The Stereocontrolled Synthesis of a 2,3,3-Trisubstituted Cyclohexanone Involving Hydroxylactonisation of a Tertiary Amide

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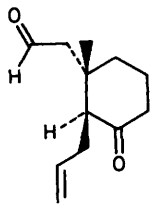
A new method for the stereocontrolled synthesis of 2,3,3-trisubstituted cyclohexanones is reported which involves the first example of hydroxylactonisation of a γ,δ-unsaturated tertiary amide followed by reductive cleavage of the lactone to produce the substituted cyclohexanone.

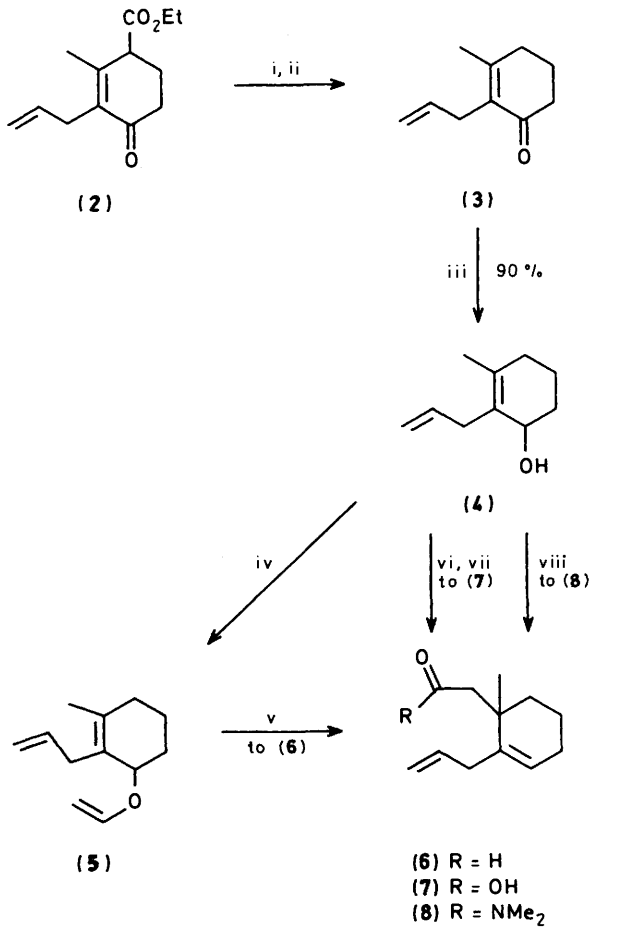
There are many literature examples of the stereocontrolled synthesis of 2,3,3-trisubstituted cyclopentanones prepared by the addition of a cuprate reagent to a 3-substituted cyclopentenone followed by trapping of the intermediate enolate with an alkyl halide.[1] As part of a synthetic programme we required the trisubstituted cyclohexanone derivative (**1**),[2] and in view of this well precedented procedure for five-membered rings we attempted to add lithium dimethylcuprate to a 3-substituted cyclohexenone and to trap the intermediate with allyl bromide. Despite considerable effort we were only able to isolate complex mixtures of products whichever order we carried out the transformation using a range of substrate molecules. Consequently, we turned out attention to the development of alternative strategies to achieve this transformation and we now disclose full details of a novel sequence leading to an ester corresponding to (**1**).



(**1**)

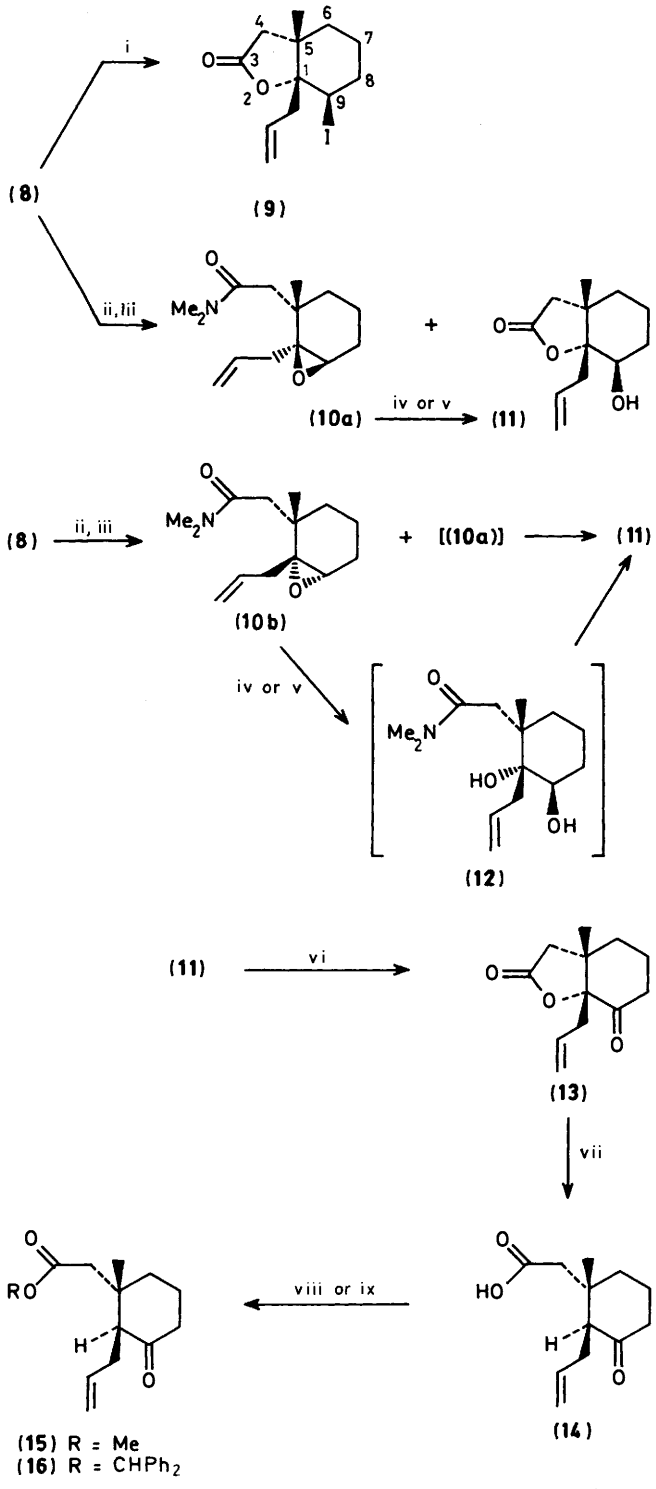
Results and Discussion

The reaction sequence is summarised in Schemes 1 and 2. Hagemann's ester was deprotonated and treated with allyl bromide according to the literature procedure[3] to provide the ester (**2**), which on hydrolysis and decarboxylation gave enone (**3**). Reduction with lithium aluminium hydride produced the allylic alcohol (**4**) in high yield. Three different variants of the Claisen rearrangement[4] were carried out on alcohol (**4**). Conversion into the allyl vinyl ether (**5**) followed by heating at 170 °C for 4.5 h gave the aldehyde (**6**) in an overall yield of 67%. Next treatment of (**4**) with triethyl orthoacetate and propionic acid at 150 °C and subsequent hydrolysis produced the acid (**7**) in modest yield. The amide acetal Claisen rearrangement[5] converted alcohol (**4**) into the amide (**8**) in 96% yield. This product was converted into the iodo lactone (**9**) Scheme 2 in 33% yield on treatment with iodine.[6] During this reaction an iodonium ion forms and it is opened by nucleophilic attack by the admide oxygen; subsequent hydrolysis of the intermediate leads to the iodo lactone (**9**). We reasoned that another means of turning the trisubstituted olefin in (**8**) into an electrophile is to form an epoxide; acid catalysed opening by the amide would then constitute a companion reaction to iodolactonisation which we call hydroxylactonisation. Although the hydroxylactonisation of acids is known[7] we believe that this is the first example of the reaction with a tertiary amide.[8] At the time of the preliminary publication of this work,[2] there were no examples of the hydroxylactonisation of a tertiary amide.[8]



Scheme 1. *Reagents:* i, KOH, EtOH, heat; ii, HCl, H_2O, heat; iii, $LiAlH_4$; iv, $Hg(OAc)_2$, $H_2C{=}CHOEt$; v, PhMe, 170 °C, 4.5 h, (**6**) R=H; vi, $H_3CC(OEt)_3$, $CH_3CH_2CO_2H$, 150 °C; vii, NaOH, H_2O, (**7**), R=OH; viii, $MeC(OMe)_2NMe_2$, heat.

Epoxidation of the amide (**8**) with *m*-chloroperbenzoic acid gave the hydroxy lactone (**11**), m.p. 84–85 °C (34%) and an epoxide (32%). There appear to be two explanations for this result. The first possibility is that we have formed only one epoxide (**10a**) in the reaction and that it opens *via* an S_N1 mechanism to give a cation which is attacked by the amide carbonyl oxygen leading to the lactone on hydrolysis. The



Scheme 2. *Reagents:* i, I_2, tetrahydrofuran (THF), H_2O; ii, *m*-chloroperbenzoic acid (MCPBA), MeCN, H_2O; iii, saturated aqueous Na_2SO_3 then saturated $NaHCO_3$; iv, H_2SO_4, H_2O, THF; v, 0.5M NaOH, ButOH, heat, then H_2SO_4, H_2O; vi, pyridinium chlorochromate (PCC), CH_2Cl_2; vii, Al–Hg, THF, H_2O, EtOH; viii, CH_2N_2; ix, Ph_2CN_2.

reason we isolate the epoxide (**10a**) would then simply be that the reaction has not gone to completion. The problem with this explanation is that we would not expect to form a single epoxide in the reaction of (**8**) with *m*-chloroperbenzoic acid. We prefer a second explanation in which two epoxides (**10a**) and (**10b**) are formed. The epoxide (**10b**) leads to the hydroxy lactone (**11**) by

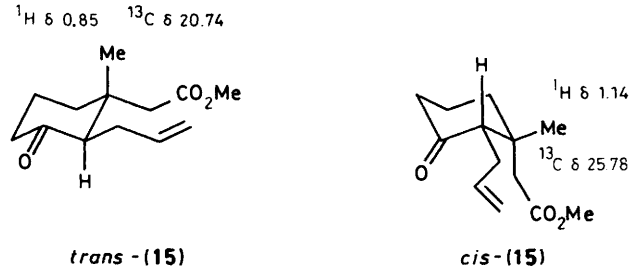
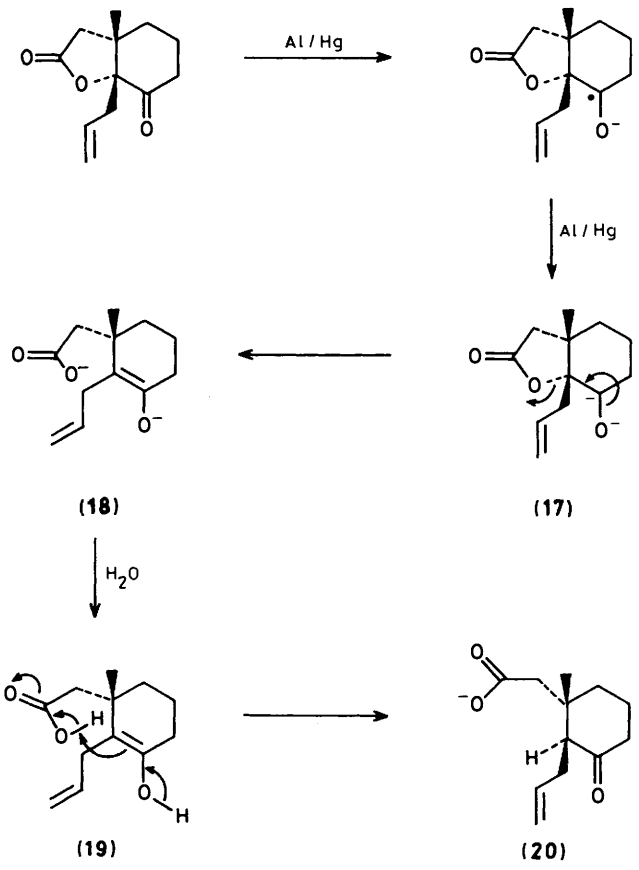


Figure.

ring-opening to give a tertiary cation; nucleophilic attack by the amide oxygen leaves the epoxide (**10a**) unchanged because the epoxide ring is on the same side as the amide side chain. The epoxide (**10a**) was converted into the hydroxy lactone (**11**), under both acidic and basic conditions, which we believe to occur *via* the diol (**12**). Similarly, reaction of the epoxide (**10a**) with methanolic HCl gave a lactone methyl ether identical with the product from reaction of the hydroxy lactone (**11**) with KH and MeI. Whereas an S_N2 opening of the epoxide (**10a**) at the least substituted carbon was expected under basic conditions, the occurrence of the same reaction under acidic conditions was at first surprising. However, several examples of the S_N2 opening of steroid epoxides under acidic conditions have been reported where the acid anion is a good nucleophile.[10] Further support for this mechanism comes from the fact that the acid hydrolysis of an epoxide to a *trans*-diol is a widely used synthetic method.[11] The stereochemistry of hydroxy lactone (**11**) was confirmed by an X-ray crystal structure determination.[2] Since our objective is the synthesis of a substituted cyclohexane, we need to cleave the C–O bond of the lactone. Methods normally used for the deoxygenation of esters[12] were unsuccessful. However, oxidation of the alcohol (**11**) with pyridinium chlorochromate gave the keto lactone (**13**)[13] which reacted with calcium in liquid ammonia to produce a 3.5:1 mixture of *trans*- and *cis*-isomers of the acid (**14**). Higher selectivity was achieved using aluminium amalgam[14] which produced the methyl ester (**15**) as a 96:4 mixture of *trans*- and *cis*-isomers after treatment of the intermediate acid (**14**) with diazomethane. The major isomer was assigned structure (**15**) where the angular methyl group would be expected to be axial in the more stable conformation, (**15**) *trans* Figure in which two groups are equatorial and one axial. The chemical shifts of the angular methyl group were δ_H 0.85 and δ_C 20.74; when the product was epimerised with NaOMe in MeOH a 3:2 mixture was obtained with additional signals at δ_H 1.14 and δ_C 25.78. From our experience with related compounds we would expect the conformation of the *cis*- and *trans*-isomers of (**15**) to be as shown in the Figure, and the axial methyl group to occur at higher field than the equatorial methyl in both ^{1}H and ^{13}C NMR spectra. This leads to the conclusion that the major isomer of (**15**) has the larger side chains *trans*. An X-ray analysis[2] on the diphenylmethyl ester (**16**), m.p. 96–98 °C, confirms the stereochemical assignment; this derivative was prepared by the reaction of the initially isolated acid (**14**) with diphenyldiazomethane.

The often quoted NMR text book by Jackman and Sternhell[15] predicts that an axial methyl group is at a lower field than the equatorial methyl in a 3-methylcyclohexanone.[16] However, it appears that this prediction is based on results obtained on 2- and 4-methylcyclohexanone derivatives[17] and certainly does not apply in the case of compounds (**15**) and (**16**). In our experience the occurrence of axial methyl groups at higher field than the corresponding equatorial methyl is the norm in both ^{1}H and ^{13}C NMR spectra for cyclohexanone derivatives.



Scheme 3.

A mechanism which explains the observed stereoselectivity in the aluminium amalgam reduction of the lactone (**13**) is outlined in Scheme 3. The transfer of two electrons from the amalgam to the lactone leads to the dianion (**17**) which opens to the carboxylate enolate (**18**) which is protonated twice at oxygen under the neutral conditions of the reaction to produce the enol (**19**). Intramolecular removal of the acid proton by the enol nucleophile delivers the proton on the same side as the acid side chain leading to the ketone (**20**) as the major product. It is significant that under the substantially more basic conditions of calcium in liquid ammonia the acid group of intermediate (**19**) would not be protonated and intermolecular protonation during work-up would be expected to lead to lower selectivity, and indeed it does (3.5:1). Our results show that the reaction is under kinetic control since base-catalysed epimerisation of the methyl ester (**15**) or its acid precursor (**14**) produces a mixture of *trans, cis*-isomers (**15**) and (**14**) (3:2 for the ester and 1:1 for the acid).

In conclusion we have developed a useful procedure for the stereoselective synthesis of trisubstituted cyclohexanones which provides an alternative to cuprate addition to a cyclohexanone.

Experimental

90 MHz ^{1}H NMR spectra were recorded on a Varian EM-390 spectrometer. Highfield ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AM-400 spectrometer in the highfield NMR service at the University of Warwick. Mass spectra were recorded on a Micromass 16B spectrometer. Elemental analysis was carried out by CHN Analysis, Wigston, Leicester. IR spectra were recorded on a Perkin-Elmer 298 spectrometer. M.p.s were determined on a Kofler hot-stage and were uncorrected.

Flash chromatography was carried out according to the method of Still *et al.*[18] using silica gel manufactured by Merck and Co., Kiesel 60, 230–400 mesh (ASTM). TLC was conducted on precoated aluminium sheets (60–254) with a 0.2 mm layer thickness, manufactured by Merck and Co.

The concentration of butyl-lithium was determined by back titration with 0.1M hydrochloric acid from solutions in dibromoethane and water using phenolphthalein as an indicator.

Light petroleum refers to the fraction b.p. 40–60 °C; both light petroleum and ethyl acetate were distilled prior to use. Tetrahydrofuran (THF) and toluene were distilled from sodium metal in the presence of benzophenone. Ether refers to diethyl ether which was distilled from $LiAlH_4$.

2-Allyl-3-methylcyclohex-2-enol (**4**).—A solution of 2-allyl-3-methylcyclohex-2-enone (**3**)[3] (10.0 g, 66.6 mmol) in dry ether (10 ml) was added dropwise over 25 min to a stirred suspension of lithium aluminium hydride (1.0 g, 26.4 mmol, 0.4 equiv.) in dry ether (60 ml) at 0 °C under N_2. After the mixture had been stirred at 0 °C for a further 1.5 h excess of hydride was destroyed by the dropwise addition of ethyl acetate (5.2 ml, 53 mmol, 2 equiv.). The resulting slurry was poured into saturated aqueous ammonium chloride (400 ml) and the phases were separated. The aqueous phase was further extracted with ether (3 × 100 ml). The combined ether extracts were washed with saturated aqueous sodium hydrogen carbonate (× 2) and brine (× 1), dried (Na_2SO_4), and evaporated under reduced pressure to leave a colourless oil (9.91 g). Distillation of crude alcohol from the enone (35.8 g) gave *the title compound* (**4**) (32.54 g, 90%) as a colourless oil, b.p. 63–66 °C/0.5 Torr, R_f 0.59 [light petroleum–ether (1:1)]; R_f 6.2 min (10% SE 30, 150 °C, 15 psi); ν_{max}(film) 3 100–3 600br s (OH), 2 970s, 2 935s, 2 860s, 2 825s, 1 635m (C=C), 1 435, 1 165s, 1 075s, 990s, 960s, 940s, 935s, and 910s cm^{-1}; δ_H(90 MHz, CCl_4) 0.9–2.1 [6 H, m, $(CH_2)_3$], 1.60 (3 H, s, CH_3), 2.67 (1 H, s, OH), 2.82 (1 H, br d, *J* 7 Hz, C=CCH$_2$C=C), 3.84 (1 H, br s, C*H*OH), 4.75–5.1 (2 H, m, C=CH$_2$), and 5.45–6.0 (1 H, m, C=CH).

The conversion of alcohol (**4**) (50 mg, 0.33 mmol) into its 3,5-dinitrobenzoate was carried out by the standard method and after recrystallisation from ether–light petroleum afforded white microcrystalline prisms (43 mg, 38%), m.p. 77–78 °C; R_f 0.81 [light petroleum–ether (2:1)]; δ_H(90 MHz, $CDCl_3$) 1.4–2.3 [6 H, m, $(CH_2)_3$], 1.75 (3 H, s, CH_3) 2.6–2.9 (2 H, m, C=CCH$_2$C=C), 4.75–5.1 (2 H, m, C=CH$_2$), 5.4–6.1 (2 H, m, C=C*H* + CH$_2$-C*H*OCO), and 9.0–9.25 (3 H, m, aromatic H) (Found: C, 58.75; H, 5.20; N, 8.10. $C_{17}H_{18}N_2O_6$ requires C, 58.96; H, 5.24; N, 8.09%).

The alcohol (**4**) (2.0 g, 13.1 mmol) was converted into its acetate by the standard method, chromatography on silica (3 × 15 cm) eluting with light petroleum–ether (9:1) gave the acetate (2.54 g, 100%). Bulb-to-bulb distillation of a sample (2.122 g) gave a colourless oil with a fruity odour (2.079 g, 98% recovery) b.p. 80–90 °C/0.75 Torr, R_f 0.38 [light petroleum–ether (6:1)] (Found: C, 74.10; H, 9.35. $C_{12}H_{18}O_2$ requires C, 74.19; H, 9.34%); ν_{max}(film) 2 930s, 1 730s (ester), 1 635w (C=C), 1 370s, 1 240s, 1 235s, and 1 015s cm^{-1}; δ_H(400 MHz, $CDCl_3$) 1.52–1.69 (3 H, m), 1.64 (3 H, s, CH_3), 1.75–1.83 (1 H, m), 1.96–2.02 (2 H, m), 1.99 (3 H, s, CH_3CO_2), 2.59 (1 H, dd, *J* 15.3, 7.0 Hz, C=CC*H*HC=C), 2.83 (1 H, dd, *J* 15.3, 5.8 Hz, C=CCH*H*C=C), 4.89–4.94 (2 H, m, C=CH$_2$), 5.21 (br s, C*H*OH), and 5.62–5.72 (1 H, m, C=CH); δ_C(100 MHz, $CDCl_3$) 18.11 (t), 19.05 (q), 21.14 (q), 28.86 (t), 31.69 (t), 34.56 (t), 69.93 (d), 114.6 (t), 125.92 (s), 135.51 (d), 135.54 (s), and 170.53 (s, C=O).

1-Allyl-2-methyl-6-vinyloxycyclohex-1-ene (**5**).—A solution of the cyclohexenol (**4**) (5.0 g, 32.8 mmol) and recrystallised mercuric acetate (2.0 g, 6.3 mmol, 0.19 equiv.) in freshly distilled

dry ethyl vinyl ether (120 ml, 1.25 mol, 38 equiv.) was stirred and heated to reflux under N_2. Every 2 h an additional portion of mercuric acetate (0.5 g) dissolved in dry ethyl vinyl ether (5 ml) was added to the refluxing mixture *via* syringe. After 2.5 g of mercuric acetate had been added (five additions over 10 h) the resulting clear colourless solution was refluxed for a further 11 h. The cooled reaction mixture was diluted with petroleum (120 ml) and washed with aqueous 2M sodium hydroxide (3 × 50 ml), dried (K_2CO_3), and evaporated under reduced pressure. The residue was chromatographed on alumina (3 × 9 cm) using light petroleum to give the title compound (**5**) (4.59 g, 78%) as a colourless oil; ν_{max}(film) 2 935s, 2 905s, 2 860s, 1 630s, 1 605s, 1 190s, 1 165s, 1 075s, and 1 025 cm^{-1}; δ_H(90 MHz, CCl_4) 1.2–2.2 [6 H, m, $(CH_2)_3$], 1.64 (3 H, s, CH_3), 2.5–3.1 (2 H, m, C=CCH_2C=C), 3.82 (1 H, dd, *J* 8, 2 Hz, *E*-OCH=CH*H*), 4.03 (1 H, m, CH_2CHOC=C), 4.13 (1 H, dd, *J* 15, 2 Hz, *Z*-OCH=C*H*H), 4.7–5.1 (2 H, m, CH=CH_2) 5.6–5.9 (1 H, m, CH_2=C*H*CH_2), and 6.17 (1 H, dd, *J* 15, 8 Hz, OC*H*=CH_2).

1-*Allyl*-2-*formylmethyl*-2-*methylcyclohex*-6-*ene* (**6**).—A solution of the cyclohexene (**5**) (1.0 g, 5.61 mmol) in dry toluene (6 ml) was heated at 170 °C for 4.5 h in a resealable Carius tube. Evaporation of solvent under reduced pressure (40 °C) and chromatography of the residue on silica (2 × 16 cm) using light petroleum–ether (95:5) gave the title compound (**6**) (829 mg, 83%) as a colourless oil with a floral odour; R_f 0.39 [light petroleum–ether (9:1)]; ν_{max}(film) 2 960s, 2 930s, 2 875s, 2 840s, 2 735m (aldehyde CH), 1 720s (aldehyde C=O), 1 640m (C=C), and 910 cm^{-1}; δ_H(90 MHz, CCl_4) 1.15 (3 H, s, CH_3), 1.3–2.1 [6 H, m, $(CH_2)_3$], 2.18 and 2.43 (2 H, both dd, *J* 15, 4 Hz, CH_2CHO), 2.6–2.9 (2 H, m, C=CCH_2C=C), 4.8–5.2 (2 H, m, C=CH_2), 5.3–6.0 (2 H, m, 2 × C=CH), and 9.59 (1 H, t, *J* 4 Hz, CHO); *m*/*z* 178 (M^+, 14), 160 (20), 134 (48), 133 (100), 132 (31), 119 (67), 107 (40), 105 (41), 93 (94), 91 (78), 81 (36), 79 (67), and 67 (36).

Conversion of the aldehyde (20 mg, 0.11 mmol) into its 2,4-dinitrophenylhydrazone was carried out by the standard method and after two recrystallisations from ethanol gave yellow prisms (34 mg, 86%), m.p. 108–109 °C. (Found: C, 60.20; H, 6.25; N, 15.50. $C_{18}H_{22}N_4O_4$ requires C, 60.32; H, 6.19; N, 15.63%); *m*/*z* 358 (M^+, 4), 136 (100), 94 (50), 79 (33), and 67 (21).

1-*Allyl*-2-*ethoxycarbonylmethyl*-2-*methylcyclohex*-6-*ene*.—A solution of the cyclohexenol (**4**) (1.52 g, 10 mmol) in dry triethyl orthoacetate (12.8 ml, 70 mmol) and dry propanoic acid (44 μl, 0.6 mmol, 6 mol%) was heated at 150 °C for 3.5 h under N_2 using a Dean–Stark trap. The solvent was removed under reduced pressure (40 °C) and the residue chromatographed on silica (3 × 15 cm) eluting with light petroleum–ether (95:5) to give the title compound (733 mg, 33%) as a colourless oil, R_f 0.52 [light petroleum–ether (19:1]; ν_{max}(film) 2 980s, 2 935s, 1 735s (ester), 1 640m (C=C), 1 195s, 1 150s, and 910 cm^{-1}; δ_H(90 MHz, $CDCl_3$) 1.11 (3 H, s, CH_3), 1.22 (3 H, t, *J* 7 Hz, CH_2CH_3), 1.3–2.4 [6 H, m, $(CH_2)_3$], 2.02 (2 H, s, CH_2CO_2), 2.6–2.9 (2 H, m, C=CCH_2C=C), 4.06 (2 H, q, *J* 7 Hz, C$H_2$$CH_3$), 4.8–5.2 (2 H, m, C=C$H_2$), and 5.26–6.05 (2 H, m, 2 × C=CH); *m*/*z* 222 (M^+, 3), 135 (52), 134 (100), 119 (42), 93 (73), 91 (52), and 88 (55).

1-*Allyl*-2-*carboxyethyl*-2-*methylcyclohex*-6-*ene* (**7**).—A 50% (w/v) aqueous solution of sodium hydroxide was added to a stirred solution of the preceding ester (0.53 g, 2.38 mmol) in methanol (12 ml). After 20 h the reaction mixture was poured into water (60 ml) and extracted with ether (40 ml). The aqueous phase was acidified with 6M hydrochloric acid to pH 1 and extracted with ether (3 × 40 ml). The combined extracts from the acidified aqueous phase were dried (Na_2SO_4) and evaporated to leave the title compound (**7**) (350 mg, 76%) as a slightly discoloured oil, R_f 0.57 [light petroleum–ether (1:1)].

1-*Allyl*-2-(N,N-*dimethylcarbamoylethyl*)-2-*methylcyclohex*-6-*ene* (**8**).—A solution of cyclohexanol (**4**) (1.0 g, 6.57 mmol) and dimethylacetamide dimethylacetal (1.44 ml, 9.85 mmol) in dry toluene (11 ml) contained in a resealable Carius tube was degassed (freeze-thaw to 0.1 Torr with liquid N_2 × 3) and heated to 150 °C (oil bath, stirrer, contact thermometer) for 4.5 h. The reaction mixture was transferred to a round-bottomed flask using ether and evaporated under reduced pressure (40 °C) to leave a yellow oil. Chromatography on silica (3 × 15 cm) eluting with ethyl acetate–light petroleum (3:2) yielded a slightly discoloured oil (2.496 g, 86%). Bulb-to-bulb distillation of a sample (3.092 g) gave the title compound (**8**) (2.970 g, 96% recovery) as a colourless mobile oil with a sweet spicy odour; R_f 0.51 [ethyl acetate–light petroleum (2:1)]; (Found: C, 75.45; H, 10.45; N, 6.20, $C_{14}H_{23}NO$ requires C, 75.97; H, 10.44; N, 6.21%); ν_{max}(film) 2 930s, 2 870s, 1 640s (amide), and 1 390s cm^{-1}; δ_H(400 MHz, $CDCl_3$) 1.07 (3 H, s, CH_3), 1.32–1.38 (1 H, m), 1.49–1.55 (2 H, m), 1.79–1.85 (1 H, m), 1.86–1.99 (2 H, m, C=CC$H_2$$CH_2$), 2.25 and 2.40 (2 H, AB system, *J* 14.4 Hz, CH_2CON), 2.64–2.66 (2 H, m, C=CCH_2C=C), 2.83 and 2.94 [each 3 H, both s, $CON(CH_3)_2$], 4.89–4.95 (2 H, m, C=CH_2), 5.29–5.32 (1 H, m, C=CH), and 5.65–5.75 (1 H, m, CH_2=C*H*); δ_C(100 MHz, $CDCl_3$) 18.58 (t), 25.38 (t), 25.89 (q, CH_3), 35.09 (q), 35.68 (t), 35.91 (t), 37.27 (s), 37.90 (q), 40.38 (t), 115.12 (t), 122.95 (d), 137.72 (d), 141.59 (s), and 171.21 (s, amide); *m*/*z* 221 (M^+, 11), 91 (13), 88 (20), and 87 (100).

1-*Allyl*-9-*Iodo*-5-*methyl*-2-*oxabicyclo*[4.3.0]*nonan*-3-*one* (**9**).—A solution of iodine (707 mg, 2.79 mmol, 3.0 equiv.) in THF–water (1:1) was added to a solution of the amide (**8**) (205 mg, 0.93 mmol) in THF–water (1:1) (8 ml). After 7 h the reaction mixture was poured into 10% aqueous sodium thiosulphate (6 ml) and extracted with ether (3 × 40 ml). The combined ether extracts were washed with brine (× 1), dried (Na_2SO_4), and evaporated under reduced pressure to leave a yellow oil. Chromatography on silica (1 × 15 cm) eluting with light petroleum–ether (4:1) gave the title compound (**9**) (97 mg, 33%) as a colourless oil which crystallised with time; R_f 0.52 [light petroleum–ether (1:1)]; δ_H(90 MHz, $CDCl_3$) 1.36 (3 H, s, CH_3), 1.3–2.2 [6 H, m, $(CH_2)_3$], 2.31 and 2.50 (2 H, AB system, *J* 17 Hz, CH_2CO_2), 2.65 (1 H, dd, *J* 15, 6 Hz, C=CC*H*H), 2.95 (1 H, dd, *J* 15, 8 Hz, C=CCH*H*), 4.42 (1 H, br t, *J* 5 Hz, CHI), 5.15–5.50 (2 H, m, C=CH_2), and 5.55–6.15 (1 H, m, C=CH); ν_{max}(film) 2 930s, 1 780s, (lactone), 1 640w (C=C), 1 220s, 950s, 940s, and 920s cm^{-1}; *m*/*z* 320 (M, 10), 279 (100, $M - C_3H_5$), 193 (129, M − I), 152 (42), 151 (54), 95 (42), and 81 (38). Further elution with light petroleum–ethyl acetate (1:1) gave unchanged starting material (127 mg, 62%).

1-*Allyl*-9-*hydroxy*-5-*methyl*-2-*oxabicyclo*[4.3.0]*nonan*-3-*one* (**11**) *and* 1-*Allyl*-6-(NN-*dimethylcarbamoylmethyl*)-6-*methyl*-1,2-*epoxycyclohexane* (**10b**).—A solution of the amide (**8**) (221 mg, 1.0 mmol) in dry chloroform (1.5 ml) was added dropwise to a stirred solution of *m*-chloroperoxybenzoic acid (259 mg, based on 80% assay, 1.2 equiv.) in dry chloroform (10 ml) under N_2. The resulting colourless solution was stirred for 2 days and then washed sequentially with aqueous 10% sodium sulphite (× 1), saturated aqueous sodium hydrogencarbonate (× 1), and brine (× 1), dried (Na_2SO_4), and evaporated under reduced pressure. Chromatography of the residue on silica (2 × 15 cm) eluting with light petroleum–ethyl acetate (1:1) gave in order of elution, a crystalline product (81 mg, 39%), recrystallisation of which from ether–light petroleum afforded the title compound (**11**) as colourless prisms, m.p. 84–85 °C; R_f 0.71 [ethyl acetate–light petroleum (2:1)]; R_f 0.60 [ether–light petroleum (2:1)]; (Found: C, 68.55; H, 8.60. $C_{12}H_{18}O_3$ requires C, 68.54; H, 8.63%); ν_{max}($CHCl_3$, 5.2 mg/100 μl) 3 620w, 3 250–3 700br w (OH), 2 940s, 1 770s, (lactone), 1 640m (C=C), 1 205s, 1 100s,

1 080s, 1 070s, 1 040s, 995s, 975s, and 925s cm^{-1}. δ_H(400 MHz, $CDCl_3$, NOSY) 1.20 (3 H, s, CH_3), 1.38–1.55 (3 H, m), 1.64–1.77 (3 H, m), 1.89 (1 H, d, *J* 4.3 Hz, OH), 2.28 and 2.46 (2 H, AB system, *J* 17.1 Hz, CH_2CO_2; *anti* and *syn* to the CH_3 group respectively), 2.42 (1 H, ddt, *J* 14.4, 5.7, 1.5 Hz, C=CC*H*H), 2.70 (1 H, dd, *J* 14.4, 8.6 Hz, C=CH*H*), 3.96 (1 H, dd, *J* 7.4, 4.4 Hz, CH_2CHOH), 5.14–5.23 (2 H, m, $C=CH_2$), 5.86–5.96 (1 H, m, C=CH); δ_C(100 MHz, $CDCl_3$) 15.87 (t), 21.06 (q, CH_3), 29.04 (t), 35.85 (t), 35.97 (t), 41.12 (s), 44.54 (t), 68.35 (d), 88.50 (s), 118.95 (t), 132.83 (d), and 175.71 (s, lactone).

An X-ray crystal structure determination has been carried out on (**11**). Full details of this X-ray crystal structure determination were submitted with the preliminary communication of some of these results.[2]

Unchanged starting material (49 mg, 22%) and the amide (**10b**) were also obtained; R_f 0.42 [ethyl acetate–light petroleum (2:1)]; ν_{max}(film) 2 935s, 1 640s (amide), 1 490s, 1 450s, 1 390s, 1 375s, and 915s cm^{-1}; δ_H(90 MHz, $CDCl_3$) 1.0–2.25 [6 H, m, $(CH_2)_3$], 1.26 (3 H, s, CH_3), 2.3–2.7 (2 H, m, $C=CCH_2$), 2.41 (2 H, s, CH_2CON), 2.8–3.2 (1 H, m, CH_2CHO), 2.89 and 3.04 [6 H, both s, $CON(CH_3)_2$], 4.8–5.2 (2 H, m, $C=CH_2$), and 5.4–6.0 (1 H, m, C=CH).

Acid Hydrolysis of the Amide (**10b**).—1M Sulphuric acid (2 ml) was added to a stirred solution of the amide (**10b**) (293 mg, 1.23 mmol) in tetrahydrofuran (10 ml) and the mixture stirred for 20 h under N_2. After evaporation of solvent under reduced pressure, the residue was taken up in brine (20 ml) and extracted with ether (3 × 10 ml). The combined organic extracts were washed with saturated aqueous sodium carbonate (× 1), dried (Na_2SO_4), and evaporated under reduced pressure to leave an oil (188 mg). Chromatography of this on silica (2 × 15 cm) eluting with light petroleum–ether (1:1) gave the crystalline ketone (**11**) (107 mg, 41%), identical in all respects to that obtained from peracid oxidation of the amide (**8**).

Acid Methanolysis of the Amide (**10b**).—1M Sulphuric acid (1 ml) was added to a stirred solution of the amide (**10b**) (177 mg, 0.75 mmol) in methanol (6 ml) and the resulting solution stirred under N_2 for 17 h. It was then poured into brine (20 ml) and extracted with ether (3 × 10 ml). The combined ether extracts were washed with saturated aqueous sodium hydrogencarbonate (× 1), dried (Na_2SO_4), and evaporated under reduced pressure to leave a yellow oil (114 mg). Chromatography of this on silica (2 × 15 cm) eluting with light petroleum–ether (1:1) gave 1-allyl-9-methoxy-5-methyl-2-oxabicyclo[4.3.0]nonan-3-one (53 mg, 32%) as a pale yellow mobile oil; R_f 0.40 [light petroleum–ether (3:1)]; ν_{max}(film) 2 940s, 1 775s (lactone), 1 640m (C=C), 1 235s, 1 205s, 995s, 965s, and 915s cm^{-1}; δ_H(90 MHz, $CDCl_3$) 1.15 (3 H, s, CH_3), 1.1–2.9 [8 H, m, $(CH_2)_3$ + $C=CCH_2$], 2.14 and 2.52 (2 H, AB system, *J* 17 Hz, CH_2CO_2), 3.24 (3 H, s, OCH_3), 3.43 (1 H, m, $w_{\frac{1}{2}}$ 7 Hz, $CHOCH_3$), 5.0–5.3 (2 H, m, $C=CH_2$), and 5.6–6.1 (1 H, m, C=CH); this compound was identical in all respects to the methoxy lactone prepared by the reaction of bicyclononanone (**11**) with MeI,KH, THF at 0 °C. The second compound from the column was the bicyclononanone (**11**) obtained as a crystalline solid (42 mg, 27%).

1-*Allyl*-5-*methyl*-2-*oxabicyclo*[4.3.0]*nonane*-3,9-*dione* (**13**).—A solution of the bicyclononan-2-one (**11**) (336 mg, 1.60 mmol) in dry dichloromethane (2 ml) was added to a stirred suspension of pyridinium chlorochromate (11.51 g, 7.01 mmol, 4.4 equiv.) in dry dichloromethane (10 ml). The resulting brown reaction mixture was stirred under N_2 for 3 h and then diluted with ether (10 ml) and stirring continued for a further 5 min. The supernatant was decanted off and the residue washed with ether (20 ml). The combined ether extracts were filtered through a plug of silica (2 × 7 cm) and evaporated under reduced pressure to afford a white crystalline solid (285 mg, 86%). Recrystallisation of this from acetone–light petroleum gave the title compound (**13**) as colourless prisms, m.p. 124–125 °C; R_f 0.41 [light petroleum–ethyl acetate (1:1)] (Found: C, 69.25; H, 7.75. $C_{12}H_{16}O_3$ requires C, 69.21; H, 7.75%); δ_H(400 MHz, $CDCl_3$) 1.17 (3 H, s, CH_3), 1.71–1.84 (3 H, m), 2.00–2.07 (1 H, m), 2.04 and 2.44 (2 H, AB system, *J* 16.8 Hz, CH_2CO_2), 2.37–2.48 (2 H, m), 2.55–2.66 (2 H, m), 5.05–5.13 (2 H, m, $C=CH_2$), and 5.62–5.72 (1 H, m, C=CH); ν_{max}($CHCl_3$, 4.8 mg/10 μl) 3 025m, 2 980m, 2 940m, 1 785s (lactone), 1 725s (ketone), 1 645w (C=C), 1 190s, 1 130s, 1 010s, and 925s cm^{-1}; δ_C(100 MHz, $CDCl_3$) 22.25 (t), 23.19 (q, CH_3), 31.98 (t), 35.19 (t), 38.73 (t), 39.09 (t), 47.65 (s), 92.65 (s, OCCO), 119.20 (t, $=CH_2$), 130.73 (d, =CH), 173.99 (s, lactone), and 207.14 (s, ketone).

2-*Allyl*-3-*methoxycarbonylmethyl*-3-*methylcyclohexanone* (**15**).—Aluminium foil (70 mg, 2.6 mmol, 10.6 equiv.) was cut into *ca.* 0.5 cm squares and placed in a 25 ml conical flask. The aluminium was etched with aqueous 5% (w/v) potassium hydroxide until vigorous hydrogen evolution occurred. The basic solution was removed by decantation and the aluminium washed once with water and covered with aqueous 0.5% (w/v) mercuric chloride solution for 1.5–2.0 min. The mercuric chloride solution was decanted, the aluminium washed with water, and the mercuric chloride solution reintroduced for 1.5–2.0 min. Once again the mercuric chloride solution was decanted and water added to rinse the aluminium; this was followed by successive rinsing with ethanol and ether. The aluminium was then covered with ethanol and a solution of the bicyclononanedione (**13**) (50 mg, 0.24 mmol) in THF–water (10:1) (3 ml) was added in one portion. After the mixture had been stirred under N_2 for 1 h (the bulk of the aluminium had dissolved) the resulting grey suspension was acidified at 0 °C with 0.1M hydrochloric acid and extracted with dichloromethane (3 × 15 ml). The combined organic extracts were washed with brine (× 2), dried (Na_2SO_4), and evaporated under reduced pressure to give essentially pure 2-allyl-3-carboxymethyl-3-methylcyclohexanone (**14**) (45 mg, 88%) as a semi-solid, R_f 0.44 [light petroleum–ethyl acetate (1:1)]; ν_{max}(film) 3 700–3 400br m (OH), 2 970s, 2 940s, 1 705br s (acid + ketone), 1 640m (C=C), and 790s cm^{-1}; δ_H(90 MHz, $CDCl_3$): 0.90 (3 H, s, CH_3), 1.3–2.1 (1 H, m), 4.8–5.1 (2 H, m, $C=CH_2$), 5.5–6.0 (1 H, m, C=CH), 8.0–8.6 (1 H, br s, CO_2H).

An ethereal solution of diazomethane was added dropwise *via* pipette to a stirred solution of the ketone (**14**) (152 mg, 0.73 mmol) in dry ether until a permanent yellow colouration was obtained. After the mixture had been stirred for a further 10 min excess of diazomethane was destroyed by the dropwise addition of glacial acetic acid. The solvent was evaporated under reduced pressure and the residue azeotroped with benzene to remove the final traces of solvent. The residue was chromatographed on silica (2 × 15 cm) eluting with light petroleum–ether (2:1) gave the title compound (**15**) (126 mg, 77%) as a colourless oil; ν_{max}(film) 2 950s, 1 735s (ester), 1 710s (ketone), 1 640m (C=C), 1 435s, 1 220s, 1 200s, and 1 180s cm^{-1}; δ_H(400 MHz, $CDCl_3$) 0.85 (3 H, s, CH_3), 1.60–1.67 (1 H, m), 1.74–1.84 (1 H, m), 1.88–2.05 (3 H, m), 2.23–2.50 (3 H, m), 2.30 and 2.44 (2 H, AB system, *J* 14.2 Hz, CH_2CO_2), 2.56 (1 H, dd, *J* 10.2, 2.5 Hz, CH_2CHCO), 3.65 (3 H, s, OCH_3), 4.91 (1 H, dm, *J* 10.1 Hz, *E*-C=CH*H*) 4.99 (1 H, dq, *J* 17, 1 1.6 Hz, *Z*-C=CH*H*), 5.68–5.79 (1 H, m, C=CH). The *cis*-isomer shows two singlets at δ 1.15 (CH_3) and δ 3.62 (OCH_3) the *trans*:*cis* ratio is 96:4 by integration; δ_C(100 MHz, $CDCl_3$) 20.73 (q, CH_3), 22.41 (t), 28.14 (t), 35.94 (t), 41.24 (t), 41.84 (s), 44.88 (t), 51.22 (q), 58.11 (d), 115.33 (t), 137.28 (d), 171.55 (s, ester), and 211.14 (s, ketone); *m*/*z* 224 (*M*, 8), 151 (100), 107 (27), 95 (39), and 81 (28).

Epimerisation of the Ketone (**15**).—A solution of the ketone

(**15**) (21 mg, 94 μmol) in dry methanol (1 ml) was added to a stirred solution of sodium methoxide (from sodium 18 mg, 0.78 mmol, 8.3 equiv.) in dry methanol (3 ml) under N_2. After 29 h the reaction mixture was poured into brine 920 ml) and extracted with ether (3 × 10 ml). The combined ether extracts were washed with brine (× 1), dried (Na_2SO_4), and evaporated under reduced pressure to leave essentially pure keto ester (20 mg, 95% recovery) as a pale yellow oil, consisting of a 3:2 mixture of *trans*- and *cis*-diastereoisomers respectively. δ_H(400 MHz, $CDCl_3$) 0.85 and 1.14 (3 H, both s, CH_3, *trans*- and *cis*-isomers respectively), 1.56–1.65 (m), 1.74–2.04 (m), 2.11–2.60 (m), 3.62 and 3.65 (3 H, both s, OCH_3, *cis*- and *trans*-isomers respectively), 4.89–5.00 (2 H, m, C=CH_2), 5.63–5.77 (1H, m, C=CH). δ_C(100 MHz, $CDCl_3$) *cis*-isomer 22.37 (t), 25.78 (q), CH_3), 28.74 (t), 35.08 (t), 39.29 (t), 40.55 (t), 41.60 (t), 51.26 (q), 61.01 (d), 115.65 (t), 136.66 (d), 171.59 (s, ester), and 211.41 (s, ketone).

trans-isomer: 20.74 (q, CH_3), 22.42 (t), 28.15 (t), 35.94 (t), 41.26 (t), 41.85 (s), 44.89 (t), 51.26 (q), 58.10 (d), 115.37 (t), 137.29 (d), 171.56 (s, ester), and 211.25 (s, ketone).

2-Allyl-3-carboxymethyl-3-methylcyclohexanone (**16**).—The ketone (**14**) was dissolved in dry benzene (15 ml) and diphenyldiazomethane (1.0 g, 4.7 mmol) was added to the solution. After 2 h, glacial acetic acid was added until the red colour had been discharged. The solution was then diluted with ether and extracted with saturated aqueous sodium hydrogen carbonate. The organic phase was dried and evaporated to give a yellow oil. This was flash chromatographed on silica eluted with light petroleum–ether (3:1) to give white crystals (0.63 g, 35.4%). Recrystallisation from light petroleum–ether gave the title compound (**16**) as white crystals, m.p. 96–98 °C (Found: C, 79.8; H, 7.5, $C_{25}H_{28}O_3$ requires C, 79.75; H, 7.49%); ν_{max}(Nujol) 2 950m, 1 730s, 1 710s, 1 640w, 1 495m, 1 455m, 1 340m, and 700s cm^{-1}; δ_H(400 $CDCl_3$) 7.25 (10 H, m), 6.85 (1 H, s), 5.7 (1 H, m), 4.9 (2 H, m), 2.6–1.5 (10 H, m), and 0.85 (3 H, s); δ_C(100 MHz, benzene) 210.5 (s), 170.02 (s), 140.8 (s), 137.9 (d), 128 (m), 115.6 (t), 76.98 (d), 58.11 (d), 45.1 (t), 41.95 (s), 41.32 (t), 36.05 (t), 28.6 (t), 22.5 (t), 20.6 (q); *m/z* 376 (*M*, 5%), 209 (2), 193 (10), 165 (100), and 151 (25).

An X-ray crystal structure determination has been carried out on (**16**), full details of which were submitted with the preliminary communication of some of these results.[2]

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