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NATURAL ACETOGENINS FROM ANNONACEAE, SYNTHESIS AND MECHANISMS OF ACTION

IN HONOUR OF THE RETIREMENT OF PROFESSOR ANDRÉ CAVÉ§

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Key Word Index—Annonaceae; linear, epoxy, mono- and bis-tetrahydrofuranic acetogenins; miscellaneous acetogenins; total synthesis; biological activity; mechanism of action.

Abstract—The search concerning Annonaceous acetogenins has increased in the last two years. The goal of the present review is to summarize the knowledge about new isolated acetogenins as well as the advances in synthesis, biological activity and mechanism of action.

INTRODUCTION

Since our last review was published [1], research in the field of Annonaceous acetogenins dealing with the isolation, structural elucidation, hemisynthesis or total synthesis, and mechanism of the cytotoxic action, has evidenced a rapid increase. In fact, to the 128 compounds then reviewed, a total of 113 new acetogenins enlarged the list of isolated compounds.

Thus, the primary aim of this review is to bring up-to-date, in graphical form, those data with the compounds described during the period from June 1995–June 1997, together with their origin and literature references. The classification is made following the same criteria and based on the structural characteristics shown in Fig. 1. Three new subgroups of acetogenins are presented, characterized by a different type of side chain: (T-G.1) (T-G.2) and (T-H). In addition, a new type of γ-lactone moiety (L-D) characterized by a γ-hydroxy-γ-methyl unsaturated-γ-lactone ring is included.

As in our previous reviews [1–5] we discuss, by considering the spectral data, several uncertain aspects on compounds described as new acetogenins. Within the tables, compounds are presented according to the chronological order of discovery. For a complete revision, both new and previously published data are reported. To improve the comprehension of the tables, only identical compounds with different names, but isolated at the same time (linked by 'or'), are maintained, for the acetogenins referred therein [1]. The great number of compounds to be added made necessary the inclusion of new subgroups but their number listed in the previous review are maintained with only one exception. Because of the subdivision of adjacent bis-THF acetogenins, in α,α'-dihydroxylated (Table 6) and α-monohydroxylated (Table 7), numbers of compounds included as panalicin type have been changed (type **15** in [1] and here considered as type **14b**). The additional new compounds are given underlined. The reliable number of acetogenins must be considered as 241 so far, 15 of them being linear, 14 epoxy, 113 mono-THF, 94 bis-THF, and 5 other acetogenins that we include in a miscellaneous group (see Tables 1–10).

Table 11 summarizes the botanical sources from which new acetogenins have been isolated independently their further isolation from other Annonaceous species. Three new genera, *Polyalthia*, *Porcelia* and *Disepalum*, were found to contain acetogenins. In Table 12 the acetogenins cited in this review are listed in alphabetical order. A survey on the last two years advances in the total synthesis, and the biological activities of acetogenins, is included.

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§ Two of the authors (B.F. and D.C.) want to express their gratitude to Prof. André Cavé for transmitting his knowledge and passion in the world of Natural Products.

*** Types of THF and THP α-hydroxylated systems:**

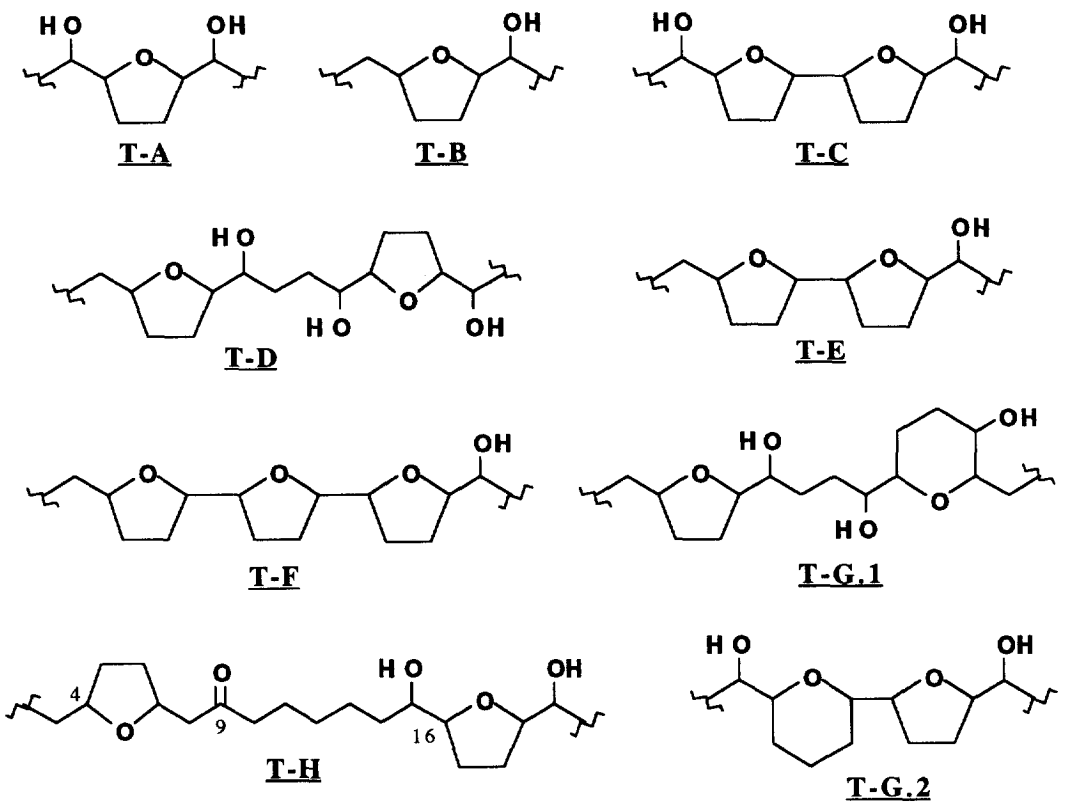


Fig. 1. Tetrahydrofuran (THF), tetrahydropyran (THP), γ-lactone and epoxy systems in Annonaceous acetogenins.

LINEAR ACETOGENINS

The isolated natural linear acetogenins, claimed as the biogenetic precursors of epoxy- and THF-acetogenins, differ in the degree of unsaturation and hydroxylation of their alkyl chain. We can consider here three subgroups [1, 6–13] (Table 1).

(i) Vicinal dihydroxylated and olefinic acetogenins (**1a**: giganin type) are the most abundant subgroup, which include eight compounds. They are characterized by the presence of a vicinal diol and, with the only exception of tonkinelin (**1.6**), by one or two double bonds. In all of these acetogenins a *cis*-geometry for the double bond and a *threo* relative configuration at the vicinal diol has been established.

Cohibins-A (**1.8**) and B (**1.9**) were obtained as a mixture and their structures established by MS/MS spectrometry [10]. Venezinone (**1.10**), with a 2-acetonyl saturated γ-lactone moiety (L-B), was described as a classical mixture of two 2,4-*cis* and 2,4-*trans* isomers. This can be rationalized by trans-lactonization of acetogenins possessing an OH at C-4 [14, 15], giving the pair of compounds currently named 'iso'-acetogenins, as mentioned below in the chapters of mono- and bis-THF actogenins.

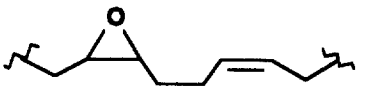
(ii) Hydroxylated (or ketonic) linear acetogenins (**1b**: reticulatamol type) in which the saturated hydrocarbon chain is substituted by one or more non-vicinal hydroxyl groups (or ketone group).

(iii) Olefinic and acetylenic acetogenins (**1c**: muridienin-1 type) without hydroxyl groups on the alkyl chain. Two non classical linear acetogenins, isolated from the Brazilian Annonaceae *Porcelia macrocarpa*, have been described here. Their structures are characterized by a short alkyl chain with a triple bond, bearing a terminal saturated β-hydroxy γ-methyl γ-lactone (L-C) [13]. It is the first report on acetogenins with an acetylenic side chain and without a C_{35}/C_{37} but a C_{25} skeleton. A biogenetic pattern involving Claisen condensation of a C_{22} fatty acid with pyruvic acid is proposed for **1.14** and **1.15** [13].

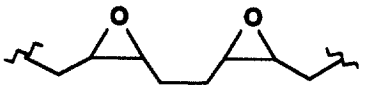
EPOXY ACETOGENINS

In the group of epoxy-acetogenins (Table 2), only epomusenins-A and B (**2.4** and **2.5**) [16], two mono-epoxy and olefinic compounds obtained as a mixture, are added. As we have described above, epoxy-acetogenins, originating by oxidation of linear and

*** Types of epoxy rings:**



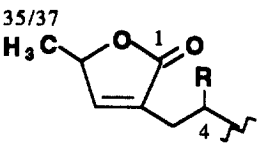
E-A



E-B

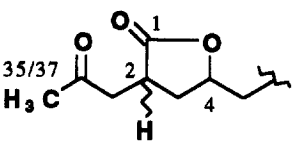
E-C

*** Types of γ-lactone rings:**

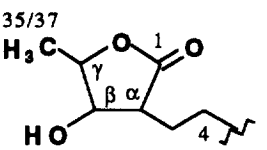


L-A

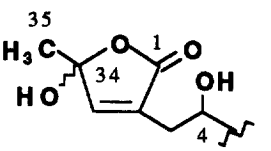
(R= H or OH)



L-B



L-C



L-D

Fig. 1. (continued).

olefinic acetogenins, are key metabolites in the biosynthesis of mono-, bis- or tri-THF acetogenins [5, 17, 18]. Their absolute configurations remain unknown and only recently, the total synthesis of (15*S*,16*R*,19*S*,20*R*,34*S*)-diepomuricanin [19] led the authors to consider that the synthesized compound should be the natural diepomuricanin-A (**3.1**).

MONO-THF ACETOGENINS

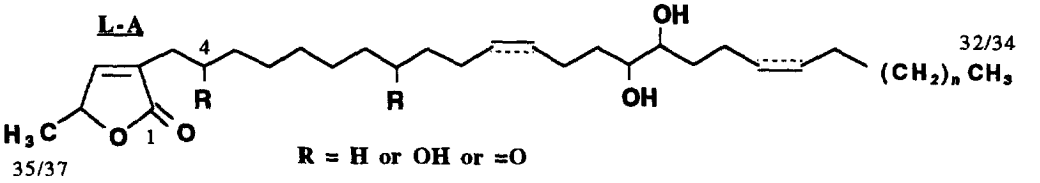
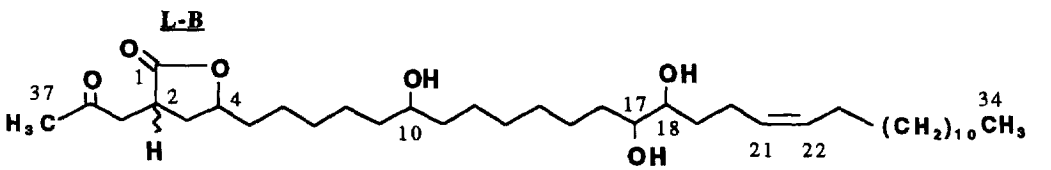
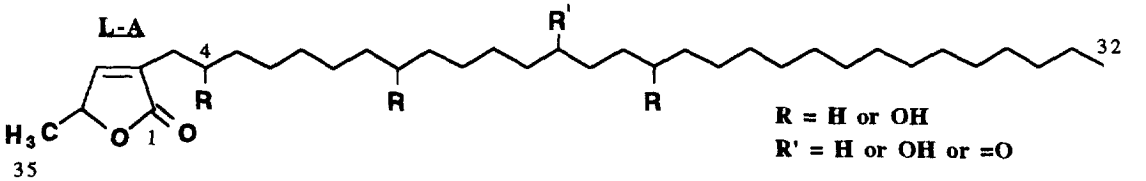
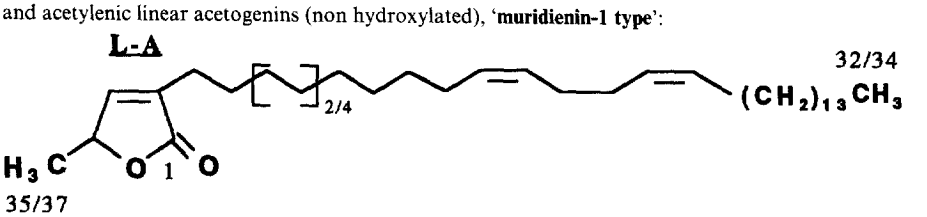
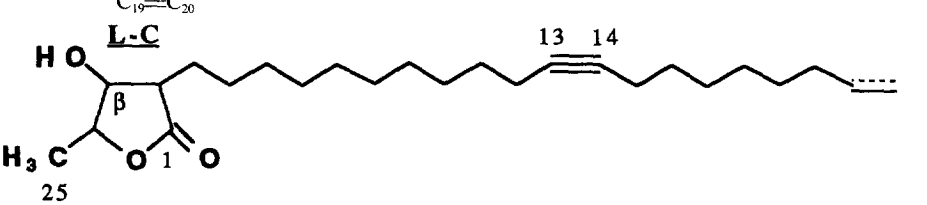
Mono-THF-α,α′-dihydroxylated acetogenins

They represent the most important subclass of mono-THF acetogenins. In the last two years a total of 40 new compounds have been described [1, 20–41] (Table 3), including two dihydroxylated (type **5**), nine trihydroxylated and dihydroxylated ketonic (type **6**), twenty one tetrahydroxylated and trihydroxylated ketonic (type **7**) and eight polyhydroxylated and tetrahydroxylated ketonic (type **8**) acetogenins. A subdivision in two groups is presented herein for the tetrahydroxylated and trihydroxylated ketonic acetogenins (type **7**) according to either the presence or the absence of a hydroxyl substituent at the C-4 position.

Although a *threo/trans/threo* or *threo/trans/erythro* relative configuration had been established for all the mono-THF-α,α′-dihydroxylated acetogenins [1–4] in this period, several acetogenins with a *threo/cis/threo* relative configuration have been reported (**6.5**, **6.7**, **7.19–7.21** compounds). The *cis* configuration was assigned by the chemical shifts observed for the two methylene protons at the THF system. Authors only argued this configuration by comparing these δ values with those observed for synthetic models: δ 1.66 and δ 1.98 in the *trans* THF, and δ 1.74 and δ 1.93 in the *cis* THF [42]. In addition, the *erythro/trans/threo* relative configuration was described for the first time for the mono-THF-α,α′dihydroxylated acetogenin, uvarigranin (**6.9**).

Two pairs of compounds, arianacin+javoricin,

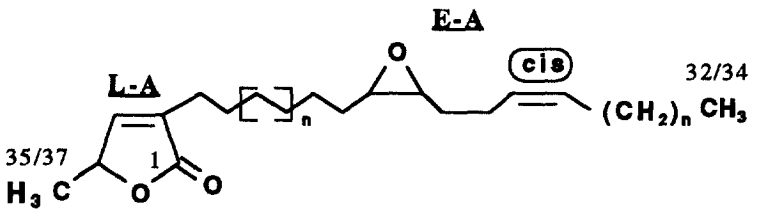
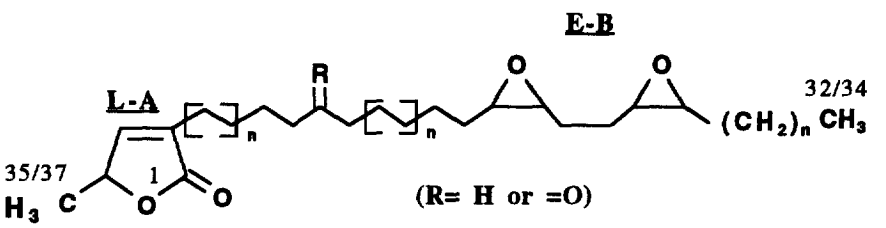
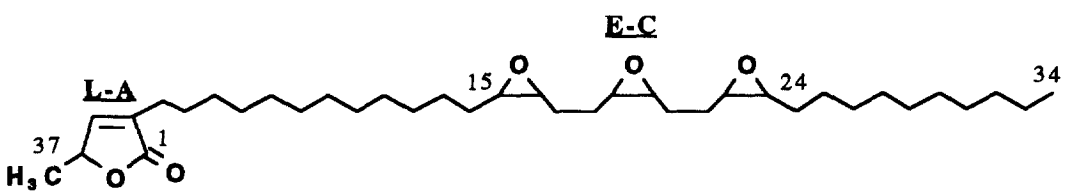
Table 1. Acetogenins without tetrahydrofuran rings: linear acetogenins

		Olefinic position	Hydroxyl positions	Relative configuration*	Molecular formula	M^+	Annonaceae species** [Ref.]
			I. Linear acetogenins				
1a. Vicinal dihydroxylated and olefinic linear acetogenins, '**giganin type**':							
							
		L-A					
		35/37	**R = H or OH or =O**				
1.1	giganin	C_{13}=C_{14}	4,10,17,18	*c-th*	$C_{35}H_{64}O_6$	580	*G. giganteus* [1, 6]
1.2	venezenin	C_{21}=C_{22}	4,17,18 (CO,10)	*th-c*	$C_{37}H_{66}O_6$	606	*X. aromatica* [1]
1.5	coriadienin	C_{13}=C_{14}; C_{17}=C_{18}	4,10,21,22	*c-c-th*	$C_{37}H_{66}O_6$	606	*A. coriacea* [7]
1.6	tonkinelin	—	17,18	*th*	$C_{37}H_{70}O_4$	578	*U. tonkinesis* [8]
1.7	montecristin	C_{17}=C_{18}; C_{21}=C_{22}	13,14	*th-c-c*	$C_{37}H_{66}O_4$	574	*A. muricata* [9]
1.8	cohibin-A	C_{19}=C_{20}	15,16	*th-c*	$C_{35}H_{64}O_4$	548	*A. muricata* [10]
1.9	cohibin-B	C_{17}=C_{18}	13,14	*th-c*	$C_{35}H_{64}O_4$	548	*A. muricata* [10]
							
		L-B					
1.10	venezinone	C_{21}=C_{22}	10,17,18	*th-c*	$C_{37}H_{68}O_6$	608	*X. aromatica* [11]
1b. Hydroxylated (or ketonic) linear acetogenins, '**reticulatamol type**':							
							
		L-A	**R = H or OH** **R' = H or OH or =O**				
		35					
1.3	reticulatamol	—	15	—	$C_{35}H_{66}O_3$	534	*A. reticulata* [1]
1.4	reticulatamone	—	(CO,15)	—	$C_{35}H_{64}O_3$	532	*A. reticulata* [1]
1.11	longanin	—	4,10,18	—	$C_{35}H_{66}O_5$	566	*As. longifolia* [6]
1c. Olefinic and acetylenic linear acetogenins (non hydroxylated), '**muridienin-1 type**':							
							
		L-A					
		35/37					
1.12	muridienin-1	C_{13}=C_{14}; C_{17}=C_{18}		*c-c*	$C_{35}H_{62}O_2$	514	*A. muricata* [12]
1.13	muridienin-2	C_{15}=C_{16}; C_{19}=C_{20}		*c-c*	$C_{37}H_{66}O_2$	542	*A. muricata* [12]
							
		L-C					
		25					
1.14	butyrolactone-1	C_{21}=C_{22}		—	$C_{25}H_{42}O_3$	390	*P. macrocarpa* [13]
1.15	butyrolactone-2	—		—	$C_{25}H_{44}O_3$	392	*P. macrocarpa* [13]

* *th*: *threo*; *c*: *cis*.

** *G*: *Goniothalamus*; *X*: *Xylopia*; *A*: *Annona*; *U*: *Uvaria*; *As*: *Asimina*; *P*: *Porcelia*.

Table 2. Acetogenins without tetrahydrofuran rings: epoxy-acetogenins

		Olefinic position	Epoxy positions	Molecular formula	M^+	Annonaceae species* [Ref.]
	II. Epoxy-acetogenins					
2. Mono-epoxy olefinic, '**epoxymurin-A type**':						
						
2.1	epoxymurin-A or epomuricenin-A	C_{19}=C_{20}	15,16	$C_{35}H_{62}O_3$	530	*A. muricata* [1]
						A. muricata [1]
2.2	epoxymurin-B	C_{15}=C_{16}	19,20	$C_{35}H_{62}O_3$	530	*A. muricata* [1]
2.3	epomuricenin-B	C_{17}=C_{18}	13,14	$C_{35}H_{62}O_3$	530	*A. muricata* [1]
2.4	epomusenin-A	C_{21}=C_{22}	17,18	$C_{37}H_{66}O_3$	558	*R. mucosa* [16]
2.5	epomusenin-B	C_{19}=C_{20}	15,16	$C_{37}H_{66}O_3$	558	*R. mucosa* [16]
3. Bis-epoxy, '**diepomuricanin-A type**':						
						
3.1	diepomuricanin-A	—	15,16,19,20	$C_{35}H_{62}O_4$	546	*A. muricata* [1]
3.2	corepoxylone	(C=O,10)	15,16,19,20	$C_{35}H_{60}O_5$	560	*A. muricata* [1]
3.3	dieporeticanin-1	—	17,18,21,22	$C_{37}H_{66}O_4$	574	*A. reticulata* [1]
3.4	dieporeticanin-2	—	19,20,23,24	$C_{37}H_{66}O_4$	574	*A. reticulata* [1]
3.5	dieporeticenin	C_{23}=C_{24}	15,16,19,20	$C_{37}H_{64}O_4$	572	*A. reticulata* [1]
3.6	diepoxymontin	—	11,12,13,14	$C_{35}H_{62}O_4$	546	*A. montana* [1]
3.7	diepomuricanin-B	—	17,18,21,22	$C_{35}H_{62}O_4$	546	*R. membranacea* [1]
3.8	diepoxyrollin	—	15,16,19,20	$C_{37}H_{66}O_4$	574	*R. membranacea* [1]
4. Tri-epoxy, '**tripoxyrollin type**':						
						
4.1	tripoxyrollin	—	15,16,19,20,23,24	$C_{37}H_{64}O_5$	588	*R. membranacea* [1]

* *A.*: *Annona*; *R*: *Rollinia*.

(**7.22**) and rollinecins-A+B (**7.23**) are claimed as 12 and 14-epimers, respectively, based only in an invaluable difference in their ^{1}H-NMR spectral data. The difference between arianacin and javoricin was established by the proton resonance of the methine at C-12, δ 3.63 and δ 3.60, respectively [29]. For rollinecins-A and B the methine resonances at C-14 were δ 3.63/3.62 and δ 71.72/71.90 in the ^{1}H-NMR and ^{13}C-NMR [30]. A similar difference was described for gigantransenins-A+B (**7.34**), reported as 23-epimers because of a difference of 0.02 ppm was observed between both H-23 [36]. In our opinion, these very minor differences in spectral shifts are insufficient, so far, to consider those compounds as different acetogenins.

Surprisingly, a methine resonance at δ 86.2 (C-16)

Table 3. Mono-THF α,α′-dihydroxylated γ-lactone acetogenins

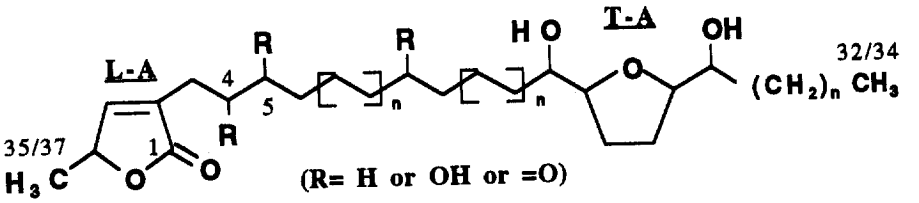
		Hydroxyl positions	THF-relative configuration*	Molecular formula	M^+	Annonaceae species* [Ref.]
III. Mono-THF α,α′-dihydroxylated acetogenins						
						
5. Dihydroxylated, '**uvariamicin-I type**':						
5.1	uvariamicin-I	15,20	*th/t/th*	$C_{37}H_{68}O_5$	592	*U. narum* [1]
5.2	uvariamicin-II or reticulatacin	17,22	*th/t/th*	$C_{37}H_{68}O_5$	592	*U. narum* [1] *A. reticulata* [1]
5.3	uvariamicin-III	19,24	*th/t/th*	$C_{37}H_{68}O_5$	592	*U. narum* [1]
5.4	solamin	15,20	*th/t/th*	$C_{35}H_{64}O_5$	564	*A. muricata* [1]
5.5	uvariamicin-IV	13,18	*th/t/th*	$C_{37}H_{68}O_5$	592	*A. bullata* [1]
5.6	bullatencin (C_{23}=C_{24})	15,20	*th/t/th*	$C_{37}H_{66}O_5$	590	*A. bullata* [1]
5.7	reticulatain-1	17,22	*th/t/er*	$C_{37}H_{68}O_5$	592	*A. reticulata* [1]
5.8	reticulatain-2	19,24	*th/t/er*	$C_{37}H_{68}O_5$	592	*A. reticulata* [1]
5.9	annotemoyin-1	17,22	*th/t/th*	$C_{35}H_{64}O_5$	564	*A. atemoya* [20]
5.10	annotemoyin-2	17,22	*th/t/er*	$C_{35}H_{64}O_5$	564	*A. atemya* [20]
6. Trihydroxylated and dihydroxylated ketonic, '**murisolin type**':						
6.1	murisolin	4,15,20	*th/t/th*	$C_{35}H_{64}O_6$	580	*A. muricata* [1]
6.2	corossolin	10,15,20	*th/t/th*	$C_{35}H_{64}O_6$	580	*A. muricata* [1]
6.3	corossolone (C=O,10)	15,20	*th/t/th*	$C_{35}H_{62}O_6$	578	*A. muricata* [1]
6.4	giganenin (C_9=C_{10})	13,18,21	*th/t/th*	$C_{37}H_{66}O_6$	606	*G. giganteus* [1]
6.5	asiminenin-A (C_{23}=C_{24})	4,15,20	*th/c/th*	$C_{37}H_{66}O_6$	606	*As. triloba* [21]
6.6	asiminenin-B (C_{23}=C_{24})	4,15,20	*th/t/th*	$C_{37}H_{66}O_6$	606	*As. triloba* [21]
6.7	*cis*-murisolin	4,15,20	*th/c/th*	$C_{35}H_{64}O_6$	580	*As. triloba* [22]
6.8	murisolin-A	4,15,20	*th/t/er*	$C_{35}H_{64}O_6$	580	*As. triloba* [22]
6.9	uvarigranin	15,OAc-17,22	*er/t/th*	$C_{39}H_{70}O_7$	650	*U. grandiflora* [23]
6.10	tonkinecin	5,17,22	*th/t/th*	$C_{37}H_{68}O_6$	608	*U. tonkinesis* [24]
6.11	longifolicin	10,13,18	*th/t/th*	$C_{35}H_{64}O_6$	580	*As. longifolia* [25]
6.12	longicoricin	10,15,20	*th/t/th*	$C_{37}H_{68}O_6$	608	*As. longifolia* [25]
6.13	4-deoxyannomontacin	10,17,22	*th/t/th*	$C_{37}H_{68}O_6$	608	*G. giganteus* [26]
7. Tetrahydroxylated and trihydroxylated ketonic:						
7a-with OH in 4 '**annonacin type**':						
7.1	annonacin	4,10,15,20	*th/t/th*	$C_{35}H_{64}O_7$	596	*A. densicoma* [1]
7.2	goniothalamicin	4,10,13,18	*th/t/th*	$C_{35}H_{64}O_7$	596	*G. giganteus* [1]
7.3	annonacinone (C=O,10)	4,15,20	*th/t/th*	$C_{35}H_{62}O_7$	594	*A. densicoma* [1]
7.4	annonacin-A	4,10,15,20	*th/t/er*	$C_{35}H_{64}O_7$	596	*A. squamosa* [1]
7.5	annomontacin	4,10,17,22	*th/t/th*	$C_{37}H_{68}O_7$	624	*A. montana* [1]
7.6	annoreticuin	4,9,15,20	*th/t/th*	$C_{35}H_{64}O_7$	596	*A. reticulata* [1]
7.7	annoreticuinone (C=O,9)	4,15,20	*th/t/th*	$C_{35}H_{62}O_7$	594	*A. reticulata* [1]
7.8	xylopianin	4,8,15,20	*th/t/th*	$C_{35}H_{64}O_7$	596	*X. aromatica* [1]
7.9	xylopiacin	4,8,15,20	*th/t/th*	$C_{37}H_{68}O_7$	624	*X. aromatica* [1]
7.10	xylomaticin	4,10,15,20	*th/t/th*	$C_{37}H_{68}O_7$	624	*X. aromatica* [1]
7.11	reticulacinone (C=O,11)	4,15,20	*th/t/th*	$C_{35}H_{62}O_7$	594	*A. reticulata* [1]
7.12	squamosten-A (C_{23}=C_{24})	4,12,15,20	*th/t/th*	$C_{37}H_{66}O_7$	622	*A. squamosa* [1]
7.13	gonionenin (C_{21}=C_{22})	4,10,13,18	*th/t/th*	$C_{37}H_{66}O_7$	622	*G. giganteus* [1]
7.14	xylopien (C_{23}=C_{24})	4,8,15,20	*th/t/th*	$C_{37}H_{66}O_7$	622	*X. aromatica* [1]
7.15	xylomatenin (C_{23}=C_{24}) or annogalene	4,10,15,20	*th/t/th*	$C_{37}H_{66}O_7$	622	*X. aromatica* [1] *A. senegalensis* [1]
7.16	annosenegalin	4,10,15,20	*th/t/er*	$C_{37}H_{68}O_7$	624	*A. senegalensis* [1]
7.17	longicin	4,10,13,18	*th/t/er*	$C_{35}H_{64}O_7$	596	*As. longifolia* [27]
7.18	annomutacin	4,10,17,22	*th/t/er*	$C_{37}H_{68}O_7$	624	*A. muricata* [28]
7.19	*cis*-annonacin	4,10,15,20	*th/c/th*	$C_{35}H_{64}O_7$	596	*A. muricata* [29]
7.20	*cis*-annonacinone (C=O,10)	4,15,20	*th/c/th*	$C_{35}H_{62}O_7$	594	*A. muricata* [29]

Table 3. (continued)

		Hydroxyl positions	THF-relative configuration*	Molecular formula	M^-	Annonaceae species* [Ref.]
7.21	*cis*-goniothalamicin	4,10,13,18	*th/c/th*	$C_{35}H_{64}O_7$	596	*A. muricata* [29]
7.22	arianacin + javoricin†	4,12,15,20	*th/t/th*	$C_{35}H_{64}O_7$	596	*A. muricata* [29]
7.23	rollinecins-A + B†	4,14,17,22	*th/t/er*	$C_{37}H_{68}O_7$	624	*R. mucosa* [30]
7.24	4-acetylannonacin	OAc-4,10,15,20	*th/t/th*	$C_{37}H_{66}O_8$	638	*As. longifolia* [31]
7.25	4-acetylxylomaticin	OAc-4,10,15,20	*th/t/th*	$C_{39}H_{70}O_8$	666	*As. longifolia* [31]
7.26	disepalin	4,10,15,OAc-20	*th/t/th*	$C_{39}H_{70}O_8$	666	*D. anomalum* [32]
7.27	mosin-B (C=O,9)	4,15,20	*th/t/er*	$C_{35}H_{62}O_7$	594	*A. squamosa* [33]
7.28	mosin-C (C=O,9)	4,15,20	*th/c/th*	$C_{35}H_{62}O_7$	594	*A. squamosa* [33]
7b-without OH in 4 '**plagionicin-A type**':						
7b.1	plagionicin-A	5,10,15,20	*th/t/th*	$C_{35}H_{64}O_7$	596	*P. plagioneura* [34]
7b.2	tonkinin-A (C=O,5)	15,17,22	*th/t/er*	$C_{37}H_{66}O_7$	622	*U. tonkinesis* [35]
7b.3	tonkinin-B (C=O,5)	15,17,22	*th/t/th*	$C_{37}H_{66}O_7$	622	*U. tonkinesis* [35]
7b.4	tonkinin-C (C=O,5)	15,OAc-17,22	*th/t/er*	$C_{39}H_{68}O_8$	664	*U. tonkinesis* [35]
7b.5	tonkinesin-A	5,15,17,22	*th/t/er*	$C_{37}H_{68}O_7$	624	*U. tonkinesis* [35]
7b.6	tonkinesin-B	5,15,17,22	*th/t/th*	$C_{37}H_{68}O_7$	624	*U. tonkinesis* [35]
7b.7	tonkinesin-C	5,15,OAc-17,22	*th/t/er*	$C_{39}H_{70}O_8$	666	*U. tonkinesis* [35]
7b.8	gigantransenins-A + B† (C_{21}=C_{22})	10,13,18,23	*th/t/th*	$C_{37}H_{66}O_7$	622	*G. giganteus* [36]
7b.9	gigantransenin-C (C_{22}=C_{23})	10,13,18,21	*th/t/th*	$C_{37}H_{66}O_7$	622	*G. giganteus* [36]
8. Polihydroxylated and tetrahydroxylated ketonic, '**annomonicin type**':						
8.1	annomonicin	4,8,13,15,20	*th/t/th*	$C_{35}H_{64}O_8$	612	*A. montana* [1]
8.2	montanacin	4,8,13,19,24	*th/t/th*	$C_{37}H_{68}O_8$	640	*A. montana* [1]
8.3	8-hydroxyannonacin	4,8,10,15,20	*th/t/th*	$C_{35}H_{64}O_8$	612	*A. densicoma* [1]
8.4	annomuricin-A	4,10,11,15,20	*th-th/t/er*	$C_{35}H_{64}O_8$	612	*A. muricata* [1]
8.5	annomuricin-B	4,10,11,15,20	*er-th/t/er*	$C_{35}H_{64}O_8$	612	*A. muricata* [1]
8.6	muricatin-C (C=O,10)	4,15,20,25	*th/t/th*	$C_{35}H_{62}O_8$	610	*A. muricata* [1]
8.7	muricatocin-A	4,10,12,15,20	ps *er-th/t/th*	$C_{35}H_{64}O_8$	612	*A. muricata* [37]
8.8	muricatocin-B	4,10,12,15,20	ps *er-th/t/er*	$C_{35}H_{64}O_8$	612	*A. muricata* [37]
8.9	muricatocin-C	4,10,12,15,20	ps *th-th/t/er*	$C_{35}H_{64}O_8$	612	*A. muricata* [38]
8.10	annomuricin-C	4,10,11,15,20	*th-th/t/th*	$C_{35}H_{64}O_8$	612	*A. muricata* [38]
8.11	annohexocin	4,8,10,12,15,20	*th/t/er*	$C_{35}H_{64}O_9$	628	*A. muricata* [39]
8.12	muricatalicin	4,7,13,15,20	*th/t/th*	$C_{35}H_{64}O_8$	612	*A. muricata* [40]
8.13	coriheptocin-A	4,7,12,14,16,19,20	*er/t/th*-an-*th*	$C_{35}H_{64}O_{10}$	644	*A. coriacea* [41]
8.14	coriheptocin-B	4,7,12,14,16,19,20	*th/t/th*-an-*th*	$C_{35}H_{64}O_{10}$	644	*A. coriacea* [41]

* *th*: *threo*; *er*: *erythro*; *t*: *trans*; *c*: *cis*; *ps*: *pseudo*; *an*: *anti*.

** *U.*: *Uvaria*; *A.*: *Annona*; *G.*: *Goniothalamus*; *As.*: *Asimina*; *X.*: *Xylopia*; *P.*: *Polyalthia*; *R.*: *Rollinia*; *D.*: *Disepalum*.

† (**7.22**): 12-epimer for the authors [29]; (**7.23**): 14-epimer for the authors [30]; (**7b.8**): 23-epimer for the authors [36].

was given for annohexocin (**8.11**) and a *threo/trans/erythro* relative configuration established [39]. This value must be erroneously reported because in mono-THF-α,α′-dihydroxylated acetogenins with this classical configuration a chemical shift value near to δ 83 has been traditionally assigned [2].

Mono-THF-α-monohydroxylated acetogenins

This subclass is represented by two groups including 4-hydroxylated acetogenins (**9a**: gigantetrocin-A type) and compounds without a 4-hydroxyl group (**9b**: gigantriocin type) [1, 43–50] (Table 4). For gigantetrocin-B (**9.6**), muricatetrocins-A + B (**9.7**), murihexocins-A + B (**9.12**) and annopentocins-A + B (**9.14**), reported as mono- or diepimers (see footnotes to Table 4), the same critical comments made above can be applied because of the very minor differences observed in their ^{1}H NMR spectral data.

Muricatalin (**9.13**) was reported as an unusual acetogenin with two vicinal diols at 14/15 and 17/18 positions, separated only by a methylene carbon [45]. This structure needs to be revised because, in our opinion, it is given without solid proof and, on the other hand, this unusual substitution is biogentically unlikely.

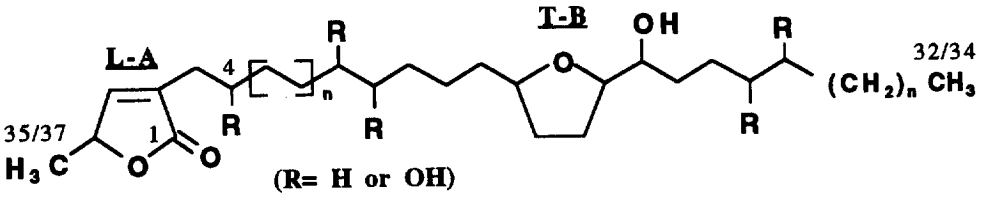
Mono-THF acetogenins with a L-B, L-C or L-D lactone moieties

In the last two years the number of 'iso' mono-THF acetogenins (**10**: isoannonacin type) has been duplicated [1, 26–28, 33, 46, 51–55] (Table 5). All

Table 4. Mono-THF α-monohydroxylated γ-lactone acetogenins

		Hydroxyl positions	THF and diols relat. config.*	Molecular formula	M^+	Annonaceae species** [Ref.]

IV. Mono-THF α-monohydroxylated acetogenins



9. THF α-monohydroxylated:

9a-with OH in 4 '**gigantetrocin-A type**':

9.1	gigantetrocin-A	4,14,17,18	*t/th-th*	$C_{35}H_{64}O_7$	596	*G. giganteus* [1]
9.3	densicomacin-1	4,14,17,18	*t/er-th*	$C_{35}H_{64}O_7$	596	*A. densicoma* [1]
9.4	gigantetronenin (C_{21}=C_{22})	4,14,17,18	*t/th-th*	$C_{37}H_{66}O_7$	622	*G. giganteus* [1]
9.6	gigantetrocin-B†	4,14,17,18	*t/th-th*	$C_{35}H_{64}O_7$	596	*A. muricata* [1]
9.7	muricatetrocins-A + B‡	4,16,19,20	*t/er* or *th-th*	$C_{35}H_{64}O_7$	596	*A. muricata* [1]
9.8	senegalene (C_{29}=C_{30})	4,12,13,21	*th-t/th*	$C_{37}H_{66}O_7$	622	*A. senegalensis* [1]
9.9	muricatin-A	4,14,17,18,23	*t/th-th*	$C_{35}H_{64}O_8$	612	*A. muricata* [1]
9.10	muricatin-B	4,14,17,18,19	*t/th-th/er*	$C_{35}H_{64}O_8$	612	*A. muricata* [1]
9.11	coriacin (C_{17}=C_{18})	4,14,21,22	*t/th-th*	$C_{37}H_{66}O_7$	622	*A. coriacea* [43]
9.12	murihexocins-A + B‡	4,7,8,16,19,20	*th-t/th-th*	$C_{35}H_{64}O_9$	628	*A. muricata* [44]
9.13	muricatalin	4,14,15,17,18	*t/er/er-th*	$C_{35}H_{64}O_8$	612	*A. muricata* [45]
9.14	annopentocins-A + B‡	4,10,16,19,20	*t/th-th*	$C_{35}H_{64}O_8$	612	*A. muricata* [46]
9.15	annopentocin-C	4,10,16,19,20	*t/th-er*	$C_{35}H_{64}O_8$	612	*A. muricata* [46]
9.16	4-acetylgigantetrocin-A	4-OAc,14,17,18	*t/th-th*	$C_{37}H_{66}O_8$	638	*G. giganteus* [47]
9.17	muricatetrocin-C	4,16,19,20	*t/th-er*	$C_{35}H_{64}O_7$	596	*R. mucosa* [48]
9.18	glaucafilin	4,16,19,20	*t/th-er*	$C_{35}H_{64}O_7$	596	*A. glauca* [49]
9.19	glabranin (C_{23}=C_{24})	4,16,19,20	*t/th-th*	$C_{37}H_{66}O_7$	622	*A. glabra* [50]

9b-without OH in 4 '**gigantriocin type**':

9.2	gigantriocin	14,17,18	*t/th-th*	$C_{35}H_{64}O_6$	580	*G. giganteus* [1]
9.5	gigantrionenin (C_{21}=C_{22})	14,17,18	*t/th-th*	$C_{37}H_{66}O_6$	606	*G. giganteus* [1]
9.20	4-deoxycoriacin (C_{17}=C_{18})	14,21,22	*t/th-th*	$C_{37}H_{66}O_6$	606	*A. coriacea* [43]
9.21	*cis*-gigantrionenin (C_{21}=C_{22})	14,17,18	*c/th-th*	$C_{37}H_{66}O_6$	606	*G. giganteus* [47]

* *th*: *threo*; *er*: *erythro*; *t*: *trans*; *c*: *cis*.

** *G.*: *Goniothalamus*; *A.*: *Annona*; *R.*: *Rollinia*.

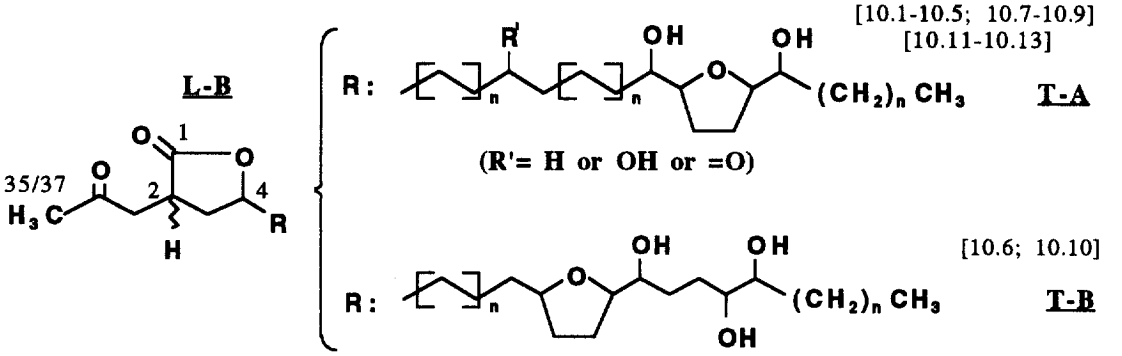
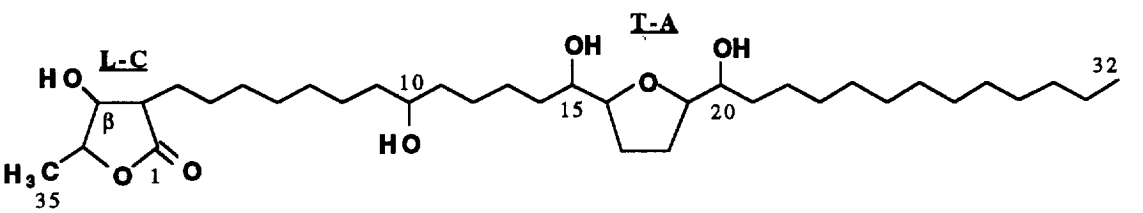
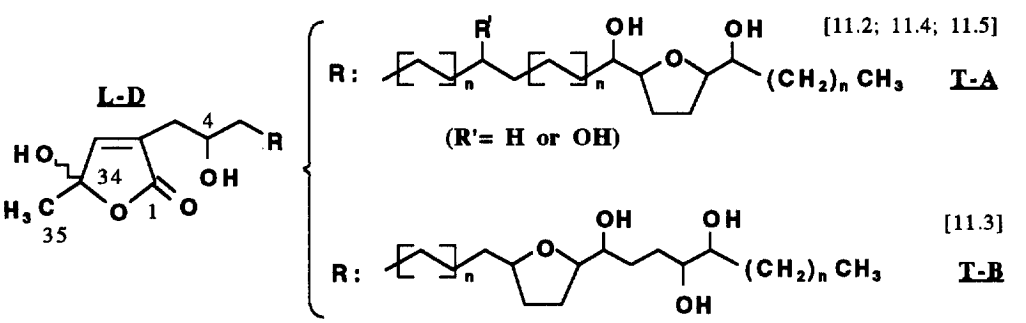
† gigantetrocin-B (**9.6**): 17,18-diepimer from gigantetrocin-A (**9.1**), for the authors [1].

‡ (**9.7**): 15-epimer for the authors [1]; (**9.12**): 19,20-diepimer for the authors [44]; (**9.14**): 19,20-diepimer for the authors [46].

these compounds described as a 2,4-*cis* and 2,4-*trans* mixture are characterized by the presence of a 2-acetonyl saturated γ-lactone moiety (L-B). Since 1994 it is well known, and further largely referred, that the 'ketolactones' or 'iso'-acetogenins, obtained as mixture of 2-epimers, are spontaneously formed by translactonization from classical 4-hydroxylated acetogenins during extraction procedures, by a simple light basic medium (for example by the presence of alkaloids), or after light heating in MeOH [1–5, 14]. So, these compounds must not be considered as natural products but as artifacts. In fact, with the exception of annomuricinone-D (**10.9**), isomurisolenin (**10.12**) and mosinone-A (**10.13**), the equivalent 4-hydroxylated acetogenins are known for all of the 'iso'-acetogenins. These exceptions as well as a different yield of the two isomers (2,4-*cis* and 2,4-*trans*) led the authors to consider 'iso'-acetogenins as natural products. In our opinion, unsubstantial reasons are given because a total lactonization might occur and then the natural aceogenins are not isolated. On the other hand, it is well known that 2-substituted γ-lactones may easily epimerize, leading to thermodynamic mixtures whose proportions strongly depend on the nature of the substituents.

The difference in C-10 stereochemistry between annonacin-A-one (**10.5**) isolated from *Asimina triloba* [51] and the compound isolated from *Annona muricata*, 10-*R*-annonacin-A-one [28], is based on differences in some of the physical data and the multiplicity of the H-10 signals: δ 3.59, pseudoquartet for 10*R* and δ 3.60, multiplet for 10*S*!!. Thus the absolute

Table 5. Mono-THF acetogenins with a L-B, L-C or L-D lactone moiety

		Hydroxyl positions	THF-relative configuration*	Molecular formula	M^+	Annonaceae species** [Ref.]
	V. Iso-acetogenins, mono-THF					
						
10. 'Iso' mono-THF, '**isoannonacin type**':						
10.1	isoannonacin	10,15,20	*th/t/th*	$C_{35}H_{64}O_7$	596	*A. densicoma* [1]
10.2	isoannonacinone (CO,10)	15,20	*th/t/th*	$C_{35}H_{62}O_7$	594	*A. densicoma* [1]
10.3	squamone (CO,9)	15,20	*th/t/th*	$C_{35}H_{62}O_7$	594	*A. squamosa* [1]
10.4	isoannoreticuin	9,15,20	*th/t/th*	$C_{35}H_{64}O_7$	596	*A. reticulata* [1]
10.5	annonacinone-A†	10,15,20	*th/t/er*	$C_{35}H_{64}O_7$	596	*As. triloba* [51] *A. muricata* [28]
10.6	gigantetrocinone	14,17,18	*t/th-th*	$C_{35}H_{64}O_7$	596	*As. triloba* [1]
10.7	goniothalamicinone	10,13,18	*th/t/th*	$C_{35}H_{64}O_7$	596	*As. longifolia* [27]
10.8	murisolinone	15,20	*th/t/th*	$C_{35}H_{64}O_6$	580	*As. triloba* [52]
10.9	annomuricinone-D	10,11,15,20	*er-th/t/th*	$C_{35}H_{64}O_8$	612	*A. muricata* [46]
10.10	gigantetroneninone (C_{21}=C_{22})	14,17,18	*t/th-th*	$C_{37}H_{66}O_7$	622	*As. longifolia* [25]
10.11	annomontacinone	10,17,22	*th/t/th*	$C_{37}H_{68}O_7$	624	*G. giganteus* [26]
10.12	isomurisolenin (C_{11}=C_{12})	15,20	*th/t/th*	$C_{35}H_{62}O_6$	578	*A. reticulata* [53]
10.13	mosinone-A (C_{23}=C_{24})	15,20	*th/t/th*	$C_{37}H_{64}O_7$	620	*A. squamosa* [33]
	VIa. β-Hydroxy-acetogenins, mono-THF					
						
11a. β-Hydroxy-γ-methyl-γ-lactones: '**jetein type**':						
11.1	jetein	10,15,20,33	*th/t/er*	$C_{35}H_{66}O_7$	598	*A. cherimolia* [1]
	VIb. 34-Hydroxy acetogenins					
						
11b. 34-Hydroxy acetogenins: '**donnaienin-A type**':						
11.2	donnaienin-A + 34 epi	4,15,20,34	*th/t/th*	$C_{35}H_{64}O_7$	596	*G. donnaiensis* [54]
11.3	donnaienin-B + 34 epi	4,14,17,18,34	*t/th-th*	$C_{35}H_{64}O_8$	612	*G. donnaiensis* [54]
11.4	goniodonin + 34 epi	4,10,15,20,34	*th/t/th*	$C_{35}H_{64}O_8$	612	*G. donnaiensis* [55]
11.5	*cis*-goniodonin + 34 epi	4,10,15,20,34	*th/c/th*	$C_{35}H_{64}O_8$	612	*G. donnaiensis* [55]

* *th*: *threo*; *er*: *erythro*; *t*: *trans*.

** *A.*: *Annona*; *As.*: *Asimina*; *G.*: *goniothalamus*.

† (**10.5**): 10-epimers for the authors [28].

Table 6. Adjacent bis-THF α,α′-dihydroxylated γ-lactone acetogenins

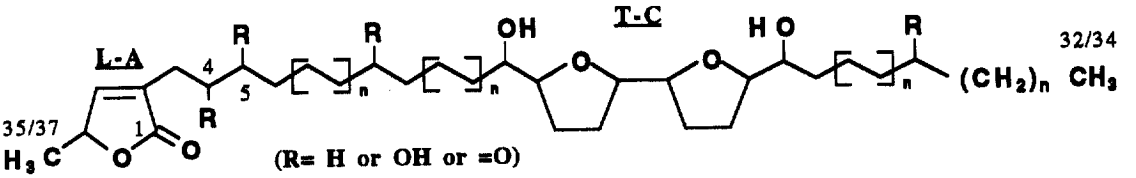
		Hydroxyl positions	THF-relative configuration*	Molecular formula	M⁻	Annonaceae species** [Ref.]
VII. Adjacent bis-THF α,α′-dihydroxylated acetogenins						
						
12. Dihydroxylated, '**uvaricin type**':						
12.1	uvaricin	15 (OAc-24)	*th/t/th/t/er*	$C_{39}H_{68}O_7$	648	*U. acuminata* [1]
12.2	desacetyluvaricin	15,24	*th/t/th/t/er*	$C_{37}H_{66}O_6$	606	*U. acuminata* [1]
12.3	neoannonin	13,22	*th/t/th/t/er*	$C_{35}H_{62}O_6$	578	*A. squamosa* [1]
12.4	isodesacetyluvaricin	15,24	*th/t/th/t/th*	$C_{37}H_{66}O_6$	606	*U. narum* [1]
12.5	membranacin	15,24	*th/c/th/c/er*	$C_{37}H_{66}O_6$	606	*R. membranacea* [1]
12.6	squamocin-I	13,22	*er/t/th/t/th*	$C_{35}H_{62}O_6$	578	*A. squamosa* [1]
12.7	squamocin-K	13,22	*th/t/th/t/th*	$C_{35}H_{62}O_6$	578	*A. squamosa* [1]
12.8	squamocin-N	15,24	*th/c/th/c/th*	$C_{37}H_{66}O_6$	606	*A. squamosa* [1]
12.9	membrarollin	13,22	*th/c/th/c/er*	$C_{35}H_{62}O_6$	578	*R. membranacea* [56]
13. Trihydroxylated and tetrahydroxylated (with OH in 4), '**asimicin type**':						
13.1	asimicin	4,15,24	*th/t/th/t/th*	$C_{37}H_{66}O_7$	622	*As. triloba* [1]
13.2	rolliniastatin-1	4,15,24	*th/c/th/c/er*	$C_{37}H_{66}O_7$	622	*R. mucosa* [1]
13.3	rolliniastatin-2 or bullatacin	4,15,24	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	*R. mucosa* [1] *A. bullata* [1]
13.4	molvizarin	4,13,22	*th/t/th/t/er*	$C_{35}H_{62}O_7$	594	*A. cherimolia* [1]
13.5	trilobacin	4,15,24	*th/t/er/c/th*	$C_{37}H_{66}O_7$	622	*As. triloba* [1] [57]
13.6	rioclarin	4,15,24,28	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*R. membranacea* [1]
13.7	purpureacin-2 (=12-OH-bullatacins-A+B)†	4,12,15,24	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. purpurea* [1] *R. mucosa* [58]
13.8	parviflorin or squamocin-E (=atemoyacin-A)	4,13,22	*th/t/th/t/th*	$C_{35}H_{62}O_7$	594	*As. parviflora* [1] *A. squamosa* [1] *A. atemoya* [59]
13.9	annoglaucin	4,10,15,24	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. glauca* [1]
13.10	glaucanisin (=squamotacin)	4,13,22	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	*A. glauca* [1] *A. squamosa* [60]
13.11	30-OH-bullatacin†	4,15,24,30	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [61]
13.12	31-OH-bullatacin	4,15,24,31	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [61]
13.13	32-OH-bullatacin	4,15,24,32	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [61]
13.14	araticulin	4,12,15,24	*th/t/th/t/th*	$C_{37}H_{66}O_8$	638	*A. crassiflora* [62]
13.15	annonisin	4,8,13,22	*th/t/th/t/th*	$C_{35}H_{62}O_8$	610	*A. atemoya* [63]
13.16	10-OH-asimicin	4,10,15,24	*th/t/th/t/th*	$C_{37}H_{66}O_8$	638	*As. triloba* [64] *A. reticulata* [65]
13.17	10-OH-trilobacin	4,10,15,24	*th/t/er/c/th*	$C_{37}H_{66}O_8$	638	*As. triloba* [64]
13.18	longimicin-A	4,11,20	*th/t/th/t/th*	$C_{37}H_{66}O_7$	622	*As. longifolia* [66]
13.19	longimicin-B	4,11,20	*th/t/th/t/th*	$C_{35}H_{62}O_7$	594	*As. longifolia* [66]
13.20	longimicin-C	4,9,18	*th/t/th/t/th*	$C_{35}H_{62}O_7$	594	*As. longifolia* [66]
13.21	rollimembrin	4,13,22	*th/c/th/c/er*	$C_{35}H_{62}O_7$	594	*R. membranacea* [67]
14. Trihydroxylated, dihydroxylated ketonic and tetrahydroxylated (without OH in 4):						
14a-without OH in 4 '**squamocin type**':						
14.1	squamocin	15,24,28	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	*A. squamosa* [1]
14.2	isorollinicin‡	15,24,28	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	*R. papilonella* [1]
14.3	squamocinone (CO,28)	15,24	*th/t/th/t/er*	$C_{37}H_{64}O_7$	620	*U. narum* [1]
14.4	motrilin or annonin-III	15,24,29	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	*A. cherimolia* [1] *A. squamosa* [1]
14.5	squamocin-B	13,22,26	*th/t/th/t/er*	$C_{35}H_{62}O_7$	594	*A. squamosa* [1]
14.6	squamocin-D or asiminacin	15,24,28	*th/t/th/t/th*	$C_{37}H_{66}O_7$	622	*A. squamosa* [1] *As. triloba* [1]
14.7	squamocin-F	12,15,24	*th/t/th/t/th*	$C_{37}H_{66}O_7$	622	*A. squamosa* [1]
14.8	asimin	10,15,24	*th/t/th/t/th*	$C_{37}H_{66}O_7$	622	*As. triloba* [1]
14.9	asiminecin	15,24,29	*th/t/th/t/th*	$C_{37}H_{66}O_7$	622	*As. triloba* [1]

Table 6. (continued)

		Hydroxyl positions	THF-relative configuration*	Molecular formula	M^+	Annonaceae species** [Ref.]
14.10	bullatin	10,15,24	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	*As. triloba* [1]
14.11	bullanin†	15,24,30	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	*As. triloba* [1][68]
14.12	bullacin	6,13,22	*th/t/th/t/th*	$C_{35}H_{62}O_7$	594	*A. bullata* [1]
14.13	trilobin	10,15,24	*th/t/er/c/th*	$C_{37}H_{66}O_7$	622	*As. triloba* [57]
14.14	asitribin	15,24,28	*th/t/er/c/th*	$C_{37}H_{66}O_7$	622	*As. triloba* [21]
14.15	uleirollin	12,15,24	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	*R. ulei* [5]
14.16	asiminocin	15,24,30	*th/t/th/t/th*	$C_{37}H_{66}O_7$	622	*As. triloba* [68]
14.17	bullatetrocin	15,24,31,32	*th/t/th/t/er-er*	$C_{37}H_{66}O_8$	638	*As. triloba* [64]
14.18	longimicin-D	10,13,22	*th/t/th/t/th*	$C_{37}H_{66}O_7$	622	*As. longifolia* [66]
14.19	mucoxin	8,14,17	*th/t/th/(c)t/th*	$C_{37}H_{66}O_7$	622	*R. mucosa* [69]
14.20	rollitacin	15,24,28,29	*th/t/th/t/er-er*	$C_{37}H_{66}O_8$	638	*R. mucosa* [70]
14.21	guanacone (CO,10)	15,24	*th/t/th/t/er*	$C_{37}H_{64}O_7$	620	*A.* aff. *spraguei* [71]
14b. without OH in 4, but with OH in 5 '**panalicin type**':						
14b.1	panalicin	5,15,24,28	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*U. narum* [1]
14b.2	narumicin-I	5,15,24	*th/t/th/t/th*	$C_{37}H_{66}O_7$	622	*U. narum* [1]
14b.3	narumicin-II	5,15,24	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	*U. narum* [1]
14b.4	espelicin	5,15,24,29	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*U. pauci-ovulata* [72]
14b.5	uvariasolin-I	5,6,15,24	*th-th/t/th/t/th*	$C_{37}H_{66}O_8$	638	*U. pauci-ovulata* [72]
14b.6	uvariasolin-II	5,6,15,24	*th-th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*U. pauci-ovulata* [72]

* *th*: *threo*; *er*: *erythro*; *t*: *trans*; *c*: *cis*.

** *U.*: *Uvaria*; *A.*: *Annona*; *R.*: *Rollinia*; *G.*: *Goniothalamus*; *As.*: *Asimina*.

† (**13.7**): 12-OH-bullatacins-A + B, 12 epimer from purpureacin-2, for the authors [58]; (**13.11**): 30 epimer for the authors [61]; (**14.11**): 30 epimers for the authors [1, 68].

‡ isorollinicin (**14.2**): would have to be a C-23 or C-24 epimer from squamocin (**14.1**) [1].

Table 7. Adjacent bis-THF α-monohydroxylated γ-lactone acetogenins

		Hydroxyl positions	THF-relative configuration*	Molecular formula	M^+	Annonaceae species** [Ref.]
VIII. Adjacent bis-THF α-monohydroxylated acetogenins						
15. Adjacent bis-THF α-monohydroxylated acetogenins, '**uvaricin type**':						
15.1	goniodenin (C_{21}=C_{22})	4,18	*t/th/t/th-c*	$C_{37}H_{64}O_6$	604	*G. giganteus* [73]
15.2	asimilobin	4,18	*t/th/t/th*	$C_{35}H_{62}O_6$	578	*G. giganteus* [73] *As. triloba* [51]
15.3	annosilin-A	20,23,24	*t/th/t/th-th*	$C_{37}H_{66}O_7$	622	*A. squamosa* [74]
15.4	rollidecin-A	4,20,23,24	*t/th/c/th-th*	$C_{37}H_{66}O_8$	638	*R. mucosa* [48]
15.5	rollidecin-B	4,20,23,24	*t/th/c/th-er*	$C_{37}H_{66}O_8$	638	*R. mucosa* [48]
15.6	rollinacin	4,10,20	*t/th/t/th*†	$C_{35}H_{62}O_7$	594	*R. mucosa* [70]

* *th*: *threo*; *er*: *erythro*; *t*: *trans*; *c*: *cis*.

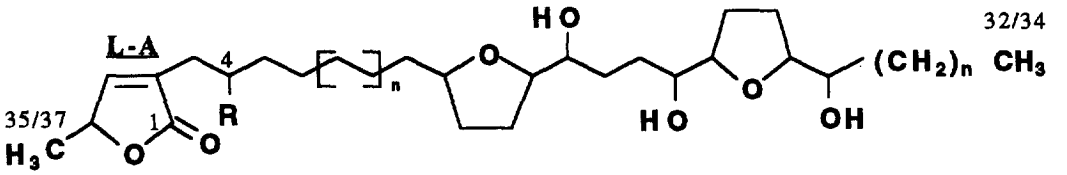
** *G.*: *Goniothalamus*; *As.*: *Asimina*; *A.*: *Annona*; *R.*: *Rollinia*.

† (**15.6**) its relative configuration has not been confirmed.

configuration indicated for 10-*R*-annonacin-A-one was given without solid proof.

A new subclass of acetogenins with a C_{35} skeleton and an unusual 34-OH-unsaturated lactone moiety (L-D) was found only in *Goniothalamus donnaiensis*. One of these acetogenins, donnaienin-B (**11.3**), showed a mono-THF-α-monohydroxylated system and the three other ones a mono-THF-α,α′-dihy-

Table 8. Non-adjacent bis-tetrahydrofuran γ-lactone acetogenins

		Hydroxyl positions	THF-relative configuration*	Molecular formula	M^+	Annonaceae species** [Ref.]
IX. Non-Adjacent bis-THF acetogenins						
			T-D			
						
16. Nonadjacent bis-THF (with OH in 4), **'sylvaticin type'**:						
16.1	sylvaticin	4,16,19,24	*t/th-th/c/er*	$C_{37}H_{66}O_8$	638	*R. sylvatica* [1] *R. mucosa* [75]
16.2	gigantecin	4,14,17,22	*t/th-th/t/th*	$C_{37}H_{66}O_8$	638	*G. giganteus* [1]
16.3	cherimolin-1 or bullatalicin	4,16,19,24	*t/th-th/t/er*	$C_{37}H_{66}O_8$	638	*A. cherimolia* [1] *A. bullata* [1]
16.4	cherimolin-2 or bullatanocin	4,16,19,24	*t/th-th/t/th*	$C_{37}H_{66}O_8$	638	*A. cherimolia* [1] *A. bullata* [1]
16.5	parvifloracin	4,14,17,22	*t/th-th/t/th*	$C_{35}H_{62}O_8$	610	*As. parviflora* [1]
16.6	12,15-*cis*-bullatalicin	4,16,19,24	*c/th-th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [1]
16.7	12,15-*cis*-bullatanocin	4,16,19,24	*c/th-th/t/th*	$C_{37}H_{66}O_8$	638	*A. bullata* [1]
16.8	12,15-*cis*-sylvaticin	4,16,19,24	*c/th-th/c/er*	$C_{37}H_{66}O_8$	638	*R. mucosa* [75]
16.9	trilobalicin	4,14,17,22	*t/th-th/t/er*	$C_{35}H_{62}O_8$	610	*As. triloba* [76]
17. Nonadjacent bis-THF (without OH in 4), **'squamostatin-A or almunequin type'**:						
17.1	squamostatin-A or almunequin	16,19,24,28	*t/th-th/t/er*	$C_{37}H_{66}O_8$	638	*A. squamosa* [1] *A. cherimolia* [1]
17.2	4-deoxygigantecin	14,17,22	*t/th-th/t/th*	$C_{37}H_{66}O_7$	622	*G. giganteus* [1]
17.3	squamostatin-D	16,19,24	*t/th-th/t/er*	$C_{37}H_{66}O_7$	622	*A. squamosa* [1]
17.4	squamostatin-E	16,19,24	*t/th-th/t/th*	$C_{37}H_{66}O_7$	622	*A. squamosa* [1]

* *th*: *threo*; *er*: *erythro*; *t*: *trans*; *c*: *cis*.
** *R.*: *Rollinia*; *G.*: *Goniothalamus*; *A.*: *Annona*; *As.*: *Asimina*.

droxylated one. All of them (**11.1–11.4**) were isolated as mixtures of 34-epimers [54, 55].

BIS-THF ACETOGENINS

Although a great number of new compounds have been included in this group, an identical classification is made in this review: adjacent acetogenins [1, 5, 21, 48, 51, 56–74] (Tables 6–7), non-adjacent acetogenins [1, 75, 76] (Table 8) and saturated lactone acetogenins [1, 61, 76, 77] (Table 9).

Adjacent bis-THF acetogenins

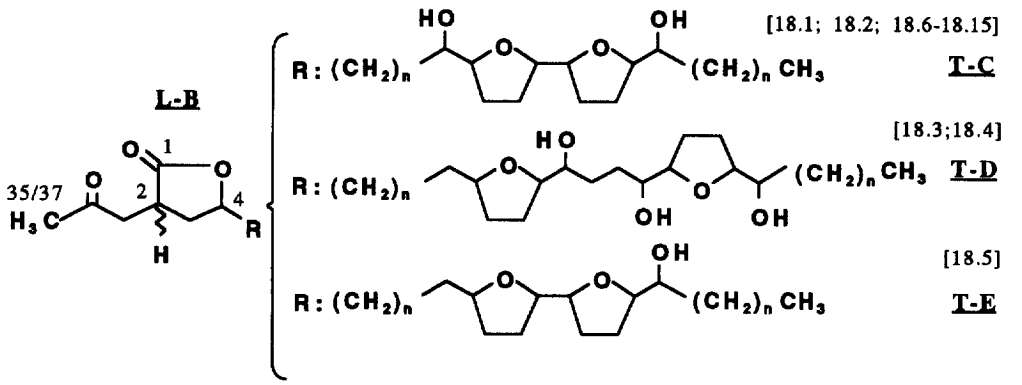
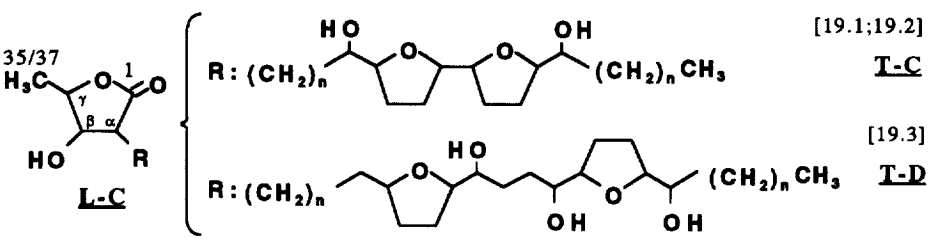
All of the adjacent bis-THF acetogenins previously described possess a bis-THF system flanked in α and α′ by two hydroxyl groups (T-C). Recently, six acetogenins with an α-monohydroxylated bis-THF ring (T-E) were isolated. This system only has been previously reported for bulladecinone (**18.5**), a bis-THF 'iso'-acetogenin [78].

The relative configuration of the known compound trilobacin (**13.5**) has been revised and established as *threo/trans/erythro/cis/threo* on the basis of COSY, NOESY and Mosher experiments of its diacetate derivative [57]. Moreover, this configuration was confirmed by synthesis [79].

Surprisingly, in a Rapid Communication published in February 1996, squamotacin is claimed by Hopp [60] as a new compound with selectivity on human prostate tumor cell lines (PC-3). The structure proposed for such compound is that of glaucasinin (**13.10**), an acetogenin already published in 1995 and included in our last review [1]. In the same line, 12-OH-bullatacins-A + B were described as new compounds with different stereochemistry at C-12 [58]. The minor differences in the ^1H NMR and ^{13}C NMR at C-12 are insufficient and led us to consider these compounds identical to purpureacin-2 (**13.7**), isolated from *Annona purpurea* [80].

Isolation of three new hydroxylated derivatives of bullatacin, at 30, 31 or 32 position (compounds **13.11–13.13**) from bark of *Annona bullata* [61] supports our hypothesis that 'iso'-acetogenins are artifacts. In fact,

Table 9. Saturated lactone bis-THF acetogenins

		Hydroxyl positions	THF-relative configuration*	Molecular formula	M^+	Annonaceae species** [Ref.]
	X. Iso-acetogenins, bis-THF					
						
	L-B					[18.1; 18.2; 18.6-18.15] **T-C**
						[18.3;18.4] **T-D**
						[18.5] **T-E**
	18. 'Iso' bis-THF, **'bullatacinone type'**:					
18.1	bullatacinone (=isoannonareticin)	15,24	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	*A. bullata* [1] *A. reticulata* [77]
18.2	rollinone	15,24	*th/c/th/c/er*	$C_{37}H_{66}O_7$	622	*R. papilionella* [1]
18.3	bullatalicinone or isocherimolin-1	16,19,24	*th-th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [1] *A. cherimolia* [1]
18.4	bullatanocinone	16,19,24	*th-th/t/th*	$C_{37}H_{66}O_8$	638	*A. bullata* [1]
18.5	bulladecinone	20,23,24	*t/th/t/th-er*	$C_{37}H_{66}O_8$	638	*A. bullata* [1]
18.6	32-OH-bullatacinone	15,24,32	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [1]
18.7	31-OH-bullatacinone	15,24,31	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [1]
18.8	30-OH-bullatacinone	15,24,30	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [1]
18.9	isomolvizarin-1	13,22	*th/t/th/t/er*	$C_{35}H_{62}O_7$	594	*A. cherimolia* [1]
18.10	isomolvizarin-2	13,22	*th/t/th/t/th*	$C_{35}H_{62}O_7$	594	*A. cherimolia* [1]
18.11	10-OH-bullatacinone	10,15,24	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [1]
18.12	12-OH-bullatacinone	12,15,24	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [1]
18.13	29-OH-bullatacinone	15,24,29	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [1]
18.14	28-OH-bullatacinone	15,24,28	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [61]
18.15	trilobacinone	15,24	*th/t/er/c/th*	$C_{37}H_{66}O_7$	622	*As. triloba* [76]
	XI. β-Hydroxy-acetogenins, bis-THF					
						
	L-C					[19.1;19.2] **T-C**
						[19.3] **T-D**
	19. β-Hydroxy methyl γ-lactones, **'laherradurin type'**:					
19.1	laherradurin	15,24,35	*th/t/th/t/er*	$C_{37}H_{68}O_7$	624	*A. cherimolia* [1]
19.2	itrabin	13,22,33	*th/t/th/t/er*	$C_{35}H_{64}O_7$	596	*A. cherimolia* [1]
19.3	otivarin	16,19,24,35	*t/th-th/t/er*	$C_{37}H_{68}O_8$	640	*A. cherimolia* [1]

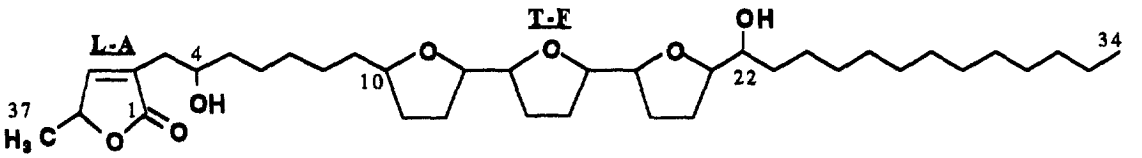
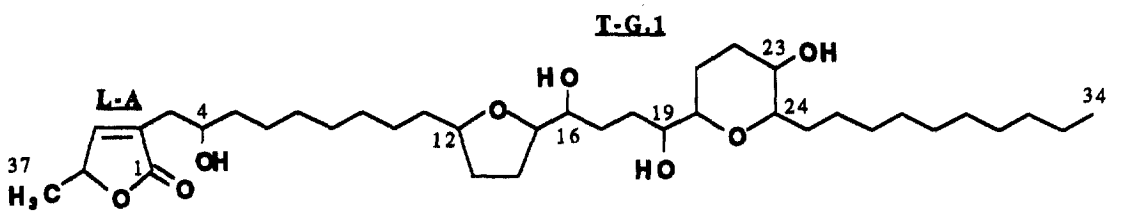
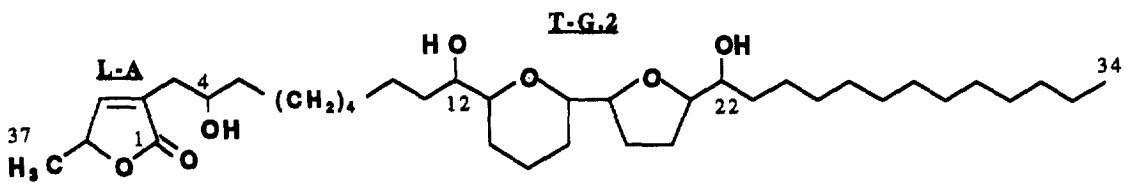
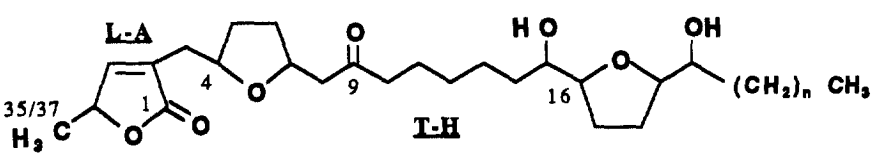
* *th*: *threo*; *er*: *erythro*; *t*: *trans*; *c*: *cis*.

** *A.*: *Annona*; *R.*: *Rollinia*; *As.*: *Asimina*.

compounds **18.6–18.8** (Table 9) previously isolated from the same plant material [1, 81] should be their respective 'iso'-acetogenins. Moreover, compounds **13.11** and **14.11** have been considered as a mixture of 30*S* and 30*R* isomers based on the doubtful double carbon signal observed in their ^{13}C-NMR spectrum [61, 68].

Finally, mucoxin (**14.19**) is the first unusual

Table 10. Miscellaneous acetogenins

	Hydroxyl positions	Relative configuration*	Molecular formula	M^+	Annonaceae species* [Ref.]
XII: Tri-THF acetogenins					
20. Tri-THF acetogenins, '**goniocin type**':					
					
20.1 goniocin	4,22	*t/th/t/th/t/th*	$C_{37}H_{64}O_7$	620	*G. giganteus* [1]
XIII. **THF-THP acetogenins**					
21. Nonadjacent THF-THP acetogenins, '**mucocin type**':					
					
21.1 mucocin	4,16,19,23	*t/th-th/c*	$C_{37}H_{66}O_8$	638	*R. mucosa* [83]
22. Adjacent THF-THP acetogenins, '**muconin type**':					
					
22.1 muconin	4,12,22	*th/c/th/t/th*	$C_{37}H_{66}O_7$	622	*R. mucosa* [69]
XIV. 4–7/16–19 Nonadjacent bis-THF acetogenins					
23. 4–7/16–19 Nonadjacent bis-THF acetogenins, '**aromin type**':					
					
23.1 aromin	15,20	*t-th/t/th*	$C_{35}H_{60}O_7$	592	*X. aromatica* [84]
23.2 aromicin	15,20	*t-th/t/th*	$C_{37}H_{64}O_7$	620	*X. aromatica* [84]

* *th*: *threo*; *t*: *trans*; *c*: *cis*.

** *G.*: *Goniothalamus*; *R.*: *Rollinia*; *X.*: *Xylopia*.

reported acetogenin with a hydroxyl group at one of the methylene carbons of the THF ring [69].

Non-adjacent bis-THF acetogenins

Only two compounds are added in the group of non-adjacent bis-THF acetogenins: 12,15-*cis*-sylvaticin (**16.8**) isolated from *Rollinia mucosa* [75] and trilobalicin (**16.9**) found in *Asimina triloba* [76]. The relative configuration *cis/threo-threo/cis/erythro* for (**16.8**) was established. In the same work, the isolation of the known sylvaticin (**16.1**) is reported and its relative configuration revised and now established as *trans/threo-threo/cis/erythro*. As in mono-THF-α,α′-dihydroxylated acetogenins, only differences in the ^{1}H-NMR chemical shifts for the methylene protons at

Table 11. Species of the Annonaceae with new acetogenins

Species	Organ		Compounds	Ref.
Annona atemoya	seed	**5.9**	annotemoyin-1	[20]
(*A. cherimolia* × *A. squamosa*)		**5.10**	annotemoyin-2	[20]
		13.15	annonisin	[63]
Annona bullata	bark	**5.5**	uvariamicin-IV	[1]
		5.6	bullatenicin	[1]
		13.3	bullatacin (or rolliniastatin-2)	[1]
		13.11	30-OH-bullatacin	[61]
		13.12	31-OH-bullatacin	[61]
		13.13	32-OH-bullatacin	[61]
		14.12	bullacin	[1]
		16.3	bullatalicin (or cherimolin-1)	[1]
		16.4	bullatanocin (or cherimolin-2)	[1]
		16.6	12,15-*cis*-bullatalicin	[1]
		16.7	12,15-*cis*-bullatanocin	[1]
		18.1	bullatacinone	[1]
		18.3	bullatalicinone (or isocherimolin-1)	[1]
		18.4	bullatanocinone	[1]
		18.5	bulladecinone	[1]
		18.6	32-OH-bullatacinone	[1]
		18.7	31-OH-bullatacinone	[1]
		18.8	30-OH-bullatacinone	[1]
		18.11	10-OH-bullatacinone	[1]
		18.12	12-OH-bullatacinone	[1]
		18.13	29-OH-bullatacinone	[1]
		18.14	28-OH-bullatacinone	[61]
Annona cherimolia	seed	**11.1**	jetein	[1]
		13.4	molvizarin	[1]
		14.4	motrilin (or annonin-III)	[1]
		16.3	cherimolin-1 (or bullatalicin)	[1]
		16.4	cherimolin-2 (or bullatanocin)	[1]
		17.1	almunequin (or squamostatin-A)	[1]
		19.1	laherradurin	[1]
		19.2	itrabin	[1]
		19.3	otivarin	[1]
	root	**18.3**	isocherimolin-1 (or bullatalicinone)	[1]
		18.9	isomolvizarin-1	[1]
		18.10	isomolvizarin-2	[1]
Annona coriacea	root	**1.5**	coriadienin	[7]
		8.13	coriheptocin-A	[41]
		8.14	coriheptocin-B	[41]
		9.11	coriacin	[43]
		9.20	4-deoxycoriacin	[43]
Annona crassiflora	seed	**13.14**	araticulin	[62]
Annona densicoma	seed	**7.1**	annonacin	[1]
		7.3	annonacinone	[1]
	bark	**8.3**	8-hydroxyannonacin	[1]
		9.3	densicomacin-1	[1]
		10.1	isoannonacin	[1]
		10.2	isoannonacinone	[1]
Annona glabra	seed	**9.19**	glabranin	[50]
Annona glauca	root	**13.9**	annoglaucin	[1]
	seed	**9.18**	glaucafilin	[49]
		13.10	glaucanisin	[1]

Table 11. (continued)

Species	Organ		Compounds	Ref.
Annona montana	seed	**7.5**	annomontacin	[1]
		8.1	annomonicin	[1]
		8.2	montanacin	[1]
	fruit	**3.6**	diepoxymontin	[1]
Annona muricata	seed	**2.1**	epomuricenin-A (or epoxymurin-A)	[1]
		2.3	epomuricenin-B	[1]
		3.1	diepomuricanin-A	[1]
		3.2	corepoxylone	[1]
		5.4	solamin	[1]
		6.1	murisolin	[1]
		6.2	corossolin	[1]
		6.3	corossolone	[1]
		7.19	*cis*-annonacin	[29]
		7.20	*cis*-annonacinone	[29]
		7.21	*cis*-goniothalamicin	[29]
		7.22	arianacin + javoricin	[29]
		8.12	muricatalicin	[40]
		9.6	gigantetrocin-B	[1]
		9.7	muricatetrocin-A + B	[1]
		9.13	muricatalin	[45]
Annona muricata	bark	**2.1**	epoxymurin-A (or epomuricenin-A)	[1]
		2.2	epoxymurin-B	[1]
		8.6	muricatin-C	[1]
		9.9	muricatin-A	[1]
		9.10	muricatin-B	[1]
	leaf	**7.18**	annomutacin	[28]
		8.4	annomuricin-A	[1]
		8.5	annomuricin-B	[1]
		8.7	muricatocin-A	[37]
		8.8	muricatocin-B	[37]
		8.9	muricatocin-C	[38]
		8.10	annomuricin-C	[38]
		8.11	annohexocin	[39]
		9.12	murihexocin-A + B	[44]
		9.14	annopentocin-A + B	[46]
		9.15	annopentocin-C	[46]
		10.9	annomuricinone-D	[46]
	root	**1.7**	montecristin	[9]
		1.8	cohibin-A	[10]
		1.9	cohibin-B	[10]
		1.12	muridienin-1	[12]
		1.13	muridienin-2	[12]
Annona purpurea	leaf	**13.7**	purpureacin-2	[1]
Annona reticulata	bark	**5.2**	reticulatacin (or uvariamicin-II)	[1]
		7.11	reticulacinone	[1]
	leaf	**7.6**	annoreticuin	[1]
		7.7	annoreticuinone	[1]
		10.4	isoannoreticuin	[1]
	seed	**1.3**	reticulatamol	[1]
		1.4	reticulatamone	[1]
		3.3	dieporeticanin-1	[1]
		3.4	dieporeticanin-2	[1]
		3.5	dieporeticenin	[1]
		5.7	reticulatain-1	[1]
		5.8	reticulatain-2	[1]
		10.12	isomurisolenin	[53]

Table 11. (continued)

Species	Organ		Compounds	Ref.
Annona senegalensis	seed	**7.15**	annogalene (or xylomatenin)	[1]
		7.16	annosenegalin	[1]
		9.8	senegalene	[1]
Annona aff. *spraguei*	seed	**14.21**	guanacone	[71]
Annona squamosa	seed	**7.4**	annonacin-A	[1]
		7.12	squamosten-A	[1]
		7.27	mosin-B	[33]
		7.28	mosin-C	[33]
		10.13	mosinone-A	[33]
		12.3	neoannonin	[1]
		12.6	squamocin-I	[1]
		12.7	squamocin-K	[1]
		12.8	squamocin-N	[1]
		13.8	squamocin-E (or parviflorin)	[1]
		14.1	squamocin	[1]
		14.4	annonin-III (or motrilin)	[1]
		14.5	squamocin-B	[1]
		14.6	squamocin-D (or asiminacin)	[1]
		14.7	squamocin-F	[1]
		15.3	annosilin-A	[74]
		17.1	squamostatin-A (or almunequin)	[1]
		17.3	squamostatin-D	[1]
		17.4	squamostatin-E	[1]
	bark	**10.3**	squamone	[1]
Asimina longifolia	leaves and twigs	**1.11**	longanin	[6]
		6.11	longifolicin	[25]
		6.12	longicoricin	[25]
		7.17	longicin	[27]
		7.24	4-acetylannonacin	[31]
		7.25	4-acetylxylomaticin	[31]
		10.7	goniothalamicinone	[27]
		10.10	gigantetroneninone	[25]
		13.18	longimicin-A	[66]
		13.19	longimicin-B	[66]
		13.20	longimicin-C	[66]
		14.18	longimicin-D	[66]
Asimina parviflora	stem	**13.8**	parviflorin (or squamocin-E)	[1]
		16.5	parvifloracin	[1]
Asimina triloba	root and seeds	**13.1**	asimicin	[1]
	bark	**10.5**	annonacinone-A	[28], [51]
		10.6	gigantetrocinone	[1]
		13.5	trilobacin	[1] [57]
		13.16	10-OH-asimicin	[64], [65]
		13.17	10-OH-trilobacin	[64]
		14.6	asiminacin (or squamocin-D)	[1]
		14.8	asimin	[1]
		14.9	asiminecin	[1]
		14.10	bullatin	[1]
		14.11	bullanin	[1] [68]
		14.16	asiminocin	[68]
		14.17	bullatetrocin	[64]
		16.9	trilobalicin	[76]
		18.15	trilobacinone	[76]

Table 11. (continued)

Species	Organ		Compounds	Ref.
Asimina triloba	seed	**6.5**	asiminenin-A	[21]
		6.6	asiminenin-B	[21]
		6.7	*cis*-murisolin	[22]
		6.8	murisolin-A	[22]
		10.8	murisolinone	[52]
		14.13	trilobin	[57]
		14.14	asitribin	[21]
		15.2	asimilobin	[52]
Disepalum anomalum	bark	**7.26**	disepalin	[32]
Goniothalamus amuyon	seed	—	known acetogenins (**6.2**, **7.1** and **9.1**)	[123]
Goniothalamus donnaiensis	root	**11.2**	donnaienin-A + 34 epi	[54]
		11.3	donnaienin-B + 34 epi	[54]
		11.4	goniodonin + 34 epi	[55]
		11.5	*cis*-goniodonin + 34 epi	[55]
Goniothalamus giganteus	bark	**1.1**	giganin	[1], [6]
		6.4	giganenin	[1]
		6.13	4-deoxyannomontacin	[26]
		7.2	goniothalamicin	[1]
		7.13	gonionenin	[1]
		7b.8	gigantransenin-A + B	[36]
		7b.9	gigantransenin-C	[36]
		9.1	gigantetrocin-A	[1]
		9.2	gigantriocin	[1]
		9.4	gigantetronenin	[1]
		9.5	gigantrionenin	[1]
Goniothalamus giganteus	bark	**9.16**	4-acetylgigantetrocin-A	[47]
		9.21	*cis*-gigantronenin	[47]
		10.11	annomontacinone	[26]
		15.1	goniodenin	[73]
		15.2	asimilobin	[73]
		16.2	gigantecin	[1]
		17.2	4-deoxygigantecin	[1]
		20.1	goniocin	[1]
Goniothalamus sesquipedalis	bark	—	known acetogenin (9.1)	[124]
Polyalthia plagioneura	seed	**7b.1**	plagionicin-A	[34]
Porcelia macrocarpa	seed	**1.14**	butyrolactone-1	[13]
		1.15	butyrolactone-2	[13]
Rollinia membranacea	seed	**3.7**	diepomuricanin-B	[1]
		3.8	diepoxyrollin	[1]
		4.1	tripoxyrollin	[1]
		12.5	membranacin	[1]
		12.9	membrarollin	[56]
		13.6	rioclarin	[1]
		13.21	rollimembrin	[67]
Rollinia mucosa	seed	**13.2**	rolliniastatin-1	[1]
		13.3	rolliniastatin-2 (or bullatacin)	[1]
	leaf	**7.23**	rollinecins-A + B	[30]
		9.17	muricatetrocin-C	[48]
		14.19	mucoxin	[69]
		14.20	rollitacin	[70]

Table 11. (continued)

Species	Organ		Compounds	Ref.
Rollinia mucosa		**15.4**	rollidecin-A	[48]
		15.5	rollidecin-B	[48]
		15.6	rollinacin	[70]
		16.8	12,15-*cis*-sylvaticin	[75]
		21.1	mucocin	[83]
		22.1	muconin	[69]
	fruit	**2.4**	epomusenin-A	[16]
		2.5	epomusenin-B	[16]
Rollinia papilionella	root	**14.2**	isorollinicin	[1]
		18.2	rollinone	[1]
Rollinia sericea	bark	—	known acetogenins (**13.2** and **14.1**)	[125]
Rollinia sylvatica	fruit	**16.1**	sylvaticin	[1, 75]
Rollinia ulei	leaf	**14.15**	uleirollin	[5]
Uvaria acuminata	root	**12.1**	uvaricin	[1]
		12.2	desacetyluvaricin	[1]
Uvaria grandiflora	root	**6.9**	uvarigranin	[23]
Uvaria narum	root	**5.1**	uvariamicin-I	[1]
		5.2	uvariamicin-II (or reticulatacin)	[1]
		5.3	uvariamicin-III	[1]
		12.4	isodesacetyluvaricin	[1]
		14.3	squamocinone	[1]
		14b.1	panalicin	[1]
		14b.2	narumicin-I	[1]
		14b.3	narumicin-II	[1]
Uvaria pauci-ovulata	root	**14b.4**	espelicin	[72]
		14b.5	uvariasolin-I	[72]
		14b.6	uvariasolin-II	[72]
Uvaria tonkinesis	root	**1.6**	tonkinelin	[8]
		6.10	tonkinecin	[24]
		7b.2	tonkinin-A	[35]
		7b.3	tonkinin-B	[35]
		7b.4	tonkinin-C	[35]
		7b.5	tonkinesin-A	[35]
		7b.6	tonkinesin-B	[35]
		7b.7	tonkinesin-C	[35]
Xylopia aromatica	bark	**1.2**	venezenin	[1]
		1.10	venezinone	[11]
		7.8	xylopianin	[1]
		7.9	xylopiacin	[1]
		7.10	xylomaticin	[1]
		7.14	xylopien	[1]
		7.15	xylomatenin (or annogalene)	[1]
		23.1	aromin	[84]
		23.2	aromicin	[84]

Table 12. Names of acetogenins from Annonaceae cited in this review (alphabetic order)

	Acetogenin	Ref.
7.24	4-Acetylannonacin	[31]
9.16	4-Acetylgigantetrocin-A	[47]
7.25	4-Acetylxylomaticin	[31]
17.1	Almunequin (or squamostatin A)	[1]
7.15	Annogalene (or xylomatenin)	[1]
13.9	Annoglaucin	[1]
8.11	Annohexocin	[39]
8.1	Annomonicin	[1]
7.5	Annomontacin	[1]
10.11	Annomontacinone	[26]
8.4	Annomuricin-A	[1]
8.5	Annomuricin-B	[1]
8.10	Annomuricin-C	[38]
10.9	Annomuricinone-D	[46]
7.18	Annomutacin	[28]
7.1	Annonacin	[1]
7.19	*cis*-Annonacin	[29]
7.4	Annonacin-A	[1]
7.3	Annonacinone	[1]
7.20	*cis*-Annonacinone	[29]
10.5	Annonacinone-A	[28] [51]
14.4	Annonin-III (or motrilin)	[1]
13.15	Annonisin	[63]
15.3	Annonsilin-A	[74]
9.14	Annopentocins-A + B	[46]
9.15	Annopentocin-C	[46]
7.6	Annoreticuin	[1]
7.7	Annoreticuinone	[1]
7.16	Annosenegalin	[1]
5.9	Annotemoyin-1	[20]
5.10	Annotemoyin-2	[20]
13.14	Araticulin	[62]
7.22	Arianacin	[29]
23.2	Aromicin	[84]
23.1	Aromin	[84]
13.1	Asimicin	[1]
15.2	Asimilobin	[51] [73]
14.8	Asimin	[1]
14.6	Asiminacin (or squamocin-D)	[1]
14.9	Asiminecin	[1]
6.5	Asiminenin-A	[21]
6.6	Asiminenin-B	[21]
14.16	Asiminocin	[68]
14.14	Asitribin	[21]
14.12	Bullacin	[1]
18.5	Bulladecinone	[1]
14.11	Bullanin	[1] [68]
13.3	Bullatacin (or rolliniastatin-2)	[1]
18.1	Bullatacinone	[1]
16.3	Bullatalicin (or cherimolin-1)	[1]
16.6	12,15-*cis*-Bullatalicin	[1]
18.3	Bullatalicinone (or isocherimolin-1)	[1]
16.4	Bullatanocin (or cherimolin-2)	[1]
16.7	12,15-*cis*-Bullatanocin	[1]
18.4	Bullatanocinone	[1]
5.6	Bullatencin	[1]
14.17	Bullatetrocin	[64]
14.10	Bullatin	[1]
1.14	Buthyrolactone-1	[13]
1.15	Buthyrolactone-2	[13]
16.3	Cherimolin-1 (or bullatalicin)	[1]
16.4	Cherimolin-2 (or bullatanocin)	[1]
1.8	Cohibin-A	[10]
1.9	Cohibin-B	[10]
3.2	Corepoxylone	[1]
9.11	Coriacin	[43]
1.5	Coriadienin	[7]
8.13	Coriheptocin-A	[41]
8.14	Coriheptocin-B	[41]
6.2	Corossolin	[1]
6.3	Corossolone	[1]
9.3	Densicomacin-1	[1]
6.13	4-Deoxyannomontacin	[26]
9.20	4-Deoxycoriacin	[43]
17.2	4-Deoxygigantecin	[1]
12.2	Desacetyluvaricin	[1]
3.1	Diepomuricanin-A	[1]
3.7	Diepomuricanin-B	[1]
3.3	Dieporeticanin-1	[1]
3.4	Dieporeticanin-2	[1]
3.5	Diporeticenin	[1]
3.6	Diepoxymontin	[1]
3.8	Diepoxyrollin	[1]
7.26	Disepalin	[32]
11.2	Donnaienin-A + 34 epi	[54]
11.3	Donnaienin-B + 34 epi	[54]
2.1	Epomuricenin-A or epoxymurin-A	[1]
2.3	Epomuricenin-B	[1]
2.4	Epomusenin-A	[16]
2.5	Epomusenin-B	[16]
2.1	Epoxymurin-A (or epomuricenin-A)	[1]
2.2	Epoxymurin-B	[1]
14b.4	Espelicin	[72]
6.4	Giganenin	[1]
1.1	Giganin	[1] [6]
16.2	Gigantecin	[1]
9.1	Gigantetrocin-A	[1]
9.6	Gigantetrocin-B	[1]
10.6	Gigantetrocinone	[1]
9.4	Gigantetronenin	[1]
10.10	Gigantetroneninone	[25]
7b.8	Gigantransenins-A + B	[36]
7b.9	Gigantransenin-C	[36]
9.2	Gigantriocin	[1]
9.5	Gigantrionenin	[1]
9.21	*cis*-Gigantrionenin	[47]
9.19	Glabranin	[50]
9.18	Glaucafilin	[49]
13.10	Glaucanisin	[1]
20.1	Goniocin	[1]
15.1	Goniodenin	[73]
11.4	Goniodonin + 34-epi	[55]
11.5	*cis*-Goniodonin + 34-epi	[55]
7.13	Gonionenin	[1]
7.2	Goniothalamicin	[1]
7.21	*cis*-Goniothalamicin	[29]
10.7	Goniothalamicinone	[27]
14.21	Guanacone	[71]
8.3	8-Hydroxy-annonacin	[1]
13.16	10-Hydroxy-asimicin	[64], [65]
13.11	30-Hydroxy-bullatacin	[61]
13.12	31-Hydroxy-bullatacin	[61]
13.13	32-Hydroxy-bullatacin	[61]

Table 12. (continued)

	Acetogenin	Ref.
18.11	10-Hydroxy-bullatacinone	[1]
18.12	12-Hydroxy-bullatacinone	[1]
18.14	28-Hydroxy-bullatacinone	[61]
18.13	29-Hydroxy-bullatacinone	[1]
18.8	30-Hydroxy-bullatacinone	[1]
18.7	31-Hydroxy-bullatacinone	[1]
18.6	32-Hydroxy-bullatacinone	[1]
13.17	10-Hydroxy-trilobacin	[143]
10.1	Isoannonacin	[1]
10.2	Isoannonacinone	[1]
10.4	Isoannoreticuin	[1]
18.3	Isocherimolin-1 (or bullatalicinone)	[1]
12.4	Isodesacetyluvaricin	[1]
10.12	Isomurisolenin	[53]
18.9	Isomolvizarin-1	[1]
18.10	Isomolvizarin-2	[1]
14.2	Isorollinicin	[1]
19.2	Itrabin	[1]
7.22	Javoricin	[29]
11.1	Jetein	[1]
19.1	Laherradurin	[1]
1.11	Longanin	[6]
7.17	Longicin	[27]
6.12	Longicoricin	[25]
6.11	Longifolicin	[25]
13.18	Longimicin-A	[66]
13.19	Longimicin-B	[66]
13.20	Longimicin-C	[66]
14.18	Longimicin-D	[66]
12.5	Membranacin	[1]
12.9	Membrarollin	[56]
13.4	Molvizarin	[1]
8.2	Montanacin	[1]
1.7	Montecristin	[9]
7.27	Mosin-B	[33]
7.28	Mosin-C	[33]
10.13	Mosinone-A	[33]
14.4	Motrilin (or annonin-III)	[1]
21.1.	Mucocin	[83]
22.1	Muconin	[69]
14.19	Mucoxin	[69]
8.12	Muricatalicin	[40]
9.13	Muricatalin	[45]
9.7	Muricatetrocins-A+B	[1]
9.17	Muricatetrocin-C	[48]
9.9	Muricatin-A	[1]
9.10	Muricatin-B	[1]
8.6	Muricatin-C	[1]
8.7	Muricatocin-A	[37]
8.8	Muricatocin-B	[37]
8.9	Muricatocin-C	[38]
1.12	Muridienin-1	[12]
1.13	Muridienin-2	[12]
9.12	Murihexocins-A+B	[108]
6.1	Murisolin	[1]
6.7	*cis*-Murisolin	[22]
6.8	Murisolin-A	[22]
10.8	Murisolinone	[52]
14b.2	Narumicin-I	[1]
14b.3	Narumicin-II	[1]
12.3	Neoannonin	[1]
19.3	Otivarin	[1]

Table 12. (continued)

	Acetogenin	Ref.
14b.1	Panalicin	[1]
16.5	Parvifloracin	[1]
13.8	Parviflorin (or squamocin-E)	[1]
7b.1	Plagionicin-A	[34]
13.7	Purpureacin-2	[1]
7.11	Reticulacinone	[1]
5.2	Reticulatacin (or uvariamicin-II)	[1]
5.7	Reticulatain-1	[1]
5.8	Reticulatain-2	[1]
1.3	Reticulatamol	[1]
1.4	Reticulatamone	[1]
13.6	Rioclarin	[1]
15.4	Rollidecin-A	[48]
15.5	Rollidecin-B	[48]
13.21	Rollimembrin	[67]
15.6	Rollinacin	[70]
7.23	Rollinecins-A+B	[30]
13.2	Rolliniastatin-1	[1]
13.3	Rolliniastatin-2 (bullatacin)	[1]
18.2	Rollinone	[1]
14.20	Rollitacin	[70]
9.8	Senegalene	[1]
5.4	Solamin	[1]
14.1	Squamocin	[1]
14.5	Squamocin-B	[1]
14.6	Squamocin-D (or asiminacin)	[1]
13.8	Squamocin-E (or parviflorin)	[1]
14.7	Squamocin-F	[1]
12.6	Squamocin-I	[1]
12.7	Squamocin-K	[1]
12.8	Squamocin-N	[1]
14.3	Squamocinone	[1]
10.3	Squamone	[1]
17.1	Squamostatin-A (or almunequin)	[1]
17.3	Squamostatin-D	[1]
17.4	Squamostatin-E	[1]
7.12	Squamosten-A	[1]
16.1	Sylvaticin	[1] [75]
16.8	12,15-*cis*-Sylvaticin	[75]
6.10	Tonkinecin	[24]
1.6	Tonkinelin	[8]
7b.5	Tonkinesin-A	[35]
7b.6	Tonkinesin-B	[35]
7b.7	Tonkinesin-C	[35]
7b.2	Tonkinin-A	[35]
7b.3	Tonkinin-B	[35]
7b.4	Tonkinin-C	[35]
13.5	Trilobacin	[1] [57]
18.15	Trilobacinone	[76]
16.9	Trilobalicin	[76]
14.13	Trilobin	[57]
4.1	Tripoxyrollin	[1]
14.15	Uleirollin	[5]
5.1	Uvariamicin-I	[1]
5.2	Uvariamicin-II (or reticulatacin)	[1]
5.3	Uvariamicin-III	[1]
5.5	Uvariamicin-IV	[1]
14b.5	Uvariasolin-I	[72]
14b.6	Uvariasolin-II	[72]
12.1	Uvaricin	[1]
6.9	Uvarigranin	[23]
1.2	Venezenin	[1]

Table 12. (continued)

	Acetogenin	Ref.
1.10	Venezinone	[11]
7.15	Xylomatenin (or annogalene)	[1]
7.10	Xylomaticin	[1]
7.9	Xylopiacin	[1]
7.8	Xylopianin	[1]
7.14	Xylopien	[1]

the THF system are argued to confirm the *cis* or *trans* THF configuration.

Saturated lactone bis-THF acetogenins

Two bis-THF 'iso'-acetogenins have been reported in this period: 28-hydroxy-bullatacinone (**18.14**) (must be derived from rioclarin, **13.6**) and trilobacinone (**18.15**) (must be derived from trilobacin, **13.5**).

In the group of β-hydroxy-acetogenins (**19**: laherradurin type) no compound is added. So far, these compounds have been considered as exclusive to *Annona cherimolia* [82], but recently, compounds **19.1** and **19.2** have been isolated, by our group, from seeds of *Annona glabra* [50].

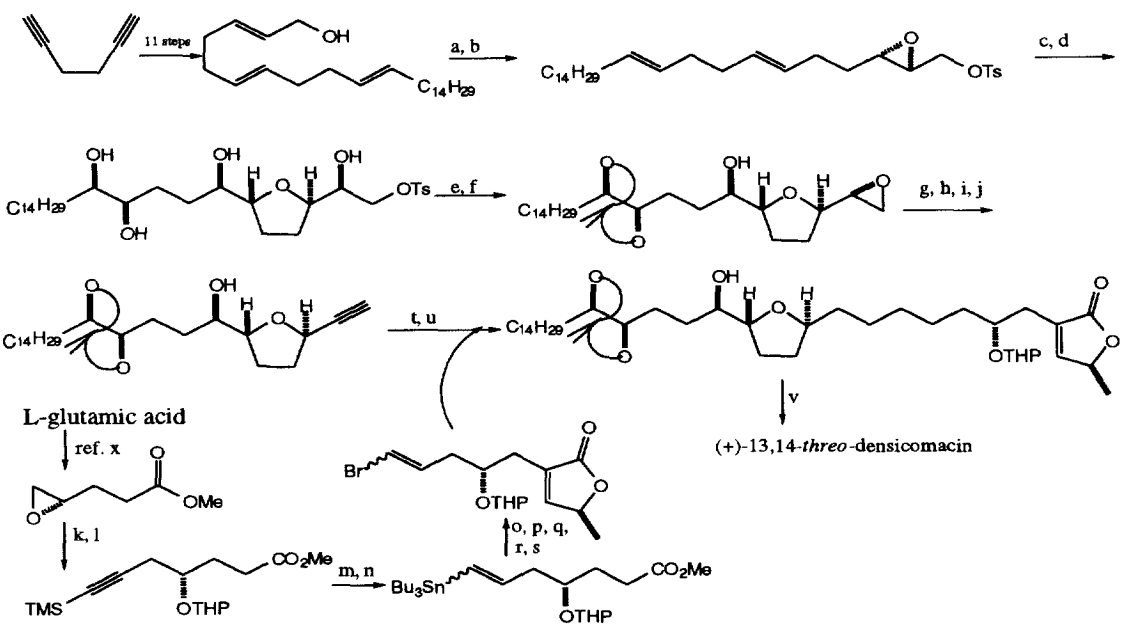
MISCELLANEOUS ACETOGENINS

In Table 10 we included a miscellaneous group of acetogenins characterized by an atypical substituted alkyl chain [1, 69, 83, 84]. Acetogenins with a THF ring and a non-adjacent (type **21**) or adjacent (type **22**) tetrahydropyran (THP) ring, were isolated from *Rollinia mucosa* [69, 83]. Mucocin (**21.1**) is the first acetogenin with an unusual hydroxylated THP ring and a relative configuration *trans/threo-threo/cis*. Finally, non-adjacent bis-THF acetogenins (**23**: aromin type) possessing a THF system between the 4/7 and 16/19 positions were found in *Xylopia aromatica* [84].

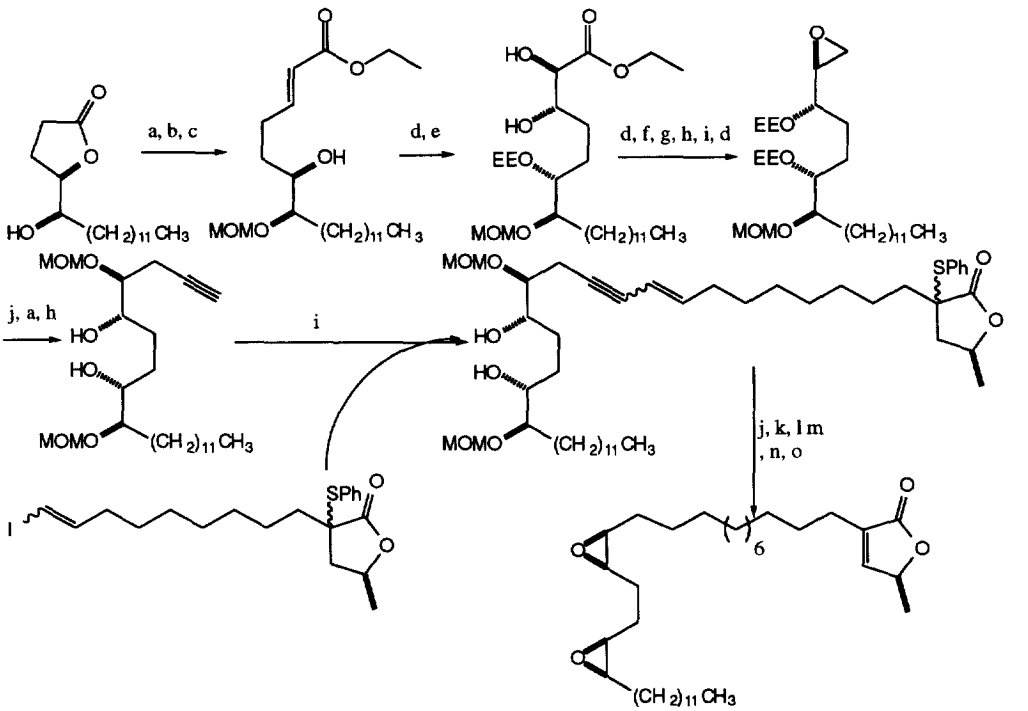
TOTAL SYNTHESIS

Since our last reviews [85, 86], numerous new approaches to Annonaceous acetogenins have appeared in the literature. We will not describe herein the preparation of key intermediates; instead we will focus on several synthetic pathways which led to the total synthesis of natural and enantiomeric acetogenins.

Cassady [87] prepared (+)-13,14-*threo*-densicomacin using a convergent strategy which required to prepare enantioselectively the THF part and the lactone moiety, prior to couple both synthons through the Sonogashira-Linstrumelle-Alami reaction (Scheme 1). The THF part of the molecule was prepared from the (*E,E,E*) triene which was obtained through an 11 step procedure from 1,5-hexadiyne. Then after asymmetric epoxidation of the allylic alcohol, a double asymmetric dihydroxylation afforded the tetraol, which upon basis treatment gave the THF pattern. After hydroxyl protection, the terminal epoxide was converted to the desired alkyne by opening with trimethylsilyl lithium acetylide. Concerning the lactone fragment, the strategy was inspired by Franck's work [88]. Indeed L-glutamic acid was converted into the corresponding epoxide [89] in five steps. Then addition of trimethylsilyl lithium acetylide, followed by



Scheme 1.



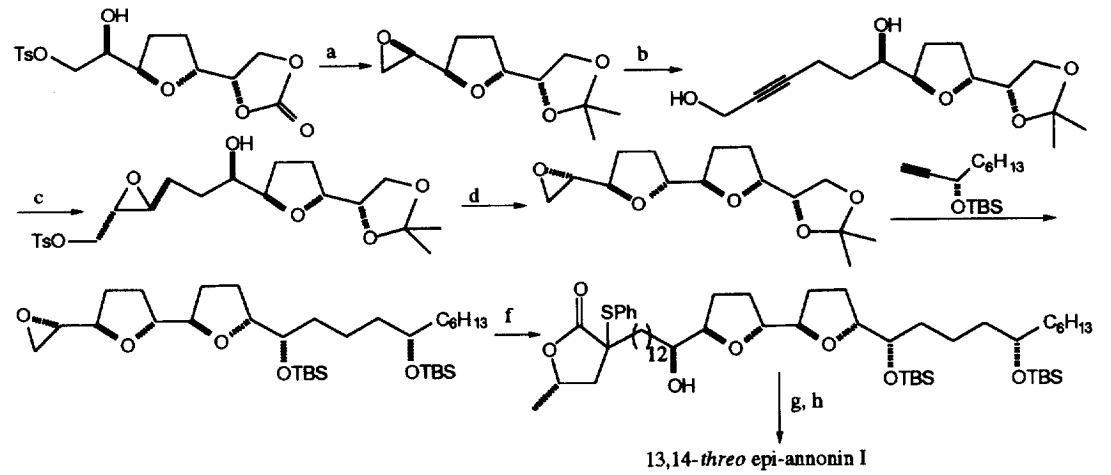
Scheme 2.

hydroxyl protection gave the bromopropargyl tetrahydropyran derivative. Addition of tri-*n*-butyl tin hydride in the presence of AIBN gave the corresponding vinyl tin compound. Introduction of the lactone was performed by enolization, followed by addition of O-MOM (*S*)-lactaldehyde, deprotection and lactonization. The tin–carbon bond was then cleaved by bromine to afford the corresponding vinyl bromine. Dehydration of the mesylate obtained from the corresponding alcohol afforded the desired synthon. The coupling reaction was performed in the presence of palladium triphenylphosphine tetrakis, copper iodide and diethylamine, leading to the enyne, which was selectively hydrogenated in the presence of Wilkinson catalyst [90]. Deprotection of the hydroxyls afforded the target molecule.

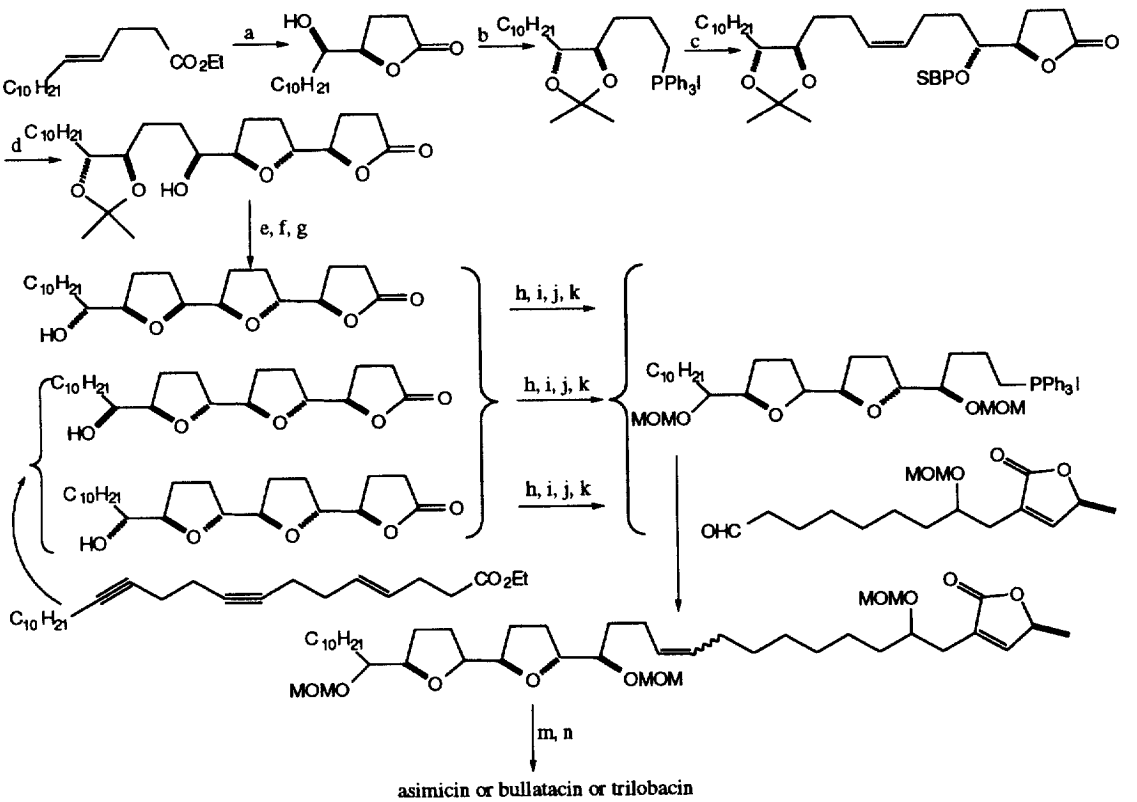
Tanaka [19, 91] (Scheme 2) described the synthesis of (15*S*,16*R*,20*R*,34*S*)-diepomuricanin, the natural bis-epoxide precursor of solamin (**5.4**), and thus was able to determine the absolute configurations of the stereogenic centers of the natural product. Since absolute configurations of solamin (**5.4**) are also known after completion of its total synthesis, it is now possible to propose that the oxirane opening followed by THF formation is under enzymatic control and that the first water attack occurs at C-15 with inversion of configuration, followed by the cascade reaction leading to the 2,5-disubstituted THF (the reverse rearrangement would have led to the opposite configuration across the THf pattern). The synthesis of the bis-epoxide started with the known muricatacin [5] which after hydroxyl protection, DIBAL reduction and Wittig reaction gave the ω-hydroxy-α,β-unsaturated ester. Hydroxyl protection and asymmetric dihydroxylation afforded the tetraol. Then several transformations led to the desired alkyne. The lactone fragment was prepared as already described as a vinyl iodide derivative [92]. Cross coupling reaction was performed between the two synthons under palladium catalysis through the Sonogashira-Linstrumelle-Alami reaction. Then hydrogenation of the enyne so obtained was performed in the presence of Wilkinson catalyst. Finally Williamson reaction and oxidative elimination afforded the desired molecule. It is worth noting that the same authors succeeded in the total synthesis of the proposed and erroneous structure for epoxyrollin-A and epoxyrollin-B [1].

Scharf [93] prepared the 15-*epi*-annonin I (Scheme 3), an unnatural isomer of the natural squamocin (**14.1**), also named annonin I. The key starting material was a building block prepared as in Ref. [94], which after leading to an epoxide gave the alylic alcohol through the propargyl alcohol. Then Sharpless epoxidation, followed by tosylation and ring rearrangement, afforded the bis-THF pattern. Opening of the epoxide by treatment with the lithiated homochiral alkyne, followed by hydrogenation and hydroxyl protections, gave the expected compound. The latter afforded the desired terminal epoxide which upon treatment with the lactone fragment [95] gave the coupled product which after deprotection afforded the target molecule.

Keinan [79, 96] prepared asimicin (**13.1**), buyllatacin or rollinistatin-2 (**13.3**) (two natural epimers at



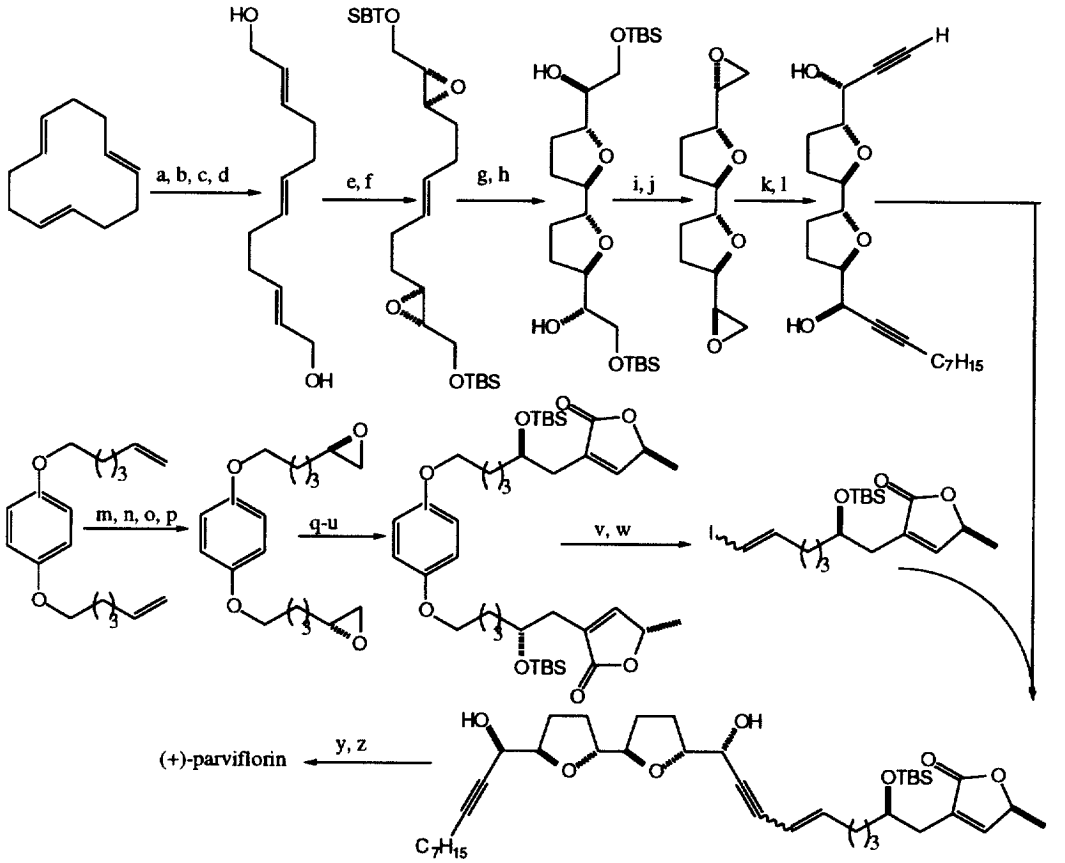
Scheme 3.



Scheme 4.

C-24) and trilobacin (**13.5**) through a similar strategy (Scheme 4): asymmetric dihydroxylation of a tris-unsaturated ester, Kennedy's oxidative-cyclization of a bis-homoallylic alcohol with rhenium oxide for the preparation of the THF synthons for bullatacin (**13.3**) and asimicin (**13.1**). For parviflorin (**13.8**), Wittig coupling reaction between a chiral aldehyde with a chiral phosphorus ylide gave the desired alkene which after di-hydroxylation and Williamson reaction afforded the THF pattern. The lactone fragment possessing at one terminus an aldehyde was prepared without any details. Then a Wittig reaction was performed for the coupling reaction between both fragments. Again, selective hydrogenation of the isolated double bond in the presence of Wilkinson catalyst, followed by deprotection of the hydroxyls led to the target molecules.

Hoye [97] prepared (+)-parviflorin (**13.8**) from a symmetrical (*E,E,E*)-triene through a double asymmetric epoxidation of allylic diol, followed by an

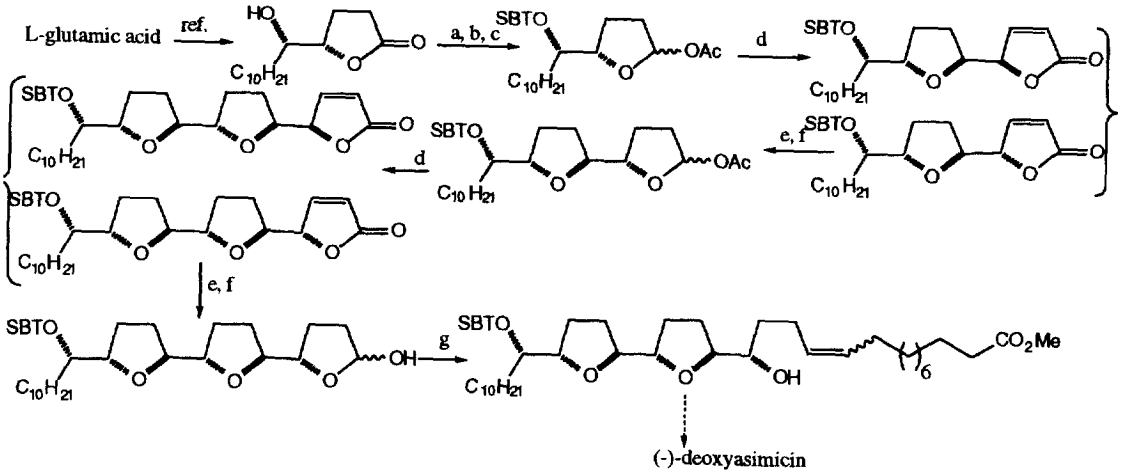


Scheme 5.

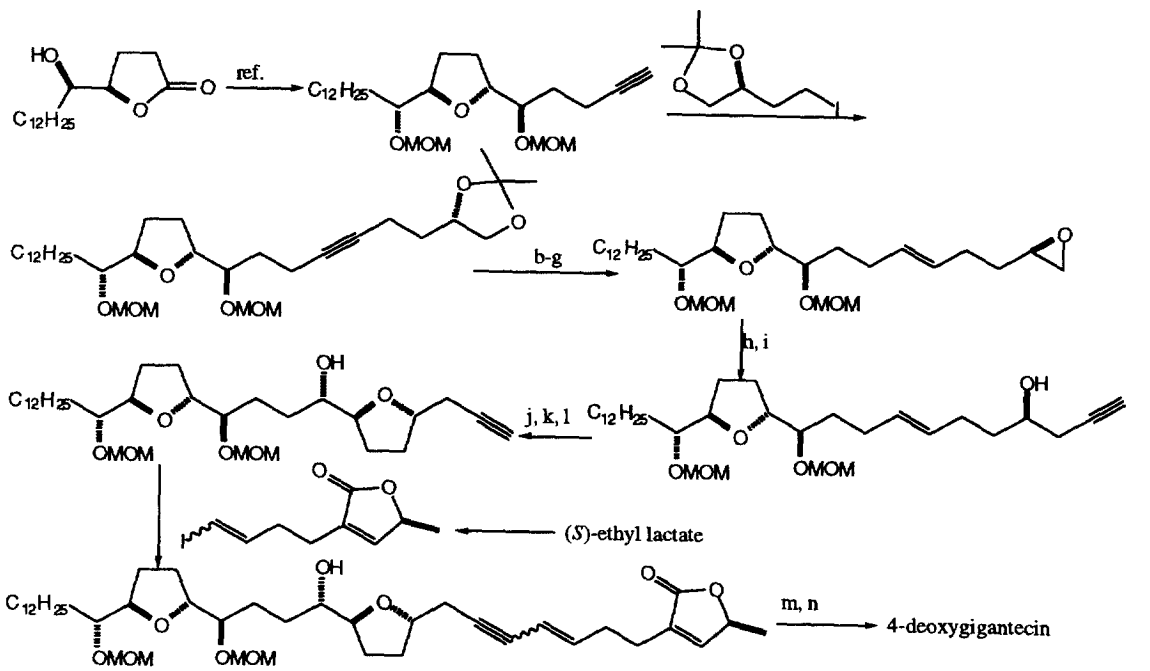
asymmetric dihydroxylation of the resultant double bond (Scheme 5). Oxiranes opening in acidic conditions led to the bis-THF pattern possessing two 1,2-diols which were easily converted into the corresponding epoxides. Then successive additions of trimethylsilyl lithium acetylide, followed by lithiated nonyne, led to the building block possessing a terminal triple bond. Since the coupling reaction with the lactone fragment was based on the Sonogashira-Linstrumelle-Alami reaction, vinyl iodide was prepared through an original approach. Namely, the 4-hydroxybutenolide was prepared from 6-iodo-hexene after bis-alkylation of hydroquinone followed by asymmetric dihydroxylation, and successive formation of the epoxides from the 1,2-diols obtained. Opening of the epoxides with lithiated optically pure 3-butyn-2-ol derivative, and selective deprotection of the propargyl hydroxyls led to the desired derivative which was ready for a Redal reduction followed by iodine treatment and Stille carbonylation to give the butenolide. Oxidative release, Swern oxidation and reaction with chromium (II) chloride and iodoform gave the required vinyl iodide with a high optical purity. The final coupling reaction under palladium catalysis (Sonogashira-Linstrumelle-Alami reaction), followed by the selective hydrogenations and hydroxyls deprotections led to (+)-parviflorin (**13.8**).

Figadère [98] (Scheme 6) prepared the C_1–C_{34} skeleton of (−)-deoxyasimicin through a repetitive stereoselective C-glycosylation of anomeric acetates with trimethylsilyloxyfuran. The starting material was prepared from L-glutamic acid as reported [99]. Then a Wittig reaction followed by hydrogenation gave the C_1–C_{34} fragment of (−)-4-deoxyasimicin. Known procedures for introduction of the C_{35}–C_{37} lactone ring [100] would lead to *ent*-asimicin.

Tanaka [101] (Scheme 7) recently reported the first synthesis of a non-adjacent bis-THF acetogenin, (+)-4-deoxygigantecin (**17.2**). The starting material was (−)-muricatacin [5] which after several steps afforded the THF moiety possessing a terminal alkyne [92]. Then alkylatin with a chiral alkyl iodide, followed by semi-hydrogenation and formation of the terminal epoxide through the 1,2-diol, afforded the desired intermediate. The latter was treated with lithiated trimethylsilyl acetylene, giving the homopropargyl alcohol, which after asymmetric dihydroxylation and Williamson reaction gave the desired terminal alkyne. The latter was directly coupled with the vinyl iodide bearing the lactone fragment (prepared from (*S*)-ethyl lactate) through the Sonogashira-Linstrumelle-Alami reaction, to afford the desired enyne. Chemoselective hydrogenation with Wilkinson catalyst, followed by hydroxyl deprotection afforded the target compound.



Scheme 6.



Scheme 7.

These recent syntheses of natural acetogenins, as well as the syntheses of epimers or enantiomers, illustrates the increasing interest in this family of compounds. More preparations are to come in order to improve the efficiency of the synthetic pathways, as well as to design new analogs with better biological specificity.

BIOLOGICAL ACTIVITY

Acetogenins of Annonaceae are potent cytotoxic agents mainly as insecticides, parasitics, fungicides, herbicides and also as antitumor compounds [1–4, 102, 103]. Since then, great efforts have been made in several directions to elucidate their mode of action.

Weiss [104] noted in 1991 the ability of Annonaceous acetogenins to inhibit the mitochondrial respiration. These results were confirmed in 1993 by other groups of workers [105, 106]. Currently it is well established that the inhibition of the mitochondrial respiration at site I is the main mode of action of the acetogenins [107]. Complex I is the limiting step in the production of energy by the mitochondria. Inhibition of this enzyme gives a rationale for the antitumor activity because most tumor cells require high-energy production. Although other additional mechanisms

have been reported [108], this specific action explains all the biological activities previously reported.

Antitumor cell line assays

The major attention to this group of natural products derives from the idea that they represent a future generation of antitumor drugs. Many studies to establish the cytotoxic potency of acetogenins for several human tumor lines are being undertaken. This has become a standard method for evaluating *in vitro* new cytotoxic acetogenins. An extensive review of all these data reveals different general tendencies for each tumor cell line. Against the human lung, breast and colon carcinoma cells (A-459, MCF-7 and HT-29 respectively) the most potent groups of acetogenins (considering DE_{50} values) are some of the adjacent bis-THF α,α'-dihydroxylated acetogenins (asimicin, squamocin and panalicin types, Table 6), followed by the non-adjacent bis-THF acetogenins (Table 8). Mono-THF α,α'-dihydroxylated acetogenins show intermediate potency (Table 3), followed by the mono-THF α-monohydroxylated ones (Table 4). Some of the polyhydroxylated and tetrahydroxylated ketonic mono-THF α,α'-dihydroxylated acetogenins (Table 3) have the weakest inhibitory potency. However, these tendencies are significantly different against human prostate adenocarcinoma (PC-3), human pancreatic carcinoma (MIA PaCa-2) and human kidney carcinoma (A-498) cells, where the mono-THF acetogenins are the most potent series (Table 3), followed by the 'iso' mono-THF acetogenins. The weakest potency against these tumor cell lines is presented in the bis-THF asimicin series (Table 6) and the linear acetogenins (Table 1).

Another type of antitumor study in cell culture was described as preliminary results by Schwaller [85] and later by Oberlies [109] who has recently reported that the bis-THF acetogenin rolliniastatin-2 (**13.3**) was effective against growth of multidrug resistance (MDR) culture cells in the adriamycin-resistant human mammary adenocarcinoma model (MCF-7). The authors indicate that rolliniastatin-2 or bullatacin (**13.3**) could not only assist in hindering normal cancerous cell growth but also in multidrug resistance tumor types as an adjuvant.

Our extensive examination of the activity of acetogenins systematized here for the first time shows that the bulk of their data are puzzling and confusing. Indeed, it does not clarify the structure–activity relationship of those compounds; moreover it is difficult to understand the antitumor test results at the molecular level. It is important to note that growth inhibition of cultured tumor cells depends on many additional factors other than the mode of action of the inhibitor molecule itself.

Mechanism of action

Although the mode of action of acetogenins is the inhibition of the mitochondrial complex I (NADH: ubiquinone oxidoreductase), few studies have explored the mechanism of action at the target enzyme level. This enzyme is the main gate for the energy production in the cell. It transfers electrons from NADH to ubiquinone and links this process with the translocation of protons across the inner membrane to generate an electrochemical gradient that drives the ATP synthesis. Complex I has assumed renewed interest by its implication in a great number of congenital and acquired diseases as encephalomyopathies, Huntington's disease, idiopathic Parkinson's disease, maturity onset diabetes and stroke-like episodes [110–112]. This interest is also growing as the selected target of a potential new generation of antitumor drugs.

Acetogenins have a high Ca^{2+} complexation ability, which has been demonstrated by NMR studies [98, 113–115]. These studies showed that the relative configuration, as well as the nature of the cation, are important factors for this complexation. Given that NADH: ubiquinone oxidoreductase is an iron cluster protein, some authors postulate that acetogenins may interfere with the enzyme by ion complexation [94]. However, this hypothetical mechanism has not been supported by experimental data up to now. Nevertheless, a Ca^{2+} plays an important role in the cell, complexation of this cation may affect other biological functions.

Landolt *et al.* [116] gave a preliminary tentative outline of the structure–activity relationship from studies of inhibition of the oxygen consumption by rat liver mitochondria. They indicated that both bis-adjacent THF and bis-nonadjacent THF acetogenins were more active than mono-THF acetogenins. In general they found that the presence of an increasing number of hydroxylations, up to by three, increased activity within all groups.

An important study on the mechanism by which the acetogenins inhibit the NADH:ubiquinone oxidoreductase was done by Degli Esposti [107]. Most acetogenins were found about one order of magnitude more potent than rotenone (a classical inhibitor of the enzyme taken as reference) and some of them (rolliniastatin-1 (**13.2**) and rolliniastatin-2 (**13.3**)) were more potent than piericidin-A (the most potent complex I inhibitor previously reported). Moreover, acetogenins inhibited complex I by different ways acting at different binding sites within the active site of the enzyme. These findings have received further support [117–119], also by genetic approaches [120].

We have recently compared the potency of three of the bis-THF acetogenins with a *threo/cis/threo/cis/erythro* configuration against the NADH oxidase activity in submitochondrial particles from beef heart [67]. This study showed that these three acetogenins: rolliniastatin-1 (**13.2**), membranacin (**12.5**) and rollimembrin (**13.21**), are potent inhibitors of the mitochondrial compled I, rollimembrin being the most potent inhibitor of the integrated respiratory chain to date, with an IC_{50} and full-inhibition concentration

significantly lower than rolliniastatin-1 (**13.2**) and rolliniastatin-2 (**13.3**). From the close chemical structures we can indicate that adjacent bis-THF acetogenins with a *threo/cis/threo/cis/erythro* relative configuration are the most potent inhibitors of mammalian complex I, and the proximity of the γ-lactone ring to the THF moiety plays an important role in the inhibitory potency as rollimembrin with a shorter alkyl chain is the most potent of the series [67].

Our most recent work has advanced in the knowledge of the structure–activity relationships of the mono-THF acetogenins at the molecular level. From these studies [50], we can conclude that if the acetogenin bears a hydroxyl in 4 position, the substitution of an hydroxyl group in 10 position by a carbonyl one, annonacin (**7.1**) vs annonacinone (**7.3**), increases up to seven times the inhibitory potency of mono-THF acetogenins over complex I, approaching the potency of rolliniastatin-1 (**13.2**). On the other hand, this substitution does not affect acetogenins without a hydroxyl in the 4 position, corossolin (**6.2**) vs corossolone (**6.3**).

Recently there has been reported a NADH oxidase activity found in liver plasma membranes. Studies carried out by Oberlies [108] shown that this NADH oxidase activity of rat liver plasma membranes was unaffected by rolliniastatin-2 (**13.3**) whereas it was strongly inhibited in several tumor cell lines like HeLa (human cervical carcinoma origin) and HL-60 (human promyelocytic leukemia origin). Authors have proposed that the inhibition of this enzymatic system could explain the selective inhibition of tumor cells [121]. However, it seems a marginal effect of rolliniastatin-2 (**13.3**), which main mode of action is the inhibition of the mitochondrial NADH:ubiquinone oxidoreductase. Interestingly, this acetogenin inhibits complex I by a mechanism that differs from that of all the complex I inhibitors known up to now. Moreover, other acetogenins currently investigated in our laboratory, as cherimolin-1 (**16.3**) [122], could have this particular mode of action.

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