

Acetogenins from Annonaceae

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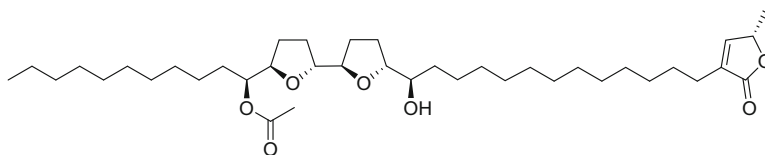
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1 Introduction

Annonaceous acetogenins (AGEs) constitute a series of polyketides found almost exclusively from plants in the family Annonaceae, with some of their species of origin being important economic crops in Asia and North and South America. The study of AGEs was initiated as a result of the first report on the bioactive uvaricin (**1**) in 1982, from the roots of *Uvaria accuminata* Oliv. by Jolad et al., which exhibited excellent bioactivity in the P-388 lymphocytic leukemia system in mice [1]. Since then, numerous AGEs have been isolated and identified from various parts of annonaceous plants, especially the seeds, by virtue of advances in separation technology. These initial results have promoted further work on the structural elucidation and classification of AGEs, as well as their biogenetic hypotheses. Annonaceous AGEs are a unique compound class of C_{35} or C_{37} secondary metabolites, derived from the polyketide pathway, which include structurally a γ -lactone ring along with several oxygenated functionalities. For example, hydroxy group, ketone, epoxide, tetrahydrofuran (THF), and tetrahydropyran (THP) moieties, and even double and triple bonds are structural features encountered among the AGEs. Annonaceous acetogenins have been found to exhibit a broad range of biological properties, such as antineoplastic, antiparasitic, cytotoxic, immunosuppressive, neurotoxic, and pesticidal effects. Among the broad array of biological properties documented in the biomedical literature for the AGEs, their cytotoxic and antitumor effects and the underlying mechanisms for such effects have received the most attention.



1 (uvaricin)

In 1997, Cavé et al. wrote a thorough contribution on AGEs in this book series, covering the classification, extraction, isolation, structure elucidation, biogenetic hypotheses, syntheses, and biological activities of these type of compounds. Altogether, they collaboratively reported 242 AGEs and described relevant studies on their synthesis and bioactivities [2].

An overall advancement in experimental techniques has led to many worldwide efforts focusing on the isolation and structural identification of new bioactive AGEs. Most importantly, organic chemists have overcome the challenges of meeting the total and rapid synthesis of AGEs with multiple stereocenters during the past 15 years. Moreover, growing interest in investigating the mechanisms of biochemical action of AGEs has been triggered by recent advances in understanding the processes involved in tumor cell death. Members of this class of natural compounds are considered as possible candidates for future anticancer drugs. Bioactivity and mechanism of action studies on annonaceous AGEs have both focused on their potent cytotoxicity against cancer cells and the inhibition of mitochondrial respiratory chain complex I. However, recent studies have reported the relation between this type of compound and sporadic neurodegenerative tau pathologies in those humans who have ingested annonaceous plants containing AGEs [3]. The purpose of this contribution is to give a short historical introduction as well as a description of current studies on AGEs and their analogues. As a result, 203 AGEs dating from 1997 to 2014 were isolated and characterized. The bioactivities of each AGE are highlighted as well. Recent investigations on the mechanisms of action of the pesticidal and antitumor effects of AGEs are reviewed within each individual section. In addition, modified analogues of AGEs and synthesized AGE mimics that were mentioned to play an important role in verifying hypotheses on the modes of action of AGEs are covered.

Annonaceous acetogenins, derivatives of the polyketide pathway, contain 35 or 37 carbons. Biogenetically, they appear to originate from polyhydroxy C_{32} or C_{34} fatty acids to which a 2-propanol unit is added to form a methylated α,β -unsaturated γ -lactone. During the past two decades, advances in chromatographic methodology, such as repeated open column chromatography and high-performance liquid chromatography (HPLC) [4–7], have made the ready and efficient separation of AGEs with only minor structural differences possible. Based on the isolation and

characterization of different acetogenins, their general structural features can be divided into various classes dependent on the nature of the γ -lactone rings, such as an α,β -unsaturated γ -lactone ring (normal form) or a ketolactone (isoform), in addition to the oxygen-bearing moieties evident [2, 8]. However, Cavé et al. suspected that acetogenins with terminal ketolactones (isoforms) are artifacts of the translactonization of 4-hydroxy-AGEs. To validate this suspicion, they performed the extraction and characterization of the initial AGEs from fresh crude materials under the effects of alkalis, other basic media, and alcohols. These reagents affected the kinetics of the translactonization [9], which was later supported by the work of Figadère and colleagues describing how 4-hydroxylated AGEs led to iso-derivatives under basic conditions [10].

In summary, the common features on the structures of AGEs are a terminal γ -lactone ring and a terminal aliphatic side chain connecting to some hydrophilic functional groups, such as one to three THF rings and several hydroxy groups. In 1998, Cavé et al. discussed the previously mentioned features in terms of two major structural factors, the terminal γ -lactone ring and the substituents on the long aliphatic chain [8]. Under such a classification system, AGEs were divided into ten subtypes: (1) AGEs without THF rings: linear AGEs; (2) AGEs without THF rings: epoxy-AGEs; (3) mono-THF α,α' -dihydroxylated γ -lactone AGEs; (4) mono-THF α -hydroxylated γ -lactone AGEs; (5) mono-THF AGEs with various lactone moieties; (6) adjacent bis-THF α,α' -dihydroxylated γ -lactone AGEs; (7) adjacent bis-THF α -hydroxylated γ -lactone AGEs; (8) non-adjacent bis-THF γ -lactone AGEs; (9) saturated lactone bis-THF AGEs; (10) miscellaneous AGEs.

2 Annonaceous Acetogenins in the Plant Kingdom

Since their first discovery over 30 years ago, phytochemists have focused their studies on AGEs in the plant family Annonaceae. The isolation of AGEs has been reported from 15 genera of this family, including *Annona* (19 species), *Asimina* (3), *Artabotrys* (2), *Cananga* (2), *Dasymaschalon* (1), *Disepalum* (1), *Fissistigma* (2), *Goniolthalamus* (5), *Mitrephora* (2), *Ophrypetalum* (1), *Polyalthia* (6), *Rollinia* (7), *Saccopetalum* (1), *Uvaria* (10), and *Xylopia* (1), up to the present (see Table 1). Among all the reported isolations of AGEs, a series of linear acetylenic C_{25} -AGEs has been found from species of four genera (i.e. *Cananga*, *Polyalthia*, *Mitrephora*, and *Saccopetalum*). Surprisingly, a paper in 2008 reported that a new AGE was isolated from the root of an *Ampelocissus* species collected in the Philippines, which belongs to the family Vitaceae [34]. However, this remains the first and only example suggesting that this type of compound could be found from plants other than in the family Annonaceae (see Table 1).

Table 1 Distribution of acetogenins in the plant kingdom

Plant source	Genus	Species	Refs.
Annonaceae	<i>Annona</i>	<i>A. atemoya</i> (<i>A. cherimola</i> x <i>A. squamosa</i>)	
		<i>A. bullata</i>	
		<i>A. cherimola</i> Mill.	
		<i>A. coriacea</i>	
		<i>A. crassiflora</i>	
		<i>A. densicoma</i>	
		<i>A. glabra</i> L.	
		<i>A. glauca</i>	
		<i>A. jahnii</i>	[11, 12]
		<i>A. montana</i> Macf.	
		<i>A. muricata</i> L.	
		<i>A. nutans</i>	[13]
		<i>A. purpurea</i>	
		<i>A. reticulata</i> L.	
		<i>A. salzmanii</i>	
		<i>A. senegalensis</i>	
		<i>A. spinescens</i>	
		<i>A. spraguei</i>	
		<i>A. squamosa</i> L.	
	<i>Asimina</i>	<i>A. longifolia</i>	
		<i>A. parviflora</i>	
		<i>A. triloba</i>	
	<i>Artabotrys</i>	<i>A. hexaptalus</i> (L.f.) Bhandari	[14]
		<i>A. uncinatus</i> (Lam.) Merr.	
	<i>Cananga</i>	<i>C. odorata</i> (Lam.) Hook.f & Thomas	
		<i>C. latifolia</i> (Hook.f. & Thomson) Finet & Gagnep	[15]
	<i>Dasymaschalon</i>	<i>D. sootepense</i>	[16]
	<i>Disepalum</i>	<i>D. anomalum</i>	[17]
		<i>D. plagineurum</i>	[18]
	<i>Fissistigma</i>	<i>F. glaucescens</i> (Hance) Merr. ^a	
		<i>F. oldhami</i> (Hemsl.) Merr. ^a	
	<i>Goniothalamus</i>	<i>G. amuyon</i> (Blanco) Merr. ^a	
		<i>G. donnaiensis</i>	[19–21]
		<i>G. giganteus</i>	
		<i>G. howii</i>	
		<i>G. undulatus</i> Ridl.	[22]
	<i>Mitrephora</i>	<i>M. glabra</i>	[23]
		<i>M. maingayi</i>	[24]
	<i>Ophrypetalum</i>	<i>O. odoratum</i>	[25]
	<i>Polyalthia</i>	<i>P. debilis</i>	[26]
		<i>P. longifolia</i> Benth. et Hook.f	
		<i>P. longifolia</i> Benth. et Hook.f ‘pendula’	
		<i>P. plagineura</i>	
		<i>P. suberosa</i> Hook.f	
		<i>P. liukiensis</i> Hatusima ^a	

(continued)

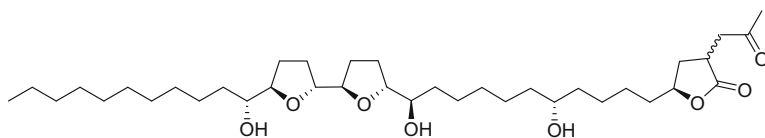
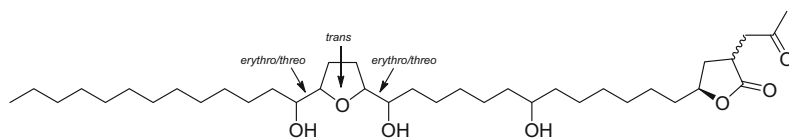
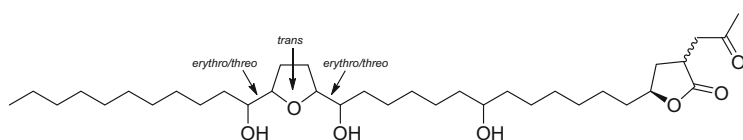
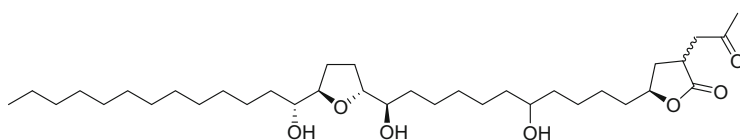
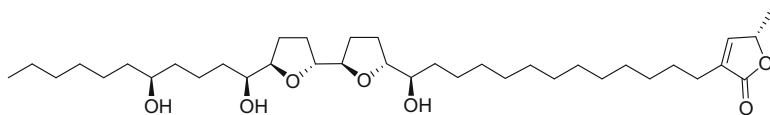
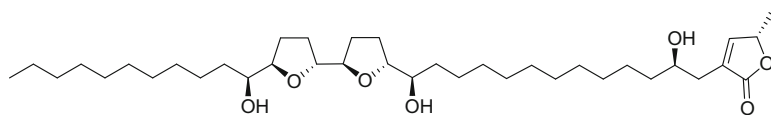
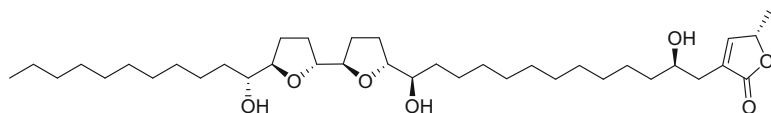
Table 1 (continued)

Plant source	Genus	Species	Refs.
	<i>Rollinia</i>	<i>R. emarginata</i>	[27]
		<i>R. membranacea</i>	
		<i>R. mucosa</i> Baill.	
		<i>R. papilionella</i>	
		<i>R. sericea</i>	
		<i>R. sylvatica</i>	
		<i>R. ulei</i>	
	<i>Saccopetalum</i>	<i>S. prolificum</i>	[28]
	<i>Uvaria</i>	<i>U. acuminata</i>	
		<i>U. boniana</i>	[29]
		<i>U. calamistrata</i>	[30]
		<i>U. grandiflora</i>	
		<i>U. hookeri</i>	
		<i>U. microcarpa</i>	
		<i>U. narum</i>	
		<i>U. pauci-ovulata</i>	[31]
		<i>U. rufa</i> Bl.	
		<i>U. tonkinensis</i>	[32]
	<i>Xylopia</i>	<i>X. aromatica</i>	
		<i>X. emarginata</i>	[33]
Vitaceae	<i>Ampelocissus</i>	<i>A. sp.</i>	[34]

^aAnnonaceous plants native to Taiwan

3 Classification of Annonaceous Acetogenins (Since 1997 Until the End of 2014)

Studies on annonaceous acetogenins (AGEs) after 1997 have focused on efficient compound identification by hyphenated chromatographic techniques and other spectroscopic methods. Although normal- and reversed-phase HPLC are powerful tools for the isolation of natural products, limitations such as the allowed amount of sample to be purified per unit time, the solvent cost, and the size of the columns, still remain. Therefore, searching for new approaches to facilitate chromatographic work is crucial. McLaughlin et al. used countercurrent chromatography (CCC) to isolate four AGEs, (2,4-*cis* and *trans*)-9-hydroxyasimicinone (**2**), (2,4-*cis* and *trans*)-squamoxinone B (**3**), (2,4-*cis* and *trans*) squamoxinone C (**4**), and isoannoreticuin (**5**), from the bark of *A. squamosa* [35]. Cavé et al. also applied high-speed countercurrent chromatography (HSCCC) to the separation of AGEs from *A. atemoya* to give two major AGEs, squamocin (**6**), bullatacin (rolliniastatin-2) (**7**), asimicin (**8**), and isodesacetyluvaricin (**9**), as well as four other known analogues **10–13** [36]. Moreover, our group introduced the recycle-HPLC system for isolating of gigantetronenin (**14**) and montalicin J (**15**) [37] in an attempt to separate mixtures of AGEs that cannot be easily purified by regular HPLC methods (unpublished data, see Fig. 1).

**2** ((2,4-*cis* and *trans*)-9-hydroxyasimicinone)**3** ((2,4-*cis* and *trans*)-squamoxinone B)**4** ((2,4-*cis* and *trans*)-squamoxinone C)**5** (isoannoreticuin)**6** (squamocin)**7** (bullatacin = rolliniastatin-2)**8** (asimicin)

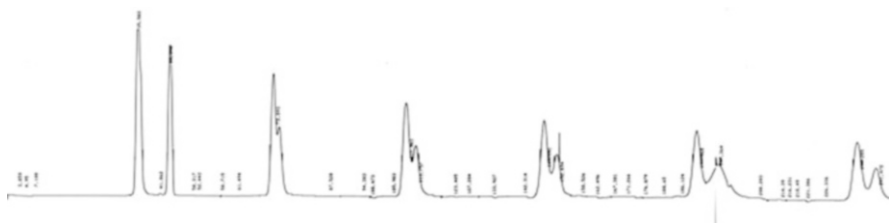
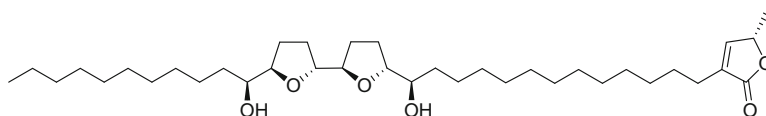


Fig. 1 HPLC separation profiles of gigantetronenin (**14**) and montalicin J (**15**) from the JAI recycling HPLC system

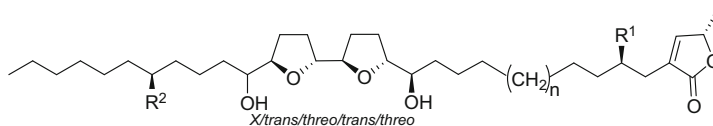
With the idea of developing a convenient yet reliable spectroscopic methodology for determining the stereochemistry of AGEs, Gawronski et al. established the absolute configuration of the γ -lactone ring moiety by analyzing the CD spectra of butenolides [38]. Cavé et al. not only modified the Mosher ester method, but they also determined the stereochemistry of asimicin (**8**) using the long-range anisotropic effect of 2-NMA (naphthylmethoxyacetic acid) [39].

Another key tool for determining the structures of AGEs is mass spectrometry (MS). Electron-impact mass spectrometry (EI-MS) has been a preferred technique for determining the location of AGE tetrahydrofuran rings and functional groups (i.e. hydroxy, ketone, acetoxy, and double bond) along the hydrocarbon chain. Derivatized AGEs, such as TMS- and acetyl derivatives, are helpful in the elucidation of these structures. In addition, the direct-inlet-probe technique (DIP) and a lower volatile energy setting (e.g. 30 eV) have been suggested for use with EI-MS scanning, as AGEs can decompose readily under thermal conditions. Such EI-MS fragmentations are quite useful to determine the planar structures of AGEs despite being a seemingly old-fashioned method. The structure of squamocin (**6**) from *A. squamosa* was characterized by a combination of chemical derivatization and precursor-ion scanning mass spectrometry. The lactone portion of squamocin (**6**) was modified with *N,N*-dimethylethylene-diamine in the vapor phase to afford a strong positive charge at one end of the skeleton [40]. In 1997, Wu et al. (Xenobiotic Laboratories, Inc.) in cooperation with the McLaughlin group, analyzed AGEs from *R. mucosa* that were subjected to liquid chromatography/mass spectrometry (LC/MS) with ionization source-atmospheric pressure in-source collision-induced dissociation (APICID). They were able to detect the presence of 40 known AGEs along with four new AGEs of diverse structures, from the bioactive crude methanol-soluble fraction of this plant extract [41]. They also observed a unique fragmentation profile for AGEs with a hydroxy group at C-4, which gave a characteristic loss of a terminal γ -lactone (m/z 112) during ESI-MS scanning [41]. This rapid and straightforward selective ionization procedure also provided a convenient and useful method for identifying AGEs with or without a hydroxy group at C-4 [41].

From a detailed literature survey, it is apparent that the structures of more than 200 AGEs have been published since 1996 until the end of 2014. Among those published, 113 AGEs were included in McLaughlin's review from the year of 1999 [42] yet excluded from chapter written by Cavé's group in 1997 [2]. In addition, AGEs with many previously unprecedented skeletons were isolated and elucidated from plants in the Annonaceae. In view of this, the criteria of Cavé et al. have been modified and the structural characteristics to classify the AGEs have been simplified [8]. Depending on the substituents along the aliphatic chain, AGEs have been classified into four groups, namely, (1) linear and epoxy AGEs, including those without any THF ring but with substitution by an epoxide ring and/or a double bond; (2) mono-THF AGEs, including AGEs with a mono-THF ring; (3) bis-THF AGEs, including those with adjacent or non-adjacent bis-THF rings; and (4) miscellaneous (see Fig. 2 and formulas 9–15).



9 (isodesacetylularicin)

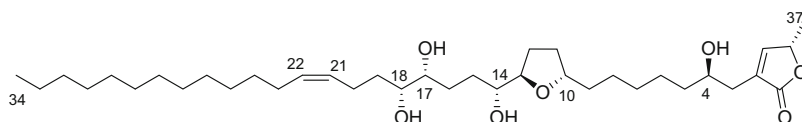


10 (molvizarin) $R^1 = \text{OH}$ $R^2 = \text{H}$ $n = 4$ $X = \text{erythro}$

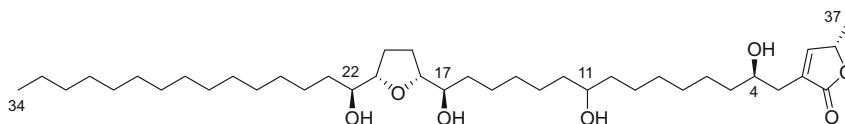
11 (neoannonin) $R^1 = \text{H}$ $R^2 = \text{H}$ $n = 4$ $X = \text{erythro}$

12 (atemoyin) $R^1 = \text{H}$ $R^2 = \text{H}$ $n = 4$ $X = \text{threo}$

13 (desacetylularicin) $R^1 = \text{OH}$ $R^2 = \text{H}$ $n = 6$ $X = \text{erythro}$



14 (gigantetronenin)



15 (montalycin J)

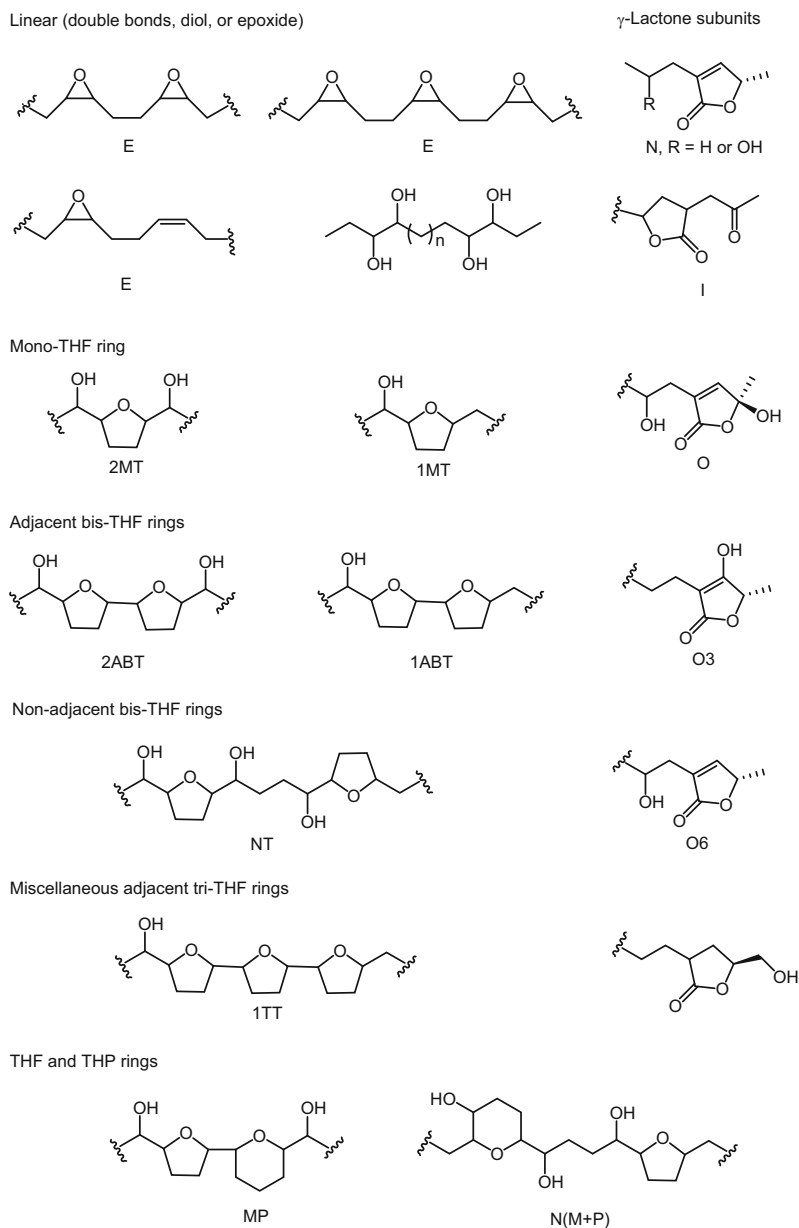


Fig. 2 γ -Lactone and tetrahydrofuran (THF), tetrahydropyran (THP), and other oxygen-bearing subunits in annonaceous acetogenins (AGEs)

3.1 Linear and Epoxy Annonaceous Acetogenins

In general, this structural sub-type of AGEs includes compounds with no THF ring but that have a substituent like an epoxide ring and/or a double bond. Fifty-two new

linear and epoxide ring-containing AGEs were isolated from 15 species in nine genera, including *Annona* (22), *Cananga* (9), *Goniothalamus* (7), *Mitrephora* (3), *Polyalthia* (6), *Rollinia* (2), *Saccopetalum* (2), *Uvaria* (2), and *Xylopia* since 1997 (1). The features of this group are double bonds, a diol group, and/or an epoxide ring in place of the THF ring (see Table 2). Notably, AGEs with an epoxide ring of this structural sub-type usually have the terminal γ -lactone ring without a C-4 hydroxy group often suggested by some specific biosynthesis pathways for these compounds. In 2002, the first linear acetylenic C₂₅-AGEs (**16** and **17**) with a new type of saturated γ -hydroxymethyl- γ -lactone terminal ring, but with no oxygenated substituents on its alkyl chain were found in *Saccopetalum prolificum* (Annonaceae) [28]. However, such compounds were later found in *Goniothalamus gardneri* (Annonaceae) [52], *Mitrephora glabra* [23], *Mitrephora maingayi* [24], *Polyalthia debilis* [26], and *Cananga latifolia* [15].

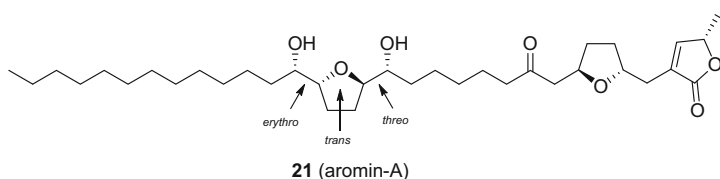
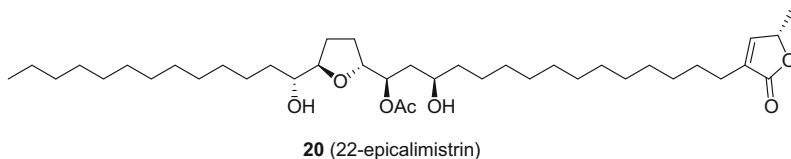
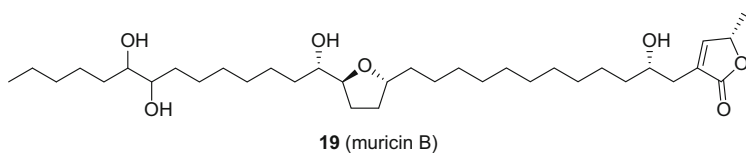
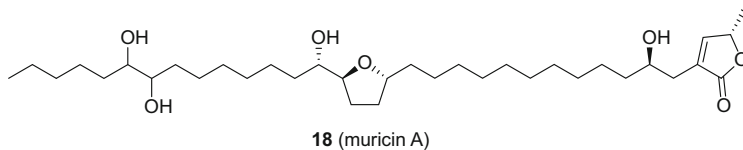
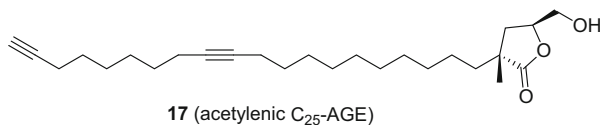
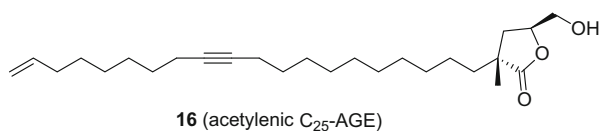


Table 2 Linear and epoxy AGEs isolated since 1997 until the end of 2014

	Name	No. of C	-OH/epoxide/double bond	Plant	Ref.
1	Annojahnin	37	10=O, (17 <i>R</i> ,18 <i>R</i>)	<i>A. jahnii</i>	[11]
2	Artemoin A	35	23,24	<i>A. atemoya</i>	[43]
3	Artemoin B	35	21,22	<i>A. atemoya</i>	[43]
4	Artemoin C	35	19,20	<i>A. atemoya</i>	[43]
5	Artemoin D	35	17,18	<i>A. atemoya</i>	[43]
6	Cananginone A	23	11T 13T 15D 19D	<i>C. latifolia</i>	[15]
7	Cananginone B	23	11T 13T 15D	<i>C. latifolia</i>	[15]
8	Cananginone C	23	11T 13T 19D	<i>C. latifolia</i>	[15]
9	Cananginone D	23	11T 13T	<i>C. latifolia</i>	[15]
10	Cananginone E	23	11T 13D 19D	<i>C. latifolia</i>	[15]
11	Cananginone F	23	11T 19D	<i>C. latifolia</i>	[15]
12	Cananginone G	21	9T 11D 17D	<i>C. latifolia</i>	[15]
13	Cananginone H	21	9T 11D	<i>C. latifolia</i>	[15]
14	Cananginone I	25	13T 15T 17D 21D	<i>C. latifolia</i>	[15]
15	Cohibin A	35	15,16	<i>A. muricata</i>	[44]
16	Cohibin B	35	13,14	<i>A. muricata</i>	[44]
17	Cohibin C	37	17,18,21	<i>A. muricata</i> <i>A. nutans</i>	[45]
18	Cohibin D	37	15,16,19	<i>A. muricata</i> <i>A. nutans</i>	[45]
19	Coronin	37	(13 <i>E</i> ,17 <i>E</i>),21	<i>A. muricata</i>	[46]
20	Debilisone A	25	13T 15T	<i>P. debilis</i>	[26]
21	Debilisone B	25	13T 15T	<i>P. debilis</i>	[26]
22	Debilisone C	25	13T 15T 17D	<i>P. debilis</i>	[26]
23	Debilisone D	25	13T 15T 17D 21D	<i>P. debilis</i>	[26]
24	Debilisone E	25	13T 15T 17D 21D	<i>P. debilis</i>	[26]
25	Debilisone F	27	15T 17T 19D	<i>P. debilis</i>	[26]
26	Diepomuricanin B	35	(15 <i>E</i> ,19 <i>E</i>)	<i>R. membranacea</i>	[47]
27	Dieposabadelin	35	(13 <i>E</i> ,17 <i>E</i>)	<i>A. squamosa</i>	[48]
28	Diepoxyrollin	37	(17 <i>E</i> ,21 <i>E</i>)	<i>R. membranacea</i>	[47]
29	Donbutocin	35	(4 <i>R</i>),10,15,16	<i>G. donnaiensis</i>	[49]
30	Donhepocin	35	(4 <i>R</i>),10,15,16,19,20	<i>G. donnaiensis</i>	[49]
31	34- <i>epi</i> -Donhepocin	35	(4 <i>R</i>),10,15,16,19,20	<i>G. donnaiensis</i>	[49]
32	Donhexocin	35	(4 <i>R</i>),10,15,16,19,20	<i>G. donnaiensis</i>	[49]
33	Epomurinin-A	35	(15 <i>E</i>)	<i>A. muricata</i>	[50]
34	Epomurinin-B	35	(13 <i>E</i>)	<i>A. muricata</i>	[50]
35	Gardnerilin A	35	(4 <i>R</i>),8,15,16,19,20	<i>G. gardneri</i>	[51]
36	Gardnerilin B	35	4 <i>R</i> ,10,17,18	<i>G. gardneri</i>	[51]
37	Goniothalamusin	25	13T	<i>G. gardneri</i>	[52]
38	9,10-Dihydrooropheolide	19	9D 11T 13T 17D	<i>M. glabra</i>	[23]
39	Mitregenin	21		<i>M. maingayi</i>	[24]
40	(+)-Monhexocin	35	4,9,15,16,19,20	<i>A. montana</i>	[53]

(continued)

Table 2 (continued)

	Name	No. of C	-OH/epoxide/double bond	Plant	Ref.
41	(–)-Monhexocin	35	4,9,15,16,19,20	<i>A. montana</i>	[53]
42	Montecristin	37	13,14	<i>A. muricata</i>	[54]
43	Muricadienin	35	15,19	<i>A. muricata</i>	[13]
44	Muridienin-3	37	13,17	<i>A. muricata</i>	[13]
45	Muridienin-4	37	17,21	<i>A. muricata</i>	[13]
46	Murihexol	35	4,10,15,16,19,20	<i>A. muricata</i>	[55]
47	Oropheolide	19	9T 11T 13T 17D	<i>M. glabra</i>	[23]
48	Sabadelin	35	13,(17E)	<i>A. muricata</i>	[56]
49	Saccopetrin A	25	13T 21D	<i>S. prolificum</i>	[28]
50	Saccopetrin B	25	13T 21D	<i>S. prolificum</i>	[28]
51	Squamocenin ^a	35	(15E,19E),23	<i>A. squamosa</i>	[48]
52	Xymarginatin	35	10=O 15D 19D	<i>X. emarginata</i>	[33]

^aThis compound has the same name as one of the mono-THF AGEs [57]

3.2 Mono-THF Annonaceous Acetogenins, Including Derivatives with a Mono-THF Ring

The structural features of this type of AGE are one THF ring with one or two flanking hydroxy groups in the long aliphatic chain (see Table 3). There are two subtypes based on the number of flanking hydroxy groups including: (1) the THF ring flanking one hydroxy group and (2) the THF ring flanking two hydroxy groups. Mono-THF acetogenins are indeed the largest single group of these plant secondary metabolites. One hundred and nineteen new mono-THF compounds were isolated from 15 species in seven genera, including *Ampelocissus* (1), *Annona* (91), *Asimina* (6), *Disepalum* (8), *Goniothalamus* (5), *Rollinia* (3), and *Uvaria*, since 1997 (5). In particular, two epimeric AGEs, muricins A (**18**) and B (**19**), were isolated from *A. muricata*, of which the absolute configurations were determined by the modified Mosher ester method [86]. Muricin B (**19**) is the first AGE to possess a hydroxy group with the (*S*)-configuration at C-4 where the typical configuration of this hydroxy group is (*R*). Moreover, 22-epicalimistrin B (**20**) is the first AGE that was isolated from the genus *Ampelocissus* (Vitaceae), which does not belong to the family Annonaceae [34].

Table 3 Mono-THF AGEs isolated since 1997 until the end of 2014

	Name	No. of C	OH	THF/epo	Plant	Ref.
1	Anmontanin A	35	(4 <i>R</i>),8=O	15,20	<i>A. montana</i>	[58]
2	Anmontanin B	35	(4 <i>R</i> ,8 <i>R</i>),10=O	(17 <i>S</i> ,22 <i>R</i>)	<i>A. montana</i>	[58]
3	Anmontanin C	35	(4 <i>R</i>),10=O,34	17–22	<i>A. montana</i>	[58]
4	Annocherimolin	37	(4 <i>R</i>),9	(13 <i>R</i> ,18 <i>R</i>)	<i>A. cherimola</i>	[59]
5	Annocatalin	35	4,28,29	19	<i>A. muricata</i>	[60]
6	Annocherin	35	(4 <i>R</i>),7=O	(15 <i>R</i> ,20 <i>R</i>)	<i>A. cherimola</i>	[61]
7	(2,4)- <i>cis</i> - and <i>trans</i> - Annocherinones	35	7=O,34=O	(15 <i>R</i> ,20 <i>R</i>)	<i>A. cherimola</i>	[61]
8	Annoglacin A	37	(4 <i>R</i> ,12 <i>R</i>)	(17 <i>R</i> ,22 <i>S</i>)	<i>A. glabra</i>	[62]
9	Annoglacin B	37	(4 <i>R</i> ,12 <i>R</i>)	(17 <i>R</i> ,22 <i>R</i>)	<i>A. glabra</i>	[62]
10	Annoglaxin	35	(8 <i>R</i>),12=O, (22 <i>S</i>)	(15 <i>R</i> ,20 <i>R</i>)	<i>A. glabra</i>	[63]
11	Annomocherin	35	(4 <i>R</i>),10,23-	(15 <i>R</i> ,20 <i>R</i>)	<i>A. cherimola</i>	[64]
12	Annomolin	35	(4 <i>R</i> ,7 <i>R</i> ,8 <i>R</i>)	(18 <i>S</i>)	<i>A. cherimola</i>	[59]
13	Annomolon A	35	11=O,34	(15 <i>R</i> ,20 <i>R</i>)	<i>A. cherimola</i>	[65]
14	34- <i>epi</i> -Annomolon A	35	11=O,34	(15 <i>R</i> ,20 <i>R</i>)	<i>A. cherimola</i>	[65]
15	Annomolon B	35	(4 <i>R</i>),11=O,34	(15 <i>R</i> ,20 <i>R</i>)	<i>A. cherimola</i>	[65]
16	34- <i>epi</i> -Annomolon B	35	(4 <i>R</i>),11=O,34	(15 <i>R</i> ,20 <i>R</i>)	<i>A. cherimola</i>	[65]
17	<i>cis</i> -Annomontacin	37	4,10	17–22	<i>A. muricata</i>	[60]
18	4-Deoxyannomontacin	37	(10 <i>R</i>)	(17 <i>R</i> ,22 <i>R</i>)	<i>G. giganteus</i>	[66]
19	(2,4- <i>cis</i> and <i>trans</i>)- Annomontacinone	37	(10 <i>S</i>)36=O	(17 <i>R</i> ,22 <i>R</i>)	<i>G. giganteus</i>	[66]
20	Annomuricin E	35	4,10,11	15–20	<i>A. muricata</i>	[67]
21	<i>cis</i> -Annoreticuin	35	4,9	15,20	<i>A. montana</i>	[68]
22	4-Deoxyannoreticuin	35	9	15–20	<i>A. squamosa</i>	[69]
23	<i>cis</i> -4- Deoxyannoreticuin	35	9	15–20	<i>A. squamosa</i>	[69]
24	<i>cis</i> -Annotemoyin-1	35		17–22	<i>A. squamosa</i>	[37]
25	Asitrilobin A	37	(4 <i>R</i>),10	(17 <i>R</i> or <i>S</i> ,22 <i>R</i> or <i>S</i>)	<i>A. triloba</i>	[70]
26	Asitrilobin B	35	(4 <i>R</i>),10	(17 <i>R</i> or <i>S</i> ,22 <i>R</i> or <i>S</i>)	<i>A. triloba</i>	[70]
27	Asitrilobin C	37	(4 <i>R</i> ,10 <i>R</i> ,15 <i>S</i>)	(17 <i>R</i> ,22 <i>R</i>)	<i>A. triloba</i>	[71]
28	Asitrilobin D	37	(4 <i>R</i> ,10 <i>R</i> ,17 <i>S</i>)	(19 <i>R</i> ,24 <i>R</i>)	<i>A. triloba</i>	[71]
29	Asitrocin	35	(4 <i>R</i> ,12 <i>R</i>)	(15 <i>S</i> ,20 <i>R</i>)	<i>A. triloba</i>	[72]
30	(2,4)- <i>cis</i> - and <i>trans</i> - Asitrocinones	35	(12 <i>R</i>),34=O	(15 <i>S</i> ,20 <i>R</i>)	<i>A. triloba</i>	[72]
31	Calamistrin A	37	(15 <i>S</i>)	(17 <i>R</i> ,22 <i>S</i>)	<i>U. calamistrata</i>	[30]
32	Calamistrin B	39	(15 <i>R</i>)	17ROAc, (22 <i>S</i>)	<i>U. calamistrata</i>	[30]
33	22- <i>epi</i> -Calamistrin B	39	15,17-OAc	(22 <i>R</i>)	<i>Ampelocissus</i> sp.	[34]

(continued)

Table 3 (continued)

	Name	No. of C	OH	THF/epo	Plant	Ref.
34	Calamistrin C	37	13	(19R,24R)	<i>U. calamistrata</i>	[73]
35	Calamistrin D	37	13	(19R,24S)	<i>U. calamistrata</i>	[73]
36	Calamistrin E	37	(5R),23-	(15R,20R)	<i>U. calamistrata</i>	[73]
37	Coriaheptocin A	35	4,14,16,19,20	7,12	<i>A. coriacea</i>	[74]
38	Coriaheptocin B	35	4,14,16,19,20	7,12	<i>A. coriacea</i>	[74]
39	<i>cis</i> -Corossolone	35	10=O	15,20	<i>A. muricata</i>	[60]
40	Dotistenin	35	23	15,20	<i>A. squamosa</i>	[48]
41	Glabrencin A	37		13,18	<i>A. glabra</i>	[75]
42	Glabrencin B	37		17,22	<i>A. glabra</i>	[75]
43	Glacin A	35	(4R,12R)	(17R,22R)	<i>A. glabra</i>	[76]
44	Glacin B	35	(4R,12R)	(15R,20S)	<i>A. glabra</i>	[76]
45	Glaucabellin	37	4	17,22	<i>A. glauca</i>	[77]
46	Glaucalflorin	37	4,19,20	16	<i>A. glauca</i>	[77]
47	Mixture of (2,4- <i>cis</i> and <i>trans</i>)-gonioneninone	37	(10R)	(13R,18R)	<i>G. giganteus</i>	[78]
48	Goniotetracin	37	(4R),10	(13R,18R)	<i>G. giganteus</i>	[78]
49	<i>cis</i> -/ <i>trans</i> -Isomurisolin	35	34=O	15,20	<i>A. reticulata</i>	[79]
50	Jimenezin	37	4,23	15,20	<i>R. mucosa</i>	[80]
51	Lepirenin	35	23	15,20	<i>A. squamosa</i>	[48]
52	Monlicin A	35	(4R,7R,8R)	(14R,18S)	<i>A. montana</i>	[53]
53	Monlicin B	35	(4R,7S,8S)	(14S,18R)	<i>A. montana</i>	[53]
54	Montacin	35	(4R),7=O,(9S)	(20S,25S)	<i>A. montana</i>	[81]
55	<i>cis</i> -Montacin	35	(4R),7=O,(9R)	(20S or R),25(R or S)	<i>A. montana</i>	[81]
56	Montalicin A	33	4	13,18	<i>A. montana</i>	[68]
57	Montalicin B	35	4	13,18	<i>A. montana</i>	[68]
58	Montalicin C	35	4,7	13,18	<i>A. montana</i>	[68]
59	Montalicin D	35	4,11	13,18	<i>A. montana</i>	[68]
60	Montalicin E	37	4,7	13,18	<i>A. montana</i>	[68]
61	Montalicin F	35	4,9	15,20	<i>A. montana</i>	[68]
62	Montalicin G	35	(4R),7,9	(15R,20R)	<i>A. montana</i>	[53]
63	Montalicin H	35	4,7,9	15,20	<i>A. montana</i>	[53]
64	Montalicin I	37	4,9	15,20	<i>A. montana</i>	[68]
65	Montalicin J	37	4,11	17,22	<i>A. montana</i>	[68]
66	Montanacin B	35	(4R,8R),10=O	(15R,20R)	<i>A. montana</i>	[82]
67	Montanacin C	35	4,8,10=O	15,(20S)	<i>A. montana</i>	[82]
68	Montanacin D	35	10=O	15R-20	<i>A. montana</i>	[82]
69	Montanacin E	35	10=O	15,20	<i>A. montana</i>	[82]
70	Montanacin F	35	(29S)	(15R,20S)	<i>A. montana</i>	[83]
71	Montanacin G	35	(8R),10=O	(15R,20S)	<i>A. montana</i>	[84]

(continued)

Table 3 (continued)

	Name	No. of C	OH	THF/epo	Plant	Ref.
72	(34- <i>epi</i>)-Montanacin H	35	4,8,10=O	(15 <i>R</i> ,20 <i>S</i>)	<i>A. montana</i>	[84]
73	(34- <i>epi</i>)-Montanacin I	35	(4 <i>R</i> ,29 <i>S</i>)	(15 <i>R</i> ,20 <i>R</i>)	<i>A. montana</i>	[84]
74	(34- <i>epi</i>)-Montanacin J	35	(4 <i>R</i> ,29 <i>S</i>)	(15 <i>R</i> ,20 <i>S</i>)	<i>A. montana</i>	[84]
75	Mosin B	35	(4 <i>R</i>)	(15 <i>R</i> or 5,20 <i>S</i> or <i>R</i>)	<i>A. squamosa</i>	[85]
76	Mosin C	35	(4 <i>R</i>)	(15 <i>R</i> ,20 <i>S</i>)	<i>A. squamosa</i>	[85]
77	(2,4- <i>cis</i> and <i>trans</i>)- Mosinone A	37	9=O	(15 <i>R</i> ,20 <i>R</i>)	<i>A. squamosa</i>	[85]
78	Muricapentocin	35	4,8,12	15,20	<i>A. muricata</i>	[67]
79	Muricin A	35	(4 <i>R</i>),26,27	(19 <i>R</i>)	<i>A. muricata</i>	[86]
80	Muricin B	35	(4 <i>S</i>),26,27	(19 <i>R</i>)	<i>A. muricata</i>	[86]
81	Muricin C	35	4,24,25	21	<i>A. muricata</i>	[86]
82	Muricin D	33	4,22,23	19	<i>A. muricata</i>	[86]
83	Muricin E	33	4,22,23	16	<i>A. muricata</i>	[86]
84	Muricin F	35	4,27,28	21	<i>A. muricata</i>	[86]
85	Muricin G	35	4,10	15,20	<i>A. muricata</i>	[86]
86	Muricin H	35	24,25	(19 <i>R</i>)	<i>A. muricata</i>	[60]
87	Muricin I	37	24,25	19	<i>A. muricata</i>	[60]
88	Muricoreacin	35	4,8,10,19,20	16	<i>A. muricata</i>	[87]
89	Murihexocin C	35	4,7,8,19,20	16	<i>A. muricata</i>	[87]
90	<i>cis</i> -Pantellin	35		13,18	<i>A. muricata</i>	[88]
91	Parisin	37	4,23,24	15,20	<i>A. salzmanii</i>	[89]
92	Plagioneurin A	39	10,15-OAc	(17 <i>R</i> ,22 <i>R</i>)	<i>D. plagioneurum</i>	[18]
93	Plagioneurin B	39	10,15-OAc	17–22	<i>D. plagioneurum</i>	[18]
94	Plagioneurin C	39	10=O,15-OAc	(17 <i>R</i> ,22 <i>R</i>)	<i>D. plagioneurum</i>	[18]
95	Plagioneurin D	39	(5 <i>R</i>),10=O,15-OAc	(17 <i>R</i> ,22 <i>R</i>)	<i>D. plagioneurum</i>	[18]
96	Plagioneurin E	39	5,10=O,15-OAc	17,22	<i>D. plagioneurum</i>	[18]
97	Plagionicin B	35	5,10=O	15,20	<i>D. plagioneurum</i>	[18]
98	Plagionicin C	35	4,5,11	15,20	<i>D. plagioneurum</i>	[18]
99	Plagionicin D	35	5=O,10,11	15,20	<i>D. plagioneurum</i>	[18]
100	<i>cis</i> -Reticulatacin	37		17,22	<i>A. muricata</i>	[88]
101	<i>cis</i> -Reticulatacin-10-one	37	10=O	17,22	<i>A. muricata</i>	[88]
102	Rolliacocin	35	(4 <i>R</i>),11	(15 <i>S</i> ,20 <i>S</i>)	<i>R. mucosa</i>	[90]
103	Rollicosin	22	(4 <i>R</i>),19=O	(15 <i>R</i>)	<i>R. mucosa</i>	[91]
104	<i>cis</i> -Solamin	35		15,20	<i>A. muricata</i>	[88]
105	Squadiolin A	37	15,16,28	19,24	<i>A. squamosa</i>	[37]
106	Squadiolin B	37	19,20,23,24	16	<i>A. squamosa</i>	[37]
107	Squadiolin C	37	4,21,22	16	<i>A. squamosa</i>	[37]

(continued)

Table 3 (continued)

	Name	No. of C	OH	THF/epo	Plant	Ref.
108	Squafosacin B	37		15,20	<i>A. squamosa</i>	[37]
109	Squafosacin C	35		17,22	<i>A. squamosa</i>	[37]
110	Squafosacin F	35		(15 <i>S</i> ,20 <i>S</i>)	<i>A. squamosa</i>	[37]
111	Squafosacin G	37		(19 <i>S</i> ,24 <i>S</i>)	<i>A. squamosa</i>	[37]
112	Squamocenin ^a	37	25B	17–22	<i>A. squamosa</i>	[57]
113	(2,4- <i>cis</i> and <i>trans</i>)- Squamoxinone	37	(11 <i>S</i>),36=O	(17 <i>R</i> ,22 <i>R</i>)	<i>A. squamosa</i>	[69]
114	(2,4- <i>cis</i> and <i>trans</i>)- Squamoxinone B	37	11,36=O	17,22	<i>A. squamosa</i>	[35]
115	(2,4- <i>cis</i> and <i>trans</i>)- Squamoxinone C	35	11,34=O	17,22	<i>A. squamosa</i>	[35]
116	Tucupentol	35	4,8,19,20	15	<i>A. montana</i>	[92]
117	<i>cis</i> -Uvariamicin I	37		15,20	<i>A. muricata</i>	[88]
118	<i>cis</i> -Uvariamicin IV	37		13,18	<i>A. muricata</i>	[88]
119	Mixture of (2,4- <i>cis</i> and - <i>trans</i>)-xylomaticinones	37	(10 <i>R</i>),36=O	(15 <i>R</i> ,20 <i>R</i>)	<i>G. giganteus</i>	[93]

^aThis compound has the same name as one of the linear AGEs [48]

3.3 Bis-THF Annonaceous Acetogenins, Including Derivatives with Adjacent or Non-adjacent Bis-THF Rings

The primary structural feature of bis-THF AGEs is two THF rings flanking one or two hydroxy groups. Two subtypes of this group can be identified based on the nature of the bis-THF moieties, namely, (1) compounds with an adjacent bis-THF moiety and (2) those with a non-adjacent bis-THF moiety, in which the latter possesses a four-carbon aliphatic chain between the THF rings. Since 1997, 63 new bis-THF AGEs were found, including 48 adjacent bis-THF AGEs isolated from 15 species in the four genera, *Annona* (35 species), *Asimina* (four species), *Rollinia* (five species), and *Uvaria* (four species), along with 15 non-adjacent bis-THF AGEs from six species in the four genera, *Annona* (11 species), *Asimina* (one species), *Goniiothalamus* (two species), and *Rollinia* (one species) (see Table 4). Interestingly, aromin-A (**21**) from *A. cherimola* possesses one THF ring that is cyclized between C-4 and C-7 by an ether linkage [116], which shares many similarities with the analogues found from *Xylopia aromatica* [120]. As a result, the bis-THF ring-containing compounds have been organized into groups of adjacent and non-adjacent compounds.

Table 4 Bis-THF AGEs isolated since 1997 until the end of 2014

	Name	No. of C	OH	THF/epo	Plant	Ref.
<i>Adjacent Bis-THF AGEs</i>						
1	Annocatacin A	35	(4 <i>S</i>)	(23 <i>S</i>)	<i>A. muricata</i>	[94]
2	Annocatacin B	35	(4 <i>S</i>)	23	<i>A. muricata</i>	[94]
3	Annonisin	35	4,8	13,22	<i>A. atemoya</i>	[95]
4	Annosquacin A	35		11,20	<i>A. squamosa</i>	[96]
5	Annosquacin B	37		13,22	<i>A. squamosa</i>	[96]
6	Annosquacin C	37	25	13,22	<i>A. squamosa</i>	[96]
7	Annosquacin D	37		13,22	<i>A. squamosa</i>	[96]
8	Annosquacin-I	37	23	10,19	<i>A. squamosa</i>	[97]
9	(2,4- <i>cis</i> and <i>trans</i>)- 9-Hydroxy- asimicinone	37	(9 <i>S</i>),36=O	(15 <i>R</i> ,24 <i>R</i>)	<i>A. squamosa</i>	[35]
10	(2,4- <i>cis</i> and <i>trans</i>)- 9-Oxo-asimicinone	35	9=O,36=O	(15 <i>R</i> ,24 <i>R</i>)	<i>A. squamosa</i>	[98]
11	Asimitrin	37	(4 <i>R</i> ,17 <i>R</i>)	(15 <i>R</i> ,24 <i>R</i>)	<i>A. triloba</i>	[99]
12	Atemotetrolin	37	28,29	15,24	<i>A. atemoya</i>	[100]
13	Bullacin B	37	(6 <i>R</i>)	(15 <i>R</i> ,24 <i>R</i>)	<i>A. squamosa</i>	[98]
14	Bulladecin	37	4,23,24	11,20	<i>A. atemoya</i>	[100]
15	27- Hydroxybullatacin	37	(4 <i>R</i> ,27 <i>S</i>)	(15 <i>R</i> ,24 <i>S</i>)	<i>A. glabra</i>	[63]
16	Calamistrin F	37	(5 <i>R</i>)	17,(26 <i>R</i>)	<i>U. calamistrata</i>	[73]
17	Calamistrin G	37	(5 <i>S</i>)	(17 <i>R</i> ,26 <i>S</i>)	<i>U. calamistrata</i>	[73]
18	Carolin A	37	28	15,24	<i>A. spinescens</i>	[101]
19	Carolin B	37	29	15,24	<i>A. spinescens</i>	[101]
20	Carolin C	35	26	1322	<i>A. spinescens</i>	[101]
21	Chamuvarinin	37		15	<i>U. chamae</i>	[102]
22	Cornifolin	37	7	17,26	<i>A. cornifolia</i>	[103]
23	9-Hydroxyfolianin	37	9	(12 <i>R</i> ,21 <i>S</i>)	<i>A. cornifolia</i>	[104]
24	Folianin B	37		12,21	<i>A. cornifolia</i>	[104]
25	Glabracin A	37	(4 <i>R</i>),23,24	(10 <i>S</i>)	<i>A. glabra</i>	[105]
26	Glabracin B	37	(4 <i>R</i>),23,24	(10 <i>S</i>)	<i>A. glabra</i>	[105]
27	Guanaconetin-1	41	24,30=OCOCH ₃	15	<i>A. aff. spraguei</i>	[106]
28	Guanaconetin-2	41	15,30=OCOCH ₃	24	<i>A. aff. spraguei</i>	[106]
29	Guanaconetin-3	39	24=OCOCH ₃ ,30	15	<i>A. aff. spraguei</i>	[106]
30	Guanaconetin-4	39	30=OCOCH ₃	15,24	<i>A. aff. spraguei</i>	[106]
31	Joolanin	37	5=O	15,24	<i>U. chamae</i>	[107]
32	Purpuracenin	37	(4 <i>R</i>)	(15 <i>R</i> ,24 <i>S</i>)	<i>A. purpurea</i>	[108]
33	Purpurediolin	37	28,29 <i>S</i>	(5 <i>R</i> ,24 <i>S</i>)	<i>A. purpurea</i>	[109]
34	Purpurenin	37	(10 <i>R</i>),28,29 <i>S</i>	(15 <i>R</i> ,24 <i>S</i>)	<i>A. purpurea</i>	[109]
35	Rollidecin C	35		20	<i>R. mucosa</i>	[110]
36	Rollidecin D	37		22	<i>R. mucosa</i>	[110]
37	Rollimusin	37	10,28	15,24	<i>R. mucosa</i>	[90]
38	Rollinacin	35	4,10	20	<i>R. mucosa</i>	[111]
39	Rollitacin	37	28,29	15,24	<i>R. mucosa</i>	[111]

(continued)

Table 4 (continued)

	Name	No. of C	OH	THF/epo	Plant	Ref.
40	Salzmanolin	37	15,17,28,29	24	<i>A. salzmanii</i>	[89]
41	Squamocin-O ₁	37	(12 <i>R</i> ,28 <i>S</i>)	(15 <i>R</i> ,24 <i>S</i>)	<i>A. squamosa</i>	[112]
42	Squamocin-O ₂	37	(12 <i>S</i> ,28 <i>S</i>)	(15 <i>R</i> ,24 <i>S</i>)	<i>A. squamosa</i>	[112]
43	(2,4- <i>cis</i> and <i>trans</i>)- Squamolinone	35	36=O	(15 <i>R</i> ,24 <i>S</i>)	<i>A. squamosa</i>	[98]
44	2,4- <i>cis</i> - Trilobacinone	37	36=O	(15 <i>R</i> ,24 <i>R</i>)	<i>A. triloba</i>	[113]
45	2,4- <i>trans</i> - Trilobacinone	37	36=O	(15 <i>R</i> ,24 <i>R</i>)	<i>A. triloba</i>	[113]
46	4-Hydroxytrilobin	37	(4 <i>R</i>),10	(15 <i>R</i> ,24 <i>R</i>)	<i>A. triloba</i>	[99]
47	Tucumanin	37		15,24	<i>A. cherimola</i>	[114]
48	Compound 1	37	5	15,24	<i>A. squamosa</i>	[115]
<i>Non-adjacent-bis-THF AGEs</i>						
1	Aromin-A	35	9=O	15,20	<i>A. cherimola</i>	[116]
2	Annosquatin A	37		13,16,21	<i>A. squamosa</i>	[96]
3	Annosquatin B	37	29	13,16,21	<i>A. squamosa</i>	[96]
4	Annosquatin-I	37	30	17,24,29	<i>A. squamosa</i>	[97]
5	Annosquatin-II	37	4	17,24,29	<i>A. squamosa</i>	[97]
6	Mixture of 20,23- <i>cis</i> -2,4- <i>cis</i> and <i>trans</i> - bullatalicinone	37		16,19,24	<i>R. mucosa</i>	[90]
7	Mixture of (2,4- <i>cis</i> and <i>trans</i>)- gigantecinone	37	36=O	(14 <i>S</i> ,17 <i>R</i> ,22 <i>R</i>)	<i>G. giganteus</i>	[117]
8	Goniotricin	37	4,18	10	<i>G. giganteus</i>	[93]
9	Squamostanin-A	37	(27 <i>R</i>)	(15 <i>R</i> ,18 <i>R</i> ,23 <i>R</i>)	<i>A. squamosa</i>	[118]
10	12,15- <i>cis</i> - Squamostatin-A	37	28	16,19,24	<i>A. atemoya</i>	[43]
11	Squamostanin-B	37	(27 <i>R</i>)	(15 <i>R</i> ,18 <i>R</i> ,23 <i>S</i>)	<i>A. squamosa</i>	[118]
12	Squamostanin-C	37	(5 <i>R</i>)	(16 <i>R</i> ,19 <i>R</i> ,24 <i>R</i>)	<i>A. squamosa</i>	[119]
13	Squamostanin-D	37	(5 <i>R</i>)	(16 <i>R</i> ,19 <i>R</i> ,24 <i>S</i>)	<i>A. squamosa</i>	[119]
14	12,15- <i>cis</i> - Squamostatin-D	37		16,19,24	<i>A. atemoya</i>	[43]
15	Trilobalicin	35	(4 <i>R</i>)	14,17,22	<i>A. triloba</i>	[113]

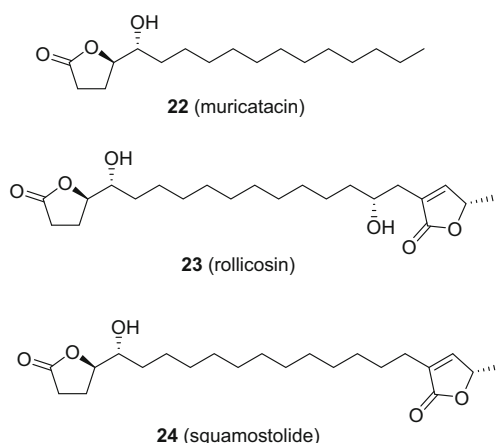
3.4 Miscellaneous

This group includes AGEs with an atypical substituted alkyl chain (see Table 5). For instance, muricatacin (**22**) appears like a normal AGE without the γ -lactone ring moiety and the aliphatic chain between the THF ring and lactone ring [122]. In 2003, our group reported a novel skeleton of an abridged AGE, rollicosin (**23**), from the unripe fruits of *Rollinia mucosa*, the first identified AGE containing lactone moieties

Table 5 Miscellaneous types of AGEs isolated since 1997 until the end of 2014

	Name	No. of C	OH	THF/epo	Plant	Ref.
1	Montanacin D	35	10=O	(15 <i>R</i>),20	<i>A. montana</i>	[82]
2	Montanacin E	35	10=O	(15 <i>R</i>),20	<i>A. montana</i>	[82]
3	Chamuvarinin	37		15,28	<i>U. chamae</i>	[102]
4	Rollicosin	22	(4 <i>R</i>),19=O	(15 <i>R</i>)	<i>R. mucosa</i>	[91]
5	Squamostolide	22	19=O	(15 <i>R</i>)	<i>A. squamosa</i>	[121]

on both sides of an aliphatic chain [91]. Soon after this report, a Chinese group communicated the second AGE of this type, squamostolide (**24**), from *A. squamosa* [121].



4 Chemotaxonomy of the Annonaceae Family

The family Annonaceae is composed of 2000 species including 129 genera found worldwide. Plants of this family are recognized sources of alkaloids, diterpenes, flavonoids, and polyketide compounds. Among them, acetogenins are regarded as characteristic secondary metabolites of this family. More than half of the annonaceous AGEs have been isolated from the genus *Annona*. A plausible biosynthesis pathway of AGEs should be related to various polyketide synthases deduced by different species of plants. Three types of AGEs were selected, including mono-THF AGEs (MT), adjacent bis-THF AGEs (ABT) and non-adjacent bis-THF AGEs (NBT). They were all isolated from the plants of the genus *Annona* according to the reported literature. By employing qualitative analysis, three patterns of radar charts were observed for deducing a cladistics chart and the phylogenetic inference of selected species in the genus *Annona*. These seem to correlate with the appearance of the fruits of these plants (see Fig. 3). For instance, the species examined may have fruits with the skin covered with many short fleshy spines (e.g. *A. montana* and

Fig. 3 Radar chart of AGEs. *MT* mono-THF AGEs, *ABT* adjacent bis-THF AGEs, *NBT* non-adjacent bis-THF AGEs

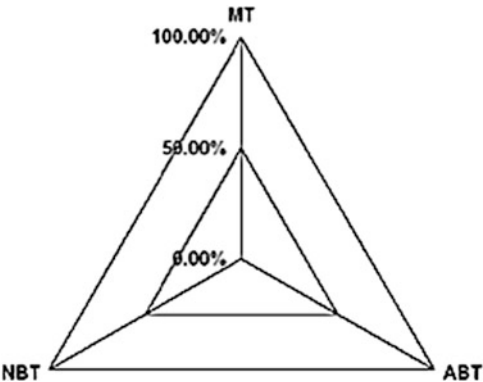
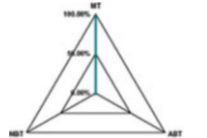

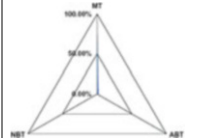

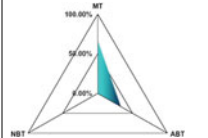

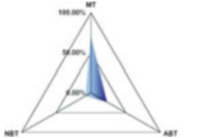

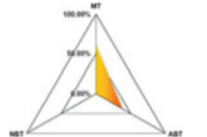
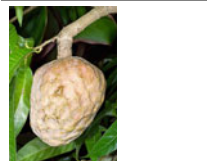
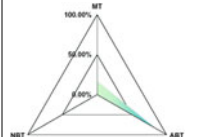

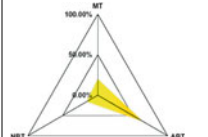

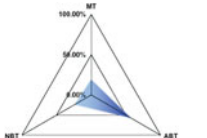



Table 6 Radar charts of AGEs of the plants in the genus *Annona* in qualitative analysis and the appearance of their fruits

<i>A. montana</i>  	<i>A. muricata</i>  	<i>A. cherimola</i>  	<i>A. glabra</i>  
<i>A. reticulata</i>  	<i>A. purpurea</i>  	<i>A. squamosa</i>  	<i>A. atemoya</i>  

Photographs by the authors: *A. montana*, *A. glabra*, *A. squamosa*; giardinaggi.it: *A. muricata*; Ken Lowe: *A. cherimola*; photomazza.com: *A. reticulata*; *A. purpurea*, *A. atemoya*: wikipedia.org

A. muricata), fruits with the skin overlapping scales or knob-like warts (e.g. *A. cherimola*, *A. glabra*, and *A. reticulata*), and fruits with many round protuberances (e.g. *A. purpurea*, *A. squamosa*, and *A. atemoya*) (see Table 6).
Based on the radar chart analysis of their AGEs, plants of the genus *Annona* can be classified into three sub-genera. Sub-genus I with mono-THF (MT) AGEs (one hydroxy group) as the major type includes *A. montana* and *A. muricata*.

Sub-genus II with mono-THF and bis-THF AGEs can be further separated into two groups, including one with mono-THF (MT) AGEs and the other with adjacent bis-THF (ABT) AGEs as the major ones. The former includes *A. reticulata*, *A. cherimola*, and *A. glabra*, whereas the latter includes *A. purpurea*, *A. atemoya* and *A. squamosa* (see Fig. 4).

The evaluation of the patterns of AGEs was extended to other plants of the Annonaceae. It was found that *Rollinia mucosa* seems to be phylogenetically related to *A. squamosa* based on the analysis of AGEs isolated from this particular plant (see Fig. 5).

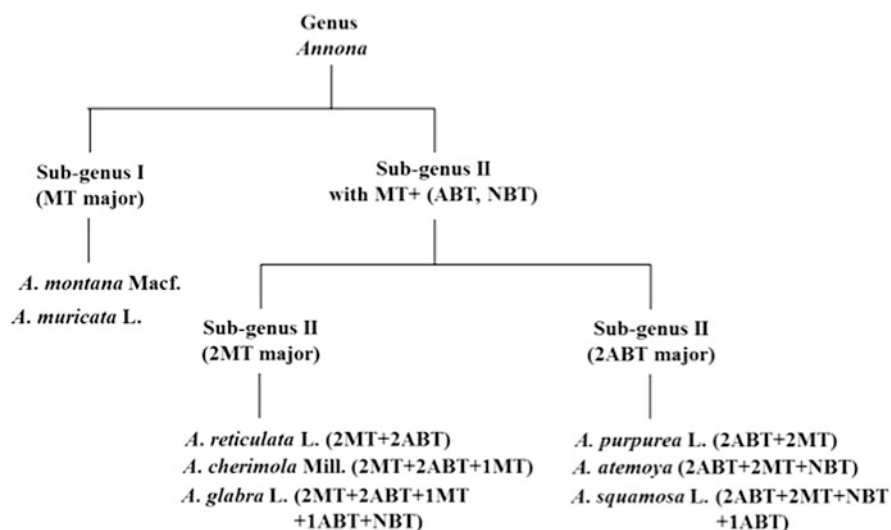


Fig. 4 Plausible interrelationships of plants of the genus *Annona*. 1MT: AGEs with a mono-THF moiety flanked by one hydroxy group, 2MT: AGEs with a mono-THF moiety flanked by two hydroxy groups, 1ABT: AGEs with an adjacent bis-THF moiety flanked by one hydroxy group, 2ABT: AGEs with an adjacent bis-THF moiety flanked by two hydroxy groups, NBT: AGEs with a non-adjacent bis-THF moiety

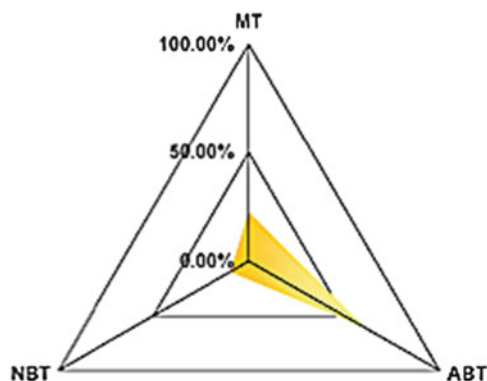


Fig. 5 Radar chart of AGEs from *R. mucosa*

5 Synthesis of Annonaceous Acetogenins

Owing to the great scientific interest in AGEs and their abundant structural types and interesting biological activities, these components have attracted the attention of many researchers working on chemical synthesis. However, the structural variations of AGEs, such as the presence of a γ -lactone ring moiety, and 1–3 THF/THP rings with multiple chiral centers, and an alkyl chain have been considered as challenging targets to utilize synthesis methods. A number of total syntheses for pure AGEs samples have also been reported in the literature since the 1990s. Since 1997, the total syntheses of AGEs achieved include those for the mono-THF AGEs: murisolin (**25**) [123, 124], longicin (**26**) [125, 126], and *cis*-solamin (**27**) [88, 127], adjacent bis-THF AGEs: bullatacin (**7**) [128], rolliniastatin 1 (**28**) [129, 130], rollimembrin (**29**) [130, 131], 10-hydroxyasimicin (**30**) [132, 133], membranacin (**31**) [130, 134], asimicin (**8**) [135, 136], longimicin D (**32**) [137, 138], and mucoxin (**33**) [139, 140], and non-adjacent bis-THF AGEs: *cis*-sylvaticin (**34**) [141, 142] and gigantecin (**35**) [143, 144], and others, jimenezin (**36**) [80, 145], mucocin (**37**) [146, 147], pyranicin (**38**) [148, 149], pyragonicin (**39**) [148, 150, 151], rollicosin (**23**) [91, 152], and squamostolide (**24**) [121, 153]. Indeed, more than 100 investigations on the synthesis of AGEs have been published during the last 15 years (see Fig. 6).

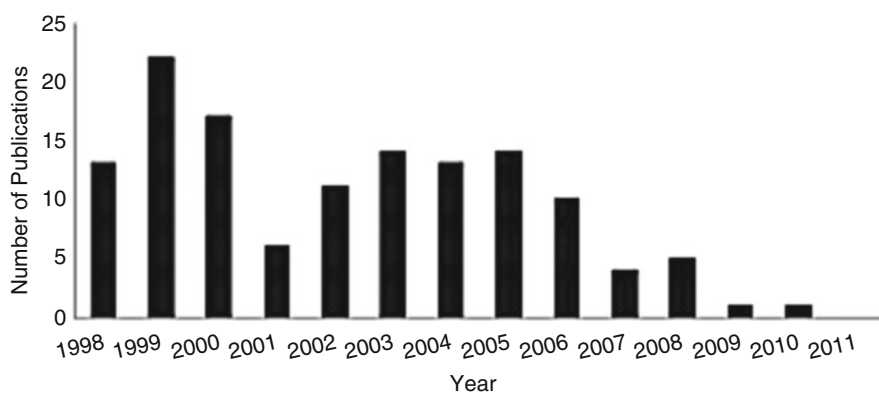
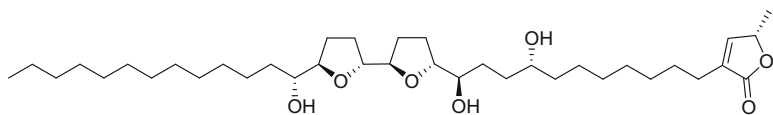
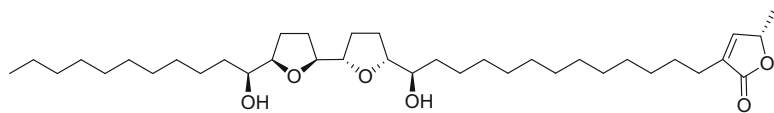
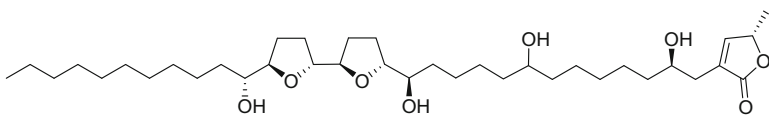
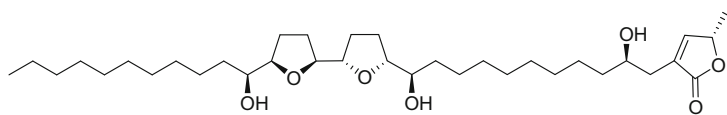
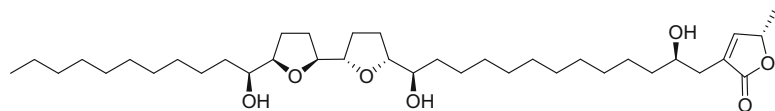
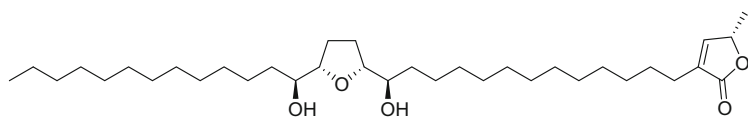
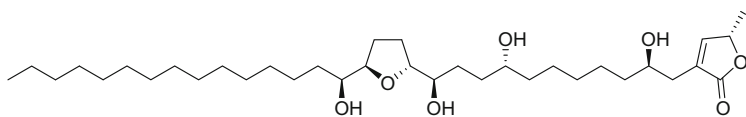
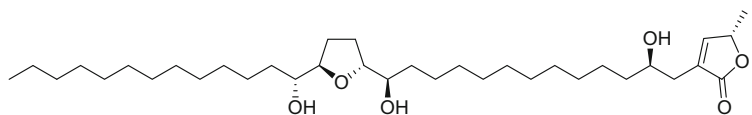
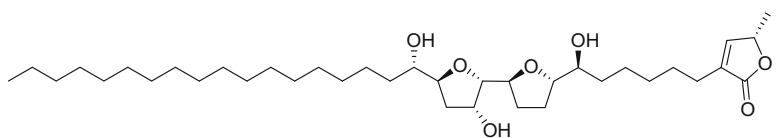
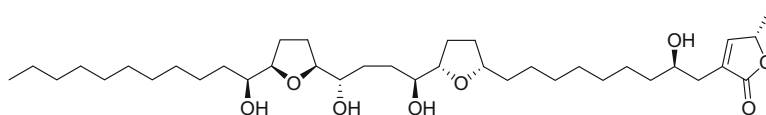
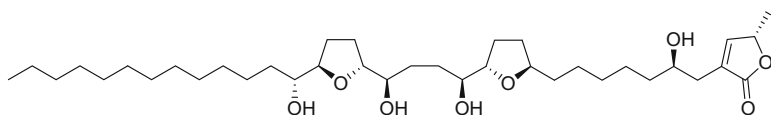
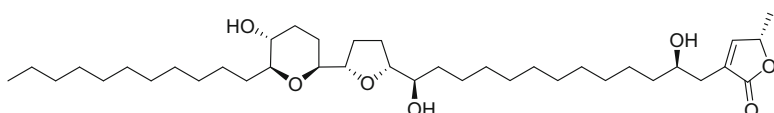
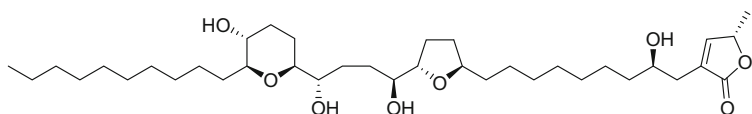
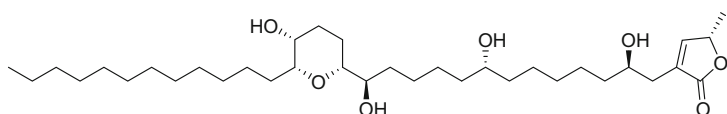
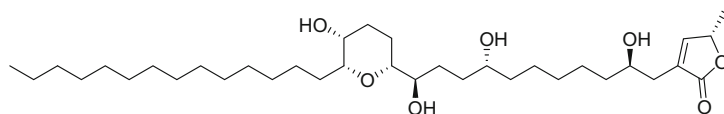


Fig. 6 Number of publications per year on the investigation of AGE synthesis from 1998 to 2011



**33** (mucoxin)**34** (*cis*-sylvaticin)**35** (gigantecin)**36** (jimenezin)**37** (mucocin)**38** (pyranicin)**39** (pyragonicin)

Most information on the synthesis of AGEs is evident for the bis-THF AGEs (BT), followed by AGEs with a THP moiety (O), then the mono-THF AGEs (MT), and the linear AGEs (L) (see Fig. 7). Moreover, the methodologies described for the synthesis of the adjacent type (ABT) are about four times more numerous than

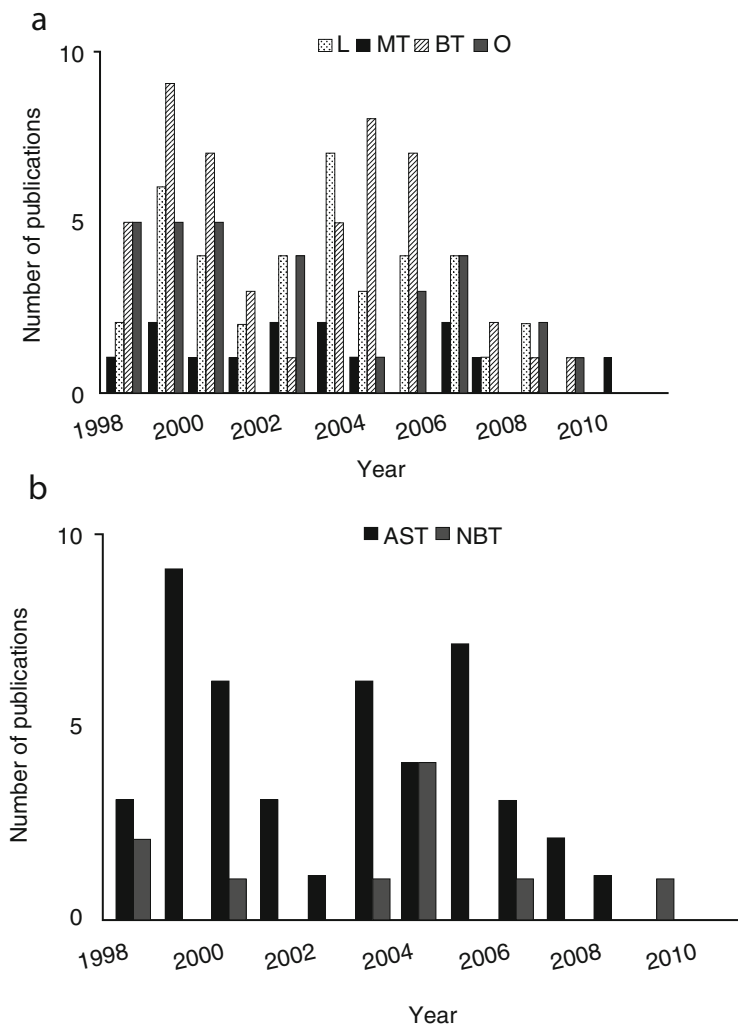


Fig. 7 Publications on AGEs divided into four major types from 1988 to 2010. (a) L linear AGEs, MT mono-THF ring of AGEs, BT bis-THF ring of AGEs, O other AGEs. (b) ABT adjacent bis-THF ring of AGEs, NBT nonadjacent bis-THF ring of AGEs

those on the non-adjacent type (NBT). Summarized below are some concepts of synthesis for AGEs presented according to the previously described classification method for these natural products.

5.1 Linear Annonaceous Acetogenins

Methods for the synthesis of three characteristic linear AGEs, including montecristin (**40**), muricatacin (**22**), and tonkinelin (**41**), have been proposed. In particular, 72% of the articles published on synthesis methods have had a special focus on muricatacin (**22**), see Chart 1.

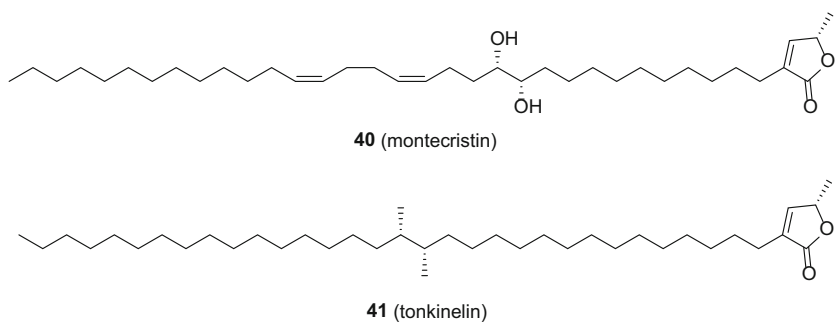
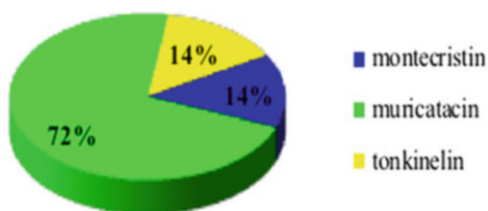


Chart 1 Analysis of linear and epoxy ACGs synthesis from 1998 to 2012



5.1.1 Montecristin

Montecristin (**40**) is a linear C_{32} -AGE with an α,β -unsaturated γ -lactone and a *syn*-form glycol moiety along with two *cis*-form $C=C$ bonds in its side chain. A rapid but effective synthesis methodology was developed by the Brückner group, which was also used to determine the stereostructure of montecristin (**40**). These investigators prepared (*S*)- and (*R*)-4-hydroxy-5-methyl-dihydrofuran-2(3*H*)-one (the lactone substructure) from a commercially available pentenoic ester under asymmetric dihydroxylation conditions and further performed an asymmetric dihydroxylation of an appropriate (*E*)-olefin to obtain an acetone iodide, which was conjugated to the lactone group while deprotecting this group simultaneously (see Table 7) [154].

Table 7 Long-chain AGE synthesis from 1998 to 2011

Compound name	Total synthesis	Synthesis method	Starting materials	Steps and yields	Other points	Ref.
5- <i>epi</i> -Montecristin and (–)-montecristin	First total synthesis	1. Asymmetric dihydroxylation 2. Nucleophile and electrophile	Pentenoic ester	5- <i>epi</i> -Montecristin (13 steps, 88%) and (–)-montecristin (13 steps, 83%)	(+)-Montecristin was established to have (11' <i>R</i> ,12' <i>R</i>) configuration.	[154]
(–)-(4 <i>R</i> ,5 <i>R</i>)-Muricatacin and (–)-(4 <i>R</i> ,5 <i>S</i>)- <i>epi</i> -muricatacin		1. New chiral Witting reagent: a β-keto-γ(δ)-hydroxy-δ-(<i>R</i>)- <i>p</i> -tolysulfinyl phosphonate 2. DIBAL-H reduction of β-hydroxy-γ-ketosulfoxides 3. Pummerer rearrangement 4. Swern oxidation	Ethyl oxalate and sulfoxide	(–)-(4 <i>R</i> ,5 <i>R</i>)-Muricatacin (13 steps, 27%) and (–)-(4 <i>R</i> ,5 <i>S</i>)- <i>epi</i> -muricatacin (13 steps, 2.5%)		[155]
(–)-(4 <i>R</i> ,5 <i>R</i>)-Muricatacin	Total synthesis	1. Sharpless epoxidation on (<i>Z</i>) or (<i>E</i>) allylic alcohol using (+)-DET or (–)-DET 2. A regio- and stereospecific ring-opening of a substituted vinyl epoxide under Lewis acid catalysis using catalytic amounts of BF ₃ ·Et ₂ O	Propargylic alcohol	11 Steps, 96%	1. The spectroscopic data (¹ H and ¹³ C NMR, IR, MS) and optical rotation were in close agreement with reported values. 2. Condensation of alcohol on vinyl epoxide using equal amounts of both units has not previously been reported in the literature.	[156]

(4 <i>R</i> ,5 <i>S</i>)- and (4 <i>S</i> ,5 <i>R</i>)-Muricatacins, and (4 <i>S</i> ,5 <i>R</i>)-aza-muricatacin, unnatural analogues		1. Sharpless asymmetric dihydroxylation 2. Grignard reaction 3. Johnson-Claisen rearrangement 4. Mitsunobu inversion or Weinreb amidation	Lauryl bromide	(4 <i>R</i> ,5 <i>R</i>)-Muricatacins (5 steps, 87%, >98% <i>ee</i>) (4 <i>R</i> ,5 <i>S</i>)-muricatacins (8 steps, 30%) (4 <i>S</i> ,5 <i>R</i>)-muricatacins (10 steps, 90%) (4 <i>S</i> ,5 <i>R</i>)-aza-muricatacins (11 steps, 84%)	[157]
(-)-Muricatacin	Total synthesis	Wittig olefination	D-Mannitol	8 Steps, 92–95%	[158]
(-)-(4 <i>R</i> ,5 <i>R</i>)-Muricatacin and the pheromone (<i>R</i>)-japonilure		Lithium salt catalyzed ring expansion of nonracemic oxaspiropentenones		6 Steps	[159]
(17 <i>S</i> ,18 <i>S</i>)-Tonkinelin and (17 <i>R</i> ,18 <i>R</i>)-Tonkinelin		1. Asymmetric dihydroxylation by the Sharpless procedure using AD mix α and spontaneous epoxidation afforded an epoxy alcohol 2. Grignard reaction 3. Sonogashira cross-coupling reaction	C ₁₆ H ₃₃ I	(17 <i>S</i> ,18 <i>S</i>)-Tonkinelin (9 steps, 56%)	[160, 161]

5.1.2 (–)-Muricatacin

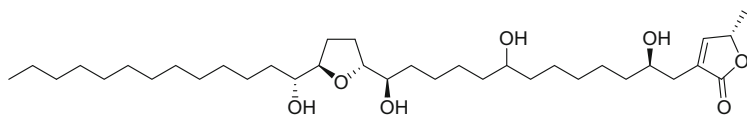
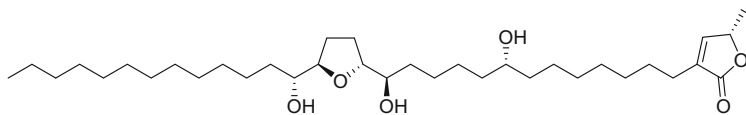
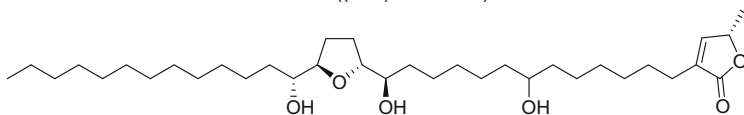
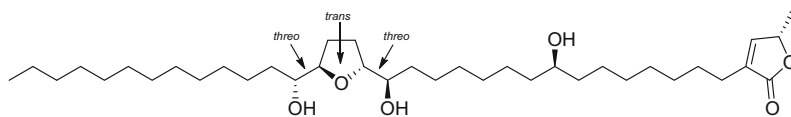
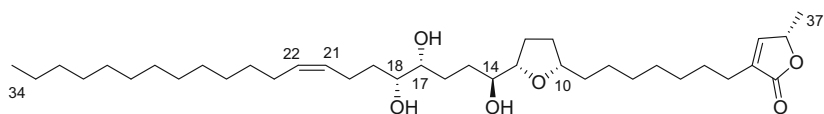
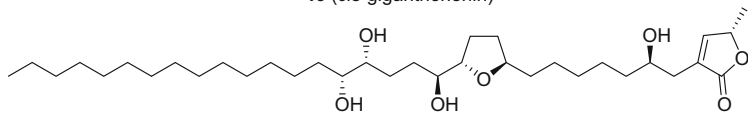
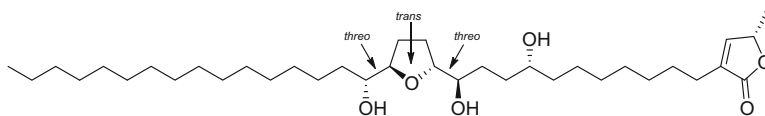
(–)-Muricatacin (**22**), an AGE with only one terminal γ -lactone unit and a long alkyl chain moiety, possesses a broad spectrum of biological activities. This particular AGE has greatly attracted many research groups to further explore its synthesis. Solladié et al. synthesized the *syn*- and *anti*-1,2-diol units of (–)-muricatacin by a highly stereoselective method, DIBAL-H reduction of β -hydroxy- γ -ketosulfoxides [155]. The Mioskowski group later produced a high yield of 96% of natural muricatacin (**22**) [156] through development of a new method, an epoxide ring-opening reaction under Lewis acid catalysis. In addition, Singh's group synthesized muricatacin (**22**) efficiently and highly stereoselectively using a 5-hydroxy-alkylbutan-4-olide obtained from D-mannitol [158]. The Konno group successfully prepared enantiomerically pure muricatacin (**22**) (87% yield, >98% *ee*) using the Sharpless asymmetric dihydroxylation method [157]. Moreover, Bernard et al. unexpectedly discovered a simple ring expansion procedure that led to the synthesis of **22**. The step involves the use of LiI to catalyze ring expansion of non-racemic oxaspiropentanes into cyclobutanones (see Table 7) [159].

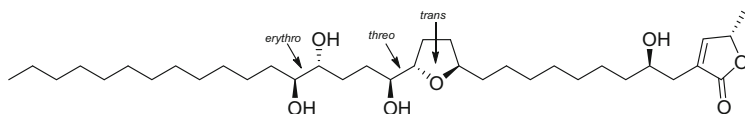
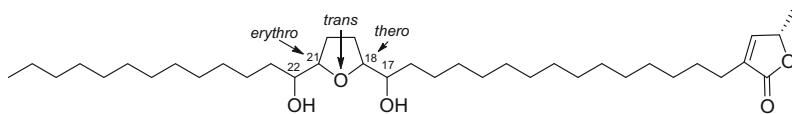
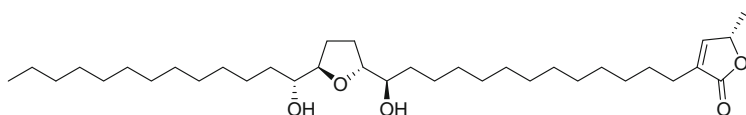
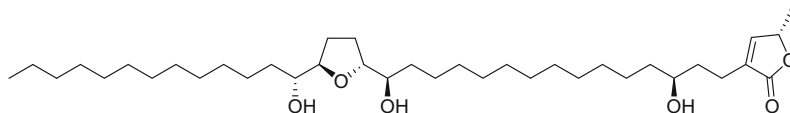
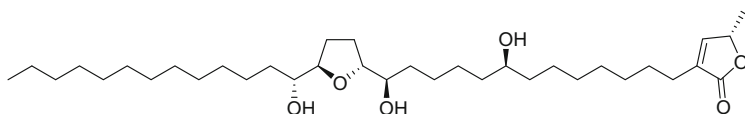
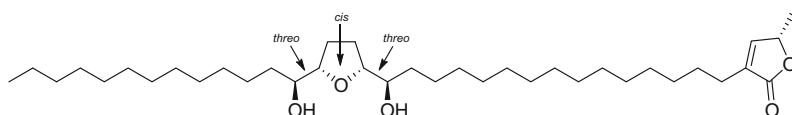
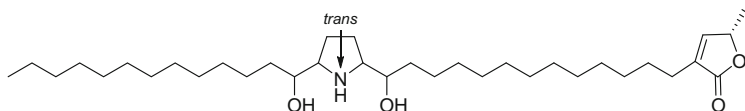
5.1.3 Tonkinelin

Tonkinelin (**41**) is a nonclassical linear C₃₇ AGE with the lactone ring in a (*S*)-configuration and with an undefined diol moiety [160]. In 2007, Makabe et al. first synthesized this compound using a Sonogashira cross-coupling reaction to link the dihydroxy and γ -lactone parts of the molecule together (see Table 7) [161].

5.2 Mono-THF Annonaceous Acetogenins

Mono-THF AGEs are one of the major types of AGEs, and have at least four stereogenic centers that have made the organic synthesis of these compounds challenging (Table 8). Several mono-THF AGEs, such as annonacin (**42**), corossolin (**43**), 4-deoxyannoreticuin (**44**), 4-deoxyannomontacin (**45**), *cis*-gigantrionenin (**46**), gigantetrocin A (**47**), (+)-longicin (**26**), longifolicin (**48**), mosin B (**49**), muricatetrocin C (**50**), murisolin (**25**), pseudoannonacin A (**51**), reticulatain (**52**), solamin (**53**), and tonkinecin (**54**) have been chosen as targets for total synthesis. Among them, solamin (**53**) (29%) was the most popular synthesis target (see Fig. 8).

**42** (annonacin)**43** ((10*R*)-corossolin)**44** (4-deoxyannoreticuin)**45** (4-deoxyannomontacin)**46** (*cis*-gigantrionenin)**47** (gigantetrocin A)**48** (longifolicin)

**50** (muricatetrocin C)**52** (reticulatain)**53** (solamin)**54** (tonkinecin)**55** ((10*S*)-corossolin)**56** (*cis*-reticulatain)**57a-57d** (aza-solamines)**57a:** erythro-trans-erythro**57b:** erythro-trans-threo**57c:** threo-trans-erythro**57d:** threo-trans-threo

In 2000, Wu et al. synthesized annoacin (**42**), a typical mono-THF AGE with seven chiral centers, via a Sharpless asymmetric dihydroxylation reaction method with the incorporation of three natural hydroxy acids, achieving a high yield of 85% [162, 163]. Wu et al. have also developed a strategy to couple the alkyne

Table 8 Mono-THF AGE synthesis from 1998 to 2011

Compound	Total synthesis	Synthesis method	Starting materials	Steps and yields	Other points	Ref.
Annonacin	First total synthesis	Sharpless AD reaction	L-Ascorbic acid; D-glucono-1,5-lactone and ethyl L-lactate	31 Steps, 85%	1. MOM protection. 2. R_f value and spectroscopic data are identical to those reported for the natural product.	[162]
Annonacin and tonkinecin	Total synthesis	1. Asymmetric dihydroxylation 2. Pd(O)-catalyzed coupling reaction with vinyl iodides 3. Introduction of the butenolide moiety by aldol condensation of protected S-lactal followed by cleavage of all MOM ethers	D-Glucono-1,5-lactone; D-xylose; (–)-(S)-ethyl lactate and L-ascorbic acid	Tonkinecin (18 steps, 86%) and annonacin (33 steps, 85%)	MOM protection.	[163]
(10 <i>R</i>)- and (10 <i>S</i>)-Corossolin	First total synthesis	1. Wittig reaction 2. Horner-Emmons reaction 3. Swern oxidation 4. Hunsdiecker reaction 5. Wilkinson reaction	D-Gluconolactone and azelic acid monoethyl ester	(10 <i>R</i>)-Corossolin (24 steps, 62%) and (10 <i>S</i>)-corossolin (24 steps, 86%)	1. Natural compound is (10 <i>R</i>)-corossolin. 2. Both compounds can cause suppression of the proliferation of the tumor cell; (<i>R</i>) > 18x (<i>S</i>) against B16BL6 cell line. 3. (10 <i>S</i>)-Corossolin was first synthesized. 4. TBS and MOM ether protection.	[164]

(continued)

Table 8 (continued)

Compound	Total synthesis	Synthesis method	Starting materials	Steps and yields	Other points	Ref.
(9 <i>R</i>)- and (9 <i>S</i>)-4-Deoxyanmoreticuin		Olefin cross-metathesis (CM) coupling reaction		(<i>R</i>)-4-Deoxyanmoreticuin (6 steps, 70–72%) and (<i>S</i>)-4-deoxyanmoreticuin (6 steps, 90%)	1. TBDPS ether protection. 2. Unfortunately, identification of one or the other epimeric structures with the natural product was not possible because of the closeness of the physical data for all three compounds. 3. Both C-9 epimeric analogues showed similar toxicity in the low molar range, against two human tumor cell lines PC-3 (prostate) and Jurkat (T-cell leukemia).	[165]
4-Deoxyanmontacin	First total synthesis	Sharpless asymmetric dihydroxylation and salen Co ^{III} -catalyzed hydrolytic kinetic resolution	D-Glucose and ethyl (<i>S</i>)-lactate	17 Steps, 88%	MOM ether protection.	[166]
<i>cis</i> -Gigantrionenin	First asymmetric total synthesis	1. An enzyme-catalyzed epoxide hydrolysis and an enzyme-triggered double cyclization 2. Sonogashira coupling with a γ -lactone segment	Sulfanyl acetic acid; 1,5-hexanediylne and pentynol	14 Steps		[167]

Gigantetrocin A	Total synthesis	1. Wittig reaction 2. Sharpless asymmetric dihydroxylation 3. Horner-Emmons reaction 4. Swern oxidation	<i>trans</i> -1,4-Dichloro-2-butene	19 Steps, 59%	MOM protection.	[168]
Gigantetrocin A	First total synthesis	1. Wittig reaction 2. Sharpless asymmetric dihydroxylation 3. Horner-Emmons reaction 4. Swern oxidation	<i>trans</i> -1,4-Dichloro-2-butene	19 Steps, 59%	MOM protection.	[169]
(+)-Longicin	First total synthesis	1. Grubbs RCM reaction 2. The butenolide subunit was constructed via an aldol reaction with a macrocyclic lactone precursor	D- and L-Glutamic acids	19 Steps, 62% [internal transac-tonization strategy (18 steps, 50%)]	These data were identical to the natural product on the basis of the reported physical constants.	[126]
Longifolicin	Total synthesis	1. Asymmetric dihydroxylation 2. Allenyl Pd hydrocarbonylation	Chiral long-chain α - and γ -OMOM allylic stannanes and (<i>E</i>)-ethyl 3-formyl-2-propenoate	29 Steps, 97%	TBS ether and MOM ether protection.	[170]
Mosin B and a diastereomer	First total synthesis	Asymmetric desymmetrization of the γ -symmetric diol and the Nozaki-Hiyama-Kishi reaction	A common intermediate, 4-cyclohexene-1,2-diol; 1; (<i>R</i>)-malic acid and (<i>S</i>)-propylene oxide	20 Steps, 72%	Natural compound type is 1a .	[171]

(continued)

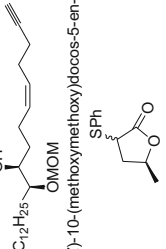
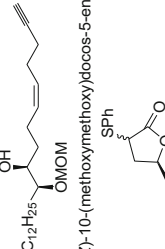
Table 8 (continued)

Compound	Total synthesis	Synthesis method	Starting materials	Steps and yields	Other points	Ref.
Mosin B and one of its diastereomers	Total synthesis	Asymmetric desymmetrization of the γ -symmetric diol and the Nozaki-Hiyama-Kishi reaction	4-Cyclohexene-1,2-diol; (<i>R</i>)-malic acid and (<i>S</i>)-propyleneoxide	Mosin B (20 steps, 72%) and one of its diastereomers (20 steps, 78%)	1. Natural type is 1a . 2. Diastereomer of mosin B (1b) exhibited a higher antiproliferative effect than Adriamycin and had a similar profile of growth inhibition as natural (1a) against the cancer cells used.	[172]
Muricatetrocin C	First total synthesis	1. Sonogashira coupling and chelated addition 2. Anomeric O–C rearrangement and HAD reaction	(<i>R,R</i>)-Dimethyltartrate, butane-1,4-diol and (<i>R</i>)-oxiran-2-yl methanol	22 Steps, 82%		[173]
Muricatetrocin C	First total synthesis	1. Sonogashira coupling and chelated addition 2. Anomeric O–C rearrangement and hetero-Diels-Alder (HAD) reaction	(<i>R,R</i>)-Dimethyltartrate, butane-1,4-diol and (<i>R</i>)-oxiran-2-yl methanol	22 Steps, 82%		[174]
Murisolin, natural 16,19- <i>cis</i> -murisolin and unnatural 16,19- <i>cis</i> -murisolin	Total synthesis	Asymmetric alkynylation of α -tetrahydrofuranic aldehyde with a diyne and Sonogashira coupling with a γ -lactone segment	1,6-Heptadiyne and α -oxaldehyde	Murisolin (4 steps, 91%), natural 16,19- <i>cis</i> -murisolin (11 steps, 85%), and unnatural 16,19- <i>cis</i> -murisolin (11 steps, 82%)	1. Three compounds showed strong inhibitory activity against lung cancer cells (DMS114). 2. Natural 16,19- <i>cis</i> -murisolin exhibited potent activity against stomach cancer cells.	[175]

Pseudo annonacin A	First total synthesis	Chiron approach	L-Glutamic acid; D-glutamic acid and L-lactic acid	36 Steps, 83%	1. Pseudo annonacin A (15 <i>R</i> ,16 <i>S</i> ,19 <i>S</i> ,20 <i>S</i>), annonacin A (15 <i>R</i> ,16 <i>R</i> ,19 <i>R</i> ,20 <i>S</i>). 2. The synthetic product (a mixture of epimers at C-10) had spectroscopic data identical to that of the natural product, but a different optical rotation.	[176]
(17 <i>R</i> ,18 <i>R</i> ,21 <i>R</i> ,22 <i>S</i>)- and (17 <i>S</i> ,18 <i>S</i> ,21- <i>S</i> ,22 <i>R</i>)-Reticulatain-1		Mitsunobu inversion and hydrolysis	Acrolein and lauryl magnesium bromide	(17 <i>R</i> ,18 <i>R</i> ,21 <i>R</i> ,22- <i>S</i>)-Reticulatain-1 (17 steps, 87%)	1. Comparison of the specific optical rotations of 1a and 1b did not allow for the strict determination of the absolute configuration. However, the bis-(<i>R</i>)-MTPA esters of 1a and 1b showed a clear difference in chemical shifts in the ¹ H NMR spectra. 2. Both compounds showed inhibitory activity against the bovine heart mitochondrial complex I.	[177]
Solamin	Total synthesis	Direct coupling between γ-lactone and mono-THF unit	D-Glutamic acid	19 steps, 97%	TBDPS ether and MOM protection.	[178]
(15 <i>R</i> ,16 <i>R</i> ,19 <i>S</i> ,20 <i>S</i>)- and (15 <i>S</i> ,16 <i>S</i> ,19 <i>R</i> ,20 <i>R</i>)- <i>cis</i> -Solamin	Concise total syntheses	Permanganate-promoted oxidative cyclization	Tridecanal and (S)-ethyl 4-hydroxypent-2-ynoate	<i>cis</i> -Solamin (13 steps, 94%)	1. No protecting groups. 2. Relative stereochemical relationship of the THF-diol portion is <i>threo</i> / <i>cis</i> / <i>threo</i> , but the absolute stereochemistry could not be defined.	[179]

(continued)

Table 8 (continued)

Compound	Total synthesis	Synthesis method	Starting materials	Steps and yields	Other points	Ref.
(15 <i>R</i> ,16 <i>R</i> ,19 <i>S</i> ,20 <i>S</i>)- and (15 <i>S</i> ,16 <i>S</i> ,19 <i>R</i> ,20 <i>R</i>)- <i>cis</i> -Solamin	Total synthesis	TBHP-VO(acac) ₂ diastereoselective epoxidation and cyclization	<p>1,8-Diiodooct-1-ene and</p>  <p>(9<i>S</i>,10<i>S</i>,<i>Z</i>)-10-(methoxymethoxy)docos-5-en-1-yn-9-ol</p> <p>(<i>S</i>)-5-methyl-3-(phenylthio)-dihydrofuran-2(3<i>H</i>)-one</p>	13 Steps, 60%	Natural <i>cis</i> -solamin is of configuration (15 <i>S</i> ,16 <i>S</i> ,19 <i>R</i> ,20 <i>R</i>) (1a).	[180]
(15 <i>R</i> ,16 <i>R</i> ,19 <i>S</i> ,20- <i>S</i> ,34 <i>S</i>)- and (15 <i>S</i> ,16 <i>S</i> ,19 <i>R</i> ,20- <i>R</i> ,34 <i>S</i>)- <i>cis</i> -Solamin	First total synthesis	VO(acac) ₂ -catalyzed diastereoselective epoxidation of (<i>Z</i>)-bis-homoallylic alcohol followed by spontaneous cyclization for the <i>cis</i> -THF ring formation.	<p>1,8-Diiodooct-1-ene and</p>  <p>(9<i>S</i>,10<i>S</i>,<i>Z</i>)-10-(methoxymethoxy)docos-5-en-1-yn-9-ol</p> <p>(<i>S</i>)-5-methyl-3-(phenylthio)-dihydrofuran-2(3<i>H</i>)-one</p>	(15 <i>R</i> ,16 <i>R</i> ,19 <i>S</i> ,20- <i>S</i> ,34 <i>S</i>)- <i>cis</i> -Solamin (13 steps, 60%)	1. Natural <i>cis</i> -solamin is of the configuration (15 <i>R</i> ,16 <i>R</i> ,19 <i>S</i> ,20 <i>S</i> ,34 <i>S</i>). 2. Both compounds showed inhibitory activity against the bovine heart mitochondrial complex I.	[181]
Solamin	Total synthesis	1. A ring-closing metathesis (RCM) reaction using a ruthenium imidazolylidene complex 2. Asymmetric epoxidation	Propargylic alcohol	24 Steps, 85%	The first application of RCM using the ruthenium catalyst for the total synthesis of solamin.	[182]

<i>cis</i> -Solamin A [(15 <i>R</i> ,16 <i>R</i> ,19 <i>S</i> ,20 <i>S</i> , 34 <i>S</i>)- <i>cis</i> -solamin]	Total synthesis	1. Olefin crossmetathesis between the tetrahy- drofuran moiety and γ -lactone moiety 2. An enzymatic kinetic transesteri- fication procedure was successfully applied to the synthe- sis of an optically pure γ -lactone moiety	(-)-Muricatacin	11 Steps, 95%	No protection/ deprotection steps.	[183]
<i>cis</i> -Solamin A, <i>cis</i> -solamin B, and reticulatacin	Total synthesis	1. Olefin crossmetathesis between the tetrahy- drofuran moiety and γ -lactone moiety 2. An enzymatic kinetic transesteri- fication procedure was successfully applied to the synthe- sis of an optically pure γ -lactone moiety	Muricatacin	<i>cis</i> -Solamin A (10 steps, 95%) and <i>cis</i> -solamin B (10 steps, 93%) and reticulatacin (9 steps, 91%)	1. No protection/ deprotection steps. 2. <i>cis</i> -Solamin A and <i>cis</i> - solamin B are of the (15 <i>R</i> ,16 <i>R</i> ,19 <i>S</i> ,20 <i>S</i> ,34 <i>S</i>) and <i>cis</i> -solamin of (15 <i>S</i> ,16 <i>S</i> ,19 <i>R</i> ,20 <i>R</i> ,34 <i>S</i>) configurations.	[184]
aza-Solamin isomers		Coupling with vinyl iodide segment and <i>trans</i> -pyrrolidine segment	2,5- <i>trans</i> -Bis(methoxycarbonyl)pyrrolidine; ethyl (5)-lactate and undecylenic acid	aza-Solamin (9 steps, 40%)	1. Solamin analogs active against several tumor cell lines were also observed. 2. Being first synthesized with a facile route.	[185]
Tonkinecin	First synthesis	Palladium-catalyzed cross-coupling reaction and Sharpless asymmetric dihydroxylation	D-Glucose; L-lactate; D-xylose	16 Steps, 81%	1. The physical data are the same as those of the natural one. 2. MOM protection.	[186]

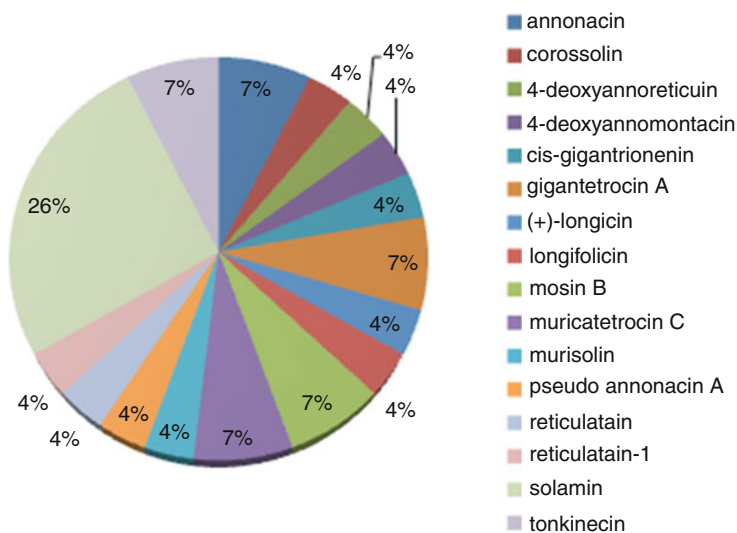


Fig. 8 Analysis of linear and epoxy AGEs synthesis from 1998 to 2011

intermediate and the terminal epoxide to produce (10*R*)-(43) and (10*S*)-corossolin (55) [164]. The comparison of the optical rotation, the ^{13}C NMR spectrum and the *in vitro* activity of the synthesized compound with the natural form allowed further postulation of the absolute configuration of the natural form at C-10 as (*R*).

Mootoo et al. employed an olefin cross metathesis method with THF and butenolide alkene to convergently synthesize the C-9 epimers of 4-deoxyannoreticuin (45) [165] since both stereoisomers exhibit similar cytotoxicity against prostate tumor and T-cell leukemia cells. However, the identification of the unassigned configuration at C-9 was unsuccessful owing to the similar physical data of the two synthetic products.

Orru et al. reported an asymmetric total synthesis of *cis*-gigantrionenin (46) by utilizing a rapid and efficient enzyme-catalyzed epoxide hydrolysis method and an enzyme-triggered double cyclization method for the construction of the THF ring and the alkyl chain with a double bond. In addition, the Sonogashira coupling method was employed to overcome a synthesis problem inherent from the linkage between the THF fragment and γ -lactone segment [167]. Various other methods were reported also for synthesizing gigantetrocin A (47), such as the Sharpless asymmetric dihydroxylation, the Horner-Emmons reaction, Swern oxidation, and the Wittig reaction [169].

Hanessian et al. used D- and L-glutamic acid as chiralons corresponding to two five-carbon segments, harboring stereogenic centers at C-4 and at C-17 of longicin (26) using the Grubbs RCM reaction as the “chain elongation” strategy, which underwent coupling and assembling of the complete aliphatic chain. The butenolide unit was subjected to an aldol reaction with a macrocyclic lactone precursor.

The synthetic product was identical to the natural product according to the reported physical constants and spectroscopic data obtained [126].

Marshall et al. designed a bidirectional synthesis strategy with minor modifications toward longifolicin (**48**), a C₃₅ mono-THF AGE with a *threo*/*trans*/*threo* configuration. The group successfully achieved a high yield. The allylic stannanes used in the experiment demonstrated the potential for converging mono-THF AGEs efficiently [170].

Tanaka et al. attempted to determine the absolute configuration of mosin B (**49**). Despite the ¹H and ¹³C NMR spectroscopic data at hand, Mosher ester methodology and X-ray analysis were not conclusive [171, 172]. An efficient asymmetric desymmetrization method of cyclic *meso*-1,2-diols using C₂-symmetric bis-sulfoxide synthesis has provided two possible candidates for determining the absolute configuration (see Fig. 9). The THF ring fragment was introduced stereoselectively by a stereodivergent synthesis starting from 4-cyclohexene-1,2-diol based on a desymmetrization strategy. The γ -lactone fragment was synthesized via coupling a triflate and a chiral α -sulfenyl γ -lactone. By plotting the difference between the chemical shifts of the ¹³C NMR spectroscopic data of natural mosin B (**49**) and both candidate structures, the THF moiety of mosin B (**49**) was even more closely matched to the **49a** configuration (see Fig. 10) [172].

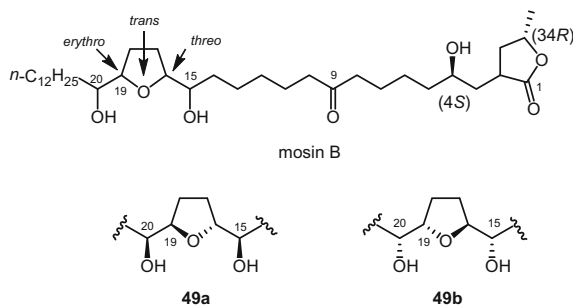


Fig. 9 Possible structures of mosin B (**49**)

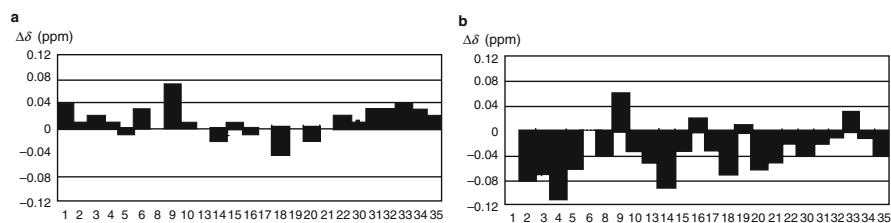
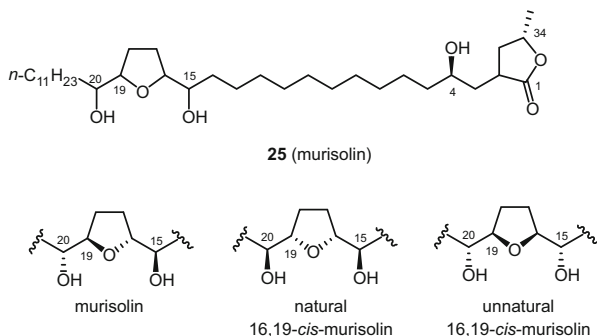


Fig. 10 Differences between the characteristic chemical shifts of the carbon atoms of natural mosin B (**49**) and those of each candidate **49a** (left) and **49b** (right) (75 MHz, CDCl₃). The x and y axes represent the carbon number and $\Delta\delta$ ($= \delta_{a,b} - \delta_{\text{mosin B}}$)

Fig. 11 Structures of analogues of murisolin (**25**)



Muricatetrocin C (**50**) exhibited excellent cytotoxic activities against three human cell lines, including PC-3, PACA-2, and A-549; thus it may be regarded as a potential antitumor agent. Ley et al. provided a stereoselective strategy with a linear sequence of 22 steps and achieved a 82% yield. They applied 2,3-butanediactal (BDA)-protected butane tetrol as a building block for the *anti*-1,2-diol units. The use of the anomeric oxygen to carbon rearrangement of alkynyl stannanes for the stereoselective construction of the 2,5-*trans*-disubstituted THF ring component, and finally the implementation of a hetero-Diels-Alder (HDA) reaction allowed construction of the hydroxy-butenolide terminus [173, 174].

Tanaka et al. provided a procedure for the total synthesis of murisolin (**25**): asymmetric alkynylation of α -tetrahydrofuranic aldehyde with a diyne and Sonogashira coupling method using a γ -lactone segment as key steps [175]. The approach achieved a good yield and high diastereoselectivity. Based on the interesting stereodivergent differences in biological activity of these compounds, unnatural murisolin with an opposite configuration from that of the natural ones was synthesized (**25a**). Using the COMPARE analysis, a tool to examine a pair of compounds in terms of their mean graphs, both compounds showed inhibitory activity against DMS114 lung cancer cells, and indicated that they share the same mode of action (see Fig. 11).

Hanessian et al. used three natural acids and took a chiron approach for the total synthesis of the *erythro,trans,threo*-(15*R*,16*S*,19*S*,20*S*)-diastereomer of annonacin A (**51a**) [176]. The inavailability of this compound made the comparison of the synthetic sample with the natural product difficult and only referred to the physical data, specifically the optical rotation (see Fig. 12). However, the undefined configuration of positions C-4, C-10, and C-34 of annonacin A (**51**) still remains a challenge.

Although Makabe et al. successfully synthesized two diastereomers of reticulatin-1 (**52**) using the Mitsunobu inversion method in 2004 (see Fig. 13) [177], the absolute configuration of natural reticulatin-1 (**52**) has not yet been resolved. However, the use of the Mosher ester method showed a clear difference between the two synthetic products in terms of their ^1H NMR chemical shifts. This demonstrated that if Mosher esters were to be prepared, the absolute configuration of naturally occurring reticulatin-1 (**52**) could be determined. Moreover, both synthetic epimers displayed very similar reactivity to bovine heart mitochondrial complex I.

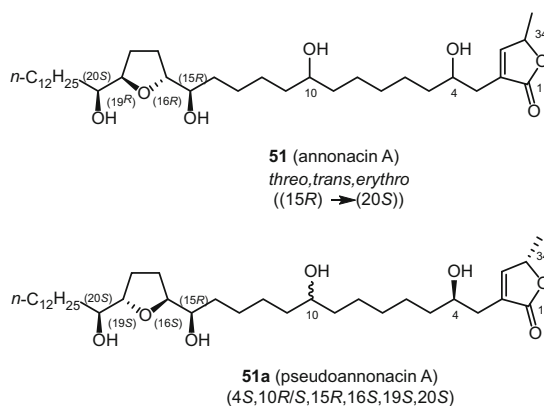


Fig. 12 Structures of analogues of annonacin A (**51** and **51a**)

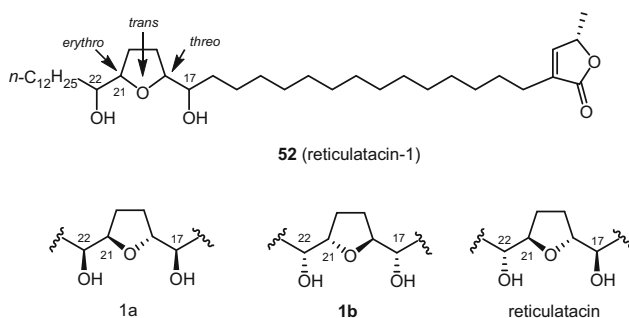


Fig. 13 Structures of analogues of reticulatin-1 (**52**)

Kitahara et al. completed the synthesis of solamin (**53**) via direct coupling between a long chain iodide and γ -lactone, which resulted in an excellent yield of 97% from D-glutamic acid in 19 steps [178]. Heck et al. further described a convergent total synthesis method for solamin (**53**) in 2004 [182]. The central THF core was obtained by means of a ring-closing metathesis (RCM) reaction using a ruthenium imidazolylidene complex. All the stereoisomers of solamin (**53**) could be obtained readily by employing this strategy using (*E*)- or (*Z*)-allyl alcohol and (+)- or (–)-DET for the asymmetric epoxidations. Brown et al. synthesized *cis*-solamin (**27**) and its diastereoisomer, 15,16-di-*epi*-solamin (also named as *cis*-solamin B, **27a**) with potassium permanganate under phase-transfer conditions with an excellent yield (94%) (see Fig. 14) [179]. No hydroxy group protection was required during this approach. The absolute configuration of *cis*-solamin (**27**) based only on the optical rotation data has remained uncertain. Makabe et al. reported the synthesis of two possible variants of *cis*-solamin (**27**) using VO(acac)₂-catalyzed diastereoselective epoxidation followed by cyclization of bis-homoallylic alcohol, in which the specific rotation ($[\alpha]_D^{21} +26^\circ \text{cm}^2/\text{g}$) of the product with the (15*R*,16*R*,19*S*,20*S*) configuration matched with the natural

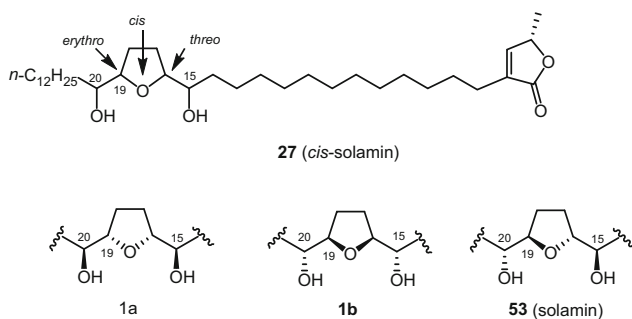


Fig. 14 Structures of solamin (**53**) and *cis*-solamin (**27**)

cis-solamin (**27**) ($[\alpha]_D +22^\circ\text{cm}^2/\text{g}$) [180, 181]. Konno et al. developed a synthesis strategy for *cis*-solamin (**27**) via the enzymatic kinetic transesterification method producing an optically pure γ -lactone moiety and the olefin cross-metathesis reaction constructing two distinct motifs between the tetrahydrofuran moiety and γ -lactone moiety [183]. This approach also favored the synthesis of solamin-type AGEs, like the isomer of *cis*-solamin (**27a**) and *cis*-reticulatacin (**56**) [184]. In addition, Shen et al. were able to couple vinyl iodide and *trans*-pyrrolidine segments to prepare the four possible relative configurations of aza-solamin (**57a–57d**), in which the THF core unit is replaced by pyrrolidine [185]. The stereochemistry proposed was supported by ^1H NMR spectroscopic analysis.

Tonkinecin (**54**) is a mono-THF AGE with an unusual C-5 carbinol center. Wu et al. reported the first total synthesis of tonkinecin (**54**) by an efficient and highly stereoselective palladium-catalyzed cross-coupling reaction [163, 186]. Four stereogenic centers were derived from three carbohydrates, D-glucose, L-lactate, and D-xylose, and two stereogenic centers were produced via Sharpless asymmetric dihydroxylation. The data of the synthetic product matched with those of natural product.

5.3 Adjacent Bis-THF Annonaceous Acetogenins

Evolution of synthesis methodology after 1998 has allowed higher yields of adjacent bis-THF AGEs (Fig. 15; Table 9).

In 1999, Mootoo et al. reported a two-directional strategy for synthesizing the bis-THF core of asimicin (**8**). This method relied on the iodoetherification reaction for desymmetrization of a C_2 -symmetric precursor in a relatively easy and inexpensive reaction through large-scale preparations [205].

Sinha et al. divided asimicin (**8**) into two major fragments, the butenolide moiety and the bis-THF component [187]. Three strategies were employed comprising: the naked carbon skeleton strategy, the convergent strategy, and the hybrid synthesis strategy to construct the bis-THF component. The advantages of the naked carbon skeleton strategy relied on the production of all stereogenic centers via specific

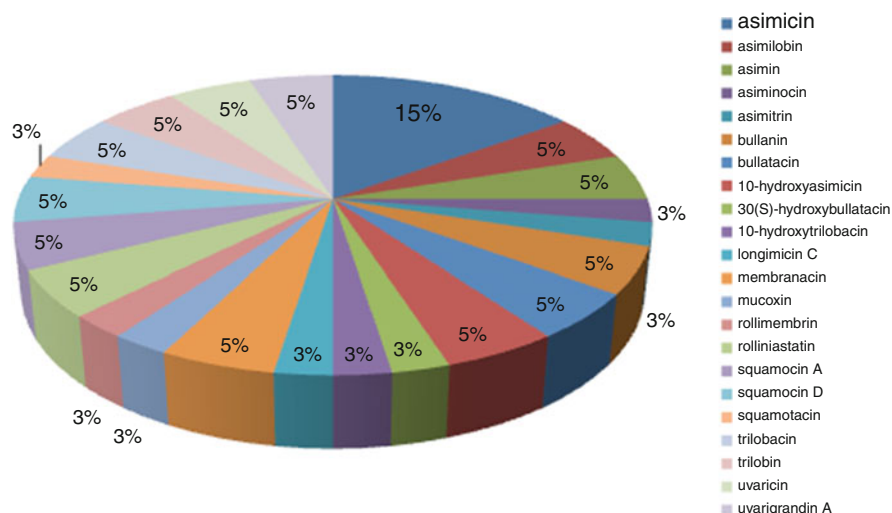


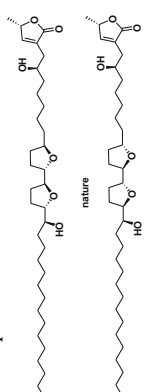
Fig. 15 Analysis of bis-THF AGEs (adjacent type) synthesis from 1998 to 2011

positioning of the oxygen functions onto the unsaturated, nonfunctionalized carbon skeleton. The convergent strategy can couple two series of diastereomeric fragments while taking into account their efficiency and versatility. The hybrid approach involves partially functionalized intermediates integrating the advantages of the linear and the convergent strategies that further improves synthesis efficiency and diversity. The butenolide fragment was prepared from deca-1,9-diene via an eight-step procedure that achieved a good yields. As a result, asimicin (**8**) was produced successfully with its spectroscopic data identical to those of the naturally occurring compound.

Roush et al. reported a double asymmetric [3 + 2]-annulation reaction toward the synthesis of asimicin (**8**), which used a bis-THF core with a *trans-threo-trans* configuration [188]. The key step with this approach is that the chiral (*E*)- γ -(dimethylphenylsilyl)allylborane reagent reacts with aldehydes to afford chiral, nonracemic *anti*- β -silyloxy allylsilanes with high enantioselectivity. In order to develop a highly stereoselective synthesis of asimicin (**8**), the coupling of a 2,5-*trans*-tetrahydrofuryl aldehyde with the chiral allylsilane was demonstrated (see Fig. 16). This approach provided the general synthesis of six diastereomeric bis-THF structures and the derived six diastereomeric desilylated bis-THF structures were related to the core sub-structure of several bis-THF type of AGEs.

Marshall et al. constructed the bis-THF core of asimicin (**8**) using a bidirectional outside-in hydroxy mesylate cascade cyclization pathway from 4-penten-1-ol, and then a subsequent Grubbs cross-metathesis reaction, which resulted in a good yield [136]. It is worth noting that almost 100% of the material was recovered from this study. They further synthesized three terminal hydroxy analogs **58a–58c** and a truncated analog **59** of asimicin (**8**) via the key Grubbs cross-metathesis reaction method [189]. Cytotoxicity testing of these analogs against HCT-116 human colon cancer cells revealed that the cytotoxic effect was not attributed to the terminal hydroxy group.

Table 9 Synthesis topics on adjacent bis-THF AGEs from 1998 to 2011

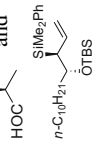
Compound name	Total synthesis	Synthesis method	Starting materials	Steps and yields	Other points	Ref.
Asimicin and bullatacin	Total synthesis	1. The naked carbon skeleton strategy 2. The convergent strategy 3. The hybrid synthetic strategy	Undecanal; deca-1,9-diene	Asimicin (8 steps, 81%) and bullatacin (9 steps, 79%)	MOM protection.	[187]
Asimicin and 12 dia-stereomeric bis-THF structures		Double stereodifferentiating [3 + 2]-annulation reactions of chiral allylsilanes with 2-tetrahydrofuryl aldehydes		Asimicin (7 steps, 80%)		[188]
Asimicin and a C ₃₂ analogue	Total synthesis	A bidirectional outside-in hydroxy mesylate cascade cyclization route and Grubbs cross-metathesis	4-Penten-1-ol and 2-(dec-9-enyl) oxirane	23 Steps, 80%	MOM protection.	[136]
Asimicin and its analogues		Grubbs cross-metathesis	10-Undecenal; 4-penten-1-ol	24 Steps, 80–91 %	The truncated asimicin analog of asimicin is some 20 times more active against HCT-116 colon cancer cells than its natural counterpart.	[189]
Asimilobin	First total synthesis	Wittig reaction	<i>trans</i> -1,4-Dichloro-2-butene	13 Steps, 79%	The natural product has the opposite absolute configuration on the bis-THF unit of that reported in the literature. 	[190]

(-)-Asimilobin and (+)-asimilobin	First total synthesis	Wittig reaction	<i>trans</i> -1,5,9-Decatriene and L-glutamic acid	(-)-Asimilobin (12 steps, 79%) and (+)-asimilobin (14 steps, 76%)	By virtue of these synthesis results, the absolute configuration of the bis(THF) unit in naturally occurring (+)-asimilobin should be corrected.	[191]
(10 <i>R</i>)-Asimin and (10 <i>S</i>)-asimin	Total synthesis	1. The addition of an enantioenriched γ -OMOM allylic indium reagent 2. The addition of a dialkyl zinc reagent 3. Aldol condensation	6-(Benzyloxy)hex-1-en-3-ol	(10 <i>R</i>)-Asimin (17 steps, 90%) and (10 <i>S</i>)-asimin (17 steps, 74%)	1. The natural compound is (10 <i>R</i>)-asimin. 2. MOM protection.	[192]
Asiminocin, asimicin, asimin, and bullanin		1. Additions of enantiopure allylic indium or tin reagents 2. Sonogashira coupling		Asiminocin (17 steps, 66%), asimicin (17 steps, 57%), asimin (17 steps, 57%), and bullanin (11 steps, 82%)	1. <i>IC</i> ₅₀ values have not previously been determined for these annonaceous acetogenins. 2. The <i>IC</i> ₅₀ activities were ca. 10 ⁻³ μ M for asimicin and asimin but only 0.1–1 μ M for bullanin and asiminocin. 3. These acetogenins have been reported to exhibit inhibitory activities of ~10 ⁻¹² μ g/cm ³ (<i>IC</i> ₅₀) against the HT-29 human colon cancer cell line.	[192]
Asimitrin (C-10-C-34 fragment)	First stereoselective synthesis	Stereoselective intramolecular oxymercuration and chelation-controlled Grignard reactions	1,2:5,6-di- <i>O</i> -Isopropylidene- α -D-glucofuranose	17 Steps, 76%		[193]

(continued)

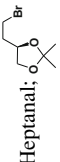
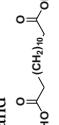


Table 9 (continued)



Compound name	Total synthesis	Synthesis method	Starting materials	Steps and yields	Other points	Ref.
(+)-(3 <i>OS</i>)-Bullainin	Total synthesis	Sharpless asymmetric dihydroxylation (AD) and Se_2' additions	(<i>E</i>)-Methyl 8-(benzyloxy)oct-4-enoate and <i>tert</i> -butyldimethyl (4-(tributylstannyl)but-3-ynyl)oxy)silane	25 Steps, 100%	The optical reaction of (3 <i>OS</i>)-bullainin, $[\alpha]_D^{24} + 24^\circ \text{cm}^2/\text{g}$, is in close agreement with the reported value for the mixture, $[\alpha]_D^{28} + 28^\circ \text{cm}^2/\text{g}$.	[194]
(+)-Bullatacin	Total synthesis	Diastereoselective [3+2]-annulation of the highly enantiomerically enriched allylsilane and racemic and aldehyde	α -Benzyloxy acetaldehyde; (<i>E</i>)-dimethyl(phenyl) (3-(tributylstannyl)prop-1-enyl)silane and decanal	11 Steps, 60%		[195]
10-Hydroxyasimicin	First total synthesis	1. Critical ring-closing metathesis (RCM) step and desymmetrization 2. Hetero-Diels-Alder (HDA) reaction	(<i>S,S</i>)-Dimethyl-tartrate and butane-1,4-diol	25 Steps, 68%	MOM protection.	[133]
(3 <i>OS</i>)-Hydroxybullatacin, uvarigrandin A and (5 <i>R</i>)-uvarigrandin A (narumicin I?)	Total synthesis	1. Additions of chiral α -oxygenated allylic stannane and indium reagents 2. Core ring closure reaction 3. Sonogashira coupling	(<i>S</i>)- or (<i>R</i>)-Malic acid	(3 <i>OS</i>)-Hydroxybullatacin (3 steps, 74%), uvarigrandin A (13 steps, 86%) and 5(<i>R</i>)-uvarigrandin A (3 steps, 57%)	Spectroscopic properties of synthetic (3 <i>OS</i>)-hydroxybullatacin and uvarigrandin A, as well as their Mosher ester derivatives, were in close agreement to the reported values of the natural substances. The synthetic (5 <i>R</i>)-uvarigrandin A is possibly identical to narumicin I, but subtle differences in the reported NMR spectra prevented an unambiguous assessment of this point.	[196]

(19 <i>R</i> ,20 <i>S</i>)-10-Hydroxytrilobacin, (19 <i>S</i> ,20 <i>S</i>)-4,10-dihydroxysquamocin N, (19 <i>R</i> ,20 <i>R</i>)-10-hydroxyasimicin and (19 <i>S</i> ,20 <i>R</i>)-an unnatural acetogenin		Stereodivergent [3 + 2] annulation reaction of tetrahydrofuran carboxaldehyde and allylsilane	Methyl-4-pentenoate; methyl adipoyl chloride;  and $n\text{-C}_{10}\text{H}_{21}\text{SiMe}_2\text{Ph}$	22 Steps, 70–87% (70–87% \geq 98% <i>ee</i>)	[197]
Longimicin C	First total synthesis	1. An iterative acetylene–epoxide coupling strategy 2. Sharpless dihydroxylations and intramolecular Williamson etherifications 3. Regioselective epoxide-openings	D-Mannitol	22 Steps, 51%	[198]
Membranacin	Total synthesis	Transition metal-oxo and metal-peroxy-mediated oxidative cyclizations	Ethyl acetoacetate and 1,4-dibromobut-2-ene	17 Steps, 78%	[199]
Mucoxin	First total synthesis	Thiophenyl-directed epoxydol cyclization, and a one-pot 1,2- <i>n</i> -triol cyclization strategy	3-Butynol	32 Steps, 80%	[140]

(continued)

Table 9 (continued)

Compound name	Total synthesis	Synthesis method	Starting materials	Steps and yields	Other points	Ref.
Rolliniastatin (bis-THF core)		Iodoetherification (modular synthesis)	Tri- <i>O</i> -acetyl-D-glucal and <i>t</i> -butanol or trifluoroethanol	19 Steps, 68%		[200]
Rolliniastatin 1, rollimembrin, and membranacin		A radical cyclization of β -alkoxyvinyl Sulfoxide-Pummerer rearrangement-allylation protocol	Butane-1,4-diol; D-malic acid and (<i>R</i>)-glycidyl tosylate or (<i>R</i>)-epichlorohydrin	Rolliniastatin 1 (29 steps, Rollimembrin (29 steps, 66%), and membranacin (25 steps, 74%)		[130]
Squamocin A and squamocin D	Total synthesis	Key reactions are additions of organomagnesium compounds to bi-THF aldehydes	Heptanal;  and 	Squamocin A (25 steps, 82%) and squamocin D (25 steps, 79%)		[201]
Squamocin A and squamocin D	Total synthesis	1. Multiple Williamson reaction 2. Addition of organomagnesium compounds to aldehyde functions	 and 	Squamocin A (23 steps, 33%) and squamocin D (23 steps, 39%)		[202]
Squamotacin	First total synthesis	Sharpless asymmetric dihydroxylation (AD) and asymmetric epoxidation (AE) reaction	(+)-Muricatacin	27 Steps, 48%	MOM protection.	[203]

Trilobacin and 36 analogues		Rhenium(VII) oxides mediated mono- or bis-oxidative cyclization, Shi mono- or bis-asymmetric epoxidation, Sharpless asymmetric dihydroxylation, Williamson's type etherification, and Mitsunobu inversion	8,9:12,13-(<i>E,E</i> and <i>Z,E</i>)-16-Benzyloxy-5-hydroxy-hexadeca-1,4-olide	43–92% (19,23-bis- <i>epi</i> -Trilobacin (78%) and 16,19-bis-trilobacin were (80%))	Using the nonsymmetrical bis-THF lactones, syntheses of two non-natural acetogenins (19,23-bis- <i>epi</i> -trilobacin and 16,19-bis- <i>epi</i> -trilobacin) were achieved.	[204]
Trilobacin and asimicin (bis-THF core)		A two-directional strategy based on the haloetherification reaction of a bis-5,6- <i>O</i> -isopropylidene alkene	Cyclooctadiene	Trilobacin (bis-THF core) (12 steps, 69%) and asimicin (bis-THF core) (14 steps, 70%)		[205]
(+)-Trilobin	Total synthesis	Carbon-carbon bond-forming steps		17 Steps, 85%		[206]
(+)-Trilobin	First total synthesis	Sharpless asymmetric dihydroxylation (AD) and asymmetric epoxidation (AE) reaction		22 Steps, 81%	MOM protection.	[207]

(continued)

Table 9 (continued)

Compound name	Total synthesis	Synthesis method	Starting materials	Steps and yields	Other points	Ref.
Uvaricin		1. Palladium-mediated, ligand-controlled double cyclization 2. The C_2 -symmetric diene produced was desymmetrized via Sharpless asymmetric dihydroxylation	D-Tartrate		Using chiral DPPBA ligands.	[208]
(+)-Uvaricin	First total synthesis	Sharpless asymmetric dihydroxylation (AD) and Williamson type etherification reaction	Ethyl pentadec-4-enoate and non-8-yn-1-ol	18 Steps, 32%		[209]

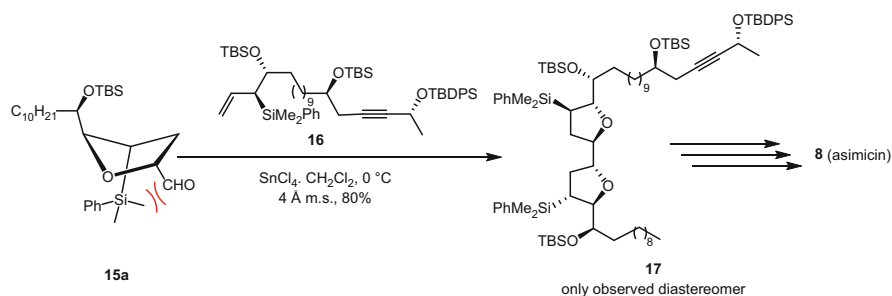
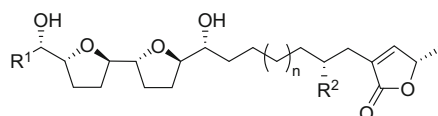


Fig. 16 [3 + 2]-Annulation reactions of chiral allylsilanes and chiral aldehydes to synthesize asimicin (**8**) and its analogues



16 $\text{R}^1 = \text{CH}_3(\text{CH}_2)_9$, $\text{R}^2 = \text{OH}$, $n = 7$

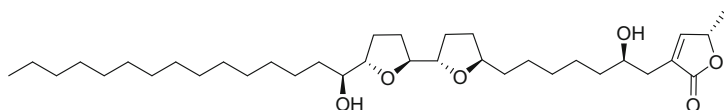
58a $\text{R}^1 = \text{HO}(\text{CH}_2)_6$, $\text{R}^2 = \text{OH}$, $n = 7$

58b $\text{R}^1 = \text{HO}(\text{CH}_2)_{11}$, $\text{R}^2 = \text{OH}$, $n = 7$

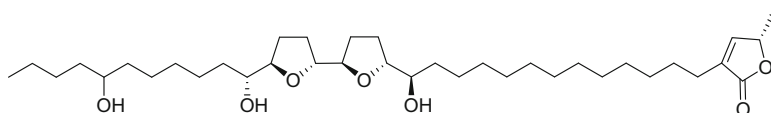
58c $\text{R}^1 = \text{HO}(\text{CH}_2)_{11}$, $\text{R}^2 = \text{H}$, $n = 6$

59 $\text{R}^1 = \text{CH}_3(\text{CH}_2)_7$, $\text{R}^2 = \text{OH}$, $n = 7$

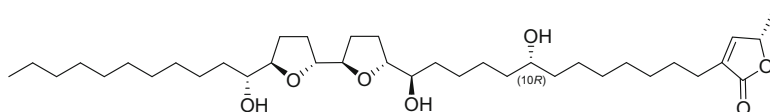
three terminal hydroxy analogs **58a-58c** and a truncated analog **59** of asimicin (**8**)



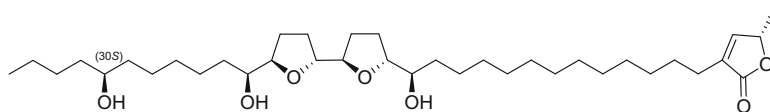
60 (asimilobin)



61 (asiminocin)



62 (asimin)



63 (bullandin)

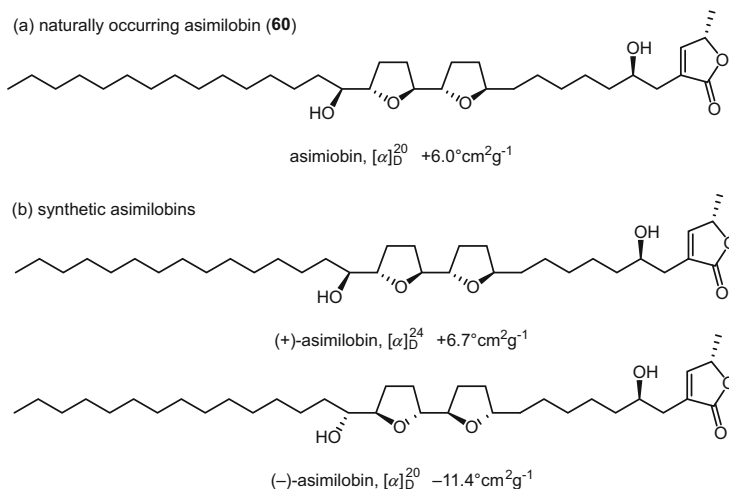


Fig. 17 Structure of asimilobin (**60**)

To investigate the structure of asimilobin (**60**), a bullatacin-type of AGE, Wang et al. published a short and convergent route to synthesize (+)- and (–)-asimilobins via a Wittig reaction [190, 191]. With this approach, the corrected absolute configuration of naturally occurring asimilobin (**60**) was clearly indicated by the optical rotation. Natural asimilobin (**60**), with an positive optical rotation value of $[\alpha]_D +6.0^\circ\text{cm}^2/\text{g}$, compares with (+)-asimilobin ($[\alpha]_D +6.7^\circ\text{cm}^2/\text{g}$), but not (–)-asimilobin ($[\alpha]_D -11.4^\circ\text{cm}^2/\text{g}$) (see Fig. 17).

Marshall et al. developed a modular synthesis for initial synthetis targets, such as asiminocin (**61**), asimin (**62**), asimicin (**8**), and bullanin (**63**) [210]. This modular synthesis focused on the effects of two pairs of allylic stannanes from parts of these AGEs, namely, their aliphatic termini and the spacer groups. The two parts were attached to the hydrofuran core precursor via allylation and cyclization methods to give bis-THF rings. Then, a Sonogashira coupling method was used to connect the butenolide termini to the bis-THF rings to result in a completed synthesis target of AGEs.

Marshall et al. also reported a study on the total synthesis of asimin (**62**) using an enantioenriched γ -OMOM allylic indium reagent, a dialkyl zinc reagent and aldol condensation, in which 12 chiral centers were constructed precisely via 17 steps along with a good overall yield [192]. Interestingly, the spectroscopic data of synthetic (10*R*)-hydroxyasimin are similar to those of natural asimin (**62**) (see Fig. 18). In addition, Marshall et al. described a convenient route to synthesize (30*S*)-bullanin (**63**). Its optical rotation of $[\alpha]_D +24^\circ\text{cm}^2/\text{g}$ is in close agreement with the natural product, $[\alpha]_D +28^\circ\text{cm}^2/\text{g}$. With this approach, a Sharpless asymmetric dihydroxylation and SE_2' additions of oxygenated nonracemic allylic

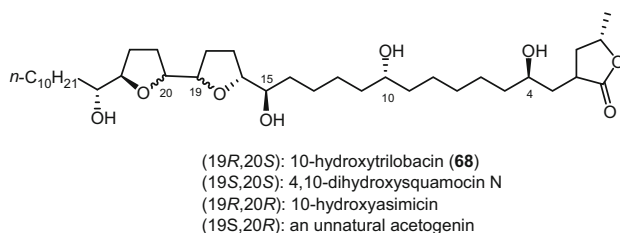


Fig. 18 Structures of stereoisomers of 10-hydroxytrilobacin (**68**)

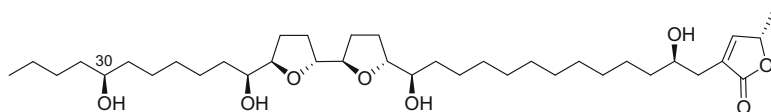
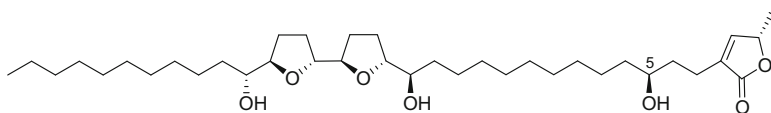
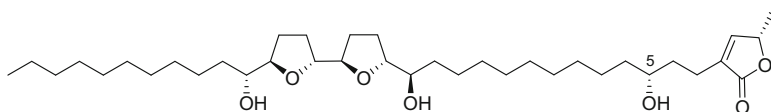
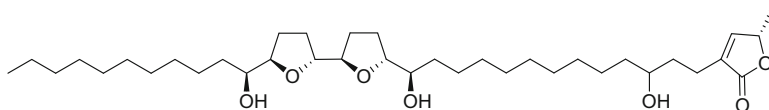
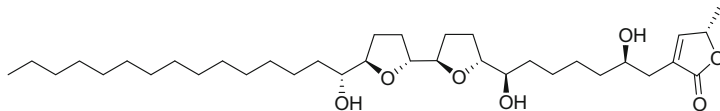
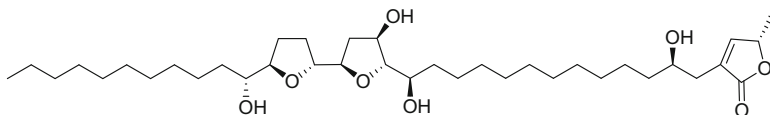
stannane and indium reagents to γ -oxygenated aldehydes were employed via a 25-step procedure to construct the stereocenters of the THF segment [194]. According to the literature, this approach resulted in a 100% yield of the synthetic sample [194].

Roush et al. completed the total synthesis of bullatacin (**7**) through sequential chelate-controlled [3 + 2]-annulation reactions. The highly enantiomerically enriched allylsilane and racemic aldehyde played a central role in the kinetic resolution obtained [195].

Ley et al. proposed a template approach to the synthesis of 10-hydroxyasimicin (**30**). The bis-THF fragment was prepared via a ring closing metathesis (RCM) reaction from the material, (*S,S*)-dimethyltartrate, which was found easy to desymmetrize for further chain extension [133]. The butenolide unit was prepared from butane-1,4-diol under a HDA reaction with a good yield. Then, selective hydrogenation and deprotection produced the target product.

Marshall et al. expedited a previously described four-component modular synthesis on the C-4,C-30-dihydroxylated and C-5-hydroxylated bis-THF units of AGEs [196]. In this work, AGEs such as (30*S*)-hydroxybullatacin (**64**), uvarigrandin A (**65**), and (5*R*)-uvarigrandin A (**66**) were successfully synthesized to confirm their structures. The main features of this method were the addition of chiral α -oxygenated allylic stannane and indium reagents to the acyclic core aldehyde precursor, followed by a THF ring closing reaction and Sonogashira coupling attaching the butenolide subunit. Among the products the synthesized (30*S*)-hydroxybullatacin (**64**) and uvarigrandin A (**65**) had physical properties identical to the literature values of the natural compounds [211, 212]. However, the data of synthesized (5*R*)-uvarigrandin A (**66**) were not identical to those of the naturally occurring narumicin I (**67**) as evidenced by the Mosher ester method [31].

A convergent and highly stereoselective route for the synthesis of 10-hydroxytrilobacin (**68**) and its three diastereomers was published by Roush et al. (see Fig. 18) [197]. In this work, a [3 + 2]-annulation reaction with simple modification from the same precursors was demonstrated as a potential method for the syntheses of these AGEs.

**64** ((30*S*)-hydroxybullatacin)**65** (uvarigrandin A)**66** ((5*R*)-uvarigrandin A)**67** ((5*R*or *S*,24*R*)-narumicin I)**69** (longimicin C)**70** (asimitrin)

Yao et al. reported for the first time the total synthesis of longimicin C (**69**) in 2005 [198]. The C_2 -symmetrical bis-THF segment of **69** was prepared via a Sharpless dihydroxylation procedure and intramolecular Williamson etherification for the incorporation of the stereocenters. An iterative acetylene–epoxide coupling strategy was used subsequently to assemble all fragments allowing the elaboration of the target compound.

Brown et al. completed the synthesis of membranacin (**31**) using metal-oxo- and metal-peroxy-mediated oxidative cyclizations as the key steps in a 17-step procedure. They achieved a good overall yield. The required starting material, triene, was prepared prior to the introduction of the (2*S*)-2,10-camphorsultam auxiliary [199].

Mucosin (**33**) was obtained as the first AGE with a hydroxy group substituted on the bis-THF rings [139]. In 2006, Borhan et al. studied the synthesis of the proposed mucosin (**33**) structure using a neighboring-group-directed regioselective cyclization approach, in which a methylene-interrupted epoxydiol and the one-pot 1,2,-*n*-triol cyclization were employed for constructing this AGE [140]. When the synthetic product was compared to the naturally occurring compound by ^1H NMR spectroscopy, differences (>0.1 ppm) in the chemical shifts of the bis-THF (C-8–C-17) region of the molecule were evident. To confirm the exact configuration of mucosin (**33**), exciton coupled circular dichroism (ECD) spectroscopy, and a 1D-NOESY NMR measurement were employed to reveal that the stereochemical discrepancies are due to a stereochemical misassignment of the natural mucosin (**33**) (see Fig. 19). Mohapatra et al. synthesized asimitrin (**70**) using the commercially available carbohydrate, 1,2:5,6-di-*O*-isopropylidene- α -D-glucofuranose, as the starting material. This was further elaborated with respect to the adjacent *trans*-bis-THF subunit via stereoselective intramolecular oxymercuration and chelation-controlled Grignard reactions [193]. The strategy was based on a retrosynthesis reaction, in which the butenolide moiety was coupled with the bis-THF fragment.

Mootoo et al. reported the synthesis of the bis-THF core of rolliniastatin (**28**) from pyranoside precursors (see Fig. 20) [200]. The C-6 allylated 2,3-dideoxypyranoside precursors were prepared via Ferrier reaction of tri-*O*-acetyl-D-glucal and *t*-butanol or

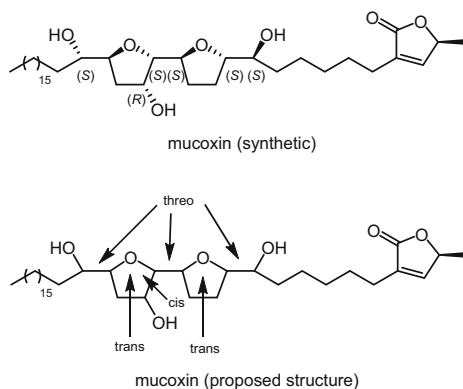


Fig. 19 Structures of synthetic mucosin and proposed mucosin (**33**)

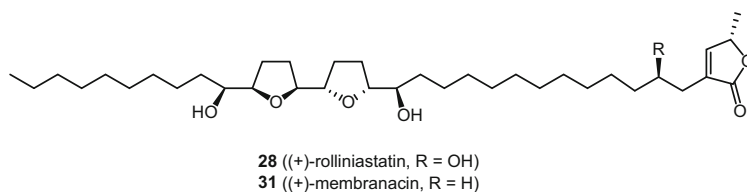


Fig. 20 Structures of AGEs with the bis-THF core as that of rolliniastatin (**28**)

trifluoroethanol. Iodoetherification reaction of the precursors was employed further to obtain a highly functionalized and selective *cis*-2,5-disubstituted THF, allowing a 68% yield of rolliniastatin (**28**) to be obtained.

Lee et al. synthesized under stereocontrol rolliniastatin (**28**), rollimembrin (**29**), and membranacin (**31**) [130]. A radical cyclization of β -alkoxyvinyl sulfoxide-Pummerer rearrangement-allylation methodology was developed to demonstrate the synthesis of the compound with a *threo,cis,threo,cis,erythro*-bis-oxolane moiety flanked by dihydroxy groups. The two major segments were then coupled by allylation-olefin cross metathesis. This approach enables an efficient and selective production of the bis-THF type of AGEs.

5.4 Non-adjacent Bis-THF Annonaceous Acetogenins

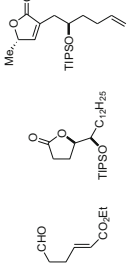
Methods of chemical synthesis for non-adjacent bis-THF structures are not yet well developed (Table 10). Since 1998, six naturally occurring structures have been investigated by total synthesis in detail, including bullatanocin (squamosstatin C) (**71**), (+)-4-deoxygigantecin (**72**), (+)-14-deoxy-9-oxygigantecin (**73**), (+)-gigantecin (**74**), squamosstatin-D (**75**), and (+)-sylvaticin (**76**) (see Fig. 21).

Bullatanocin (squamosstatin C) (**71**) is a typical example of a non-adjacent 2,5-*trans*-disubstituted THF. Mootoo et al. described a preparation of the bis-THF element of this AGE using the construction of THF-allylic alcohol moieties (see Fig. 22), which underwent iodoetherification of two 1,2-*O*-isopropylidene-5-alkene precursors that emerged from two relatively simple mono-THF structures [213, 214]. This approach showed enantiodivergence and resulted in a good yield.

The potent antitumor agent AGE, (+)-gigantecin (**74**), has remained a big challenge to investigators because of the unclear configuration of the THF moieties (see Fig. 23). Crimmins et al. chose an enantioselective methodology utilizing a modified asymmetric aldol reaction with chlorotitanium enolates of oxazolidinone glycolates to synthesize three key subunits of this molecule, namely, the butenolide, the C-9–C-16 fragment, and the C-17–C-34 fragment. These were synthesized individually using different starting materials (see Fig. 24a) [216]. The fragments were assembled to give (+)-gigantecin (**74**) as the final product achieving a 71% yield. Furthermore, Hoye et al. reported a more convenient one-pot reaction to synthesize gigantecin (**74**) by coupling three component olefin metatheses via a 13-step protocol, resulting in an 87% yield (see Fig. 24b) [144]. This method was also employed reversely to construct 14-deoxy-9-oxygigantecin (**73**), a constitutional isomer of gigantecin (**74**).

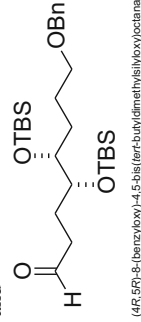
(+)-4-Deoxygigantecin (**72**) possesses a similar structure to gigantecin (**74**) (see Fig. 23). Makabe et al. used a convergent route to determine the absolute configuration of (+)-4-deoxygigantecin (**72**) (see Fig. 24c) [215], in which the synthesis of (+)-4-deoxygigantecin (**72**) from (–)-muricatacin (**22**) and (–)-(*S*)-ethyl lactate had been reported previously [220]. The optical rotation value of the synthetic

Table 10 Synthesis topics on non-adjacent bis-THF AGEs from 1998 to 2011

Compound name	Total synthesis	Synthesis method	Starting materials	Steps and yields	Other points	Ref.
Bullatanocin (squamosatin C) [213]		Olefin cross-metathesis as the segment coupling (The plan centers on the olefin cross-metathesis of THF allylic alcohol two derivatives as the key segment coupling step and the assembly of two derivatives through the iodoetherification of 1,2- <i>O</i> -isopropylidene-5-alkene precursors)	Ethyl (<i>E</i>)-4,6-heptadienoate	24 Steps, 95%		[213]
Bullatanocin (squamosatin C)	First total synthesis	Olefin cross-metathesis and Wittig olefination as the segment-coupling reactions.	Ethyl (<i>E</i>)-4,6-heptadienoate	13 Steps, 71%	The synthesis confirms the structure of the natural product.	[214]
(+)-4-Deoxy-gigantecin	Total synthesis	Retrosynthetic synthesis with Pd(0)-catalyzed cross coupling reaction	(-)-Muricatacin and (<i>S</i>)-(-)-ethyl lactate	30 Steps, 95%	1. The synthesis confirms the structure of the natural product. 2. MOM protection.	[215]
(+)-Gigantecin	First total synthesis	The synthesis exploits a modified asymmetric aldol protocol using chlorotitanium enolates of oxazolidinone glycolates.	Commercially available benzyl glycidyl ether	19 Steps, 71%		[216]
(+)-Gigantecin or (+)-14-deoxy-9-oxygigantecin	Total synthesis	1. A three-component ring-closing/cross-metathesis sequence that differs only in the ordering of the RCM vs. CM events 2. Another notable aspect		(+)-Gigantecin (13 steps, 87%) or (+)-14-deoxy-9-oxygigantecin (14 steps, 48%)		[144]

(continued)

Table 10 (continued)

Compound name	Total synthesis	Synthesis method	Starting materials	Steps and yields	Other points	Ref.
Squamosstatin-D	Total synthesis	is the use of in situ epoxide-closing and -opening of iodohydrins with dimethylsulfonium methyliide to provide inverted allylic alcohols 1. Sharpless asymmetric dihydroxylation (C-19/C-20) 2. BF_3 -Promoted addition of a γ -alkoxy allylic stannane (C-23/C-24) 3. Addition of a γ -alkoxy allylic indium chloride C-15/C-16 4. Addition of an organozinc reagent catalyzed by a chiral titanium triflic amide C-12	(S)-Lactate; ethyl undec-10-enoate and  (4R,5R)-5-(benzoyloxy)-4,5-bis((tert-butyldimethylsilyloxy)octanal	14 Steps, 97% (>90% ee)		[217]
(+)- <i>cis</i> -Sylvaticin and (+)-sylvaticin	First total synthesis	1. Double oxidative cyclization of a protected tetraol onto a diene unit that forms two rings in one reaction 2. The <i>trans</i> -THF ring of sylvaticin was prepared by utilizing a one-pot hydride shift/intramolecular oxo-carbenium ion reduction protocol	(<i>E,E</i>)-Tetradecatetraene and (<i>E,E,E</i>)-cyclododecatriene	(+)- <i>cis</i> -Sylvaticin (13 steps, 87%) and (+)-sylvaticin (19 steps, 76%)	A similar sequence on the C-4,36 bis-epimer of sylvaticin (for which the NMR data, but not specific rotation data, matched the literature) gave a synthetic sample that also had a poor match of its di-(<i>R</i>) and di-(<i>S</i>)-Mosher esters.	[218]

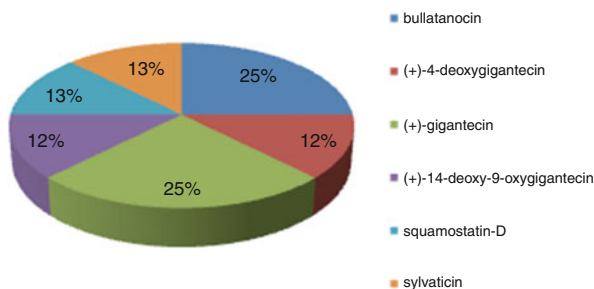


Fig. 21 Synthesis topics on bis-THF AGEs (nonadjacent type) since 1998

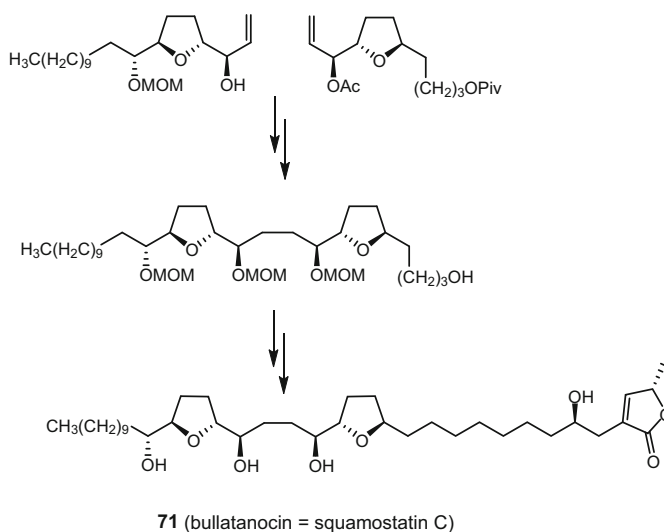


Fig. 22 Synthesis of the non-adjacent bis-THF core of bullatanocin (**71**) using THF-allylic alcohol moieties

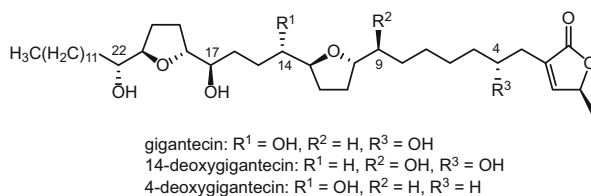


Fig. 23 Structures of gigantecin (**74**), 14-deoxy-9-oxygigantecin (**73**), and 4-deoxygigantecin (**72**)

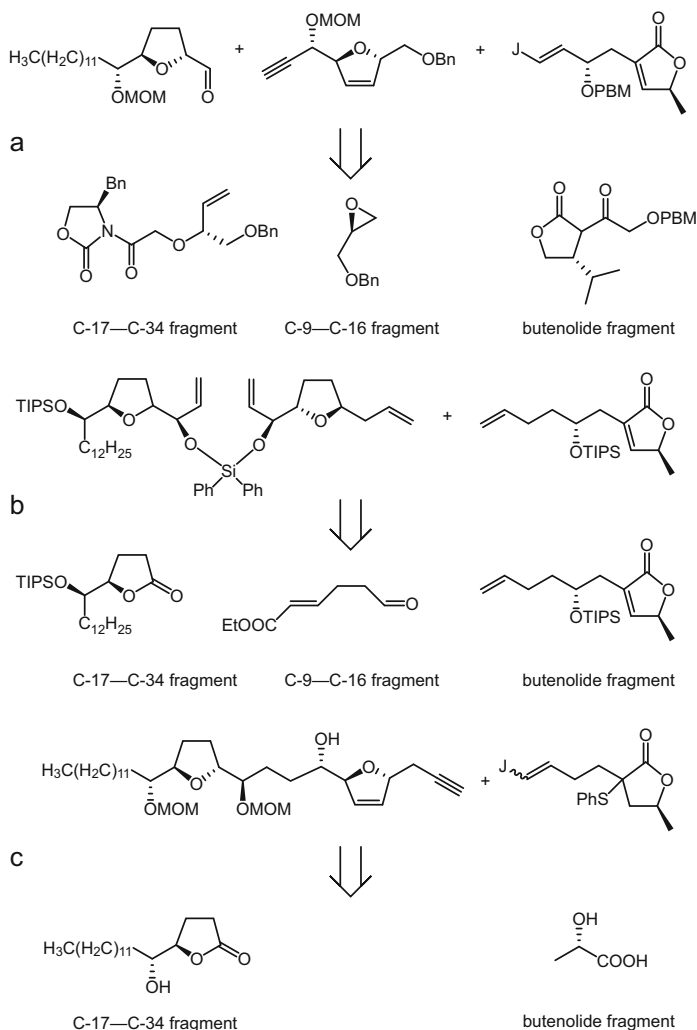


Fig. 24 Synthesis strategies of (a) (+)-gigantecin (**74**) by Crimmins and She [216], (b) (+)-14-deoxy-9-oxygigantecin (**74**) by Hoye et al. [144], and (c) (+)-4-deoxygigantecin (**73**) by Makabe et al. [215]

compound ($[\alpha]_D^{23} +16.0^\circ\text{cm}^2/\text{g}$) matched with that of the natural product ($[\alpha]_D +15.5^\circ\text{cm}^2/\text{g}$).

Marshall et al. proposed a synthesis strategy for squamostatin D (**75**) by constructing chiral centers incorporating several groups and steps. The strategy included a C-36 methyl group from (*S*)-lactic acid, a γ -alkoxy allylic stannane (C-23/C-24) by a BF_3 -promoted addition, a Sharpless asymmetric dihydroxylation (C-19/C-20), a γ -alkoxy allylic indium chloride (C-15/C-16) addition, and an addition of an organozinc reagent catalyzed by a chiral titanium triflic amide (C-12) (see Fig. 25) [217].

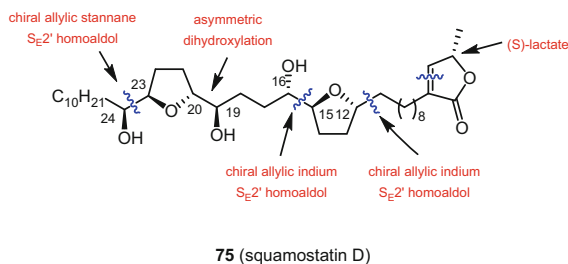


Fig. 25 Retrosynthesis analysis of squamostatin D (**75**)

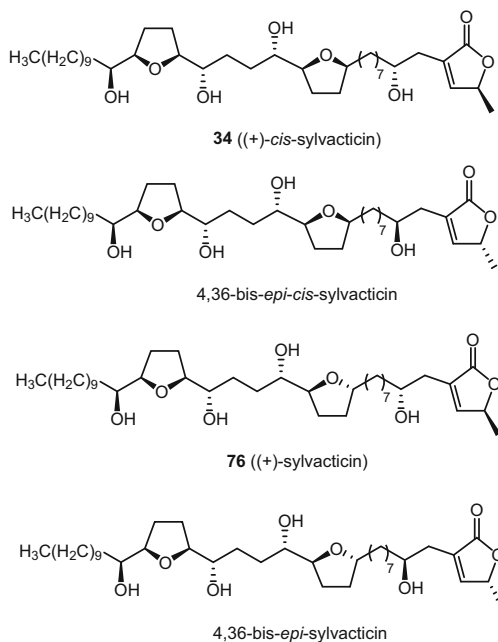
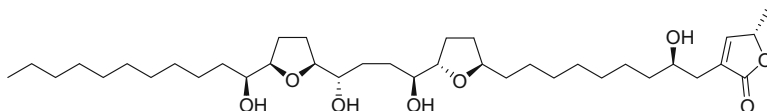


Fig. 26 Structures of sylvactin (**76**) and its epimers

Both *cis*-sylvactin (**34**) and sylvactin (**76**) (Fig. 26) show potent antitumor activity containing the non-adjacent THF rings. Sylvactin (**76**) bears one *cis*- and one *trans*-THF ring, while *cis*-sylvactin (**34**) possesses two *cis*-THF moieties. Donohoe et al. used an oxidative cyclization strategy and a cross-metathesis reaction as efficient and concise routes for the synthesis of these AGEs [218]. The starting material, (*E,E*)-tetradecatetraene, was utilized to protect the tetraol group for constructing the two THF rings with >95% stereoselectivity. In addition, the *trans*-THF ring of sylvactin (**76**) was prepared via a one-pot hydride shift/intramolecular oxo-carbenium ion reduction methodology using *cis*-THF as

precursor [221]. This work provides a shortcut for producing both natural products, in which *cis*-sylvaticin (**34**) was synthesized in only 13 steps with a commercially available diene product while 19 steps were needed for sylvaticin (**76**). The optical rotation values and NMR data of the synthesized products and their Mosher esters were similar to those reported in literature [141], which confirmed the configurations of these two compounds. In addition, the C-4,C-36 bis-epimers of *cis*-sylvaticin (**34**) and sylvaticin (**76**) showed a poor consistency of their optical rotation values with those in the literature.



76 (sylvaticin)

5.5 Other AGEs

Except for the above mentioned type AGEs, we summarize procedures for the synthesis of five classes of other AGEs, like the adjacent THF–THP, nonadjacent THF–THP, THP, tri-THF, and bis-lactone types of AGEs, performed during 1998–2011. In the subgroups, synthesis of the THF–THP type AGEs have been reported the most (see Fig. 27). Related studies for other AGEs are listed in Table 11.

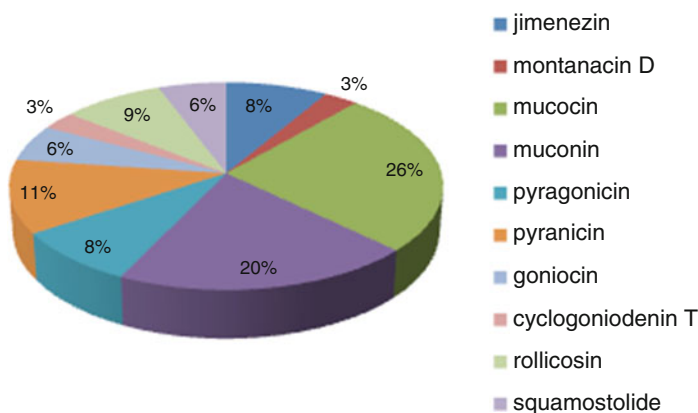


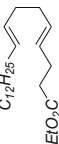
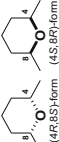

Fig. 27 Analysis of other AGEs syntheses from 1998 to 2011

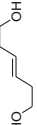
Table 11 Synthesis topics on other AGEs from 1998 to 2011

Compound name	Total synthesis	Synthesis method	Starting materials	Steps and yields	Other points	Ref.
<i>THF-THP (adjacent type)</i>						
Jimenezin	Total synthesis	1. A highly stereoselective intramolecular allylboration 2. An intramolecular Williamson reaction	(S)-Glycidol	24 Steps, 99%		[145]
Jimenezin (19 α -H and 19 β -H)	First total synthesis	1. A stereoselective condensation between the pyranaldehyde and the acetylene derivative 2. A palladium-catalyzed coupling reaction	D-Galactose, L-arabinose, and L-rhamnose	Jimenezin [19 α -H (12 steps, 56%) and 19 β -H (13 steps, 68%)]	Natural compound is (19 α -H)-jimenezin.	[222, 223]
(+)-Muconin	Total synthesis	A novel α -C-H hydroxyalkylation and α' -C-H oxidation of tetrahydrofuran	(-)-Muricatacin	17 Steps, 96%		[229]
Muconin	Total synthesis	The key reactions include successive ether-ring formation reaction under acidic and basic conditions or one-pot double cyclization promoted by TBAF and stereoselective reduction of acyclic ketones adjacent to the 2,6- <i>cis</i> -THP with Zn (BH ₄) ₂		25 Steps, 78%		[224]

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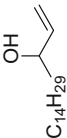
Table 11 (continued)

Compound name	Total synthesis	Synthesis method	Starting materials	Steps and yields	Other points	Ref.
Muconin	Total synthesis	1. Ether-ring formation reaction under acidic and basic conditions 2. Stereoselective reduction of acyclic ketone	$C_{12}H_{25}$ 	25 Steps, 65%		[225]
(+)-Muconin	Total synthesis	A Pd(0)-mediated cross diene coupling reaction	D-Glutamic acid	26 Steps, 82%	MOM protection.	[226]
(+)-Muconin	Total synthesis	Dess-Martin oxidation/ <i>l</i> -selectride reduction	D-Glutamic acid	25 Steps, 82%		[227]
Muconin	Total synthesis	Hydrolytic kinetic resolution (HKR) of terminal epoxides catalyzed by cobalt complex	Tetradecene oxide, epichlorohydrin, and propylene oxide	19 Steps, 70%		[228]
(+)-Muconin		By means of the KSAE (Katsuki-Sharpless asymmetric epoxidation) and SAD (Sharpless asymmetric dihydroxylation) reaction	5-Hexen-1-ol	15 Steps, 70%		[230]
<i>THF-THP (nonadjacent type)</i>						
Montanacin D and (4 <i>S</i> ,8 <i>R</i>)-montanacin D 	First total synthesis	Cross-metathesis; intermolecular metathesis of an α,β -unsaturated ketone carrying a tetrahydropyranyl lactone with a tetrahydrofuran derivative		22 Steps, 83–86%	Natural compound montanacin D is the (4 <i>R</i> ,8 <i>S</i>)-isomer.	[231]

Mucocin		1. Cross-metathesis 2. Julia–Kocienski olefination		10 Steps, 51%		[240]
(–)-Mucocin	Total synthesis	1. The temporary silicon- tethered (TST) ring- closing metathesis (RCM) cross-coupling reaction 2. The enantioselective alkyne/aldehyde addition 3. Bismuth tribromide- mediated reductive etherification		12 Steps, 95%	First application of the temporary silicon- tethered (TST) ring- closing metathesis (RCM) cross-coupling reaction for an acetogenin.	[239]
Mucocin	Total synthesis	1. Chiron approach 2. Palladium-catalyzed cross-coupling reaction	D-Galactose, 2,5-anhydro-D-manni- tol, and L-rhamnose	30 Steps, 77%		[233]
(–)-Mucocin	Total synthesis	1. 6- <i>endo</i> -Epoxide cycli- zation 2. Wittig-type reaction	(<i>E</i>)-Dihydromuconic acid	(–)-Mucocin (53%) and 16- <i>epi</i> -mucocin (75%)	Natural compound is (–)-mucocin.	[234]
Mucocin	Total synthesis	1. Palladium-catalyzed cross coupling reaction 2. Radical cyclization	L-Rhamnose	19 Steps, 76%	MOM protection.	[235]
Mucocin	Total synthesis	1. Naked carbon skeleton strategy 2. Double AE reaction and double AD reaction	Cyclododecatriene	20 Steps, 64%	Simultaneous two-ring closure reactions provided both the THP and THF rings in a single step.	[232]
Mucocin	Total synthesis	1. Swern reaction 2. L-Selectride reduction	D-Galactose and L- rhamnose	31 Steps, 76%	MOM protection.	[238]
(–)-Mucocin	Total synthesis	1. Highly convergent synthetic strategy 2. Metalloorganic cou- pling reaction 3. Sharpless epoxidation 4. Dess–Martin oxidation	β -Ketoester and 	32 Steps, 91%	(–)-Mucocin was found to be identical to the nat- urally occurring product in respect to the spectro- scopic data.	[237]

(continued)

Table 11 (continued)

Compound name	Total synthesis	Synthesis method	Starting materials	Steps and yields	Other points	Ref.
<i>THP</i>						
Pyragonicin		Olefin cross-metathesis	 $C_{14}H_{29}$	19 Steps, 73%	A novel MOM-migrating reaction found in a cyclization reaction is also discussed.	[241]
Pyragonicin		1. Asymmetric Horner-Wadsworth-Emmons (HWE) methodology 2. A key feature of the synthesis is a mild, stereoselective coupling reaction using Carreira's asymmetric acetylide addition with a substrate bearing an adjacent unprotected hydroxy group and a base-sensitive butenolide moiety	Cyclohexadiene	9 Steps, 34%	Zinc-mediated stereoselective coupling.	[150]
Pyranicin		1. Achmatowicz oxidation—Kishi reduction 2. Fu's alkyl-alkyl Suzuki coupling		13 Steps, 89%	Pyranicin shows activity against the PACA-2 (pancreatic cancer) cell line (ED_{50} 1.3 ng/cm ³).	[244]
Pyranicin and pyragonicin		1. An asymmetric HWE desymmetrization 2. An uncommon, yet highly efficient, protective group [(TMS)(CH ₂) ₂] 3. Carreira's asymmetric acetylide additions to construct 1,4- and 1,6-diols	Cyclohexadiene	Pyranicin (31 steps, 72%) and pyragonicin (27 steps, 34%)		[243]

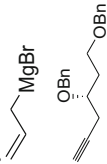


Pyranicin	Total synthesis	1. Asymmetric Homer-Wadsworth-Emmons (HWE) reactions followed by a Pd-catalyzed allylic substitution 2. The C-10/C-15 1,6-diol motif was installed using Carreira's asymmetric acetylide addition methodology	Cyclohexadiene	32 Steps, 72%	[149]
Pyranicin	First total synthesis	1. SmI ₂ -induced reductive cyclization 2. Mitsunobu lactonization 3. Wittig reaction	2,3- <i>O</i> -Isopropylidene-D-threitol allylmagnesium bromide and chiral acetylene 	30 Steps, 95%	[242]
<i>Tri-THF</i>					
Goniocin	Total synthesis	Rhenium oxo complexes involves tandem cyclization	4,8,12-Trienol substrate	A mixture of trifluoroacetyl perhenate and trifluoroacetic anhydride (TFAA) has proven to be an effective reagent for promoting triple-oxidative cyclizations.	[245] (continued)

Table 11 (continued)

Compound name	Total synthesis	Synthesis method	Starting materials	Steps and yields	Other points	Ref.
Goniocin and cyclogoniodenin T	First asymmetric total synthesis	Sharpless asymmetric dihydroxylation (AD)8 and epoxidation (AE)9 reactions as well as the Williamson etherification reaction	Polypoxide	Goniocin (17 steps, 58%) and cyclogoniodenin T (17 steps, 17%)	The synthetic materials, goniocin and cyclogoniodenin T, were found to be identical to the naturally occurring compounds, thereby confirming their proposed absolute configurations.	[247]
<i>Two butenolides</i>						
Rollicosin	First total synthesis	1. A highly regio- and stereoselective tandem RCM/CM reaction for construction of the east-wing lactone and incorporation of alkyl spacer 2. Establishment of the C-4 stereocenter and addition of the west-wing lactone were achieved by Sharpless asymmetric dihydroxylation and enolate alkylation	Hexa-1,5-diene-3,4-diol	12 Steps, 86%		[152]
(4 <i>R</i> ,15 <i>R</i> ,16 <i>R</i> ,21 <i>S</i>)- and (4 <i>R</i> ,15 <i>S</i> ,16 <i>S</i> ,21 <i>S</i>)-Rollicosin	Total synthesis	Convergent synthesis	4-Pentyn-1-ol;  and 5-hexen-1-ol	(4 <i>R</i> ,15 <i>R</i> ,16 <i>R</i> ,21 <i>S</i>)-Rollicosin (23 steps, 85%)	Both compounds showed inhibitory activity against the bovine heart mitochondrial complex I.	[248]

Squamostolide	Total synthesis	Tandem ring-closing metathesis (RCM)/cross metathesis (CM) step in which lactone formation and fragment coupling	Mannitol	9 Steps, 56%	[219]
Squamostolide, (4 <i>R</i> ,15 <i>R</i> ,16 <i>R</i> ,21 <i>S</i>)- and (4 <i>R</i> ,15 <i>S</i> ,16 <i>S</i> ,21 <i>S</i>)-rollicosin	Total synthesis	A convergent stereoselective synthesis with Pd-catalyzed cross-coupling reaction	4-Pentyn-1-ol; 5-hexen-1-ol or 1,6-hexanediol; 	(4 <i>R</i> ,15 <i>R</i> ,16 <i>R</i> ,21 <i>S</i>)-Rollicosin (23 steps, 66%); (4 <i>R</i> ,15 <i>S</i> ,16 <i>S</i> ,21 <i>S</i>)-rollicosin (23 steps, 78%) and squamostolide (15 steps, 62%)	[153] These compounds showed weak activity against bovine heart mitochondrial NADH-ubiquinone oxidoreductase.
Solamin, reticulatin, asimicin, bullatacin, trilobin, trilobacin, squamotacin, rolliniastatin, uvaricin, rollidecins C and D, mucocin, goniocin, and cyclogoniodenin T, as well as ensembles of non-natural analogues		Sharpless asymmetric dihydroxylation (AD) and the asymmetric epoxidation (AE) reactions	Cyclohexadiene	20 Steps	[246] Oxidative polycyclization reaction with rhenium (VII) oxides.

5.5.1 Adjacent Type THF–THP AGEs

Takahashi et al. successfully conducted the first total synthesis of jimenezin (**36**) and its 19-epimer (**36a**) through a convergent route by Pd-catalyzed cross-coupling reaction of a THP–THF segment and a vinyl iodide butenolide, of which both were synthesized from carbohydrates, L-rhamnose and D-galactose [222, 223]. However, the physical data of H-19 α of jimenezin (**36a**) were different from the natural jimenezin (**36**) so that the latter compound was corrected with a H-19 β configuration. To resolve the stereochemistry of the THP moiety of jimenezin (**36**), Bandur et al. synthesized (–)-jimenezin via a stereocontrolled process, such as the intramolecular allylboration for building the THP ring and an intramolecular Williamson reaction for closing the THF ring [146]. The synthesized product, (–)-jimenezin, was found to be identical with respect to its spectroscopic data with the naturally occurring jimenezin (**36**) (Fig. 28).

Another example is muconin (**77**) due to its broad bioactivities and unique structure. Schaus et al. synthesized **77** by an advanced methodology from chiral building blocks. It was attempted to synthesize the THF–THP fragment using the hydrolytic kinetic resolution (HKR) of tetradecene oxide and to synthesize the butenolide segment via HKR of racemic epoxide [224]. Yang and Kitahara et al. succeeded in the total synthesis of **77** via a convergent route, in which two key building blocks I and II were derived from D-glutamic acid (see Fig. 29) [225, 226]. Also, Takahashi et al. proposed a new synthetic strategy of **77** via a successive ether-ring formation reaction under acidic and basic conditions or a

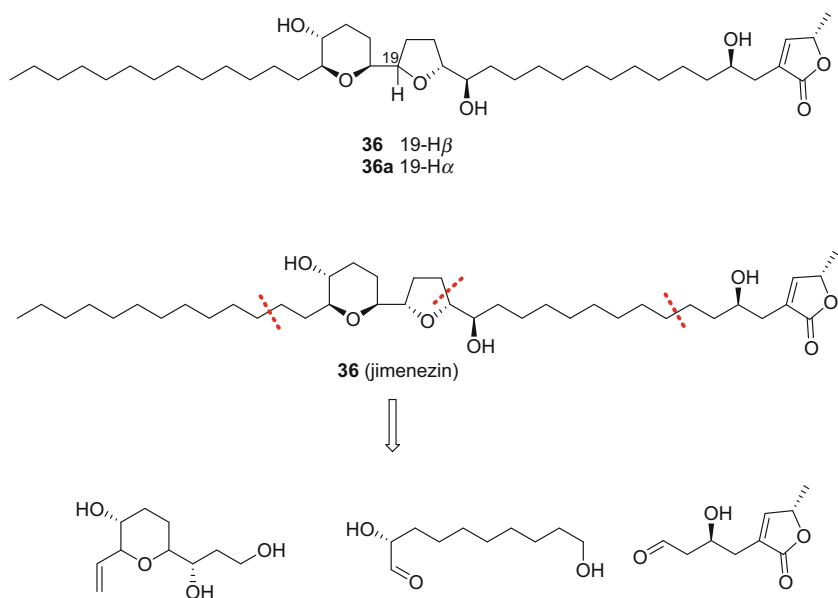


Fig. 28 Jimenezin (**36**) and its 19- $H\alpha$ isomer and retrosynthesis analysis of jimenezin (**36**)

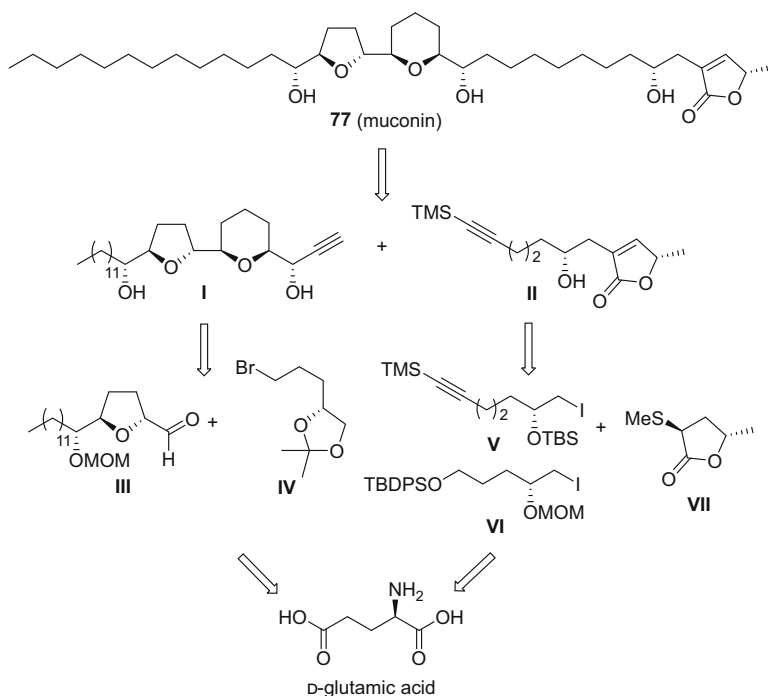


Fig. 29 Retrosynthesis analysis of muconin (77)

one-pot double cyclization utilizing the TBAF reagent and diastereoselective reduction of acyclic ketones with $\text{Zn}(\text{BH}_4)_2$ [227, 228]. Yoshimitsu et al. designed a synthesis strategy for **77** from (–)-muricatacin (**22**), in which the novel α -C-H hydroxyalkylation and α' -C-H oxidation of tetrahydrofuran were developed and achieved as key processes [229].

Crisóstomo et al. reported the synthesis of muconin (**77**) based on Sonogashira coupling between a terminal alkyne with the THF–THP fragment and iodine in the γ -lactone fragment [230]. The precursor of the THF–THP fragment was synthesized from 5-hexen-1-ol as the starting material, and the stereoselective *exo*-cyclization of the THF ring was mediated by means of the Katsuki–Sharpless asymmetric epoxidation and Sharpless asymmetric dihydroxylation. The unique characteristic of the method was established based on the consecutive enantioselective reaction to ensure the high enantiomeric purity of the products.

5.5.2 Non-adjacent THF–THP Type

In 1999 Wang et al. published the first non-adjacent THF–THP AGE, montanacin D (**78**), but the absolute configuration of the THP ring of the naturally occurring AGE was undefined. Takahashi et al. reported the total synthesis of montanacin D (**78**)

and its (4*S*,8*R*) isomer for the first time (Fig. 30) [231]. They designed a cross-metathesis strategy for the synthesis of an α,β -unsaturated ketone bearing a THP lactone unit with a THF derivative (Fig. 31). Thus, the synthesized product suggested that the naturally occurring montanacin D (**78**) should be assigned from its spectroscopic data to be of the (4*R*,8*S*) configuration (Fig. 30).

Neogi et al. demonstrated the total synthesis of mucocin (**37**) from cyclododecatriene and verified the proposed structure [232]. Through the “naked” carbon

Fig. 30 Structure of montanacin D (**78**)

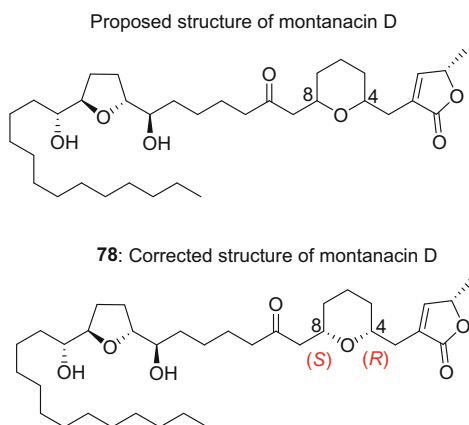


Fig. 31 Retrosynthesis analysis of montanacin D (**78**)

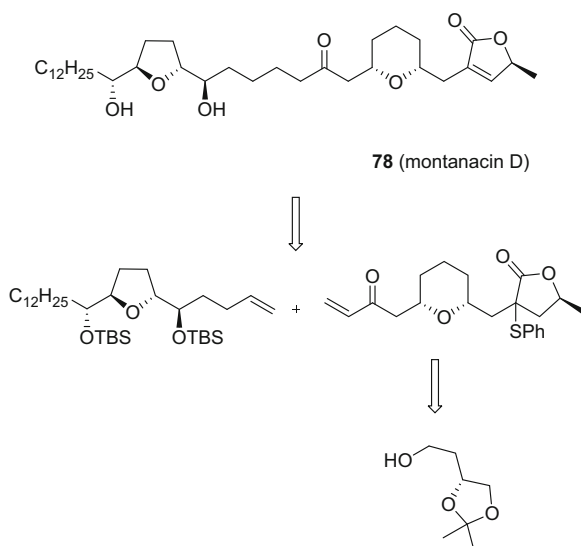
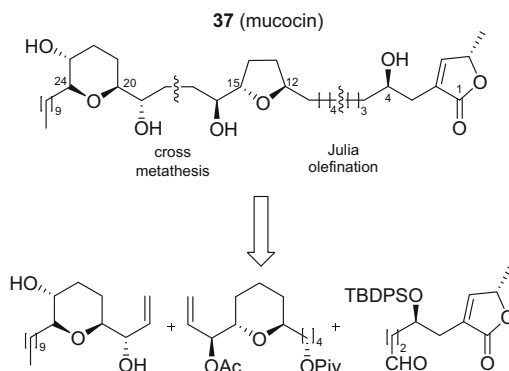


Fig. 32 Retrosynthesis analysis of mucocin (**37**) by Zhu and Mootoo et al.



skeleton strategy, the seven stereocenters on the center fragment were prepared from double AE and double AD reactions. The THF and THP ring were closed and produced in one step as the key feature. In the continued conformational studies of mucocin (**37**), Takahashi and Nakata et al. proposed a series of synthesis methodologies for mucocin (**37**) [233–236]. Takahachi et al. synthesized mucocin (**37**) by using carbohydrates as the key starting point, in which the THP and THF moieties were synthesized from β -selective C-glycosidation and a chelation-controlled addition of an ethynyl group, respectively, and the γ -lactone was prepared via radical cyclization from commercial rhamnose.

Baurle et al. synthesized mucocin (**37**) by the addition of a THP organometallic compound to a THF aldehyde by an appropriate metalloorganic coupling reaction [237]. Four years later, Evans et al. synthesized **37** by means of a temporary silicon-tethered ring-closing metathesis homo-coupling reaction and an enantioselective alkyne/aldehyde addition [239]. Zhu and Mootoo et al. developed a modular synthesis of **37** by olefinic coupling reaction [240]. The cross metathesis reaction on the terminal alkene moiety of THP and THF segments was employed to assemble the non-adjacently-linked five and six membered rings. Then, the nonadjacent THP and THF rings and the butenolide unit were connected by Julia–Kocienski olefination, which was similar to the Wittig-reduction method for bullantanocin synthesis (Fig. 32). The synthesized product showed the identical spectroscopic data with natural mucocin (**37**).

5.5.3 THP Type

Strand and Rein et al. synthesized pyragonicin (**39**) by stereoselective coupling and hydrogenation of the key asymmetric Horner–Wadsworth–Emmons (HWE) approach (Fig. 33) to confirm the proposed structure and for further bioactivity

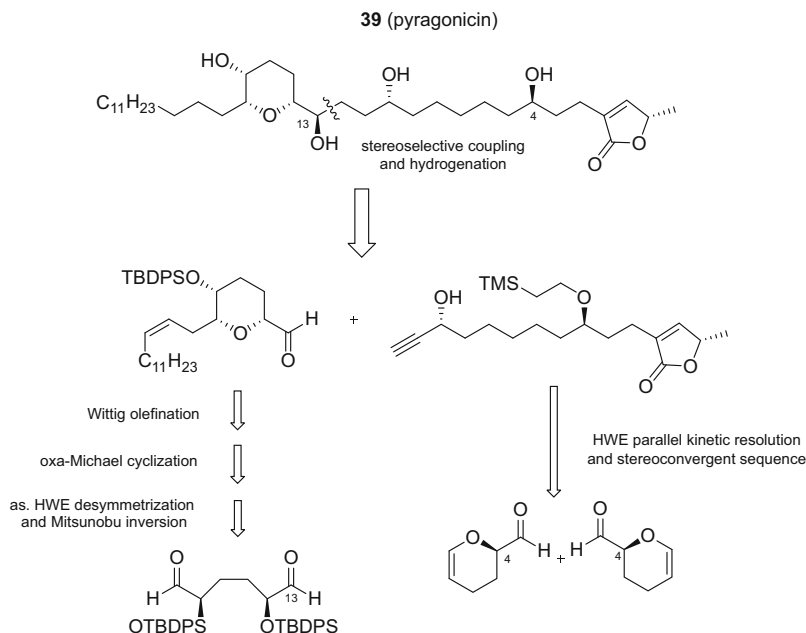


Fig. 33 Retrosynthesis analysis of pyragonicin (**39**) by Strand and Rein et al.

studies [150]. The major characteristic of the coupling reaction was to use an adjacent unprotected hydroxy group and a base-sensitive butenolide moiety to undergo Carreira's asymmetric acetylide addition, which generally can be used for a fragment with a 1,4-diol subunit. The spectroscopic data of synthesized product were the same as for the proposed pyragonicin (**39**).

In 2006, Takahashi et al. synthesized pyragonicin (**39**) via an olefin cross-metathesis between THP fragment and terminal γ -lactone unit in the presence of a Grubbs second-generation catalyst (Fig. 34) [241]. The THP fragment was obtained from asymmetric dihydroxylation and 6-exo-cyclization, and the γ -lactone unit was prepared by an alkylation of γ -lactone with iodide. A twofold yield increase in comparison with that of the previous study was obtained [150].

Pyranicin (**38**) is the first AGE with a THP moiety and an *axial* hydroxy group on the THP ring. Takahashi et al. showed the first total synthesis of **38** in a stereocontrolled manner [242]. A retrosynthesis analysis suggested **38** may be synthesized by a Wittig reaction of the phosphonium salt of a 16,20-*syn*-19,20-*cis*-THP ring, which could be cyclized via a SmI_2 -induced reduction of a β -alkoxyacrylate derivative, and an aldehyde of the lactone unit. Strand and Rein et al. synthesized **38** from cyclohexadiene with an overall yield of 6.3% [149] by a similar principle to one Takahashi et al. proposed [150]. Strand and co-workers

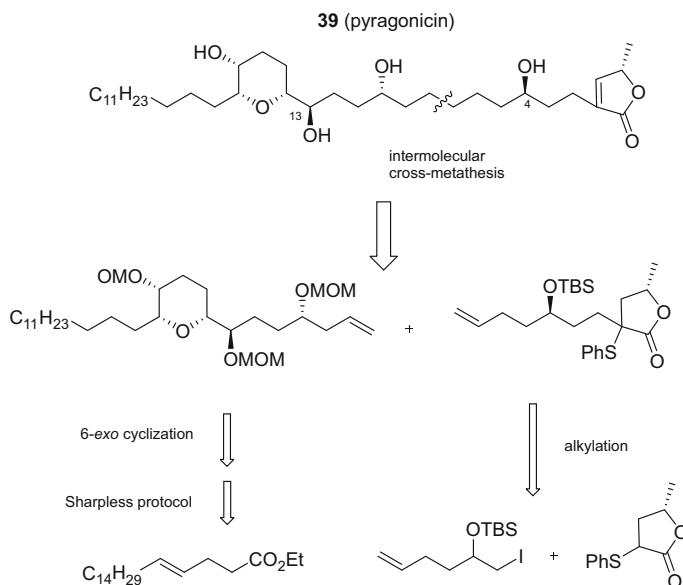


Fig. 34 Takahashi's retrosynthesis analysis of pyragoninic (**39**)

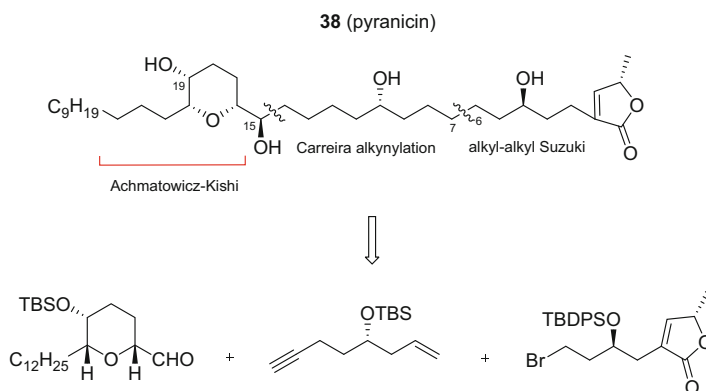


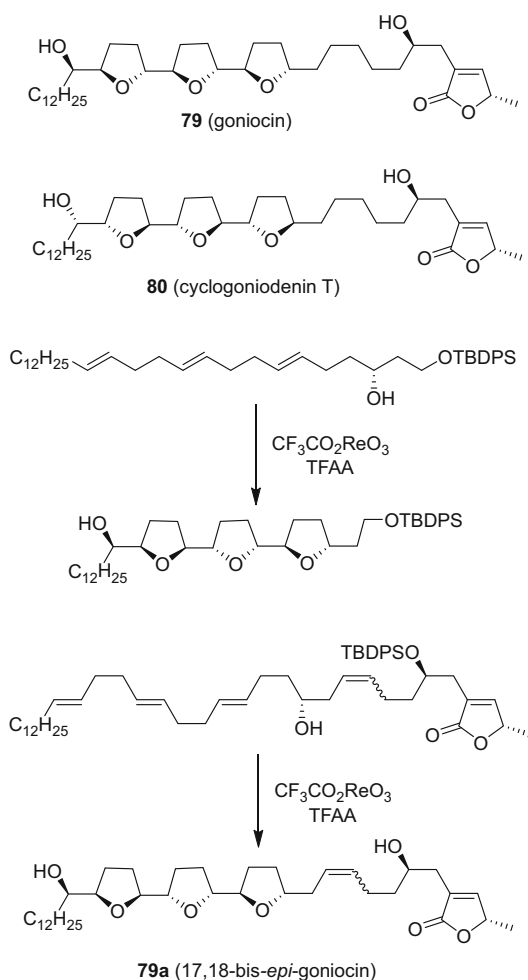
Fig. 35 Pyranicin (**38**) and its overall synthesis strategy

further summarized the divergence en route to pyragoninic (**39**) and pyranicin (**38**) in detail [243]. Soon afterwards, Griggs and Phillips proposed a convenient 13-step and efficient synthesis of pyranicin (**38**) (Fig. 35), in which the pyran subunit was prepared by an Achmatowicz oxidation-Kishi reduction and the other two subunits were made by Fu's alkyl-alkyl Suzuki coupling reaction and Carreira alkylation to give the desired compound [244]. The physical data of the synthesized compound were in excellent agreement with those of naturally occurring pyranicin (**38**).

5.5.4 Tri-THF Type

Goniocin (**79**) and cyclogoniodenin T (**80**) are a new subgroup of the AGEs that possesses three adjacent THF rings. Initially, Sinha et al. planned to synthesize goniocin (**79**) using rhenium oxide in tandem oxidative polycyclizations [245, 246]. A mixture of trifluoroacetylperhenate and trifluoroacetic anhydride (TFAA) was proven to increase the efficiency of triple-oxidative cyclizations (Fig. 36). However, they obtained 17,18-bis-*epi*-goniocin (**79a**) rather than **79**. Later on, Sinha et al. proposed an asymmetric total synthesis of goniocin (**79**) and cyclogoniodenin T (**80**) from a trienol and its *ent*-form via a tandem epoxide opening cascade of Sharpless asymmetric dihydroxylation (AD) and epoxidation (AE) reaction as well as Williamson etherification [247]. Both synthetic materials were found to be

Fig. 36 Sinha's strategy to synthesize the stereoisomer **79a** of goniocin (**79**)



identical with the naturally occurring compounds **79** and **80**, thereby confirming the proposed absolute configurations. The only disadvantage of this work was the low yield obtained.

5.5.5 Bis-lactone Type

Rollicosin (**23**) and squamostolide (**24**) are of the characteristic subclass of AGEs that are composed of two terminal γ -lactone rings linked to an alkyl chain. They can be regarded as derivatives of classical THF-containing AGEs stemming from the oxidative cleavage in biosynthesis. Quinn et al. synthesized rollicosin (**23**) using the tandem ring-closing/crossmetathesis (RCM/CM) strategy [152], in which the allyl butenolide segment was obtained by a site-selective initiation of the catalyst as the key step. Sequentially, the C-4 stereocenter of **23** was introduced by an AD-mix- β reaction. Coupling the triflate with the enolate, oxidation, and deprotection, **23** was obtained in 9% yield over 12 steps from the C_2 -symmetric dienediol. To obtain **23**, Makabe et al. reported a synthesis of **23** and its (4*R*,15*S*,16*S*,21*S*)-configured isomer (Fig. 37) [248]. The retrosynthesis analysis indicated that rollicosin (**23**) could be dissected into two building blocks, a hydroxy lactone with a terminal alkyne fragment and an iodine substituted α,β -unsaturated lactone. Both building blocks could be prepared from the corresponding primary alcohols. By palladium-catalyzed coupling of the two building blocks the target products were obtained. The ^1H and ^{13}C NMR spectra of the (4*R*,15*R*,16*R*,21*S*) product showed good agreement with those of the naturally occurring rollicosin (**23**). Interestingly, both synthetic compounds displayed the same activity ($IC_{50} = 0.6 \mu\text{M}$) with the bovine heart mitochondrial complex I. The same approach was also applied to the rollicosin analogue, squamostolide (**24**), resulting in a good yield [153]. In addition,

Fig. 37 Retrosynthesis of rollicosin (**23**) [91, 152]

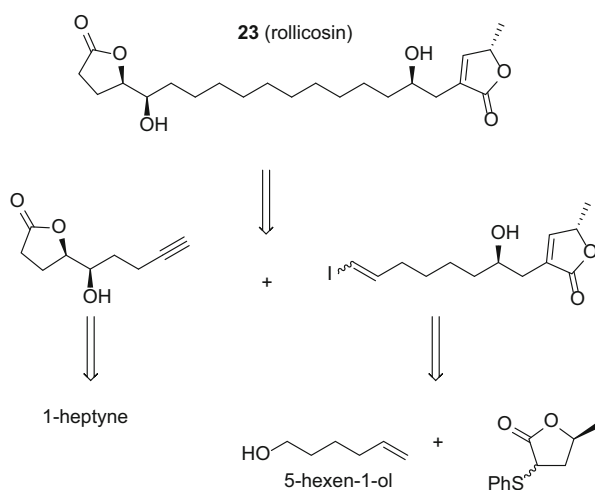
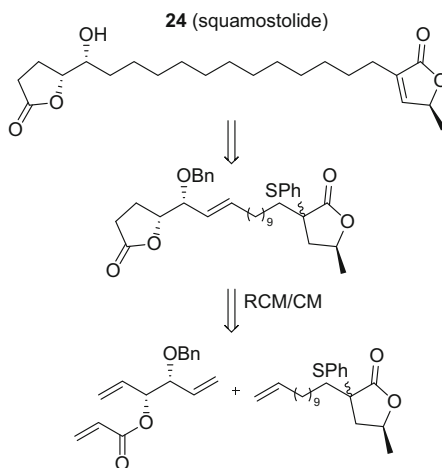


Fig. 38 Retrosynthesis of squamostolide (**24**) [121, 153]



Wu and Quinn et al. proposed a total synthesis of **24** [219]. Quinn et al. synthesized **24** from D-mannitol as the starting material over nine steps, in which the catalyst ($L_nRu=$) plays an important role in the inherent selectivity of the five-membered ring formation, which is the key step for the highly selective tandem ring-closing/cross metathesis reaction used (Fig. 38).

6 Biological Activity and Mechanism of Action of Annonaceous Acetogenins

In this section, the biological function and mechanism of action of AGEs are both discussed in addition to the clarification of the linkage between the mitochondrial respiratory chain and cellular apoptosis [249]. Apoptosis, also known as programmed cell death, is a normal physiological process that selectively and desirably destroys cells and tissues without triggering any inflammatory response, as opposed to necrotic cell death. Instead of focusing on the well-established inhibition of bullatacin (**7**) on mitochondrial complex I, this compound was found capable of inducing apoptotic cell death. This is based on the morphological changes observed with bullatacin (**7**)-treated Hep 2.2.15 cells, as determined by double staining using fluorescein-isothiocyanate (FITC)-labeled annexin V and propidium iodide (PI) [250]. These findings have opened a new means of exploring the mechanism of action of AGEs on apoptosis.

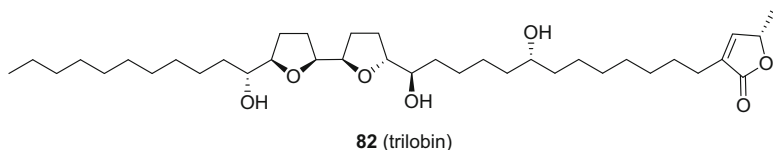
Although AGEs have exhibited diverse biological activities, including antibacterial [251], insecticidal [252], cytotoxic [1], and immunosuppressive effects [253], investigators have developed a particular interest on their potential anticancer effects and on the underlying mechanisms of activity. However, both the

cytotoxic and pesticidal activities are related to ATP generation and NADH-oxidation in the mitochondria. Therefore, several studies have focused on the interaction of AGEs with mitochondrial complex I.

6.1 Pesticidal Activities

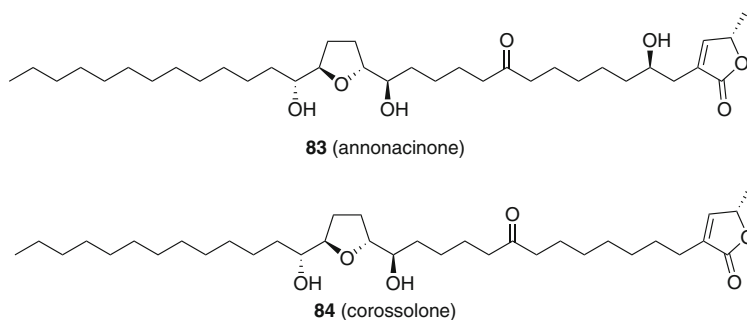
Annonaceous plants have potential use as pesticides, and McLaughlin et al. were the first group to report this application. They determined the pesticidal potencies of extracts from the paw paw tree (*Asimina triloba*) by the brine shrimp lethality test (*Artemia salina* L. larvae). Also, similar pesticidal activities were found against the striped cucumber beetle (*Acalymma vittatum* F.), the Mexican bean beetle (*Epilachna varivestis* Mulsant), mosquito larvae (*Aedes aegypti* L.), blowfly larvae (*Calliphora vicina* Meigen), the melon aphid (*Aphis gossypii* Glover), the two-spotted-spider mite (*Tetranychus urticae* Koch) and the free-living nematode (*Caenorhabditis elegans* Maupas). During preliminary screening work, asimicin (**8**) was isolated and its pesticidal action was evaluated [135]. Utilizing a bioactivity-guided isolation and fractionation method, bullatacin (**7**) was purified and its pesticidal effects were observed at a fairly low concentration (1 ppm), whereas bullatacinone (**81**) lacked any discernible pesticidal activity at the concentrations tested [254]. McLaughlin et al. conducted a controlled study to investigate the pesticidal potencies of extracts from various parts of plant of the paw paw tree (*Asimina triloba*) using the brine shrimp test [255].

McLaughlin et al. further evaluated the pesticidal properties of 44 AGEs using a yellow fever mosquito larvae (YFM) assay [256]. The results clearly demonstrated that many AGEs possess pesticidal properties. In addition, the results focused on adjacent bis-THF AGEs with three hydroxy groups. For example, bullatacin (**7**) and trilobin (**82**) were the most potent AGEs in this aspect. They further used AGEs of the mono-THF, adjacent bis-THF, and nonadjacent bis-THF types as insecticidal baits for testing the potent toxicity of these compounds against insecticide-susceptible and -resistant German cockroaches. The resultant pesticidal activities were compared with conventional synthetic insecticides [257]. Ohsawa et al. evaluated the insecticidal activities of AGEs from the seeds of the pond apple, *A. glabra* with a micro-sprayer on the cabbage leaf or with a filter paper [258]. Guadano et al. also found that annonacin (**42**) showed antifeedant effects on *L. decemlineata*, whereas squamocin was toxic to *L. decemlineata* and *M. persicae*. They also proved that both AGEs were not mutagenic but indeed toxic to the insects in the absence of a metabolic energy-activating system [259].



Londershausen et al. also determined how extracts of the ground seeds of *A. squamosa* revealed interesting insecticidal properties, in which AGEs were determined to be the active components through an activity-monitored fractionation procedure. The measurement of ATP-levels (at the LT_{50} value) in *Plutella xylostella* under treatment with squamocin (**6**) and antimycin A were 1.45 and 1.35 $\mu\text{mol/g}$ weight [4]. Further studies demonstrated that squamocin (**6**) showed an inhibitory effect on NADH-cytochrome *c*-reductase and complex I of insect mitochondria with IC_{50} values of 4–8 $\mu\text{mol/g}$ protein and 0.8 μM , respectively. Similar results were observed for the inhibition of squamocin (**6**) on complex I in bovine heart muscle ($IC_{50} < 0.1 \mu\text{M}$) or *Neurospora crassa* cells (IC_{50} : 0.3 μM). However, no effects on other coupling sites of mitochondrial complexes were observed [4]. These experimental results were established by Lewis et al. in 1993 [260]. Friedrich et al. and McLaughlin et al. simultaneously reported that the insecticidal action is attributed to the inhibition of AGEs on mitochondria complex I [261, 262]. Friedrich et al. found the inhibition of mitochondrial and bacterial NADH:ubiquinone oxidoreductase (complex I) by AGEs did not rely on pure competition [261]. They demonstrated how AGEs also affect the electron-transfer step from the high-potential iron-sulphur cluster to ubiquinone by directly acting on the ubiquinone-catalytic site of complex I [261].

Recently, a Brazilian group has found that two AGEs, annonacinone (**83**) and corossolone (**84**) from *A. muricata*, showed IC_{50} values ranging from 25.9 to 37.6 $\mu\text{g/cm}^3$ against the promastigote form of *Leishmania chagasi*, whereas the IC_{50} values ranged from 13.5 to 28.7 $\mu\text{g/cm}^3$ against the amastigote form of this protozoan [263].



6.2 Cytotoxic, Cancer-Related, and Ionophore Activities (Anticancer Activity)

Jolad et al. first reported the significant in vivo cytotoxic activity of uvaricin (**1**) using the murine P-388 lymphocytic leukemic test system [1]. In 1993, McLaughlin et al. reported the usage of normal mice bearing L1210 murine leukemia and athymic mice bearing A2780 conventional ovarian cancer xenografts as models to study the cytotoxic action of bullatacin (**7**) and its analogues. These compounds also demonstrated potential insecticidal activity in insect-derived Sf9 cells. It was

postulated that the toxicity of AGEs in both cases is due to the strong inhibitory effect on the mitochondrial electron transport with specific action at complex I [264]. Degli Esposti et al. first used mammalian mitochondria to study the action of AGEs on NADH:ubiquinone reductase (complex I). They reported that bullatacin (7) inhibited the proton pumping function of complex I with similar efficiency under steady-state and non-steady-state conditions, while comparing to the action of rotenone and piericidin [265]. Their ability to inhibit mitochondrial complex I, the main gate for cellular energy production, has helped promote AGEs as candidates for the development of a new class of antitumor drugs with a different mechanism of action than conventional cancer chemotherapeutic agents.

Besides blocking NADH:ubiquinone oxidoreductase (complex I) in the electron transport system, AGEs are also considered as powerful inhibitors of NADH oxidases peculiar to the plasma membranes of cancer cells. Both mechanisms of action led to the inhibition of ATP production and may also be accountable for the observation on the effectiveness of AGEs killing multiple-drug resistant (MDR) tumors than their non-resistant counterparts. This effect was due to the requirement of ATP for the MDR pumps on cell membranes. In addition, Oberlies et al. observed that AGEs can inhibit selectively cell growth in in vitro cell inhibition assays against three murine (P388, PO3, and M17/Adr) and two human (H8 and H125) cancer cell lines [266]. Interestingly, the work of McLaughlin et al. showed that certain members of this class of natural products exhibit inhibitory activity against some drug-resistant cancers. Currently, MDR cancers are hard to cure due to the mechanism developed by the cancer cells in overcoming the anticancer agents being administered therapeutically. Owing to the biochemical differences between MDR and parental cancer cells, the ATP-dependent P-glycoprotein mediated pumps (P-gp) found in MDR cancer cells require a higher demand for ATP. Also, Oberlies et al. tested the effect of bullatacin (7) on two cell lines, MDR human mammary adenocarcinoma (MCF-7/Adr) cells and parental, non-resistant wild-type (MCF-7/wt) cells [267]. Thus, ATP depletion could be another mode of action that offers an advantage for AGEs to be developed into novel chemotherapeutic agents for MDR tumors.

McLaughlin et al. also proposed a model for explaining the action of AGEs [268]. They suspected that the lactone ring alone could directly interact with the binding to complex I, while the THF rings with flanking OH groups function as hydrophilic anchors at the membrane surface that allow lateral diffusion (or random distribution) of the lactone ring in the interior membrane. To verify this model, Kuwabara et al. synthesized a series of analogues with two terminal γ -lactone rings [269]. However, the bioassay results showed that these analogues did not have the same degree of effectiveness as the AGEs. For the AGEs abundant in plants from Taiwan, our group has collaborated with biochemists and pharmacologists countrywide to clarify their mechanism of actions. Yuan et al. found that annonacin (42) could arrest T24 bladder cancer cells at the G1 phase and cause cytotoxicity in a Bax- and caspase-3-related pathway [270]. In addition, squamocin (6) was also observed to arrest the same cancer cells at the G1 phase and resulted in a selective cytotoxicity in S-phase-enriched T24 cells via the same pathway of cleaving the

functional protein of PARP thus inducing cellular apoptosis [271]. Squamocin (**6**) was also found to inhibit the proliferation of K562 cells via G2/M arrest in association with the induction of p21 and p27 and the reduction of Cdk1 and Cdc25C kinase activities [271].

6.3 Neurotoxic Activities

In 1999, Caparros-Lefebvre et al. found an unexpectedly high percentage of atypical parkinsonism in Guadeloupe, French West Indies, by a 1-year epidemiological study from August 1995 to August 1996. The study reported that progressive supranuclear palsy (PSP) and atypical parkinsonism were apparent in those patients who had drunk herbal tea or eaten the fruits from annonaceous plants (custard apple or paw paw family) in Guadeloupe [272]. Originally, a relationship was speculated between dietary neurotoxins from the tropical herbal teas and fruits of *Annona muricata*, *A. squamosa*, and *A. reticulata* and atypical parkinsonism of patients as being due to chronic poisoning by benzyl-tetrahydro-isoquinolines thought to be potent dopaminergic neurotoxins [272–274]. In addition, in 2002, Lannuzel et al. found that both a crude extract and pure compounds, such as the alkaloids, coreximine, and reticuline, from *A. muricata* root bark could affect physiological functions and the survival of mesencephalic dopaminergic neurons. This finding matched closely with Caparros-Lefebvre's hypothesis [275]. On the other hand, the major AGE, annonacin (**42**), in *A. muricata*, a potent inhibitor of mitochondrial respiratory chain at the level of complex I was investigated for potential neurotoxic activity in vitro. Annonacin (**42**) was highly toxic to the dopaminergic and other mesencephalic neurons, and **42**-treated neurons, by impairment of energy production [276]. Subsequently, in 2004, Champy et al. found that neurodegeneration in the rat brain was induced under a chronic systemic exposure of annonacin (**42**) intravenously for 28 days [277]. The aforementioned in vitro and in vivo studies provided evidence that neurotoxicity between the consumption of annonaceous products and the occurrence of atypical Parkinson's disease. Similarly, atypical Parkinson's disease also occurred in people who consumed traditionally annonaceous fruits in Guam and New Caledonia [278]. Moreover, a temperate annonaceous plant in Eastern United States named paw paw fruit (*A. triloba*) also contains a high percentage of annonacin (**42**). Its ethyl acetate extract possesses about 10% annonacin (**42**), which induced 50% death of cortical neurons in an in vitro experiment [279]. Did this side effect come from the alkaloids and/or acetogenins of annonaceous plants? If true, is the edible pulp of various ripe annonaceous fruits suitable for dietary food? The edible pulp of these plants are important and delicious fruit resources of many countries in the world. Meanwhile, the seeds of these plants are well-known for their toxicity and abundance of acetogenins. The content of annonaceous acetogenins and dopaminergic alkaloids in the pulp of the fruits should be investigated in future studies to clarify their potential for chronic neurotoxicity. As of now, no reports on the chemical composition of the edible pulp of annonaceous fruits are available.

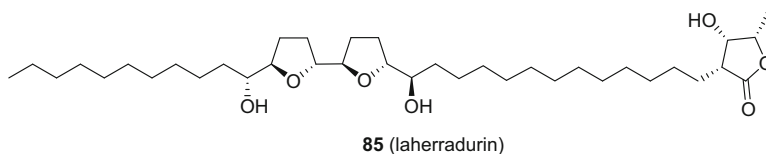
6.4 Other Activities

6.4.1 Anti-inflammatory Effects

In a search for phytochemicals with anti-inflammatory activity, 15 representative AGEs were evaluated for their COX-2 inhibitory activity. Among them, isodesacetyluvaricin (**9**), from the Formosan tropical fruit tree, *Annona glabra*, exhibited the most potent inhibitory activity. Reverse transcription PCR in cultures of A431 human epidermoid carcinoma cells and luciferase assays on lipopolysaccharide-stimulated expression of COX-2 in RAW 264.7 mouse leukemic monocyte-macrophages revealed that the treatment of isodesacetyluvaricin (**9**) reduced the activities of two COX-2 promoter-transcription factors: cAMP response element-binding factor and nuclear factor of activated T-cells. In these tests, isodesacetyluvaricin (**9**) did not affect cell proliferation, as measured by a colorimetric assay, or intracellular store-operated calcium influx, as determined by fluorescence imaging. Thus, isodesacetyluvaricin (**9**) may serve as a lead compound for targeting inflammatory diseases as well as angiogenesis and cancer metastasis [280].

6.4.2 Promotion of Biofilm Formation in Microbes

An Argentinian group found that *Pseudomonas aeruginosa* PA100 and *P. plecoglossicida* J26 increased their biofilm formation when squamocin (**6**) was added to the culture medium [251]. Although the evaluated AGEs possessed similar structures as the autoinducer, AHL, bioassays using *C. violaceum* showed that squamocin (**6**) is not an autoinducer agonist. It was proposed that this compound is indirectly involved in a quorum sensing mechanism by inducing a stress-related increase in AI production for a given incubation time. Therefore, the exacerbation of biofilm formation was found to be due to increased production of AI-1 [281]. Squamocin (**6**) and laherradurin (**85**) stimulated *P. plecoglossicida* J26 biofilm formation, which led to an increase in consumption of naphthalene in the absence of planktonic cells. The authors proposed that the AGEs, squamocin (**6**) and laherradurin (**85**), can be used as biofilm formation promoters to allow more efficient, safe, and durable naphthalene bioremediation processes [282].



6.4.3 Interaction of AGEs with Membranes

With regard to the interaction of AGEs with membranes, McLaughlin's group used NMR spectroscopy to measure the space between AGEs and a bilayer membrane. ^1H difference NOE NMR spectra indicated that the lactone rings of asimicin (**8**) and parviflorin (**86**), of which the latter has two fewer carbons in its alkyl chain, were located below the glycerol backbone in the membrane [268]. An Argentinian group designed an FTIR experiment and provided molecular dynamics simulations of the interactions of AGEs with artificial lipid bilayers. According to their results, AGEs can interact to different extents with the phosphate and carbonyl groups of membranes in the liquid crystalline state. The THF rings, through their flanking hydroxy groups, form the hydrogen bond interactions that act as hydrophilic anchors in the lipid membrane [283, 284]. Our group used dipalmitoylphosphatidylcholine (DPPC) as a monolayer membrane to measure the change of surface pressure of membrane after treatment with squamocin (**6**). These preliminary data showed that AGEs can disrupt the integrity of such membranes (see Fig. 39). These studies should be helpful in clarifying the mechanisms of action of AGEs in the membrane environment.

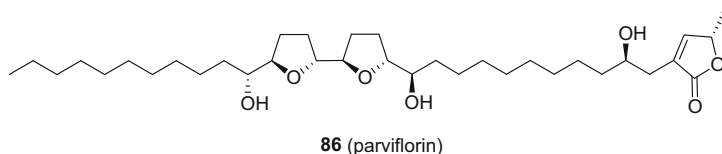
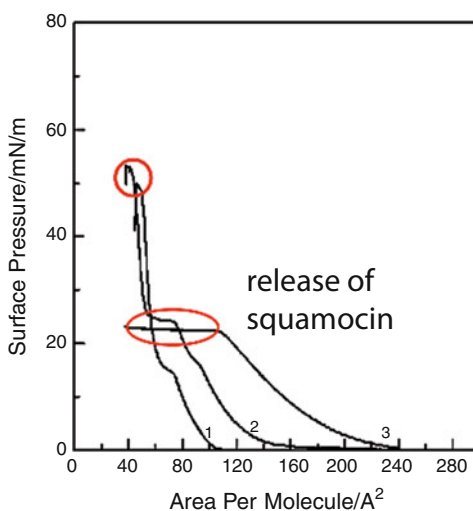


Fig. 39 Changes of membrane surface pressure after treatment with squamocin (**6**). (1) Pure DPPC, (2) squamocin (**6**) (C001)/DPPC = 1/4, 3) squamocin (**6**) (unpublished data)



6.4.4 AGEs as Cation Ionophores

Although many research investigators have examined the mechanisms of actions of the AGEs, such as the inhibitory action of mitochondria complex I (NADH: ubiquinone oxidoreductase) [285], induction of programmed cell death by the expression of pro-apoptotic Bax, Bad, and caspase-3 [270], and the structure-activity relationships of either natural, semi-synthetic or synthetic compounds, the diverse bioactivities of the various types of AGEs still remain to be elucidated in more detail. Several researchers have investigated the physicochemical features of various AGEs, and have provided direct evidence for new structure-activity relationships for these compounds.

Sasaki et al. first reported the ionophore activity of AGEs, and NMR studies revealed that the structurally related analogues of AGEs form supramolecular complexes with metal cations [286]. These studies indicated that hydroxylated bis-THF derivatives, the structural components of the more potent cytotoxic AGEs, may form supramolecular complexes with metal cations. In particular, some formed 2:1 ligand:metal complexes with calcium cations with high selectivity [286]. Earlier, in 1995, however, Araya et al. evaluated the ion-transport and ion-binding activities of AGEs using a W-08 apparatus and did not find any particular activity [287], Sasaki et al. later indicated that the two AGEs bullatacin (7) and asimicin (8) and their structurally related analogues assembled with bivalent cations, such as Ca^{2+} and Mg^{2+} [288, 289]. Peyrat et al. evaluated the ^{13}C NMR longitudinal relaxation times (T_1) for both annonacin (42) and squamocin (6) in the absence and presence of Ca^{2+} ions to assess the structural changes that accompany complexations. They considered that the potent cytotoxic activities shown by the THF- γ -lactone derivatives could be explained by their ionophoric ability. Their results also showed differences in the stoichiometry of the complexes for mono-THF AGEs and bis-THF AGEs with Ca^{2+} ions [290].

In biological studies of living cells, a point often considered was how AGEs could play a role in the bioavailability of the cations in cell membranes due to their amphiphilic nature. While culturing smooth muscle cells of the human coronary artery, our group observed that squamocin (6) could induce a transient but strong increase in the large-conductance Ca^{2+} -activated K^+ channels [291]. In a whole-cell configuration, this AGE (0.3–100 μM) induced a Ca^{2+} -activated K^+ current ($I_{\text{K(Ca)}}$) in a concentration-dependent manner with an EC_{50} value of 4 μM . When cells were exposed to a Ca^{2+} -free solution, squamocin (6) (3 μM) induced a transient increase in $I_{\text{K(Ca)}}$. In the continued presence of squamocin (6), an additional increase in extracellular Ca^{2+} (1 mM) caused a significant increase in $I_{\text{K(Ca)}}$. In the cell-attached configuration of single-channel recordings, squamocin (6) applied to the bath increased the activity of large-conductance Ca^{2+} -activated K^+ (BK_{Ca}) channels without altering the single-channel conductance. These findings provide evidence that squamocin (6) can activate $I_{\text{K(Ca)}}$ in coronary arterial smooth muscle cells. The initial transient activation of $I_{\text{K(Ca)}}$ may reflect squamocin (6)-induced Ca^{2+} release from intracellular Ca^{2+} stores, whereas the sustained activation of $I_{\text{K(Ca)}}$ may arise

from the squamocin (**6**)-induced Ca^{2+} influx across the cell membrane. The stimulatory effects of squamocin (**6**) on these channels would affect the functional activity of vascular smooth muscle cells [287].

We speculated that AGEs may use their hydrophilic centers (THF rings with flanking hydroxy groups) to bind with cations like Ca^{2+} and surround the ion core by the peripheral hydrophobic regions (long chains). This arrangement allows the AGE molecules to dissolve effectively in the membrane and diffuse transversely into cells as ionophores. The interaction was clarified between mono-THF AGEs and Ca^{2+} by isothermal titration calorimetry, which is a powerful and sensitive technique for measuring the heat of interaction of reacting species in dilute solution. Interestingly, it was found that the mono-THF AGEs, annonacin (**42**) and uvariamicin-I (**87**), interacted with Ca^{2+} by an exothermic process, indicating the formation of AGE-calcium complexes [37]. Furthermore, our group used various types of AGEs, including three mono-THF AGEs, two adjacent bis-THF AGEs, two non-adjacent bis-THF AGEs, and one linear AGE to clarify the relationship between the Ca^{2+} -chelating ability and their cytotoxicity. From the results, NMR spectroscopy and isothermal titration calorimetry showed that calcium ions are chelated by the hydroxylated THF ring of acetogenins, which results from formation of complexes that aid the Ca^{2+} cations in penetrating cell membranes and in elevating the intracellular calcium level (see Fig. 40). This disruption of intracellular calcium homeostasis induces mitochondrial depolarization and mediates cell toxicity [292].

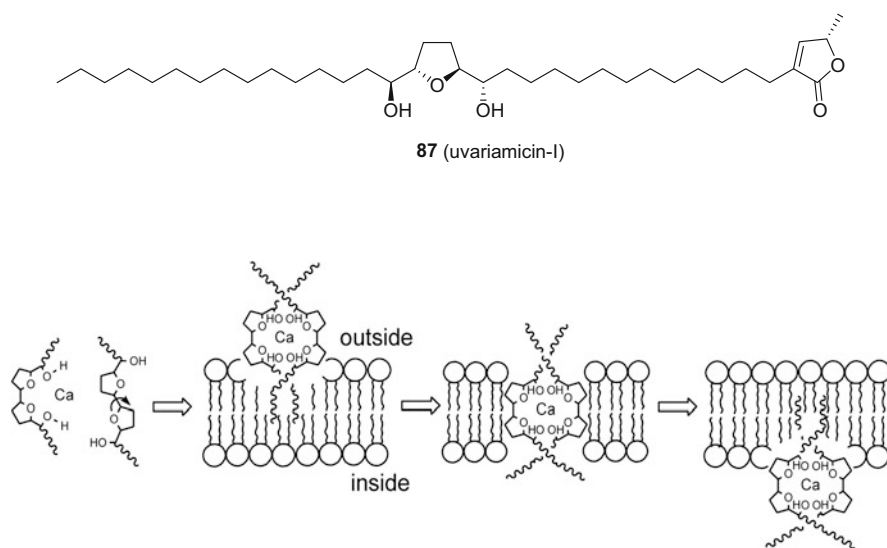
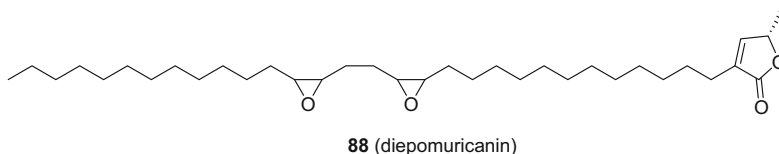


Fig. 40 Calcium-chelation model for an adjacent bis-THF AGE/ Ca^{2+} complex that enhances cell-membrane penetration. The lipid bilayer can be that of the cell membrane or the mitochondrial membrane

7 Medicinal Chemistry of Annonaceous Acetogenins (Annonaceous Acetogenin Mimics)

7.1 Structure-Activity Relationship

The structure-activity relationship studies of AGEs have proven to be interesting to medicinal and natural products chemists alike. Miyoshi et al. noted that the alkyl spacer between the γ -lactone and hydroxylated THF ring moieties play an important role for AGEs to elicit potent inhibitory activities on the NADH oxidase [293]. They summarized several structure-activity relationship observations of AGEs as follows: (1) the adjacent bis-THF ring moiety is not an essential structural factor for inhibition, and the mono-THF-containing compounds can maintain potent activities; (2) this stereochemical configuration of the THF ring moiety is also not essential for potent activity irrespective of the number (one or two) of THF rings; (3) The THF rings of the AGEs have strong interactions with the interface of lipid bilayers irrespective of the configuration in the THF region; (4) the length of the alkyl side chain is very important for the elicitation of potent activity [294]. Takada et al. also tested the NADH oxidase activity of two naturally occurring AGEs, bullatacin (**7**) and diepomuricanin (**88**), and several synthesized analogues in a comparison with piericidin A [295]. They concluded that both ring moieties, the γ -lactone ring and the tetrahydrofuran ring, acted in a cooperative manner on the enzyme and that the optimal length of the alkyl spacer is 13 carbon atoms. These results supported the above hypothesis that Miyoshi et al. offered.



To consider solely the role of the THF ring moieties, Murai et al. synthesized Δ lac-AGE (**89**) (an acetogenin derivative without the α,β -unsaturated γ -lactone ring). This was also shown to be a novel type of inhibitor that acts at the terminal electron transfer step of mitochondrial NADH:ubiquinone oxidoreductase (complex I). They also prepared a photolabile Δ lac-AGE (**90**) connected to a biotin probe to trace the labeled peptide without the use of a radioisotope. This photolabile Δ lac-AGE elicited potent inhibition of bovine heart mitochondrial complex I at nanomolar levels (see Fig. 41) [296]. Ichimaru et al. further synthesized a series of Δ lac-AGEs, in which the stereochemistry around the hydroxylated tetrahydrofuran ring moiety was systematically modified, and examined their inhibitory effects on complex I. The results revealed that the bis-THF ring analogues are much more potent than are the mono-THF ring analogues and that the stereochemistry around the bis-THF ring moiety plays a significant role in the inhibitory effects on

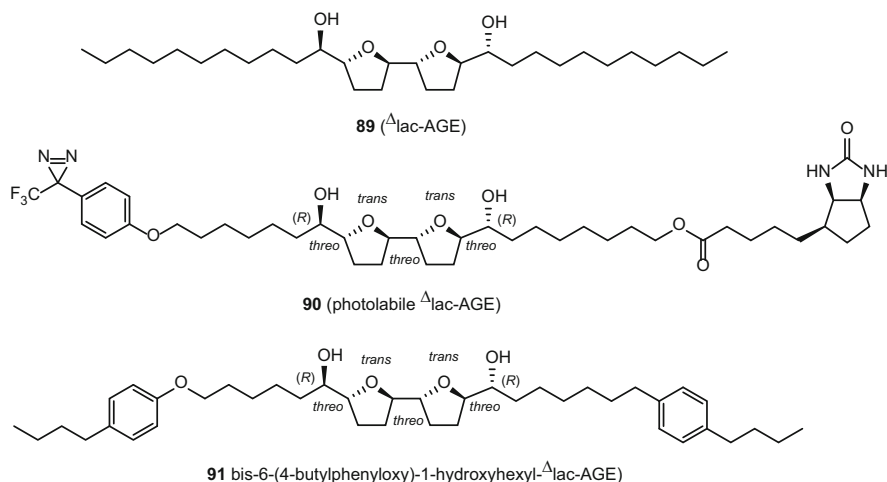


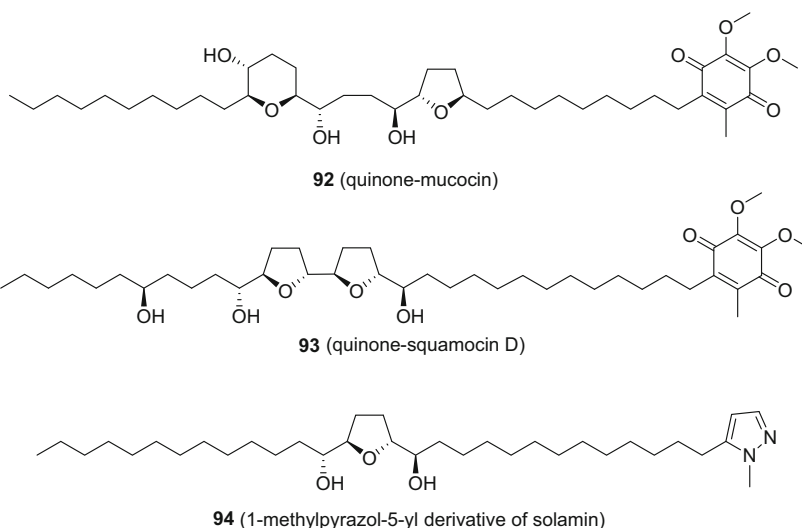
Fig. 41 Structures of Δ lac-AGE (**89**) and modified analogues **90** and **91**

complex 1 [297]. The synthetic bis-6-(4-butylphenyloxy)-1-hydroxyhexyl Δ lac-AGE (**91**) showed a similar IC_{50} value to that observed for bullatacin (**7**) in terms of the reduction of NADH oxidase activity (0.60–0.65 mmol NADH/min/mg of protein) in submitochondrial particles (see Fig. 41). Intriguingly, Ichimaru et al. demonstrated that the inhibitory site of complex I on which the Δ lac-AGEs act might be different from that of the natural AGEs [296, 297].

In addition to the total syntheses of various AGEs, some specialized analogues were designed to improve the bioactivities through, for example, modifications of the γ -lactone ring, the THF ring, and the hydroxy group moieties on the aliphatic chain.

7.2 Modifications of the γ -Lactone Ring Moiety

Hoppen et al. designed and prepared quinone-mucocin (**92**) and quinone-squamocin D (**93**) to elucidate the mechanisms of action of the AGEs. The IC_{50} values of quinone-mucocin (**92**) and quinone-squamocin D (**93**) in the inhibition of the mitochondrial NADH-ubiquinone oxidoreductase complex were 3.6 and 1.7 nM [298]. These results supported their hypothesis: AGEs are competitive inhibitors at the ubiquinone binding site of complex I based on the structural similarity between the butenolide and the quinone. Arndt et al. synthesized a systematic variation of featured structures, the butenolide and the ether components, to evaluate the critical factors for the interaction of the AGEs with complex I. Their results and data from the smaller substructures indicated that the substructures of the AGEs require the polyether component and the lipophilic side chain for strong binding of the AGEs to complex I [299].



In addition, aromatic heterocycles are commonly found as base structures of potent complex I inhibitors. Duval et al. thus replaced the α,β -unsaturated γ -lactone moiety of squamocin (**6**) with benzimidazole via an unusual condensation-oxidative decarboxylation reaction with 1,2-diamines in the presence of acetic acid and oxygen. Although they did not clarify the inhibitory ability of modified squamocin toward complex I, one of the benzimidazole analogues showed cytotoxicity (KB 3-1 cells) with an IC_{50} value of $2.2 \times 10^{-3} \mu M$ and induced a 61% accumulation of the G1 phase of the cell cycle at concentrations of 1–5 nM, with apoptosis above 10 nM [300]. In 2006, this same group of investigators partially synthesized a series of heterocyclic analogues of squamocin (**6**). Their results suggested that the binding of this hybrid inhibitor was responsible for a negative allosteric effect at the level of the first ubiquinone-binding site of mitochondrial complex I [301]. This group also prepared a small assembly of the γ -ketoester derivatives of squamocin (**6**) and screened their biological activities, including their cytotoxicity against KB 3-1 cells, and also evaluated the inhibition of mitochondrial complexes I and III. However, these modified analogues with an open γ -lactone ring did not show any better activity than that of the parent compound, squamocin (**6**) [302].

Except for the adjacent bis-THF and non-adjacent bis-THF AGEs, Kojima et al. prepared a series of α,β -unsaturated- γ -lactone-free, nitrogen-containing heterocyclic analogues of solamin (**53**). The cytotoxic activities of the compounds were investigated against 39 tumor cell lines. One of these, a 1-methylpyrazol-5-yl derivative (**94**) showed a selective increase in cytotoxicity against NCI-H23 cells with potency a 80 times greater than that of solamin (**53**) [303].

7.3 Modification of the THF Ring Moiety of Acetogenins

In 2000, two independent groups proposed replacing the ethylene bridge in the AGE THF rings with normal- and iso-terminal lactone moieties, respectively, based on both the difficulty associated with total syntheses of AGEs and the straightforward means by which their structures can be simplified [304, 305].

Yao and co-workers studied two other series of simplified acetogenin derivatives, AA005 (**95**) and its analogues, which showed potent antitumor activities and significant selectivity between normal cells and cancer cells (see Fig. 42) [306]. Zeng et al. designed and synthesized a series of (4*R*)-hydroxy analogues of AGEs based on the naturally occurring lead compound, bullatacin (**7**). Preliminary screening data showed that the IC_{50} values of (4*R*)-hydroxylated AA005 (**96**) were 1.6×10^{-3} and 8×10^{-2} $\mu\text{g}/\text{cm}^3$ against HT-29 and HCT-8 cells (see Fig. 42). A remarkable enhancement effect was observed for AA005 (**95**) and its (4*R*)-hydroxylated analogues **96** and **97** (see Fig. 42) [307]. The results obtained indicated that both the butenolide and ethylene glycol subunits play essential roles in mediating the cytotoxicity of those compounds against selected tumor cell lines. Recently, additional evidence has indicated that AA005 (**95**) can cause growth inhibition and autophagy of colon cancer cells by depleting ATP, activating AMP-activated protein kinase (AMPK) and inhibiting the mTOR complex 1 (mTORC1) signal pathway. Compound AA005 (**95**) also inhibits cisplatin-triggered up-regulation of mTOR and synergizes with this cancer chemotherapeutic drug in the suppression of proliferation and induction of apoptosis of colon cancer cells [307]. However, the presence of a hydroxy group at C-10 and the absolute configuration of the methyl group on the butenolide moiety are less important for their activities [308].

While Rodier et al. introduced a benzoyl group to adjust the moiety between the ether linkage, analogues **98a–98g** of this type (Fig. 43) displayed interesting cell cycle effects. The analogues were found to be less potent than the cytotoxic agent,

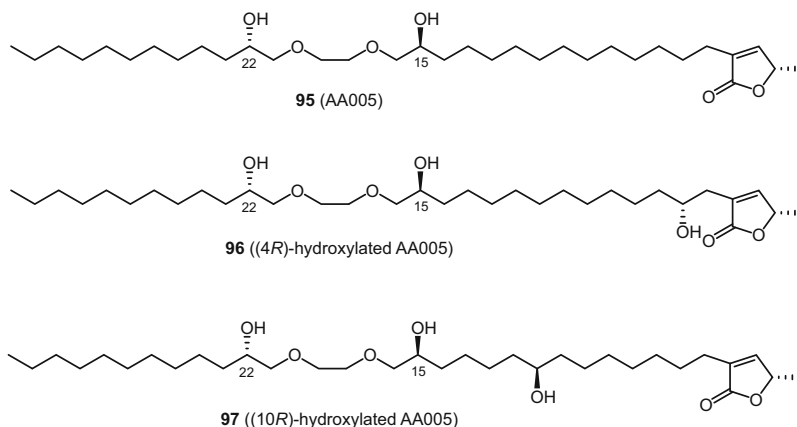


Fig. 42 The structures of Zeng-type simplified mimics **95–97** of AGEs

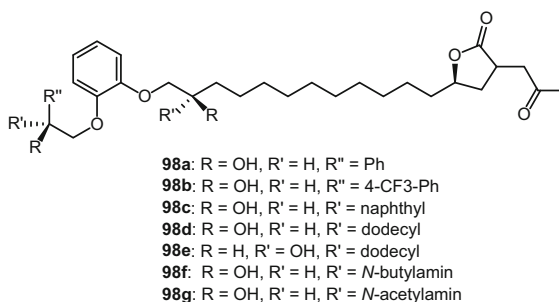


Fig. 43 The structures of Rodier-type simplified mimics of AGEs **98a–98g**

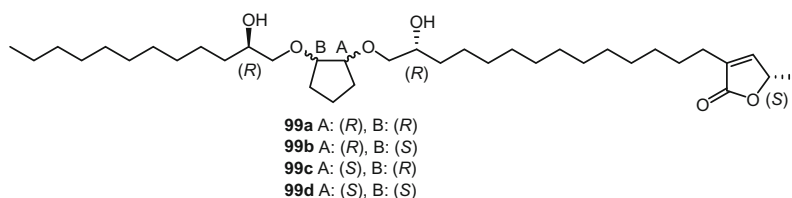


Fig. 44 The structures of Fujita-type simplified mimic of AGEs **99a–99d**

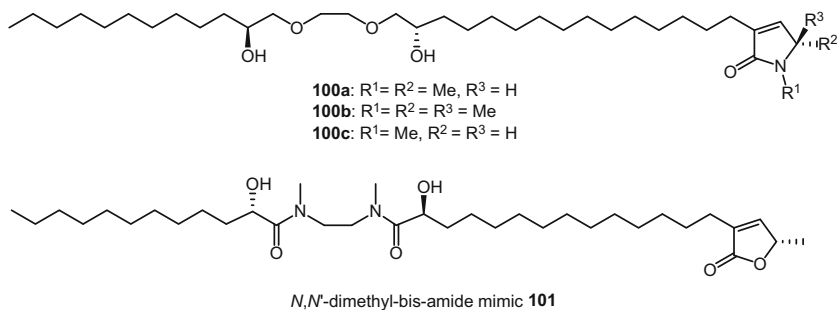


Fig. 45 The structures of modified analogues **100a–100c** and **101** of AA005 (**95**)

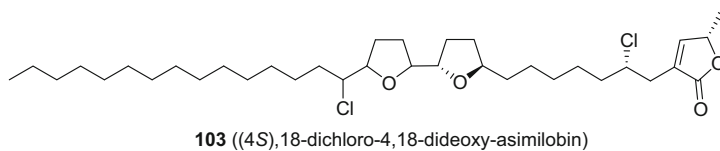
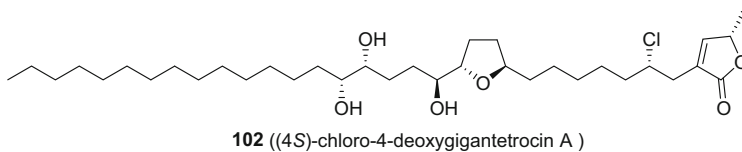
bullatacinone (**81**), a compound with the same terminal lactone unit [309]. Fujita et al. replaced the bis-adjacent THF ring by a 1,2-cyclopentanediol bis-ether skeleton to obtain simplified mimics **99a–99d** (see Fig. 44). Based on the evaluation of the inhibitory effects on mitochondrial NADH:ubiquinone oxidoreductase (complex I), compounds containing the 1,2-cyclopentanediol bis-ether motif also showed very potent inhibitory activity at the nanomolar level [310].

For a study of AGE mimics, Liu et al. designed, synthesized, and evaluated a new series of compounds containing a terminal lactam [311]. They found that the *N*-methylated lactam-containing mimics of AGEs **100a–100c** and **101** (see Fig. 45), the modified analogues of AA005 (**95**), exhibited comparable potencies to that of

the parent compound and similar selectivity for the cancer cells represented. It was also revealed that the stereogenic center on the lactam is not essential for cytotoxic activity. Liu et al. synthesized a series of analogues by replacing the acyclic bis-ether functionality of AA005 (**95**) with certain conformationally constrained fragments. Interestingly, most newly synthesized mimetics were found to exhibit potent activities against breast cancer cells and showed selectivity between cancerous and non-cancerous cells. Among those, an *N,N'*-dimethyl bis-amide mimic **101** of AGE exhibited greater potency against MDA-MB-468 cells than did its parent molecule, AA005 (**95**) (see Fig. 42). Xiao et al. indicated that certain bis-amide analogues of AA005 (**95**) make this unique class of anticancer agents simpler and allow more flexibility for their future development [312]. Also, analogues bearing a biphenyl moiety in the hydrocarbon chain part of AA005 (**95**) exhibit more potent antiproliferative activity and preferentially target cancer cells over normal cells [312].

7.4 Replacement of the Hydroxy Group on the Aliphatic Chain

Investigators have studied the effects of the replacement of the hydroxy groups on the aliphatic chain of AGEs. Ye et al. obtained the halogen-substituted AGEs, (4*S*)-chloro-4-deoxygigantetrocin A (**102**) and (4*S*)-18-dichloro-4,18-dideoxyasimilobin (**103**), by treating gigantetrocin A (**47**) with triphenylphosphine and CCl₄. However, the chlorinated products showed decreased bioactivities in the brine shrimp lethality test and when evaluated against selected human tumor cell lines [313]. In contrast, Kojima et al. made C-4-fluorinated solamin (**104**) and evaluated its cytotoxic activities against 39 cancer cell lines (see Fig. 46). They found **104** to show more potent growth inhibitory activity against cancer cell lines than solamin (**53**) [314].



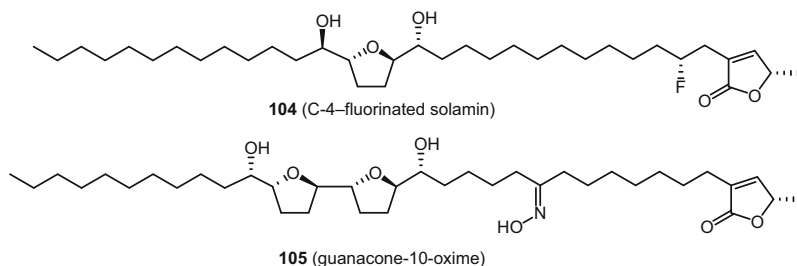


Fig. 46 The structures of C-4-fluorinated solamin (**104**) and guanacone-10-oxime (**105**)

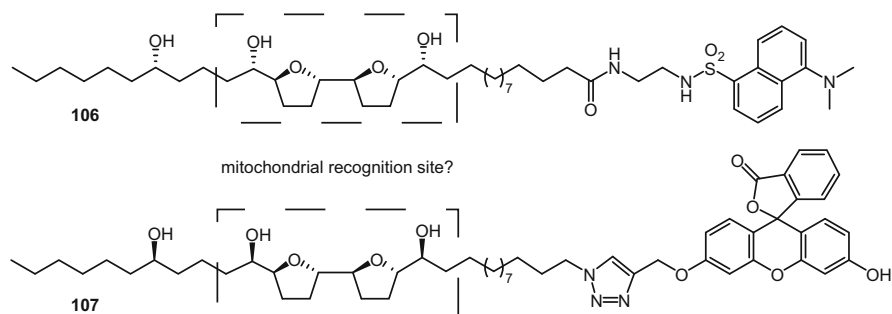
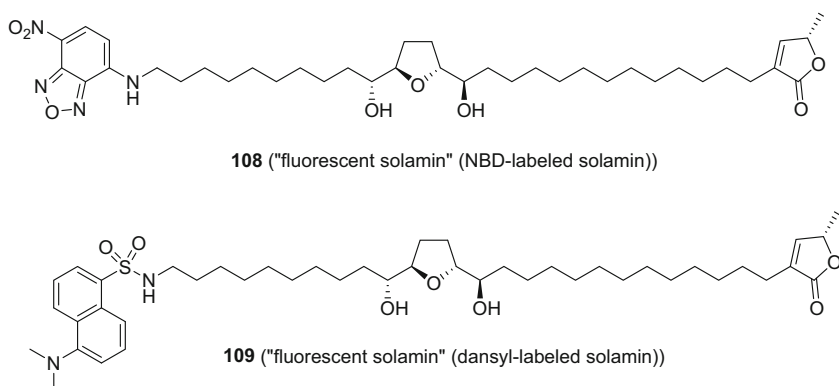


Fig. 47 The structures of fluorescent-hybridized AGEs **106** and **107**

In related work, Gallardo et al. made 10-oximeguanacone (**105**), the first bioactive nitrogenated AGE, which showed potent inhibition toward complex I by the titration of the NADH oxidase and NADH:ubiquinone oxidoreductase activities (see Fig. 46) [315]. Duret et al. partially synthesized amino derivatives from two natural AGEs, rolliniastatin-1 (**28**) and squamocin (**6**). Although it is noteworthy that these amino-AGEs still retain some activity, more studies are required to confirm the potencies of these derivatives as new specific and efficient anticancer agents [316].

A variety of chemical strategies have been applied to investigate biological processes. Recently, fluorescent modifications became powerful tools for visualizing the distribution of bioactive natural products in cells and investigating their targeting. In 2005, Derbre et al. synthesized hybrids consisting of an AGE tail connected to a fluorescent tag (see Fig. 47). Using fluorescence microscopy, two of the fluorescent-hybridized AGEs **106** and **107** were observed initially in Jurkat cell mitochondria, but they diffused into the cytosol of apoptotic cells, supporting the conclusion that squamocin (**6**) passes through the plasma membrane and targets the mitochondria. Indeed, both semi-synthetic fluorescent derivatives were shown to be potent apoptosis inducers that were directed to this organelle. Moreover, they proposed that the lactone moiety seems not to interfere with mitochondrial

targeting but apparently influenced the activity [317]. Alexander et al. attached ethyl 7-dimethylaminocoumarin-4-acetate to the diols of (–)-mucocin (**37**) through amide coupling chemistry. Although coumarin-labeled-mucocin can also induce fluorescently coded morphogenic responses, no expected response was found [318]. This result might be due to the occupation of the mitochondrial recognition site by the fluorescent coumarin group. To overcome this above disadvantage, Tanaka et al. labeled the terminal aliphatic chain of solamin (**53**) with the fluorescent groups, 7-nitrobenzo[c][1,2,5]oxadiazol-4-yl-amino (NBD-NH-) and 5-dimethylaminonaphthalen-1-yl-sulfonamide (dansyl-NH-), to produce NBD-labeled solamin (**108**) and dansyl-labeled solamin (**109**), in 2007 and 2009 [319, 320]. It was anticipated that these compounds may be used to explore the cellular targeting of AGEs.



Liu et al. modified the C-10 hydroxy group of some AGE mimics to introduce a label based on the results of the cytotoxicity screening of parallel synthetic analogues. Fluorescent-imaging studies revealed that the AA005-flu derivatives **110** and **111** (AA005 (**95**) connected with fluorescent groups) in normal human cells was significantly different from that in cancer cells (see Fig. 48). AA005-flu accumulated in the mitochondria of the cancer cells. This direct and visible evidence suggests that membrane recognition of AA005 (**95**) is involved in its selective bioactivity [321].

The Yao group recently also developed three representative AA005-like molecules **112–114** via formation of small nitrogen-containing heterocycles or amide bond based on the concept of click chemistry, which was introduced by Sharpless in 2001, describing the tailored chemistry to generate compounds quickly and reliably by joining small units together (see Fig. 49) [322]. These nitrogen-containing analogues exhibited significantly inhibitory activities against several cancer cell lines in low micromolar concentrations.

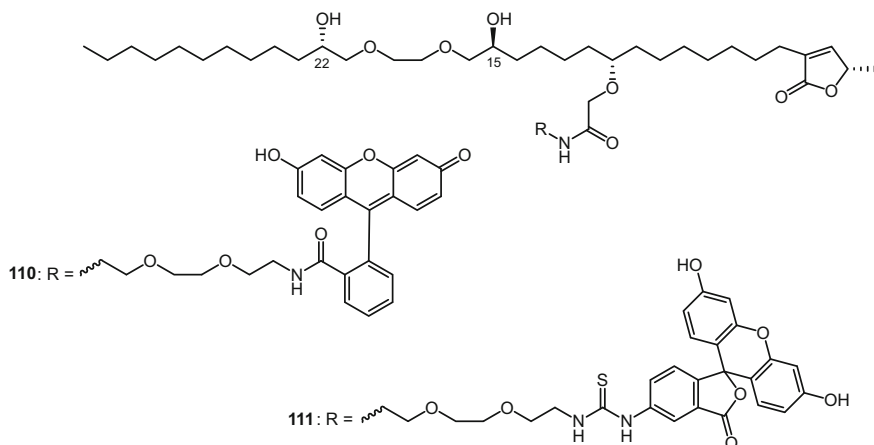


Fig. 48 The structures of AA005-flu derivatives **110** and **111**

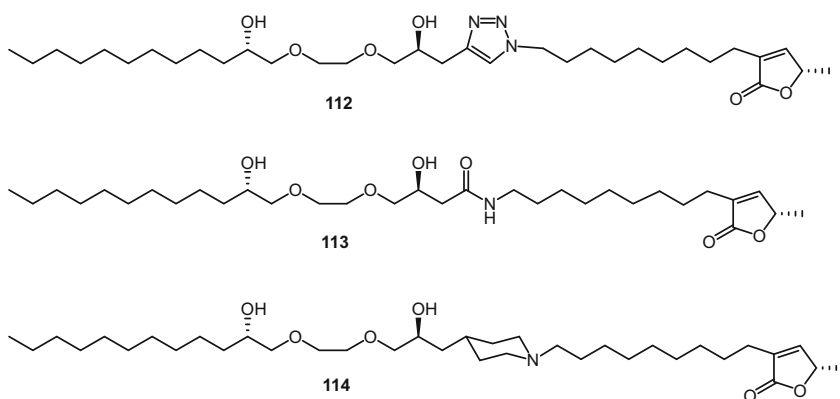


Fig. 49 Three newly proposed AA005-like molecules, **112–114**

7.5 Mimic Synthesis Study

Yao's group further designed a series of linear dimeric compounds mimicking naturally occurring AGEs, for example the AGE mimic **115** (see Fig. 50), and evaluated the cytotoxic activities of these analogues toward the growth of cancer cells by the MTT method. Interestingly enough, these compounds showed selective action favoring the human cancer cell lines used. The authors pointed out that with appropriate conformational constraint their assembled moieties of AGEs might be useful to optimize the potential anticancer properties of this class of compounds [323].

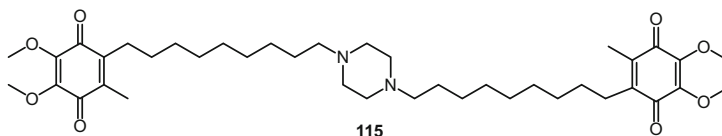


Fig. 50 A new mimicking AGE **115**, the linear dimeric compound with bis-terminal benzoquinone

8 Annonaceous Acetogenin-Containing Products and Their Potential Development

On many websites, paw paw extract-containing products are commonly available; however, there are only a few reports that mention quality control studies for annonaceous acetogenin-containing products [324]. In 1976, McLaughlin et al. found that extracts of the leaves and twigs of the U.S. native paw paw tree, *Asimina triloba*, were active in the cytotoxicity screens of the U.S. National Cancer Institute (NCI). Following their phytochemical study to determine the compounds present [255], McLaughlin et al. used the three most active AGEs, bullatacin (**7**), asimicin (**8**), and trilobacin (**116**) (Fig. 51), to serve as marker compounds for the examination of various extracts of the paw paw tree by LC/MS/MS. In this work, they demonstrated that small twigs collected in the months of May and June were the optimum plant sources for the commercial harvesting of paw paw biomass for extraction. McLaughlin further developed some useful commercial products containing the AGEs, including a head lice shampoo (in 2001), and ointment, lotion, and spray for plant pests, as well as paw paw capsules (in 2003) for human administration. The entire process from the safety and toxicology of the AGEs to the introduction of commercial products was described in McLaughlin's 2008 review [325]. More recently, Cuendet et al. reported the potential of a standardized extract from the twigs of *A. triloba* to mediate a cancer chemopreventative effect in the *N*-methyl-*N*-nitrosourea-induced mammary carcinogenesis model. As McLaughlin et al. did before, they used three potent bioactive AGEs, bullatacin (**7**), asimicin (**8**), and trilobacin (**116**) in their standardized extract. Mammary tumor latency was increased from 55 to 66 days in Sprague-Dawley rats given a diet containing paw paw extract (1250 and 2500 mg/kg diet; based on maximum tolerated dose studies) [326].

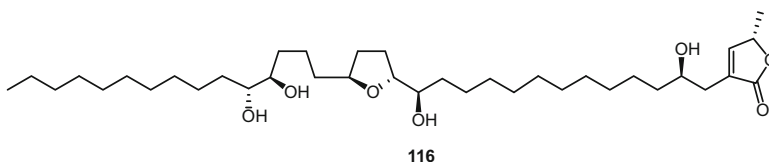


Fig. 51 Structure of trilobacin (**116**)

In Taiwan and elsewhere, plants of the genus *Annona* are important economic crops for their edible fruits. The abundant material obtained from the seeds and the potent cytotoxic effects of the AGEs from this material has stimulated the possible further development of these compounds as pharmaceutical products. In addition to the aforementioned studies, oral gavage (p.o.) animal studies have been performed by MDS Pharma Services-Taiwan for which our group provided the material (unpublished data). An extract powder from *A. muricata*, WYC-AA07, was applied to a xenograft tumor in a SCID mouse model using implanted human MCF-7 breast tumor cells. WYC-AA07 at 10 mg/kg was administered p.o. daily for a total of ten doses. The tumor sizes, body weights and signs of overt animal toxicity after dosing were monitored and recorded for 25 days. This extract caused significant decreases in tumor weights as measured from days 13 to days 25. However, it also caused significant decreases in body weight on days 9, 13, 17, and 21 (unpublished data). Another SCID mouse xenograft experiment was performed on this extract using implanted human HT-29 colon tumor cells. Extract WYC-AA07 at 20 mg/kg p.o. caused death in half of the animals and a significant decrease in body weight on day 8 (unpublished data). Recently, the acute toxicity of squamocin (**6**) was evaluated in nude mice at 20 mg/kg p.o. Most of the animals showed an abnormal movement pattern that caused the mice to move uncontrollably in a lateral direction. However, the mice apparently recovered after the administration of squamocin (**6**) was stopped. Moreover, a Chinese group also investigated the antitumor activities of AGEs in vivo using S180 and HepS xenografts in mice. Their results revealed that three types of AGEs effectively suppressed tumor growth in a dose-dependent fashion. Interesting, their results also matched with those of previous studies: adjacent bis-THF AGEs were more active than nonadjacent bis-THF AGEs, nonadjacent bis-THF AGEs were more active than mono-THF AGEs [327]. Furthermore, the present authors performed a pharmacokinetic study using LC-MS to validate the quantification of AGEs in rats [328].

On the other hand, an ethnopharmacological investigation reported a similar side effect of AGEs in that a neurodegenerative tauopathy endemic to the Caribbean island of Guadeloupe was suspected to be linked to the consumption of annonaceous plants [274], Escobar-Khondiker et al. further found that annonacin induced the retrograde transport of mitochondria to decrease ATP levels, which induces changes in the intracellular distribution of tau in a way that shares characteristics with some neurodegenerative diseases [329]. The demonstrated adverse effects of AGEs on neuronal cells should be of major concern when considering their potential commercial development.

9 Summary and Perspectives

The annonaceous acetogenins (AGEs) are one of the most interesting classes of plant-derived natural products to have been investigated during the last three decades. They exhibit a wide variety of biological activities. Impressively, some

of them have comparable cytotoxic potency to the widely used anticancer agent, paclitaxel, against various cancer cells. Two structural features, the hydroxylated tetrahydrofuran (THF) and γ -lactone ring moieties, are considered to be the pharmacophores that block the electron transport system of mitochondrial complex I. Much effort has been dedicated to elucidating the underlying cytotoxic mechanisms of the AGEs and to synthesizing AGE analogues by altering the spacing between the two pharmacophores, or removing either one of these units (Δ Lac AGEs or muricatacin (**22**)), or mimicking the THF rings by ether linkages. Although none of the modified AGEs obtained thus far has demonstrated activities comparable to those of the naturally occurring AGEs, studies on the synthesis and mechanisms of action of these compounds have provided solid fundamental knowledge and drug discovery insights. For example, some of the studies on analogues of AGEs have created a series of compounds that are based on completely different skeletons, of which some also show excellent bioactivities against various cancer cells. Not only promising antitumor effects, but also serious side effects of the AGEs have been found, such as neurotoxicity and the generation of symptoms of atypical parkinsonism. These may greatly limit prospects for the drug development of the AGEs. It is recommended that the composition of AGEs and dopaminergic alkaloids in the edible pulps of commercially used annonaceous fruits be evaluated so that their potential for causing neurotoxicity-related side effects can be clarified.

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