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α-LONGIPINENE DERIVATIVES FROM *SANTOLINA VISCOSA*. A CONFORMATIONAL ANALYSIS OF THE CYCLOHEPTANE RING

A.F. BARRERO,* M.M. HERRADOR, J. MOLINA MOLINA, J.F. QUÍLEZ,

Departamento de Química Orgánica

and M. QUIRÓS

*Departamento de Química Inorgánica, Facultad de Ciencias,
Universidad de Granada, 18071, Granada, Spain*

ABSTRACT.—The aerial parts of *Santolina viscosa* afforded the new longipinene derivatives, methyl longipin-9-en-15-oate [1], methyl 14-hydroxylongipin-9-en-15-oate [2], methyl 12-hydroxylongipin-9-en-15-oate [3], methyl 14-methoxylongipin-9-en-15-oate [4], and methyl 12-methoxylongipin-9-en-15-oate [5]. Their structures were established by 2D nmr experiments and chemical correlations. The conformational analysis of the seven-membered ring was achieved through the use of nmr techniques and molecular mechanics calculations. Furthermore, a single-crystal X-ray diffraction study of the *p*-bromobenzoyl derivative **9** established the absolute stereochemistry of these compounds.

The genus *Santolina* has been reported to possess compounds with diverse biological and pharmacological properties (1,2). As a continuation of our previous work on aromatic and medicinal plants endemic to Southern Spain (3), this paper describes the isolation and structural elucidation of five longipinene derivatives [1–5] found in the aerial parts of *Santolina viscosa* Lag. (Compositae). So far, stereochemical and conformational studies of longipinene derivatives have been described only in compounds with substituents at the seven-membered ring (4). We describe herein a conformational study of the new longipinene derivatives using nmr techniques and molecular mechanics calculations.

RESULTS AND DISCUSSION

Compounds **1–5**, previously esterified with CH_2N_2, were isolated from the hexane extract of the aerial parts of *S. viscosa*. Allylic oxidation of **1** with SeO_2 gave **6**, whose molecular formula was established by its mass ([M]$^+$ at *m/z* 262) and ^{1}H- and ^{13}C-nmr spectra. Analysis of the ^{13}C-nmr spectrum of **6** indicated it was the methyl ester of a tricyclic sesquiterpene. The ir bands at 2714 and 1677 cm^{-1}, together with the nmr signals at δ 9.38 and 6.67 ppm (^{1}H nmr) and 190.17 ppm (^{13}C nmr), revealed the presence of an α,β-unsaturated aldehyde. The methyl ester was shown in its ir (1727 cm^{-1}), ^{1}H-nmr (methoxyl group at δ 3.57, s) and ^{13}C-nmr (carbonyl group at δ 177.69) spectra. The correlations observed in HETCOR and COSY nmr measurements allowed the determination of connectivities I and II in the molecule of compound **6** (Figure 1).

	R_1	R_2	R_3
1	CH_3	CH_3	COOMe
2	CH_3	CH_2OH	COOMe
3	CH_2OH	CH_3	COOMe
4	CH_3	CH_2OMe	COOMe
5	CH_2OMe	CH_3	COOMe
6	CHO	CH_3	COOMe
7	CH_3	COOH	COOMe
8a	CH_3	H	COOMe
8b	CH_3	COOMe	H
9	CH_3	p-Br-Bz	COOMe
10	CH_3	CH_3	COOMe

$$OHC - C = CH - CH_2 - CH - \quad - C - CH_2 - CH_2 - CH_2 - C -$$

$$- CH -$$

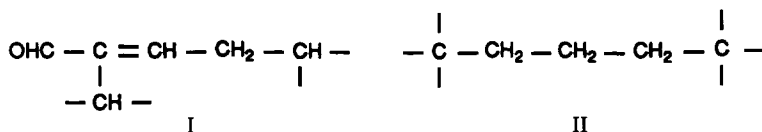I   II
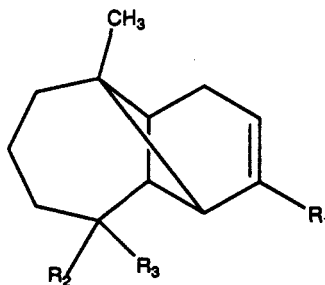
FIGURE 1.   Connectivities Determined by HETCOR and COSY Nmr Measurements
for **6**.

Assignment of the methyl 12-oxo-longipin-9-en-15-oate structure to **6** was achieved on the basis of the long-range correlations observed in the ^{1}H-^{13}C COLOC nmr experiment (Figure 2).
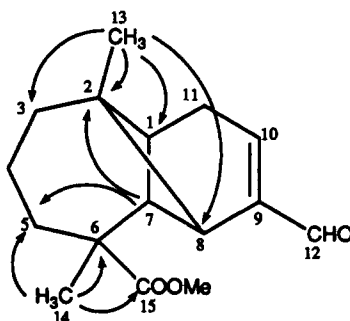

FIGURE 2.   Long-Range Correlations Observed for **6** in the ^{1}H-^{13}C COLOC Experiment.

Natural compound **1** showed a methyl group attached to a trisubstituted double bond (^{1}H nmr, q, δ 1.68 ppm; ^{13}C, δ 23.01) instead of the aldehyde group of **6**. The spectroscopic data of **2** were very similar to those of **1**, showing in its ms the presence of an additional oxygen, [M]$^+$ at m/z 264 ($C_{16}H_{24}O_3$), which was attributed to the presence of a -CH$_2$OH group attached to a quaternary carbon (^{1}H, d, δ 3.53; ^{13}C, δ 66.65). The chemical shift variations experienced by the signals corresponding to C-6, C-7, and C-5 with respect to the values of **1** (Tables 1 and 2), were those theoretically predictable according to the β and γ-effects produced by the presence of a hydroxyl at C-14. This permitted the location of the CH$_2$OH at C-6. The presence of a hydroxyl group at C-14 was confirmed by oxidation of **2** with pyridinium dichromate (PDC), leading to the formation of the monomalonyl ester, **7**, which decarboxylated in refluxed toluene to give a mixture of diastereomers, **8**. On the other hand, the chemical correlation of **2** with **1** was achieved by oxidation of **2** with PDC/DMF and subsequent reduction of the resulting aldehyde following the Huang-Minlon procedure (5).

The spectroscopic features of **3** resembled those of **2**. The molecular ion appeared at m/z 262 in both compounds, indicating that they were isomers. The hydroxyl group in **3** was located at C-12 on the grounds of the chemical shift and multiplicity of the signal corresponding to H-12 (δ 4.0 ppm, q, J=1.7 Hz) in the ^{1}H-nmr spectrum, and the shielding experienced by C-8 (δ 42.7 ppm) with regard to the chemical shift of C-8 in compound **1** (δ 47.2 ppm).

Compounds **4** and **5** were the corresponding methyl ethers of alcohols **2** and **3**, respectively. Their structures were confirmed by methylation of **2** and **3**, respectively, with MeI in the presence of NaH.

Because the 4- and 6-membered bicyclic system is rigid for longipinenes, each

TABLE 1.   ¹H-Nmr Chemical Shifts of Compounds **1–5**.[a]

Proton	1	2	3	4	5
1	1.96–2.15 m	2.17 d (6.0)	2.05–2.15 m	2.01–2.17 m	2.08–2.17 m
3	1.49–1.64 m	1.55–1.72 m	1.50–1.65 m	1.48–1.71 m	1.50–1.73 m
5a.	1.28–1.38 m	1.43–1.52 m	1.33–1.42 m	1.28–1.37 m	1.28–1.37 m
5b	1.96–2.15 m	2.00–2.11 m	2.05–2.15 m	2.01–2.17 m	2.08–2.17 m
7	1.96–2.15 m	2.06 s	2.03 s	2.01–2.17 m	2.15 s
8	1.96–2.15 m	2.17 d (6.0)	2.30–2.36 m	2.01–2.17 m	2.28 d (6.3)
10	5.18–5.22 m	5.18–5.21 m	5.18–5.22 m	5.16–5.19 m	5.49–5.51 m
11	2.23–2.27 m	2.22–2.25 m	2.30–2.36	2.20–2.24 m	2.31–2.34 m
12	1.67 q (2.0)	1.66 q (2.0)	3.99 q (1.52)	1.64 q (2.0)	3.75–3.78 m
13	0.82 s	0.84 s	0.83 s	0.80 s	0.83 s
14	1.07 s	3.53 d (6.40)	1.08 s	3.26 s	1.08
COO*Me*	3.64 s	3.69 s	3.65 s	3.65 s	3.64 s
CH₂O*Me*				3.22 s	3.27 s

[a]Data are δ (ppm), multiplicity and *J* (in parentheses) in Hz.

structure can have the four A–D main conformations of the cycloheptane ring (Figure 3). Conformations C and D have a close resemblance to the classical, chair and boat, respectively; yet A and B do not correspond to any of the four classical conformers, but are an intermediate state between chair and twist-chair, which could be called "chair, twist-chair transition conformation A" and "chair, twist-chair transition conformation B", respectively. Molecular mechanics calculations were carried out for structures **2, 6, 8, 9**, and longipinene **10**. For compounds **2** and **10**, calculations were performed on the four conformations. We observed that A and B were the most stable ones, showing similar stability (Table 3). As can be seen in this table, the contribution to the total population of C and D conformers was negligible due to their high energy values (relative populations less than 10^{-3}). Accordingly, these two conformations were not considered in the study for the rest of the structures.

TABLE 2.   ¹³C-Nmr Chemical Shifts of Compounds **1–5**.[a]

Carbon	Compound				
	1	2	3	4	5
1	40.0	39.8	40.0	40.2	40.2
2	39.7	40.0	39.7	39.9	39.6
3	40.7	40.5	40.5	40.6	40.5
4	22.5	22.0	22.4	22.2	22.4
5	34.9[b]	30.0	34.9	30.8	34.8[d]
6	46.6	52.8	46.5	51.8	46.4
7	54.4	49.9	54.8	50.1	54.3
8	47.2	47.3	43.7	46.7	43.4
9	147.6	147.3	150.7	147.3	148.2
10	117.2	117.3	119.7	117.2	120.9
11	34.3[b]	34.0	35.0	34.1	34.3[d]
12	23.0[c]	23.0	66.1	22.9	75.2
13	23.4[c]	23.2	23.6	23.3	23.6
14	24.7	66.6	24.7	77.7	24.8
15	178.6	177.4	178.6	176.1	178.2
COO*Me*	51.6	51.8	51.6	51.6	51.4
CH₂O*Me*				59.3	57.8

[a]Chemical shifts in δ (ppm). Assignments were supported by DEPT experiments.
[b–d]Signal assignments with the same letter may be interchanged.

Conformation A   Conformation B   Conformation C   Conformation D
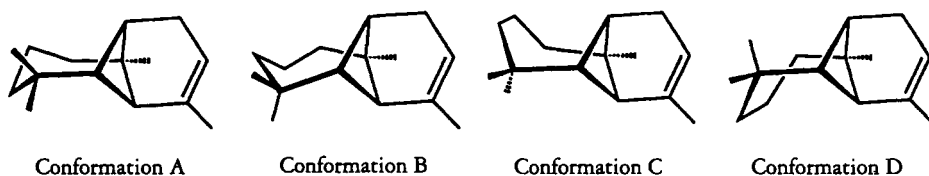
FIGURE 3.   Main Conformations for the Cycloheptane Ring.

TABLE 3.   Steric Energies of the Most Stable Ring Disposition for Compounds **2**, **6**, **8a**, **8b**, **9**, and **10**, Obtained by Molecular Mechanics Calculations.

Conformer	Energy (kcal/mol)	Relative population (%)
2A	54.54	52.47
2B	54.82	47.52
2C	60.58	
2D	63.00	
6A	55.60	69.39
6B	56.07	30.60
8aA	50.63	93.06
8aB	52.13	6.93
8bA	52.18	6.78
8bB	50.75	93.21
9A	80.96	32.97
9B	80.54	67.02
10A	52.60	52.11
10B	52.65	47.88
10C	59.60	
10D	59.63	

From the different A and B conformations obtained for each compound by molecular mechanics, theoretical coupling constants were obtained using the 3JHH2 program (see computational aspects in Experimental). When we compared these data with the coupling constants calculated for conformers A and B (Table 4) with the experimental data measured in CDCl$_3$ solution, we observed a remarkable resemblance between the average and the experimental data. This together with the energy figures obtained for the different conformations (Table 3) led us to conclude that these molecules present a rapid balance between A and B conformations.

The existence of only A and B conformations in equilibrium for these natural products facilitated the assignment of the relative configuration at C-6. Thus, in compound **6**, the nOe observed between H-1 and H-14 could only be explained if the molecule adopted the dispositions depicted in Figure 4.

A view of the molecular structure of the *p*-bromobenzoate **9**, as determined by X-ray diffraction, is shown in Figure 5. Bond distances and angles within the molecule were

TABLE 4.   Comparison Between Theoretical Coupling Constants for Conformer A (J_A), B (J_B) and Average Data (J_{Av}) and the Corresponding Experimental Values (J_{Exp}) Measured for Compounds **6** and **8**.

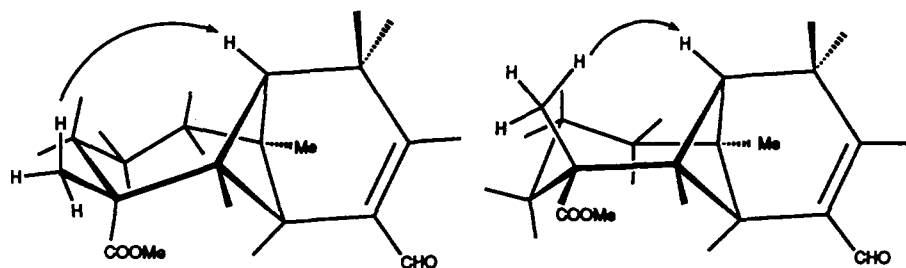|	Compound 6				Compound 8a			Compound 8b		
	H$_{5a}$-H$_{4a}$	H$_{5a}$-H$_{4b}$	H$_{5b}$-H$_{4a}$	H$_{5b}$-H$_{4b}$	H$_6$-H$_7$	H$_6$-H$_{5a}$	H$_6$-H$_{5b}$	H$_6$-H$_7$	H$_6$-H$_{5a}$	H$_6$-H$_{5b}$
J_A	2.2	12.4	6.1	1.9	2.2	4.9	11.6	4.4	3.5	5.0
J_B	2.2	5.7	12.6	2.4	4.9	3.6	3.8	2.2	11.6	4.9
J_{Av}	2.2	10.4	8.1	2.1	2.4	4.9	11.0	2.4	11.0	5.0
J_{Exp}	1.5	11.3	7.9	0.0	2.5	5.2	9.7	2.7	9.3	5.6

FIGURE 4.   Most Stable Conformations Obtained by Molecular Mechanics Calculations (the observed nOes, indicated by arrows, led to the establishment of the configuration at C-6).
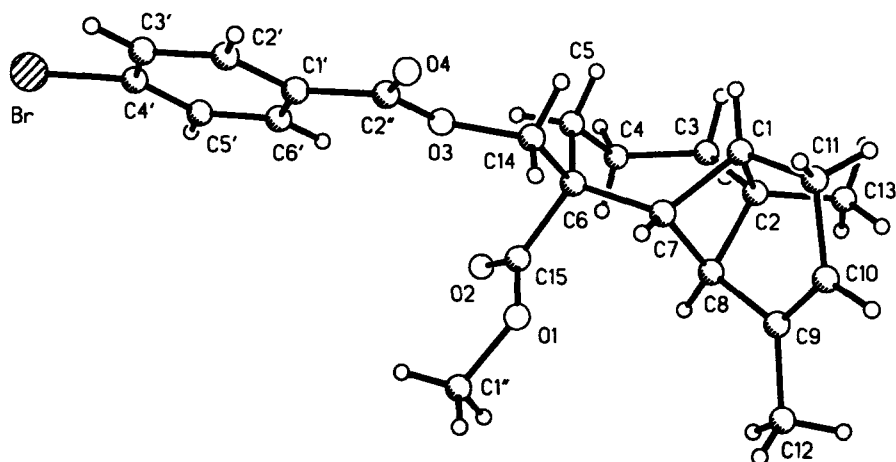

FIGURE 5.   Perspective View of the Molecular Structure of **9**.

those expected (6) in accordance with the sp^2 or sp^3 nature of the atoms involved and the geometric constraints imposed by the rings. The dispositions of the substituents at C-6 is indicated by the torsion angles: C-2″–O-3–C-14–C-7=169.4°, O-3–C-14–C-6–C-5=64.6°, O-2–C-15–C-6–C-5=−1.5°.

The deviations of atoms C-4 and C-5 from the C-2–C-3–C-6–C-7 plane (see Table 5) allowed us to determine as type B the conformation of the seven-membered ring in **9**. The same conformation was found in the crystal structure of three other longipinene derivatives (7–9), whereas type A conformation was found in only one case (10). The differences between both conformations are also evident from the torsion angles in the seven-membered ring, also included in Table 5.[1]

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mps were measured with a Reichert Kofler microscope and are uncorrected. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter. Ir spectra were obtained on a Perkin-Elmer 983G instrument. Eims were determined on a Hewlett-Packard 5988A mass spectrometer. Nmr (¹H, ¹³C, NOEDIF and 2D experiments) were recorded on a Bruker AM 300 spectrometer using TMS as internal standard. Cc was carried out using Si gel Merck 60 (70–230 mesh) and eluting with mixtures of hexane/Et₂O/EtOAc of increasing polarity. Anal. tlc was performed on layers of Si gel Merck 60 G of 0.25 mm thickness, using a 7% phosphomolybdic acid solution in EtOH to visualize the spots.

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[1]Coordinates for these compounds were obtained via the Cambridge Structural Data Base (11).

TABLE 5.   Comparison of A and B Conformations for Compound **9**, as Determined by X-Ray Diffraction, with Those of Previously Reported Longipinene Derivatives.

	9	Ref. (7)	Ref. (8)	Ref. (9)	Ref. (10)
$\phi_{1,2}$[a]	88.9 (5)	88.1 (3)	87.4 (7)	85.1	88.8
$\phi_{2,3}$	−64.8 (7)	−67.3 (3)	−67.2 (9)	−62.1	−27.2
$\phi_{3,4}$	54.7 (7)	61.0 (3)	60.3 (10)	57.1	−59.2
$\phi_{4,5}$	−75.5 (6)	−79.7 (3)	−80.4 (9)	−82.2	76.9
$\phi_{5,6}$	52.3 (6)	50.3 (3)	57.2 (9)	52.5	−45.8
$\phi_{6,7}$	35.1 (6)	39.1 (4)	37.9 (10)	40.0	60.0
$\phi_{1,7}$	−96.4 (4)	−99.7 (3)	−98.2 (8)	−99.6	−95.8
d (C$_4$)[b]	−0.388	−0.491	−0.488	−0.445	0.537
d(C$_5$)	0.398	0.351	0.344	0.410	−0.255

[a]$\phi_{1,2}$ is the abreviation for the torsion angle C-7–C-1–C-2–C-3. Analogous definitions for the torsion angles in the C-1–C-2–C-3–C-4–C-5–C-6–C-7 ring.
[b]Distances of C-4 and C-5 from the least-square C-2–C-3–C-6–C-7 plane. Positive values indicate deviations toward C-1. Negative values indicate deviations toward C-8.

PLANT MATERIAL.—*Santolina viscosa* Lag. (Compositae) was collected in Las Yeserías (Almería, Spain) and was identified by Professor J. Molero, Departamento de Biología Vegetal, Universidad de Granada. A voucher specimen is available for inspection at the Herbarium of the Facultad de Farmacia, Universidad de Granada.

EXTRACTION AND ISOLATION.—The air-dried material (7.9 kg) was extracted in a Soxhlet apparatus, resulting in 510 g of extract. A 60 g portion was defatted, dissolved in Et$_2$O, and extracted with a 1 N NaOH solution to yield 35 g of a neutral fraction and 10.5 g of an acid one. The latter was treated with CH$_2$N$_2$ to obtain the mixture of the methyl esters of the corresponding acids. This mixture was subjected to cc over Si gel using mixtures of hexane/Et$_2$O of increasing polarity as eluents. Six main fractions were collected (A-F). The less polar fraction contained **1** {hexane-Et$_2$O (9:1)}. Fraction B yielded **2** {hexane-Et$_2$O (8:2)}. The third fraction {hexane-Et$_2$O (7:3)} was rechromatographed with hexane and increasing amounts of Et$_2$O to give **3** {hexane-Et$_2$O (95:5)}. Fraction D afforded **4** {hexane-Et$_2$O (6:4)}. The following fraction, E, contained a mixture of **4** and **5** {hexane-Et$_2$O (6:4)}. Finally, F was pure **5** {hexane-Et$_2$O (1:1)}.

Methyl longipin-9-en-15-oate {**1**}.—Syrup; $[\alpha]^{25}$D +17.5° (c=1.0, CHCl$_3$); eims (70 eV) m/z 248 (2), 216 (5), 189 (5), 173 (6), 145 (12), 119 (100), 105 (38), 91 (54), 59 (31); ir ν max (film) 2925, 1730, 1414, 1372, 1252, 1195, 1149, 1114 cm^{-1}; ^{1}H nmr and ^{13}C nmr, see Tables 1 and 2.

Methyl 14-hydroxylongipin-9-en-15-oate {**2**}.—Syrup; $[\alpha]^{25}$D +16.5° (c=1.0, CHCl$_3$); eims (70 eV) m/z 264 (2), 214 (4), 186 (8), 158 (14), 145 (21), 131 (24), 119 (100), 105 (48), 91 (72), 59 (24); ir ν max (film) 3424, 2922, 2837, 1722, 1434, 1374, 1211, 1149, 1102, 979 cm^{-1}; ^{1}H nmr and ^{13}C nmr, see Tables 1 and 2.

Methyl 12-hydroxylongipin-9-en-15-oate {**3**}.—Syrup; $[\alpha]^{25}$D +10.8° (c=1.0, CHCl$_3$); eims (70 eV) m/z 264 (1), 246 (10), 214 (8), 186 (30), 172 (61), 158 (37), 145 (30), 131 (61), 119 (40), 105 (68), 101 (56), 95 (47), 91 (100), 79 (69), 59 (51); ir ν max (film) 3437, 2925, 1727, 1455, 1433, 1373, 1256, 1150, 1113, 981, 911, 857, 801 cm^{-1}; ^{1}H nmr and ^{13}C nmr, see Tables 1 and 2.

Methyl 14-methoxylongipin-9-en-15-oate {**4**}.—Syrup; $[\alpha]^{25}$D +4.8° (c=1.0, CHCl$_3$); eims (70 eV) m/z 279 (4), 278 (3), 267 (3), 251 (2), 221 (10), 187 (21), 186 (14), 173 (27), 159 (32), 158 (30), 145 (38), 131 (48), 119 (99), 105 (63), 91 (77), 43 (100); ir ν max (film) 2921, 2837, 1734, 1438, 1375, 1258, 1207, 1150, 1113, 1021, 983, 913 cm^{-1}; ^{1}H nmr and ^{13}C nmr, see Tables 1 and 2.

Methyl 12-methoxylongipin-9-en-15-oate {**5**}.—Syrup; $[\alpha]^{25}$D +12.0° (c=1.0, CHCl$_3$); eims (70 eV) m/z 279 (2), 246 (3), 214 (5), 187 (21), 186 (19), 145 (39), 131 (57), 119 (67), 105 (71), 91 (100), 55 (63), 43 (74); ir ν max (film) 2923, 1736, 1435, 1374, 1258, 1203, 1150, 1113, 1019, 982, 912 cm^{-1}; ^{1}H nmr and ^{13}C nmr, see Tables 1 and 2.

PREPARATION OF **3** AND **6**.—A solution of 106 mg of SeO$_2$ in 95% EtOH (11 ml) and 120 mg of **1** was refluxed for 24 h. Work up as usual gave 28 mg of **3** and 44 mg of the aldehyde, **6**. Syrup; $[\alpha]^{25}$D +49.5° (c=1.0, CHCl$_3$); eims (70 eV) m/z 262 (9), 230 (5), 202 (26), 172 (20), 147 (39), 131 (27), 119 (28), 105 (52), 91 (100), 77 (75), 59 (53); ir ν max (film) 2926, 2714, 1727, 1677, 1453, 1432, 1397, 1369, 1255, 1201, 1148, 1129, 1035, 984, 883, 865, 810, 765, 711 cm^{-1}; ^{1}H nmr (C$_6$D$_6$) δ 0.53 (3H, s, H-13), 0.99

(3H, s, H-14), 1.12–1.22 (1H, ddd, J=13.5, 11.3, and 1.5 Hz, H-5a), 1.24–1.33 (1H, m, H-3a), 1.45–1.68 (3H, m, H-3b, H-4), 1.71–1.76 (1H, m, H-1), 1.87 (1H, s, H-7), 2.07 (2H, q, J=3.2 Hz, H-11), 2.27–2.35 (1H, dd, J=13.5 and 7.9 Hz, H-5b), 3.31 (1H, d, J=5.9 Hz, H-8), 3.38 (3H, s, -COO*Me*), 5.88–5.92 (1H, m, H-10); ^{13}C nmr δ 22.20 (C-4), 23.36 (C-13), 24.71 (C-14), 34.70 (C-5), 36.03 (C-11), 38.35 (C-3), 39.28 (C-2), 39.93 (C-3), 39.98 (C-1), 46.33 (C-6), 51.69 (-COO*Me*), 54.36 (C-7), 148.45 (C-10), 154.13 (C-9), 177.69 (-*C*OOMe), 190.17 (C-12).

CONVERSION OF **2** TO **1**.—A solution of **2** (175 mg) in CH$_2$Cl$_2$ (2 ml) was stirred for 24 h with PDC (378 mg) to obtain 75 mg of the corresponding aldehyde which was mixed with hydrazine hydrate (100 mg), diethylene glycol (2 ml), and KOH (285 mg) and heated at 200° for 2 h under N$_2$. The usual work-up gave a crude product which, after treatment with CH$_2$N$_2$, was subjected to cc to yield 15 mg of **1**.

CONVERSION OF **2** TO **9**.—A solution of 274 mg of N,N'-carbonyldiimidazole and 340 mg of p-bromobenzoic acid in THF (5 ml) was stirred for 1 h under N$_2$. Then 240 mg of **2** in 2 ml of THF were added dropwise. The reaction mixture was allowed to stand 24 h at room temperature. The THF solution was concentrated and, after addition of H$_2$O, extracted with Et$_2$O. Cc of the crude product afforded **9** (380 mg). Colorless crystals, mp 93–95°; [α]^{25}D +7.5° (c=1.0, CHCl$_3$); eims (70 eV) *m/z* 448 (1), 446 (1), 388 (1), 386 (1), 301 (1), 145 (39), 299 (1), 263 (1), 246 (15), 214 (27), 185 (100), 183 (92), 119 (97), 91 (52); ir ν max (film) 2923, 2838, 1726, 1590, 1482, 1434, 1397, 1374, 1269, 1213, 1192, 1174, 1152, 1115, 1102, 1062, 1012, 984, 915, 848, 802, 756, 682 cm^{-1}; ^{1}H nmr (CDCl$_3$) δ 0.85 (3H, s, H-13), 1.47–1.76 (5H, m, H-3, H-4, H-5a), 1.68 (3H, q, J=1.9 Hz, H-12), 3.69 (3H, s, -OCO*Me*), 4.26 (1H, d, J=4.0 Hz, H-14a), 4.32 (1H, d, J=4.0 Hz, H-14b), 5.19–5.22 (1H, m, H-10), 7.56 (2H, d, J=8.0 Hz, H-3', H-5'), 7.82 (2H, d, J=8.0 Hz, H-2', H-6'); ^{13}C nmr (CDCl$_3$) δ 21.94 (C-4), 22.90 (C-12), 23.24 (C-13), 30.47 (C-5), 33.97 (C-11), 40.04 (C-2), 40.20 (C-1), 40.32 (C-3), 46.86 (C-1), 50.12 (C-7), 50.65 (C-6), 51.91 (-COO*Me*), 68.88 (C-14), 117.36 (C-10), 128.22 (C-1'^{a}), 128.86 (C-4'^{a}), 131.13 (C-2', C-6'^{b}), 131.94 (C-3', C-5'^{b}), 147.10 (C-9), 165.49 (-*C*O-Ph-Br), 175.27 (-*C*OOMe). (^{a,b}Signal assignments with the same letter may be interchanged).

CONVERSION OF **2** TO **8a** AND **8b**.—Pyridinium dichromate (2.0 g) was added to a solution of **2** (400 mg) in DMF (5 ml). The mixture was stirred for 12 h at room temperature. The usual work-up gave 300 mg of a product, which was refluxed in toluene for 50 h. After removing the toluene, the residue was redissolved in Et$_2$O and extracted with 10% NaOH. Evaporation of the organic layer and cc of the product afforded a mixture of **8a** and **8b** (100 mg). Syrup; [α]^{25}D +13.6° (c=1.0, CHCl$_3$); eims (70 eV) *m/z* 234 (2), 221 (10), 207 (6), 173 (6), 147 (46), 119 (60), 105 (31), 91 (33), 73 (100); ir ν max (film) 2920, 2838, 1735, 1436, 1373, 1318, 1260, 1097, 1032, 804 cm^{-1}. **8a**: ^{1}H nmr (CDCl$_3$) δ 0.86 (3H, s, H-13), 1.46–1.83 (6H, m, H-3, H-4, H-5), 1.66 (3H, q, J=2.0 Hz, H-12), 2.14–2.34 (5H, m, H-1, H-7, H-8, H-11), 2.59 (1H, ddd, J=9.7, 5.2, and 2.5 Hz, H-6), 3.63 (3H, s, -COO*Me*), 5.16–5.20 (1H, m, H-10); ^{13}C nmr (CDCl$_3$) δ 22.95 (C-12), 23.41 (C-13), 24.32 (C-4), 27.98 (C-5), 33.64 (C-11), 40.21 (C-3), 40.60 (C-2), 41.52 (C-1), 46.35 (C-6^a), 47.24 (C-7^a), 48.21 (C-1^a), 51.41 (-COO*Me*), 117.66 (C-10), 147.16 (C-9), 176.71 (-*C*OOMe). **8b**: ^{1}H nmr (CDCl$_3$) δ 0.83 (3H, s, H-13), 1.46–1.83 (6H, m, H-3, H-4, H-5), 1.66 (3H, q, J=2.0 Hz, H-12), 2.03 (1H, s, H-8), 2.14–2.34 (4H, m, H-1, H-7, H-11), 2.70 (1H, ddd, J=9.3, 5.6, and 2.7 Hz, H-6), 3.61 (3H, s, -COO*Me*), 5.16–5.20 (1H, m, H-10); ^{13}C nmr (CDCl$_3$) δ 22.87 (C-12), 23.35 (C-13), 24.12 (C-4), 27.98 (C-5), 33.59 (C-11), 40.35 (C-3), 40.56 (C-2), 40.66 (C-1), 46.45 (C-6^b), 47.89 (C-7^b), 48.12 (C-1^b), 51.41 (-COO*Me*), 117.14 (C-10), 146.74 (C-9), 176.48 (-*C*OOMe). (^{a,b}Signal assignments with the same letter may be interchanged).

METHYLATION OF **2** AND **3**.—A solution of 160 mg of the alcohol **2** in 5 ml of THF was treated with MeI (0.25 ml) followed by 40 mg of NaH (20% paraffin liquid). The mixture was stirred for 2 h at room temperature. The usual workup yielded a crude product which was purified by cc to give **4** (125 mg). Compound **3** was treated as **2** to give **5**.

X-RAY DIFFRACTION ANALYSIS OF COMPOUND **9**.—Crystal data: C$_{23}$H$_{27}$BrO$_4$, mol wt=447.4, triclinic, space group P1, a=6.669 (2), b=9.235 (3), c=10.462 (4) Å, α=67.05 (1), β=73.43 (2), γ=69.22 (2)° (from 20 random oriented reflections), V=546.6 (3) Å^3, Z=1, F(000)=232, D$_c$=1.359 g/cm^{-3}, MoKα radiation (λ=0.71069 Å), μ=18.83 cm^{-1}. Crystal dimensions 0.28×0.26×0.46 mm.

A total of 5817 reflections with −10<h<10, −14<k<14, −2<l<16, 2θ<70° were recorded using a Siemens R3m/V diffractometer (MoKα radiation, ω scan). Three standard reflections measured every 90 min showed no significant change during the data collection. 2426 reflections with |F|>5σ(|F|) were retained for solving and refining the structure, and corrected for Lorentz and polarization effects and empirically for absorption (maximum and minimum transmission coefficients, 0.578 and 0.498).

The bromine atom was used to fix the arbitrary origin, the remaining atoms being readily located in successive ΔF maps. Non-hydrogen atoms were refined anisotropically by full-matrix least squares calculations, minimizing Σw (F$_o$-F$_c$)^2, with w^{-1}=σ^2 (F)+0.0006 F^2. Hydrogen atoms were idealized with

a fixed isotropic thermal parameter 1.2 times the equivalent isotropic thermal parameter of their parent carbon atoms. An isotropic extinction parameter was introduced and refined up to a value $\chi = 4.6(8) \times 10^{-3}$. A multiplier for the $\Delta f''$ values was also refined, the value $\eta = 0.98(4)$ being obtained, indicating that the chosen absolute configuration is correct. Final residues are: $R = 0.042$, $R_w = 0.042$, $GOF = 1.36$, $|\Delta\rho| < 0.49$ $e/\mathring{A}^3$.

   All calculations and drawings were performed with the SHELXTL PLUS program package (12) on a Micro VAX II computer. Final non-hydrogen atomic coordinates are included in Table 6.[2]

TABLE 6.   Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Coefficients ($\mathring{A}^2 \times 10^3$).

Atom	x	y	z	U(eq)*
Br	0	0	0	97 (1)
C-1	−334 (6)	7243 (6)	6768 (5)	53 (2)
C-2	−2480 (7)	7193 (5)	7878 (5)	51 (2)
C-3	−2871 (10)	5477 (6)	8596 (6)	69 (3)
C-4	−3242 (10)	4664 (6)	7712 (6)	67 (2)
C-5	−1489 (8)	4505 (5)	6447 (5)	61 (2)
C-6	−1562 (6)	6113 (6)	5213 (4)	41 (2)
C-7	−1600 (6)	7546 (4)	5627 (4)	38 (2)
C-8	−3623 (6)	8289 (4)	6584 (4)	40 (2)
C-9	−3603 (8)	10052 (5)	6220 (5)	59 (2)
C-10	−1694 (9)	10244 (6)	6155 (6)	75 (3)
C-11	246 (7)	8805 (7)	6463 (6)	73 (3)
C-12	−5671 (11)	11379 (6)	5957 (9)	100 (4)
C-13	−2830 (10)	7838 (8)	9089 (6)	75 (3)
C-14	444 (7)	5876 (5)	4069 (5)	49 (2)
C-15	−3522 (7)	6571 (6)	4532 (5)	51 (2)
O-1	−3648 (5)	7966 (5)	3481 (4)	74 (2)
O-2	−4797 (6)	5788 (5)	4878 (5)	87 (2)
C-1″	−5363 (10)	8433 (11)	2670 (8)	104 (4)
O-3	280 (5)	4700 (3)	3524 (3)	55 (1)
C-2″	1649 (8)	4514 (6)	2378 (6)	59 (2)
O-4	3110 (7)	5112 (7)	1873 (6)	·118 (3)
C-1′	1183 (8)	3423 (5)	1819 (5)	55 (2)
C-2′	2583 (9)	3052 (7)	651 (6)	71 (3)
C-3′	2220 (9)	2023 (6)	114 (6)	69 (3)
C-4′	481 (9)	1410 (5)	734 (5)	60 (2)
C-5′	−943 (9)	1788 (6)	1856 (6)	64 (3)
C-6′	−579 (8)	2808 (6)	2399 (6)	63 (3)

   *Equivalent isotropic U defined as one-third of the trace of the orthogonalized U_{ij} tensor.

   COMPUTATIONAL ASPECTS.—The Allinger-Molecular mechanics methodology (13) for theoretical calculations was used through the PC-Model software (14) on an IBM-PC-compatible computer. Minimization was performed using the MMX forcefield, which is a modification of the MM2 (15) and MMP1 (16) Allinger's programs by J.J. Gajewski and K.E. Gilbert. The current version of MMX recognizes nearly 60 different atom types. Conformational analyses were performed using the MULTOR option of the PC-Model program, rotating all the possible side-chains of the structures considered. In some cases, a collection of conformers of minimum energies and their corresponding Cartesian coordinates could be obtained. The theoretical ^3J H-H coupling constants and the relative populations were calculated through the 3JHH2 PROGRAM (17), which is set up in the use of an extended multiparametric Karplus equation (18) mixing the above minimum energy Cartesian coordinates.

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