REVIEW

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Acetogenins from Annonaceae: recent progress in isolation, synthesis and mechanisms of action

Almudena Bermejo,[a] Bruno Figadère,*[b] Maria-Carmen Zafra-Polo,[a] Isabel Barrachina,[a,b] Ernesto Estornell[c] and Diego Cortes*[a]

[a] *Departamento de Farmacología, Facultad de Farmacia, Universidad de Valencia, 46100, Burjassot, Valencia, Spain. E-mail: dcortes@uv.es; Fax: (34) 96354 4943; Tel: (34) 96354 4975*

[b] *Laboratoire de Pharmacognosie, associé au CNRS (BIOCIS), Faculté de Pharmacie, Université Paris-Sud, 92296, Châtenay-Malabry, France. E-mail: bruno.figadere@cep.u-psud.fr; Fax: (33) 1 4683 5399; Tel: (33) 1 4683 5592*

[c] *Departamento de Bioquímica y Biología Molecular, Facultad de Farmacia, Universidad de Valencia, 46100, Burjassot, Valencia, Spain. E-mail: ernesto.estornell@ uv.es; Fax: (34) 96354 4943; Tel: (34) 96354 3481*

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Covering: the literature from 1998 to 2004

The aim of the present review is to summarise the knowledge about newly isolated acetogenins (ACGs) in the last six years. It will also report the total syntheses that have allowed either the confirmation or the revision of some structures, together with the biological activities and mechanism of action of such interesting natural products. In fact, of the 417 isolated compounds reviewed, over 176 have been added during the period from 1998 to 2004.

Almudena Bermejo obtained her PhD degree from the Universidad de Valencia-Facultad de Farmacia (1997) under the guidance of Professor Diego Cortes. After a postdoctoral position financially supported by the Servier Laboratory (1997–2003), she obtained a Scientific position at IVIA (Instituto Valenciano de Investigaciones Agrarias) in 2004. Her research interests are in natural products (isolation, structure determination, synthesis and biological properties).

Bruno Figadère was educated in Paris (Université Pierre et Marie Curie, Dr Sc. J. Normant) and at University of California Riverside (postdoctoral, W. H. Okamura, 1988–1990). In 1990, he was appointed to the CNRS as Chargé de Recherche and promoted Directeur de Recherche in 1997. Since then he has worked at the Université Paris Sud-Faculté de Pharmacie, and received several awards for his achievements in the chemistry of bioactive natural products (Bronze Medal 1994 of CNRS, Servier Award 1995 of the Société de Chimie Thérapeutique, Acros Award 2000 of Société Française de Chimie). Along with studies on naturally occurring products (isolation, structure determination and total synthesis) he is also interested in the development of new, practical and non-toxic methods for synthesis. He is author of 95 publications and chapters and holds two patents in the field.

Maria-Carmen Zafra-Polo received her PhD degree from the Universidad de Valencia-Facultad de Farmacia (1980). After a postdoctoral position with Professor C. Galeffi in Rome (Italy) in 1981, she is since 1985 Profesora Titular (Assistant Professor) in Farmacologia at the Universidad de Valencia-Facultad de Farmacia. Her main interests concern the chemistry and biological properties of natural products. She is the author of 60 publications in the field.


Dr Alumudena Bermejo


Dr Bruno Figadère


Dr Maria-Carmen Zafra-Polo

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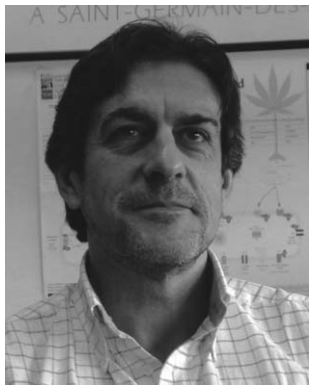
Isabel Barrachina received a MSc degree in Pharmacy from the Universidad de Valencia-Facultad de Farmacia (2000), and a MSc degree from the Université Paris-Sud (2001). She is now carrying out her PhD research with Professors Cortes and Figadère on the isolation and synthesis of natural mitochondrial complex I inhibitors.

Ernesto Estornell obtained his PhD from the Universidad de Valencia-Facultad de Farmacia (1991), and spent two years (1992–1993) with Professor M. Degli Esposti in Bologna (Italy). He is since 1996 Profesor Titular (Assistant Professor) in the Department of Biochemistry and Molecular Biology of the Facultad de Farmacia at the Universidad de Valencia. His research interests are the inhibitors of the mitochondrial respiratory chain. He is the author of 45 publications.

Diego Cortes received two PhD degrees, one from the Universidad de Valencia-Facultad de Farmacia (1980) and the another from the Université Paris-Sud with Professor André Cavé (1985). After accepting a professorship at the Université de Rouen (1988–1993), he joined the Universidad de Valencia in 1993 where he is currently Professor (Catedratico). His scientific interests are the discovery of new natural products, their synthesis and their biological properties. He is author of 120 publications and 1 patent in the field.

Isabel Barrachina

Dr Ernesto Estornell



Dr Diego Cortes

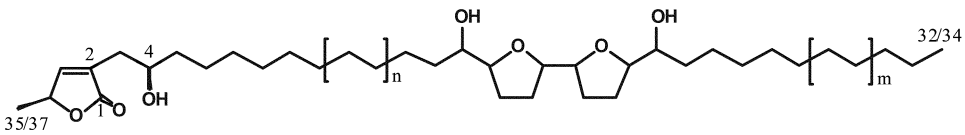
1 Introduction

Annonaceous acetogenins (ACGs) constitute a series of natural products isolated exclusively from Annonaceae species[1–6] that are widely distributed in tropical and sub-tropical regions. The common skeleton is most often characterised by an unbranched C_{32} or C_{34} fatty acid ending in a γ-lactone. Several oxygenated functions, such as hydroxyl, ketone, epoxide, tetrahydrofuran (THF) and tetahydropyran (THP), may be present, as well as double and triple bonds. Thus several types of ACG have been characterised, based on the nature of the functional groups which are present. ACGs exhibit a broad range of biological properties such as cytotoxic, antitumoural, antiparasitic, pesticidal, antimicrobial and immunosuppresive activities. Mechanism of action studies have shown that ACGs are the most potent inhibitors of the mitochondrial respiratory chain complex I. The biogenetic pathway of such unusual secondary metabolites is postulated, since no systematic studies have been carried out so far. Starting from a very long chain fatty acid, introduction of the terminal γ-lactone appears first, then by oxidation of the unsaturated units present, followed by opening and closing reactions, the THF and THP rings are introduced.[1–6]

The purpose of this review is to list all the annonaceous ACGs known up to now. Since our last review was published,[2] research in the field of annonaceous ACGs dealing with the isolation, structural elucidation, semi-synthesis or total synthesis, and mechanism of the cytotoxic action has shown a rapid increase. In fact, of the 417 compounds reviewed, over 176 new ACGs have been added to the list of isolated compounds during the period from 1998 to 2004.

The classification is made following the same criteria and based on the structural characteristics shown in Fig. 1. Three new types of γ-lactone moiety, L-B2 (α-acetonyl-α,β-unsaturated-γ-lactone), L-E (saturated γ-hydroxy methyl-γ-lactone) and L-F (β-methoxy-γ-methylene-α,β-unsaturated-γ-butyrolactone), as well as a new type of tetrahydropyran (THP) system (T-G.3) are included. In addition, two new subgroups of ACGs are presented, characterised by a different type of side chain: 1d (bis-lactonic linear ACG), and 22a (mono-THP ACG).

As in our previous reviews[1,2] we discuss herein, by considering the published spectral data, several uncertain aspects of compounds described as new ACGs. Within the tables, compounds are presented in chronological order of discovery. For a complete revision, both new and previously published data are reported. To make the reading of tables easier, multiple names for ACGs (shown as, *e.g.* "epoxymurin-A or epomuricenin-A") have only been given when two research groups isolated the compound at the same time.[1,2] The great number of compounds to be added made necessary the inclusion of new subgroups, and in general their numbers listed in the previous review are maintained.[2] The additional new compounds are given in bold. The number of



General structure of acetogenins.

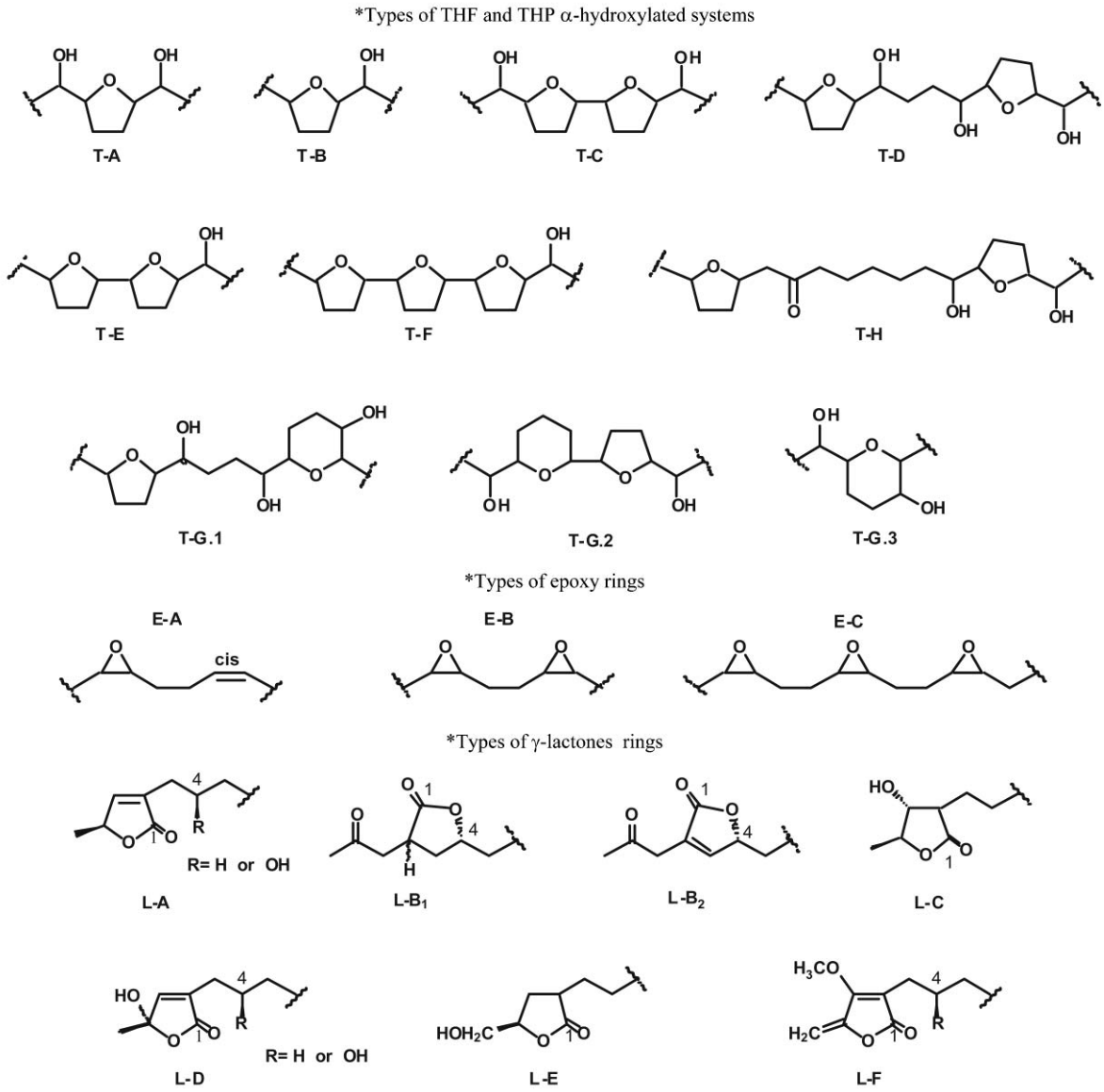


Fig. 1 Tetrahydrofuran (THF), tetrahydropyran (THP), epoxy and γ-lactone systems in Annonaceous acetogenins.

'reliable' ACGs must be considered as 417 so far, 40 of them being linear, 16 epoxy, 206 mono-THF, 146 bis-THF, 1 tri-THF, and 8 other ACGs belonging to the THP group (see Tables 1–11). Table 12 summarises the species from the Annonaceae family from which new ACGs have been isolated. Four new genera, *Artabotrys*, *Dasymaschalon*, *Ophrypetalum* and *Sassopetalum* were found to contain ACGs. In Table 13 the ACGs cited in this review are listed in alphabetical order. In addition, a survey on the advances in cytotoxic and antitumour mechanisms, as well as in the total synthesis of ACGs in recent years, is included.

2 Extraction, isolation and purification

The classic extraction of ACGs from plants is carried out by successive solvent extractions with increasingly polar solvents, or by liquid/liquid partition from an initial alcoholic extract. The separation of ACGs is then performed by chromatography on silica gel or by preparative HPLC.[3–5] Positional isomeric and epimeric ACGs have been successfully separated by preparative HPLC. Countercurrent chromatography (CCC or CPC) has also been used for isolating ACGs.[7] This method is highly efficient since large amounts of mixtures and crude extracts, when purified by this method, have afforded pure compounds. Again, positional isomers, epimers and homologous ACGs have been successfully separated by CPC.[8] Recently, chiral HPLC has been used with success for the separation of epimeric ACGs obtained by synthesis,[9] which will allow in the future the determination of the absolute configurations of natural ACGs (*vide infra*).

3 Structural elucidation

The structural elucidation of ACGs has already been summarised in previous reviews.[3–5] This consists of analysis of the mass spectra to determine the exact molecular formula, followed by EI-MS and FAB-MS, which allow one to determine the position of the functional groups on the alkyl chain. Elucidation of the relative stereochemistry of the stereogenic centres by careful analysis of the ^{1}H- and ^{13}C-NMR spectra is now straightforward, due to the possible comparisons of the spectra between those of the natural products and synthetic models. For the determination of the absolute configurations, the advanced Mosher ester methodology has allowed several authors to determine unambiguously the absolute configuration of the carbinols present in the vicinity of the THF rings, and thus to assign the whole configuration of the THF units. For isolated carbinols, the use of 2-NMA (2-napthylmethoxy acetic acid) esters is of great interest, since the influence of the aromatic rings can extend to five carbon–carbon bonds.[10]

Concerning the absolute configuration of the terminal γ-lactone, several methods have been used and described in the

preceding reviews, but they all required the degradation of the natural ACGs in order to obtain lactic acid derivatives, which can be analysed by chromatography. Recently, it has been proposed to analyse ACGs by ^{1}H-NMR spectroscopy, in the presence of a chiral solvating agent (CSA), and deduce the absolute configuration of the terminal γ-lactone by analysing the chemical shift differences of the carbinolic proton of the lactone in the presence of the (*R*)- and (*S*)-CSA.[11]

Circular dichroism has also been used for the determination of the absolute configuration of the terminal γ-lactone.[12]

4 Types of acetogenins and new compounds

Compounds previously covered in reviews[1,2] and new compounds[8,13–104] have been included in Tables 1–11. The reliable number of reported ACGs must now be considered as 417, with 176 of these being new.

4.1 Linear ACGs (Group 1)

The isolated natural linear ACGs, claimed as the biogenetic precursors of epoxy- and THF-ACGs, differed in the degree of unsaturation and hydroxylation of their alkyl chains. We can consider here four subgroups (1a to 1d) (see Table 1).

Group 1a – Vicinal dihydroxylated and olefinic acetogenins (giganin type). This is the most abundant subgroup, which includes 21 compounds. They are characterised by the presence of a vicinal diol, and some of them by one or two double bonds. In all of these ACGs a *Z*-geometry for the double bond and a *threo* relative configuration at the vicinal diol have been established, except for murihexol (1a.13), which possesses two vicinal diols containing *threo* and *erythro* configurations. Cohibins-C and D (1a.15),[56] donhepocin + 34-*epi*-donhepocin (1a.19),[22] donnaienin-D + 34-*epi*-donnaienin-D (1a.20),[27] and artemoins A–D (1a.21)[51] were obtained as mixtures. Moreover, the position of the acetyl group at C-4 in 1a.20 in our opinion must be revised. It is interesting to note that two new ACGs in this group, 1a.19 and 1a.20, present an L-D lactone type.[22,27]

Group 1b – Hydroxylated (or ketonic) linear acetogenins (reticulatamol type). These are characterised by one or more non-vicinal hydroxyl groups (or a ketone group), and only three compounds belong to this subgroup.

Group 1c – Olefinic and acetylenic acetogenins (muridienin-1 type). Without hydroxyl groups on the alkyl chain, four novel ACGs with a γ-lactone L-A type have been reported, three of them isolated as mixtures (1c.5, 1c.6, 1c.8).[21] Moreover, six compounds with an interesting new type of terminal lactone, L-E or L-F, are described for the first time. Goniothalamusin (1c.9), saccopetrin-A (1c.10) and saccopetrin-B (1c.11) are ACGs containing an L-E lactone, and have a shorter alkyl chain (C25 skeleton) and one or two triple bonds. The only difference between the 1c.9 and 1c.10 isomers is the positive or negative sign of the specific rotation $[\alpha]_D$.[44,88] On the other hand, artapetalin-A (1c.12), -B (1c.13) and -C (1c.14), possess a terminal L-F lactone and three double bonds. Compounds 1c.12 and 1c.13 are the first ACGs containing a C22 skeleton,[61] whereas 1c.14 is the only ACG containing an unusual moiety on the aliphatic chain, a 4-*epi*-cubebol group.[61]

Group 1d – Bis-lactonic linear acetogenins (rollicosin type). Bis-lactonic linear ACGs are a new subgroup of ACGs with one or two hydroxyl groups, characterised by the presence of two terminal lactone moieties on both sides of the aliphatic chain and the lack of either THF or THP rings. Compounds 1d.1 and 1d.2 contain a classical γ-methyl, α,β-unsaturated γ-lactone (L-A type) and a simple saturated γ-lactone.[72,95]

4.2 Epoxy-ACGs (Groups 2–4)

In the group of epoxy-ACGs (Table 2), only two compounds, sabadelin (2.6) and coronin (3.9) have been added.[45,70] As we have disclosed above, epoxy-ACGs, probably originating by oxidation of linear and olefinic ACGs, are key metabolites in the biosynthesis of mono-, bis- and tri-THF ACGs.[1–5]

4.3 Mono-THF ACGs (Groups 5–11)

Groups 5–8 – Mono-THF-α,α′-dihydroxylated acetogenins (Table 3). These represent the most important subclass of mono-THF ACGs, now enlarged by the addition of 9 new dihydroxylated ACGs (type 5), 13 trihydroxylated and dihydroxylated ketonic ACGs (type 6), 26 tetrahydroxylated and trihydroxylated ketonic ACGs (type 7) and 13 polyhydroxylated and tetrahydroxylated ketonic ACGs (type 8).

A *threo–trans–threo* or *threo–trans–erythro* or *threo–cis–threo* relative configuration has been established for all the mono-THF-α,α′-dihydroxylated ACGs, although there is one compound with an *erythro–trans–threo* relative configuration (6.9).[1,2] The relative configuration of two new compounds, 15-palmitoylsolamin (5.17) and 15-oleylsolamin (5.18) has not been determined. Their structures were determined by MS/MS.[86]

It is interesting to note that the relative configuration of asitrocin (7a.41) was reported as *erythro–trans–threo*. The authors comment that the location of the *threo* assignment should be at C-19/20 rather than C-15/16 because δ_H value of the *threo* carbinol methine in the ^{1}H NMR spectra of 7a.41 was 3.40 ppm; if the reverse was true, this value would have been 3.44 ppm.[62] This comment is also valid for the corresponding *iso*-derivative, asitrocinone (10.18) (Table 5). In our opinion these arguments are ambiguous, because of the minimal differences in the NMR values.[62]

Donnaiein (8.15), is an ACG with a hydroxyl group in the THF ring. The relationship at C-13/14 for 8.15 was deduced as *threo*, the ring as *trans*, and at C-14/15 as *threo*, and applying Born's rule, the relation at C-17/8 was confirmed as *threo*.[19]

Group 9 – Mono-THF-α-monohydroxylated acetogenins (Table 4). Fourteen novel ACGs have been added in this group, which is presented in two subgroups: 4-hydroxylated ACGs (9a: gigantetrocin-A type) and compounds without a 4-hydroxyl group (9b: gigantriocin type)[1,2] (Table 4). Muricin-B (9a.23) is the first ACG with a 4*S* absolute configuration, whereas muricin-C (9a.24), was reported as an unusual ACG with the THF ring at the C-17 position.[63] On the other hand, it is interesting to note that muricin-D (9a.25) and muricin-E (9a.26) are the first mono-THF ACGs reported with a C_{33} skeleton.[63]

Groups 10 and 11 – Mono-THF acetogenins with a L-B1, L-B2, L-C or L-D lactone moiety (Table 5). The number of "*iso*"-mono-THF ACGs (10: isoannonacin type) has been increased by nine novel compounds[1,2] (Table 5). All these compounds, described as 2,4-*cis* and 2,4-*trans* mixtures, are characterised by the presence of a 2-acetonyl saturated γ-lactone moiety (L-B) with sole exception of montanicin-F (10.22), which contains a novel subtype of terminal lactone unit, an unsaturated lactone L-B2 type.[74] Since 1994, it has been well-known, and further largely accepted, that the "ketolactones" or "*iso*"-ACGs, obtained as a mixture of C-2-epimers, are spontaneously formed by translactonisation from classical 4-hydroxylated ACGs during extraction procedures by a simple mildly basic medium (for example by alkaloids), or after gentle heating in MeOH. Therefore, these compounds must not be considered as natural products but as artefacts, with some exceptions.[1,2,4]

Another important subclass of ACGs contain a 34- or 36-OH-α,β-unsaturated lactone moiety (L-D). All ACGs of this type, due to the presence of the hemi-acetal function, have been isolated as mixtures of the C-34 or C-36 epimers (Fig. 1). Since our last review, 9 ACGs are reported as belonging to this

Table 1 Acetogenins without tetrahydrofuran rings: linear acetogenins (Group 1)

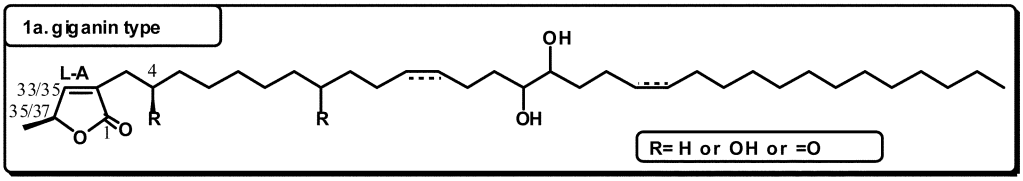
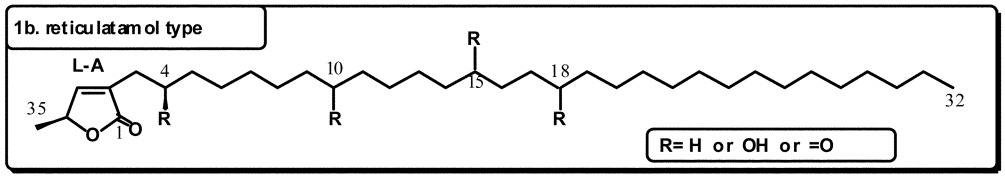
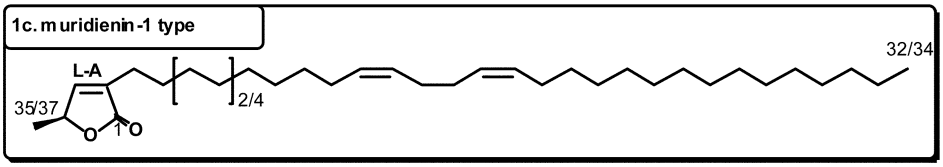
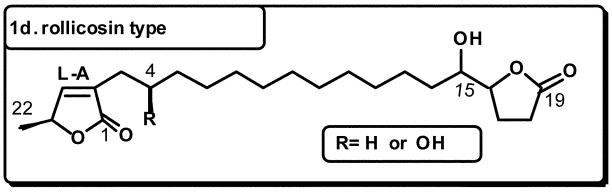
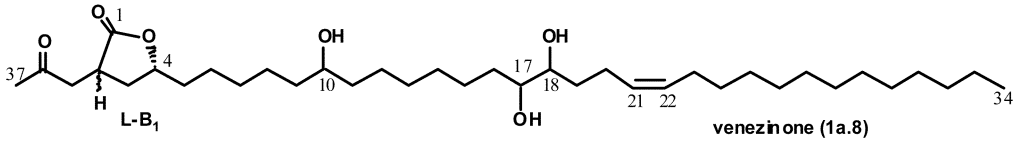
		Olefinic position	Hydroxyl positions	Relative configuration[a]	Molecular formula	M+	Species[b] [Ref.]
Group 1a – Vicinal dihydroxylated and olefinic linear acetogenins (giganin type)							
							
1a.1	giganin	Δ_{13}	4,10,17,18	*c-th*	$C_{35}H_{64}O_6$	580	*G. giganteus* [1]
1a.2	venezenin (CO,10)	Δ_{21}	4,17,18	*th-c*	$C_{37}H_{66}O_6$	606	*X. aromatica* [1]
1a.3	coriadienin	Δ_{13}; Δ_{17}	4,10,21,22	*c-c-th*	$C_{37}H_{66}O_6$	606	*A. coriacea* [2]
1a.4	tonkinelin		17,18	*th*	$C_{37}H_{70}O_4$	578	*U. tonkinesis* [2]
1a.5	montecristin	Δ_{17}; Δ_{21}	13,14	*th-c-c*	$C_{37}H_{66}O_4$	574	*A. muricata* [2]
1a.6	cohibin-A	Δ_{19}	15,16	*th-c*	$C_{35}H_{64}O_4$	548	*A. muricata* [2]
1a.7	cohibin-B	Δ_{17}	13,14	*th-c*	$C_{35}H_{64}O_4$	548	*A. muricata* [2]
1a.8	venezinone[c]	Δ_{21}	10,17,18	*th-c*	$C_{37}H_{68}O_6$	608	*X. aromatica* [2]
1a.9	**gardnerilin-A**		4,8,15,16,19,20	*th-th*	$C_{35}H_{66}O_8$	614	***G. gardneri*** [16]
1a.10	**gardnerilin-B**		4,10,17,18	*th*	$C_{35}H_{66}O_6$	582	***G. gardneri*** [16]
1a.11	**donhexocin**		4,10,15,16,19,20	*th-th*	$C_{35}H_{66}O_8$	614	***G. donnaiensis*** [22]
1a.12	**donbutocin**		4,10,15,16	*th*	$C_{35}H_{66}O_6$	582	***G. donnaiensis*** [22]
1a.13	**murihexol**		4,10,15,16,19,20	*th-er*	$C_{35}H_{66}O_8$	614	***A. muricata*** [23]
1a.14	**annojahnin** (CO,10)	Δ_{21}	17,18	*th-c*	$C_{37}H_{66}O_5$	590	***A. jahnii*** [39]
1a.15	**cohibin-C + D**[d]	$\Delta_{21/19}$	17/15,18/16	*th-c*	$C_{37}H_{68}O_4$	576	***A. muricata***, ***A. nutans*** [56]
1a.16	**annodienin** (CO,10)	Δ_{17}; Δ_{21}	13,14	*th*	$C_{37}H_{64}O_5$	588	***A. jahnii*** [85]
1a.17	**jahnonacin**	Δ_{21}	4,10,17,18	*th*	$C_{37}H_{68}O_6$	608	***A. jahnii*** [85]
1a.18	**muricatenol**	Δ_{14}	4,10,18,19	*c-th*	$C_{37}H_{68}O_6$	608	***A. muricata*** [89]
1a.19	**donhepocin + 34-*epi***[e]		4,10,15,16,19,20,34	*th-th*	$C_{35}H_{66}O_9$	630	***G. donnaiensis*** [22]
1a.20	**donnaienin-D + 34-*epi***[e]		(OAc-4),10,15,16,19,20,34	*th-th*	$C_{37}H_{66}O_{10}$	672	***G. donnaiensis*** [27]
1a.21	**artemoin-A + B + C + D**		19,20/17,18	*th*	$C_{35}H_{66}O_4$	550	***A. atemoya*** [51]
Group 1b – Hydroxylated (or ketonic) linear acetogenins (reticulatamol type)							
							
1b.1	reticulatamol		15		$C_{35}H_{66}O_3$	534	*A. reticulata* [1]
1b.2	reticulatamone (CO,15)				$C_{35}H_{64}O_3$	532	*A. reticulata* [1]
1b.3	longanin		4,10,18		$C_{35}H_{66}O_5$	566	*As. longifolia* [2]
Group 1c – Olefinic and acetylenic linear acetogenins (non-hydroxylated) (muridienin-1 type)							
							
1c.1	muridienin-1	Δ_{13}; Δ_{17}		*c-c*	$C_{35}H_{62}O_2$	514	*A. muricata* [2]
1c.2	muridienin-2	Δ_{15}; Δ_{19}		*c-c*	$C_{37}H_{66}O_2$	542	*A. muricata* [2]
1c.3	butyrolactone-1[f]	Δ_{21}; $\Delta_{13}(\equiv)$			$C_{25}H_{42}O_3$	390	*P. macrocarpa* [2]
1c.4	butyrolactone-2[f]	$\Delta_{13}(\equiv)$			$C_{25}H_{44}O_3$	392	*P. macrocarpa* [2]
1c.5	**chatenaytrienin-1 + 2**	$\Delta_{13/11}$; $\Delta_{17/15}$; $\Delta_{21/19}$			$C_{35}H_{60}O_2$	512	***A. nutans***, ***A. muricata*** [21]
1c.6	**chatenaytrienin-3 + 4**	$\Delta_{13/15}$; $\Delta_{17/19}$; $\Delta_{21/23}$			$C_{37}H_{64}O_2$	540	***A. nutans***, ***A. muricata*** [21]
1c.7	**muricadienin**	Δ_{15}; Δ_{19}			$C_{35}H_{62}O_2$	514	***A. nutans***, ***A. muricata*** [21]
1c.8	**muridienin-3 + 4**	$\Delta_{13/17}$; $\Delta_{17/21}$			$C_{37}H_{66}O_2$	542	***A. nutans***, ***A. muricata*** [21]
1c.9	**goniothalamusin**[g]	$\Delta_{13}(\equiv)$; Δ_{21}		[h]	$C_{25}H_{42}O_3$	390	***G. gardneri*** [44]
1c.10	**saccopetrin-A**[g]	$\Delta_{13}(\equiv)$; Δ_{21}		[h]	$C_{25}H_{42}O_3$	390	***S. prolificum*** [88]
1c.11	**saccopetrin-B**[g]	$\Delta_{13}(\equiv)$; $\Delta_{21}(\equiv)$			$C_{25}H_{40}O_3$	388	***S. prolificum*** [88]
1c.12	**artapetalin-A**[i]	Δ_9; Δ_{12}; Δ_{15}		*c-c-c*	$C_{22}H_{32}O_3$	344	***Ar. hexapetalus*** [61]
1c.13	**artapetalin-B**[i]	Δ_9; Δ_{12}; Δ_{15}	18	*c-c-c*	$C_{22}H_{32}O_4$	360	***Ar. hexapetalus*** [61]
1c.14	**artapetalin-C**[i]	Δ_9; Δ_{12}; Δ_{15}	18[j]	*c-c-c*	$C_{37}H_{54}O_4$	562	***Ar. hexapetalus*** [61]

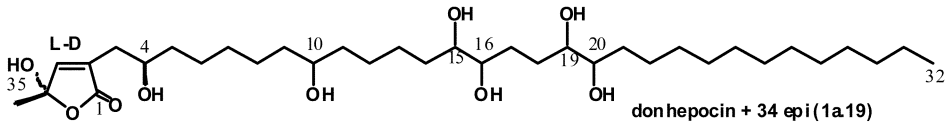
Table 1 (*Cont.*)

		Olefinic position	Hydroxyl positions	Relative configuration[a]	Molecular formula	M^+	Species[b] [Ref.]
Group 1d – Bis-lactonic linear acetogenins (rollicosin type)							
							
1d.1	rollicosin		4,15		$C_{22}H_{36}O_6$	396	*R. mucosa* [72]
1d.2	squamostolide		15		$C_{22}H_{36}O_5$	380	*A, squamosa* [95]

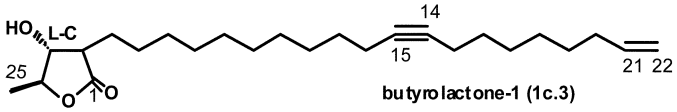
[a] *th* = *threo*; *c* = *cis*. [b] *G.* = *Goniothalamus*; *X.* = *Xylopia*; *A.* = *Annona*; *U.* = *Uvaria*; *As.* = *Asimina*; *P.* = *Porcelia*; *S.* = *Saccopetalum*; *Ar.* = *Artabotrys*.

[c] 

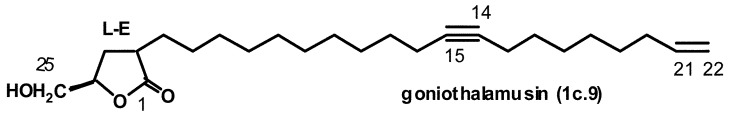
(linear ACG with lactone type L-B_1: 1a.8). [d] **1a.15** is a mixture of isomers C and D.

[e] 

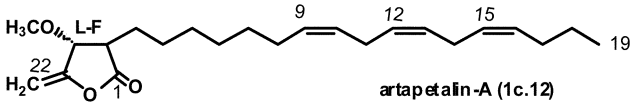
(linear ACG with lactone type L-D: **1a.19** and **1a.20**).

[f] 

(linear ACG with lactone type L-C: 1c.3 and 1c.4).

[g] 

(linear ACG with lactone type L-E: **1c.9**, **1c.10** and **1c.11**). [h] Compounds **1c.9** and **1c.10** are isomers, which only differ in the sign of $[\alpha]_D$.

[i] 

(linear ACG with lactone type L-F: **1c.12**, **1c.13** and **1c.14**). [j] **1a.14**: at C18 there is a 4-*epi*-cubebol group.

subgroup (11b.5 to 11b.13). Donnaiein-C + 34-*epi* (11b.6) has been reported as an unusual ACG with an acetyl group at the C-4 position,[27] but in our opinion this structure needs to be revised.

4.4 Bis-THF ACGs (Groups 12–20)

New compounds have been included in this group, and these have been classified into adjacent ACGs (Table 6 and Table 7), non-adjacent ACGs (Table 8) and saturated lactone ACGs (Table 9).

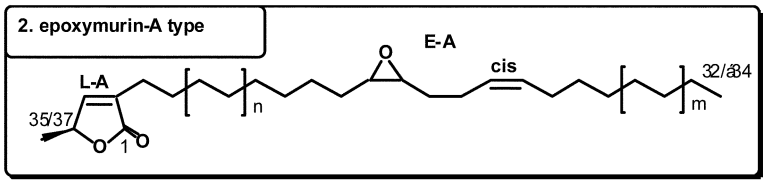
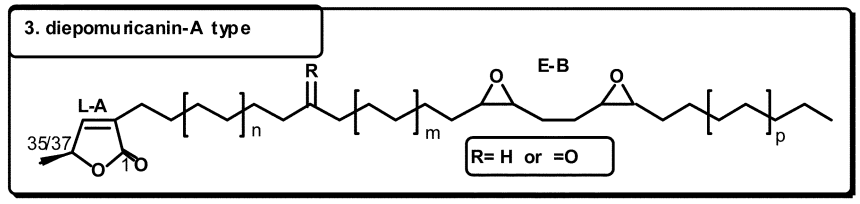
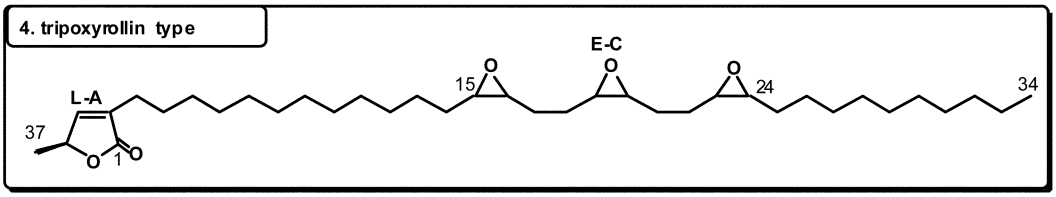
Groups 12–15 – Adjacent bis-THF acetogenins (Tables 6 and 7). Most of the adjacent bis-THF ACGs possess a bis-THF system flanked at the α and α′ positions by two hydroxyl groups; 31 new compounds have been thus reported (Table 6). Nine new α-monohydroxylated bis-THF ACGs have been described with a T-E ring system (Table 7).

The absolute configurations of squamocin-O_1 (14a.31) and squamocin-O_2 (14a.32) have been reported as 12*R* and 12*S*, respectively,[71] whereas salzmanolin (14a.38) is reported as an unusual ACG with a hydroxyl group on one of the THF rings, at the C-17 position.[93] The last six new compounds isolated by our group from *Annona* aff. *spraguei*, 14a.39 to 14a.44, present different and unusual degrees of acetylation, with one or two acetyl groups at several positions. The elucidation of their structures has been used to corroborate the acetylation positions of the other previously isolated compounds.[99]

Annocatacin-A (15.12) and annocatacin-B (15.13) are reported as the first ACGs with the THF ring at the C-15 position.[78] Glabracin-A (15.10) and glabracin-B (15.11) are the first ACGs with an α (and not α′) monohydroxylated bis-THF system.[77]

Groups 16–18 – Non-adjacent bis-THF acetogenins (Table 8). Only three new compounds have been added to the group of non-adjacent bis-THF ACGs: goniotriocin (16.10), with an hydroxyl in the THF ring, and characterised by the absence of hydroxyl group flanking the second THF ring,[36] 12,15-*cis*-squamostatin-D (17.5), and 12,15-*cis*-squamostatin-A (17.6).[51] Thus, in the

Table 2 Acetogenins without tetrahydrofuran rings: epoxy-acetogenins (Groups 2–4)

		Olefinic positions	Epoxy positions	Molecular formula	M^+	Species[a] [Ref.]
Group 2 – Mono-epoxy olefinic acetogenins (epoxymurin-A type)						
						
2.1	epoxymurin-A or epomuricenin-A	Δ_{19}	15,16	$C_{35}H_{62}O_3$	530	*A. muricata* [1] *A. muricata* [1]
2.2	epoxymurin-B	Δ_{15}	19,20	$C_{35}H_{62}O_3$	530	*A. muricata* [1]
2.3	epomuricenin-B	Δ_{17}	13,14	$C_{35}H_{62}O_3$	530	*A. muricata* [1]
2.4	epomusenin-A	Δ_{21}	17,18	$C_{37}H_{66}O_3$	558	*R. mucosa* [2]
2.5	epomusenin-B	Δ_{19}	15,16	$C_{37}H_{66}O_3$	558	*R. mucosa* [2]
2.6	**sabadelin**	Δ_{13}	17,18	$C_{35}H_{62}O_3$	530	***A. muricata*** [45]
Group 3 – Bis-epoxy acetogenins (diepomuricanin-A type)						
						
3.1	diepomuricanin-A[b]		15,16,19,20	$C_{35}H_{62}O_4$	546	*A. muricata* [1]
3.2	corepoxylone (CO,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	Δ_{23}	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]
3.9	**coronin**	Δ_{21}	13,14,17,18	$C_{37}H_{64}O_4$	572	***A. muricata*** [70]
Group 4 – Tri-epoxy acetogenins (tripoxyrollin type)						
						
4.1	tripoxyrollin		15,16,19,20,23,24	$C_{37}H_{64}O_5$	588	*R. membranacea* [1]

[a] *A.*. = *Annona*; *R.*. = *Rollinia*. [b] Mixture of *syn*- and *anti*-diepomuricanin A; see Scheme 7 (ref. 160).

group of 4–7/16–19 non-adjacent bis-THF ACGs, only one new compound has been reported, aromin-A (18.3), isolated from *Annona cherimolia*, and characterised by the presence of a carbonyl group at the C-9 position.[46]

Groups 19 and 20 – Saturated lactone bis-THF acetogenins (Table 9). Five new "*iso*"-bis-THF ACGs have been reported in this period, 19.16–19.20 (Table 9).

In the group of β-hydroxy-ACG (20: laherradurin type) one compound has been isolated, by our group: tucumanin (20.4), from the seeds of *Annona cherimolia*.[96]

4.5 Tri-THF ACGs (Group 21)

Only one compound is included in this group, goniocin (21.1). See Table 10.

4.6 THP ACGs (Group 22)

In Table 11 we have included the group of ACGs characterised by an atypical substituted alkyl chain with tetrahydropyran (THP) ring systems.[2] A new subtype of ACGs containing only one THP ring has been described (22a: pyranicin type), and two compounds, 22a.1 and 22a.2, were isolated from *Goniothalamus giganteus*.[38] Both compounds represent the first mono-THP bearing ACG, and this finding adds a new structural type to this family of natural products. These ACGs are characterised by the presence of a hydroxylated THP moiety with one flanking hydroxyl group.

New ACGs with a THF ring and an adjacent (type 22b) or non-adjacent (type 22c) THP ring were recently reported.[17,68,97]

5 Cytotoxic and antitumour mechanisms

Annonaceous ACGs are very interesting compounds due to their well-known cytotoxic activity. In fact, uvaricin, the first isolated ACG,[105] was announced as a new antitumour compound. Since then, ACGs have been always judged as promising candidates for a future generation of drugs to fight against the current chemotherapy-resistant tumours. However, more than

Table 3 Mono-THF α,α′-dihydroxylated γ-lactone acetogenins (Groups 5–8)

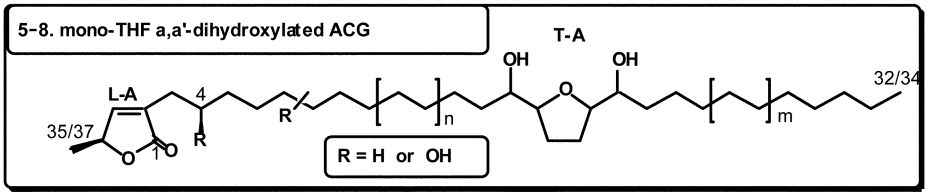
		Hydroxyl positions	Relative configuration of THF[a]	Molecular formula	M^+	Annonaceae species[b] [References]
						
Group 5 – Dihydroxylated acetogenins (uvariamicin-I type)						
5.1	uvariamicin-I	15,20	*th/t/th*	$C_{37}H_{68}O_5$	592	*U. narum* [1]
5.2	uvariamicin-II or reticulatacin	17,22	*th/t/th*	$C_{37}H_{68}O_5$	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 (Δ_{23})	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* [2]
5.10	annotemoyin-2	17,22	*th/t/er*	$C_{35}H_{64}O_5$	564	*A. atemoya* [2]
5.11	***cis*-solamin**	15,20	*th/c/th*	$C_{35}H_{64}O_5$	564	***A. muricata*** [30]
5.12	***cis*-panatellin**	13,18	*th/c/th*	$C_{35}H_{64}O_5$	564	***A. muricata*** [30]
5.13	***cis*-uvariamicin-IV**	13,18	*th/c/th*	$C_{37}H_{68}O_5$	592	***A. muricata*** [30]
5.14	***cis*-uvariamicin-I**	15,20	*th/c/th*	$C_{37}H_{68}O_5$	592	***A. muricata*** [30]
5.15	***cis*-reticulatacin**	17,22	*th/c/th*	$C_{37}H_{68}O_5$	592	***A. muricata*** [30]
5.16	**laurifolin**	19,24	*th/t/th*	$C_{35}H_{64}O_5$	564	***R. laurifolia*** [73]
5.17	**15-palmitoylsolamin**	15-palmitic,20	[c]	$C_{51}H_{94}O_6$	802	***A. muricata*** [86]
5.18	**15-oleylsolamin**	15-oleic,20	[c]	$C_{53}H_{96}O_6$	828	***A. muricata*** [86]
5.19	***cis*-bullatencin** (Δ_{23})	15,20	*th/c/th*	$C_{37}H_{66}O_5$	590	***U. chamae*** [90]
Group 6 – Trihydroxylated and dihydroxylated ketonic acetogenins (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 (CO,10)	15,20	*th/t/th*	$C_{35}H_{62}O_6$	578	*A. muricata* [1]
6.4	giganenin (Δ_9)	13,18,21	*th/t/th*	$C_{37}H_{66}O_6$	606	*G. giganteus* [1]
6.5	asiminenin-A (Δ_{23})	4,15,20	*th/c/th*	$C_{37}H_{66}O_6$	606	*As. triloba* [2]
6.6	asiminenin-B (Δ_{23})	4,15,20	*th/t/th*	$C_{37}H_{66}O_6$	606	*As. triloba* [2]
6.7	*cis*-murisolin	4,15,20	*th/c/th*	$C_{35}H_{64}O_6$	580	*As. triloba* [2]
6.8	murisolin-A	4,15,20	*th/t/er*	$C_{35}H_{64}O_6$	580	*As. triloba* [2]
6.9	uvarigranin	15,(OAc-17),22	*er/t/th*	$C_{39}H_{70}O_7$	650	*U. grandiflora* [2]
6.10	tonkinecin	5,17,22	*th/t/th*	$C_{37}H_{68}O_6$	608	*U. tonkinesis* [2]
6.11	longifolicin	10,13,18	*th/t/th*	$C_{35}H_{64}O_6$	580	*As. longifolia* [2]
6.12	longicoricin	10,15,20	*th/t/th*	$C_{37}H_{68}O_6$	608	*As. longifolia* [2]
6.13	4-deoxyannomontacin	10,17,22	*th/t/th*	$C_{37}H_{68}O_6$	608	*G. giganteus* [2]
6.14	**4-deoxyannoreticuin**	9,15,20	*th/t/th*	$C_{35}H_{64}O_6$	580	***A. squamosa*** [24]
6.15	***cis*-4-deoxyannoreticuin**	9,15,20	*th/c/th*	$C_{35}H_{64}O_6$	580	***A. squamosa*** [24]
6.16	***cis*-reticulatacin-10-one** (CO,10)	17,22	*th/c/th*	$C_{37}H_{66}O_6$	606	***A. muricata*** [30]
6.17	**calamistrin-A**	15,17,22	*th/t/er*	$C_{37}H_{68}O_6$	608	***U. calamistrata*** [32]
6.18	**calamistrin-B**	15,(OAc-17),22	*th/t/er*	$C_{39}H_{70}O_7$	650	***U. calamistrata*** [32]
6.19	**glaucabellin**	4,17,22	*th/t/er*	$C_{37}H_{68}O_6$	608	***A. glauca*** [33]
6.20	**uvarigrin**	15,17,22	*th/t/th*	$C_{37}H_{68}O_6$	608	***U. grandiflora*** [34]
6.21	**calamistrin-C**	13,19,24	*th/t/th*	$C_{37}H_{68}O_6$	608	***U. calamistrata*** [57]
6.22	**calamistrin-D**	13,19,24	*th/t/er*	$C_{37}H_{68}O_6$	608	***U. calamistrata*** [57]
6.23	**calamistrin-E** (Δ_{23})	5,15,20	*/t/th*	$C_{37}H_{66}O_6$	606	***U. calamistrata*** [57]
6.24	**montalicin-A**	4,13,18	*th/t/th*	$C_{33}H_{60}O_6$	552	***A. montana*** [98]
6.25	**montalicin-B**	4,13,18	*th/t/th*	$C_{35}H_{64}O_6$	580	***A. montana*** [98]
6.26	**uvaribonianin**	13,(OAc-15),20	*er/t/th*	$C_{37}H_{66}O_8$	644	***U. boniana*** [104]
Group 7 – Tetrahydroxylated and trihydroxylated ketonic acetogenins						
Group 7a – With OH at C4 (annonacin type)						
7a.1	annonacin	4,10,15,20	*th/t/th*	$C_{35}H_{64}O_7$	596	*A. densicoma* [1]
7a.2	goniothalamicin	4,10,13,18	*th/t/th*	$C_{35}H_{64}O_7$	596	*G. giganteus* [1]
7a.3	annonacinone (CO,10)	4,15,20	*th/t/th*	$C_{35}H_{62}O_7$	594	*A. densicoma* [1]
7a.4	annonacin-A	4,10,15,20	*th/t/er*	$C_{35}H_{64}O_7$	596	*A. squamosa* [1]
7a.5	annomontacin	4,10,17,22	*th/t/th*	$C_{37}H_{68}O_7$	624	*A. montana* [1]
7a.6	annoreticuin	4,9,15,20	*th/t/th*	$C_{35}H_{64}O_7$	596	*A. reticulata* [1]
7a.7	annoreticuinone (CO,9)	4,15,20	*th/t/th*	$C_{35}H_{62}O_7$	594	*A. reticulata* [1]
7a.8	xylopianin	4,8,15,20	*th/t/th*	$C_{35}H_{64}O_7$	596	*X. aromatica* [1]
7a.9	xylopiacin	4,8,15,20	*th/t/th*	$C_{37}H_{68}O_7$	624	*X. aromatica* [1]
7a.10	xylomaticin	4,10,15,20	*th/t/th*	$C_{37}H_{68}O_7$	624	*X. aromatica* [1]
7a.11	reticulacinone (CO,11)	4,15,20	*th/t/th*	$C_{35}H_{62}O_7$	594	*A. reticulata* [1]
7a.12	squamosten-A (Δ_{23})	4,12,15,20	*th/t/th*	$C_{37}H_{66}O_7$	622	*A. squamosa* [1]
7a.13	gonionenin (Δ_{21})	4,10,13,18	*th/t/th*	$C_{37}H_{66}O_7$	622	*G. giganteus* [1]

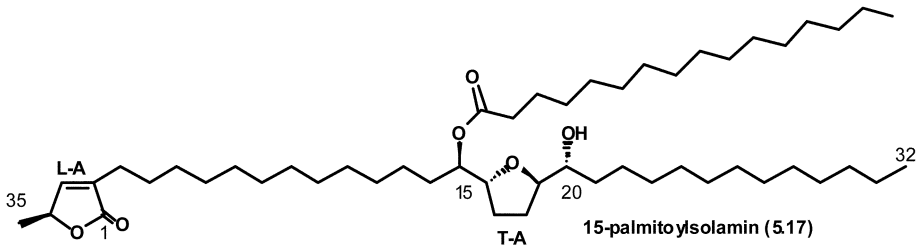
Table 3 (*Cont.*)

		Hydroxyl positions	Relative configuration of THF[a]	Molecular formula	M^+	Annonaceae species[b] [References]
7a.14	xylopien (Δ_{23})	4,8,15,20	*th/t/th*	$C_{37}H_{66}O_7$	622	*X. aromatica* [1]
7a.15	xylomatenin (Δ_{23}) or annogalene	4,10,15,20	*th/t/th*	$C_{37}H_{66}O_7$	622	*X. aromatica* [1] *A. senegalensis* [1]
7a.16	annosenegalin	4,10,15,20	*th/t/er*	$C_{37}H_{68}O_7$	624	*A. senegalensis* [1]
7a.17	longicin	4,10,13,18	*th/t/er*	$C_{35}H_{64}O_7$	596	*As. longifolia* [2]
7a.18	annomutacin	4,10,17,22	*th/t/er*	$C_{37}H_{68}O_7$	624	*A. muricata* [2]
7a.19	*cis*-annonacin	4,10,15,20	*th/c/th*	$C_{35}H_{64}O_7$	596	*A. muricata* [2]
7a.20	*cis*-annonacinone (CO,10)	4,15,20	*th/c/th*	$C_{35}H_{62}O_7$	594	*A. muricata* [2]
7a.21	*cis*-goniothalamicin	4,10,13,18	*th/c/th*	$C_{35}H_{64}O_7$	596	*A. muricata* [2]
7a.22	arianacin + javoricin	4,12,15,20	*th/t/th*	$C_{35}H_{64}O_7$	596	*A. muricata* [2]
7a.23	rollinecins-A + B	4,14,17,22	*th/t/er*	$C_{37}H_{68}O_7$	624	*R. mucosa* [2]
7a.24	4-acetylannonacin	(OAc-4),10,15,20	*th/t/th*	$C_{37}H_{66}O_8$	638	*As. longifolia* [2]
7a.25	4-acetylxylomaticin	(OAc-4),10,15,20	*th/t/th*	$C_{39}H_{70}O_8$	666	*As. longifolia* [2]
7a.26	disepalin	4,10,15,OAc-20	*th/t/th*	$C_{39}H_{70}O_8$	666	*D. anomalum* [2]
7a.27	mosin-B (CO,9)	4,15,20	*th/t/er*	$C_{35}H_{62}O_7$	594	*A. squamosa* [2]
7a.28	mosin-C (CO,9)	4,15,20	*th/c/th*	$C_{35}H_{62}O_7$	594	*A. squamosa* [2]
7a.29	**glacin-A**	4,12,17,22	*th/t/th*	$C_{35}H_{64}O_7$	596	***A. glabra*** [31]
7a.30	**glacin-B**	4,12,15,20	*th/t/er*	$C_{35}H_{64}O_7$	596	***A. glabra*** [31]
7a.31	**goniotetracin**	4,10,13,18	*th/t/th*	$C_{37}H_{68}O_7$	624	***G. giganteus*** [37]
7a.32	**asitrilobin-A**	4,10,17,22	*th*[d]*/c/er*[d]	$C_{37}H_{68}O_7$	624	***As. triloba*** [41]
7a.33	**asitrilobin-B**	4,10,15,20	*th*[d]*/c/er*[d]	$C_{35}H_{64}O_7$	596	***As. triloba*** [41]
7a.34	**annoglacin-A**	4,12,17,22	*th/t/er*	$C_{37}H_{68}O_7$	624	***A. glabra*** [49]
7a.35	**annoglacin-B**	4,12,17,22	*th/t/th*	$C_{37}H_{68}O_7$	624	***A. glabra*** [49]
7a.36	**annocherin** (CO,7)	4,15,20	*th/t/th*	$C_{35}H_{62}O_7$	594	***A. cherimolia*** [52]
7a.37	**annomontanin-A** (CO,8)	4,15,20	*th/t/th*	$C_{35}H_{62}O_7$	594	***A. montana*** [53]
7a.38	**rolliacocin**	4,11,15,20	*th/t/th*	$C_{35}H_{64}O_7$	596	***R. mucosa*** [58]
7a.39	***cis*-annomontacin**	4,10,17,22	*th/c/th*	$C_{37}H_{68}O_7$	624	***A. muricata*** [59]
7a.40	**annocherimolin** (Δ_{21})	4,9,13,18	*th/t/th*	$C_{37}H_{66}O_7$	622	***A. cherimolia*** [60]
7a.41	**asitrocin**	4,12,15,20	*er/t/th*	$C_{35}H_{64}O_7$	596	***As. triloba*** [62]
7a.42	**muricin-G** (Δ_{23})	4,10,15,20	*th/t/th*	$C_{35}H_{62}O_7$	594	***A. muricata*** [63]
7a.43	**asitrilobin-C**	4,15,17,22	*th/t/th*	$C_{37}H_{68}O_7$	624	***As. triloba*** [75]
7a.44	**montalicin-C**	4,7,13,18	*th/t/th*	$C_{35}H_{64}O_7$	596	***A. montana*** [98]
7a.45	**montalicin-D**	4,11,13,18	*th/t/th*	$C_{35}H_{64}O_7$	596	***A. montana*** [98]
7a.46	***cis*-annoreticuin**	4,9,15,20	*th/c/th*	$C_{35}H_{64}O_7$	596	***A. montana*** [98]
7a.47	**montalicin-E**	4,7,13,18	*th/t/th*	$C_{37}H_{66}O_7$	622	***A. montana*** [98]
7a.48	**montalicin-F**	4,9,15,20	*th/t/er*	$C_{35}H_{64}O_7$	596	***A. montana*** [98]
7a.49	**montalicin-I**	4,9,15,20	*th/t/th*	$C_{37}H_{68}O_7$	624	***A. montana*** [98]
7a.50	**montalicin-J**	4,11,17,22	*th/c/th*	$C_{37}H_{68}O_7$	624	***A. montana*** [98]
Group 7b – Without OH at C4 (plagionicin-A type)						
7b.1	plagionicin-A	5,10,15,20	*th/t/th*	$C_{35}H_{64}O_7$	596	*P. plagioneura* [2]
7b.2	tonkinin-A (CO,5)	15,17,22	*th/t/er*	$C_{37}H_{66}O_7$	622	*U. tonkinesis* [2]
7b.3	tonkinin-B (CO,5)	15,17,22	*th/t/th*	$C_{37}H_{66}O_7$	622	*U. tonkinesis* [2]
7b.4	tonkinin-C (CO,5)	15,(OAc-17),22	*th/t/er*	$C_{39}H_{68}O_8$	664	*U. tonkinesis* [2]
7b.5	tonkinesin-A	5,15,17,22	*th/t/er*	$C_{37}H_{68}O_7$	624	*U. tonkinesis* [2]
7b.6	tonkinesin-B	5,15,17,22	*th/t/th*	$C_{37}H_{68}O_7$	624	*U. tonkinesis* [2]
7b.7	tonkinesin-C	5,15,(OAc-17),22	*th/t/er*	$C_{39}H_{70}O_8$	666	*U. tonkinesis* [2]
7b.8	gigantransenin-A + B (Δ_{21})	10,13,18,23	*th/t/th*	$C_{37}H_{66}O_7$	622	*G. giganteus* [2]
7b.9	gigantransenin-C (Δ_{22})	10,13,18,21	*th/t/th*	$C_{37}H_{66}O_7$	622	*G. giganteus* [2]
7b.10	**sootepensin-A**	5,15,(OAc-17),22	*th/c/er*	$C_{39}H_{70}O_8$	666	***Ds. sootepense*** [67]
7b.11	**sootepensin-B**[e] (CO,5)	15,(OAc-17),22	*th/t/th*	$C_{39}H_{68}O_8$	664	***Ds. sootepense*** [67]
7b.12	**asitrilobin-D**	10,17,19,24	*th/t/th*	$C_{37}H_{68}O_7$	624	***As. triloba*** [75]
7b.13	**uvaribonin**	5,15,(OAc-17),22	*er/t/th*	$C_{39}H_{70}O_8$	666	***U. boniana*** [104]
Group 8 – Polyhydroxylated and tetrahydroxylated ketonic acetogenins (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-OH-annonacin	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 (CO,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* [2]
8.8	muricatocin-B	4,10,12,15,20	ps *er-th/t/er*	$C_{35}H_{64}O_8$	612	*A. muricata* [2]
8.9	muricatocin-C	4,10,12,15,20	ps *th-th/t/er*	$C_{35}H_{64}O_8$	612	*A. muricata* [2]
8.10	annomuricin-C	4,10,11,15,20	*th-th/t/th*	$C_{35}H_{64}O_8$	612	*A. muricata* [2]
8.11	annohexocin	4,8,10,12,15,20	*th/t/er*	$C_{35}H_{64}O_9$	628	*A. muricata* [2]
8.12	muricatalicin	4,7,13,15,20	*th/t/th*	$C_{35}H_{64}O_8$	612	*A. muricata* [2]
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* [2]
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* [2]
8.15	**donnaienin**[f]	4,10,13,15,18	*th-(th)-t,th*	$C_{35}H_{64}O_8$	612	***G. donnaiensis*** [19]
8.16	**annomuricin-E**	4,10,11,15,20	*er-th/t/th*	$C_{35}H_{64}O_8$	612	***A. muricata*** [26]
8.17	**muricapentocin**	4,8,12,15,20	*th/t/th*	$C_{35}H_{64}O_8$	612	***A. muricata*** [26]
8.18	**araticin**	15,20,23,24,28	*er-th/t/th*	$C_{37}H_{68}O_8$	640	***A. spinescens*** [43]
8.19	**annoglaxin** (CO,12)	8,15,20,22	*th/t/th*	$C_{35}H_{62}O_8$	610	***A. glabra*** [50]

Table 3 (*Cont.*)

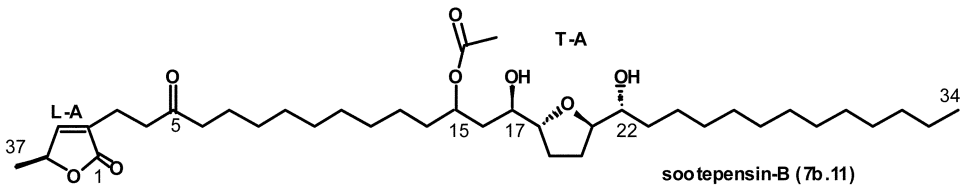
		Hydroxyl positions	Relative configuration of THF[a]	Molecular formula	M^+	Annonaceae species[b] [References]
8.20	**annomontanin-B** (CO,10)	4,8,17,22	*th*/*c*/*th*	$C_{35}H_{62}O_8$	610	***A. montana*** [53]
8.21	**montanacin-B** (CO,10)	4,8,15,20	*th*/*t*/*th*	$C_{35}H_{62}O_8$	610	***A. montana*** [68]
8.22	**montanacin-C** (CO,10)	4,8,15,20	*th*/*c*/*th*	$C_{35}H_{62}O_8$	610	***A. montana*** [68]
8.23	**annoheptocin-A**	4,9,14,16,21,22	*er*/*t*/*th*	$C_{37}H_{68}O_{10}$	672	***A. coriacea*** [87]
8.24	**annoheptocin-B**	4,9,14,16,21,22	*th*/*t*/*th*	$C_{37}H_{68}O_{10}$	672	***A. coriacea*** [87]
8.25	**muricatatin-C** (CO,10)	4,15,20,25	*th*/*t*/*th*	$C_{35}H_{66}O_8$	614	***A. muricata*** [100]
8.26	**montacin** (CO,7)	4,9,20,25	*th*/*t*/*th*	$C_{35}H_{62}O_8$	610	***A. montana*** [101]
8.27	***cis*-montacin** (CO,7)	4,9,20,25	*th*/*c*/*th*	$C_{35}H_{62}O_8$	610	***A. montana*** [101]

[a] *th* = *threo*; *er* = *erythro*; *t* = *trans*; *c* = *cis*; *ps* = *pseudo*; *an* = *anti*. [b] *U.* = *Uvaria*; *A.* = *Annona*; *G.* = *Goniothalamus*; *As.* = *Asimina*; *X.* = *Xylopia*; *P.* = *Polyalthia*; *R.* = *Rollinia*; *D.* = *Disepalum*; *Ds.* = *Dasymaschalon*. [c] The relative configuration of compounds 5.17 and 5.18 was not determined by the authors.

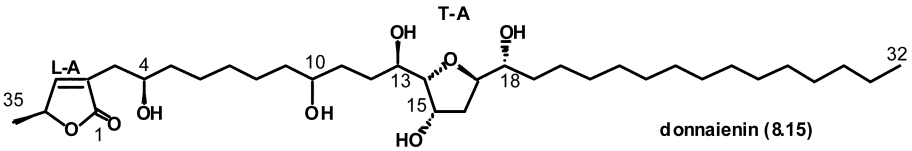


[d] For **7.32** and **7.33** the relative configurations are either *th*/*t*/*er* or *er*/*t*/*th*.

[e]



[f] **8.15**: The OH is on the THF ring (C15 position).

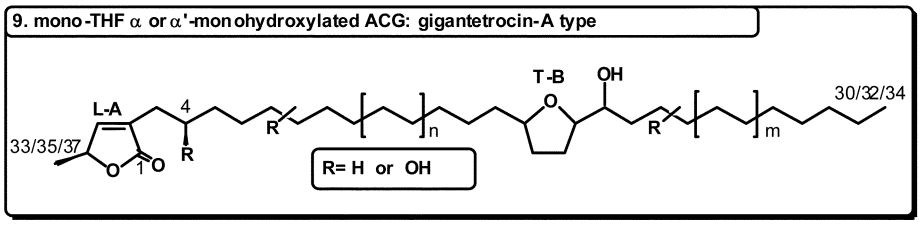


twenty years later and after hundreds of studies concerning many aspects, it seems that this promise is far from being accomplished, and ACGs still remain "potential" candidates. Although twenty years of expectation seem a long time, it is true that only in recent years has the knowledge of the processes involved in tumour cell death experienced the greatest progress. Therefore, the "old" ACGs sustain their candidature. Moreover, it seems that as the mechanism of cell death becomes better understood, ACGs become more promising. Why have ACGs taken so much time to reveal their possibilities as antitumour drugs? There are two main reasons: (i) an enzyme-inhibiting mechanism of action affecting the key metabolic process, and (ii) the consequences of this inhibitory mechanism on the maintenance of the cellular function. Both events are very complicated to understand, and thus, progress has been hindered for years.

In 1991, the mitochondrial complex I (NADH:ubiquinone oxidoreductase) of the respiratory chain was identified as the target enzyme for ACGs.[106] A few years later, ACGs were characterised as one of the most powerful groups of complex I inhibitors.[107] Complex I plays an important role in the maintenance of the bioenergetic function of the cell by driving the ATP synthesis from the mitochondrial reduced equivalents produced in the central metabolic oxidative pathways. Its relevance for the whole cellular function has been verified due to its implication in the pathogenesis of a wide spectrum of human neurodegenerative diseases, in which even a even slight decrease in complex I activity produces dramatic and deleterious effects on the cells.[108] Surprisingly, although structural studies have driven great advances in the knowledge of this enzymatic complex,[109] its functional mechanism remains elusive, in huge contrast with the other mitochondrial enzymatic complexes involved in oxidative phosphorylation.[110] Certainly, the exploration of this mysterious mechanism has been one of the main stimuli to extend the research on new natural or synthetic inhibitors of complex I in an attempt to elucidate its internal electron-transfer and energy-coupling pathways.[111] As consequence, an enormous number of inhibitory compounds have been identified in recent years. To date, mitochondrial complex I is probably the enzyme with the greatest number of inhibitors. The reason why this enzyme can accommodate such variety of inhibitors in the active site, where the main oxidoreductive reactions take place, is not clear.[112] It could be due to the existence of a wide active site, probably formed by more than one protein subunit of the complex, a shuttle or channel for the ubiquinone substrate, or more likely, a conformational change in the catalytic turnover cycle.[110,113] Therefore, the inhibitory compounds could obstruct the enzymatic activity in many ways, and interact with one or more active sites. Indeed, it seems that all relevant inhibitors of complex I bind the enzyme at the same site, or at least in a very close site in the same domain, which causes mutual interference.[112,114–116]

Taking into account the structural and functional characteristics of complex I that are briefly stated above, it is not surprising that clarification of a general structure–activity relationship for inhibitory compounds is a very

Table 4 Mono-THF α- or α′-monohydroxylated γ-lactone acetogenins (Group 9)

		Hydroxyl positions	THF–diol relative configuration[a]	Molecular formula	M$^+$	Species[b] [Ref.]
Group 9 – THF α-monohydroxylated acetogenins						
						
Group 9a – With OH at C4 (gigantetrocin-A type)						
9a.1	gigantetrocin-A	4,14,17,18	*t/th-th*	$C_{35}H_{64}O_7$	596	*G. giganteus* [1]
9a.2	densicomacin-1	4,14,17,18	*t/er-th*	$C_{35}H_{64}O_7$	596	*A. densicoma* [1]
9a.3	gigantetronenin (Δ_{21})	4,14,17,18	*t/th-th*	$C_{37}H_{66}O_7$	622	*G. giganteus* [1]
9a.4	gigantetrocin-B	4,14,17,18	*t/th-th*	$C_{35}H_{64}O_7$	596	*A. muricata* [1]
9a.5	muricatetrocins-A + B	4,16,19,20	*t/er* or *th-th*	$C_{35}H_{64}O_7$	596	*A. muricata* [1]
9a.6	senegalene (Δ_{29})	4,12,13,21	*th-t/th*	$C_{37}H_{66}O_7$	622	*A. senegalensis* [1]
9a.7	muricatin-A (= **muricatatin-A**)	4,14,17,18,23	*t/th-th*	$C_{35}H_{64}O_8$	612	*A. muricata* [1] *A. muricata* [100]
9a.8	muricatin-B (= **muricatatin-B**)	4,14,17,18,19	*t/th-th/er*	$C_{35}H_{64}O_8$	612	*A. muricata* [1] *A. muricata* [100]
9a.9	coriacin (Δ_{17})	4,14,21,22	*t/th-th*	$C_{37}H_{66}O_7$	622	*A. coriacea* [2]
9a.10	murihexocins-A + B	4,7,8,16,19,20	*th-t/th-th*	$C_{35}H_{64}O_9$	628	*A. muricata* [2]
9a.11	muricatalin	4,14,15,17,18	*t/er/er-th*	$C_{35}H_{64}O_8$	612	*A. muricata* [2]
9a.12	annopentocins-A + B	4,10,16,19,20	*t/th-th*	$C_{35}H_{64}O_8$	612	*A. muricata* [2]
9a.13	annopentocin-C	4,10,16,19,20	*t/th-er*	$C_{35}H_{64}O_8$	612	*A. muricata* [2]
9a.14	4-acetylgigantetrocin-A	(OAc-4),14,17,18	*t/th-th*	$C_{37}H_{66}O_8$	638	*G. giganteus* [2]
9a.15	muricatetrocin-C	4,16,19,20	*t/th-er*	$C_{35}H_{64}O_7$	596	*R. mucosa* [2]
9a.16	glaucafilin	4,16,19,2	*t/th-er*	$C_{35}H_{64}O_7$	596	*A. glauca* [2]
9a.17	glabranin (Δ_{23})	4,16,19,20	*t/th-th*	$C_{37}H_{66}O_7$	622	*A. glabra* [2]
9a.18	**goniotrionin** (Δ_{17})	4,14,16	*t/th-ps th*	$C_{35}H_{62}O_6$	578	***G. giganteus*** [38]
9a.19	**muricoreacin**	4,8,10,16,19,20	*ps er-t/th-er*	$C_{35}H_{64}O_9$	628	***A. muricata*** [40]
9a.20	**murihexocin-C**	4,7,8,16,19,20	*th*[c]*-t/th-er*[c]	$C_{35}H_{64}O_9$	628	***A. muricata*** [40]
9a.21	**annomolin**	4,7,8,18	*th-t/th*	$C_{35}H_{64}O_7$	596	***A. cherimolia*** [60]
9a.22	**muricin-A**	4,19,26,27	*t/th-th*	$C_{35}H_{64}O_7$	596	***A. muricata*** [63]
9a.23	**muricin-B**[d]	4,19,26,27	*t/th-th*	$C_{35}H_{64}O_7$	596	***A. muricata*** [63]
9a.24	**muricin-C**	4,21,24,25	*t/th-th*	$C_{35}H_{64}O_7$	596	***A. muricata*** [63]
9a.25	**muricin-D**	4,19,22,23	*t/th-th*	$C_{33}H_{60}O_7$	568	***A. muricata*** [63]
9a.26	**muricin-E**	4,16,22,23	*t/th-th*	$C_{33}H_{60}O_7$	568	**A. muricata** [63]
9a.27	**muricin-F** (Δ_{24})	4,21,27,28	*t/th-th*	$C_{35}H_{62}O_7$	594	**A. muricata** [63]
Group 9b – Without OH at C4 (gigantriocin type)						
9b.1	gigantriocin	14,17,18	*t/th-th*	$C_{35}H_{64}O_6$	580	*G. giganteus* [1]
9b.2	gigantrionenin (Δ_{21})	14,17,18	*t/th-th*	$C_{37}H_{66}O_6$	606	*G. giganteus* [1]
9b.3	4-deoxycoriacin (Δ_{17})	14,21,22	*t/th-th*	$C_{37}H_{66}O_6$	606	*A. coriacea* [2]
9b.4	*cis*-gigantrionenin (Δ_{21})	14,17,18	*c/th-th*	$C_{37}H_{66}O_6$	606	*G. giganteus* [2]
9b.5	**muricin-H**	19,24,25	*t/th-th*	$C_{35}H_{64}O_6$	580	***A. muricata*** [59]
9b.6	**muricin-I** (Δ_{28})	19,24,25	*t/th-th*	$C_{37}H_{66}O_6$	606	***A. muricata*** [59]
9b.7	**coriacyclodienin** (Δ_{17}; Δ_{21})	14	*t/th*	$C_{37}H_{64}O_4$	572	***A. coriacea*** [91]
9b.8	**coriacycloenin** ((Δ_{17})	14	*t/th*	$C_{35}H_{62}O_4$	546	***A. coriacea*** [91]

[a] *th* = *threo*; *er* = *erythro*; *t* = *trans*; *c* = *cis*. [b] *G.* = *Goniothalamus*; *A.* = *Annona*; *R.*. = *Rollinia*. [c] For **9a.20** the relative configuration is either *th-t/th-er* or *er-t/th-th*; [d] **9a.23** is the first ACG with the 4*S* configuration (Mosher method).

difficult task. The main common feature is that they must be lipophilic molecules, because the part of complex I where ubiquinone reacts is likely to be immersed in the inner mitochondrial membrane or at least, ubiquinone accesses the reaction site through the membrane. Therefore, the inhibitory potency of each compound is determined by specific interactions with the enzyme, and also by non-specific factors that affect the access to the inhibitor-binding site.[117]

ACGs deserve an eminent position among the great variety of complex I inhibitors due to several reasons: (i) several ACGs are the most potent inhibitors of complex I, some of them with a stoichiometry close to one unit,[118] (ii) some ACGs show inhibitory properties clearly different from the rest of complex I inhibitors,[107,119] (iii) there are hundreds of natural ACGs with significant structural variations to allow extensive structure–activity relationship studies,[6] and (iv) relatively easy semi-synthetic procedures increase greatly the natural variation of these compounds to provide thousands of new compounds to study.

However, ACGs also have some inconveniences. Although they are not very complex molecules, there are many chiral centres that affect the spatial structure, in addition to the inherent flexibility of the molecule due to the long carbon chains. In the absence of a structural model of the inhibitor binding site of complex I, it is very difficult to predict the inhibitory potency of a new acetogenin. Extensive studies using a large variety of natural ACGs and semi-synthetic derivatives have shown that ACGs retain a potent inhibitory activity for complex I, irrespective of most changes in their chemical structure. Structural differences, regarding mainly the number and stereochemistry of the tetrahydrofuran units, flanked hydroxyl groups, the terminal lactone and groups placed along the alkyl chain, and the length of the alkyl-chain spacer between tetrahydrofurans and the lactone, have yielded at least some

potent inhibitory compounds.[117,118,120–129] It seems that there is not a restrictive structural requirement for binding and inhibiting the enzyme, and different molecular arrangements can produce an "optimal" ACG spatial structure very effective at exerting inhibitory action. Therefore, as previously suggested,[121] ACG binding to the enzyme depends on a very complex combination of structural factors, mainly involving the tetrahydrofuran group and the terminal lactone group, both likely to be the points of direct interaction or fixation to the enzyme, which need an appropriate spatial orientation mediated by the spacer alkyl chain.

ACGs, as potent inhibitors of the mitochondrial respiratory chain complex I, are compounds with potential to become a new generation of antitumour drugs, as stated above. Nevertheless, their mechanism of selective cytotoxicity, and the factors that modulate the efficacy against cancer cells are unknown. The antitumour activity of ACGs and other respiratory chain inhibitors could be due, at first sight, to the following reason: the tumour cells with higher energetic demand and/or those with higher oxidative-phosphorylation dependence would be the most sensitive to the cytotoxic effects of these compounds. Nevertheless, efficiency to control tumour cell growth implies additional mechanisms beyond mitochondrial energy production in which induction of programmed cells death or apoptosis is involved. Unfortunately, it is poorly understood how different inhibitors could switch on this complicated process and also, how cells could activate the defensive mechanisms against oxidative stress injury and control both the signalling and execution pathways of the apoptotic process.[130]

Most studies on the antitumour activity of ACGs are carried out by treating tumour cell cultures with lethal amounts of the compounds, and thus, they yield abundant data on LD_{50} values. Extensive examination of these data does not give any conclusive results. At first sight, it would be expected that there would be a good correlation between the capacity for killing tumour cells and the inhibitory potency on complex I activity. However, this hypothetical correlation has not been found.[6,131,132] Some authors have claimed alternative mechanisms for ACG cytotoxicity to explain this inconsistency, but cause–effect relationships are often forced to match the proposed alternative mechanism at author convenience, and many times the proposal seems rather indirect.[133] Moreover, different tumour cell lines show notable differences in their susceptibility to be killed by the same ACG.[131,132,134] Actually, there are multiple factors involved in cell death caused by enzymatic inhibitors of mitochondrial complex I (such as ACGs), from the access of the toxic compound to the target enzyme, to the defensive cellular mechanism against this poisoning. Moreover, cell death can be produced by two substantially different modes: necrosis or apoptosis.

Table 5 Mono-THF acetogenins with a L-B_1, L-B_2, L-C or L-D lactone moiety (Groups 10 and 11)

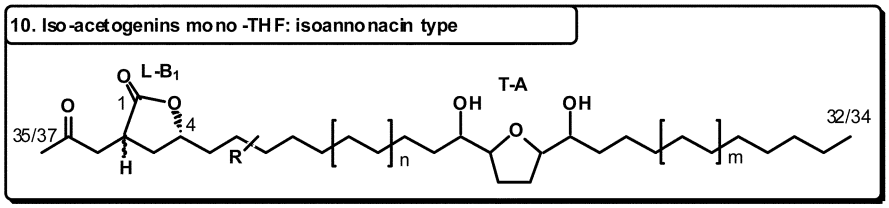
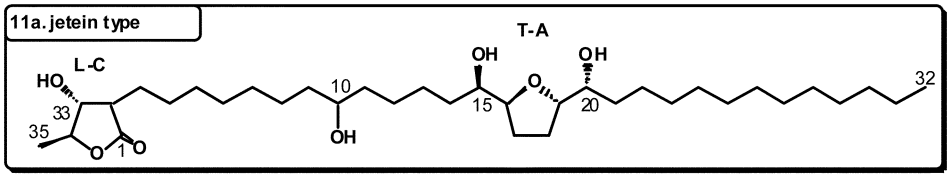
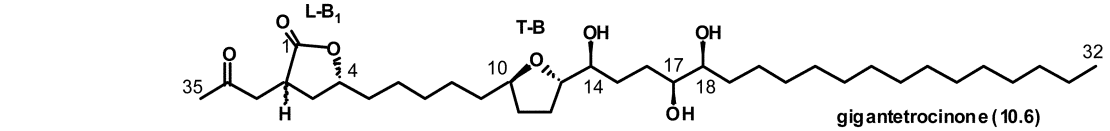
		Hydroxyl positions	Relative configuration of THF[a]	Molecular formula	M^+	Species[b] [Ref.]
Group 10 – Mono-THF *iso*-acetogenins (isoannonacin type)						
						
10.1	isoannonacin	10,15,20	*th/t/th*	$C_{35}H_{64}O_7$	596	*A. densicoma* [1]
10.2	isoannonacinone (CO,10)	15,20	*th/t/th*	$C_{35}H_{62}O_7$	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* [2] *A. muricata* [2]
10.6	gigantetrocinone[c]	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* [2]
10.8	murisolinone	15,20	*th/t/th*	$C_{35}H_{64}O_6$	580	*As. triloba* [2]
10.9	annomuricinone-D	10,11,15,20	*er-th/t/th*	$C_{35}H_{64}O_8$	612	*A. muricata* [2]
10.10	gigantetroneninone[c] (Δ_{21})	14,17,18	*t/th-th*	$C_{37}H_{66}O_7$	622	*As. longifolia* [2]
10.11	annomontacinone	10,17,22	*th/t/th*	$C_{37}H_{68}O_7$	624	*G. giganteus* [2]
10.12	isomurisolenin (Δ_{11})	15,20	*th/t/th*	$C_{35}H_{62}O_6$	578	*A. reticulata* [2]
10.13	mosinone-A (Δ_{23})	15,20	*th/t/th*	$C_{37}H_{64}O_7$	620	*A. squamosa* [2]
10.14	**squamoxinone**	11,17,22	*th/t/th*	$C_{37}H_{68}O_7$	624	***A. squamosa*** [24]
10.15	**xylomaticinone**	10,15,20	*th/t/th*	$C_{37}H_{68}O_7$	624	***G. giganteus*** [36]
10.16	**gonioneninone** (Δ_{21})	10,13,18	*th/t/th*	$C_{37}H_{66}O_7$	622	***G. giganteus*** [37]
10.17	**annocherinone** (CO,7)	15,20	*th/t/th*	$C_{35}H_{62}O_7$	594	***A. cherimolia*** [52]
10.18	**asitrocinone**	12,15,20	*er/t/th*	$C_{35}H_{64}O_7$	596	***As. triloba*** [62]
10.19	**squamoxinone-B**	11,17,22	*th[d]/t/er[d]*	$C_{37}H_{68}O_7$	624	***A. squamosa*** [8]
10.20	**squamoxinone-C**	11,17,22	*th[d]/t/er[d]*	$C_{35}H_{64}O_7$	596	***A. squamosa*** [8]
10.21	**montanacin-G** (CO,10)	8,15,20	*th/t/th*	$C_{35}H_{62}O_8$	610	***A. montana*** [69]
10.22	**montanacin-F**[e]	15,20,29	*th/t/er*	$C_{35}H_{62}O_7$	594	***A. montana*** [74]
Group 11a – Mono-THF β-hydroxy acetogenins (jetein type)						
						
11a.1	jetein	10,15,20	*th/t/er*	$C_{35}H_{66}O_7$	598	*A. cherimolia* [1]

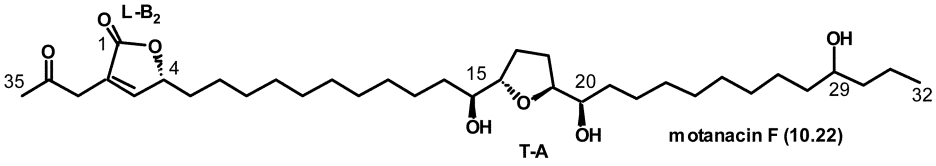
Table 5 (*Cont.*)

		Hydroxyl positions	Relative configuration of THF[a]	Molecular formula	M^+	Species[b] [Ref.]
Group 11b – 34- or 36-Hydroxy acetogenins (donnaienin-A type)						
11b.1	donnaienin-A + 34-*epi*	4,15,20,34	*th*/*t*/*th*	$C_{35}H_{64}O_7$	596	*G. donnaiensis* [2]
11b.2	donnaienin-B + 34-*epi*	4,14,17,18,34	*t*/*th*-*th*	$C_{35}H_{64}O_8$	612	*G. donnaiensis* [2]
11b.3	goniodonin + 34-*epi*	4,10,15,20,34	*th*/*t*/*th*	$C_{35}H_{64}O_8$	612	*G. donnaiensis* [2]
11b.4	*cis*-goniodonin + 34-*epi*	4,10,15,20,34	*th*/*c*/*th*	$C_{35}H_{64}O_8$	612	*G. donnaiensis* [2]
11b.5	**gardnerinin + 34-*epi*[f]**	4,10,16,19,20,34	*t*/*th*-*er*	$C_{35}H_{64}O_9$	628	***G. gardneri*** [25]
11b.6	**donnaienin-C + 34-*epi***	(OAc-4),10,15,20,34	*th*/*t*/*th*	$C_{37}H_{66}O_9$	654	***G. donnaiensis*** [27]
11b.7	**annomontanin-C** (CO,10)	4,17,22,34	*th*/*t*/*th*	$C_{35}H_{62}O_8$	610	***A. montana*** [53]
11b.8	**montanacin-H + 34-*epi*** (CO,10)	4,8,15,20,34	*th*/*t*/*er*	$C_{35}H_{62}O_9$	626	***A. montana*** [69]
11b.9	**montanacin-I + 34-*epi***	4,15,20,29,34	*th*/*t*/*th*	$C_{35}H_{64}O_8$	612	***A. montana*** [69]
11b.10	**montanacin-J + 34-*epi***	4,15,20,29,34	*th*/*t*/*er*	$C_{35}H_{64}O_8$	612	***A. montana*** [69]
11b.11	**parisin**	4,15,20,23,24,36	*th*/*t*/*th*-*th*	$C_{37}H_{68}O_9$	656	***A. salzmani*** [93]
11b.12	**annomolon-A + 34-*epi*** (CO,11)	15,20,34	*th*/*t*/*th*	$C_{35}H_{62}O_7$	594	***A. cherimolia*** [94]
11b.13	**annomolon-B + 34-*epi*** (CO,11)	4,15,20,34	*th*/*t*/*th*	$C_{35}H_{62}O_8$	610	***A. cherimolia*** [94]

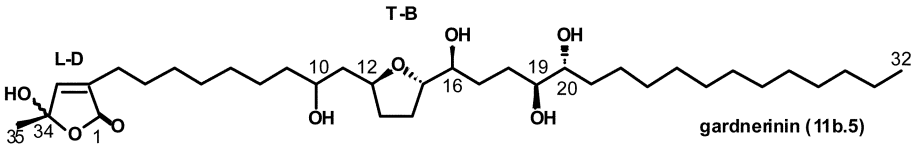
[a] *th* = *threo*; *er* = *erythro*; *t* = *trans*. [b] *A.* = *Annona*; *As.* = *Asimina*; *G.* = *Goniothalamus*.



[c] (*iso*-mono-THF acetogenins with T-B ring system: 10.6 and 10.10). [d] 10.19 and 10.20: interchangeable relative configuration for the authors.



[e] (*iso*-mono-THF acetogenins with T-A ring system: 10.22).



[f]

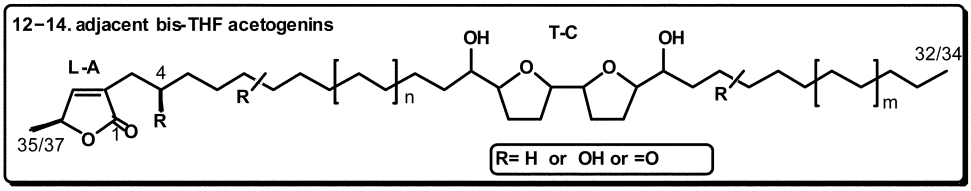
When mitochondrial complex I is fully inhibited, cells suffer an extensive failure of the mitochondrial oxidative metabolism that yields ATP depletion, and thus a fast energetic collapse of the cellular functions: cells die by necrosis. It can occur even under slight complex I inhibition in a time-dependent manner. Resistance of the cells to this energetic collapse mainly depends on their ability to obtain energy from the anaerobiotic metabolism. Contrarily, the apoptotic process or programmed cell death involves a complex sequence of events that produce selective elimination of the damaged cell in which the cell exerts some relative control, and it can activate more complicated defensive mechanisms. One of the main apoptotic pathways can be initiated by mitochondrial complex I inhibition.[135,136]

Recently, it has been shown that inhibition of mitochondrial complex I increases the amount of the reduced or semi-reduced chemical species of the electron transporters which react with molecular oxygen to generate superoxide anion and hydrogen peroxide. These reactive oxygen species attack the enzymatic complexes of the respiratory chain, the mitochondrial membranes and the mitochondrial genome that codifies essential components of the respiratory chain, and thus promote a notable amplification of the deleterious effects. Lowering of the mitochondrial membrane potential induces the opening of transition pores followed by cytochrome c liberation, pro-apoptotic factor launching, and caspase activation. This complicated signaling cascade induces the programmed cell death process.[135–137]

Nevertheless, cells respond to the oxidative damage by complex I inhibition activating defensive mechanisms such as enzymatic systems, anti-apoptotic factors, and alternative metabolic processes to oxidative phosphorylation to accomplish their energetic demand. These defensive mechanisms include enzymes such as superoxide dismutase, catalase and glutathione peroxidase, protective anti-apoptotic factors, and the capacity for switching on the anaerobiotic metabolism. The ability of each cell type, including the great variety of tumour cells, to overcome the deficient functionality of the respiratory chain and the subsequent oxidative damage is the key factor in staying alive.[130]

Recent studies on the cytotoxic mechanism of rotenone, the most known complex I inhibitor, and other inhibitory compounds, have shown induction of programmed cell death[138] mediated by caspase-3 activation, one of the main executor proteases of this process, through an oxidative-stress dependent initiation,[136] a common feature of neurodegenerative diseases.[139,140] Although ACGs are less well studied, it seems that the cytotoxic mechanism could be very similar to that

Table 6 Adjacent bis-THF α,α′-dihydroxylated γ-lactone acetogenins (Groups 12–14)

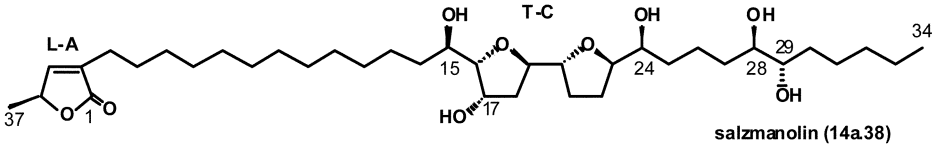


		Hydroxyl positions	Relative configuration of THF[a]	Molecular formula	M^+	Species[b] [Ref.]
Group 12 – Dihydroxylated acetogenins (uvaricin type)						
12.1	uvaricin	15,(OAc-24)	*th/t/th/t/er*	$C_{39}H_{68}O_7$	648	*U. acuminata* [1]
12.2	desacetyluvaricin	15,24	*th/t/th/t/er*	$C_{37}H_{66}O_6$	606	*U. 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* [2]
Group 13 – Trihydroxylated and tetrahydroxylated acetogenins (with OH at C4) (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* [1,2]
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	4,12,15,24	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. purpurea* [1]
13.8	parviflorin or squamocin-E	4,13,22	*th/t/th/t/th*	$C_{35}H_{62}O_7$	594	*As. parviflora* [1] *A. squamosa* [1]
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	4,13,22	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	*A. glauca* [1]
13.11	30-OH-bullatacin	4,15,24,30	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [2]
13.12	31-OH-bullatacin	4,15,24,31	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [2]
13.13	32-OH-bullatacin	4,15,24,32	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [2]
13.14	araticulin	4,12,15,24				
13.15	annonisin	4,8,13,22	*th/t/th/t/th*	$C_{35}H_{62}O_8$	610	*A. atemoya* [2]
13.16	10-OH-asimicin	4,10,15,24	*th/t/th/t/th*	$C_{37}H_{66}O_8$	638	*As. triloba* [2] *A. reticulata* [2]
13.17	10-OH-trilobacin	4,10,15,24	*th/t/er/c/th*	$C_{37}H_{66}O_8$	638	*As. triloba* [2]
13.18	longimicin-A	4,11,20	*th/t/th/t/th*	$C_{37}H_{66}O_7$	622	*As. longifolia* [2]
13.19	longimicin-B	4,11,20	*th/t/th/t/th*	$C_{35}H_{62}O_7$	594	*As. longifolia* [2]
13.20	longimicin-C	4,9,18	*th/t/th/t/th*	$C_{35}H_{62}O_7$	594	*As. longifolia* [2]
13.21	rollimembrin	4,13,22	*th/c/th/c/er*	$C_{35}H_{62}O_7$	594	*R. membranacea* [2]
13.22	**glaucanetin**	4,13,22	*th/t/th/t/th*	$C_{37}H_{66}O_7$	622	***R. glauca*** [13]
13.23	**10-OH-glaucanetin**	4,10,13,22	*th/t/th/t/th*	$C_{37}H_{66}O_8$	638	***R. glauca*** [13]
13.24	**purpuracenin**	4,10,15,24	*th/c/th/c/er*	$C_{37}H_{66}O_8$	638	***A. purpurea*** [48]
13.25	**27-OH-bullatacin**	4,15,24,27	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	***A. glabra*** [50]
13.26	**atemoyacin-C**	4,15,24,28	*th/c/th/c/er*	$C_{35}H_{62}O_8$	610	***A. atemoya*** [84]
Group 14 – Trihydroxylated, dihydroxylated ketonic, tetrahydroxylated and pentahydroxylated acetogenins						
Group 14a – Without OH at C4 (squamocin type)						
14a.1	squamocin	15,24,28	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	*A. squamosa* [1]
14a.2	isorollinicin	15,24,28	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	*R. papilionella* [1]
14a.3	squamocinone (CO,28)	15,24	*th/t/th/t/er*	$C_{37}H_{64}O_7$	620	*U. narum* [1]
14a.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]
14a.5	squamocin-B	13,22,26	*th/t/th/t/er*	$C_{35}H_{62}O_7$	594	*A. squamosa* [1]
14a.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]
14a.7	squamocin-F	12,15,24	*th/t/th/t/th*	$C_{37}H_{66}O_7$	622	*A. squamosa* [1]
14a.8	asimin	10,15,24	*th/t/th/t/th*	$C_{37}H_{66}O_7$	622	*As. triloba* [1]
14a.9	asiminecin	15,24,29	*th/t/th/t/th*	$C_{37}H_{66}O_7$	622	*As. triloba* [1]
14a.10	bullatin	10,15,24	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	*As. triloba* [1]
14a.11	bullanin	15,24,30	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	*As. triloba* [1,2]
14a.12	bullacin	6,13,22	*th/t/th/t/th*	$C_{35}H_{62}O_7$	594	*A. bullata* [1]
14a.13	trilobin	10,15,24	*th/t/er/c/th*	$C_{37}H_{66}O_7$	622	*As. triloba* [2]
14a.14	asitribin	15,24,28	*th/t/er/c/th*	$C_{37}H_{66}O_7$	622	*As. triloba* [2]
14a.15	uleirollin	12,15,24	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	*R. ulei* [2]
14a.16	asiminocin	15,24,30	*th/t/th/t/th*	$C_{37}H_{66}O_7$	622	*As. triloba* [2]
14a.17	bullatetrocin	15,24,31,32	*th/t/th/t/er-er*	$C_{37}H_{66}O_8$	638	*As. triloba* [2]
14a.18	longimicin-D	10,13,22	*th/t/th/t/th*	$C_{37}H_{66}O_7$	622	*As. longifolia* [2]
14a.19	mucoxin	8,14,17	*th/t/th/(c)t/th*	$C_{37}H_{66}O_7$	622	*R. mucosa* [2]

Table 6 (*Cont.*)

		Hydroxyl positions	Relative configuration of THF[a]	Molecular formula	M^+	Species[b] [Ref.]
14a.20	rollitacin (= **purpurediolin**)	15,24,28,29	*th/t/th/t/er-er*	$C_{37}H_{66}O_8$	638	*R. mucosa* [2] ***A. purpurea*** [29]
14a.21	guanacone (CO,10)	15,24	*th/t/th/t/er*	$C_{37}H_{64}O_7$	620	*A. aff. spraguei* [2]
14a.22	**spinencin** (= **uvarigrin**)	15,24,28,29	*th/t/th/c/er-th*	$C_{37}H_{66}O_8$	638	***A. spinescens*** [15] ***U. grandiflora*** [104]
14a.23	**carolin-A**	15,24,28	*th/t/th/c/er*	$C_{37}H_{66}O_7$	622	***A. spinescens*** [18]
14a.24	**carolin-B**	15,24,29	*th/t/th/c/er*	$C_{37}H_{66}O_7$	622	***A. spinescens*** [18]
14a.25	**carolin-C**	13,22,26	*th/t/th/c/er*	$C_{35}H_{62}O_7$	594	***A. spinescens*** [18]
14a.26	**atemotetrolin**	15,24,28,29	*th/t/th/t/er-th*	$C_{37}H_{66}O_8$	638	***A. atemoya*** [28]
14a.27	**purpurenin**	10,15,24,29	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	***A. purpurea*** [29]
14a.28	**ophrypetalin**	15,24,28	*h/c/th/c/er*	$C_{37}H_{66}O_7$	622	***O. odoratum*** [47]
14a.29	**salzmanin**	12,15,24,28	*th/t/er/c/er*	$C_{37}H_{66}O_8$	638	***A. salzmanii*** [54]
14a.30	**rollimusin**	10,15,24,28	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	***R. mucosa*** [58]
14a.31	**squamocin-O_1**[c]	12,15,24,28	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	***A. squamosa*** [71]
14a.32	**squamocin-O_2**[c]	12,15,24,28	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	***A. squamosa*** [71]
14a.33	**bullacin-B**	6,15,24	*th/t/th/t/th*	$C_{37}H_{66}O_7$	622	***A. squamosa*** [76]
14a.34	**6-OH-desacetyl-uvaricin**	6,15,24	*th/t/th/t/er*	$C_{35}H_{62}O_7$	594	***A. glabra*** [80]
14a.35	**6-OH-4-deoxy-squamotacin**	6,13,22	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	***A. glabra*** [80]
14a.36	**microcarpacin-A**	15,24,28,33	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	***U. microcarpa*** [82]
14a.37	**microcarpacin-B** (CO,33)	15,24,28	*th/t/th/t/er*	$C_{37}H_{64}O_8$	636	***U. microcarpa*** [83]
14a.38	**salzmanolin**[d]	15,17,24,28,29	*th/(t)/er-er*	$C_{37}H_{66}O_9$	654	***A. salzmanii*** [93]
14a.39	**15-acetylguanacone** (CO,10)	(OAc-15),24	*th/t/th/t/er*	$C_{39}H_{66}O_8$	662	***A.* aff. *spraguei*** [99]
14a.40	**24-acetylguanacone** (CO,10)	15,(OAc-24)	*th/t/th/t/er*	$C_{39}H_{66}O_8$	662	***A.* aff. *spraguei*** [99]
14a.41	**guanaconetin-1**	15,(OAc-24,30)	*th/t/th/t/er*	$C_{41}H_{70}O_9$	706	***A.* aff. *spraguei*** [99]
14a.42	**guanaconetin-2**	24,(OAc-15,30)	*th/t/th/t/er*	$C_{41}H_{70}O_9$	706	***A.* aff. *spraguei*** [99]
14a.43	**guanaconetin-3**	15,(OAc-24),30	*th/t/th/t/er*	$C_{39}H_{68}O_8$	664	***A.* aff. *spraguei*** [99]
14a.44	**guanaconetin-4**	15,24,(OAc-30)	*th/t/th/t/er*	$C_{39}H_{68}O_8$	664	***A.* aff. *spraguei*** [99]
14a.45	**atemoyacin-B**	13,22,27	*th/t/th/t/er*	$C_{35}H_{62}O_7$	594	***A. atemoya*** [102]
Group 14b – Without OH at C4, but with OH at C5 (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 (= **uvarigrandin-A**)	5,15,24	*th/t/th/t/th*	$C_{37}H_{66}O_7$	622	*U. narum* [1] ***U. grandiflora*** [103]
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* [2]
14b.5	uvariasolin-I	5,6,15,24	*th-th/t/th/t/th*	$C_{37}H_{66}O_8$	638	*U. pauci-ovulata* [2]
14b.6	uvariasolin-II	5,6,15,24	*th-th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*U. pauci-ovulata* [2]
14b.7	**calamistrin-F**	5,17,26	*th/t/th/t/th*	$C_{37}H_{66}O_7$	622	***U. calamistrata*** [57]
14b.8	**calamistrin-G**	5,17,26	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	***U. calamistrata*** [57]

[a] *th* = *threo*; *er* = *erythro*; *t* = *trans*; *c* = *cis*; [b] *U.* = *Uvaria*; *A.* = *Annona*; *R.* = *Rollinia*; *G.* = *Goniothalamus*; *As.* = *Asimina*; *O.* = *Ophrypetalum*. [c] 14a.31 and 14a.32 are C12-epimers for the authors. [d] 14a.38: The OH is on the THF ring (at C17).



of rotenone and the neurotoxic cation methylphenylpyridinium (MPP^+). In fact, ACGs such as annonacin are extremely toxic for dopaminergic neurones,[141] and they mimic the typical nigral and striatal neurodegeneration induced by rotenone and MPP^+ that cause experimental Parkinsonism.[142] However, it is not clear if the mechanism of cell death is necrosis or apoptosis, although the same ACG, annonacin, has been described as an apoptosis inductor in a human tumour cell line,[143] as well as squamocin,[144] and bullatacin (or rolliniastatin-2).[145,146] However, taking into account that the mechanism of induction of the programmed cell death process by ACG should not be different from that of rotenone, it is surprising to observe the different effects on the cell cycle described,[143,147] and the hypothetical mediating pathways involved.[144,145] It is more likely that the production of reactive oxygen species by mitochondrial complex I partially inhibits the initiator event, and thus, caspase-3 activation as main executor process[143,144] drives apoptosis induction in tumour cells by ACGs.

In summary, if these preliminary data are confirmed, potent ACGs could induce the programmed cell death process in tumour cells at very low concentration. Therefore, ACGs are not only cytotoxic compounds with expanding use as pesticides because of their capacity of inhibiting mitochondrial complex I and collapsing the bioenergetic metabolism – if they are actually potent apoptotic inductors, their potential as antitumour drugs is renewed, although a better knowledge of the cellular processes involved in the modulation of the selectivity of ACGs against the various tumour cells is required.

6 Total synthesis of ACGs‡

Because of their structural diversity and the numerous biological properties, many authors are working on the total synthesis of ACGs; previous reviews on the total synthesis of ACGs have already been published.[148–152] Since 1998 over 60 total syntheses of all types of ACGs have appeared in the literature, illustrating the creativity of chemists (to be published elsewhere as a review).

‡ Note: the compound numbers corresponding to those in the rest of the review are given within brackets in the titles.

Table 7 Adjacent bis-THF α-monohydroxylated γ-lactone acetogenins (Groups 15 and 16)

		Hydroxyl positions	Relative configuration of THF[a]	Molecular formula	M^+	Species[b] [Ref.]
Group 15 – Adjacent bis-THF α-monohydroxylated acetogenins (goniodenin type)						
15.1	goniodenin (Δ_{21})	4,18	*t/th/t/th-c*	$C_{37}H_{64}O_6$	604	*G. giganteus* [2]
15.2	asimilobin	4,18	*t/th/t/th*	$C_{35}H_{62}O_6$	578	*G. giganteus* [2] *As. triloba* [2]
15.3	annonsilin-A	20,23,24	*t/th/t/th-th*	$C_{37}H_{66}O_7$	622	*A. squamosa* [2]
15.4	rollidecin-A	4,20,23,24	*t/th/c/th-th*	$C_{37}H_{66}O_8$	638	*R. mucosa* [2]
15.5	rollidecin-B	4,20,23,24	*t/th/c/th-er*	$C_{37}H_{66}O_8$	638	*R. mucosa* [2]
15.6	rollinacin	4,10,20	*t/th/t/th*	$C_{35}H_{62}O_7$	594	*R. mucosa* [2]
15.7	**rollidecin-C**	4,20	*t/th/c/th*	$C_{35}H_{62}O_6$	578	***R. mucosa*** [20]
15.8	**rollidecin-D**	4,22	*t/th/c/th*	$C_{37}H_{66}O_6$	606	***R. mucosa*** [20]
15.9	**bulladecin**	4,20,23,24	*t/th/t/th-er*	$C_{37}H_{66}O_8$	638	***A. atemoya*** [28]
15.10	**glabracin-A**[c]	4,10,23,24	*th/t/th/t-er*	$C_{37}H_{66}O_8$	638	***A. glabra*** [77]
15.11	**glabracin-B**	4,10,23,24	*th/t/th/t-th*	$C_{37}H_{66}O_8$	638	***A. glabra*** [77]
15.12	**annocatacin-A**	4,23	*t/th/t/th*	$C_{35}H_{62}O_6$	578	***A. muricata*** [78]
15.13	**annocatacin-B**	4,23	*c/th/c/th*	$C_{35}H_{62}O_6$	578	***A. muricata*** [78]
15.14	**atemoyacin-E**	4,20,23,26	*t/th/t/th*	$C_{37}H_{66}O_8$	638	***A. atemoya*** [79]
15.15	**robustocin**	18	*t/th/c/th*	$C_{35}H_{62}O_5$	562	***A. muricata*** [81]

[a] *th = threo*; *er = erythro*; *t = trans*; *c = cis*. [b] *G. = Goniothalamus*; *As. = Asimina*; *A. = Annona*; *R. = Rollinia*.
[c]

Convergent, linear, and biomimetic approaches have been used, relying on the use of cheap chiral starting materials (*e.g.* amino acids, sugars, tartaric acid, *etc.*) or on asymmetric reactions (*e.g.* Sharpless asymmetric epoxidation, Sharpless asymmetric dihydroxylation, diastereoselective Williamson etherification, *etc.*). Semi-synthesis of natural ACGs as well as derivatised ACGs (*e.g.* amines, esters, and glucosylated ACGs) and preparation of structural analogues (*e.g.* simplified mimics, chimeras) have also been reported. The aim of the present work is thus not to discuss these numerous reports, but rather to describe the key syntheses that have contributed to the structural elucidation of natural ACGs. Indeed, total synthesis is a key tool for the complete structure determination of ACGs, since several absolute configurations of stereogenic centres are rather difficult to determine without comparison of the spectroscopic data, and/or the chromatographic properties of several stereomers.

Total synthesis of asimilobin (15.2, Table 7) and its penta-epimer[153,154]

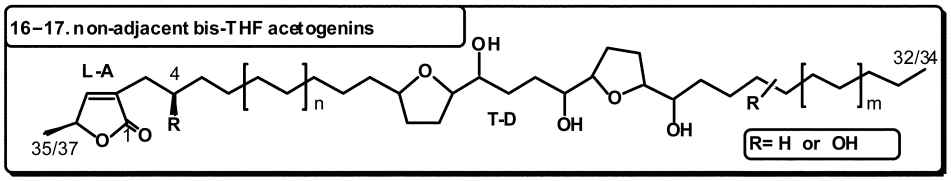
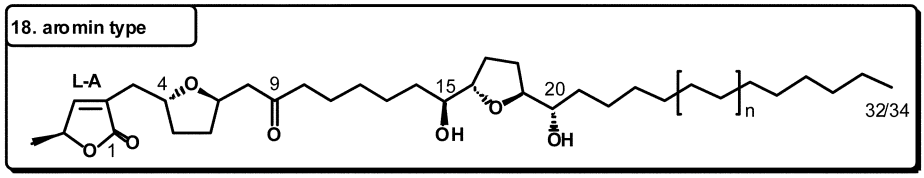
The convergent synthesis of asimilobin relies on the Sharpless asymmetric dihydroxylation (AD-mix) of an *E*-alkene, followed by a highly diastereoselective epoxidation–opening–cyclisation of the dien-diol intermediate to produce the bis-THF core of the target molecule. Preparation of the butenolide terminus by known procedures, followed by a Wittig-type reaction between the two fragments, led to the desired compound, which after functionalisation gave the expected product **1a**. The spectroscopic data were in accord with those of the natural product except for the specific rotation, which was of opposite sign. Thus by modifying the absolute configuration of the five stereogenic centres of the bis-THF unit, a new compound, **1b**, was obtained, whose data were in complete accord with the natural product (Scheme 1).

Scheme 1 Total synthesis of asimilobin **1b** and its penta-epimer **1a**.

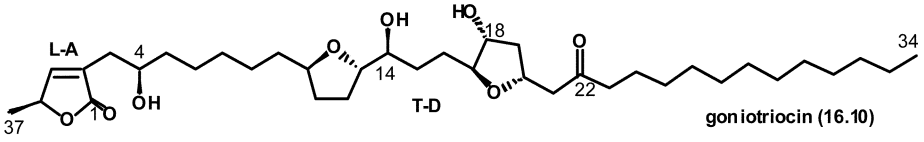
Total synthesis of corossolin (6.2, Table 3) and its (10*S*)-epimer[155]

The synthesis of both epimers was performed from gluconolactone, which led to the mono-THF fragment, terminated by an alkyne. The latter, after metallation, opened up a chiral epoxide containing the butenolide terminus, to give the expected products. Functional manipulation gave the two target molecules, whose spectroscopic data were in accord with the natural compound. However, the specific rotation of compound (10*R*)-**2a** ($[\alpha]_D = +19.1$) was in better agreement with that of the

Table 8 Non-adjacent bis-tetrahydrofuran γ-lactone acetogenins (Groups 16–18)

		Hydroxyl positions	Relative configuration of THF[a]	Molecular formula	M^+	Species[b] [Ref.]
						
Group 16 – Non-adjacent bis-THF acetogenins (with OH at C4) (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* [2]
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* [2]
16.9	trilobalicin	4,14,17,22	*t/th-th/t/er*	$C_{35}H_{62}O_8$	610	*As. triloba* [2]
16.10	**goniotriocin**[c] (CO,22)	4,14,18	*t/th/(c)/t*	$C_{37}H_{64}O_8$	636	***G. giganteus*** [36]
Group 17 – Non-adjacent bis-THF acetogenins (without OH at C4) (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]
17.5	**12,15-*cis*-squamostatin-D**	16,19,24	*c/th-th/t/er*	$C_{37}H_{66}O_7$	622	***A. atemoya*** [51]
17.6	**12,15-*cis*-squamostatin-A**	16,19,24,28	*c/th-th/t/er*	$C_{37}H_{66}O_8$	638	***A. atemoya*** [51]
Group 18 – 4–7/16–19 Non-adjacent bis-THF acetogenins (aromin type)						
						
18.1	aromin	15,20	*t-th/t/th*	$C_{35}H_{60}O_7$	592	*X. aromatica* [2]
18.2	aromicin	15,20	*t-th/t/th*	$C_{37}H_{64}O_7$	620	*X. aromatica* [2]
18.3	**aromin-A** (CO,9)	15,20	*t-th*[d]*/t/er*[d]	$C_{35}H_{60}O_7$	592	***A. cherimolia*** [46]

[a] *th* = *threo*; *er* = *erythro*; *t* = *trans*; *c* = *cis*. [b] *R.* = *Rollinia*; *G.* = *Goniothalamus*; *A.*. = *Annona*; *As.* = *Asimina*. [c] **16.10**: The OH is on the THF ring (C18 position).



[d] For **18.3** the relative configuration is either *th/t/er* or *er/t/th*.

natural product ($[\alpha]_D = +19$) than the (10*S*)-epimer **2b** ($[\alpha]_D = +24.6$) (Scheme 2).

Total synthesis of asimin (14a.8, Table 6) and its C-10 epimer[156]

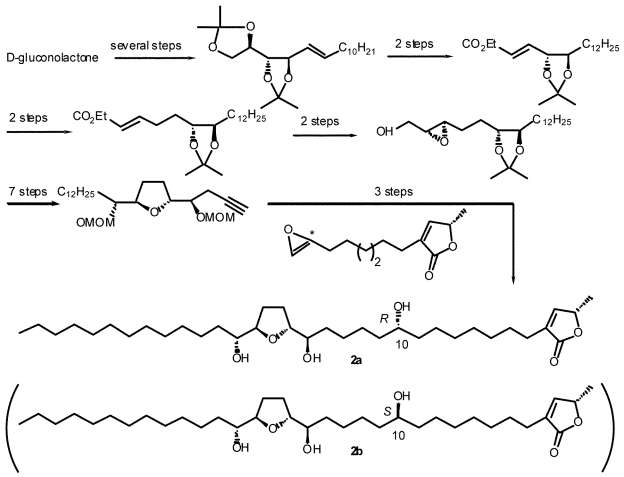
The synthesis of both possible C-10 epimers of asimicin, **3a** and **3b**, allowed the authors to determine the absolute configuration of the natural product as being 10*R* (compound **3b**), based on the comparison of the specific rotations and on the ^{1}H-NMR spectra of the MTPA ester derivatives of **3a** and **3b**. The synthesis of both epimers relies on the key enantioenriched addition of γ-OMOM allylic indium reagents to a core aldehyde, and to a Williamson reaction for the THF ring-closing reaction, followed by an asymmetric addition of a dialkyl zinc reagent to stereoselectively introduce the C-10 carbinol group. Aldolisation with (*S*)-lactaldehyde and functional manipulation then gave the expected products **3a** and **3b** (Scheme 3).

Total synthesis of jimenezin (22b.2, Table 11) and its C-19 epimer[157]

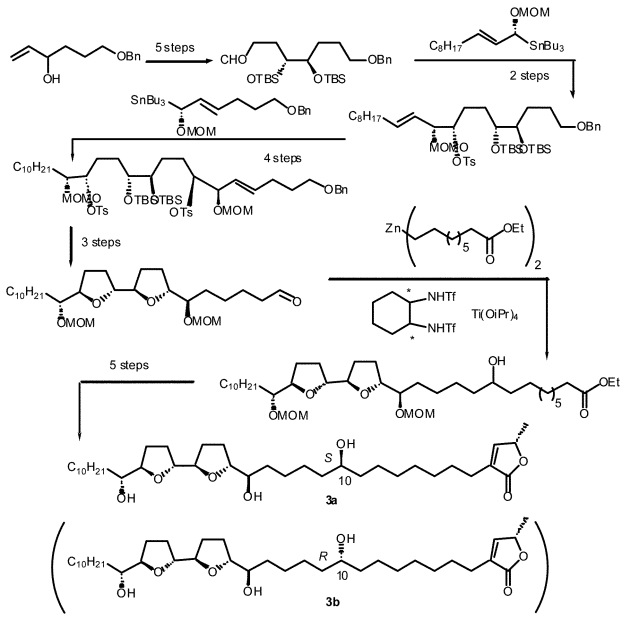
The synthesis of both C-19 epimers of jimenezin, from L-rhamnose and D-galactose, allowed the authors to revise the structure of the natural product. Comparison of the spectroscopic data (chemical shifts and coupling constants in the ^{1}H NMR spectra, as well as ^{13}C NMR chemical shifts and $[\alpha]_D$ values) of the two synthetic products **4a** and **4b** with those of the natural compound, supported unambiguously the structural revision, which corresponds to the product **4b** (Scheme 4).

Total synthesis of muricatetrocins A and B (9a.5, Table 4)[158]

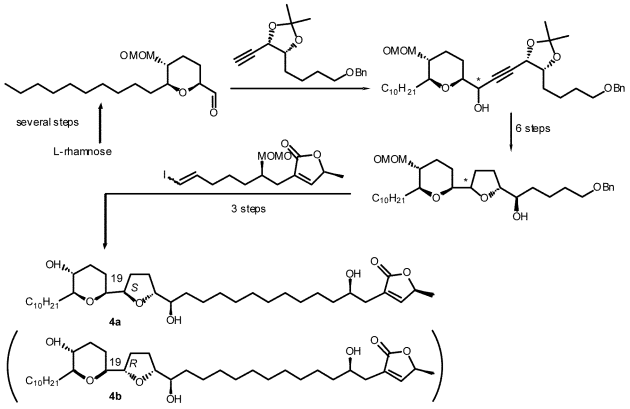
Muricatetrocins A and B are epimers at C-12, and thus possess *cis* and *trans* THF rings, respectively. The THF fragments, with the desired configurations, were obtained by the enantioselective



Scheme 2 Total synthesis of corossolin **2a** and its (10*S*)-epimer **2b**.

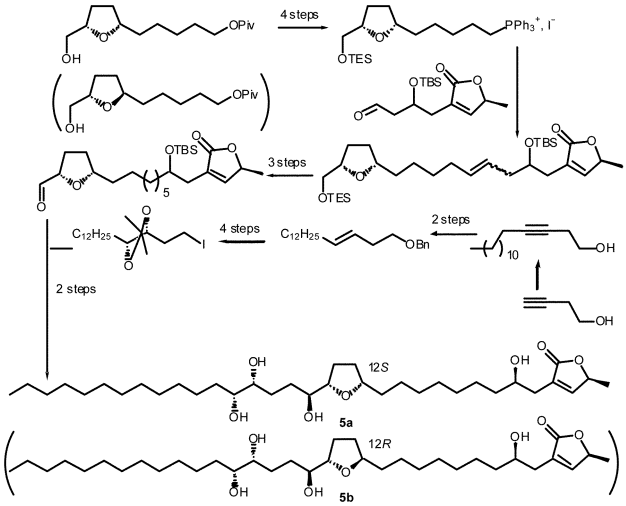


Scheme 3 Total synthesis of asimin **3b** and its (10*S*)-epimer **3a**.



Scheme 4 Total synthesis of jimenezin **4b** and its (19*R*)-epimer **4a**.

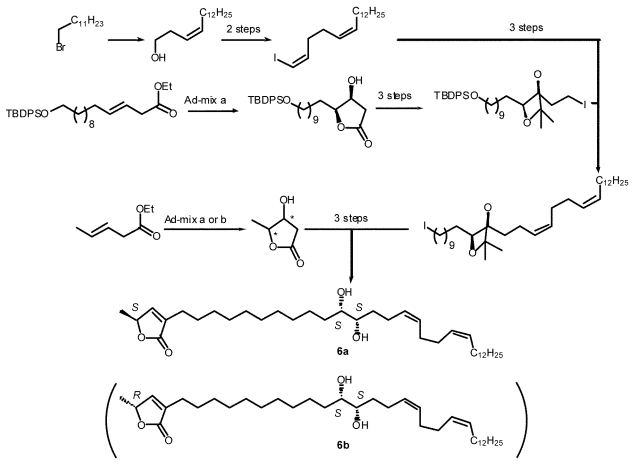
addition of an organozinc reagent on a chiral aldehyde, followed by a Williamson cyclisation. The butenolide fragment was prepared from acetoacetic acid and (*S*)-propylene oxide by enantioselective Noyori hydrogenation to secure the C-carbinol centre. Then, coupling reaction of the fragments bearing the required THF and butenolide parts with the common aliphatic diol moiety afforded the expected products **5a** and **5b**. The ^{1}H and ^{13}C NMR data of **5a** are in close agreement with those of the natural muricatetrocin A, whereas those of **5b** matched closely those of muricatetrocin B. Furthermore, authors concluded that howiicin E is similar to muricatetrocin A (Scheme 5).



Scheme 5 Total synthesis of muricatetrocins A and B.

Total synthesis of (−)-montecristin (1a.5, Table 1) and its *ent*-5-epimer[159]

The synthesis of the two stereomers, **6a** and **6b**, of natural (+)-montecristin allowed the authors to elucidate the structure of the natural compound. The key reactions rely on the Sharpless asymmetric dihydroxylation and an alkylation of a β-hydroxy butanolide. Comparison of the spectroscopic data (^{1}H and ^{13}C NMR data, and $[\alpha]_D$ values) of the two synthetic products with those of the natural compound allowed the authors to secure the complete structural elucidation of montecristin as *ent*-**6b** (Scheme 6).



Scheme 6 Total synthesis of (−)-montecristin **6b** and its *ent*-5-epimer **6a**.

Semi-synthesis of *cis* and *trans* solamin (5.11 and 5.4, Table 3)[160]

Semi-synthesis of *cis*- and *trans*-solamin by $H_2{}^{18}O$ acidic opening of natural diepomuricanin A (3.1, Table 2) has provided evidence for the presence of an unexpected diepomuricanin A isomer in the reaction mixture. The acidic S_N2 opening by $H_2{}^{18}O$ of the bis-epoxide unit of diepomuricanin A, followed by mass analysis of the products so obtained, has shown that the natural product was in fact a mixture of *syn*- and *anti*-diepomuricanins A **7a** and **7b**, whose absolute configurations remain unknown (Scheme 7).

Table 9 Saturated lactone bis-THF acetogenins (Groups 19 and 20)

		Hydroxyl positions	Relative configuration of THF[a]	Molecular formula	M^+	Species[b] [Ref.]
Group 19 – "Iso"-bis-THF acetogenins (bullatacinone type)						
19.1	bullatacinone	15,24	*th/t/th/t/er*	$C_{37}H_{66}O_7$	622	*A. bullata* [1]
19.2	rollinone	15,24	*th/c/th/c/er*	$C_{37}H_{66}O_7$	622	*R. papilionella* [1]
19.3	bullatalicinone[c] or isocherimolin-1	16,19,24	*th-th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [1] *A. cherimolia* [1]
19.4	bullatanocinone[c]	16,19,24	*th-th/t/th*	$C_{37}H_{66}O_8$	638	*A. bullata* [1]
19.5	bulladecinone[d]	20,23,24	*t/th/t/th-er*	$C_{37}H_{66}O_8$	638	*A. bullata* [1]
19.6	32-OH-bullatacinone	15,24,32	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [1]
19.7	31-OH-bullatacinone	15,24,31	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [1]
19.8	30-OH-bullatacinone	15,24,30	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [1]
19.9	isomolvizarin-1	13,22	*th/t/th/t/er*	$C_{35}H_{62}O_7$	594	*A. cherimolia* [1]
19.10	isomolvizarin-2	13,22	*th/t/th/t/th*	$C_{35}H_{62}O_7$	594	*A. cherimolia* [1]
19.11	10-OH-bullatacinone	10,15,24	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [1]
19.12	12-OH-bullatacinone	12,15,24	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [1]
19.13	29-OH-bullatacinone	15,24,29	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [1]
19.14	28-OH-bullatacinone	15,24,28	*th/t/th/t/er*	$C_{37}H_{66}O_8$	638	*A. bullata* [2]
19.15	trilobacinone	15,24	*th/t/er/c/th*	$C_{37}H_{66}O_7$	622	*As. triloba* [2]
19.16	**gigantecinone**[c]	14,17,22	*t/th-th/t/th*	$C_{37}H_{66}O_8$	638	***G. giganteus*** [14]
19.17	**20,23-*cis*-bullatalicinone**[c]	16,19,24	*t/th-th*[e]*/c/er*[e]	$C_{37}H_{66}O_8$	638	***R. mucosa*** [58]
19.18	**9-OH-asimicinone**	9,15,24	*th/t/th/t/th*	$C_{37}H_{66}O_8$	638	***A. squamosa*** [8]
19.19	**squamolinone**	15,24	*th/t/th/t/er*	$C_{35}H_{62}O_7$	594	***A. squamosa*** [76]
19.20	**9-oxo-asimicinone** (CO,9)	15,24	*th/t/th/t/th*	$C_{37}H_{64}O_8$	636	***A. squamosa*** [76]
Group 20 – β-Hydroxy methyl γ-lactones (laherradurin type)						
20.1	laherradurin	15,24,35	*th/t/th/t/er*	$C_{37}H_{68}O_7$	624	*A. cherimolia* [1]
20.2	itrabin	13,22,33	*th/t/th/t/er*	$C_{35}H_{64}O_7$	596	*A. cherimolia* [1]
20.3	otivarin[f]	16,19,24,35	*t/th-th/t/er*	$C_{37}H_{68}O_8$	640	*A. cherimolia* [1]
20.4	**tucumanin**[f]	15,24,35	*th/t/th/t/th*	$C_{37}H_{68}O_7$	624	***A. cherimolia*** [96]

[a] *th* = *threo*; *er* = *erythro*; *t* = *trans*; *c* = *cis*. [b] *A.*. = *Annona*; *R.*. = *Rollinia*; *As.* = *Asimina*; *G.* = *Gonothalamus*.

[c] Isobullatalicinone or isocherimolin-1 (19.3)

(*iso*-bis-THF-acetogenins with T-D ring system: 19.3, 19.4, **19.16** and **19.17**).

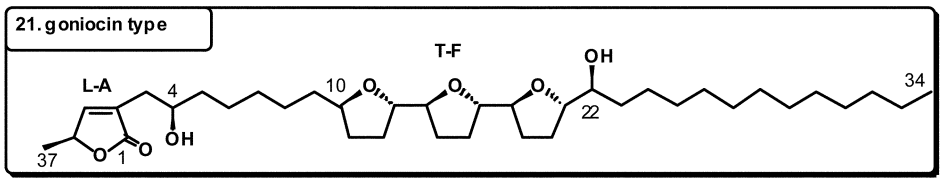
[d] bulladecinone (19.5)

(*iso*-bis-THF-acetogenins with T-A ring system: 19.5). [e] For **19.17** the relative configuration is either *t/th-th/c/er* or *t/th-er/c/th*.

[f] otivarin (20.3)

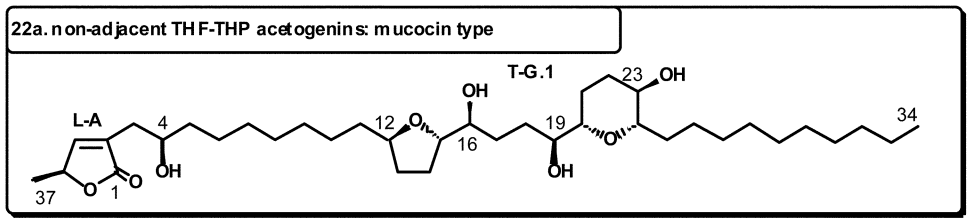
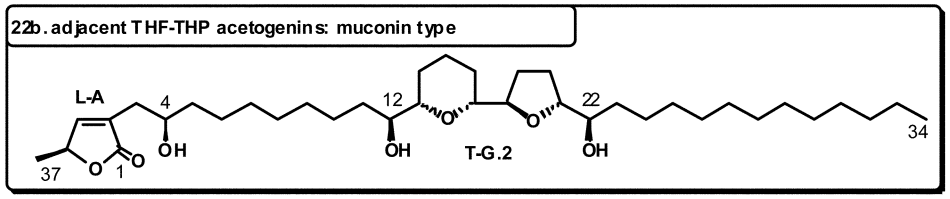
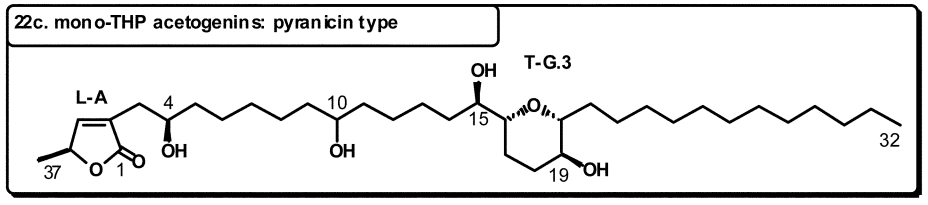
tucumanin (20.4)

Table 10 Tri-tetrahydrofuran acetogenins (Group 21)

		Hydroxyl positions	Relative configuration of THF[a]	Molecular formula	M+	Species[b] [Ref.]
Group 21 – Tri-THF acetogenins (goniocin type)						
						
21.1	goniocin	4,22	*t/th/t/th/t/th*	$C_{37}H_{64}O_7$	620	*G. giganteus* [1]

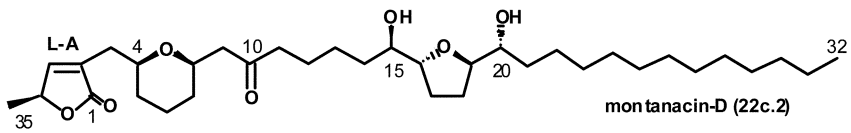
[a] *th* = *threo*; *t* = *trans*. [b] *G.* = *Goniothalamus*.

Table 11 Tetrahydropyran acetogenins (Group 22)

		Hydroxyl positions	Relative configuration[a]	Molecular formula	M+	Species[b] [Ref.]
Group 22a – Mono-THP acetogenins (pyranicin type)						
						
22a.1	**pyranicin**	4,10,15,19	*th-c-t*	$C_{35}H_{64}O_7$	596	***G. giganteus*** [38]
22a.2	**pyragonicin**	4,10,13,17	*th-c-t*	$C_{35}H_{64}O_7$	596	***G. giganteus*** [38]
Group 22b – Adjacent THF–THP acetogenins (muconin type)						
						
22b.1	muconin	4,12,22	*th/c/th/t/th*	$C_{37}H_{66}O_7$	622	*R. mucosa* [2]
22b.2	**jimenezin**	4,15,23	*th/t/er/c-t*	$C_{37}H_{66}O_7$	622	***R. mucosa*** [17]
	Configuration revised following synthesis; see Scheme 4.		*th/c/th/c-t*			[157]
22b.3	**chamuvarinin**	15	*nd*	$C_{37}H_{64}O_6$	604	***U. chamae*** [97]
Group 22c – Non-adjacent THF–THP acetogenins (mucocin type)						
						
22c.1	mucocin	4,16,19,23	*t/th-th/c*	$C_{37}H_{66}O_8$	638	*R. mucosa* [2]
22c.2	**montanacin-D** (CO,10)[c]	15,20	*c-th/t/th*	$C_{35}H_{60}O_7$	592	***A. montana*** [68]
22c.3	**montanacin-E** (CO,10)	15,20	*c-th/c/th*	$C_{35}H_{60}O_7$	592	***A. montana*** [68]

[a] *th* = *threo*; *er* = *erythro*; *t* = *trans*; *c* = *cis*; *nd* = configuration not determined. [b] *G.* = *Goniothalamus*; *R.*. = *Rollinia*; *X.* = *Xylopia*.

[c]



(Non-adjacent THF–THP acetogenins with separated rings system: **22c.2** and **22c.3**).

Table 12 Species from the Annonaceae family which hav provided new acetogenins

Species	Organ	Compounds		Ref.
Annona atemoya	Seed	**1a.21**	**artemoin-A + B + C + D**	[51]
		5.9	annotemoyin-1	[2]
(*A. cherimolia* × *A.squamosa*)		5.10	annotemoyin-2	[2]
		13.15	annonisin	[2]
		14a.26	**atemotetrolin**	[28]
		14a.45	**atemoyacin B**	[102]
		15.9	**bulladecin**	[28]
		15.14	**atemoyacin-E**	[79]
		17.5	**12,15-*cis*-squamostatin-D**	[51]
		17.6	**12,15-*cis*-squamostatin-A**	[51]
	Root	**13.26**	**atemoyacin-C**	[84]
Annona bullata	Bark	5.5	uvariamicin-IV	[1]
		5.6	bullatencin	[1]
		13.3	bullatacin (or rolliniastatin-2)	[1]
		13.11	30-OH-bullatacin	[2]
		13.12	31-OH-bullatacin	[2]
		13.13	32-OH-bullatacin	[2]
		14a.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]
		19.1	bullatacinone	[1]
		19.3	bullatalicinone (or isocherimolin-1)	[1]
		19.4	bullatanocinone	[1]
		19.5	bulladecinone	[1]
		19.6	32-OH-bullatacinone	[1]
		19.7	31-OH-bullatacinone	[1]
		19.8	30-OH-bullatacinone	[1]
		19.11	10-OH-bullatacinone	[1]
		19.12	12-OH-bullatacinone	[1]
		19.13	29-OH-bullatacinone	[1]
		19.14	28-OH-bullatacinone	[2]
Annona cherimolia	Seed	**7a.36**	**annocherin**	[52]
		7a.40	**annocherimolin**	[60]
		9a.21	**annomolin**	[60]
		10.17	**annocherinone**	[52]
		11a.1	jetein	[1]
		11b.12	**annomolon-A + 34-*epi***	[94]
		11b.13	**annomolon-B + 34-*epi***	[94]
		13.4	molvizarin-1	[1]
		14a.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]
		20.1	laherradurin	[1]
		20.2	itrabin	[1]
		20.3	otivarin	[1]
		20.4	**tucumanin**	[96]
	Stem	**18.3**	**aromin-A**	[46]
	Root	19.3	isocherimolin-1 (or bullatalicinone)	[1]
		19.9	isomolvizarin-1	[1]
		19.10	isomolvizarin-2	[1]
Annona coriacea	Root	1a.3	coriadienin	[2]
		8.13	coriheptocin-A	[2]
		8.14	coriheptocin-B	[2]
		8.23	**annoheptocin-A**	[87]
		8.24	**annoheptocin-B**	[87]
		9a.9	coriacin	[2]
		9b.3	4-deoxycoriacin	[2]
		9b.7	**coriacyclodienin**	[91]
		9b.8	**coriacycloenin**	[91]
Annona crassiflora	Seed	13.14	araticulin	[2]
Annona densicoma	Seed	7a.1	annonacin	[1]
		7a.3	annonacinone	[1]
	Bark	8.3	8-OH-annonacin	[1]
		9a.2	densicomacin-1	[1]
		10.1	isoannonacin	[1]
		10.2	isoannonacinone	[1]
Annona glabra	Seed	9a.17	glabranin	[2]
	Leaf	**7a.29**	**glacin-A**	[31]
		7a.30	**glacin-B**	[31]
		7a.34	**annoglacin-A**	[49]
		7a.35	**annoglacin-B**	[49]

Table 12 (*Cont.*)

Species	Organ	Compounds		Ref.
		8.19	**annoglaxin**	[50]
		13.25	**27-OH-bullatacin**	[50]
		14a.34	**6-OH-desacetyluvaricin**	[80]
		14a.35	**6-OH,4-deoxysquamotacin**	[80]
		15.10	**glabracin-A**	[77]
		15.11	**glabracin-B**	[77]
Annona glauca	Root	13.9	annoglaucin	[1]
	Seed	**6.19**	**glaucabellin**	[33]
		9a.16	glaucafilin	[2]
		13.10	glaucanisin	[1]
		13.22	**glaucanetin**	[13]
		13.23	**10-OH-glaucanetin**	[13]
Annona jahnii	Twig	**1a.14**	**annojahnin**	[39]
		1a.16	**annodienin**	[85]
		1a.17	**jahnonacin**	[85]
Annona montana	Seed	**6.24**	**montalicin-A**	[98]
		6.25	**montalicin-B**	[98]
		7a.5	annomontacin	[1]
		7a.44	**montalicin-C**	[98]
		7a.45	**montalicin-D**	[98]
		7a.46	***cis*-annoreticuin**	[98]
		7a.47	**montalicin-E**	[98]
		7a.48	**montalicin-F**	[98]
		7a.49	**montalicin-I**	[98]
		7a.50	**montalicin-J**	[98]
		8.1	annomonicin	[1]
		8.2	montanacin	[1]
		8.26	**montacin**	[101]
		8.27	***cis*-montacin**	[101]
	Fruit	3.6	diepoxymontin	[1]
	Leaf	**7a.37**	**annomontanin-A**	[53]
		8.20	**annomontanin-B**	[53]
		8.21	**montanacin-B**	[68]
		8.22	**montanacin-C**	[68]
		10.21	**montanacin-G**	[69]
		10.22	**montanacin-F**	[74]
		11b.7	**annomontanin-C**	[53]
		11b.8	**montanacin-H + 34-*epi***	[69]
		11b.9	**montanacin-I + 34-*epi***	[69]
		11b.10	**montanacin-J + 34-*epi***	[69]
		22c.2	**montanacin-D**	[68]
		22c.3	**montanacin-E**	[68]
Annona muricata	Seed	**1a.13**	**murihexol**	[23]
		1a.15	**cohibin-C + D**	[56]
		1a.18	**muricatenol**	[89]
		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]
		5.17	**15-palmitoylsolamin**	[86]
		5.18	**15-oleylsolamin**	[86]
		6.1	murisolin	[1]
		6.2	corossolin	[1]
		6.3	corossolone	[1]
		7a.19	*cis*-annonacin	[2]
		7a.20	*cis*-annonacinone	[2]
		7a.21	*cis*-goniothalamicin	[2]
		7a.22	arianacin + javoricin	[2]
		7a.39	***cis*-annomontacin**	[59]
		7a.42	**muricin-G**	[63]
		8.12	muricatalicin	[2]
		8.25	**muricatatin-C**	[100]
		9a.4	gigantetrocin-B	[1]
		9a.5	muricatetrocin-A + B	[1]
		9a.11	muricatalin	[2]
		9a.22	**muricin-A**	[63]
		9a.23	**muricin-B**	[63]
		9a.24	**muricin-C**	[63]
		9a.25	**muricin-D**	[63]
		9a.26	**muricin-E**	[63]
		9a.27	**muricin-F**	[63]
		9b.5	**muricin-H**	[59]
		9b.6	**muricin-I**	[59]
		15.12	**annocatacin-A**	[78]

Table 12 (*Cont.*)

Species	Organ	Compounds		Ref.
		15.13	**annocatacin-B**	[78]
		15.15	**robustocin**	[81]
	Bark	2.1	epoxymurin-A (or epomuricenin-A)	[1]
		2.2	epoxymurin-B	[1]
		8.6	muricatin-C	[1]
		9a.7	muricatin-A	[1]
		9a.8	muricatin-B	[1]
	Leaf	7a.18	annomutacin	[2]
		8.4	annomuricin-A	[1]
		8.5	annomuricin-B	[1]
		8.7	muricatocin-A	[2]
		8.8	muricatocin-B	[2]
		8.9	muricatocin-C	[2]
		8.10	annomuricin-C	[2]
		8.11	annohexocin	[2]
		8.16	**annomuricin-E**	[26]
		8.17	**muricapentocin**	[26]
		9a.10	murihexocin-A + B	[2]
		9a.12	annopentocin-A + B	[2]
		9a.13	annopentocin-C	[2]
		9a.19	**muricoreacin**	[40]
		9a.20	**murihexocin-C**	[40]
		10.9	annomuricinone-D	[2]
	Root	1a.5	montecristin	[2]
		1a.6	cohibin-A	[2]
		1a.7	cohibin-B	[2]
		1c.1	muridienin-1	[2]
		1c.2	muridienin-2	[2]
		1c.5	**chatenaytrienin-1 + 2**	[21]
		1c.6	**chatenaytrienin-3 + 4**	[21]
		1c.7	**muricadienin**	[21]
		1c.8	**muridienin-3 + 4**	[21]
		2.6	**sabadelin**	[45]
		3.9	**coronin**	[70]
		5.11	***cis*-solamin**	[30]
		5.12	***cis*-panatellin**	[30]
		5.13	***cis*-uvariamicin-IV**	[30]
		5.14	***cis*-uvariamicin-I**	[30]
		5.15	***cis*-reticulatacin**	[30]
		6.16	***cis*-reticulatacin-10-one**	[30]
Annona nutans	Root	**1a.15**	**cohibin-C + D**	[56]
		1c.5	**chatenaytrienin-1 + 2**	[21]
		1c.6	**chatenaytrienin-3 + 4**	[21]
		1c.7	**muricadienin**	[21]
		1c.8	**muridienin-3 + 4**	[21]
Annona purpurea	Leaf	13.7	purpureacin-2	[1]
	Seed	**13.24**	**purpuracenin**	[48]
		14a.27	**purpurenin**	[29]
Annona reticulata	Bark	5.2	reticulatacin (or uvariamicin-II)	[1]
		7a.11	reticulacinone	[1]
	Leaf	7a.6	annoreticuin	[1]
		7a.7	annoreticuinone	[1]
		10.4	isoannoreticuin	[1]
	Seed	1b.1	reticulatamol	[1]
		1b.2	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	[2]
Annona salzmanii	Root	**11b.11**	**parisin**	[93]
		14a.29	**salzmanin**	[54]
		14a.38	**salzmanolin**	[93]
Annona senegalensis	Seed	7a.15	annogalene (or xylomatenin)	[1]
		7a.16	annosenegalin	[1]
		9a.6	senegalene	[1]
Annona spinescens	Seed	**8.18**	**araticin**	[43]
		14a.22	**spinencin**	[15]
		14a.23	**carolin-A**	[18]
		14a.24	**carolin-B**	[18]
		14a.25	**carolin-C**	[18]
Annona aff. *spraguei*	Seed	14a.21	guanacone	[2]
		14a.39	**15-acetylguanacone**	[99]
		14a.40	**24-acetylguanacone**	[99]

Table 12 (*Cont.*)

Species	Organ	Compounds		Ref.
		14a.41	**guanaconetin-1**	[99]
		14a.42	**guanaconetin-2**	[99]
		14a.43	**guanaconetin-3**	[99]
		14a.44	**guanaconetin-4**	[99]
Annona squamosa	Seed	**1d.2**	**squamostolide**	[95]
		7a.4	annonacin-A	[1]
		7a.12	squamosten-A	[1]
		7a.27	mosin-B	[2]
		7a.28	mosin-C	[2]
		10.13	mosinone-A	[2]
		10.19	**squamoxinone-B**	[8]
		10.20	**squamoxinone-C**	[8]
		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]
		14a.1	squamocin	[1]
		14a.4	annonin-III (or motrilin)	[1]
		14a.5	squamocin-B	[1]
		14a.6	squamocin-D (or asiminacin)	[1]
		14a.7	squamocin-F	[1]
		14a.31	**squamocin-O_1**	[71]
		14a.32	**squamocin-O_2**	[71]
		15.3	annonsilin-A	[2]
		17.1	squamostatin-A (or almunequin)	[1]
		17.3	squamostatin-D	[1]
		17.4	squamostatin-E	[1]
	Bark	**6.14**	**4-deoxyannoreticuin**	[24]
		6.15	***cis*-4-deoxyannoreticuin**	[24]
		10.3	squamone	[1]
		10.14	**squamoxinone**	[24]
		14a.33	**bullacin-B**	[76]
		19.18	**9-OH-asimicinone**	[8]
		19.19	**squamolinone**	[76]
		19.20	**9-oxo-asimicinone**	[76]
Artabotrys hexapetalus	Aerial parts	**1c.12**	**artapetalin-A**	[61]
		1c.13	**artapetalin-B**	[61]
		1c.14	**artapetalin-C**	[61]
Asimina longifolia	Leaf; twig	1b.3	longanin	[2]
		6.11	longifolicin	[2]
		6.12	longicoricin	[2]
		7a.17	longicin	[2]
		7a.24	4-acetylannonacin	[2]
		7a.25	4-acetylxylomaticin	[2]
		10.7	goniothalamicinone	[2]
		10.10	gigantetroneninone	[2]
		13.18	longimicin-A	[2]
		13.19	longimicin-B	[2]
		13.20	longimicin-C	[2]
		14a.18	longimicin-D	[2]
Asimina parviflora	Stem	13.8	parviflorin (or squamocin-E)	[1]
		16.5	parvifloracin	[1]
Asimina triloba	Roots and seed husks	13.1	asimicin	[1]
		10.5	annonacinone-A	[2]
		10.6	gigantetrocinone	[1]
		13.5	trilobacin	[1,2]
		13.16	10-OH-asimicin	[2]
		13.17	10-OH-trilobacin	[2]
		14a.6	asiminacin (or squamocin-D)	[1]
		14a.8	asimin	[1]
		14a.9	asiminecin	[1]
		14a.10	bullatin	[1]
		14a.11	bullanin	[1,2]
		14a.16	asiminocin	[2]
		14a.17	bullatetrocin	[2]
		16.9	trilobalicin	[2]
		19.15	trilobacinone	[2]
	Seed	6.5	asiminenin-A	[2]
		6.6	asiminenin-B	[2]
		6.7	*cis*-murisolin	[2]
		6.8	murisolin-A	[2]

Table 12 (*Cont.*)

Species	Organ	Compounds		Ref.
		7a.32	**asitrilobin-A**	[41]
		7a.33	**asitrilobin-B**	[41]
		7a.41	**asitrocin**	[62]
		7a.43	**asitrilobin-C**	[75]
		7b.12	**asitrilobin-D**	[75]
		10.8	murisolinone	[2]
		10.18	**asitrocinone**	[62]
		14a.13	trilobin	[2]
		14a.14	asitribin	[2]
		15.2	asimilobin	[2]
Dasymaschalon sootepense	Leaf	**7b.10**	**sootepensin-A**	[67]
		7b.11	**sootepensin-B**	[67]
Disepalum anomalum	Bark	7a.26	disepalin	[2]
Goniothalamus amuyon	Seed		known acetogenins (**6.2**, **7a.1** and **9a.1**)	[2]
Goniothalamus donnaiensis	Root	**1a.11**	**donhexocin**	[22]
		1a.12	**donbutocin**	[22]
		1a.19	**donhepocin + 34-*epi***	[22]
		1a.20	**donnaienin-D + 34-*epi***	[27]
		8.15	**donnaienin**	[19]
		11b.1	donnaienin-A + 34-*epi*	[2]
		11b.2	donnaienin-B + 34-*epi*	[2]
		11b.3	goniodonin + 34-*epi*	[2]
		11b.4	*cis*-goniodonin + 34-*epi*	[2]
		11b.6	**donnaienin-C + 34-*epi***	[27]
Goniothalamus gardneri	Root	**1a.9**	**gardnerilin-A**	[16]
		1a.10	**gardnerilin-B**	[16]
		11b.5	**gardnerinin + 34-*epi***	[25]
	Aerial parts	**1c.9**	**goniothalamusin**	[44]
Goniothalamus giganteus	Bark	1a.1	giganin	[1,2]
		6.4	giganenin	[1]
		6.13	4-deoxyannomontacin	[2]
		7a.2	goniothalamicin	[1]
		7a.13	gonionenin	[1]
		7a.31	**goniotetracin**	[37]
		7b.8	gigantransenin-A + B	[2]
		7b.9	gigantransenin-C	[2]
		9a.1	gigantetrocin-A	[1]
		9a.3	gigantetronenin	[1]
		9a.14	4-acetylgigantetrocin-A	[2]
		9a.18	**goniotrionin**	[38]
		9b.1	gigantriocin	[1]
		9b.2	gigantrionenin	[1]
		9b.4	*cis*-gigantrionenin	[2]
		10.11	annomontacinone	[2]
		10.15	**xylomaticinone**	[36]
		10.16	**gonioneninone**	[37]
		15.1	goniodenin	[2]
		15.2	asimilobin	[2]
		16.2	gigantecin	[1]
		16.10	**goniotriocin**	[36]
		17.2	4-deoxygigantecin	[1]
		19.16	**gigantecinone**	[14]
		21.1	goniocin	[1]
		22a.1	**pyranicin**	[38]
		22a.2	**pyragonicin**	[38]
Goniothalamus sesquipedalis	Bark		known acetogenin (**9a.1**)	[2]
Ophrypetalum odoratum	Leaf	**14a.28**	**ophrypetalin**	[47]
Polyalthia plagioneura	Seed	7b.1	plagionicin-A	[2]
Porcelia macrocarpa	Seed	1c.1	butyrolactone-1	[2]
		1c.2	butyrolactone-2	[2]
Rollinia laurifolia	Leaf	**5.16**	**laurifolin**	[73]
Rollinia membranacea	Seed	3.7	diepomuricanin-B	[1]
		3.8	diepoxyrollin	[1]
		4.1	tripoxyrollin	[1]
		12.5	membranacin	[1]
		12.9	membrarollin	[2]
		13.6	rioclarin	[1]
		13.21	rollimembrin	[2]
Rollinia mucosa	Seed	13.2	rolliniastatin-1	[1]
		13.3	rolliniastatin-2 (or bullatacin)	[1]
		22b.2	**jimenezin**	[17]
	Leaf	7a.23	rollinecin-A + B	[2]
		9a.15	muricatetrocin-C	[2]
		14a.19	mucoxin	[2]

Table 12 (*Cont.*)

Species	Organ	Compounds		Ref.
		14a.20	rollitacin	[2]
		15.4	rollidecin-A	[2]
		15.5	rollidecin-B	[2]
		15.6	rollinacin	[2]
		15.7	**rollidecin-C**	[20]
		15.8	**rollidecin-D**	[20]
		16.8	12,15-*cis*-sylvaticin	[2]
		22c.1	mucocin	[2]
		22b.1	muconin	[2]
	Fruit	**1d.1**	**rollicosin**	[72]
		2.4	epomusenin-A	[2]
		2.5	epomusenin-B	[2]
		7a.38	**rolliacocin**	[58]
		14a.30	**rollimusin**	[58]
		19.17	**20,23-*cis*-bullatilicinone**	[58]
Rollinia papilionella	Root	14a.2	isorollinicin	[1]
		19.2	rollinone	[1]
Rollinia sericea	Bark		known acetogenins (**13.2** and **14a.1**)	[2]
Rollinia sylvatica	Fruit	16.1	sylvaticin	[1,2]
Rollinia ulei	Leaf	14a.15	uleirollin	[2]
Saccopetalum prolificum	Root	**1c.10**	**saccopetrin-A**	[88]
		1c.11	**saccopetrin-B**	[88]
Uvaria acuminata	Root	12.1	uvaricin	[1]
		12.2	desacetyluvaricin	[104]
Uvaria boniana	Bark	**6.26**	**uvaribonianin**	[104]
		7b.13	**uvaribonin**	[32]
Uvaria calamistrata	Root	**6.17**	**calamistrin-A**	[32]
		6.18	**calamistrin-B**	[57]
		6.21	**calamistrin-C**	[57]
		6.22	**calamistrin-D**	[57]
		6.23	**calamistrin-E**	[57]
		14b.7	**calamistrin-F**	[57]
		14b.8	**calamistrin-G**	[90]
Uvaria chamae	Root	**5.19**	***cis*-bullatencin**	[97]
		22b.3	**chamuvarinin**	[2]
Uvaria grandiflora	Root	6.9	uvarigranin	[34]
		6.20	**uvarigrin**	[82]
Uvaria microcarpa	Seed	**14a.36**	**microcarpacin-A**	[83]
		14a.37	**microcarpacin-B**	[1]
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	[2]
		14b.5	uvariasolin-I	[2]
		14b.6	uvariasolin-II	[2]
Uvaria tonkinesis	Root	1a.4	tonkinelin	[2]
		6.10	tonkinecin	[2]
		7b.2	tonkinin-A	[2]
		7b.3	tonkinin-B	[2]
		7b.4	tonkinin-C	[2]
		7b.5	tonkinesin-A	[2]
		7b.6	tonkinesin-B	[2]
		7b.7	tonkinesin-C	[2]
Xylopia aromatica	Bark	1a.2	venezenin	[1]
		1a.8	venezinone	[2]
		7a.8	xylopianin	[1]
		7a.9	xylopiacin	[1]
		7a.10	xylomaticin	[1]
		7a.14	xylopien	[1]
		7a.15	xylomatenin (or annogalene)	[1]
		18.1	aromin	[2]
		18.2	aromicin	[2]

Total synthesis and structure confirmation of the Annonaceous acetogenins (30*S*)-hydroxybullatacin (13.11, Table 6), uvarigrandin A, and (5*R*)-uvarigrandin A (narumicin I) (14b.2, Table 6).[161]

The synthesis of all three acetogenins **8a–c** through the connection of four fragments, already used for other syntheses of ACGs in this group, afforded the expected products. The spectroscopic data (^{1}H and ^{13}C NMR spectra of the underivatised products and the Mosher esters) of **8a** were in agreement with those of the natural product (30*S*)-hydroxybullatacin, whereas those of **8b** were in accord with uvarigrandin A. It was then postulated that narumicin I is identical to uvarigrandin A, or its 5-epimer **8c** (Scheme 8).

Table 13 Names of acetogenins from Annonaceae cited in this review (in alphabetic order)

	Acetogenins	Ref.		Acetogenins	Ref.
7a.24	4-Acetylannonacin	[2]	**7a.33**	**Asitrilobin-B**	[41]
9a.14	4-Acetylgigantetrocin-A	[2]	**7a.43**	**Asitrilobin-C**	[75]
14a.39	**15-Acetylguanacone**	[99]	**7b.12**	**Asitrilobin-D**	[75]
14a.40	**24-Acetylguanacone**	[99]	**7a.41**	**Asitrocin**	[62]
7a.25	4-Acetylxylomaticin	[2]	**10.18**	**Asitrocinones**	[62]
17.1	Almunequin (or Squamostatin-A)	[1]	**14a.26**	**Atemotetrolin**	[28]
15.12	**Annocatacin-A**	[78]	**14a.45**	**Atemoyacin-B**	[102]
15.13	**Annocatacin-B**	[78]	**13.26**	**Atemoyacin-C**	[84]
7a.40	**Annocherimolin**	[60]	**15.14**	**Atemoyacin-E**	[79]
7a.36	**Annocherin**	[52]	14a.12	Bullacin	[1]
10.17	**Annocherinone**	[52]	**14a.33**	**Bullacin-B**	[76]
1a.16	**Annodienin**	[85]	**15.9**	**Bulladecin**	[28]
7a.15	Annogalene (or Xylomatenin)	[1]	19.5	Bulladecinone	[1]
7a.34	**Annoglacin-A**	[49]	14a.11	Bullanin	[1,2]
7a.35	**Annoglacin-B**	[49]	13.3	Bullatacin (or Rolliniastatin-2)	[1]
13.9	Annoglaucin	[1]	19.1	Bullatacinone	[1]
8.19	**Annoglaxin**	[50]	16.3	Bullatalicin (or Cherimolin-1)	[1]
8.23	**Annoheptocin-A**	[87]	16.6	12,15-*Cis*-Bullatalicin	[1]
8.24	**Annoheptocin-B**	[87]	19.3	Bullatalicinone (or Isocherimolin-1)	[1]
8.11	Annohexocin	[2]	**19.17**	**20,23-*Cis*-Bullatalicinone**	[58]
1a.14	**Annojahnin**	[39]	16.4	Bullatanocin (or Cherimolin-2)	[1]
9a.21	**Annomolin**	[60]	16.7	12,15-*Cis*-Bullatanocin	[1]
11b.12	**Annomolon-A + 34-*epi***	[94]	19.4	Bullatanocinone	[1]
11b.13	**Annomolon-B + 34-*epi***	[94]	5.6	Bullatencin	[1]
8.1	Annomonicin	[1]	**5.19**	***Cis*-Bullatencin**	[90]
7a.5	Annomontacin	[1]	14a.17	Bullatetrocin	[2]
7a.39	***Cis*-Annomontacin**	[59]	14a.10	Bullatin	[1]
7a.37	**Annomontanin-A**	[53]	1c.3	Buthyrolactone-1	[2]
8.20	**Annomontanin-B**	[53]	1c.4	Buthyrolactone-2	[2]
11b.7	**Annomontanin-C**	[53]	**6.17**	**Calamistrin-A**	[32]
10.11	Annomontacinone	[2]	**6.18**	**Calamistrin-B**	[32]
8.4	Annomuricin-A	[1]	**6.21**	**Calamistrin-C**	[57]
8.5	Annomuricin-B	[1]	**6.22**	**Calamistrin-D**	[57]
8.10	Annomuricin-C	[2]	**6.23**	**Calamistrin-E**	[57]
8.16	**Annomuricin-E**	[26]	**14b.7**	**Calamistrin-F**	[57]
10.9	Annomuricinone-D	[2]	**14b.8**	**Calamistrin-G**	[57]
7a.18	Annomutacin	[2]	**14a.23**	**Carolin-A**	[18]
7a.1	Annonacin	[1]	**14a.24**	**Carolin-B**	[18]
7a.19	*Cis*-Annonacin	[2]	**14a.25**	**Carolin-C**	[18]
7a.4	Annonacin-A	[1]	**22b.3**	**Chamuvarinin**	[97]
7a.3	Annonacinone	[1]	**1c.5**	**Chatenaytrienin-1 + 2**	[21]
7a.20	*Cis*-Annonacinone	[2]	**1c.6**	**Chatenaytrienin-3 + 4**	[21]
10.5	Annonacinone-A	[2]	16.3	Cherimolin-1 (or Bullatalicin)	[1]
14a.4	Annonin-III (or Motrilin)	[1]	16.4	Cherimolin-2 (or Bullatanocin)	[1]
13.15	Annonisin	[2]	1a.6	Cohibin-A	[2]
15.3	Annonsilin-A	[2]	1a.7	Cohibin-B	[2]
9a.12	Annopentocin-A + B	[2]	**1a.15**	**Cohibins-C + D**	[56]
9a.13	Annopentocin-C	[2]	3.2	Corepoxylone	[1]
7a.6	Annoreticuin	[1]	9a.9	Coriacin	[2]
7a.46	***Cis*-Annoreticuin**	[98]	**9b.7**	**Coriacyclodienin**	[91]
7a.7	Annoreticuinone	[1]	**9b.8**	**Coriacycloenin**	[91]
7a.16	Annosenegalin	[1]	1a.3	Coriadienin	[2]
5.9	Annotemoyin-1	[2]	8.13	Coriheptocin-A	[2]
5.10	Annotemoyin-2	[2]	8.14	Coriheptocin-B	[2]
8.18	**Araticin**	[43]	**3.9**	**Coronin**	[70]
13.14	Araticulin	[2]	6.2	Corossolin	[1]
7a.22	Arianacin	[2]	6.3	Corossolone	[1]
18.2	Aromicin	[2]	9a.2	Densicomacin-1	[1]
18.1	Aromin	[2]	6.13	4-Deoxyannomontacin	[2]
18.3	**Aromin-A**	[46]	**6.14**	**4-Deoxyannoreticuin**	[24]
1c.12	**Artapetalin-A**	[61]	**6.15**	***Cis*-4-Deoxyannoreticuin**	[24]
1c.13	**Artapetalin-B**	[61]	9b.3	4-Deoxycoriacin	[2]
1c.14	**Artapetalin-C**	[61]	17.2	4-Deoxygigantecin	[1]
1a.21	**Artemoin-A + B + C + D**	[51]	12.2	Desacetyluvaricin	[1]
13.1	Asimicin	[1]	3.1	Diepomuricanin-A	[1]
15.2	Asimilobin	[2]	3.7	Diepomuricanin-B	[1]
14a.8	Asimin	[1]	3.3	Dieporeticanin-1	[1]
14a.6	Asiminacin (or Squamocin-D)	[1]	3.4	Dieporeticanin-2	[1]
14a.9	Asiminecin	[1]	3.5	Dieporeticenin	[1]
6.5	Asiminenin-A	[2]	3.6	Diepoxymontin	[1]
6.6	Asiminenin-B	[2]	3.8	Diepoxyrollin	[1]
14a.16	Asiminocin	[2]	7a.26	Disepalin	[2]
14a.14	Asitribin	[2]	**1a.12**	**Donbutocin**	[22]
7a.32	**Asitrilobin-A**	[41]	**1a.19**	**Donhepocin + 34-*epi***	[22]

Table 13 (*Cont.*)

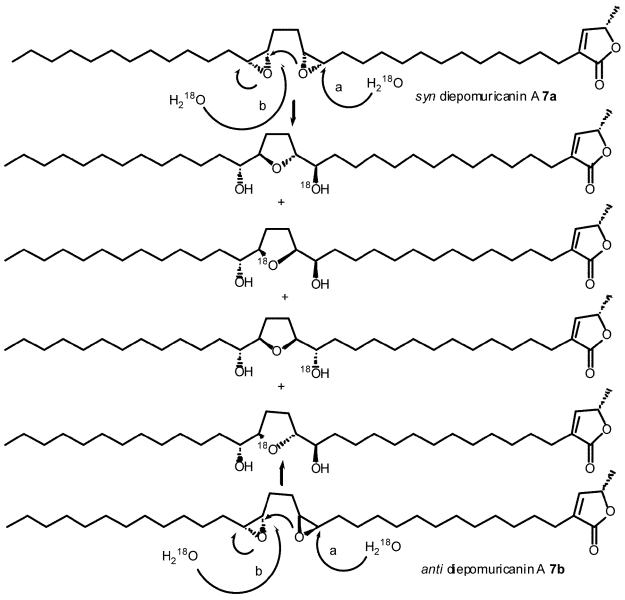
	Acetogenins	Ref.		Acetogenins	Ref.
1a.11	**Donhexocin**	[22]	10.1	Isoannonacin	[1]
8.15	**Donnaienin**	[19]	10.2	Isoannonacinone	[1]
11b.1	Donnaienin-A + 34-*epi*	[2]	10.4	Isoannoreticuin	[1]
11b.2	Donnaienin-B + 34-*epi*	[2]	19.3	Isocherimolin-1 (or Bullatalicinone)	[1]
11b.6	**Donnaienin-C + 34-*epi***	[27]	12.4	Isodesacetyluvaricin	[1]
1a.20	**Donnaienin-D + 34-*epi***	[27]	10.12	Isomurisolenin	[2]
2.1	Epomuricenin-A or Epoxymurin-A	[1]	19.9	Isomolvizarin-1	[1]
2.3	Epomuricenin-B	[1]	19.10	Isomolvizarin-2	[1]
2.4	Epomusenin-A	[2]	14a.2	Isorollinicin	[1]
2.5	Epomusenin-B	[2]	19.2	Itrabin	[1]
2.1	Epoxymurin-A (or Epomuricenin-A)	[1]	**1a.17**	**Jahnonacin**	[85]
2.2	Epoxymurin-B	[1]	7a.22	Javoricin	[2]
14b.4	Espelicin	[2]	11a.1	Jetein	[1]
1a.9	**Gardnerilin-A**	[16]	**22b.2**	**Jimenezin**	[17]
1a.10	**Gardnerilin-B**	[16]	20.1	Laherradurin	[1]
11b.5	**Gardnerinin + 34-*epi***	[25]	**5.16**	**Laurifolin**	[73]
6.4	Giganenin	[1]	1b.3	Longanin	[2]
1a.1	Giganin	[1,2]	7a.17	Longicin	[2]
16.2	Gigantecin	[1]	6.12	Longicoricin	[2]
19.16	**Gigantecinone**	[14]	6.11	Longifolicin	[2]
9a.1	Gigantetrocin-A	[1]	13.18	Longimicin-A	[2]
9a.4	Gigantetrocin-B	[1]	13.19	Longimicin-B	[2]
10.6	Gigantetrocinone	[1]	13.20	Longimicin-C	[2]
9a.3	Gigantetronenin	[1]	14a.18	Longimicin-D	[2]
10.10	Gigantetroneninone	[2]	12.5	Membranacin	[1]
7b.8	Gigantransenin-A + B	[2]	12.9	Membrarollin	[2]
7b.9	Gigantransenin-C	[2]	**14a.36**	**Microcarpacin-A**	[82]
9b.1	Gigantriocin	[1]	**14a.37**	**Microcarpacin-B**	[83]
9b.2	Gigantrionenin	[1]	13.4	Molvizarin	[1]
9b.4	*Cis*-Gigantrionenin	[2]	**8.26**	**Montacin**	[101]
9a.17	Glabranin	[2]	**8.27**	***Cis*-Montacin**	[101]
15.10	**Glabracin-A**	[77]	**6.24**	**Montalicin-A**	[98]
15.11	**Glabracin-B**	[77]	**6.25**	**Montalicin-B**	[98]
7a.29	**Glacin-A**	[31]	**7a.44**	**Montalicin-C**	[98]
7a.30	**Glacin-B**	[31]	**7a.45**	**Montalicin-D**	[98]
6.19	**Glaucabellin**	[33]	**7a.47**	**Montalicin-E**	[98]
9a.16	Glaucafilin	[2]	**7a.48**	**Montalicin-F**	[98]
13.22	**Glaucanetin**	[13]	**7a.49**	**Montalicin-I**	[98]
13.10	Glaucanisin	[1]	**7a.50**	**Montalicin-J**	[98]
21.1	Goniocin	[1]	8.2	Montanacin	[1]
15.1	Goniodenin	[2]	**8.21**	**Montanacin-B**	[68]
11b.3	Goniodonin + 34-*epi*	[2]	**8.22**	**Montanacin-C**	[68]
11b.4	*Cis*-Goniodonin + 34-*epi*	[2]	**22c.2**	**Montanacin-D**	[68]
7a.13	Gonionenin	[1]	**22c.3**	**Montanacin-E**	[68]
10.16	**Gonioneninone**	[37]	**10.22**	**Montanacin-F**	[74]
7a.31	**Goniotetracin**	[37]	**10.21**	**Montanacin-G**	[69]
7a.2	Goniothalamicin	[1]	**11b.8**	**Montanacin-H + 34-*epi***	[69]
7a.21	*Cis*-Goniothalamicin	[2]	**11b.9**	**Montanacin-I + 34-*epi***	[69]
10.7	Goniothalamicinone	[2]	**11b.10**	**Montanacin-J + 34-*epi***	[69]
1c.9	**Goniothalamusin**	[44]	1a.5	Montecristin	[2]
16.10	**Goniotriocin**	[36]	7a.27	Mosin-B	[2]
9a.18	**Goniotrionin**	[38]	7a.28	Mosin-C	[2]
14a.21	Guanacone	[2]	10.13	Mosinone-A	[2]
14a.41	**Guanaconetin-1**	[99]	14a.4	Motrilin (or Annonin-III)	[1]
14a.42	**Guanaconetin-2**	[99]	22c.1	Mucocin	[2]
14a.43	**Guanaconetin-3**	[99]	22b.1	Muconin	[2]
14a.44	**Guanaconetin-4**	[99]	14a.19	Mucoxin	[2]
8.3	8-Hydroxy-Annonacin	[1]	**1c.7**	**Muricadienin**	[21]
13.16	10-Hydroxy-Asimicin	[2]	**8.17**	**Muricapentocin**	[26]
19.18	**9-Hydroxy-Asimicinone**	[8]	8.12	Muricatalicin	[2]
13.25	**27-Hydroxy-Bullatacin**	[50]	9a.11	Muricatalin	[2]
13.11	30-Hydroxy-Bullatacin	[2]	**8.25**	**Muricatatin-C**	[100]
13.12	31-Hydroxy-Bullatacin	[2]	**1a.18**	**Muricatenol**	[89]
13.13	32-Hydroxy-Bullatacin	[2]	9a.5	Muricatetrocin-A + B	[1]
19.11	10-Hydroxy-Bullatacinone	[1]	9a.15	Muricatetrocin-C	[2]
19.12	12-Hydroxy-Bullatacinone	[1]	9a.7	Muricatin-A	[1]
19.14	28-Hydroxy-Bullatacinone	[2]	9a.8	Muricatin-B	[1]
19.13	29-Hydroxy-Bullatacinone	[1]	8.6	Muricatin-C	[1]
19.8	30-Hydroxy-Bullatacinone	[1]	8.7	Muricatocin-A	[2]
19.7	31-Hydroxy-Bullatacinone	[1]	8.8	Muricatocin-B	[2]
19.6	32-Hydroxy-Bullatacinone	[1]	8.9	Muricatocin-C	[2]
14a.34	**6-Hydroxy-Desacetyluvaricin**	[80]	**9a.22**	**Muricin-A**	[63]
14a.35	**6-Hydroxy,4-Deoxysquamotacin**	[80]	**9a.23**	**Muricin-B**	[63]
13.23	**10-Hydroxy-Glaucanetin**	[13]	**9a.24**	**Muricin-C**	[63]
13.17	10-Hydroxy-Trilobacin	[2]	**9a.25**	**Muricin-D**	[63]

Table 13 (*Cont.*)

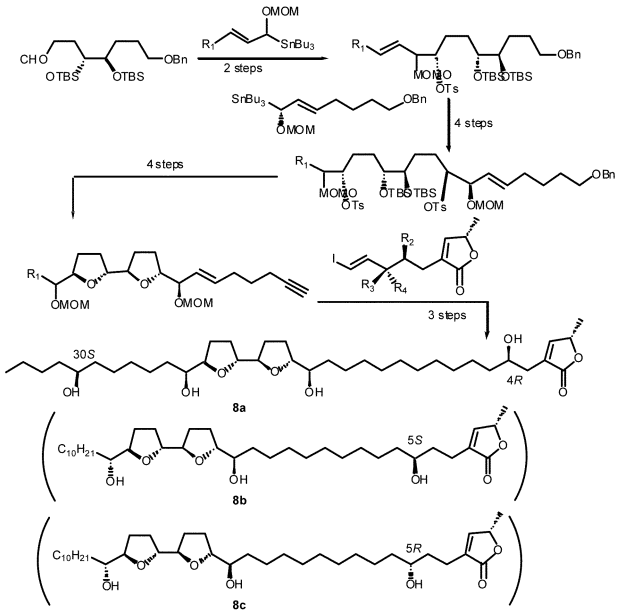
	Acetogenins	Ref.		Acetogenins	Ref.
9a.26	**Muricin-E**	[63]	**7b.11**	**Sootepensin-B**	[67]
9a.27	**Muricin-F**	[63]	**14a.22**	**Spinencin**	[15]
7a.42	**Muricin-G**	[63]	14a.1	Squamocin	[1]
9b.5	**Muricin-H**	[59]	14a.5	Squamocin-B	[1]
9b.6	**Muricin-I**	[59]	14a.6	Squamocin-D (or Asiminacin)	[1]
9a.19	**Muricoreacin**	[40]	13.8	Squamocin-E (or Parviflorin)	[1]
1c.8	**Muridienin-3 + 4**	[21]	14a.7	Squamocin-F	[1]
1c.1	Muridienin-1	[2]	12.6	Squamocin-I	[1]
1c.2	Muridienin-2	[2]	12.7	Squamocin-K	[1]
9a.10	Murihexocin-A + B	[2]	12.8	Squamocin-N	[1]
9a.20	**Murihexocin-C**	[40]	**14a.31**	**Squamocin-O_1**	[71]
1a.13	**Murihexol**	[23]	**14a.32**	**Squamocin-O_2**	[71]
6.1	Murisolin	[1]	14a.3	Squamocinone	[1]
6.7	*Cis*-Murisolin	[2]	**19.19**	**Squamolinone**	[76]
6.8	Murisolin-A	[2]	10.3	Squamone	[1]
10.8	Murisolinone	[2]	17.1	Squamostatin-A (or Almunequin)	[1]
14b.2	Narumicin-I	[1]	**17.6**	**12,15-*Cis*-Squamostatin-A**	[51]
14b.3	Narumicin-II	[1]	17.3	Squamostatin-D	[1]
12.3	Neoannonin	[1]	**17.5**	**12,15-*Cis*-Squamostatin-D**	[51]
5.18	**15-Oleylsolamin**	[86]	17.4	Squamostatin-E	[1]
14a.28	**Ophrypetalin**	[47]	7a.12	Squamosten-A	[1]
20.3	Otivarin	[1]	**1d.2**	**Squamostolide**	[95]
19.20	**9-Oxo-Asimicinone**	[76]	**10.14**	**Squamoxinone**	[24]
5.17	**15-Palmitoylsolamin**	[86]	**10.19**	**Squamoxinone-B**	[8]
14b.1	Panalicin	[1]	**10.20**	**Squamoxinone-C**	[8]
5.12	***Cis*-Panatellin**	[30]	16.1	Sylvaticin	[1,2]
11b.11	**Parisin**	[93]	16.8	12,15-*Cis*-Sylvaticin	[2]
16.5	Parvifloracin	[1]	6.10	Tonkinecin	[2]
13.8	Parviflorin (or Squamocin-E)	[1]	1a.4	Tonkinelin	[2]
7b.1	Plagionicin-A	[2]	7b.5	Tonkinesin-A	[2]
13.24	**Purpuracenin**	[48]	7b.6	Tonkinesin-B	[2]
13.7	Purpureacin-2	[1]	7b.7	Tonkinesin-C	[2]
14a.27	**Purpurenin**	[29]	7b.2	Tonkinin-A	[2]
22a.2	**Pyragonicin**	[38]	7b.3	Tonkinin-B	[2]
22a.1	**Pyranicin**	[38]	7b.4	Tonkinin-C	[2]
7a.11	Reticulacinone	[1]	13.5	Trilobacin	[1,2]
5.2	Reticulatacin (or Uvariamicin-II)	[1]	19.15	Trilobacinone	[2]
5.15	***Cis*-Reticulatacin**	[30]	16.9	Trilobalicin	[2]
6.16	***Cis*-Reticulatacin-10-one**	[30]	14a.13	Trilobin	[2]
5.7	Reticulatain-1	[1]	4.1	Tripoxyrollin	[1]
5.8	Reticulatain-2	[1]	**20.4**	**Tucumanin**	[96]
1b.1	Reticulatamol	[1]	14a.15	Uleirollin	[2]
1b.2	Reticulatamone	[1]	5.1	Uvariamicin-I	[1]
13.6	Rioclarin	[1]	**5.14**	***Cis*-Uvariamicin-I**	[30]
15.15	**Robustocin**	[81]	5.2	Uvariamicin-II (or Reticulatacin)	[1]
7a.38	**Rolliacocin**	[58]	5.3	Uvariamicin-III	[1]
1d.1	**Rollicosin**	[72]	5.5	Uvariamicin-IV	[1]
15.4	Rollidecin-A	[2]	**5.13**	***Cis*-Uvariamicin-IV**	[30]
15.5	Rollidecin-B	[2]	14b.5	Uvariasolin-I	[2]
15.7	**Rollidecin-C**	[20]	14b.6	Uvariasolin-II	[2]
15.8	**Rollidecin-D**	[20]	**6.26**	**Uvaribonianin**	[104]
13.21	Rollimembrin	[2]	**7b.13**	**Uvaribonin**	[104]
14a.30	**Rollimusin**	[58]	12.1	Uvaricin	[1]
15.6	Rollinacin	[2]	6.9	Uvarigranin	[2]
7a.23	Rollinecins-A + B	[2]	**6.20**	**Uvarigrin**	[34]
13.2	Rolliniastatin-1	[1]	1a.2	Venezenin	[1]
13.3	Rolliniastatin-2 (or Bullatacin)	[1]	1a.8	Venezinone	[2]
19.2	Rollinone	[1]	7a.15	Xylomatenin (or Annogalene)	[1]
14a.20	Rollitacin	[2]	7a.10	Xylomaticin	[1]
2.6	**Sabadelin**	[45]	**10.15**	**Xylomaticinone**	[36]
1c.10	**Saccopetrin-A**	[88]	7a.9	Xylopiacin	[1]
1c.11	**Saccopetrin-B**	[88]	7a.8	Xylopianin	[1]
14a.29	**Salzmanin**	[54]	7a.14	Xylopien	[1]
14a.38	**Salzmanolin**	[93]			
9.A8	Senegalene	[1]			
5.4	Solamin	[1]			
5.11	***Cis*-Solamin**	[30]			
7b.10	**Sootepensin-A**	[67]			

Total synthesis of mosin B (7a.27, Table 3) and its tetra-epimer[162,163]

The synthesis of the natural product **9a** and its tetra-epimer **9b** from a *meso* cyclic diol (by desymmetrisation with a C_2-symmetric bis-sulfoxide) and coupling of an intermediate epoxide containing the THF core with a vinyl iodide possessing the butenolide terminus, allowed the authors to obtain the expected products. The ^{1}H NMR data of both products were identical with those of the natural product, but a careful



Scheme 7 Semi-synthesis of *cis*- and *trans* solamins: evidence for *syn*- and *anti*-diepomuricanins A **7a** and **7b**.

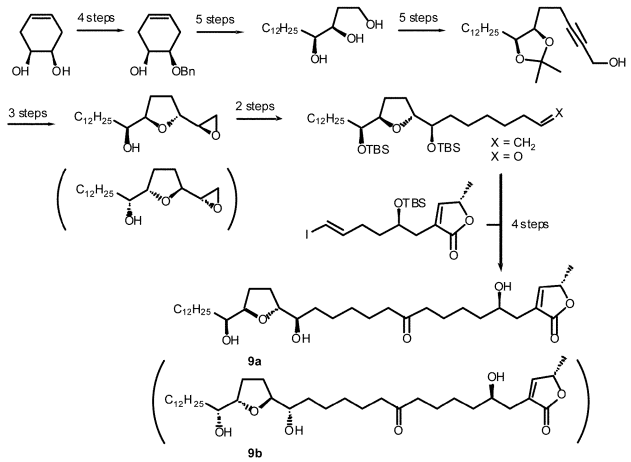


Scheme 8 Total synthesis of (30*S*)-hydroxybullatacin, uvarigrandin A, and (5*R*)-uvarigrandin A (narumicin I).

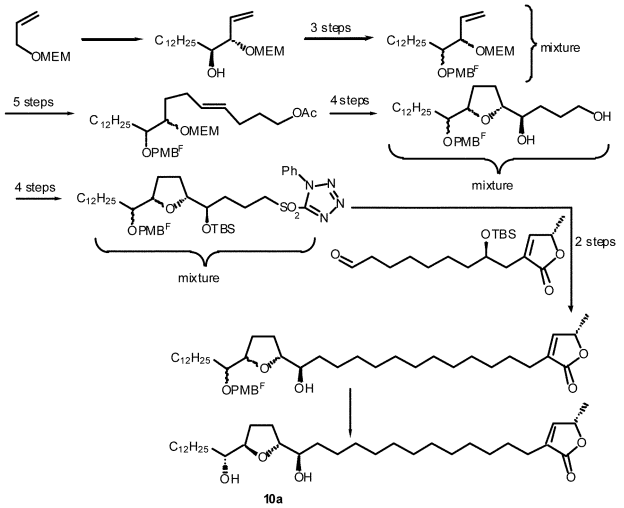
comparison, and analysis of the ^{13}C NMR data and the $[a]_D$ values allowed the authors to postulate that **9a**, with the (15*R*,16*R*,19*R*,20*S*) absolute configuration ($[a]_D = +18.7$), was in better agreement with the natural product ($[a]_D = +11.5$) than the (15*S*,16*S*,19*S*,20*R*) tetra-epimer **9b** ($[a]_D = +2$) (Scheme 9).

Total synthesis of (+)-murisolin (6.1, Table 3) and its fifteen diastereomers[164]

The synthesis of a mixture of 16 isomers (around the THF unit) of murisolin using a fluorous tag, followed by Chiracel-OD HPLC separation, provided the expected products, which presented only six different sets of ^{1}H and ^{13}C NMR spectra. Specific rotations were not reliable, but co-injection of natural murisolin with the (15*R*,16*R*,19*R*,20*R*)-isomer **10a** confirmed its stereochemical assignment. Thus, HPLC analysis of natural *cis*-murisolin and murisolin A should secure their stereochemical assignments (Scheme 10). Independently, T. Tanaka synthesised (15*R*,16*R*,19*R*,20*R*)-murisolin.[165]



Scheme 9 Total synthesis of mosin B and its tetra-epimer.



Scheme 10 Total synthesis of murisolin **10a** and its 15 diastereomers.

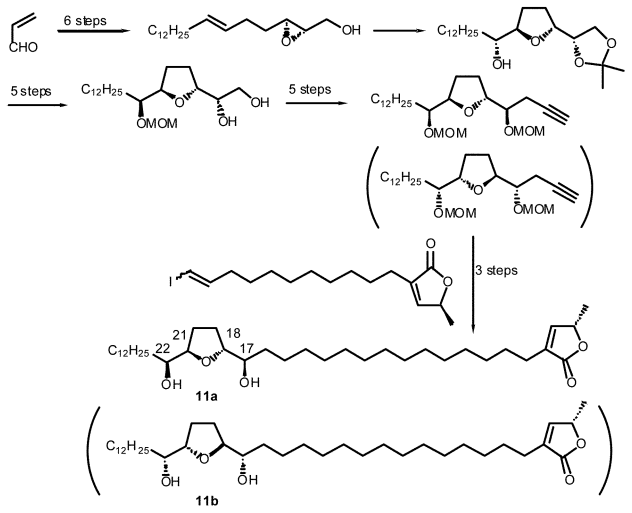
Synthesis of two possible diastereomers of reticulatain-1 (5.7, Table 3)[166]

The total synthesis of two stereomers of reticulatain-1, tetra-epimers around the THF core, has been performed. The ^{1}H and ^{13}C NMR spectra of the Mosher esters showed a clear difference, however, the *erythro* relationship between C-21 and C-22 (*vs.* C-17 and C-18) in the natural product, has still not been unambiguously determined. Comparison of spectroscopic data of the synthesised products **11a** and **11b** with those of the natural product would help in the completion of the stereochemical assignment (Scheme 11).

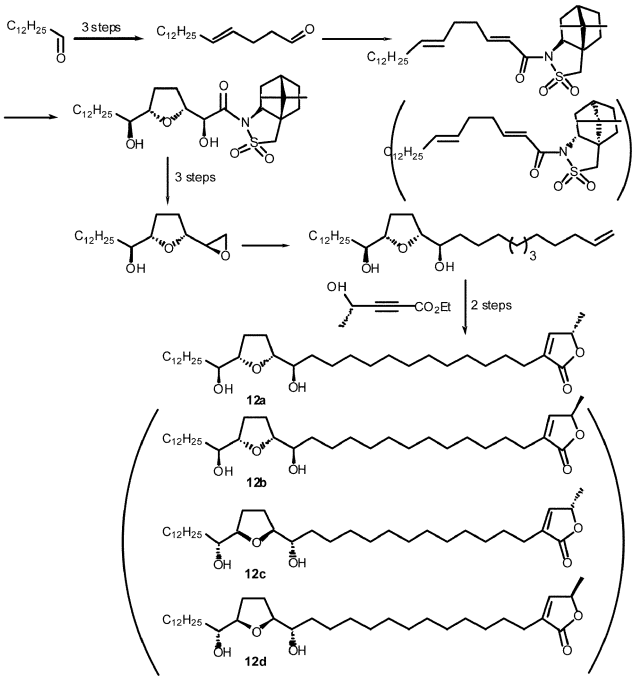
Total synthesis of all four possible stereomers of *cis*-solamin (5.11, Table 3)[9,167,168]

The total synthesis of all four possible isomers **12a–d** of *cis*-solamin by $KMnO_4$ oxidation of a chiral 1,5-dienoate derivative, followed by the Trost connection with a chiral butenolide acyclic precursor was achieved. The IR, MS and ^{1}H and ^{13}C NMR data of the isomers was indistinguishable, and specific rotations were not reliable. However, all four isomers **12a–d** were separable by chiral HPLC. Therefore, co-injection HPLC analysis of the natural compound would definitively secure the stereochemical assignment of natural *cis*-solamin (Scheme 12).

Independently, A. Tanaka and T. Oritani have prepared the two isomers **12a** and **12c** of *cis*-solamin,[169,170] and have determined the stereochemical assignment of the THF core, based on comparison of the specific rotations of two synthetic products with that of the natural product. However, due to a



Scheme 11 Synthesis of two possible diastereomers of reticulatain-1.



Scheme 12 Synthesis of all possible stereomers of *cis*-solamin.

poor match of specific rotations, this conclusion should be taken with caution.

Pyranicin (22a.1, Table 11) has been synthesised by S. Takahashi and T. Nakata, but although they concluded that its spectroscopic data, as well as the ^{1}H and ^{13}C NMR of its Mosher ester, were identical to those of the natural product, the specific rotations of the synthetic and natural products were opposite in sign. Thus, in our view the absolute configuration of pyranicin remains uncertain.[171]

Besides these syntheses, which have allowed the structural elucidation of natural ACGs, much work on the synthesis of unnatural derivatives, mimics, and advanced intermediates has been published, and will be reported elsewhere.

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