Available online at www.sciencedirect.com

SCIENCE DIRECT

Tetrahedron Letters 47 (2006) 2937–2939

Tetrahedron Letters

Sinularectin, a new diterpenoid from the soft coral *Sinularia erecta*

Amira Rudi,[a] Guy Shmul,[a] Yehuda Benayahu[b] and Yoel Kashman[a,*]

[a] *School of Chemistry, Tel-Aviv University, Ramat Aviv 69978, Israel*
[b] *Department of Zoology, Tel-Aviv University, Ramat Aviv 69978, Israel*

Received 21 December 2005; revised 15 February 2006; accepted 17 February 2006
Available online 10 March 2006

Abstract—A new norcembrane, designated sinularectin **3**, was isolated from the Kenyan soft coral *Sinularia erecta*. Sinularectin is a chlorinated highly oxygenated norcembrane with an unprecedented functionalisation of the cembrane isopropyl group. The structure of sinularectin was elucidated by interpretation of the HRESMS results as well as 1D and 2D NMR spectra.

As part of our continuing program to discover bioactive compounds from marine invertebrates, we examined the Kenyan soft coral *Sinularia erecta* (Tixier-Durivault, 1945, family Alcyoniidae). *Sinularia* is among the most abundant soft coral genera on many soft coral reefs and it tends to form large monospecific 'carpets' of up to several square meters.[1,2] Previously, we investigated *S. erecta* samples collected from the Northern Red Sea[3] and the lagoon of Mayotte, in the Indo-Pacific.[4] The latter two samples, differing in the composition of their isoprenoids, afforded several sesquiterpenes, cembranoids and C-4 norcembranoids. Variations in the chemical composition within specific soft corals is well known, yet the reason for this phenomenon is speculative[5].

The ethyl acetate/MeOH/H_2O, 10:10:1, extract (750 mg) of the freeze-dried soft coral (15 g)[6] was solvent partitioned[7] and the CH_2Cl_2 fraction was separated by chromatography on Sephadex LH-20 (eluting with hexane/CH_2Cl_2/MeOH, 2:1:1) to afford decaryiol **1**[8] (6 mg), scabrolide A **2**[9] (4 mg) and a new compound designated as sinularectin (**3**, 8 mg) (Fig. 1). Sinularectin[10] was obtained as a colourless oil. Its CIMS exhibited pseudomolecular ions at *m*/*z* 443/445 (3:1) consistent with the *m*/*z* 442/444 (3:1) peaks observed in the EIMS, thus suggesting a molecular formula of $C_{20}H_{23}O_9Cl$. However, the HRESMS, together with the ^{13}C NMR data, established a formula of $C_{20}H_{25}O_{10}Cl$ with eight degrees of unsaturation. The ESMS spectrum exhibited peaks at 483.1033 $[M+Na]^+$ (calcd 483.1034) and 943.2170 [2M+Na], both in a cluster of peaks which are in full agreement with the calculated cluster for the suggested formula. The ^{13}C NMR spectrum of **3** contains two methyl groups, six methylenes, five methines and seven non-protonated carbon atoms, together accounting for 20 carbon atoms

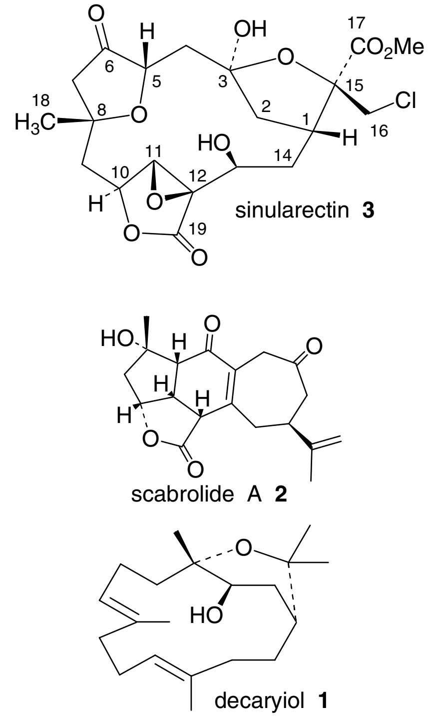

Figure 1.

---

[*] Corresponding author. Tel.: +972 3 6408419; fax: +972 3 6409293; e-mail: kashman@post.tau.ac.il

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.02.118

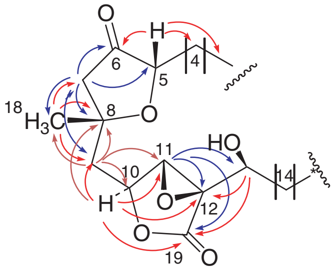

Figure 2. C_{11} Segment with key HMBC correlations.

and 23 protons. Two additional protons, belonging to two hydroxyl groups, were observable in the ^{1}H NMR spectrum taken in DMSO-d_6 (δ 5.48 d and 5.94 s). Analyzing the 1D and 2D NMR spectra, revealed a dominant part of the molecule comprising a $C_{11}H_{12}O_5$ unit as shown in Figure 2. The latter C_{11}-unit includes a ketone (δ 214.2 s), incorporated in a trisubstituted 3-oxo-THF ring, and a lactone (δ 169.7 s) that is, a butanolide. The latter butanolide incorporates an epoxy group, the chemical shifts of which (Table 1) were quite different from the ones known for an isolated epoxy moiety but are in full agreement with a 2,3-epoxybutanolide.[11] The 3-oxo-THF ring was found to be connected to the epoxybutanolide moiety via a methylene group (C-9). The entire C_{11}-unit was unequivocally determined from the HMBC correlations (Fig. 2 and Table 1) and was found to be identical to the same moiety in the C-4 norcembranoid scabrolide D.[9] Vicinal to the epoxybutanolide moiety is a secondary alcohol group (C-13) as established by CH correlations (Fig. 2 and Table 1).[12]

The $^1J_{CH}$ coupling constants of the various methinoxy groups of **3** were very helpful in the structure elucidation. The 125 Hz value for alkane-sp^3 carbon atoms increases with oxygen substitution and a decrease in the ring size.[13] Characteristic values for alcoholic, lactone, methinoxy α- to carbonyl, anomeric and epoxy methinoxy groups are around 135, 140, 155, 170 and 180 Hz, respectively.[13,14] Values of 155, 141, 197 and 135 Hz were measured for C-5, C-10, C-11 and C-13, respectively. The epoxy 197 Hz ^1J-value is very large, however, it is in agreement with the value measured for 2,3-epoxybutanolide ($J = 202$ and 198 Hz).[15] The various increments affecting the ^1J-values are additive, increasing with the type and number of oxygen atoms and decreasing size of the ring. Searching the literature for natural compounds with the above C_{11}-unit, we found several C-4 norcembranoids[9,12] suggesting that **3** is also a norcembranoid, a notion that was further supported by the isolation from the soft coral of scabrolide A **2**—a compound that can be looked upon as a norcembranoid derivative. COSY and HMBC correlations (Fig. 2, Table 1) expanded the C_{11}-unit by a methylene group on both sides of the segment [CH_2(4) and CH_2(14)]. A methoxycarbonyl group and a $-CH_2Cl$ functionality were readily identifiable from the MS and mainly from the NMR data. The remaining atoms and residual degree of unsaturation, to complete the structure of **3**, required an extra ring, in the absence of a double bond.

Table 1. ^{1}H NMR (500 MHz), ^{13}C NMR (100 MHz), ^{1}H–^{1}H COSY, NOESY and HMBC spectral data for sinularectin **3** in DMSO-d_6

Position	δ_H, mult (J in Hz)	δ_C (mult)[a]	^{1}H–^{1}H COSY	NOESY	HMBC
1	2.63 (m)	41.7 (CH)	14α, 14β, 2α, 2β	5, 2α, 16α, 2β, 14β, 18, 16β	15, 16, 17, 14, 2
2α	1.67 (t, 12.8)	42.1 (CH_2)	2β, 1	3, 18, 2β, 1, 13	1, 3, 14
2β	2.31 (dd, 12.8, 6.7)		2α, 1	2α, 1, 13, 11	1, 15
3		106.2 (C)			
4α	1.67 (t, 13.3)	41.1 (CH_2)	4β, 5	4β, 5	6, 5, 3, 2
4β	2.07 (d, 13.3)		4α, 5	4α, 5, 3	2, 3
5	4.04 (d, 11.3)	75.8 (CH)	4α, 4β	18, 2α, 4β, 1, 16α, 7β	6, 4, 3
6		214.8 (C)			
7α	2.40 (s)	50.6 (CH_2)	18, 7β	9α	6, 18, 9, 8
7β	2.43 (s)		18, 7α	18	6, 18, 9, 8
8		78.2 (C)			
9α	2.13 (s)	40.6 (CH_2)	9β, 18, 10	9β, 10, 11	18, 7, 11, 10, 8
9β	2.47 (d, 5.4)		9α, 10	18, 9β, 10	18, 11, 8
10	4.83 (d, 6.1)	78.3 (CH)	9α, 9β	14β, 9β	9, 11, 12, 8, 19
11	4.70 (s)	66.4 (CH)		9α, 2β, 13α	12, 10, 19, 8
12		61.6 (C)			
13	3.37 (m)	67.5 (CH)	14α, 14β	2α	12, 19
14α	1.40 (td, 10.9, 5.4)	32.4 (CH_2)	14β, 13	14β, 13	1, 12, 13, 15
14β	2.16 (m)		14α, 13	14α, 16β, 1	12, 1
15		88.2 (C)			
16α	3.51 (d, 11.3)	48.0 (CH_2)	16β	14β, 16β	1, 15, 17
16β	3.96 (d, 11.3)		16α	16α, 18, 1	1, 2, 15
17		170.8 (C)			
18	1.32 (s)	24.0 (CH_3)	9α, 7α, 7β	7α, 13, 1, 16α, 5	9, 7, 8
19		169.7 (C)			
20	3.73 (s)	53.3 (CH_3)			17
(C3)-OH	5.94 (s)			4β, 2α	2, 3, 4
(C13)-OH	5.48 (d)		13	14α	12, 13, 14, 19

[a] C-atom multiplicity was determined by DEPT and HMQC experiments.

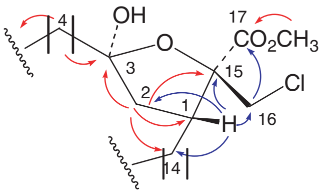

Figure 3. C_7 Segment with key HMBC correlations.

The chemical shifts of the remaining atoms, the COSY and especially the HMBC correlations suggested another substituted THF ring (Fig. 3), connected to the C_{11}-unit via the two terminal CH_2 groups of the latter moiety.

The low field resonance of C-3, α to the oxygen of the second THF ring (δ 106.2 s), required an additional electron-withdrawing group close to it, implying a lactol. The 88.2 ppm value of the α′ carbon atom proposed a heavily tetrasubstituted C-atom (C-15). This data indicated that the α′ carbon carries the CO_2CH_3 and CH_2Cl groups, a suggestion that was well supported by the HMBC correlations (Fig. 3 and Table 1). Joining the two segments created the 14-membered ring as in cembranoids and C-4 norcembranoids (as in compounds **1** and norcembrane[4]). Unique in the structure of **3** is the methylene chloride group on the five-membered lactol moiety. The suggested stereochemistry of **3** is based on NOE measurements (Fig. 4). An outline of a plausible biogenesis is given in Figure 5.

Sinularectin is a new class of cembranoid-derived diterpenes and is another example of the many oxidations and cyclisation modes of cembranoids within the *Sinularia* genera[5,9,16] with the unprecedented in soft corals, methylene chloride functionality.

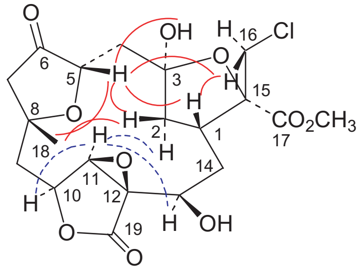

Figure 4. Sinularectin **3** with key NOEs.

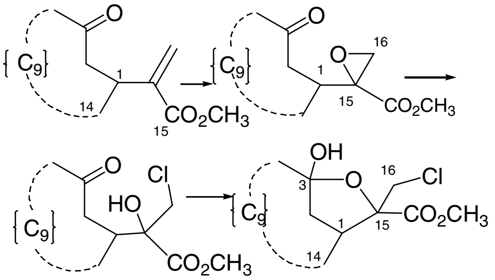

Figure 5. Suggested biogenesis for **3**.

Acknowledgements

We thank Dr. A. Tishbi, Weizmann Institute for the HRESMS and PharmaMar Madrid for financial support and a reviewer for a correction in the structure of **3**. Special thanks are due to Mr. C. O. Oduol, Assistance Director of Fisheries, Mombasa, Ministry of Agriculture, Kenya, for issuing the collection permit for the research expedition.

Supplementary data

Supporting information available: NMR and MS data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.02.118.

References and notes

1. Benayahu, Y. *Galaxea JSRP* **2002**, *4*, 1–21.
2. Benayahu, Y.; Jeng, M.-S.; Perkl-Finkel, S.; Dai, C.-F. *Zool. Stud.* **2004**, *43*, 548–560, and references cited therein.
3. Kashman, Y.; Loya, Y.; Bodner, M.; Groweiss, A.; Benayahu, Y.; Naveh, N. *Mar. Biol.* **1980**, *55*, 255–259.
4. Rudi, A.; Lev-Ari Dayan, T.; Aknin, M.; Gaydou, E. M.; Kashman, Y. *J. Nat. Prod.* **1998**, *61*, 872–875.
5. Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2003**, *20*, 1–48, and previous papers in this series.
6. The soft coral *Sinularia erecta* Tixier-Durivault, 1945 was collected in Shundo, southern Kenya, 04°52′53″S 39°18′10″E (11 February 2004). A voucher specimen has been deposited at the Zoological Museum, Tel Aviv University, Israel (SMTAU Co 32252). This soft coral was collected on a reef, at a depth of 10–12 m, characterised by a very diverse fauna comprised of other soft corals, sponges and tunicates.
7. Kupchan, S. M.; Komoda, Y.; Branfman, A. R.; Sneden, A. T.; Court, W. A.; Thomas, G. J.; Hintz, H. P. J.; Smith, R. M.; Karim, A.; Howie, G. A.; Verma, A. K.; Nagao, Y., ; Dailey, R. G., Jr.; Zimmerly, V. A.; Summer, W. C., Jr. *J. Org. Chem.* **1977**, *42*, 2349–2357.
8. Carmely, S.; Groweiss, A.; Kashman, Y. *J. Org. Chem.* **1981**, *46*, 4279–4284.
9. Sheu, J.-H.; Ahmed, A. F.; Shinu, R.-T.; Dai, C.-F.; Kuo, Y.-H. *J. Nat. Prod.* **2002**, *65*, 1904–1908.
10. Sinularectin, an oil, $[\alpha]_D$ −14 (*c* 0.001, $CHCl_3$), *m/z* (%) (CIMS) 445 (35), 443 (100), 427 (7), 425 (22), 409, 407, 393, 391.
11. Ahmed, A. F.; Su, J.-H.; Kuo, Y.-H.; Sheu, J.-H. *J. Nat. Prod.* **2004**, *67*, 2079–2082.
12. Mono acetylation of **3** with Ac_2O/pyridine afforded the 13-acetoxy derivative, δ_H 4.78 dd ($J = 14.5, 7.2$ Hz).
13. Pretsch, E.; Bühlmann, P.; Affolter, C. *Structure Determination of Organic Compounds*, 3rd ed.; Springer: Berlin, 2000.
14. Serianni, A. S.; Wu, J.; Carmichael, I. *J. Am. Chem. Soc.* **1995**, *117*, 8645–8650.
15. Bols, M.; Lundt, I. *Acta Chem. Scan.* **1990**, *44*, 252–256.
16. Tseng, Y.-J.; Ahmed, A. F.; Dai, C.-F.; Chiang, M. Y.; Sheu, J.-H. *Org. Lett.* **2005**, *7*, 3813–3816.