Hydrolysis and Reversible Isomerization of Humulene Epoxides II and III

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The hydrolysis reactions of humulene epoxide II (3) and humulene epoxide III (4) were studied in aqueous solution at pH 4.0. Twelve compounds from the hydrolysis of humulene epoxide II and 16 from humulene epoxide III were separated and identified. All of the compounds identified from hydrolysis of 3 also were found among the hydrolysis products of 4. A reversible transformation between these two epoxides proceeding through a bicyclic diol (15) as intermediate is responsible for producing the same products. Hydrolysis reactions further yielded diols and a number of different ring systems. The apparent intermediacy of carbocations also led to several elimination reaction products. Among the products identified from these epoxides, six have not been reported before. These are 1,5,8,8-tetramethyl-12-oxa-5-tricyclo[7.2.1.$0^{6,9}$]dodecene (1), 4,8,11,11-tetramethyl-8-tricyclo-[7.2.0.$0^{2,5}$]undecen-4-ol (5), stereoisomers of 2,6,6,9-tetramethyltricyclo[6.3.0.$0^{2,4}$]undecane-5,9-diol (10, 14), 1,5,8,8-tetramethyl-8-bicyclo[8.1.0]undecene-2,9-diol (15), and the stereoisomeric pair 4,8,11,11-tetramethyltricyclo[6.3.0.$0^{2,4}$]undecane-5,9-diol (16).

Introduction

(2*E*,6*E*,9*E*)-3,7,11,11-Tetramethylcycloundeca-2,6,9-triene (α-humulene) is an important biogenetic precursor of a large number of sesquiterpenoids particularly in fungi. It is found also in hops, and when the concentration of this sesquiterpene is high (30–40% of the essential oil) the cultivar is prized among brewers as an aroma hop. Humulene epoxides also are found in hops possibly as a result of biosynthesis but more likely from the post-harvest oxidation of humulene which occurs upon storage for 3–6 months or longer. These epoxides, 1,5,5,8-tetramethyl-12-oxabicyclo[9.1.0]dodeca-3,7-diene (humulene epoxide II) and 3,7,10,10-tetramethyl-12-oxabicyclo[9.1.0]-dodeca-3,7-diene (humulene epoxide III), several humulene diepoxides, and humulene triepoxide have previously been reported from our laboratory.[1]

The acid-catalyzed hydrolysis of humulene epoxide II (3) was previously studied with sulfuric acid in acetone.[2,3] Seven compounds were identified in the product mixture. Tricyclohumuladiol (11), a *vic*-diol (12), and humulenol II (8) were identified by McKervey and co-workers.[2] In addition to these compounds Namikawa and co-workers[3] isolated four other compounds and identified three of them, i.e., the *vic*-diol 13 or stereoisomer of 12, the acetonide of 12 or 13, and compound 17. The acid-catalyzed hydrolysis reaction of humulene epoxide III (4) has not been reported. Reactions of epoxides are significant in bioorganic chemistry and in the biosynthesis of terpenes and sterols.[4] Accordingly, we wish to report our studies on the hydrolysis and apparent interconversion of epoxides 3 and 4 under hydrolytic conditions.

Results and Discussion

Humulene epoxide II (3) was synthesized by epoxidation of (2*E*,6*E*,9*E*)-3,7,11,11-tetramethylcycloundeca-2,6,9-triene (α-humulene) using *m*-chloroperbenzoic acid.[5] In this reaction, the three possible racemic humulene monoepoxides were produced in a ratio of 59(II):15(I):8(III). These epoxides were separated and purified by liquid chromatography. Because the yield of humulene epoxide III (4) was low by this method a more specific reaction was used to produce this compound. α-Humulene was oxidized to a stereoisomeric mixture of humulene triepoxides which were subsequently reduced in a solution of WCl_6/BuLi/THF.[6,7] Humulene epoxide III (4) was isolated in 57%

Chart I

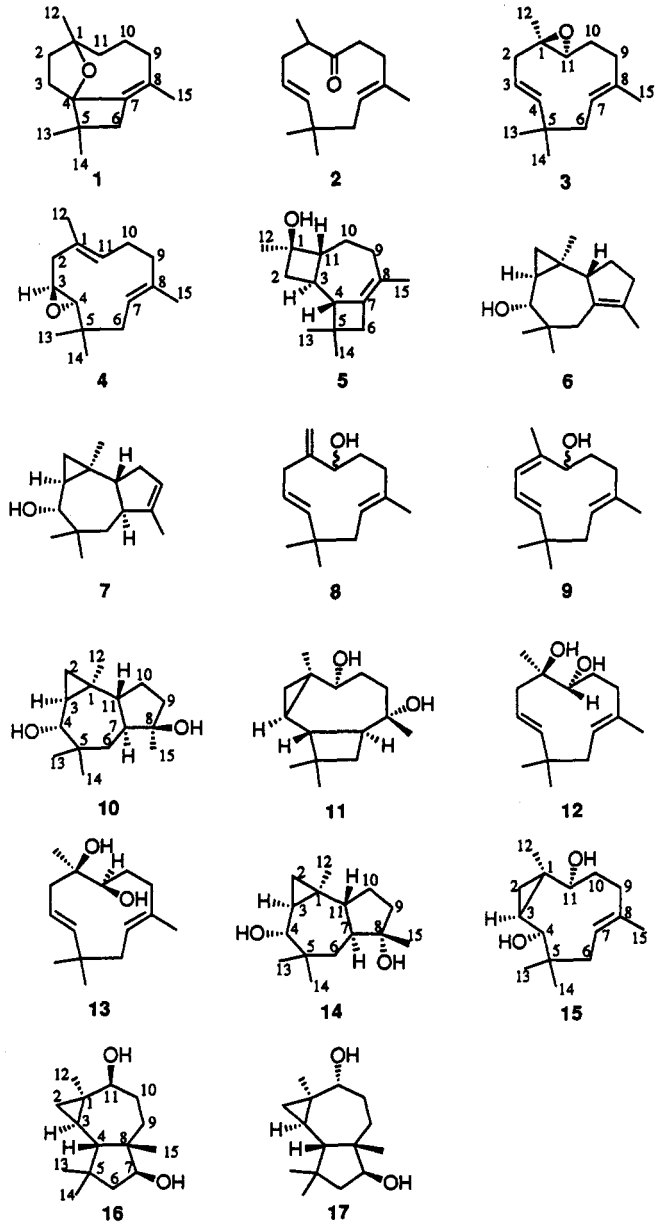

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Table I. Humulene Epoxide II and III Hydrolysates

compd	I_k[a]	A[b]	B[b]	IUPAC Name
1	1771	1.0	0.8	1,5,8,8-tetramethyl-12-oxa-5-tricyclo[7.2.1.0^{6,9}]dodecene
2	2013	0.9	1.1	2,6,6,9-tetramethyl-4,8-cycloundecadien-1-one (humuladienone)
3	2064	4.4	6.7	1,5,5,8-tetramethyl-12-oxabicyclo[9.1.0]dodeca-3,7-diene (humulene epoxide II)
4	2076	1.8	16.2	3,7,10,10-tetramethyl-12-oxabicyclo[9.1.0]dodeca-3,7-diene (humulene epoxide III)
5	2101	2.4	1.2	4,8,11,11-tetramethyl-8-tricyclo[7.2.0.0^{2,5}]undecen-4-ol
6	2165		3.2	2,6,6,9-tetramethyl-8-tricyclo[6.3.0.0^{2,4}]undecen-5-ol
7	2186		1.3	2,6,6,9-tetramethyl-9-tricyclo[6.3.0.0^{2,4}]undecen-5-ol
8	2287	8.6	6.0	6,6,9-trimethyl-2-methylene-4,8-cycloundecadien-1-ol (humulenol II)
9	2401	1.5	1.6	2,6,6,9-tetramethyl-2,4,8-cycloundecatrien-1-ol
10	2655		2.1	2,6,6,9-tetramethyltricyclo[6.3.0.0^{2,4}]undecane-5,9-diol
11	2664	14.0	13.5	4,8,11,11-tetramethyltricyclo[7.2.0.0^{2,4}]undecane-5,8-diol
12	2698	19.0	14.3	(1*RS*,2*SR*)-2,6,6,9-tetramethyl-4,8-cycloundecadiene-1,2-diol
13	2726	6.1	3.5	(1*SR*,2*SR*)-2,6,6,9-tetramethyl-4,8-cycloundecadiene-1,2-diol
14	2733		2.3	2,6,6,9-tetramethyltricyclo[6.3.0.0^{2,4}]undecane-5,9-diol
15	2843	2.5	7.3	1,5,8,8-tetramethyl-8-bicyclo[8.1.0]undecene-2,9-diol
16, 17	2901	21.0	11.5	4,8,11,11-tetramethyltricyclo[6.3.0.0^{2,4}]undecane-5,9-diol

[a] The retention indices were determined under the GC condition: Carbowax, 30 m, 0.32-mm i.d. 0.25-μm film; 140 °C (2 min) to 250 °C at 2 °C/min. [b] A, B: GC peak area percentage for hydrolysates of humulene epoxides II and III, respectively.

yield, and only trace amounts of the other two monoepoxides were produced.

Product Identification. Heating **3** or **4** under reflux for 3 h in buffer solutions (pH 4) consisting of sodium acetate–acetic acid or of potassium dihydrogen phosphate resulted in complex product mixtures. Analysis of these mixtures by gas chromatography (FID) showed more than 30 compounds were present in each case. Twelve of the products produced from **3** and 16 from **4** comprised 83% and 93%, respectively, of the mixture as measured by gas chromatographic peak area (Table I). All of the compounds identified from the hydrolysis of **3** were present in the hydrolysis product mixture of **4**. These were isolated by liquid chromatography and identified. High-resolution mass spectrometry showed that all of the isolated compounds can be assigned to two groups. The first group includes **1–9** with empirical formula $C_{15}H_{24}O$, and the second includes **10–17** with empirical formula $C_{15}H_{26}O_2$.

Upon silylation with (trimethylsilyl)imidazole the GC retention times and mass spectra changed for **5–17** but not for **1–4**. This indicates that **5–17** are alcohols. All of the silyl derivatives showed an intense ion peak with m/z 73 corresponding to the fragment $(CH_3)_3Si^+$. Several compounds, i.e., **5–9**, had molecular ions with m/z 292 corresponding to one hydroxyl group. The molecular ions with m/z 382 for silylated **10–17** indicated that they were diols. In addition, the spectra of **12** and **13** showed a peak at m/z 147 due to the formation of $[(CH_3)_2SiOSi(CH_3)_3]^+$ which indicates that two hydroxyl groups are on adjacent carbon atoms or in close proximity to one another.[8]

The numbers of hydroxyl groups in the compounds were confirmed by deuterium isotope exchange as observed in the ^{1}H-NMR spectra and by their ^{13}C-NMR chemical shifts. The products **5–9** each have one signal and **10–17** have two signals in the 70–90 ppm region of their carbon-13 spectra indicating heteroatom-substituted sp^3 carbons. In this region, **1**, **3**, and **4** also show two resonance lines. However, their IR spectra show they are not alcohols; hence, they must be epoxides or ethers. A resonance line at 216 ppm in **2** is consistent with a carbonyl carbon atom.

The structures of **2–4**, **6–9**, **11–13**, and **17** were determined from their ^{1}H- and ^{13}C-NMR spectra and their ^{1}H^{1}H and ^{1}H^{13}C correlation NMR data. The ^{1}H-NMR data for these compounds match those reported in the literature.[3,9-11]

There are carbon-13 resonances at 71.52 and 90.60 ppm in **1** indicating heteroatom-substituted carbons and two resonances at 133.84 ppm and 133.13 ppm indicating the presence of a double bond in the molecule. The DEPT spectrum indicates the presence of six methylene, four methyl groups, and four carbons that are nonprotonated. These results, together with the connectivities established by ^{1}H^{1}H- and ^{1}H^{13}C-correlation data and the IR data, are consistent with the proposed cyclic ether structure. Compound **5** which is hydroxylated shows two nonprotonated carbon resonances at 128.69 and 133.51 ppm, indicating the presence of a double bond, and connectivities from ^{1}H^{1}H- and ^{1}H^{13}C-correlation data are consistent with the proposed structure.

Two compounds, i.e., **10** and **14**, have almost identical NMR spectra. They contain two hydroxyl groups connected to nonadjacent carbon atoms. These compounds are saturated three-ring systems, one of which is a trisubstituted cyclopropane. The compounds are stereoisomers. The ^{1}H-NMR spectra show that methyl group 15 is shifted significantly further downfield in **10** (1.26 ppm) than in **14** (1.07 ppm). This suggests an axial methyl group and an equatorial hydroxyl group on C-8 of **14** and the opposite configuration for **10**. Because of the opposing effects exerted by the hydroxyl and methyl groups on C-8, the corresponding ^{13}C chemical shifts for the two compounds are similar.

The two hydroxyl groups on **15** are connected to nonadjacent carbons. Carbon-13 resonances at 132.60 and 124.72 ppm are consistent with the presence of a double bond, and high-field proton resonances show the presence of a cyclopropyl ring. Underivatized **16** and **17** could not be separated by gas chromatography, but the silylated derivatives were resolved. The compounds were separated and isolated by semipreparative HPLC. These saturated diols are stereoisomers as shown by the similarities in their NMR spectra. The chemical shifts for C-11 are 78.03 ppm in **16** and 73.91 ppm in **17**. This difference is believed due to the orientation of the hydroxyl groups, i.e., equatorial in **16** and axial in **17**.[12,13]

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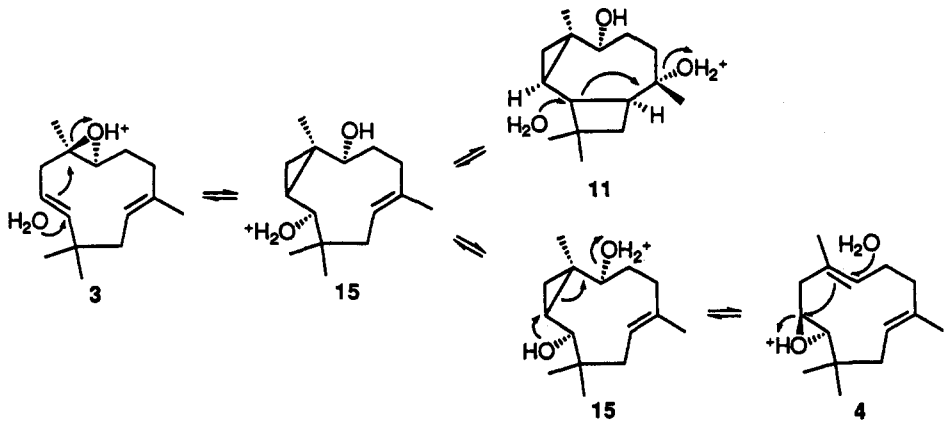
Scheme I

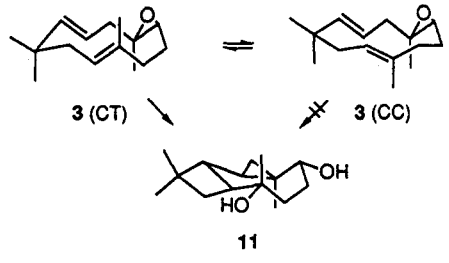


Reaction Mechanisms. Mlotkiewicz and co-workers[14] have studied the boron trifluoride etherate-catalyzed rearrangement of 4 and found 6 and 7 as the major products. Shirahama and co-workers[15,16] treated 4 with boron trifluoride etherate in acetic acid and found 6, 7, the acetates of 8 and 12, as well as a diacetate among the products. The present acid-catalyzed investigations, however, show that the final product mixture of 4 contains a significant amount of 3 and the product mixture from 3 also contains 4 (Table I). This clearly suggests a transformation between 3 and 4 involving equilibrium processes.[17]

Compound 15 was considered to be an intermediate, and indeed, it was noted that when pure 15 was allowed to stand in chloroform solution at room temperature for three months, 3, 4, 8, and 11 were produced with 4 predominating (70%). When pure 15 was refluxed at pH 4 for 30 min under the same conditions as used for the hydrolysis of 3 and 4, the product mixture consisted of only 50% 15. The balance of the product mixture consisted of 3, 4, and 11. These results are consistent with a series of equilibria (Scheme I) in which 15 acts as a common intermediate. After reluxing 15 for 3 h, 2, 5, 8, 9, 13, 16, and 17 also were prominently present. These products apparently arise mainly from the hydrolysis of 3 and 11. Pure 3, 4, and 11 were refluxed separately at pH 4 for 0.5, 1, 2, and 3 h. Gas chromatographic analyses of the product mixture showed that 11 produced mostly 3 and 17 and lesser amounts of 4, 8, 9, 13 and 15. No significant difference in the product ratio from the hydrolysis of 3 and 11 was observed after refluxing for 1 h. An equilibrium apparently also is established between 3 and 11. Hydrolysis of 4 gives mostly 15 in the first 30 min, which in turn produces 3 and 11 and the rest of the products as the reaction proceeds. To verify that the reactions are acid catalyzed, 3, 4, 11, and 15 were individually refluxed at pH 10. After 30 min the starting materials remained practically unchanged.

The acid-catalyzed hydrolysis of 1,5,9,9-tetramethyl-12-oxabicyclo[9.1.0]dodeca-4,7-diene (humulene epoxide I) does not result in the same products as those produced from 3 and 4. This compound also is more resistant to hydrolysis since after 3 h of refluxing a large amount of the starting material remained.

Scheme II



The first step in the hydrolysis reactions of epoxides involves protonation of the oxygen atom. This is normally followed by an S_N2 displacement reaction which in the case of 3 is more likely to occur on the more substituted C-1 position because of the stabilizing effect of the methyl group on the partial positive charge.[18] Just one pair of enantiomeric (1*RS*,2*SR*)-diols can be produced through inversion of configuration[18-20] upon addition of a water molecule to racemic 3. Thus, the racemate 12 amounting to 32% by weight is the major product in the hydrolysis reaction mixture. Interestingly, the corresponding *vic*-diols of humulene epoxide III (4) were not observed among the hydrolysis products.

The diastereomeric (1*SR*,2*SR*)-diol 13 is unlikely to be produced by direct ring opening of the epoxide. Generally speaking, S_N1 reactions for epoxides are unlikely in nucleophilic media, but the formation of a carbocation is possible after nucleophilic attack by the π electrons of double bonds. The alcohols from the hydrolysis of epoxides also could undergo S_N1 reactions with a protonated hydroxyl leaving group. Products 2, 8, 9, and 13 are suggestive of the formation of a carbocation as intermediate with the positive charge on C-1. This carbocation probably was formed by protonation of the hydroxyl group on 11 followed by dehydration and retrocyclization. The formation of 16 and 17 probably involves cyclobutyl carbinyl ring expansion from 11. In the case of 4 nucleophilic attack easily occurs on C-11 and leads to formation of 15. A large number of compounds was formed through internal consecutive S_N2 displacements and ring formation. It is well-known that cyclopropanes are normally more readily formed than cyclobutanes regardless of the degree of substitution of the epoxide ring:[21] nucleophilic attack on

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C-1 of 3 and C-3 of 4 by the π electrons of the double bonds is, therefore, no exception. From a gas chromatographic analysis of the hydrolysis product mixture, it appears that only a small amount of 5 results from nucleophilic attack at C-11 of 3 to form the cyclobutyl ring system.

In the hydrolysis product mixture of 4, a considerable amount of 6, 7, 10, and 14 was formed in addition to the hydrolysis products identified in the product mixture of 3. The structures of 6 and 7 were determined previously by NMR. X-ray analysis of the *p*-bromobenzoate of 6 confirmed the stereochemistry as shown (Chart I).[14] X-ray analysis of the silver nitrate adduct of α-humulene has shown that it has the CT conformation,[22,23] in which the hydrogen on C-11 and the methyl group on C-8 are on the same side of the molecule while the hydrogen atoms on C-7 and C-4 are on opposite sides. Calculations suggested that the CC conformation of humulene also is stable in solution.[24] Although the CT and CC conformations of humulene epoxides II (Scheme II) and III can exist in equilibrium with one another, the stereochemistry of 6 and 11, as shown by X-ray crystal structural analysis,[14,25] indicates that they were most likely produced from the CT conformation of the epoxides. Compounds 6, 7, 10, and 14 probably are formed through a common intermediate, i.e., the carbocation with the positive charge on C-8. Compounds 6 and 7 are the elimination products while 10 and 14 are probably formed by the attack of a water molecule on either side of the carbonium ion. Thus 6, 7, 10, and 14 should have the stereochemistry shown (Chart I). The ring formation of these compounds is probably due to a reaction similar to the one that produced 11 from 3. The 8.7 Hz proton coupling constant indicates that H-3 and H-11 of compound 5 are trans. Therefore, 5 also is likely derived from the CT conformer.

The diacetate of 15 was found to be the main product when 4 was treated with boron trifluoride etherate in acetic anhydride.[15] X-ray analysis showed that the diacetate would logically have arisen from a nucleophilic displacement reaction on the CC conformer of 4. The acetate of 8 could not be produced by action of acetic acid and boron trifluoride etherate on the isolated diacetate of 15.[15,16] The acetate of 8, however, was identified in an acetic acid solution containing boron trifluoride etherate and was proposed to have been formed via an intermediate stereoisomeric diacetate of 15 from the CT conformer, though no other stereoisomers of 15 could be isolated. In the present study 8 was identified as a product of 15. Morever, 11; whose stereochemistry has been established,[25] interconverts with 15. This leads to the conclusion that 15 arises from the CT conformer and has the stereochemistry shown (Chart I).

Experimental Section

^{1}H-NMR spectra were recorded in CD_3OD, $CDCl_3$, or DMSO-d_6 as solvents at 400 MHz. Chemical shifts (ppm) are reported relative to tetramethylsilane. ^{13}C-NMR data were recorded at 100 MHz and are summarized in Table II for the new compounds 1, 5, 10, 14, 15, and 16.

GC/MS analyses were carried out with a 0.32-mm i.d. × 30-m DB-5 fused silica capillary column (J&W Scientific, Inc., Rancho Cordova, CA) for the trimethylsilylimidazole-derivatized samples and a 0.32-mm i.d. × 30-m Supelcowax 10 fused silica capillary column (Supelco, Inc., Bellefonte, PA) for the hydrolysis products of 3 and 4. Helium was used as carrier gas at a flow rate of 25 cm/s. Silylated samples were injected with a split ratio of 1:50. Temperature program: 120 °C (2 min); 120–250 °C at 2 °C/min; the electron energy was 70 eV. CI spectra were obtained in the positive ion mode using ammonia as reagent gas at a pressure of 0.6 Torr.

Table II. Carbon-13 Chemical Shifts δ (ppm) for Compounds 1, 5, 10, 14, 15, 16

carbon	1	5	10	14	15	16
1	71.52	73.43	19.34	19.51	28.45	20.96
2	33.51	42.81	22.62	22.56	17.56	23.14
3	36.34	34.05	29.76	29.73	31.88	20.59
4	90.60	59.77	80.95	81.15	74.76	57.56
5	35.98	32.32	37.96	38.13	39.68	35.34
6	35.49	41.68	42.13	43.53	40.10	47.62
7	133.13	133.51	48.19	48.83	124.72	79.81
8	133.84	128.69	81.07	79.91	132.60	48.37
9	34.44	27.03	41.37	41.8	38.26	40.37
10	23.20	35.02	23.13	22.74	23.20	30.09
11	37.60	58.26	49.12	48.76	82.47	78.03
12	31.73	21.34	19.43	19.55	13.68	12.46
13	25.41	23.62	28.68	28.67	30.06	28.11
14	23.63	30.48	19.05	18.75	18.38	33.95
15	13.90	20.98	25.64	22.27	16.39	18.12

1,5,5,8-Tetramethyl-12-oxabicyclo[9.1.0]dodeca-3,7-diene (3) (Humulene Epoxide II). This compound was prepared as described by Peacock and Deinzer.[5] Humulene monoepoxides were separated from unreacted humulene and humulene diepoxides by liquid chromatography with a 2.5- × 25-cm column filled with silica gel (silica gel 60, Universal Scientific Incorporated, 32–63 μm) that was equilibrated with hexane. The flow rate was 6 mL/min, and 20 mL fractions were collected. The solvents used were 200 mL of hexane and 200 mL of hexane/ethyl acetate (93:7). The three isomers of humulene epoxides were then separated by liquid chromatography with a 2.5- × 25-cm column filled with 10% $AgNO_3$-impregnated silica gel (silica gel 60, Universal Scientific Incorporated, 32–63 μm) that was equilibrated with hexane. The solvent systems used were the following: hexane/ethyl acetate, 250 mL (95:5), 250 mL (90:10), 250 mL (85:15), 250 mL (70:30).

The chromatographic process was monitored by TLC which was developed by CH_2Cl_2 and visualized by I_2 vapor. Epoxide 3 was further purified to 99.7% (GC/FID) by using reversed-phase HPLC with a 250- × 10-mm column (C18, 5 μm) and a solvent mixture consisting of methanol/water (80:20) programmed at a flow rate of 3 mL/min.

3,7,10,10-Tetramethyl-12-oxabicyclo[9.1.0]dodeca-3,7-diene (4) (Humulene Epoxide III). Humulene (4.4 g, 21.6 mmol) in 50 mL of $CHCl_3$ was slowly added to a solution containing 16.5 g of *m*-CPBA (ca. 70%, 64.7 mmol) in 200 mL of $CHCl_3$. The solution was heated at reflux for 30 min and then washed with 5% Na_2CO_3 solution and again with water two times. The solvent was removed by rotary evaporation. The purity of the triepoxides was 99.2% according to GC analysis (yield > 95%).

A solution of WCl_6 (6.3 g, 15.9 mmol) in 100 mL of THF was stirred and cooled at 0 °C. Butyllithium (1.6 M in hexane, 20 mL) was added, and the mixture was warmed slowly to rt. This solution was added slowly to 50 mL of THF containing humulene triepoxides (1 g, 4 mmol). The reaction mixture was stirred for 2 h and then extracted with 100 mL of an aqueous solution of 2 M NaOH solution containing 1.5 M potassium sodium tartrate (72% yield by GC). The solvent was removed by evaporation. The crude product was purified by flash chromatography using a 2.5- × 25-cm silica gel column (silica gel 60, 32–63 m, 8% water) and 5% and 25% CH_2Cl_2 in hexane as solvent. The structure of the product was confirmed by ^{1}H-NMR. The purity was >99% according to GC analysis (0.5 g, 57%).

Hydrolysis of Epoxides 3 and 4. Distilled water buffered at pH 4.0 by 0.02 M NaOAc/HOAc or 0.002 M KH_2PO_4 was added to an ethanol solution of 3 or 4 with vigorous stirring. This mixture containing 0.2–0.4 mg/mL of the epoxide and 3% ethanol was boiled for 3 h under reflux. After being cooled the solution was neutralized and extracted with pentane followed by CH_2Cl_2 or

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diethyl ether three times. The solvent was removed.

The pentane extract of the hydrolysis mixture, containing compounds 1–9, was fractionated by liquid chromatography with a 1.5- × 50-cm silica gel column (silica gel 60, 32–63 μm) at a flow rate of 6 mL/min. Fraction (20 mL) were collected. The solvent system used was 50 mL of hexane, 100 mL of hexane/CH_2Cl_2 (2:1), 200 mL of hexane/CH_2Cl_2 (1:1), 200 mL of hexane/CH_2Cl_2 (1:2), 100 mL of CH_2Cl_2, and 100 mL of CH_2Cl_2/ethyl acetate (1:1). Elution was monitored by TLC which was visualized by I_2 vapor or concentrated H_2SO_4. After combining the fractions into six portions, the compounds were further purified by reversed-phase HPLC with a 250- × 10-mm column (C18, 5 μm) using methanol and methanol/water as solvent.

The CH_2Cl_2 extract containing compounds 11–17 was fractionated by liquid chromatography with a 2.5- × 25-cm silica gel column (silica gel 60, 32–63 μm) at a flow rate of 6 mL/min. Fractions (20 mL) were collected. The solvent systems used were as follows: 100 mL of CH_2Cl_2, 200 mL of CH_2Cl_2/ethyl acetate (2:1), 200 mL of CH_2Cl_2/ethyl acetate (1:1), and 200 mL of ethyl acetate. Further purification of individual compounds was carried out by reversed-phase HPLC (250- × 10-mm column, C18) with a solvent system of methanol/water (70:30) at a flow rate of 3 mL/min. The elution was monitored at 205 nm. Weights of the purified products were obtained in the range of 5–50 mg. Compound **16** is a minor component in the product mixture (ca. 1%). Its separation from **17** by HPLC is very difficult. The purified **16** still contained ca. 30% of **17**. By comparison of the NMR spectra of **16** and pure **17**, the spectra of **16** could be obtained.

The molecular ions in the mass spectra were confirmed by chemical ionization. The purified compounds were then analyzed by HRMS. The molecular mass for compounds 1–9 is 220.1827 (±0.0003), which corresponds to the composition $C_{15}H_{24}O$ (220.182 715), and 238.1933 (±0.0004) for compounds 10–17 corresponding to the composition $C_{15}H_{26}O_2$ (238.193 28).

Silylation of the Hydrolysis Products. The hydrolysis product mixture and the isolated pure compounds were derivatized with *N*-(trimethylsilyl)imidazole/pyridine (1:1) for 30 min at 60 °C. The reaction mixture was then injected directly onto a GC column.

The ^{1}H-NMR and MS data are summarized as follows for new compounds. The proton coupling constants (*J*, Hz) were determined from phase-sensitive COSY spectra. The numbers in the parentheses indicate the proton coupling.

1,5,8,8-Tetramethyl-12-oxa-5-tricyclo[7.2.1.0^{6,9}]dodecene (1). ^{1}H NMR (400 MHz, $CDCl_3$): H-2a, 1.55, dd, 1 H, *J* = 13.9 (2b), 5.6 (3b); H-2b, 1.82, dddd, 1 H, *J* = 14.2 (3b), 13.9 (2a), 6.2 (3a), 2.5 (11a); H-3a, 1.27, dd, 1 H, *J* = 14.2 (3b), 6.2 (2b); H-3b, 1.93, ddd, 1 H, *J* = 14.2 (3a), 14.2 (2b), 5.6 (2a); H-6, 2.17, s, 2 H; H-9a, 1.60, dd, 1 H, *J* = 18.5 (9b), 7.7 (?); H-9b, 2.17, dd, 1 H, *J* = 18.5 (9a), 6.2 (?); H-10a, 2.43, ddd, 1 H, *J* = 14.8 (10b), 7.7 (11a), 2.0 (11b); H-10b, 2.51, m, broad, 1 H, *J* = 14.8 (10a), 7.7 (10a), 6.5 (11b); H-11a, 1.56, ddd, 1 H, *J* = 13.9 (11b), 7.7 (10a), 2.5 (2b); H-11b, 1.70, ddd, 1 H, *J* = 13.9 (11a), 6.5 (10b), 2.0 (10a); H-12, 1.15, s, 3 H; H-13, 0.74, s, 3 H; H-14, 1.12, s, 3 H; H-15, 1.64, s, 3 H. Coupling constant J < 2 Hz: H-2a/H-3a; H-3b/H-14; H-13/H-14; H-10a/H-15; H-10b/H-15. Cross peaks in COSY spectrum give unclear pattern for: H-10a/H-9b; H-10b/H-9b; H-11a/H-10b. EIMS: *m/e* 220 (M^+, 45), 164 (71), 149 (100), 131 (31), 55 (23). CIMS, NH_3: *m/e* 238 ($M + NH_4^+$, 27), 221 ($M + H^+$, 100).

4,8,11,11-Tetramethyl-8-tricyclo[7.2.0.0^{2,5}]undecen-4-ol (5). ^{1}H NMR (400 MHz, $CDCl_3$): H-2a, 1.57, dd, 1 H, *J* = 9.8 (2b), 9.5 (3); H-2b, 2.03, dd, 1 H, *J* = 9.8 (2a), 7.3 (3); H-3, 1.26, dddd, 1 H, *J* = 10.5 (4), 9.5 (2a). 8.7 (11), 7.3 (2b); H-4, 2.41, dd, broad, 1 H, *J* = 10.5 (3), 5.1 (6a); H-6a, 2.12, dd, broad, 1 H, *J* = 14.6 (6b), 5.1 (4); H-6b, 2.24, d, broad, 1 H, *J* = 14.6 (6a); H-9a, 2.05, ddd, 1 H, *J* = 15.3 (9b), 7.3 (10b), 3.3 (10a); H-9b, 2.15, dd, broad, 1 H, *J* = 15.3 (9a), 12.0 (10a); H-10a, 1.21, dddd, 1 H, *J* = 14.6 (10b), 12.7 (11), 12.0 (9b), 3.3 (9a); H-10b, 1.70, dd, 1 H, *J* = 14.6 (10a), 7.3 (9a); H-11, 1.64, dd, 1 H, *J* = 12.7 (10a), 8.7 (3); H-12, 1.25, s, 3 H; H-13, 0.96, s, 3 H; H-14, 1.12, s, 3 H; H-15, 1.50, s, broad, 3 H. Coupling constant *J* < 2 Hz: H-4/H-15, H-6a/H-15, H-6b/H-15; H-10b/H-11; H-9b/H-10b; H-13/H-14; H-6b/H-13. EIMS: *m/e* 220 (M^+, 5), 162 (76), 147 (61), 135 (21), 134 (47), 133 (20), 121 (44), 120 (27), 119 (98), 107 (68), 106 (51), 105 (80), 95 (29), 93 (62), 92 (21), 91 (100), 79 (56), 77 (42), 71 (63), 69 (33), 67 (30), 65 (21), 57 (30), 55 (65), 53 (37). CIMS, NH_3: *m/e* 238 ($M + NH_4^+$, 10), 220 (M^+, 82), 203 (100). EIMS, silylated: *m/e* 292 ($M^+ + (CH_3)_3Si^+ - H^+$, 2), 162 (40), 143 (75), 134 (43), 119 (46), 73 ($(CH_3)_3Si^+$, 100).

2,6,6,9-Tetramethyltricyclo[6.3.0.0^{2,4}]undecane-5,9-diol (10). ^{1}H NMR (400 MHz, $CDCl_3$): H-2a, 0.44, dd, 1 H, *J* = 4.9 (3), 3.6 (2b); H-2b, 0.73, dd, 1 H, *J* = 8.2 (3), 3.6 (2a); H-3, 0.54, ddd, 1 H, *J* = 8.7 (4), 8.2 (2b), 4.9 (2a); H-4, 3.13, d, 1 H, *J* = 8.7 (3); H-6a, 1.19, dd, 1 H, *J* = 14.0 (6b), 11.4 (7); H-6b, 1.45, dd, 1 H, *J* = 14.0 (6a), 5.3 (7); H-7, 1.60, ddd, 1 H, *J* = 11.4 (6a), 9.7 (11), 5.3 (6b); H-9a, 1.58, ddd, 1 H, *J* = 13.7 (9b), 11.2 (10b), 8.8 (10a); H-9b, 1.69, m, 1 H, *J* = 13.7 (9a), 8.8 (10a); H-10a, 1.70, ddd, 1 H, *J* = 12.4 (10b), 8.8 (9), 4.4 (11); H-10b, 1.82, dddd, 1 H, *J* = 12.4 (10a), 11.2 (9a), 10.5 (11), 8.8 (9b); H-11, 1.43, ddd, 1 H, *J* = 10.5 (10b), 9.7 (7), 4.4 (10a); H-12, 0.98, s, 3 H; H-13, 1.01, s, 3 H; H-14, 0.97, s, 3 H; H-15, 1.26, s, 3 H. Coupling constant *J* < 2 Hz: H-12/H-2a, H-12/H-2b, H-12/H-3, H-4/H-2a, H-4/H-13, H-4/H-14. EIMS: *m/e* 220 ($M^+ - H_2O$, 4), 164 (22), 163 (91), 135 (22), 123 (31), 121 (44), 110 (43), 109 (73), 108 (41), 107 (48), 95 (70), 93 (66), 91 (29), 84 (41), 83 (31), 81 (73), 79 (37), 77 (27), 71 (38), 69 (49), 67 (51), 59 (53), 57 (58), 55 (100), 53 (38). CIMS, NH_3: *m/e* 256 ($M + NH_4^+$, 12), 238 (M^+, 100), 221 (25), 203 (90). EIMS, silylated: *m/e* 382 ($M^+ - 2H^+ + 2(CH_3)_3Si^+$, 9), 163 (75), 143 (34), 131 (23), 129 (28), 75 (36), 73 ($(CH_3)_3Si^+$, 100).

2,6,6,9-Tetramethyltricyclo[6.3.0.0^{2,4}]undecane-5,9-diol (14). ^{1}H NMR (400 MHz, $CDCl_3$): H-2a, 0.39, dd, 1 H, *J* = 5.6 (3), 4.5 (2b); H-2b, 0.73, dd, 1 H, *J* = 8.2 (3), 4.5 (2a); H-3, 0.54, ddd, 1 H, *J* = 8.8 (4), 8.2 (2b), 5.6 (2a); H-4, 3.06, d, 1 H, *J* = 8.8 (3); H-6a, 0.97, dd, 1 H, *J* = 14.1 (6b), 13.0 (7); H-6b, 1.53, dd, 1 H, *J* = 14.1 (6a), 3.2 (7); H-7, 1.81, ddd, 1 H, *J* = 13.0 (6a), 10.2 (11), 3.2 (6b); H-9, 1.67, dd, 2 H, *J* = 16.2 (10b), 7.8 (10a); H-10a, 1.52, ddd, 1 H, *J* = 10.2 (11), 7.8 (9), 5.0 (10b); H-10b, 1.73, ddd, 1 H, *J* = 16.2 (9), 5.4 (11), 5.0 (10a); H-11, 1.10, ddd, 1 H, *J* = 10.2 (7), 10.2 (10a), 5.4 (10b); H-12, 19.55 1.04, s, 3 H; H-13, 0.99, s, 3 H; H-14, 0.96, s, 3 H; H-15, 1.07, s, 3 H. Coupling constant J < 2 Hz: H-12/H-2a, H-12/H-2b, H-12/H-3, H-11/H-2a, H-11/H-9, H-4/H-2a, H-4/H-13, H-4/H-14. EIMS: *m/e* 220 ($M^+ - H_2O$, 1), 138 (35), 126 (26), 125 (29), 111 (26), 109 (52), 96 (33), 95 (51), 93 (22), 83 (100), 82 (38), 81 (33), 74 (66), 70 (24), 69 (55), 68 (42), 67 (71), 55 (83), 53 (33). CIMS, NH_3: *m/e* 256 ($M + NH_4^+$, 100), 235 (5), 221 (12). EIMS, silylated: *m/e* 382 ($M^+ - 2H^+ + 2(CH_3)_3Si^+$, 6), 197 (57), 163 (34), 143 (33), 129 (60), 75 (37), 73 ($(CH_3)_3Si^+$, 100).

1,5,8,8-Tetramethyl-8-bicyclo[8.1.0]undecene-2,9-diol (15). ^{1}H NMR (400 MHz, $CDCl_3$): H-2a, 0.42, dd, 1 H, *J* = 5.9 (3), 4.4 (2b); H-2b, 0.63, dd, 1 H, *J* = 10.0 (3), 4.4 (2a); H-3, 1.17, ddd, 1 H, *J* = 10.0 (2b), 7.2 (4), 5.9 (2a); H-4, 2.97, d, 1 H, *J* = 7.2 (3); H-6a, 1.86, dd, 1 H, *J* = 15.0 (6b), 5.3 (7); H-6b, 2.20, dd, 1 H, *J* = 15.0 (6a), 11.7 (7); H-7, 5.26, dd, 1 H, *J* = 11.7 (6b), 5.3 (6a); H-9a, 2.07, ddd, 1 H, *J* = 12.9 (10b), 12.9 (9b), 2.5 (10a); H-9b, 2.16, ddd, 1 H, *J* = 12.9 (9a), 6.3 (10a), 3.9 (10b); H-10a, 1.70, dddd, 1 H, *J* = 13.6 (10b), 6.3 (9b), 2.5 (9a), 2.3 (11); H-10b, 1.93, dddd, 1 H, *J* = 13.6 (10a), 12.9 (9a), 10.1 (11), 3.9 (9b); H-11, 2.81, dd, 1 H, *J* = 10.1 (10b), 2.3 (10a); H-12, 0.98, s, 3 H; H-13, 1.07, s, 3 H; H-14, 1.07, s, 3 H; H-15, 1.66, s, 3 H. Coupling constant *J* < 2 Hz: H-7/H-15; H-6a/H-15; H-6b/H-14; H-6b/H-13; H-4/H-14; H-4/H-13; H-12/H-2b. EIMS: *m/e* 220 ($M^+ - H_2O$, 1), 178 (31), 138 (30), 135 (25), 125 (33), 121 (22), 111 (64), 109 (33), 107 (41), 98 (34), 95 (60), 93 (32), 83 (29), 82 (32), 81 (46), 79 (27), 71 (27), 69 (54), 68 (31), 67 (62), 57 (53), 55 (100), 53 (44). CIMS, NH_3: *m/e* 256 ($M + NH_4^+$, 8), 238 (M^+, 35), 221 (100), 203 (35). EIMS, silylated: *m/e* 382 ($M^+ - 2H^+ + 2(CH_3)_3Si^+$, 5), 157 (60), 156 (40), 143 (25), 75 (30), 73 ($(CH_3)_3Si^+$, 100).

4,8,11,11-Tetramethyltricyclo[6.3.0.0^{2,4}]undecane-5,9-diol (16). ^{1}H NMR (400 MHz, $CDCl_3$): H-2a, 0.38, dd, 1 H, *J* = 4.5 (2b), 4.5 (3); H-2b, 0.76, dd, 1 H, *J* = 8.0 (3), 4.5 (2a); H-3, 0.52, ddd, 1 H, *J* = 11.0 (4), 8.0 (2b), 4.5 (2a); H-4, 0.92, d, 1 H, *J* = 11.0 (3); H-6a, 1.52, dd, 1 H, *J* = 11.1 (7), 11.1 (6b); H-6b, 1.80, dd, 1 H, *J* = 11.1 (6a), 7.4 (7); H-7, 3.58, dd, 1 H, *J* = 11.1 (6a), 7.4 (6b); H-9a, 1.10, ddd, 1 H, *J* = 13.2 (10b), 13.2 (9b), 4.6 (10a); H-9b, 1.75, ddd, 1 H, *J* = 13.2 (a), 6.6 (10a), 5.6 (10b); H-10a, 1.52, ddd, 1 H, *J* = 12.2 (10b), 6.6 (9b), 4.6 (9a); H-10b, 2.00, dddd, 1 H, *J* = 13.2 (9a), 12.2 (10a), 10.9 (11), 5.6 (9b); H-11, 3.30, d, 1 H, *J* = 10.9 (10b); H-12, 0.86, s, 3 H; H-13, 1.06, s, 3 H; H-14, 0.99, s, 3 H; H-15, 1.11 s, 3 H. Coupling constant *J* < 2 Hz: H-11/H-10a. EIMS, silylated: *m/e* 382 ($M^+ - 2H^+ + 2(CH_3)_3Si^+$,

7), 367 (51), 223 (26), 157 (87), 156 (53), 143 (30), 75 (31), 73 ($(CH_3)_3Si^+$, 100).

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Supplementary Material Available: GC graphs of hydrolysis products, ^{13}C and ^1H NMR data of compounds **2-4**, **6-9**, and **11-13**, and ^{13}C and ^1H NMR spectra of compounds **1**, **5**, **10**, and **14-17** (18 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.

Cyclization Reactions of the *o*-Naphthoquinone Diterpene Aethiopinone. A Revision of the Structure of Prionitin[1]

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The 4,5-seco-20(10→5)-*abeo*-abietane derivative aethiopinone (1), a natural *o*-naphthoquinone isolated from some *Salvia* species, was subjected to a series of acid-catalyzed reactions which yielded phenalene derivatives (**2**, **6**, **9**, and **11**) and other cyclization products (**3** and **10**). The 11-nor derivative **3** is formed by an intramolecular [4 + 2] cycloaddition reaction, and a mechanistic pathway for the formation of the phenalene derivatives **6** and **11** is also proposed. These transformations of aethiopinone (1) allowed the partial syntheses of the naturally occurring diterpenes salvipisone (**8**), salvilenone (**9**), and the racemic form of prionitin (**11**), a rearranged abietane diterpenoid previously isolated from the root of *Salvia prionitis*, to which structure **12** had been attributed only on the basis of NMR spectroscopic studies. In the light of the results reported herein, including an X-ray analysis of compound **11**, the structure **12** assigned to prionitin must be changed to **11**.

The roots of various species of sage, *Salvia* spp. (Labiatae), are used throughout the world in folk medicine to treat a wide variety of ailments.[4] The chemical composition of these plant materials has been studied extensively over the last 50 years, and their organic extracts are particularly rich in abietanoids and diterpene quinone pigments. These substances have attracted considerable attention because many of them exhibit significant cytotoxic,[5] antibacterial,[6] antioxidant,[7] antiinflammatory,[8] antineoplastic,[9] and antiplatelet aggregation[10] activities.

Aethiopinone[5a,11] (1, Chart I, 4,5-seco-20(10→5)-*abeo*-abieta-4(18),5(10),6,8,13-pentaene-11,12-dione[12]) is a rearranged diterpenoid easily available from the root of *Salvia aethiopis*.[13] We have focused our attention on the utility of this substance (1) as an expedient starting material for obtaining several biologically active rearranged abietane derivatives previously isolated from the roots of some *Salvia* species. In this paper, we report some acid-catalyzed cyclizations of aethiopinone (1) which allowed the formation of compounds **2**, **3**, and **6-11**. Two of these substances have previously been isolated from the roots of *S. aethiopis*[11b] (compound **8**, salvipisone), *Salvia moorcraftiana*[14a] and *Salvia miltiorrhiza*[14b] (compound **9**,

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(12) The nomenclature and numbering system for all these compounds are based on those in abietane diterpenes. This decision was taken since the substances described herein can be biogenetically generated from an abietane derivative.

(13) Aethiopinone (1) was isolated as the extract.[11b]) constituent of the acetone extract of the root of *Salvia aethiopis* (0.58% on dry plant material, 24.8% of the extract).[11b] This sage is profusely widespread in Southern and South-Eastern Europe and North Africa.

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