A Stereocontrolled Synthesis and *X*-Ray Crystal Structure of a 2,3,3-Trisubstituted Cyclohexanone

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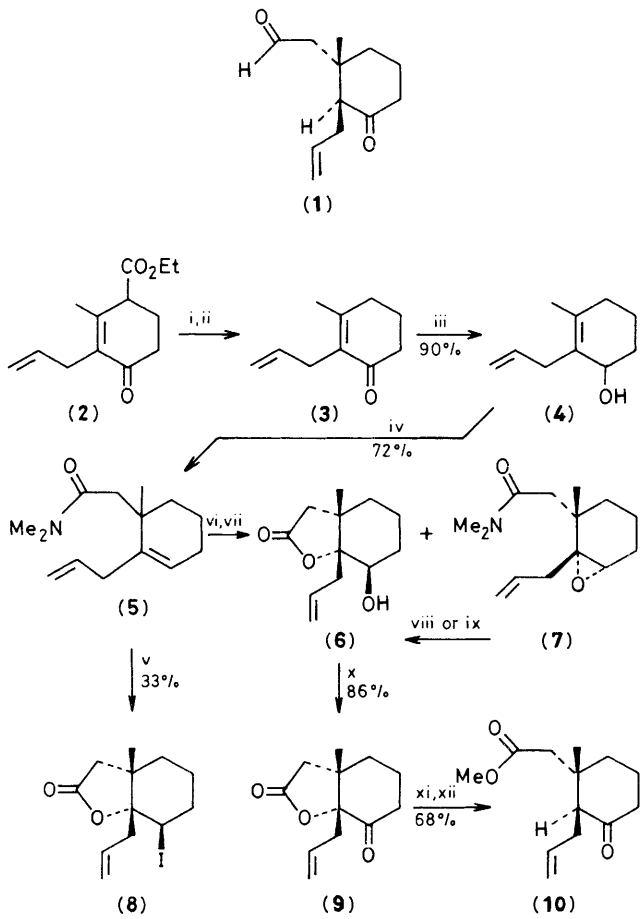
A γ,δ-unsaturated amide, prepared by an amide acetal Claisen rearrangement, has been subjected to hydroxy-lactonisation, and reductive cleavage of the corresponding keto-lactone with aluminium amalgam has led to a trisubstituted cyclohexanone derivative with retention of configuration, thus establishing a new method for the stereocontrolled synthesis of 2,3,3-trisubstituted cyclohexanones.

As part of a synthetic approach to the taxane ring system[1] using 2-lithiobutadiene[2] we are interested in the stereocontrolled construction of the trisubstituted cyclohexane derivative (**1**).

Attempts to prepare compounds like (**1**) by addition of lithium dimethylcuprate to a wide variety of appropriate 2,3-disubstituted cyclohexenones and 3-substituted cyclohexenones followed by trapping with allyl bromide led to mixtures of stereo- and regio-isomers. Consequently, we turned our attention to alternative strategies and now report a novel sequence to an ester corresponding to (**1**) outlined in Scheme 1.



Scheme 1. *Reagents:* i, KOH, EtOH, heat; ii, HCl, H_2O, heat; iii, $LiAlH_4$; iv, PhMe, $MeCH(OMe)_2NMe_2$, heat; v, I_2, tetrahydrofuran (THF), H_2O; vi, *m*-chloroperbenzoic acid (MCPBA), MeCN, H_2O; vii, saturated Na_2SO_3 then saturated $NaHCO_3$; viii, H_2SO_4, H_2O, THF; ix, 0.5 M NaOH, Bu^tOH, heat, then H_2SO_4, H_2O; x, pyridinium chlorochromate (PCC), CH_2Cl_2; xi, Al–Hg, THF, H_2O, EtOH; xii, CH_2N_2.

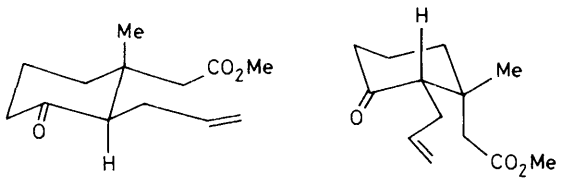
Hagemann's ester was prepared[3] and allylated[4] according to literature procedure to give (**2**). Hydrolysis and decarboxylation were then followed by reduction of enone (**3**) to the allylic alcohol† (**4**) in high yield.

Amide acetal Claisen rearrangement[5] on alcohol (**4**) gave amide (**5**) in 72% yield. Iodolactonisation of the amide using literature procedure[6] leads to iodolactone (**8**) in which some of the required stereochemistry has been introduced. However, an iodine atom is clearly not required in the final molecule. Alternatively, epoxidation of the amide followed by treatment with dilute acid gave a mixture of an epoxide (32%) assigned the structure (**7**) and a hydroxy-lactone (**6**), m.p. 84–85 °C (34%). This mixture was separated, and under both acidic and basic conditions epoxide (**7**) was converted into the hydroxy-lactone (**6**) [overall yield of (**6**) was 62% using acid], presumably *via* an S_N2 type mechanism under both conditions.[7] Nuclear Overhauser effect experiments indicated that lactone (**6**) was indeed the *cis*-lactone and this was subsequently confirmed by *X*-ray analysis.‡ Although hydroxy-lactonisation is known for unsaturated acids[8] we believe that the conversion of (**5**) into (**6**) is the first example of this reaction with a tertiary amide.[9]

Reductive cleavage of the lactone (**6**) using methods developed for the deoxygenation of alcohols[10] was unsuccessful. However, more rewarding results were obtained using the keto-lactone (**9**).[11] Calcium in ammonia reduction of (**9**) gave a 3.5 : 1 mixture of *trans*- and *cis*-isomers and the best result was obtained with aluminium amalgam[12] which gave the ester (**10**) as a 96 : 4 mixture of stereoisomers. We assign structure (**10**) as the major isomer in which the angular methyl group would be expected to be axial in the more stable conformation (**11**) where two groups are equatorial and one axial. The chemical shifts of the angular methyl group were δ (^1H) 0.85 and δ (^{13}C) 20.74; when the product was epimerised with NaOMe in MeOH a 3 : 2 mixture was obtained with additional

† All new compounds gave satisfactory ^1H, ^{13}C n.m.r., i.r., and mass spectral data; compounds (**8**), (**9**), and (**10**), as its diphenylmethyl ester, gave correct microanalysis data.

‡ An *X*-ray crystal structure determination has been carried out on (**6**). All crystals so far examined have shown varying degrees of twinning; however, a data set has been collected on the best crystal found so far. The unit cell contains two molecules in the asymmetric unit which are apparently related by a non-crystallographic symmetry operation. Refinement of the two molecules has so far reached $R = 0.13$ and further study is needed to understand the nature of the twinning. However, the molecular stereochemistry of (**6**) is clearly established. *Crystal data:* $C_{12}H_{18}O_3$, $M = 384.2$, monoclinic, space group $C2/m$, $a = 15.05(1)$, $b = 7.96(12)$, $c = 38.19(1)$ Å, $\beta = 90.45(5)°$, $U = 4600$ Å^3, $Z = 16$, $\lambda(\text{Mo-}K_\alpha) = 0.7107$ Å. The intensities of reflections with $7 \leq 2\theta \leq 50°$ were measured using a Stoe STADI-2 Weissenberg diffractometer; of these 2857 had $|F_0^2| \geq 3\sigma(|F_0^2|)$.



(11) *trans* (12) *cis*

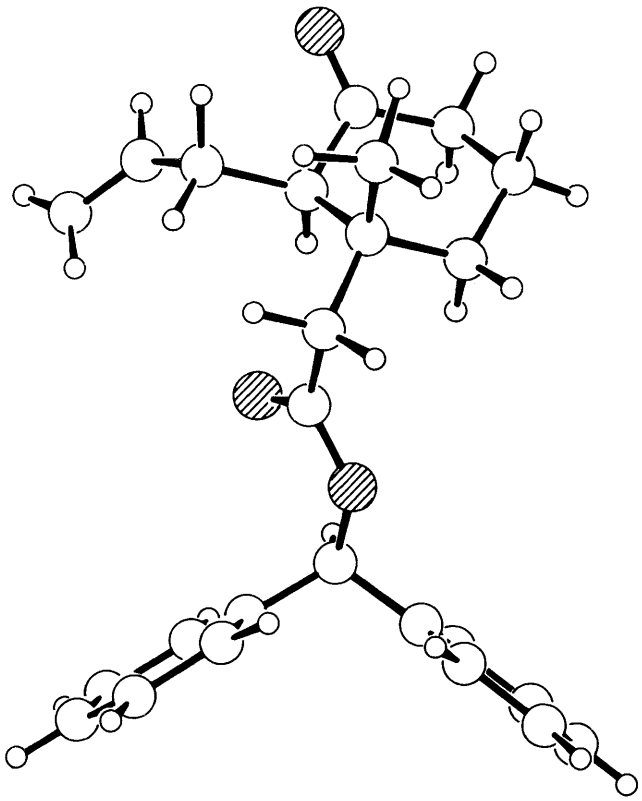


Figure 1. A view of the molecular structure of (**10**) as its diphenylmethyl ester. Atoms are represented by circles of arbitrary radius. The shaded atoms are oxygen and the remaining atoms carbon (large circles) or hydrogen.

methyl signals at δ (^{1}H) 1.14 and δ (^{13}C) 25.78 (^{1}H n.m.r. spectra at 400 MHz and ^{13}C at 100 MHz were run in $CDCl_3$). From our results on the epimerisation of related cyclohexane derivatives we would expect the *trans*- and *cis*-isomers to be most stable in the conformations (**11**) and (**12**), and the axial methyl group to occur at higher field than the equatorial methyl in both ^{1}H and ^{13}C n.m.r. spectra. This leads us to assign the *trans* stereochemistry to the larger side chains in the keto-ester (**10**). We have now confirmed this assignment by *X*-ray analysis of the diphenylmethyl ester of (**10**), m.p. 96—98 °C, prepared by treating the corresponding acid with diphenyl diazomethane (see Figure 1).

Crystal data: (**10**) as its diphenylmethyl ester, $C_{25}H_{28}O_3$, M = 376.47, monoclinic, space group $C2/c$, a = 22.536(1), b = 12.210(1), c = 17.834(5) Å, β = 118.9(1)°, U = 4294.08 Å^3, Z = 8, λ (Mo-K_α) = 0.7107 Å. The intensities of 2663 unique reflections with $2\theta < 45°$ were measured using a Stoe STADI-2 Weissenberg diffractometer; of these 1616 reflections had $|F_0| > 4\sigma(|F_0|)$. The structure was solved by direct methods and refined to R = 0.0656, R_w 0.0661.§ All hydrogen atoms were included, in calculated positions (methylene and phenyl), or refined with constraints.

These results appear to clarify some confusion in the literature where other authors[13] have reached the opposite conclusion on the relative chemical shifts in the ^{1}H n.m.r. spectra of the axial and equatorial methyl groups in 3-methylcyclohexanones related to (**10**) by applying results obtained with 2- and 4-methylcyclohexanone derivatives.[14]

A plausible reaction mechanism may be envisaged for the conversion of (**9**) into (**10**), with aluminium amalgam, in which the proton at the 2-position is delivered by the acid group from the same side as that group. We believe the reaction is under kinetic control as base-catalysed epimerisation of the methyl ester (**10**) or its acid precursor produces a mixture of *trans–cis*-isomers (**11**) and (**12**) (3 : 2 for the ester and 1 : 1 for the acid).

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§ The atomic co-ordinates for this work are available from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.