Pergamon

Tetrahedron Letters, Vol. 35, No. 47, pp. 8855-8858, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01906-1

Xeniafaraunol A and B, and Faraunatin; Three New Cytotoxic Diterpenes from the Soft Coral *XENIA FARAUNENSIS*

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Abstract: The organic extract of *Xenia faraunensis* was found to contain besides xeniolide A and B three novel diterpenes: xeniafaraunol A (**1**), -B (**2**) and faraunatin (**3**). The structure of compounds **1-3** was defined by spectral methods and mainly 1D and 2D NMR experiments. Xeniafaraunol A and B (**1** and **2**) are of a novel bicyclo[7.4.0] tridecane carbon skeleton and faraunatin (**3**) is an unprecedented prenylated bicyclogermacrene. Compounds **1-3** are cytotoxic against P388 cells.

Soft corals of the genus *Xenia* have produced a range of xenicane diterpenes of which xenicin[1], xeniolides A and B and the xeniaphyllanes[2,3] are a few examples. In the course of our continuing investigation of soft corals[4,5] we have investigated a specimen of *Xenia faraunensis* (Octocoralia, Alcyonacea) from the Red Sea.

In the course of fractionating and purifying the constituents of the ethyl acetate extract of *X.faraunensis*, we isolated five diterpenoids, namely, the earlier reported by us xeniolide A and B[2,3] and the new xeniafaraunol A (1), -B (2) and faraunatin (3).[6]

Xeniafaraunol (1) was isolated as a colorless, optically active glass.[7] HREIMS provided *m/z* 300.2089 [M$^+$] for a molecular formula of $C_{20}H_{28}O_2$. The IR spectrum showed a OH stretch (3380 cm^{-1}), an exocyclic methylene (890 cm^{-1}) and a characteristic absorption for a conjugated carbonyl moiety at 1688 cm^{-1}. Proton resonances at δ 9.26s and 5.90s and carbon lines at 192.0d, 150.1d, and a very weak and broad signal at 140.0s determined an αβ-unsaturated aldehyde moiety (A). The presence of six additional olefin carbons in the ^{13}C NMR spectrum (Table 1) revealed that the molecule was bicyclic. Analysis of the ^{1}H NMR data (Table 1) showed three vinyl methyl groups in addition to the above functionalities suggesting that xeniafaraunol A was of diterpene biogenesis.

Interpretation of NMR spectra (DEPT, COSY, TOCSY, NOE, HMQC and HMBC - Table 1) suggested in addition to A, moieties B & C: B $-CHCH_2CH_2C(CH_3)=CHCH_2CH_2C(=CH_2)-$; C $(Me)_2C=CHCHCH(OH)CH-$ which together with A account for all 20 carbon atoms of 1. Comparison of the ^{13}C data of fragment B with the corresponding carbon lines in 9-desacetyl xeniculins[2] suggested also for 1 the same nine membered ring. However, it was evident that the rest of the molecule differs. Based on long range couplings and NOE's the bicyclo[7.4.0]tridecane system was suggested for 1. This structure is in full agreement with a head-to-tail isoprene array.

With the planar structure of 1 in hand, the relative stereochemistry was probed by assignment of almost all coupling constants and by a series of NOE enhancements as summarized in Table 1. Assuming a twisted chair conformation of the cyclohexene ring, the coupling constants of 9Hz between H-1 and -9; H-9 and -10; and H-10 and -11 indicated a pseudo axial conformation of H-1, -9, -10 and 11 and

TABLE 1. NMR Data of xeniafaraunol A (1)[a]

H#	δ ^{13}C	δ ^{1}H	m	J(Hz)	COSY, TOCSY	HMBC(C to H#)	nOe
1	36.6	2.80	m		2′,9,10,11,12,16	12	5,6′
2	36.3	1.20	ddt	3, 1.5, 13.5	1,2′,3,3′,9,10		2′,9
2′		1.65	dq	13.5, 3	1,2,3,3′,10		2
3	40.6	2.10	dt	12, 3	2,2′,3′,10	1,2,14	3′
3′		2.72	dt	3.5,12	2,2′,3,10		3
4	136.0	-				2,3,3′,6,14	
5	125.1	5.40	dd	11, 4.5	6,6′,7,7′,14	3,3′,6, 7′,14	1,6,6′,7
6	28.5	1.88	dq	12.5, 5	5,6′,7′,14	5,7,15	5,6′,15
6′		2.30	dq	5.5, 12	5,7,7′,14		5,6
7	32.2	1.62	dd	13, 10	5,6,6′,7′	5,6,6′,9,15	5,7′,10
7′		2.06	dt	4.7, 13	5,6′,7		7
8	146.9	-				1,9,15	
9	61.0	1.87	t	9	1,2,3,10,11,16	1,2,3,7′,8,15	2[c],11
10	73.3	3.03	t	9	1,2′,3,9[b]	9,11,12,15,16	16[c],7
11	44.0	3.06	m		1,2′,3,9[b]	9,10,12,16	9,16,18
12	150.1	5.90	s		1,10,11,16	1,9,10,11,20	10,11,16,20[c]
13	146.0	-				11,9,20	
14	18.4	1.53	s		5,6′,7′	3,3′,5	15
15	118.0	4.80	s (2H)		6,7	6,7′	6,7′,9,14
16	125.6	4.90	d	7.5	1,10,11,18,19	10	10,11,12,19
17	135.6	-				18,19	
18	18.5	1.60	s		11,16	16,19	11
19	26.0	1.67	s		11,16	16,18	16
20	192.0	9.26	s		12	12	12[c]

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[a] C_6D_6 (and for 2D studies $CDCl_3/C_6D_6$, 3:1), 500 MHz for ^1H, 125 MHz for ^{13}C. Carbon resonances by HMQC experiment. [b] Overlapping. [c]Strong nOe effect, over 2%.

TABLE 2. NMR Data of faraunatin {3}[a]

H#	δ ^{13}C	δ ^{1}H	m	J(Hz)	COSY, TOCSY	HMBC(C to H#)	nOe
1	24.2[b]	1.568	ddd	11.5, 9, 1	2,8,9,9′,10,18	4,10,18	12,19
2	125.3	4.482	dd	11.5, 1	1,8,8′,9,9′,10,19	4,12,19	18
3	134.0	-					
4	41.4	1.958	dt	4, 12.5	4′,5,5′,6,20	2,19	
4′		2.271	dt	12.5, 3.5	4′,5,5′,6,20		20
5	26.3	2.096	brdq	11, 4	5′,4,4′	20	
5′		2.192	dt	4, 11	5′,4,4′		20
6	125.1	4.905	ddd	11, 5, 1	4,4′,5,5′,20	4′,5′,20	
7	140.0					9,20	
8	37.4	2.547	brdt	13, 2	1,2,8′,9,9′,10	9′,20	
8′		1.807	ddt	3.5, 1, 13	1,2,8,9′,10		
9	27.0	1.875	ddq	13, 1, 3	1,2,8,8′,9′,10,20		
9′		1.286	ddq	4.5, 1, 13	1,2,8,8′,9,10		18,20
10	27.5[b]	0.713	dddd	12.5, 8.5, 2.5, 1	1,2,8,9,9′	12	
11	28.3					18	
12	80.7	2.895	dd	6.5, 6	13,13′,14,16,17,18	1,10,13,18	1
13	33.2	2.456	m		12,14,16,17,18	14	18
13		2.434	m		12,14,16,17,18		
14	121.6	5.372	tq	8, 1	12,13,13′,16,17	12,13,13′,16,17	17
15	133.0	-				13,13′,16,17	
16	17.7	1.652	s		12,13,13′,14	14,17	
17	25.9	1.770	s		12,13,13′,14	14,16	14
18	8.4	1.192	s		1,12,13,13′	1,11,12	2,9′,13
19	16.6	1.735	d	1.5	2	2	
20	21.0	1.588	s		4,5,6,9		4′,5′,9′

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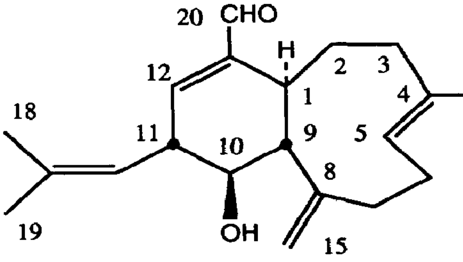
[a] C_6D_6, 500 MHz for ^1H, 125 MHz for ^{13}C. Carbon resonances assigned by HMQC experiment.

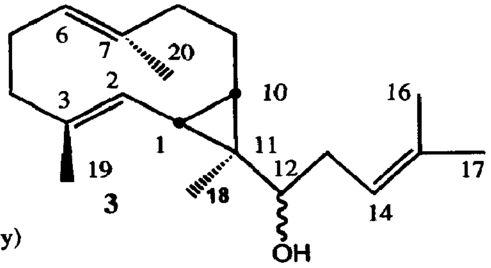
[b] $^{1}J_{C(1)H} = 160$ Hz, $^{1}J_{C(10)H} = 156$ Hz

thus also defining the relative stereochemistry of the four chiral centers of the molecule. The above suggested conformation of the cyclohexene ring, is in full agreement with a 90° angle between H-11 and -12 as concluded from their 0Hz mutual coupling constant. As in caryophyllene and the xenicanes the cyclononane ring may adopt several different conformations according to the conformation of Me-14 and methylene-15 (αα, αβ, βα,ββ) relative to H-1(α) and -9(β).[8] In case of **1** the major conformation seems to be the ββ one as determined from the following NOE's between H-9 and H-2, -11 and -15 (β); between H-15 and Me-14, H-6 and -7′ (β) and between H-5 and H-1, -6′ and -7 (α). Molecular modeling, using Dreiding models as a guide and NOE data as constraints, provided the three-dimensional conformation illustrated in Figure 1. The latter conformation is in good agreement with the measured coupling constants. Xeniafaraunol A represents an unprecedented diterpene skeleton.



1

2 (4,5-epoxy)



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Xeniafaraunol B (**2**) which was isolated in smaller amounts[6] proved to be the 4,5-epoxy derivative of **1**, possessing very similar spectral data to **1** except for the $\Delta^{4,5}$ olefin[9]; NMR analysis indicated replacement of the double bond by an epoxide (δ 2.85 dd, H-5, δ 59.0s and 63.0d). Similar epoxidations have earlier been observed for the xenicanes.[2,3]

Compound **3**, faraunatin had the molecular formula $C_{20}H_{32}O$ (M^+ at m/z 288.2460) indicating five degrees of unsaturation. The IR, ^1H NMR and ^{13}C NMR spectra (Table 2) indicated the presence of a secondary hydroxyl group (3500 cm^{-1}, δ 80.7d). One tertiary methyl group (δ 1.19s), two olefinic methyl groups (δ 1.588s, 1.735s) coupled with two olefinic protons (δ 4.48dd and 4.91ddd, respectively) on two trisubstituted double bonds (δ 125.3d, 134.0s and 125.1d, 140.0s ppm). And an isopropenyl group (δ1.652s, 1.770s, each 3H, and 5.372tq, 1H; δ 17.7q, 25.9q; 121.6d and 133.0s). These spectral data suggested **3** was also a bicyclic diterpene.

Careful studies of the 2D NMR spectra of **3** (COSY, TOCSY, HMQC and HMBC) (Table 2) established, unequivocally, a substituted bicyclo[8.1.0]undecane structure for faraunatin (**3**) - a prenylated bicyclogermacrene. Bicyclogermacrenes[10-12] and iso-bicyclogermacrenes[13-15] have earlier been reported from marine organisms, compound **3** however is the first bicyclogermacrene diterpene.

The suggested cyclopropane, of **3**, was confirmed from the characteristic cyclopropane one-bond CH-coupling of 156Hz and 160Hz for C-10 and C-1 respectively.[16] Furthermore, a coupling constant of 8.7Hz between H-1 and H-10 (against a 5.5Hz for the *trans* isomer) determined a *cis* substitution[13,14].

The *E* geometries of both trisubstituted ring double bonds were determined from the diagnostic shifts of the olefinic methyl carbons (16.6 and 21.0 ppm)[11,12], and the relative high-field resonances of the corresponding vinyl protons (δ 4.48 and 4.90 ppm)[11,12] due to the mutual transannular diamagnetic effects of the double bonds (in case of a *E,Z* stereochemistry values of ca. 16 and 26 ppm are expected). The relative low-field resonance of CH_3-20 (δ 21 ppm in comparison to 16.6 for CH_3-19), due to the anisotropic effect of the C(2)=C(3) bond, is also characteristic for the bicyclogermacrenes[12].

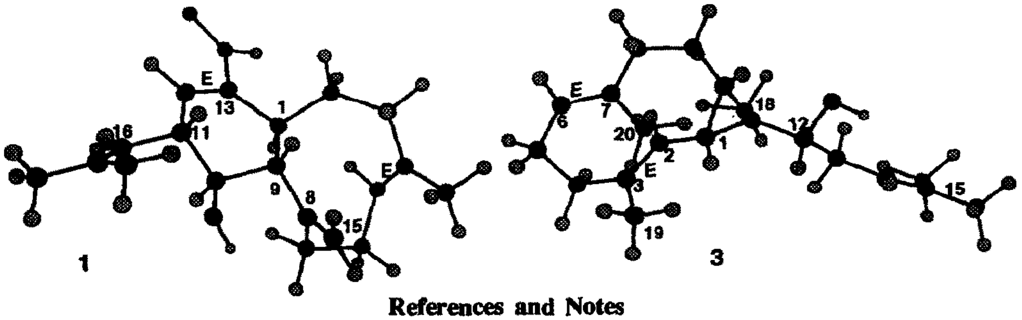
The stereochemistry at C-11 as well as the conformation of the ten-membered ring were determined on the basis of NOESY and d-NOE measurements. An NOE between H-12 and H-1 determined the β configuration of the side chain, the same direction as H-1 and -10.

Furthermore, an NOE between H-1(β) and CH_3-19, which thus, has to be β too, and between CH_3-18 (α) and H-2 and H-9′ and between CH_3-20 and H-4′, -5′ and -9′ all α (as also H-8′) and in a pseudo axial conformation suggested that **3** adopts a conformation in which CH_3-19, the prenyl side chain, H-1, and H-10 are on one side of the ring and CH_3-20, H-4′, 5′ and 9′ on the opposite side. The configuration of C-12 could not be determined due to insufficient material.

The measured coupling constants of the entire bicyclic system (Table 2) are in full agreement with the suggested stereochemistry (i.e. (φ/J) H-1/2 ≈ 180°, 11.5; H-1/10=0°, 8.5; H-8/9′ ≈ 170°, 13; H-9/10 ≈ 50°, 2.5; H-9′/10 ≈ 170°, 13) as seen in the computer generated model (Figure 1).

All three compounds are cytotoxic to P388 murine leukemia cells (IC_{50} = 1.2 μg/mL).

Figure 1. Models of **1** and **3**
(minimized using MM2 force field)



1

3

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6. Crude extract (450mg) was sequentially partitioned among hexane, CCl_4 and $CHCl_3$, and increasingly polar mixtures of $MeOH/H_2O$. The CCl_4 solubles (100mg) were applied first to a Sephadex LH-20 column, eluted with $CH_2Cl_2/MeOH$ (1:1) and then to a silica gel H column eluted with hexane and increasing percentages of ethyl acetate to yield xeniolides A and B, 15mg, xeniafaraunol A (**1**) 8mg, -B (**2**), 4mg and faraunatin (**3**) 8mg.
7. Colorless glass: $[\alpha]_D$+5° (c 0.01, $CHCl_3$); *m/z* (%) 300 (100), 283(M-OH, 7), 288(M-H_2O, 8), 232(M-C_3H_8,15), 105(C_8H_9, 56), 91(C_7H_7, 100).
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9. Colorless glass; *m/z* 316 [M^+], δ (C_6C_6). 2.65(m,H-1), 2.85(ddd, J=11, 2.5Hz, H-5), 1.90(t, J=10Hz, H-9), 2.95(dd, J=10, 9Hz,H-10), 3.05(m, H-11), 5.90(s, H-12), 1.09(s, Me-14), 4.72 and 4.85(s, each, H-15,15′), 4.90(d,J=7Hz, H-16), 1.60(s, Me-18), 1.68(s, Me-19), 9.20(s, H-20); δ 35.1d, 32.0t, 39.2t, 59.3s, 62.9d, 27.0t, 26.5t, 146.0s, 60.6d, 71.4d, 44.0d, 149.6d, 146.3s, 19.0q, 119.0t, 124.3d, 135.1s, 25.7q, 18.2q, 192d.
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(*Received in UK* 5 *August* 1994; *revised* 19 *September* 1994; *accepted* 23 *September* 1994)