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PHOTOLYSIS OF α-DIAZOCYCLOPENTANONES. RING CONTRACTION TO FUNCTIONALISED CYCLOBUTANES AND SYNTHESIS OF JUNIONONE, GRANDISOL AND PLANOCOCCYL ACETATE

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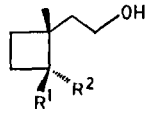
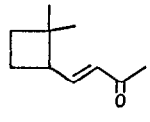
Abstract: Photolysis of diazoketone **19** in methanol furnished the cyclobutane carboxylate **20**. Photolysis in aqueous sodium bicarbonate-THF afforded the acid **21** in better yield. Reduction of the ester followed by oxidation and a subsequent Wittig reaction furnished (±) junionone (**3**). Photolysis of the diazoketone **24** resulted in a 1:1 mixture of cyclobutane carboxylates **25**. Treatment of the corresponding carboxylic acids with hydriodic acid furnished the bicyclic lactone **27**, a known precursor of grandisol (**1**). The diazoketone **28**, on photolysis yielded a mixture of cyclobutane carboxylates **29** and **30**. Conversion of the trans acid **31** to a methyl ketone followed by oxidative functionalisation of the phenyl group gave the keto ester **36** which was isomerised under acid catalysis to **37**, which in optically active form had been a precursor to (-) grandisol. Photolysis of diazoketone **38** afforded the cyclobutane carboxylates **39** and **40** in 2:1 proportion. The corresponding mixture of acids on treatment with methyl lithium and subsequent acetylation furnished the keto acetates **43** and **44**, resulting in a formal synthesis of planococcyl acetate (**4**).

The importance of functionalised cyclobutanes stems from their intrinsic potential as precursors to the natural compounds of recent origin enclosing a cyclobutane framework. These are exemplified in grandisol (**1**)[1], the most important of the components of the pheromone of boll weevil, fragranol (**2**)[2], the trans isomer of (**1**), junionone (**3**)[3], the first vegetable monocyclic cyclobutane monoterpenoid and planococcyl acetate (**4**)[4], the pheromone of citrus mealy bug. In connection with our synthetic efforts directed to these natural products, we have been concerned with exploring methodologies for formation of appropriately substituted, functionalised cyclobutanes. One particularly attractive route to such compounds is through ring contraction of fairly easily accessible substituted cyclopentanones. But unlike the case of ring expansion, methods for ring contraction are far too limited and the well-known Favorskii reaction is not applicable to simple cyclopentanones[5]. The photolytic Wolff rearrangement of α-diazocyclopentanones is a very



1, R^1=H, R^2=C(Me)=CH_2
2, R^1=C(Me)=CH_2, R^2=H



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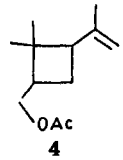

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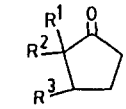
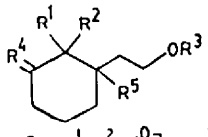


5, R^1=R^2=CH_3, R^3=H
6, R^1=CH_3, R^2=CH_2CH_2OMe, R^3=H
7, R^1=CH_3, R^2=Ph, R^3=H
8, R^1=R^2=CH_3, R^3=$CH_2OSiMe_2Bu^t$

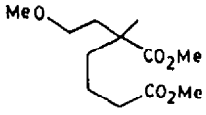
practical protocol for generation of functionalised cyclobutances through ring contraction[6]. The applicability of this procedure in the case of simple cyclopentanones has not been explored. In this paper we report on the successful application of this methodology to a few representative cyclopentanones[7] and subsequent transformations leading to the synthesis of junionone, grandisol and planococcyl acetate.

The cyclopentanones chosen for this study were **5–8**. Dimethyl cyclopentanone **5** was chosen as the basic substrate for initial experimentation since the ring contracted product, a functionalised cyclobutane can be used for a synthesis of junionone (**3**). The cyclopentanone **6** was expected to provide, depending on the stereochemical outcome, a synthon for transformation to grandisol (**1**). The presence of the phenyl substituent in **7** makes it amenable to oxidative functionalisation for additional transformations after ring contraction and the cyclopentanone **8** was envisaged, though dependent on stereochemical outcome, as a precursor for planococcyl acetate (**4**).

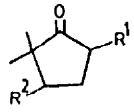
The cyclopentanones **5**[8] and **7**[9] are known compounds. However **7** was prepared in improved yield through methylation of 2-phenylcyclopentanone with methyl iodide in presence of sodium hydride in DME. The cyclopentanone **6** was prepared through a step-down sequence from a cyclohexanone precursor, based on the methodology evolved by Johnson[10]. The acetal alcohol **9**[11] was converted to the methyl ether **10** in excellent yield through reaction with methyl iodide in DME in presence of sodium hydride. Deacetalisation with methanolic hydrochloric acid provided the keto-ether **11** in 93%. Condensation with benzaldehyde afforded the benzylidene derivative **12** in 60% yield which was methylated to **13** with methyl iodide in presence of potassium-t-butoxide in t-butanol[10] in 85% yield. Oxidative cleavage of **13** using potassium permanganate followed by esterification resulted in the dimethyl adipate **14** in 55% yield which was cyclised



9, $R^1=R^2=$, $R^3=R^4=R^5=H$
10, $R^1=R^2=$, $R^3=Me$, $R^4=R^5=H$
11, $R^1=R^2=O$, $R^3=Me$, $R^4=R^5=H$
12, $R^1=R^2=O$, $R^3=Me$, $R^4=CHPh$, $R^5=H$
13, $R^1=R^2=O$, $R^3=Me$, $R^4=CHPh$, $R^5=Me$



14



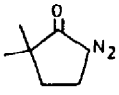
15, $R^1=R^2=CO_2Et$
16, $R^1=H$, $R^2=CO_2H$
17, $R^1=H$, $R^2=CO_2Me$
18, $R^1=H$, $R^2=CH_2OH$

(Dieckmann) and demethoxycarbonylated[12] in an overall yield of 70% to the cyclopentanone **6**. The remaining cyclopentanone **8** was synthesised starting from the dicarboxylate **15**[13]. Acidic hydrolysis of **15** followed by esterification furnished the keto-ester **17** in excellent yield. Protection of the ketone in **17** as the ethylene acetal, reduction with LAH followed by deprotection led to the keto-alcohol **18** in 84% overall yield. This was converted in more than 90% yield to the silylether **8** following Corey's[14] procedure.

Ring contraction studies

Ring contraction of 2,2-dimethylcyclopentanone (5) and synthesis of (±) junionone (3).

Reaction of 5 with ethyl formate in presence of sodium hydride furnished the α-formyl derivative which was transformed to **19** through reaction with tosyl azide[15] and was purified by chromatography on neutral alumina. Photolysis of this diazo ketone **19** in methanol using a Hanovia 450W mercury lamp furnished methyl 2,2-dimethylcyclobutane carboxylate (**20**) in 40% overall yield from 5[7]. The product showed in the IR an ester carbonyl absorption at 1725 cm^{-1} and in the ^1HNMR a three proton singlet at δ 3.63 for the methyl ester, attesting to the formation of desired ring contraction product. The yield was not reproducible and the compound was difficult to handle on account of its volatility.



19

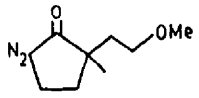
20, R=CO_2Me
21, R=CO_2H
22, R=CH_2OH
23, R=CHO

Hence, we decided to prepare the corresponding acid **21**. Photolysis of **19** in an aqueous sodiumbicarbonate-THF mixture and work-up afforded the cyclobutane carboxylic acid **21** in 64% overall yield from 5. The acid was completely characterised and displayed spectral features (^1H NMR) consistent with those reported[16]. Treatment of the acid **21** with diazomethane furnished the methyl ester **20**. Reduction of **20** with LAH furnished the alcohol **22** in 81% yield which was oxidised with PCC to the aldehyde **23** in near quantitative yield. The volatile aldehyde was immediately subjected to a Wittig reaction[17] with acetylmethylene triphenyl phosphorane. Preparative layer chromatographic purification of the product afforded (±) junionone (**3**) in 76% yield. The structure was established from comparison of the ^1H NMR spectrum with the spectrum of the natural compound.

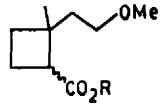
Ring contraction of 2-methyl-2(2-methoxyethyl)cyclopentanone (6) and a formal synthesis of grandisol

Following the previous procedure the cyclopentanone **6** was transformed to the diazo ketone **24**. Photolysis in methanol afforded the cyclobutane carboxylates **25** in 36% overall yield from **6**. This was an epimeric mixture of esters in almost equal proportion as evidenced from the ^1H NMR spectrum which showed in equal proportions two singlets at δ 1.03 and 1.2 for the methyl group and two singlets at δ 3.2 and 3.23 for the methoxy protons. Hydrolysis with alcoholic KOH did not lead to any change in the epimeric composition. The 1:1 epimeric acid mixture **26** was treated at reflux with hydriodic acid

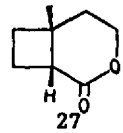
and acetic acid. This led to demethylation and concommittant lactonisation of the cis isomer affording the cis bicyclic lactone **27** as a neutral component in 78% yield (based on



24



25, R=Me
26, R=H

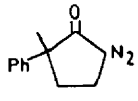


27

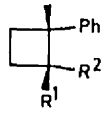
cis isomer in **26**). The lactone **27** displayed characteristics (IR, ^{1}H NMR) in accord with reported data[1b]. Since **27** has already been converted to grandisol (**1**), this completed a formal synthesis of this pheromone component. The acidic fraction from the above reaction was found to be a mixture of products containing iodine (Beilsteins test), acetate and hydroxy groups (^{1}H NMR), arising from demethylation and further reaction. This mixture was not further investigated.

Ring contraction of 2-methyl-2-phenylcyclopentanone (7)

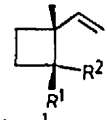
Conversion of the cyclopentanone **7** to the diazo ketone **28** was carried out as previously described. Photolysis of **28** in methanol furnished a cyclobutane carboxylate[18] in 80% yield. However, high field (200 MHz) NMR analysis revealed that the product was not a single compound but mixture. The spectrum displays two singlets (δ 1.4 and 1.66) for



28



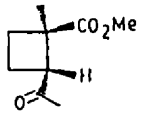
29, R^1=H, R^2=CO_2Me
30, R^1=CO_2Me, R^2=H
31, R^1=CO_2H, R^2=H
32, R^1=$COCH_3$, R^2=H
33, R^1=H, R^2=$COCH_3$



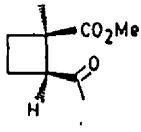
34, R^1=H, R^2=CO_2Me
35, R^1=CO_2Me, R^2=H

the methyl group in a proportion of 85:15. There is a strong singlet at δ 3.8 due to the ester methyl group and a smaller singlet at δ 3.36 . These peaks together account for three protons again in a proportion of 85:15. This proves that we are dealing with a mixture of isomers and the major product is not cis **29** but trans **30**. The singlet at δ 1.4 arises from shielding of the methyl group by the ester in **30** in comparison to that in **29**. Similarly the upfield singlet at δ 3.36 is due to the ester methyl protons in the cis **29** arising from shielding by the phenyl group. Once again hydrolysis under alcoholic KOH did not change the epimeric composition and from the mixture of epimeric acids, the pure trans acid **31** could be isolated by repeated crystallisation, m.p. 91-93°C. Esterification with diazomethane furnished the pure trans methyl ester which showed only two singlets (δ 1.4 and 3.8 corresponding to the methyl and methyl ester groups). The

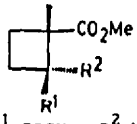
formation of **30** as the major product of ring contraction of **28** proved counter productive to its use for synthesis of grandisol. However, Meyers et al[19] observed that the trans(-) **A** can be isomerised under acidic condition to a separable mixture (55:45) of (-) **A** and cis (+) **B** and the separated (-) **A** once again isomerised. To this end, the trans acid **31** was reacted with methyllithium and afforded the methyl ketone **32** in 71% yield. GC analysis showed the presence of another component to the extent of about 4%, presumed to



(-) **A**



(+) **B**

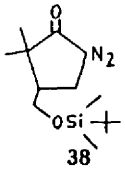


36, R^1=$COCH_3$, R^2=H
37, R^1=H, R^2=$COCH_3$

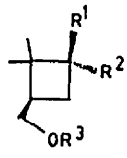
be the cis isomer **33**, arising from minor epimerisation. No effort was made at separation and the mixture was oxidised with ruthenium (III) chloride and sodium metaperiodate following Sharpless procedure[20] and the product esterified with diazomethane to provide the keto ester **36** in 76% yield. This was contaminated (GC) with the isomer **37** (4%) arising from oxidation of **33**. The keto ester **36** was confirmed from comparison of the NMR spectrum with an authentic sample [(-) **A**] kindly provided by Professor Meyers. Compound **36** was treated with methanolic H_2SO_4 to yield a mixture of **36** and **37** in 55:45 proportions. The product was corroborated from comparison with the individual spectra of authentic samples [(-) **A** and (+) **B**]. This successful isomerisation thus completes another formal synthesis of **1**.

Ring contraction of 2,2-Dimethyl-3[t-butyldimethylsiloxy)methyl]cyclopentanone (8) and a synthesis of planococcyl acetate (4)

Following the earlier procedure the cyclopentanone **8** was converted to the diazo ketone **38** and photolysis in methanol afforded in 69% overall yield the cyclobutane



38



39, R^1=CO_2Me, R^2=H, R^3=$SiMe_2Bu^t$
40, R^1=H, R^2=CO_2Me, R^3=$SiMe_2Bu^t$
41, R^1=COMe, R^2=R^3=H
42, R^1=R^3=H, R^2=COMe
43, R^1=COMe, R^2=H, R^3=Ac
44, R^1=H, R^2=COMe, R^3=Ac

carboxylates **39** and **40** in 2:1 proportion. This assignment was arrived at from the ^1H NMR spectrum where the methyl groups of the cis **39** appear as singlets at δ 0.99 and

1.26 while for the trans isomer these are at δ 1.07 and 1.20. This assignment for the cis and trans isomer is based on similar reported observations relating to methyl groups in the trans isomer appearing closer than for the cis isomer in cognate intermediates in previous synthesis of 4[4]. Separation of these isomers proved difficult. We, therefore, decided to proceed with further transformations to complete the synthesis of **4** with the mixture since in an earlier report[4c] an efficient separation of the final compound from the trans isomer has been achieved. Basic hydrolysis of the mixture of **39** and **40** furnished the corresponding acids which were directly reacted with methyllithium to give the methyl ketones. The product, obtained in a yield of 62% showed complete loss of the silyl protecting group and corresponded to the hydroxy ketones **41** and **42**. Acetylation furnished the mixture of acetates **43** and **44** in 84% yield. In the ^{1}H NMR spectrum the characteristic peaks for the isomer **43** corresponded well with reported[4] data. Transformation of **43** to **4** having already been realised[4], this concludes a formal synthesis of **4**.

In conclusion the viability of photolysis of α-diazocyclopentanones to provide functionalised cyclobutanes has been demonstrated in the case of simple cyclopentanones and applied to synthesis of cyclobutanoid natural products. In the case of differently substituted cyclopentanones, no generalisation could be drawn on the stereochemical outcome in the ring contraction.

EXPERIMENTAL SECTION

The compounds described are all racemates. Melting points and boiling points are uncorrected and melting points were taken in open capillary in sulphuric acid bath. Petroleum refers to the fraction of b.p. 60-80°C. Preparative layer chromatography was done with silica gel 60 HF_{254} (E. Merck) plates. Drying of organic layers was done with sodium sulphate. Photolysis was done using a medium pressure 450W Hanovia lamp. ^{1}H NMR spectra were determined at 60 MHz on a Varian T-60A, at 100 MHz on a Jeol FX-100 and at 200 MHz on a Varian XL-200 spectrometers. Peak positions are indicated in ppm downfield from internal TMS in δ units. NMR spectra were taken in carbon tetrachloride for T-60A and in $CDCl_3$ for FX-100 and XL-200 spectrometers. IR spectra were recorded on a Perkin Elmer 298 or Beckman IR 20A infrared spectrometer and were taken in chloroform. UV absorption spectra were measured in 95% ethanol solution on Beckmann DU-2 spectrophotometer (manually operated). Gas chromatographic analyses were done on a Shimadzu GC-9A instrument using column OV-17 (2 m) and nitrogen as carrier gas. GC/MS was performed with a Shimadzu GC-MS QP 1000 instrument using column 3% OV-225 (2 m) and helium as carrier gas and mass at 70 ev.

2-Methyl-2-phenylcyclopentanone (7) :- 2-Phenylcyclopentanone[21] (5.6 g, 35 mmol) was added dropwise under nitrogen to ice-cold suspension of sodium hydride (844 mg, 35 mmol) in DME (40 ml) with stirring for 1 h. Methyl iodide (10 ml) was added and the solution was refluxed for 2 h, poured into ice-cold water and extracted with ether. The ethereal extracts were washed with water, dried and solvent removed to afford an oil which was fractionally distilled to afford the cyclopentanone **7** (3.5 g, 63%), b.p. 105-110°C/6 mm Hg; (lit[9] b.p. 90-98°C/1-2 mm Hg); ν_{max} 1735, 1600 cm^{-1}; δ(60 MHz), 1.33 (s, 3H), 7.23 (m, 5H). Found: C, 82.53; H, 7.93, $C_{12}H_{14}O$ requires C, 82.72; H, 8.10%.

1,1-Ethylenedioxy-2-(2-methoxyethyl)cyclohexane (10) :- A mixture of the alcohol **9**[11] (22 g, 120 mmol) and methyl iodide (13 g, 250 mmol) was taken in anhydrous DME (200 ml) and sodium hydride (3 g, 130 mmol) added portionwise under nitrogen with stirring. Ten minutes after the last of the hydride had been added, a further quantity of methyl

iodide (9 g, 120 mmol) was added and stirring continued for 2 h. DME was distilled out, ether added and the organic layer separated by filtration. Solvent was removed and the material distilled to provide the ether **10** (20 g, 83%), b.p.94-6°C/7 mm Hg; δ (60 MHz) 3.2-3.7 (m, 5H), 3.87 (s, 4H). Found: C, 65.94; H, 10.33, $C_{11}H_{20}O_3$ requires C, 65.97; H, 10.07%.

2-(2-Methoxyethyl)cyclohexanone (11) :- The acetal-ether **10** (20 g, 100 mmol) was heated at 80°C with methanolic hydrochloric acid (5% 100 ml) for 1-2 h. The solution was concentrated and extracted with ether and the combined organic layer washed with water and dried. The residue after removal of solvent was distilled to furnish ketone **11** (14 g, 93%), b.p.100-5°C/10 mm Hg; ν_{max} 1710 cm^{-1}; δ (60 MHz) 3.23-3.4 (m, 5H). Found: C, 69.43; H, 10.28, $C_9H_{16}O_2$ requires C, 69.19; H, 10.32%.

2-(2-Methoxyethyl)-6-benzalcyclohexanone (12) :- A stirred mixture of **11** (14 g, 90 mmol), benzaldehyde (19 g, 180 mmol), aqueous sodium hydroxide (10%, 60 ml) and ethanol (95%, 30 ml) was heated at 90°C for 3 h. The reaction mixture was cooled, organic layer separated and aqueous layer extracted with ether. The combined organic layers were washed with hydrochloric acid (6N) followed by water, dried and solvent removed. Distillation of the residue, b.p.170-5°C/0.1 mm Hg, afforded **12** (13 g, 60%); ν_{max} 1680, 1600 cm^{-1}; δ (60 MHz) 3.23-3.4 (m, 5H), 7.3 (s, 6H). Found: C, 78.82; H, 8.54, $C_{16}H_{20}O_2$ requires C, 78.65; H, 8.25%.

2-Methyl-2-(2-methoxyethyl)-6-benzalcyclohexanone (13) :- To a solution of potassium (3.9 g, 0.1 g atom) in t-butanol (150 ml), benzal derivative **12** (12 g, 50 mmol) was added at room temperature under nitrogen. After stirring for a few minutes the red solution was cooled (0°C) and methyl iodide (14 g, 100 mmol) added. After 30 min the mixture was refluxed on a steam-bath for 2 h. The residue after removal of the t-butanol was diluted with water and extracted with ether. Ethereal layer was washed with a dilute sodium thiosulphate solution (5%) followed by water and dried. Removal of solvent and distillation of the residue yielded the methylated product **13** (11 g, 85%), b.p. 160-6°C/0.1 mm Hg; λ_{max} 288 nm (ε = 11090), ν_{max} 1680, 1600 cm^{-1}; δ (60 MHz) 1.13 (s, 3H), 2.6-2.9 (br, 2H), 3.17-3.4 (m, 5H), 7.1-7.27 (m, 6H). Found: C, 79.31; H, 8.72, $C_{17}H_{22}O_2$ requires C, 79.03; H, 8.58%.

Dimethyl-2-methyl-2-(2-methoxyethyl)adipate (14) :- A solution of the benzal ketone **13** (52 g, 200 mmol) in acetone (250 ml) was stirred magnetically below 10°C and treated with potassium permanganate (63 g, 400 mmol) portionwise and the mixture stirred for another 1 h. The mixture was acidified with dilute sulphuric acid (9N). The product was filtered, organic layer separated from the filtrate and aqueous layer extracted with ether after saturation with sodium chloride. The combined organic layers were washed with saturated aqueous sodium bicarbonate. The alkaline extract was acidified with dilute hydrochloric acid (6N), saturated with sodium chloride and extracted with ether. Ethereal layer was washed with water, dried and evaporated to afford a mixture of 2,2-disubstituted adipic acid and benzoic acid.

The above mixture of acids was esterified with methanol (30 ml) in benzene (100 ml) in presence of sulphuric acid (36 N, 3 ml) under reflux for 12 h. Excess methanol was removed and residue diluted with water. Organic layer was separated and aqueous layer extract with ether. The combined organic layers were washed with saturated aqueous sodium bicarbonate followed by water. Solvents were distilled off and the residue fractionally distilled to produce the dimethyladipate **14** (25 g, 50%), b.p.160-6°C/15 mm Hg; ν_{max} 1735 cm^{-1}; δ (60 MHz) 1.13 (s, 3H), 3.23-3.4 (m, 5H), 3.6 (s, 6H). Found: C, 58.73; H, 9.01, $C_{12}H_{22}O_5$ requires C, 58.51; H, 9.00%.

2-Methyl-2-(2-methoxyethyl)cyclopentanone (6) :- The diester **14** (25 g, 100 mmol) was added to sodium dust (0.08 g atom) in anhydrous benzene (100 ml) and left overnight. Next day, the reaction mixture was refluxed for 2 h, cooled and poured into crushed ice. Organic layer was washed with water and the combined aqueous layers were acidified with hydrochloric acid (6N) and extracted with ether. The ether extract was washed with water, dried and evaporated to yield the crude β-keto ester.

The above β-keto ester was taken in DMSO (100 ml) and heated at 120-130°C for 5 h in presence of sodium chloride (3 g) and water (5 ml). The reaction mixture was poured into cold water and extracted with ether after saturation with sodium chloride. Organic layer was dried and fractionated to afford the cyclopentanone **6** (11 g, 70%), b.p.170-5°C; ν_{max} 1735 cm^{-1}; δ (60 MHz) 0.97 (s, 3H), 3.2-3.47 (m, 5H). Found: C, 69.12; H, 10.44; $C_9H_{16}O_2$ requires C, 69.19; H, 10.32%.

2,2-Dimethylcyclopentanone-3-carboxylic acid (16) :- The β-keto ester **15**[13] (20 g, 80 mmol) was refluxed with ethanolic potassium hydroxide (10%, 135 ml) for 12-15 h. Most of the alcohol was removed under reduced pressure, diluted with water and extracted once with ether. The aqueous layer was acidified with hydrochloric acid (6N) in cold condition and extracted with ether. The ether layer was washed with brine, dried and concentrated to afford a slightly coloured product, which was purified by sublimation under vacuum (105°C/0.5 mm Hg). Multiple crystallisation (benzene) afforded an analytical sample of the acid **16** (10.2 g, 82%), m.p. 110-112°C; ν_{max} 1740, 1720 cm^{-1}; δ (60 MHz) 0.96 (s, 3H), 1.16 (s, 3H), 8.33 (br s, 1H). Found: C, 61.71; H, 7.72, $C_8H_{12}O_3$ requires C, 61.52; H, 7.75%.

Methyl-2,2-dimethylcyclopentanone-3-carboxylate (17) :- A mixture of the acid **16** (10 g, 64 mmol) and methanolic sulphuric acid (10%, 100 ml) was refluxed for 15 h. Most of the alcohol was removed and the residue poured into ice-cold water and extracted repeatedly with ether. The combined organic layer was washed once with water followed by dilute sodium bicarbonate solution and finally with brine. Removal of ether and distillation of the residue afforded the ester **17** (9.2 g, 83%), b.p.150-5°C/40 mm Hg; ν_{max} 1735 cm^{-1}; δ(200 MHz) 0.90 (s, 3H), 1.16 (s, 3H), 2.77 (t, J = 8 Hz, 1H), 3.68 (s, 3H). Found: C, 63.60; H, 8.09, $C_9H_{14}O_3$ requires C, 63.51; H, 8.29%.

2,2-Dimethyl-3-hydroxymethyl cyclopentanone (18) :- A mixture of the keto ester **17** (9 g, 50 mmol), ethylene glycol (6.2 g, 100 mmol), p-toluenesulphonic acid (50 mg) and dry benzene (150 ml) was refluxed for 5 h using a Dean-Stark water separator. After completion of the reaction (TLC), it was cooled, washed with water and benzene removed. Distillation of the residue furnished the corresponding acetal ester (9.4 g, 88%), b.p. 160-6°C/20 mm Hg; ν_{max} 1735 cm^{-1}; δ (60 MHz) 0.83 (s, 3H), 1.00 (s, 3H), 3.63 (s, 3H), 3.86 (s, 4H).

The above acetal ester (9 g, 40 mmol) was added dropwise to a stirred suspension of LAH (1.5 g, 40 mmol) in dry ether (40 ml) at room temperature. After addition was complete, stirring was continued for another 1 h at room temperature and then the mixture was heated under reflux for 3 h. The reaction mixture was chilled to 0°C and slowly decomposed with saturated aqueous sodium sulphate. Organic layer was decanted and concentrated in vacuo to furnish the crude acetal alcohol.

The above acetal alcohol was heated at 80°C with methanolic hydrochloric acid (5%, 50 ml) for 1-2 h. The solution was concentrated and extracted with ether and the combined organic layer washed with water. The residue after removal of ether was distilled to afford the keto alcohol **18** (4.8 g, 84.5%), b.p.130-5°C/10 mm Hg; ν_{max} 1735 cm^{-1}; δ (200 MHz) 0.92 (s, 3H), 1.12 (s, 3H), 1.58-1.74 (m, 1H), 3.64-3.87 (m, 2H). Found: C, 67.47; H, 9.87, $C_8H_{14}O_2$ requaires C, 67.57; H, 9.93%.

2,2-Dimethyl-3[(t-butyldimethylsiloxy)methyl]cyclopentanone (8) :- To a solution of the keto alcohol **18** (1.42 g, 10 mmol) in dry DMF (3 ml), t-butyldimethylchlorosilane (1.8 g, 12 mmol) and imidazole (1.7 g, 25 mmol) were added. The mixture was stirred at 35°C for 10 h and then partitioned between ether and water. The organic layer was washed with water and brine and dried. Removal of the solvent yielded (2.38 g, 93%) of the silylated material. This material was passed through a short column of neutral alumina to afford an analytical sample; ν_{max} 1735 cm^{-1}, δ (200 MHz) 0.05 (s, 6H), 0.87 (s, 9H), 0.95 (s, 3H), 1.11 (s, 3H), 3.68-3.72 (m, 2H). Found: C, 65.21; H, 10.8, $C_{14}H_{28}O_2Si$ requires C, 65.58; H, 11.01%.

Methyl-2,2-dimethylcyclobutane carboxylate (20) :- To a stirred and cooled (0°C) suspension of sodium hydride (1.7 g, 35 mmol) in dry ether (20 ml) was added ethyl

formate (5.2 g, 70 mmol) followed by a few drops of methanol. To the above, 2,2-dimethylcyclopentanone **(5)** (3.4 g, 30 mmol) was added dropwise and the mixture was stirred for 3 h at 0°C and left overnight. It was poured into ice-cold water and extracted with ether once. The basic aqueous part was acidified in the cold with dilute hydrochloric acid (6N) and extracted with ether. The extracts were washed with brine, dried and concentrated to yield the formyl derivative (3.4 g).

The above crude formyl ketone (3.4 g, 24 mmol) was dissolved in methylene chloride (20 ml) and triethyl amine (7.3 g, 72 mmol) was added. The solution was stirred and cooled to -10°C and a methylene chloride (5 ml) solution containing tosyl azide (4.7 g, 24 mmol) was added slowly. The mixture was stirred for 4 h at 0°C and left for 12 h in the freezer (10°C). After adding aqueous potassium hydroxide (10%, 20 ml) it was again stirred for 15 min at 0°C. The layers were separated and the aqueous layer was extracted with ether. The combined ether layer was washed twice with water, dried and ether distilled off. The residual oil was chromatographed over neutral alumina with ether-petroleum ether (1:1) to furnish the diazo ketone **19** (3.1 g) ν_{max} 2090 cm^{-1}.

The above diazo ketone **19** was dissolved in methanol (250 ml) and irradiated with ice-bath cooling under nitrogen. The reaction was complete after 3-4 h. Removal of solvent afforded the cyclobutane carboxylate **20** (1.7 g, 40%); b.p. 100°C/10 mm Hg; ν_{max} 1735 cm^{-1}; δ (100 MHz) 1.01 (s, 3H), 1.18 (s, 3H), 2.81 (t, J = 8 Hz, 1H), 3.64 (s, 3H).

2,2-Dimethylcyclobutane carboxylic acid (21) :- The diazo ketone **19** obtained from **5** (3.4 g, 30 mmol) was dissolved in a solution of sodium bicarbonate (2 g) in water (75 ml) and THF (140 ml) and with ice-bath cooling irradiated under nitrogen. After the reaction was complete (4 h), the THF was removed under reduced pressure and the aqueous part was extracted once with ether. The aqueous layer was then acidified in the cold with hydrochloric acid (6N) and extracted with ether after saturating with sodium chloride. The combined ether extract was dried, concentrated and the residue distilled to provide the acid **21** (2.46 g, 64%), b.p. 90°C/2 mm Hg (lit[16] b.p. 85-86°C/1.5 mm Hg); δ (60 MHz) 1.12 (s, 3H), 1.23 (s, 3H), 2.9 (t, J = 8 Hz, 1H), 10.65 (br, 1H). Found: C, 65.81; H, 9.25. $C_7H_{12}O_2$ requires C, 65.59; H, 9.44%.

The methyl ester **20** obtained by treatment of above acid with diazomethane in ether contained no detectable impurities, GLC, column temp. 80°C, R_t 2.17 min.

2,2-Dimethylcyclobutyl methanol (22) :- A solution of the ester **20** (1.4 g, 10 mmol) in dry ether (10 ml) was added dropwise to a stirred slurry of LAH (0.38 g, 10 mmol) in dry ether (30 ml). The mixture was heated under reflux for 3 h, cooled and decomposed with ice-cold saturated aqueous sodium sulphate solution. The ether layer was decanted and the residue after removal of ether was distilled to furnish the alcohol **22** (920 mg, 81%), b.p. 65-67°C/8 mm Hg (lit[16] b.p. 76-78°C/17 mm Hg); GLC, column temp. 80°C, R_t 1.69 min; δ (100 MHz) 1.04 (s, 3H), 1.12 (s, 3H), 3.48-3.84 (m, 2H).

1-(2,2-Dimethylcyclobutyl)but-1-en-3-one, (±) junionone (3) :- To a stirred suspension of PCC (650 mg, 3 mmol) in methylene chloride (4 ml) was added the alcohol **22** (230 mg, 2 mmol) in methylene chloride (1 ml). The mixture was stirred for 1 h at 30°C, diluted with dry ether (20 ml) and filtered through a short column of silica gel to get sufficiently pure (TLC) **23** for the next step, (213 mg, 95%); ν_{max} 1710 cm^{-1}; δ (60 MHz) 1.13 (s, 3H), 1.32 (s, 3H), 2.81 (t, J = 8 Hz, 1H), 9.78 (s, 1H).

To a solution of acetylmethylene triphenylphosphorane (650 mg, 2 mmol) in dry methylene chloride (5 ml) under nitrogen was added a solution of the above aldehyde **23** (190 mg, 1.7 mmol) in dry methylene chloride (5 ml). The mixture was then refluxed for 3 h and left overnight. The solvent was removed under reduced pressure and the residue diluted with petroleum ether (10 ml). The crystalline residue was separated through filtration and the organic filtrate was concentrated. The residue was subjected to preparative layer chromatography [2% ethyl acetate in petroleum, two developments] to afford (±) junionone **(3)** (196 mg, 76%) as a colourless liquid, GLC (GC/MS), column temp.

40°C - 2 min - 6°C/min-200°C, R_t 6.5 min; ν_{max} 1670 cm^{-1}; δ (100 MHz) 1.01 (s, 3H), 1.12 (s, 3H), 2.24 (s, 3H), 2.70 (m, 1H), 6.0 (d, J = 16 Hz, 1H), 6.86 (dd, J = 16 Hz and 8 Hz, 1H); MS (GC/MS) m/z 152 (M^+).

Methyl-2-methyl-2-(2-methoxyethyl)cyclobutane carboxylates (25) :- The diazo ketone **24** prepared from **6** (624 mg, 4 mmol) on irradiation in methanol and work up as before furnished **25** (268 mg, 36%); b.p. 125°C/5 mm Hg; ν_{max} 1725 cm^{-1}; δ (60 MHz) 1.03, 1.2 (2s, in a ratio 1:1, 3H), 3.2, 3.23 (2s, in a ratio 1:1, 3H), 3.67 (s, 3H). Found: C, 64.32; H, 9.56, $C_{10}H_{18}O_3$ requires C, 64.49; H, 9.47%.

2-Methyl-2-(2-methoxyethyl)cyclobutane carboxylic acid (26) :- The mixture of esters **25** (268 mg, 1.4 mmol) was taken in ethanolic potassium hydroxide (5%, 20 ml) and refluxed for 6 h, water was added and the solution concentrated. The solution was cooled and extracted with ether. Aqueous layer was acidified with hydrochloric acid (6N) and extracted with ether after saturation with sodium chloride. Ethereal solution was dried and concentrated to leave the acid **26** (225 mg, 90%); δ (60 MHz) 1.16, 1.26 (2s, in a ratio 1:1, 3H), 3.30, 3.33 (2s, 3H), 8.33 (br s, 1H).

The identical epimeric composition, before and after hydrolysis, was confirmed from esterification of **26** with diazomethane and comparison (^1H NMR) with **25**.

cis-6-Methyl-3-oxabicyclo(4.2.0)octan-2-one (27) :- The cyclobutane carboxylic acid **26** (220 mg, as 1:1 mixture) was taken in glacial acetic acid (1 ml) and treated with hydriodic acid (2 ml, freshly decolourised with red phosphorus) and the mixture heated on an oil bath at 120°C for 45 min. Reaction mixture was poured into cold water and neutralised with solid sodium bicarbonate. The separated oil was taken in ether and the aqueous layer was extracted with ether. Combined ethereal layer was washed with saturated sodium thiosulphate solution and brine. Concentration of solution afforded the cis bicyclic lactone, further purified by passing down a column of silica gel with ether - petroleum ether (1:1) (70 mg, 78%), ν_{max} 1740 cm^{-1}; δ (60 MHz) 1.26 (s, 3H), 4.10-4.50 (m, 2H).

Methyl-2-methyl-2-phenyl cyclobutane carboxylates (29) and (30) :- The diazo ketone **28**, prepared from **7** (1 g, 6 mmol) on irradiation in methanol and work up as before furnished the cyclobutane carboxylates **29** and **30** (954 mg, 78%), b.p. 110-120°C/3 mm Hg; ν_{max} 1725, 1600 cm^{-1}; δ (200 MHz) 1.40 (major), 1.66 (2s, at the ratio of 85:15, 3H), 2.82-3.02 and 3.44-3.57 (2m, 1H), 3.36, 3.80 (major) (2s, at the ratio of 15:85, 3H).

Hydrolysis of the esters 29 and 30 and separation of acid 31 :- The mixture of esters **29** and **30** (2 g, 10 mmol) was taken in ethanolic potassium hydroxide (5%, 20 ml) and refluxed for 6 h, water was added and the solution concentrated. The concentrated solution was cooled and extracted once with ether. The basic aqueous layer was then acidified with hydrochloric acid (6N) and extracted with ether after saturation with sodium chloride. Removal of solvent yielded the crude acid in an (cis-trans) isomeric mixture as a semisolid mass. The major isomer was separated by repeated crystalisation from petroleum ether to give the cyclobutane carboxylic acid **31**, m.p. 91-93°C, δ (60 MHz) 1.39 (s, 3H), 3.23-3.56 (m, 1H), 7.06-7.29 (m, 5H), 8.61 (br s, 1H). Found: C, 75.89; H, 7.58, $C_{12}H_{14}O_2$ requires C, 75.76; H, 7.42%.

Pure methyl ester **30** was obtained from esterification with diazomethane; ν_{max} 1725, 1600 cm^{-1}; GLC, column temp. 140°C, 8.14 min; δ (200 MHz) 1.40 (s, 3H), 3.46-3.56 (m, 1H), 3.80 (s, 3H), 7.20-7.42 (m, 5H).

The mother liquor after partial separation of the major isomer was again esterified to afford mixture of **29** and **30** (46:54); GLC, column temp. 140°C, R_t 6.27 and 8.11 min at the ratio of 46:54; δ (200 MHz) 1.40 (major), 1.66 (2s, in a ratio of 54:46, 3H), 2.82-3.02 and 3.44-3.57 (2m, 1H), 3.36, 3.80 (major) (2s, in a ratio of 46:54, 3H), 7.20-7.42 (m, 5H).

1-Acetyl-2-methyl-2-phenylcyclobutane (32) :- To a cooled (0°C) and stirred solution of the acid **31** (760 mg, 4 mmol) in ether (40 ml) under nitrogen was added 1 ml of 1.1 M (12 mmol) solution of methyllithium in ether. The mixture was stirred for 0.5 h at 0°C,

then for 3 h at room temperature. A portion (ca. one-third) of the reaction mixture was then added dropwise to 100 ml of rapidly stirred ice-water. This process was repeated until all the reaction mixture was quenched, the ice-water being replaced every time.

The aqueous layer was separated and extracted with ether. The combined ether extracts were washed with saturated brine. The product after removal of ether was chromatographed through a column of silica gel (5% ethyl acetate-petroleum) to get the desired ketone **32** (530 mg, 71%); ν_{max} 1705, 1600 cm^{-1}; GLC column temp. 150°C, R_t 5.04 and 5.43 min (major) at the ratio of 4:96; δ (100 MHz) 1.36 (s, 3H), 2.08 (s, 3H), 3.49 (t, J = 8 Hz, 1H), 7.20-7.38 (m, 5H). Found: C, 82.74; H, 8.51, $C_{13}H_{16}O$ requires C, 82.93; H, 8.57%.

Methyl-2-acetyl-1-methyl cyclobutane carboxylates (36) and (37) :- To a stirred solution of ketone **32** (206 mg, 1.1 mmol) in a mixture of carbontetrachloride (4 ml) and acetonitrile (4 ml), ruthenium (III) chloride (50 mg, 0.24 mmol) was added followed by a solution of sodium periodate in water (20 ml), in one portion, and left overnight. Sufficient water was then added to dissolve the separated sodium iodate. The solution was extracted with ether and the combined ethereal extracts concentrated. The residue was dissolved in ether (10 ml) and filtered through a short column of alumina. The crude acid thus obtained was esterified with an ethereal solution of diazomethane and again passed through a short column of alumina. Removal of solvent furnished the keto ester **36** (133 mg, 70%), contaminated with ca. 4% of the other epimer **37** (^{1}H NMR), ν_{max} 1720 cm^{-1}; GLC, column temp. 100°C, R_t 6.34 (major) and 7.03 min at the ratio of 96:4; δ (100 MHz) 1.25 (major), 1.49 (2s, in a ratio of 96:4, 3H), 2.07, 2.09 (2s, 3H), 3.65, 3.73 (major) (2s, 3H). Found: C, 63.07; H, 7.66, $C_9H_{14}O_3$ requires C, 63.51; H, 8.29%.

Isomerisation of methyl-2-acetyl-1-methyl cyclobutane carboxylates (36) and (37) :- The keto esters **36** and **37** were dissolved in 5% methanolic sulphuric acid and left stirring for 12 h. Next it was diluted with equal volume of water, neutralised with saturated sodium bicarbonate solution and extracted with ether. The solvent was removed to afford a product consisting of **36** and **37** in a proportion of 55:45; GLC, column temp. 100°C, R_t 6.34 (major) and 7.03 min at the ratio of 55:45; δ (100 MHz) 1.25 (major), 1.49 (2s, in a ratio of 55:45, 3H), 2.07, 2.09 (2s, 3H), 3.65, 3.73 (2s, 3H).

Methyl-2,2-dimethyl-3-[(t-butyldimethylsiloxy)methyl]cyclobutane carboxylates (39) and (40):- The diazo ketone **38**, prepared from ketone **8** (2.6 g, 10 mmol), on irradiation in methanol and work up as before furnished the carboxylates **39** and **40** (1.9 g, 69%), b.p. 100-110°C/5 mm Hg; ν_{max} 1725 cm^{-1}; δ (200 MHz) 0.04, 0.06 (2s, in 2:1 proportion, 3H), 0.88, 0.90 (2s, in 2:1 proportion, 9H), 0.99 (major), 1.07, 1.20 and 1.26 (major) (4s, 6H), 3.69 (major), 3.71 (2s, 3H). Found: C, 63.05; H, 10.86, $C_{15}H_{30}O_3Si$ requires C, 62.88; H, 10.56%.

2,2-Dimethyl-3-acetylcyclobutylmethanol acetates, (±) pinononyl acetate (43) and (44) :- The mixture of esters **39** and **40** (1.9 g, 6 mmol) was taken in ethanolic potassium hydroxide (5%, 10 ml) and refluxed for 6 h. Usual work up furnished the crude acid which was subjected to methyllithium treatment as in the case of **32**. The product showed (^{1}H NMR) complete loss of silyl protecting group and corresponded to the hydroxy ketones **41** and **42** (580 mg, 62%), ν_{max} 1705 cm^{-1}. To this mixture of ketones **41** and **42** (468 mg, 3 mmol) was added acetic anhydride (2 ml) and pyridine (4 ml) and stirred overnight at room temperature. The reaction mixture was diluted with water, extracted with ether and the ether layer washed with dilute sodium bicarbonate solution followed by water. The ether layer was dried and concentrated and the residual oil was subjected to preparative layer chromatography [5% ethyl acetate in petroleum, two developments] to afford **43** and **44** (2:1) (488mg, 87%); ν_{max} 1705, 1735 cm^{-1}; δ (200 MHz) 0.91 (major), 1.04, 1.24, 1.34 (major) (4s, 6H), 2.03 (major), 2.04, 2.05 (major), 2.07 (4s, 6H), 2.9 (m, 1H), 4.1 (m, 2H). Found: C, 66.10; H, 9.48, $C_{11}H_{18}O_3$ requires C, 66.64; H, 9.15%.

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