The Thermal Isomerization of the Sesquiterpenes Isovelleral and Merulidial. A Reversible Ring Opening of the *cis*-Methylcyclopropanecarbaldehyde Group via an Intramolecular Ene Reaction

Thomas Hansson, Olov Sterner, and Börje Wickberg*

Organic Chemistry 2, Lund Institute of Technology, P.O.B 124, S-221 00 Lund, Sweden

Rolf Bergman

Division of Organic Chemistry, AB Hässle, S-431 83 Mölndal, Sweden

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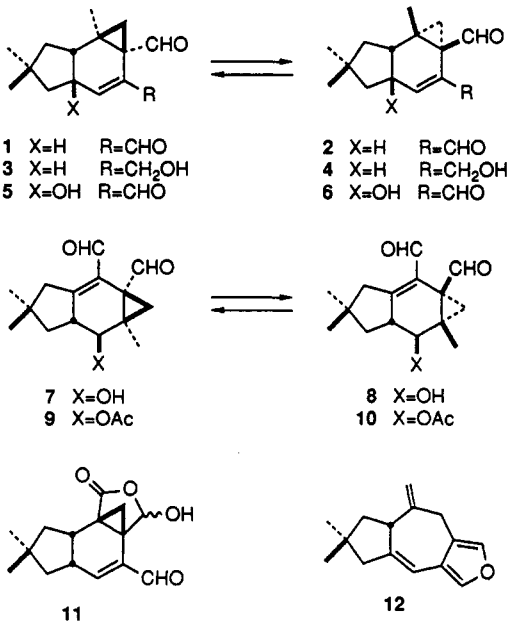
Fungal sesquiterpene dialdehydes of marasmane and isolactarane types, such as isovelleral (1) and merulidial (7), undergo a reversible thermal rearrangement to products (e.g., 2 and 8) with inverted orientations of the cyclopropane rings. The process is shown to involve an intramolecular ene reaction with a bicyclic enol intermediate 13 which was trapped as an *E*-silyl ether 17. In the presence of D_2O, deuterium is incorporated quantitatively into the C-12 methyl groups of 1 and 2. A high kinetic isotope effect is observed for the rearrangement of 1 and its deuterated analogue 24, and the reaction parameters are comparable to those reported for the thermal ring-opening reactions of *cis*-alkylvinylcyclopropanes and *cis*-alkyl cyclopropyl ketones. In the presence of weak acid or base, an equilibrium is established between 1, 2, and the hydroazulenic dialdehydes 14 and 15. Dialdehyde 7 reacts less cleanly and incorporates deuterium not only at C-13 but also at C-1 (26). The latter process presumably involves enolization via a [1,5] sigmatropic hydrogen shift.

Introduction

Isovelleral[1] (1), marasmic acid[2] (11), and merulidial[3] (7) are three sesquiterpenes of fungal origin (Basidiomycetes) which have unusual tricyclic marasmane and isolactarane α,β-unsaturated dialdehyde structures[4] and which possess antifeedant, mutagenic, and antimicrobial activities.[5] As a part of studies of the chemistry and biological activities of sesquiterpenes from Lactarius and Russula species, we recently reported a total synthesis of (+)-isovelleral (1),[6,7] which relied upon a thermal rearrangement of its diastereoisomer 2 as the final step.

It was known earlier that when heated neat 1 would undergo a rearrangement–elimination reaction to give pyrovellerofuran (12).[8] It was suggested that this reaction was initiated by a [1,5] homodienyl hydrogen shift giving an enol (cf. 13, Scheme II) as the first intermediate. However, we found that when the thermal reaction was performed in toluene solution, our synthetic sample of 2 isomerized neatly into 1 and vice versa prior to the formation of the furan. At equilibrium, which was attained after 2 h at 175 °C, the ratio between 1 and 2 was ca. 1:1. Small quantities of the furan 12 and the epimeric lactarane dialdehydes 14 and 15 were occasionally observed. The generality of the novel isomerization reaction was demonstrated in a qualitative sense by the thermal conversion of 9-hydroxyisovelleral (5)[9] into its stereoisomer 6[5a] and of merulidial 7 and its acetate 9[3] into 8 and 10,[5c] respectively, in order to provide samples for the study of structure–activity relationships.



If these isomerizations follow the pericyclic route indicated for the formation of pyrovellerofuran, they would be special cases of the well-known intramolecular ene reaction of enones (Scheme I, $n = 1$), which is sometimes useful for closing five- or six-membered rings.[10] Due to ring strain, the reverse reaction normally takes place when $n \leq 2$, and thus γ,δ-unsaturated carbonyl compounds may be obtained by thermal ring cleavage of *cis*-2-alkyl-1-

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(6) Bergman, R.; Hansson, T.; Sterner, O.; Wickberg, B. *J. Chem. Soc., Chem. Commun.* **1990**, 865.
(7) For a recent synthesis of (±)-isovelleral, see: Thompson, S. K.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 3004.
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(10) (a) Conia, J. M.; Le Perchec, P. *Synthesis* **1975**, 1. (b) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476.

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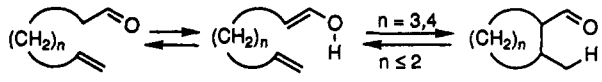
Table I. Thermal Equilibration of Marasmane and Isolactarane Derivatives[a]

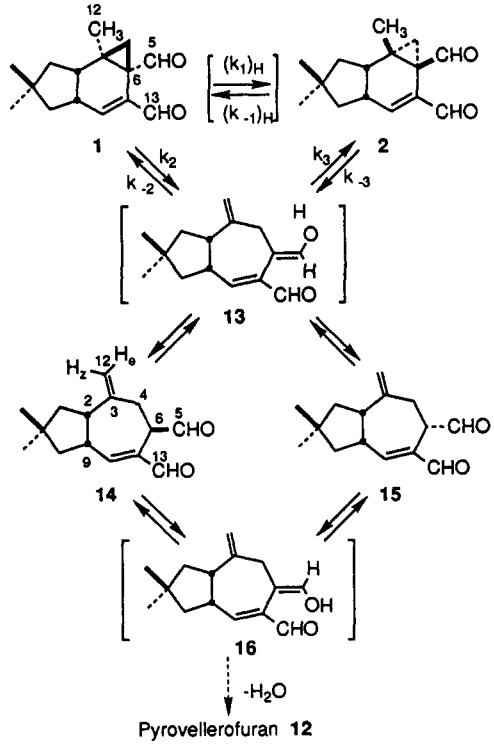
entry	equilibrating system	starting material (concn, M)	TEA, M	temp, °C	time, h	prods analyzed (rel amounts, %)[b]	unidentified part of total material,[c] %
1	1 and 2	1 (0.045) or		180	11	1 (49), 2 (47), 14 (2), 15 (2)	0
		2 (0.045)		180	11		
2	1, 2, 14, and 15	1 (0.110) or	0.05	170	2.5	1 (25), 2 (25), 14 (35), 15 (15)	10
		2 (0.110) or	0.05	170	2.5		
		14 (0.110) or	0.05	170	2.5		
		15 (0.110)	0.05	170	2.5		
3	7 and 8	7 (0.085)		170	4.5	7 (40), 8 (30), 21 (30)	20
4	7, 8, and 21	7 (0.005)	0.05	175	4	21 (100)	90
		21 (0.0044)	0.02	175	4	21 (100)	90
5	9 and 10	9 (0.007) or		170	3	9 (10), 10 (35), 22 (55)	25
		10 (0.007)		170	3		
6	9, 10, and 22	9 (0.010) or	0.02	170	3	9 (5), 10 (20), 22 (50), 23 (30)	25
		22 (0.0034)					

[a] Toluene was used as a solvent. [b] Analyses were made with NMR spectroscopy. [c] Calculated as the difference between the quantities of starting material and of products, as analyzed by NMR.

Scheme I



Scheme II

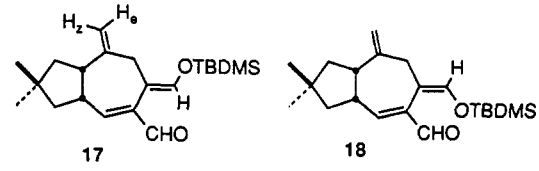


carbonylcyclopropane derivatives.[11] With this in mind, we felt it proper to undertake a more careful study of the isovelleral isomerization.[12]

Methods and Results

Thermal Isomerizations. The low temperature at which the isovelleral isomerization sets in (120–130 °C) supports an ene mechanism (Scheme II) rather than a homolytic cleavage of the cyclopropane ring with a stabilized diradical as an intermediate (vinylcyclopropane rearrangement).[13] This was further supported by our observation that marasmic acid (11) failed to isomerize under similar conditions (toluene, 170 °C).

While the same equilibrium ratio of 51:49 was reached between 1 and 2 on heating either isomer (in a carefully purified state) for several hours at 170 °C (Table I, entry 1), a similar treatment in the presence of a 10-fold excess of a neutral silylating agent such as *N*-methyl-*N*-(*tert*-butyldimethylsilyl)trifluoroacetamide (MTBSTFA), afforded exclusively the silyl ether 17 having an *E*-configuration. Apparently, the silylation was faster than re-



cyclization of the enol 13 since no isomerization of 1 into 2 or vice versa was observed. Desilylation of 17 with fluoride ion gave convenient access to the aldehydes 14 and 15 in a 2:1 ratio. Silylation of 14 with MTBSTFA on the other hand gave a 1.4:1 mixture of *E*- and *Z*-ethers 17 and 18, respectively, thus confirming that the exclusive formation of *E*-product 17 from 1 or 2 was a kinetic rather than a thermodynamic effect. The configurations at C-6 in 14 and 15 and at C-5 in 17 and 18 were established with NOESY experiments.[14]

Thermal treatment (175 °C) of isovelleral (1) or its stereoisomer 2 in toluene containing catalytic amounts of triethylamine (TEA) or acetic acid (to catalyze keto–enol conversions) eventually afforded identical product mixtures of 1, 2, 14, and 15 as determined by NMR spectroscopy (Table I, entry 2). This apparently represents a true equilibrium, since when either of the bicyclic aldehydes 14 or 15 was subjected to the same treatment (TEA catalyst), the same product mixture of 1, 2, 14, and 15 was obtained again. More vigorous conditions, i.e., higher temperatures or higher concentration of acetic acid, resulted in a formation of pyrovellerofuran (12) together with decomposition products.

The hydroxyaldehyde isovellerol (3)[15] also underwent a thermal rearrangement in toluene to its stereoisomer 4 to give an approximately 2:1 ratio of 3 to 4 at equilibrium. Both compounds were present as 1:1:1 mixtures of the

(11) Roberts, R. M.; Landolt, R. G.; Greene, R. N.; Heyer, E. W. *J. Am. Chem. Soc.* **1967**, *89*, 1404. See also: McGreer, D. M.; Chiu, N. W. K. *Can. J. Chem.* **1968**, *46*, 2217.

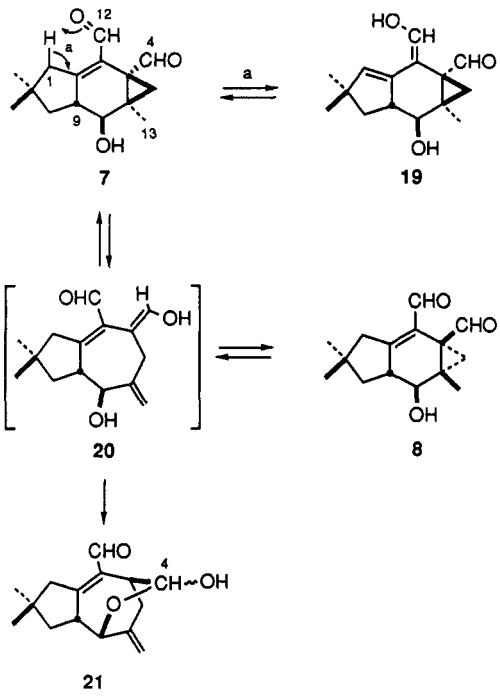
(12) Preliminary report: Hansson, T.; Bergman, R.; Sterner, O.; Wickberg, B. *J. Chem. Soc., Chem. Commun.* **1990**, 1260.

(13) For a review, see: Hudlicky, T.; Kutchan, T. M.; Naqvi, S. M. *Org. React.* **1985**, *33*, 247.

(14) The most indicative NOE's were observed between H-5 and H-9 in 14; H-6 and H-2 in 15; H-5 and H-13 in 17; and H-5 and H-4α in 18.

(15) Sterner, O.; Bergman, R.; Kihlberg, J.; Wickberg, B. *J.* Nat. *Prod.* **1985**, *48*, 279.

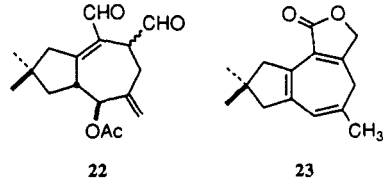
Scheme III



respective hydroxyaldehyde and its 5-epimeric cyclic hemiacetals; therefore, NMR analysis was not suited for a more accurate estimation of the equilibrium composition.

The thermal reaction[5c] of merulidial (7) was monitored with NMR on an analytical scale (Table I, entry 3). The isomerization to 8, presumably via enol 20, was accompanied by formation of the hydroazulene hemiacetal 21 (as a 10:3 mixture of the C-4 epimers) (Scheme III). Thermal treatment of merulidial 7 in the presence of TEA initially yielded the hemiacetal 21, but eventually resulted in extensive formation of byproducts. No reversion of 21 into 7 or 8 could be observed on a similar treatment of 21 alone (Table I, entry 4).

On heating toluene solutions of either merulidial acetate 9 or its isomer 10, a steady-state ratio of ca. 1:4 was established between them, but at the same time increasing amounts of the vellerane dialdehyde 22 were formed (Table I, entry 5). Similar treatment of either 9 or 22 in the presence of triethylamine demonstrated that the bicyclic dialdehyde 22 would indeed revert to 9 and 10 (Table I, entry 6). However, on prolonged heating a new product was formed quite cleanly. It was identified as the hydroazulene lactone 23. The formation of this is probably initiated by elimination of the acetoxy group followed by prototropic shifts; it was enhanced in a preparative run with a reduced amount of TEA present, as compared to the analytical experiment (see Experimental Section).

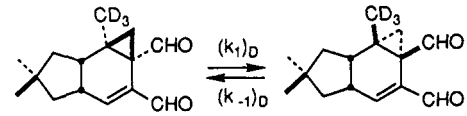


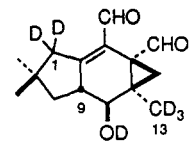
Deuterations. In the anticipation that the intermediate exomethylenic enols such as 13 might be able to undergo a diffision-controlled protium–deuterium exchange, isovelleral (1) was heated in toluene in the presence of an excess of D_2O. The isovelleral analogue 24 and its isomer 25 were obtained (ca. 60% recovery) with deuterium incorporated in the C-12 methyl groups. With exclusion of acid or base, the presence of D_2O did not significantly increase the formation of the furan 12 or the aldehydes 14 and 15, and the isotopic purity of the deuterated products was better than 97% as determined by NMR spectroscopy.

Table II. Rate Constants and Deuterium Isotope Effects for the Isomerization of Isovelleral (1) into 2 and [12-$^2H_3$]-Isovelleral (24) into 25

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, $K_H = K_D = 0.96$. Activation parameters in the direction 2 → 1: E_a 126.0 ± 2.0 kJ mol^{-1}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 mol1^{-1} K^{-1}.





The analogous deuteration of merulidial (7) gave a lower total recovery (ca. 30%), and the analysis was hampered by the very poor chromatographic resolution of merulidial and its isomer 8. NMR spectroscopy showed that the recovered merulidial was the product 26 with deuterium incorporated not only in the C-13 methyl group (ca. 80%), but also in the methylene group at C-1 (ca. 90%). The deuteration in the latter position is most likely caused by a protium–deuterium exchange in a dienol intermediate 19 (Scheme III) formed via a [1,5] sigmatropic rearrangement of the *cis*-γ-methylene-α,β-unsaturated aldehyde system. It might be noted that we have not observed deuterium exchange at C-9 of 1 or 7 which could be involved in alternative dienol tautomerizations.

Kinetics. The isomerizations of 1 and its deuterated analogue 24 into 2 and 25, respectively, were chosen for kinetic studies because under neutral conditions 1 and 24 give relatively clean reactions and are readily prepared from natural sources. The reactions were run in [$^2H_8$]-toluene and were monitored with ^1H NMR spectroscopy by integrating the well resolved NMR signals from H-5 and H-13 in the aldehyde region. The isomerization followed reversible first-order kinetics (Table II) with the apparent rate constants $(k_1)_H$ and $(k_1)_D$, respectively. The activation parameters were obtained by a least-squares treatment of the experimental data (Table II).

In principle, the parameters for the ring-opening reaction steps (1 → 13 and 2 → 13) are of the most direct interest for comparison purposes; the lower limits of the corresponding rate constants k_2 and k_{-3} could be estimated by following the disappearance of 1 and 2, respectively, when these were heated in [$^2H_8$]-toluene containing an excess of *O,N*-bis(trimethylsilyl)trifluoroacetamide. The reaction was monitored with ^1H NMR by periodic integration of the aldehyde signals. (It appears that under these con-

ditions the silylation of the intermediate enol 13 is much faster than its cyclization to 1 or 2.) Due to experimental complications, the values found this way, constants $k_2 = 1.2 \times 10^{-4}$ s^{-1} and $k_{-3} = 5.4 \times 10^{-5}$ s^{-1} at 407.8 K, are only approximate and not suited for exact kinetic analysis. However, the rate constants of the pericyclic reaction steps are related to the apparent first-order rate constants of the isomerization of 1 and 2 as shown for k_{-3} in eq 1: With

$$k_{-3} = (1 + k_3/k_{-2})(k_{-1})_H \quad (1)$$

$(k_{-1})_H/(k_1)_H = 0.96$ and the rate constants k_2 and k_{-3} approximately known, one finds that $k_3/k_{-2} \approx 0.43$. Therefore, the apparent activation parameters for the isomerization reaction 2 → 1 should give a fair approximation of the true parameters for the ring-opening reaction 2 → 13.

En route from 1 to 2 or vice versa, the cycloheptene ring in the enol 13 has to undergo a ring inversion. In the improbable case that the rate of this were of the same order as that of the cyclization reactions (rate constants k_{-2} and k_3), then the true values of k_2 and k_{-3} might be larger than the estimates from the silylation experiments. However, molecular mechanics calculations on enol 13, using the MM2 force field,[16] indicated that besides a low-energy conformation, 13 has two conformations of 12.7 and 5.9 kJ mol^{-1} higher energy, which approach the anticipated transition-state conformations leading to 1 and 2, respectively. The inversion barrier was evaluated to be less than 36 kJ mol^{-1} and therefore of no significance for the observed reaction rates.

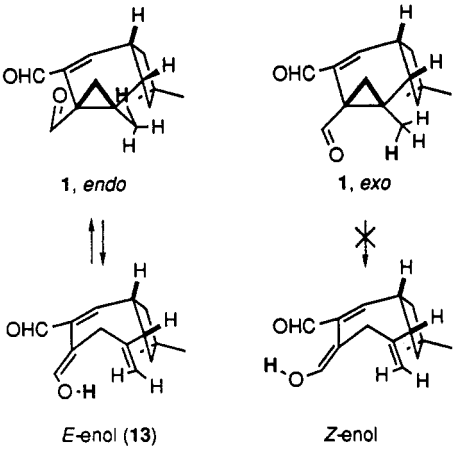
Discussion

Our experimental data are all consistent with with a pericyclic mechanism (Scheme II) for the thermal isomerizations of isovelleral and related compounds. Apart from the qualitative evidence provided by the trapping of of the *Z*-enol 13 by silylation and the deuterium incorporation at C-12 of isovelleral (1) and C-13 of merulidial (7), the kinetic results also support the suggested mechanism. The reaction parameters for the ring-opening step 2 → 13, as approximated by the values for the 2 → 1 conversion (Table II), compare well with the corresponding values reported for the thermal opening of 1-acetyl-2,2-dimethylcyclopropane,[11] $E_a = 131$ kJ mol^{-1} and $\Delta S^{\ddagger} = -42$ J mol^{-1} K^{-1}, and of *cis*-1-alkenyl-2-methylcyclopropanes, $E_a = 131$ kJ mol^{-1} and log $A = 11.0$ (A, s^{-1}).[17,18]

The primary kinetic isotope effect (Table II) is large and is close to the maximum value ($k_H/k_D \approx 3.9$ at 139 °C) expected from a loss of vibrational zero-point energy in the transition state. It is consistent with a concerted hydrogen migration proceeding through a symmetrical transition state but does not permit any definite conclusions about the transition-state geometry. In the related case of the thermal [1,5]-H-shift in *cis*-1,3-pentadienes, the deuterium isotope effect is unexpectedly high, which has been suggested to be caused by contributions from vibrational assisted tunneling to the mechanism.[19]

cis-1-Methyl-2-vinylcyclopropyl systems are known to undergo thermal ring opening with almost exclusive formation of *Z*-1,4-dienes via an endo transition state (cf. Scheme IV). The difference in energy between the endo and exo transition states has been determined experimentally[20] to be at least 50 kJ mol^{-1} and by theoretical calculations[21] for the simplest case to be ca. 71 kJ mol^{-1}. It has been pointed out that, with respect to conformational preferences, the endo transition state is analogous to a seven-membered ring containing a cis double bond, while the exo transition structure is analogous to a seven-membered ring with a trans double bond.[21,22] By analogy, the exclusive formation of the *E*-enol silyl ether 17 in the trapping experiments with aldehydes 1 and 2 is not surprising. However, the stereochemical course of the retro-ene reaction of *cis*-alkylcyclopropyl carbonyl systems has not been observed earlier due to rapid enol–carbonyl tautomerization.

Scheme IV



It is obvious that the isovelleral isomerization is closely related to the so called "abnormal Claisen" or "enolene" rearrangement, which may be observed in thermal rearrangements of allyl aryl ethers possessing an alkyl group in the γ-position or in γ,δ-unsaturated ketones with a β-alkyl substituent.[23] This rearrangement is considered to involve a homodienyl [1,5] sigmatropic hydrogen shift or, in other words, an intramolecular ene reaction with a cyclopropane intermediate. However, to the best of our knowlege, the latter has never been intercepted before the present investigation.

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 practical route to hydroazulene sesquiterpenes.[24] In the hydroazulene dialdehydes 14, 15, and 22, ring strain presumably helps to shift the equilibria partly toward the tricyclic cyclopropane derivatives, even though the balance may be delicate. In the merulidial isomerization, the hydroazulene isomer 21 is obviously sufficiently stabilized by hemiacetal formation to resist detectable reversion to the tricyclic isolactaranes 7 and 8.

The [1,5] sigmatropic enolization mechanism suggested for the selective deuterium incorporation at C-1 of merulidial (7) gets further support by a very recent report on a similar deuteration of the methyl group in different cyclic γ-methyl α,β-unsaturated aldehydes.[25] Such reversible [1,5] sigmatropic hydrogen migrations have also been

(16) (a) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. (b) The 1991 version MM2(91) of the force field was used.
(17) Ellis, R. J.; Frey, H. M. *J. Chem. Soc.* **1964**, 5578.
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(23) (a) March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley: New York, 1985; p 1029. (b) Hansen, H. J. In *Mechanisms of Molecular Migrations*; Thyagarajan, B. S., Ed.; John Wiley: New York, 1971; Vol. 3, p 177ff.
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(25) Curtin, M. L.; Okamura, W. H. *J. Am. Chem. Soc.* **1991**, *113*, 6958.

identified in the thermal deuteration of 2-vinylphenols.[26] Due to the greater stability of the carbonyl tautomers, the thermal enolization of α,β-unsaturated carbonyl systems will only be detected when the enol intermediate is intercepted, e.g., in secondary ene reactions.[10,27]

Apart from the mechanistic implications, the deuteration of the naturally occurring sesquiterpene aldehydes 1 and 7 gives convenient access to isotopically labeled marasmanes and isolactaranes for biological studies. The [12-$^2H_3$]-isovelleral (24) has recently been used for the study of the bioconversion of sesquiterpenes in *Lactarius* sp.[28]

Experimental Section

Chemical shifts are relative to Me_4Si.[29] Kinetic ^1H NMR measurements were performed in [$^2H_8$]-toluene with an acquisition time of 6.0 s, a relaxation delay of 20 s, and a 45° pulse. Molecular mechanics calculations were made with the MacMimic/MM2(91) package.[30] Melting points are uncorrected. TLC was performed on Merck DC-Alufolien Kieselgel 60F_{254}. Column chromatography was carried out on Merck Kieselgel 60 (0.040–0.063 mm), Grace Amicon Kieselgel 60 (0.035–0.070 mm), or on Merck Aluminiumoxid 90 (0.036–0.200 mm). Unless stated otherwise, reactions were performed in sealed glass ampules, and Na_2SO_4 was used as a drying agent. Marasmic acid (11) was kindly provided by Prof. H. Anke, University of Kaiserslautern, Germany. Compounds 3,[15] 7,[3] and 9[3] were prepared according to published methods. Isovelleral (1) was isolated by a modification of a published method.[15] Full assignments of NMR data are published since some confusion exists in the literature.[5d]

General Procedure for Equilibrium Measurements. Samples were prepared in toluene according to Table I, sealed in glass tubes, and heated in a thermostatic oil bath (±0.5 °C). At intervals the tubes were withdrawn and cooled and the nonvolatile contents taken in $CDCl_3$ and analyzed by integration of the aldehyde region in the NMR spectra.

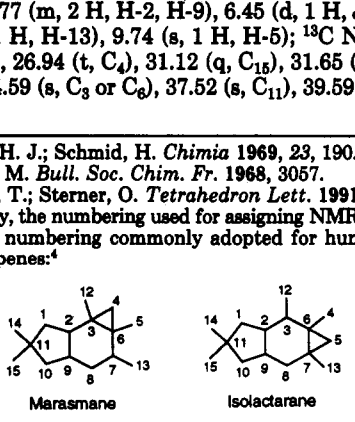
Isolation of (+)-Isovelleral (1). Fruit bodies of *Lactarius vellereus* Fr. were ground in a meat grinder without the addition of solvent. After 20 min at room temperature the mush was extracted with hexane. After concentration the extract was taken in diethyl ether and the solution filtered through Al_2O_3 (activity II–III) in order to remove stearic acid from the terpenoids. The eluate was subjected to chromatography (SiO_2, 1:4 EtOAc–heptane) to give 1 as white crystals: mp 100–103 °C; $[\alpha]^{20}_D$ 251° (*c* 1.0, $CHCl_3$); IR (CCl_4) cm^{-1} 3010, 2960, 2940, 2880, 2820, 2720, 1720, 1695, 1635, 1200, 1080; ^1H NMR ($CDCl_3$) δ 0.94 (d, 1 H, $J_{4\beta-4\alpha}$ = 4.4 Hz, H_β-4), 1.05 (s, 3 H, H_3-14), 1.07 (s, 3 H, H_3-15), 1.12 (s, 3 H, H_3-12), 1.20 (dd, 1 H, $J_{1\alpha-1\beta}$ = 12.2 Hz, $J_{1\alpha-2}$ = 12.2 Hz, H_α-1), 1.58 (dd, 1 H, $J_{10\alpha-10\beta}$ = 13.5 Hz, $J_{10\alpha-9}$ = 2.1 Hz, H_α-10), 1.75 (dd, 1 H, $J_{1\beta-1\alpha}$ = 12.6 Hz, $J_{1\beta-2}$ = 6.8 Hz, H_β-1), 1.90 (d, 1 H, $J_{4\alpha-4\beta}$ = 4.4 Hz, H_α-4), 1.99 (dd, 1 H, $J_{10\beta-10\alpha}$ = 13.5 Hz, $J_{10\beta-9}$ = 8.8 Hz, H_β-10), 2.63–2.77 (m, 2 H, H-2, H-9), 6.45 (d, 1 H, J_{8-9} = 2.2 Hz, H-8), 9.48 (s, 1 H, H-13), 9.74 (s, 1 H, H-5); ^{13}C NMR ($CDCl_3$) δ 18.67 (q, C_{12}), 26.94 (t, C_4), 31.12 (q, C_{15}), 31.65 (q, C_{14}), 34.17 (s, C_3 or C_6), 34.59 (s, C_3 or C_6), 37.52 (s, C_{11}), 39.59 (d, C_9), 41.77 (d, C_2), 45.63 (t, C_1), 46.95 (t, C_{10}), 140.34 (s, C_7), 153.59 (d, C_8), 192.30 (s, C_{13}), 197.83 (s, C_5); MS (EI) *m/z* 232 (M^+, 4.4), 217 ($M^+ - CH_3$, 0.9), 204 (6.0), 189 (5.6), 175 (10.9), 161 (5.8), 147 (9.6), 133 (11.1), 119 (20.4), 105 (34.7), 91 (47.6), 77 (32.4), 55 (39.3), 41 (100). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.6; H, 8.68. Found: C, 77.4; H, 8.82.

Isomerization of Isovelleral to [1a*R*-(1aα,3aα,6aα,6bα)]-3a,4,5,6,6a,6b-Hexahydro-5,5,6b-trimethylcycloprop[*e*]indene-1a,2(1*H*)-dicarboxaldehyde (2). A solution of 1 (300 mg, 1.29 mmol) in toluene (10 mL) was heated for 1 h at 200 °C. After being cooled the solution was concentrated and the residue was purified by chromatography (SiO_2, 1:4 EtOAc–heptane) affording recovered 1 (98 mg, 33%, higher R_f) and 2 (113 mg, 38%, lower R_f) as white crystals, mp 68–70 °C; $[\alpha]^{20}_D$ −79.1° (*c* 1.0, $CHCl_3$); IR (CCl_4) cm^{-1} 2950, 2930, 2860, 2810, 2740, 1710, 1690, 1640, 1460, 1370, 1200, 1080, 1075, 1035, 860; ^1H NMR ($CDCl_3$) δ 0.55 (d, 1 H, $J_{4\alpha-4\beta}$ = 4.4 Hz, H_α-4), 1.02 (dd, 1 H, $J_{10\alpha\beta}$ = 12.5 Hz, $J_{10\alpha-9}$ = 12.5 Hz, H_α-10), 1.05 (s, 3 H, H_3-14), 1.10 (s, 3 H, H_3-15), 1.16 (s, 3 H, H_3-12), 1.43 (dd, 1 H, $J_{1\alpha-1\beta}$ = 12.9 Hz, $J_{1\alpha-2}$ = 8.1 Hz, H_α-1), 1.85 (ddd, 1 H, $J_{10\beta-10\alpha}$ = 12.0 Hz, $J_{10\beta-9}$ = 7.1 Hz, $J_{10\beta-1\beta}$ = 2.0 Hz, H_β-10), 1.88 (dd, 1 H, $J_{4\beta-4\alpha}$ = 4.4 Hz, $J_{4\beta-2}$ = 1.3 Hz, H_β-4), 2.12 (ddd, 1 H, $J_{1\beta-1\alpha}$ = 12.9 Hz, $J_{1\beta-2}$ = 8.5 Hz, $J_{1\beta-10\beta}$ = 1.9 Hz, H_β-1), 2.43 (dddd, 1 H, $J_{2-4\beta}$ = 0.9 Hz, $J_{2-1\alpha}$ = 8.3 Hz, $J_{2-1\beta}$ = 8.3 Hz, J_{2-9} = 8.3 Hz, H-2), 3.15–3.03 (m, 1 H, H-9), 6.85 (d, 1 H, J_{8-9} = 4.6 Hz, H-8, 9.51 (s, 1 H, H-13), 9.64 (s, 1 H, H-5); ^{13}C NMR ($CDCl_3$) δ 20.36 (q, C_{12}), 27.61 (q, C_{14}), 29.10 (q, C_{15}), 30.21 (t, C_4), 37.30 (s, C_3 or C_6), 37.93 (s, C_{11}), 38.37 (s, C_3 or C_6), 39.05 (d, C_9), 39.15 (d, C_2), 48.19 (t, C_1), 49.12 (t, C_{10}), 139.94 (s, C_7), 152.41 (d, C_8), 192.63 (d, C_{13}), 197.87 (d, C_5); MS (EI) *m/z* 232 (M^+, 5.8), 217 ($M^+ - CH_3$, 1.5), 204 (4.9), 189 (4.9), 175 (8.8), 161 (6.2), 147 (9.3), 133 (13.5), 119 (23.5), 105 (40.5), 91 (50.2), 77 (35.4), 69 (21.0), 55 (46.0), 41 (100). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.6; H, 8.68. Found: C, 77.4; H, 8.80.

***tert*-Butyldimethylsilyl Ether of *E*-Enol 13 (17).** A solution of 1 (300 mg, 1.29 mmol) and *N*-methyl-*N*-(*tert*-butyldimethylsilyl)trifluoroacetamide (1.02 g, 4.24 mmol) in toluene (7 mL) was heated in a sealed Teflon vessel for 3 h at 180 °C. Usual workup by chromatography (SiO_2, 1:9 Et_2O–heptane) gave 17 (170 mg, 38%) as a syrup with $[\alpha]^{20}_D$ 176.3° (*c* 1.0, $CHCl_3$): IR (neat) cm^{-1} 3080, 2950, 2930, 2900, 2860, 2710, 1690, 1630, 1590, 1460, 1250, 1170, 840, 780; ^1H NMR ($CDCl_3$) δ 0.18 (s, 3 H, SiMe), 0.19 (s, 3 H, SiMe), 0.95 (s, 9 H, SiC*Me*$_3$), 1.05 (s, 3 H, H_3-15), 1.13 (s, 3 H, H_3-14), 1.51–1.68 (m, 3 H, H_2-1 and H_α-10), 1.87 (ddd, 1 H, $J_{10\beta-10\alpha}$ = 13.0 Hz, $J_{10\beta-9}$ = 8.0 Hz, $J_{10\beta-1\beta}$ = 1.2 Hz, H_β-10), 3.01 (ddd, 1 H, $J_{4\beta-4\alpha}$ = 16.1 Hz, $J_{4\beta-5}$ = 2.3 Hz, $J_{4\beta-12e}$ = 0.9 Hz, H_β-4), 3.05–3.14 (m, 1 H, H-2), 3.23–3.32 (m, 1 H, H-9), 3.29 (ddd, 1 H, $J_{4\alpha-4\beta}$ = 16.1 Hz, $J_{4\alpha-5}$ = 2.1 Hz, $J_{4\alpha-12e}$ = 0.9 Hz, H_α-4), 4.70 (dd, 1 H, $J_{12z-12e}$ = 1.8 Hz, J_{12z-2} = 1.8 Hz, H_z-12), 4.75 (dddd, 1 H, $J_{12e-12z}$ = 1.8 Hz, J_{12e-2} = 1.0 Hz, $J_{12e-4\alpha}$ = $J_{12e-4\beta}$ = 0.9 Hz, H_e-12), 6.31 (d, 1 H, J_{8-9} = 5.6 Hz, H-8), 6.77 (dd, 1 H, $J_{5-4\alpha}$ = 2.1 Hz, $J_{5-4\beta}$ = 2.1 Hz, H-5), 9.35 (s, 1 H, H-13); ^{13}C NMR ($CDCl_3$) δ −5.24 (q, $SiMe_2$), 18.20 (s, SiCMe$_3$), 25.62 (q, SiC*Me*$_3$), 29.37 (q, C_{15}), 30.46 (q, C_{14}), 33.88 (t, C_4), 38.21 (s, C_{11}), 42.59 (d, C_9), 45.21 (t, C_1), 48.12 (t, C_{10}), 49.22 (d, C_2), 111.52 (t, C_{12}), 112.07, (s, C_3 or C_6 or C_7), 139.62 (s, C_3 or C_6 or C_7), 141.54 (d, C_5), 148.20 (s, C_3 or C_6 or C_7), 158.66 (d, C_8), 193.86 (d, C_{13}); MS (EI) *m/z* 346 (M^+, 51), 317 (23), 289 (100), 233 (23.5), 214 (21), 201 (17), 184 (26), 129 (23), 91 (20), 77 (100), 75 (100), 58 (41), 43 (92); HRMS *m/z* exact mass calcd for $C_{21}H_{34}O_2Si$ 346.2328, found 346.2331.

[3a*S*-(3aα,6aα,8aα)]-1,2,3,3a,6,7,8,8a-Octahydro-2,2-dimethyl-8-methylene-5,6-azulenedicarboxaldehyde (14) and Its 6-Epimer 15. Tetrabutylamonium fluoride trihydrate (1.0 g, 3.17 mmol) was added to a solution of 17 (113 mg, 0.33 mmol) in $CHCl_3$ (15 mL) and H_2O (3 mL). The mixture was kept at room temperature for 1 h with stirring. The organic phase was washed with H_2O (3 × 10 mL) and then dried and concentrated. Column chromatography (SiO_2, 1:4 EtOAc–heptane) of the residue gave 14 (26.2 mg, 35%) and 15 (10.8 mg, 14%) as syrups. For 14: $[\alpha]^{20}_D$ 136.9° (*c* 1.0, $CHCl_3$); IR (neat cm^{-1} 3080, 2950, 2930, 2860, 2820, 2720, 1720, 1680, 1640, 1460, 1365, 1150, 900; ^1H NMR ($CDCl_3$) δ 1.03 (s, 3 H, H_3-15), 1.14 (s, 3 H, H_3-14), 1.49–1.65 (m, 3 H, H_2-1, H_α-10), 1.91 (ddd, 1 H, $J_{10\beta-10\alpha}$ = 12.9 Hz, $J_{10\beta-9}$ = 7.9 Hz, J = 1.2 Hz, H_β-10), 2.54 (dd, 1 H, $J_{4\alpha-4\beta}$ = 13.9 Hz, $J_{4\alpha-6}$ = 7.9 Hz, H_α-4), 2.92 (ddd, 1 H, $J_{4\beta-4\alpha}$ = 13.9 Hz, $J_{4\beta-12e}$ = 1.0 Hz, $J_{4\beta-6}$ = 5.7 Hz, H_β-4), 2.96–3.02 (m, 1 H, H-2), 3.12–3.21 (m, 1 H, H-9), 3.93 (dd, 1 H, $J_{6-4\alpha}$ = 7.9 Hz, $J_{6-4\beta}$ = 5.7 Hz, H-6), 4.79 (dd, 1 H, J_{12z-2} =

(26) Hansen, H. J.; Schmid, H. *Chimia* **1969**, *23*, 190.
(27) Conia, J. M. *Bull. Soc. Chim. Fr.* **1968**, 3057.
(28) Hansson, T.; Sterner, O. *Tetrahedron Lett.* **1991**, *32*, 2541.
(29) For clarity, the numbering used for assigning NMR signals follows the "biogenetic" numbering commonly adopted for humulene-derived fungal sesquiterpenes:[4]



(30) InStar Software, Ideon Research Park, S-223 70 Lund, Sweden.

1.5 Hz J_{12z-9} = 1.5 Hz, H_z-12), 4.81 (dd, 1 H, $J_{12e-4\beta}$ = 0.9 Hz, J_{12e-2} = 0.9 Hz, H_e-12), 6.74 (d, 1 H, J_{8-9} = 4.1 Hz, H-8), 9.39 (s, 1 H, H-13), 9.55 (s, 1 H, H-5); ^{13}C NMR ($CDCl_3$) δ 29.06 (q, C_{15}), 30.33 (q, C_{14}), 31.83 (t, C_4), 37.80 (s, C_{11}), 42.03 (d, C_9), 44.85 (t, C_{10}), 47.87 (d, C_2), 48.03 (t, C_1), 48.16 (d, C_6), 112.77 (t, C_{12}), 137.72 (s, C_3 or C_7), 146.46 (s, C_3 or C_7), 162.88 (d, C_8), 193.43 (d, C_{13}), 198.96 (d, C_5); MS (CI-NH_3) m/z 233 (M^+ + 1, 39), 215 (50), 204 (33), 189 (20), 187 (18), 175 (14), 160 (14), 145 (13), 133 (12), 119 (20), 105 (24), 91 (19), 75 (100), 59 (100), 58 (87), 45 (49), 43 (100); HRMS m/z exact mass calcd for $C_{15}H_{20}O_2$ 232.1463, found 232.1486.

For **15**: $[\alpha]^{20}_D$ 26.2° (c 0.5, $CHCl_3$); IR (neat) cm^{-1} 3080, 2950, 2930, 2860, 2720, 1720, 1680, 1640, 1460, 1365, 900; ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 3 H, H_3-15), 1.14 (s, 3 H, H_3-14), 1.49 (dd, 1 H, $J_{10\alpha-10\beta}$ = 12.7 Hz, $J_{10\alpha-9}$ = 10.3 Hz, H_α-10), 1.60–1.66 (m, 2 H, H_2-1), 1.90 (ddd, 1 H, $J_{10\beta-10\alpha}$ = 12.5 Hz, $J_{10\beta-9}$ = 7.7 Hz, $J_{10\beta-1\beta}$ = 1.3 Hz H_β-10), 2.55 (dd, 1 H, $J_{4\beta-4\alpha}$ = 13.7 Hz, $J_{4\beta-6}$ = 6.1 Hz, H_β-4), 2.68 (dd, 1 H, $J_{4\alpha-4\beta}$ = 14.0 Hz, $J_{4\alpha-6}$ = 8.9 Hz, H_α-4), 3.04 (ddd, 1 H, J = 8.8 Hz, J = 9.1 Hz, J = 9.4 Hz, H-2), 3.30–3.42 (m, 1 H, H-9), 3.52 (ddddd, 1 H, $J_{6-4\beta}$ = 6.5 Hz, $J_{6-4\alpha}$ = 8.9 Hz, J_{6-8} = J_{6-5} = J_{6-9} = 1.0 Hz, H-6), 4.81 (s, 1 H, H_e-12), 4.82 (d, 1 H, J_{12z-2} = 1.2 Hz, H_z-12), 6.80 (dd, 1 H, J_{8-6} = 1.1 Hz, J_{8-9} = 5.0 Hz, H-8), 9.36 (s, 1 H, H-13), 9.73 (d, 1 H, J_{5-6} = 1.0 Hz, H-5); ^{13}C NMR ($CDCl_3$) δ 27.70 (q, C_{15}), 29.32 (q, C_{14}), 33.05 (t, C_4), 38.09 (s, C_{11}), 42.38 (d, C_9), 45.01 (t, C_1), 47.13 (d, C_2), 48.31 (t, C_{10}), 49.73 (d, C_6), 112.94 (t, C_{12}), 139.51 (s, C_3 or C_7), 145.99 (s, C_3 or C_7), 161.13 (d, C_8), 193.55 (d, C_{13}), 199.71 (d, C_5); MS (CI-NH_3) m/z 233 (M^+ + 1), 219 (50), 215 (48), 204 (57), 189 (56), 175 (53), 161 (45), 159 (46), 147 (57), 133 (72), 119 (96), 105 (100), 95 (68), 91 (86), 81 (43), 69 (41), 59 (45); HRMS m/z exact mass calcd for $C_{15}H_{20}O_2$ 232.1463, found 232.1478.

***tert*-Butyldimethylsilyl Ether of *Z*-Enol 16 (18).** A solution of **14** (115 mg, 0.50 mmol) and *N*-methyl-*N*-(*tert*-butyldimethylsilyl)trifluoroacetamide (2.35 g, 5.4 mmol) in toluene (1.7 mL) was heated for 2 h at 175 °C. Usual workup by chromatography (SiO_2, 1:20 Et_2O–heptane) afforded **17** (33.6 mg, 19%, higher R_f) and **18** (45.3 mg, 26%, lower R_f). For **18**, a syrup with $[\alpha]^{20}_D$ 41.2° (c 1.0, $CHCl_3$): IR (neat) cm^{-1} 3080, 2950, 2930, 2900, 2860, 2700, 1690, 1670, 1610, 1460, 1360, 1250, 1170, 840, 780; ^{1}H NMR ($CDCl_3$) δ 0.11 (d, 6 H, $SiMe_2$), 0.85 (s, 9 H, $SiCMe_3$), 1.01 (s, 3 H, H_3-15), 1.13 (s, 3 H, H_3-14), 1.46 (dd, 1 H, $J_{10\alpha-10\beta}$ = 12.4 Hz, $J_{10\alpha-9}$ = 9.4 Hz, H_α-10), 1.52 (ddd, 1 H, $J_{1\beta-1\alpha}$ = 12.6 Hz, $J_{1\beta-2}$ = 7.4 Hz, $J_{1\beta-10\beta}$ = 1.5 Hz, H_β-1), 1.70 (dd, 1 H, $J_{1\alpha-1\beta}$ = 12.6 Hz, $J_{1\alpha-2}$ = 10.1 Hz, H_α-1), 1.75 (ddd, 1 H, $J_{10\beta-10\alpha}$ = 12.5 Hz, $J_{10\beta-9}$ = 7.4 Hz, $J_{10\beta-1\beta}$ = 1.6 Hz, H_β-10), 2.91 (d, 1 H, $J_{4\alpha-4b}$ = 15.6 Hz, H_a-4), 3.03 (dd, 1 H, J_{4b-4a} = 15.6 Hz, J_{4b-5} = 1.1 Hz, H_b-4), 3.04–3.23 (m, 2 H, H-2 and H-9), 4.74–4.75 (m, 1 H, H_z-12), 4.77–4.78 (m, 1 H, H_e-12), 6.37 (ddd, 1 H, J_{5-4a} = J_{5-4b} = 1.5 Hz, J_{5-8} = 0.9 Hz, H-5), 6.65 (d, 1 H, J_{8-9} = 5.4 Hz, H-8), 9.37 (s, 1 H, H-13); ^{13}C NMR ($CDCl_3$) δ –5.25 (q, $SiMe_2$), 17.98 (s, $SiCMe_3$), 25.48 (q, $SiCMe_3$), 28.00 (q, C_{15}), 29.44 (q, C_{14}), 37.50 (t, C_4), 38.03 (s, C_{11}), 43.37 (d, C_9), 44.63 (t, C_1), 46.54 (d, C_2), 47.72 (t, C_{10}), 111.03 (s, C_3 or C_6 or C_7), 112.39 (t, C_{12}), 137.93 (d, C_5), 140.75 (s, C_3 or C_6 or C_7), 148.10 (s, C_3 or C_6 or C_7), 155.00 (d, C_8), 191.86 (d, C_{13}); MS (EI) m/z 346 (M^+, 100), 317 (48), 289 (100), 233 (58), 217 (39), 214 (37), 197 (38), 129 (59), 91 (59), 77 (100), 75 (100), 57 (50), 43 (59); HRMS m/z exact mass calcd for $C_{21}H_{34}O_2Si$ 346.2328, found 346.2336.

Isomerization of Isovellerol (3) to [1a*R*-(1aβ,3aβ,6aβ,6bβ)]-3a,4,5,6,6a,6b-Hexahydro-2-(hydroxymethyl)-5,5,6b-trimethylcycloprop[*e*]indene-1a(1*H*)-carboxaldehyde (4). A solution of **3** (300 mg, 1.28 mmol) in toluene (10 mL) was heated in a sealed Teflon vessel for 3 h at 170 °C. Usual workup by chromatography (SiO_2, 1:4 EtOAc–heptane) afforded recovered **3** (185 mg, 62%, higher R_f) and **4** (86 mg, 29%, lower R_f) as a syrup with $[\alpha]^{20}_D$ 161° (c 1.0, $CDCl_3$). Because of extensive hemiacetal formation, a detailed interpretation of the spectra of **4** was prohibited: IR (neat) cm^{-1} 3100–3600, 2950, 2880, 1700, 1470, 1450, 1370, 1010, 910; ^{1}H NMR ($CDCl_3$) δ 0.99 (s), 1.06 (s) and 1.07 (s, 6 H, H_3-15, H_3-14), 1.17 (s), 1.26 (s) and 1.33 (s, 3 H, H_3-12), 2.11–0.47 (m, 6 H, H_2-1, H_2-4, H_2-10), 2.27 (ddd, 1 H, $J_{2-1\alpha}$ = 8.5 Hz, $J_{2-1\beta}$ = 8.5 Hz, J_{2-9} = 8.5 Hz, H-2), 2.77 (m, 1 H, H-9), 4.36–4.17 (m, 1 H, H-13), 4.72–4.62 (m, 1 H, H-13), 5.32 (m), 5.41 (m) and 5.70 (d, 1 H, J_{8-9} 4.4 Hz, H-8), 5.26 (s), 5.30 (s) and 9.40 (s, 1 H, H-5); ^{13}C NMR ($CDCl_3$) δ 20.45, 21.83, 22.71 (q, C_{12}), 25.98, 27.89, 28.33, 28.52, 29.47, 29.79, 29.88, 30.45, 30.91 (m, C_{14}, C_{15}, C_4), 34.38 (s, C_{11}), 37.42, 37.61, 37.76, 38.42, 39.19, 39.73 (d, C_2, C_9), 37.81, 38.42, 38.81, 39.27, 41.13 (s, C_3, C_6), 38.93, 47.65, 47.83, 48.38, 49.92, 50.89 (t, C_1, C_{10}), 66.20, 68.83, 69.57 (t, C_{13}), 114.62, 119.27, 128.19 (d, C_8), 134.81, 138.31, 139.74 (s, C_7), 98.45, 102.27, 202.30 (d, C_5); MS (EI) m/z 234 (M^+, 26), 219 (100), 216 (47), 200 (60), 187 (55), 173 (87), 159 (44), 145 (46), 133 (71), 119 (69), 105 (69); HRMS m/z exact mass calcd for $C_{15}H_{22}O_2$ 234.1619, found 234.1621.

[8*S*-(5β,8β,8aβ)]-1,2,3,5,6,7,8,8a-Octahydro-8-hydroxy-2,2-dimethyl-7-methylene-4,5-azulenedicarboxaldehyde (as Hemiacetals, 21). A solution of merulidial (**7**) (100 mg, 0.40 mmol) and triethylamine (18 mg, 0.18 mmol) in toluene (5 mL) was heated for 1.5 h at 170 °C. Usual workup by chromatography (SiO_2, 2:3 EtOAc–heptane) afforded a 5:2 mixture of **7** and **8** (11 mg, 11%, lower R_f) and **21** (39 mg, 39%, higher R_f) as colorless crystals with mp 118 °C: $[\alpha]^{20}_D$ 131° (c 0.20, Et_2O). The hemiacetal **21** exists as a 10:3 ratio of two isomers, differing in the configuration at the C-4 stereocenter. NMR data are given for the major isomer: IR (neat) cm^{-1} 3100–3600, 2950, 2920, 2860, 1660, 1460, 1430, 1370, 1250, 1180, 1100, 1040, 910; ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 3 H, H_3-14 or H_3-15), 1.15 (s, 3 H, H_3-14 or H_2-15), 1.35 (dd, 1 H, J_{10b-9} = $J_{10b-10a}$ = 12 Hz, H_b-10), 1.68 (ddd, 1 H, $J_{10a-10b}$ = 12 Hz, J_{10a-1b} = 1 Hz, J_{10a-9} = 7.8 Hz, H_a-10), 2.36 (dm, 1 H, J_{5b-5a} = 17.4 Hz, H_b-5), 2.51 (dm, 1 H, J_{5a-5b} = 17.4 Hz, H_a-5), 2.68 (dd, 1 H, J_{1b-1a} = 18.6 Hz, J_{1b-9} = 2.4 Hz, H_b-1), 2.77 (dm, 1 H, J_{1a-1b} = 18.6 Hz, H_a-1), 2.88 (d, 1 H, J_{OH-4} = 5.5 Hz, OH), 3.59 (ddd, 1 H, J_{6-4} = 5.4 Hz, J_{6-5a} = J_{6-5b} = 3.5 Hz, H-6), 3.74–3.63 (m, 1 H, H-9), 4.31 (d, 1 H, J_{8-9} = 1 Hz, H-8, 4.76 (m, 1 H, H_b-13), 4.92 (m, 1 H, H_a-13), 5.42 (dd, 1 H, $J_{4-}OH$ = 5.4 Hz, J_{4-6} = 5.4 Hz, H-4), 9.83 (s, 1 H, H-12); ^{13}C NMR ($CDCl_3$) δ 29.19 (q, C_{14} or C_{15}), 29.91 (q, C_{14} or C_{15}), 32.42 (d, C_6), 33.74 (t, C_5), 36.70 (s, C_{11}), 43.30 (t, C_{10}), 43.55 (t, C_1), 54.05 (d, C_9), 77.70 (d, C_8), 95.94 (d, C_4), 111.70 (t, C_{13}), 130.74 (s, C_3), 141.76 (s, C_7), 168.12 (s, C_2), 190.44 (s, C_{12}); MS (EI) m/z 248 (M^+, 44), 230 (60), 219 (22), 215 (51), 208 (78), 205 (29), 202 (63), 201 (57), 187 (67), 173 (100), 159 (62), 145 (32), 136 (37), 131 (48), 117 (57), 105 (51), 95 (75), 91 (75), 77 (46), 59 (32), 57 (51), 41 (83); HRMS m/z exact mass calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1415.

[8*S*-(5ξ,8β,8aβ)]-8-Acetoxy-1,2,3,5,6,7,8,8a-octahydro-2,2-dimethyl-7-methylene-4,5-azulenedicarboxaldehyde (22) and Hydroazulene Lactone 23. A solution of merulidial acetate **9** (37 mg, 0.13 mmol) and triethylamine (11 mg, 0.11 mmol) in toluene (5 mL) was kept for 3 h at 170 °C. After removal of solvents, chromatography of the residue (SiO_2, 1:4 EtOAc–heptane) afforded **22** (5.6 mg, 15%, lower R_f) and **23** (10.0 mg, 34%, higher R_f) as syrups. For **22**: $[\alpha]^{20}_D$ 173° (c 0.56, $CHCl_3$); IR (CCl_4) cm^{-1} 2960, 2920, 2870, 1740, 1670, 1650, 1460, 1370, 1230, 1040, 910; ^{1}H NMR ($CDCl_3$) δ 0.98 (s, 3 H, *Me*), 1.19 (s, 3 H, *Me*), 1.36 (dd, 1 H, $J_{10a-10b}$ = 12.6 Hz, J_{10a-9} = 10.3 Hz, H_a-10), 1.85 (ddd, 1 H, $J_{10a-10b}$ = 12.6 Hz, J_{10b-9} = 7.9, J_{10b-1b} = 2.4 Hz, H_b-10), 2.11 (s, 3 H, CO*Me*), 2.37 (dd, 1 H, J_{5a-5b} = 14.2 Hz, J_{5a-6} = 4.8 Hz, H_a-5), 2.53 (dd, 1 H, J_{1a-1b} = 16.9 Hz, J_{1a-9} = 2.5 Hz, H_a-1), 3.03 (m, 1 H, H-9), 3.10 (dd, 1 H, J_{1b-1a} = 16.6 Hz, J_{1b-10b} = 2.2 Hz, H_b-1), 3.14 (dd, 1 H, J_{5b-5a} = 14.0, J_{5b-6} = 5.9 Hz, H_b-5), 4.20 (dd, 1 H, J_{6-5a} = 5.3 Hz, J_{6-5b} = 5.3 Hz, H-6), 4.98 (s, 1 H, H_a-13), 5.01 (d, 1 H, J_{8-9} = 10.7 Hz, H-8), 5.07 (s, 1 H, H_b-13) 9.54 (s, 1 H, H-12), 9.95 (s, 1 H, H-4); ^{13}C NMR ($CDCl_3$) δ 20.94 (q, CO*Me*), 26.54 (q, *Me*), 28.20 (q, *Me*), 33.44 (t, C_{10}), 37.66 (s, C_{11}), 44.00 (t, C_5 or C_1), 45.48 (t, C_5 or C_1), 47.21 (d, C_4), 49.11 (d, C_9), 75.54 (d, C_8), 112.91 (t, C_{13}), 132.73 (s, C_3), 144.28 (s, C_7), 169.52 (s, C_2), 169.80 (s, COMe), 190.46 (s, C_{12}), 199.21 (s, C_4); MS (EI) m/z 290 (M^+, 5), 248 (14), 230 (47), 215 (55), 202 (100), 197 (48), 187 (79), 173 (100), 159 (75), 145 (39), 131 (39), 117 (39), 105 (42), 95 (35), 84 (28), 79 (16), 69 (16), 55 (13); HRMS m/z exact mass calcd for $C_{17}H_{22}O_4$ 290.1518, found 290.1517.

For **23**: $[\alpha]^{20}_D$ 0° (c 1.0, $CHCl_3$); UV (EtOH) λ_{max} 266 (ϵ 2400), 217 nm (ϵ 23 000); IR (CCl_4) cm^{-1} 3010, 2960, 2920, 2860, 2840, 1765, 1625, 1465, 1450, 1385, 1360, 1330, 1260, 1215, 1060, 1040, 1020; ^{1}H NMR ($CDCl_3$) δ 1.14 (s, 6 H, H_3-14 and H_3-15), 1.97 (s, 3 H, H_3-13), 2.43 (s, 2 H, H_2-1), 2.80 (s, 2 H, H_2-5), 2.84 (s, 2 H, H_2-10), 4.73 (s, 2 H, H_2-4), 5.92 (s, 1 H, H-8); ^{13}C NMR ($CDCl_3$) δ 25.24 (q, C_{13}), 29.27 (q, C_{14} and C_{15}), 32.26 (t, C_5), 37.67 (s, C_{11}), 47.89 (t, C_{10}), 51.32 (t, C_1), 70.45 (t, C_4), 123.89 (s), 124.01 (d, C_8), 128.03 (s), 130.94 (s), 142.74 (s), 148.83 (s), 171.99 (s, C_{12}); MS (EI) m/z 230 (M^+, 100), 215 (74), 197 (15), 186 (43), 171 (29), 141 (38), 128 (49), 115 (54), 103 (13), 91 (32), 84 (28), 77 (28), 63 (18),

51 (20), 39 (43); HRMS m/z exact mass calcd for $C_{15}H_{18}O_2$ 230.1307, found 230.1306.

[12-$^2H_3$]-Isovelleral (24) and [12-$^2H_3$]-2 (25). A mixture of 1 (300 mg, 1.29 mmol), D_2O (1.11 g, 55.4 mmol), and toluene (9 mL) was heated at 200 °C for 1 h. The organic phase was separated, dried over molecular sieves (4A), and concentrated. Chromatography (SiO_2, 1:4 EtOAc–heptane) gave **24** (96.3 mg, 32%) and **25** (82.5 mg, 27%) as white crystals. For **24**: mp 95–97 °C; $[\alpha]^{20}_D$ 237° (c 1.0, CCl_4); IR (CCl_4) as for **1** but with C–D absorption at 2220 cm^{-1} (weak), diminished absorption at 2940 cm^{-1}, and peak at 1080 cm^{-1} shifted to 1100 cm^{-1}; ^1H NMR ($CDCl_3$) as for **1** but not peak at δ 1.12 ppm; ^{13}C NMR ($CDCl_3$) as for **1** but very weak multiplet at δ 18.67 ppm and weakened singlets at δ 34.17 and 34.59 ppm; MS (EI) m/z 235 (M^+, 4.2), 217 ($M^+ - CD_3$, 0.7), 207 (5.8), 189 (5.6), 175 (9.1), 161 (5.6), 147 (11.1), 133 (12.2), 122 (17.6), 105 (28.0), 91 (42.2), 79 (28.9), 69 (28.4), 55 (43.6), 41. (100).

For **25**: mp 67–69 °C $[\alpha]^{20}_D$ −88.3° (c 1.0, CCl_4); IR (CCl_4) as for **2** but with C–D absorption at 2210 cm^{-1} (weak); ^1H NMR ($CDCl_3$) as for **2** but no peak at δ 1.16 ppm; ^{13}C NMR ($CDCl_3$) as for **2** but very weak multiplet at δ 19.77 ppm and weakened singlets at δ 37.30 and 38.37 ppm; MS (EI) m/z 235 (M^+, 4.9), 217 ($M^+ - CD_3$, 1.5), 106 (5.8), 189 (4.9), 175 (7.1), 165 (6.6), 147 (9.3), 133 (13.3), 122 (19.0), 105 (27.9), 91 (39.4), 79 (28.8), 69 (26.1), 55 (46.9), 41 (100).

[1-$^2H_2$,13-$^2H_3$]-Merulidial (26). A mixture of **7** (19 mg, 0.077 mmol), D_2O (0.22 g, 12.2 mmol), and toluene (1.80 mL) was heated at 185 °C for 1.5 h. The organic phase was separated, dried over molecular sieves (4A), and concentrated. The residue was purified by HPLC using LiChrosorb Si 60 (10 μm, mobile phase EtOAc/heptane (25/75), flow rate 1.0 mL/min, detection at 254 nm) affording **21** (0.8 mg, 4%; the deuterium content of this fraction could not be determined), **26** (2.6 mg), and a 1:2 mixture (3.0 mg) of **26** and [1-$^2H_2$, 13-$^2H_3$]-**8**. Although the mixture in the later fraction was not separated further, ^1H NMR indicated deuteration at C_1 and C_{13} of **8**, since the peaks at δ 2.86, 2.60, and 1.28 were greatly diminished.

Relevant data for **26**: ^1H NMR ($CDCl_3$) as for **7**[3] but diminished peaks at δ 2.75, 2.66, and 1.17 ppm; ^{13}C NMR ($CDCl_3$) as for **7** but weakened singlets at δ 164.65, 130.73, and 15.86 ppm. Peaks absent at δ 44.27 and 34.22 ppm; MS (EI) m/z 254 ($M^+ + 1$, 6), 253 (M^+, 26), 252 (38), 235 ($M^+ - CD_3$, 31), 223 (88), 205 (100), 192 (61), 177 (59), 163 (56), 149 (57), 137 (39), 121 (44), 107 (48), 93 (60), 79 (43), 69 (23), 55 (25), 41 (31).

Kinetic Determinations. 0.045 M solutions of **1** and **24** in [$^2H_8$] toluene were introduced in thoroughly cleaned and oven-dried NMR tubes. The samples were degassed and sealed under vacuum. At each of four temperatures duplicate samples were immersed in a thermostatic and stirred oil bath. Temperatures of the oil bath were measured with a Siebert & Kühn scientific mercury thermometer calibrated within ±0.2 °C and were constant to ±0.5 °C as checked with a Chromel-Alumel thermocouple in conjunction with a potentiometer. The samples were withdrawn periodically and cooled rapidly, and the progress of the reaction was monitored by integration of the well-resolved NMR signals from H-5 and H-13. The NMR shifts of the H-5 and H-13 aldehyde shifts in [$^2H_8$]-toluene with $SiMe_4$ as internal standard were, respectively, δ **1** (9.70, 9.17); **2** (9.79, 9.08); **14** (9.20, 9.03); **15** (9.60, 8.98).

The activation parameters were obtained by a least-squares treatment of the experimental data (36 points). The results are given with a 95% confidence interval in Table II.

The measurements of k_2 and k_{-3} were performed by introducing 0.045 M solutions of **1** and **2** in [$^2H_8$]-toluene into washed and oven-dried NMR tubes. *N,O*-Bis(trimethylsilyl)trifluoroacetamide (70 μL, 0.26 mmol) was added to each tube. The solutions were degassed, and the tubes were sealed under vacuum. Duplicate samples were immersed at 407.8 K in the same oil bath as was used for the kinetic experiments described above. The samples were withdrawn periodically and cooled rapidly, and the reaction was monitored by integration of the well-resolved NMR signals from H-5.

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Registry No. **1**, 37841-91-1; **2**, 109956-89-0; **3**, 96910-70-2; **3** (α-hemiacetal), 141315-78-8; **3** (β-hemiacetal), 141315-79-9; **4**, 141315-80-2; **4** (α-hemiacetal), 141315-81-3; **4** (β-hemiacetal), 141315-82-4; **7**, 68053-32-7; **8**, 121843-89-8; [1-$^2H_2$,13-$^2H_2$]-**8**, 141315-85-7; **9**, 108893-54-5; **10**, 121843-90-1; **11**, 2212-99-9; **12**, 69905-56-2; **13**, 131367-57-2; **14**, 131367-58-3; **15**, 131434-67-8; **16**, 141315-83-5; **17**, 131367-60-7; **18**, 131434-69-0; **19**, 141223-42-9; **20**, 141223-43-0; **21** (isomer 1), 141223-44-1; **21** (isomer 2), 141315-84-6; **22**, 141223-45-2; **23**, 141223-46-3; **24**, 131434-68-9; **25**, 131367-59-4; **26**, 141223-47-4.

Supplementary Material Available: ^{13}C and ^1H NMR spectra of **2**, **4**, **14**, **15**, **17**, **18**, and **21–26** (24 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Theopederins A–E, Potent Antitumor Metabolites from a Marine Sponge, *Theonella* sp.[1]

Nobuhiro Fusetani,* Takeo Sugawara, and Shigeki Matsunaga

Laboratory of Marine Biochemistry, Faculty of Agriculture, The University of Tokyo, Bunkyo-ku, Tokyo, Japan

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Theopederins A–E (**1–5**) has been isolated from a marine sponge *Theonella* sp. and their structures established mainly by extensive 2D NMR analyses as well as by comparison with spectral data of mycalamides A and B. Theopederins A–E are highly cytotoxic against P388 murine leukemia cells. Theopederins A and B (**1** and **2**) showed promising antitumor activity.

Marine sponges of the genus *Theonella* have proved to be a rich source of bioactive secondary metabolites possessing novel structural features; e.g., cytotoxic macrolides (swinholide A[2] and bistheonellide A[3]), cyclic peptides (theonellamide F,[4] keramamide A,[5] and theonellapeptolides[6]), and alkenyl pyridines (theonelladins[7]).

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