GONIODENIN, A NEW BIOACTIVE ANNONACEOUS ACETOGENIN FROM *GONIOTHALAMUS GIGANTEUS* AND ITS CONVERSION TO TRI-THF ACETOGENINS

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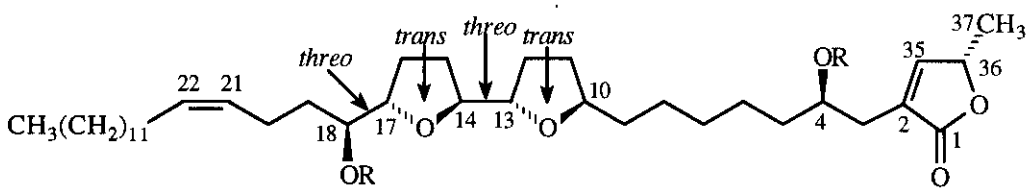
Abstract- Using activity-directed fractionation, a novel bioactive bis-THF acetogenin, goniodenin (**1**), has been isolated from the bark of *Goniothalamus giganteus* (Annonaceae). **1** is the first reported bis-THF acetogenin which bears a double bond in the aliphatic chain. The *cis* C-21/22 double bond in **1** was efficiently oxidized to the epoxides and cyclized to produce a pair of tri-THF acetogenins, cyclogoniodenins T and C (**8** and **13**). These are the first reported semi-synthesized tri-THF acetogenins, and **13** represents a new type of acetogenin. The absolute stereochemistries were assigned using Mosher ester and nmr analyses. **8** and **13** show interesting selectivities among several human tumor cell lines. Asimilobin (**19**), concurrently found in the seeds of *Asimina triloba*, was also isolated and characterized.

Goniothalamus giganteus Hook. f. & Thomas (Annonaceae) is a tropical tree which has a great reputation as a drug among the Malays.[1] The bark of this plant, obtained from Thailand, showed toxicities in the brine shrimp lethality test (BST) and showed murine toxicities in the 3PS (P388) leukemia bioassay.[2] Thirteen bioactive Annonaceous acetogenins have been previously isolated from the bark.[3] In our further bioactivity-directed search for antitumor compounds, two additional bioactive acetogenins,

goniodenin (**1**) and asimilobin (**19**), have been isolated. Both have adjacent bis-THF rings with only one flanking hydroxyl group. Prior to this work, only a mixture of two acetogenins, (2, 4-*cis* and *trans*) - bulladecinones, of this type had been reported.[4] **1** and **19** differ in that **1** has a double bond at C-21/22, **19** is saturated at this position, and **1** has 37 carbons while **19** has 35 carbons. While this work was in progress, **19** was concurrently isolated and characterized from the seeds of *Asimina triloba*.



Compound	1	2	3	4	5
R	H	Ac	TMS	(S)-MTPA	(R)-MTPA

Figure 1. Structures of compounds (**1-5**).

Goniodenin (**1**) is the first example of a bis-THF acetogenin bearing a double bond in the aliphatic chain. The double bond in the C-21/22 position (Figure 1) was oxidized to give a pair of adjacent bis-THF epoxides (**6**, **7**). The epoxides were converted into tri-THF acetogenins (**8**, **13**) with toluenesulfonic acid. The epoxides of unsaturated mono-THF acetogenins had been previously converted to bis-THF acetoge-

Table 1. ^{1}H Nmr (500 MHz, $CDCl_3$) Data of **1**, **2**, **4**, **5** [δ ppm (J = Hz)]

proton	1	2	4	5	$\Delta\delta_H(\delta_4-\delta_5)$
37	1.44 d (7)	1.40 d (7)	1.28 d (7)	1.30 d (7)	-0.02
36	5.06 qq (7, 1.5)	5.01 qq (7, 1.5)	4.86 qq (7, 1.5)	4.92 qq (7, 1.5)	-0.06
35	7.20 q (1.5)	7.08 q (1.5)	6.72 q(1.5)	6.97 q (1.5)	-0.25
3a	2.53 dddd	2.56 dddd	2.60 dddd	2.66 dddd	-0.06
3b	2.40 dddd	2.52 dddd	2.54 dddd	2.59 dddd	-0.05
4	3.85 m	5.10 m	5.30 m	5.36 m	R
5	1.45 m	1.55 m	1.64 m	1.62 m	+0.02
10	3.93 m	3.89 m	3.95-3.89 m	3.95-3.89 m	-
11a, 12a	2.02 m				
11b, 12b	1.60 m				-
13, 14	3.92 - 3.83	3.96 - 3.82 m	3.92 - 3.80 m	3.78 -3.56 m	-
15a, 16a	1.96 m	1.96 m	2.03 m	1.92 m	+0.11
15b, 16b	1.64 m	1.60 m	1.58 m	1.52 m	+0.06
17	3.83 m	4.04 m	4.07 m	4.07 m	-0
18	3.41 m	4.90 m	5.08 m	5.08 m	S
19	1.47 m	1.56 m	1.50 m	1.62 m	-0.12
20	2.19 m	2.00 m	1.88 m	2.08 m	-0.20
21	5.36 m	5.32 m	5.22 m	5.28 m	-0.06
22	5.39 m	5.37 m	5.34 m	5.40 m	-0.06
23	2.03 m	2.00 m	1.88 m	1.95 m	-0.07
33	1.28 m	1.28 m	1.28 m	1.28 m	-
34	0.88 t (7)	0.88 t (7)	0.88 t (7)	0.88 t (7)	-
4-OAc	-	2.02	-	-	-
18-OAc	-	2.08	-	-	-

nins by using perchloric acid.[5] However, **6** and **7** were not stable to perchloric acid, and, using toluenesulfonic acid as the ring closure reagent, the yield was *ca.* 90%. So far, only one natural tri-THF acetogenin, goniocin (**18**), has been reported.[6] Thus, the conversion of **1** to **8** and **13** conclusively determined the position of the double bond at C-21/22 and also provided two new examples of tri-THF acetogenins.

Goniodenin (**1**) was obtained as a colorless oil-like substance with slight optical activity, $[\alpha]_D$ + 0.5°. The molecular formula was deduced as $C_{37}H_{64}O_6$ by HRCIms which gave the MH^+ ion at *m/z* 605.4792 (calcd 605.4781). The prominent absorption peak at 3435 cm^{-1} in the ir spectrum and sequential losses of H_2O (*m/z* 18) from the molecular ion in the CIms (m/z 587, 569) indicated the presence of two hydroxyls. These were further confirmed by preparation of the diacetyl derivative (**2**). The ^1H nmr spectrum of **2** showed the protons for two isolated methyl groups at δ 2.02 (H-4-OAc) and 2.08 (H-18-OAc) and two multiple proton resonances at δ 5.10 (H–4) and δ 4.90 (H-18) which were shifted downfield compared with **1**. The existence in **1** of an α, β–unsaturated γ–lactone with an OH group at C-4 was indicated by a strong ir absorption at 1755 cm^{-1}, a uv maximium at 227 nm, the ^1H nmr absorptions at δ 7.20 (q, H-35), 5.06 (qq, H-36), 3.85 (H-4), 2.53 and 2.40 (H-3a and 3b) and ^{13}C nmr absorptions at δ 174.62 (C-1), 131.13 (C-2), 151.83 (C-35), 77.97 (C-36), 69.97 (C-4) and 19.09 (C-37) (Tables 1 and 2). The presence of an adjacent bis-THF ring with only one flanking OH was indicated by the proton signals at δ 3.41 (H-18), 3.93–3.83 (H–10, 13, 14, 17), 2.02–1.96 (4H, H–11a, 12a, 15a, 16a), 1.64-1.60 (4H, H-11b, 12b, 15b, 16b) in the ^1H nmr spectrum (Table 1) and by the carbon signals at δ 83.09 (C-17), 82.04 (C-14), 81.25 (C-13), 73.57 (C-18) and 79.90 (C-10) in ^{13}C nmr spectrum (Table 2).[4] These nmr data also indicated that the relative stereochemistries between C-13 and C-14, C-17 and C-18 were *threo* and that the configurations across the THF rings (C-10/13 and C-14/17) were *trans*, by comparisons with compounds of known relative stereochemistry.[5, 7] The placement of the adjacent bis-THF ring system was determined by the EIms fragmentation of **3** (Figure 2).

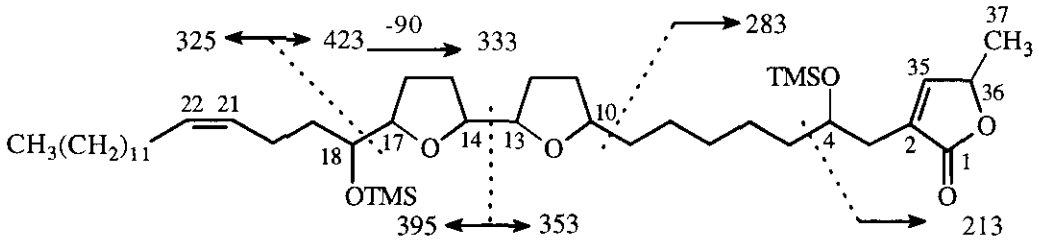
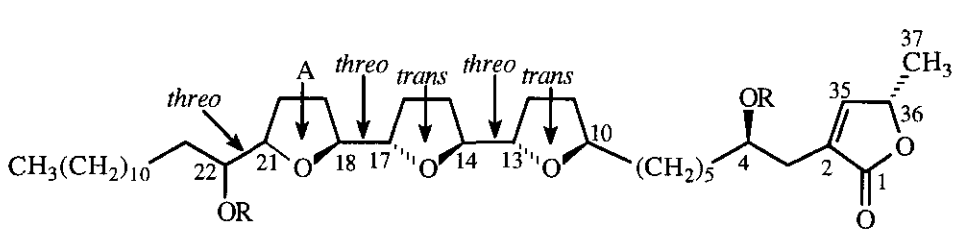


Figure 2. EIms fragmentation of the TMS derivative (**3**) of **1**.

Table 2. ^{13}C Nmr (125 MHz, $CDCl_3$) of **1**, **8**, **13**.

carbon	1	8	13	carbon	1	8	13
37	19.09	19.11	19.12	13	81.24	81.10	80.72
36	77.97	77.98	77.95	14	82.09	81.73	81.31
35	151.83	151.82	151.76	17	83.02	81.83	81.51
1	174.62	174.64	174.60	18	73.57	82.24	82.29
2	131.13	131.18	131.20	19	33.33		
3	33.30	33.29	33.29	21	129.09	83.98	82.47
4	69.97	69.94	69.86	22	130.62	74.15	74.72
5	37.28	37.28	37.28	23		33.35	33.35
9	35.66	35.64	35.64	32	31.90	31.91	31.91
10	79.90	79.63	79.75	33	22.67	22.68	22.68
11	32.04	32.13	32.11	34	14.11	14.12	14.12
12, 15, 16	28.89-28.37						

The presence of an isolated double bond in **1** was indicated by proton nmr signals at δ 5.39 and 5.36 and the carbon nmr signals at δ 130.62 and 129.09. The *cis* configuration was indicated by the coupling constant (J = 11.0 Hz) between H-21 and 22. The coupling constant was measured by selectively decoupling the protons at δ 2.19 (H-20), which showed correlation cross peaks with the proton at δ 5.36 (H-21) in the COSY spectrum. The position of the double bond was placed at C-21/22 after observing the double-relayed COSY spectrum, which showed correlation peaks between H-18 (δ 3.43) and H-21 (δ 5.36). The absolute stereochemistries of the carbinol centers at C-4 and C-18 were determined as 4R, 18S by using Mosher ester methodology.[17] The absolute configuration at C-36 was determined as S by comparison of the magnitude of Δ (δH_{35}) and Δ (δH_{36}) between the (R)- and (S)- per-Mosher esters (**4, 5**) of **1**, according to the recent paper of Hoye *et al.*[8b] (Table 1). From the above spectral data, the structure of **1** was determined as illustrated and named goniodenin.



Compds	8	9	10	11	12	13	14	15	16	17
R	H	Ac	TMS	(S)-MTPA	(R)-MTPA	H	Ac	TMS	(S)-MTPA	(R)-MTPA
A	*trans*	*trans*	*trans*	*trans*	*trans*	*cis*	*cis*	*cis*	*cis*	*cis*

Figure 3. Structures of the semisynthetic tri-THF acetogenins (**8, 13**) and their derivatives (**9-12, 14-17**).

According to the proposed biogenetic pathway,[3d,15] the THF rings of acetogenins are biosynthesized in plants from double bonds through epoxide intermediates. Since in **1** the double bond is appropriately

located two methylenes away from the flanking OH of the adjacent bis-THF ring system, we assumed that if the double bond were oxidized to the epoxides, the flanking OH group could attack the epoxide, forming a pair of tri-THF acetogenins, one having a *cis*-THF and the other a *trans*-THF ring at C-18/21.

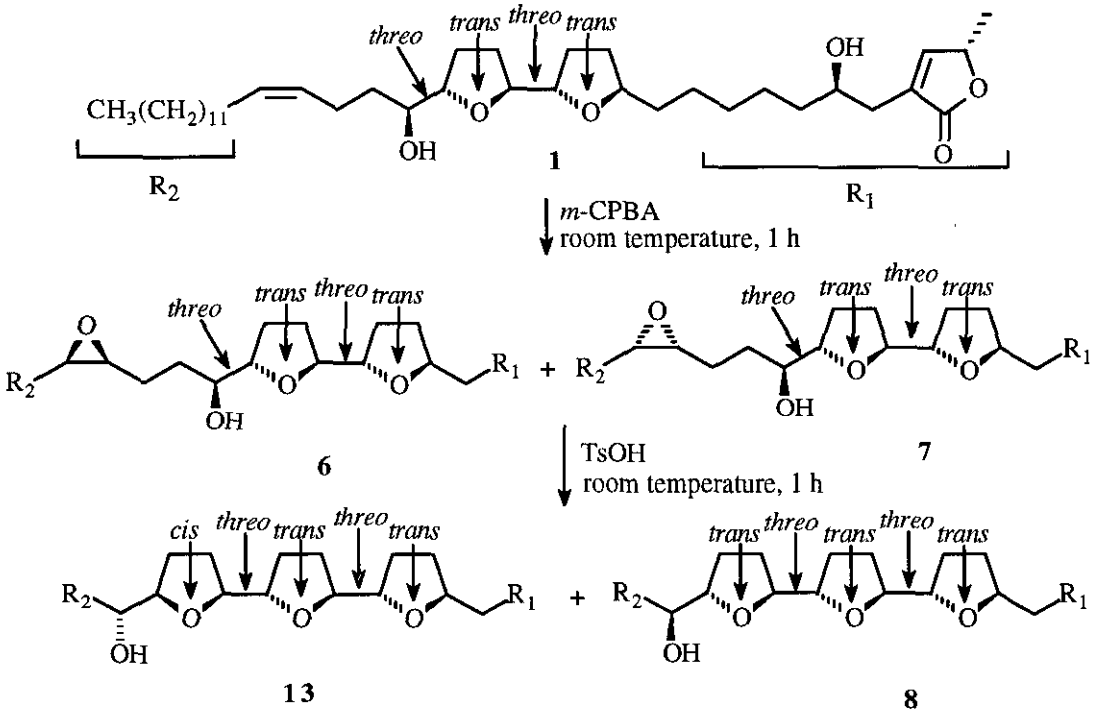
Table 3. ^{1}H Nmr (500 MHz, $CDCl_3$) Data of **8, 9, 11, 12** [δ ppm (J = Hz)]

proton	**8**	**9**	**11**	**12**	$\Delta\delta_H(\delta_{11}-\delta_{12})$
37	1.44 d (7)	1.40 d (7)	1.28 d (7)	1.30 d (7)	-0.04
36	5.06 qq (7, 1.5)	5.01 qq (7, 1.5)	4.85 qq (7, 1.5)	4.91 qq (7, 1.5)	-0.06
35	7.20 q (1.5)	7.08 q (1.5)	6.73 q (1.5)	6.97 q (1.5)	-0.26
3a	2.53 dddd	2.56 dddd	2.60 dddd	2.66 dddd	-0.06
3b	2.40 dddd	2.52 dddd	2.55 dddd	2.60 dddd	-0.05
4	3.84 m	5.10 m	5.31 m	5.37 m	*R*
5	1.45 m	1.55 m	1.63 m	1.62 m	+0.01
10	3.93 m	3.98 m	-	-	-
11a, 12a	2.02 m	1.95 m	-	-	-
11b, 12b	1.62 m	1.56 m	-	-	-
15a, 16a	1.96 m	1.94 m	-	-	-
15b, 16b	1.64 m	1.56 m	-	-	-
13, 14	3.92 - 3.83 m	3.93 m	-	-	-
17, 18	3.94 - 3.82 m	3.94 m	-	-	-
19a, 20a	1.94 m	1.92 m	2.02 m	1.90 m	+0.12
19b, 20b	1.58 m	1.55 m	1.56 m	1.49 m	+0.07
21	3.81 m	4.01 m	4.05 m	4.05 m	~0
22	3.37 m	4.86 m	5.05 m	5.05 m	*S*
23	1.38 m	1.55 m	1.50 m	1.61 m	-0.11
33	1.28 m	1.28m	1.28 m	1.28 m	-
34	0.88 t (7)	0.88 t (7)	0.88 t (7)	0.88 t(7)	-
4-OAc	-	2.02	-	-	-
22-OAc	-	2.08	-	-	-

Gu *et al.* had similarily oxidized unsaturated mono-THF acetogenins into epoxides using *m*-perchlorobenzoic acid (*m*-CPBA) and then treated the epoxides with perchloric acid to make pairs of bis-THF acetogenins.[5] After treatment of **1** with *m*-CPBA and separation by hplc, a pair of epoxides (**6, 7**) were obtained; but **6** and **7** decomposed upon addition of perchloric acid. However, using toluenesulfonic acid, the reaction was accomplished within 30 minutes (Scheme 1), and the conversion rate was *ca.* 90%. After hplc separation, **8** and **13** were obtained.

8 and **13** were isolated as colorless oils, and their molecular formulae were both determined as $C_{37}H_{64}O_7$ based on the accurate mass *m/z* 620.4730 (found) for their MH^+ from HRCIms (calcd 620.4749). ^{1}H Nmr of **8** and **13** showed that the integration ratio of signals at δ 3.35 (H-22) to those at *ca.* δ 3.90 (H-4, 10, 13, 14, 17, 18, 21) was 1:7, and the double bond signals at δ 5.36 and δ 5.39 had disappeared, indicating that the third THF ring had been formed (Tables 2 and 3). The formation of the third THF ring was also confirmed by comparing the ^{13}C nmr spectra of **8** and **13** (Table 2) with that of **1**; with **8** and **13** the

signal at *ca.* δ 130 and δ 129.0 had disappeared and two more signals appeared at *ca.* δ 80. The above ^1H and ^{13}C nmr data also indicated that the relative stereochemistries between C-13 and C-14, C-17



Scheme 1. The conversion reaction of **1** to **6**, **7**, **8** and **13**.

and C-18, and C-21 and C-22 were all *threo*.[7] The presence of two hydroxyls in **8** and **13** was also confirmed by preparation of the diacetate derivatives (**9**, **14**). The ^1H nmr spectra of both **9** and **14** showed the signals for the two isolated methyl groups at δ 2.02 (H-4-OAc) and 2.08 (H-22-OAc) and two multiple proton resonances at *ca.* δ 5.10 (H–4) and δ 4.89 (H-22) which were shifted downfield compared with **8** and **13.** Since during the ring closure reaction, the configuration of the original two THF rings remained the same, only the configuration of the third ring needed to be determined. This was accomplished by comparing the ^1H nmr chemical shifts of **8** and **13** with those of model compounds. In compound (**8**), H-19 and H-20 absorbed at δ 1.60 and δ 1.96, so the ring between H-18 and H-21 was *trans*.[5] In **13**, H-19 and H-20 absorbed at δ 1.74 and δ 1.87, so the ring between H-18 and H-21 was *cis*.[5] Thus, the relative stereochemistries of **8** and **13** across the tri-THF ring, from C-10 to C-22, are *trans/threo/trans/threo/trans/threo* and *trans/threo/trans/threo/cis/threo*, respectively.

The placement of the tri-THF ring system of **8** and **13** was confirmed by EIms of the TMS derivatives (Figure 4). The absolute stereochemistries of **8** and **13** were determined as 36S, 4R, 22S, and 36S, 4R, 22R, respectively by nmr analysis of the per-(S)- and (R)- Mosher esters, as described above (Tables

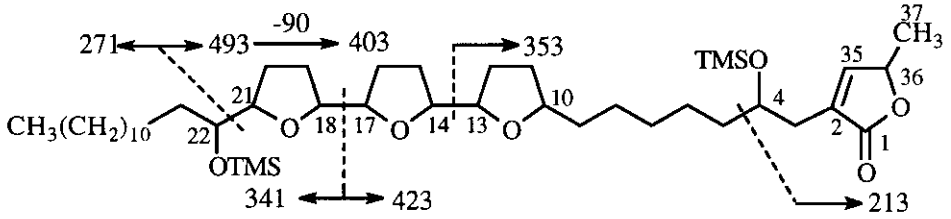


Figure 4. Diagnostic EIms fragmentation of the TMS derivatives of **8** and **13**.

3 and 4). Therefore, **8** and **13** are new tri-THF acetogenins and were named cyclogoniodenins T and C, respectively. **13** also represents a new type of acetogenin ring system.

Table 4. ^{1}H Nmr (500 MHz, $CDCl_3$) Data of **13, 14, 16, 17** [δ ppm (J = Hz)].

proton	**13**	**14**	**16**	**17**	$\Delta\delta_H(\delta_{16}-\delta_{17})$
37	1.44 d (7)	1.40 d (7)	1.28 d (7)	1.32 d (7)	-0.04
36	5.06 qq (7, 1.5)	5.01 qq (7, 1.5)	4.86 qq (7, 1.5)	4.91 qq (7, 1.5)	-0.05
35	7.20 q (1.5)	7.08 q (1.5)	6.72 q (1.5)	6.98 q (1.5)	-0.24
3a	2.53 dddd	2.56 dddd	2.60 dddd	2.67 dddd	-0.07
3b	2.40 dddd	2.52 dddd	2.55 dddd	2.60 dddd	-0.05
4	3.84 m	5.10 m	5.31 m	5.38 m	*R*
5	1.45 m	1.56 m	1.65 m	1.65 m	~0
10	3.93 m	3.98 m	-	-	-
11a, 12a	2.02 m	1.96 m	-	-	-
11b, 12b	1.62 m	1.56 m	-	-	-
15a, 16a	1.96 m	1.92 m	-	-	-
15b, 16b	1.64 m	1.54 m	-	-	-
13, 14	3.94 - 3.82 m	3.94 m	-	-	-
17, 18	3.94 - 3.82 m	3.94 m	-	-	-
19	1.85, 1.74 m	1.82, 1.72	-	-	-
20	1.85, 1.74 m	1.82, 1.72	1.80, 1.60	1.88, 1.65	-0.08, -0.05
21	3.88 m	3.98 m	3.97 m	3.97 m	~0
22	3.35 m	4.89 m	5.08 m	5.12 m	*R*
23	1.46 m	1.56 m	1.63 m	1.50 m	+0.13
33	1.28 m	1.28 m	1.28 m	1.28 m	-
34	0.88 t (7)	0.88 t (7)	0.88 t (7)	0.88 t (7)	-
4-OAc	-	2.02	-	-	-
22-OAc	-	2.08	-	-	-

Only one tri-THF acetogenin, goniocin (**18**) (Figure 5), has been previously reported.[6] After careful examination of their spectral data, it was found that **8** and **18** differ in the absolute stereochemistry at C-22. Because their relative stereochemistries across the tri-THF rings were both *trans/threo/trans/threo/trans/threo,* their absolute sterochemistries, surprisingly, must be the mirror images of each other.

Asimilobin (**19**) was isolated as a white wax during hplc purification of goniodenin (**1**). The polarity of **19** is very close to that of **1**. The ^{1}H and ^{13}C nmr spectral patterns of **19** were nearly the same as those of

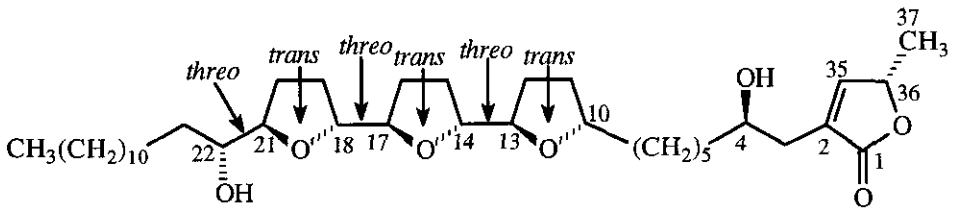


Figure 5. Structure of goniocin (**18**).

1 except that the signals for the C-21/22 double bond were missing. This suggested that **19** has the same carbon skeleton as **1** but has no double bond. HRCIms of **19** gave a *m/z* of 579.4608 for the MH^{+} which corresponds to the molecular formula of $C_{35}H_{62}O_6$ (calcd 579.4625) and showed that the hydrocarbon chain of **19** is shorter than **1** by two methylenes. From the EIms fragmentation of the TMS derivative, it was determined that the bis-THF ring of **19** was at C-10 to C-17, which was in the same position as **1** and demonstrates that the missing methylenes in **19** are from the end of the molecule bearing the terminal methyl.

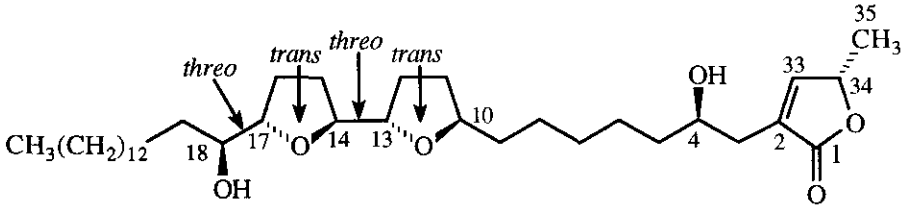


Figure 6. Structure of Compound **19**.

The absolute stereochemistries of the chiral centers at C-4, C-18 and C-36 of **19** were determined as 4R, 18S and 36S by the same Mosher ester methods as described above. **19** was concurrently isolated from the seeds of *Asimina triloba*, and the details of its characterization and its acetate, TMS, and Mosher ester derivatives will be published elsewhere.

Bioactivity data obtained with **1**; **8**, **13** and **19** are listed in Table 5. **1** and **19** were cytotoxic and also showed activities similar to adriamycin against six solid tumor cell lines. **8** and **13** demonstrated good selectivities against PC-3 (human prostate carcinoma) and PACA-2 (human pancreatic carcinoma). **8** was also selectively cytotoxic against A-549 (human lung carcinoma). Comparing the bioactivities of **8**, **13** and **18**, the bioactivities of **18** are more similar to those of **8**. The acetogenins exert their biological

effects through inhibition of mitochondrial electron transport (complex I) and the inhibition of the plasma membrane NADH oxidase of tumor cells. [16]

Table 5. Bioactivities of Compounds **1**, **8**, **13**, **18** and **19** (LC_{50}, μg/ml).

Compd	BST[a]	A-549[b]	MCF-7[c]	HT-29[d]	A-498[e]	PC-3[f]	PACA-2[g]
1	0.85	1.86×10^{-2}	8.40	4.45×10^{-3}	8.98×10^{-2}	1.21	1.88×10^{-1}
8	35.33	6.37×10^{-4}	7.63×10^{-1}	4.67×10^{-1}	1.67×10^{-1}	9.38×10^{-4}	$< 10^{-8}$
13	40.12	4.27×10^{-1}	2.57	3.64×10^{-1}	1.07	5.21×10^{-5}	3.83×10^{-5}
18[h]	57	9.42×10^{-1}	4.85	1.61×10^{-2}	-	-	-
19	7.12	2.84×10^{-3}	3.87	1.28×10^{-3}	3.10×10^{-3}	2.27	3.59×10^{-1}
adriamycin[i]	8×10^{-2}	2.06×10^{-3}	3.65×10^{-1}	3.27×10^{-2}	6.07×10^{-3}	3.19×10^{-2}	2.35×10^{-2}

a) Brine shrimp lethality test[2a, 14] b) Lung carcinoma[9] c) Breast carcinoma[10]
d) Colon adenocarcinoma[11] e) Kidney carcinoma[9] f) Prostate adenocarcinoma[12]
g) Pancreatic carcinoma[13] h) Data taken from [7] i) Positive control standard

EXPERIMENTAL

Instrumentation

Optical rotations were determined on a Perkin Elmer 241 polarimeter. Ir spectra (film) were measured on a Perkin-Elmer 1600 FTIR spectrophotometer. Uv spectra were taken in EtOH on a Beckman DU-7 UV spectrophotometer. ^{1}H Nmr, ^{1}H - ^{1}H COSY, and ^{13}C nmr spectra were obtained on a Varian VXR-500S spectrometer. Low resolution ms data were collected on a Finnigan 4000 spectrometer. Low resolution EIms for TMS derivatives and high resolution FABms were performed on a Kratos MS50. Hplc separations were performed with a Rainin hplc using a Dynamax software system and a silica gel column (250 x 21 mm) equipped with a Rainin UV-1 detector set at 225 nm. Analytical tlc was carried out on silica gel plates (0.25 mm) developed with hexane:acetone (3:2) and $CHCl_3$:MeOH (9.5:0.5), respectively, and visualized with 5% phosphomolybdic acid in EtOH .

Bioassays

The extracts, fractions and pure compounds were routinely tested for lethality to brine shrimp larvae (BST).[2a,14] In vitro cytotoxicities, against human tumor cell lines, were carried out at the Purdue Cancer Center, Cell Culture Laboratory, using standard protocols for A-549 (lung carcinoma),[9] MCF-7 (breast carcinoma),[10] HT-29 (colon adenocarcinoma),[11] A-498 (kidney carcinoma),[9] PC-3 (prostate adenocarcinoma),[12] and PACA-2 (pancreatic carcinoma).[13]

Plant material

The stem bark of *Goniothalamus giganteus* (B-826538, PR-50604) was collected in Thailand in Sept. 1978 under the auspices of Dr. Robert E. Perdue, Medicinal Plant Laboratory, USDA, Beltsville, MD, where voucher specimens are maintained.

Extraction and isolation

The stem bark (10 kg) was ground into powder and percolated in 95% ethanol (25 l). The dry extract (900 g) (F001) was partitioned between H_2O (5.0 l) and CH_2Cl_2 (5.0 l) to give a H_2O layer (F002) (102 g), an insoluble interface (F004) (270 g) and a CH_2Cl_2 layer (430 g). The residue of the CH_2Cl_2 layer was partitioned between 90% aqueous MeOH (3.0 l) and hexane (3.0 l), giving a MeOH layer (F005) (400 g) and a hexane layer (F006) (15 g). The MeOH layer (F005) was the most active fraction in the BST (LC_{50} 1.02 µg/ml). Thus, a portion (190 g) of F005 was repeatedly chromatographed over silica gel columns directed by the BST test, using gradients of hexane-acetone, hexane-EtOAc and $CHCl_3$-MeOH and purified by normal phase hplc eluted with 10% THF in MeOH -hexane (4-6%) to give the colorless oil (**1**) (55 mg) and the white wax (**19**) (50 mg).

Oxidization and cyclization of goniodenin (1)

15 mg of *m*-chloroperbenzoic acid (*m*-CPBA) was added to 30 mg (0.05 m mol) of **1** in 10 ml of CH_2Cl_2. The mixture was stirred for 1 h at room temperature and then washed with 1% $NaHCO_3$ (5 ml) and H_2O (2 x 5 ml). The CH_2Cl_2 layer was dried under vacuum and injected into the hplc for purification. **6** and **7** were isolated as a mixture. 3 mg of toluenesulfonic acid was added into 13.5 mg of **6** and **7** in 4 ml of CH_2Cl_2, and the mixture was stirred for 1 h at room temperature and then washed with 1% $NaHCO_3$ (3 x 5 ml) and H_2O (2 x 5 ml). The CH_2Cl_2 layer was dried under vacuum. 6.0 mg of **8** and 6.0 mg of **13** were obtained through normal phase hplc separation.

Preparation of Mosher esters

To an acetogenin (0.5-1 mg, in 0.3 ml of CH_2Cl_2) were sequentially added pyridine (0.2 ml), 4-(dimethylamino)pyridine (0.5 mg), and 25 mg of (R)-(-)-α-methoxy-α-(trifluomethyl)phenylacetyl chloride. The mixture was stirred at room temperature for 4 h and passed through a disposable pipet (0.6 x 6 cm) containing silica gel (60- 200 mesh) and eluted with 3 ml of CH_2Cl_2. The CH_2Cl_2 residue, dried *in vacuo*, was redissolved in CH_2Cl_2 and washed in 1% $NaHCO_3$ (5 ml) and H_2O (2 x 5ml); the CH_2Cl_2 layer was dried under vacuum to give

the (S)-Mosher esters. Using (S)-(+)-α-methoxy-α-(trifluomethyl)phenylacetyl chloride gave the (R)-Mosher esters. Both yields were typically higher than 90%.

Acetylations

Compounds (**1**, **8**, and **13** (0.5 mg of each)) were mixed with anhydrous pyridine/Ac_2O (0.2 ml of each) at room temperature overnight and, through the usual workup, give *ca.* 0.5 mg each of the diacetates (**2**, **9**, and **14**), respectively. ^1H Nmr are shown in Tables 1, 3, and 4.

Preparation of TMS derivatives

Compounds (**1**, **8** and **13** (ca. 0.3 mg of each)) were treated with *N,O*-bis(trimethylsilyl)acetamide (20 µl) and pyridine (2 µl) and heated at 70 °C for 30 min to yield the respective di-TMS derivatives (**3**, **10**, and 15). EIms fragmentations are shown in Figures 2 and 4.

Goniodenin (1)

Colorless oil, $[\alpha]_D$ +5.0° (c 1.10, CH_2Cl_2); uv λ_{max} (EtOH) 209 nm (log ε, 3.0); ir ν_{max} (film) 3435, 2926, 2856, 1755, 1454, 1320 cm^{-1}; HRFABms (glycerol): found *m/z* 605.4792, calcd 506.4781. ^1H and ^{13}C nmr, see Tables 1 and 2, respectively.

Asimilobin (19)

White wax, $[\alpha]_D$ +11.3° (c 1.00, CH_2Cl_2); uv λ_{max} (EtOH) 209 nm (log ε, 3.0); ir ν_{max} (film) 3437, 2924, 2853, 1752, 1596, 1454 cm^{-1}; HRFABms (glycerol): found *m/z* 579.4608, calcd 579.4625. For ^1H and ^{13}C nmr, diacetate, TMS, and Mosher esters, see Woo *et al.*[5]

C-21/22-Epoxides of goniopenin(6, 7)

Colorless oil; CIms *m/z* 621 (MH^+); ^1H nmr (500 MHz, $CDCl_3$) δ 7.19 [q, 1H, J = 1.5 Hz, H-35], 5.04 [qq, 1H, J = 7.0, 1.5 Hz, H-36], 3.93-3.82 [m, 5H, H-4, H-10, H-13, H-14, H-17], 3.46-3.40 [m, 1H, H-18], 2.95-2.87 [m, 2H, H-21, H-22], 2.50 [dddd, 1H, J = 15 , 8.0, 1.5, 1.1 Hz, H-3a], 2.39 [ddt, 1H, J = 15.0, 8.0, 1.4 Hz, H-3b], 2.04-1.92 [m, 4H, H-11a, H-12a, H-15a, H-16a], 1.85-1.22 [m, 45H], 0.88 [t, 3H, J = 7.0 Hz, H-34].

Cyclogoniodenin T (8)

Colorless oil, $[\alpha]_D$ +1.5 °(c 1.20, CH_2Cl_2), uv λ_{max} (EtOH) 223 nm (log ε, 6.0); ir ν_{max} (film) 3400, 2925, 2854, 1757, 1064 cm^{-1}; HRFABms (glycerol): found *m/z* 620.4730, calcd 620.4749. ^1H and ^{13}C nmr: see Tables 2 and 3, respectively.

*Cyclogoniodenin C (**13**)*

Colorless oil, $[\alpha]_D$ +0.6 °(c 1.00, CH_2Cl_2), uv λ_{max} (EtOH) 223 nm (log ε, 6.0); ir ν_{max} (film) 3400, 2925, 2854, 1756, 1059 cm^{-1}; HRFABms (glycerol): found 620.4730, calcd 620.4749. ^1H and ^{13}C nmr: see Tables 2 and 4, respectively.

*(S)- and -(R)-MTPA Esters of **1, 8** and **13***

Colorless oil. ^1H Nmr: see Tables 1, 3 and 4.

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