Goniotriocin and (2,4-*cis*- and -*trans*)-Xylomaticinones, Bioactive Annonaceous Acetogenins from *Goniothalamus giganteus*

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Goniotricin (**1**) and a mixture of (2,4-*cis* and -*trans*)-xylomaticinones (**2**), new bioactive annonaceous acetogenins, were isolated from the bark of *Goniothalamus giganteus* (Annonaceae) by activity-directed fractionation using the brine shrimp lethality test. Compound **1** is the first nonadjacent ring-hydroxylated bis-tetrahydrofuran (THF) acetogenin to be reported. Compound **2** is the *cis*- and *trans*-ketolactone mixture of xylomaticin, a known compound whose absolute stereochemistry has not been previously determined. The absolute stereochemistry of **2** was determined by the advanced Mosher's ester method. Both **1** and **2** showed significant and selective cytotoxicities among the six tumor cell lines in our seven-day MTT human solid tumor panel. In the yellow fever mosquito larvae microtiter assay, **1** was quite active, with an ED_{50} value of 3.5 μg/mL.

Goniothalamus giganteus Hook. f. et Thomas (Annonaceae) is a tropical tree widely distributed in southeast Asia. It has been called "black medicine" and has a reputation as a drug plant among the Malays.[1] Extracts of the bark, obtained from Thailand, showed toxicities in the brine shrimp lethality test (BST)[2,3] and showed murine toxicities in the 3PS (P-388) leukemia bioassay.[4] In previous work, a number of unusual styryllactones and 24 highly cytotoxic annonaceous acetogenins were isolated from this species and reported by our group.[5−7] The annonaceous acetogenins are a relatively new class of promising anticancer, antiinfective, and pesticidal natural compounds that are potent inhibitors of oxidative and substrate level ATP production.[8−10] Structurally, most of these C_{35}−C_{37} fatty acid derivatives may be classified into three major groups, that is, the mono-THF, adjacent bis-THF, and nonadjacent bis-THF subclasses.[8−10] Four acetogenins, found to date, bear tetrahydropyran (THP) rings[7,11,12] and extend the structural diversity of this class of compounds.

Continuing our search for novel antitumor agents, directed by the BST, we have now isolated, from the bark of this species, two additional bioactive acetogenins, goniotriocin (**1**), bearing the first hydroxylated ring of the nonadjacent bis-THF type, and a mixture of (2,4-*cis* and -*trans*)-xylomaticinones (**2**), the ketolactones of xylomaticin, which has been previously reported without determination of its absolute stereochemistry.[13] The absolute stereochemistry of **2** was determined by the advanced Mosher's ester method.[14,15]

Results and Discussion

Compound **1** was isolated as a white wax. Its molecular weight was suggested by the mass peak at *m/z* 637 $[MH]^+$ in the CIMS. The HRCIMS gave *m/z* 637.4672 for the $[MH]^+$ ion (calcd 637.4679), corresponding to the molecular formula $C_{37}H_{65}O_8$.

Compound **1** showed an IR carbonyl absorption at 1750 cm^{-1}, a UV (MeOH) λ_{max} at 217 nm (log ϵ, 3.32), the proton resonances at δ 7.18, 5.06, 3.84, 2.53, 2.40, and 1.44, and the carbon resonances at δ 174.6, 151.9, 131.1, 78.0, 69.9, and 19.1, all of which provided characteristic spectroscopic features for an α,β-unsaturated γ-lactone fragment with an OH-4 (see Table 1).[8−10]

Table 1. NMR Spectral Data (δ, $CDCl_3$) for **1**

proton/carbon	^{13}C NMR[a]	^1H NMR (*J* in Hz)
1	174.6	
2	131.1	
3a		2.53 m
3b	33.3	2.40 m
4	69.9	3.84 m
5	37.2	1.47 m
6−8	b	1.20−1.63
9	35.4	1.42 m, 1.52 m
10	79.3	3.88 m
11	32.4	1.60 m, 1.98 m
12	28.4	1.60 m, 1.98 m
13	81.9	3.75 q (7.0)
14	74.7	3.41 dt (2.0, 8.5)
15	b	1.28 m
16	b	1.81 m
17	82.7	3.80 dt (2.5, 7.0)
18	72.4	4.29 br q ($J = J' = J'' = 3.0$)
19a		2.22 dd (13.5, 6.0)
19b	41.2	1.77 m
20	73.4	4.62 dddd
21a		2.74 dd (15.5, 6.5)
21b	49.0	2.53 dd (15.5, 6.0)
22	209.6	
23	43.5	2.44 t (7.5)
24−31	b	1.20−1.63
32	31.9	1.20−1.63
33	22.6	1.20−1.63
34	14.1	0.88 t (7.0)
35	151.9	7.18 q (1.0)
36	78.0	5.06 qq (6.5, 1.5)
37	19.1	1.44 d (7.0)

[a] Assignments assisted by HMQC. [b] Signals observed at δ 23.6, 24.9, 25.5, 26.1, 29.1, 29.2, 29.3, 29.4, 29.5, 29.59, 29.60, and 29.63.

The presence of three OH groups in **1** was suggested by a prominent OH absorption at 3378 cm^{-1} in the IR spectrum and was confirmed by three successive losses of H_2O (*m/z* 18) from the $[MH]^+$ in the CIMS. A ketone group was identified by an IR absorption at 1718 cm^{-1}, a methylene triplet (J = 7.5 Hz) at δ 2.44 in the ^1H NMR spectrum, and a carbonyl signal at δ 209.6 in the ^{13}C NMR spectrum. A unique position for the keto group, that is, one carbon away from a THF ring, was proposed by COSY correlation cross peaks between δ 4.62 (later assigned to H-20) and two doublet of doublet protons at δ 2.74 (dd, 15.5, 6.5 Hz) (H-21a) and δ 2.53 (dd, 15.5, 6 Hz) (H-21b) (Table 1).

The presence in **1** of two THF rings with two associated hydroxyls was suggested by both the degree of unsaturation and by six oxymethine resonances between δ 72.4 and 82.7 in the ^{13}C NMR spectrum. Careful analysis of ^1H NMR,

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Table 2. ^{1}H NMR Spectral Data (δ, $CDCl_3$) for **2**, **2a**, and **2b**

	^{1}H NMR (*J* in Hz)				
proton	**2** cis	**2** trans	**2a**	**2b**	$\Delta\delta$**2a**−**2b**
1					
2	3.03 m	3.00 m			
3a	2.61 m	2.27 m			
3b	1.49 m	2.00 m			
4	4.40 dddd	4.55 dddd	4.38 cis	4.36 cis	+0.02
	(10.5, 7.5, 5.5, 5.3)	(8.5, 8.5, 5.5, 3.5)	4.54 trans	4.52 trans	+0.02
5a	1.62 m	1.58 m	1.60 cis, 1.54 trans	1.53 cis, 1.49 trans	+0.07, +0.05
5b	1.72 m	1.71 m	1.72 cis, 1.67 trans	1.69 cis, 1.64 trans	+0.03, +0.03
6−9	1.17−1.80				
10	3.59 m		5.05 m	5.00 m	*R*[a]
11−13	1.17−1.80				
14	1.43 m		1.55 m	1.54 m	+0.01
15	3.41 m		4.90 m	5.00 m	*R*[a]
16	3.80 m		3.90 m	4.00 m	−0.10
17e, 18e	1.68 m		1.36 m	1.56 m	−0.20
17a, 18a	2.00 m		1.64 m	1.92 m	−0.28
19	3.80 m		3.90 m	4.00 m	−0.01
20	3.41 m		4.96 m	5.00 m	*R*[a]
21	1.43 m		1.48 m	1.47 m	+0.01
22−33	1.17−1.80				
34	0.88 t (7.0)				
35a	2.61 dd (18.5, 8.5)	2.67 dd (19.0, 9.0)			
35b	3.10 dd (18.5, 3.5)	3.03 dd (9.0, 3.5)			
36					
37	2.20 s				

[a] Absolute configuration of carbinol centers.

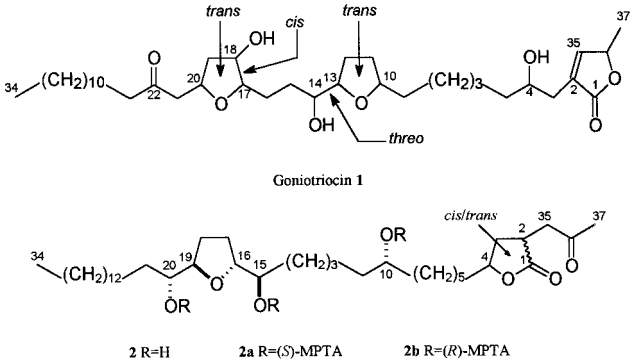

Figure 1. Chemical structures of **1**, **2**, **2a**, and **2b**.

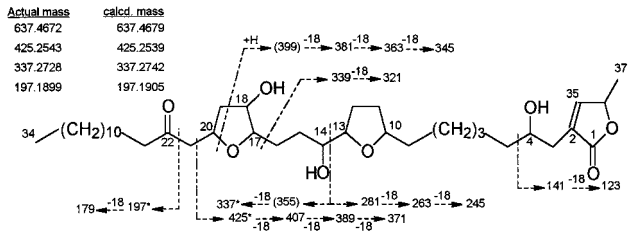

Figure 2. Diagnostic CIMS, and EIMS (*m*/*z*) fragments of **1**; ions in parentheses were not observed; * ions confirmed by HRCIMS or EIMS.

COSY, ^{13}C NMR, HMQC, and EIMS spectra led to the identification of one typical THF ring flanked by one hydroxyl group,[8−10] and another unusual nonadjacent hydroxylated ring THF without flanking hydroxyls was identified by COSY cross peaks between δ 3.80 (H-17) and two other protons at δ 4.29 (H-18) and δ 1.81 (H-16); by COSY cross peaks between δ 4.29 (H-18) and two other protons at δ 3.80 (H-17) and 1.77 (H-19b); also between δ 4.62 (H-20) and four other protons at δ 2.74 (H-21a), 2.53 (H-21b), 2.22 (H-19a), and 1.77 (H-19b); and by analyzing the *J* coupling patterns at δ 3.80 (td 7, J = 2.5 Hz) (H-17) and 4.29 (br quartet, J = 3 Hz) (H-18).

The placements of the two THF ring systems, the three hydroxyls, and the keto group of **1** along the aliphatic chain were determined based on the EIMS fragmentation pattern and the HREIMS of certain diagnostic peaks (Figure 2).

The relative stereochemistries at C-13/C-14 and across C-10/C-13 in the THF ring were determined as threo and trans, respectively, by comparing ^{1}H NMR and ^{13}C NMR data to those of the Cavé and Fujimoto models of known mono-THF relative stereochemistries.[16,17] To determine the relative stereochemistries across the second THF ring at C-17/C-20 and between C-17/C-18, a 2D NOESY experiment was conducted. Correlations between H-17 and H-18 and the lack of correlations between H-17 and H-20 indicated cis and trans configurations, respectively. Although negative NOESY results are generally indecisive, oxymethines on cis THF rings always have shown strong NOESY correlations in our experience. Thus, the structure of **1** was elucidated as illustrated (Figure 1), and it was named goniotriocin. Compound **1** is the second hydroxylated THF-bearing acetogenin and the first nonadjacent bis-THF acetogenin with a hydroxylated THF to be reported.[12] Insufficient material was available to permit preparations of Mosher's esters to solve the absolute stereochemistry of **1**.

The mixture of (2,4-*cis* and -*trans*)-xylomaticinones (**2**) was isolated in the form of an amorphous waxy powder. The molecular weight of **2** was indicated by a peak at *m*/*z* 625 for the $[MH]^+$ in the CIMS. The HRCIMS gave *m*/*z* 625.5061 (calcd 625.5043) for the $[MH]^+$ corresponding to the molecular formula $C_{37}H_{69}O_7$. The IR spectrum showed a strong absorption at 1756 cm^{-1} for a γ-lactone carbonyl and 1716 cm^{-1} for a ketone carbonyl. Compound **2** was transparent under UV light at 225 nm, suggesting that the lactone ring is not α,β-unsaturated. In comparison with (2,4-*cis* and -*trans*)-annomontacinones[5] and (2,4-*cis* and -*trans*)-gigantecinones,[6] the ^{1}H and ^{13}C NMR spectra of **2** clearly indicated the presence of a ketolactone moiety. In the ^{1}H NMR spectrum of **2** (Table 2), the resonances at δ 4.40 and 4.55, with combined integrations for one proton, were assigned to H-4 and suggested the presence of the mixture of (2,4-*cis* and -*trans*)-diastereoisomers, as is typical with these ketolactones.[8−10] In the ^{13}C NMR spectra (Table 3), signal pairs at δ 178.3 and 178.9, 43.8 and 44.2, 79.3 and 78.9, and 205.7 and 205.6 were assigned to C-1, C-35, C-4, and C-36, respectively, and also confirmed the presence of the mixture of (2,4-*cis* and -*trans*)-isomers. The assignments of the NMR signals for H-2, H3a, H3b,

Table 3. ^{13}C NMR Spectral Data (δ, $CDCl_3$) for **2**

carbon	**2** cis		**2** trans
1	178.3		178.9
2	34.4		36.7
3a, b		25.2−37.4	
4	79.3		78.9
5−9		25.2−37.4	
10		71.7	
11−14		25.2−37.4	
15		73.97[a]	
16		82.60[b]	
17−18		25.2−37.4	
19		82.66[b]	
20		74.04[a]	
21−31		25.2−37.4	
32		31.9	
33		22.6	
34		14.1	
35a, b	43.7		44.2
36	205.7		205.6
37		30.0	

[a,b] Signals are interchangeable.

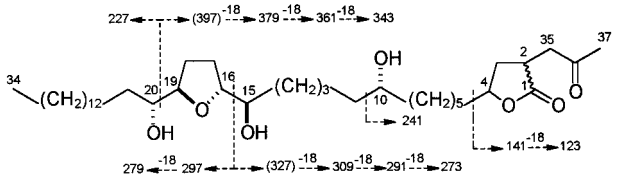

Figure 3. Diagnostic EIMS (m/z) fragments of **2**.

H-5a, H-5b, H-35a, and H-35b were based on the analysis of the COSY spectrum of **2**.

The remaining part of the structure of **2** exhibited identical ^1H and ^{13}C NMR signals for a long aliphatic chain bearing a mono-THF ring and three OH groups. The existence of the three OH moieties was indicated by an IR hydroxyl absorption at 3454 cm^{-1} and three successive losses of H_2O from the $[MH]^+$ in the CIMS. Furthermore, the ^{13}C NMR spectrum of **2** showed three resonances due to oxygen-bearing carbons at δ 71.7, 73.97, and 74.04, indicating the existence of three secondary hydroxyls. The presence of a mono-THF ring, with two OH groups flanking the ring, was suggested by proton resonances at δ 3.41 (H-15 and H-20) and 3.80 (H-16 and H-19) and the carbon signals at δ 82.60 (H-16) and 82.66 (H-19); these directly matched similar peaks of other mono-THF acetogenins[16] and of xylomaticin[13] and annonacin.[18] The carbon skeleton and placement of the ring and the three OH groups along the hydrocarbon chain were determined based on the EIMS spectral analysis of **2** (Figure 3).

The relative stereochemisties at C-15/C-16 and C-19/C-20 of **2** were determined to be threo, and the stereochemistry of the THF ring was determined as trans by comparing ^1H and ^{13}C NMR data to those of the Cavé and Fujimoto models.[16,17] The absolute stereochemistries of the carbinol centers of compound **2** were elucidated as C-10*R*, C-15*R*, C-16*R*, C-19*R*, and C-20*R* by using the advanced Mosher's ester methodology (Table 2).[14,15] Ketolactone annonaceous acetogenins are derived from the OH-4 α,β-unsaturated γ-lactone acetogenins through translactonization;[19,20] the absolute stereochemistry at C-4 is conserved after the reaction,[20] and, because all C-4 hydroxyl acetogenins found, so far, have the *R* stereochemistry at C-4,[8−10] the *R* configuration has been postulated for C-4 in **2**. Consequently, the structure of **2** is proposed as illustrated, and it was named (2,4-*cis* and -*trans*)-xylomaticinone, honoring the parent acetogenin, xylomaticin,[13] which has previously been found in *Xylopia aromatica*,[13] *Asimina longifolia*,[21] and *Goniothalamus giganteus*.[5] We, thus, suggest that xylomaticin, whose absolute stereochemistry has not been previously determined,[13] has the same absolute stereochemistry as that of (2,4-*cis* and -*trans*)-xylomaticinone (**2**) reported herein.

The biological activities of **1** and **2** are summarized in Table 4. These compounds were quite active in the BST.[2,3] Although **2** showed moderate activity in the yellow fever mosquito larvae (YFM) assay,[22] **1** was significantly more active, with an ED_{50} of 3.5 μg/mL. Both **1** and **2** also showed significant and selective cytotoxicities among the six human tumor cell lines in our seven-day MTT human solid tumor panel.[23−27] Both exhibited potent and selective cytotoxicities against the human breast adenocarcinoma (MCF-7)[24] and human colon adenocarcinoma (HT-29)[25] cell lines with 10−10 000 times the potency of Adriamycin.

All of the acetogenins tested so far decrease oxygen uptake in mitochondrial tests.[28,29] These results indicate that they act, at least in part, as potent inhibitors of ATP production via blocking at complex I in mitochondria.[30−32] In addition, they act as potent inhibitors of the plasma membrane NADH oxidase of cancerous cells; and this action decreases cytosolic ATP production.[33] The consequence of such ATP deprivation is apoptosis (programmed cell death).[34] Recently, we have shown that the acetogenins also inhibit cells that are multiple-drug resistant (MDR) due to ATP-dependent efflux mechanisms, and, thus, they offer a unique mechanism of action for cancer chemotherapy.[35−37] They are also very effective against pesticide-resistant German cockroaches, possibly by the same mechanism.[38]

Experimental Section

General Experimental Procedures. Optical rotations were determined on a Perkin−Elmer 241 polarimeter. IR spectra (film) were measured on a Perkin−Elmer 1600 FTIR spectrometer. UV spectra were obtained in MeOH on a Beckman DU 640 series spectrophotometer. ^1H NMR, $^1H-^1H$ COSY, and ^{13}C NMR spectra were obtained on a Varian VXR-500S spectrometer. LRMS data were collected on a Finnigan 4000 spectrometer. HRCIMS were performed on a Kratos MS50. HPLC separations were performed with a Rainin Dynamax solvent delivery system (model SD-200) using a Dynamax software system and a Si gel column (Dynamax 60-A 250 × 21 mm) equipped with a Dynamax absorbance detector (model UV-1) set at 225 nm. Analytical TLC was

Table 4. Biological Data for **1** and **2**

			cytotoxicity (ED_{50}, μg/mL)					
compound	BST[a] LC_{50} (μg/mL)	YFM[b] LC_{50} (μg/mL)	A-549[c]	MCF-7[d]	HT-29[e]	A-498[f]	PC-3[g]	PACA-2[h]
1	2.7	3.6	3.3×10^{-2}	3.3×10^{-5}	1.2×10^{-3}	1.1	2.6×10^{-1}	1.4
2	0.4	54.2	1.4×10^{-2}	7.6×10^{-4}	7.4×10^{-4}	1.2×10^{-1}	5.7×10^{-2}	7.4×10^{-2}
rotenone[i]	NT	0.3	NT	NT	NT	NT	NT	NT
adriamycin[j]	NT	NT	1.7×10^{-2}	2.1×10^{-1}	3.1×10^{-2}	1.9×10^{-2}	6.2×10^{-2}	2.3×10^{-2}

[a] Brine shrimp lethality test.[2,3] [b] Yellow fever mosquito larvae test.[22] [c] Human lung carcinoma.[23] [d] Human breast carcinoma.[24] [e] Human colon adenocarcinoma.[25] [f] Human kidney carcinoma.[23] [g] Human prostate adenocarcinoma.[26] [h] Human pancreatic carcinoma.[27] [i,j] Positive control standards; NT: not tested.

carried out on Si gel plates (0.25 mm), developed with $CHCl_3$−MeOH (9:1) and visualized with 5% phosphomolybdic acid in EtOH.

Bioassays. The bioactivities of extracts, fractions, and pure compounds were routinely assayed using a test for lethality to brine shrimp larvae.[2,3] The yellow fever mosquito larvae microtiter plate assay[22] was used to determine the relative pesticidal activities of compounds **1** and **2**; rotenone was used as the positive pesticidal control standard. In vitro cytotoxicities, against six human tumor cell lines, were carried out at the Purdue Cancer Center, Cell Culture Laboratory, using standard seven-day MTT assays for A-549 (human lung carcinoma),[23] MCF-7 (human breast carcinoma),[24] HT-29 (human colon adenocarcinoma),[25] A-498 (human kidney carcinoma),[23] PC-3 (human prostate adenocarcinoma),[26] and PACA-2 (human pancreatic carcinoma).[27] Adriamycin is always used as a positive antitumor control in the same runs.

Plant Material. The stem bark of *G. giganteus* (B-826538, PR-50604) was collected in Thailand in September 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 (10.7 kg) was ground into powder and percolated with 95% EtOH. The dry extract (900 g) (F001) was partitioned between H_2O and CH_2Cl_2 to give a H_2O layer (F002) and a CH_2Cl_2 layer. The residue of the CH_2Cl_2 layer (430 g) (F003) was partitioned between 90% MeOH and hexane, giving a MeOH layer (400 g) (F005) and a hexane layer (30 g) (F006). 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 open Si gel columns directed by the BST test, using gradients of hexane−Me_2CO, 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 waxy compounds **1** and **2**.

Preparation of Mosher's Esters. To an acetogenin (0.5−1 mg, in 0.5 mL of CH_2Cl_2) were sequentially added pyridine (0.1 mL), 4-(dimethylamino)pyridine (0.1 mg), and 15 mg of (*R*)-(−)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride. The mixture was stirred at room temperature from 4 h to overnight, checked with TLC to make sure that the reaction was complete, and passed through a disposable pipet (0.6 × 4 cm) containing Si gel (60−200 mesh) and eluted with 3 mL of CH_2Cl_2. The CH_2Cl_2 residue, dried in vacuo, was redissolved in 1% $NaHCO_3$ (5 mL) and H_2O (2 × 5 mL); the CH_2Cl_2 layer was dried in vacuo to give the (*S*)-Mosher esters. Using (*S*)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetyl chloride gave the (*R*)-Mosher esters. Both yields were typically higher than 90%. For partial ^{1}H NMR assignments of **2a** and **2b**, see Table 2.

Goniotriocin (1): white, waxy solid (2 mg); $[\alpha]^{23}_D$ +10.0° (*c* 0.03, $CHCl_3$); IR (film on NaCl plate) ν_{max} 3378, 2925, 2853, 1750, 1718, 1458, 1066; ^{1}H, ^{13}C NMR ($CDCl_3$), see Table 1; CIMS (isobutane) *m/z* 637 $[MH]^+$ (23), 619 $[MH - H_2O]^+$ (47), 601 $[MH - 2H_2O]^+$ (100), 583 $[MH - 3H_2O]^+$ (38); HRCIMS (isobutane) *m/z* 637.4672 for $C_{37}H_{65}O_8$ $[MH]^+$ (calcd 637.4679); EIMS see Figure 2.

(2,4-*cis* and *trans*)-Xylomaticinone (2): white, waxy solid (7 mg); $[\alpha]^{23}_D$ +26.2° (*c* 0.08, $CHCl_3$); IR (film on NaCl plate) ν_{max} 3454, 2916, 2848, 1756, 1716, 1470, 1070; ^{1}H, ^{13}C NMR ($CDCl_3$), see Tables 2 and 3; CIMS (isobutane) *m/z* 625 $[MH]^+$ (100), 607 $[MH - H_2O]^+$ (35), 589 $[MH - 2H_2O]^+$ (73), 571 $[MH - 3H_2O]^+$ (14); HRCIMS (isobutane) *m/z* 625.5061 for $C_{37}H_{69}O_7$ $[MH]^+$ (calcd 625.5043); EIMS see Figure 3.

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