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STEREOCHEMISTRY AND CONFORMATION OF DOLABELLANE DITERPENES: AN NMR AND MOLECULAR MECHANICS STUDY

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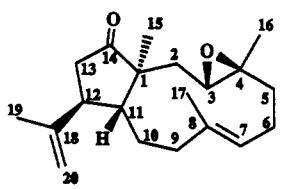
ABSTRACT.—The preferred conformations in solution of five dolabellane diterpenes [**4–8**] previously isolated from marine organisms have been determined on the basis of a complete ^{1}H- and ^{13}C-nmr analysis, including NOESY and lanthanide-induced shift experiments, in combination with MM2 calculations. This study led also to a revision of the stereochemistry for three of these dolabellanes.

Dolabellanes are metabolites with restricted distribution possessing a trans-fused bicyclo[9.3.0] skeleton. After the original isolation from the herbivorous opistobranch mollusc *Dolabella californica* (1,2) they were found in brown algae of the family Dictyotaceae (3–17), a possible dietary source for the mollusc, and in other marine organisms (18–25). The only terrestrial sources known at present are primitive plant species of the liverworts (Hepaticae) (26–28). Members of the dolabellane family have important biological properties, namely, cytotoxic, antibacterial, antifungal, antiviral, molluscicidal, and phytotoxic activity (19,22,26,29). In particular, the major component of the extract obtained from the brown alga *Dictyota dichotoma* (Huds.) Lamouroux (family Dictyotaceae), which has been assigned structure **1**, possesses interesting bioactivities (antibiotic against both Gram-positive and Gram-negative bacteria, cytotoxic against KB cells, antiviral against influenza and adenovirus viruses) (29). The structures of this metabolite and four co-occurring dolabellanes, one of them originally isolated from the mollusc *D. californica* (2), were established as **1–5** (4) before the introduction of 2D nmr techniques, and therefore their ^{1}H- and ^{13}C-nmr spectral data have been reported only in part; moreover, no data have been reported concerning their preferred conformation in solution. For this reason we decided to re-isolate these compounds from *D. dichotoma* and submit them to a complete nmr analysis and a conformational study. As will be detailed, the results of this analysis have led to the revision of the stereochemistry at C-3 and C-4 for structures **1–3**, which have been reassigned as **6–8**, respectively.

RESULTS AND DISCUSSION

3,4-Epoxy-14-oxo-7,18-dolabelladiene [**6**] was the first compound to be examined as it was the most abundant. The initial step was to assign unambiguously all of the peaks in the ^{1}H- and ^{13}C-nmr spectra. Assignments were based largely on the integrated use of COSY and one-bond and long-range HETCOR experiments, using some straightfor-



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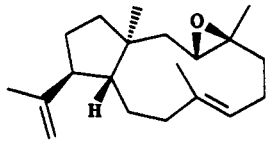

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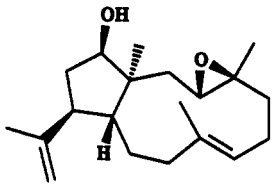

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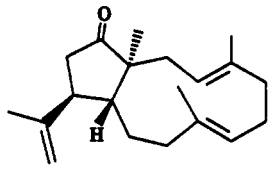

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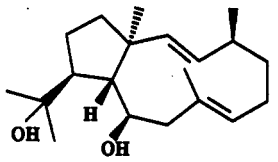

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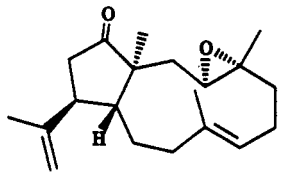

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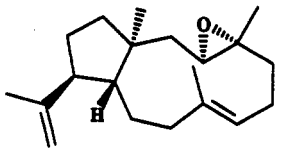

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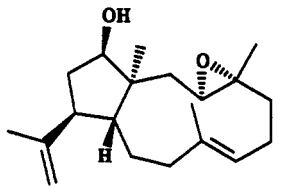

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ward assignments as starting points. Table 1 summarizes the ^{1}H- and ^{13}C-nmr chemical shifts, ^{1}H-^{1}H coupling constants, and long-range HETCOR, COSY, and NOESY correlations. On the whole, these data confirm the previous assignments of the proton resonances, aside from those for Me-15 and Me-16 which are interchanged. The new assignments are based on a long-range HETCOR correlation between C-3 at 62.9 ppm and Me-16 at 1.27 ppm, as well as between C-15 (18.5 ppm) and one of the methylene protons at position 2 (H-2a, 1.93 ppm).

The inversion of the ^{1}H-nmr assignments for Me-15 and Me-16 prompted a re-examination of the stereochemical assignments, which were based on these resonances. This inversion does not invalidate the considerations leading to the assignments of the stereochemistry at positions 1, 11, and 12 (1*S*, 11*R*, and 12*S* for **1**) (4), which is the same as that found for all the dolabellanes so far described. Thus, only a re-examination of the stereochemistry at C-3 and C-4 had to be considered. Because **6** can be obtained from the corresponding alkene **4** by epoxidation with *m*-CPBA, only two possibilities had to be taken into consideration, namely, 3*S*,4*S* (as in **1**) and 3*R*,4*R* (as in **6**). To discriminate between them, we resorted to an integrated use of NOESY data (Table 1) and the results of a conformational search performed on both diastereoisomers **1** and **6** by means of MM2 molecular mechanics calculations (30). A similar approach, where the determination of both configuration and conformation in solution relies on the concerted use of ^{1}H-nmr data and molecular mechanics calculations, has been recently applied to *neo*-clerodane and lactarane terpenoids (31,32).

The global minimum energy conformation for each stereoisomer was found by conformational search at 60° resolution using the MacroModel V 2.5 molecular modeling program (33). During the searches all bonds within the eleven-membered ring were rotated, as well as the C-12-C-18 bond. Relative steric energies, equilibrium

TABLE 1. ^{1}H- and ^{13}C-Nmr Data for Compound **6**.[a]

Position	δ_C	δ_H	Multiplicity	Long-range HETCOR	COSY	NOESY
1	51.9			1.34, 1.54, 1.93, 2.18, 2.31		
2a		1.93	dd (14.0, 2.6)		1.34, 2.99	1.27, 2.99
	36.0			2.31, 2.99		
2b		1.34	dd (14.0, 11)		1.93, 2.99	1.79, 2.99
3	62.9	2.99	dd (11.0, 2.6)	1.27, 1.34, 1.93, 2.18	1.34, 1.93	1.25, 1.33, 1.34, 1.93
4	61.2			1.27, 1.93, 2.18		
5a		2.18			1.25, 2.38	2.38
	38.8			2.38, 2.99, 5.11		
5b		1.25			2.18	2.99
6a		2.38			2.18, 2.22, 5.11	2.18
	24.1			1.25, 2.18, 5.11		
6b		2.22			2.38	
7	126.9	5.11	br d (11.0)	1.67, 2.15	1.67, 2.38	1.33, 1.67
8	133.2			1.35, 1.67, 2.15		
9a		2.27			1.54	
	36.8			1.67, 5.11		
9b		2.15			1.35, 1.54	
10a		1.54			1.35, 2.27	4.74, 5.03
	21.2			2.15, 2.27, 2.82		
10b		1.35			1.54, 2.15	4.74
11	39.8	2.31		1.33, 1.54, 1.93, 2.44, 2.82	2.82	1.27, 1.67, 2.44
12	44.0	2.82	dt (14.0, 7.0)	1.79, 2.44, 4.74, 5.03	1.79, 2.18, 2.31, 2.44, 4.74	2.44, 2.18
13a		2.44	dd (14.0, 15.0)		2.18, 2.82	1.79, 2.31, 2.82, 4.74
	39.9			2.82		
13b		2.18	dd (14.0, 7.0)		2.44, 2.82	2.82
14	220.9			1.33, 1.93, 2.18, 2.31, 2.44		
15	18.5	1.33	s	1.93		2.99, 5.11
16	15.6	1.27	s	2.18, 2.99		1.67, 1.93, 2.31
17	15.8	1.67	s	2.15, 2.27, 5.11	5.11	1.27, 1.79, 2.31, 5.11
18	143.2			1.79, 2.44, 2.82		
19	22.4	1.79	s	4.74, 5.03	2.82, 4.74, 5.03	1.34, 1.67 2.44, 4.74, 5.03
20a		5.03	br s		1.79	1.54, 1.79
	111.9			1.79		
20b		4.74	br s		1.79, 2.82	1.35, 1.54, 1.79, 2.44

[a]Run at 250 (^{1}H) and 62.89 (^{13}C) MHz, in $CDCl_3$. Chemical shifts are in ppm from TMS. Coupling constants (Hz) are reported in parentheses. Cross-peaks obtained in 2D NMR experiments are reported within the columns: long-range HETCOR, COSY, NOESY. The NOESY cross-peaks due to geminal protons are not reported.

percentages, and selected dihedral angles for the low energy conformers based on structures **1** and **6** in a range of 5 kcal/mol above the global minima **1A** and **6A** are reported in Table 2. For each diastereoisomer, conformers that total at least 97% of the population (**1A**,**1B** and **6A**,**6B**) differ essentially in the orientation of the Me-19 group, which in both cases points in the same direction as H-11, while the eleven-membered ring remains almost unmodified. The small and large coupling constants (2.6 and 11.0 Hz) of the protons at position 2 with H-3 agree with this conclusion, indicating a predominant conformation in solution for the eleven-membered ring. Thus, we used the lowest energy conformers **1A** and **6A** (stereoviews in Figures 1 and 2, respectively) to measure interproton distances (see Experimental), which were compared with the nOe correlations. This comparison, in particular with reference to the nOe cross-peaks [H-2b] Me-19, [H-3] Me-15, [H-7] Me-15, [H-11] Me-17, [Me-17] Me-19, was clear evidence in favor of 3*R*,4*R* stereochemistry (structure **6**).[1]

Further evidence supporting the revision of stereochemistry at C-3, C-4 came from the study of the co-occurring metabolites 3,4-epoxy-7,18-dolabelladiene [**7**] and 3,4-epoxy-14-hydroxy-7,18-dolabelladiene [**8**], previously related to the epoxy-oxo-dolabelladiene [**6**] on the basis of chemical conversions (4). The nmr spectra of these compounds were assigned using a variety of two-dimensional techniques (see Experimental for relevant data and a list of selected dipolar correlations extracted from NOESY

TABLE 2. Relative Steric Energies, Equilibrium Percentages, and Selected Dihedral Angles for the Low Energy Conformers of Diastereoisomers **1** (3*S*,4*S*) and **6** (3*R*,4*R*).[a]

	1A	1B	1C	1D	6A	6B	6C	6D
ΔE	0.00	0.01	2.07	4.42	0.00	0.23	1.81	4.62
%	49.77	48.75	1.45	0.03	58.27	39.07	2.64	0.02
C-11-C-1-C-2-C-3	−46.2	−46.2	−42.9	−44.1	60.4	58.8	73.0	56.8
C-1-C-2-C-3-C-4	141.5	139.0	140.6	96.2	−126.9	−125.8	−114.3	−116.8
C-3-C-4-C-5-C-6	98.2	99.8	98.0	17.4	−98.6	−98.8	−92.0	−93.7
C-4-C-5-C-6-C-7	−57.8	−57.2	−46.6	52.0	57.5	57.8	53.0	46.5
C-5-C-6-C-7-C-8	114.1	114.1	−119.5	−128.4	−116.9	−116.6	−122.0	67.7
C-7-C-8-C-9-C-10	96.7	94.6	−25.8	−61.9	−61.4	−63.3	−120.9	14.3
C-8-C-9-C-10-C-11	−76.0	−76.0	−59.1	−70.8	−67.9	−65.8	45.7	53.4
C-9-C-10-C-11-C-1	140.2	142.7	152.8	142.5	150.5	151.3	73.9	56.3
C-10-C-11-C-1-C-2	−80.2	−80.5	−82.1	−98.2	−95.7	−96.3	−130.1	−118.0
C-11-C-12-C-16-C-19	71.0	−110.4	66.9	68.1	74.3	−113.3	68.6	58.0

[a]ΔE (kcal/mol) and dihedral angles (degrees) have been calculated for the MM2 conformers in a range of 5 kcal/mol above the global minima **1A** and **6A**.

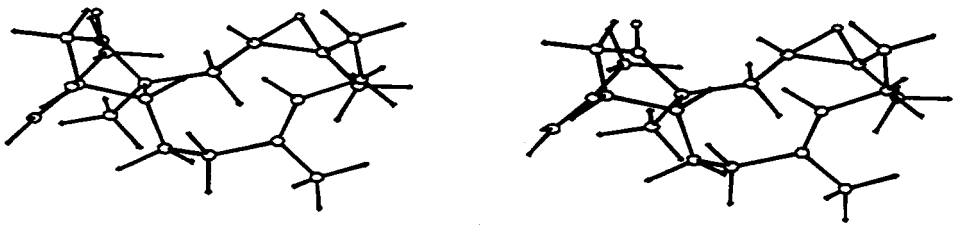

FIGURE 1. Stereoview of the MM2 lowest energy conformer **1A**.

[1]An examination of the literature for related epoxides reveals that in earlier papers (12–15), inconsistencies occur between structure drawings and chemical names. Subsequently, an X-ray study (17) definitively proved that the carbons at positions 3 and 4 of those compounds have the same stereochemistry (1*S**,3*R**,4*R**) as we are proposing here for dolabellanes **6–8**.

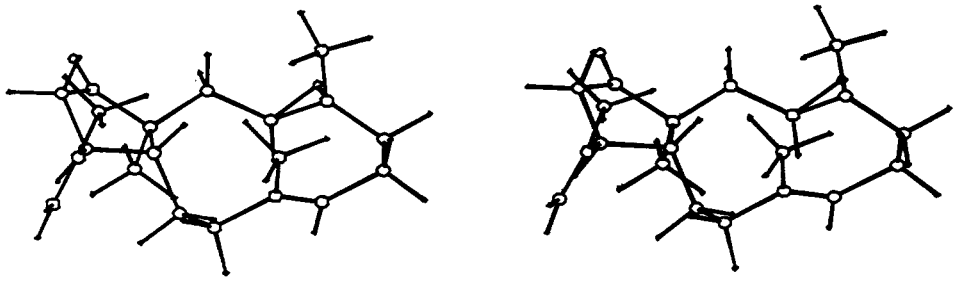

FIGURE 2. Stereoview of the MM2 lowest energy conformer **6**A.

spectra). On the whole, the previously published proton assignments have been confirmed, apart from inversion of those relative to Me-15 and Me-16 for **7**.

Following the same methodology illustrated above, the lowest energy conformers for **2** and **3** and their 3*R*,4*R* diastereoisomers **7** and **8** were obtained by MM2 calculations, and NOESY data were compared with crucial interproton distances. In both cases, this comparison clearly favored the 3*R*,4*R* stereochemistry. In addition, considering that the epoxydolabelladiene **7** contains a single heteroatom, a fact that facilitates the interpretation of the results, a study of the lanthanide-induced shifts (LIS) was performed to corroborate the revision of the stereochemistry at positions 3 and 4. To this end, we resorted to the '$1/r^2$' method (34). Measurements of shifts induced by $Eu(fod)_3$ in the ^1H-nmr spectrum of this metabolite led to the LIS values (see Experimental). The relevant proton-oxygen distances (r, see Experimental) have been calculated from the MM2 lowest energy conformers of **2** and **7**, assuming that the conformation does not significantly change during the complexation with $Eu(fod)_3$ (35). Comparison of the correlation coefficients between measured LIS and calculated 10^2r^{-2} values for **2** and **7** (0.86 and 0.94, respectively) favored again the 3*R*,4*R* stereochemistry. Thus, the structures **2** and **3** have been revised in **7** and **8**, respectively.

The analysis of the ^1H- and ^{13}C-nmr spectra of **4** (14-oxo-3,7,18-dolabellatriene) and **5** (10,18-dihydroxy-2,7-dolabelladiene) led to the assignments summarized in the Experimental. By extension of the above methodology, the MM2 lowest energy conformations of these further dolabellanes have been determined and found to be compatible with NOESY data (see Experimental). Figure 3 shows a least-square superimposition (common heavy atoms) of the lowest energy conformations of the dolabellanes **4**, **6**, **7**, and **8**; these are very similar and can be described as 'crown' conformations with Me-16 and Me-17 in the pseudo-axial position, anti- to Me-15. The

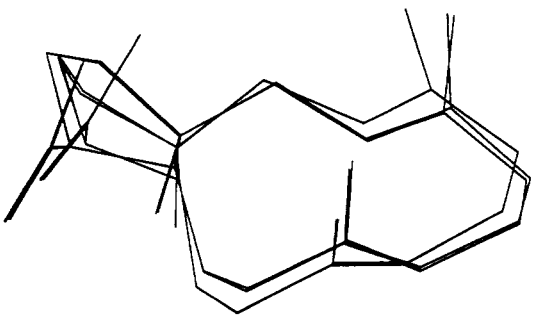

FIGURE 3. Least-square superimposition (common heavy atoms) of the preferred conformations of dolabellanes **4**, **6**, **7**, and **8**.

preferred conformation of **5** (Figure 4) is quite different, with Me-16 in a pseudoequatorial position, while Me-17 is pseudo-axial and syn- to Me-15. It is worth noting that an X-ray diffraction analysis has been previously reported for the 10-acetoxy derivative of **5** and its solid-state conformation differs from that depicted in Figure 4 only in the orientation of Me-17 (2). An MM2 calculation performed on the acetate gave as lowest energy minimum a conformer closely resembling that based on X-ray crystallography.

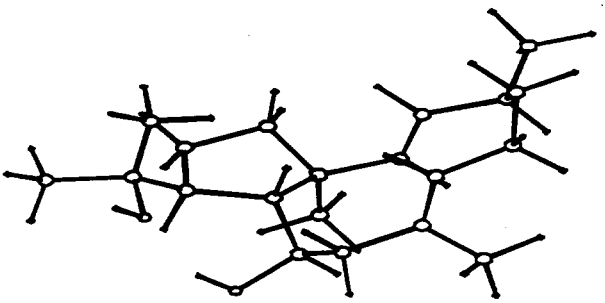

FIGURE 4. MM2 lowest energy conformer of compound **5**.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—The nmr spectra were recorded in $CDCl_3$ on a Bruker AC-250 nmr spectrometer operating at 250.13 (^1H) and 62.89 (^{13}C) MHz, with TMS as internal standard. All 1D and 2D experiments were performed using software supplied by the manufacturer. For each compound, standard ^1H, ^{13}C (BB and DEPT) spectra, and the following 2D experiments were run: COSY-45, NOESY, HETCOR one-bond, and HETCOR long-range. All spectra were acquired at constant temperature (298° K). For COSY and NOESY spectra, a data matrix of 1024 data points for 256 increments was used, expanded to 512 in F_1 (zero-filling) prior to Fourier transformation. Relaxation delays of 1 sec (COSY) and 2 sec (NOESY) were used. For the NOESY experiment, a mixing time of 0.8 sec was used. The HETCOR spectra were acquired with 1024 data points for 256 increments, and a relaxation delay of 1.5 sec. For the HETCOR spectra, polarization transfer delays optimized for $J_{C,H}$=135 Hz (one-bond) and $J_{C,H}$=7.5 Hz (long-range) were used. A final matrix of 1024×512 points after zero-filling was subjected to Fourier transformation. The ^1H- and ^{13}C-nmr assignments, signal multiplicity and ^1H-^1H coupling constants (when detectable), and selected NOESY correlations are reported below.

PLANT MATERIAL.—As described previously (4). A voucher specimen is stored at the Dipartimento di Botanica of the University of Catania.

EXTRACTION AND ISOLATION.—Extraction and chromatographic fractionation of *Dictyota dichotoma* were carried out as described previously (4).

14-Oxo-3,7,18-dolabellatriene [**4**].—^1H nmr δ 5.16 (1H, dd, J=11.4 and 4.6 Hz, H-3), 4.95 (1H, br s, H-20a), 4.87 (1H, br d, J=10.6 Hz, H-7), 4.68 (1H, br s, H-20b), 2.91 (1H, dt, J=10.4 and 7.6 Hz, H-12), 2.36 (2H, H_2-13), 2.30 (1H, H-6a), 2.20 (1H, H-5a), 2.18 (1H, H-2a), 2.17 (2H, H-9a and H-11), 2.16 (1H, H-5b), 2.10 (1H, H-6b), 2.03 (1H, H-9b) 1.82 (1H, dd, J=13.4 and 4.6 Hz, H-2b), 1.73 (3H, s, Me-19), 1.57 (3H, s, Me-17), 1.55 (3H, s, Me-16), 1.48 (1H, H-10a), 1.30 (1H, H-10b), 1.13 (3H, s, Me-15, s); ^{13}C nmr δ 222.9 (s, C-14), 144.8 (s, C-18), 136.5 (s, C-4), 133.1 (s, C-8), 128.3 (d, C-7), 122.8 (d, C-3), 112.1 (t, C-20), 54.5 (s, C-1), 43.8 (d, C-12), 41.6 (t, C-13), 40.5 (d, C-11), 39.9 (t, C-5), 37.1 (t, C-9), 36.8 (t, C-2), 24.4 (t, C-6), 23.9 (t, C-10), 22.8 (q, C-19), 18.4 (q, C-15), 16.7 (q, C-17), 15.7 (q, C-16). Selected NOESY correlations: [H-2b] H-11; [H-3] Me-15; [H-10b] Me-15; [H-12] Me-19; [H_2-13] Me-19; [H_2-13] H-20b; [Me-17] Me-19; [Me-17] H-20a; [Me-17] H-20b.

10,18-Dihydroxy-2,7-dolabelladiene [**5**].—^1H nmr δ 5.18 (1H, dd, J=16.0 and 7.0 Hz, H-3), 5.02 (1H, d, J=16 Hz, H-2), 4.98 (1H, t, J=6.8 Hz, H-7), 3.41 (1H, H-10), 2.53 (1H, ddd, J=11.0, 7.0, and 6.0 Hz, H-12), 2.16 (2H, H_2-9), 2.13 (3H, H-4 and H_2-6), 1.88 (1H, qd, J=11.0 and 2.0 Hz, H-13a), 1.61 (1H, H-11), 1.59 (3H, s, Me-17), 1.57 (2H, H-5a and H-14a), 1.44 (1H, H-5b), 1.33 (1H, H-14b), 1.25

(3H, s, Me-20), 1.22 (1H, H-13b), 1.21 (3H, s, Me-19), 0.95 (3H, s, Me-15), 0.93 (3H, d, J=7.0 Hz, Me-16); ^{13}C nmr δ 135.3 (d, C-2), 134.1 (d, C-3), 129.4 (d, C-7), 128.4 (s, C-8), 73.4 (s, C-18), 68.5 (d, C-10), 57.2 (d, C-11), 49.4 (t, C-9), 47.6 (d, C-12), 46.6 (s, C-1), 38.9 (t, C-14), 37.4 (d, C-4), 35.6 (t, C-5), 31.7 (q, C-20), 27.0 (t, C-6), 26.2 (t, C-13), 23.4 (q, C-19), 21.2 (q, C-16), 19.4 (q, C-15), 18.5 (q, C-17). Selected NOESY correlations: [H-4] Me-16; [H-5a] H-7; [H-9] Me-17; [H_2-10] Me-15; [H_2-10] Me-17; [H-12] Me-15; [H-12] Me-19; [H-12] Me-20; [H-13a] Me-15.

3,4-Epoxy-14-oxo-7,18-dolabelladiene [**6**].—Nmr data for compound **6** are reported in Table 1. Selected nOe correlations and the related proton-proton distances (Å) calculated for the MM2 lowest energy conformers (in parentheses: **1A** and **6A**, respectively) are as follows: [H-2b] Me-19 (6.22, 4.98); [H-3] Me-15 (4.81, 3.23); [H-7] Me-15 (6.09, 4.96); [H-11] Me-17 (4.53, 3.31); [Me-17] Me-19 (6.80, 4.04).

3,4-Epoxy-7,18-dolabelladiene [**7**].—^{1}H nmr δ 5.05 (1H, br d, J=11.0 Hz, H-7), 4.87 (1H, br s, H-20a), 4.66 (1H, br s, H-20b), 2.88 (1H, dd, J=11.0 and 2.5 Hz, H-3), 2.52 (1H, dt, J=11.3 and 5.6 Hz, H-12), 2.31 (1H, H-6a), 2.19 (1H, H-9a), 2.15 (2H, H-5a and H-6b), 2.07 (1H, H-9b), 1.77 (1H, H-11), 1.76 (1H, H-2a), 1.70 (3H, s, Me-19), 1.67 (1H, H-13a), 1.59 (1H, H-14a), 1.58 (3H, s, Me-17), 1.55 (1H, H-13b), 1.43 (1H, H-2b), 1.39 (1H, H-10a), 1.38 (1H, H-14b), 1.28 (1H, H-10b), 1.27 (3H, s, Me-15), 1.23 (3H, s, Me-16); ^{13}C nmr δ 145.7 (s, C-18), 133.7 (s, C-8), 126.2 (d, C-7), 111.1 (t, C-20), 64.0 (d, C-3), 61.6 (s, C-4), 51.3 (d, C-12), 43.9 (t, C-2), 42.9 (s, C-1), 42.7 (t, C-14), 41.5 (d, C-11), 38.7 (t, C-5), 37.2 (t, C-9), 27.4 (t, C-13), 24.6 (q, C-15), 24.2 (t, C-6), 23.4 (q, C-19), 22.0 (t, C-10), 16.0 (q, C-17), 15.7 (q, C-16). Selected NOESY correlations: [H-2b] H-11; [H-2b] H-14b; [H-2b] Me-16; [H-3] Me-15; [H-10b] H-13a; [H-13a] Me-15; [Me-16] Me-17; [Me-16] Me-19; [Me-17] Me-19.

3,4-Epoxy-14-hydroxy-7,18-dolabelladiene [**8**].—^{1}H nmr δ 5.05 (1H, br d, J=10.5 Hz, H-7), 4.86 (1H, br s, H-20a), 4.67 (1H, br s, H-20b), 3.85 (1H, t, J=6.5 Hz, H-14a), 2.93 (1H, H-3), 2.87 (1H, H-12), 2.28 (1H, H-6a), 2.18 (2H, H-5a and H-9a), 2.17 (1H, H-6b), 2.01 (1H, H-13a), 1.98 (1H, H-11), 1.96 (1H, H-9b), 1.95 (1H, H-2a), 1.72 (3H, s, Me-19), 1.59 (3H, s, Me-17), 1.58 (1H, H-13b), 1.38 (1H, H-10a), 1.36 (1H, H-2b), 1.25 (6H, s, Me-15 and Me-16), 1.24 (2H, H-5b and H-10b); ^{13}C nmr δ 145.9 (s, C-18), 133.9 (s, C-8), 126.2 (d, C-7), 112.1 (t, C-20), 81.4 (d, C-14), 64.1 (d, C-3), 62.1 (s, C-4), 51.3 (s, C-12), 46.3 (s, C-1), 46.3 (d, C-12), 42.0 (d, C-11), 38.8 (t, C-5), 36.9 (t, C-9), 36.4 (t, C-13), 34.6 (t, C-2), 24.2 (t, C-6), 23.4 (t, C-10), 23.0 (q, C-19), 22.3 (q, C-15), 16.5 (q, C-17), 15.8 (q, C-16). Selected NOESY correlations: [H-3] Me-15; [H-12] Me-15; [H-14] Me-15; [Me-16] Me-19; [Me-17] Me-19.

LANTHANIDE SHIFT STUDY.—The LIS values were determined by adding progressive aliquots of Eu(fod)$_3$ (0.274 M in $CDCl_3$) to a solution of compound **7** (10 mg in 0.5 ml $CDCl_3$). The 250 MHz ^{1}H-nmr spectra were recorded at 16 different reagent concentrations, and the assignments of the proton signals were confirmed, when necessary, by the use of 2D nmr experiments. The LIS values were calculated by linear extrapolation to a (1:1) substrate: reagent molar ratio. LIS values closer than three bonds to the coordination site were not included in calculations on account of possible through-bond contact shift. The measured LIS were correlated with distances r of the protons from the oxygen atom, calculated for the MM2 lowest energy conformers determined on the basis of structures **2** (3*S*,4*S*) and **7** (3*R*,4*R*). For the methyl protons, a mean position was considered along the Me-C bond at 1.94 Å from the quaternary carbon. Plots of LIS vs. 10^2r^{-2} were constructed for both cases and the correlation coefficients obtained with least-square analysis were 0.86 and 0.94 for **2** and **7**, respectively. The following list indicates, in sequence: proton position [LIS] (H-O distance in Å, r, for diastereoisomer **2**; H-O distance in Å, r, for diastereoisomer **7**); 6a [2.12] (4.62; 4.59); 6b [3.38] (4.19; 4.19); 7 [3.23] (4.29; 3.97); 9a [1.17] (6.59; 6.43); 9b [1.70] (5.92; 6.38); 10a [1.32] (6.26; 6.01); 10b [not determined]; 11 [4.03] (3.82; 3.78); 12 [2.23] (6.24; 6.40); 13a [0.93] (6.05; 6.56); 13b [1.09] (4.72; 5.04); 14a [1.02] (5.04; 5.84); 14b [1.26] (3.58; 4.88); 15 [1.54] (5.31; 4.63); 16 [5.52] (2.75; 2.79); 17 [1.50] (5.51; 6.07); 19 [1.09] (6.29; 6.11); 20a [0.63] (8.46; 8.28); 20b [0.78] (8.08; 8.03).

MOLECULAR MECHANICS CALCULATIONS.—The molecular mechanics studies employed the MacroModel V2.5 program running on a DEC Vax-Station 3100 computer, equipped with a Tektronix 4211 graphic system. For each structure (**1–8**), a randomly drawn conformation was energy minimized with the block-diagonal matrix Newton-Raphson procedure using the MM2 force field, until the energy gradient was lower than 0.01 kJ/Å mol, and then used as starting geometry for a search conducted at 60° resolution. During the search, the relevant bonds within the eleven-membered ring were rotated, as was the C-12-C-18 bond.

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