Unusually cyclized triterpenes: occurrence, biosynthesis and chemical synthesis

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The biosynthetic origin of most of triterpenes lies in cascade cyclizations and rearrangements of the acyclic precursors squalene (S) and 2,3-oxidosqualene (OS), processes leading to tetra- and pentacyclic triterpene skeleta. Apart from these, a number of triterpenoid structures derived from cyclization processes, that are different from those leading to tetra- and pentacyclic triterpenes, are also found in Nature. We have defined these processes as unusual cyclizations, and grouped them in three blocks, namely, incomplete cyclizations of the corresponding S-derived precursors, cyclizations of S or OS towards polycyclic triterpenes and subsequent cleavage of the preformed ring systems, and two independent cyclizations of the S- or OS-derived precursor. Apart from the molecules obtained from intact organisms, we will also consider the compounds obtained from *in vitro* cyclizations promoted by enzyme systems. After establishing which compounds could unambiguously be grouped under the term 'unusually cyclized triterpenes', this review moves on to the advances achieved in this kind of structure during the last ten years. These advances are presented in three parts. The first one presents the structure and biological properties of the unusual triterpenes reported in the last decade. The second part considers the main biosynthetic pathways which justify the formation of these triterpenes from their corresponding acyclic precursors. Finally, we look at the achievements made in different synthetic strategies directed at some of these molecules. One hundred and twenty-three references are cited.

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1 Introduction

Triterpenes are one of the most structurally diverse groups of terpenes, with more than 100 skeleta described as natural products.[1–4] The origin of this diversity is the type of mechanism that takes part in their biosynthesis – the enzymatic systems generically named terpenoid synthases act on acyclic polyprene precursors generating carbocations that, by electrophilic additions on double bonds, produce processes of cyclization and rearrangements. In the specific case of the triterpenes, the triterpenoid synthases act on the most common precursors – squalene (S) and oxidosqualene (OS) – and biosynthesis is initiated by enzymatic protonation of the terminal double bond or the oxirane respectively. As those precursors contain five or six double bonds, the possibilities of cyclization accompanied by rearrangement are theoretically very great.[5–7] This has generated a good deal of interest amongst scientists. In this context, the hypothesis of isoprene as a biogenetic precursor for triterpenes by Ruzicka, Eschenmoser, Arigoni *et al.*[8,9] was a significant milestone which was complemented by the characterization of

some thirty OS cyclases (OSCs) and various studies of mutations on the genes involved in these cyclization processes.[5,10–12]

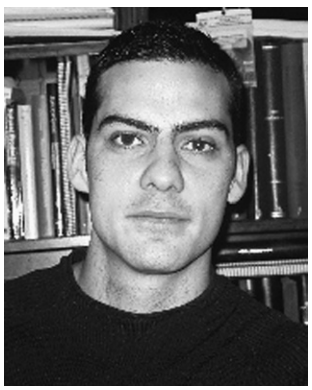
Most of the triterpenes contain tetra- or pentacyclic skeletons, but together with these a number of triterpenoid structures derived from cyclization processes different to those leading to tetra- and pentacyclic triterpenes have also been reported from Nature. We have named these structures 'unusually cyclized triterpenes', and have grouped them as follows:

a) Triterpenes arising *via* an incomplete cyclization of the corresponding S-derived precursors. These processes start at the terminal isopropylidene unit or at its corresponding epoxide and lead to mono-, bi- and tricyclic triterpenic skeletons.

b) Triterpenes arising *via* cyclization of S or OS towards polycyclic triterpenes and subsequent cleavage of the preformed ring systems.

c) Triterpenes arising *via* two independent cyclizations of the S- or OS-derived precursor.

The aim of this review is to cover the structure, biological properties, biosynthesis and chemical synthesis of the unusually cyclized triterpenes described in the last ten years. Apart from the molecules obtained from live organisms, compounds obtained

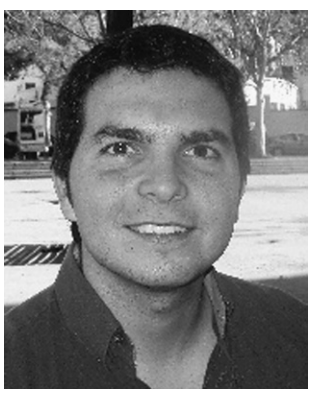


Victoriano Domingo

Victoriano Domingo was born in Granada (Spain) in 1981 and graduated in Chemistry in 2006 at the University of Granada. He is a Ph.D. student at the same University under the supervision of Prof. Alejandro F. Barrero and Dr José F. Quílez. Currently, he is in the process of completing the total synthesis of various triterpenes. His interests lie in modern synthetic methodologies with application in the field of bioactive natural products.

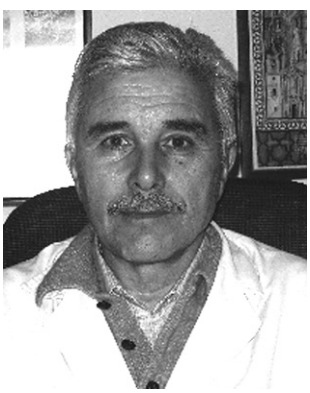
José F. Quìlez del Moral

José F. Quílez del Moral was born in Linares (Spain) in 1967 and studied Chemistry at the University of Granada, where he graduated in 1990. He received his Ph.D. degree in 1996 under the supervision of Prof. A. F. Barrero. In 1997, he started a 20 month post-doctoral fellowship with Prof. S. Arseniyadis at the Institut de Chimie des Substances Naturelles at Gif-sur Yvette (France) working on the total synthesis of taxol. He returned to Granada as an assistant professor and joined Prof. A. F Barrero's group in 1998. He is currently a Senior Lecturer and his research interests are directed towards the development of new methods for the synthesis of molecules having biological activity.



Jesús F. Arteaga

Jesús F. Arteaga was born in Salamanca (Spain) in 1979 and he graduated in Chemistry in 2002 at the University of Granada. He received his Ph. D. degree in 2006 under the supervision of Prof. Alejandro F. Barrero at the same university. From 2006–2007 he formed part of a post-doctoral team at the Institut de Chimie des Substances Naturelles (Gif-sur-Yvette, France) with Prof. Simeon Arseniyadis working on the total synthesis of biologically active natural products. He is currently a post-doctoral investigator at the University of Huelva (Spain). His research interests are mainly focused on the development of new applications of free-radical chemistry in the synthesis of natural products and homogeneous catalysis.



Alejandro F. Barrerro

Alejandro F. Barrerro was born in Orense (Spain) in 1949. He obtained his Ph.D. degree in 1975 at the University of Salamanca under the guidance of Professors Joaquín Pascual de Teresa, Arturo San Feliciano and Inés Sánchez Bellido. After working as a research scientist at the Compañía Española de Petróleos Research Center in San Fernando de Henares (Spain), he returned to the University of Salamanca as a Lecturer. He moved to the University of Granada as Full Professor in 1983, where he is Head of the Organic Chemistry Department. He is also President of the Natural Product Group of the Royal Spanish Society of Chemistry. His work includes the direction of more than 40 doctoral theses. His current interests are the chemistry and biotechnology of terpenoids and the application of both radical cyclization reactions and new couplings catalyzed by transition metals to the synthesis of natural bioactive products.

from *in vitro* cyclizations of S or OS promoted by enzymatic systems are also included.

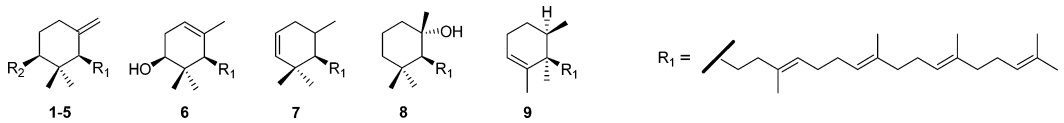
2 Occurrence and biological activities of unusually cyclized triterpenes

2.1 Triterpenes resulting from incomplete cyclizations of S and OS

Monocyclic triterpenes: Achillanes and neoachillane. Although achilleol A **1**, the first monocyclic triterpene to be described, was isolated from the plant *Achillea odorata* (Asteraceae) in 1989,[13] it is worth noting the recently described production of this compound by a number of mutants of lanosterol and cycloartenol synthase (Table 1). Compound **1** and some derivatives were also found in other species of the Umbelliferae,[17] Asteraceae,[18] Theaceae,[19] and Gramineae.[20] Camelliol C **6**, first found in *Camellia sasanqua* (Theaceae),[19] has also been isolated from *in vitro* cyclizations promoted by enzymatic systems.

Monocyclosqualene **7** was isolated from the herb *Ligularia fischeri* var. *spiciformis* (Compositae),[30] and 3-deoxyachilleol A **5** from a squalene hopene cyclase (SCH) mutant of the prokaryotic bacterium *Alicyclobacillus acidocaldarius*.[29] Only camelliol C **6** was reported to present a slight inhibitory effect

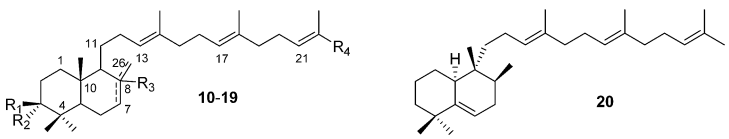
Table 1 Monocyclic triterpenes with the achillane skeleton



1-5 6 7 8 9

Compound	R^2	Source
Achilleol A (**1**)	OH	*Bupleurum spinosum*,[17] *Santolina elegans*,[18] *Camellia sasanqua*, *C. japonica*,[19] wheat germ oil and rice bran oil,[20] SHC mutant [*Alicyclobacillus acidocaldarius* ΔG600],[21] OSLC mutant [*S. cerevisiae* H234 (M/Y/F), Y510 (A/K/W/H),[22,23] V454A, V454G],[24] CAS1 mutant [*Arabidopsis thaliana* I481 (A/G),[25] Y410C Y532H[26]], Gene expression: CAMS1 [*At1g78955*],[27] BARS1 [*At4g15370*][28]
Achilleol A esterified derivative (**2**)	$CH_3(CH_2)_{10}COO$	*B. spinosum*,[17] *S. elegans*,[18] *C. sasanqua*,[19] *C. japonica*,[19] wheat germ oil and rice bran oil[20]
Achilleol A esterified derivative (**3**)	$CH_3(CH_2)_{12}COO$	
Achilleol A esterified derivative (**4**)	$CH_3(CH_2)_{14}COO$	
3-Deoxyachilleol (**5**)	H	SHC Mutant [*Alicyclobacillus acidocaldarius* D377 (C/N), Y612A][29]
Camelliol C (**6**)	—	*C. sasanqua*,[19] *C. japonica*,[19] OSLC mutant: [*S. cerevisiae* Y510 (K/W)],[22] CAS1 [*Arabidopsis thaliana* I481 (A/G)],[25] Gene expression: CAMS1 [*At1g78955*],[27] BARS1[*At4g15370*][28]
Monocyclosqualene (**7**)	—	*Ligularia fischeri*[30]
6α-Hydroxyachilla-9,13,17,21-tetraene (**8**)	—	SHC mutants [*Alicyclobacillus acidocaldarius* L607(F/W)][31]
Neoachillapentaene (**9**)	—	SHC mutants [*Alicyclobacillus acidocaldarius* L607(F/W), Y420W][31]

Table 2 Bicyclic triterpenes with the polypodane skeleton



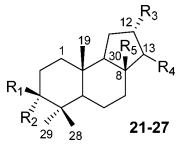
10-19 20

Compound	Δ	R^1	R^2	R^3	R^4	Source
α-Polypodatetraene (**10**)	$\Delta^{8(26)}$	H	H	—	H	SHC mutants [*A. acidocaldarius*Y420A, Y609F][34,35]
γ-Polypodatetraene (**11**)	Δ^7	H	H	—	H	SHC mutants [*A. acidocaldarius* F365A,[36] Y420A,[34] Y609 (A/L/C/S),[37,38] Y612A,[37] L607K[39,40]]
3β-Hydroxy γ-polypodatetraene (**12**)	Δ^7	OH	H	—	H	*Cratoxylum cochinchinense*[41]
Myrrhanol A (**13**)	—	OH	H	α-OH	CH_2OH	*Balsamodendron mukul*[33,42]
Myrrhanone A (**14**)	—	O	O	α-OH	CH_2OH	*B. mukul*[33,42]
Myrrhanone A acetate (**15**)	—	O	O	α-OH	CH_2OAc	*B. mukul*[43]
Myrrhanol B (**16**)	—	OH	H	α-OH	COOH	*B. mukul*[43]
Myrrhanone B (**17**)	—	O	O	α-OH	COOH	*B. mukul*[43]
21,22-Dihydro α-polypodatetraene (**18**)	$\Delta^{8(26)}$	H	H	—	H	*Tetrahymena pyriformis*[44]
21,22-Dihydro γ-polypodatetraene (**19**)	Δ^7	H	H	—	H	*T. pyriformis*[44]
Neopolypodatetraene (**20**)	—	—	—	—	—	SHC mutant [*A. acidocaldarius* F365A][37]

on the HIV transcriptase.[14] It is possible that these compounds may have a biological role as reinforcers of the cell membranes.[15,16]

Bicyclic triterpenes: Polypodanes. Table 2 lists the structures of eleven bicyclic triterpenes with the polypodane skeleton. Herein, neopolypodatetraene **20**, a rearranged polypodane described in SHC mutants from *Alicyclobacillus acidocaldarius*,[37] is also included. Although previously described in species of the Polypodaceae family,[32] α- and γ-polypodatetraene have also been isolated recently from mutated enzymes. The polypodanes oxygenated at C-3 (**12–17**) were found in *Balsamodendron mukul* (Burseraceae),[33,42] and *Cratoxylum cochinchinense* (Hypericaceae).[41] Of these, myrrhanol A **13** and myrrhanol B **16** possess interesting anti-inflammatory activity in various assays. The former is more potent than hydrocortisone, and is considered a plausible candidate as an anti-inflammatory agent, and probably with fewer side effects.[33]

Table 3 Triterpenes with the malabaricane skeleton



21-27

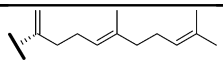
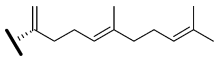
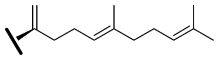
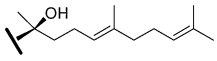
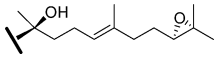
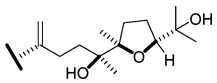
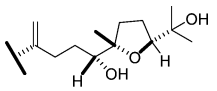
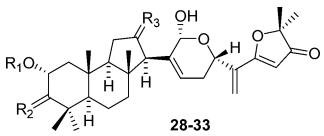
Compound	R^1	R^2	R^3	R^4	R^5	Source
Malabarica-14(27),17,21-trien-3-ol (**21**) (13*R* or 13*S*)	OH	H	H		Me	SHC mutant [*A. acidocaldarius* ΔG600],[21] Gene expression: BARS1[*At4g15370*][28]
13β-Malabaricatriene (**22**)	H	H	H		Me	SHC mutant [*A. acidocaldarius* F601A][45]
13α-Malabaricatriene (**23**)	H	H	H		Me	SHC mutants [*A. acidocaldarius* F601A, Y420A, I261A],[31,45,46] sediment lake Cadagno[47]
Arabidiol (**24**)	OH	H	H		Me	Gene expression: [*At4g15340*],[48] SHC mutant [*A. acidocaldarius* ΔG600][21]
Arabidiol 20,21-epoxide (**25**)	OH	H	H		Me	Gene expression: [*At4g15340*][48]
26	O	O	H		Me	*Caloncoba echinata*[49]
27	O	O	H		Me	*C. echinata*[49]

Table 4 Triterpenes with the malabaricane skeleton (sodagnitins)



28-33

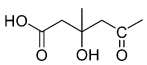
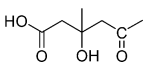
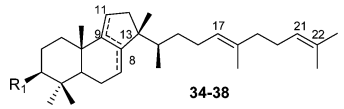
Compound	R^1	R^2	R^3	Source
Sodagnitin A (**28**)	H	O	H_2	*Cortinarius sodagnitus*, *C. fulvoincarnatus*, *C. arcuatorum*[50]
Sodagnitin B (**29**)	H	O	O	*C. sodagnitus*, *C. fulvoincarnatus*, *C. arcuatorum*[50]
Sodagnitin C (**30**)		O	H_2	*C. sodagnitus*, *C. fulvoincarnatus*, *C. arcuatorum*, *C. cf. calochrous*[50]
Sodagnitin D (**31**)		O	O	*C. sodagnitus*, *C. fulvoincarnatus*, *C. arcuatorum*[50]
Sodagnitin E (**32**)	H	H, β-OH	H_2	*C. sodagnitus*, *C. fulvoincarnatus*, *C. arcuatorum*[50]
Sodagnitin F (**33**)	H	H, β-OH	O	*C. sodagnitus*, *C. fulvoincarnatus*, *C. arcuatorum*[50]

Table 5 Triterpenes with the rearranged malabaricane skeleton



34-38

Compound	R^1	Source
Thalianol (**34**), podioda-8,17,21-trien-3β-ol	OH	Gene expression: [*At5g48010*],[51] SHC mutant [*A. acidocaldarius* ΔG600][21]
(21*S*)-21,22-Epoxy-malabarica-8,17-dien-3-ol (**35**)	OH	Gene expression: [*At5g48010*][51]
Podioda-9(11)-17,21-trien-3β-ol (**36**)	OH	SHC mutant [*A. acidocaldarius* ΔG600][21]
7,17,21-Podiodatriene (**37**)	H	SHC mutant [*A. acidocaldarius* F605A],[52,53] Gene expression: BARS1 [*At4g15370*][28]
8,17,21-Podiodatriene (**38**)	H	SHC mutant [*A. acidocaldarius* F605A][52,53]

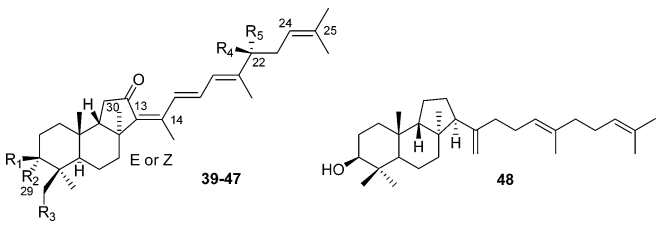
Tricyclic 6,6,5 triterpenes: Malabaricanes and rearranged isomalabaricanes. Tricyclic triterpenes containing the fused 6,6,5 system are grouped in malabaricanes (Table 3 and Table 4) (**21–33**), rearranged malabaricanes (Table 5) (**34–38**), and isomalabaricanes (Tables 6–8) (**39–76**). The difference between malabaricanes and isomalabaricanes is the stereochemistry of the B–C ring junction – *trans-anti-trans* and *trans-syn-trans* respectively – while in the rearranged malabaricanes Me-30 is absent at C-8 but at C-13. Table 4 displays a group of malabaricanes of marine origin possessing a similar side chain named sodagnitins. In two cases, compounds **30–31**, esters of hydroxymethylglutaric acid were found at C-2. The side chain of these molecules presents different degrees of oxidation. Thus, up to four oxygens can be found in this moiety, mostly as hydroxyls or tetrahydrofurans. Compounds **26–27**, isolated from *Caloncoba echinata* (Flacourtiaceae),[49] inhibited *Plasmodium falciparum*, while sodagnitins A and C are active against *Bacillus subtilis*, *B. brevis*, and *Nematospora coryli.*[50]

Isomalabaricanes have been found exclusively in marine sponges, mostly from the Pacific, and in many cases form their yellow pigmentation. The substances possessing this skeleton are characterised structurally by a carbonyl group on C-12, an *E* or *Z* double bond on C-13 (which can undergo light-induced isomerization), and highly unsaturated systems on the side chain, which in many cases are four and five double bonds conjugated with the carbonyl on C-12. Moreover, oxygenated functions are frequently present on the ring at C-3 and on the C-29 methyl group.

They have been classified into three groups according to their structure and origin. Stelliferins (Table 6) have a methylene on C-23, and an oxygenated function on C-22. The second group comprises globostellatic acids (Table 7), isolated almost exclusively from *Rhabdastrella globostellata*. Most of these compounds contain a carboxylic acid or a methyl ester on C-29 and a highly unsaturated side chain with 4 or 5 conjugated double bonds. The third group – jaspolides and stelletins (Table 8) – either contain side chains with terminal pyrone rings (**66–67**) or a carboxylic acid in place of one of the terminal methyls of the side chain (**70–72**), or are *nor*-triterpenes that have lost the last carbon of the side chain, forming methylketones (**73–76**).

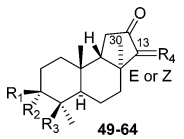
Numerous examples of isomalabaricanes have been found with cytotoxic activity. Mixtures of 29-hydroxystelliferin

Table 6 Triterpenes with the isomalabaricane skeleton (stelliferins)



Compound	Δ^{13}	R^1	R^2	R^3	R^4	R^5	Source
3-*Epi*-29-hydroxystelliferin A (**39**)	*Z*	H	OH	OH	OH	H	*Stelleta globostellata*[55]
Stelliferin G (**40**)	*Z*	H	H	OH	OAc	H	*Jaspis* species [54]
29-Hydroxystelliferin E (**41**)	*Z*	OAc	H	OH	OAc	H	*Jaspis* species,[54] *S. globostellata*[55]
29-Hydroxystelliferin A (**42**)	*Z*	OAc	H	OH	OH	H	*Jaspis* species[54]
29-Hydroxystelliferin D (**43**)	*Z*	OH	H	OH	OH	H	*S. globostellata*[55]
Stelliferin riboside E (**44**)	*Z*	H	OAc	H	H or O-ribose	O-ribose or H	*R. globostellata*[56]
3-*O*-Deacetyl-13*Z*-stelliferin riboside (**45**)	*Z*	H	OH	H	H or O-ribose	O-ribose or H	*R. globostellata*[56]
Stelliferin riboside (**46**)	*E*	H	OAc	H	H or O-ribose	O-ribose or H	*R. globostellata*,[56] *G. globostellifera*[57]
3-Hydroxy-13*E*-stelliferin riboside (**47**)	*E*	H	OH	H	H or O-ribose	O-ribose or H	*R. globostellata*,[56] *G. globostellifera*[57]
13α*H*-Isomalabarica-14(27),17*E*,21-trien-3β-ol (**48**)	—	—	—	—	—	—	OSLC [*S. cerevisiae* H234 (L/M/N/D),[58,59] F445 (C/M/N/T/D),[60] Y510(F/H)[23,61,62]]

Table 7 Triterpenes with the isomalabaricane skeleton (globostellatic acids)



49-64

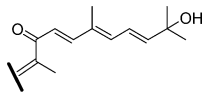
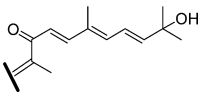
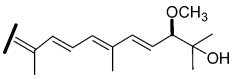
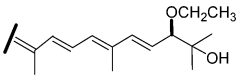
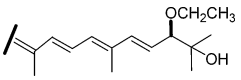
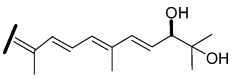
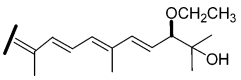
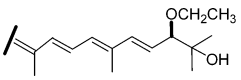
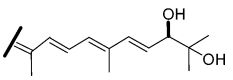
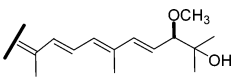
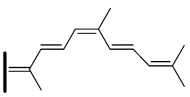
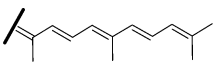
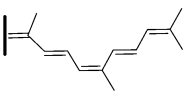
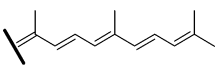
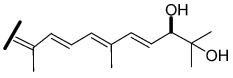
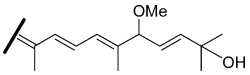
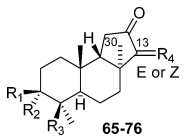
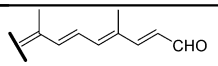
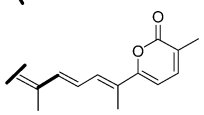
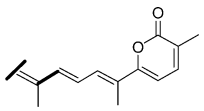
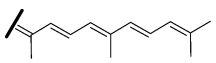
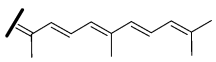
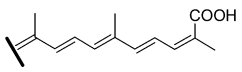
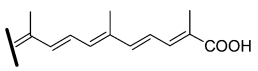
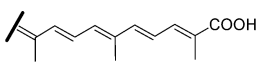
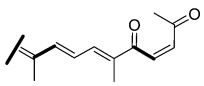
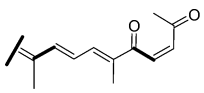
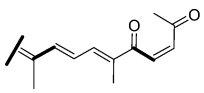
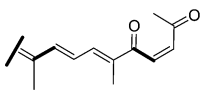
Compound	Δ^{13}	R^1	R^2	R^3	R^4	Source
Globostellatic acid F (**49**)	*Z*	H	OH	COOH		*R. globostellata*[56]
Globostelletin (**50**)	*Z*	H	OH	CH_3		*R. globostellata*[56]
Globostellatic acid G (**51**)	*Z*	H	OH	COOH		*R. globostellata*[56]
Globostellatic acid I (**52**)	*Z*	H	OH	COOH		*R. globostellata*[56]
Globostellatic acid K (**53**)	*Z*	H	OAc	COOH		*R. globostellata*[56]
Globostellatic acid M (**54**)	*Z*	H	OH	COOH		*R. globostellata*[56]
Globostellatic acid H (**55**)	*E*	H	OH	COOH		*R. globostellata*[56]
Globostellatic acid J (**56**)	*E*	H	OAc	COOH		*R. globostellata*[56]
Globostellatic acid L (**57**)	*E*	H	OH	COOH		*R. globostellata*[56]
Globostellatic acid E (**58**)	*Z*	H	OAc	$COOCH_3$		*Jaspis* species[63]
13*Z*,17*Z*-Globostellatic acid X methyl ester (**59**)	*Z*	H	OAc	$COOCH_3$		*R. globostellata*[64]
13*Z*,17*E*-Globostellatic acid X methyl ester (**60**)	*Z*	H	OAc	$COOCH_3$		*R. globostellata*[64]
13*E*,17*Z*-Globostellatic acid X methyl ester (**61**)	*E*	H	OAc	$COOCH_3$		*R. globostellata*[64]
13*E*,17*E*-Globostellatic acid X methyl ester (**62**)	*E*	H	OAc	$COOCH_3$		*R. globostellata*[64]
Globostellatic acid F methyl ester (**63**)	*E*	H	OAc	$COOCH_3$		*R. globostellata*[64]
Globostellatic acid B methyl ester (**64**)	*E*	H	OAc	$COOCH_3$		*R. globostellata*[64]

Table 8 Triterpenes with the isomalabaricane skeleton (jaspolides-stelletins)



65-76

Compound	Δ^{13}	R^1	R^2	R^3	R^4	Source
3-*O*-Acetyl-jaspiferal B methyl ester (**65**)	*Z*	H	OAc	$COOCH_3$		*Jaspis* species[63]
Jaspolide A (**66**)	*Z*	OH	H	CH_3		*Jaspis* species[65]
Jaspolide B (**67**)	*E*	OH	H	CH_3		*Jaspis* species [65]
Stelletin J (**68**)	*Z*	OH	H	CH_2OH		*R. globostellata*[66]
Stelletin K (**69**)	*Z*	OH	H	COOH		*R. globostellata*[66]
Stelletin I (**70**)	*Z*	OAc	H	CH_3		*R. globostellata*[67]
Stelletin L (**71**)	*E*	OH	H	CH_3		*Stelletta tenuis*[68]
Stelletin M (**72**)	*Z*	OH	H	CH_3		*S. tenuis*[68]
Isogeoditin A (23*Z*) (**73**)	*Z*,*E*	O	O	CH_3		*R.* aff. *distincta*[69]
Isogeoditin B (23*Z*) (**74**)	*Z*	OAc	H	CH_3		*R.* aff. *Distincta*[69]
Geoditin A (23*E*) (**75**)	*Z*	O	O	CH_3		*R.* aff. *distincta*,[69] *G. japonica*[70]
Geoditin B (23*E*) (**76**)	*Z*	OAc	H	CH_3		*R.* aff. *distincta*,[69] *G. japonica*[70]

A/29-hydroxystelliferin B and stelliferin G/13 E-stelliferin G showed antiproliferative activity against melanoma cells (MALME-3M),[104] with an IC_{50} value of 0.11 and 0.23 μg/mL respectively. Stelliferin riboside **44** and 3-*O*-deacetyl-13, 14 *Z*-stelliferin riboside **45** showed potent activity against the mouse lymphoma cell line L5178Y.[56]

Stelliferin riboside **44** and the 3-*epi*-acetate derivative of 29-hydroxystelliferin **E 41** were shown to induce 29% and 23% DNA-polymerase β binding, respectively, at 28 μg/mL. These compounds displayed varying levels of activity toward the A2780 ovarian cancer cell line, revealing structure-based effects on both the level of cytotoxicity and DNA-polymerase β binding.[66]

Globostellatic acids E–M showed potent activity against the mouse lymphoma cell lne L5178Y, with ED_{50} values of 0.3–10.4 nM. They were weakly active or inactive against a human cervix carcinoma HeLa and rat pheochromocytoma PC-12 cell lines.[56] Six globostellatic acids methyl esters **59–64**, especially those with 13*E* geometry **61–64**, exhibited a high selective index value in antiangiogenic activity, inhibiting proliferation of human umbilical vein endothelial cells selectively in comparison with other cell lines.[64]

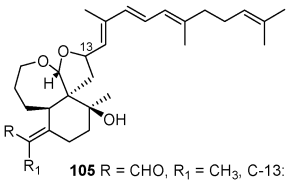
Stelletins L and M (**71–72**) also showed interesting cytotoxic activity against stomach cancer.[68] Some isomalabaricanes possess antimicrobial activities, thus stelliferin ribosides **44–46** show activity against *E. coli*, presenting an inhibition zone of 12 mm at a loading concentration of 10 μg. Globostelletin (**50**) and globostellatic acids G and I (**51–52**) show moderate activities against *E. coli*, and globostelletin also inhibits *Bacillus subtilis*,

with inhibition zones of 12 and 13 mm at concentrations of 5 and 10 μg.[56]

2.2 Triterpenes derived from processes of cyclization of S or OS towards polycyclic triterpenes and subsequent retrocyclization reactions from pentacyclic carbocation intermediates

Oxidosqualene cyclases (OSCs) have been recognized to catalyze carbon-carbon bond formations and rearrangements including hydride and methyl groups to finally produce different polycyclic structures. However, recent reports by Matsuda and Ezibuka's groups of the identification of a marneral synthase yielding the A-ring-*seco*-triterpene marneral on one hand, and an OSCs yielding *seco*-amyrins revealed that OSCs have the ability to cleave preformed ring systems in addition to forming multiring systems. Bearing these findings in mind, we have established a new group of triterpenes which includes those structures derived from an OSC-mediated annulation of S or OS to give, in an earlier part of the reaction, a carbenium ion intermediate possessing bi-, tetra- or pentacyclic systems, which in a later process undergo fragmentations of the previously generated rings to produce *seco*-bi-, tetra- and pentacyclic triterpenes. However, those *seco*-triterpenoids arising from postcyclization steps,[71,72] are not included here.

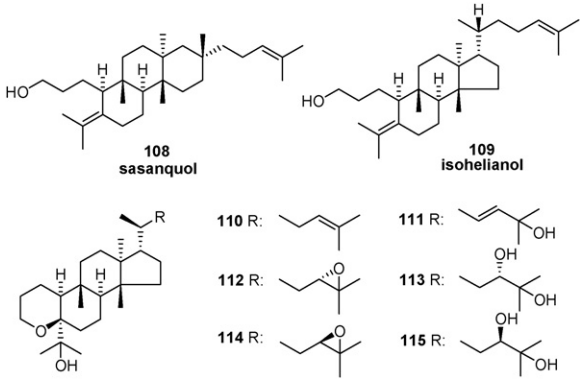
***Seco*-bicyclic triterpenes: Iridals.** The iridal skeleton is a 3,4-*seco*-abeo-10→9,27 polypodane, and most of the iridals are characterized by a carbonyl function on position C-1, and an alcohol, ester, or glucoside on C-3, often accompanied by different epoxide-, alcohol-, ketone-type oxygenated functions (Table 9). They can be classified into four broad groups: simple iridals **77–91**, spiroiridals **92–97**, glycoside iridals **98–104**, and oxaspiroiridals **105–107**. Iridals are found only in plants of the family Iridaceae, mainly in the genus *Iris*, although some were found in the genera *Belamcanda* and *Tigridia*. Marneral (**77**) and marnerol (**78**) were produced by a new OSC encoded by the gene *At5g42600* of *Arabidopsis thaliana*.[72]



105 R = CHO, R_1 = CH_3, C-13: *S*
106 R = CHO, R_1 = CH_3, C-13: *R*
107 R = CH_3, R_1 = CHO, C-13: *S*

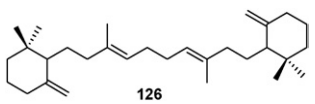
***Seco*-tetracyclic triterpenes.** Sasanquol (**108**) was isolated from sasanqua oil, obtained from the seeds of *Camellia sasanqua*.[84] The remaining 3,4-*seco* tetracyclic triterpenes reported (**109–115**) were isolated from the diethyl ether extract of the pollen grains of sunflower (*Helianthus annuus*). Compounds **109–115** showed potent inhibitory effects of the induction of Epstein-Barr virus early antigen induced by the tumor promoter 12-*O*-tetradecanoylphorbol 13-acetate.[85]

***Seco*-pentacyclic triterpenes.** Ten compounds listed in Table 10 have been considered as *seco*-pentacyclic triterpenes. Eight of them were isolated from plants of the families Asteraceae and Polypodaceae, and two were obtained in the laboratory using *Arabidopsis thaliana* OSC mutants.[87] The structures of **116** and **117** were confirmed by X-ray diffraction analysis of the corresponding ketone at C-3.[86]



2.3 Triterpenes deriving from two independent cyclization processes of S or OS derivatives

Bis-(6,11-cyclofarnesa-2,7(14)-diene) **126**, isolated from an anoxic sulfur-rich sediment, is a unique example of the cycloachillane skeleton.[90]



Cycloiridals. Although a number of cycloiridals were reported before 1998, only two of these triterpenes have been described in the last ten years, namely, hoogianal (**127**) from *Iris hoogiana*[91] and iridotectoral B (**128**) from *Iris tectorum*.[80]

The oxidative degradation of hoogianal yielded β-irone, a compound of interest in perfumery due to its violet aroma.[91]

Onoceranes. Two onoceranes (**129–130**), tetracyclic triterpenes with a symmetrically substituted bisdecalin skeleton, and one *seco*-onocerane (**131**) were isolated in 2002 from the fruit peel of *Lansium domesticum*.[92]

These triterpenoids exhibited mild toxicity against brine shrimp (*Artemia salina*).[92]

Sipholanes. Kashman *et al.* defined the sipholane skeleton as the assembling of two tetramethyl perhydrogenated bicyclic

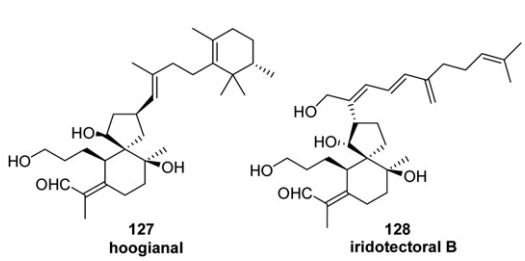
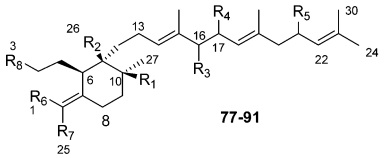
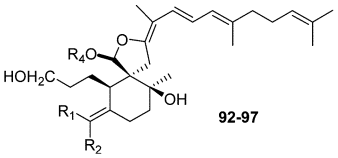
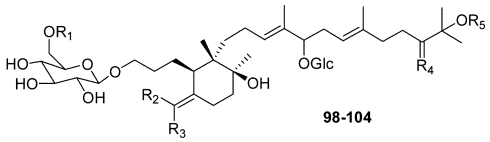


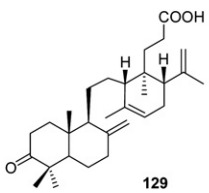
Table 9 *Seco*-Bicyclic triterpenes with the iridal skeleton

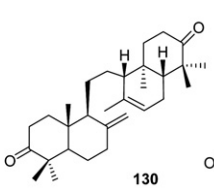


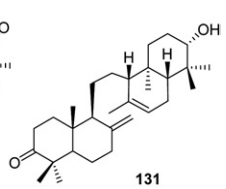




Compound	R^1	R^2	R^3	R^4	R^5	R^6	R^7	R^8	Source
Marneral (**77**)	H	CH_3	H	H	H	CH_3	CH_3	CHO	Gene expression: [*At5g42600*][72]
Marnerol (**78**)	H	CH_3	H	H	H	CH_3	CH_3	CH_2OH	Gene expression: [*At5g42600*][72]
23-Hydroxyiridal (**79**)	OH	CH_3	H	H	Δ^{21}	CHO	CH_3	CH_2OH	*I. variegata*[73]
18,19-Epoxy-10- deoxyiridal (**80**)	H	CH_3	H	H	H	CHO	CH_3	CH_2OH	*I. germanica*[74]
18,19-Epoxyiridal (**81**)	OH	CH_3	H	H	H	CHO	CH_3	CH_2OH	*I. versicolor*[75]
16,26-Dihydroxyiridal (**82**)	OH	CH_2OH	OH	H	H	CHO	CH_3	CH_2OH	*I. versicolor*[75]
22,23-Epoxi-21-hydroxyiridal (**83**)	OH	CH_3	H	H	OH	CHO	CH_3	CH_2OH	*I. cristata*[76]
22,23-Epoxyiridal (**84**)	OH	CH_3	H	H	H	CHO	CH_3	CH_2OH	*I. cristata*[76]
22,23-Epoxy-10-deoxy-21-hydroxyiridal (**85**)	H	CH_3	H	H	OH	CHO	CH_3	CH_2OH	*I. cristata*[76]
Iritectol A (**86**)	OH	CH_3	OH	H	H	CHO	CH_3	CH_2OH	*I. tectorum*[77]
Iritectol B (**87**)	OH	CH_3	O	H	H	CHO	CH_3	CH_2OH	*I. tectorum*[77]
Iridobelamal A (**88**)	OH	CH_3	α-OH	H	H	CH_3	CHO	CH_2OH	*B. chinensis*,[79] *I. tectorum*[77]
3-*O*-Decanoyl-16-*O*-acetylisoiridogermanal (**89**)	OH	CH_3	β-OAc	H	H	CHO	CH_3	Myristic acid	*B. chinensis*[78]
3-*O*-Tetradecanoyl-16-*O*-acetylisoiridogermanal (**90**)	OH	CH_3	β-OAc	H	H	CHO	CH_3	Capric acid	*B. chinensis*[78]
Iristectorone K (**91**)	—	—	—	—	—	—	—	—	*I. germanica*[79]
Iridotectoral A (**92**)	CH_3	CHO	—	H	—	—	—	—	*I. tectorum*,[80]
(13*R*)-Iridotectoral C (**93**)	CHO	CH_3	—	CH_3	—	—	—	—	*I. tectorum*[81]
(13*R*)-Iridotectoral D (**94**)	CH_3	CHO	—	CH_3	—	—	—	—	*I. tectorum*[81]
(13*S*)-Iridobelamal B (**95**)	CHO	CH	—	CH_3	—	—	—	—	*B. chinensis*[80]
Belachinal (**96**)	CHO	CH_3	—	H	—	—	—	—	*B. chinensis*[78]
Tigridal (**97**)	CHO	CH_3	—	H	—	—	—	—	*Tigridia pavonea*[82]
98	Glc	CHO	CH_3	O	H	—	—	—	*I. spuria*[83]
22-Oxo-23-hydroxy-iridal-3,16-di-β-D-glucopyranoside (**99**)	H	CHO	CH_3	O	H	—	—	—	*I. spuria*[83]
22,23-Dihydroxy-iridal-3,16-di-β-D-glucopyranoside (**100**)	H	CHO	CH_3	H,OH	H	—	—	—	*I. spuria*[83]
22-Oxo-isoiridal-3,16,23-tri-β-D-glucopyranoside (**101**)	H	CH_3	CHO	O	Glc	—	—	—	*I. spuria*[83]
102	Glc	CH_3	CHO	O	H	—	—	—	*I. spuria*[83]
22-Oxo-23-hydroxy-isoiridal-3,16-di-β-D-glucopyranoside (**103**)	H	CH_3	CHO	O	H	—	—	—	*I. spuria*[83]
22,23-Dihydroxy-isoiridal-3,16-di-β-D-glucopyranoside (**104**)	H	CH_3	CHO	H,OH	H	—	—	—	*I. spuria*[83]



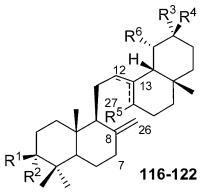




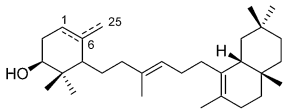
systems, namely a benzoxepine and a *cis*-azulene linked by a two carbon bridge. The structure of the sipholane skeleton was established by X-ray diffraction analysis.[93] In the last ten years, four sipholenols (**132–135**) were isolated, as for the rest of the sipholanes, from the Red Sea sponge *Siphonochalina siphonella*.[94–96]

Siphonellines. Two recently reported siphonellines were also isolated *S. siphonella*.[95,96] Their structures coincide in the

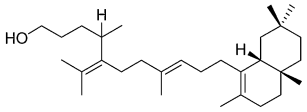
Table 10 *Seco*-pentacyclic triterpenes



116-122

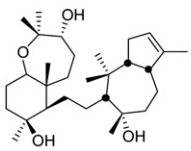


123-124

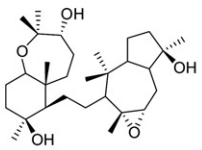


125

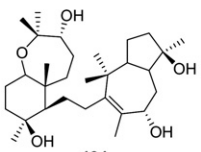
Compound	Δ	R^1	R^2	R^3	R^4	R^5	R^6	Source
8,14-*Seco*-oleana-8(26),13-dien-3β-ol (**116**)	$\Delta^{14(27)}$	OH	H	CH_3	CH_3	CH_3	H	*Stevia viscida*[86]
8,14-*Seco*-oleana-8(26),13-dien-3β-acetyl (**117**)	$\Delta^{14(27)}$	OAc	H	CH_3	CH_3	CH_3	H	*S. eupatoria*[86]
β-*Seco*-amyrin (**118**)	Δ^{7},$\Delta^{14(27)}$	OH	H	CH_3	CH_3	CH_3	H	Gene expression: [*At1g78500*][87]
α-*Seco*-amyrin (**119**)	Δ^{7},$\Delta^{14(27)}$	OH	H	CH_3	H	CH_3	CH_3	Gene expression: [*At1g78500*][87]
8,14-*Seco*taraxastane (**120**)	$\Delta^{8(26)}$,Δ^{12}	OH	H	H	CH_3	CH_3	CH_3	*Koelpinia linearis*[88]
8,14-*Seco*taraxastane (**121**)	$\Delta^{8(26)}$,Δ^{13} isomer	OH	H	H	CH_3	CH_3	CH_3	*K. linearis*[88]
8,14-*Seco*-20-hydroxy-taraxastane (**122**)	Δ^{12}	OH	H	OH	CH_3	H	CH_3	*K. linearis*[88]
Achilleol B (**123**)	$\Delta^{6(25)}$	—	—	—	—	—	—	*Achillea odorata*[89]
Camelliol A (**124**)	$\Delta^{1(6)}$	—	—	—	—	—	—	*Camellia sasanqua*[19]
Camelliol B (**125**)	—	—	—	—	—	—	—	*C. sasanqua*[19]



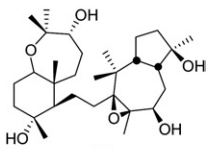
132
sipholenol F



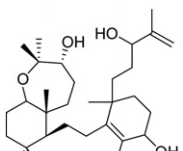
133
sipholenol G



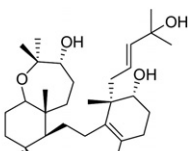
134
sipholenol H



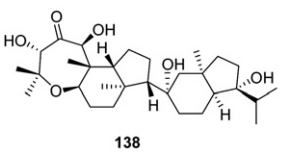
135
sipholenol I



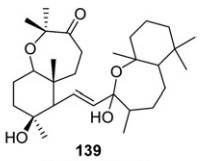
136
siphonellinol B



137
siphonellinol C



138
neviotine B



139
dahabinone A

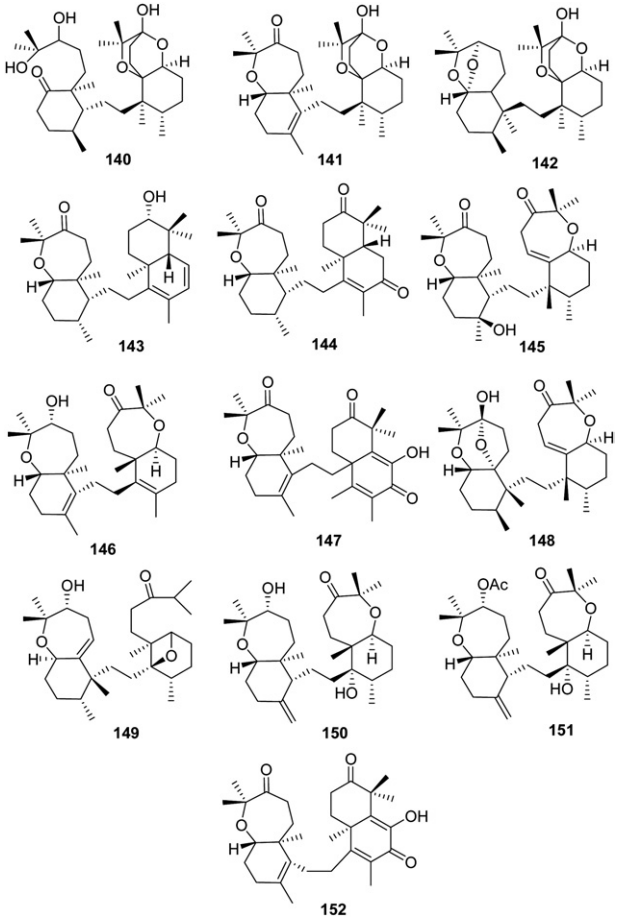
presence of a decahydrotetramethylbenzooxepine linked by an ethylene bridge to a cyclohexenol derivative. No significant bioactivities were reported for these siphonellines.

Neviotines and dahabinone A. Structurally related to sipholanes and siphonellines, neviotine B (**138**) and dahabinone A (**139**) are, respectively, pentacyclic and tetracyclic triterpenes isolated from *S. siphonella*.[95]

Sodwanones. Six new sodwanones (**140–145**) were isolated from the marine sponge *Axinella weltneri* and seven from an unnamed species of *Axinella* collected in the Indo-Pacific (**146–152**).[97,98,99] With structural similarities to sipholanes, both carbo- and heterocyclic rings are present in the skeleta of the different sodwanones that have been described – their number varying from four to six. However, two different ring systems are always present in this kind of compound. The structures of some sodwanones were confirmed by X-ray diffraction analysis.[100]

A number of sodwanones have been found to possess cytotoxic activity against different cell lines. The cytotoxic activities of sodwanone S (**145**) were evaluated against 13 human tumor lines.[98] Sodwanone V (**148**) inhibited hypoxia-induced HIF-1 activation in T47D breast tumor cells and PC-3 prostate tumor cells (IC_{50} 15 μM).[99]

Yardenones. Yardenones are pentacyclic triterpenes isolated from three Red Sea sponges belonging to the same Axenilledae family, namely, *Ptilocaulis spiculifer*, *Axinella cf. bidderi* and a new species of *Axinella* (Table 11).[97,99,101,102] These compounds are similar to other marine terpenes in that they are comprised of two halves, the left one being again a perhydro-tetramethylbenzooxepine. Yardenone A and B showed weak activity with the human lung carcinoma cell line NSCLC-N6.[102]



Abudinols and muzitone. Abudinol A (**158**) and B (**159**) are two pentacyclic structures also isolated from *P. spiculifer*.[97,101] It is also found in the same species muzitone (**160**), which is a tetracyclic triterpene thought to be derived from abudinol B.

Raspacionins. Eight raspacionins (**161–168**) have been isolated from *Raspaciona aculeata*, a Mediterranean sponge collected on the Sicilian coast (Table 12).[103] These compounds are comprised of two benzoxepine-derived moieties linked by an ethylene bridge. The structure of the first raspacionin reported was confirmed by X-ray analysis.[104] Raspacionins possess moderate antifeedant and cytotoxic activities.[103]

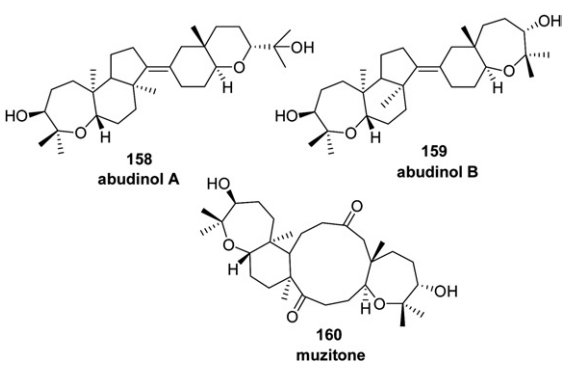
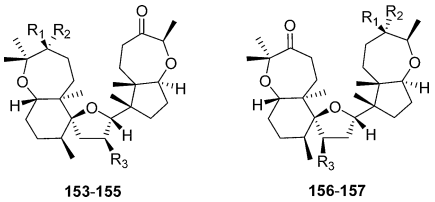


Table 11 Triterpenes with the yardenone skeleton



Compound	R^1	R^2	R^3	Source
Yardenone (**153**)	O	O	H	*Ptilocaulis spiculifer*,[97] Axinella *species*,[99] Axinella cf. bidderi[102]
Yardenone A (**154**)	O	O	OH	*A. cf. bidderi*[102]
Yardenone B (**155**)	H	OH	H	*A. cf. bidderi*[102]
Dihydroyardenone (**156**)	H	OH	H	*P. spiculifer*[97,101]
12*R*-Hydroxyyardenone (**157**)	O	O	OH	*Axinella* species[99]

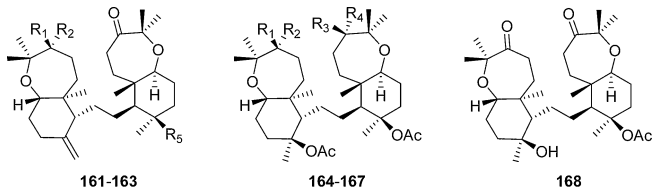
3 Biosynthesis of unusually cyclized triterpenes

Since the postulation of the isoprene biogenetic rule by Ruzicka *et al.*,[8,9] considerable progress has been made in understanding the biogenesis of the more than 100 known triterpene skeletons.[4–7,10,105,106] The cyclization mechanism is initiated by protonation of S or OS or other related initiators. The carbocation thus formed triggers a cascade of cyclizations by electrophilic addition to olefins, generating carbocations. The corresponding cyclic cations are stabilized by loss of a proton or by addition of water or other nucleophiles, just after the cyclization or after going through different 1,2-antiperiplanar rearrangements. The interest in this type of mechanism has led to the involvement of molecular biology, genetics, biochemistry, etc. in this topical scientific field, thus more than 30 OSCs and SCs have been characterized. Cloning of different OSCs and SCs has led to the identification of poly- and monofunctional cyclases that yield a single product or various, and experiments of directed mutagenesis have shown that changes in a single amino acid can cause profound alterations in their specificity.[27,87,105,107]

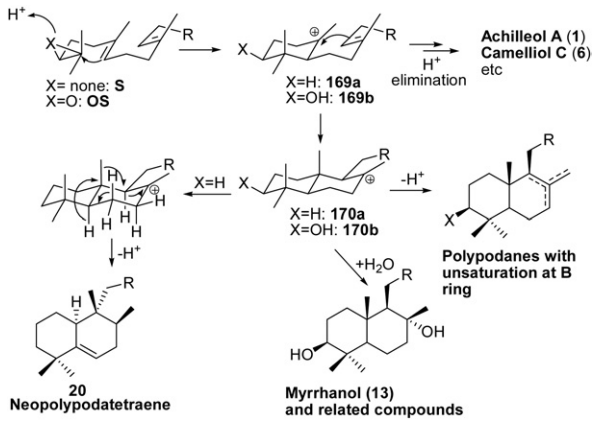
It is currently accepted that in the mechanism of cyclizations[105] mediated by OSC and SC, the cyclases provide a template that folds the flexible acyclic substrate and the carbocation intermediates in a series of conformations which define the regio- and stereospecificity of the process. The carbocation intermediates generated are stabilized with electron-rich environments, namely cation-π interactions with aromatic residues of Phe, Tyr, and Trp. This stabilization favours the cyclization kinetics, making the process more selective.[52,108,109] Finally, the terminal carbocations are neutralised either by the selective loss of a proton from a basic center of the enzyme or by addition of water.

In this review, we have highlighted summarized schemes of the main biosynthetic routes, either established or proposed, towards unusually cyclized triterpenes. In this context, the most recent advances in the enzymatic synthesis of cyclic triterpenes have been reviewed by Abe.[105]

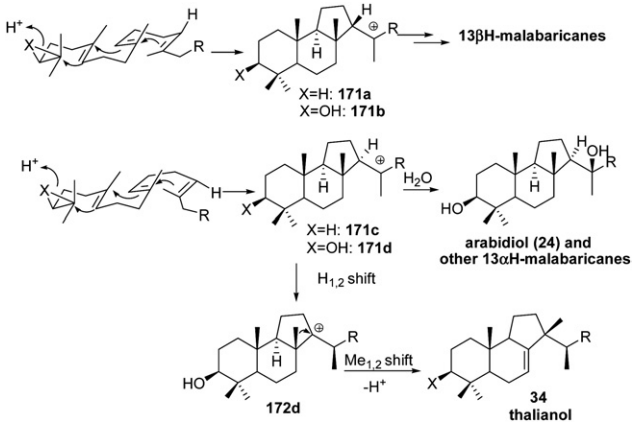
Table 12 Triterpenes with the raspacionin skeleton



Compound	R^1	R^2	R^3	R^4	R^5
21-Deacetyl-21-oxoraspacionin (**161**)	OH	H	—	—	OAc
15-Deacetyl-21-oxoraspacionin (**162**)	OH	H	—	—	OH
4,21-Dioxoraspacionin (**163**)	O	O	—	—	OAc
10-Acetoxy-4-acetyl-21-oxo-28-hydroraspacionin (**164**)	OAc	H	O	O	—
10-Acetoxy-4-acetyl-28-hydroraspacionin (**165**)	OAc	H	H	OAc	—
10-Acetoxy-28-hydroraspacionin (**166**)	OH	H	H	OAc	—
10-Acetoxy-21-deacetyl-4-acetyl-21-oxo-28-hydroraspacionin (**167**)	OAc	H	H	OH	—
10-Hydroxy-4,21-dioxo-28-hydroraspacionin (**168**)	—	—	—	—	—



Scheme 1 Proposed biosynthesis of achillanes and polypodanes.



Scheme 2 Proposed biosynthesis of malabaricanes.

3.1 Biosyntheses mediated by OSC and SC. Triterpenes originating from a single cyclization

Monocyclic triterpenes. It has been proposed that achillanes are biosynthesized as a result of a monocyclization of OS either towards achilleol A and derivatives **1–4**, or towards camelliol C **6**, *via* the monocyclic carbocation **169** (Scheme 1).[13,19,20] At the same time, 3-deoxyachilleol A **5**, monocyclosqualene **7**, and **8** would be formed in a similar transformation by monocyclization from S. More recently, Matsuda *et al.* reported that the *Arabidopsis thaliana* gene *Atl78955* encodes an enzyme that transforms OS mainly into camelliol C **5**, together with small amounts of achilleol A **1** and β-amyrin. This enzyme was named camelliol C synthase (CAMS1).[27] Sequence alignments show that nearly all plant cyclases contain Val or Ile at the position corresponding to Ala484 in CAMS1. The decreased steric bulk at this position is postulated to justify the formation of the monocycle.

It has also been found that several mutants of SHC,[21] lanosterol synthase,[24] and cycloartenol synthase[25,26] produce achilleol A **1** or camelliol C **6**. Mutants of *Alicyclobacillus acidocaldarius* generate achillanes **5**, **7** and **8**.[31]

Bicyclic triterpenes. The formation of all the bicyclic triterpenes, polypodanes with or without an oxygenated function on C-3, should involve a cyclization of either OS or S, respectively. The acyclic precursors are postulated to adopt a chair-chair conformation, that would produce after the cyclization process, carbocation intermediates **170a** and **170b**. From these, deprotonations, hydrations, rearrangement-deprotonations and, in some cases oxidations, would lead to all the known polypodanes (Scheme 1).

While it has not been demonstrated experimentally that an OSC makes polypodanes, SHC mutants from *A. acidocaldarius*[29,34,38,40,110] produce polypodatetraenes **10** and **11**, as well as from the rearranged derivative **20**.

Tricyclic triterpenes. The malabaricane tricyclic triterpenes are thought to be formed in a triple cyclization of OS or S *via* chair-chair-chair conformations or chair-chair-boat conformations

leading to the tricyclic 6,6,5 carbocations **171a–171d** (Scheme 2). Deprotonations or hydration of tricyclic cations **171a–171b**, accompanied in some cases by epoxidations of the side chain and opening of epoxides to tetrahydrofuran derivatives produce the natural 13β-H malabaricanes. Similarly, intermediates **171c** and **171d** can evolve to either 13α-H malabaricanes or, after hydride- and methyl-shifts, to the so-called rearranged malabaricanes such as thalianol **34**.

It has been found that two *A. thaliana* genes, namely *At4g15340* and *At5g4810*, encode OSCs that produce arabidiol **24** and its 20,21-epoxide **25**, and thalianol **34** and its 21,22 epoxide **35**, respectively.[48,51] The mechanism of their formation is rationalized *via* the tricyclic carbenium ion **168d**, which either rearranges to **172d** and, by a subsequent H-9 elimination, affords **34**, or undergoes stereospecific addition of water to give **24**. In an *A. acidocaldarius* SHC elimination of the residue Gly600, which is located close to the place of formation of ring D, generated a mutant that was incubated with OS to produce malabaricanes **21** and **24** and rearranged malabaricanes **34** and **36**, together with achilleol A **1**.[21] Similarly, a number of malabaricanes and rearranged malabaricanes have been obtained by site-directed mutagenesis of *A. acidocaldarius* SCH, which includes point mutants of Phe601, Ile261, Tyr420, etc.[11,105]

Isomalabaricanes, the other large group of 6,6,5 tricyclic triterpenes, have the opposite stereochemistry at C-8 and C-9 to that of the malabaricanes. The biogenetic origin of these compounds is thought to involve cyclizations of chair-boat conformations of S or OS leading to the tricyclic carbocations **173a,b**. Deprotonation of H-13, oxidation on C-12 to carbonyl group, and different dehydrogenations and oxidations, mainly on the side chain, generate the great variety of natural isomalabaricanes (Scheme 3). Tyr510 mutants were proved to afford isomalabaricatrienol **48**, which is considered a putative precursor of isomalabaricane triterpenoids in sponges.[23]

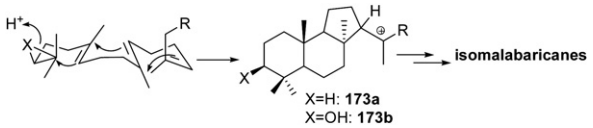
3.2 Biosynthesis of triterpenes *via* processes of cyclization of S or OS towards polycyclic triterpenes and subsequent retrocyclization reactions

***Seco*-bicyclic triterpenes: Iridals.** Marner postulated that the biosynthetic origin of iridals present in the *Iris* family involves an intermediate similar to that of polypodanes, although the stereochemistry of the majority of 10-deoxyiridals indicates that the double cyclization must proceed *via* a chair-boat conformation of OS leading to bicyclic cation **173c**. A series of 1,2-shifts would lead to **173d**, which would then undergo a Grob fragmentation to produce the aldehyde precursor of iridals (Scheme 4).[111,112]

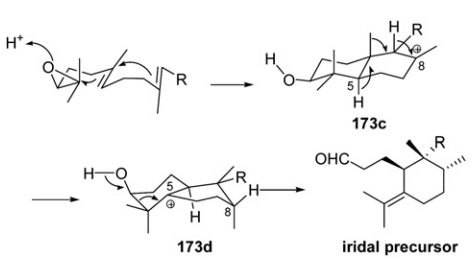
Reduction of the aldehyde group, oxidation by monooxygenases at C-1 and/or C-25, C-10, C-16, C-17, C-26, and C-13, or dehydrogenation on the side chain, would give rise to many of the iridals described. In support of Marner's hypothesis, it has recently been established that the *A. thaliana* gene *At5g42600* encodes a new OSC (called marneral synthase)[72] that catalyses the formation of the iridal marneral **77** and its reduction product marnerol **78**. Analysis of the sequence alignments for marneral synthase showed that this cyclase contains Gly at the position corresponding to Cys456 in other OSCs. The crystal structure of HLC showed that Cys456 is linked by a hydrogen bond to the Asp455 catalytic center which protonates the oxirane. This change may facilitate the mobility of Asp455 and would then help the deprotonation of H-5 and the fragmentation of the A ring.

***Seco*-tetracyclic triterpenes.** Sasanquol (**105**) is the only 3,4-*seco* triterpene thought to be biosynthesized by Grob fragmentation from a 6-6-6-6-fused ring cationic intermediate (**175**). The rest of the 3,4-*seco* tetracyclic triterpenes that have been reported arise from the corresponding 6-6-6-5-ring-fused cations (**174**) (Scheme 5).[87]

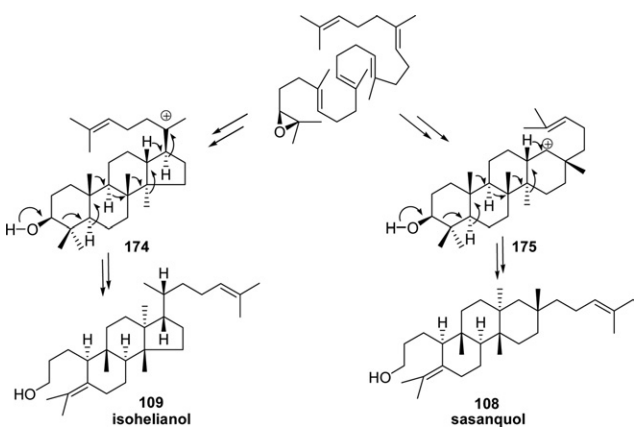
***Seco*-pentacyclic triterpenes.** Although preliminary reports on the biosynthetic proposal of some *seco*-oleananes isolated from *Stevia viscida* and *Stevia eupatoria* (**113–114**) include two different cyclization proccesses for the generation of the A–B and D–E bicyclic systems,[86] Ebizuka *et al.* have recently reported that the *A. thaliana* gene *At1g78500* encodes an OSC-homologue that is able to catalyse both the cyclization of OS leading to pentacyclic triterpenes and the subsequent cleavage of the C ring to afford α-*seco*-amyrin and β-*seco*-amyrin.[87] It was thus proposed that the pentacyclic oleanyl carbocation **171a** could lead to β-*seco*-amyrin (**115**) and the *seco*-oleanane **113** through C-8–C-14 bond cleavage and subsequent elimination of H-7 or H-25,



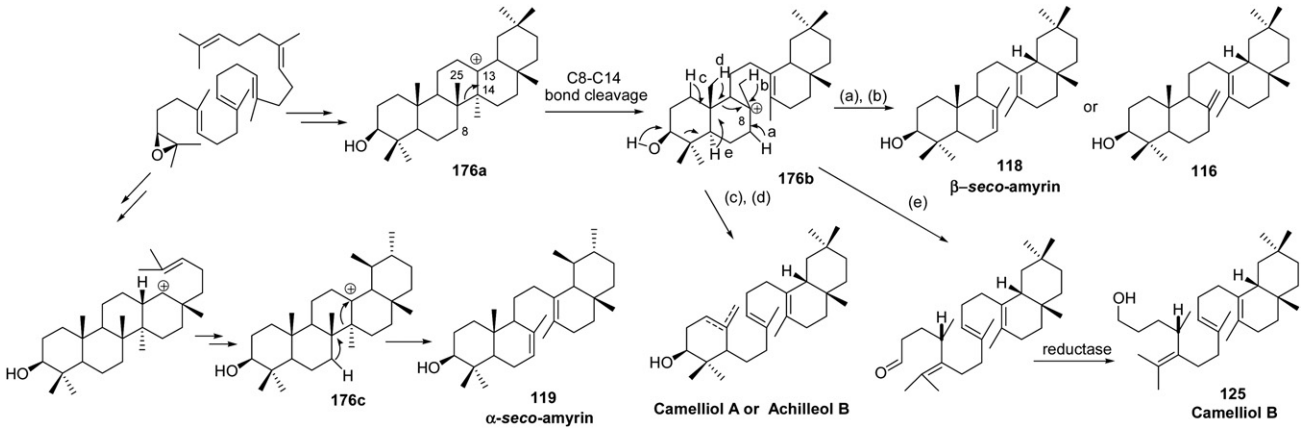
Scheme 3 Proposed biosynthesis of isomalabaricanes.



Scheme 4 Proposed biosynthesis of iridals.



Scheme 5 Proposed *seco*-tetracyclic triterpene biosynthesis.



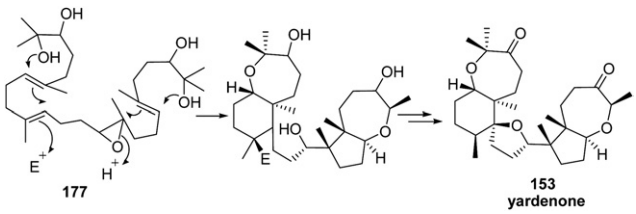
Scheme 6 Proposed biosynthesis of *seco*-pentacyclic triterpenes.

respectively (Scheme 6, pathway (a) and (b)). Moreover, camelliol A (**121**) or achilleol B (**120**) could be produced after a double retrocyclization process (Scheme 6, pathway (c) and (d)). The fragmentation of the B ring of these compounds could involve cleavage of the C-9–C-10 bond triggered by deprotonation of H-1 or H-25. A third pathway, which could include a Grob fragmentation, could lead to camelliol B **122**. On the other hand, the biogenesis of α-*seco*-amyrin (**116**) could involve the existence of intermediate **171c**, produced after the corresponding cyclization and methyl-shift.

3.3 Biosynthesis of triterpenes involving two independent cyclization processes

Cycloiridals are considered to be derived from iridals. It has been suggested that the biosynthesis of hoogianal proceeds *via* the corresponding iridals, which suffer a *S*-adenosylmethionine-mediated monocyclization initiated on the terminal double bond of the farnesyl side chain (Scheme 7). This proposal may well account for the presence of the additional carbon in these homotriterpenes.[111]

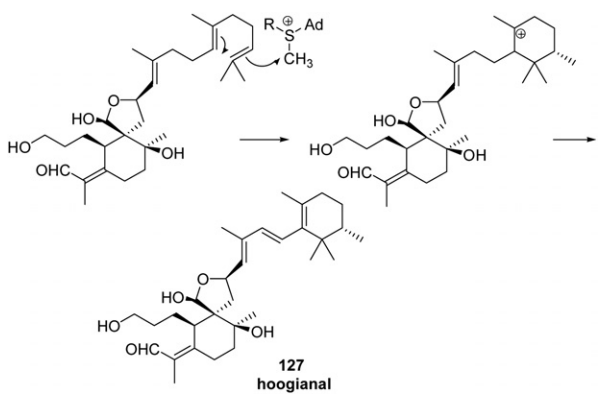
10,11-Epoxy-2,3-22,23-squalenetetraol as precursor. As seems to happen with most marine triterpenoids, the yardenone skeleton is presumably obtained after two separate cyclizations. In this case the precursor would be a squalene derivative dihydroxylated at both terminal isopropylidene moieties and possessing an epoxide at C-10–C-11 (**177**). Thus, the right and left parts formed during the biogenesis are proposed to start after activation of the internal 10,11-epoxide and the Δ^{14} double bond, respectively (Scheme 8).[94]



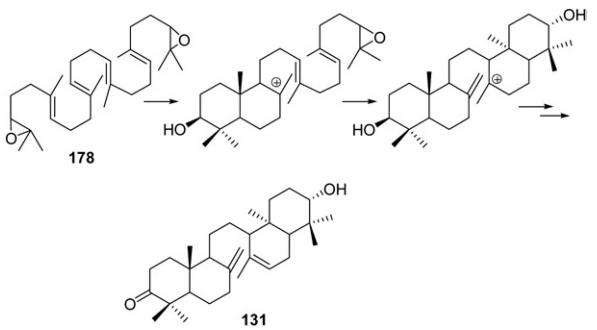
Scheme 8 Proposed biosynthesis of yardenones.

2,3-22,23-Diepoxysqualene as precursor. The origin of onoceranes such as **131** is thought to occur through an initial cyclization of bis-OS (**178**) to afford a bicyclic cation that is stabilized by deprotonation (Scheme 9). The bicyclic compounds which then arise could undergo a second process of cyclization at the epoxide located at the end of the chain, forming the tetracyclic carbocation, precursors of the natural product.

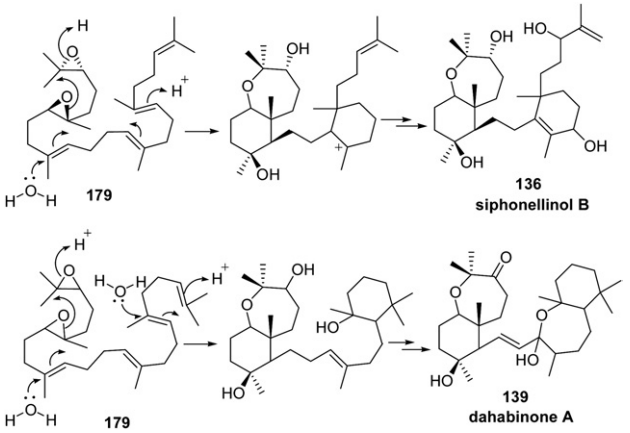
2,3-6,7-Diepoxysqualene as precursor. In the case of siphonellines (**136–137**) and dahabinone A (**139**), the two cyclizations



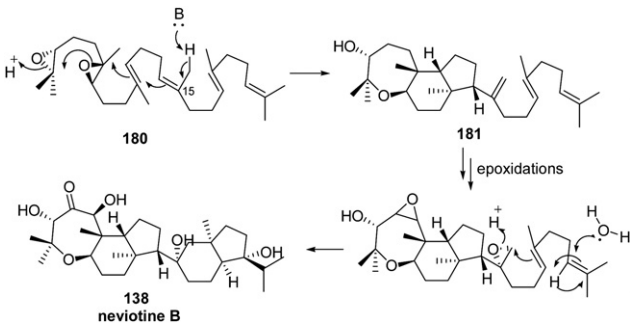
Scheme 7 Proposed biosynthesis of cycloiridals.



Scheme 9 Proposed biosynthesis of onoceranes.



Scheme 10 Proposed biosynthesis of siphonellinol B and dahabinone.



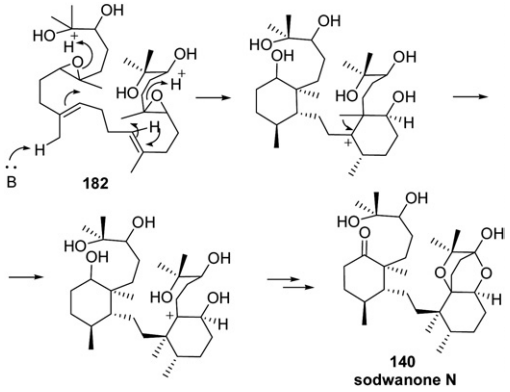
Scheme 11 Proposed biosynthesis of neviotine B.

which make up their skeleton take place in a common diepoxysqualene precursor (**179**) (Scheme 10).[94] It is worth noting that whereas the cyclization of the left part of this molecule would start from a terminal epoxide for both skeleta, the second cyclization could arise after protonation of an internal double bond in the case of the siphonellines, whereas the protonation could take place in the terminal isopropylidene for dahabinone A.

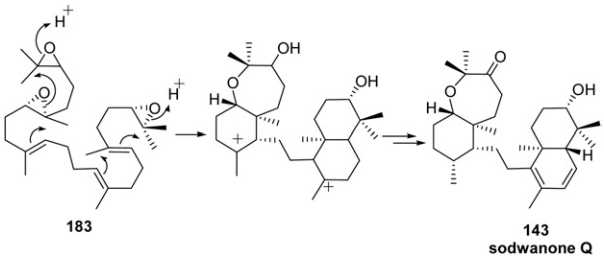
A more complex pathway seems to be involved in the biogenesis of neviotine B (**138**) (Scheme 11).[94] Thus, starting from the same diepoxide (**180**), a first cyclization could occur to give the intermediate tricyclic structure **181**. Then, the epoxide resulting derived from the methylene at C-15 could undergo a proton-induced opening, leading after a cascade cyclization process to the neviotane skeleton.

6,7-18,19-Diepoxy-2,3-22,23-squalenetetraol as precursor. Most of the sodwanones are thought to be derived from tri- or tetraepoxides. Nevertheless, in some of these natural products, i.e., sodwanone N (**140**), the left and right hand cyclizations may be limited to the formation of one cyclohexane ring which is formed after the acid activation of the corresponding epoxide (**182**) (Scheme 12).

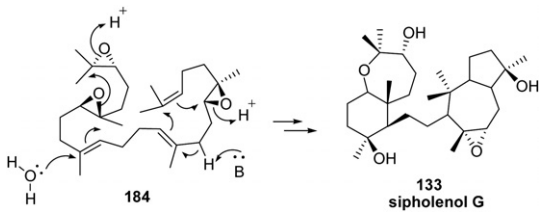
2,3-6,7-22,23-Triepoxysqualene as precursor. A significant number of sodwanones are biosynthesized after protonation of both terminal epoxides of a triepoxysqualene precursor (**183**) (Scheme 13).



Scheme 12 Proposed biosynthesis of sodwanone N.

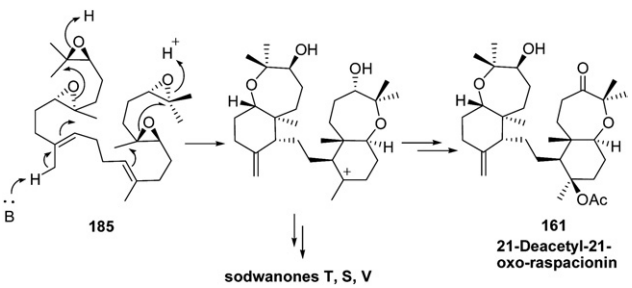


Scheme 13 Proposed biosynthesis of sodwanone Q.

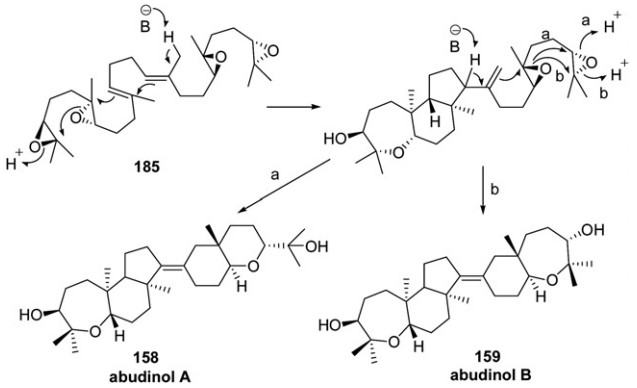


Scheme 14 Proposed shipolenol G biosynthesis.

2,3-6,7-18,19-Triepoxysqualene as precursor. Although the sipholanes share with siphonellines and some sodwanones the proposal for the origin of the left part, interestingly, the biogenesis of the right part would be induced by the protonation of an internal epoxide (**184**) (Scheme 14).



Scheme 15 Proposed biosynthesis of raspacionin.



Scheme 16 Proposed biosynthesis of abudinol.

2,3-6,7-18,19-22,23-Tetraepoxysqualene as precursor. The biogenesis of a number of tetracyclic sodwanones and all the reported raspacionins are thought to involve the presence of a tetraepoxy precursor (**185**). Symmetric acid-induced opening of the epoxides located at the terminal position of each C-15 subunit could lead to the corresponding tetracyclic structure (Scheme 15).

It has been proposed that the biosynthesis of abudinols involves the same tetraepoxyderivative of squalene (**185**). Once the first tandem cyclization takes place, abstraction of H-14 could trigger the generation of the tricyclic moiety (Scheme 16).

Kashman *et al.* proposed that abudinol B (**159**) could be involved in the biosynthesis of muzitone (**160**).[94]

4 Chemical syntheses of unusually cyclized triterpenes

Although a number of impressive syntheses of unusually cyclized triterpenes has been achieved in the last ten years,[113] we have included here only the syntheses of compounds whose occurrence has been reported since 1998 (shown in section 2).

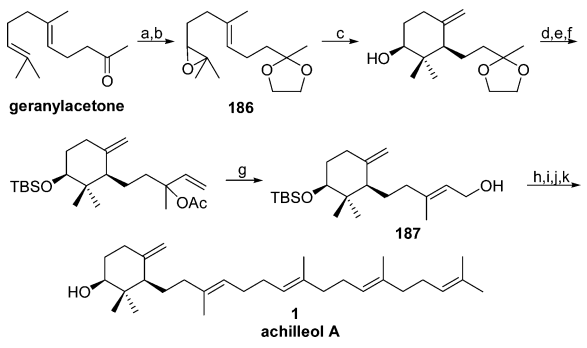
4.1 Achillanes

The synthesis of achilleol A **1** was planned on the basis of a C_{15}-C_{15} convergent strategy (Scheme 17).[114] The monocyclic sesquiterpenic elegansidiol (**187**) was obtained through a Ti-mediated radical cyclization of oxirane **186**, prepared from commercially available geranylacetone. Alcohol **175** was converted into allylic bromide which was then coupled with farnesylsulfone. Desulfonation with NaHg in MeOH and deprotection of the silyl ether with TBAF led to achilleol A **1**.

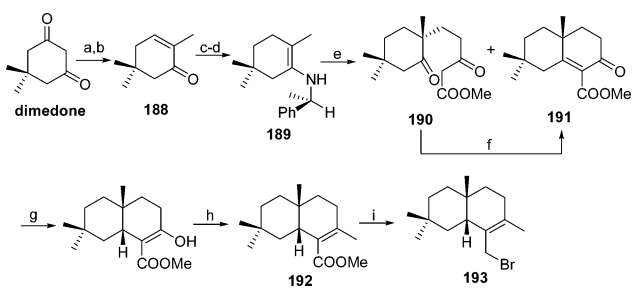
Very recently, our research group carried out the first total synthesis of (−)-achilleol B,[115] an achievement that led us to reassign the relative stereochemistry of the interannular junction as *cis*. The key steps employed in our synthesis were an enantioselective Robinson annelation for the construction of the bicyclic moiety,[116] and a Ti(III)-mediated cyclization of a chiral monoepoxide to construct the monocyclic moiety.

Scheme 18 summarizes the formation of the bicyclic synthon. Thus, based on the work of Heathcock,[117] ketone **188** was prepared from dimedone. Treatment of **188** with (*S*)-phenylethylamine led to enamine **189** which reacts with freshly prepared Nazarov reagent to obtain a mixture of the desired keto ester and its acyclic precursor **190**, which was converted into the keto ester by treatment with KF in MeOH. Reduction with H_2-Pd/C and treatment with the corresponding enol triflate with MeLi in the presence of $CuBr \cdot SMe_2$ gave the *cis*-decalin **192**. Subsequent reduction with $LiAlH_4$ and treatment with PBr_3 led to the allylic bromide **193**.

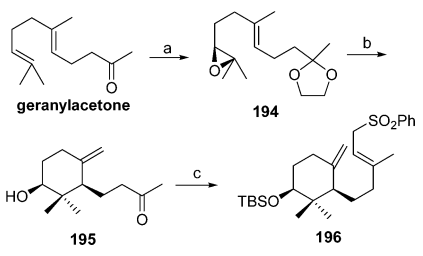
The monocyclic synthon was synthesized starting from geranylacetone (Scheme 19). Sharpless asymmetric dihydroxylation of this acyclic precursor led to the corresponding asymmetric diol. Protection of the carbonyl group, and



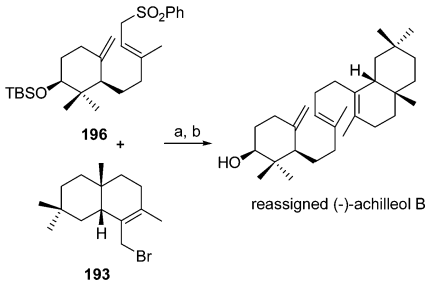
Scheme 17 *Reagents and conditions*: (a) Ethylene glycol, TsOH, 93%; (b) NBS, K_2CO_3, 71%; (c) Cp_2TiCl, 65%; (d) $CeCl_3$, NaI, 95%; (e) TBSCl, imidazole, DMAP, 72%; (f) i. allylmagnesium bromide; ii. Ac_2O, 68%; (g) i. $PdCl_2(MeCN)_2$; ii. K_2CO_3, MeOH, 88%; (h) PBr_3, DMAP, 75%; (i) *n*BuLi, $PhSO_2$-farnesyl, 74%; (j) NaHg, MeOH, 55%; (k) TBAF, 95%.



Scheme 18 *Reagents and conditions*: (a) i. NaOH, CH_3I, H_2O; ii. LAH, Et_2O; (b) PDC, DCM; (c) H_2, Pd/C, EtOAc; (d) (*S*)-phenylethylamine, PhH, 74%; (e) methyl 3-oxo-4-pentenoate, PhH, 41%; (f) KF, MeOH, 99%; (g) H_2, Pd/C, EtOAc, 91%; (h) i. Tf_2O, *i*Pr_2EtN; ii. $CuBr \cdot SMe_2$, MeLi, 91%; (i) i. DIBALH, 94%; ii. PBr_3, 90%.



Scheme 19 *Reagents and conditions*: (a) i. AD-mix-β, $CH_3SO_2NH_2$, *t*BuOH/H_2O, 0 °C, 67%, ii. ethylene glycol, TsOH, 82%; iii. MsCl, Py, DMAP, K_2CO_3, MeOH, 74%, (b) i. Cp_2TiCl, 77%; ii. $CeCl_3$, NaI, 95%; (c) i. TBSCl, imidazole, DMAP, 91%; ii. diethyl phosphonoacetate, NaH, DIBALH, 74%; iii. PBr_3, DMAP, 75%; iii. $NaSO_2Ph$, DMF, 72%.



Scheme 20 *Reagents and conditions*: (a) i. *n*BuLi, THF, 71%; (b) i. Li, $EtNH_2$, THF; ii. TBAF, 86%.

treatment of the corresponding diol with mesyl chloride and subsequent treatment with base gave rise to oxirane **194**. Ti(III)-mediated cyclization of this epoxide led after deprotection of the ketyl group led to ketoalcohol **195**. Application of the Horner–Wadsworth–Emmons protocol to the corresponding silyl derivative provided the requisite two-carbon homologation. The corresponding unsaturated ester was converted to bicyclic sulfone **196** following straightforward transformations.

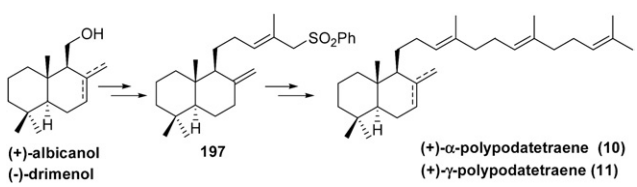
Finally, the target (−)-achilleol B was efficiently assembled as shown in Scheme 20.

4.2 Polypodanes

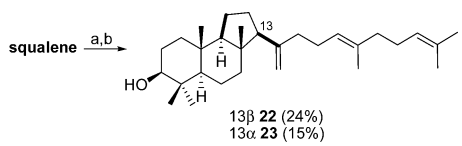
Akita *et al.* reported the synthesis of (+)-α-polypodatetraene **10** and (+)-γ-polypodatetraene **11**.[118] Starting from (+)-albicanol and (−)-drimenol respectively, the hydrocarbon chain was lengthened following straightforward transformations, including a Wittig reaction (Scheme 21). The subsequent formation of sulfone **197** enabled coupling with geranyl bromide to give, after desulfonation, the desired final products.[119]

4.3 Malabaricanes

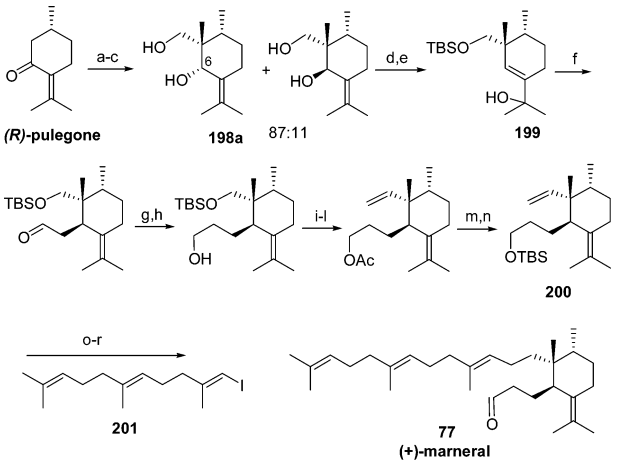
In our laboratories malabaricanes **22** and **23** were prepared through a titanocene-catalyzed cyclization of 2,3-oxidosqualene, mimicking the enzyme lanosterol synthase.[120] Treatment of OS with a catalytic quantity of Cp_2TiCl_2 led to a mixture of 13α- and 13β- malabaricanes in 39% yield (Scheme 22).



Scheme 21



Scheme 22 *Reagents and conditions*: (a) i. NBS, $MeOH/H_2O$; ii. K_2CO_3, MeOH; (b) Cl_2TiCp_2, Mn, TMSCl, collidine, THF, 39%.



Scheme 23 *Reagents and conditions*: (a) LDA, $ClCO_2Et$; (b) NaH-MeI (40%, 2 steps); (c) $LiAlH_4$; (d) AcOH (75%); (e) TBSCl (88%); (f) vinyl ether, $Hg(OAc)_2$, sealed tube, 190 °C, 2 d (80%); (g) Wittig (92%); (h) 9-BBN, $NaOH-H_2O_2$ (80%); (i) Ac_2O-DMAP (90%); (j) HF-MeCN; (k) Swern; (l) Wittig (79%, 3 steps); (m) K_2CO_3, MeOH, (n) TBSCl, DMAP (77%, 2 steps), (o) 9-BBN, THF, (p) $Pd(dppf)Cl_2$, $AsPh_3$, Cs_2CO_3, H_2O, DMF, 25 °C, 12 h (67%), (q) TBAF (87%); (r) Swern (96%).

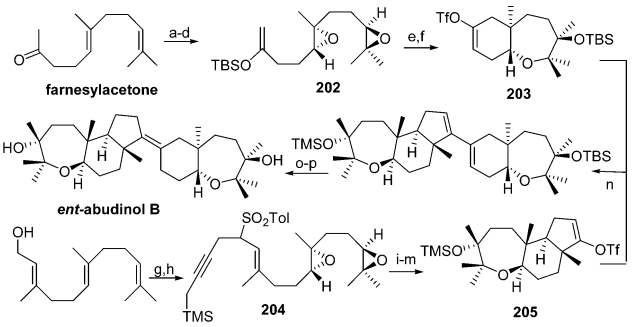
4.4 Marneral

In 2008, Arseniyadis *et al.* reported the convergent synthesis of (+)-marneral (Scheme 23).[121] This achievement was based on the B-alkyl Suzuki–Miyaura coupling of vinyl iodide **201** and the corresponding monocyclic counterpart **200**. Central to the elaboration of the monocyclic moiety was the mercury-catalyzed Claisen rearrangement of the allylic alcohol **199**, efficiently prepared from commercially available (*R*)-pulegone. X-Ray analysis of intermediate **198a** established the relative configuration of the final product.

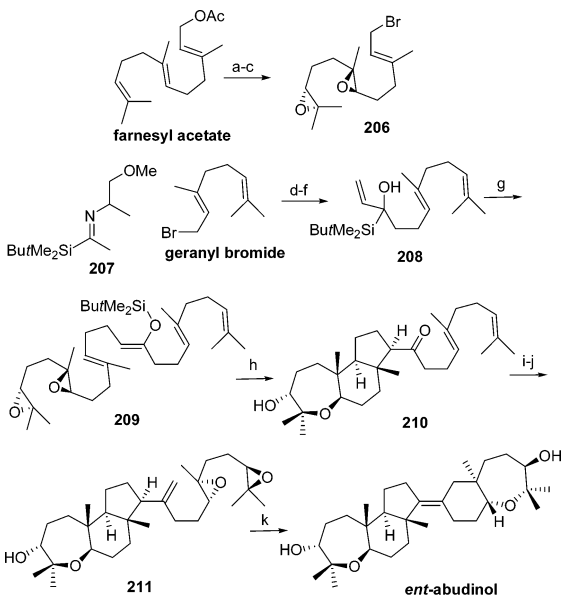
4.5 *ent*-Abudinol B

McDonald *et al.*[122] carried out the first synthesis of *ent*-abudinol B inspired by the biosynthesis proposed for abudinols A (**158**) and B (**159**), using cascade cyclizations of di-epoxides coupled to the corresponding enol-silane **202** or ene-propargylsilane **204** to construct the different carbocycles of the structure (Scheme 24). The key step was the Pd-catalyzed cross-coupling of ABC (**205**) and DE (**203**) units, which proceeded in 70% yield. Hydrogenation of the diene occurred in low yield (30%). Final desilylation provided the structure corresponding to *ent*-abudinol B.

In 2008 the same research group reported a total synthesis of the same triterpene *ent*-abudinol (Scheme 25).[123] The synthesis relies on Lewis acid promoted tandem oxa- and carbacyclizations of the squalene-like substrate **209**. This 29-carbon substrate was prepared by coupling of diepoxybromide **206** with the Brook rearrangement product of the lithium alkoxide of **207**. Compounds **206** and **208** were prepared from farnesyl acetate and geranyl bromide, respectively (Scheme 25). Me_3SiOTf-promoted tandem cyclization of **209** afforded tricyclic ketone **210** as the major product. Ketone **210** was converted to diepoxide **211** by methylenation and double enantioselective epoxidation of the



Scheme 24 *Reagents and conditions*: (a) $NaBH_4$, MeOH, 0 °C, 90%; (b) Shi catalyst, Oxone, K_2CO_3, Na_2EDTA, DMM/MeCN/H_2O, 0 °C, 95%; (c) SO_3-pyridine, DMSO, Et_3N, DCM, 0 °C, 95%; (d) KHMDS, TBSCl, THF, −78 °C, 87%; (e) TBSOTf, DTBMP, DCM, −78 °C, 60%; (f) KHMDS, THF, −78 °C, then $PhNTf_2$, −78 °C, 95%; (g) Ph_3P, NBS, THF, 0 °C, then cat. Bu_4NI, $NaSO_2Tol$, 99%; (h) *n*BuLi, THF, −78 to −40 °C, then 1-bromo-4-trimethylsilyl-2-butyne, −78 to 20 °C, 92%; (i) Shi catalyst, Oxone, K_2CO_3, Na_2EDTA, DMM/MeCN/H_2O, 0 °C, 76%; (j) Cl_2Pd(dppp), $LiEt_3BH$, THF, 0 °C, 71%; (k) TMSOTf, DTBMP, DCM, −78 °C, 75%; (l) Bu_4NF, THF, 99%; (m) O_3, DCM, −78 °C, then Me_2S, −78 to 20 °C, 88%; (f) 95%; (n) **205**, $Cl_2Pd(PPh_3)_2$, Ph_3P, PhOK, bis(neopentylglycolato)diboron, toluene, 50 °C, then **203**, Cl_2Pd(dppf), K_3PO_4, DMF, 80 °C, 70%; (o) 10% Pd/C, toluene, H_2, 0 °C, 30%; (p) Bu_4NF, THF, 60 °C, 84%.



Scheme 25 *Reagents and conditions*: a) D-Epoxone (0.5 equiv), Oxone, pH 10.5 buffer, DMM/MeCN/H_2O, −5 °C, 54%; b) K_2CO_3, MeOH, 99%; c) MsCl, Et_3N, −40 °C, then LiBr, THF, 0 °C, 60%; d) LDA, THF, −30 °C, then **207**; e) NaOAc, HOAc, 84% (2 steps); f) $H_2C{=}CHMgCl$, Et_2O, 0 °C, then HCl, 88%; g) *n*BuLi, hexane/THF, −78 °C, then **206**, 50%. DMM = dimethoxymethane; h) Me_3SiOTf, DTBMP, CH_2Cl_2, −78 °C, then Bu_4NF, 50%; i) Ph_3PMeBr, KO*t*Bu, benzene, 80 °C, 30% (+55% C-14 epimer); j) D-Epoxone (0.5 equiv), Oxone, pH 10.5 buffer, DMM/MeCN/H_2O,−5 °C, 50%; k) Me_3SiOTf, DTBMP, CH_2Cl_2, −78 °C, then Bu_4NF.

trisubstituted double bonds. Again, trimethylsilyl triflate promoted a tandem oxa- and carbocyclization of **211** to provide *ent*-abudinol in modest yield.

5 Conclusions

There has been an increase in the description of new natural triterpenes derived from partial cyclization of squalene or 2,3-oxidosqualene in the last few years. In addition, the confirmation of the existence of OSCs specific for the formation of these compounds seems to indicate that these molecules are more widely distributed in Nature than might be expected *a priori*. At the same time, the biosynthetic proposals that suggest new retrocyclization mechanisms are involved in the biosynthesis of these molecules seem to widen the range of structural diversity in these irregular triterpenes, a possibility that should be explored in the future.

Marine organisms, mainly sponges, prove to be a remarkable source of triterpenes, which are structurally distant from those having a terrestrial origin. Many of these compounds, which often possess interesting biological properties, derive from cyclization of polyepoxides of squalene or 2,3-oxidosqualene. In our opinion, the scientific research into these unusually cyclized triterpenes constitutes a valid strategy for the advance in the understanding of the metabolism of natural products. This research should also contribute to the discovery of new bioactive molecules with potential applications.

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