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IDENTITY OF SANADAOL WITH β-CRENULAL, A DITERPENE FROM THE BROWN ALGA *DICTYOTA CRENULATA*

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Key Word Index—*Dictyota crenulata*; Dictyotaceae; diterpene; β-crenulal; sanadaol.

Abstract—β-Crenulal is a minor constituent of the marine brown alga *Dictyota crenulata* from Hawaii and is identical with sanadaol isolated from *Pachydictyon coriaceum* in Japan.

INTRODUCTION

Dictyodial A (**1**) is the major diterpene in the brown alga *Dictyota crenulata* found in Hawaii [1]. This dialdehyde is also present in *D. flabellata* found in the Gulf of Mexico [1]. During the winter months *D. crenulata* contains a minor aldehydic diterpene, β-crenulal, which has the same elemental composition as **1** and is obtained when **1** is treated with boron trifluoride etherate [2]. Some time ago we proposed that β-crenulal has the structure and relative stereochemistry (1*R**,2*R**,6*R**,10*S**,11*S**) shown in **2** [2, 3]. Recently Japanese chemists isolated a diterpene from *Pachydictyon coriaceum* and established its structure as **2** [4, 5]. Unaware of our findings, the Kakisawa group named their diterpene sanadaol. There is no doubt, however, after comparison of our data for β-crenulal with the data published for sanadaol that the two diterpenes are identical.

We had withheld publication of our results in the primary literature, since the data that we had obtained in 1978, which was essentially the same as that reported by the Japanese [4], did not unambiguously rule out a 1*S**, 6*S** stereochemistry for the bridgehead carbons. In their communication the Kakisawa group did not address this possibility and we feel a comment is in order.

RESULTS AND DISCUSSION

If the acid-catalysed cyclization of **1** to **2** by boron trifluoride etherate [2] or silica gel [4] proceeds without epimerization of C-1 in **1** prior to cyclization, then one would expect the bridgehead stereochemistry in **2** to be 1*R**, 6*R**. Cyclizations analogous to **1** → **2** are known and in one case it has been suggested that the ene and al functionalities react in a concerted manner [6]. We were concerned, however, that epimerization of C-1 in **1** might have to occur before cyclization, thereby leading to the 1*S**, 6*S** stereochemistry. Examination of a Dreiding model of dictyodial A, in the preferred conformation indicated from X-ray data [1], showed that C-1 would have to epimerize to allow interaction of the al and 5(*E*)-ene functionalities. In order for the aldehydic group to approach the Δ^5-double bond without epimerization of C-1 first, the trisubstituted double bond in **1** would have to isomerize to *Z* so that **1** could assume a conformation where C-10 and C-6 were close enough for reaction.

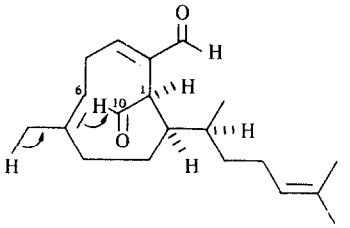
We find that it is not possible to determine the bridgehead stereochemistry on the basis of *W*-coupling between H-1 and H-6 and homoallylic coupling between H-1 and each proton on C-7 alone. Several other couplings can be observed in the 300 MHz ^{1}H NMR spectrum of **2** (Table 1), however, and all considered show that the proposed 1*R**, 6*R** stereochemistry is correct. First of all, no coupling is observed between H-1 and H-2, suggesting that the dihedral angle between these two hydrogens is around 90°. Secondly, the same coupling is seen between H-8 and each proton on C-7; this means that the dihedral angles between H-8 and each H on C-7 are the same. Thirdly, H-6 shows large (7.4 Hz) and small (~ 1 Hz) couplings to the protons on C-7, indicating dihedral angles between H-6 and each C-7 proton of about 30° and 90°, respectively. Next, only one H on C-4 shows allylic coupling (1.2 Hz) to an H on C-20; this suggests that one H on C-4 is more than 30° above the plane and that the other C-4 H is near or in the plane of the terminal methylene group. Finally each H on C-4 exhibits similar couplings (9.8 and 5.2 Hz for 4α and 9.1 and 5.5 Hz for 4β) to the protons on C-3; this suggests that the protons on C-4 are eclipsing the protons on C-3 in the preferred conformation of **2**. Dreiding models show that only when the relative stereochemistry is 1*R**, 2*R**, 6*R** can **2** have all of these conformational requirements fulfilled (see **2a**).

Additional support for this structure is obtained from NMR data of several derivatives of **2** and α-crenulal (**3**), the acid-catalysed rearrangement product of **2**. The ^{1}H NMR spectrum of the derivative **4** (Table 2), for example, shows couplings that are consistent only with the 1*R**, 6*R** stereochemistry.

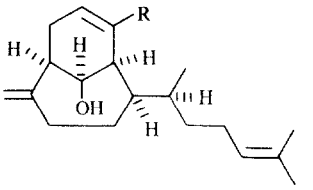
Lanthanide-induced proton chemical shift (LIS) studies of compounds **3**–**6** support the 10*S** stereochemistry (Table 3). The protons on C-20 shift faster than H-8 in **2** and **5** and H-4 moves twice as fast as H-8 in **3**. As expected H-8 shifts much faster than H-4 in **4**. These experiments clearly demonstrate that the hydroxyl on C-10 is endo in compounds **2**–**6**.

EXPERIMENTAL

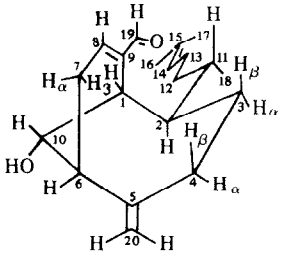
β-Crenulal (**2**). This minor diterpene was isolated [7] as a viscous, colorless oil, $[\alpha]_D^{25}$ +89° (*c* 0.82; EtOH); IR ν^{CHCl_3} cm^{-1}: 3940–3710, 1685, 1635, 895; UV λ_{max}^{EtOH} nm(ε):



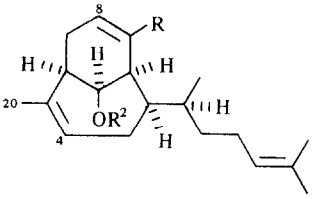
1



2 R = CHO
5 R = CH_2OAc



2a



3 R^1=CHO, R^2 = H
4 R^1=CH_2OH, R^2 = Ac

Table 1. NMR spectral data for β-crenulal

^{13}C δ*		^1H δ†	^{13}C δ*		^1H δ†
192.86 *d*	19	9.457 *s*	36.21 *t*‡	12	1.197 *m*
					1.58 *m*
150.24 *d*	8	6.788 *br t*	36.17 *d*‡	6	2.865 *br dd*
146.10 *s*	9		31.70 *d*	11	1.53 *m*
143.63 *s*‡	5		29.67 *t*‡	3	1.57 *m* (α)
130.60 *s*	15				0.989 *dddd* (β)
			25.30 *q*	16	1.611 *br m*
124.96 *d*	14	5.157 *t septets*	25.25 *q*	13	2.06 *br m*
116.33 *t*	20	4.900 *dd*			1.96 *br m*
		4.885 *d*			
68.69 *d*	10	3.771 *ddd*	24.04 *t*‡	4	2.297 *ddd* (α)
45.88 *d*	2	1.59 *m*			2.230 *dddd* (β)
39.10 *d*‡	1	3.181 *br d*	17.61 *q*	17	1.675 *br q*
37.51 *dd*‡	7	2.747 *dddd* (α)	17.61 *q*	18	0.760 *d*
		2.550 *br d* (β)			

*25.2 MHz, $CDCl_3$, $CDCl_3$ as internal reference.
†300 MHz, $CDCl_3$, residual $CHCl_3$ as internal reference = 7.25.
‡Tentative assignments.
$J_{H,H}$ (Hz): 1, 2 = 0; 1, 3α = ~ 1, 6 ~ 1, 7 ~ 1.5; 1, 10 = 5.0; 2, 3α ~ 1–2; 2, 3β = 12.1; 2, 11 ~ 10; 3α, 3β = −14.0; 3α, 4α = 9.8; 3α, 4β = 5.5; 3β, 4α = 5.2; 3β, 4β = 9.1; 4α, 4β = −15.0; 4β, 20 = 1.2; 6, 7α = 7.4; 6, 7β ~ 1; 6, 10 = 5; 7α, 7β = −20.8; 7α, 8 = 7β, 8 = 3.7; 10, OH = 10; 11, 18 = 6.4; 13, 16 = 13′, 16 = 13, 17 = 13′, 17 = 14, 17 = 1.4; 14, 16 = 1.

234 (7000); EIMS (probe) 70 eV, *m/z* (rel. int.): 302 (40), 284 (30), 69 (100).

Conversion of **1** *to α- and β-crenulal.* Dictyodial A in dry C_6H_6 at 5° was treated with redistilled BF_3 etherate and the reaction quenched with H_2O after 1 min. The organic material was immediately extracted into $CHCl_3$, dried ($MgSO_4$) and concd to an oil (54.2 mg, 98.5%). ^1H NMR analysis indicated that the product was a 3:1 mixture of β- and α-crenulal. Separation was achieved by HPLC on a Whatman Partisil 10/50 M-9 column using $CHCl_3$. The synthetic β-crenulal was identical with the natural product in all respects, except that its optical rotation, $[\alpha]_D^{20}$ + 78.3° (*c* 0.86; EtOH), was slightly lower.

Conversion of **2** *to α-crenulal.* The 3:1 mixture of β- and α-crenulal obtained above in dry C_6H_6 was refluxed with *p*-toluenesulfonic acid under N_2 for 5–10 min. After cooling, H_2O was added and the $CHCl_3$ layer washed (H_2O, saturated $NaHCO_3$ and H_2O), dried ($MgSO_4$) and concd to an oil ^1H NMR and TLC analysis (silica gel, $CHCl_3$) revealed that the

Table 2. ^{1}H NMR spectral data for α-crenulol 10-acetate (**4**)

	δ*		δ*
H-8	5.834 *br t*	H-3α	2.043 *ddm*
H-4	5.468 *ddq*	2H-13	1.94 *m*
H-10	5.120 *dd*	H-3β	1.835 *dm*
H-14	5.093 *t septets*	H-2	1.76 *m*
H-19	4.042 *br dq*	3H-20	1.704 *br t*
H-19′	4.006 *br dq*	3H-17	1.673 *br q*
H-1	3.009 *br dm*	3H-16	1.586 *br m*
H-6	2.45–2.55 *m*	H-12	1.53 *m*
H-7α	2.45–2.55 *m*	H-11	1.355 *m*
H-7β	2.20 *m*	H-12′	1.141 *dtd*
OAc	2.065 *s*	3H-18	0.891 *d*

*300 MHz, $CDCl_3$, residual $CHCl_3$ as internal reference = 7.25. *J* (Hz): 1, 2 ~ 1, 3α ~ 1, 6 ~ 1, 7α ~ 1, 7β = 1–1.5; 2, 3α = 1; 1, 10 = 6.0; 3α, 3β = −15.9; 3α, 4 = 8.8; 3α, 20 = 1; 3β, 20 = 1.5; 4, 20 = 1.5; 6, 10 = 4.0; 7α, 8 ~ 7β, 8 ~ 3.0; 11, 12′ = 8.8; 11, 18 = 6.5; 12, 12′ = −13.7; 12′, 13 = 8.8; 12′, 13′ = 5.4; 13, 16 = 13′, 16 = 14, 16 = 13, 17 = 13′, 17 = 14, 17 = 1–1.5.

Table 3. Lanthanide-induced shifts for β-crenulal and derivatives

	Δδ*, ppm			
	2	**3**	**4**	**5**
H-1	9.15	5.67	5.44	8.66
H-4		3.33	1.02	
H-6	8.85	5.67	2.00	6.86
H-8	1.70	1.66	4.10	2.08
H-10	10.24	9.55	4.66	10.70
2H-20	3.75	2.12	1.02	3.80
	2.70			2.66

*100 MHz, shifts induced by 1 equivalent of $Eu(fod)_3$ in $CDCl_3$.

product was pure α-crenulal; ^{1}H NMR ($CDCl_3$): δ 9.43 (1H, *s*), 6.932 (1H, *t*, *J* = 3.8 Hz), 5.623 (1H, *v br t*), 5.127 (1H, *t septets*, *J* = 6.5 and 1.5 Hz), 3.835 (1H, *t*, *J* = 5.4 Hz), 3.35 (1H, *br d*, 5 Hz), 2.813 (1H, *dddd*, *J* = −21, 7, 3.8, and 1.5 Hz), 2.646 (m), 2.58 (1H, *br dd*, *J* = −21 and 3.8 Hz), 1.80 (3H, *br m*), 1.69 (3H, *br m*), 1.61 (*br m*), 2.0–1.0 (8H, complex multiplets), 0.65 (3H, *d*, *J* = 6.5 Hz); EIMS (probe) 70 eV, *m/z* (rel. int.): 302 (25), 284 (22), 69 (100); UV λ_{max}^{EtOH} nm (ε): 234 (6000).

β-Crenulol was prepared from **2** by reduction with $NaBH_4$. Work-up after 30 min gave a glass which crystallized from 3% $CHCl_3$–hexane as thin needles (40 mg, 93%), mp 65–65.5°, $[\alpha]_D^{25}$ +54.8°; EIMS (probe) 70 eV, *m/z* (rel. int.): 304 (5), 286 (10), 85 (99), 83 (100), 69 (49). ^{1}H NMR ($CDCl_3$, 100 MHz): δ 5.68 (1H, *br m*), 5.10 (1H, *br t*, *J* = 6.5 Hz), 4.82 (2H, *br s*), 4.05 (1H, *br s*), 3.89 (1H, *br m*), 2.68 (1H, *br m*), 2.35 (*br m*), 2.30 (*br m*), 2.01 (*q*, *J* = 7 Hz), 1.68 (3H, *br s*), 1.59 (3H, *br s*), 1.6–1.0 (complex multiplets), 0.88 (3H, *d*, *J* = 6 Hz); ^{13}C NMR ($CDCl_3$): δ 147.09 (*s*), 139.34 (*s*), 131.34 (*s*), 124.72 (*d*), 121.90 (*d*), 115.51 (*t*), 69.15 (*d*), 66.56 (*t*), 46.24 (*d*), 41.41 (*d*), 37.01 (*d*), 37.00 (*d*), 35.51 (*t*), 30.32 (*t*), 29.26 (*d*), 25.62 (*t*), 25.31 (*q*), 25.21 (*t*), 17.99 (*q*), 17.72 (*q*). Attempts to analyse these crystals by X-ray crystallography were not possible due to the unusually large unit cell.

β-Crenulol 19-*acetate* (**5**). This acetate (Ac_2O–pyridine) is an oil, which was purified on Partisil 10 using 50% $CHCl_3$–hexane as the eluant. IR ν^{neat} cm^{-1}: 3460, 1735, 895, 800; EIMS (probe) 70 eV, *m/z* (rel. int.): 346 (5), 328 (4), 69 (100); ^{1}H NMR ($CDCl_3$, 100 MHz): δ 5.79 (1H, *br m*), 5.07 (1H, *br t*, *J* = 6 Hz), 4.93 (2H, *br s*), 4.51 (2H, *br s*), 3.92 (1H, *ddd*, 11, 5, 5), 2.63 (1H, *br m*), 2.03 (3H, *s*), 1.67 (3H, *br s*), 1.59 (3H, *br s*), 0.89 (3H, *d*, *J* = 6 Hz).

α-Crenulol. α-Crenulal was reduced as above yielding a glass which readily crystallized from hexane, mp 77–79°, $[\alpha]_D^{25}$ +68° (EtOH; *c* 0.47); IR ν^{neat} cm^{-1}: 3340, 825, 800; ^{1}H NMR ($CDCl_3$, 100 MHz): δ 5.92 (1H, *br m*), 5.68 (1H, *br m*), 5.10 (1H, *br t*, *J* = 7 Hz), 3.01 (3H, *br m*), 2.89 (1H, *br d*, *J* = 4 and 5 Hz), 2.5 (*br m*), 2.28 (*br m*), 2.1–1.8 (complex multiplets), 1.79 (3H, *s*), 1.69 (3H, *s*), 1.58 (3H, *s*), 1.2 (*br m*), 0.92 (3H, *d*, *J* = 6.5 Hz); EIMS (probe) 70 eV, *m/z* (rel. int.): 304 (5), 286 (48), 91 (100), 69 (65).

α-Crenulol 10-*acetate* (**4**). The acetate (Ac_2O–pyridine plus a little **4** (*N*,*N*-dimethylamino)pyridine for 10 hr at room temp. and then refluxed under N_2 for 15 min) was an oil which showed only one spot by TLC (silica gel, $CHCl_3$). The crude aldehyde was reduced with excess $NaBH_4$. Work-up and purification on Partisil 10 using 10% EtOAc–CH_2Cl_2 yielded 12 mg of **4**; IR ν^{neat} cm^{-1}: 3400, 1740, 815; EIMS (probe) 70 eV, *m/z* (rel. int.): 346 (12), 328 (7), 69 (100).

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