Chinese Chemical Letters Vol. 11, No. 4, pp. 327–330, 2000

Ent-untenospongin A, a New C_{21} Furanoterpene from the Indian Marine Sponge *Hippospongia* sp.

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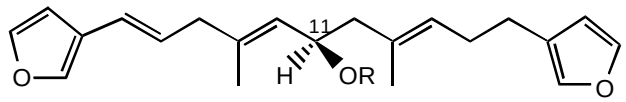
Abstract: A new C_{21} furanoterpene, *ent*-untenospongin A (**2**), together with a known related compound, tetradehydrofurospongin-1 (**1**), has been isolated from the Indian marine sponge *Hippospongia* sp. and its structure was determined on the basis of spectroscopic data.

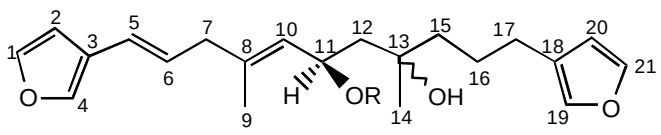
Keywords: Sponge, C_{21} furanoterpene, *ent*-untenospongin A.

Many marine sponges of the family Spongiidae, in particular, the genus *Hippospongia* frequently afford terpenoids containing 21 carbons and displaying two β-substituted furan moieties at the end of the molecule[2]. These unusual compounds are probably derived from higher terpenoids from a biogenetic point of view. During our studies on bioactive substances from marine organisms, we investigated the extracts of the Indian sponge *Hippospongia* sp. and isolated a new C_{21} furanoterpene, named *ent*-untenospongin A (**2**), together with a known related compound, tetradehydrofurospongin-1 (**1**). Here we describe the isolation and structure elucidation of **2**.

The sponge (400 g, wet weight) was collected by SCUBA off Goa, India in the Indian ocean and stored frozen at –80°C until processed. Me_2CO extract of the sponge was partitioned between Et_2O and water. The Et_2O-soluble fraction was subjected to column chromatography on Silica gel eluting with petroleum ether-Et_2O system to afford, in the order of increasing polarity, compounds **1** and **2**, respectively.



1 R=H, **1**R R=(*R*)-MTPA, **1**S R=(*S*)-MTPA



2

Compound **1** was identified as tetradehydrofurospongin-1[2,3] by comparing the NMR data of **1** with those reported for tetradehydrofurospongin-1as well as the NMR data of MTPA esters of **1** with those of the corresponding MTPA esters of tetradehydrofurospongin-1[2], confirming the structure including absolute stereochemistry assignment of **1**.

Table 1. ^{1}H- and ^{13}C-NMR Data of Compounds **1** and **2**[a,b]

position	**1**		**2**	
	δ ^{1}H	δ ^{13}C	δ ^{1}H	δ ^{13}C
1	7.34 s	143.3 d	7.34 s	143.3 d
2	6.49 s	107.6 d	6.49 s	107.5 d
3	-	124.3 s	-	124.2 s
4	7.36 s	133.6 d	7.36 s	139.7 d
5	6.24 d	121.1 d	6.24 d	121.3 d
6	5.89 dt	127.6 d	5.89 dt	127.3 d
7	2.82 d	42.9 t	2.82 d	42.8 t
8	-	136.9 s	-	136.5 s
9	1.70 s	16.7 q	1.70 s	16.6 q
10	5.23 d	128.2 d	5.28 d	128.6 d
11	4.44 dt	65.8 d	4.71 dt	66.4 d
12	2.16 dd	46.1 t	1.74 dd	46.5 t
			1.55 dd	
13	-	132.3 s	-	73.3 s
14	1.64 s	16.2 q	1.20 s	28.5 q
15	5.27 dd	128.0 d	1.69 m	40.6 t
16	2.29 ddd	28.5 t	1.64 m	25.6[c] t
			1.52 m	
17	2.48 dd	24.8 t	2.45 m	25.2[c] t
18	-	124.6 s	-	124.8 s
19	7.20 s	138.9 d	7.22 s	138.8 d
20	6.26 s	110.9 d	6.26 s	110.9 d
21	7.34 s	142.7 d	7.34 s	142.7 d

[a] In ppm from internal TMS in $CDCl_3$ (δ 7.26) solution.

[b] Assignments aided by 2D experiments.

[c] Assignments may be interchangeable.

The high resolution electric impact MS (HREIMS) data of **2** established the molecular formula $C_{21}H_{28}O_4$ (*m*/*z* 344.2035, Δ+3.1 mmu) which was supported by the ^{13}C

–NMR spectrum showing 21 carbon signals. The UV spectrum of **2** showed absorptions at 208 (ε 21000) and 226 sh nm. The IR spectrum demonstrated the presence of hydroxy groups (3400 cm-1). From a comparison of the ^{1}H- and ^{13}C-NMR data of **1** and **2** (**Table 1**), the structure of **2** was considered to be quite similar to that of **1** revealing cross peaks of H-6 to H-5 and H_2-7; H-11 to H-10 and H_2-12. In fact, the structure difference between compounds **1** and **2** was found only in the C-12 to C-16 segment. HMBC experiment revealed three-bond couplings for C-12 to H_3-14, H_2-15 and C-13 to H-11, in addition to C-4 to H-5, C-9 to H-7 and H-10, C-19 to H_2-17, confirming this assignment. The two hydroxy groups were attached to C-11 and C-13 due to the lower field sp^3 carbon chemical shifts of C-11 (δ 66.3) and C-13 (δ 73.3). Furthermore, the *E*-configuration of 5, 6-double bond was assigned on the basis of coupling constants (*J*=16.1 Hz) between H-5 and H-6 while the configuration of 8, 10 double bond was assigned to be *E*, since a NOE was observed between H-7 and H-10 according to the structure **2**.

Checking the literature revealed that the NMR data of **2** were identical to those reported for untenospongin A[4] isolated from a Japanes *Hippospongia* sp. but the optical rotation was different (**2**$[\alpha]^{20}_{D}$=+4.5; untenospongin A$[\alpha]^{20}_{D}$=-3.0). This fact suggests that **2** is enantiomeric with untenospongin A. To confirm this, **2** was treated with (*S*)- and (*R*)-MTPA chloride in order to converse it to the corresponding MTPA esters for analyzing its absolute stereochemistry. Unfortunately every attempt was failed probably due to the stereo impediments between 11-OH and 13-OH, while the effort to transfer **2** to the corresponding acetonide,[5] for a purpose of understanding the relative stereochemistry between 11-OH and 13-OH, was also unsuccessful. However, considering that the co-occurring metabolite **1** possessed an *R* absolute stereochemistry at C-11, and moreover, all the C_{21} furanoterpene isolated so far also possessed *R* configuration at C-11[4], so most likely the configuration at C-11 of **2** should also be *R*. The absolute stereochemistry at C-13 remained undefined.

The metabolite pattern of the Indian sample is very similar to that of the Japanese one[4] that also contained compounds (-)-**1** (named untenospongin B) and (-)-**2** (named untenospongin A). Recently, the structural ambiguity of tetradehydrofurospongin-1[3] and untenospongin B[4] has been corrected[2]. In fact, both compounds are actually the same as represented by structure **1**. As a consequence, it raises the necessity to re-measure the $[\alpha]_D$ value of untenospongin A and to study its absolute stereochemistry by chemical methods.

Experimental

General experimental procedures.– The following instruments were used: Varian DMS 90 double beam spectrophotometer (UV), Bio-Rad FTS 7 spectrometer (IR), Bruker AM-500 spectrometer (500 MHz for ^{1}H- and 125 MHz for ^{13}C), CARLO ERBA VG TRIO 2000 instrument (EIMS), Jasco DIP-370 digital polarimeter ($[\alpha]_D$). Commercial Merck Si gel plates were used for TLC. The chromatograms were sprayed with 0.1% $Ce(SO_4)_2$ in 2N H_2SO_4 and heated at 80 ^{o}C for 5 minutes to detect the spots.

***Collection of Hippospongia* sp.**– The sponges were collected by Dr. E. Mollo off Goa, India on the Indian Ocean using SCUBA–diving at a depth of –10 m. They were

immediately frozen and transferred to Naples and kept at –80° until extraction. Voucher specimens are available for inspection at ICMIB of Naples.

Isolation and purification of 1 and 2.– A frozen sponge (30 g, dry weight after extraction) was extracted with Me_2CO (2.5 Liters). After concentration, the aqueous residues were extracted with Et_2O (3 × 150 ml). The combined ether extracts were taken to dryness, yielding oily residues (1.8 g) which was chromatographed on silica gel column using eluents of increasing polarity from light petroleum ether to Et_2O. The faction eluted with petroleum ether-Et_2O (8:2) yielded crude tetradehydrofurospongin-1 (**1**) that was again chromatographed on a silica gel column eluted with the same eluents as mentioned above to afford pure tetradehydrofurospongin-1 (**1**). The petroleum ether-Et_2O (7:3) fraction afforded *ent*-untenospongin A (**2**).

Spectral Data of 1.–$[\alpha]_D^{20}$ +18 (*c* 2.0, $CHCl_3$), (Found M^+, 326.1911, $C_{21}H_{26}O_3$ requires M^+, 326.1082). UV (MeOH) λ_{max} 207 (ε 21000), 230 sh nm.; IR (liquid film) ν 3400 cm^{-1}; ^{1}H- and ^{13}C-NMR (**Table 1**).

Preparation of (R) and (S) –MTPA esters of 1.– (*R*) (**1**R) and (*S*) (**1**S)–MTPA esters of **1** were prepared by treating the compound (each 5 mg in two vials) with (*S*) and (*R*)–MTPA chloride (0.05~0.1 ml) in dry pyridine (0.5 ml) for about 16 hours under stirring at room temperature, respectively. The esters were purified by chromatography in Pasteur pipette (SiO_2, petroleum/Et_2O) obtaining **1**R and **1**S, respectively.

1R: ^{1}H-NMR (500 MHz, $CDCl_3$) δ6.47 (H-2), 6.24 (H-5), 5.83 (H-6), 2.84 (H_2-7), 1.79 (H_3-9), 5.24 (H-10), 5.87 (H-11), 2.21, 2.40 (H_2-12), 1.57 (H_3-14), 5.16 (H-15), 2.16 (H_2-16), 2.36 (H_2-17), 7.16 (H-19), 6.23 (H-20).

1S: ^{1}H-NMR (500 MHz, $CDCl_3$) δ6.46 (H-2), 6.22 (H-5), 5.80 (H-6), 2.80 (H_2-7), 1.78 (H_3-9), 5.10 (H-10), 5.85 (H-11), 2.26, 2.46 (H_2-12), 1.64 (H_3-14), 5.25 (H-15), 2.23 (H_2-16), 2.41 (H_2-17), 7.18 (H-19), 6.24 (H-20).

Spectral Data of 2.–$[\alpha]_D^{20}$ +4.5 (*c* 1.5, $CHCl_3$), (Found M^+, 344.2025, $C_{21}H_{28}O_4$ requires M^+, 344.1987). UV (MeOH) λ_{max} 208 (ε 21000), 226 sh nm.; IR (liquid film) ν 3400 cm^{-1}; ^{1}H- and ^{13}C-NMR (**Table 1**).

Acknowledgments

Dr. Y.W. Guo thanks Dr. G. Cimino and Dr. M. Gavagnin for helpful discussions on the work. Thanks are also due to Dr. E. Mollo, Mr. F. Castelluccio for their valuable technical help. The NMR and the mass spectra were obtained from the "ICMIB-NMR Service" and from the "Servizio di Spettrometria di Massa del CNR e dell'Università di Napoli". The staff of both services is gratefully acknowledged.

References and Notes

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Received 11 November 1999
Revised 3 January 2000