Total Synthesis of (±)-Fenchone, a Synthesis of (+)-Fenchone and of (+)-*cis*-2,2,5-Trimethyl-3-vinylcyclopentanone, a Photoisomer of (−)-*trans*-Caran-4-one

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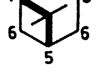
Summary (+)-*cis*-3-(2-Hydroxyethyl)-2,2,5-trimethylcyclopentanone and its racemic form are synthesised from (+)-α-2,3-epoxypinane or (−)-*trans*-pinocarveol, and (±)-2,2,5-trimethyl-1-oxocyclopentane-3-carboxylic acid, respectively; treatment with base of the chloroketone, derived from the (+)-hydroxyketone, affords (+)-fenchone, while pyrolysis of the (+)-acetoxyketone gives (+)-*cis*-2,2,5-trimethyl-3-vinylcyclopentanone, the latter and its *trans*-isomer being photo-products of (−)-*trans*- and (−)-*cis*-caran-4-one, respectively.

TREATMENT of (+)-α-2,3-epoxypinane (**1**) with ethereal hydrogen bromide yields (−)-6-*endo*-bromo-1,5,5-trimethylbicyclo[2,2,1]heptan-2-*exo*-ol (**2**) as major product, and *p*-cymene (**3**), (−)-2,2,3-trimethylcyclopent-3-enylacetaldehyde (**4**), (+)-pinocamphone (**5**) and (−)-6-*endo*-bromo-1,7,7-trimethylbicyclo[2,2,1]heptan-2-*endo*-ol (**6**) in smaller yields. Similar treatment of (−)-*trans*-pinocarveol (**7**) gives slightly different proportions of the same products (*cf*. ref. 1).

Reaction of the bromo-alcohol (**2**) with silver acetate in acetic acid affords (*cf*. ref. 1) (−)-2,2,4-trimethylcyclopent-3-enylacetaldehyde (**8a**). Reduction of this with lithium aluminium hydride gives the alcohol (**8b**) which with peroxyacetic acid gives an almost quantitative yield of the (−)-*cis*-epoxy-alcohol (**9**) (*cf*. ref. 2), slightly contaminated with its acetate. Assignment of configuration of (**9**) is based on the intramolecular hydrogen bonding manifested in its i.r. spectrum in CCl_4. Isomerisation of (**9**) with BF_3–Et_2O gives (+)-*cis*-3-(2-hydroxyethyl)-2,2,5-trimethylcyclopentanone (**10a**) in 70% yield, which with thionyl chloride and pyridine affords the chloro-ketone (**10b**). Treatment of the last with ethoxide gives (+)-fenchone (**11**).

Racemic *cis*-3-(2-hydroxyethyl)-2,2,5-trimethylcyclopentanone, identical in spectra with its (+)-form (**10a**), is formed from (±)-2,2,5-trimethyl-1-oxocyclopentane-3-carboxylic acid[3] by Arndt–Eistert chain extension to the corresponding acetic ester, alkaline hydrolysis of which gives mainly the racemic *cis*-acetic acid corresponding to the active form (**10c**). Diborane reduction of the mainly *cis*-racemic acid gives solely the *cis*-racemic alcohol. This completes a new total synthesis of racemic fenchone.

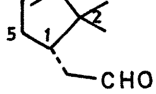
Pyrolysis at 480° of the (+)-acetate (**10d**), of the keto-alcohol (**10a**), gives (+)-*cis*-2,2,5-trimethyl-3-vinylcyclopentanone (**12a**) as principal product (> 80% by g.l.c.). A recent report[4] claims the synthesis of a similar cyclopentanone of unspecified configuration.



(1)

(2)

(3)



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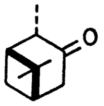

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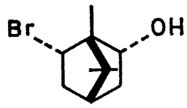

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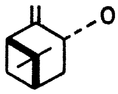

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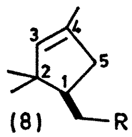
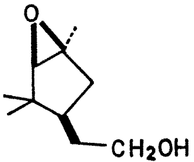
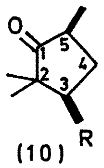


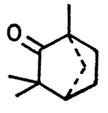
(8)
a; R = CHO
b; R = CH_2OH



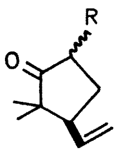
(9)



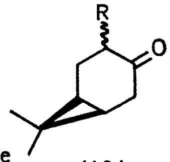
(10)
R
a;R=$[CH_2]_2OH$
b;R=$[CH_2]_2Cl$
c;R= CH_2CO_2H
d;R=$[CH_2]_2OCOMe$
e;R=CH_2CO_2H,5α-Me



(11)



(12)
a; R =β-Me
b; R =α-Me



(13)
a;R=β-Me
b;R=α-Me

The corresponding *trans*-ketone (**12b**) was previously shown[5,6] to be the major photo-product of (−)-*cis*-caran-4-one (**13a**), its configuration being correctly assigned on mechanistic grounds.[6] It is, however, not stable to base as we earlier believed,[5] for we have converted it with sodium methoxide in methanol into the *cis*-isomer (**12a**), which is also obtained by the photolysis of (−)-*trans*-caran-4-one (**13b**).

We assign the configurations of the *cis*- and *trans*-ketones (**12a**) and (**12b**) (a) on mechanistic grounds (*cf.* ref. 6), (b) by analogy with the *cis*- and *trans*-2,2,5-trimethyl-1-oxocyclopentane-3-acetic acids (**10c** and **e**), the *cis*-form being the more stable,[7] and (c) on o.r.d. evidence, the molecular amplitude of the Cotton effect of the *cis*-ketone (**12a**) (+ 66·8) being greater than that of the *trans*-ketone (**12b**) (+ 50·8), as is the case with the corresponding oxocyclopentaneacetic acids (**10c**) (+ 96) and (**10e**) (+ 27) respectively.[8]

Satisfactory spectra were obtained for the compounds described.

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