**17**) *and Acetylation to Isomeric Enones* **13**, **14**, **18**, *and* **19**. To a soln. of **17** [17] (2.5 g, 6.34 mmol) in AcOH (500 ml) was added dropwise 5N H_2SO_4 (125 ml), and the resulting mixture was heated at 65° for 15 min. The cooled soln. was then poured into H_2O (1 l), and 20% NaOH soln. (170 ml) was cautiously added and extracted with Et_2O. After evaporation, the crude residue was dissolved in dry pyridine (15 ml) and cooled at 0°. Ac_2O (1.2 ml) was added all at once and the mixture stirred at r.t. overnight. Usual workup gave a yellowish oil (2.77 g). TLC (*C*): 4 more polar compounds at R_f 0.31 (**19**), 0.27 (**14**), 0.23 (**18**), and 0.19 (**13**). The residue was repeatedly chromatographed (*C*) to give pure **13**, **14**, **18**, and **19**.

(22E)-6-Oxo-5α,14β-ergosta-7,22-dien-3β-yl Acetate (**19**): 1.038 g (36%) of colourless needles. M.p. 114–116° (i-Pr_2O). UV (MeOH): 246 (4.2). IR ($CHCl_3$): 1740 (ester), 1680 (unsat. C=O). ^{1}H-NMR (80 MHz, $CDCl_3$): 0.81 (*d*, *J* = 7.0, CH_3(27)); 0.83 (*s*, CH_3(19)); 0.84 (*d*, *J* = 7.0, CH_3(26)); 0.91 (*d*, *J* = 7.0, CH_3(28)); 0.93 (*d*, *J* = 7.1, CH_3(21)); 0.97 (*s*, CH_3(18)); 2.00 (*s*, OAc); 4.67 (*m*, $w_{1/2}$ = 18, H–C(3)); 5.25 (*m*, H–C(22), H–C(23)); 5.77 (br. *d*, *J* = 2.9, H–C(7)). ^{13}C-NMR ($CDCl_3$): 36.4 (C(1)); 26.7 (C(2)); 72.8 (C(3)); 26.3 (C(4)); 52.9 (C(5)); 198.6 (C(6)); 125.7 (C(7)); 164.6 (C(8)); 46.4 (C(9)); 38.6 (C(10)); 20.6 (C(11)); 35.4 (C(12)); 44.9 (C(13)); 54.5 (C(14)); 26.0 (C(15)); 33.1 (C(16)); 55.4 (C(17)); 22.0 (C(18)); 13.0 (C(19)); 38.0 (C(20)); 20.5 (C(21)); 134.0 (C(22)); 132.6 (C(23)); 43.2 (C(24)); 33.1 (C(25)); 20.1 (C(26)); 19.7 (C(27)); 17.6 (C(28)); 170.3 (C=O); 21.3 (CH_3CO). EI-MS: 454 ($M^{+\cdot}$).

(22E)-6-Oxo-5α-ergosta-7,22-dien-3β-yl Acetate (**14**): 760 mg (26%) of colourless needles. M.p. 182° (EtOH). UV (MeOH): 243 (4.21). IR ($CHCl_3$): 1740, 1680. ^{1}H-NMR (80 MHz, $CDCl_3$): 0.59 (*s*, CH_3(18)); 0.89 (*d*, *J* = 7.0, CH_3(28)); 1.00 (*d*, *J* = 7.2, CH_3(21)); 2.01 (*s*, OAc); 4.67 (*m*, $w_{1/2}$ = 18, H–C(3)); 5.18 (*m*, H–C(22), H–C(23)); 5.69 (*t*, *J* = 2.2, H–C(7)). EI-MS: 454 ($M^{+\cdot}$).

(22E)-6-Oxo-5β,14β-ergosta-7,22-dien-3β-yl Acetate (**18**): 418 mg (14%); after crystallization from AcOEt/pentane, colourless needles. M.p. 137°. UV (MeOH): 248 (4.2). IR ($CHCl_3$): 1740, 1680. ^{1}H-NMR (80 MHz, $CDCl_3$): 0.81 (*d*, *J* = 7.0, CH_3(27)); 0.83 (*d*, *J* = 7.0, CH_3(26)); 0.92 (*d*, *J* = 7.0, CH_3(28)); 0.93 (*s*, CH_3(19)); 0.94 (*d*, *J* = 7.1, CH_3(21)); 0.98 (*s*, CH_3(18)); 2.02 (*s*, OAc); 5.03 (br. *quint.*, *J* = 3.5, H–C(3)); 5.26 (*m*, H–C(22), H–C(23)); 5.73 (*d*, *J* = 2.3, H–C(7)). ^{13}C-NMR ($CDCl_3$): 29.0 (C(1)); 25.6 (C(2)); 67.7 (C(3)); 29.7 (C(4)); 51.2 (C(5)); 201.7 (C(6)); 124.1 (C(7)); 166.1 (C(8)); 34.5 (C(9)); 36.3 (C(10)); 21.3 (C(11)); 36.1 (C(12)); 45.9 (C(13)); 55.0 (C(14)); 25.7 (C(15)); 32.6 (C(16)); 55.6 (C(17)); 22.0 (C(18)); 24.0 (C(19)); 37.9 (C(20)); 20.3 (C(21)); 134.1 (C(22)); 132.5 (C(23)); 43.2 (C(24)); 33.1 (C(25)); 20.0 (C(26)); 19.1 (C(27)); 17.6 (C(28)); 170.1 (C=O); 21.3 (CH_3CO). EI-MS: 454 ($M^{+\cdot}$).

(22E)-6-Oxo-5β-ergosta-7,22-dien-3β-yl Acetate (**13**): 304 mg (10%) of colourless needles. M.p. 193° (EtOH). UV (MeOH): 246 (4.2). IR ($CHCl_3$): 1740, 1680. ^{1}H-NMR (80 MHz, $CDCl_3$): 0.59 (*s*, CH_3(18)); 0.80 (*d*, *J* = 7.0, CH_3(27)); 0.82 (*d*, *J* = 7.0, CH_3(26)); 0.88 (*d*, *J* = 7.0, CH_3(28)); 0.97 (*s*, CH_3(19)); 0.99 (*d*, *J* = 7.1, CH_3(21)); 2.02 (*s*, OAc); 5.03 (*quint.*, *J* = 3.2, H–C(3)); 5.18 (*m*, H–C(22), H–C(23)); 5.60 (br. *t*, *J* = 1.9, H–C(7)). EI-MS: 454 ($M^{+\cdot}$).

9. *Base-Catalyzed Autooxidation of (22E)-5α-Ergosta-6,8(14),22-trien-3β,6-diyl Diacetate* (**22**) *to* **23**. To **22** (1.25 g, 2.52 mmol; prepared according to [20]) and MeOH (100 ml) was added K_2CO_3 (3.12 g) in H_2O (10 ml). The flask was then filled with O_2 and allowed to stand at r.t. After 3 h, more K_2CO_3 (1.5 g) was added and stirring continued for 10 min. The mixture was then evaporated at < 35° and neutralized by addition of 5% H_3PO_4 soln. Extraction with Et_2O, evaporation, and FC (AcOEt/C_6H_6 7:3) of the crude residue yielded pure *(22E)-14α-hydroperoxy-3β-hydroxy-5α-ergosta-7,22-dien-6-one* (**23**; 319 mg, 67%). R_f (AcOEt/C_6H_6 7:3) 0.22 (pink spot with *N*,*N*-dimethyl-*p*-phenylendiammonium hydrochloride spray). M.p. 173–175° (dec.; i-Pr_2O). UV (MeOH): 241. IR ($CHCl_3$): 1665, 1630. ^{1}H-NMR (80 MHz, $CDCl_3$): 0.72 (*s*, CH_3(18)); 0.78 (*d*, *J* = 7.0, CH_3(26)); 0.80 (*d*, *J* = 7.0, CH_3(27)); 0.82 (*s*, CH_3(19)); 0.91 (*d*, *J* = 7.0, CH_3(28)); 0.95 (*d*, *J* = 7.2, CH_3(21)); 2.58 (br. *t*, *J* = 8.0, H–C(9)); 3.58 (*m*, $w_{1/2}$ = 18, H–C(3)); 5.20 (*m*, H–C(22), H–C(23)); 5.84 (br. *d*, *J* = 2.2, H–C(7)). FAB-MS: 445 ($(M + H)^+$).

10. *Acid-Catalyzed Autooxidation of* **13**/**18** *to* **15**. Through a soln. of **13**/**18** (260 mg, 0.57 mmol) in 0.01M $HClO_4$ in EtOAc (30 ml) at r.t., air was bubbled. TLC monitoring (C_6H_6/EtOAc 7:3) showed the formation of a major slower-moving spot (R_f 0.43). After 8 h, the soln. was diluted with further EtOAc and washed with 5% $NaHCO_3$ soln. Usual workup gave an oily residue which was subjected to FC (C_6H_6/EtOAc 7:3): 180 mg (71%) of pure *(22E)-14α-hydroperoxy-6-oxo-5β-ergosta-7,22-dien-3β-yl acetate* (**15**). M.p. 151° (i-Pr_2O). UV (MeOH): 241. IR ($CHCl_3$): 1740, 1665. ^{1}H-NMR (80 MHz, $CDCl_3$): 0.74 (*s*, CH_3(18)); 0.80 (*d*, *J* = 7.0, CH_3(27)); 0.82 (*d*, *J* = 7.0, CH_3(26)); 0.89 (*d*, *J* = 7.0, CH_3(28)); 0.98 (*s*, CH_3(19)); 1.00 (*d*, *J* = 7.2, CH_3(21)); 2.05 (*s*, OAc); 2.35 (*dd*,

J = 11.2, 5.1, H–C(5)); 3.03 (br. *t*, J = 8.0, H–C(9)); 5.05 (br. *quint.*, J = 3.6, H–C(3)); 5.24 (*m*, H–C(22), H–C(23)); 5.88 (br. *s*, H–C(7)). FAB-MS: 487 ($(M + H)^+$).

11. *Fe(II)-Induced Rearrangement of* **8**. A soln. of $FeSO_4 \cdot 7\ H_2O$ (120 mg, 0.42 mmol) in acetic buffer (pH 3) (5 ml) was added to **8** (200 mg, 0.40 mmol) in 20 ml of THF/H_2O 3:2 with stirring. Brown Fe(III) salts precipitated immediately, and the reaction was complete at this stage (TLC (*A*): only 2 new spots). The mixture was poured into H_2O and thoroughly extracted with EtOAc. Usual workup and prep. TLC (*A*) gave 164 mg (85%) of **4**, identical with that obtained by photolysis in H_2O of **1**, and 9 mg (5%) of **1**.

12. *(20*R*,22*R*)-25-Hydroxy-2β,3β:20,22-bis[(1-methylethylidene)dioxy]-8,13-*cyclo-*13,14-*seco-*5β-cholestane-6,14-dione* (**12**) was prepared from **4** in 89% yield according to [4]. Colourless foam. R_f (AcOEt) 0.38. IR (KBr): 3500, 1720. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.95 (*s*, CH_3(18)); 1.23 (*s*, CH_3(26), CH_3(27)); 1.25 (*s*, CH_3(19)); 1.27, 1.28 (2*s*, $(CH_3)_2$C); 1.31 (*s*, CH_3(21)); 1.33 (*dd*, J = 15.2, 4.5, H_α–C(1)); 1.46 (*ddd*, J = 13.4, 9.5, 4.7, H_β–C(4)); 1.66 (*dd*, J = 15.2, 2.1, H_β–C(1)); 1.86 (*dddd*, J = 14.0, 12.5, 12.5, 4.2, H_β–C(16)); 1.98, 2.81 (*AB*, J = 13.5, 2 H–C(7)); 2.25 (*ddd*, J = 13.4, 6.8, 3.2, H_α–C(4)); 2.33 (*ddd*, J = 13.4, 12.5, 5.9, H_β–C(15)); 2.51 (*dd*, J = 4.7, 3.2, H–C(5)); 2.80 (*ddd*, J = 13.4, 4.2, 3.0, H_α–C(15)); 2.85 (br. *t*, J = 8.2, H–C(9)); 4.04 (*ddd*, J = 5.5, 4.5, 2.1, H_α–C(2)); 4.35 (*ddd*, J = 9.5, 6.8, 5.5, H_α–C(3)). EI-MS: 560 ($M^{+\cdot}$).

13. *Fe(II)-Induced Rearrangement of* **15**. Reaction of **15** (210 mg, 0.43 mmol) as described in *Exper. 11* gave, after separation by prep. TLC (C_6H_6/EtOAc 3:2), **20** (168 mg, 83%; R_f 0.47) and **21** (18 mg, 9%; more polar).

*(8*R*,22*E*)-6,14-Dioxo-8,13-*cyclo-*13,14-*seco-*5β-ergost-22-en-3β-yl acetate* (**20**): M.p. 201° (i-Pr_2O). IR ($CHCl_3$): 1740, 1717. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.73 (*s*, CH_3(18)); 0.77 (*d*, J = 7.0, CH_3(27)); 0.80 (*d*, J = 7.0, CH_3(26)); 0.86 (*d*, J = 7.0, CH_3(28)); 1.11 (*d*, J = 7.0, CH_3(21)); 1.13 (*s*, CH_3(19)); 1.96 (*s*, OAc); 4.78 (*tt*, J = 12.0, 5.7, H–C(3)); 5.22 (*m*, H–C(22), H–C(23)). FAB-MS: 471 ($(M + H)^+$).

*(22*E*)-14α-Hydroxy-6-oxo-5β-ergosta-7,22-dien-3β-yl acetate* (**21**): M.p. 215° (MeOH). UV (MeOH): 248. IR ($CHCl_3$): 1732, 1665, 1630. ^{1}H-NMR (80 MHz, $CDCl_3$): 0.70 (*s*, CH_3(18)); 0.83 (*d*, J = 7.0, CH_3(26)); 0.84 (*d*, J = 7.0, CH_3(27)); 0.91 (*d*, J = 7.0, CH_3(28)); 0.97 (*s*, CH_3(19)); 1.00 (*d*, J = 7.2, CH_3(21)); 2.04 (*s*, OAc); 5.07 (*m*, $w_{1/2}$ = 8, H–C(3)); 5.24 (*m*, H–C(22), H–C(23)); 5.88 (br. *d*, J = 2.4, H–C(7)). EI-MS: 470 ($M^{+\cdot}$).

Treatment of **15** with Me_2S in CH_2Cl_2 (r.t., overnight) or of **13** with SeO_2 in dioxane (70°, 5 h) gave, after prep. TLC of the crude mixtures, in each case **21**, identical in all respects with the sample prepared above.

14. *Fe(II)-Induced Rearrangement of* **23**. In a similar manner as described in *Exper. 11*, **23** (886 mg, 2.0 mmol) was reacted with $FeSO_4 \cdot 7\ H_2O$ (554 mg, 2.0 mmol). After 15 min, prep. TLC (EtOAc/C_6H_6 7:3) indicated complete disappearance of **23** (R_f 0.22) and the formation of **24** (R_f 0.34) and **25** (R_f 0.20). FC (EtOAc/C_6H_6 7:3) gave 674 mg (79%) of **24** and 102 mg (12%) of **25**.

*(8*R*,22*E*)-3β-Hydroxy-8,13-*cyclo-*13,14-*seco-*5α-ergost-22-en-6,14-dione* (**24**): After crystallization from i-Pr_2O, colourless needles. M.p. 123°. IR ($CHCl_3$): 1710. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.79 (*d*, J = 7.2, CH_3(27)); 0.81 (*d*, J = 7.2, CH_3(26)); 0.83, 0.90 (2*s*, CH_3(18), CH_3(19)); 0.89 (*d*, J = 7.0, CH_3(28)); 1.05 (*d*, J = 6.9, CH_3(21)); 1.24 (*q*, J = 13.2, H_β–C(4)); 2.06 (*dd*, J = 12.0, 3.8, H–C(5)); 2.18 (br. *dt*, J = 13.2, 4.2, H_α–C(4)); 2.38 (*m*, H–C(2)); 2.29, 2.47 (*AB*, J = 17.8, 2 H–C(7)); 2.63 (*dd*, J = 9.5, 7.0, H–C(9)); 3.57 (*tt*, J = 11.0, 4.4, H–C(3)); 5.24 (*m*, H–C(22), H–C(23)). ^{13}C-NMR ($CDCl_3$): *inter alia* 70.3 (C(3)); 216.5 (C(6)); 61.3 (C(8)); 35.1 (C(10)); 54.2 (C(13)); 210.0 (C(14)); 23.4 (C(18)); 16.9 (C(19)); 37.3 (C(20)); 16.9 (C(21)); 134.6 (C(22)); 132.3 (C(23)); 43.2 (C(24)); 33.0 (C(25)); 20.0 (C(26)); 19.6 (C(27)); 17.6 (C(28)). FAB-MS: 429 ($(M + H)^+$).

*(22*E*)-3α,14α-Dihydroxy-5α-ergosta-7,22-dien-6-one* (**25**): M.p. 178° (AcOEt). UV (MeOH): 241. IR ($CHCl_3$): 1665, 1630. ^{1}H-NMR (80 MHz, $CDCl_3$): 0.64 (*s*, CH_3(18)); 0.76 (*d*, J = 7.0, CH_3(26)); 0.78 (*d*, J = 7.0, CH_3(27)); 0.80 (*s*, CH_3(19)); 0.87 (*d*, J = 7.0, CH_3(28)); 0.97 (*d*, J = 7.2, CH_3(21)); 3.56 (*m*, $w_{1/2}$ = 18, H–C(3)); 5.20 (*m*, H–C(22), H–C(23)); 5.85 (br. *d*, J = 2.4, H–C(7)). EI-MS: 428 ($M^{+\cdot}$).

This compound was identical in all respects with that obtained by reduction (KI, AcOH, r.t.) of the corresponding **23**.

15. *Acetylation of* **24** *to (8*R*,22*E*)-6,14-Dioxo-8,13-*cyclo-*13,14-*seco-*5α-ergost-22-en-3β-yl Acetate* (**26**). At r.t. **24** (150 mg, 0.53 mmol) was acetylated in dry pyridine (5 ml) with Ac_2O (1 ml) for 10 h. Evaporation, codistillation with toluene and FC (C_6H_6/EtOAc 3:2) afforded **26** (156 mg, 95%). M.p. 128° (EtOH). IR ($CHCl_3$): 1734, 1710. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.79 (*d*, J = 7.0, CH_3(26)); 0.82 (*d*, J = 7.0, CH_3(27)); 0.84, 0.89 (2*s*, CH_3(18), CH_3(19)); 0.89 (*d*, J = 7.0, CH_3(28)); 1.06 (*d*, J = 7.0, CH_3(21)); 2.00 (*s*, OAc); 4.65 (br. *tt*, J = 11.2, 5.3, H–C(3)); 5.26 (*m*, H–C(22), H–C(23)). EI-MS: 470 ($M^{+\cdot}$).

16. *Photolysis of* **4** *to* **5**. A soln. of **4** (25 mg, 0.052 mmol) in 2 ml of EtOH was irradiated through quartz with a 125-W high-pressure Hg lamp for 1 h under N_2 at r.t. The solvent was evaporated and the residue purified by prep. TLC (*B*) to yield 16 mg (65%) of pure **5**, identical in all respects with that obtained by photolysis of **1** in H_2O.

17. *X-Ray Crystallographic Data for* **26**. *Crystallographic Data.* $C_{30}H_{46}O_4$. Mol.wt. 470.7. Monoclinic, $a = 7.509(2)$, $b = 10.980(3)$, $c = 17.085(5)$ Å, $\beta = 97.78(3)°$, $U = 1396$ Å^3, $Z = 2$. Space group $P2_1(C_2^2)$, $D_x = 1.12$ g cm^{-3}. Cell parameters were obtained from diffractometer measurements (25 reflections, MoK_α radiation).

Data Collection. Intensities were measured on a *Nonius CAD4* diffractometer with graphite-monochromatized MoK_α radiation using ω/ϑ scan mode, scan width 1.3°, variable scan speed between 1.3 and 6.7 deg·min^{-1}, ϑ range from 3 to 30°. One check reflection was monitored periodically to test the crystal stability, and three to test the crystal orientation. No absorption corrections were applied ($\mu = 0.68$ cm^{-1} for MoK_α radiation). Of the 4239 independent reflections measured, 2639 having $F_o \geqslant 2\sigma(F_o)$ were considered as observed.

Structure Solution and Refinement. The structure was solved by direct methods (program MULTAN 80 [35]) and by subsequent cycles of least-squares and difference *Fourier* syntheses (program SHELX 76 [36]). Indeed, the 'best' E-map allowed to localize 25 heavy atoms over a total of 34. In the following isotropic refinement, it became soon evident that the side chain at C(17) was affected by disorder, the terminal part of the chain (atoms C(25) to C(28)) being splitted over two different orientations.

Owing to the number of parameters, in the following anisotropic refinement, the blocked-matrix technique was employed, three groups of atoms being refined in separate subsequent cycles. Most of the H-atoms bonded to non-disordered C-atoms were located on difference maps; some of them were placed in calculated positions. They were not refined, but included in the structure-factor calculations with an isotropic temperature factor equal to the U(equiv.) value for the bonded C-atom.

To refine the disordered part of the structure, some constraints were imposed. To all the 'primed' atoms (see *Fig. 3*), a unique variable site-occupation factor (s.o.f.) was assigned, and the same was done for all the 'doubly primed' atoms: both s.o.f. values were allowed to refine, their sum being tied to unity. The C–C bond lengths involving disordered atoms were tied to two values (one for 'primed', one for 'doubly primed' atoms, respectively) which were allowed to refine. Finally, for the partially overlapping couples C(27′)/C(27″) and C(28′)/C(28″), a unique isotropic thermal factor was refined for the atoms in each couple.

At the end of the refinement, a difference map showed 2 residual electron-density peaks of 0.49 and 0.35 eÅ^{-3} in the disordered region, ranging otherwise between +0.26 and −0.32 eÅ^{-3}. The discrepancy index over the 2693 observed reflections converged to $R = 0.059$. The final s.o.f. values for the 'primed' and 'doubly primed' atoms was 0.54 and 0.46, respectively; corresponding values for the two tied C–C bond lengths were 1.570 and 1.568 Å. The final isotropic thermal parameter U for atoms C(27′)/C(27″) was 0.1263 Å^2 and that for atoms C(28′)/C(28″) 0.1105 Å^2.

Tables of observed and calculated structure amplitudes, anisotropic and equivalent thermal parameters, and H-atom coordinates are available on request *(A.M.)*.

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