Pergamon

Tetrahedron Letters, Vol. 35, No. 30, pp. 5367-5368, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01085-4

Goniocin from *Goniothalamus Giganteus*: The First Tri-THF Annonaceous Acetogenin

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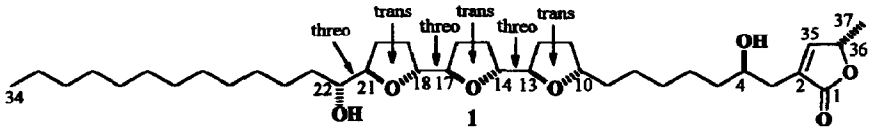
Abstract: A novel cytotoxic Annonaceous acetogenin, the first member of this class of compounds having a tri-tetrahydrofuran (THF) moiety, has been isolated from *Goniothalamus giganteus*. The structure was elucidated by spectral data, and the absolute configuration was determined by advanced Mosher's methodology.

The Annonaceous acetogenins are a class of promising anticancer, antiinfective, and pesticidal natural compounds which are potent mitochondrial inhibitors.[1] Over ninety acetogenins, usually belonging to mono-THF, adjacent bis-THF, and nonadjacent bis-THF subclasses, have been reported.[1] Until now, no tri-THF acetogenins have appeared in the literature, although their existence in nature has been predicted by their proposed biogenetic pathway (Figure 1).[1,2] In our continuous search, directed by lethality to brine shrimp, for new bioactive components from the bark of *Goniothalamus giganteus* Hook. f. & Thomas (Annonaceae), a tree from Thailand, a novel cytotoxic acetogenin possessing a tri-THF moiety was isolated and named goniocin (**1**).



On the basis of spectral data (Table 1), **1**[3] was suggested to be a new acetogenin possessing a terminal α,β-unsaturated γ-lactone with a 4-OH group like gigantecin and gigantetronenin.[1] The molecular formula of **1**, $C_{37}H_{64}O_7$, having one more index of hydrogen deficiency than the bis-THF acetogenins, indicated that there were, not two, but three THF rings in **1** since no extra double bond proton or carbon signals were observed in the NMR spectra. The adjacent tri-THF moiety in **1** was further identified by six proton signals at δ 3.96-3.78 and six oxygenated carbon signals at δ 83.0-79.6 (Table 1). The carbinol carbon signal at δ 74.2 (C-22), with its corresponding proton signal at δ 3.37 (H-22) which had correlation cross peaks with the proton at δ 3.80 (H-21) in the ^1H-^1H COSY spectrum, showed that there was only one OH group in **1** adjacent to a THF ring. The carbon signal for C-10 at δ 79.6 demonstrated that there was no OH group adjacent to this side of the THF system. The placement of the tri-THF rings at C-10 through C-21 was determined by the EIMS fragmentation of the bis-TMSi derivative[4] of **1**.

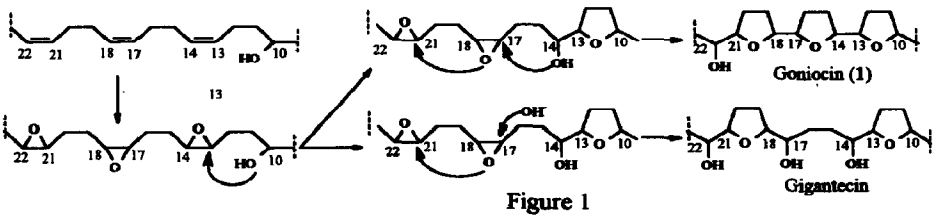


Figure 1

Table 1. ^{13}C NMR and ^{1}H NMR Data of 1 and its *S*- and *R*-Mosher Esters.

	^{13}C (125 MHz)	^{1}H (500 MHz)			$\Delta\delta_H$
	1	1 (*J* in Hz)	*S*-MPTA-1	*R*-MPTA-1	$\delta_S - \delta_R$
37	19.1	1.35 d (6.5)	1.28	1.31	neg
36	78.0	5.06 qq (6.5, 1.5)	4.86	4.91	neg
35	151.9	7.20 q (1)	6.72	6.97	neg
1	174.3	-	-	-	-
2	131.1	-	-	-	-
3	33.2	2.53 dddd, 2.40 dddd	2.57	2.64	neg
4	69.8	3.85 m	5.31	5.37	*R*
5	37.2	1.47 m	1.65	1.62	pos
6 - 8	29.7 - 25.4	1.60 - 1.20 m	1.60 - 1.20	1.60 - 1.20	-
9	35.6	1.44 m	1.43	1.42	-
10	79.6	3.93 m	3.89	3.87	-
11	32.1	2.02 m, 1.62 m	1.96, 1.62	1.96, 1.63	-
12,15,16	28.5 - 28.3	1.96 m, 1.70 - 1.64 m	1.88 - 1.58	1.92 - 1.60	-
13, 14, 17, 18	82.3 - 81.1	3.92 - 3.83 m	3.92 - 3.82	3.98 - 3.84	-
19	28.5	1.96 m, 1.64 m	1.88 - 1.58	1.92 - 1.60	-
20	28.8	1.96 m, 1.60	1.91, 1.49	2.02, 1.56	neg
21	83.0	3.80 m	4.04	4.05	neg
22	74.2	3.37 m	5.05	5.05	*R*
23	33.3	1.38 m	1.62	1.50	pos
24	25.6	1.60 - 1.20 m	1.29	1.18	pos
25 - 31	29.7 - 29.3	1.60 - 1.20 m	1.60 - 1.20	1.60 - 1.20	-
32	31.9	1.60 - 1.20 m	1.60 - 1.20	1.60 - 1.20	-
33	22.7	1.28 m	1.28	1.28	-
34	14.1	0.879 t (7.0)	0.880	0.880	-

The Ha and Hb proton signals of the THF methylenes (C-11, 12, 15, 16, 19, and 20) at δ 2.02-1.96 and 1.70-1.62, respectively, those of H-13, 14, 17 and 18 at δ 3.92-3.83, and that of H-22 at δ 3.37 suggested that the relative stereochemistry around the tri-THF rings was *trans-threo-trans-threo-trans-threo*, from C-10 through C-22, by comparisons with the ^{1}H NMR data of model compounds[1] and other known acetogenins.[1] Both of the absolute configurations of the carbinol stereocenters at C-4 and C-22 were determined to be *R* by preparation of Mosher ester derivatives (MTPA, Table 1).[5] As the C-4 *R* and C-36 *S* relationship has always been found in the acetogenins,[5] the absolute stereochemistry of 1 was proposed to be 4*R*, 10*S*, 13*R*, 14*R*, 17*R*, 18R, 21*R*, 22*R*, and 36*S*, as illustrated.

Acknolwdgement: This work was supported by grant no. R01CA30909 from the National Cancer Institute, NIH.

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2. Gu, Z.-M.; Fang, X.-P.; Zeng, L.; Song, R.; Ng, J. H.; Wood, K. V.; Smith, D. L.; McLaughlin, J. L. *J. Org. Chem.* **1994** (accepted for publication).
3. Goniocin (1) was obtained as a whitish wax. The molecular formula of 1 was established to be $C_{37}H_{64}O_7$ by HRFABMS [obsd 621.4735, calcd 621.4730, for (M+H)]. 1 exhibited toxicity LC_{50} value 57 μg/ml to brine shrimp and showed cytotoxic ED_{50} values 9.42×10^{-1}, 4.85, and 1.61×10^{-2} μg/ml against A-549, MCF-7, and HT-29 human solid tumor cells, respectively; adriamycin gave respective ED_{50} values of 8.50×10^{-3}, 5.19×10^{-1}, and 3.72×10^{-2} μg/ml.
4. EIMS of bi-TMSi-1 m/z (%): 764 (2.2), 749 (4.0), 659 (4.8), 653 (5.7), 563 (6.8), 493 (48.6), 423 (23.6), 421 (40.3), 403 (55.5), 392 (16.0), 385 (62.9), 353 (40.3), 341 (18.2), 323 (8.0), 315 (30.0), 271 (100.0), 263 (26.9), 245 (31.7), 213 (44.8).
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(*Received in USA* 27 *April* 1994; *revised* 1 *June* 1994; *accepted* 2 *June* 1994)