Preparation of Moreliane-Derived Volatile Sesquiterpenes†

Carlos M. Cerda-García-Rojas,*,‡ María A. Bucio,‡ Luisa U. Román,§ Juan D. Hernández,§ and Pedro Joseph-Nathan‡

Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apartado 14-740, México, D. F., 07000 Mexico, and Instituto de Investigaciones Químico-Biológicas, Universidad Michoacana de San Nicolás de Hidalgo, Apartado 137, Morelia, Michoacán, 58000 Mexico

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A series of six volatile sesquiterpenes (**9**−**13** and **15**) was prepared by thioketalization of (4*R*,5*S*,9*S*,10*S*,11*S*)-morel-2-en-1,7-dione (**2**) and of (4*R*,5*S*,7*R*,9*R*,11*R*)-moreli-2,10-dien-7-ol-1-one (**3**), followed by Raney-nickel desulfurization. The structures of the new substances were determined by 1D and 2D NMR including COSY, NOESY, HSQC, and HMBC experiments. The geometry of (3*S*,4*R*,5*R*,9*S*,10*R*,11*S*)-morelian-7-one (**11**), which exhibited an intense woody odor, was calculated by density functional theory at the B3LYP/6-31G* level.

Volatile mono-oxygenated tricyclic sesquiterpenes are important materials in the perfume industry.[1,2] In particular, fractions containing oxygenated compounds exhibit more interesting odors and possess higher commercial values than fractions containing the respective hydrocarbon products.[3] Several efforts to obtain new volatile substances with interesting fragrance properties have been focused on variations in the oxidation degree as well as in molecular rearrangements of natural sesquiterpenes.[3−8] In previous work, we have explored the molecular rearrangements of longipinene derivative **1**[9] obtained by alkaline hydrolysis of the natural diesters produced by several plants of the genus *Stevia*.[10−12] The rearrangements afforded a series of new carbocyclic structures, including moreliane derivatives **2** and **3** (Scheme 1).[9,13] Given that both substances can be obtained in good yields, it was considered of interest to prepare a series of volatile derivatives and to carry out a preliminary olfactory evaluation. Preparation of the new compounds was accomplished by removal of the carbonyl groups of **2** and **3** by means of thioketalization followed by Raney-nickel desulfurization.

Results and Discussion

Treatment of diketone **2** with 1,2-ethanedithiol and *p*-toluenesulfonic acid in benzene afforded 1,7-bis(ethylenedithioketal) (**4**) and 1-ethylenedithioketal (**5**) as the major products (52% and 16%, respectively), together with 7-ethylenedithioketal (**6**, 5%) and the addition products **7** and **8** in 8% and 3% yield, respectively (Scheme 1). The major products **4** and **5** were subjected to desulfurization with Raney-nickel in methanol. Compound **4** gave hydrocarbon **9**, while compound **5** afforded the expected product **10** together with the saturated ketone **11**, which must arise from an over-reduction process promoted by the Raney-nickel. Treatment of ketone **10** with sodium borohydride in methanol afforded the epimeric compounds **12** and **13** in 49% and 27% yield, respectively. A preliminary olfactory evaluation of compounds **9**−**13** revealed that the saturated ketone **11** possesses an intense woody odor, while the other sesquiterpenoids exhibited only a moderate root-like odor. Therefore, to increase the yield of compound **11**, its precursor **5** was obtained in 85% yield by treatment of compound **3** with 1,2-ethanedithiol and *p*-toluenesulfonic acid in benzene (Scheme 2). It is known that, under acidic conditions, compound **3** isomerizes to **2** throughout a hydride transfer from C-7 to C-10.[9] Thus, the preferred formation of **5** from **3** shows that the ethylenedithioketalization at C-1 is faster than the transannular 1,4-hydride migration. Alcohol **14** was obtained in only 10% yield and was also subjected to the thioketalization−desulfurization process to afford **15** in 72% yield, which exhibited a moderate root-like odor (Scheme 2).

The determination of the stereostructure of the new substances **4**−**15** was not trivial since in some cases only a single functional group is present on the sesquiterpene framework. The structures were determined by 1D and 2D NMR spectroscopy, including COSY, NOESY, HSQC, and HMBC, in combination with HRMS. Addition of the two ethyleneketal moieties in **4** was evident from the absence of carbonyl IR absorption bands and the presence of two ^{13}C NMR signals at δ 74.5 and 75.1 for C-1 and C-7, respectively, instead of the carbonyl carbon signals at δ 214.2 and 201.7 present in **2**. Their individual assignment followed from HMBC correlations between C-1 and the vinylic proton H-2 and between C-7 and the proton signals of the *gem*-dimethyl groups Me-12 and Me-13. Similarly, the positional assignment of the ethylenedithioketal moiety in **5** and **6** followed from IR carbonyl absorptions and from the HMBC correlations between C-1 in **5** at δ 72.6 and H-2 and between C-7 in **6** at δ 74.4 and the *gem*-dimethyl groups Me-12 and Me-13.

The stereostructure,[9,10] conformation,[13,14] and absolute configuration[14,15] of compounds **1**−**3** have been well established by NMR,[9,10,14] X-ray diffraction analyses,[9,13] CD measurements,[14] and chemical correlations.[9,15] This information was essential for the full stereochemical assignment of products **4**−**15**. The stereochemistry for the new chiral centers generated at C-3 in **7** and **8** was assigned according to NOESY correlations. The β-methyl group Me-15 in compound **7** displayed a strong correlation with H-9, which is located on the β-side of the molecule, while the α-methyl group in compound **8** showed a correlation with H-5, which is located on the α-side of the structure. The ^{1}H NMR spectrum of compound **9** displayed, even at 500 MHz, a strongly coupled spin−spin system in particular for the hydrogen atoms attached to the seven-membered ring. The analysis of this spectrum was carried out with the aid of

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* To whom correspondence should be addressed. Tel: (+52-55)-5747-7112. Fax: (+52-55)-5747-7137. E-mail: ccerda@mail.cinvestav.mx.

‡ Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional.

§ Universidad Michoacana de San Nicolás de Hidalgo.

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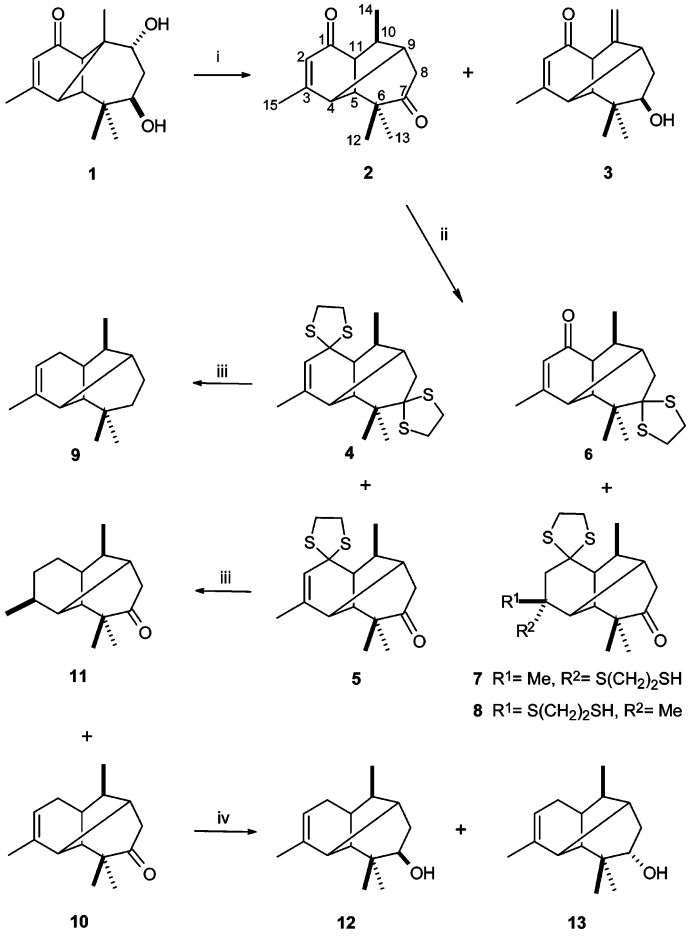
Scheme 1[a]



[a] (i) TsOH, C_6H_6 (see ref 9); (ii) $HSCH_2CH_2SH$, TsOH, C_6H_6, reflux 9 h; (iii) Raney-Ni, MeOH, reflux 0.5−1.0 h; (iv) $NaBH_4$, MeOH, rt 2 h.

Table 1. ^{13}C NMR Data for Compounds **4**−**15** in $CDCl_3$

compd	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	C-13	C-14	C-15
4[a]	74.5	127.4	139.3	45.9	63.8	43.3	75.1	49.1	49.6	35.3	52.8	29.6	25.3	21.9	21.9
5[a]	72.6	126.6	137.3	46.6	60.8	47.7	215.5	47.2	47.9	40.8	54.0	27.2	22.0	20.6	21.9
6[a]	202.1	126.1	165.5	50.3	62.7	43.7	74.4	50.0	45.2	32.9	54.8	30.0	25.3	19.0	23.5
7[a,b]	70.6	48.1	50.8	53.1	56.1	48.2	214.9	50.1	42.1	41.3	55.1	28.3	22.5	17.6	29.0
8[a,b]	71.0	49.8	50.9	53.3	56.1	48.2	214.6	50.1	42.4	41.3	55.1	28.2	22.7	17.5	27.7
9	31.5	119.5	140.9	46.9	56.6	33.2	32.6	29.6	48.1	35.4	37.7	27.7	29.6	18.3	22.6
10	30.4	119.2	138.9	47.1	56.7	47.7	216.9	48.4	47.7	38.9	38.3	27.4	22.0	17.6	22.6
11	27.8	28.4	35.1	50.9	59.4	48.6	218.3	51.3	39.3	39.4	40.4	28.1	22.3	13.5	20.8
12	31.8	119.7	139.7	46.4	57.9	38.2	73.2	39.0	48.2	37.2	37.3	20.8	26.1	18.7	22.7
13	31.9	119.8	140.7	46.5	55.8	38.2	73.6	38.3	47.4	35.4	37.3	29.6	23.7	18.5	22.7
14[a]	73.7	125.5	138.4	45.2	58.6	37.9	72.0	39.4	48.6	153.2	53.2	20.1	25.6	110.0	22.0
15	38.6	117.9	140.2	45.7	55.5	37.8	72.6	39.4	49.7	159.0	40.6	20.4	25.7	104.8	22.8

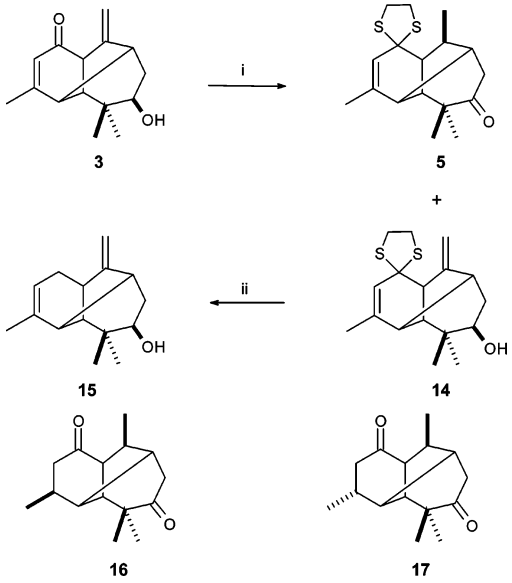
[a] Ethyleneketal signals for **4**: 41.6, 41.3, 37.8, and 36.8; **5**: 41.2 and 37.8; **6**: 41.9 and 37.2; **7**: 39.3 and 39.1; **8**: 39.8 and 37.9; **14**: 39.8 and 39.3. [b] 2-Mercaptoethyl signals for **7**: 33.4 and 24.9; **8**: 31.8 and 25.3.

spectral simulation using the MestRe−C program.[16] A system of 12 nuclei was calculated for the protons attached to the C4−C5−C6−C7−C8−C9−C10(C14)−C11 fragment, affording a more complete set of ^1H NMR parameters with a root-mean-square (rms) error of only 0.34 Hz, which allowed the structure of this tricyclic hydrocarbon (**9**) to be secured. The assigned ^1H NMR data of this compound and all the new substances are listed in the Experimental Section, while the corresponding ^{13}C NMR chemical shifts are listed in Table 1. Additionally, the ^1H NMR spectra of **4**−**15** are shown in Figures S1−S12 of the Supporting Information.

The stereochemistry of the chiral center at C-3 in **11** was assigned when the ^{13}C NMR chemical shifts of this substance were compared with those of diketones **16** and **17**[9] (Scheme 2), which are the known dihydro derivatives of **2**. In compound **11**, the signal for the C-15 methyl group appeared at δ 20.8, which is very close to the C-15 chemical shift of the 3β-isomer **16** (δ 19.9). In contrast, in the 3α-isomer **17**, the methyl group signal appeared shifted downfield at δ 23.6. The stereochemistry at C-7 in **12** and **13** was deduced by comparing the coupling constant values of H-7 for both substances with compounds having a β-oriented hydroxyl group at C-7 such as **15**. Thus, the signal for H-7 in **12** appeared at δ 3.63 as a double doublet of $J_{7\alpha,8\alpha} = 6.1$ Hz and $J_{7\alpha,8\beta} = 10.8$ Hz, resembling that of compound **15**, which appeared at δ 3.56 as a double doublet of $J_{7\alpha,8\alpha} = 5.4$ Hz and $J_{7\alpha,8\beta} = 10.7$ Hz. On the contrary, the signal for H-7 in compound **13**, which possesses an α-oriented hydroxyl group at C-7, appeared at δ 3.48 as a double doublet of $J_{7\beta,8\alpha} = 1.5$ Hz and $J_{7\beta,8\beta} = 4.9$ Hz.

For compound **11**, we decided to carry out density

Scheme 2[a]



[a] (i) $HSCH_2CH_2SH$, TsOH, C_6H_6, reflux 2 h; (ii) Raney-Ni, MeOH, reflux 0.5 h.

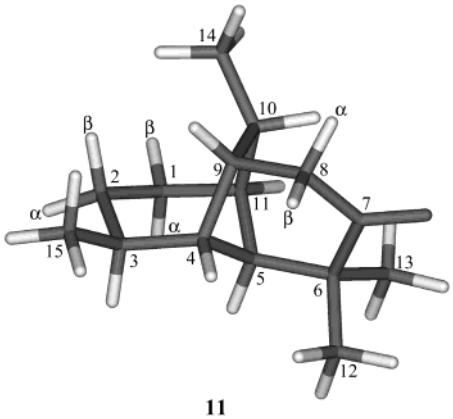


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Figure 1. Density functional theory (B3LYP/6-31G*) molecular model of (3*S*,4*R*,5*R*,9*S*,10*R*,11*S*)-morelian-7-one (**11**).

functional theory calculations at the B3LYP/6-31G* level of theory. The minimum energy structure is shown in Figure 1, and the corresponding Cartesian coordinates are listed in the Supporting Information (Table S1). The conformation of **11** in chloroform solution is found to be similar to the DFT geometry, as reflected by comparison between the observed and the calculated $^1H-^1H$ vicinal coupling constants and the corresponding dihedral angles (Table 2), which were obtained using the Altona equation.[17,18] This procedure has recently been successfully applied to the conformational analysis of several natural products.[19−22] In addition, the long-range coupling constants $J_{4,11} = 1.2$ Hz and $J_{5,9} = 2.8$ Hz were in agreement with the W-type geometries[23] found in the molecular model of **11** (Figure 1) for the H4−C4−C5−C11−H11 and H5−C5−C4−C9−H9 fragments, respectively. In particular, the large value for $J_{5,9}$ is characteristic of a W-fragment that is slightly distorted toward planarity and that is located in the Heq-Cβ-Cγ-Cβ-Heq positions of a cyclohexanone moiety.[24] The molecular model of **11** indicates that the C5−C4−C9 bond angle has a value of 99°.

Experimental Section

General Experimental Procedures. Organic layers were dried using anhydrous Na_2SO_4. Column chromatography was carried out on Merck silica gel 60 (230−400 mesh ASTM).

Table 2. Dihedral Angles (ϕ_{DFT} in deg) and Calculated and Observed Vicinal Coupling Constants (J_{calc} and J_{obs} in Hz) for (3*S*,4*R*,5*R*,9*S*,10*R*,11*S*)-Morelian-7-one (**11**)

H(x)−C−C−H(y) x,y	ϕ_{DFT}	J_{calc}	J_{obs}[a]
1α,2α	−43	6.4	5.9
1α,2β	−158	11.7	13.2
1α,11	+60	3.0	2.4
1β,2α	+73	1.1	1.0
1β,2β	−43	6.4	5.4
1β,11	−55	3.7	4.0
2α,3	−47	5.3	*b*
2β,3	+162	11.4	12.7
3,4	−64	2.2	2.4[c]
4,5	+75	1.0	1.0[d]
4,9	−84	0.6	1.0[e]
5,11	−73	1.2	1.3
8α,9	−58	3.3	3.4
8β,9	+62	2.8	2.9
9,10	+119	3.4	3.1
10,11	−35	6.9	5.9

[a] Measured at 300 MHz in $CDCl_3$. [b] Not observed due to signal overlapping. [c] Measured under irradiation of H-11. [d] Estimated from the width at half-height of the broad doublet of H-4 observed under irradiation of H-11. [e] Estimated from the width at half-height of the H-9 signal.

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$ on a Perkin-Elmer 241 polarimeter. IR spectra were recorded in $CHCl_3$ on a Perkin-Elmer 16F PC spectrophotometer. NMR spectra were measured at 300 MHz for ^1H and 75.4 MHz for ^{13}C on Varian Mercury spectrometers in $CDCl_3$ solution unless stated otherwise. Chemical shifts (δ) are given in ppm relative to tetramethylsilane, and coupling constants (J) are in Hz. The ^1H NMR spectrum of hydrocarbon **9** was also measured at 500 MHz on a Bruker DMX500 spectrometer. Low-resolution mass spectra were recorded at 20 eV on Hewlett-Packard 5989A or at 70 eV on Varian Saturn 2000 spectrometers. High-resolution mass spectra were measured on a VG 7070 high-resolution mass spectrometer at the UCR Mass Spectrometry Facility, University of California, Riverside, CA, except for compound **9**, which was measured on a JEOL-DX 300 mass spectrometer. The starting compounds **2** and **3** were prepared by alkaline hydrolysis of the natural mixture of longipinene diesters isolated from *Stevia salicifolia*[10] to afford **1**, followed by treatment with *p*-toluenesulfonic acid to promote the molecular rearrangement.[9]

Thioketalization of 2. A solution of **2** (1.30 g) in benzene (20 mL) was treated with 1,2-ethanedithiol (0.93 mL) and *p*-toluenesulfonic acid (1.30 g). The reaction mixture was refluxed for 9 h, poured over ice/H_2O, and extracted with EtOAc. The organic layer was washed with aqueous NaOH (10%) and H_2O, dried, and filtered. After solvent evaporation, the residue was chromatographed on silica gel eluting with mixtures of hexane and increasing amounts of EtOAc to give **4** (1118 mg, 52%), **5** (274 mg, 16%), **6** (103 mg, 5%), **7** (192 mg, 8%), and **8** (78 mg, 3%).

(4*R*,5*S*,9*S*,10*S*,11*S*)-Morel-2-en-1,7-dione 1,7-bis(ethylenedithioketal) (4): white powder; mp 134−136 °C; $[\alpha]_D$ +210° (*c* 0.66); IR ν_{max} 1646 (C=C) cm^{-1}; ^1H NMR δ 5.42 (1H, dq, $J_{2,4} \approx J_{2,15} \approx 1.4$ Hz, H-2), 3.38−3.07 (8H, complex m, 2 SCH_2CH_2S), 3.04 (1H, br dq, $J_{10,11} = 7.4$ Hz, $J_{10,14} = 7.2$ Hz, H-10), 2.98 (1H, dd, $J_{5,11} = 1.6$ Hz, $J_{10,11} = 7.4$ Hz, H-11), 2.46 (2H, m, H-8α and H-8β), 2.27 (1H, br d, $J_{5,9} = 2.2$ Hz, H-5), 2.08 (1H, br s, H-4), 1.82 (1H, m, H-9), 1.68 (3H, d, $J_{2,15} = 1.4$ Hz, Me-15), 1.28 (3H, s, Me-13), 1.20 (3H, s, Me-12), 1.19 (3H, d, $J_{10,14} = 7.2$ Hz, Me-14); ^{13}C NMR, see Table 1; EIMS *m*/*z* 384 $[M]^+$ (11), 356 (100), 328 (50), 291 (21), 264 (20), 158 (34), 130 (20); HREIMS *m*/*z* 385.1156 $[M + 1]^+$ (calcd for $C_{19}H_{29}S_4$, 385.1152).

(4*R*,5*S*,9*S*,10*S*,11*S*)-Morel-2-en-1,7-dione 1-ethylenedithioketal (5): white powder; mp 96−98 °C; $[\alpha]_D$ +233° (*c*

1.92); IR ν_{max} 1702 (C=O), 1652 (C=C) cm^{-1}; ^1H NMR δ 5.43 (1H, br m, H-2), 3.35−3.04 (4H, complex m, SCH_2CH_2S), 2.78 (1H, br d, $J_{10,11}$ = 6.8 Hz, H-11), 2.50 (1H, br dd, $J_{8\alpha,8\beta}$ = 16.6 Hz, $J_{8\beta,9}$ = 1.9 Hz, H-8β), 2.43 (1H, br d, $J_{5,9}$ = 2.4 Hz, H-5), 2.36 (1H, dd, $J_{8\alpha,8\beta}$ = 16.6 Hz, $J_{8\alpha,9}$ = 3.9 Hz, H-8α), 2.32 (1H, br s, H-4), 1.84 (1H, br m, H-9), 1.77 (1H, br dq, $J_{10,11}$ = 6.8 Hz, $J_{10,14}$ = 7.3 Hz, H-10), 1.72 (3H, d, $J_{2,15}$ = 1.0 Hz, Me-15), 1.18 (3H, d, $J_{10,14}$ = 7.3 Hz, Me-14), 1.34 (3H, s, Me-12), 1.34 (3H, s, Me-13); ^{13}C NMR, see Table 1; EIMS *m/z* 308 $[M]^+$ (2), 280 (100), 247 (4), 216 (6), 197 (30), 164 (5); HREIMS *m/z* 309.1349 $[M + 1]^+$ (calcd for $C_{17}H_{25}OS_2$, 309.1347).

(4*R*,5*S*,9*S*,10*S*,11*S*)-Morel-2-en-1,7-dione 7-ethylenedithioketal (6): colorless oil; $[\alpha]_D$ +152° (*c* 1.83); IR ν_{max} 1664 (C=O), 1628 (C=C) cm^{-1}; ^1H NMR δ 5.43 (1H, $J_{2,4} \approx J_{2,15} \approx$ 1.5 Hz, H-2), 3.34 (1H, br dq, $J_{10,11} = J_{10,14}$ = 6.8 Hz, H-10), 3.15 (1H, br d, $J_{10,11}$ = 6.8 Hz, H-11), 3.35−3.08 (4H, complex m, SCH_2CH_2S), 2.62 (2H, d, $J_{8,9}$ = 3.4 Hz, H-8), 2.58 (1H, br s, H-4), 1.99 (3H, d, $J_{2,15}$ = 1.5 Hz, Me-15), 1.99 (1H, br s, H-5), 1.93 (1H, br s, H-9), 1.22 (3H, s, Me-12), 1.17 (3H, s, Me-13), 0.87 (3H, d, $J_{10,14}$ = 6.8 Hz, Me-14); ^{13}C NMR, see Table 1; EIMS *m/z* 308 $[M]^+$ (12), 280 (100), 265 (26), 248 (4), 199 (10), 172 (20), 158 (9), 147 (35), 119 (11), 105 (26); HREIMS *m/z* 308.1262 (calcd for $C_{17}H_{24}OS_2$, 308.1268).

(3*R*,4*R*,5*S*,9*S*,10*S*,11*S*)-3-*S*-(1,2-Dimercaptoethyl)-morelian-1,7-dione 1-ethylenedithioketal (7): colorless oil; $[\alpha]_D$ +60° (*c* 1.45); IR ν_{max} 1700 (C=O) cm^{-1}; ^1H NMR δ 3.29−3.11 (4H, complex m, SCH_2CH_2S), 2.91 (1H, br d, $J_{5,9}$ = 2.4 Hz, H-5), 2.84−2.69 (4H, complex m, SCH_2CH_2SH), 2.54 (1H, br d, $J_{10,11}$ = 6.3 Hz, H-11), 2.52 (1H, dd, $J_{8\alpha,8\beta}$ = 17.6 Hz, $J_{8\alpha,9}$ = 3.4 Hz, H-8α), 2.42 (1H, br ddd, $J_{8\alpha,8\beta}$ = 17.6 Hz, $J_{8\beta,9}$ = 2.5 Hz, $J_{5,8\beta}$ = 1.5 Hz, H-8β), 2.30 (1H, br d, $J_{2\alpha,2\beta}$ = 16.1 Hz, H-2α), 2.22 (1H, d, $J_{2\alpha,2\beta}$ = 16.1 Hz, H-2β), 2.07 (1H, br s, H-4), 1.93 (1H, m, H-9), 1.70 (1H, m, H-10), 1.44 (3H, s, Me-15), 1.37 (3H, d, $J_{10,14}$ = 7.3 Hz, Me-14), 1.17 (3H, s, Me-12), 1.10 (3H, s, Me-13); ^{13}C NMR, see Table 1; EIMS *m/z* 402 $[M]^+$ (46), 341 (26), 309 (100), 280 (25), 249 (32), 197 (13), 165 (16), 145 (17), 105 (29); HREIMS *m/z* 402.1191 (calcd for $C_{19}H_{30}OS_4$, 402.1179).

(3*S*,4*R*,5*S*,9*S*,10*S*,11*S*)-3-*S*-(1,2-Dimercaptoethyl)morelian-1,7-dione 1-ethylenedithioketal (8): colorless oil; $[\alpha]_D$ +67° (*c* 2.0); IR ν_{max} 1700 (C=O) cm^{-1}; ^1H NMR δ 3.38−3.02 (4H, complex m, SCH_2CH_2S), 2.84−2.66 (4H, complex m, SCH_2-CH_2SH), 2.61 (1H, br d, $J_{10,11}$ = 6.4 Hz, H-11), 2.51 (1H, dd, $J_{8\alpha,8\beta}$ = 17.6 Hz, $J_{8\alpha,9}$ = 3.9 Hz, H-8α), 2.46 (1H, m, H-8β), 2.45 (1H, br m, H-9), 2.37 (1H, d, $J_{2\alpha,2\beta}$ = 14.6 Hz, H-2β), 2.32 (1H, br d, $J_{5,9}$ = 2.4 Hz, H-5), 2.25 (1H, br d, $J_{2\alpha,2\beta}$ = 14.6 Hz, H-2α), 2.04 (1H, br s, H-4), 1.74 (3H, s, Me-15), 1.69 (1H, br m, H-10), 1.30 (3H, d, $J_{10,14}$ = 7.3 Hz, Me-14), 1.15 (3H, s, Me-12), 1.10 (3H, s, Me-13); ^{13}C NMR, see Table 1; EIMS *m/z* 402 $[M]^+$ (14), 309 (100), 280 (8), 249 (15), 215 (6), 165 (7), 145 (10), 105 (19); HREIMS *m/z* 402.1178 (calcd for $C_{19}H_{30}OS_4$, 402.1179).

(4*R*,5*R*,9*S*,10*S*,11*S*)-Morel-2-ene (9). A solution of **4** (173 mg) in MeOH (5 mL) was treated with W-2 Raney-nickel (2.42 g). The reaction mixture was refluxed for 30 min, filtered over Celite, and evaporated, giving a colorless oil, which was chromatographed. The fractions eluted with pentane afforded **9** (39.7 mg, 43%) as a colorless oil; $[\alpha]_D$ +68° (*c* 2.14); IR ν_{max} (C=C) 1666 cm^{-1}; ^1H NMR δ 5.13 (1H, br m, H-2), 2.30 (1H, br m, $J_{4,11}$ = −0.4 Hz, $J_{5,11}$ = 0.5 Hz, $J_{10,11}$ = 7.8 Hz, H-11), 2.08 (1H, complex m, H-1α), 2.00 (1H, complex m, H-2β), 1.95 (1H, ddq, $J_{9,10}$ = 0.5 Hz, $J_{10,11}$ = 7.8 Hz, $J_{10,14}$ = 7.4 Hz, H-10), 1.82 (1H, br s, $J_{4,9}$ = 1.2 Hz, $J_{4,5}$ = 1.3 Hz, $J_{4,11}$ = −0.4 Hz, H-4), 1.81 (1H, ddddd, $J_{8\alpha,9}$ = 4.4 Hz, $J_{8\beta,9}$ = 1.95 Hz, $J_{4,9}$ = 1.2 Hz, $J_{5,9}$ = −0.5 Hz, $J_{9,10}$ = 0.5 Hz, H-9), 1.64 (3H, q, $J_{3,15}$ = 1.7 Hz, Me-15), 1.59 (1H, dddd, $J_{5,7\beta}$ = −0.9 Hz, $J_{5,9}$ = −0.5 Hz, $J_{4,5}$ = 1.3 Hz, $J_{5,11}$ = 0.5 Hz, H-5), 1.47 (1H, dddd, $J_{8\alpha,8\beta}$ = −13.4 Hz, $J_{7\alpha,8\beta}$ = 13.0 Hz, $J_{7\beta,8\alpha}$ = 5.5 Hz, $J_{8\beta,9}$ = 1.95 Hz, H-8β), 1.39 (1H, dddd, $J_{8\alpha,8\beta}$ = −13.4 Hz, $J_{8\alpha,7\alpha}$ = 6.0 Hz, $J_{8\alpha,7\beta}$ = 1.1 Hz, $J_{8\alpha,9}$ = 4.4 Hz, H-8α), 1.38 (1H, ddd, $J_{7\alpha,7\beta}$ = −13.4 Hz, $J_{7\alpha,8\alpha}$ = 6.0 Hz, $J_{7\alpha,8\beta}$ = 13.0 Hz, H-7α), 1.09 (1H, dddd, $J_{5,7\beta}$ = −0.9 Hz, $J_{7\beta,7\alpha}$ = −13.4 Hz, $J_{7\beta,8\alpha}$ = 1.1 Hz, $J_{7\beta,8\beta}$ = 5.5 Hz, H-7β), 0.99 (3H, d, $J_{10,14}$ = 7.4 Hz, Me-14), 0.94 (3H, s, Me-12), 0.91 (3H, s, Me-13) (the C4−C5−C6−C7−C8−C9−C10(C14)−C11 spin−spin system was assigned by spectral simulation, rms error = 0.34); ^{13}C NMR, see Table 1; EIMS *m/z* 204 $[M]^+$ (100), 189 (71), 175 (13), 161 (28), 148 (45), 133 (51), 119 (44), 105 (47), 93 (65); HREIMS *m/z* 204.1880 (calcd for $C_{15}H_{24}$, 204.1878).

Hydrogenolysis of 5. A solution of **5** (50 mg) in MeOH (5 mL) was treated with Raney-nickel W-2 (390 mg). The reaction mixture was refluxed for 1 h, filtered over Celite, and evaporated to dryness, giving a colorless oily residue, which was chromatographed. Fractions eluted with hexane−EtOAc (97:3) afforded **10** (25 mg, 71%) and **11** (7.5 mg, 21%).

(4*R*,5*R*,9*S*,10*R*,11*S*)-Morel-2-en-7-one (10): colorless oil; $[\alpha]_D$ +142° (*c* 1.58); IR ν_{max} 1698 (C=O) cm^{-1}; ^1H NMR δ 5.19 (1H, br m, H-2), 2.52 (1H, ddd, $J_{8\alpha,8\beta}$ = 16.2 Hz, $J_{8\alpha,9}$ = 2.8 Hz, $J_{8\alpha,10}$ = 1.1 Hz, H-8α), 2.41 (1H, br m, H-11), 2.31 (1H, dd, $J_{8\alpha,8\beta}$ = 16.2 Hz, $J_{8\beta,9}$ = 3.8 Hz, H-8β), 2.29 (1H, br s, H-4), 2.13 (1H, complex, H-1α), 2.02 (1H, complex m, H-1β), 1.98 (1H, br s, H-5), 1.96 (1H, br m, H-9), 1.72 (3H, dddd, $J_{1\alpha,15} \approx J_{1\beta,15} \approx J_{2,15} \approx J_{4,15} \approx$ 2.2 Hz, Me-15), 1.68 (1H, br dq, $J_{10,11} = J_{10,14}$ = 7.4 Hz, H-10), 1.16 (3H, s, Me-12), 1.09 (3H, s, Me-13), 1.01 (3H, d, $J_{10,14}$ = 7.4 Hz, Me-14); ^{13}C NMR, see Table 1; EIMS *m/z* 218 $[M]^+$ (100), 203 (7), 190 (15), 175 (20), 147 (30), 133 (35), 119 (30), 105 (24), 93 (79), 43 (28); HREIMS *m/z* 218.1671 (calcd for $C_{15}H_{22}O$, 218.1671).

(3*S*,4*R*,5*R*,9*S*,10*R*,11*S*)-Morelian-7-one (11): colorless oil; $[\alpha]_D$ +13° (*c* 0.75); IR ν_{max} 1692 (C=O) cm^{-1}; ^1H NMR δ 2.47 (1H, dd, $J_{8\alpha,8\beta}$ = 17.0 Hz, $J_{8\alpha,9}$ = 3.4 Hz, H-8α), 2.36 (1H, ddd, $J_{5,8\beta}$ = 1.5 Hz, $J_{8\alpha,8\beta}$ = 17.0 Hz, $J_{8\beta,9}$ = 2.9 Hz, H-8β), 2.14 (1H, ddddd, $J_{1\alpha,11}$ = 2.4 Hz, $J_{1\beta,11}$ = 4.0 Hz, $J_{4,11}$ = 1.2 Hz, $J_{5,11}$ = 1.3 Hz, $J_{10,11}$ = 5.9 Hz, H-11), 1.95 (1H, br s, H-4), 1.74 (1H, br dddd, $J_{5,9}$ = 2.8 Hz, $J_{8\alpha,9}$ = 3.4 Hz, $J_{8\beta,9}$ = 2.9 Hz, $J_{9,10}$ = 3.1 Hz, H-9), 1.70 (1H, m, H-3), 1.68 (1H, dddd, $J_{1\alpha,1\beta}$ = 13.6 Hz, $J_{1\beta,2\alpha}$ = 1.0 Hz, $J_{1\beta,2\beta}$ = 5.4 Hz, $J_{1\beta,11}$ = 4.0 Hz, H-1β), 1.40 (1H, m, H-2α), 1.51 (1H, br m, H-5), 1.49 (1H, br m, H-10), 1.34 (1H, dddd, $J_{1\alpha,1\beta}$ = 13.6 Hz, $J_{1\alpha,2\alpha}$ = 5.9 Hz, $J_{1\alpha,2\beta}$ = 13.2 Hz, $J_{1\alpha,11}$ = 2.4 Hz, H-1α), 1.05 (1H, ddd, $J_{1\alpha,2\beta}$ = 11.7 Hz, $J_{1\beta,2\beta}$ = 5.4 Hz, $J_{2\beta,3}$ = 11.4 Hz, H-2β), 1.11 (3H, s, Me-12), 1.06 (3H, d, $J_{10,14}$ = 7.3 Hz, Me-14), 1.02 (3H, s, Me-13), 0.90 (3H, d, $J_{3,15}$ = 6.8 Hz, Me-15); ^{13}C NMR, see Table 1; EIMS *m/z* 220 $[M]^+$ (100), 176 (65), 161 (50), 149 (26), 137 (98), 121 (24), 107 (28), 95 (52), 81 (91); HREIMS *m/z* 220.1832 (calcd for $C_{15}H_{24}O$, 220.1827).

Reduction of 10. A solution of **10** (50 mg) in MeOH (2 mL) was treated with $NaBH_4$ (61 mg) at room temperature for 2 h, poured into ice/H_2O, and extracted with EtOAc. The organic layer was washed with H_2O, dried, filtered, and evaporated. The oily residue was chromatographed. Fractions eluted with hexane−EtOAc (9:1) afforded **12** (25.0 mg, 49%) and **13** (13.6 mg, 27%).

(4*R*,5*R*,7*R*,9*S*,10*R*,11*S*)-Morel-2-en-7-ol (12): colorless oil; $[\alpha]_D$ +32° (*c* 1.42); IR ν_{max} 3534 (OH), 1666 (C=C) cm^{-1}; ^1H NMR δ 5.19 (1H, br m, H-2), 3.63 (1H, dd, $J_{7\alpha,8\alpha}$ = 6.1 Hz, $J_{7\alpha,8\beta}$ = 10.8 Hz, H-7), 2.33 (1H, br m, H-11), 2.10 (1H, complex m, H-1α), 2.02 (1H, complex, H-1β), 1.91 (1H, ddq, $J_{9,10}$ = 1.2 Hz, $J_{10,11}$ = 6.9 Hz, $J_{10,14}$ = 7.3 Hz, H-10), 1.90 (1H, br ddd, $J_{4,5}$ = 1.2 Hz, $J_{4,9}$ = 1.6 Hz, $J_{4,11}$ = −0.8 Hz, H-4), 1.86 (1H, ddddd, $J_{4,9}$ = 1.6 Hz, $J_{5,9}$ = −0.8 Hz, $J_{8\alpha,9}$ = 4.8 Hz, $J_{8\beta,9}$ = 3.0 Hz, $J_{9,10}$ = 1.2 Hz, H-9), 1.83 (1H, ddd, $J_{8\alpha,7\alpha}$ = 6.1 Hz, $J_{8\alpha,8\beta}$ = −13.0 Hz, $J_{8\alpha,9}$ = 4.8 Hz, H-8α), 1.74 (1H, dddd, $J_{4,5}$ = 1.2 Hz, $J_{5,8\beta}$ = −0.6 Hz, $J_{5,9}$ = −0.8 Hz, $J_{5,11}$ = 0.6 Hz, H-5), 1.64 (3H, dddd, $J_{1\alpha,15} \approx J_{1\beta,15} \approx J_{2,15} \approx J_{4,15} \approx$ 1.5 Hz, Me-15), 1.40 (1H, br s, OH), 1.30 (1H, dddd, $J_{5,8\beta}$ = 0.6 Hz, $J_{7\alpha,8\beta}$ = 10.8 Hz, $J_{8\alpha,8\beta}$ = −13.0 Hz, $J_{8\beta,9}$ = 3.0 Hz, H-8β), 1.03 (3H, s, Me-12), 1.01 (3H, d, $J_{10,14}$ = 7.3 Hz, Me-14), 0.92 (3H, s, Me-13) (the C4−C5−C6−C7−C8−C9−C10(C14)−C11 spin−spin system was assigned by spectral simulation, rms error = 0.35); ^{13}C NMR, see Table 1; EIMS *m/z* 220 $[M]^+$ (100), 205 (13), 187 (13), 177 (17), 159 (23), 149 (20), 133 (62), 119 (36), 107 (38), 93 (58), 81 (14), 70 (12), 55 (12), 43 (19); HREIMS *m/z* 220.1831 (calcd for $C_{15}H_{24}O$, 220.1827).

(4*R*,5*R*,7*S*,9*S*,10*R*,11*S*)-Morel-2-en-7-ol (13): colorless oil; $[\alpha]_D$ +68° (*c* 2.14); IR ν_{max} 3536 (OH), 1666 (C=C) cm^{-1}; ^1H NMR δ 5.16 (1H, br m, H-2), 3.48 (1H, dd, $J_{7\beta,8\alpha}$ = 1.5 Hz, $J_{7\beta,8\beta}$ = 4.9 Hz, H-7β), 2.72 (1H, dq, $J_{10,11} = J_{10,14}$ = 7.8 Hz, H-10); 2.40 (1H, br m, H-11), 2.10 (1H, complex m, H-1α), 2.01 (1H, complex m, H-1β), 1.86 (1H, ddd, $J_{8\alpha,8\beta}$ = 13.7 Hz, $J_{7\beta,8\beta}$ = 4.9 Hz, $J_{8\beta,9}$ = 1.9 Hz, H-8β), 1.81 (1H, br s, H-4), 1.79 (1H, br s, H-9), 1.74 (1H, ddd, $J_{7\beta,8\alpha}$ = 1.5 Hz, $J_{8\alpha,8\beta}$ = 13.7 Hz, $J_{8\alpha,9}$

= 3.4 Hz, H-8α), 1.64 (3H, dddd, $J_{1\alpha,15} \approx J_{1\beta,15} \approx J_{2,15} \approx J_{4,15} \approx$ 2.0 Hz, Me-15), 1.64 (1H, br s, H-5), 1.46 (1H, br s, OH), 1.04 (3H, s, Me-13), 0.92 (3H, d, $J_{10,14}$ = 7.8 Hz, Me-14), 0.95 (3H, s, Me-12); ^{13}C NMR, see Table 1; EIMS *m*/*z* 220 $[M]^+$ (55), 202 (53), 187 (52), 173 (22), 159 (50), 145 (47), 133 (100), 119 (93), 108 (94), 93 (47), 81 (22), 43 (15); HREIMS *m*/*z* 220.1830 (calcd for $C_{15}H_{24}O$, 220.1827).

Thioketalization of 3. A solution of **3** (100 mg) in benzene (10 mL) was treated with 1,2-ethanedithiol (35 μL) and *p*-toluensulfonic acid (100 mg). The reaction mixture was refluxed for 2 h, poured over ice/H_2O, and extracted with EtOAc. The organic layer was washed with aqueous NaOH (10%) and H_2O, dried, and filtered. After solvent evaporation, the residue was chromatographed on silica gel eluting with hexane−EtOAc (9:1) to give **5** (112 mg, 85%) and **14** (14.2 mg, 10%).

(4*R*,5*S*,7*R*,9*R*,11*R*)-Moreli-2,10-dien-7-ol-1-one 1-ethylenedithioketal (14): colorless oil; $[\alpha]_D$ +37° (*c* 1.56); IR ν_{max} 3462 (OH), 1652 (C=C) cm^{-1}; ^{1}H NMR δ 5.42 (1H, br s, H-14), 5.31 (1H, quint, $J_{2,4} \approx J_{2,15} \approx$ 1.4 Hz, H-2), 5.02 (1H, br s, H-14′), 3.59 (1H, dd, $J_{7\alpha,8\alpha}$ = 5.5 Hz, $J_{7\alpha,8\beta}$ = 11.0 Hz, H-7α), 3.35−3.25 (4H, complex m, SCH_2CH_2S), 3.03 (1H, br s, H-11), 2.67 (1H, br s, H-9), 2.15 (1H, br s, H-4), 2.05 (1H, br s, H-5), 1.82 (1H, ddd, $J_{7\alpha,8\alpha}$ = 5.5 Hz, $J_{8\alpha,8\beta}$ = 12.2 Hz, $J_{8\alpha,9}$ = 5.4 Hz, H-8α), 1.68 (3H, d, $J_{2,15}$ = 1.4 Hz, Me-15), 1.64 (1H, br s, OH), 1.55 (1H, ddd, $J_{7\beta,8\beta}$ = 12.4 Hz, $J_{8\alpha,8\beta}$ = 12.2 Hz, $J_{8\beta,9}$ = 1.9 Hz, H-8β), 1.08 (3H, s, Me-13), 0.95 (3H, s, Me-12); ^{13}C NMR, see Table 1; EIMS *m*/*z* 308 $[M]^+$ (100), 291 (16), 280 (93), 247 (21), 195 (26), 168 (86), 131 (28), 105 (22); HREIMS *m*/*z* 308.1262 (calcd for $C_{17}H_{24}OS_4$, 308.1268).

(4*R*,5*R*,7*R*,9*R*,11*R*)-Moreli-2,10-dien-7-ol (15). A solution of **14** (90 mg) in MeOH (8 mL) was treated with W-2 Raney-nickel (630 mg) as for **9**. The oily residue was chromatographed eluting with hexane−EtOAc (4:1) to give **15** (45.7 mg, 72%) as colorless oil; $[\alpha]_D$ −10° (*c* 1.1); IR ν_{max} 3454 (OH), 1654 (C=C) cm^{-1}; ^{1}H NMR δ 5.09 (1H, br m, H-2), 4.90 (1H, br s, H-14), 4.89 (1H, br s, H-14′), 3.56 (1H, dd, $J_{7\alpha,8\alpha}$ = 5.4 Hz, $J_{7\alpha,8\beta}$ = 10.7 Hz, H-7α), 2.77 (1H, br s, H-11), 2.74 (1H, br m, H-9), 2.33 (1H, complex m, H-1α), 2.11 (1H, br s, H-4), 1.96 (1H, complex m, H-1β), 1.82 (1H, ddd, $J_{7\alpha,8\alpha}$ = 5.4 Hz, $J_{8\alpha,8\beta}$ = 12.2 Hz, $J_{8\alpha,9}$ = 3.4 Hz, H-8α), 1.67 (1H, br s, H-5), 1.67 (3H, dddd, $J_{1\alpha,15} \approx J_{1\beta,15} \approx J_{2,15} \approx J_{4,15} \approx$ 2.2 Hz, Me-15), 1.51 (1H, td, $J_{7\alpha,8\beta} = J_{8\alpha,8\beta}$ = 12.2 Hz, $J_{8\beta,9}$ = 2.0 Hz, H-8β), 1.02 (3H, s, Me-13), 0.94 (3H, s, Me-12); ^{13}C NMR, see Table 1; EIMS *m*/*z* 218 $[M]^+$ (100), 203 (24), 175 (26), 146 (83), 131 (76), 119 (33), 105 (59), 93 (56), 70 (33), 55 (19); HREIMS *m*/*z* 218.1668 (calcd for $C_{15}H_{22}O$, 218.1671).

Molecular Modeling Calculations. The structure of **11** was framed and minimized in the Spartan 02 molecular modeling software from Wavefunction, Inc. (Irvine, CA) using MMFF94 force-field calculations.[25−29] A systematic conformational search for the six- and seven-membered rings was conducted with the aid of Dreiding models considering torsion angle movements of ca. 10° and using the E_{MMFF} values as the convergence criterion. A further search with the Monte Carlo protocol[30] was carried out considering an energy cutoff of 5 kcal/mol above the global minimum, whose geometry was optimized by the DFT method at the B3LYP/6-31G* level of theory.[31,32] The minimum energy structure has a total energy value E_T = −661.28386 hartrees and the partition coefficient log *P* = 4.10, calculated according to the Ghose−Crippen method.[33,34]

Preliminary Olfactory Evaluation. Solutions of compounds **9**−**13** and **15** (30 mg) in acetone (1 mL) were placed in 20 mL glass vials of 25 mm i.d. × 55 mm height. A portion (10 mm × 10 mm) of Whatman No. 1 filter paper strips (10 mm × 100 mm) was impregnated with the solutions. The strips were allowed to dry for 5 min and subjected to olfactory evaluation for 5 s by five healthy nonsmoker volunteers between 25 and 65 years of age. At least 3 min was left between each evaluation. The tests were repeated in triplicate. Samples of (+)-aromadendrene, (+)-ledene, (−)-β-panasinsene, (−)-globulol, (+)-longifolene, (−)-patchouli alcohol, and (+)-α-longipinene having higher than 97% purity were used as the reference compounds. Compound **11** exhibited an intense woody odor. Compounds **9**, **10**, **12**, **13**, and **15** exhibited moderate root-like odor, like that shown by (−)-β-panasinsene.[19]

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Supporting Information Available: ^{1}H NMR spectra of compounds **4**−**15** and a table of density functional theory (B3LYP/6-31G*) Cartesian coordinates of (3*S*,4*R*,5*R*,9*S*,10*R*,11*S*)-morelian-7-one (**11**). Figures S1−S12 and Table S1 are available free of charge via the Internet at http://pubs.acs.org.

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