

Chiral 2,2-Disubstituted Cyclohexanones; Annulation *via* Claisen Rearrangement Products

T. J. Grattan and J. S. Whitehurst*

Department of Chemistry, The University, Exeter EX4 4QD, U.K.

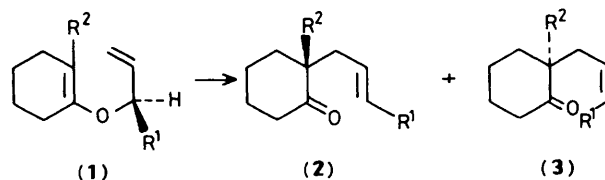
The methyl enol ether of 2-methylcyclohexanone reacts regiospecifically and enantioselectively with (*R*)- and (*S*)-but-3-en-2-ol to give respectively, the (*R*)- and (*S*)- forms of 2-methyl-2-(*trans*-but-2-enyl)cyclohexanone.

We considered it likely that a compound of type (1) would undergo the Claisen rearrangement¹ stereoselectively, because its two possible chair-like transition states² differ in that the R' group is quasi-equatorial in one and quasi-axial in the other. The expected products are (2) (major) and (3) (minor), respectively (see Scheme 1).

For a synthetic project based on this idea the literature was not encouraging. For example, the methyl enol ether of 2-methylcyclohexanone (4) exists as a tautomeric mixture of 1-methoxy-2-methylcyclohexene (39.4%) and 2-methoxy-3-methylcyclohexene (60.6%).³ By analogy, similarly constituted allyl-type enol ethers would also be expected to exist as equilibrium mixtures of tautomers. However it does not follow that the products of Claisen rearrangement of such a mixture would necessarily reflect its composition. Apart from steric factors, the electron densities at the two available sites should influence the course of reaction.

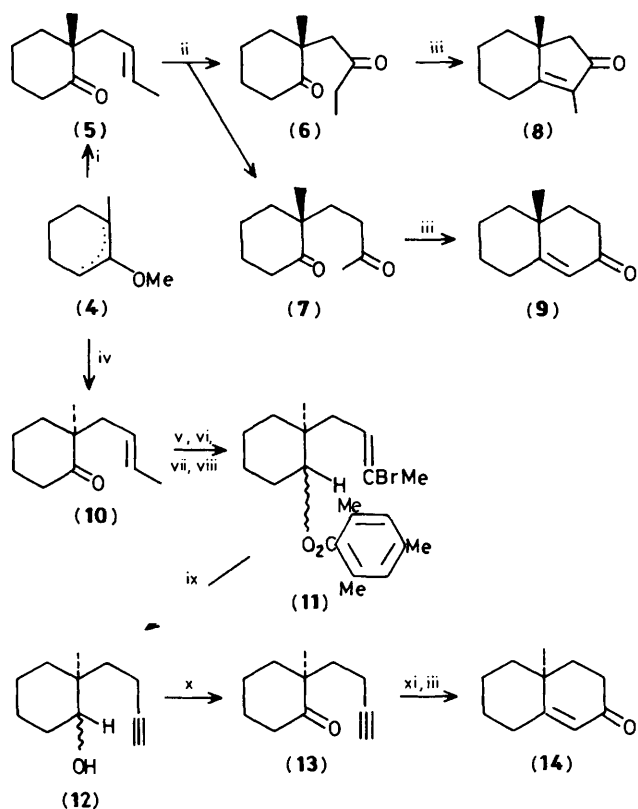
In practice, the tautomeric mixture (4), when heated with (*R*)-(-)-but-3-en-2-ol and a trace of toluene-*p*-sulphonic acid, (ptsa), gave an oil (77–84% yield) which after chromatography furnished the pure, optically active ketone (5) (62% yield), $[\alpha]_D^{21} + 52.1^\circ$ (CHCl₃, *c* 1.0). The ¹H n.m.r. spectrum showed a singlet at δ 1.04 (3H, quaternary methyl), a doublet of doublets at δ 1.64 (3H, *J* 1.5 and 7 Hz, CH₃CH=CHCH₂) and multiplets at δ 5.31 (1H, MeCH=CHCH₂) and 5.41 (1H,

MeCH=CHCH₂).[†] On irradiation at δ 1.61, the δ 5.41 multiplet became a doublet, *J* 15 Hz, clearly indicating a *trans*-configuration at the double bond, supported by a strong i.r. absorption at 975 cm⁻¹. The quaternary methyl signal remained a singlet when the compound in deuteriochloroform was treated with tris-3-(trifluoromethylhydroxymethylene)-(+)-camphoratoeuropium(III); the corresponding racemate gave two methyl signals. The ¹³C n.m.r. spectrum of the material prior to chromatography revealed the presence of the *cis*-isomer. The relative amounts were obtained by the summation of intensities of the eleven signals for each compound. Slow reaction at 95 °C gave *ca.* 3% of the *cis* compound; at 135 °C, *ca.* 7%. Besides chromatography, the



Scheme 1

[†] We thank Dr. I. Sadler, University of Edinburgh, for a 360 Mz ¹H n.m.r. spectrum of this compound.



Scheme 2. i, (*R*)-(-)-but-3-en-2-ol, ptsa; ii, O₂, PdCl₂, CuCl₂, H₂O, dimethylformamide, iii, 2% NaOH, MeOH, H₂O; iv, (*S*)-(+)-but-3-en-2-ol, ptsa; v, NaBH₄, MeOH, H₂O, NaOH; vi, mesityl chloride, petroleum; vii, Br₂, CCl₄; viii, Bu^tOK, Bu^tOH; ix, NaNH₂; x, (COCl)₂, dimethyl sulphoxide, CH₂Cl₂; xi, HgO, BF₃·Et₂O, CCl₃CO₂H, MeOH.

cis-compound could be removed by preparation of the ketone semicarbazone and regeneration with hot 20% oxalic acid.

Wacker-type oxidation⁴ of (5) furnished, apart from unchanged starting material, a readily separable mixture of

ketones (6) and (7) (57%) in the ratio 91 : 9, which were in turn cyclised to the optically active ketones (8) {[α]_D²⁵ -12° (ethanol, *c* 0.3)} and (9) {[α]_D²⁵ -188° (ethanol, *c* 0.4)} (Scheme 2).⁵ Preparation of the octalone as sole product was carried out in the enantiomeric series employing (*S*)-(+)-but-3-en-2-ol to yield (10). Reduction to a 60:40 mixture of alcohols (94%), mesitylation (95%), and addition of bromine (100%) produced a diastereoisomeric mixture of dibromo-compounds which, with Bu^tOK, gave the monobromides (84%) of (11) (side chain Me δ 2.23 in the ¹H n.m.r. spectrum⁶). Reaction of (11) with sodamide produced the acetylenes (12) (67%) and mesitylene as virtually the only products and Swern oxidation⁷ then gave (13) (92% yield). Purification of compounds in the sequence from (10) to (12) was not necessary and (13) was purified simply by low pressure distillation. Hydration⁸ and cyclisation produced the octalone (14), {[α]_D²⁰ +198° (ethanol, *c* 0.8)} (80% yield).

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