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STRUCTURE AND ABSOLUTE CONFIGURATIONS OF *DICTYOTA* SP. DITERPENES

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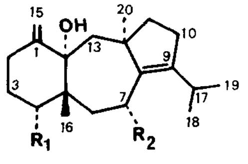
Abstract—Eight diterpenes belonging to the dolostane carbon skeleton have been isolated from the Canary Island brown alga *Dictyota* sp. The structures including absolute configuration of these diterpenes were secured by X-ray analysis of the triol derivative 7 followed by chemical interconversions.

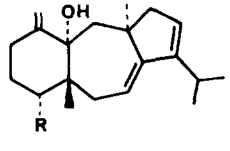
The genus *Dictyota*, brown seaweeds of the Dictyotaceae family, is yielding an expanding variety of interesting diterpenoids.[1] We wish to describe here the structures including absolute configuration of seven diterpenoids (**2–3** and **5–9**) isolated from the *Dictyota* sp. collected near La Graciosa, Canary Islands, during the Bentos I Expedition.[2] Air-dried alga was extracted with acetone and the condensed extract chromatographed over silica gel (open column), using solvents of increasing polarity from *n*-hexane to ethyl acetate.[3]

Concentration of the extract yielded the triol 7 ($C_{20}H_{32}O_3$) as a pure crystalline substance (long needles, m.p. 220°, $\{\alpha\}_D = -189$ (*c*, 0.1 MeOH). The detailed ^{1}H-NMR and ^{13}C-NMR analyses (Experimental) were consistent with the structure 7, which was confirmed by X-ray studies of the single crystal. Compound 7 crystallizes in orthorhombic system with four molecules in the cell $a = 22.6211(4)$, $b = 11.4528(2)$ and $c = 7.4452(2)$ Å; $\rho_x = 1.104\,\mathrm{g\,cm^{-3}}$. A crystal of $0.32 \times 0.30 \times 0.18$ mm was used to measure the intensities of the 1899 independent Friedel pairs up to $\theta = 65°$. Data were collected on a computer-controlled four-circle diffractometer, using graphite-monochromated CuKα radiation ($\lambda = 1.5418$ Å) and $\omega/2\theta$ scan at $\sim 2°$/min. No crystal decomposition was observed during the experiment. No absorption correction ($\mu = 5.36\,\mathrm{cm^{-1}}$) was done. The structure was solved by Multan[4] and refined using the 1796 observed reflections with $1 > 2\sigma(1)$. The H atoms were located on a difference map. After the molecular model was completed, a weighting scheme for the refinement was applied to prevent bias in $\langle w\Delta^2F\rangle$ vs $\langle F_0\rangle$ and vs $\langle \sin\theta/\lambda\rangle$. A last weighted anisotropic refinement (fixed isotropic contribution for H atoms), using both hkl and $\overline{hkl}$, reflections converged to $R_{obs} = 0.042$ and $Rw_{obs} = 0.054$.[5]

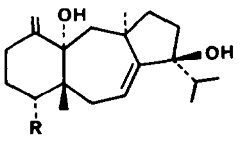
Figure 1 shows the X-ray molecular model with the right absolute configuration, which was determined using those Bijvoet pairs (BP) with $F_0 > 10\sigma(F_0)$ and greater ΔF_c.[6] The averaged Bijvoet difference, ⟨BD⟩, between



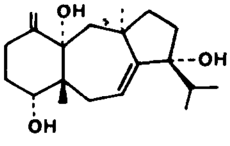
1 R_1=OH; R_2=H
2 R_1=OH; R_2=OH
3 R_1=OAc; R_2=OH
4 R_1=OAc; R_2=OAc



5 R=OH
6 R=OAc



7 R=OH
8 R=OAc



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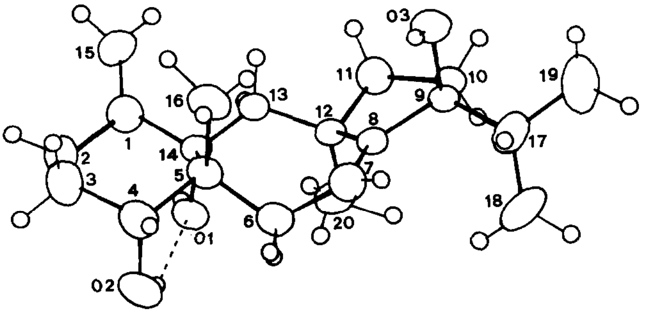

Fig. 1.

the 46 BP with $\Delta F_c > 0.15$ is 0.19 for the right enantiomer vs 0.33 for the wrong one. Using the 80 BP with $\Delta F_c > 0.13$, $\langle BD \rangle$ is 0.20 vs 0.29.

The 6-membered ring is a chair with the best plane through the atoms 1–2–4–5. The 7-membered ring is also a chair with its best plane through atoms 5–6–12–13. The 5-membered ring is a distorted envelope with the flap at C-10. The length of the two double bonds C-1-C-15 and C7–C8 is 1.321(3) Å. The three OH groups are linked through H-bonds, two intermolecular: 01H.... 03 of 2.75 Å and 03H...02 of 2.77 Å; and one intermolecular 02H...01 of 2.64 Å.

Treatment of **7** with Ac_2O/Py gave the also isolated monoacetate **8** which was dehydrated to the previously known compound **6**.[7] The absolute configuration of **6** is then determined as: 4(*R*), 14(*S*)-dihydroxy-dolast-1 (15), 7, 9-triene.

The isolation of **7**, was recently reported from a mixture of the seaweeds *D. linearis* and *D. divaricata* collected in the Honduras Bay Islands.[8] The structure was given on chemical and spectroscopic basis and the absolute configuration was undetermined.

The triol isomer **9** ($C_{20}H_{32}O_3$), m.p. 160–161°, $\{\alpha\}_D$-59 (*c*, 0.1 $CHCl_3$) gave on acetylation with Ac_2O/Py the monoacetate **6** as a result of concomitant dehydration at C-9. The $C_9(OH)$ substituent and stereochemistry were confirmed by comparison of the ^1H-NMR and ^{13}C-NMR spectra with those of the related triol **7** (Experimental). The absolute configuration of **9** was established by the chemical correlation with **7** through the common dehydration derivative **6**.

The remaining compounds were identified with the previously reported amijiol (**1**)[9], the triol **2** reported by Crews *et al.*,[8] and their corresponding monoacetate (**3**).[7] The chemical correlation within **2**–**4** was achieved by acetylation of **2** and **3** to give **4** and the absolute configuration determined by transformation of **4** into **6** by heating with DMSO.

EXPERIMENTAL

M.ps were determined on a Kofler block and are uncorr. IR spectra were recorded on a Perkin–Elmer Model 237 and Model 681 spectrophotometer. UV spectra were recorded on a Perkin-Elmer Model 137 or a Unicam SP800. Opical rotations were determined for solns in $CHCl_3$ and MeOH with a Perkin–Elmer 141 polarimeter. ^1H-NMR spectra were recorded on Perkin-Elmer R-32 (90 MHz) and with a Brucker Mod WM 360 spectrometers, chemical shifts are reported relative to Me_4Si ($\delta 0$) and coupling constants are given in hertz. ^{13}C-NMR spectra were obtained on a Brucker Mod WM 360 and the chemical shifts are reported relative to Me_4Si ($\delta 0$). Low and high resolution mass spectra were obtained from a VG Micromass ZAB-2F. Column and dry column chromatography were performed in silica gel 0.2–0.5 and 0.005–0.20 mm respectively, and tlc and plc on silica gel G, all Merck products. Tlc plates were developed by spraying with 6N-HSO_4 and heating. All solvents were purified by standard techniques. Anhyd Na_2SO_4 and $MgSO_4$ were used for drying solns.

Collection and extraction. Collections were from a depth of − 5 to − 10m, and location was near LaGraciosa Island (Canary Islands), October 1981, during the Bentos I expedition. The collection was immediately frozen and stored until extracted with acetone in a Soxhlet apparatus. Removal of solvent *in vacuo* yielded 48 g of dark green extract, which was subsequently chromatographed over silica gel (open column), using solvents of increaing polarity from *n*-hexane to EtOAc.

Amijol or (4S*, 14S*)-4, 14-Dihydroxydolast-1(15), 9 diene (**1**). Crystalline compound, m.p. 180°, $\{\alpha\}_D = -163$ (*c*, 0.3, $CHCl_3$). This compound showed spectral features similar to those reported,[9] and was identified by direct comparison with the natural product.

(4R, 14S)-*Dihydroxydolast*-1 (15), 7, 9-*triene* (**5**). This crystalline compound showed spectral features similar to those reported,[7] m.p. 145°, $\{\alpha\}_D = -220°$(*c*, 0.15, $CHCl_3$). MS: *m/z*: 302 (M^+–H_2O), 284, 266, 241 and 223. ^1H-NMR (360 MHz, $CDCl_3$) δ : 0.80 (s, Me_{16}) 1.07 (d, $J = 6.8$ Hz, Me_{18}); 1.09 (d, $J = 6.8$ Hz, Me_{19}); 1.40 (s, Me_{20}); 2.40 (qq, $J = 6.8$ Hz, H_{17}); 2.90 (ddd, $J = 5.3$ and 13.7 Hz, $H_{2\alpha}$); 3.48 (*dd*, $J = 4$ and 14 Hz, $H_{6\alpha}$); 3.87 (bs, H_4) 4.77 (s, H_{15}); 4.91 (s, H_{15}); 5.45 (dd, $J = 4.5$ and 9.5 Hz, H_7); 5.57 (s, H_{10}). CMR ($CDCl_3$; 360 MHz): 153.8 (C-1); 31. 67 (C-2); 31.35 (C-3); 80.31 (C-4); 44.03 (C-5); 27.23 (C-6); 114.17 (C-7); 149.8 (C-8); 152.4 (C-9); 109.5 (C-10); 50.95 (C-11); 45.5 (C-12); 43.5 (C-13); 82.05 (C-14); 109.6 (C-15); 19.9 (C-16); 26.74 (C-17); 22.13 (C-18); 22.3 (C-19); 25.7 (C-20). UV (EtOH) λ_{max}: 243 nm (ϵ 8.000).

(4R, 14S) 4-*Acetoxy*-14-*hydroxydolast*-1 (15), 7, 9-*triene* (**6**). This viscous oil showed spectral features similar to those reported.[7] $\{\alpha\}_D = -140°$ (*c*, 0.1, $CHCl_3$). ^1H-NMR (90 MHz, $CDCl_3$) δ : 1.00 (s, Me_{16}); 1.1 (d, $J = 6.8$ Hz; Me_{18}); 1.4 (d, $J = 6.8$ Hz; Me_{19}); 2.2 (s, − OAc); 3.75 (bs, D_2O exch.); 4.90 (m, 3H); 5.39 (dd, $J = 9$ and 5 Hz, H_7); 5.65 (bs, H_{10}); UV (EtOH) λ_{max} : 243 nm (ϵ : 10.000).

(4R, 7R, 14S)-4-*Acetoxy*-7, 14-*dihydroxydolast*-1 (15), 8-*diene* (**3**). A crystalline compound, m.p. 150°, $\{\alpha\}_D = -122°$ (*c*, 0.1, $CHCl_3$). MS: *m/z*: 362 (M^+), 344, 320, 319, 302, 301, 259, 241, 223. IR ($CHCl_3$): 3550, 2940, 1730, 1640, 1410, 960 and 910 cm^{-1}. ^1H-NMR: 0.78 (s, Me_{16}): 0.89 (dd, $J = 6.8$ Hz, Me_{18})*; 1.01 (d, $J = 6.8$ Hz, Me_{19})*; 145 (s, Me_{20}); 2.10 (s, C_4–OAc); 2.60 (ddd, $J = 5$ and 14 Hz, $H_{2\alpha}$); 2.68 (dd, $J = 11$ and 14.3 Hz, $H_{6\alpha}$); 2.78 (qq, $J = 6.8$ and 6.8 Hz, H_{17}); 4.60 (t, $J = 9$ Hz); 4.75 (s, H_{15}); 4.79 (s, H_4); 4.85 (s, H_{15}); CMR ($CDCl_3$, 360 MHz): 150.8 (C-1); 27.45 (C-2)$^{\#}$; 27.25 (C-3)$^{\#}$; 82.3 (C-4); 42.6 (C-5); 36.32 (C-6); 65.0 (C-7); 147.5 (C-8)$^+$; 141.1 (C-9)$^+$; 26.6 (C-10); 42.9 (C-11); 50.4 (C-12); 45.68 (C-13); 79.3 (C-14); 109.7 (C-15); 17.9 (C-16); 26.9 (C-17); 20.5 (C-18)*; 21.42 (C-19)*; 28.44 (C-20); 169.3 (C_4–OAc); 22.18 (C_4–OAc) (chemical shifts marked with *, $^{\#}$ and $^+$ are interchangeable). High resolution mass measurement: Found: 362.2440. Calc. for $C_{22}H_{34}O_4$: 362.2456.

(4R, 7R, 14S)-4, 7, 14-*Trihydroxydolast*-1 (15), 8-*diene* (**2**). A crystalline compound, m.p. 172°, $\{\alpha\}_D = -140°$ (c, 0.05, $CHCl_3$). MS: *m/z*: 320 (M^+), 302, 284, 259, 241 and 223. IR (KBr): 3500, 3200, 2990, 1640 and 910 cm^{-1}. ^1H-NMR ($CDCl_3$, 360 MHz): 0.69 (s, H_{16}); 0.90 (d, J = 6.8 Hz, Me_{18})*, 1.03 (d, J = 6.8 Hz, Me_{19})*; 1.47 (s, Me_{20}); 2.83 (ddd, J = 5 and 14 Hz, $H_{2\alpha}$); 2.87 dd, J = 11 and 14.2 Hz, $H_{6\alpha}$); 2.90 (qq, J = 6.8 and 6.8 Hz, H_{17}); 3.45 (bs, H_4); 4.63 (dd, J = 11 and 7 Hz, H_7); 4.78 (s, H_{15}); 4.87 (s, H_{15}) (chemical shifts marked with * are interchangeable). High resolution mass measurement: Found: 320.2356. Calc for $C_{20}H_{32}O_3$: 320. 2351.

(4R, 9S, 14S)-4, 9, 14-*Trihydroxydolast*-1 (15), 7-*diene* (**7**). A crystalline compound, m.p. 220°, $\{\alpha\}_D = -189°$ (*c*, 0.1, MeOH); IR (KBr): 3660, 2940, 1640, 1300, 1220, 1050, 970 and 910 cm^{-1}. $H_{2\alpha}$); 3.35 (dd, J = 4 and 15 Hz; $H_{6\alpha}$); 3.74 (d, J = 8 Hz; C_{14}–Me_{18})*; 1.03 (d, J = 6.8 Hz, Me_{19})*; 1.23 (s, Me_{20}); 1.97 (qq, J = 6.8 and 6.8 Hz, H_{17}); 2.65 (s, C_4–0$\underline{H}$); 2.89 (ddd, J = 5.5 and 13.6 Hz; H_{2a}); 3.35 (dd, *J* = 4 and 15 Hz; H_{6a}); 3.74 (d, *J* = 8 Hz; C_{14}–O$\underline{H}$); 3.47 (bs, H_4); 4.79 (s, H_{15}); 4.93 (s, H_{15}); 5.63 (dd, J = 4 and 10 Hz; H_7). CMR ($CDCl_3$, 360 MHz): 152. 3 (C-1); 31.2 (C-2)$^{\#}$; 26.6 (C-3)$^+$; 79.9 (C-4); 42.5 (C-5); 29.1 (C-6)$^+$; 119.5 (C-7); 156.3 (C-8); 86.1 (C-9); 31.3 (C-10)$^{\#}$; 41.3 (C-11); 46.0 (C-12); 44.9 (C-13); 81.6 (C-14); 109.7 (C-15); 17.3 (C-16); 37.7 (C-17); 19.1 (C-18)*; 19.9 (C-19)*; 24.4 (C-20) (chemical shifts marked with *, $^{\#}$ and $^+$ are interchangeable). MS: *m/z*: 320 (M^+); 302, 284, 277, 259, 241 and 223. High resolution mass measurement: Found: 320.2351. Calc for $C_{20}H_{32}O_3$: 320.2336.

(4R, 9S, 14S)-4-*Acetoxy*-9, 14-*dihydroxydolast*-1 (15), 7-*diene* (**8**). A viscous and colourless oil, $\{\alpha\}_D = -159°$ (*c*, 0.11, $CHCl_3$). IR ($CHCl_3$): 3570, 2950, 1730, 1640 and 920 cm^{-1}. ^1H NMR ($CDCl_3$, 360 MHz): 0.83 (d, J = 6.8 Hz, Me_{18}): 0.89 (s, Me_{16})*; 1.03 (d, J = 6.8 Hz, Me_{19})*; 1.23 (s, Me_{20}); 2.15 (s, 4-OAc); 2.71 (ddd, J = 5 and 14 Hz; $H_{2\alpha}$); 1.95 (qq, J = 6.8 and 6.8 Hz, H_{17}); 3.06 (dd, J = 4 and 15 Hz, $H_{6\alpha}$); 3.73 (d, J = 2.4 Hz, C_{14}-OH); 4.82 (bs, H_{15}); 4.85 (brt, H_4); 4.92 (bs, H_{15}); 5.53 (dd, J = 4 and 9.5 Hz, H_7). CMR ($CDCl_3$, 360 MHz): 151.3 (C-1); 30.4 (C-2)*; 26.8 (C-3)$^{\#}$; 82.0 (C-4); 42.7 (C-5); 28.3 (C-6)$^{\#}$; 117.9 (C-7); 157.4 (C-8); 86.4 (C-9); 29.3 (C-10)*; 41.4 (C-11); 46.3 (C-12); 43.3 (C-13); 79.7 (C-14); 109.8 (C-15); 17.3 (C-16); 37.8 (C-17); 19.1 (C-18)$^+$; 19.9 (C-19)$^+$; 24.4 (C-20); 169.5 (C_4-OAc); 21.4 (C_4-OAc) (chemical shifts marked with *, # and $^+$ are interchangeable). MS: *m/z*: 362 (M^+), 344, 319, 301, 259, 241 and 223. High resolution mass measurement: Found: 362.2445. Calc for $C_{22}H_{34}O_4$: 362.2456.

(4R, 9R, 14S)-4, 9, 14-*Trihydroxydolast*-1 (15), 7-*diene* (**9**). A crystalline compound, m.p. 160–161°, $\{\alpha\}_D = 59°$ *c*, 0.1, $CHCl_3$). IR ($CHCl_3$); 3500, 2980, 1640, 1040, 960 and 920 cm^{-1}. ^1H-NMR ($CDCl_3$, 360 MHz): 0.76 (s, Me_{16}); 0.83 (d, J = 6.8 Hz, Me_{18})*; 0.99 (d, J = 6.8 Hz, Me_{19})*; 1.40 (s, Me_{20}); 1.83 (qq, J = 6.8 and 6.8 Hz; H_{17}); 2.84 (ddd, J = 4.5 and 13.6 Hz; $H_{2\alpha}$); 3.21 (bs, H_4); 3.29 (dd, J = 4 and 15 Hz, $H_{6\alpha}$); 4.71 (s, H_{15}); 4.86 (s, H_{15}); 5.65 (dd, J = 4 and 9 Hz; H_7). CMR ($CDCl_3$, 360 MHz): 152.4 (C-1); 31.2 (C-2)$^+$; 27.7 (C-3); 80.0 (C-4); 43.1 (C-5); 31.9 (C-6); 120.8 (C-7); 157.6 (C-8); 85.0 (C-9); 32.5 (C-10)$^+$; 42.06 (C-11); 45.5 (C-12); 43.4 (C-13); 81.6 (C-14); 109.5 (C-15); 17.16 (C-16); 34.8 (C-17); 19.0 (C-18)$^{\#}$; 20.17 (C-19)$^{\#}$; 26.6 (C-20) (chemical shifts marked with *, $^{\#}$ and $^+$ are interchangeable). MS: *m/z*: 320 (M^+), 284, 277, 259, 241 and 223. High resolution mass measurement: Found: 320.2300. Calc. for $C_{20}H_{32}O_3$: 320.2351.

Acetylation of **2** *and* **3** *to* **4**. 20 Mg of **2** and 35 mg of **3** were treated separately with excess Ac_2O in pyridine at room temp overnight and diluted with ether. The mixtures were washed with several portions of 1% HCl followed by sat. $NaHCO_3$aq. The ethereal layer was dried with $MgSO_4$ and the solvent removed under vacuum in both cases. The residues were chromatographed on silica gel (open column) to give **4** in both reactions, and whose ^1H-NMR and physical constants were similar to those reported.[7]

Acetylation of **7** *to* **8**. By employment of the above procedure, **7** (30 mg) (0.09 mmole) yielded **8** (30.5 mg) (0.081 mmole, 90%), which was identified by direct comparison with the natural product.

Acetylation of **9** *to* **6**. Triol **9** (20 mg; 0.06 mmole) was treated with Ac_2O/Py under conditions described for the conversion of **7**–**8**. Standard work-up gave **6** as a colourless oil, which was identified by direct comparison with the natural product.

Conversion of **4** *to* **6**. A soln of 28 mg (0.068 mmole) of **3** in 3 ml DMSO was heated at 120° for 0.5 hr. H_2O was added and the mixture was extracted with CCl_4. After drying with $MgSO_4$, it was concentrated *in vacuo* and chromatographed over silica gel to yield 18 mg (65%) of **6**, identical with the natural product.

Conversion of **8** *to* **6**. Compound **8** (40 mg, 0.1 mmole) was warmed in DMSO under the conditions described for the conversion of **3**–**6**. Removal of solvents *in vacuo* gave 21 mg (60%) of an oil identified as **6** by direct comparison.

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