Synthesis of Unsaturated Aldehydes by Sequential Claisen and Cope Rearrangements

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Summary The reaction of hexa-1,5-dien-3-ols with 2-methyl-1,1,3-triethoxybutane gives unsaturated aldehydes by a Claisen rearrangement which undergo two Cope rearrangements to give 2,5,9-unsaturated aldehydes; the reactions proceed with high stereospecificity when secondary hexa-1,5-dien-3-ols are used, resulting in the 2-*trans*-5-*trans* isomer.

THE succession of a Claisen rearrangement by a Cope rearrangement, known for many years in the isomerisation of 2,6-disubstituted phenyl allyl ethers to 4-allyl phenols,[1] has been applied with great effect by Thomas[2] to the synthesis of terpenes. The overall reaction amounts to a simple γ-allylation of an $\alpha\beta$-unsaturated carbonyl compound. We now draw attention to two other systems that allow a Claisen rearrangement to be followed by one or two Cope rearrangements and hold promise in the synthesis of straight chain unsaturated aldehydes and ketones.

In principle any enol ether of a 2,5,8, . . . *n*—3,*n* polyen-1-ol or dienol ether of a 1,5,8, . . . *n* — 3,*n* polyen-3-ol can undergo successive [3,3]sigmatropic shifts to form a straight chain aldehyde or ketone, in which each allyl unit has been inverted with respect to the following one. In practice only the first members of the series are likely to be of value in synthesis. We describe here some examples of the latter process, starting with a hexa-1,5-dien-3-ol, easily made by the addition of an allylic Grignard reagent to an unsaturated carbonyl compound.[3]

Three different hexa-1,5-dien-3-ols (Ia–c) were prepared to test the generality and stereospecificity of the reaction. The hexa-1,5-dien-3-ols react with 2-methyl-1,1,3-triethoxybutane† under acid catalysis‡ at 110° to give unsaturated aldehydes (II) in good yields (50—76%). These aldehydes§ are converted at 190° into the straight chain isomers (IV) as the result of two Cope rearrangements [30—50% yield based on (II)].

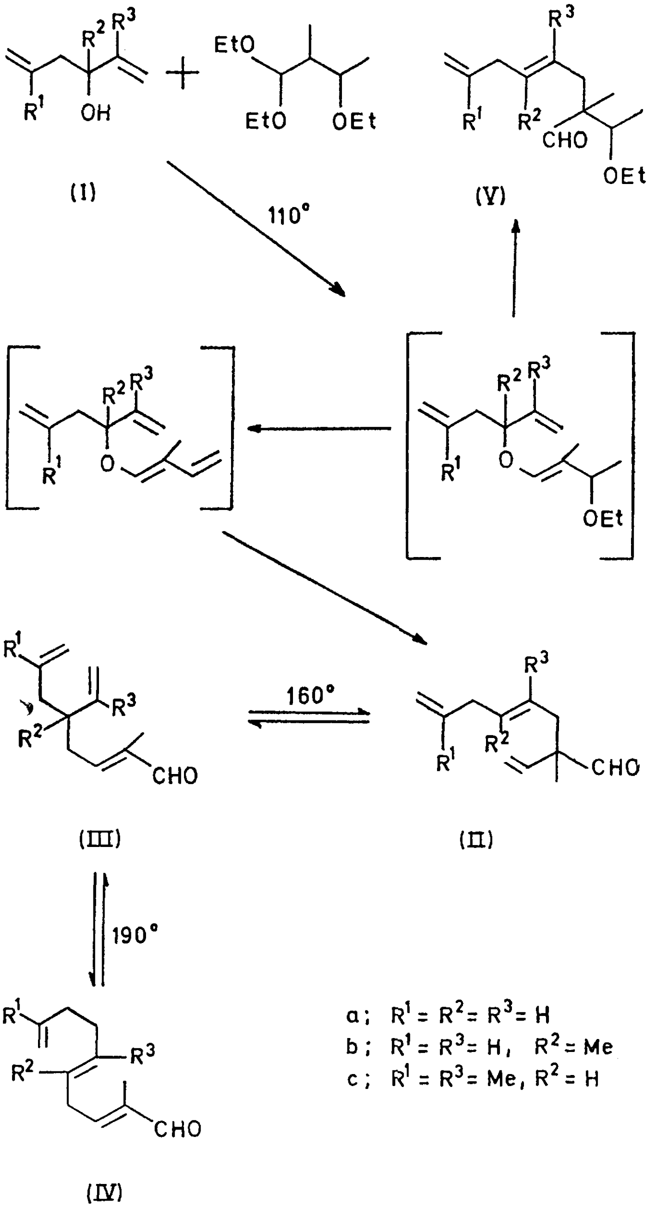
The intermediate aldehyde (III), from one Cope rearrangement, is the major product at 160°. All three aldehydes (II), (III), and (IV) were isolated for each of the dienols studied, and characterised by their n.m.r. (60 MHz and/or 100 MHz), i.r. and mass spectra.

A minor product of the reaction (5—7%) to give (II) was the aldehyde (V) from the Claisen rearrangement of an intermediate enol ether. (Vb) was isolated and shown to be a mixture of the 4-*cis*- and 4-*trans*-aldehydes. The crude aldehydic mixture from reaction of (Ib) with the acetal at 110° contained (IIb) (92·5%), (IIIb) (0·6%), and (Vb) (6·9%).

The stereochemistry of the aldehydes (II)—(V) was indicated from their n.m.r. and/or i.r. spectra (Table). The 2-double bond of the aldehydes (III) and (IV) was shown to be predominantly ($\geqslant$ 95%) *trans* [^{1}H n.m.r. (CCl$_4$) τ 0·65—0·8 (s) and 3·65, *J* 6—7 Hz, further split into quartets, *J* 1·5 Hz] together with a small amount ($\leqslant$ 5%) of the *cis*-isomer [τ (CCl$_4$) 0 to −0·25 (s)].[5]

The configuration of the 4- or 5-double bond in the aldehydes (IIa) and (IVa) was determined from the i.r. spectra which showed only the *trans*-disubstituted olefinic stretch at 980—990 cm^{-1}.

A study of the n.m.r. spectra of the remaining products led to the assignments given in the Table.



a; R^1 = R^2 = R^3 = H
b; R^1 = R^3 = H, R^2 = Me
c; R^1 = R^3 = Me, R^2 = H

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† *Cf.* the use of 3,3-dimethoxybutenes and allylic alcohols in Claisen rearrangements.[4]

‡ *o*-Nitrobenzoic acid (pK_a 2·16) was the most successful of many catalysts tried (including mercuric salts and Lewis as well as other protonic acids).

§ Condensation of the dienols with 1,1,3-trimethoxybutane lacking the 2-methyl group gave good yields of the $\alpha\beta$-unsaturated aldehydes corresponding to (II). Further rearrangement of these to analogues of (III) and (IV) could not be achieved by heating with acid catalysts, which might have equilibrated them with the $\beta\gamma$-isomers, capable of Cope rearrangement (*cf.* ref. 2).

TABLE

Aldehyde	(II)	(III)	(IV)
a	4-*trans*	2-*trans*	2-*trans*-5-*trans*
b	4-*trans* 4-*cis*	2-*trans*	2-*trans*-5-*trans* 2-*trans*-5-*cis*
c	4-*trans* (?)	2-*trans*	2-*trans*-5-*trans*

These results are consistent with chair-like transition states for the three rearrangements, with the bulky groups occupying pseudo-equatorial positions.[5] In the rearrangement (II) → (III) the formyl group must be equatorial, forming the 2-*trans* isomer, in agreement with the results obtained by Thomas.[2] The lack of stereospecificity in the Claisen rearrangement of vinyl ethers derived from tertiary alcohols and the high stereospecificity for the ethers of secondary alcohols has been previously reported.[2,4,5]

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