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

Christine A. Barron, Nazir Khan, and James K. Sutherland*

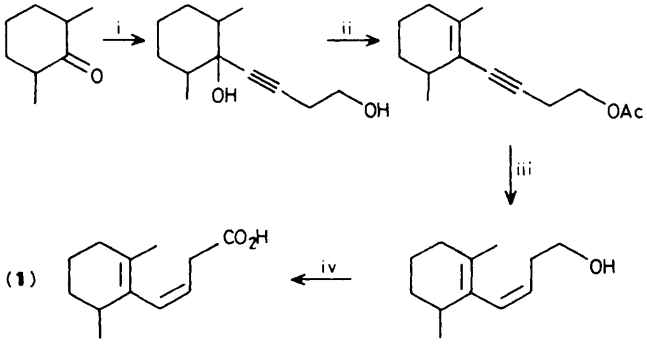
Chemistry Department, The Victoria University of Manchester, Manchester M13 9PL, U.K.

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 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_3N–CH_2Cl_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_3PCHCO_2Me.[7] When the acid chloride of (**1**) was treated with Ph_3PCHCO_2Me–Et_3N–CH_2Cl_2, the ketone mixture (**2**) was isolated (15% yield), but the major



Scheme 1. *Reagents:* i, $HC{\equiv}CCH_2CH_2OH$, KOH, tetrahydrofuran; ii, Ac_2O–pyridine, then $POCl_3$–pyridine; iii, H_2–Lindlar catalyst, then Na_2CO_3–MeOH; iv, CrO_3–H_2SO_4–Me_2CO

† *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*

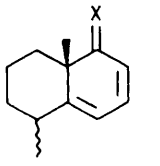
[a] C = chair conformation; T = twist-boat conformation. [b] 'Steroid' conformation. [c] 'Non-steroid' conformation.

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 Ph_3PCHCO_2Me.

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 ($AlCl_3$ catalysed)[8] reacted with $LiC{\equiv}C(CH_2)_2OTHP$ (THP = tetrahydropyran-2-yl) to give (**4β**) (83% yield). Acidic hydrolysis gave the alcohol (**5β**) (90% yield) which was reduced with Lindlar catalyst and H_2 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 SmI_2[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.

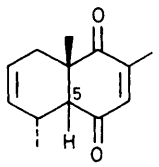
In the event, reaction of the acid chloride of (**8β**) with Et_3N–CH_2Cl_2 gave a 2 : 1 mixture (81% yield) of the diones (**9β**) and (**11β**). Similar cyclisation of (**8α**) gave a 2 : 1 mixture (75% yield) of the diones (**9α**) and (**11α**).† The relative stereochemistry in the series was established 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 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 sp^2 hybridised atoms in the ring we attempted to convert the C(6) carbonyl group of (**8**) into sp^3 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 $NaBH_4$ gave diols which were oxidised with MnO_2 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



(**2**)

a; X = O

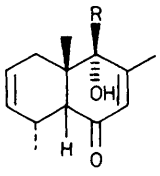
b; X = CH·CO_2Me



(**3**)

α is the 5α series (*trans*)

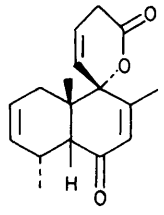
β is the 5β series (*cis*)



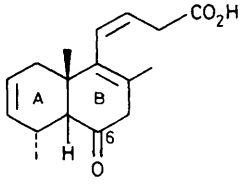
(**4**; R = $C{\equiv}CCH_2CH_2OTHP$)

(**5**; R = $C{\equiv}CCH_2CH_2OH$)

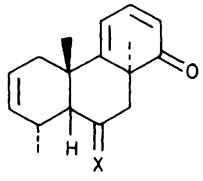
(**6**; R = $CH{=}^{Z}CHCH_2CH_2OH$)



(**7**)

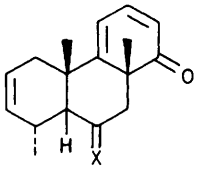


(**8**)

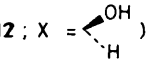


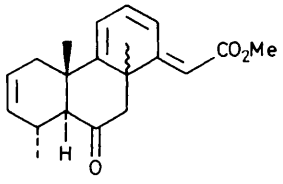
(**9**; X = O)

(**10**; X = )



(**11**; X = O)

(**12**; X = )



(**13**)

‡ 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]

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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