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Sesquiterpene Epoxidation: Rearrangement of (+)-Ledene Epoxy Compounds

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Oxidation of (+)-ledene by *m*-chloroperbenzoic acid was carried out to produce two diastereoisomer epoxides along with another sesquiterpene, an allylic alcohol and an epoxy alcohol, rearrangement products of epoxide in acidic medium. Reduction of epoxides yielded several epoxy ring opening flavoring products, including an ether, an enol, and a diol. The determination of the structure of all the compounds was achieved by 2D-NMR experiments.

Keywords: *Sesquiterpene; epoxide; sesquiterpenol; oxidation; isomerization; reduction; flavoring compounds; 2D-NMR; MS*

INTRODUCTION

During the course of syntheses of new olfactory sesquiterpenols (Bombarda *et al.*, 1994), we have observed the formation of some rearrangement products presenting new structural formulas and original odor. We have therefore attempted a new investigation on a commercial sesquiterpene, ledene, which is the dehydration product of ledol (Dolejs *et al.*, 1958; Dolejs and Sorm, 1959; Graham *et al.*, 1960). Ledol is a sesquiterpenol which was first isolated from the essential oil of *Ledum palustre* L. leaves or from *L. columbianum* Piper and *L. groenlandicum* Veder (Cain and Lynn, 1934). During the epoxidation reaction of ledene with *m*-chloroperbenzoic acid, we have observed the formation of a new sesquiterpene isomer, two epoxides, an allylic alcohol, and an epoxy alcohol. From reduction of epoxides by lithium aluminum hydride, we have obtained three new epoxy ring opening products including a diol, an ether, and an enol.

MATERIALS AND METHODS

General Oxidation Procedure. *m*-Chloroperbenzoic acid (MCPBA; Fluka Chemicals, Switzerland, 65% purity) was used as the oxidant. In the different experiments a solution of ledene (Fluka, Chemicals) in methylene chloride was stirred at various temperatures (0 °C to reflux of solvent) during the addition of small aliquots of MCPBA (1–1.3 equiv, with regard to MCPBA purity) in methylene chloride. The reaction mixture was allowed to stand between 0.5 to 144 h. Unreacted MCPBA and byproduct *m*-chlorobenzoic acid were removed by using an aqueous solution containing first 10% sodium sulfite and then 10% sodium bicarbonate. The organic layer was dried over magnesium sulfate and then concentrated under vacuum on a rotavapor.

Reaction is realized with 110 μ L (0.5 mmol) of ledene **1** [(1*S*,2*R*,4*R*,11*R*)-3,3,7,11-tetramethyltricyclo[6.3.0.0^{2,4}]undec-7-ene] and 175 mg (0.65 mmol, 1.3 equiv) of MCPBA (48 h, reflux of methylene chloride). The reaction mixture contained 12% hydrocarbon **4** [(1*S*,2*R*,4*R*,11*R*)-4-isopropenyl-7,11-dimethyltricyclo[4.4.0.0^{1,8}]dec-6-ene], 22% epoxide **3** [(1*S*,2*R*,4*R*,11*R*)-7 β ,8 β -epoxy-3,3,7,11-tetramethyltricyclo[6.3.0.0^{2,4}]undecane], 24% allylic alcohol **5** [(1*S*,2*R*,4*R*,11*R*)-3,3,7,11-tetramethyltricyclo[6.3.0.0^{2,4}]undec-8-en-5 β -ol], and 24% epoxy

alcohol **6** [(1*S*,2*R*,4*R*,11*R*)-8 β ,9 β -epoxy-3,3,7,11-tetramethyltricyclo[6.3.0.0^{2,4}]undecan-8 β -ol].

Synthesis of Allylic Alcohol 5 and of Compound 4. Better yield in allylic alcohol **5** and in compound **4** can be obtained with 1 equiv of peracid. Under these conditions, 220 μ L of ledene react with 260 mg of MCPBA (144 h, ambient temperature) to afford 21% of epoxide **3**, 46% of allylic alcohol **5**, and 26% of compound **4**.

Purification of Epoxide 3 and Allylic Alcohol 5. A mixture containing 25% epoxide and 27% allylic alcohol, 112 mg, is submitted to column chromatography (CC) over silica gel, eluent pentane–diethyl ether (70:30 v/v, 350 mL). We isolated 20 mg of epoxide **3** (94.5% purity GC, *R*_f 0.87) and 10 mg of allylic alcohol **5** (92.5% purity GC, *R*_f 0.54).

Purification of Compound 4. Compound **4** was purified from 40 mg of a mixture containing 51% **4** and 26% epoxide **3**. CC (eluent, pentane 100%) allowed isolation of **4** in tubes 5–9, 22 mg (91% purity GC, *R*_f 0.90).

Purification of Compound 6. Compound **6** was isolated by CC, eluent pentane–diethyl ether (70:30 v/v, 600 mL), and from 233 mg of a mixture containing 21% epoxide **3**, 40% allylic alcohol **5**, and 7% **6**. Tubes 21–25 contained 26 mg of **3**, tubes 45–50 contained 24 mg of **5**, and tubes 54–68 contained 15 mg of **6** (*R*_f 0.52, 91% purity GC).

Synthesis of Epoxide 2. Reaction was realized with 110 μ L (0.5 mmol) of ledene and 175 mg (0.65 mmol, 1.3 equiv) of MCPBA and in biphasic solution (CH₂Cl₂/NaHCO₃, 0.3 N, 70:30, v/v). After 1 h at 0 °C, we obtained a mixture containing 17% epoxide **3** and 76% epoxide **2** [(1*S*,2*R*,4*R*,11*R*)-7 α ,8 α -epoxy-3,3,7,11-tetramethyltricyclo[6.3.0.0^{2,4}]undecane].

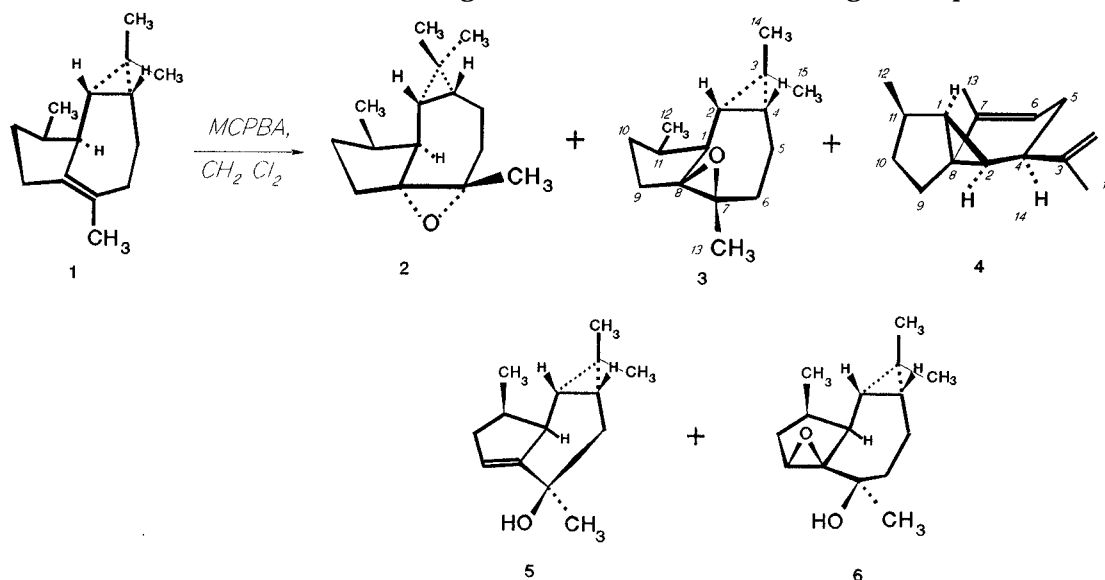
Purification of Compound 2. 157 mg of reaction mixture containing 55% of epoxide **2**, eluent pentane–diethyl ether (90:10 v/v, 300 mL), was submitted to CC. Tubes 31–36 contained 53 mg of epoxide **2** (*R*_f 0.73).

General Reduction Procedure. Sesquiterpene epoxides, 220 mg (1 mmol), were reduced with lithium aluminum hydride (LiAlH₄, Fluka Chemicals, Switzerland), 76 mg (2 equiv), in THF (10 mL) at reflux during a 12 h period. The complex LiAl–alcoholate was hydrolyzed with 10% sulfuric acid and reduction products were isolated by diethyl ether extraction.

Reduction reaction using lithium triethyl borohydride (Et₃BHLi, Aldrich Chemical Company Inc.) was achieved by using the method of Brown *et al.* (1980). The reaction was carried out under helium atmosphere. Sesquiterpene epoxides, 220 mg (1 mmol) in 3 mL of tetrahydrofuran (THF) were added with a syringe to a solution containing 2 mL (2 mmol, 2 equiv) of a 1 mol L⁻¹ solution of LiEt₃BH in 1 mL of THF. The mixture was vigorously stirred at room temperature. After 12 h, the reaction mixture was hydrolyzed with 1 mL of water.

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Scheme 1. Oxidation Reaction of Ledene 1 Using MCPBA and Carbon Numbering of Compounds 3 and 4

The triethylborane formed was oxidized with 1 mL of 30% hydrogen peroxide. The aqueous phase was extracted with 2×5 mL diethyl ether. After volatile material evaporation under vacuum, the crude material was analyzed by GC and then analyzed by NMR and GC-MS.

Reduction Reaction of Epoxide 3. Reduction reaction of epoxide **3**, 26 mg (0.118 mmol), with LiAlH_4 , 9 mg (0.236 mmol), lead to diol **9** with 63% yield. Purification by CC, eluent pentane–diethyl ether (60:40 v/v, 100 mL), allowed isolation, from 30 mg of reaction mixture, of diol **9** [(1*S*,2*R*,4*R*,11*R*)-3,3,7,11-tetramethyltricyclo[6.3.0.0^{2,4}]undecan-7 α ,8 β -diol] in tubes 16–21, 12 mg (91% purity GC, R_f 0.60).

Reduction Reaction of Epoxide 2. Epoxide **2**, 17 mg (0.08 mmol), was reduced by LiAlH_4 (6 mg, 0.16 mmol). Compounds **7** [(1*S*,2*R*,4*R*,11*R*)-4-(1-hydroxy-1-methylethyl)-7,11-dimethyltricyclo[4.4.0.0^{1,8}]dec-6-ene] and **8** are formed in 29% and 33% yield, respectively. Purification by CC, eluent pentane–diethyl ether (70:30 v/v, 200 mL), allowed isolation, from 29 mg of a reaction mixture, of compound **7** in tubes 6 and 7, 8 mg (99% purity GC, R_f 0.87), and compound **8** [5,9,11,11-tetramethyl-12-oxatricyclo[6.3.1.0^{1,2}]dodec-5-ene] in tubes 11–15, 10 mg (99% purity GC, R_f 0.48).

Gas Chromatography (GC) and Gas Chromatography–Mass Spectrometry (GC-MS). A Delsi 300 gas chromatograph equipped with a flame ionization detector (FID) was used for compound separations with a fused silica capillary column (0.32 mm i.d.) coated with Carbowax 20 M (25 m; phase thickness, 0.20 μm ; column temperature, 170 $^\circ\text{C}$ or 60–220 $^\circ\text{C}$, 4 $^\circ\text{C min}^{-1}$). Detector and inlet temperatures were 250 $^\circ\text{C}$. Helium was used as carrier gas at an inner pressure of 0.4 bar. The injections averaged 1 μL of a 2% solution of crude mixtures in pentane. Combined GC-MS was recorded on a Delsi gas chromatograph linked to a Ribermag R-10–10C mass spectrometer equipped with a quadrupole mass analyzer (15.6 mm (i.d.) \times 350 mm, 10^{-6} mmHg) and coupled with a Sidar data computer. The GC column was a 0.32 mm (i.d.) \times 25 m fused capillary column coated with Wax 51 (0.20- μm phase thickness). The column temperature was 150–220 $^\circ\text{C}$, 3 $^\circ\text{C min}^{-1}$; carrier gas, helium; ion source, 220 $^\circ\text{C}$; ionizing voltage, 70 eV.

Thin Layer Chromatography. Analytical TLC was performed on precoated plates (5 \times 10 cm, silica gel 60 F₂₅₄, 0.25 mm, Merck). Spots were visualized by examination under ultraviolet light and/or sulfuric acid spray reagent (5% solution of sulfuric acid in diethyl ether) followed by brief heating.

Nuclear Magnetic Resonance Spectroscopy. All spectra were recorded on a Bruker AMX-400 spectrometer. The NMR spectra were measured as solutions in chloroform-*d* in 5-mm-o.d. tubes for ^{13}C and ^1H . Tetramethylsilane was used as internal standard in both measurements. Proton–proton coupling constants were extracted from high-field resolution-

Table 1. Ledene Oxidation Conditions and Yields of Products^a

entry	1:MCPBA ^b	temp ($^\circ\text{C}$)	time (h)	composition, % ^c					
				2	3	4	5	6	ni ^d
a	1:1.3	0	0.5	73	20	0	5	nd ^e	2
b	1:1 ^f	0	1	76	17	0	2	nd	5
c	1:1.3	reflux ^g	48	nd	22	12	24	24	18
d	1:1	reflux	48	nd	21	24	40	7	8
e	1:1.3	25	144	nd	25	17	27	13	18
f	1:1	25	144	nd	21	26	46	2.5	4.5

^a For compounds identification, see Scheme 1. ^b Mole ratio, with regard to MCPBA purity. ^c Relative percentage obtained by GC on a Carbowax 20M column. ^d Not identified. ^e Not detected. ^f Biphasic experiment, methylene chloride–sodium bicarbonate (10%) (70:30 v/v). ^g Reflux of methylene chloride (38 $^\circ\text{C}$).

enhanced ^1H spectra by using the Gaussian multiplication technique (Ferridge and Lindon, 1978). Standard Bruker pulse sequences were used for homonuclear and heteronuclear correlation experiments. For other experimental details, see Faure *et al.* (1991).

RESULTS AND DISCUSSION

Oxidation Reaction. The reaction of ledene **1** with *m*-chloroperbenzoic acid (MCPBA) affords a mixture of a hydrocarbon **4**, two epoxides endo **2** and exo **3**, an allylic alcohol **5**, and an epoxy alcohol **6** (Scheme 1).

Epoxide endo **2** was obtained in good yield (73–76%) when the reaction was carried out at low temperature (Table 1, entry a). Epoxide **3**, stereoisomer of **2**, was obtained in a lower yield (17–20%). Yield of allylic alcohol **5**, the rearrangement product of epoxide **3**, increased when reaction temperature raised from ambient to reflux of solvent (entries d and f). The higher yields for hydrocarbon **4** (24–26%) were obtained at ambient temperature or reflux of methylene chloride (entries d and f). When we worked with an excess of MCPBA, epoxy alcohol **6** was produced, resulting from the oxidation of allylic alcohol **5** (entries c and e). At ambient temperature, we observed, first, formation of compounds **2**, **3**, **5**, and **6**. But yield of **2** decreased when the reaction proceeded and, simultaneously, yield of **4** increased. This fact showed that epoxide **2** was the kinetic product and epoxidation occurs preferentially at the α -face of the C₇–C₈ double bond of the olefin, which was less hindered.

Table 2. Retention Indices and Mass Spectra of Oxidation–Reduction Products of Ledene

compd ^a	I _R ^b	mass spectral data ^c
2	1684	M ⁺ 220, 43 (100), 41 (66.9), 55 (36.4), 107 (26.2), 39 (22.9), 93 (20.0), 29 (19.3), 53 (19.2), 69 (19.1), 81 (18.0), 67 (17.1), 79 (16.3), 123 (15.9), 95 (15.5), 91 (15.4), 27 (14.6)
3	1670	M ⁺ 220, 41 (100), 55 (47.9), 69 (34.9), 109 (29.0), 39 (28.9), 43 (25.8), 29 (25.7), 81 (25.5), 122 (24.3), 135 (23.2), 53 (22.1), 67 (21.1), 121 (20.0), 93 (19.8), 79 (19.6), 27 (19.2)
5	1887	M ⁺ 220, 43 (100), 41 (40.8), 159 (33.6), 131 (21.8), 145 (20.5), 105 (20.2), 125 (18.3), 55 (18.1), 202 (16.8), 91 (16.4), 39 (13.7), 117 (13.4), 138 (13.0), 133 (12.6), 95 (12.2), 220 (12.0)
7	1947	M ⁺ 220, 105 (100.0), 59 (48.7), 159 (28.3), 41 (26.4), 43 (25.3), 91 (25.0), 106 (22.9), 147 (17.3), 119 (15.8)
8	1706	M ⁺ 220, 220 (100), 105 (66.8), 41 (49.1), 91 (44.5), 43 (41.1), 107 (37.1), 147 (33.4), 93 (31.1), 135 (26.2), 205 (26.1), 162 (25.7), 150 (25.1), 221 (18.2), 106 (16.8), 79 (16.7), 159 (15.8), 29 (14.8), 55 (14.4), 133 (14.0), 39 (13.5), 120 (13.1)
9	2150	M ⁺ 238, 43 (100), 41 (45.0), 83 (31.8), 96 (30.7), 109 (27.6), 55 (26.7), 81 (22.5), 69 (21.6), 107 (20.6), 95 (20.1), 112 (19.1), 111 (18.2), 97 (17.8), 125 (17.0), 93 (14.6), 177 (14.4), 82 (13.0), 29 (12.6), 67 (12.4), 121 (12.4), 165 (11.8), 123 (10.0), 122 (10.0), 220 (3.6)

^a See Figure 1 for structure formula. ^b Determined on a Carbowax 20 M silica capillary column. ^c *m/z* (relative intensity).

Table 3. ¹H and ¹³C NMR Chemical Shifts of Epoxides **2 and **3****

compound							
2				3			
δ ¹³ C ^a	group ^b	assignment ^c	δ ¹ H ^a	δ ¹³ C ^a	group ^b	assignment ^c	δ ¹ H ^a
79.08	C	C-7		73.72	C	C-7	
63.04	C	C-8		60.77	C	C-8	
44.74	CH	C-1	1.78	41.76	CH	C-1	2.01
36.28	CH	C-11	2.25	36.64	CH	C-11	2.14
35.86	CH ₂	C-6	2.13(β) and 1.81(α)	33.11	CH ₂	C-6	2.02(α) and 1.80(β)
31.91	CH ₂	C-10	1.78(α) and 1.34(β)	31.31	CH ₂	C-10	1.63(β) and 1.52(α)
31.30	CH ₂	C-9	2.03(β) and 1.58(α)	30.17	CH ₂	C-9	1.97(α) and 1.64(β)
28.41	CH ₃	C-14	0.96	28.69	CH ₃	C-14	1.00
27.00	CH	C-4	0.50	24.96	CH ₃	C-13	1.21
24.70	CH ₃	C-13	1.21	24.30	CH	C-4	0.53
24.11	CH	C-2	0.45	22.26	CH	C-2	0.45
19.44	CH ₂	C-5	1.44(α) and 0.97(β)	21.95	CH ₂	C-5	1.61(α) and 1.26(β)
18.08	C	C-3		19.45	C	C-3	
15.48	CH ₃	C-15	0.93	15.87	CH ₃	C-12	0.98
15.36	CH ₃	C-12	0.95	15.34	CH ₃	C-15	0.97

^a In ppm with regard to TMS. ^b Determined from DEPT analyses. ^c Determined from 2D-NMR experiments. For carbon numbering, see Scheme 1.

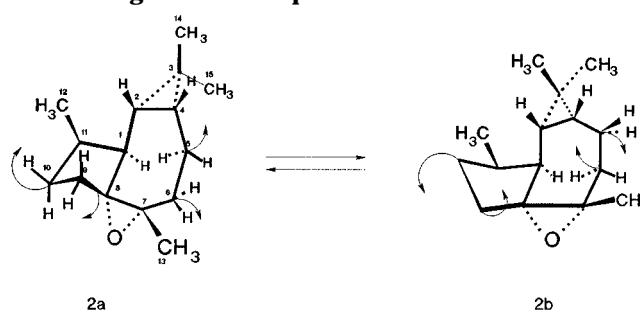
Table 4. Coupling Constants^a of Compounds **2, **3**, and **6–9****

pairs ^b	compounds					
	2	3	6	7	8	9
1–2	10.1	10.1	9.5	4.3	8.0	11.2
1–10					11.4	
1–11	7.0	7.0	6.0 ^c	4.3		
2–3α					13.1	
2–3β					5.1	
2–4	9.1	9.4	9.5	2.0		8.9
4–5α	4.2	4.6	11.6			11.2
4–5β	10.1	11.8	5.6			6.2
5α–5β	14.4		13.5			14.8
5α–6α	3.4	3.8	<1.5			1.2
5α–6β	4.0	3.5	13.5			12.6
5β–6α	13.4	13.8	6.0			
5β–6β	2.8	3.5	<1.5			
6α–6β	15.4	–15.3	13.5			
9α–9β	14.3					
9α–10α	6.0	7.0			4.7	
9α–10β	12.2					
9β–10α	<0.8	2.2				
9β–10β	8.6					
9α–15					7.0	
10α–10β	12.2	–12.5	12.8			
10α–11	6.8	7.0	9.0			
10β–11	12.2					
11–12	6.8	6.9	6.5			

^a *J* in hertz.

Structures, Configurations, and Conformations.

The structures of compounds **2–6** and their ¹H and ¹³C NMR spectral parameters were deduced from concerted application of homonuclear and both direct and long-rang heteronuclear chemical shift correlation experi-

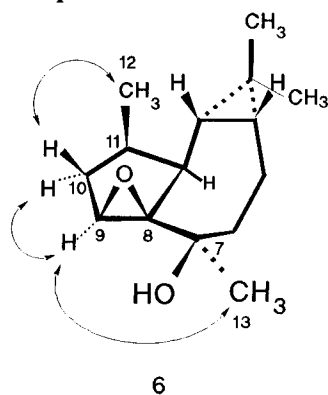
Scheme 2. Conformational Equilibrium and Carbon Numbering of Ledene Epoxide **2**

ments. First, the establishment of proton connectivities was deduced from the COSY spectrum (Aue *et al.*, 1976; Nagayama *et al.*, 1980). Then, one-bond proton–carbon chemical shift correlations were achieved by using proton-detected C,H-correlation experiments (HMQC sequence) (Bax and Subramanian, 1986), while assignments of the CH_{*n*} groups were obtained from analysis of the long-range correlation responses over two or three bonds (²*J* or ³*J* couplings) by using the HMBC techniques (Bax and Summers, 1986). The ¹H and ¹³C chemical shifts of **2** and **3** are given in Table 3 and the ¹H–¹H coupling constants in Table 4. The retention time and mass spectral data are given in Table 2. The endo stereochemistry for epoxide **2** was fully supported by a COSY-correlation peak observed between H-6α and CH₃-13 (1.81 and 1.21 ppm respectively), indicative of a trans diaxial disposition of the methyl group and proton (Platzer *et al.*, 1987). We confirmed (*vide infra*)

Table 5. Coupling Constant Values and Comparison of Dihedral Angle Values Obtained from Karplus Curve with Those Obtained by Molecular Modelization

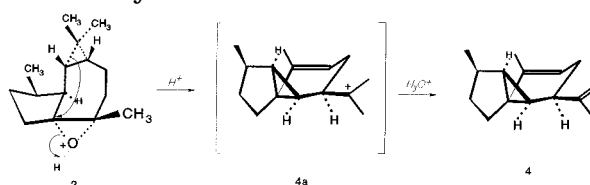
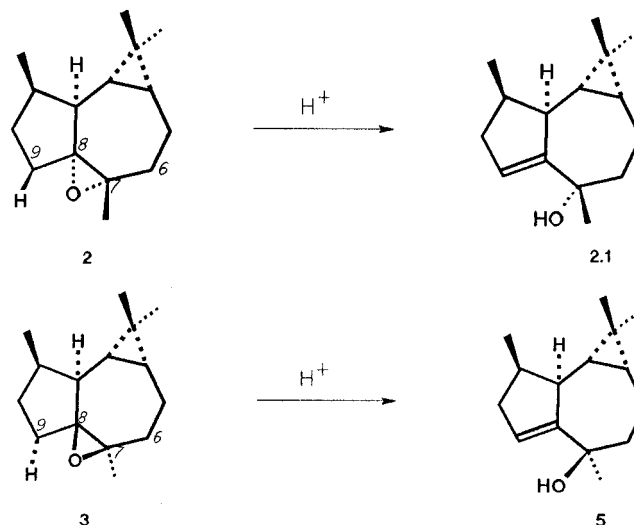
H-H	3J , ^a Hz	θ , deg		
		Karplus ^b	Alchemy ^c	
			2a	2b
5 α -6 β	4.0	40	170	49.5
5 β -6 α	13.4	180	64	180
9 α -10 β	12.2	180	83	170
9 β -10 α	<0.8	90	161	95

^a Coupling constant from NMR ^1H spectrum. ^b Determined from Karplus curve and from experimental coupling constant value obtained by NMR spectra. ^c Obtained from Alchemy II program.

Scheme 3. Selected Through-Space Interaction Pathways Deduced from the Phase-Sensitive NOESY Spectrum of Compound 6

that CH_3 -13 is in a β position and, consequently, the oxirane ring is endo. In fact, CH_3 -13 in epoxide **3** is in an α position and, consequently, the oxirane ring is exo (Scheme 1). The *trans* antiparallel geometry between the proton H-6 α and the CH_3 -13 methyl group in epoxide **2** has been nicely confirmed by a conformation study, carried out by the Alchemy II program (Evans and Sutherland, 1988). Two conformers, **2a** and **2b**, have been optimized (Scheme 2).

Examination of the ^1H NMR data, particularly the coupling constants $^3J = 13.4$, 12.2, and 0.8 Hz, for coupling between H-5 β and H-6 α , H-9 α and H-10 β , and H-9 β and H-10 α , respectively, indicate that conformer **2b** prevails. In fact, the Karplus curve (Günther, 1993) indicates that, for an angle of 180° , $^3J = 9$ Hz, for an angle of 50° , $^3J = 3$ Hz, and, for an angle of 95° , 3J is

Scheme 4. Synthesis Mechanism of 4**Scheme 5. Allylic Alcohol Isomers from Ledene Epoxides 2 and 3**

near 0 Hz. The values obtained, 13.4, 12.2, 4.0, and 0.8 Hz, are in agreement with structure **2b**. The Alchemy program gives 180° , 170° , 49.5° , and 95° , respectively, for dihedral angle values (Table 5). For conformer **2b**, we found 176° for the H(6 α)-C(6)-C(7)-C(13) dihedral angle value, which is in agreement with a *trans* antiparallel geometry between H-6 α and methyl-13.

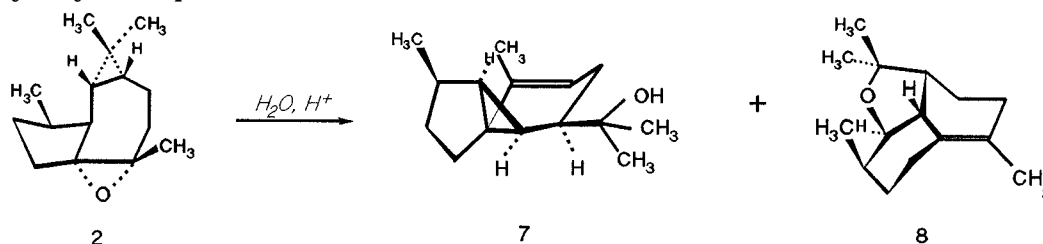
The β -configuration of the oxirane ring and the hydroxy group in compound **6** (Scheme 3) was deduced from the phase-sensitive NOESY spectrum (Bodenhausen et al., 1984). The ^1H and ^{13}C chemical shifts are given in Table 6. Thus, correlation peak between CH_3 -12 (0.89 ppm) and H-10 (1.33 ppm) differentiates H-10 β from H-10 α (1.94 ppm). A correlation peak between H-10 α and H-9 of the oxirane ring was in good agreement with the β position of the epoxide. Finally, the correlation peak between CH_3 -13 and H-9 α indicates that hydroxy group is β (Scheme 3).

Table 6. ^1H and ^{13}C NMR Chemical Shifts of Epoxy Alcohol 6 and Alcohol 9

compound				compound			
6				9			
δ $^{13}\text{C}^a$	group ^b	assignment ^c	δ $^1\text{H}^a$	δ $^{13}\text{C}^a$	group ^b	assignment ^c	δ $^1\text{H}^a$
73.57	C	C-8		87.70	C	C-8	
73.10	C	C-7		75.02	C	C-7	
64.44	CH	C-9	3.50	40.58	CH	C-1	2.11
40.31	CH_2	C-6	1.98(α) and 1.59(β)	37.81	CH_2	C-6	1.83(β) and 1.43(α)
39.11	CH	C-1	2.05	35.17	CH	C-11	2.12
33.71	CH_2	C-10	1.94(β) and 1.33(α)	33.69	CH_2	C-9	1.81(β) and 1.62(α)
30.14	CH	C-11	2.01	33.07	CH_2	C-10	1.73(α) and 1.44(β)
29.64	CH	C-4	0.64	28.96	CH_3	C-14	1.03
28.47	CH_3	C-14	1.01	27.10	CH_3	C-13	1.24
27.45	CH_3	C-13	1.08	26.68	CH	C-4	0.66
22.18	CH	C-2	0.04	21.78	CH	C-2	0.44
20.00	C	C-3		20.45	C	C-3	
18.42	CH_2	C-5	1.69(β) and 1.45(α)	19.18	CH_2	C-5	1.65(β) and 1.38(α)
16.01	CH_3	C-15	1.00	18.02	CH_3	C-12	0.97
14.02	CH_3	C-12	0.89	15.81	CH_3	C-15	1.04

^a In ppm with regard to TMS. ^b Determined from DEPT analysis. ^c Determined from NMR 2D analyses. For carbon numbering, see Schemes 1 and 9.

Scheme 6. Hydrolysis of Epoxide 2

Table 7. ^{13}C NMR Signals of Compound 4

δ $^{13}\text{C}^a$	group ^b	assignment
150.46	C	C-3
137.24	C	C-7
116.99	CH	C-6
109.57	CH_2	C-15
38.77	CH	C-4
34.62	CH	C-11
33.21	CH	C-1
31.05	C	C-8
29.80	CH_2	C-9
29.80	CH_2	C-10
27.63	CH_2	C-5
23.76	CH	C-2
21.58	CH_3	C-13
20.78	CH_3	C-14
18.04	CH_3	C-12

^a In ppm with regard to TMS. ^b Determined from DEPT analysis. For carbon numbering, see Scheme 1.

Epoxy alcohol **6** is an oxidation product of allylic alcohol **5**. The *syn* relationship between the oxirane ring and the hydroxy group in **6** is in agreement with the generalization proposed by Henbest and Wilson (1957), where they conclude that epoxidation of allylic alcohol proceeds in the direction from the *syn*-directing effect of the hydroxyl group. The β -configuration of the hydroxy group in alcohol **5** was supported by the consideration of the stereochemistry of **6**.

Formation of compound **4** involves opening of cyclopropane and oxirane rings. The ^{13}C chemical shifts are given in Table 7. Treatment of epoxide **2** in an acidic medium favors oxirane ring opening to form carbocation **4a**, which led to hydrocarbon **4** by dehydration (Scheme 4).

We note that only endo epoxide **2** can produce hydrocarbon **4**. When reactions were carried out at 25 °C or at reflux of methylene chloride, **2** was not detected

(Table 1, entries c–f). At 0 °C, sesquiterpene **4** was not obtained and the yield of **2** was about 75%. In fact, in the epoxide **2** structure, cyclopropane and oxirane rings present a *trans* antiparallel geometry, which is in agreement with the mechanism involved. In epoxide **3**, cyclopropane and oxirane rings are quasi-perpendicular.

Isomerization of Epoxides 2 and 3 to Allylic Alcohols. In acidic medium, epoxides can yield products of rearrangement and ring opening of the starting epoxy compounds. By proton *anti* elimination, an allylic alcohol can be formed (Cabrera *et al.*, 1988). In this work, we have obtained allylic alcohol **5** with a β -hydroxy group. This compound could be obtained from epoxides **2** or **3** (Scheme 5).

From epoxide **2**, only allylic alcohol **2.1** could be formed by the rearrangement of proton H-9 β , *anti* to the epoxide (Scheme 5). From epoxide **3**, the rearrangement of the *anti* proton H-9 α produced allylic alcohol **5**. We concluded that allylic alcohol **5** was formed from β epoxide **3**.

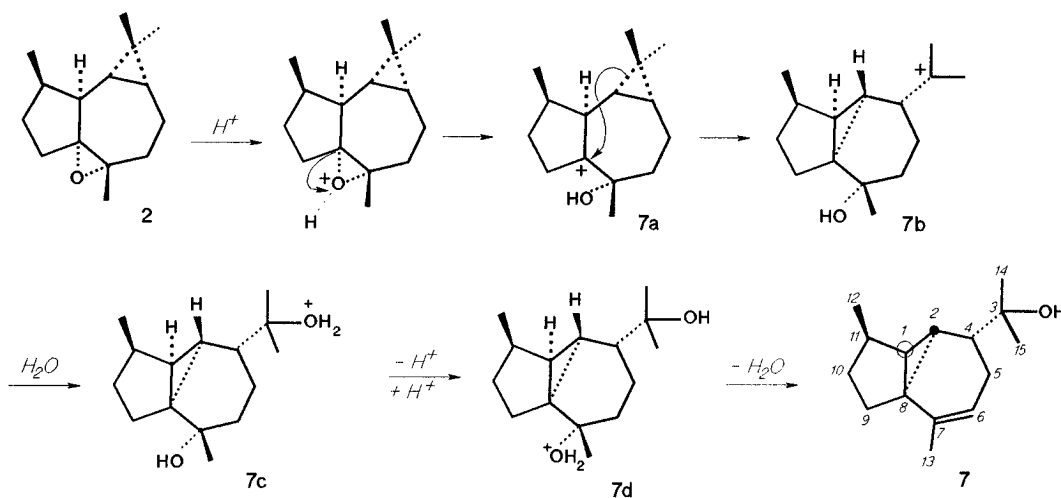
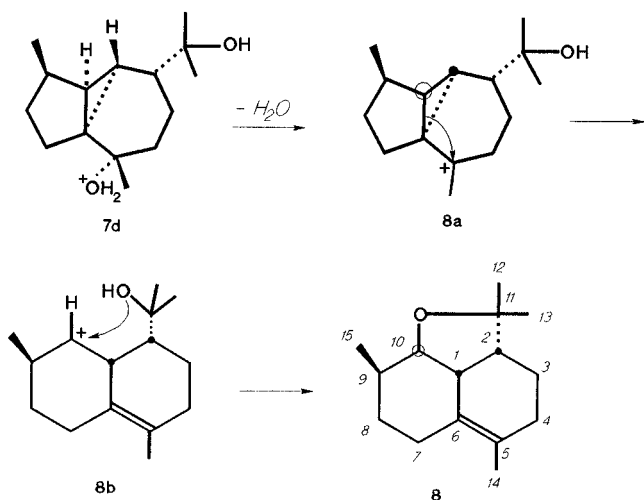
Reduction Reactions. We study then reduction reaction of epoxides **2** and **3**. Lithium aluminum hydride (LiAlH_4), commonly used for reduction of sesquiterpene epoxides (aromadendrene, alloaromadendrene, or δ -cadinene epoxides) (Tressl *et al.*, 1983), arrested our attention. Reduction of α -epoxide **2** with LiAlH_4 afforded alcohol **7** and ether **8** in 29 and 42.5% yield, respectively (Scheme 6). The ^1H and ^{13}C chemical shifts are given in Table 8 and the retention time and mass spectral data in Table 2.

These compounds are not reduction products. They are formed during acidic hydrolysis of the reaction mixture. When reduction is attempted with lithium triethylborohydride (LiEt_3BH), the epoxide is not reduced and we do not observed formation of **7** or **8**, since

Table 8. ^1H and ^{13}C NMR Chemical Shifts of Dienol 7 and Ether 8

compound							
7				8			
δ $^{13}\text{C}^a$	group ^b	assignment ^c	δ $^1\text{H}^a$	δ $^{13}\text{C}^a$	group ^b	assignment ^c	δ $^1\text{H}^a$
136.69	C	C7		130.16	C	C6 ^d	
117.17	CH	C6	5.23	123.69	C	C5 ^d	
73.72	C	C3		82.96	CH	C10	3.53
41.72	CH	C4	1.69	82.60	C	C11	
34.48	CH	C11	2.27	45.29	CH	C2	1.91
33.99	CH	C1	1.48	41.53	CH	C1	2.27
30.64	C	C8		31.84	CH_2	C4	2.02 and 1.59
29.83	CH_2	C9	2.03 and 1.74	31.57	CH_2	C8	1.62 and 1.43
29.83	CH_2	C10	1.65 and 0.87	31.43	CH_3	C12	1.25
28.05	CH_3	C15	1.25	31.21	CH	C9	2.28
27.38	CH_3	C14	1.24	23.89	CH_3	C13	1.20
23.04	CH_2	C5	1.95 and 1.53	23.71	CH_2	C7	2.29 and 1.82
21.44	CH_3	C13	1.81	22.84	CH_2	C3	1.56(α) and 1.45(β)
20.13	CH	C2	1.16	18.15	CH_3	C14	1.59
18.40	CH_3	C12	1.00	10.40	CH_3	C15	0.99

^a In ppm with regard to TMS. ^b Determined from DEPT analyses. ^c Determined from NMR 2D analyses. ^d Assignments could be reversed. For carbon numbering, see Schemes 7 and 8.

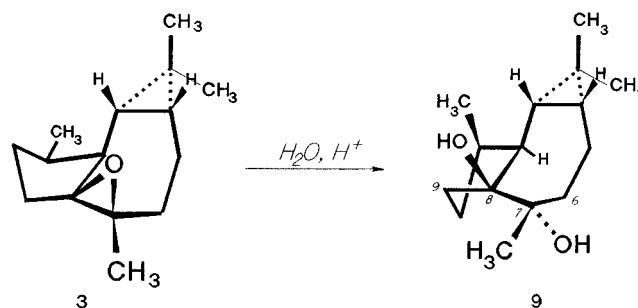
Scheme 7. Mechanism of the Formation of Alcohol 7**Scheme 8. Mechanism of the Formation of 8**

reaction mixture is only washed with water. The mechanism of formation of alcohol **7** can be rationalized as followed (Scheme 7).

The reaction was initiated by protonation of the oxygen atom of the epoxide ring and simultaneous opening of the epoxide ring to form carbocation **7a**. By opening of the cyclopropane ring, carbocation **7b** is formed and then diol **7c** by addition of water. Mono-dehydration of this diol lead to enol **7**. The structure and configuration of enol **7** were unequivocally determined by simple consideration based on the configuration of the starting epoxide, mechanism of its formation, and examination of its ^1H NMR spectra (coupling constant). Stereochemistry α assigned to H-1 is supported by $^3J(\text{H}_1-\text{H}_{11}) = 4.3$ Hz. $^3J(\text{H}_2-\text{H}_4) = 4.3$ Hz shows that H-2 and H-4 are cis. From **7d**, we can explain formation of ether **8** (Scheme 8).

The lose of a water molecule lead to carbocation **8a**, which rearranges to carbocation **8b** after opening of the cyclopropane ring. The spacial proximity of the hydroxy group and carbocation favor cyclization and formation of a furanic ring. The stereochemistry of **8** is determined by examination of its ^1H NMR spectra (coupling constant). In fact, $^3J(\text{H}_2-\text{H}_{3\alpha}) = 13.1$ Hz and $^3J(\text{H}_2-\text{H}_{3\beta}) = 5.1$ Hz are in agreement with H-2 in a β position. $^3J(\text{H}_1-\text{H}_{10}) = 11.4$ Hz and $^3J(\text{H}_1-\text{H}_2) = 8.0$ Hz put to the fore the β and α positions of H-1 and H-10, respectively.

Reduction of β -epoxide **3** with LiAlH_4 do not afford the alcohol expected but a diol **9** in 63% yield (Scheme

Scheme 9. Hydrolysis of Epoxide 3

9). The ^1H and ^{13}C chemical shifts are given in Table 6 and the retention time and mass spectral data in Table 2. In acidic medium, ring opening of the epoxide by a nucleophile begins by protonation of the epoxidic oxygen atom followed by an attack of the hydroxy group on the carbon atom susceptible to give the more stable carbocation according to the diaxial opening rules. In ledene epoxide, carbons C-7 and C-8 of the oxirane ring could provide two tertiary carbocations with one at the bridgehead. Configuration of diol **9** was unequivocally determined by examination of its 2D-NOESY spectra. A correlation peak between methyl-13 (1.24 ppm) and H-9 α (1.62 ppm) was in agreement with α hydroxy group for C₇. β -Configuration of the hydroxy group on C-8 was assigned on the basis of the configuration of the starting epoxide.

Odor Properties. These newly described sesquiterpenes derived from (+)-ledene were submitted to olfactive evaluation. A precious fruity woody odor appears to be important.

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