Tetrahedron Vol 45, No 21, pp 6833 to 6840, 1989
Printed in Great Britain

0040-4020/89 $3 00+ 00

A FORMAL STEREOCONTROLLED SYNTHESIS OF (±) ISOCLOVENE

Zafeer Ahmad, Pannalal Goswami and R.V. Venkateswaran*

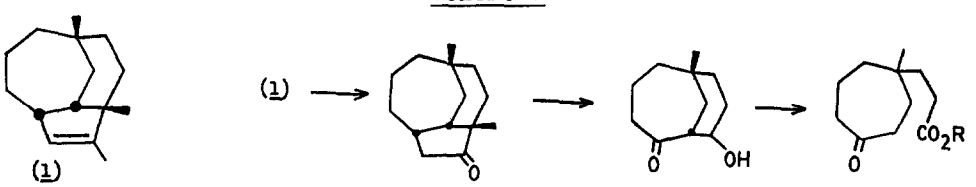
Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta - 700 032, INDIA

(*Received in UK* 1 *June* 1989)

Abstract: Starting from a seven-membered ring compound, the synthesis of the tricyclic ketone (25) is described concluding a formal total synthesis of (±) isoclovene, the major sesquiterpene from extensive rearrangement of caryophyllene. Enroute, a facile base promoted epimerisation and consequent ketone assisted hydrolysis of ketonitrile (12) under mild conditions was observed.

Isoclovene (1)[1], the sesquiterpene artifact isolated from the rearrangement panorama of caryophyllene encloses an unusual tricyclo(6.2.2.$0^{5,12}$)dodecane skeleton seldom encountered in natural products or artifacts. The structure and stereochemistry of (1) was unravelled through x-ray crystallographic investigation[2] of the corresponding hydrochloride. Mechanistic proposals relating to mode of formation of (1) have also been advanced[3]. Efforts relating to synthesis of (1) were earlier reported from this[4] and other

Scheme-1

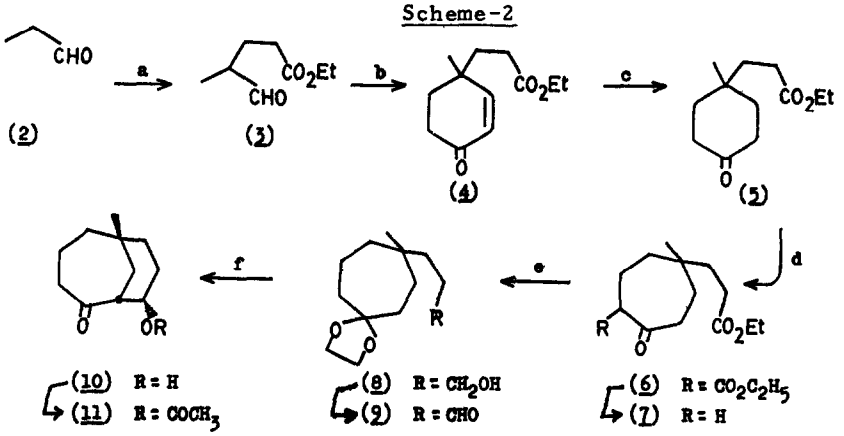


laboratories[5]. In a previous occasion[4b] we had detailed a strategy for the construction of the tricyclododecane network present in (1). More recently its total synthesis has been disclosed by others[6] and our own studies[7] have culminated in a formal synthesis. We present herein the full details of our synthesis.

Our approach is presented retrosynthetically in Scheme-1. This envisaged the final incorporation of the five-membered ring onto a properly functionalised bicyclo(4.3.1)decane unit which in turn entailed starting from a preformed seven-membered ring compound, and was realised as follows. Propionaldehyde (2) was converted to the aldehyde-ester (3) through condensation of the corresponding piperidino-enamine[8] with ethyl acrylate. This was again converted to an enamine and a Michael reaction with methyl vinyl ketone (MVK) followed by cyclisation furnished the cyclohexenone-ester (4) in a satisfactory overall yield which was hydrogenated to the keto-ester (5). Ring enlargement of (5) with ethyl diazoacetate in presence of triethyl oxonium fluoroborate[9]

furnished the β-keto-ester (6) which was smoothly de-ethoxycarbonylated under Krapcho's[10] conditions to the cycloheptanone-ester (7). The ketone in (7) was next protected as the ethylene-ketal and reduction of the ensued ketal-ester with lithium aluminium hydride (LAH) to the alcohol (8) was followed by oxidation with PCC to the ketal-aldehyde (9). Exposure of this aldehyde to acetic acid (90%) on a steam bath

Scheme-2



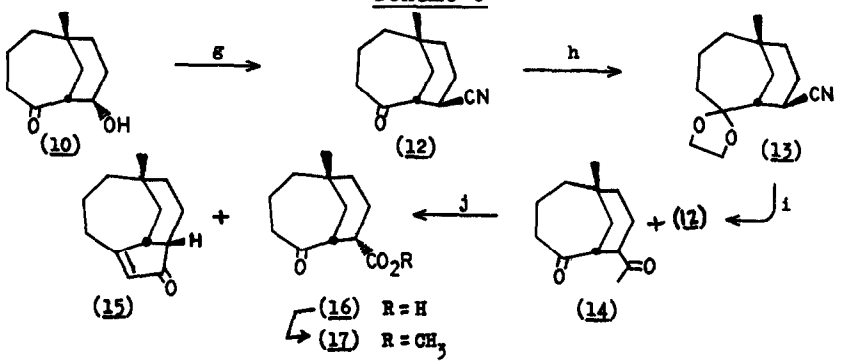
(a) Piperidine/K_2CO_3, ethyl acrylate; HOAc/H_2O (b) piperidine, MVK; HOAc (c) Pd-C, H_2 (d) $Et_3O^+ BF_4^-$, $N_2CHCO_2C_2H_5$, CH_2Cl_2; NaCl, DMSO, H_2O, heat (e) $(CH_2OH)_2$, p-TsOH, benzene; LAH, ether; PCC (f) HOAc (90%)

resulted in de-protection and concomittant internal aldol cyclisation to afford the bicyclic ketol (10) (Scheme-2). Based on well appreciated mechanism of the reaction[11] the hydroxy group in (10) should be disposed equatorially. The ketol (10) was well characterised from analytical and spectral data and additionally furnished a crystalline acetate (11).

Having thus a ready route to the bicyclic ketol (10), we next addressed to further transformations to develop the tricarbocyclic network of (1). To this end (10) was converted to the keto-nitrile (12) through first formation of a toluene-p-sulphonate followed by displacement with sodium cyanide. The assigned β-axial configuration for the nitrile group in (12) follows from course of reaction and further from the ^1H NMR spectrum where the α-hydrogen appeared as an unresolved multiplet at δ 3.4 whose $W_{\frac{1}{2}}$ (9 Hz)[12] value suggested an equatorial nature. At this juncture of the synthetic programme, the keto-nitrile (12) was further harnessed to study the feasibility of incorporating the remaining five-membered ring. To this end the derived ketal-nitrile (13) was reacted with methyl lithium and the product de-protected to afford the diketone (14) contaminated with traces of (12), as evidenced from the IR spectrum. Treatment of the mixture of (14) and (12) with methanolic KOH led to clean cyclisation of (14) to furnish the tricyclic ketone (15) as the neutral component (Scheme-3). This incorporates the

tricarbocyclic framework of (1) and displayed characteristic peak in IR for cyclopentenone at 1700 cm^{-1} and in the ^1H NMR the olefin proton appeared as a doublet at δ 5.8. The stereochemistry of the newly created chiral centre stems from requirement

Scheme-3



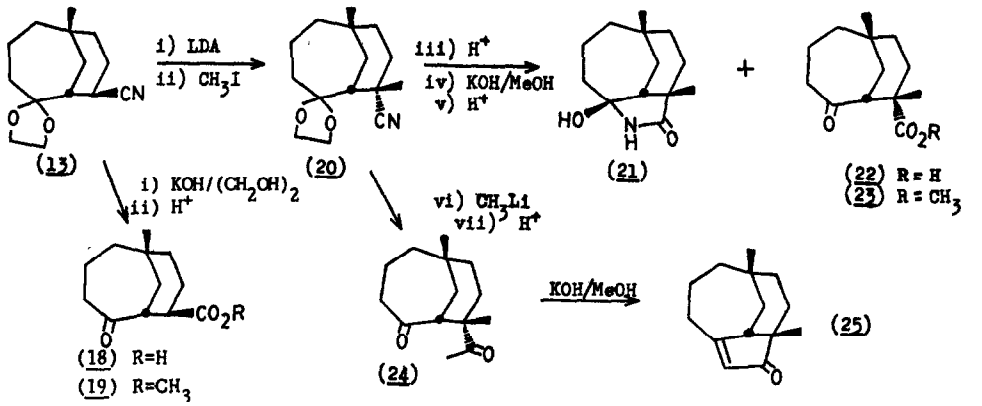
(g) p-TsCl, pyridine; NaCN, DMSO (h) $(CH_2OH)_2$, p-TsOH, benzene (i) CH_3Li; H^+ (j) KOH/MeOH; H^+

of α-equatorial geometry of the side chain for cyclisation to lead to (15). The tricyclic ketone (15) on standing displayed some unusual phenomonon which has already been reported[4c]. From the alkaline portion of the above cyclisation was obtained on acidification a crystalline keto-acid, arising from facile hydrolysis of traces of (12) and assigned structure (16). This very easy hydrolysis of (12) to (16) provided the crucial clue on which was based the successful synthesis of (1) as detailed later.

Encouraged by the success attending the assemblage of the tricarbocyclic unit of (1) we turned our attention to incorporate the crucial methyl group α to the nitrile in (13). It was assumed that methylation of the bicyclo(4.3.1)decane system of (13) will result in the incoming methyl group possessing the required β-axial configuration from preferential attack from the more accessible β-face. Additional support for this tenet came from the detailed studies on the hydrolysis profile of the keto-nitrile (12). This underwent very easy hydrolysis with methanolic KOH (7%) to provide in excellent yield (16), m.p. 166°C. This ready hydrolysis of (12) clearly involves a base induced prior epimerisation followed by participation[13] from the proximal ketone. The corresponding methyl ester (17) showed in the ^1H NMR two singlets at δ 0.96 and 3.63 for the methyl and methoxycarbonyl groups respectively. The ketal-nitrile (13) was totally unaffected under the above conditions of mild hydrolysis (KOH/MeOH), but drastic hydrolysis in presence of KOH in ethylene glycol under reflux followed by de-protection furnished a different keto-acid, m.p. 98-99°C, isomeric with (16) and hence assigned the β-carboxylic acid structure (18) (Scheme-4). The corresponding methyl ester (19) showed in the ^1H NMR two singlets at δ 0.93 and 3.63 for the methyl and methoxycarbonyl groups respectively. Evidence in favour of assigned structures (16) and (18) was further secured from the aromatic solvent induced shifts (ASIS)[14] in the ^1H NMR of the corresponding methyl esters (17) and (19). In the event when the solvent was changed from CCl_4 to benzene in the

^{1}H NMR the methoxycarbonyl (19), situated far behind the reference carbonyl plane showed a pronounced upfield shift ($\Delta \overset{C_6H_6}{\underset{CCl_4}{}} = \delta\, C_6H_6 - \delta\, CCl_4 = -0.27$ ppm) whereas that in (17) showed only a low upfield shift($\Delta \cong -0.03$ ppm). Based on this the formation of acid (18) can be explicated in terms of additional steric inhibition from the ketal group which precludes epimerisation. Following on above cue, methylation of the ketal-nitrile (13) using lithium diisopropylamide (LDA) as base furnished a single methylated nitrile (20) in good yield (Scheme-4). The homogeniety was evident from the ^{1}H NMR (200 MHz) which showed only two singlets for the methyl groups in (20) at δ 0.92 and 1.5. For further confirmation a portion of this was de-protected and the resulting keto-nitrile

Scheme-4



subjected to the previous mild hydrolysis (KOH/MeOH). This furnished essentially a neutral crystalline compound, m.p. 154-56°C, assigned the lactamol structure (21) from analytical and spectral considerations. Since formation of (21) readily corroborated the assigned structure to (20), no further studies on (21) were pressed for. The alkaline portion from above hydrolysis furnished very small ($\lesssim$ 10%) of an acidic material which was treated with diazomethane to provide a methyl ester. This showed a molecular ion at 238 and in the ^{1}H NMR a singlet at δ 3.68 due to a methoxycarbonyl group. On this basis has been assigned structure (23). On account of very low yield this could not be further purified for a more detailed characterisation. Treatment of the ketal-nitrile (20) with an excess of methyl lithium followed by de-protection and p.l.c. afforded the diketone (24), initially as an oil. In course of time this solidified and crystallisation furnished a solid, m.p. 72-73°C (lit.[6a] m.p. 73-74°C). Internal aldol cyclisation of this diketone (24) yielded the tricyclic ketone (25) (Scheme-4) as a low melting solid, m.p. 49-51°C[15]. On account of difficulty in retaining this as solid and high solubility, this could not be further improved upon. The ^{1}H NMR spectra of the diketone (24) and the tricyclic ketone (25) were fully consonant with authentic spectra. The diketone (24) and cyclised (25) served as advanced intermediates in an earlier synthesis[6a] of isoclovene (1), thus constituting in the present case a formal total synthesis of this hydrocarbon.

EXPERIMENTAL SECTION

Melting points and boiling points are uncorrected and melting points were taken in open capillary in sulphuric acid bath or Reichert hot stage. Preparative layer chromatography was performed using silica gel 60 HF_{254} (E.Merck), plate thickness 1 mm. UV spectra were measured in 95% ethanol solution on Beckmann DU spectrophotometer (manually operated) or Hitachi model 200-20 spectrophotometer. IR spectra were recorded in $CHCl_3$ solution on a Perkin-Elmer 298 or Beckmann Acculab-4 instrument. ^1H NMR spectra were recorded against TMS as internal standard in CCl_4 solution at 60 MHz on a Varian T-60A and in $CDCl_3$ solution at 100 MHz on Jeol FX-100 and at 200 MHz on a Varian XL-200 spectrometers. Gas chromatography was carried out on a Shimadzu GC-9A model using OV-17 on 1.5% shimalite W 80-100 Silanized column (6 m x 3 mn). Mass spectra were recorded on a Hitachi RMU-6 Mass spectrometer at 70 ev. Petroleum ether refers to fraction boiling in the range 60-80°C unless otherwise mentioned. General work-up involves dilution with water, extraction with ether (unless otherwise mentioned), washing with brine, drying and removal of solvent using a rotavapor. All organic extracts were dried over anhydrous sodium sulphate.

Ethyl-4-formyl valerate (3):- A well-stirred mixture of piperidine (200 ml) and anhydrous K_2CO_3 (45 g) was cooled to 0°C and propionaldehyde (2, 55 g, 950 mmol) added dropwise. Stirring was continued for 2 h at room temperature, left overnight and filtered under N_2, and washed with dry ether. The filtrate was concentrated and residue dissolved in dry thiophene free benzene (600 ml) under N_2, cooled to 0°C and ethyl acrylate (125 g, 1250 mmol) added dropwise with stirring. After addition the mixture was stirred at room temperature for 4 h and refluxed for 36 h. To this mixture was next added water (400 ml) and acetic acid (60 ml) and again refluxed for 8 h. The product was cooled to room temperature, the organic layer separated, washed with brine, hydrochloric acid (2N) and again with brine. The residue left after removal of solvent was fractionated to provide (3) (90 g, 60%), b.p. 88-90°C/8 mm; IR 1735 cm^{-1}. Anal. calcd. for $C_8H_{14}O_3$: C, 60.7; H, 8.9. Found: C, 60.6; H, 8.9.

Ethyl-3-(1-methyl-4-oxocyclohex-2-enyl)propionate (4):- A mixture of (3) (85 g, 540 mmol), piperidine (73 ml, 740 mmol) and benzene (600 ml) was refluxed under N_2 using a Dean-Stark water separator till complete separation of water. The volume was reduced by distilling off benzene (300 ml) from the flask. This was next cooled to 5°C and MVK (55 g, 780 mmol) was added dropwise with stirring. The mixture was left overnight and then refluxed for 16 h, cooled to room temperature, acetic acid (70 ml) added and refluxed for another 6 h. The product was washed with brine, hydrochloric acid (2N) and again with brine. Benzene was removed and the residual liquid distilled to furnish (4) (69 g, 60%), b.p. 125-135°C/0.8 mm. UV_{max} 226 nm ε 13,140. IR 1730, 1675 cm^{-1}. ^1H NMR δ (CCl_4) 1.2 (s, 3H), 1.28 (t, J 7 Hz, 3H), 4.04 (q, J 7 Hz, 2H), 5.74 (d, J 10 Hz, 1H), 6.55 (d, J 10 Hz, 1H). Anal. calcd. for $C_{12}H_{18}O_3$: C, 68.5; H, 8.6. Found: C, 68.4; H,8.7.

Ethyl-3-(1-methyl-4-oxocyclohexyl)propionate (5):- The above unsaturated keto-ester (4) (50 g) was hydrogenated in ethanol (200 ml) in presence of Pd-C (2 g, 10%). The product was filtered, solvent removed and the residue distilled. The keto-ester (5) passed over at 125-130°C/0.5 mm (48 g, 96%); IR 1725 cm^{-1}; ^1H NMR δ (CCl_4) 1.07 (s, 3H), 1.24 (t, J 7 Hz, 3H), 4.05 (q, J 7 Hz, 2H). Anal. calcd. for $C_{12}H_{20}O_3$: C, 67.9; H, 9.5. Found: C, 67.8; H, 9.4.

Ethyl-3-(1-methyl-4-oxocycloheptyl)propionate (7):- Freshly prepared triethyl oxonium fluoroborate (16.7 g, 88 mmol) was dissolved in CH_2Cl_2 (150 ml) under N_2. The solution was cooled to 0°C and the keto-ester (5) (10.6 g, 50 mmol) in CH_2Cl_2 (25 ml) was added. The reaction mixture was stirred for 3-4 min and then ethyl diazoacetate (10.1 g, 95 mmol) added dropwise. After addition was complete the mixture was stirred for 3 h more at 0°C. The reaction was quenched with saturated aqueous $NaHCO_3$ (150 ml). After stirring for half hour CH_2Cl_2 layer was separated, washed several times with water and dried ($CaCl_2$). On removal of the solvent the material was distilled. The β-keto-ester (6) (12 g, 80%) was collected at 165-175°C/0.2 mm. It gave a deep violet colour with alcoholic ferric chloride solution. Anal. calcd. for $C_{16}H_{26}O_5$: C, 64.4; H, 8.8. Found: C, 64.6; H, 8.7.

A mixture of the β-keto-ester (6) (19.3 g, 66 mmol), DMSO (100 ml), NaCl (6 g) and water (3.5 ml) was stirred and heated at 165°C in an oil bath for 6 h. The reaction mixture was cooled and worked-up with petroleum ether (80-100°C) and ether (4:1). Distillation of the residue furnished the keto-ester (7) (12.5 g, 85%), b.p. 123-29°C/0.4 mm. IR 1725, 1690 cm^{-1}; ^1H NMR δ(CCl_4) 0.90 (s, 3H), 1.21 (t, J 7 Hz, 3H), 4.06 (q, J 7 Hz). Anal. calcd. for $C_{13}H_{22}O_3$: C, 69.0; H, 9.8. Found: C, 68.8, H, 9.9.

3-(1-Methyl-4-ethylenedioxy cycloheptyl)propionaldehyde (9):- A mixture of keto-ester (7) (16 g, 70 mmol), benzene (200 ml), ethane diol (9.5 g, 150 mmol) and toluene-p-sulphonic acid (0.2 g) was refluxed for 25 h using a Dean-Stark water separator. It was cooled, washed with aqueous Na_2CO_3 and brine and fractionated to obtain the corresponding ketal-ester (17 g, 85%), b.p. 133-142°C/0.4 mm. IR 1725 cm^{-1}; ^1H NMR δ (CCl_4) 0.91 (s, 3H), 1.21 (t, J 7 Hz, 3H), 3.78 (s, 4H), 4.02 (q, J 7 Hz, 2H).

To a stirred slurry of LAH (2.8 g, 75 mmol) in ether (200 ml) was added dropwise a solution of the above ketal-ester (27 g, 95 mmol) in ether (50 ml). After addition a further volume of ether (100 ml) was added and the whole mixture refluxed for 4 h. It was then decomposed with saturated aqueous sodium sulphate, ethereal layer decanted, dried and the product fractionated to furnish the ketal-alcohol (8) (21 g, 99%), b.p. 109-114°C/0.01 mm. ^1H NMR δ (CCl_4) 0.91 (s, 3H), 3.1 (br s, 1H, exchangeable with D_2O), 3.5 (t, J 6 Hz, 2H), 3.78 (s, 4H). Anal. calcd. for $C_{13}H_{24}O_3$: C, 68.4; H, 10.6. Found: C, 68.6; H, 10.6.

To a mechanically stirred suspension of PCC (25.8 g, 120 mmol) in CH_2Cl_2 (250 ml) was added the above ketal-alcohol (8) (15.9 g, 70 mmol) in CH_2Cl_2 (40 ml) in one portion. After 2 h, dry ether (200 ml) was added and the supernatant liquid decanted. The insoluble residue was washed with ether. The combined organic extract was concentrated and distilled to afford the ketal-aldehyde (9) (11.05 g, 70%), b.p. 104-109°C/0.01 mm. IR 1730 cm^{-1}; ^1H NMR δ (CCl_4) 0.90 (s, 3H), 3.78 (s, 3H), 9.66 (t, J 2 Hz, 1H). Anal. calcd. for $C_{13}H_{22}O_3$: C, 69.0; H, 9.8. Found: C, 68.7; H, 10.0.

1β-Methyl-7α-hydroxybicyclo(4.3.1)decan-5-one (10):- A solution of the ketal-aldehyde (9) (7.5 g, 33 mmol) in acetic acid (40 ml, 90%) was heated on a boiling water-bath for 3 h. It was worked-up after neutralising with Na_2CO_3 and residue distilled. The ketol (10) was collected at 101-104°C/0.2 mm. (4.8 g, 80%). IR 1690 cm^{-1}; ^1H NMR δ(CCl_4) 0.92 (s, 3H), 3.4 (q, J 6 Hz, 1H), 3.63 (s, 1H, exchangeable with D_2O). Anal. calcd. for $C_{11}H_{18}O_2$: C, 72.5; H, 9.9. Found: C, 72.5; H, 10.2.

The acetate (11) was prepared from (10) and acetic anhydride and pyridine, and crystallised from benzene - petroleum ether, m.p. 83°C. IR 1730, 1690 cm^{-1}, ^1H NMR δ (CCl_4) 0.91 (s, 3H), 1.9 (s, 3H), 4.2 (m, 1H). Anal. calcd. for $C_{13}H_{20}O_3$: C, 69.6; H, 9.0. Found: C, 69.4; H, 9.1.

1β-Methyl-7β-cyanobicyclo(4.3.1)decan-5-one (12):- To an ice-cooled solution of the ketol (10) (3 g, 16.5 mmol) in pyridine (30 ml), toluene-p-sulphonyl chloride (4.2 g, 22.5 mmol) was added and the mixture stirred overnight at room temperature. Next day it was warmed at 60-70°C for 2 h. Work-up afforded a gummy residue which solidified on scratching. The tosylate was crystallised from benzene-petroleum ether, (4.3 g, 84%), m.p. 84-87°C, IR 1700, 1600, 1175, 1100 cm^{-1}.

To a solution of the above keto-tosylate (3.6 g, 11.1 mmol) in anhydrous DMSO (35 ml) NaCN (0.75 g, 15mmol) was added and the mixture stirred at room temperature for 12 h and then warmed at 75°C for 4 h. Work-up with petroleum ether-ether (3:1) followed by distillation afforded the keto-nitrile (12) (1.5 g, 70%), b.p. 98-102°C/0.2 mm. IR 2215, 1690 cm^{-1}, ^1H NMR δ (CCl_4) 0.95 (s, 3H), 3.4 (m, 1H). Anal. calcd. for $C_{12}H_{17}ON$: C, 75.4; H, 8.9. Found: C, 75.2; H, 9.1.

1β-Methyl-5-ethylenedioxy-7β-cyanobicyclo(4.3.1)decane (13):- Prepared from keto nitrile (12) (1.51 g, 7.8 mmol) following procedure adopted on (7) to afford the ketal-nitrile (13) (1.53 g, 85%), b.p. 120-25°C/0.3 mm. IR 2215 cm^{-1}; ^1H NMR δ (CCl_4) 0.95 (s, 3H), 3.4 (m, 1H), 3.86 (s, 4H). Anal. calcd. for $C_{14}H_{21}O_2N$: C, 71.5; H, 9.0. Found: C, 71.5, H, 8.9.

1β-Methyl-8βH-cis-tricyclo(6.2.2.0^{5,12})dodec-5-en-7-one (15):- Methyl lithium [prepared from Li (0.56 g, 80 mmol) and methyl iodide (5.6 g, 40 mmol) in ether (20 ml)] was added dropwise to a stirred solution of the ketal-nitrile (13) (0.94 g, 4 mmol) in ether (20 ml) kept in a freezing mixture under N_2. The reaction mixture was stirred at room temperature for 24 h and refluxed for 3 h. It was then decomposed with saturated aqueous NH_4Cl and worked-up. The product showed in the IR 2210 (low intensity), 1710 cm^{-1}. This was directly used for the next step.

The above crude product was de-ketalised by heating in acetic acid (10 ml, 80%) for 3 h. Work-up as for (10) afforded a liquid material which was evaporatively distilled at 84-86°C/0.1 mm (bath temp.) to furnish the diketone (14) containing traces of (12) (0.69 g). IR 2215 (low intensity), 1710, 1690 cm^{-1}; ^1H NMR δ (CCl_4) 0.90 (s, 3H), 2.13 (s, 3H).

A mixture of (14) and (12) as above (1 g) was mixed with methanolic KOH (7%) and refluxed for 3 h under N_2. Work-up followed by evaporative distillation of the residue afforded the tricyclic ketone (15) (0.6 g, 65%), b.p. 120-25°C/0.02 mm (bath temp.); UV_{max} 242 nm, ε 10,480; IR 1700, 1620 cm^{-1}; ^1H NMR δ (CCl_4) 0.91 (s, 3H), 5.8 (d, J 2 Hz, 1H). Anal. calcd. for $C_{13}H_{18}O$: C, 82.1; H, 9.5. Found: C, 82.4; H, 9.5.

1β-Methyl-5-oxo-7α-carboxybicyclo(4.3.1)decane (16):- The alkaline fraction from the above cyclisation step was acidified with dilute hydrochloric acid and worked-up. This furnished (16) (0.008 g) as a colourless solid and was crystallised from benzene-petroleum ether, m.p. 166°C.

The same acid (16) was obtained in 85% yield from direct hydrolysis of keto-nitrile (12) under the above conditions (MeOH/KOH, 7%, reflux 3 h), IR 1700 cm^{-1}; ^1H NMR δ ($CDCl_3$, 60 MHz) 0.92 (s, 3H), 8.5 (br s, 1H). Anal. calcd. for $C_{12}H_{18}O_3$: C, 68.5; H, 8.6. Found: C, 68.6; H, 8.4. HRMS required for $C_{12}H_{18}O_3$: 210.1255; Found: 210.1264.

Methyl ester (17) (from diazomethane) was purified by p.l.c. IR 1725, 1690 cm^{-1}; 1H NMR δ(CCl_4) 0.96 (s, 3H), 3.63 (s, 3H). Using benzene as solvent this showed peaks at δ0.63 (s, 3H), 3.60 (s, 3H). Anal. calcd. for $C_{13}H_{20}O_3$: C, 69.6; H, 8.9. Found: C, 69.5; H, 9.1.

1β-Methyl-5-oxo-7β-carboxybicyclo(4.3.1)decane (18):- A mixture of the ketal-nitrile (13) (0.475 g, 2mmol) and KOH (1.12 g) in ethylene glycol (11.5 ml) was refluxed for 16 h. The reaction mixture was diluted with water and extracted once with ether. The alkaline fraction was acidified with dilute hydrochloric acid and left for 1 h at room temperature. It was then worked-up to furnish (18) as a colourless solid (0.34 g, 82%). and crystallised from ether-petroleum ether, m.p. 98-99°C, IR 1700 cm^{-1}; ^1H NMR δ ($CDCl_3$, 60 MHz) 0.93 (s, 3H), 9.0 (br s, 1H). HRMS required for $C_{12}H_{18}O_3$: 210.1255; Found: 210.1259.

Methyl ester (19) (from diazomethane) was purified by p.l.c. IR 1725, 1690 cm^{-1}; 1H NMR δ (CCl_4) 0.93 (s, 3H), 3.63 (s, 3H). Using benzene as solvent this showed peaks at δ0.73 (s, 3H), 3.36 (s, 3H).

1β-7β-Dimethyl-5-ethylenedioxy-7α-cyanobicyclo(4.3.1)decane (20):- To a magnetically stirred solution of diisopropylamine (2.6 g, 25 mmol) in ether (40 ml) under N_2 was added n-butyl lithium (15 ml of 1.6 M solution in hexane, 25mmol) at 0°C followed after 15min by a solution of ketal-nitrile (13) (1.18 g, 5mmol) in ether (5ml) at -20°C. After stirring for 15 min methyl iodide (3.5 g, 25mmol) was added at a moderately rapid rate at the same temperature. Stirring was allowed to continue at -20°C for 0.5 h and then brought to room temperature and stirred for 15 min. Work-up followed by careful distillation of the residue afforded the methylated ketal-nitrile (20) (1.01 g, 80%); b.p. 120-30°C/0.1mm. IR 2215 cm^{-1}; ^1H NMR δ (200 MHz) 0.92 (s, 3H), 1.5 (s, 3H), 3.96 (s, 4H). Anal. calcd. for $C_{15}H_{23}O_2N$: C, 72.2; H, 9.2. Found: C, 72.1; H, 9.2.

1β-7β-Dimethyl-4β-hydroxy-4α-amino-7α-carboxybicyclo(4.3.1)decane lactam (21):- A mixture of the ketal-nitrile (20) (0.25 g, 1 mmol) and acetic acid (1.2 ml, 80%) was heated on a steam bath for 3 h. Work-up as for (10) afforded a keto-nitrile (0.15 g), b.p. 100-10°C/0.2 mm. IR 2220, 1695 cm^{-1}; ^1H NMR δ (200 MHz) 0.97 (s, 3H), 1.51 (s, 3H). GC R_t, 3.48 min at 150°C, 98.9%.

The above product was mixed with methanolic KOH (7%) and refluxed for 3 h. Work-up furnished the lactamol (21) (0.11 g, 80%), crystallised from ethyl acetate-petroleum ether, m.p. 155-56°C. IR 3400, 1690 cm^{-1}; ^1H NMR δ ($CDCl_3$) 0.89 (s, 3H), 1.22 (s, 3H), 7.08 (br s, 1H); MS, m/z 223 M^+. Anal. calcd. for $C_{13}H_{21}O_2N$: C, 69.9; H, 9.4. Found: C, 69.6; H, 9.5.

The alkaline fraction from above hydrolysis was acidified with dilute hydrochloric acid and extracted with ether. The product was subjected to p.l.c. (benzene-petroleum ether 1:9) to afford acid (22) (0.026 g). IR 1700 cm^{-1}. This was treated with diazomethane to furnish an ester, assigned (23) which showed the following spectral features, IR 1720, 1690 cm^{-1}; ^1H NMR δ ($CDCl_3$) 0.94 (s, 3H), 3.68 (s, 3H), MS, m/z 230 M^+.

1β,7β-Dimethyl-5-oxo-7α-acetylbicyclo(4.3.1)decane (24):- Methyl lithium (prepared from Li (0.42 g, 60 mmol) and methyl iodide (4.2 g, 30 mmol) in ether (20 ml)) was added drop-wise to a stirred solution of the ketal-nitrile (20) (0.75 g, 3 mmol) in ether (20 ml) cooled by an ice-salt bath under N_2. The reaction mixture was stirred overnight at room temperature and then refluxed for 3 h. It was decomposed with saturated aqueous NH_4Cl and work-up. The product showed IR 1710 cm^{-1}; ^1H NMR δ (CCl_4) 0.95 (s, 3H), 1.13 (s, 3H), 2.0 (s, 3H), 3.8 (s, 4H). This was directly de-ketalised[4] by heating on a steam bath with acetic acid (90%) for 3 h. Work-up as for (10) furnished an oil which was evaporatively distilled at 100-110°C/0.1 mm (bath temp.). This material was subjected to p.l.c. (benzene-ethyl acetate 1:1) to afford the diketone (24) (0.40 g, 60%) as an oil which eventually solidified. It was crystallised from petroleumether, m.p. 72-73°C (lit.[6a], m.p. 73.5-74°C). IR 1700 cm^{-1}; ^1H NMR δ ($CDCl_3$) 0.95 (s, 3H), 1.06 (s, 3H), 2.15 (s, 3H); MS, m/z 222 M^+; GC R_t 8.29 at 180°C, 98%. Anal. calcd. for $C_{14}H_{22}O_2$: C, 75.6: H, 9.9. Found: C, 75.4; H, 10.5.

1β,8β-Dimethyl-cis-tricyclo(6.2.2.0^{5,12})dodec-5-en-7-one (25):- A mixture of the diketone (24) (0.38 g, 1.7 mmol) and methanolic KOH (1.5 ml, 7.5%) was refluxed for 3 h under N_2. Work-up furnished an oil which was subjected to p.l.c. (benzene) to furnish the tricyclic ketone (25) (0.22 g, 65%), b.p. 110-15°C/0.2 mm. On keeping for a few days this solidified, m.p. 49-51°C. UV λ_{max} 244.5 nm. IR 1690, 1610 cm^{-1}; ^1H NMR δ ($CDCl_3$) 0.90 (s, 3H), 1.1 (s, 3H), 6.01 (d, J 2.2 Hz, 1H). GC R_t 1.99 at 210°C, 98.6%. MS, m/z 204 M^+.

Acknowledgement: We solemnly recall the inspiration provided by the (late) Professor P.C. Dutta during the early part of this investigation. We thank Dr. E.W. Colvin, Glasgow University for the HRMS of the keto-acids (16) and (18), Prof. H.J.E. Loewenthal for the ^1H NMR spectra of (24) and (25) and Prof. U.R. Ghatak for stimulating discussions.

REFERENCES AND NOTES

1 (a) Henderson, G.G.; Osborne, R.; McCone, R.O.O.; Robertson, J.M. J. Chem. Soc. (1929), 1368. (b) Lutz, A.W.; Reid, E.B. ibid. (1954), 2265.
2 Clunie, J.S.; Robertson, J.M. J. Chem.Soc. (1961), 4382.
3 Baines, D.; Eck, C.; Parker, W. Tetrahedron Lett. (1973), 3933.
4 (a) Mahalanabis, K.K. Indian J. Chem. (1968), 5, 124. (b) Goswami,P.; Venkateswaran, R.V.; Dutta, P.C., ibid. (1976), 14B, 299. (c) Goswami, P.; Venkateswaran, R.V. Tetrahedron Lett. (1977), 1943.
5 Traverso, G.; Pollini, G.P.; Barco, A.; Anastasia, M.; Bothner-By, A.A. Gazz. Chim. Ital. (1969), 99, 863.
6 (a) Kellner, D.; Loewenthal, H.J.E. Tetrahedron Lett. (1983), 22, 3397. (b) Baraldi, P.G.; Barco, A.; Benetti, S.; Pollini, G.P.; Simoni, D. ibid. (1983), 22, 5669. (c) Baraldi, P.G.; Barco, A.; Benetti, S.; Pollini, G.P.; Polo, E.; Simoni,D. J. Org. Chem. (1985), 50, 23.
7 Ahmad, Z.; Goswami, P.; Venkateswaran, R.V. Tetrahedron Lett. (1987), 28, 4329.
8 Stork, G.; Brijjolara, A.; Landesman, S.; Szmuszkovicz, J.; Terrel, R. J. Am. Chem. Soc. (1963), 85, 207.
9 Mock, W.L.; Hartman, M.E. J. Am. Chem. Soc., (1970), 92, 5767.
10 Krapcho, A.P. Synthesis (1982), 805.
11 Buchanan, G.L.; McKillop, A.; Raphael, R.A. J. Chem. Soc. (1965), 833.
12 Marshall, J.A.; Pike, M.T.; Carrol, R.D. J. Org. Chem. (1966), 31, 2933.
13 (a) Nagata, W.; Hirai, S.; Itazaki, H.; Takeda, K. J. Org. Chem. (1961), 26, 2413. (b) Meyer, W.L.; Schnautz, N.G. ibid. (1962), 27, 2011. (c) Rodig, O.R.; Johnston, N.J. ibid. (1969), 34, 1942.
14 Bhacca, N.S.; Williams, D.H. "Application of NMR Spectroscopy in Organic Chemistry"; Holden-Day,San Fransisco (1964); Connoly, J.D.; McCrindle, R. Chem. Ind. (1965), 379.
15 Professor Loewenthal has informed us that his sample of (25) has also crystallised.