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TRICYCLIC DITERPENOIDS OF THE DOLASTANE RING SYSTEM FROM THE MARINE ALGA *DICTYOTA DIVARICATA*

H. H. SUN,† O. J. MCCONNELL‡ and WILLIAM FENICAL*
Institute of Marine Resources, Scripps Institution of Oceanography, La Jolla, CA 92093, U.S.A.

and

KEN HIROTSU and JON CLARDY*
Department of Chemistry, Cornell University, Ithaca, NY 14853, U.S.A.

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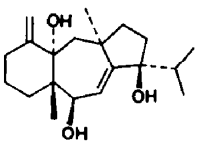
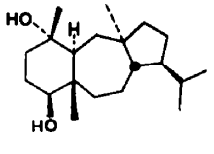
Abstract—Four new oxygenated tricyclic diterpenoids have been isolated from the Caribbean brown alga *Dictyota divaricata*. The structures of these new compounds were secured by an X-ray analysis of a convenient diol derivative, followed by interconversion where possible. The new diterpenoids belong to the dolastane group first isolated from the herbivorous mollusc *Dolabella auricularia*, and their isolation here indicates that the sea hare most likely derived these compounds from brown seaweeds of the family Dictyotaceae.

Brown seaweeds of the family Dictyotaceae are an unusually prolific source of biologically active secondary metabolites. In particular, the cosmopolitan and semitropical genus *Dictyota* is yielding an expanding variety of interesting diterpenoids.[1-7] We wish to describe here the structures of four new diterpenoids isolated from the Caribbean alga *Dictyota divaricata* Lamouroux (Dictyotaceae). These four new compounds are closely related to dolatriol (I) and the corresponding C-6 acetate, which are cytotoxic diterpenoids earlier isolated from the digestive gland of the sea hare *Dolabella auricularia*.[8] In a parallel study of the digestive gland components of *Dolabella californica*, a series of related bicyclic diterpenoids, the dolabelladienes, have been described.[9,10] Our recent report of dolabelladienes from the brown alga *Glossophora galapagensis*[11] (Dictyotaceae), coupled with this report of dolastane derivatives from *D. divaricata*, further support the contention that *Dolabella* species, like some sea hares of the genus *Aplysia*, prefer grazing on brown seaweeds of the family Dictyotaceae.[10]

It is interesting to note that some very closely related compounds, the clavularanes, typified by II have been isolated from the Indo-Pacific stoloniferan soft-coral *Clavularia inflata*.[13]



I



II

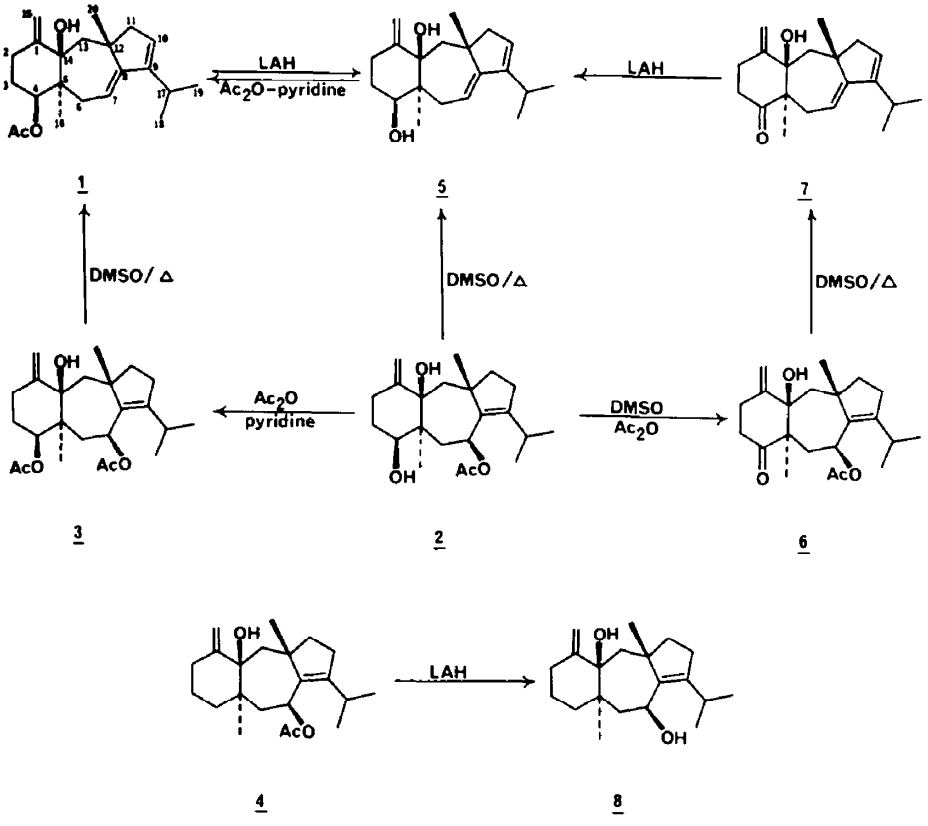
Two collections of *D. divaricata* were made in the Virgin Islands in late 1976 and early 1977. Air-dried algae from both collections were extracted with chloroform/methanol (1/1) and the condensed extracts were separately chromatographed over silica gel (open-column). The first collection (Tague Bay) yielded only the monoacetate **1** in 0.2% yield of the dry alga. The second collection yielded a small amount of **1** (0.008%) in addition to fractions containing complex mixtures. Subsequent preparative hplc yielded **2** (0.25%), **3** (0.12%) and **4** (0.004%) from this latter collection.

The acetate **1**, an oil, showed $[\alpha]_D$-128° (*c* 9.5, $CHCl_3$) and analysed for $C_{22}H_{32}O_3$ by high resolution mass spectrometry. The IR spectrum of **1** showed absorptions for OH (3400 cm^{-1}), ester CO (1740 cm^{-1}) and exomethylene (1640 and 915 cm^{-1}) functionalities. UV absorption at 243 nm (ϵ 7000) suggested the presence of a conjugated heteroannular diene. Consideration of ^1H and ^{13}C data (Tables 1 and 2, and Experimental) indicated the seven degrees of unsaturation inherent in the molecular formula to consist of three double bonds, one acetate CO and three carbocyclic rings. LAH reduction gave the diol **5** which formed X-ray-suitable crystals from ethanol. Acetylation of **5** (Ac_2O/py) yielded **1**, which was identical to the natural product.

The structure of diol **5** was solved by X-ray crystallography. Figure 1 shows a computer generated perspective drawing of the final X-ray model. Hydrogens are omitted for clarity, and the X-ray experiment did not define the absolute configuration. According to the nomenclature proposed by Pettit,[8] diol **5** would 4(S*), 14(S*)-dihydroxydolast-1(15),7,9-triene. The relative configurations at C-5 and C-12 are both S*. In general, the bond distances agree well with accepted values although there is some evidence of bond shortening due to thermal motion in the isopropyl group. An intramolecular H-bond appears to exist between O(21)H · · · O(22) with a distance of 2.67 Å, as well as an intermolecular H-bond between O(21)H · · · O(22), with a distance of 2.835 Å. The 6-membered ring is in the chair conformation with

†Present address: New York Aquarium, Boardwalk West 8th Street, Brooklyn, NY 11224, U.S.A.

‡Present address: Skidaway Institute of Oceanography, P.O. Box 13687, Savannah, GA 31406, U.S.A.



Scheme 1.

Table 1. Selected 220 MHz ^{1}H NMR data for compounds 1–5[a]

#C	1 δ, (m Hz)	2	3	4	5
4	4.86 (bs)	3.49 (bs)	4.76 (bs)	b	3.83 (bs)
6α	3.22(dd 14,4)	2.93(dd 14,11)	2.70(dd 14,11)	2.59(dd 14,11)	3.50(dd 14,4)
6β	1.59(dd 14,9)	b	1.55(dd 14,7)	b	1.78(dd 14,9)
7	5.39(dd 9,4)	5.92(dd 11,7)	5.88(dd 11,7)	5.89(dd 11,7)	5.48(dd 9,4)
10	5.64 (bs)	2.28(dd 9,6)	2.26(dd 9,6)	2.27(dd 9,6)	5.61 (bs)
15	4.83 (s) 4.95 (s)	4.85 (s) 4.93 (s)	4.86 (s) 4.91 (s)	4.77 (s) 4.83 (s)	4.81 (s) 4.94 (s)
16	0.95 (s)	0.78 (s)	0.88 (s)	0.70 (s)	0.82 (s)
17	2.41 (hp 6.5)	2.86 (hp 6.5)	2.79 (hp 6.5)	2.82 (hp 6.5)	2.43 (hp 6.5)
18	1.07[c](d 6.5)	0.93[c](d 6.5)	0.91[c](d 6.5)	0.93[c](d 6.5)	1.09[c](d 6.5)
19	1.11[c](d 6.5)	0.96[c](d 6.5)	0.94[c](d 6.5)	0.95[c](d 6.5)	1.11[c](d 6.5)
20	1.36 (s)	1.49 (s)	1.47 (s)	1.47 (s)	1.35 (s)
4-OAc	2.18 (s)	--	2.15 (s)	--	--
7-OAc	--	2.02 (s)	2.02 (s)	2.01 (s)	--

[a] assignments by spin-decoupling measurements

[b] assignment not made

[c] assignments may be reversed

Table 2. Selected 20 MHz ^{13}C NMR assignments for compounds 1–4[a]

#C	1	2	3	4
1	149.6 s	149.0 s	149.2 s	148.8 s
4	82.3 d	80.2 d	82.4 d	unassigned
5	43.9 s	42.9 s	42.9 s	40.4 s
7	112.5 d[b]	68.1 d	67.4 d	67.9 d
8	151.6 s[c]	151.8 s[b]	150.7 s[b]	153.4 s[b]
9	155.0 s[c]	137.1 s[b]	137.1 s[b]	137.2 s[b]
10	125.6 d[b]	unassigned	unassigned	unassigned
12	45.8 s	50.2 s	50.3 s	50.3 s
14	80.1 s	80.8 s	79.2 s	78.6 s
15	109.4 t	109.6 t	109.8 t	108.9 t
17	27.6 d	26.9 d	26.9 d	26.9 d
4-OAc	169.3 s	--	169.1 s	--
7-OAc	--	170.5 s	170.1 s	170.4 s

[a]recorded in $CDCl_3$ solution, and multiplicities by off-resonance decoupling.

[b,c]assignments may be reversed

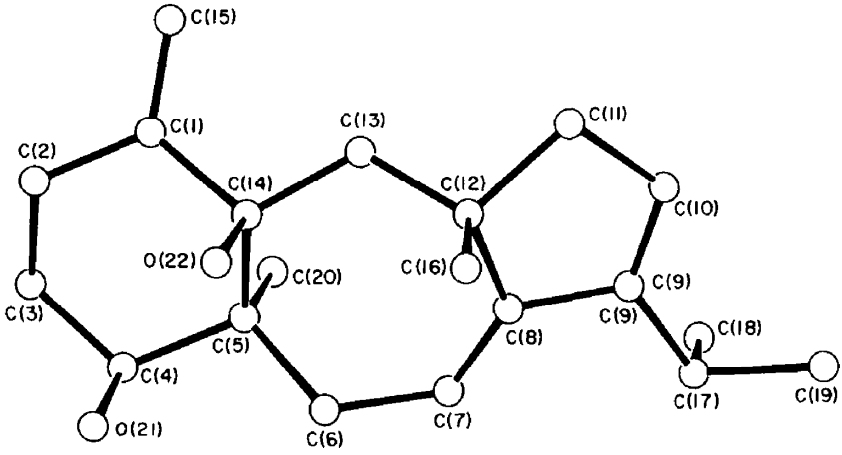


Fig. 1.

O(21), O(22) and CH_3(20) in axial positions. The cyclopentene ring has a flattened C_2 conformation.

Compound 2 analysed for $C_{22}H_{34}O_4$ by high resolution mass spectrometry, and exhibited IR absorptions for OH (3400 cm^{-1}), acetate (1740 cm^{-1}), and exomethylene (1640 and 905 cm^{-1}) functionalities, in close analogy to 1. This compound lacked UV absorption however, and by ^{13}C NMR analysis (Table 2), it appeared to possess only two double bonds. The ^1H NMR features of 2, as summarized in Table 1, indicated that the C-7 to C-10 conjugated diene was replaced by an allylic acetate functionality with acetate at C-7. The relative sterochemistry of the acetoxyl group was assigned as S* based upon the 11 and 7 Hz coupling constants with the C-6 methylene-group indicating pseudo axial–axial and pseudo axial–equatorial coupling.

Mild oxidation of 2 with DMSO/Ac_2O[14] afforded the cyclohexanone 6 ($\nu_{C=O}$ 1715 cm^{-1}) which placed the secondary OH group at C-4. During the workup of the oxidation product 4, the crude product was warmed under vacuum to remove traces of DMSO. Unexpectedly, this treatment resulted in a facile elimination of acetic acid to yield the diene–ketone 7. In confirmation that the C-7–C-10 diene chromophore was produced, 7 was reduced with LAH to yield the diol 5. The reduction proceeded with stereo-selectivity yielding only the C-4 = S* alcohol. Hence compound 2 can be assigned as 7(S*)-acetoxy-4(S*), 14(S*)-dihydroxy-dolast-1(15),8-diene.

Compound 3 analysed for $C_{24}H_{36}O_5$ by high resolution mass spectrometry and was confirmed as a diacetate derivative by its IR (two CO absorptions at 1730 and 1740 cm^{-1}) and ^1H and ^{13}C NMR features (Tables 1 and

2). Treatment of compound **2** with Ac_2O/pyridine yielded **3**, and analysis of the ^1H NMR shifts for the C-4 methine confirmed the C-4 esterification. Capitalizing upon the DMSO-induced elimination[15] of acetic acid in **2**, **3** was heated under identical conditions to yield **1**. Hence compound **3** can be assigned as 4(S*), 7(S*)-diacetoxy-14(S*)-hydroxydolast-1(15), 8-diene.

Minor amounts of another dolastane diterpene, **4**, were also isolated. Compound **4** analysed for $C_{22}H_{32}O_3$ by high resolution mass spectrometry and displayed similar IR bands at 3500, 1730, 1640 and 915 cm^{-1} for OH, acetate and exomethylene functionalities, respectively. The ^1H NMR spectrum showed an exomethylene group (δ 4.77, s; 4.83, s), an acetate Me (δ 2.01; s), an allylic acetoxyl methine proton (δ 5.89, dd), an allylic isopropyl group, (δ 0.93, d; 0.95, d; 2.82, heptet), a bridgehead Me (δ 0.70, s), and an unusually deshielded bridgehead Me group (δ 1.47, s). These characteristics allowed assignments of unsaturation at C-1–C-15 and C-8–C-9, and an acetoxyl group at C-7. Here again, the C-7 methine proton showed 11 and 7 Hz couplings in analogy to **2** and **3**, which established its stereochemistry as S* by analogy to **1–3**. The configuration of the C-20 Me and C-14 OH was securely established by the unusual C-20 Me shift mentioned above. In **4**, as in **1–3**, the C-14 OH and C-20 Me group are 1,3-diaxial substituents, and hence the Me resonance is considerably deshielded. In **1–3** the comparable Me group resonance is located between δ 1.35–1.49. LAH reduction of **4** gave the diol **8**, the ^1H NMR characteristics of which further confirmed placement of the ester functionality at C-7 in **4**. Specifically, the δ 5.89 dd in **4** was shifted, as expected, to δ 4.66 in **8**. While compound **4** could not be interconverted to **5** or **1–3**, its ^1H and ^{13}C NMR features strongly support our assignment as 7(S*)-acetoxy-14(S*)-hydroxydolast-1(15), 8-diene.

EXPERIMENTAL

IR spectra were determined on a Perkin–Elmer 137 NaCl spectrophotomer. ^1H NMR spectra were recorded on a Varian HR-220 spectrometer with computerized Fourier transform and spin-decoupling capabilities. ^{13}C NMR spectra were obtained on a Varian CFT-20 spectrometer. Chemical shifts are reported as δ values in ppm relative to TMS = 0. UV spectra were measured on a Perkin–Elmer 124 spectrophotometer and optical rotations were recorded on a Perkin–Elmer 1410 polarimeter. Low resolution mass spectra were recorded at 70 eV on a Hewlett–Packard 5930 mass spectrometer and high resolution mass measurements were supplied by the Chemistry Department, UCLA. High pressure liquid chromatography was performed using a Waters 6000 HPLC with 2 × 25 cm μ-Porasil as the support. Silica gel, Grade 62, 60–2000 mesh (W. R. Grace) was used for column chromatography and Brinkman pre-coated TLC plates (silica gel 60 F-254, 2 mm) for preparative TLC. M.ps were obtained using a Fisher–Johns apparatus and are reported uncorrected.

Collection and extraction. Dictyota divaricata, (0.86 kg) collected at Tague Bay, October, 1976, was air dried and repeatedly extracted with $CHCl_3$–MeOH (1:1). Removal of solvents *in vacuo* yielded 30 g of dark green extract, which was subsequently chromatographed over silica gel. Fractions eluted with 5% Et_2O in C_6H_6 contained **1**, and hplc (50 cm μ-Porasil, 15% EtOAc/Trimethylpentane (TMP)) yielded pure **1** (1.8 g) as a viscous, colorless oil which failed to crystallize.

A second collection (1.3 kg) of *D. divaricata* made in February 1977, from another locale near Christiansted, St. Croix, Virgin Islands, was also repeatedly extracted with $CHCl_3$–MeOH (1:1). Removal of solvents *in vacuo* gave 40 g of concentrated extract which was chromatographed over silica gel in a fashion identical with the first extract. Complex fractions were eluted from which **1–4** were subsequently isolated by preparative hplc. The dry-wt. yields were **1** (0.008%), **2** (0.12%) and **4** (0.004%).

4(S)-Acetoxy-14(S*)-hydroxydolast-1(15), 7, 9-triene* (**1**). Compound **1** was isolated as a viscous oil which showed the following spectral features: $[\alpha]_D^{25} - 128.5$ (*c* 9.5, $CHCl_3$); UV: $\lambda_{max}^{hexanes}$ 243 nm (ϵ 7,000); IR (CCl_4): ν_{max} 3500, 2920, 2860, 1740, 1640, 1460, 1380, 1240, 1175, 1130, 1050, 990, 965, 915 and 865 cm^{-1}; ^1H NMR ($CDCl_3$, 220 MHz): δ 0.95 (3H, s), 1.07 (3H, d, J = 6.5 Hz), 1.11 (3H, d, J = 6.5 Hz), 1.3 (m), 1.36 (3H, s), 1.59 (1H, dd, J = 14, 9 Hz), 1.7–2.0 (several m), 2.18 (3H, s), 2.18 (1H, bd, J = 18 Hz), 2.33 (1H, bd, J = 18 Hz), 2.41 (1H, hp, J = 6.5 Hz), 2.75 (1H, ddd, J = 12, 12, 6.5 Hz), 3.22 (1H, dd, J = 14, 4 Hz), 3.79 (1H, bs, D_2O exch), 4.83 (1H, s), 4.86 (1H, bs), 4.95 (1H, s), 5.39 (1H, dd, J = 9, 4 Hz) and 5.64 (1H, bs), ppm; ^1H NMR (benzene-d_6, 220 MHz); δ 0.77 (3H, s), 1.09 (3H, d, J = 6.5 Hz), 1.11 (3H, d) J = 6.5 Hz), 1.3 (m), 1.5 (1H, dd, J = 14, 9 Hz), 1.55 (3H, s), 1.60 (3H, s), 1.7 (m), 1.86 (1H, d, J = 13.5 Hz), 2.00 (1H, d, J = 13.5 Hz), 2.16 (1H, bd, J = 18 Hz), 2.30 (1H, bd, J = 18 Hz), 2.41 (1H, hp, J = 6.5 Hz), 2.95 (1H, ddd, J = 12, 12, 6.5 Hz), 3.34 (1H, dd, J = 14, 4 Hz), 3.67 (1H, bs, D_2O exch), 4.75 (1H, s), 4.82 (1H, s), 4.87 (1H, bs), 5.34 (1H, dd, J = 9, 4 Hz) and 5.57 (1H, bs) ppm; ^{13}C NMR ($CDCl_3$, 20 MHz): δ 20.2 (q), 21.3 (q), 22.1 (q, 2C), 25.6 (q), 26.9 (t), 27.6 (d), 28.4 (t), 30.8 (t), 41.9 (t) 43.9 (s), 45.8 (s), 51.1 (t), 80.1 (s), 82.3 (d), 109.4 (t), 112.5 (d), 125.6 (d), 149.6 (s), 151.6 (s), 155.0, (s) and 169.3 (s) ppm; MS *m/e*: 344 (M^+), 326, 301, 284, 266, 251, 243, 223, 149, 133, 119, 105, 91, 81, 79, 55 and 43; high resolution mass measurement: (Found: 344.234. Calc. for $C_{22}H_{32}O_3$: 344.235).

7(S)-Acetoxy-4(S*), 14(S*)-dihydroxydolast-1(15), 8-diene* (**2**). Compound **2** was purified by hplc (30%) EtOAc/TMP) to yield a viscous and colorless oil with the following spectral features: $[\alpha]_D^{25} - 35.3$ (*c* 1.1, $CHCl_3$); IR (CCl_4): ν_{max} 3400, 2900, 1730, 1640, 1450, 1370, 1240, 950 and 905 cm^{-1}; UV: λ_{max}^{MEOH} 208 nm (ϵ 6700): ^1H NMR ($CDCl_3$, 220 MHz): δ 0.78 (3H, s), 0.93 (3H, d, J = 6.5 Hz), 0.96 (3H, d, J = 6.5 Hz), 1.3 (m), 1.49 (3H, s), 1.5–1.8 (several m), 2.02 (3H, s), 2.1 (m), 2.28 (2H, dd, J = 9, 6 Hz), 2.81 (1H, ddd, J = 13, 13, 7 Hz), 2.86 (1H, hp, J = 6.5 Hz), 2.93 (1H, dd, J = 14, 11 Hz), 3.10 (1H, s, D_2O exch), 3.49 (1H, bs), 3.95 (1H, bs, D_2O exch), 4.85 (1H, s), 4.93 (1H, s) and 5.92 (1H, dd, J = 11, 7 Hz) ppm; ^1H NMR (benzene-d_6, 220 MHz): δ 0.68 (3H, s), 0.87 (3H, d, J = 6.5 Hz), 1.01 (3H, d, J = 6.5 Hz), 1.2–1.6 (several m), 1.68 (3H, s), 1.77 (3H, s), 1.9–2.1 (m), 2.16 (2H, dd, J = 9, 6 Hz), 2.87 (1H, ddd, J = 13, 13, 17 Hz), 3.00 (1H, hp, J = 6.5 Hz), 3.17 (1H, dd, J = 14, 11 Hz), 3.29 (1H, bs), 3.45 (1H, s, D_2O exch), 3.68 (1H, bs, D_2O exch), 4.73 (1H, s), 4.78 (1H, s) and 6.15 (1H, dd, J = 11, 7 Hz) ppm; ^{13}C NMR ($CDCl_3$, 20 MHz): δ 17.8 (q), 20.3 (q), 21.6 (q, 2C), 26.5 (t), 26.9 (d), 27.4 (t, q), 30.2 (t), 34.3 (t), 42.9 (s, t), 47.1 (t), 50.2 (s), 68.1 (d), 80.2 (d), 80.8 (s), 109.6 (t), 137.1 (s), 149.0 (s), 151.8 (s) and 170.5 (s) ppm; MS *m/e*: 362 (M^+), 344, 302, 284, 259, 241, 229, 149, 133, 121, 105, 91, 81, 79, 69, 55 and 43; High resolution mass measurement: (Found: 362.2457. Calc. for $C_{22}H_{34}O_4$: 362.2457).

4(S), 7(S*)-Diacetoxy-14(S*)-hydroxydolast-1(15), 8-diene* (**3**). Compound **3** was purified by hplc (20% EtOAc/TMP) to yield a viscous and colorless oil with the following spectral features: $[\alpha]_D^{25} - 44.0$ (*c* 1.1, $CHCl_3$); IR (CCl_4): ν_{max} 3650, 2960, 2880, 1740, 1730, 1650, 1450, 1370, 1240, 1020, 950 and 905 cm^{-1}; UV λ_{max}^{MEOH} 208 nm (ϵ 6,000); ^1H NMR ($CDCl_3$, 220 MHz): δ 0.88 (3H, s), 0.91 (3H, d, J = 6.5 Hz), 0.94 (3H, d, J = 6.5 Hz), 1.47 (3H, s), 1.55 (1H, dd, J = 14, 7 Hz), 1.6–1.8 (m), 1.70 (1H, d, J = 13 Hz), 1.93 (1H, dd, J = 13, 2 Hz), 2.02 (3H, s), 2.15 (3H, s), 2.26 (2H, dd, J = 9, 6 Hz), 2.63 (1H, ddd, J = 13, 13, 7 Hz), 2.70 (1H, dd, J = 14, 11 Hz), 2.79 (1H, hp, J = 6.5 Hz), 3.71 (1H, d, J = 2 Hz, D_2O exch), 4.76 (1H, bs), 4.86 1H, s), 4.91 (1H, s) and 5.88 (1H, J = 11, 7 Hz) ppm; ^1H NMR (benzene-d_6): δ 0.66 (3H, s), 0.87 (3H, d, J = 6.5 Hz), 1.04 (3H, d, J = 7 Hz), 1.42 (3H, s), 1.6–1.7 (m), 1.71 (3H, s), 1.80 (1H, dd, J = 14, 7 Hz), 1.86 (1H, d, J = 15 Hz), 1.87 (3H, s), 1.97 (1H, d, J = 15 Hz), 2.16 (2H, dd, J = 9, 6 Hz), 2.63 (1H, ddd, J = 13, 13, 7 Hz), 3.09 (1H, hp, J = 6.5 Hz), 3.10 (1H, dd, J = 14, 11 Hz), 3.69 (1H, bs, D_2O exch), 4.79 (1H, s), 4.82 (2H, bs) and 6.17 (1H, dd, J = 11, 7 Hz) ppm; ^{13}C NMR ($CDCl_3$, 20 MHz): δ 17.9 (q), 20.2 (q), 21.4 (q), 21.5 (q, 2C), 26.5 (t), 26.9 (d), 27.1 (t), 27.4 (t), 27.6 (q), 33.3 (t), 42.9 (s, t), 45.7 (t), 50.3 (s), 67.4 (d), 79.2 (s), 82.4 (d), 109.8 (t), 137.1 (s), 149.2 (s), 150.7 (s), 169.1 (s) and 170.1 (s) ppm; MS *m/e*: 404 (M^+), .386, 344, 326, 301, 288, 284, 266, 241, 223, 177, 149, 133, 121, 105, 93, 91, 81, 73, 61, 55 and 43;

high resolution mass measurement: (Found: 404.2563. Calc. for $C_{24}H_{36}O_5$: 404.2563).

7(S*)-*Acetoxy*-14(S*)-*hydroxydolast*-1(15), 8-*diene* (**4**). Compound **4** was purified by hplc (15% EtOAc/TMP) to yield a viscous and colorless oil with the following spectral features: $[\alpha]_D^{25}$ −9.4 (*c* 0.9, $CHCl_3$); IR (CCl_4): ν_{max} 3500, 2900, 1730, 1640, 1370, 1240 and 910 cm^{-1}; UV: λ_{max}^{EtOH} 208 nm (ϵ 6,000); ^1H NMR ($CDCl_3$, 220 MHz): δ 0.70 (3H, s), 0.93 (3H, d, J = 6.5 Hz), 0.95 (3H, d, J = 6.5 Hz), 1.3 (m), 1.47 (3H, s), 1.5–2.0 (several m), 2.01 (3H, s), 2.14 (1H, d, J = 14 Hz), 2.27 (2H, dd, J = 9, 6 Hz), 2.56 (1H, ddd, J = 13, 13, 7 Hz), 2.59 (1H, dd, J = 14, 11 Hz), 2.82 (1H, hp, J = 6.5 Hz), 4.77 (1H, s), 4.83 (1H, s) and 5.89 (1H, dd, J = 11, 7 Hz) ppm; ^1H NMR (benzene-d_6, 220 MHz): δ 0.82 (3H s), 0.88 (3H, d, J = 6.5 Hz), 1.03 (3H, d, J = 6.5 Hz), 1.26 (1H, d, J = 14 Hz), 1.4 (m), 1.58 (3H, s), 1.66 (1H, dd, J = 11, 7 Hz), 1.75 (3H, s), 1.8–1.9 (m), 2.10 (1H, d, J = 14 Hz), 2.18 (2H, dd, J = 9, 6 Hz), 2.51 (1H, ddd, J = 13, 13, 7 Hz). 2.91 (1H, dd, J = 14, 11 Hz), 3.06 (1H, hp, J = 6.5 Hz), 4.66 (1H, s), 4.75 (1H, s) and 6.19 (1H, dd, J = 11, 7 Hz) ppm; ^{13}C NMR ($CDCl_3$, 20 MHz): δ 17.8 (q), 20.3 (q), 21.6 (q), 22.4 (q), 26.9 (d), 27.4 (t), 27.6 (q), 29.7 (t), 31.9 (t), 37.3 (t), 37.8 (t), 40.4 (s), 43.0 (t), 47.4 (t), 50.3 (s), 67.9 (d), 78.6 (s), 108.9 (t), 137.2 (s), 148.8 (s), 153.4 (s) and 170.4 (s) ppm; MS *m/e*: 346 (M^+), 286, 243, 231, 225, 149, 133, 121, 107, 105 91, 81, 67, 55, 43 and 41; high resolution mass measurement: (Found: 286.2299. Calc. for $C_{20}H_{30}O$: (M^+–HOAc) 286.2297).

4(S*), 14(S*)-*Dihydroxydolast*-1(15),7,9-*triene* (**5**). A suspension of 30 mg (0.087 mmoles) of **1** and 33 mg (0.87 mmoles) LAH in 5 ml anhyd ether was stirred for 1 hr at RT. The reaction was quenched by the cautious addition of dist H_2O and the aqueous phase was extracted with 3×5 ml Et_2O. The combined Et_2O layers were then dried ($MgSO_4$) and reduced *in vacuo*. Purification by tlc using 5:5:1 hexanes–CH_2Cl_2–EtOAc provided 21 mg (80%) of **5**: m.p. 145° (recrystallized from 95% EtOH): $[\alpha]_D^{25}$ −190.0 (*c* 3.35 $CHCl_3$); IR (CCl_4): ν_{max} 3500, 2940, 1640, 1460, 1380, 1080, 1050, 970, 915 and 865 cm^{-1}; UV: $\lambda_{max}^{hexanes}$ 243 nm (ϵ 7000); ^1H NMR ($CDCl_3$, 220 MHz): δ 0.82 (3H, s), 1.09 (3H, d, J = 6.5 Hz), 1.11 (3H, d, J = 6.5 Hz), 1.35 (3H, s), 1.70 (1H, d, J = 13.5 Hz), 1.78 (1H, dd, J = 14, 9 Hz), 2.00 (1H, d, J = 13.5 Hz), 1.9–2.1 (m), 2.19 (1H, bd, J = 18 Hz), 2.33 (1H, bd, J = 18 Hz), 2.43 (1H, hp, J = 6.5 Hz), 2.74 (1H, s, D_2O exch), 2.93 (1H, ddd, J = 12, 12, 6.5 Hz), 3.50 (1H, dd, J = 14, 4 Hz), 3.83 (1H, bs), 4.81 (1H, s), 4.94 (1H, s), 5.48 (1H, dd, J = 9, 4 Hz) and 5.61 (1H, bs) ppm; ^1H NMR (benzene-d_6,, 220 MHz): δ 0.75 (3H, s), 1.11 (3H, d, J = 6.5 Hz), 1.13 (3H, d, J = 6.5 Hz), 1.44 (3H, s), 1.59 (1H, d, J = 13, 5 Hz), 1.70 (1H, dd, J = 14, 9 Hz), 1.88 (1H, d, J = 13, 5 Hz), 2.11 (1H, bd, J = 18 Hz), 2.24 (1H, bd, J = 18 Hz), 2.43 (1H, hp, J = 6.5 Hz), 2.91 (1H, ddd, J = 12, 12, 6.5 Hz), 2.93 (1H, s,D_2O exch), 3.34 (1H, bs), 3.65 (1H, dd, J = 14, 4 Hz), 4.65 (1H, s), 4.80 (1H, s), 5.48 (1H, dd, J = 9, 4 Hz) and 5.55 (1H, bs) ppm; MS *m/e*: 302 (M^+), 284, 263, 251, 241, 223, 209, 207, 157, 149, 133, 121, 119, 105, 91, 77, 69, 55 and 43.

Acetylation of **5**. To insure that unwanted rearrangements had not accompanied the conversion of **1** to **5**, diol **5** (5 mg) was treated with excess Ac_2O (1 ml) in pyridine at RT for 24 hr. Removal of the excess reagents *in vacuo* yielded a single product identified as **1** by comparison of its physical and spectral properties with the natural product.

X-ray analysis of diol **5**. Single crystals of **5** suitable for a single crystal X-ray diffraction experiment, were grown by slow evaporation of an EtOH soln. Preliminary X-ray photographs showed orthorhombic symmetry, and accurate lattice constants, determined by a least-squares fit of fifteen diffractometer measured 2θ-values, were **a** = 8.594(1), **b** = 8.626(1) and **c** = 24.377(4)Å. Systematic extinctions and the presence of chirality fixed the space group as $P2_12_12_1$ and density considerations indicated one molecule of $C_{20}H_{30}O_2$ per assymetric unit. All unique diffraction maxima with $2\theta \leq 45°$ were recorded using a variable speed ω-scan technique and graphite monochromated MoKα radiation (0.71069 Å). Of the 1403 reflections surveyed, 1234 (88%) were judged observed after correction for Lorentz, polarization and background effects.

An initial phasing model was achieved using a multisolution, wieghted tangent formula approach.[17] All H atoms were located in a difference electron density synthesis and included in subsequent calculations. Full-matrix least-squares refinements with anisotropic temperature factors for non-H atoms have converged to a conventional crystallographic discrepancy index of 0.064. Additional crystallographic details have been deposited with the Cambridge Crystallographic Data Centre (Ref. 18).

Oxidation of 7(S*)-*acetoxy*-4(S*)-*dihydroxydolast*-8-*ene* (**2**). A soln of 20 mg (0.055 mmoles) of **2** and excess Ac_2O in 2 ml DMSO was stirred at room temp for 20 hr. Approximately 5 ml distilled water was added, and the mixture was extracted with three 5 ml portions CCl_4. After drying with $MgSO_4$, concentration *in vacuo*, and tlc in 5:5:1 hexanes–CH_2Cl_2–EtOAc, 15 mg (75%) of **6** was obtained as an oil: IR (CCl_4): ν_{max} 3500, 2960, 1730, 1715, 1640, 1460, 1370, 1230 and 910 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.92 (3H, d, J = 6 Hz), 0.95 (3H, d, J = 6 Hz), 1.01 (3H, s), 1.45 (3H, s), 1.6–1.7 (4H, M), 2.26–2.50 (4H, m), 2.62–3.08 (4H, m), 5.06 (1H, s), 5.09 (1H, s) and 5.86 (1H, dd, J = 11, 7 Hz) ppm; MS *m/e*: 360 (M^+), 318, 300, 285, 275, 267, 257, 244, 239 and 216. During the work-up of this reaction, a vacuum distillation at 80° was used to remove DMSO. Compound **7** was isolated, along with **6** as a minor product.

The ketone **7**. A soln of **6** (26 mg, 0.072 mmoles) in 2 ml DMSO was heated at 120° for 0.5 hr. Approximately 5 ml distilled H_2O was added, and the mixture was extracted with three 5 ml portions of CCl_4. After drying with $MgSO_4$, concentration *in vacuo*, and TLC in 5:5:1 hexanes–CH_2Cl_2–EtOAc, 15 mg (70%) of **7** was obtained as a colorless oil, which illustrated the following spectral features: IR(CCl_4): ν_{max} 3550, 2960, 1715, 1640, 1460, 1380, 1240, 1010, 910 and 840 cm^{-1}; UV: λ_{max}^{MeOH} 243 nm (ϵ 7,500); ^1H NMR ($CDCl_3$, 220 MHz): δ 1.04 (3H, s), 1.07 (3H, d, J = 6 Hz), 1.09 (3H, d, J = 6 Hz), 1.33 (3H, s), 1.80 (1H, d, J = 15 Hz), 2.27 (1H, d, J = 15 Hz), 2.36–3.75 (6H, m), 2.90–3.10 (3H, m), 5.00 (1H, s), 5.10 (1H, s), 5.46 (1H, dd, J = 9, 4 Hz) and 5.60 (1H, bs) ppm; MS *m/e*: 300 (M^+), 282, 267, 257, 239, 222 and 177.

LAH reduction of ketone **7** *to* **5**. Ketone **7** (10 mg; 0.033 mmoles) was treated with excess LAH (20 mg) in dry Et_2O for 1 hr. Standard workup gave 5 mg (51%) of crystalline compound identified as **5** by direct comparison.

Conversion of **2** *to diol* **5**. Compound **2** (32 mg, 0.088 mmoles) was warmed in DMSO under conditions already described above for the conversion of **6** to **7**. Removal of solvents *in vacuo* gave 17 mg (64%) of a crystalline compound identified as **5** by direct comparison.

Conversion of **2** *to* **3**. A soln of 28 mg (0.077 mmoles) of **2** and excess Ac_2O in 2 ml pyridine was allowed to react at room temp for 24 hr. Approximately 5 ml distilled water was added, and the mixture was extracted with three 5 ml portions CCl_4. After drying with $MgSO_4$ and concentration *in vacuo*, 25 mg (80%) of a colorless oil was obtained. Its ^1H NMR, IR and $[\alpha]_D$ were identical with those of **3**.

Conversion of **3** *to* **1**. A soln of **3** (21 mg 0.052 mmoles) in DMSO was heated as described above for the conversion of **6** to **7**. Removal of solvents *in vacuo* gave 12 mg (67%) of an oil which was identified as **1** by direct comparison with the natural product.

LAH reduction of **4**. A suspension of **4** (19 mg; 0.055 mmoles) and excess LAH in 5 ml anhyd Et_2O were stirred for 0.5 hr at room temp. The reaction was worked up according to the procedure described above for the conversion of **1** to **2**. Approximately 11 mg (65%) of **8** was obtained as an oil, which showed the following spectral features: IR (CCl_4): ν_{max} 3600, 2960, 1640, 1450, 1380, 1120 and 915 cm^{-1}; ^1H NMR ($CDCl_3$, 220 MHz): δ 0.77 (3H, s), 0.95 (3H, d, J = 6.5 Hz), 1.06 (3H, d, J = 6.5 Hz), 1.25 (m), 1.50 (3H, s), 1.5–1.7 (m), 1.8–2.1 (2H, m), 2.11 (1H, d, J = 14 Hz), 2.27 (2H, dd, J = 9, 6 Hz), 2.54 (1H, m), 2.62 (1H, dd, J = 14, 11 Hz), 2.86 (1H, hp, J = 6.5 Hz), 4.66 (1H, dd, J = 11, 7 Hz), 4.74 (1H, s) and 4.83 (1H, s) ppm; MS *m/e*: 304 (M^+), 302, 286, 268, 253, 243, 225, 133, 105, 95 and 91.

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[18]Tables of fractional coordinates, temperature factors, bond distances, bond angles and observed and calculated structure factors are available from the director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 IEW and from Prof. Clardy.