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DITERPENES BASED ON THE DOLABELLANE SKELETON FROM *DICTYOTA DICHOTOMA*†

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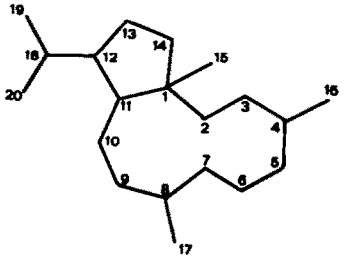
Abstract—From a variety of *Dictyota dichotoma* we have isolated, in addition to previously reported dolabellane (**6–8**) and perhydroazulene diterpenes (**9**, **10**), four new diterpenoids (**2–5**). Their structure have been elucidated by spectral analysis and chemical degradation. All the new dolabellane derivatives possess antimicrobial activity against gram-positive and gram-negative organisms.

In the course of our continuing studies for constituents of the brown seaweeds of the family Dictyotaceae, in July 1978 we made collections of an alga that, although different in colour and general appearance from the other varieties of *Dictyota dichotoma*, has been classified as the same species. Chemical investigation of this alga showed that it contained only minor amounts of perhydroazulene diterpenes, which are the major constituents of the Mediterranean Dictyotaceae *Dictyota dichotoma* var. *implexa* (Desf.) J. Ag. and *Dilophus ligulatus* (Kütz.) Feldm.,[1-3] and that it is instead a rich source of diterpenes possessing the dolabellane skeleton **1**. Compounds of this type had been originally isolated



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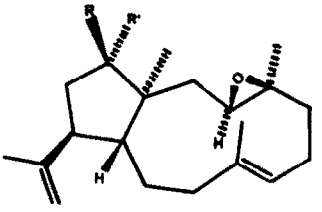
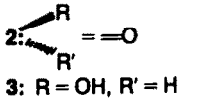
from the herbivorous sea hare *Dolabella californica*[4-5] and successively from the brown alga *Glossophora galapagensis* Taylor (Dictyotaceae)[6] upon which (or related species) the sea hare probably feeds. In this paper we report the isolation and structure determination of four new dolabellane diterpenes, **2–5**, from *D. dichotoma*. In addition to these compounds, extracts of the alga have also yielded three known dolabellane derivatives, **6–8**, as well as two perhydroazulene diterpenes, namely dictyol C (**9**) and dictyol E (**10**).

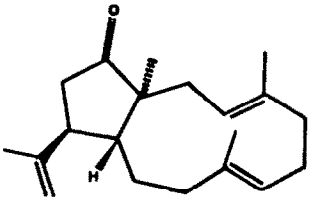
The alga was freeze-dried and the chloroform extracts purified by silica gel column chromatography using increasing concentrations of ether in hexane as the eluent.





2: R = , =O

3: R = OH, R' = H
5: R = R' = H
11: R = H, R' = OH
12: R = OAc, R' = H



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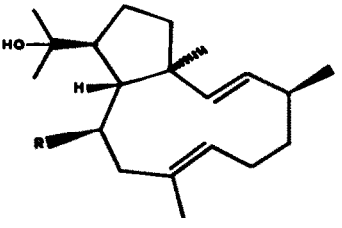
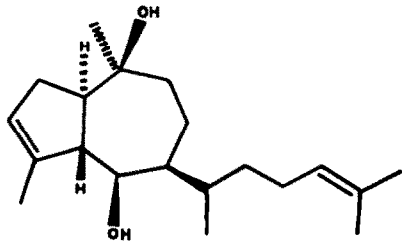
Individual components were then obtained by rechromatography and, whenever possible, final recrystallization. All the spectral data suggested that compounds **2–8** were closely related.



6: R = H
7: R = OAc
8: R = OH

†Dedicated to Professor L. Panizzi on his 70th birthday.



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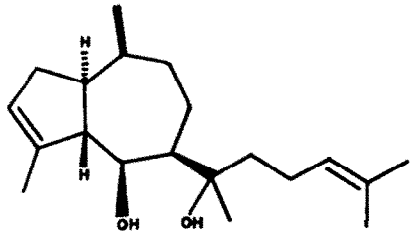

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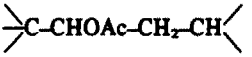
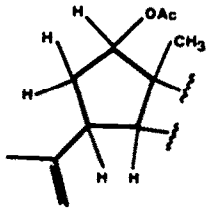
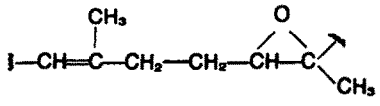
Compound 2 [m.p. 132–133°; $[\alpha]_D$ +109°], which is the component of greatest abundance, has the molecular formula $C_{20}H_{30}O_2$ from the high resolution mass measurement of the parent ion. Its IR spectrum displayed bands at 1740 (5-membered ring ketone) and 1650, 887 (terminal methylene). The ^{13}C NMR spectrum confirmed the presence of an epoxide [63.08 (d) and 61.35 (s) ppm] and a CO in a 5-membered ring (220.99 ppm), and in addition established the presence of two double bonds [143.94 (s), 133.35 (s), 127.19 (d) and 112.10 (t) ppm]. Hence 2, having six degree of unsaturation, must possess a carbobicyclic skeleton. In the ^1H NMR spectrum of 2 four Me signals appeared as singlets at δ 1.77 and 1.66 (vinyl methyls), 1.33 (Me on epoxide) and 1.24 (Me on quaternary carbon); a terminal methylene was observed as two one-proton broad singlets at δ 4.73 and 5.02, and a vinyl proton on a trisubstituted double bond as a broad doublet at δ 5.10. Homonuclear decoupling experiments showed that the vinyl Me at δ 1.77 is allylically coupled to the terminal methylene thus establishing the presence of a terminal isopropenyl grouping in 2; as a consequence, the vinyl Me at δ 1.66 has to be placed on the trisubstituted double bond.

Sodium borohydride reduction of 2 afforded two isomeric alcohols, 3 and 11, $C_{20}H_{32}O_2$, which were separated by silica gel column chromatography. The epimer 3, obtained in lower relative yield ($[\alpha]_D$ +48°) was also a natural product. Treatment of this alcohol with acetic anhydride-pyridine yielded the acetate 12, whose ^1H NMR spectrum gave further structural information. The α-acetoxy proton was seen as a double doublet at δ 4.86 (J = 7 and 3 Hz); irradiation at δ 1.55 collapsed this signal to a doublet (J = 7 Hz) and at the same time simplified a double double doublet at δ 2.79 (J = 11, 7 and 7 Hz) to a double doublet (J = 11 and 7 Hz), while irradiation at δ 2.06 likewise converted the α-acetoxy proton signal into a doublet (J = 3 Hz) and the signal at δ 2.79 into a double doublet (J = 7 and 7 Hz). Thus, the  sequence is present in the 5-membered ring of 12. Decoupling revealed that the methine group, which on account of the multiplicity of the signal at δ 2.79 must be adjacent to another methine, is allylically coupled with the terminal methylene. This and the consideration that the bridgehead Me at δ 1.24 must be linked to the lone quaternary carbon not bearing oxygen which in the ^{13}C NMR spectrum of 2 is seen as a singlet at 52.09 ppm allowed to expand the above partial structure to the system A. Information on the relative position of the

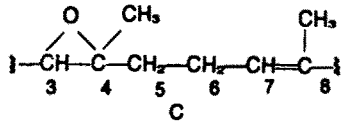


A

trisubstituted double bond and the epoxide ring was obtained from permanganate-periodate oxidation of 2. Formation of levulinic acid is only compatible with part structures B or C.



B



C

Structure B could be eliminated since the epoximethine proton at δ 2.91 was shown by spin decoupling to be coupled (J = 11.5 and 3 Hz) to the protons of a methylene (δ 1.79 and 1.42) that interact further only with each other (J = 14.5 Hz), thereby demonstrating that C-3 of part structure C must be adjacent to a methylene which in turn is adjacent to a fully substituted C-1. The two remaining methylene groups that are deduced from the ^{13}C NMR spectrum must be linked between C-8 and C-11 to form an 11-membered ring. Combination of the foregoing conclusions led to the gross structures 2 and 3 for two of the novel algal metabolites. Their stereochemistry was deduced from the following evidences. Application of the Horeau method allowed to determine the chirality at C-14 in 3 as R, while a lanthanide shift study of both the natural alcohol and its epimer (11) indicated that in the former the bridgehead methyl and the isopropenyl are respectively *trans* and *cis* to the OH. Moreover, in the ^1H NMR spectrum of the acetate 12 the magnitude of the coupling constant for $J_{11,12}$ (7 Hz) in comparison with those for $J_{12,13}$ (7 Hz) and $J_{12,13'}$ (11 Hz) (all these values were deduced from decoupling experiments) pointed to a *trans*-relationship between H-11 and H-12. Finally, the high field position (15.92 ppm, identified by selective decoupling) of the Me-8 resonance in the ^{13}C NMR demonstrated that in 3, and consequently in 2, the C-7 double bond is of the E configuration,[7] as supported by the lack of nuclear Overhauser enhancement between H-7 and Me-8. On the whole, these data allowed to determine the stereochemistry of 2 and 3, apart from the chirality at C-3 and C-4 which was deduced from the relationship between 2 and 4 (*vide infra*).

Table 1. ^{1}H NMR assignements for compounds 2–5, 11, 12*

	2	3	4	5	11	12
H-2	1.28†					dd 1.42 (14.5, 11.5)
H-2′	dd 1.93 (15, 3)		dd 1.83 (13.5, 4.2)			dd 1.79 (14.5, 3)
H-3	dd 2.99 (11.5, 3)	2.94†	dd 5.17 (11.4, 4.2)	dd 2.89 (11.4, 2.5)	dd 2.94 (11.5, 3)	dd 2.91 (11.5, 3)
H-7	d(br) 5.10 (12)	d(br) 5.02 (11)	d(br) 4.88 (10.5)	d(br) 5.05 (11)	d(br) 5.01 (11)	d(br) 5.04 (10.5)
H-12	ddd 2.87 (14, 7, 7)	2.89†	ddd 2.90 (10.2, 7.8, 7.8)	ddd 2.52 (11.4, 5.7, 5.7)	2.34†	ddd 2.79 (11, 7, 7)
H-13						1.55†
H-13′						2.06†
H-14		dd 3.87 (7, 6.5)			dd 3.62 (9, 5)	dd 4.86 (7, 3)
H-20	s(br) 4.73	s(br) 4.67	s(br) 4.69	s(br) 4.66	s(br) 4.66	s(br) 4.65
H-20′	s(br) 5.02	s(br) 4.87	s(br) 4.96	s(br) 4.87	s(br) 4.89	s(br) 4.90
Me-1	s 1.24	s 1.25	s 1.12	s 1.23	s 1.21	s 1.24
Me-4	s 1.33	s 1.25	s(br) 1.54	s 1.27	s 1.21	s 1.32
Me-8	s(br) 1.66	s(br) 1.60	s(br) 1.57	s(br) 1.58	s(br) 1.56	s(br) 1.57
Me-18	s(br) 1.77	s(br) 1.72	s(br) 1.73	s(br) 1.69	s(br) 1.69	s(br) 1.72
OAc						s 2.04

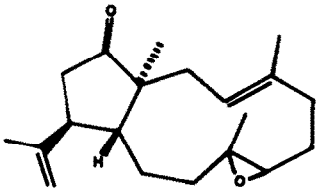
* Chemical shifts are in parts per million (δ) relative to internal TMS. Multiplicities are indicated by the usual simbols. Coupling constants (hertz) are in parentheses.

† Overlapped with other signals.

Table 2. Antimicrobial activity of the dolabellane 2–5

Organism	Compound			
	2	3	4	5
Gram-positive:				
Staphylococcus aureus	+	+	-	-
Gram-negative:				
Klebsiella pneumoniae	-	-	+	+
Pseudomonas aeruginosa	-	-	-	-
Proteus mirabilis	-	-	-	-
Escherichia coli	-	++	-	++
Enterobacter cloacae	+	-	+	-
Citrobacter freundii	++	++	-	-

Compound **4**, isolated in yield of 0.13% based on dry seaweed weight, [m.p. 53–54°; $[\alpha]_D$ −54.5°], had the molecular formula $C_{20}H_{30}O$ (precise mass measurement). In the IR region the compound showed bands for a 5-membered ring ketone (1740 cm^{-1}) and a terminal methylene (1640 and 885 cm^{-1}). The ^{13}C NMR spectrum (Experimental) and the ^1H NMR spectrum (Table 1) suggested a close relatedness to **2**. This was confirmed by the following chemical conversions. Treatment of **2** with Zn–Cu couple in boiling ethanol for 4 days resulted in the smooth reductive elimination of the 3,4-epoxide to give **4**. On the other hand, epoxidation of **4** with *m*-chloroperbenzoic acid afforded essentially two monoepoxides which were separated by column chromatography; the less polar compound was identical to the natural product **2** (m.m.p., $[\alpha]_D$, IR, NMR) while the second monoepoxide was assigned structure **13** on the basis of its spectral properties and the conversion by further treatment with *m*-chloroperbenzoic acid to the same diepoxide **14** obtained from **2** in the same conditions. These



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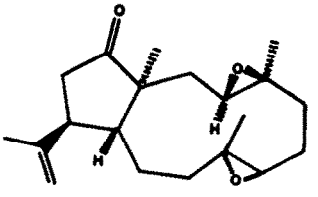

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results confirmed the structure and stereochemistry of **4**, except for the configuration of the C-3 double bond which was deduced from spectroscopy. The Me-4 and Me-8 signals in the ^{13}C NMR spectrum (16.98 and 15.68 ppm, identified by selective decoupling) were at high field which indicated that both the endocyclic double bonds are *trans* with respect to the continuous chain of carbons.[7] Considering now the stereochemistry of the epoxidation with peracids,[8] it can be deduced that in **2** the proton and the Me on the oxirane ring are *trans* each other and this requires the chirality of the relevant centers to be either 3*S*,4*S* or 3*R*,4*R*. The choice between these alternatives was made on the basis of the following argument. The 11-membered ring, which is probably more rigid than expected,[5] is in **2** in a conformation that places the bridgehead Me and the epoximethine proton in spatial proximity, as revealed by measurement of nuclear Overhauser effect. With this restriction imposed, an examination of molecular models (Stuart) revealed that only the 3*S*,4*S*-configuration is possible without unduly steric hindrance. Thus the stereochemistry of the epoxide in **2** and **3** was assumed to be as shown.

Compound **5** [m.p. 63–64°; $[\alpha]_D$ +76.9°], $C_{20}H_{32}O$ (precise mass measurement), was isolated in yield of 0.20% dry weight of the alga. Comparison of the ^1H NMR spectral data for **5** (Table 1) with **2** and **3** clearly showed their similarities, while in the IR spectrum there was no evidence for either a CO or a OH group. Since an attempt to convert **2** into **5** via sodium borohydride reduction of the corresponding *p*-toluensulfonylhydrazone[9] was unsuccessful, we resorted to the Wolff–Kishner reduction, in the version proposed by Nagata and Itazaki[10] for sterically hindered ketones. In spite of the complications due to the opening of the epoxide ring by base, we could isolate a small amount of semisynthetic **5** identical with the natural product (^1H NMR, IR, TLC), thus establishing its structure as drawn including absolute stereochemistry.

Identification of compound **6–8** was based on comparison of their physical properties (m.p., $[\alpha]_D$, MS and NMR) with those reported in the literature.[5] It is to be noted that for these compounds only the relative stereochemistry has been determined.[4,5] In the light of the established structures of the co-occurring **2–5**, the configurations shown are considered more probable than the enantiomeric ones.

Dictyol C (**9**) and dictyol E (**10**) were identified by direct comparison with authentic samples.

Table 2 summarizes the results of antimicrobial activity test against gram-positive and gram-negative organisms carried out on the new dolabellane derivatives isolated in the course of the present study.

EXPERIMENTAL

General procedures. ^1H and ^{13}C NMR spectra were run at 270 (unless otherwise stated) and 68 MHz, respectively, with TMS as internal standard. Optical rotations were measured on a Perkin–Elmer 141 polarimeter.

Extraction and isolation of constituents. The alga (1.4 kg), collected in July 1978 at Acicastello near Catania, Sicily, Italy, was freeze-dried and ground to a fine powder with a blender. The dried alga (150 g) was extracted 3x with $CHCl_3$ with continuous stirring. The extracts were combined and evaporated to give a dark green oil (15 g). The crude extract was applied to a column (5 × 120 cm) of Si gel. The column was eluted with a solvent gradient system from hexane to ether. Fractions of 50 ml were collected and those exhibiting similar tlc profiles were combined. The following compounds were isolated in order of increasing polarity.

14-*Oxo*-3,7,18-*dolabellatriene* (**4**). Fractions 50–55 were pooled and subjected to column chromatography (Si gel, 1 × 60 cm) with C_6H_6. Crystallization from EtOH gave pure **4** (195 mg, 0.13% dry weight); m.p. 53–54°; $[\alpha]_D$ −54.5° (c = 1, $CHCl_3$); IR ($CHCl_3$) 1740 (5-membered ring ketone), 1640 and 885 cm^{-1}; mass spectrum m/e 286.2292 (M^+ calc. for $C_{20}H_{30}O$, 286.2296): ^1H NMR (Table 1); ^{13}C NMR ($CDCl_3$) (off resonance mult.) ppm 222.80 (s), 144.89 (s), 136.70 (s), 133.16 (s), 128.40 (d), 122.90 (d), 112.17 (t), 54.49 (s), 43.80 (d), 41.62 (t), 40.95 (d), 39.96 (t), 37.13 (t), 36.78 (t), 24.36 (t), 23.95 (t), 22.81 (q), 18.35 (q), 16.98 (q), 15.68 (q).

3,4-*Epoxy*-7,18-*dolabelladiene* (**5**). Compound **5** was obtained from fractions 63–72 by rechromatography (Si gel, C_6H_6). Crystallization from EtOH gave 300 mg of **5** (0.2% dry weight), m.p. 63–64°; $[\alpha]_D$ +76.9° (c = 1, $CHCl_3$); IR 1650, 890 cm^{-1}; mass spectrum m/e 288.2458 (M^+ calc. for $C_{20}H_{32}O$, 288.2453); ^1H NMR (Table 1).

18-*Hydroxy*-2,7-*dolabelladiene* (**6**). Fractions 94–100 were rechromatographed on Si gel to give **6** (52 mg, 0.03% dry weight), oily; $[\alpha]_D$ −76° (c = 1, $CHCl_3$) (lit.[5] −75.1°).

3,4 - *Eopxy* - 14 - *oxo* - 7,18 - *dolabelladiene* (**2**). Fractions 101–128 were evaporated to give a crystalline material. Recrystallization from EtOH gave pure **2** (1.8 g, 1.2% dry weight), m.p. 132–133°; $[\alpha]_D$ +109° (c = 1, $CHCl_3$); mass measurement observed m/e 302.2244, $C_{20}H_{30}O_2$ requires m/e 302.2246; ^1H NMR (Table 1); ^{13}C NMR ($CDCl_3$) ppm 220.99 (s), 143.94 (s), 133.35 (s). 127.19 (d), 112.10 (t), 63.08 (d), 61.35 (s), 52.09 (s), 44.30 (d), 40.23 (t), 40.03 (d), 38.90 (t), 36.97 (t), 36.17 (t), 24.25 (t), 22.99 (q), 21.92 (t), 18.99 (q), 15.92 (q), 15.79 (q).

10 - *Acetoxy* - 18 - *hydroxy* - 2,7 - *dolabelladiene* (**7**). Fractions 128–133 gave on evaporation 100 mg of a brown oil which was purified by column chromatography on Si gel (Et_2O–$CHCl_3$ 1:20) followed by TLC (Et_2O–C_6H_6 1:6) to give pure **7** (21 mg, 0.014% dry weight), m.p. 77–78° (lit.[5] 78°); $[\alpha]_D$ −100.2° (c = 1, $CHCl_3$) (lit.[5] −101°).

Dictyol E (**9**). Repeated column chromatography of fractions 134–157 gave dictyol E (48 mg, 0.032% dry weight), oily; $[\alpha]_D$ +26.5° (c = 1, $CHCl_3$) (lit.[2] +26.8°).

10,18 - *Dihydroxy* - 2,7 - *dolabelladiene* (**8**). Fractions 158–171 were evaporated to give an oily residue (380 mg, 0.25% dry weight) which was chromatographed on Si gel (EtOAc–hexane 1:6). The appropriate fractions were pooled and evaporated to dryness. Recrystallization of the residue from EtOH gave pure **8** (55 mg, 0.025% dry weight), m.p. 150–151° (lit.[5] 152–153°); $[\alpha]_D$ −70.5° (c = 1, $CHCl_3$) (lit.[5] −71.8°).

Dictyol C (**10**). Fractions 172–183 were evaporated and the residue purified by column chromatography (Et_2O–C_6H_6 1:3) to give dictyol C (52 mg, 0.035% dry weight), m.p. 67–68° (lit.[2] 68°); $[\alpha]_D$ −16.4° (c = 1, $CHCl_3$) (lit.[2] −16.6°).

3,4 - *Epoxy* - 14 - *hydroxy* - 7,18 - *dolabelladiene* (**3**). Evaporation of fractions 185–200 gave a green oily residue (280 mg) which was subjected to repeated Si gel column chromatography to give **3** as an oil (120 mg, 0.08% dry weight); $[\alpha]_D$ +48° (c = 0.5, EtOH); IR (neat liquid) 3400, 1250, 890 cm^{-1}; M^+ m/e 304.2408 (calc. for $C_{20}H_{32}O_2$ 304.2402); ^1H NMR (Table 1).

3,4 - *Epoxy* - 14 - *acetoxy* - 7,18 - *dolabelladiene* (**12**). Conventional acetylation of **3** (Ac_2O-pyridine, overnight at room temp) gave the acetate **12**, oily; M^+ m/e 346.2501 (calc. for $C_{22}H_{34}O_3$ 346.2508); IR (neat liquid) 1735, 1250, 890 cm^{-1}; ^1H NMR (Table 1).

Sodium borohydride reduction of **2** *to produce* **3** *and* **11**. $NaBH_4$ (200 mg) was added to a soln of **2** (200 mg) in EtOH (20 ml) and the mixture was stirred for 2 hr. After addition of H_2O (50 ml), excess reagent was destroyed by addition of dil HCl and the organic material was extracted 3x with Et_2O. The combined extracts were dried over Na_2SO_4 and evaporated *in vacuo* to yield an oil (195 mg). Chromatography of the oil on Si gel (hexane–Et_2O 1:1) gave **3** (35 mg) and the epimeric alcohol **11** (120 mg). The latter had m.p. 70–72° (hexane); $[\alpha]_D$ +74.8° (c = 1, $CHCl_3$); ^1H NMR (Table 1).

Permanganate-periodate oxidation of **2**. The procedure of Lemieux-von Rudloff[11] was used. To **2** (50 mg) in t-BuOH was added 30 ml of stock oxidant soln and enough 0.05 M K_2CO_3 to give a pH of 8. After standing 18 hr at room temp, the mixture was acidified (1 M H_2SO_4) to pH 4 and treated with solid sodium metabisulfite until a nearly colourless soln was obtained. The resulting soln was extracted with ether and the extract injected into a gas chromatograph in which the stationary phase was 2.5% OV-1 on Chromosorb, and the temp kept at 130°. Under these conditions, the retention time of the single component detected was identical with that of levulinic acid. The mass fragmentation patterns of the oxidation product and levulinic acid were also identical.

Application of the Horeau method to **3**. **3** (10 mg) was treated with excess racemic α-phenylbutyric anhydride (20 mg) in pyridine (0.2 ml). Conventional workup[12] led to the isolation of a preponderance of (+) α-phenylbutyric acid (optical yield 14%).

Zinc–copper couple reduction of **2** *to produce* **4**. The procedure described by Kupchan and Maruyama[13] was followed. Compound **2** (150 mg) was dissolved in EtOH (5 ml), Zn–Cu couple (6 g) was added with stirring and the mixture refluxed for 4 days. The ppt was filtered off and the soln was evaporated. The crystalline residue was purified by column chromatography to give 114 mg of **4** (80%), identified by comparison of the physical properties (m.m.p., $[\alpha]_D$, IR, NMR) with those of a reference sample, and 20 mg of starting material.

Epoxidation of **4**. A soln of *m*-chloroperbenzoic acid (100 mg) in benzene (1 ml) was added dropwise at 25° to a stirred soln of **4** (100 mg) in benzene (2 ml). After 45 min excess peracid was destroyed by addition of 10% Na_2SO_3aq and the organic layer washed with 5% $NaHCO_3$aq followed by water, dried (Na_2SO_4) and evaporated *in vacuo*. The residue was chromatographed on column (Si gel, Et_2O–hexane 1:4) to give **2** and the isomeric **13** m.p. 173–174°; $[\alpha]_D$ −139° (c = 1, $CHCl_3$); M^+ m/e 302.2249 (calc. for $C_{20}H_{30}O_2$ m/e 302.2246); 60 MHz ^1H NMR ($CDCl_3$) δ 5.42 (dd, 1 H, J = 11 and 4 Hz, H-3), 4.98 (bs, 1 H, H-20), 4.73 (bs, 1 H, H-20'), 2.75 (dd, 1 H, J = 9 and 2 Hz, H-7), 1.76 (bs, 3 H, Me-18), 1.67 (bs, 3 H, Me-4), 1.33 (s, 3 H, Me-8), 1.12 (s, 3 H, Me-1).

When the isomeric monoepoxides **2** and **13** were each treated again with *m*-chloroperbenzoic acid, they gave the same diepoxide **14**, m.p. 151–153°; $[\alpha]_D$ +127° (c = 1, $CHCl_3$); M^+ m/e 318.2191 (calc. for $C_{20}H_{30}O_3$ m/e 318.2195); 60 MHz NMR ($CDCl_3$) δ 5.12 (bs, 1 H, H-20). 4.81 (bs 1 H, H-20'), 3.07 (dd, 1 H, J = 11 and 3 Hz, H-3), 2.80 (bd, 1 H, J = 7 Hz, H-7), 1.82 (bs, 3 H, Me-18), 1.36, 1.33 and 1.27 (s, 3 H each, Me-1, Me-4, Me-8).

Wolff–Kishner reduction of **2** *to produce* **5**. A mixture of **2** (150 mg), 85% hydrazine hydrate (3 ml), hydrazine dihydrochloride (500 mg) and 15 ml of triethyleneglycol was heated at 130° for 1.5 hr. After adding KOH pellets (1.3 g) the temp was raised at 170° and heating continued for 2 hr. After cooling H_2O (50 ml) was added and the mixture extracted with 3 × 10 ml of Et_2O. The combined ether layers were dried (Na_2SO_4) and reduced *in vacuo*. Si gel chromatography (1 × 40 cm; Et_2O–hexane 1:9) of the residue afforded 10 mg of material identical (m.p., $[\alpha]_D$, ^1H NMR, MS) with the epoxide **5**.

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