Synthesis and Stereochemistry of Polycyclic Cyclohexa-2,4-dienones

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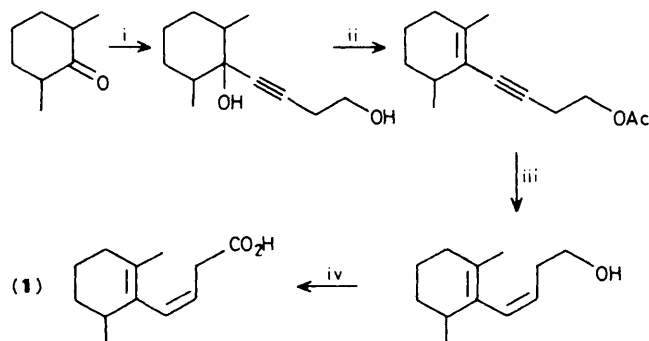
The spontaneous cyclisation of divinyl ketenes to cyclohexadienones and the interception of the intermediate ketenes with Ph_3PCHCO_2Me to form allenes which cyclise to methylenecyclohexadienes has been investigated.

Many of the alicyclic and terpenoid compounds which have significant biological activity are highly oxygenated, making polyunsaturated compounds attractive synthetic precursors. The thermal transformation of hexa-1,3,5-triene into cyclohexa-1,3-diene has limited use as a synthetic method owing to the relatively high temperatures required for reaction and consequent side reactions.[1] However, it is now well established[2] that hexa-1,3,5-triene-1-ones cyclise with great facility and recently it has been shown that hepta-1,2,4,6-tetraenes spontaneously cyclise[3] at ambient temperature. It appears that changing the hybridisation of a bonding atom from sp^2 to sp lowers E_a by 15—20 kcal mol^{-1} (cal = 4.184 J).[4]

The divinyl ketene cyclisation has been extensively used for the synthesis of phenols[5,6] but there have been few reports[6] of

Scheme 1. *Reagents:* i, HC≡CCH$_2$CH$_2$OH, KOH, tetrahydrofuran; ii, Ac$_2$O–pyridine, then POCl$_3$–pyridine; iii, H$_2$–Lindlar catalyst, then Na$_2$CO$_3$–MeOH; iv, CrO$_3$–H$_2$SO$_4$–Me$_2$CO

its use for cyclohexadienone synthesis. We decided to investigate its usefulness for the synthesis of polycycles. Initially we prepared the *cis*-acid (**1**) by the route shown in Scheme 1. Conversion of the acid (**1**) into the corresponding acid chloride with (COCl)$_2$ followed by reaction with Et$_3$N–CH$_2$Cl$_2$ gave a *ca.* 1:1 mixture of the dienones (**2a**) (44% yield).†

Previous work has shown that ketenes can be converted into allenic esters with Ph$_3$PCHCO$_2$Me.[7] When the acid chloride of (**1**) was treated with Ph$_3$PCHCO$_2$Me–Et$_3$N–CH$_2$Cl$_2$, the ketone mixture (**2**) was isolated (15% yield), but the major

† *Spectral data* for (**2a**): ν$_{max}$ 1660 cm^{-1}, λ$_{max}$ 315 nm; δ$_H$ 7.12 and 7.01 (1H, dd, *J* 10 and 6 Hz), 6.03 (2H, m), 1.35 and 1.29 (3H, s), 1.28 and 1.12 (3H, d, *J* 7 Hz).

For (**2b**): ν$_{max}$ 1710 cm^{-1}, λ$_{max}$ 350, 225 nm; δ$_H$ 7.70 and 7.58 (1H, d, *J* 7 Hz), 6.20 (1H, m), 5.87 (1H, m), 5.80 (1H, m), 1.26 and 1.27 (3H, s), 1.19 and 0.99 (3H, d, *J* 6 Hz).

For (**7β**): ν$_{max}$ 1740, 1675 cm^{-1}, λ$_{max}$ 228 nm, δ$_H$ 6.09 (1H, dt, *J* 10 and 3.5 Hz), 6.01 (1H, dt, *J* 10 and 2 Hz), 5.79 (1H, bs), 5.64 (1H, m), 5.56 (1H, m), 3.20 (2H, m), 1.83 (3H, d, *J* 1 Hz), 1.45 (3H, d, *J* 8 Hz), 1.08 (3H, s).

For (**9β**): δ$_H$ 7.12 (1H, dd, *J* 10 and 6 Hz), 6.28 (1H, d, *J* 6 Hz), 6.04 (1H, d, *J* 10 Hz), 5.52 (2H, m), 1.62 (3H, s), 1.43 (3H, s), 1.20 (3H, d, *J* 7 Hz).

For (**11β**): δ$_H$ 7.08 (1H, dd, *J* 10 and 6 Hz), 6.41 (1H, d, *J* 6 Hz); 5.96 (1H, d, *J* 10 Hz), 1.44 (3H, s), 1.36 (3H, s), 1.20 (3H, d, *J* 7 Hz).

For (**9α**): δ$_H$ 7.08 (1H, dd, *J* 10 and 6 Hz), 6.25 (1H, d, *J* 6 Hz), 5.93 (1H, d, *J* 10 Hz), 5.54 (2H, m), 1.57 (3H, s), 1.07 (3H, d, *J* 7 Hz), 0.93 (3H, s).

For (**11α**): δ$_H$ 7.08 (1H, dd, *J* 10 and 6 Hz), 6.20 (1H, d, *J* 6 Hz), 6.00 (1H, d, *J* 10 Hz), 5.54 (2H, m), 1.38 (3H, s), 1.09 (3H, s), 0.91 (3H, d, *J* 7 Hz).

Table 1.

Ketene ex	C–C bond formation	B ring conformation[a]	Angular Me stereochemistry
8α	α	C	syn
8α	β	T	anti
8β[b]	α	C	syn
8β[b]	β	T	anti
8β[c]	α	T	syn
8β[c]	β	C	anti

[a] C = chair conformation; T = twist-boat conformation. [b] 'Steroid' conformation. [c] 'Non-steroid' conformation.

product (41% yield) was a ca. 1 : 1 mixture of the esters‡ (2b).†
A control experiment demonstrated that, as anticipated, the ketones (2a) did not react with Ph₃PCHCO₂Me.

With the viability of the cyclisations established we investigated their usefulness for preparing tricyclic compounds and whether stereochemistry could be controlled. The Diels–Alder adduct (3β) of penta-1,3-diene and 2,6-dimethylbenzoquinone (AlCl₃ catalysed)[8] reacted with LiC≡C(CH₂)₂OTHP (THP = tetrahydropyran-2-yl) to give (4β) (83% yield). Acidic hydrolysis gave the alcohol (5β) (90% yield) which was reduced with Lindlar catalyst and H₂ to the alkene (6β) (96% yield). Jones's oxidation converted (6β) into the spiro-lactone (7β)† (83% yield). We were unable to hydrogenolyse (7β) using standard reagents but reduction with SmI₂[11] gave the acid (8β) (84% yield). Using the trans-dione (3α) as starting material the acid (8α) was prepared by a similar route and in similar yield.§

In cyclising the ketenes derived from (8α) and (8β) the C–C bond can form on either face of the endocyclic double bond thus forming a syn or an anti relationship between the two angular methyl groups. The face of the molecule on which C–C bond formation occurs also has consequences for the conformation of ring B. Thus cyclisation on one face will lead to ring B in a chair conformation, while cyclisation on the other leads to a twist-boat conformation. This follows from bicyclo[4.4.0]dec-1-enes being unable to adopt a chair–½chair conformation with the bridgehead hydrogen equatorial. The stereochemical and conformational outcomes of the different cyclisations of the two A : B cis and the A : B trans-½chair–½chair conformations are summarised in Table 1.

In the event, reaction of the acid chloride of (8β) with Et₃N–CH₂Cl₂ gave a 2 : 1 mixture (81% yield) of the diones (9β) and (11β). Similar cyclisation of (8α) gave a 2 : 1 mixture (75% yield) of the diones (9α) and (11α).† The relative stereochemistry in the series was established by base catalysed isomerisation of the (9β,11β) mixture to the (9α, 11α) mixture of similar relative composition. That (11α) was the syn-dimethyl compound followed from the strong nuclear Overhauser effects observed between the angular methyl groups. From these results it is apparent that the conformation of ring B is not a major determinant in the stereochemistry of cyclisation. There are a number of possible reasons for this which we shall not discuss here. However, it is of interest to determine whether the isomer distribution is kinetically or thermodynamically controlled. Since the triene cyclisation is

‡ The isomers (2b) are suggested to be E-isomers epimeric at C(4); if they were Z-E isomers then the chemical shift difference between the C(8) hydrogens would be expected[10] to be ca. 1 p.p.m. Small amounts of probable Z-isomers were detected in the crude product.
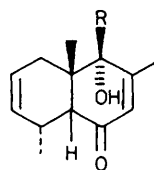
§ The stereochemistry of acetylide attack on the (3α) isomer is probably the reverse of that on the (3β).[9]
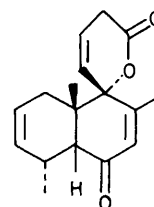

(2)

a; X = O
b; X = CH·CO₂Me
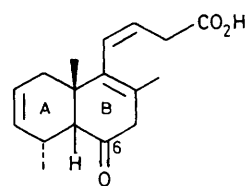

(3)
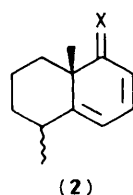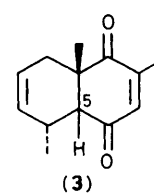
α is the 5α series (trans)
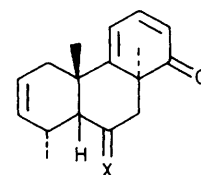β is the 5β series (cis)

(4; R = C≡CCH₂CH₂OTHP)
(5; R = C≡CCH₂CH₂OH)
(6; R = CH=̲CHCH₂CH₂OH)

(7)

(8)

(9; X = O)

(10; X = ⟨OH⟩)

(11; X = O)

(12; X = ⟨OH⟩)
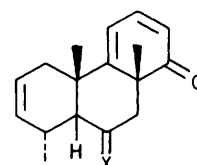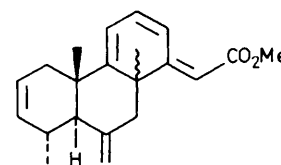
(13)

formally a reversible reaction, the (9α, 11α) mixture was heated in 1,2-dichlorobenzene, and a ratio change from 2 : 1 to 2 : 3 was observed. Thus the isomer (11β) with a chair ring B is shown to be marginally more stable than (9α). Since the energy difference between chair and twist-boat conformations often decreases with an increasing number of sp² hybridised atoms in the ring we attempted to convert the C(6) carbonyl group of (8) into sp³ hybridised derivatives; so far we have been unsuccessful. However, this approach is effective in improving the thermodynamic stability of the syn- relative to anti-dimethyl compounds. Reduction of the diones (9α) and (11α) with NaBH₄ gave diols which were oxidised with MnO₂ to the hydroxyenones (10α) and (12α) (86% yield). Thermal equilibration in dichlorobenzene transformed the (10α) : (12α) ratio of the mixture from 2 : 1 to 1 : 10. How such

a change will influence the cyclisation stereochemistry under kinetic control remains to be tested.

Reaction of the acid chloride of (8α) in the presence of Ph_3PCHCO_2Me–Et_3N formed the dienones (9α) and (11α) (24% yield) and a 2:1 mixture of the esters (13) (54% yield). As judged by δ_H values of the angular methyl groups, the major isomer (0.95 and 1.52) is the *anti*-dimethyl compound and the minor (1.07 and 1.39) the *syn*-isomer. Equilibration of the isomers has not yet been examined.

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