# The Mechanism of the Thermal Rearrangement of the Marasmane Sesquiterpene (+)-Isovelleral. Cyclopropane Ring Closure *via* an Intramolecular Ene Reaction[1]

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The reversible thermal conversion of the fungal sesquiterpene isovelleral (**2**) into (**1**) is a unique intramolecular ene reaction proceeding *via* the bicyclic enol (**3**), which is demonstrated by kinetic studies, deuterium incorporation, and the trapping of (**3**).

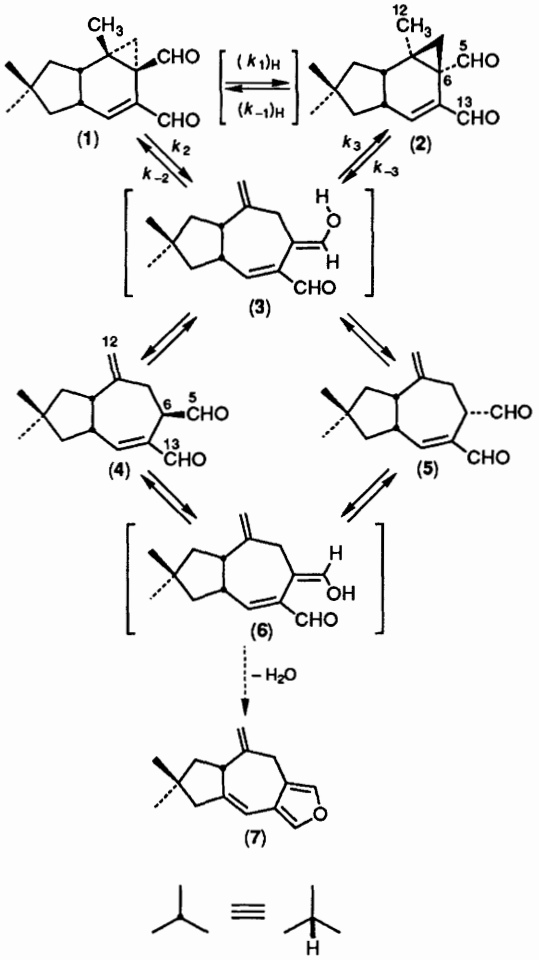
In the course of a total synthesis of (+)-isovelleral (**2**)[1] an unexpected thermal rearrangement reaction was discovered (Scheme 1). When heated neat, isovelleral (**2**) has earlier been shown to undergo a thermal rearrangement–elimination reaction to give the furanohydroazulene pyrovellerofuran (**7**).[2] This reaction was presumed to be initiated by a [1,5]homodienyl hydrogen shift giving an enol [*cf.* (**3**)] as the first intermediate. We have now found that, when the thermal reaction is performed in toluene solution, the synthetic diastereoisomer (**1**) isomerises reversibly into (**2**) prior to the formation of the furan. At equilibrium the ratio between (**1**) and (**2**) is 49 : 51. Eventually, small quantities of the furan (**7**) and the epimeric lactarane dialdehydes (**4**) and (**5**) are formed as by-products. The low temperature at which the isomerisation takes place (120—130 °C), as well as the nature of the by-products, is reconcilable with a reversible sigmatropic[1,5]homodienyl hydrogen shift mechanism (or synonymously, a retro-ene reaction).

In order to test the pericyclic mechanism, a toluene solution of (**2**) was heated in the presence of excess of $D_2O$. The intermediate exomethylenic enol (**3**) was expected to undergo a diffusion controlled proton–deuterium exchange at the hydroxy group, eventually to yield (**8**) and (**9**) having deuteriated C-12 methyl groups. With careful exclusion of acid or base, the presence of $D_2O$ did not significantly increase the formation of the furan (**7**) or of the aldehydes (**4**) and (**5**), and the isotopic purity of the deuteriated products (**8**) and (**9**) was better than 97% as determined by NMR spectroscopy. Thus the reaction also makes isotopically labelled isovelleral (**2**) readily available.

**Table 1.** Rate constants and deuterium isotope effects for the isomerisation of isovelleral (**2**) into (**1**) and (**9**) into (**8**).[a]

| Temp./°C | $(k_{-1})_H/s^{-1}$ | $(k_{-1})_D/s^{-1}$ | $(k_{-1})_H/(k_{-1})_D$ |
|---|---|---|---|
| 128.0 ± 0.5 | (2.16 ± 0.11) × $10^5$ | (6.19 ± 0.25) × $10^{-6}$ | 3.5 ± 0.2 |
| 134.8 ± 0.5 | (4.30 ± 0.07) × $10^5$ | (1.30 ± 0.05) × $10^{-5}$ | 3.3 ± 0.2 |
| 142.8 ± 0.5 | (8.59 ± 0.06) × $10^5$ | (2.41 ± 0.05) × $10^{-5}$ | 3.6 ± 0.1 |
| 150.0 ± 0.5 | (1.57 ± 0.02) × $10^4$ | (4.43 ± 0.08) × $10^{-5}$ | 3.5 ± 0.1 |

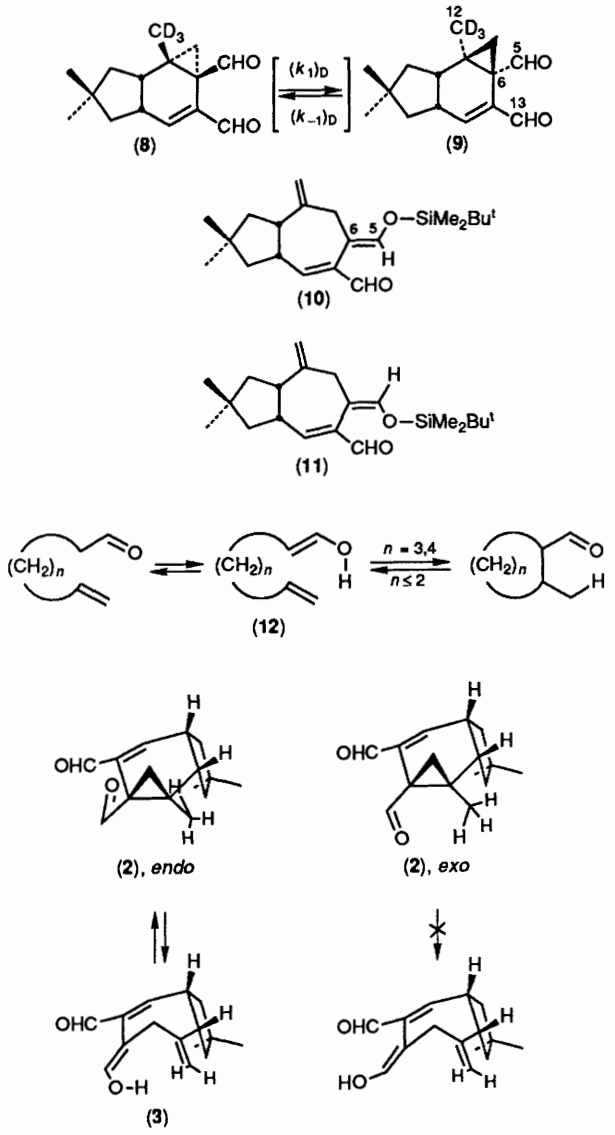
[a] The rate constants $(k_1)_H$ and $(k_1)_D$ follow from the observed equilibrium constant $K = k_1/k_{-1}$ for the interconversion of (**1**) and (**2**) or (**8**) and (**9**), $K_H = K_D = 1.04$.




**Scheme 1.** The thermal interconversion of (**1**) and (**2**) was studied in the temperature range 128—150 °C.

The intermediacy of enol (**3**) was confirmed by it being trapped exclusively as the *E*-silyl enol ether (**10**) when either (**1**) or (**2**) was heated in toluene with a 10-fold excess of *N*-methyl-*N*-(t-butyldimethylsilyl)trifluoroacetamide. The silylation was in fact faster than recyclisation of the enol (**3**), since no isomerisation of (**1**) into (**2**) or *vice versa* was observed. [Analogous experiments using *N,O*-bis(trimethylsilyl)trifluoroacetamide allowed the estimation of the lower limits of rate constants $k_2$ and $k_{-3}$ (Scheme 1).]†

† *En route* from (**1**) to (**2**) or *vice versa*, the enol (**3**) has to undergo a ring inversion. If the rate of this were of the same order or slower than the cyclisation reactions (rate constants $k_{-2}$ and $k_3$), then the true values of $k_2$ and $k_{-3}$ would be larger than those indicated by the silylation experiments (*ca.* 5.4 × $10^{-5}$ and 1.2 × $10^{-4}$ $s^{-1}$, respectively, at 407.8 K). The kinetic evaluation of these has been hampered by experimental difficulties.




**Scheme 2.** Stereochemical restrictions on the isovelleral rearrangement.

On the other hand, when the dialdehyde (**4**) was heated in toluene in the presence of $CF_3(C:O)N(Me)SiBu^tMe_2$ a mixture of the *E*- and *Z*-enol ethers (**10**) and (**11**) was obtained, the *Z*-isomer (**11**) predominating in a *ca.* 1.4:1 ratio. Cleavage of (**10**) or (**11**) with tetrabutylammonium fluoride afforded the dialdehydes (**4**) and (**5**) in *ca.* 2:1 ratio.‡

The kinetics of the isomerisation of (**2**) and its deuteriated analogue (**9**) into (**1**) and (**8**), respectively, in approximately 0.045 M solutions in [$^2H_8$]toluene, were studied by $^1H$ NMR spectroscopy at 300 MHz. Duplicate samples in sealed NMR tubes were immersed in a thermostatic oil bath with efficient stirring. Periodically, the samples were withdrawn and cooled rapidly, and the progress of the reaction was monitored by integration of the well resolved NMR signals from H-5 and

‡ The configurations at C-6 in (**4**) and (**5**) and at C-5 in (**10**) and (**11**) were established with nuclear Overhauser enhancement (NOE) and NOESY experiments. New compounds were chromatographically homogeneous and gave spectroscopic and analytical and/or high-resolution mass spectral data in accordance with their assigned structures.

H-13 in the aldehyde region.§ The reaction followed reversible first-order kinetics (Table 1).

The large primary kinetic isotope effect, which is close to the maximum kinetic isotope effects based on the loss of vibrational zero-point energy in the transition state, is consistent with a concerted hydrogen migration proceeding through a symmetrical transition state. The activation parameters were calculated for the reverse reaction [(**1**)→(**2**), $E_a$ 126.0 ± 2.0 kJ mol$^{-1}$, log $A$ 11.8 ± 0.2 s$^{-1}$; $\Delta H^{\ddagger}$ 122.6 ± 2.0 kJ mol$^{-1}$, $\Delta S^{\ddagger}$ −30.5 ± 3.8 J mol$^{-1}$ K$^{-1}$] and were obtained by a least-squares treatment of the experimental data. The reaction parameters are comparable to the corresponding values reported for the thermal opening of 1-acetyl-2,2-dimethylcyclopropane[3] and of *cis*-1-alkenyl-2-methylcyclopropanes.[4]¶

The low tendency for formation of the dialdehydes (**4**) and (**5**) during the isomerisation of (**1**) and (**2**) in pure toluene was somewhat unexpected, and, even more surprisingly, when a toluene solution of either (**4**) or (**5**) and a small amount of triethylamine (to catalyse the keto–enol equilibrium) was heated for 2.5 h at 175 °C, partial cyclisation to (**1**) and (**2**) took place in a reversible process (Scheme 1). At equilibrium the approximate ratio between (**1**), (**2**), (**4**), and (**5**) was 25 : 25 : 35 : 15 as determined by NMR spectroscopy. When (**1**) or (**2**) was heated in the presence of a catalytic amount of acetic acid, pyrovellerofuran (**7**) was the main product.

Presumably, a high ring strain in the hydroazulene dialdehydes (**4**) and (**5**) shifts the equilibrium towards the tricyclic cyclopropane derivatives (**1**) and (**2**). This is to our knowledge the first direct observation of a cyclopropyl ring formation *via* an intramolecular ene reaction of a γ-olefinic carbonyl compound. Whereas enones permitting the formation of five- or six-membered rings easily undergo an ene cyclisation *via* their enols [(**12**), $n$ = 3 or 4], the reverse reaction normally takes over for $n \leq 2$ (Scheme 2).[5,6] The so-called 'abnormal Claisen rearrangement,' sometimes observed in thermal rearrangements of allyl aryl ethers possessing an alkyl group in the γ-position, apparently involves an ene–retroene reaction sequence with a spirocyclopropane intermediate, but the latter has never been intercepted.[3,7] When applied to suitably substituted bicyclo[3.1.0]heptanes, the retro-ene reaction of the *cis*-1-acyl-2-alkylcyclopropane system has been suggested as a synthetic route to hydroazulene sesquiterpenes.[8]

For steric reasons, *cis*-1-methyl-2-vinylcyclopropyl systems undergo thermal ring opening with almost exclusive formation of *Z*-1,4-dienes[4] *via* an *endo*-transition state (*cf.* Scheme 2), which according to theoretical calculations for the simplest case should have *ca.* 71 kJ mol$^{-1}$ lower energy than the corresponding *exo*-transition state.[9] By analogy with this, the exclusive formation of the silyl ether (**10**) of *E*-enol (**3**) in our trapping experiments with aldehydes (**1**) and (**2**) is not surprising and is also suggested on inspection of molecular models.

Synthetic work utilizing these findings for synthesis of sesquiterpenes containing the methylcyclopropyl-carbaldehyde group from hydroazulenic precursors is now underway in this laboratory.

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§ H-5 and H-13 NMR shifts of the dialdehydes in [$^2H_8$]toluene with $SiMe_4$ as internal standard were respectively (δ): (**1**) (9.70, 9.17); (**2**) (9.79, 9.08); (**4**) (9.20, 9.03); (**5**) (9.60, 8.98).

¶ In a strict sense, this comparison is only valid for the ring-opening steps (**1**) → (**3**) or (**2**) → (**3**) with rate constants $k_2$ and $k_{-3}$, respectively. However, $(k_1)_H = k_2/(1 + k_{-2}/k_3)$, and the silylation experiments indicate that $k_{-2}/k_3 \approx 0.45$. Therefore the apparent activation parameters for the isomerisation reaction should give a fair approximation of the true parameters for the ring-opening reaction (**1**) → (**3**).

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