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HIGHER ISOPRENOIDS—IV*

MODIFICATION OF RING-*A* OF CYCLOLAUDANOL AN IMPROVED SEQUENCE FOR RING-*A* MODIFICATION OF TRITERPENOIDS†‡

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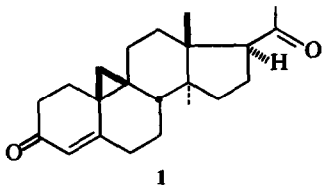
Abstract—By a 12-step sequence of reactions (24 *S*)-9β,19-cyclo-14α,24-dimethyl-cholest-4-en-3-one (**14**) has been obtained from cyclolaudenol (**4**) in overall yields of 8%. This sequence of reactions includes a new procedure for the expansion of the *A*-nor-3-oxo-derivative **10** to the above $\alpha\beta$-unsaturated ketone (**14**). A case of facile ring-opening of the 9,19-cyclopropane moiety has been observed. An interesting dependence of abnormal shielding of one of the 9β,19-cyclopropyl methylene protons on the *A*/*B* stereochemistry in the case of *A*-nor-3-substituted-9β,19-cyclolanostanes was uncovered and is discussed.

With the ultimate objective of preparing steroid hormone analogues, such as ½, we have already reported[1] an efficient, new sequence of reactions for the degradation of side chain of cycloartenol (**3**) and cyclolaudenol (**4**). In furtherance of our objective we now describe an eleven-step sequence of reactions for the conversion of cyclolaudanol into (24 *S*)-9β,19-cyclo-14α,24-dimethyl-9β-cholest-4-en-3-one (**14**). Fig 1 depicts the sequence of reactions and the most successful reagents.

Since, the action of PCl_5 on triterpenoids having 3β-hydroxy-4,4-dimethyl substituted ring A (**15**) is a standard procedure[2] for effecting transformation into the *A*-nor-3-isopropylidene derivative (**16**), cyclolaudanol (**5**) was exposed to this reagent with the hope of obtaining **17** in satisfactory yields. However, the product from such a reaction proved to be complex and on inverted-dry-column-chromatography[3] (IDCC; $AgNO_3$-silica gel) yielded two pure olefins in yields of ~ 16% and 4% only.



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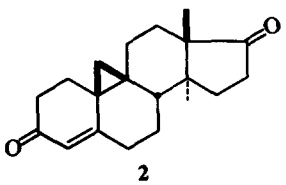

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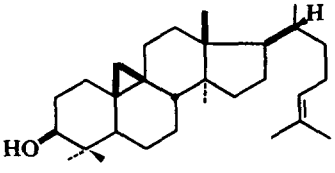

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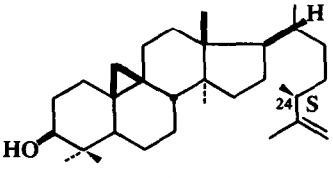

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From their PMR spectral characteristics (Table 1), the major olefin was recognised as **6** and the minor one as the expected isopropylidene isomer (**17**); cyclopropane ring has remained in tact (PMR, Table 1) in both the products.§ In an alternative approach[5] cyclolaudanyl tosylate (**18**) was subjected to dehydrosulphonylation with AcONa-AcOH when superior total yield resulted, though the crude product was still unexpectedly complex,

*Part III, ref. 1.

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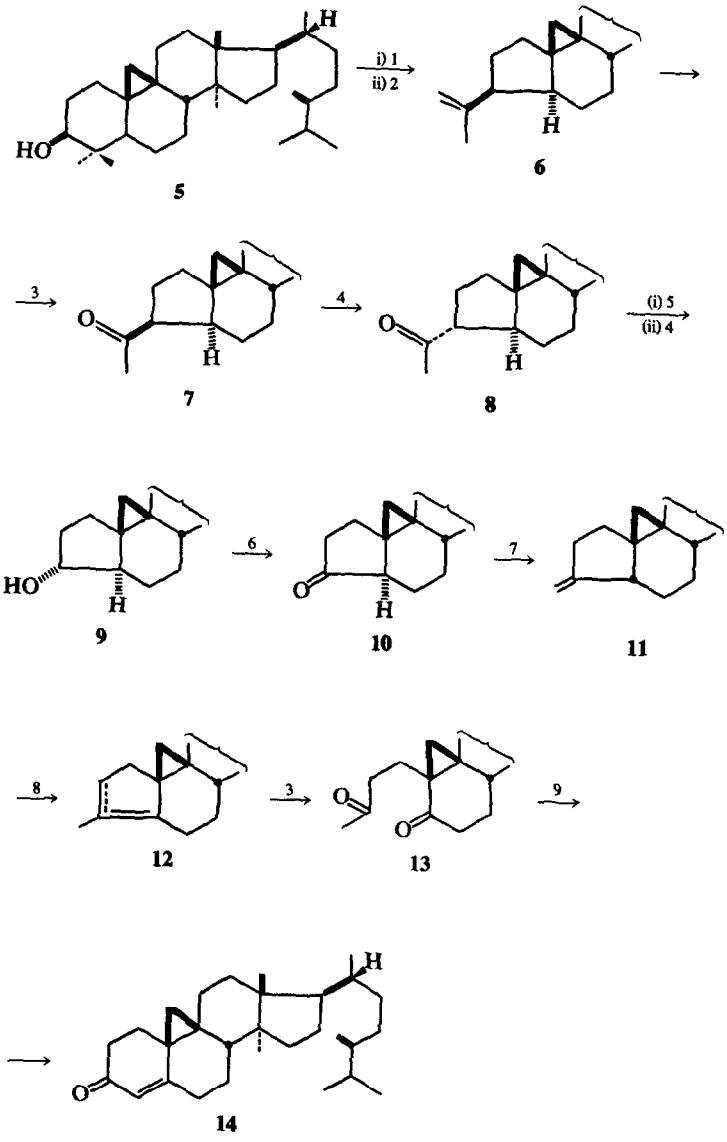
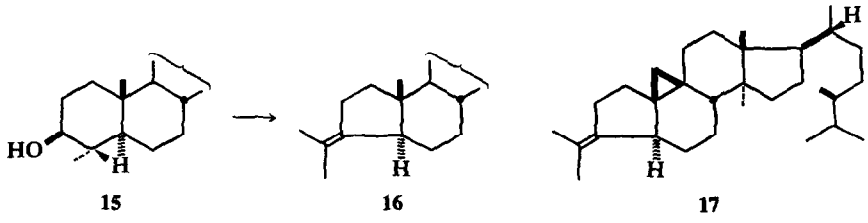
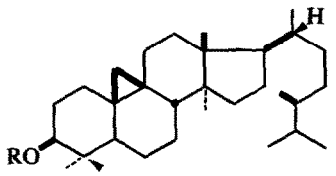
§In a recent publication, D.H.R. Barton and D. Kumari[4] describe similar results from the action of PCl_5 on cycloartanol.



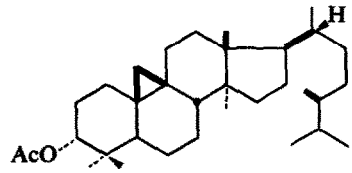
Reagents: (1) *p*-TsCl, pyr. (2) Pyridine (3) O_3/MeOH-CH_2Cl_2; CrO_3—work up (4) EtOH-KOH (5) $F_3CCOOOH$ (6) CrO_3 (7) ϕ_3 $P^+CH_3I^-$, Bu^tOK (8) Li, $NH_2CH_2CH_2$-NH_2 (9) MeOH-KOH aq.

Fig 1. Modification of ring-*A* of cyclolaudanol.





18: R = Ts
19: R = Ac



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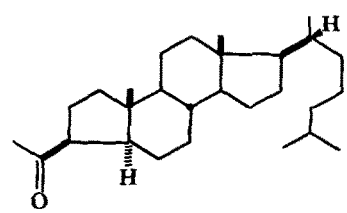
containing not more than 50% olefins. This product could be separated (IDCC;$AgNO_3$-silica gel) to furnish ~ 40% yield of the isopropenyl isomer (6) and ~ 3% yield of the isopropylidene isomer (17). Besides these, an acetate (m.p. 118–119°; $C_{33}H_{56}O_2$, $M^{\oplus}$, *m/e* 484. IR in CS_2: 1740, 1250 cm^{-1}), considered (PMR, Table 1, note that *J* value for -CHOAc signal) to be the simple S_N2 displacement product*, the 3α-isomer (20) of cyclolaudanyl acetate, and another unidentified compound (m.p. 122–125°), could be isolated as minor products from the more polar fractions. In another series of reactions, cyclolaudanyl tosylate (18) was heated with dry pyridine over a prolonged period, when to our great surprise† and advantage, we obtained the *A*-nor-3-isopropenyl derivative (6) in over 90% yield.

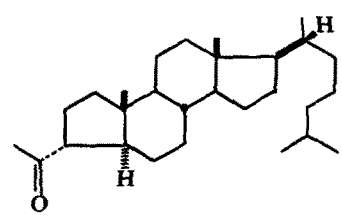
Having failed to get the required *A*-nor-3-isopropylidene derivative (17) in workable yields‡ from cyclolaudanol, attention was next directed to utilization of the readily accessible isopropenyl isomer 6, for the purpose on hand. The 3β-configuration depicted in 6 is based on mechanistic reasoning and has ample analogy,[5a,8] and, is further supported by the behaviour of the derived methyl ketone (7), described below.

The possibility of base-catalyzed isomerization[9] of 6 to 17 was first examined. Exposure of olefin 6 to N-lithioethylenediamine[1,10] for various time periods (30 min, 15 min, 5 min) led to complex olefin mixtures, and hence, this approach was abandoned. Next, the standard sequence depicted in Fig 1 was successfully adopted to get the ketone 10.

Hydroxylation (OsO_4-H_2S)[11] of olefin 6 yielded the expected α-glycol, which on cleavage with $Pb(OAc)_4$ gave the methyl ketone (7) in ~ 85% overall yield. However, ozonolysis of olefin at −70° in CH_2Cl_2-MeOH (1:1)[13], followed by oxidative work-up with Jones reagent,[14] is most expeditious and convenient and furnishes the methyl ketone (7) in over 90% yield. The methyl ketone, as formulated in 7 has the acetyl group in quasi-axial position, leading to serious non-bonded interactions with the cyclopropyl methylene. This is reflected in its almost quantitative epimerization, under alkaline conditions (MeOH-KOH), to the 3α-epimer (8), in which the acetyl group has quasi-equatorial configuration, thus minimising the non-bonded interactions. The situation has a close parallel in the corresponding C_{10}-Me series.[7] Structures 7, 8 are fully supported by spectral data. The 3β-configuration in 7 is also corroborated by its circular dichroism $\Delta\epsilon_{285.5}$ (EtOH) = +1·02 which may be compared with the similar value recorded[15] for *A*-nor cholestane derivative 21. However the 3α-isomer (8) shows a negative Cotton effect $\Delta\epsilon_{285}$



Δε max = +1·3
21



Δε max = +0·11
22

*Apparently, simple displacement of the 3β-tosylate in the triterpenes or the 4,4′-dimethyl steroids has not been observed so far and this has been commented upon[5a].

†F. Kohn and R. Stevenson[6] had earlier subjected α- and β-amyrin methanesulphonates and 4,4-dimethyl cholestan-3β-yl tosylate (or methanesulphonate) to the action of hot pyridine and in each case they obtained products of simple elimination (Δ^2-olefins) and $C_4Me \rightarrow C_3$ Wagner elimination (3-methyl-4-methylene-derivative). No *A*-nor-rearranged product was obtained. On the other hand, *A*-nor-rearranged derivative (6) is essentially the only product in the present case.

‡It is not clear why, in the case of cyclolaudanol and cycloartanol,[4] the isopropenyl isomer is formed in preference to the isopropylidene isomer. In this connection it may be pointed out that reaction of PCl_5 with 19-nor-4,4-dimethyl-17β-acetoxy-5α-androstane, under condition which convert the corresponding C_{10}-methyl compound almost quantitatively into the isopropylidene derivative, furnishes a mixture of olefins containing ~ 33% of the isopropenyl isomer (and ~ 44% isopropylidene derivative); however, this difference in behaviour is readily rationalised.[7]

Table 1. PMR spectral characteristics of various 9β,19-cyclolanostane derivatives

No.	Compound	Chemical shift in ppm (δ)		
		Cyclopropane CH_2* (J in Hz)	—C—Me†	Other signals¶
1	Cyclolaudenol (4)	0·28, 0·57 (4)	0·75, 0·86, 0·93 and 0·93	Me—C=C, bs, 1·61; C=CH_2, bs, 4·63
2	Cyclolaudanol (5)	0·30, 0·59 (5)	0·78, 0·90, 0·95 and 0·95	CHOH, bt (J = 5 Hz), 3·16
3	Cyclolaudanyl acetate (19)	0·32, 0·59 (4)	0·85, 0·87, 0·90 and 0·95	—OCOMe, s, 1·96
4	Cyclolaudanyl tosylate (18)	0·29, 0·55 (5)	0·81, 0·81, 0·87 and 0·93	p—Me—C_6H_4, s, 2·43; C_6H_4: 2H, m, 7·23 − 7·39 and 2H, m, 7·71 − 7·85
5	(24 *S*)-3α-Acetoxy-24-methyl-9β, 19-cyclo-5α-lanostane (20)	0·32, 0·59 (5)	0·86, 0·86, 0·90 and 0·95	—OCOMe, s, 1·96; —CH—OAc, diffused triplet (J = 5 Hz), 4·46
6	(24 *S*)-*A*-nor-3-isopropylidine-24-methyl-9β,19-cyclo-5α-lanostane (17)	−0·35, 0·55 (5)	0·87 and 0·92	Me_2—C=C, bs, 1·58
7	(24 *S*)-*A*-nor-3β-isopropenyl-24-methyl-9β,19-cyclo-5α-lanostane (6)	−0·17, § (4)	0·85 and 0·90	Me—C=C, s, 1·66; CH_2=C, bs, 4·66
8	(24 *S*)-*A*-nor-3α-isopropenyl-24-methyl-9β,19-cyclo-5α-lanostane‡	−0·25,) (4)	0·88 and 0·92	Me—C=C, s, 1·70; CH_2=C, bs, 4·66
9	(24 *S*)-*A*-nor-3β-isopropyl-24-methyl-9β,19-cyclo-5α-lanostane‡	−0·17, § (4)	0·82 and 0·92	—
10	(24 *S*)-*A*-nor-3α-isopropyl-24-methyl-9β,19-cyclo-5α-lanostane‡	−0·33, 0·52 (4)	0·82 and 0·88	—
11	(24 *S*)-*A*-nor-3β-acetyl-24-methyl-9β,19-cyclo-5α-lanostane (7)	−0·11, 0·55 (4)	0·82 and 0·90	—COMe, s, 1·98; —CH—COMe (pseudo-equatorial), bm, 2·78 − 3·21
12	(24 *S*)-*A*-nor-3α-acetyl-24-methyl-9β,19-cyclo-5α-lanostane (8)	−0·28, 0·56 (4)	0·92 and 0·92	—COMe, s, 2·03; —CH—COMe (pseudo-axial), bm, 2·66 − 3·33
13	(24 *S*)-*A*-nor-3β-ol-24-methyl-9β,19-cyclo-5α-lanostane	−0·13,§ (5)	0·85 and 0·92	—CHOH (pseudo-equatorial), m (W_H = 9 Hz), 3·96
14	(24 *S*)-*A*-nor-3α-ol-24-methyl-9β,19-cyclo-5α-lanostane (9)	−0·33, 0·53 (4)	0·85 and 0·88	—CHOH (pseudo-axial), bt (J = 8 Hz), 3·61.
15	(24 *S*)-*A*-nor-3-oxo-24-methyl-9β,19-cyclo-5α-lanostane (10)	−0·17, 0·60 (4)	0·87 and 0·92	—
16	(24 *S*)-*A*-nor-3-oxo-24-methyl-9β,19-cyclo-5β-lanostane	§, 0·59 (4)	0·88 and 1·02	—
17	(24 *S*)-*A*-nor-3-methylene-24-methyl-9β,19-cyclo-5β-lanostane (11)	0·39, 0·55 (4)	0·85 and 0·90	CH_2=C: 1H, bs, 4·75 and 4·90
18	Olefin 12	0·26, 0·61 (4)	0·73 and 0·83	Me—C=C, d (J = 2 Hz), 1·60; CH; C=CH—CH_2, m (very weak signal), 5·0
19	Diketone 13	0·41, — (5)	0·85 and 0·92	—COMe, s, 2·09
20	(24 *S*)-9β,19-cyclo-14α-24-dimethyl-cholest-4-en-3-one (14)	— —	0·82 and 0·92	O=C—CH=C—, s, 6·03

*Each signal integrates for ~1H and is a doublet. Negative sign indicates that the signal is on the upfield side of TMS signal.

†Most likely assignment.

‡Though, these are new compounds, they are not described in the experimental. However, we plan to describe them in our next communication.

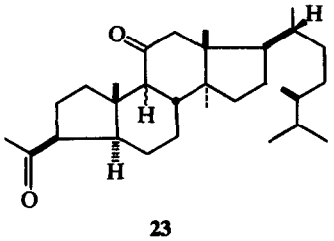
§Not clear, partly obscured by other absorptions.

¶Signals are donated by s, singlet; d, doublet; m, multiplet; bs, broad singlet; bt, broad triplet and bm, broad multiplet.

(EtOH) = −0·43 in contrast to the known[15] weak positive CD of 22.

Next step envisaged Baeyer-Villiger oxidation of both methyl ketones (7, 8) so as to determine the most suitable substrate for this reaction. It was soon found that both ketones react quite slowly, though the 3β-isomer (7) is much more resistant. Thus after exposure to *m*-chloroperbenzoic acid for 60 days at room temp (~ 27°), the 3α-isomer (8) furnished, after hydrolysis, the corresponding alcohol (9) in ~ 68% yield, while the 3β-isomer (7) afforded after hydrolysis, the 3β-ol in no more than 20% yield. The PMR spectral data (Table 1) of these two alcohols are in accord with their structures and configurations.

In order to expedite the above reaction, action of the more potent trifluoroperacetic acid[16] (1·2 mole equiv, 5 hr), in refluxing CH_2Cl_2, in presence of K_2HPO_4, on the two ketones (7, 8) was investigated. Surprisingly, the two ketones gave completely different results. Thus, whereas the 3α-methyl ketone (8) yielded, after saponification, the 3α-ol (9) in ~ 50% yield (with 2 mole equiv. of $F_3C{\cdot}CO_3H$, 80% yield is obtained), the 3β-methyl ketone (7) gave, in almost quantitative yield, a product (m.p. 143–145°) analysing for $C_{30}H_{50}O_2$ ($M^{\oplus}$, $m/e = 442$). This product (IR: no OH; C=O 1700 cm^{-1}) shows in its PMR spectrum (CCl_4) signals for *three* tertiary Me's (singlet at 0·81, 0·90 and 1·0 ppm), and one COMe (3H, s, 2·06 ppm) and hence, is formulated as 23. This structure is supported by its electron-impact-induced fragmentation (e.g. 24, $M^{\oplus}$ is base peak). Evidently product 23 must have arisen from the corresponding $\Delta^{9(11)}$-olefin resulting from the cleavage of the cyclopropane ring. The possible reasons for this facile cleavage of the cyclopropane ring have been examined in some detail and we propose to report on this aspect in a later communication.



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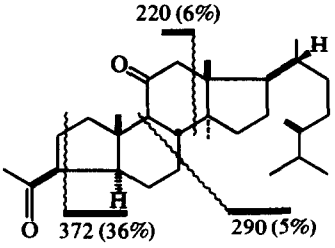

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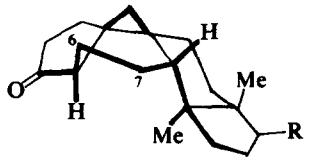
CrO_3 oxidation of either of the *A*-nor-3-ols (9 or its β-epimer) furnished the same mixture (TLC) of ketones, in which one isomer predominated and could be readily isolated by crystallisation. This major product is considered to be *trans*-configurated (10),* in view of the known *trans*-locking of the A/B rings in the precursors (e.g. 9) and, its ready epimerization (acid or base catalyzed) to the more stable isomer, which must be the 5β-epimer. An inspection of molecular models (Dreiding) shows that both ketones (25, 26) are sterically strained, though clearly in the 5β-epimer (26) ring-B



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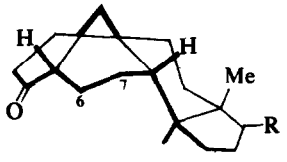

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can now adopt a half-chair conformation, which almost completely relieves the non-bonded interactions between C_6-methylene and the cyclopropane ring-methylene, present in the 5α-epimer (25) (which has ring-B in a twist-boat conformation). Thus, the epimerization, 5α → 5β, in the present case, is borne out by conformational considerations.†

Thus, one can obtain *A*-nor-ketone (10) in ~ 45% yield starting with cyclolaudanol and using the reagents recommended in Fig 1. Next, conversion of this hydrindanone to 3-oxo-4-ene system was investigated. The standard procedure[2a] involves reaction of the hydrindanone with MeMg I and dehydration of the resulting tertiary alcohol to $\Delta^{3(5)}$-olefin. Two recent publications[4,19] try to avoid this bottle neck by adopting altogether new routes from the hydrindanone. We have by-passed this difficulty by a modification of the procedure of Voser *et al*[2a] and this is described below.

*Thus, in the system under discussion, no appreciable epimerization at C_5 occurred during oxidation/isolation. In this connection it may be pointed out that in the cholestane series,[5c] *A*-nor-3-ketone epimerizes to the 5β-ketone during oxidation/isolation, unless special precautions are taken. On the other hand, no such precautions are necessary in the preparation of *trans*-hydrindanones in the 19-nor-cholestane[7] or lupeol series.[17]

†In the case of α-hydrindanones incorporated in fused ring systems, the equilibrium picture, as one may anticipate, varies with structure and, conformational analysis has served to rationalize and predict equilibrium.[18]

The hydrindanone (**10** or its 5β-epimer) was treated with methylene-triphenylphosphorane, when olefin **11** resulted in over 90% yield; in the case of 5α-hydrindanone (**10**), epimerization at C_5 also took place, as anticipated. The olefin on exposure to N-lithioethylene-diamine[10] at 120° for 7 min gave a product in which the tetrasubstituted olefin **12** predominated (PMR). This, without further purification, was subjected to ozonolysis to get the diketone **13** (~ 34% based on hydrindanone). IR (Nujol): C=O 1705, 1670 cm^{-1}. PMR (CCl_4): Cyclopropyl $C\underline{H}_2$ (1H, d, 0·56 ppm, $J = 5$ Hz; second H under Me signals), CO$\underline{Me}$ (3H, S, 2·09 ppm) Mass: M^+, $m/e = 428$ (100%). The diketone, on treatment with MeOH-KOH aq. readily furnished the targetted compound: (24*S*)-9β,19-cyclo-14α,24-dimethyl-9β-cholest-4-en-3-one (**14**), m.p. 73–75°, $[\alpha]_D + 26·6°$. The compound, as expected,* shows λ_{max} 275 nm, ε 12,700. IR (melt): C=O 1660 cm^{-1}; C=C 1600 cm^{-1}. PMR (CCl_4): —C=C$\underline{H}$—C=O, 1H, S, 6·03 ppm; cyclopropane CH_2, signal under Me absorptions†.

'Abnormally' high shielding of one of the cyclopropane methylene protons in C_3-substituted A-nor-9β,19-cyclo-5α-lanostanes.

A perusal of Table 1 will reveal that in *all* 3 (α or β)-substituted *A*-nor-9β,19-cyclolanostanes, one of the cyclopropyl methylene protons has moved up, well beyond the TMS signal, *provided* the A/B locking is *trans* (items 6 to 15, Table 1). No such shift is observed in the corresponding A/B-*cis*-series (item 16, 17, Table 1). This shielding is independent of the nature of the C_3-substituent (cf. items 6–15, Table 1), though 3α-substituents appear to enhance the effect in comparison to the corresponding 3β-substituent. It may further be noted that when ring A is 6-membered, there is no 'abnormal' shielding even when the A/B rings are *trans*-fused (items 1 to 5, Table 1).

It is obvious from the above that the reason for this 'abnormal' shielding‡ must be sought in the conformational differences in the A/B rings of *cis* and *trans A*-nor derivatives, as any significant contribution from the anisotropy of the C_3-substituent is clearly ruled out. A reference to conformational projections **25** and **26** will show that in the *trans*-series (e.g. **25**) (ring-B twist boat), the front cyclopropane methylene hydrogen is being subjected to long-range shielding by the C_5—C_6 and C_6—C_7 C—C bonds[29] and the relevant C—H bonds.[29] These factors essentially disappear in the half-chair conformation adopted by the B-ring in the 5β-series (e.g. **26**).

cf cycloart-1-en-3-one (λ_{max}^{EtOH} 269 nm; ε, 8700)[20] and, (20 S)-4,16α-dihydroxy-14α-methyl-20-methylamino-9β,19-cyclo-pregn-4en-3-one (λ_{max}^{EtOH} 296·5 nm, ε, 9000).[21]

†This is expected for the structure **14**, as 3-oxo-4-ene system is expected to deshield the 9β,19-cyclopropane methylene. The situation can be likened to the known deshielding effect[22] (0·417 ppm) of the 3-oxo-4-ene system on the C-19 methyl.

‡Some cases of highly shielded cyclopropane ring protons are on record[4,23–28]. In one case[25] (cyclovirobuxeine A) the shielding is associated with a suitably located C=C bond. No comments have been made in other cases.

EXPERIMENTAL

All m.ps are uncorrected. Light petroleum refers to the fraction b.p. 40–60°. Optical rotations were measured in $CHCl_3$.

UV spectra were taken on a Beckman spectrophotometer, model DU, in EtOH. IR were recorded as Nujol mulls on a Perkin–Elmer Infracord model 137 E. PMR spectra were taken in CCl_4, on a Varian A-60 spectrometer, using TMS as the internal standard; chemical shifts are expressed in ppm (δ) relative to TMS as zero. Mass spectra were recorded on a CEC mass spectrometer, model 21-110B using an ionizing potential of 70 eV and a direct inlet system; besides, the molecular ion, ten most abundant ions are mentioned with their relative intensities.

Silica gel for column chromatography was of 100–200 mesh and was activated at 130–140° (6 hr) and then standardized.[30] $AgNO_3$-impreganted silica gel was made by the method of Gupta and Dev[31] and activated at 100–110° (4 hr). TLC was carried out on silica gel or silica gel–$AgNO_3$ (10% $AgNO_3$) layers (0·3 mm) containing 15% gypsum; the plates were activated at 100–115° (45 min) and then stored in a desiccator. Conc H_2SO_4 spray, followed by heating (120°, 15 min) was used for visualization of TLC spots.

Cyclolaudanol (5). Cyclolaudenyl acetate (m.p. 120–121°, 7 g; from cyclolaudenol[32], Ac_2O and pyridine) in glacial AcOH (200 ml), dry ether (25 ml) mixture, was shaken with H_2 over 5% Pd–C (1·2 g) at ~ 25° and 760 mm pressure till absorption of H_2 ceased (4 hr). After usual work-up, the product (7·2 g, m.p. 123–126°) was crystallized from MeOH—$CHCl_3$ to give pure **19**, m.p. 132–133°, $[\alpha]_D + 50°$ (c, 0·8%). IR: OAc 1745, 1245 cm^{-1}. (Found: C, 81·76; H, 11·75. $C_{33}H_{56}O_2$ requires: C, 81·80; H, 11·60%). (Lit.[32]: m.p. 132–133°, $[\alpha]_D + 50°$).

Hydrolysis (5% EtOH–KOH, 4 hr reflux) of **19** gave **5** which crystallizes from MeOH as needles, m.p. 132–134°, $[\alpha]_D + 44°$ (c, 0·91%). IR: OH 3300 cm^{-1} (Found: C, 83·86; H, 12·12. $C_{31}H_{54}O$ requires: C, 84·10; H, 12·30%). (Lit.[32]: m.p. 133–134°, $[\alpha]_D + 43°$).

Action of PCl_5 on cyclolaudanol. A mixture of cyclolaudanol (2·6 g), PCl_5 (5 g) in dry light petroleum (800 ml) was stirred (45 min; N_2) at 0°. The product obtained (2·6 g) after usual work-up[2c] showed on TLC ($AgNO_3$–SiO_2-gel; solvent: light petroleum) two spots at R_f 0·18 and 0·37, besides much tailings and other minor components. This mixture was subjected to IDCC[3] (5% $AgNO_3$–SiO_2-gel/I; 45 cm × 5 cm; solvent: 2% C_6H_6 in hexane) and the following pooled fractions were obtained (bands in the increasing order of R_f):

Fr.1	1·68 g	lower most band (0·0 cm–4·5 cm from origin), tailings, discarded.
Fr.2	420 mg	next band (4·5 cm–6·5 cm), compd. with R_f 0·18.
Fr.3	30 mg	next band (6·5 cm–7·0 cm), mixture of compds. with R_f 0·18 and 0·37.

Fr.4	97 mg	next band (7·0 cm–8·0 cm), compd. with R_f 0·37.
Fr.5	70 mg	next band (8·0 cm–10·0 cm), mixture of compds. with R_f 0·37 and $R_f > 0·37$.

Fr. 2 (420 mg) was crystallized from MeOH-aq. to give (24 *S*)-A-*nor*-3β-*isopropenyl*-24-*methyl*-9β,19-*cyclo*-5α-*lanostane* (**6**), m.p. 60°, $[\alpha]_D$ +65° (*c*, 0·9%). IR: C=CH$_2$ 890, 1645 cm^{-1}. Mass: *m/e* 424 (M$^+$; 26%), 43 (100%), 95 (71%), 55 (56%), 53 (50%), 41 (50%), 107 (39%), 81 (37%), 298 (37%), 203 (33%), 109 (32%). (Found: C, 87·48; H, 12·20. $C_{31}H_{52}$ requires: C, 87·66; H, 12·34%).

Fr. 4 (97 mg) was crystallized from MeOH to furnish (24*S*)-A-*nor*-3-*isopropylidene*-24-*methyl*-9β,19-cyclo-5α-*lanostane* (**17**), m.p. 95–97°, $[\alpha]_D$ +54° (c, 0·74%). (Found: C, 87·48; H, 12·23. $C_{31}H_{52}$ requires: C, 87·66; H, 12·34%).

Cyclolaudanyl tosylate (**18**). To a soln of 5 (3·5 g) in dry pyridine (100 ml) was added *p*-toluenesulphonyl chloride (7·0 g) at 0°. After 4 days at ~25°, crushed-ice (200 g) was added and the mixture set aside for 1·5 hr. The white solid which had separated was collected by filtration, redissolved in ether (100 ml × 3) and the resulting soln washed with water (30 ml × 4), brine and dried (Na_2SO_4). Removal of solvent furnished a solid (4·2 g) which on crystallization from acetone gave needles, m.p. 107° (dec), $[\alpha]_D$ +55° (c, 0·89%). IR: Ar·SO$_2$·O[33]; 1350, 1185, 1172 cm^{-1}. (Found: C, 76·26; H, 10·02; S, 5·5. $C_{38}H_{60}O_3S$ requires: C, 76·46; H, 10·13; S, 5·3%).

Acetolysis of cyclolaudanyl tosylate. The above tosylate (7·5 g) in glacial AcOH (500 ml) containing anhyd NaOAc (3·75 g) was heated at 95° for 3 hr (N_2). Solvent was flashed off (~ 95°/100 mm) and the mixture was worked-up with ether (125 ml × 3) in the usual manner. The gum (5·2 g), thus obtained, showed on TLC ($AgNO_3$-SiO_2-gel; solvent: 2% C_6H_6 in hexane) besides tailings and minor components ($R_f > 0·49$) two clear spots at R_f 0·24 and 0·48. This mixture (5 g) was subjected to IDCC on 5% $AgNO_3$–SiO_2–gel/I (45 cm × 6·5 cm) using 2% C_6H_6 in hexane as solvent system. The following pooled fractions were obtained:

Fr. 1	2·02 g	lower most band (0·0 cm–4·5 cm from origin), tailings.
Fr. 2	2·56 g	next band (4·5 cm–6·5 cm), compd. with R_f 0·24
Fr. 3	50 mg	next band (6·5 cm–7·0 cm), mixture of compds. with R_f 0·24 to 0·49
Fr. 4	160 mg	next band (7·0 cm–8·0 cm), compd. with R_f 0·49
Fr. 5	50 mg	upper most band (> 8·0 cm), mixture of compds. with $R_f > 0·49$, discarded.

Fr. 2 (2·56 g) was recrystallized from MeOH-aq to give olefin **6**, m.p. 60°.

Fr. 4 (160 mg) was recrystallized from MeOH to yield olefin **17**, m.p. 95–97°.

Fr. 1 (2·02 g) on TLC (silica gel; solvent: benzene) showed, besides lot of polar material, four spots at R_f 0·22, 0·29, 0·42 and 0·49. This mixture was subjected to IDCC on SiO_2-gel/I (45 cm × 6·5 cm) using C_6H_6 as solvent. Only two compds. (A and B) with R_f 0·22 and 0·49 were obtained in a state of purity.

Compound A (210 mg) after several crystallizations from ethanol-aq gave a compd, m.p. 122–125°, $[\alpha]_D$ +72·5° (c, 0·83%). IR: weak band at 3350 cm^{-1}. PMR: no cyclopropane methylene. This was not examined further.

Compd. B (320 mg) was crystallized from MeOH and afforded pure (24*S*)-3α-*acetoxy*-24-*methyl*-9β,19-*cyclo*-5α-*lanostane* (**20**), m.p. 118–119°, $[\alpha]_D$ +58·8° (c, 0·68%). (Found: C, 82·30; H, 11·71. $C_{33}H_{56}O_2$ requires: C, 81·75; H, 11·64%).

Dehydrosulphonylation of cyclolaudanyl tosylate with dry pyridine. The tosylate **18** (15 g) in dry pyridine (500 ml) was heated on a steam bath for 6 days and then refluxed (bath temp 130°) for 20 hr (N_2). Solvent was flashed off (~ 95°/110 mm), and the mixture diluted with ice cold water (200 ml). It was worked up as usual[6] with ether (150 ml × 3) and the product purified by chromatography over SiO_2-gel/I (30 cm × 2·5 cm): light petroleum (500 ml × 2) eluted olefin **6** (9·2 g, m.p. 60°; TLC pure) which was used directly for ozonolysis.

(24 *S*)-A-*Nor*-3β-acetyl-24-*methyl*-9β,19-*cyclo*-5α-*lanostane* (**7**)

(i) *By hydroxylation*-Pb(OAc)$_4$ *cleavage.* A mixture of **6** (0·51 g), OsO_4 (352 mg), pyridine (2·2 ml), ether (10 ml) and light petroleum (10 ml) was kept at room temp (~ 25°) in the dark for 48 hr. The precipitated osmate-ester, collected by filtration, was dissolved in benzene (45 ml) and treated with H_2S gas.[34] It was worked-up in the usual manner to give a product (0·49 g) which was TLC pure (silica gel; solvent: 25% EtOAc in C_6H_6). On crystallization from MeCN it afforded pure α-glycol, m.p. 126–128°, $[\alpha]_D$ +48·4° (c, 0·66%). IR: OH 3300 cm^{-1}. Mass: *m/e* 458 (M$^+$, 0·5%), 43 (100%), 41 (40%), 55 (38%), 75 (37%); 95 (34%), 57 (33%), 71 (28%), 81 (21%), 69 (18%), 109 (17%). (Found: C, 81·76; H, 11·76. $C_{31}H_{54}O_2$ requires: C, 81·16; H, 11·87%).

The above α-glycol (0·23 g) in benzene (15 ml) was stirred (2 hr) with Pb(OAc)$_4$[35] (0·24 g) at ~ 25°. The neutral product (0·21 g) obtained after usual work-up was taken up in benzene (0·5 ml) and filtered through a column of SiO_2–gel/I (10 cm × 2 cm): 50% light petroleum in C_6H_6 (200 ml) eluted the main fraction (0·17 g) which was crystallized from MeOH to give pure **7**, m.p. 88–89°, $[\alpha]_D$ +112° (c, 0·64%). IR: C=O 1710 cm^{-1}. Mass: *m/e* 426 (M$^+$; 29%), 43 (100%), 95 (53%), 55 (42%), 411 (41%), 109 (36%), 71 (34%), 107 (30%), 81 (30%), 69 (28%), 57 (28%), (Found: C, 84·09; H, 12·24. $C_{30}H_{50}O$ requires: C, 84·44; H, 11·81%).

(ii) *By ozonolysis in* CH_2Cl_2–MeOH *solvent mixture.* The olefin **6** (3·1 g) in 1:1 CH_2Cl_2–MeOH mixture (200 ml) containing dry ether (20 ml) was treated with ozonized oxygen (O_3 conc 0·8 g/hr) at −70° for 30 min. The crude "ozonide" isolated by solvent removal (~ 30°/50 mm) was decomposed[14] with Jones reagent. The neutral product (3·2 g) obtained after usual work-up,[14] was chromatographed on SiO_2–gel/I (50 cm × 3·5 cm): (i) light petroleum (500 ml), 160 mg (**6**), TLC pure; (ii) 50% C_6H_6 in light petroleum (250 ml × 4), 2·45 g (**7**), m.p. 84–86°; (iii) benzene (500 ml × 2), 0·3 g, gum, rejected. Fraction (ii) (2·45 g) was recrystallized from MeOH and furnished pure ketone **7**, m.p. 88–89°.

(24 *S*)-A-*Nor*-3α-*acetyl*-24-*methyl*-9β,19-*cyclo*-5α-*lanostane* (**8**)

The ketone **7** (0·2 g) was refluxed (2 hr) with 5% EtOH–KOH (25 ml, N_2) and the product was worked-up in the usual manner. The neutral fraction (0·19 g) was chromatographed on SiO_2–gel/I (10 cm × 1 cm) and the main fraction (0·17 g) after crystallization from MeOH afforded plates of pure **8**, m.p. 102–104°, $[\alpha]_D$ +54° (c, 1·1%). IR: C=O 1710 cm^{-1}. Mass: *m/e* 426 (M$^+$, 40%), 43 (100%), 95 (46%), 383 (44%), 55 (37%), 41 (33%), 299

(28%), 81 (25%), 109 (23%), 107 (25%), 411 (23%). (Found: C, 84·14; H, 11·70. $C_{30}H_{50}O$ requires: C, 84·44; H, 11·81%).

(24 *S*)-A-*Nor*-3α-*hydroxy*-24-*methyl*-9β,19-*cyclo*-5α-*lanostane* (**9**)

A mixture of **8** (3·2 g), 85% *m*-chloroperbenzoic acid (1·94 g) and ether (30 ml) was kept at room temp (~ 27°) in the dark for 60 days. It was diluted with ether (100 ml) and worked-up[36] to give a neutral fraction (3·37 g) which on TLC (silica gel; solvent: benzene) showed two spots. Hydrolysis (5% EtOH–KOH) of the above mixture gave a product (3·35 g), which was chromatographed on SiO_2–gel/I (30 cm × 2 cm): (i) 20% C_6H_6 in light petroleum (250 ml × 3), 0·55 g (**8**); (ii) benzene (250 ml × 3), 2·1 g (**9**), m.p. 92–97°; (iii) 10% MeOH in C_6H_6 (250 ml), 0·13 g, mixture, discarded. Fraction (ii) was recrystallized with MeCN and gave **9** as plates. m.p. 96–98°, $[\alpha]_D$ +44° (c, 0·9%). IR: OH 3250 cm^{-1}. (Found: C, 83·33; H, 11·92. $C_{28}H_{48}O$ requires: C, 83·83; H, 12·08%).

(24 *S*)-A-*Nor*-3β-*hydroxy*-24-*methyl*-9β,19-*cyclo*-5α-*lanostane*

A mixture of **7** (3·2 g), 85% *m*-chloroperbenzoic acid (1·94 g) and ether (30 ml) was kept at room temp (~ 27°) in dark for 60 days and then worked up and hydrolyzed as described above. The neutral fraction (3·38 g), thus obtained, was chromatographed on SiO_2–gel/I (20 cm × 4 cm): (i) 10% C_6H_6 in light petroleum (250 ml × 2), 120 mg, TLC mixture; (ii) 20% C_6H_6 in light petroleum (250 ml × 7), 2·12 g (**8**), m.p. 84–86°; (iii) 5% EtOAc in benzene (250 ml × 3), 0·6 g, TLC pure. Fraction (iii) (0·6 g) was recrystallized from MeOH–MeCN to give the title compound, m.p. 68–70°, $[\alpha]_D$ +77° (c, 0·8%). IR: OH 3450 cm^{-1}. (Found: C, 84·12; H, 11·95. $C_{28}H_{48}O$ requires: C, 83·98; H, 12·08%).

Action of trifluoroper-acetic acid on ketone (**7**): (24 *S*)-A-*nor*-3β-*acetyl*-24-*methyl*-5α-*lanostan*-11-*one* (**23**).

A soln of CF_3CO_3H (1 ml) [prepared[37] from $(CF_3CO)_2O$ (6·8 ml), 90% H_2O_2 (1 ml) and CH_2Cl_2 (20 ml)] was added, to a stirred suspension of finely powdered anhyd K_2HPO_4 (0·6 g) in a solution of **7** (0·35 g) in CH_2Cl_2 (10 ml), and the mixture gently refluxed (5 hr). The mixture was filtered and worked-up with CH_2Cl_2 in the usual manner, to furnish a product (0·33 g) which was TLC pure (silica gel; solvent: benzene). On crystallization from MeOH, it furnished as plates 0·19 g **23**, m.p. 143–145°, $[\alpha]_D$ +63° (*c*, 0·95%). Mass: *m/e* 442 (M^+; 100%), 43 (83%), 41 (46%), 95 (44%), 55 (44%), 372 (36%), 91 (32%), 107 (28%), 93 (28%), 79 (28%), 121 (24%). (Found: C, 81·87; H, 11·71. $C_{30}H_{50}O_2$ requires: C, 81·39; H, 11·38%).

(24 *S*)-*A-Nor*-3α-*hydroxy*-24-*methyl*-9β,19-*cyclo*-5α-*lanostane* (**9**)

A soln of CF_3CO_3H (1·8 ml) [prepared as described above] was added to a stirred suspension of finely powdered anhyd. K_2HPO_4 (0·8 g) in a solution of **8** (0·3 g) in CH_2Cl_2 (10 ml) and gently refluxed (5 hr). The mixture after usual work-up gave a product (0·3 g) which showed on TLC (silica gel; solvent: benzene) two spots at R_f 0·63 and 0·56. It was chromatographed on SiO_2-gel/I (14·5 cm × 2 cm): (i) light petroleum (100 ml), nil; (ii) 5% C_6H_6 in light petroleum (50 ml × 4), 245 mg (R_f 0·63); (iii) 20% C_6H_6 in light petroleum (60 ml), 20 mg (R_f 0·56). Fraction (iii) (20 mg) was shown (IR) to be slightly impure sample of **8**, m.p. 92–98°.

Fraction (ii) (245 mg) on hydrolysis (5% EtOH–KOH) (2 hr reflux; N_2), followed by usual work-up, gave a product (225 mg; TLC pure) which was chromatographed on SiO_2–gel/I (14 cm × 2 cm) and the major fraction (195 mg, m.p. 93–98°) was crystallized from MeCN to give pure **9** as plates, m.p. 101–103°.

(24 *S*)-*A-Nor*-3-*oxo*-24-*methyl*-9β,19-*cyclo*-5α-*lanostane* (**10**)

Alcohol **9** (0·3 g) in acetone (15 ml)–ether (5 ml) mixture was cooled to 0° and then treated with Jones reagent (1 ml; N_2) [stock soln; prepared by dissolving 26·72 g CrO_3 "in 23 ml of conc HSO_4 diluted with water to a volume of 100 ml".] The mixture after 5 min was diluted with MeOH (5 ml)-water (50 ml), and extracted with ether (30 ml × 3). After usual washings and drying (Na_2SO_4) it furnished, on solvent removal, a product (296 mg) which on TLC (silica gel; solvent: 20% C_6H_6 in hexane, double irrigation) showed two spots at R_f 0·18 (major) and 0·27 (minor). This product was crystallized from MeCN–MeOH and gave as plates 0·18 g **10**, m.p. 79–80°, $[\alpha]_D$ −20° (*c*, 1·9%). IR: C=O 1745 cm^{-1}. Mass: *m/e* 398 (M^+; 43%), 271 (100%), 43 (75%), 95 (52%), 55 (43%), 107 (34%), 81 (34%), 109 (27%), 93 (27%), 91 (27%), 41 (27%). (Found: C, 84·61; H, 11·79. $C_{28}H_{46}O$ requires: C, 84·35; H, 11·63%).

(24 *S*)-*A-Nor*-3-*oxo*-24-*methyl*-9β,19-*cyclo*-5β-*lanostane*

(i) *By the action of basis* Al_2O_3 *on* **10**. The above mother liquor (0·11 g) was loaded on a column of basis Al_2O_3/I (9 cm × 2 cm) and eluted with light petroleum (150 ml) after 1 hr. The product (80 mg, m.p. 86–89°), thus obtained was crystallized from MeOH and gave as plates pure β-epimer of **10**, m.p. 94–96°, $[\alpha]_D$ +200° (*c*, 0·66%). IR: C=O 1745 cm^{-1}. Mass: *m/e* 398 (M^+; 27%), 271 (100%), 43 (83%), 96 (41%), 41 (33%), 55 (31%), 95 (29%), 81 (21%), 91 (17%), 69 (17%), 57 (16%). (Found: C, 85·04; H, 11·40. $C_{28}H_{46}O$ requires: C, 84·35; H, 11·63%).

(ii) *By the action of* p-*toluenesulphonic acid on ketone* **10**. The ketone **10** (7·54 g) in CH_2Cl_2 (50 ml) was treated with *p*-toluene-sulphonic acid (25 mg) at room temp (~ 27°) for 36 hr. The product after usual work-up, was purified over a column of SiO_2-gel/I (20 cm × 4 cm): benzene (500 ml) eluted as the major fraction (6·65 g), the β-epimer of **10** (m.p. 93–95°), which was recrystallized from MeOH, m.p. 94–96°.

(24 *S*)-*A-Nor*-3-*methylene*-24-*methyl*-9β,19-*cyclo*-5β-lan-*ostane* (**11**)

The β-epimer of **10** (2·53 g) in dry ether (20 ml) was added to a suspension of triphenyl-phosphonium methyl iodide[38] (6·7 g) and dried (freshly prepared) t-BuOK (1·74 g) in dry ether (100 ml) in an atmosphere of N_2 gas. After addition was complete (10 min), the product was stirred for another 2 hr (~ 27°), filtered and the residue washed with ether (~ 150 ml). The combined ether extracts were washed with water (25 ml × 7), brine (20 ml × 2) and dried (Na_2SO_4). Solvent removal furnished a product which was chromatographed over SiO_2-gel/I (35 cm × 2 cm): light petroleum (250 ml × 2) eluted olefin **11** (2·44 g, TLC pure), which solidifies m.p. 46–48° on keeping (1 week) at 0°; $[\alpha]_D$ +12·8° (*c*, 1·05%). IR: CH_2=C 890, 1645 cm^{-1}. Mass: *m/e* 396 (M^+; 80%), 147 (100%), 43 (90%), 95 (53%), 55 (51%), 269 (50%), 41 (50%), 91 (42%), 107 (40%), 93 (39%), 81

(34%). (Found: C, 87·48; H, 12·27. $C_{29}H_{48}$ requires: C, 87·80; H, 12·20%).

Diketone (13). The olefin 11 (2 g) was added in one lot to a stirred soln. of N-lithioethylenediamine complex[10] (from Li 2 g, $NH_2{\cdot}CH_2{\cdot}CH_2{\cdot}NH_2$ 60 ml; N_2) at 120–125° (bath temp) and the mixture maintained at this temp for 7 min. The product obtained after usual work-up was subjected to a stream of ozonized O_2 (O_3 conc 0·8 g/hr) in a 1:1 CH_2Cl_2-MeOH (230 ml) mixture at −70° for 25 min. The crude "ozonide" after solvent removal (~ 35°/50 mm) was oxidatively decomposed with Jones reagent. The neutral fraction (1·88 g) obtained after usual work-up was chromatographed on SiO_2-gel/I (50 cm × 2 cm):

Fr. 1	Light petroleum	500 ml	nil
Fr. 2	25% C_6H_6 in light petroleum	500 ml	80 mg, TLC mixture, rejected.
Fr. 3	50% C_6H_6 in light petroleum	500 ml	
Fr. 4	benzene	250 ml	0·1 g, essentially (13) TLC pure.
Fr. 5	benzene	250 m × 3	0·53 g (13), m.p. 96–99°.
Fr. 6	benzene	250 ml	0·15 g essentially (13) TLC pure.
Fr. 7	20% EtOAc in C_6H_6	500 ml	0·5 g, tailings, rejected.

Fr. 5 (0·53 g) was crystallized from MeOH–MeCN and furnished as needles, the diketone 13, m.p. 101–102°, $[\alpha]_D$ +42° (*c*, 1%). Mass: *m/e* 428 (M^+; 43%), 43 (100%), 55 (43%), 41 (38%), 95 (36%), 107 (34%), 69 (25%), 161 (22%), 93 (22%), 81 (22%), 57 (21%). (Found: C, 80·58; H, 11·21. $C_{29}H_{48}O_2$ requires: C, 81·25; H, 11·29%).

(24 *S*)-9β,19-*Cyclo*-14α,24-*dimethyl-cholest*-4-*en*-3-*one* (14)

A mixture of 13 (0·36 g) in dry MeOH (75 m) containing 4 m of 10% KOH aq, was refluxed on a steam bath (4 hr; N_2). The reaction product after usual work-up was chromatographed on SiO_2-gel/I (15 cm × 1 cm): (i) light petroleum (400 ml), 50% C_6H_6 in light petroleum (100 ml), 50 mg, TLC mixture, rejected; (ii) benzene (100 ml), 175 mg, TLC pure; (iii) 5% EtOAc in C_6H_6 (150 ml), 30 mg, *tailing, discarded*. Fraction (ii) (175 ml) was rechromatographed over SiO_2-gel/I (10 cm × 1 cm) and the major fraction (120 mg) eluted with 50% C_6H_6 in light petroleum (50 ml × 3) was recrystallized from MeCN–Me_2CO to give 83 mg of pure 14, m.p. 73–75°, $[\alpha]_D$ +27° (*c*, 1·3%). Mass: *m/e* 410 (M^+; 71%), 43 (100%), 283 (77%), 55 (67%), 122 (62%), 41 (58%), 161 (57%), 95 (57%), 107 (54%), 93 (54%), 81 (52%). (Found: C, 84·70; H, 11·28. $C_{29}H_{46}O$ requires: C, 84·87; H, 11·22%).

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