

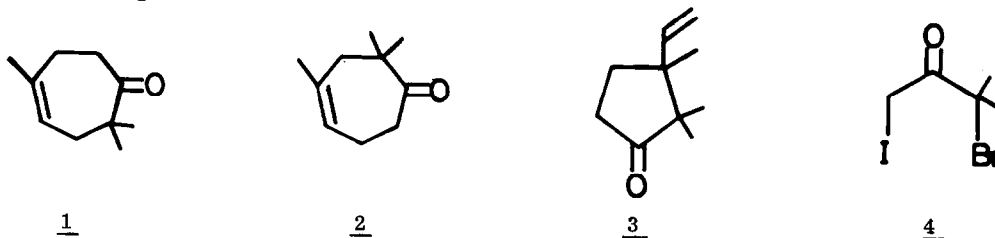
Monoterpenoids via Concurrent 4+3→7 and 3+2→5 Cyclizations¹

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Karahanaenone (1), a constituent of hop oil,⁴ belongs to a small group of naturally occurring seven-membered monoterpenes, the best known of which is eucarvone.⁵ We have begun to use the allyl cation route to seven-membered rings² as an approach to this class of compounds and describe the synthesis of 1 and of two previously unknown isomers 2 and 3 from α, α' -dihaloketone 4 and isoprene in a single flask reaction.



A solution of 3-bromo-1-iodo-3-methyl-2-butanone⁶ (4) (6.06 g, 0.021 mol), isoprene (10.2 g, 0.15 mol), 1,2-dimethoxyethane (3.5 g, 0.038 mol), and isopentane⁷ (redistilled, 25 ml) was passed down a water-cooled glass column packed with finely divided zinc-copper couple on alumina in a nitrogen atmosphere.⁸ This process was repeated to ensure complete dehalogenation. The column was flushed with isopentane (20 ml portions) and the combined isopentane extracts were washed 3-4 times with an equal volume of distilled water to ensure complete removal of the zinc complexes. The collected aqueous layers were re-extracted with isopentane, and the combined organic extracts were dried (MgSO_4) and filtered, the bulk of isopentane being distilled at atmospheric pressure (water bath 40°) to yield the crude oily product. Preparative glc (20 ft x 0.375 inch i.d. dinitrophenyl naphthyl ether column, 120°) gave three isomeric $\text{C}_{10}\text{H}_{16}\text{O}$ hydrocarbons 1 (53.9%), 2 (23.5%) and 3 (22.6%) (12% combined yield by glc, internal standard cycloheptanone).

The main product 1 proved to be spectroscopically identical (nmr, ir and ms⁹) to naturally occurring karahanaenone (1) (2,2,5-trimethylcyclohept-4-enone).

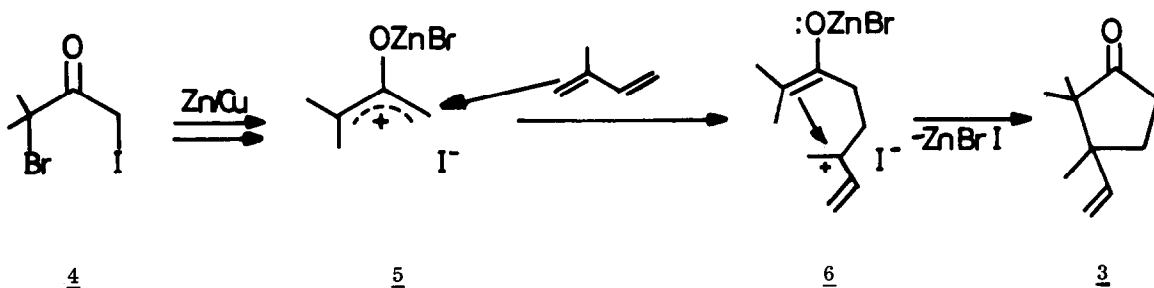
The second, minor isomer which had very similar physical properties, but a slightly longer glc retention time on the most effective columns used was 2,2,4-trimethylcyclohept-4-enone (2).

Nmr: δ (TMS, CCl_4 , 100 MHz) 1.05 (s, 6H), 1.75 (3H, brs), 2.21 (4H, m), 2.55-2.68 (2H, m), 5.29-5.47 (1H, m). Mass spectrum (20 eV, rel. intensities, glc-ms) 152 (83) (M^+), 137 (13), 109 (62), 96 (79),

95 (100), 81 (45), 70 (43), 69 (18), 68 (37), 67 (54), 55 (34), 43 (27), 41 (48). Anal. Calcd for $C_{10}H_{16}O$: C, 78.9; H, 10.6. Found: C, 79.1; H, 10.5.

Interestingly, the third isomer was a five-membered ring, which was isolated from three independent experiments and identified as 2,3,3-trimethyl-3-vinylcyclopentanone (3). Nmr δ (TMS, CCl_4 , 100 MHz) 0.81 (s, 3H), 0.86 (s, 3H), 0.94 (s, 3H), 1.73 (m, 2H), 2.09-2.27 (m, 2H), 4.91-5.09, 5.69-5.97 (ABC pattern, 3H). Ir (CCl_4 , cm^{-1}) 1741 (s). Mass spectrum (20 eV, glc-ms) 152 (56) (M^+), 137 (56), 109 (71), 97 (27), 96 (100) ($M-C_2H_4-CO$), 95 (60), 81 (81), 70 (96), 67 (82), 55 (61), 43 (67), 41 (70). The complex ABCD pattern for the ring protons in the nmr spectrum and the mass spectral fragmentation pattern [inter al. base peak at m/e 96:($M-C_2H_4-CO$)] establish 3 as the crowded isomer. Anal. Calcd. for $C_{10}H_{16}O$: C, 78.9; H, 10.6. Found: C 78.2, H, 10.6.

With regard to the mechanism of the present and related reactions we have for some time postulated zinc oxyallyl (5) as the key electrophilic intermediate.^{2,6} Attack of 5 on isoprene can be visualized to give a second intermediary allyl cation 6, which enjoys maximum stabilization by virtue of its intramolecular interaction with the fully alkylated, nucleophilic double bond. In the final step covalent



collapse of 6 produces 3 with formation of the crowded diquaternary carbon-carbon bond.

Previously, Noyori and his coworkers have described the $Fe_2(CO)_9$ induced dehalogenation of dibromoketones in the presence of conformationally mobile dienes including isoprene and reported the isolation of 4-cycloheptenones in high yield.¹⁰ Is the formation of a vinylcyclopentanone as described here just a side reaction characteristic for the use of zinc and, for that matter, is the $Fe_2(CO)_9$ promoted reaction preparatively superior to the zinc-copper couple reaction, perhaps as a result of d-orbital participation or π -complexing, as has been occasionally implied in the past?

In a brief comparative study we investigated the dehalogenation of 4 by $Fe_2(CO)_9$ in the presence of isoprene in solvent benzene (Table 1).

Table 1. Products from the Reaction of 4 with $\text{Fe}_2(\text{CO})_9$ in the Presence of Isoprene/Benzene.^a

Temp. [$^{\circ}\text{C}$]	Reaction time [hr]	Products [%]		
		<u>1</u>	<u>2</u>	<u>3</u>
60-80	12	28	11	61
57	10	46	24	30
57	20	43	22	30

^a When $\text{Fe}_2(\text{CO})_9$ was added batchwise to the refluxing mixture of isoprene-benzene over a period of 4.5 hr at 70° , the ratio of vinylcyclopentanone 3 to karahanaenone (1) was as high as 3.6:1 and ketone 2 was again the minor isomer.

Again, the two isomeric seven-membered ketones 1 and 2 were isolated under various conditions in addition to a substantial amount of a vinylcyclopentanone which proved identical in all respects to 2,2,3-trimethyl-3-vinylcyclopentanone (3), obtained from the zinc-initiated reaction.¹¹

The data in Table 1 suggest that increasing temperature favours formation of the five-membered ketone. It will become clear in subsequent communications that leakage into vinylcyclopentanones is also favoured in nonpolar solvents such as benzene which has been used for the iron carbonyl induced reactions.^{10,13}

References and Notes

- (1) (a) The Allyl Cation Route to Seven-membered Rings, 15. A. Busch and H. M. R. Hoffmann, Tetrahedron Lett., 2379 (1976) is considered to be Part 14.
(b) Experiments 1970-1973. Aspects of this work were briefly discussed in a review.²
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- (3) Present address: Institut für Organische Chemie der Technischen Universität, Schneiderberg 1 B, 3000 Hannover, Germany.
- (4) (a) Y. Naya and M. Kotake, Tetrahedron Lett., 1645 (1968);
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- (7) Similar results were obtained with benzene instead of isopentane as a solvent.
- (8) This dehalogenation technique which is especially effective for α, α' -dihaloketones that are reluctant to form allyl cations and allows dehalogenations in nonpolar solvents, e. g. isopentane, benzene, was developed by Dr. J. G. Vinter; see J. G. Vinter and H. M. R. Hoffmann, J. Am. Chem. Soc., 96, 5466 (1974). Column dimensions in the present experiments: 22 cm length, 2.5 cm diameter. A mixture of 12g Zn-Cu couple and 4 g alumina, activity 2-3, Merck, was used.
- (9) We thank Dr. B. Willhalm of Firmenich SA, Geneva, for the mass spectrum of authentic 1 and for high resolution glc-ms work.
- (10) R. Noyori, S. Makino and H. Takaya, J. Am. Chem. Soc., 93, 1272 (1971).
- (11) Since we have used zerovalent bis(cyclooctatetraene)iron¹² in place of $\text{Fe}_2(\text{CO})_9$ for related reactions under mild conditions, it is likely that the key electrophilic intermediate of the $\text{Fe}_2(\text{CO})_9$ promoted procedure is free from carbonyl ligands (5: FeBr instead of ZnBr).
- (12) A. Carbonaro, A. L. Segre, A. Greco, C. Tosi, G. Dall'Asta, J. Am. Chem. Soc., 90, 4453 (1968) and subsequent publications.
- (13) We thank the Science Research Council for financial support of our work.