Tetrahedron Vol. 38, No. 1, pp. 201 to 208, 1982
Printed in Great Britain.

0040-4020/82/010201-08$03.00/0

HIGHER ISOPRENOIDS—XII[a]

PARTIAL SYNTHESES FROM CYCLOARTENOL, CYCLOLAUDENOL-PART 4: A NOVEL METHOD FOR FUNCTIONALIZATION OF C-4 METHYL IN TRITERPENOIDS, AND SYNTHESIS OF CYCLODEUCALANONE[b,c,d]

MANOJ C. DASAI, CHANDAN SINGH,[e] H. P. S. CHAWLA and SUKH DEV
Malti-Chem Research Centre, Nandesari, Vadodara, India

(*Received in UK 29 June* 1981)

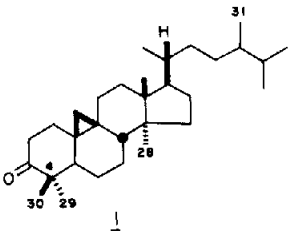
Abstract—A general method for selective oxygenation of C-4-Me in triterpenes, leading finally to 4α-carboxyl/4α-hydroxymethyl functionalities, is described. The key-step involved is phytolysis of hypoiodite derived from 3β-hydroxymethyl derivative of the triterpene. The method is illustrated by the conversion of cyclolaudanone (1) into methyl 3-oxo-cyclolaudan-29-oate (2). The latter has been converted into the known cycloeucalanone (3) by a simple sequence of reactions.

A number of triterpenoids having a 4α-hydroxymethyl or 4α-carboxyl function and the corresponding 4-desmethyl derivatives are known to occur in nature.[1,2] As a matter of fact, demethylation at C-4 during the bioconversion of triterpene precursors to sterols (e.g. lanosterol → cholesterol) is known to proceed by way of 4α-Me hydroxylation.[3] Thus, 4α-Me oxygenation is an important biosynthetic operation, and it was the purpose of the present investigation to mimic this in the laboratory. Indeed, considerable effort in this direction has been expended earlier by several groups. However, most of the known methods for the functionalization of a C-4 Me group, whether proceeding *via* 3,4-secotriterpenoids[4–7] or directly[8–11] suffer from one or more of the following shortcomings: the methods either require difficulty accessible starting materials obtainable by multi-step sequences (from the triterpene), or were non-regioselective or gave poor yields. We now describe a general, reasonably efficient method for the functionalization of 4α-Me group (in triterpenoids) with high regioselectivity: specifically, cyclolaudanone (1) has been converted into methyl 3-oxo-cyclolaudan-29-oate (2) and thence into the known[12] cycloeucalanone (3).

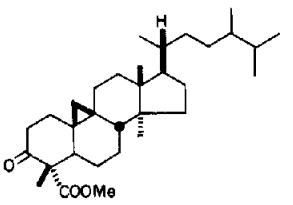
[a]Part XI: *Tetrahedron* 37, 2935 (1981).
[b]MRC Communication No. 26.
[c]Abstracted from the Ph.D Thesis of Chandan Singh (Poona University, 1976) and Manoj C. Desai (M. S. University, Baroda, 1980).
[d]Preliminary Communication: *Tetrahedron Letters* 5047 (1979).
[e]Present address: Central Drug Research Institute, Lucknow, India.

Strategy

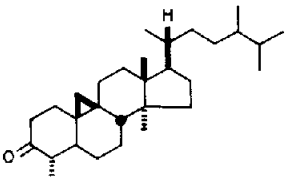
It was envisaged that photolytic decomposition of hypoiodite[13] derived from an OH function suitably disposed with respect to the 4-Me in a triterpene, could result in the desired functionalization. The structural and stereochemical requirements of such reactions have been extensively studied,[13,14] and it is well-recognized that the



1



2



3

reaction proceeds well in the desired direction only if the internuclear distance between the O and the concerned C falls between 2.5–2.7 A°, and a 6-membered chair conformation transition state is possible.

In terms of above considerations, molecular models (Dreiding) of three possible substrates (**4–6**) for functionalization of C-29 Me in cyclolaudane, were examined. 2α-Hydroxycyclolaudane (**4**) can fulfil the requirements *albeit* after forcing ring A into a boat-like conformation[15] (as in **7**); this, however, does not appear to be a significant constraint, as cases of efficient functionalization of an unactivated carbon requiring chair→boat flipping are on record.[16] 3α-Hydroxymethylcyclolaudane (**5**) would appear to be ideal for the purpose on hand. On the other hand, the 3β-epimer (**6**) can adopt conformations (**8**, **9**) so as to functionalise either of the two Me groups at C-4. However, a closer scrutiny reveals that functionalisation of C-29 Me should be preferred for the following reasons: (a) in conformation **8**, the 6-membered transition state simulates a *trans*-fused relationship with ring A and hence should experience less 1,3-diaxial type interactions and should be preferred over **9** which has a similar "*cis*-fused" disposition, (b) in **8** C–OH (of CH_2OH group) is flanked (**10**) by a "small" (H atom) and a "large" (C-4) groups in contrast to **9** in which these groups are "medium" (C-2) and "large" (C-4) (see **11**).

From practical considerations, it was obvious that the choice of **6** would only be appropriate. However, **4** was also synthesised and examined for the functionalisation reaction and the results fully vindicate the reasoning given above; for obvious reasons no attempt was made to pursue further transformation of this product to the desired goal.

RESULTS

Synthesis and functionalisation reaction of 2α-hydroxy-3β-methylcyclolaudane (**14**)

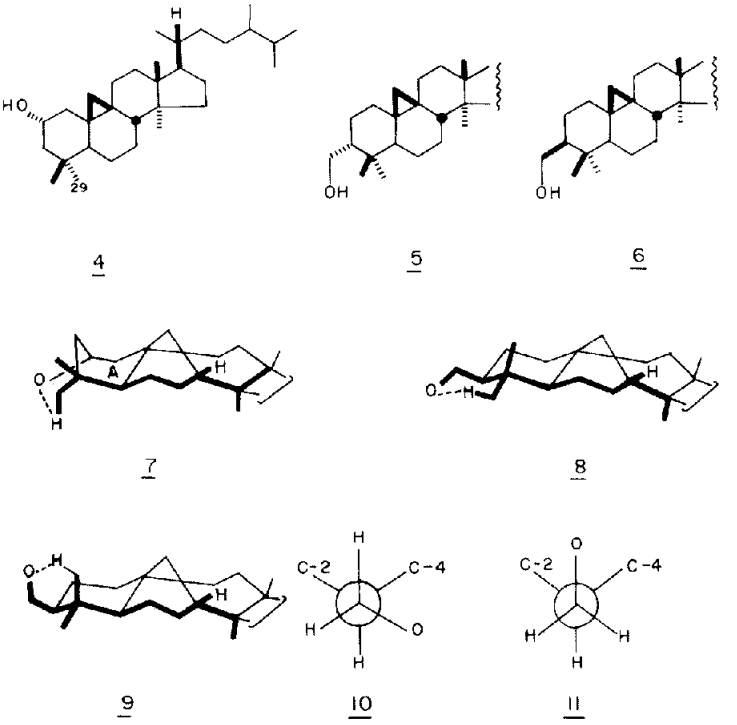
Treatment of cyclolaudanone (**1**) with methylenetriphenylphosphorane yielded **12** (84%), which readily isomerised on exposure to silica gel to furnish **13** (91%). Hydroboration of **13** with a stoichiometric quantity of B_2H_6 gave, as expected, an epimeric mixture, in which the required 2α-isomer (**14**) predominated (75%; 9:1, PMR). Assignment of stereochemistry to **14** rests on the expected preferential attack of the reagent from the α-face of the molecule and the PMR spectral characteristics[17] CHOH; (Table 1) of the two isomers.

Irradiation of **14** in presence of $Pb(OAc)_4$ and I_2, followed by Jones' oxidation of the product, gave a compound, characterised as the lactone **15** (40%) on the basis of analytical and spectral data. IR: γ-lactone, 1782 cm^{-1}; PMR (Table 1), CHOCO (1H, bd, 4.33 ppm, J = 4 Hz). That **15** has the stereochemistry shown, follows from that of the substrate (**14**).

Synthesis and functionalization reaction of 3β-*hydroxyalkylcyclolaudanes*

In the initial phases of this work hydroxyethyl alcohol (**17**), rather than the hydroxymethyl alcohol (**6**), was selected as the substrate. The choice was dictated by the expected more efficient Baeyer–Villiger oxidation of the intermediate carbonyl compound (Fig. 1), when it was a methyl ketone (**20**), rather than an aldehyde (**21**). Additional consideration was regioselectivity for the intermediate ether to lactone (**18**/**19**) oxidation. Added stereochemical complexity in **17** was considered unimportant, as the new centre will be finally lost. However, the route from the hydroxymethyl alcohol (**6**) was, finally, found to be much more convenient. Figure 1 depicts the reaction sequence employed.

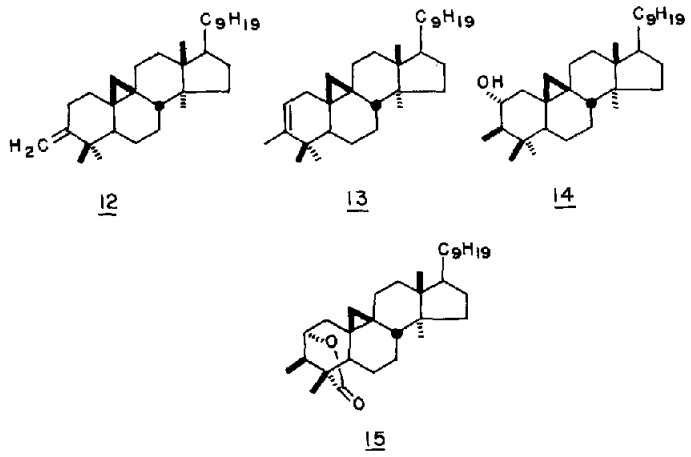
Cyclolaudanone (**1**) on exposure to ethylidenetripenylphosphorane gave a mixture of olefins **16** (*E*/*Z*) which on hydroboration, followed by oxidative (H_2O_2) work-up gave, as expected, a mixture of four alcohols, which were separated. The most abun-



4 5 6

7 8

9 10 11



12 13 14 15

dant alcohol (**17**, m.p. 145–148°; 32*R*)[18] was assigned 3β-configuration, in view of the preferred α-face attack in such systems.[18] This alcohol when irradiated in presence of $Pb(OAc)_4$ and I_2 furnished an iodotetrahydrofuran, which without isolation was oxidised (Jones' reagent) to get the desired lactone **18** (32*R*) in ~50% yield: C=O (IR; 1773 cm^{-1}), C<u>H</u>(Me) OCO (PMR: 1H, m, 4.10–4.40 ppm). The formation of a tetrahydrofuran or an iodotetrahydrofuran is largely dependent[13,14] on the conformation of the intermediate iodohydrin radical of the type **22**. In the present case, of the three conformations (**22a–22c**) relevant to our discussion, **22c**

Table 1. PMR spectral characteristics of various cyclolaudane derivatives

Compound	Chemical shift in ppm (δ)		
	Cyclopropyl CH_2*	C-Me's§	Other signals†
Cyclolaudanone (1)	0.56, >0.75¶	0.84,0.92,1.0,1.07	
3-Methylenecyclolaudane (12)	0.40, 0.67	0.78,0.84,0.91,1.0,1.08	C=C<u>H</u>$_2$,bs,4.62&4.69
3-Methylcyclolaud-2-ene (13)	0.33, 0.62	0.84,0.93,0.94,1.0	CH_3C=C,s,1.69; C=C<u>H</u>,m,5.20-5.42
2β-Hydroxy-3α-methylcyclolaudane	0.38, 0.53	0.76,0.81,0.84,0.93, 0.98,1.07	C<u>H</u>OH,m,3.64-3.84 ($\bar{W}_H$=8Hz)
2α-Hydroxy-3β-methylcyclolaudane (14)	0.36, 0.56	0.71,0.84,0.93,0.98,1.02	C<u>H</u>OH,m,3.20-3.50 ($\bar{W}_H$=13Hz)
Lactone (15)	0.11,>0.75¶	0.76,0.82,0.84,0.89, 0.96,1.08	C<u>H</u>OCO,bd,4.33(J=4Hz)
3α-Hydroxymethylcyclolaudane	0.33, 0.57	0.78,0.85,0.91,0.93, 0.99,1.0	C<u>H</u>$_2$OH,m,3.61-3.90
3β-Hydroxymethylcyclolaudane (6)	0.33, 0.53	0.71,0.78,0.85,0.93,0.94	C<u>H</u>$_2$OH,m,3.70-3.98
Lactone (19)	0.18,>0.78¶	0.78,0.84,0.93,0.96,1.09	C<u>H</u>$_2$OCO,m,3.78-4.28
Methyl 3β-hydroxymethylcyclolaudan-29-oate (23)	0.36, 0.56	0.76,0.84,0.91,0.98,1.09	C<u>H</u>$_2$OH,d,3.47(J=8Hz); CO_2C<u>H</u>$_3$,s,3.71
Methyl 3β-formylcyclolaudan-29-oate (21)	0.37, 0.60	0.78,0.84,0.93,0.97,1.07	CO_2C<u>H</u>$_3$,s,3.74;C<u>H</u>O, s,9.46
Methyl 3-oxocyclolaudan-29-oate	0.55,>0.78¶	0.78,0.84,0.91,0.96,1.0	4β-C<u>H</u>$_3$,s,1.33; CO_2C<u>H</u>$_3$, s, 3.73
32R-3β-(1-Hydroxyethyl)cyclolaudane (17)	0.31, 0.53	0.78,0.84,0.87,0.92, 0.98,1.02	C<u>H</u>OH,m,3.55-3.75
Lactone 18	0.22,>0.77¶	0.77, 0.78,0.84,0.91, 0.93,1.11	CH_3C-O,d,1.37(J=6Hz); C<u>H</u>OCO,m,4.13-4.38
Methyl 3β(1-hydroxyethyl)-cyclolaudan-29-oate (24)	0.27, 0.50	0.70,0.72,0.78,0.86, 0.91,1.03	CO_2C<u>H</u>$_3$,s,3.60
Methyl 3β-acetylcyclolaudan-29-oate (20)	0.31, 0.54	0.70,0.78,0.84,0.89,0.98	COC<u>H</u>$_3$,s,1.96;CO_2C<u>H</u>$_3$, s,3.64
Methyl 3β-hydroxycyclolaudan-29-oate (25)	0.32, 0.58	0.72,0.80,0.87,0.92,1.07	CO_2C<u>H</u>$_3$,s,3.68;C<u>H</u>OH, m, 4.0-4.18
Diester 26	0.36, 0.58	0.76,0.82,0.90,0.93,1.02	CO_2C<u>H</u>$_3$,singlets at 3.60 and 3.67
Cycloeucalanone (3)	0.32, 0.62	0.77,0.84,0.93,1.02	

*Each signal integrates for 1H and is a doublet (J=4Hz).
§Includes all the signals due to -C-Me's and HC-Me's.
†Signals are denoted by s, singlet, d, doublet, m, multiplet and b, broad.
¶Masked under other lower field signals.

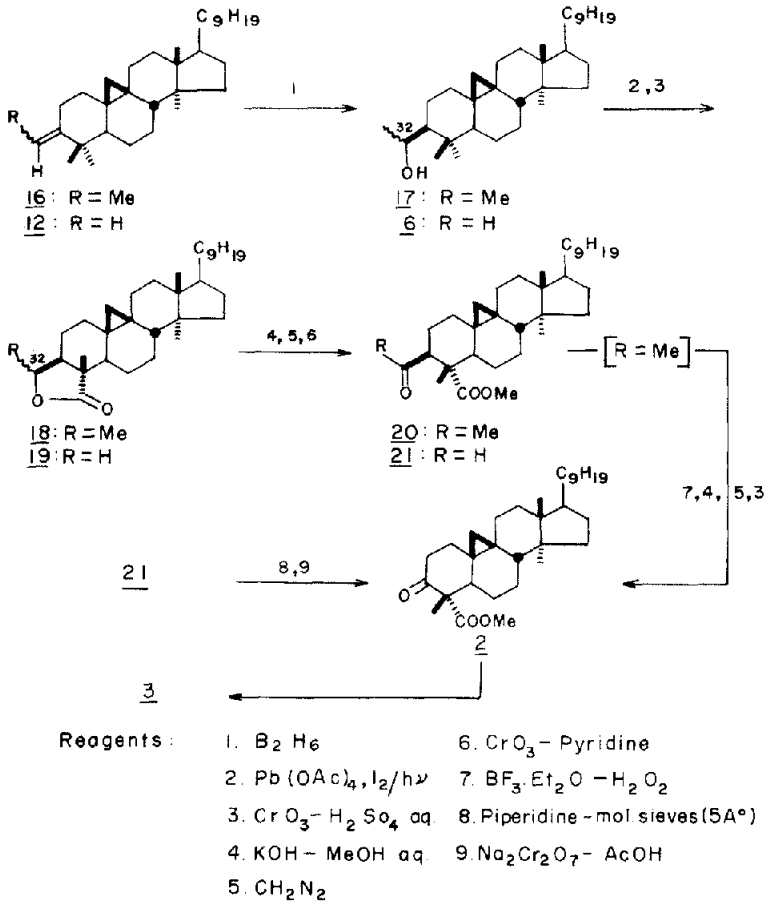


Fig. 1. 4α-Methyl functionalisation in cyclolaudane and synthesis of cycloeucalanone (3).

would be preferred (because of fewer non-bonded interactions)—a situation, known to favour formation of iodotetrahydrofurans.[13,14]

Likewise, olefin **12** on hydroboration with 9-borabicyclo[3,3,1]-nonane (9-BBN),[20] followed by oxidation, gave a mixture (86%) of 3α- and 3β-hydroxymethyl derivatives in which the latter (**6**) predominated (15:85).[21] The stereochemical assignments for these alcohols were confirmed by their ^{13}C-NMR spectra [$\underline{C}H_2OH$: β-isomer (equatorial), 61.4 ppm; α-isomer (axial), 64.5 ppm; see Ref. 22], as well as PMR spectra of the corresponding aldehydes, obtained by CrO_3-pyridine oxidation [$\underline{C}HO$: β-isomer (equatorial), 9.77 ppm; α-isomer (axial), 10.00 ppm; Table 1; see Ref. 23]. Irradiation of **6** in presence of $Pb(OAc)_4$ iodine, followed by oxidation, gave a product from which the required lactone **19** (IR: C=O 1779 cm^{-1}. PMR: $\underline{C}H_2OCO$, 2H, m, 3.78–4.28 ppm) was isolated in ~50% yield.

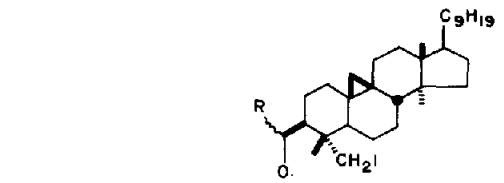
Conversion of lactones **18**, **19** *to cycloeucalanone* (**3**)

The fact that in both lactones (**18**, **19**) it is 4α-Me that has been functionalised becomes clear from the spectral data collected for the intermediates during their conversion to the β-ketoester (**2**), as described below, as well as their ultimate transformation to cycloeucalanone (**3**).

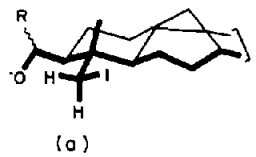
Lactone **19** was hydrolysed and esterified (CH_2N_2) to give hydroxy ester **23**. The methoxycarbonyl group in **23** was easily assigned α-configuration based on its spectral characteristics. IR: C=O 1720 cm^{-1}, C–O 1245 cm^{-1} (no adsorption due to an axial CO_2Me[24] at 1155 cm^{-1}); PMR: (Table 1), cyclopropyl $\underline{C}H_2$ (0.30 and 0.56 ppm) experience no upfield shift expected from an axial CO_2Me group.[25] The most convincing evidence was provided by the appearance of a signal at 10.34 ppm in ^{13}C-NMR of **23** because in 3β-hydroxy-triterpenoids carrying 4,4-dimethyl groups, 4β-methyl C atom signal appears comparatively upfield (14.00–16.00 ppm)[19,26] and a further upfield shift of ~5.0 ppm is observed[19] when 4α-Me group is replaced by 4α-CO_2Me group.

Oxidation of **23** with CrO_3-pyridine, smoothly furnished the corresponding formyl ester **21** (IR: CHO 2710, 1728 cm^{-1}. PMR: $\underline{C}HO$, 1H, s, 9.46 ppm). This was converted into the corresponding enamines (*E*/*Z*) which were directly oxidised ($Na_2Cr_2O_7$-AcOH) to furnish the desired β-keto ester **2** (IR: C=O 1705 cm^{-1}; CO_2Me 1735 cm^{-1}) in an overall yield of 50% from the hydroxy ester **23**.

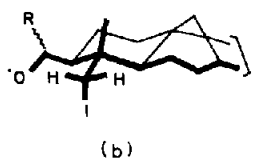
The β-keto ester (**2**) was also obtained from the lactone **18** which was hydrolysed and esterified (CH_2N_2) to give the hydroxyester **24** (IR: OH 3470 cm^{-1}; C=O 1715 cm^{-1}, C–O 1251 cm^{-1}). The latter was oxidised to the keto ester **20** (IR: C=O 1705 cm^{-1}. PMR: $\underline{C}OMe$ 3H, s, 1.96 ppm; $\underline{C}OCH$ 1H, t, 2.91 ppm; Table 1) Baeyer–Villiger oxidation[27] (BF_3·Et_2O–H_2O_2) of **20**, followed by hydrolysis and reesterification (CH_2N_2) gave a mixture of methyl 3β-hydroxycyclolaudan-29-oate **25** (PMR: $\underline{C}HOH$, 2H, m, 4.0–4.18 ppm, Table 1) and the diester **26** (PMR:



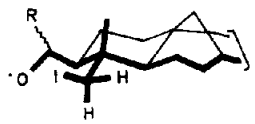
22



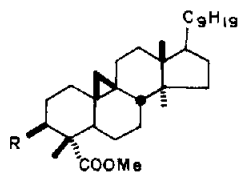
(a)



(b)



(c)



23 : R = CH_2OH
24 : R = CH(OH)Me
25 : R = OH
26 : R = CO_2Me

CO_2Me, two 3H singlets at 3.60 and 3.67 ppm). Oxidation of **26** with Jones' reagent gave the β-ketoester **2** which was identical with that obtained from lactone **19**.

Exposure of **2** to NaCN in hexamethylphosphoric triamide resulted[28] in hydrolysis with concomittant decarboxylation to furnish the known[12] cycloeucalanone (**3**) in 81% yield: m.p. 109–110°, $[\alpha]_D$ +49.7° ($CHCl_3$). (Lit.[12]: m.p. 107–108°, $[\alpha]_D$ +49.0°.

EXPERIMENTAL

All m.ps are uncorrected. Light petroleum refers to the fraction of b.p. 60–80°. Optical rotations were measured in $CHCl_3$ on a Schmidt-Haensch electronic polarimeter (model Polartronic-I).

The following instruments were used for spectral/analytical data: Perkin Elmer spectrophotometer model 402 (UV); Perkin-Elmer Infracord model 267; Perkin-Elmer model R32 (90 MHz) NMR spectrometer; Varian Mat CH7 mass spectrometer (70 eV, direct inlet system). While summarising mass spectral data, besides the molecular ion, nine most abundant ions (*m/e*) are reported with their relative intensities (Table 2).

Silica gel for column chromatography (−100, +200 mesh) was washed with hot water till sulphate-free, dried and activated at 125–130° for 6 hr and standardised.[33] Tlc was carried out on SiO_2-gel layers (0.25 mm) containing 15% gypsum and activated at 110–115° (2 hr).

Cyclolaudanone (**1**). A soln of cyclolaudanol[29] (21.0 g, 0.047 mole) in a mixture of acetone-isopropyl ether (1:1, 160 ml) cooled to 0°, was treated (N_2) with Jones' reagent[30] (40 ml). The mixture was stirred (1 hr), diluted with water (150 ml) and worked up in the usual manner to give a product which was crystallised from Et_2O–MeOH to furnish **1** (18.8 g, 90%), m.p. 107–109°. IR (CCl_4): C=O 1700 cm^{-1}. (Found: C, 84.70; H, 12.03. $C_{31}H_{52}O$ requires: C, 84.55; H, 11.83%).

3-Methylenecyclolaudane (**12**). To a suspension of methyltriphenylphosphonium iodide (18.6 g, 0.046 mole) and t-BuOK (5.1 g, 0.046 mole) in 100 ml of anhydrous THF was added (30°, N_2, 0.5 hr) a soln of **1** (14.0 g, 0.032 mole) in THF (40 ml). After stirring (30°) for 2.5 hr, most of THF was distilled off and the residue was worked up in the usual manner to give a product which was chromatographed over SiO_2-gel (I, 3.5 cm × 30 cm). Elution with light petroleum provided the desired olefin **12** (11.7 g, 84%), m.p. 100–102° (Et_2O–MeOH). IR (CCl_4): C=CH_2 1640, 896 cm^{-1}. (Found: C, 87.50; H, 12.21. $C_{32}H_{54}$ requires: C, 87.67; H, 12.33%).

3-Methylcyclolaud-2-ene (**13**). A soln of **12** (6.0 g, 0.014 mole) in light petroleum (20 ml) was loaded on a SiO_2-gel column (50 g, 2.3 cm × 25 cm) and allowed to stand for 0.5 hr at room temp (27°). The column was then eluted with light petroleum (200 ml) and the eluate stripped free of solvent to provide **13** (5.5 g, 91.6%), m.p. 123–125° (Et_2O–MeOH). (Found: C, 87.54; H, 12.12. $C_{32}H_{54}$ requires: C, 87.67; H, 12.33%).

Hydroboration of olefin **13**. To a cooled (0–5°) soln of the olefin **13** (5.0 g, 0.011 mole) in dry THF (100 ml) was added a stock soln of diborane (5.86%, 1.4 ml, 0.0057 mole) and the contents were stirred (~27°) for 5 hr. After cooling (0°), the mixture was decomposed with water (5 ml) and then treated with 3N NaOH aq (7.5 ml) and H_2O_2 (30% w/v, 7.5 ml). It was stirred (~27°) for 4 hr, diluted with water (50 ml) and extracted with ether (100 ml × 3). Usual work-up furnished a semisolid (3.9 g)

Table 2. Mass spectral data for various cyclolaudane derivatives

Compound	m/e (%)
Cyclolaudanone (1)	440(M^+,100), 426(43), 313(83), 121(32), 109(60), 107(34), 95(60), 83(32), 71(36), 69(38).
3-Methylenecyclolaudane (12)	438(M^+,75), 312(52), 135(52), 121(64), 109(75), 107(64), 95(100), 83(49), 81(44), 69(45).
3-Methylcyclolaud-2-ene (13)	438(M^+,100), 424(28), 423(62), 311(18), 136(16), 135(75), 133(16), 121(16), 109(23), 95(23).
2α-Hydroxy-3β-methylcyclolaudane (14)	456(M^+,100), 441(51), 438(51), 329(51), 302(42), 175(43), 163(40), 109(55), 95(85), 71(64).
Lactone 15	468(M^+,96), 341(100), 121(40), 109(35), 107(49), 95(72), 93(28), 81(35), 69(30), 55(35).
3α-Hydroxymethylcyclolaudane	456(M^+,100), 442(49),441(77), 329(32), 302(54), 175(43), 121(32), 109(48), 107(34), 95(71).
3β-Hydroxymethylcyclolaudane (6)	456(M^+,100), 442(49), 441(70), 329(59), 302(59), 175(38), 121(33), 109(51), 107(35), 95(75).
Lactone 19	468(M^+,55), 454(21), 453(12), 342(27), 341(100), 192(19), 163(12), 109(13), 107(15), 95(22)
Methyl 3β-hydroxymethylcyclolaudan-29-oate (23)	500(M^+,82), 486(45), 441(54), 373(57), 341(39), 121(44), 109(55), 107(53), 95(100), 81(42)
Methyl-3-oxocyclolaud-29-oate (2)	484(M^+,100), 470(39), 425(50), 397(46), 358(28), 357(96), 302(33), 297(35), 175(28), 95(33).
32R-3β-(1-Hydroxyethyl)cyclolaudane (17)	470(M^+,13), 123(27), 121(32), 109(47), 107(44), 95(100), 83(24), 81(44), 71(35), 69(80).
Cycloeucalanone (7)	426(M^+,100), 411(24), 299(74), 136(33), 123(36), 121(29), 109(33), 107(34), 95(59), 81(28).

which was chromatographed on SiO_2-gel (II, 2.7 cm × 55 cm) with tlc monitoring (solvent, C_6H_6): (i) 10% light petroleum in C_6H_6, 100 ml × 6, 0.39 g of 2β-hydroxy-3α-methylcyclolaudane, R_f: 0.3, m.p. 121–123°; (ii) 10% light petroleum in C_6H_6, 3.51 g of **14**, R_f: 0.25, m.p. 132–134 (Et_2O–MeOH). IR (CCl_4): OH 3600 cm^{-1}. (Found: C, 84.53; H, 12.49. $C_{32}H_{56}O$ requires: C, 84.21; H, 12.28%).

Photocyclisation of alcohol **14**. A mixture of alcohol **14** (4.0 g, 0.088 mole), $Pb(OAc)_4$ (11.1 g, 0.025 mole) and iodine (2.9 g, 0.011 g atom) in anhydrous cyclohexane (200 ml) was stirred (N_2) and irradiated, with a 100 watt tungsten lamp, from below till refluxing ensued. The reaction mixture was irradiated and refluxed for a total of 2.5 hr after which it was cooled and filtered. The residue was washed with cyclohexane (100 ml). The combined cyclohexane extracts were washed with 10% $Na_2S_2O_3$ aq (50 ml), followed by water (75 ml × 2) and brine (25 ml) and passed through a small bed of anhyd Na_2SO_4. To the filtrate, pyridine (3 ml) was added and the solvents were removed by distillation under reduced pressure (100 mm, 30°). The residue was dissolved in acetone (5 ml), cooled to 0° and treated with Jones' reagent (10 ml, 5 min). The mixture was stirred for 1 hr and worked up in the usual manner to give a gummy product which was chromatographed over SiO_2-gel (II, 2.5 cm × 50 cm) with tlc monitoring (solvent, C_6H_6): (i) C_6H_6, 50 ml × 6, 1.63 g of lactone **15**, R_f, 0.25 (ii) EtOAc, 50 ml × 7, 2.5 g, mixture of more polar compounds (not investigated further). Frac. (i) was crystallised from Et_2O-MeOH to give **15** (39.8%), m.p. 187–189°. (Found: C, 82.37; H, 11.40. $C_{32}H_{52}O_2$ requires: C, 82.05; H, 11.11%).

Hydroboration of olefin **12**. *With* B_2H_6: Olefin **12** (5.0 g) was treated (N_2, ~27°, 12 hr) with diborane (5.86%, 1.7 ml) and after decomposition with water (5 ml), was oxidised (3N NaOH aq, 7.5 ml; 30% H_2O_2, 7.5 ml; 25°, 4 hr). Usual work-up gave a semisolid (3.73 g) which was chromatographed on SiO_2-gel (I, 2.7 cm × 55 cm) while monitoring with tlc (2% EtOAc in C_6H_6): (i) light petroleum, 100 ml × 5, 0.11 g of **12**; (ii) C_6H_6, 50 ml × 10, 0.96 g of a solid, R_f: 0.37; (iii) C_6H_6, 50 ml × 3, 0.21 g mixture, R_f, 0.37 and 0.33; (iv) C_6H_6, 50 ml × 12, 2.45 g, solid, R_f 0.33. Frac. (ii) was crystallised from Et_2O–MeOH to give 3α-hydroxymethylcyclolaudane, m.p. 136–38°. IR (Nujol): 3260, 1035 cm^{-1} (Found: C, 84.47; H, 12.38. $C_{32}H_{56}O$ requires: C, 84.21; H, 12.28%). Frac. (iv) was crystallised from Et_2O–MeOH to yield 3β-hydroxymethylcyclolaudane (**6**), m.p. 153–155°. IR (Nujol) OH 3300, 1040 cm^{-1} (Found: C, 84.37; H, 12.36. $C_{32}H_{56}O$ requires: C, 84.21; H, 12.28%).

With 9-BBN. Hydroboration with 9-BBN[20] gave a mixture (15:85) of 3α- and 3β-hydroxymethylcyclolaudanes (85%).

Photocyclisation of alcohol **6**. A mixture of **6** (1.9 g, 4.16 mmole), Pb $(OAc)_4$ (5.4 g, 12.19 mmole) and (1.39 g, 0.011 g atom) in cyclohexane (150 ml) was irradiated and worked up as described earlier to furnish a brown gum (2.2 g) which was chromatographed over SiO_2-gel (II, 2 cm × 50 cm) while monitoring with tlc (2% EtOAc in C_6H_6): (i) C_6H_6, 50 ml × 5, 0.9 g solid, R_f: 0.34; (ii) EtOAc, 100 ml × 2, 1.15 g, mixture of more polar compounds. Crystallisation of frac. (i) from Et_2O–MeOH furnished lactone **19** (46%), m.p. 205–207° (Found: C, 82.28; H, 11.19; $C_{32}H_{52}O_2$ requires: C, 82.05; H, 11.11%).

Methyl 3β-*hydroxymethylcyclolaudan*-29-*oate* (**23**). The lactone **19** (423 mg) was hydrolysed by refluxing (N_2, 3.5 hr) with 10% KOH ethanolic (15 ml) and after the usual work up with ether, the resulting hydroxy acid was esterified (CH_2N_2) to yield **23** (400 mg, 88.5%), m.p. 165–167° (Et_2O–MeOH). IR (CCl_4): OH 3600 cm^{-1}, CO_2Me 1720, 1245 cm^{-1}. ^{13}C-NMR ($CDCl_3$): 4β-Me (10.4 ppm), CO_2Me (51.6 ppm), CH_2OH (64.5 ppm), CO_2Me (178.7 ppm). (Found: C, 79.05; H, 11.19. $C_{35}H_{56}O_3$ requires: C, 79.20; H, 11.20%).

Methyl 3β-formylcyclolaudan-29-oate (**21**). To a stirred soln of CrO_3[31] (0.4 g, 4 mmole) and pyridine (0.316 g, 4 mmole) in CH_2Cl_2 (25 ml) cooled to 25° was added in one lot a soln of **23** (0.2 g, 0.4 mmole) in CH_2Cl_2 (2 ml) and the mixture was stirred (25°) for 1 hr. Usual workup gave a solid which was crystallised from Et_2O–MeOH to give the formylester **21** (0.156 g, 78%), m.p. 116–119°. IR (CCl_4): CO_2Me 1735, 1250 cm^{-1}. (Found: C, 79.69; H, 11.03. $C_{33}H_{54}O_3$ requires: C, 79.52; H, 10.84%).

Methyl 3-oxocyclolaudan-29-oate (**2**). A mixture of formylester **21** (100 mg, 0.2 mmole), piperidine (85 mg, 1 mmole) and molecular sieves (5A-type, 7 g, activated at 330° for 8 hr) in benzene (20 ml) was stirred (N_2) at room temp. (27°) until aliquots showed the absence of formyl proton in PMR (12 hr).[32] The mixture was then filtered and molecular sieves were washed with ether. The removal of solvents from the combined organic extracts gave a mixture of enamines which were redissolved in benzene (2.5 ml) and added dropwise (1 hr) to a soln of $Na_2Cr_2O_7 \cdot 2H_2O$ (150 mg) and AcOH (5 ml) in benzene (7 ml) at 0°. The mixture was further stirred (12 hr) at 30–35° and diluted with water (75 ml). The organic layer was washed with 10% NaOH aq (20 ml) and water (20 ml × 3) and dried. Removal of solvent and chromatography of the residue on alumina-II gave a product which on crystallisation from Et_2O–MeOH gave **2** (62 mg, 63.8%), m.p. 146–147°. (Found: C, 79.52; H, 10.83. $C_{32}H_{52}O_3$ requires: C, 79.34; H, 10.74%).

3β-(1-Hydroxyethyl)cyclolaudane (**17**). A soln of **1** (8.1 g, 0.018 mole) in THF (20 ml) was added in one lot to a suspension of ethylidenetriphenylphosphorane (0.033 mole, prepared from ethyltriphenylphosphonium iodide and t-BuOK) in THF (60 ml) at 35–40° and stirred at the temp for 24 hr. After refluxing for 6 hr the mixture was worked up in the usual manner to obtain a brown gummy product (16.5 g) which was chromatographed on SiO_2-gel (II, 3.5 cm × 25 cm) using light petroleum as eluant to get a colourless product (7.9 g) which was found to be a mixture of two compounds (R_f: 0.48 and 0.58) by tlc (SiO_2-gel-15% $AgNO_3$: solvent C_6H_6–light petroleum 1:1).

A part (2.68 g, 0.6 mmole) of mixture of olefins (**16**) obtained above was dissolved in THF (20 ml) and a soln of diborane (0.24 mmole) in THF (3 ml) was added to it in one lot. The mixture was stirred (25°) for 12 hr, cooled (0°), water (5 ml) added (dropwise, 10 min) followed by 3N NaOH aq (10 ml) and H_2O_2 (30%, 10 ml), stirred (30°, 1 hr) and extracted with ether (100 ml × 3). The ether extract was worked up as usual to get a white solid (2.65 g); the latter was shown to be a mixture of four compounds (R_f: 0.37, 0.47, 0.52 and 0.67) by tlc (SiO_2-gel; solvent 2% EtOAc in C_6H_6) and was chromatographed over SiO_2-gel (II, 2.5 cm × 80 cm): (i) light petroleum, 200 ml × 5, 20 mg of unreacted olefins; (ii) C_6H_6, 50 ml × 5, 150 mg, R_f 0.67 (iii) C_6H_6, 20 ml, 57 mg mixture of two compounds, R_f: 0.67 and 0.52; (iv) C_6H_6, 20 ml × 2, 180 mg, R_f: 0.52; (v) C_6H_6, 20 ml × 5; 286 mg, mixture of two compounds, R_f 0.47 and 0.37; (vi) C_6H_6, 20 ml × 5, 275 mg, mixture of two compounds, R_f 0.47 and 0.37; (vii) C_6H_6, 100 ml × 5, 1.265 g, R_f 0.37.

Frac. (ii) was crystallised from Et_2O–MeOH to give 32R-3α(1-hydroxyethyl)cyclolaudane, m.p. 117–118°, $[\alpha]_D$ + 56 (*c*, 0.7). IR (Nujol): OH 3400 cm^{-1}. Frac. (iv) was crystallised from MeOH to give 32S-3β-(1-hydroxyethyl)cyclolaudane, m.p. 158–160°, $[\alpha]_D$ + 64° (*c*, 0.87). IR (Nujol): OH 3490 cm^{-1}. (Found: C, 83.77; H, 12.76. $C_{33}H_{58}O$ requires: C, 84.24; H, 12.34%). Frac. (vii) was crystallised from Et_2O–MeOH to give 32R-3β-(1-hydroxyethyl)-cyclolaudane (**17**), m.p. 145–148°, $[\alpha]_D$ + 55° (*c*, 0.97) (Found: C, 83.60; H, 12.95. $C_{33}H_{58}O$ requires: C, 84.24; H, 12.34%).

Photocyclisation of alcohol (**17**). A suspension of **17** (500 mg), $Pb(OAc)_4$ (4.0 g), I_2 (500 gm) and $CaCO_3$ (2.0 g) in cyclohexane (100 ml) was irradiated with 250 watt tungsten lamp. The mixture was maintained at reflux till the colour of I_2 was discharged (1.5 hr). After cooling, it was worked up as usual to give a gummy product (700 mg) which was chromatographed on SiO_2-gel (II, 1.5 cm × 25 cm): (i) C_6H_6, 50 ml × 4, 240 mg, lactone **18**. (ii) EtOAc, 50 ml × 4, 420 mg, mixture of polar compounds, not investigated further. Frac. (i) was crystallised from Et_2O–MeOH to give pure lactone **18**, m.p. 176–77°. (Found: C, 82.28; H, 10.95. $C_{33}H_{54}O_2$ requires: C, 82.16; H, 11.20%).

Conversion of lactone **18** *to β-ketoester* **2**. Lactone **18** (200 mg) was hydrolysed with 5% KOH ethanolic (10 ml, 2 hr), worked up in the usual manner and esterified (CH_2N_2) to give **24** (185 mg). IR (Nujol) OH 3470 cm^{-1}, CO_2Me 1715 cm^{-1}.

The hydroxyester obtained above was dissolved in acetone (10 ml) and oxidised with Jones' reagent (2 ml). Usual work-up and crystallisation of the product from Et_2O–MeOH gave **20** (180 mg), m.p. 145–148°. IR (Nujol) C=O 1705 cm^{-1}; CO_2Me 1728 cm^{-1}.

A soln of **20** (100 mg) in ether (1 ml) was added to $BF_3 \cdot Et_2O$ (2 ml) and H_2O_2 (95%, 0.5 ml) in Et_2O (10 ml). The mixture was stirred (25°) for 4 hr and worked up to give a gummy product (95 mg) which was hydrolysed with 5% KOH ethanolic (10 ml, reflux, 2 hr) and the product after work-up was reesterified (CH_2N_2). The mixture (90 mg) obtained was chromatographed over SiO_2-gel (II, 1.0 × 10.0 cm): (i) C_6H_6, 25 ml × 2, 50 mg, diester **26**; (ii) 9:1 C_6H_6–EtOAc, 30 mg, hydroxyester **25**.

Hydroxyester **25** in acetone (10 ml) was treated with Jones' reagent (2 ml) at 25° for 2 hr. Usual work-up and crystallisation of the product from Et_2O–MeOH gave **2** (29 mg) which was identical (m.p., IR, PMR) with that obtained from lactone **19** (*vide supra*).

Cycloeucalanone (**3**). Compound **2**, (50 mg, 0.1 mmole) was added (N_2) to a soln of NaCN (10 mg, 0.2 mmole) in hexamethylphosphoric triamide (7 ml) at 75° and the mixture stirred at that temp for 3 hr. After cooling, it was poured into 2N HCl aq (20 ml), the aqueous layer was saturated with NaCl and extracted with ether (20 ml × 4). The ether layer was washed with brine (20 ml × 5) and dried. Removal of solvent gave a product (45 mg) which was passed through a small bed of SiO_2-gel using light petroleum to get cycloeucalanone (**3**, 35 mg, 79.5%), m.p. 109–110°. IR (CCl_4): C=O 1709 cm^{-1}.

REFERENCES

[1]See e.g.: [a]T. K. Devon and A. I. Scott, *Handbook of Naturally Occurring Compounds*, Vol. II, pp. 281–384. Academic Press, New York (1972); [b]J. Tomko and Z. Voticky, *The Alkaloids* (Edited by R. H. F. Manske) Vol. 14, pp. 1–82. Academic Press, New York (1973).

[2]The earlier C-4β-configuration for the hydroxymethyl group in many Buxus alkaloids[1b] has since been proved to be 4α: [a]M. Sangare, F. Khuong-Huu, D. Herlem, A. Milliet, B. Septe, G. Berenger and G. Lukacs, *Tetrahedron Letters* 1791 (1975); [b]J. Guilhem, *Ibid.* 2937 (1975).

[3a]H. H. Rees and T. W. Goodwin, *Biosynthesis* (Specialist Periodical Reports), Vol. 1, p. 76. The Chemical Society, London (1972); [b]J. A. Nelson, S. Kahn, T. A. Spencer, K. B. Sharpless and R. B. Clayton, *Biorganic Chem.* **4**, 363 (1975).

[4]R. Kazlauskas, J. T. Pinhey, J. J. H. Simes and T. G. Watson, *Chem. Comm.* 945 (1969).

[5]K. F. Cohen, R. Kazlauskas and J. T. Pinhey, *J. Chem. Soc.* Perkin I 2076 (1973).

[6]G. R. Pettit and J. R. Dias, *J. Org. Chem.* **37**, 973 (1972).

[7]D. H. R. Barton and D. Kumari, *Liebig's Ann.* **737**, 108 (1970).

[8]J. A. Nelson, S. Chou and T. A. Spencer, *J. Am. Chem. Soc.* **97**, 648 (1975).

[9]A. J. Jones, P. E. Alewood, M. Benn and J. Wong, *Tetrahedron Letters* 1655 (1976).

[10]M. R. Czarny, B. W. Benson and T. A. Spencer, *J. Org. Chem.* **42**, 556 (1977).

[11]J. M. Midgley, J. E. Perkin and W. B. Whalley, *J. Chem. Soc.* Perkin I 834 (1977).

[12]J. S. G. Cox, F. E. King and T. J. King, *Ibid.* 1384 (1956); 514 (1959).

[13]See e.g.: K. Heusler and J. Kalvoda, *Angew. Chem.* Intern. Edit. **3**, 525 (1964).

[14]See e.g.: K. Heusler and J. Kalvoda, *Organic Reactions in Steroid Chemistry* (Edited by J. Fried and J. A. Edwards), Vol. II, p. 237. Van Nostrand Reinhold, New York (1972).

[15]There is sufficient evidence to conclude that in simple derivatives based on cycloartane, rings B and C are in boat conformation: A. Ducruix, C. Pascard-Billy, M. Devys, M. Barbier and E. Lederer, *J. Chem. Soc.* Chem. Comm. 929 (1973); Also see: Ref. 2*b*.

[16]See e.g.: H. Immer, M. L. Mihailovic, K. Schaffner, D. Arigoni and O. Jeger, *Helv. Chim. Acta* **45**, 753 (1962); R. Lukes and M. Ferles, *Coll. Czech.* Chem. Comm. **20** 1227 (1955); Also see; M. E. Wolff, *Chem. Rev.* **63**, 55 (1963).

[17]See e.g.: A. Gaudemer, *Stereochemistry, Fundamental and Methods* (Edited by H. B. Kagan), Vol. I, p. 99. George Thieme, Stuttgart (1977).

[18]In a separate study, *E*- and *Z*-isomers of **16** were separated by inverted-dry-column-chromatography on $AgNO_3$-SiO_2 gel. Each isomer was hydroborated to get two alcohols, in which one predominated (β-isomer). To reinforce the β-assignment and the inter-relationship, the four alcohols were oxidised to get two methyl ketones, the minor one of which could be base-isomerised to the major methyl ketone. The latter on Baeyer–Villiger oxidation ($BF_3 \cdot Et_2O$–H_2O_2), followed by hydrolysis gave cyclolaudanol. Information about the configuration at C-32 in alcohols (**17**) could be gleaned from the PMR[17] and ^{13}C-NMR[19] spectral characteristics of the lactones (**18**), in which the quasi-axial proton or methyl group at C-32 can be easily identified. This work is not being reported here as it is not relevant to the purpose on hand.

[19]See e.g.: F. W. Wehrli and T. Nishida, *Progress in the Chemistry of Organic Natural Products* **36**, 1 (1979).

[20]C. G. Scouten and H. C. Brown, *J. Org. Chem.* **38**, 4092 (1973).

[21]The relative proportions of 3α- and 3β-isomers formed were largely effected by the nature and quantities of the hydroborating agents used. Their relative ratio improved from 4:6 with excess diborane to 3:7 with stoichiometric quantities of the reagent. In the latter case, much bulkier mono and dialkylboranes also take part in the reaction, thus improving the stereoselectivity.

[22]G. W. Buchanan, J. B. Stothers and S. T. Wa, *Can. J. Chem.* **47**, 3113 (1969).

[23]G. W. Buchanan, J. B. Stothers, S. T. Wu, *Ibid.* **45**, 2955 (1967).

[24]S. Bory and M. Fetizon, *Bull. Soc. Chim. Fr.* 570 (1964).

[25]A. H. Kapadi and Sukh Dev, *Tetrahedron Letters* 1171 (1964); E. Wenkert, A. Afonso, P. Beak, R. W. J. Carney, P. W. Joffs and J. D. McChesney, *J. Org. Chem.* **30**, 713 (1965); C. R. Narayanan and N. K. Venkatasubramanian, *Tetrahedron Letters* 3639 (1965); T. A. Spenser, D. Weaver, R. M. Villarica, R. J. Friary, J. Posler and M. A. Schwartz, *J. Org. Chem.* **33**, 712 (1968).

[26]Replacement of 3β-hydroxyl by 3β-hydroxymethyl group should have only a little effect. J. B. Stothers, *Carbon*-13 *NMR Spectroscopy*, p. 58, 142. Academic Press, New York (1972).

[27]Baeyer-Villiger Oxidation with HCO_3H, CH_3CO_3H, CF_3CO_3H–Na_2HPO_4 and permaleic acid failed while the reaction with $BF_3 \cdot Et_2O$–H_2O_2 seems to be sterically controlled as the products formed by migration of Me groups (with comparatively low migratory aptitude) are predominant.

[28]P. Muller and B. Seigfried, *Tetrahedron Letters* 3565 (1973).

[29]H. R. Bentley, J. A. Henry, D. S. Irvine, D. Mukherji and F. S. Spring, *J. Chem. Soc.* 596 (1955).

[30]K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *Ibid.* 39 (1946); R. G. Curtis, I. M. Heilbron, E. R. H. Jones and G. F. Woods, *Ibid.* 457 (1953).

[31]J. C. Collins, W. W. Hess and F. J. Frank, *Tetrahedron Letters* 3363 (1968); R. Ratcliffe and R. Rodehorst, *J. Org. Chem.* **35**, 4000 (1970).