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Sarcoglane, A New Cytotoxic Diterpene from Sarcophyton glaucum

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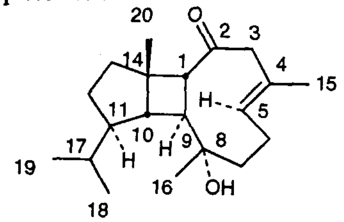
Abstract: Sarcoglane (1) a new tricyclo[7,5,$0^{10,14}$]tetradecane diterpenoid has been isolated from the Indo-Pacific soft coral *Sarcophyton glaucum*. The structure of compound **1**, which is cytotoxic to fertilized sea urchin eggs, was defined by spectral methods and mainly 1D and 2D NMR experiments. Sarcoglane possesses an unprecedented tricyclic carbon skeleton, biogenetically, closely related to the cembrane and xeniaphyllane diterpenoids. Copyright © 1996 Elsevier Science Ltd

The interest in the chemistry of soft coral metabolites[1] brought us to reinvestigate *Sarcophyton glaucum*. Since the isolation of sarcophine, deoxysarcophine and several other cembranoid alcohols from the Red Sea *S.glaucum*[2] a whole series of other cembranoids have been isolated from *S.glaucum* collected in other seas[3]. Investigation of a Indo-Pacific *S.glaucum* collected in Sodwana Bay, Durban, South Africa during January 1995 (IBS-72) afforded in addition to common cembrane and sterol soft coral metabolites[1] a new cytotoxic, to fertilized sea urchin eggs[4], diterpenoid designated sarcoglane (**1**). Compound **1** was obtained from the EtOAc extract of the soft coral by solvent partitioning followed by silica gel chromatography (hexane-EtOAc). Sarcoglane m.p.138^0, $[\alpha]_D$ 110^0, ν_{max} 3540 (OH), 1690 (CO) cm^{-1} had a molecular formula of $C_{20}H_{32}O_2$ as revealed by both EIMS and NMR data (Table 1). The IR and NMR spectra implied the presence of a ketone, a trisubstituted double bond and one hydroxyl group, thus, according to the five degrees of unsaturation, **1** had to be tricyclic. Interpretation of the 1D and 2D NMR spectra (COSY, TOCSY, HMQC and HMBC) suggested two moieties: **$-CH_2CH_2CH(iPr)\overset{|}{C}H\overset{|}{C}H\overset{|}{C}H-$** and **$-CH_2CH_2CH{=}CMeCH_2CO-$** (Table **1**, C-1 to-13 and C-2 to-7) which together with two tertiary methyl groups ($\geq C-CH_3$ and $HO-C-CH_3$) accounted for all 20 carbon and 32 hydrogen atoms of **1**. Connection of the partial structures of **1** based on CH-correlations (HMBC spectrum, Table 1) established a tricyclic structure for sarcoglane. Most significant were the strong ^2J and ^3J CH-couplings of the five methyls and six methines with their neighbors in the molecule. Consequently, a 8-hydroxy-11-isopropyl-4,8,14-trimethyltricyclo-[7,5,$0^{10,14}$] tetradec-4-ene-2-one structure was unambiguously determined for **1**.

With the planar structure of **1** in hand, the relative stereochemistry was probed by assignment of H-H coupling constants and by a series of NOE enhancements as summarized in Table 1. The NOE's between Me-20(β) and H-1 and H-10 established the β-orientation of the latter two protons and, hence, also the *cis* junction between the cyclobutane and cyclopentane rings. A NOE between H-1β and Me-16 determined the β-conformation of the latter methyl group. As in caryophyllene[5] and the xeniaphyllanes[6] the cyclononene ring may adopt several different conformations. In case of 1 the major conformation seem to be the one with the Me-15β orientation based on a NOE between the latter methyl and Me-16β (a NOE which also determined the 8S* configuration). The carbon chemical shift of Me-15 (δ_c 19.8ppm - due to a γ-effect with CH$_2$-6) established the *E*-configuration of the double bond, thus, H-5 has to be α. Finally, NOE enhancements between H-5α and H-9 and H-11 determined the relative configuration of C-9 and C-11, and the *trans* ring junction between the four and nine membered rings. Further support for the cyclobutane ring came from the one bond CH-coupling constants[7] of 132, 132 and 135 Hz for C-1, 9 and 10, respectively, as well as from characteristic MS-fragmentations of this ring[8]. Biogenetically, it is difficult to make the distinction whether sarcoglane is obtained from geranyl geraniol *via* a cembrane or xeniaphyllane precursor[9].



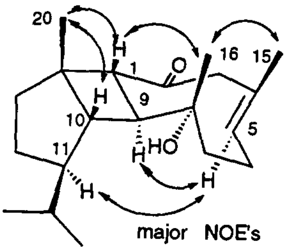


TABLE 1. NMR Data of sarcoglane (1) (500 MHz, in CDCl$_3$)

H#	δ_C	δ_H	J(Hz)	COSY TOCSY	HMBC (C to H#)	NOE
1	54.1d	2.45d	8.5	9	13′,20	
2	208.6s	-			1,3,3′	
3	53.7t	2.65d	15.4	3′		
		3.15brd	15.4	3,5		
4	126.3s	-			3,3′,15	
5	134.9d	4.79d	11.7	3,6,15	3,15	9,11
6	25.3t	2.08brd	13.8	6′,5,7	7	
		2.28dt	4.0,13.8	6,7,7′		
7	46.8t	1.65dt	4.0,13.8	6,6′,7′		
		1.95dt	14.0,4.0	6′,7	16	
8	75.5s	-			1,7,9,10,16	
9	56.3d	2.02dd	8.5,7.5	1,10	1,7,10,16	
10	49.4d	1.98m		9,11	9,19,20	
11	55.2d	1.50m		10,12,12′	17,18,19	
12	29.5t	1.64m		11,12′,13,13′		
		2.20m		11,12,13,13′	10,13	
13	33.3t	1.19m		12,12′,13′		
		2.30m		12,12′,13	12,20	
14	44.3s	-			1,10,13,20	
15	19.8q	1.85s		5		3,16
16	29.3q	1.15s				1,6,15
17	30.6d	1.38sep	6.5	18,19	18,19	
18	20.5q	1.10s		17	17,19	1,10
19	20.6q	0.85d	6.5	17	18	
20	21.8q	0.90d	6.5		1	

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