Pergamon

Tetrahedron Letters 40 (1999) 6033–6035

TETRAHEDRON LETTERS

# A novel cytotoxic norditerpenoid from the Formosan soft coral *Sinularia inelegans*

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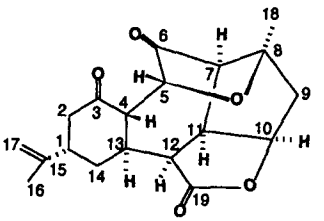
Received 10 May 1999; accepted 8 June 1999

**Abstract**

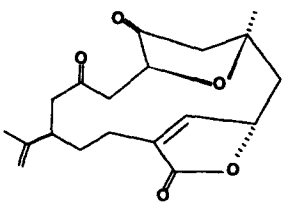
A novel cytotoxic norditerpenoid, ineleganolide (**1**), has been isolated from the soft coral *Sinularia inelegans*. The structure of **1** (novel carbon skeleton) was determined by spectral and X-ray diffraction analysis. 

*Key words:* Soft coral, *Sinularia inelegans*, cytotoxic, norditerpenoid, ineleganolide

In a search for bioactive substances from marine organisms, the Formosan soft coral *Sinularia inelegans* (Tixier-Durivault) (Family Alcyoniidae) was selected for study since its $CH_2Cl_2$ extracts showed significant cytotoxicity in several tumor cell lines as determined by standard procedures.[1-2] Bioassay-guided fractionation resulted in the isolation of a novel cytotoxic norditerpenoid, ineleganolide (**1**), which was obtained as colorless prisms, mp 190-



**1**



**2**

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0040-4039/99/$ - see front matter 
*PII:* S0040-4039(99)01194-6

192°C; $[\alpha]^{25}_D$ +26.4° (*c* 0.05, $CHCl_3$). Analysis of HREIMS revealed a molecular formula of $C_{19}H_{22}O_5$ [$M^+$ *m/z* 330.1451 (Δ –0.3 mmu)], which indicated nine degrees of unsaturation. The $^{13}$C-NMR spectral data (Table 1) of **1** revealed two ketones (δ 211.9 s and 206.2 s), an ester carbonyl (δ 175.8 s) in addition to an olefinic double bonds (δ 145.8 s, 113.6 t). The molecule was thus pentacyclic. Inspection of $^1$H-NMR spectrum of **1** revealed an isopropenyl group [δ 1.71 (3H, s), and 4.62 and 4.94 (each 1H, s)] and a tertiary methyl connected to an oxygenated carbon at δ 1.28. The $^{13}$C-NMR spectrum showed the presence of three $sp^3$ carbon carrying oxygen (δ 77.4 d, 83.0 d, 90.9 s), which confirmed the ester already indicated, and identified the remaining oxygen as an ether. Comparison of the $^1$H- and $^{13}$C-NMR spectra of **1** with those of a norcembrenolide (**2**) isolated from *Sinularia numerosa*[3] revealed that **1** may contain two additional C–C single bonds in the norcembrane skeleton of **2**. In the HMBC spectrum, long-range $^1$H-$^{13}$C correlations of H-4 to C-3, C-5, C-6, C-13 and of H-13 and H-14 to C-4 indicated that C-4 was connected to C-13. HMBC correlations of H-7 to C-6, C-8, C-11 and of H-11 to C-8, C-9, C-19 revealed the conectivity between C-7 and C-11. NOESY correlations of H-7 to H-11, H-11 to H-10, H-11 to H-12, H-12 to H-13, H-7 to $H_3$-18 indicated that H-7, H-10, H-11, H-12, H-13, and $H_3$-18 had the same orientation. The relative configuration of **1** was finally established by X-ray diffraction analysis[4] (Figure 1). Ineleganolide (**1**) exhibited cytotoxicity against P-388 cell culture system with $ED_{50}$ of 3.82 μg/ml.

**Table 1.** $^1$H- and $^{13}$C-NMR data of ineleganolide (**1**) (400 MHz and 100.6 MHz, respectively). The chemical shifts are given in ppm relative to TMS, and coupling constants (*J*) in Hz.

| pos. | $\delta_H$; mult.; *J* | $\delta_C$;mult. | HMBC | NOESY | COSY |
|---|---|---|---|---|---|
| 1 | 2.78; brs | 40.2; d | 13, 14 | 14β | 2, 14 |
| 2 | 2.63; m | 44.3; t | 1, 15 | 1 | 1, 17 |
| 3 | | 206.2; s | | | |
| 4 | 2.70; d; 13.0 | 49.7; d | 3, 5, 6, 13 | 5 | 13, 14β |
| 5 | 5.07; s | 77.4; d | 3, 4, 6, 13 | 4 | |
| 6 | | 211.9; s | | | |
| 7 | 2.59; d; 9.3 | 62.4; d | 6, 8, 11 | 11, 12, 18 | 10, 11 |
| 8 | | 90.9; s | | | |
| 9α | 2.10; dd; 15.6, 7.2 | 45.4; t | | 10, 18 | 9β, 10, 18 |
| β | 2.51; d; 15.6 | | 7, 10 | | 9α |
| 10 | 5.13; t; 7.2 | 83.0; d | 7, 8, 9 | 9α, 11, | 7, 9α, 11 |
| 11 | 3.42; ddd; 12.3, 9.3, 7.2 | 43.7; d | 8, 9, 19 | 7, 10, 12 | 7, 10, 12 |
| 12 | 3.02; dd; 12.3, 2.5 | 46.9; d | 4, 7, 11, 13, 19 | 7, 11, 13 | 11, 13 |
| 13 | 2.24; tt; 13.0, 2.5 | 33.1; d | 4, 19 | 12 | 4, 12, 14 |
| 14α | 3.00; m | 32.6; t | | | 1, 13, 14β |
| β | 1.79; m | | 4 | 1 | 1, 4, 13,14α |
| 15 | | 145.8 s | | | |
| 16 | 1.71; s | 22.5 q | 1, 17 | 17 | 17 |
| 17 | 4.62; s<br>4.94; s | 113.6 t | 1, 16 | 16 | 2, 16 |
| 18 | 1.28; s | 20.1 q | 7, 8, 9 | 7, 9α, 11 | 9β |
| 19 | | 175.8 s | | | |

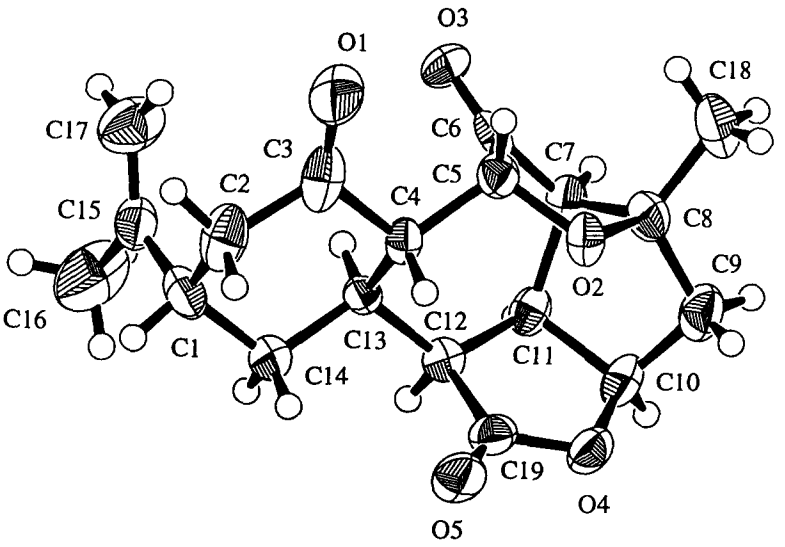


**Figure 1.** ORTEP Drawing of Ineleganolide (1)

**Acknowledgements**

We wish to think Professor Chang-Feng Dai in Institute of Oceanography, National Taiwan University, for the identification of the soft coral sample. This work was supported by grants from the National Science Council of Taiwan.

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4. Single crystal X-ray analysis of Ineleganolide (1): Cyrstal data: $C_{19}H_{22}O_5$, space group $P2_12_12_1$ (#19),$a$ = 10.755(5) Å, $b$ =10.833(5) Å, $c$ = 13.99(1) Å, $V$ = 1630(1) Å$^3$, $Z$ = 4, Dcalc = 1.347 g/cm$^3$, λ (Mo Kα) = 0.71069 Å. Intensity data were measured on a Rigaku AFC6S diffractometer up to 2θ of 49.9°. A total of 1658 reflections were observed [$I$ <3σ($I$)]. The structure was solved by the direct methods (SIR92),[5] and the final structure parameters were obtained by a full-matrix least-squares process. In view of the absence of heavy atom in the structure, Friedel pairs were not collected and the absolute configuration of ineleganolide (1) was not determined via diffraction method. Calculated hydrogen positions were put in the final cycle of structure factor calculation but not refined. The agreement indices were $R$(F) = 0.057, $Rw$(F) = 0.041 with anisotropic refinement done on all non-hydrogen atoms. Complete details of the structure investigation are available at request from the Cambridge Crystal Data Centre, 12 Union Road , Cambridge, CB1EZ England.
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