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CONFORMATIONAL ANALYSIS OF MORELIENE DERIVATIVES

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ABSTRACT.—The conformation of a series of 4,8,8-trimethyl-9-methyleneperhydro-1,5-methanonaphthalene (moreliene) derivatives [1–6] was determined from ¹H-nmr coupling constants in combination with molecular modeling calculations. While the conformation of ring A remains essentially the same within the series, the conformation of ring B is sensitive to stereochemical changes either at C-4 or at C-9. In compounds 1–3, ring B has a preferred conformation midway between chair and half-chair, in compounds 5 and 6 ring B has a preferred conformation midway between boat and half-chair, and in compound 4 it exists in an equilibrium between the two conformations. In addition, the X-ray diffraction analysis of diketone 7 supports the stereochemistry of the new chiral center at C-9 in compounds 2–3 and 5–6.

Several 4,8,8-trimethyl-9-methyleneperhydro-1,5-methanonaphthalene (moreliene) derivatives have been reported recently as products from the Wagner-Meerwein rearrangement of naturally occurring longipinene derivatives (1,2). In the present paper we discuss the conformational analysis in solution of some selected derivatives [1–6]. This group of substances is composed of two series [1–3] and [4–6], according to the stereochemistry at C-4. Furthermore, each series covers the various stereochemical possibilities at C-9.

The results from this study provide information about the dependence of the conformation on the stereochemistry of this new skeleton, as was concluded in previous work for longipinene derivatives (3).

RESULTS AND DISCUSSION

Epimeric dihydrodiolones 5 and 6 were obtained in a 2:3 ratio, respectively, from 4 (1) by catalytic hydrogenation with PtO$_2$ in EtOH. The stereochemistry at C-9 in both compounds was determined from the H-1/H-9 coupling constant and application of a generalized Karplus-type relationship (4,5). The calculated H-C-1-C-9-H dihedral angles were 117° (from $J_{1,9}$=3.2 Hz) for 5 and −26° (from $J_{1,9}$=8.6 Hz) for 6. X-ray diffraction analysis on diketone 7 (2) is summarized in Figure 1 and Table 1. The data indicated that the methyl group at C-9 has a β-orientation and that the H-C-1-C-9-H dihedral angle was −24°, in agreement with a calculated value of −26° from $J_{1,9}$=8.6 Hz, providing support for the stereochemistry at C-9 for diketones 2 and 3 and diolones 5 and 6. Diketone 1 was obtained by oxidation of 8 (2) with CrO$_3$ in AcOH and compounds 2–4 were prepared as described in previous papers (1,2).

The vicinal coupling constants of the moreliene derivatives listed in Table 2 allowed for calculation of the corresponding dihedral angles using a generalized Karplus-type equation which further considers the coupling constant dependence on the electronegativity and the stereochemistry of the atoms near the coupled protons (4,5). Such angles, together with the information provided by computer-generated molecular models (see Figures 2 and 3), gave the preferred conformations for the series [1–6].

Molecular models were generated using PCMODEL, which operates using MMX force field calculations as a derived version of the MM2 program developed by N.L.
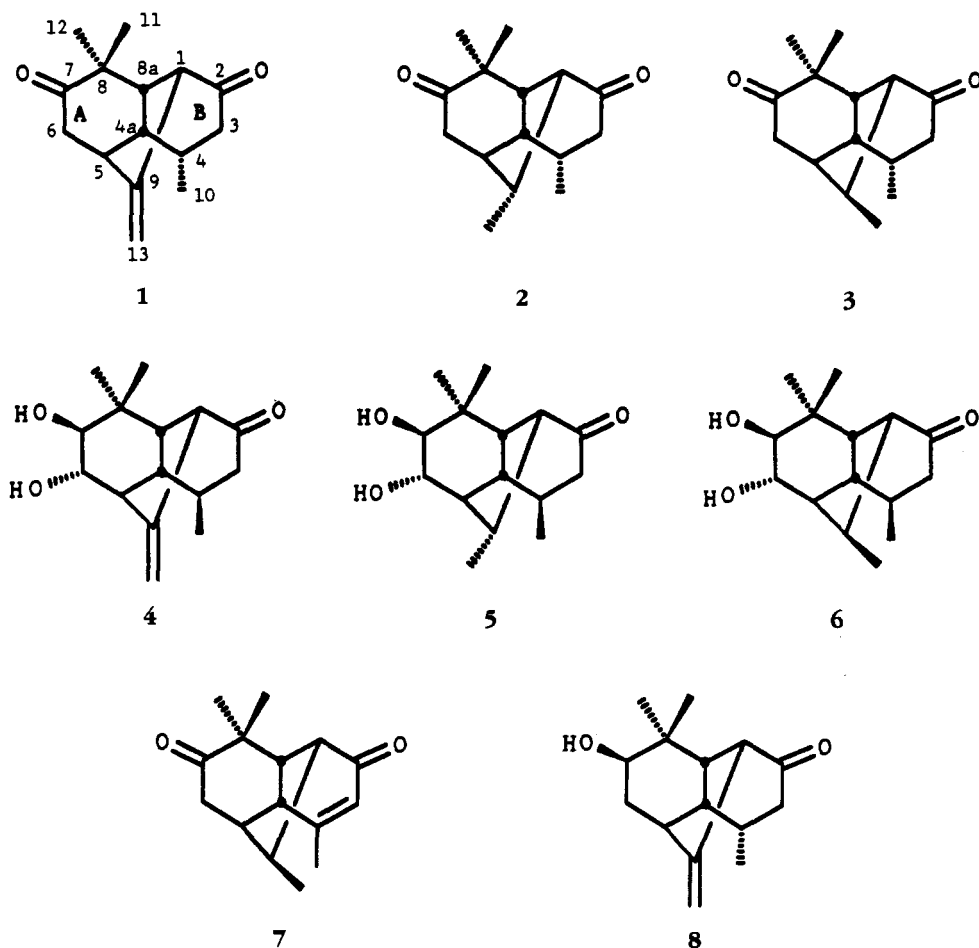
TABLE 1. Experimentally Refined Final Fractional Atomic Coordinates ($\times 10^4$) of **7**.[a]

Atom	x	y	z
O-1	11440 (7)	−329 (5)	4941 (3)
O-7	4845 (8)	−3221 (6)	3036 (3)
C-1	10127 (10)	−17 (8)	4533 (3)
C-2	9670 (10)	1379 (7)	4344 (3)
C-3	8265 (9)	1664 (6)	3885 (3)
C-4	7267 (8)	496 (5)	3507 (3)
C-5	8548 (9)	−743 (6)	3410 (3)
C-6	7591 (9)	−1867 (7)	2949 (3)
C-7	5586 (11)	−2144 (8)	3164 (4)
C-8	4482 (10)	−1026 (7)	3529 (4)
C-9	5736 (9)	−120 (7)	4000 (3)
C-10	6873 (9)	−1012 (7)	4556 (3)
C-11	8846 (8)	−1105 (7)	4225 (3)
C-12	7614 (10)	3066 (6)	3720 (3)
C-13	7493 (10)	−1387 (7)	2147 (3)
C-14	8748 (10)	−3205 (7)	2990 (4)
C-15	6810 (10)	−503 (6)	5346 (3)

[a]Estimated standard deviations in the least significant digits are shown in parentheses.
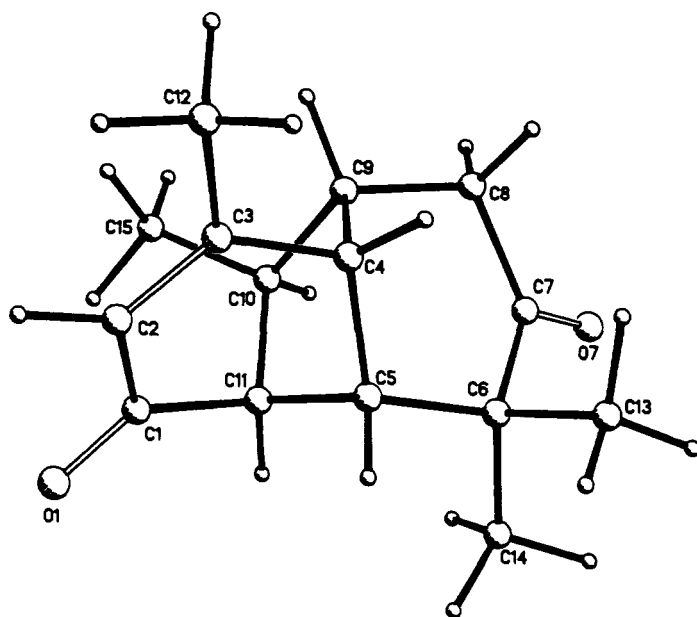
FIGURE 1.   X-ray structure of endione [7]. (Atom numbering of this structure is different from the formula numbering given as **7**).

Allinger (QCPE 395; University of Georgia). In order to find all the local minima, the minimization procedure was carried out starting from every conformer that could be formed using Dreiding models. While structures **1–3** and **5–6** converged in each case to a single energetic minimum, as shown in Figures 2 and 3, structure **4** had two energy minima as depicted in Figure 3.

In all the moreliene derivatives [**1–6**] studied, ring A exists in a chair conformation and essentially shows no influence from stereochemical changes at C-9. In contrast, the conformation of ring B is modified by changes of the stereochemistry either at C-4 or at C-9. In the three compounds having an α-orientated methyl group at C-4 [**1–3**], ring B exists in a conformation midway between chair and half-chair in which the methyl

TABLE 2.   Selected Vicinal Coupling Constants (J in Hz), H-C-C-H Dihedral Angles Calculated from J (ϕ_J in degrees) and H-C-C-H Dihedral Angles Calculated by MMX(ϕ_{MMX} in degrees) for Moreliene Derivatives [**1–3, 5,** and **6**].

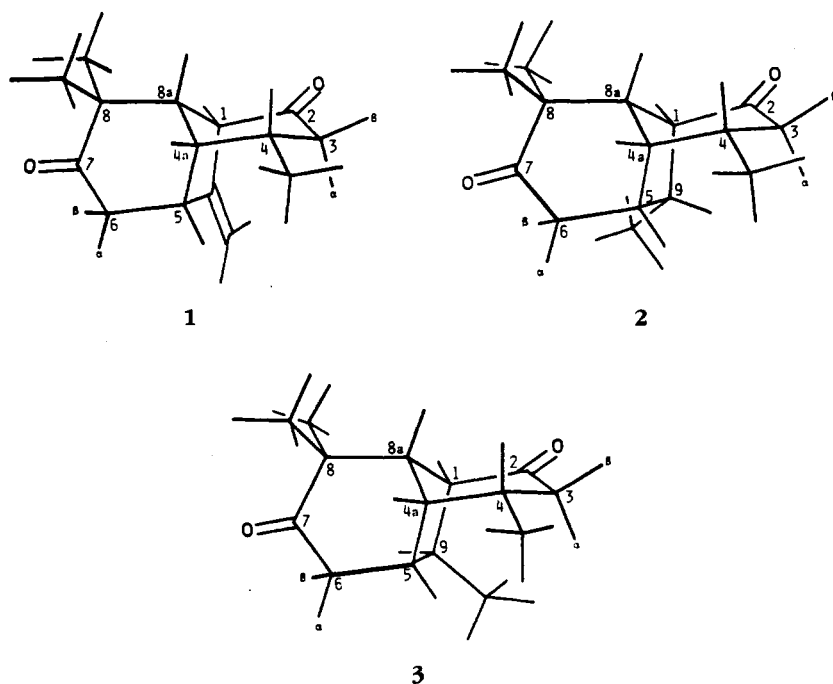| Compound	Parameters	H_1CCH_9	$H_{3\alpha}CCH_4$	$H_{3\beta}CCH_4$	$H_5CCH_{6\alpha}$	$H_5CCH_{6\beta}$	H_5CCH_9	H_6CCH_7
1	J^a	—	11.2	7.7	3.7	3.1	—	—
	ϕ_J	—	+160	+33	−55	+59	—	—
	ϕ_{MMX}	—	+163	+44	−55	+62	—	—
2	J^a	2.0	10.5	8.0	3.6	3.0	7.5	—
	ϕ_J	+109	+155	+30	−56	+60	−31	—
	ϕ_{MMX}	+103	+156	+39	−59	+58	−22	—
3	J^b	7.0	11.2	7.6	3.6	3.0	2.4	—
	ϕ_J	−36	+160	+33	−56	+60	+113	—
	ϕ_{MMX}	−33	+153	+37	−59	+59	+118	—
5	J^b	3.2	7.8	8.6	—	2.9	6.0	9.0
	ϕ_J	+117	−31	−144	—	+64	−42	−177
	ϕ_{MMX}	+119	−36	−154	—	+62	−34	−164
6	J^a	8.6	7.9	9.2	—	2.9	2.0	8.8
	ϕ_J	−26	−31	−147	—	+65	+109	−175
	ϕ_{MMX}	−21	−37	−154	—	+63	+103	−164

[a] In C_6D_6.
[b] In $CDCl_3$.

FIGURE 2.   MMX molecular models of 4-*epi*-moreliene derivatives [1–3] showing the
             preferred conformation.

group at C-4 has a *quasi*-equatorial orientation. As can be seen in Table 2, there is a
consistence in the coupling constant values of the C-3–C-4 fragment and, therefore,
changes of stereochemistry at C-9 have essentially no influence on the ring conformation
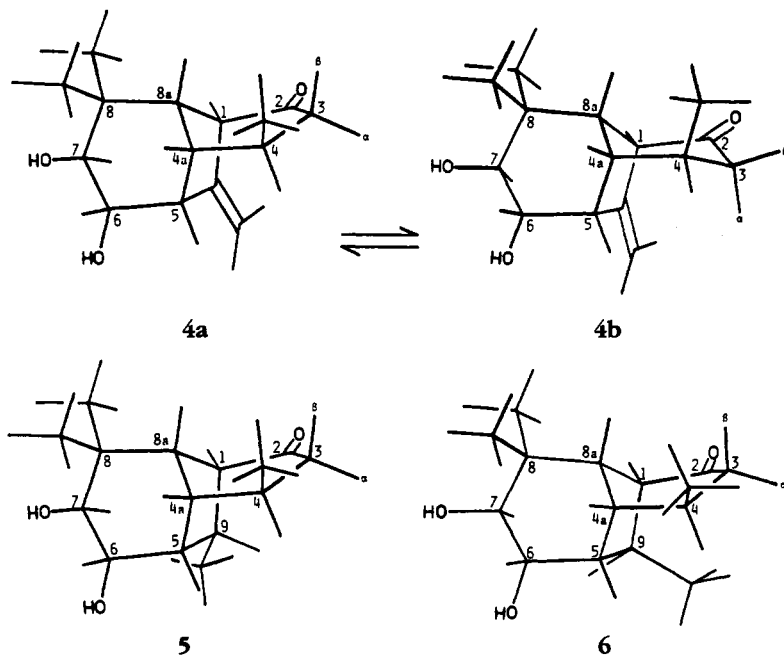

FIGURE 3.   MMX molecular models of moreliene derivatives [4–6] showing the
             preferred conformations.

TABLE 3.   Selected Experimental Coupling Constants (J in Hz) of Endiolone [4],
H-C-C-H Dihedral Angles from MMX Calculations (ϕ_{MMX} in degrees), and
Coupling Constants Calculated from ϕ_{MMX} (J in Hz) of Conformers 4a and 4b.

H(X)-C-C-H(Y) X,Y	Compound					
	4[a]	4a[b]		4b[c]		
	J[a]	ϕ_{MMX}	J_{MMX}	ϕ_{MMX}	J_{MMX}	
3α,4	8.6	−40	6.5	+35	7.0	
3β,4	3.9	−158	10.9	−81	1.0	
5,6β	3.0	+65	2.7	+65	2.7	
6,7	9.0	−165	7.7	−165	7.7	

[a]In CDCl₃.
[b]MMX energy=32.09.
[c]MMX energy=31.32.

for these three substances [1–3]. In compounds having the β-oriented methyl group at C-4, a large difference in the coupling constants of the C-3–C-4 fragment is observed between compound 4 (Table 3), in which C-9 is sp², and compounds 5–6 (Table 2) having C-9 sp³. Calculations from the nmr data show that in compounds 5 and 6 ring B exists in a conformation midway between boat and half-chair, while in 4 ring B exists in an equilibrium of conformers midway between boat and half-chair [4a] and a conformer midway between chair and half-chair [4b], in agreement with the MMX calculations (Table 3). In compounds 1–3, long-range coupling was observed between H-1 and H-3β as expected for a W-type arrangement (see Figure 2). Such coupling is not observed in 5 and 6, but is present in 4 which experimentally supports the existence of conformer 4b, in which there is a W-arrangement between H-1 and H-3β (see Figure 3).

Finally, the conformation of the five-membered ring for this series can not be fully evaluated from the coupling constants, because, with the exception of $J_{1,9}$ and $J_{5,9}$, they show very small values. However, the *C-C-C-C* torsion angles listed in Table 4, which are obtained from the molecular models, can supply the complementary conformational information.

TABLE 4.   Calculated C-C-C-C Torsion Angles (degrees)
of the Five-membered Ring for Moreliene Derivatives [1–6].[a]

Atoms	Compound						
	1	2	3	4a	4b	5	6
C1-C8a-C4a-C5	−51	−52	−51	−53	−53	−53	−53
C8a-C4a-C5-C9	+40	+44	+36	+46	+43	+53	+46
C4a-C5-C9-C1	−13	−17	−5	−21	−17	−30	−20
C5-C9-C1-C8a	−19	−16	−27	−12	−15	−3	−14
C9-C1-C8a-C4a	+44	+43	+50	+40	+41	+35	+42

[a]From the MMX calculations.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Chromatographic separation was performed with Merck Si gel 60 (70–230 mesh ASTM). Mps are uncorrected. Ir spectra were obtained in CHCl₃ on a Nicolet MX-1 spectrophotometer. Specific rotations were determined in CHCl₃ on a Perkin-Elmer 241 polarimeter. The nmr spectra were recorded at 300 MHz for ¹H and 75.4 MHz for ¹³C from CDCl₃ and/or C₆D₆ solutions

containing TMS as the internal reference on a Varian Associates XL-300GS spectrometer. Mass spectra were recorded at 70 eV on a Hewlett Packard HP-5988A spectrometer and elemental analyses were conducted by the Microanalytical Laboratory, Elbach, Germany. Molecular models were obtained using PCMODEL (4.50) available from Serena Software. The program is a derived version of the MM2 program developed by N.L. Allinger (QCPE 395), University of Georgia.

4-*EPI*-MORELI-9-ENE-2,7-DIONE [1].—A solution of **8** (2) (100 mg) in AcOH (1 ml) was treated with a solution of CrO_3 (100 mg) in H_2O (0.2 ml) at 0°. The reaction mixture was allowed to react at room temperature for 1 h, poured over ice-H_2O and extracted with Et_2O. The organic layer was washed with aqueous $NaHCO_3$ and H_2O, dried with Na_2SO_4, filtered and evaporated to dryness to give oily **1** (93 mg, 93%). Ir ν max 1707 (C=O) cm^{-1}; $[\alpha]_{589} +13°, [\alpha]_{578} +14°, [\alpha]_{546} +16°, [\alpha]_{436} +35°, [\alpha]_{365} +83° (c=4.5)$; ^{1}H nmr (CDCl$_3$) δ 5.12 (1H, br m, H-13), 5.08 (1H, m, H-13'), 3.39 (1H, br s, H-1), 3.08 (1H, br m, H-5), 2.74 (1H, dd, $J_{5,6\beta}=3.1, J_{6\alpha,6\beta}=16.2$ Hz, H-6β), 2.52 (1H, br s, H-4a), 2.47 (1H, dd, $J_{5,6\alpha}=3.8, J_{6\alpha,6\beta}=16.2$ Hz, H-6α), 2.26–2.10 (3H, complex m, H-3α, H-3β and H-4), 1.96 (1H, br d, $J_{5,8a}=2.3$ Hz, H-8a), 1.21 (3H, s, Me-11), 1.14 (3H, d, $J_{4,10}=7.3$ Hz, Me-10), and 1.06 ppm (3H, s, Me-12); ^{1}H nmr (C$_6$D$_6$) δ 4.83 (1H, br m, H-13), 4.65 (1H, m, H-13'), 3.41 (1H, br s, H-1), 2.40 (1H, br m, H-5), 2.22 (1H, dd, $J_{5,6\alpha}=3.7, J_{6\alpha,6\beta}=16.1$ Hz, H-6α), 2.12 (1H, dd, $J_{5,6\beta}=3.1, J_{6\alpha,6\beta}=16.1$ Hz, H-6β), 1.98 (1H, br dd, $J_{3\alpha,3\beta}=15.5, J_{3\beta,4}=7.7$ Hz, H-3β), 1.90 (1H, dd, $J_{3\alpha,3\beta}=15.5, J_{3\alpha,4}=11.2$ Hz, H-3α), 1.88 (1H, br m, H-4a), 1.53 (1H, dddq, $J_{3\alpha,4}=11.2, J_{3\beta,4}=7.7, J_{4,4a}=2.7, J_{4,10}=7.3$ Hz, H-4), 1.46 (1H, br d, $J_{5,8a}=2.3$ Hz, H-8a), 0.96 (3H, s, Me-11), 0.80 (3H, s, Me-12) and 0.62 ppm (3H, d, $J_{4,10}=7.3$ Hz, Me-10); ^{13}C nmr (CDCl$_3$) δ 213.5 (C-7), 208.2 (C-2), 149.9 (C-9), 111.3 (C-13), 60.0 (C-1), 57.1 (C-8a), 49.3 (C-4a), 48.4 (C-8), 47.6 (C-6), 42.3 (C-3), 39.8 (C-5), 34.6 (C-4), 27.2 (C-11), 22.3 (C-12), and 19.5 ppm (C-10); ms m/z [M]$^+$ 232 (100), 217 (16), 204 (10), 189 (15), 161 (22), 133 (23).

9-*EPI*-MORELIANE-6α,7β-DIOL-2-ONE [5] AND MORELIANE-6α,7β-DIOL-2-ONE [6].—A solution of **4** (2) (160 mg) in EtOH (50 ml) was stirred in the presence of prehydrogenated PtO$_2$ under H$_2$ at room temperature and normal pressure until uptake of the gas ceased. The catalyst was removed by filtration and the solvent evaporated to dryness. Cc, eluting with CHCl$_3$, afforded **5** (40 mg, 25%) as white prisms, mp 200–201°, and **6** (60 mg, 37%), as a white powder mp 96–98°.

Recrystallizations from Me$_2$CO-hexane provided pure **5**: mp 201–203°; ir ν max 3620 and 3460 (OH), 1700 (C=O) cm^{-1}; $[\alpha]_{589} 0°, [\alpha]_{578} +4°, [\alpha]_{546} +8°, [\alpha]_{436} +12°, [\alpha]_{365} +73° (c=1.3)$; ^{1}H nmr (CDCl$_3$) δ 3.72 (1H, dt, $J_{5,6}=J_{6,OH}=3.0, J_{6,7}=9.4$ Hz, H-6), 3.54 (1H, dd, $J_{6,7}=9.4, J_{7,OH}=4.8$ Hz, H-7), 2.50 (1H, dd, $J_{1,8a}=2.0, J_{1,9}=3.2$ Hz, H-1), 2.09 (1H, br m, H-5), 2.03 (1H, br dq, $J_{1,9}=3.2, J_{9,13}=7.0$ Hz, H-9), 1.97 (1H, br s, H-8a), 1.94 (1H, d, $J_{6,OH}=3.4$ Hz, OH-6), 1.91 (1H, dd, $J_{3\alpha,3\beta}=18.9, J_{3\beta,4}=8.6$ Hz, H-3β), 1.87 (1H, d, $J_{7,OH}=4.8$ Hz, OH-7), 1.75 (1H, m, H-4), 1.67 (1H, br s, H-4a), 1.34 (3H, d, $J_{9,13}=7.0$ Hz, Me-13), 1.05 (3H, d, $J_{4,10}=6.8$ Hz, Me-10), 1.04 (3H, s, Me-12), and 0.99 ppm (3H, s, Me-11); ^{13}C nmr (CDCl$_3$) δ 210.7 (C-2), 76.6 (C-7), 76.5 (C-6), 56.3 (C-1), 51.7 (C-5), 50.8 (C-4a), 47.1 (C-8a), 42.8 (C-3), 37.4 (C-8), 35.1 (C-9), 30.7 (C-4), 24.8 (C-11), 23.8 (C-10), 21.8 (C-12), and 15.7 ppm (C-13); *anal.* calcd for C$_{15}$H$_{24}$O$_3$, C 71.39, H 9.59, O 19.02; found C 71.48, H 9.42, O 18.96%; ms m/z [M]$^+$ 252 (42), 219 (13), 191 (8), 151 (27).

Recrystallizations of **6** from CH$_2$Cl$_2$-hexane gave a pure sample: mp 101–103°, ir ν max 3620 and 3470 (OH), 1700 (C=O) cm^{-1}; $[\alpha]_{589} -24°, [\alpha]_{578} -20°, [\alpha]_{546} -17°, [\alpha]_{436} -20°, [\alpha]_{365} -48° (c=1.2)$; ^{1}H nmr (CDCl$_3$) δ 3.63 (1H, dd, $J_{5,6}=2.9, J_{6,7}=8.8$ Hz, H-6), 3.22 (1H, d, $J_{6,7}=8.8$ Hz, H-7), 2.75 (1H, dd, $J_{1,8a}=1.5, J_{1,9}=8.6$ Hz, H-1), 2.39 (1H, br dq, $J_{1,9}=8.6, J_{9,13}=7.6$ Hz, H-9), 2.31 (1H, complex signal, H-3α), 2.25 (1H, br s, OH), 2.02 (1H, br s, OH), 1.92 (1H, br s, H-8a), 1.90 (1H, complex signal, H-3β), 1.86 (1H, complex signal, H-4), 1.84 (1H, br m, H-5), 1.18 (1H, br s, H-4a), 1.07 (3H, d, $J_{4,10}=6.7$ Hz, Me-10), 1.02 (3H, s, Me-12), 0.98 (3H, s, Me-11), and 0.96 ppm (3H, d, $J_{9,13}=7.6$ Hz, Me-13); ^{1}H nmr (C$_6$D$_6$) δ 3.21 (1H, dd, $J_{5,6}=2.9, J_{6,7}=8.8$ Hz, H-6), 2.77 (1H, d, $J_{6,7}=8.8$ Hz, H-7), 2.66 (1H, dd, $J_{1,8a}=1.5, J_{1,9}=8.6$ Hz, H-1), 2.15 (1H, br dq, $J_{1,9}=8.6, J_{9,13}=7.6$ Hz, H-9), 2.08 (1H, dd, $J_{3\alpha,3\beta}=19.0, J_{3\alpha,4}=7.9$ Hz, H-3α), 1.60 (1H, dd, $J_{3\alpha,3\beta}=19.0, J_{3\beta,4}=9.2$ Hz, H-3β), 1.49 (1H, br s, H-8a), 1.40–1.20 (5H, complex m, H-4, H-4a, H-5 and OH's), 0.89 (3H, d, $J_{4,10}=6.7$ Hz, Me-10), 0.80 (3H, s, Me-12), 0.78 (3H, s, Me-11), and 0.66 ppm (3H, d, $J_{9,13}=7.6$ Hz, Me-13); ^{13}C nmr (CDCl$_3$) δ 213.5 (C-2), 79.0 (C-7), 76.0 (C-6), 55.3 (C-5), 54.7 (C-1), 51.6 (C-4a), 45.7 (C-3), 43.4 (C-8a), 37.1 (C-8), 32.3 (C-9), 29.8 (C-4), 26.1 (C-11), 24.2 (C-10), 21.8 (C-12), and 18.8 ppm (C-13); ms m/z [M]$^-$ 252 (39), 237 (46), 219 (14), 191 (9), 151 (15).

X-RAY ANALYSIS.[1]—A single crystal of moreli-3-ene-2,7-dione [7] was grown by slow crystallization from CH$_2$Cl$_2$-hexane. It was orthorhombic P, space group $P2_12_12_1$ with $a=7.179$ (3), $b=9.871$ (4),

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[1]Atomic coordinates for the structure of **7** are deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, 12 Union Road, Cambridge CB2 1EZ, UK.

$c=18.446 (9)$ Å, cell volume $=1307 (1)$ Å^3, ρ (calcd) $=1.17$ g/cm^3 for Z$=4$, MW 232.32, and F(000)e$^-$ $=504$. The intensity data were measured on a Nicolet R3m four-circle diffractometer equipped with CuKα radiation ($\lambda=1.54178$ Å) operating in the θ:2θ scanning mode. The size of the crystal used was ca. $0.25 \times 0.15 \times 0.10$ mm^3. No absorption correction was necessary ($\mu=5.7$ cm^{-1}). A total of 1046 reflections were measured for $3° < \theta < 110°$, scan width below $K_{\alpha1}=1.2$ and above $K_{\alpha2}=1.0°$, scan speed from 4.0 to 29.3°/min and exposure time$=23.6$ h. A total of 701 reflections were considered to be observed [I$>3\sigma$(I)]. The data measured were corrected for background, Lorentz, and polarization effects, while crystal decay and absorption were negligible. The structure was solved by direct methods using the software provided by the diffractometer manufacturer. For the structural refinement the non-hydrogen atoms were treated anisotropically and the hydrogen atoms bonded to carbon, included in the structure factor calculation, were refined isotropically. Final discrepancy indices were R$=4.8\%$ using a unit weight of 595 reflections. The final difference Fourier map was essentially featureless, the highest residual peaks having densities of 0.14 e/Å^3. Several reflections were excluded from the final refinement calculation to improve the fit.

ACKNOWLEDGMENT

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