








Cite this: *Nat. Prod. Rep.*, 2018, 35, 955

Halimane diterpenoids: sources, structures, nomenclature and biological activities†

Alejandro M. Roncero,  Ignacio E. Tobal,  Rosalina F. Moro,  David Díez 
and Isidro S. Marcos *

Covering: 1970 to 2017

Diterpenes with a halimane skeleton constitute a small group of natural products that can be biogenetically considered as being between labdane and clerodane diterpenoids. Some of these compounds show biological activities, such as antitumour, mosquito repellency, germination inhibition and antimicrobial, as well as being biomarkers for tuberculosis. To the best of our knowledge, there are no reviews on these compounds. In this review, halimane skeleton diterpenoids are classified according to their biogenetic origin, characterization and/or the enzymes involved in their biosynthesis. Herein, a review of their synthesis or synthetic approaches is communicated.

Received 22nd February 2018

DOI: 10.1039/c8np00016f

rsc.li/npr

1. Introduction and background
 - 1.1. Sources of halimane diterpenoids
 - 1.2. Biological activities of halimanes
 - 1.2.1. Biomarkers for tuberculosis
 - 1.2.2. Halimane purines bioactivity
 - 1.2.3. Other bioactivities
2. Biosynthesis
 - 2.1. Biosynthesis overview
 - 2.2. Enzymatic and genetic experimental studies
3. Classification
4. Natural halimanes
 - 4.1. Halim-1(10)-enes group
 - 4.1.1. *ent*-Halim-1(10)-enes
 - 4.1.2. Halim-1(10)-enes
 - 4.1.3. 8-*epi*-Halim-1(10)-enes
 - 4.1.4. 8-*epi-ent*-Halim-1(10)-enes
 - 4.2. Halim-5(10)-enes group
 - 4.2.1. *ent*-Halim-5(10)-enes
 - 4.2.2. Halim-5(10)-enes
 - 4.2.3. 8-*epi*-Halim-5(10)-enes
 - 4.2.4. 8-*epi-ent*-Halim-5(10)-enes
 - 4.3. Halim-5-enes group
 - 4.3.1. *ent*-Halim-5-enes
 - 4.3.2. Halim-5-enes
 - 4.3.3. 8-*epi*-Halim-5-enes
 - 4.4. Dihydrohalimenes group
- 4.5. Secohalimenes and norhalimenes group
- 4.6. Rearranged halimane group
5. Halimane diterpenoids: synthesis and transformation into bioactive compounds
 - 5.1. *ent*-Halimic acid as precursor of biologically active compounds and other derivatives of interest
 - 5.1.1. *ent*-Halimanolides synthesis
 - 5.1.2. Chettaphanins synthesis
 - 5.1.3. Halimane purine synthesis: (+)-agelasine C
 - 5.2. Synthesis of 3 α -hydroxy-5 β ,10 β -epoxychiliolide (214)
 - 5.3. Synthesis of (+)-agelasimine A (217) and (+)-agelasimine B (218)
 - 5.4. Biomimetic synthesis of scopariusin A (246) and isoscoparin N (143)
 - 5.5. Synthesis of tuberculosinol (182) and isotuberculosinol (183)
 - 5.5.1. Snider's synthesis of tuberculosinol (182) and isotuberculosinol (183)
 - 5.5.2. Sorensen's synthesis of tuberculosinol (182) and isotuberculosinol (183)
 - 5.6. 1-Tuberculosinyl adenosine (1-TbAd; 200) and N⁶-tuberculosinyl adenosine (N⁶-TbAd; 201) syntheses
6. Conclusion
7. Conflicts of interest
8. Acknowledgements
9. Notes and references

Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad de Salamanca, Plaza de los Caídos 1-5, 37008 Salamanca, Spain. E-mail: ismarcos@usal.es

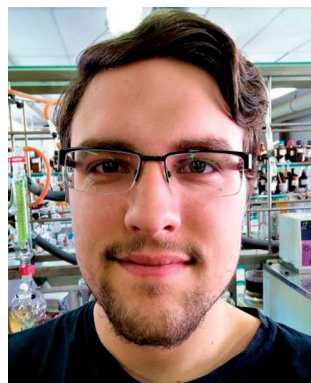
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c8np00016f

1. Introduction and background

Among natural products, terpenes are one of the most numerous and structurally diverse groups. They can be found in



nearly all life forms showing a great number of functional activities. Currently, tens of thousands of compounds in this class^{1,2} (around 55 000) are known. As soon as new compounds are discovered, from terrestrial or marine origin,³ they are included in reviews on different terpene classes (monoterpenes, sesquiterpenes,⁴ diterpenes,^{5,6} sesterterpenes⁷ and triterpenes⁸).

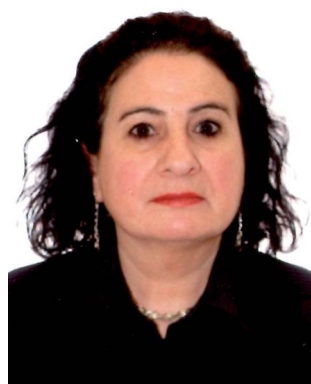


Alejandro Martín Roncero received his B.Sc. in Chemistry with Honours from the University of Salamanca in 2015. In 2016 he completed an M.Sc. in Evaluation and Development of New Drugs at the same university. Currently, he is a researcher at the University of Salamanca carrying out his PhD under the supervision of Professor I. S. Marcos focusing on the synthesis and biological evaluation of new antitumour lipids.



Ignacio E. Tobal obtained his BSc in Chemistry in 2015 at the University of Salamanca and completed his Masters studies in drug discovery and pharmaceutical sciences at the same university. He has worked in antitumour alkyl-phosphocholines and bioconjugates. Currently, he is a researcher at the University of Salamanca and has initiated his PhD in the area of organic

synthesis and natural products under the supervision of Prof. Isidro S. Marcos and Prof. David Diez.



Rosalina Fernández-Moro obtained her PhD in Organic Chemistry from the Universidad de Salamanca in 1986 under the supervision of Professors J. G. Urones and P. Basabe. She then carried out her postdoctoral research with Professor Steven V. Ley at Imperial College of Science, Technology and Medicine in London (1989–1991), obtaining the D.I.C. in September 1991. Currently she is a Lecturer

in Organic Chemistry at the University of Salamanca, where she is researching the synthesis of bioactive compounds, especially indole alkaloids and organocatalysis.

Within terpenes, diterpenes are one of the largest families of natural molecules, with more than 18 000 compounds derived from GGPP (*E,E,E*-geranylgeranyl diphosphate). Classification of these compounds is done according to their biogenesis, leading to 126 different carbon skeletons known until now.⁹

Two big groups can be distinguished among the diterpenes family: those diterpenes in which a pyrophosphate ion is involved in the first biogenetic step and those diterpenes that are generated as a consequence of cyclizations that do not include pyrophosphate ion in the first step.^{10–13} Labdanes and related diterpenes (like clerodanes^{14,15}) are included in this second group. According to Peters,¹⁶ halimanes are found within the labdane and clerodane group, as indicated in the general biogenetic scheme (Scheme 1). The halimane-type



David Diez received his B.Sc. with Honours in Chemistry from the University of Salamanca in 1982. In 1986 he completed his PhD with Honours at the same University under the supervision of Professors J. G. Urones and I. S. Marcos. Then, he carried out a postdoctoral post (1988–1990, British Council Fellowship) with Professor Steven V. Ley at Imperial College of Science, Technology and Medicine (London),

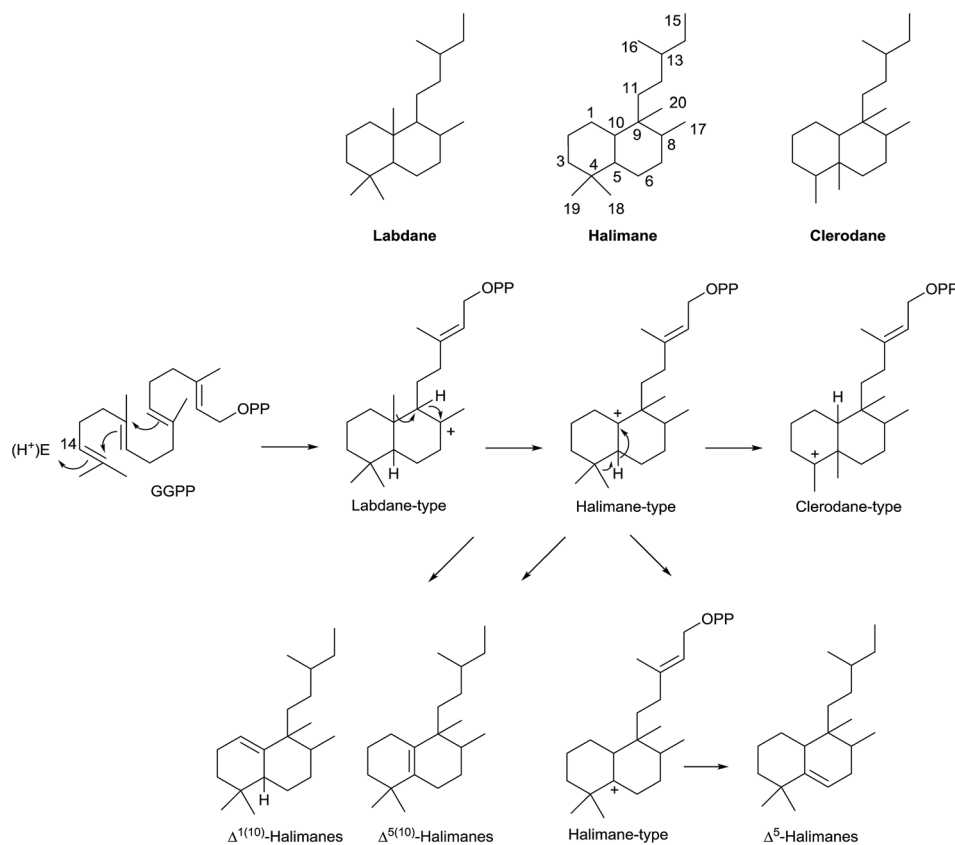
DIC 1991. He became Associate Professor in 1991 at the University of Salamanca and full Professor in 2008 at the same university. He is co-author of more than 180 papers and he acts as referee for many international scientific journals. Currently he is the Dean of the Chemistry Faculty at the University of Salamanca. His current research interests are focused on the transformation of natural products into biologically active compounds, the chemistry of cyclopropanes, sulfones, tetrahydropyrans, and chiral amides, and recently organocatalysis and nanoparticles.



Isidro Sánchez Marcos received his B.Sc. in Chemistry at the University of Salamanca in 1976 and obtained his PhD from the same University in 1979 under the supervision of Professors J. de Pascual Teresa and J. G. Urones. He was promoted to Lecturer in 1986 and to Full Professor in 2010. The area where he has developed his research is Natural Products. He has isolated and characterized more than 200

compounds and described six new carbon skeletons, in more than 180 publications. Now he is interested in the synthesis of bioactive natural products and the synthesis of structural and functional hybrid compounds of antitumour lipidic ethers and terpenolides.





Scheme 1

carbocation can be in position 10 leading to $\Delta^{1(10)}$ or $\Delta^{5(10)}$ halimanes or in position 5, due to a hydride 1,2-shift, leading to Δ^5 halimanes. Other halimanes can be understood from these intermediates or derivatives, as reported later on.

The name 'halimane' was introduced in order to provide a simple nomenclature for the isolated *ent*-halimic acid compound series¹⁷ in *Halimium viscosum* (Fig. 1). Previously in the literature, these compounds were known by generic

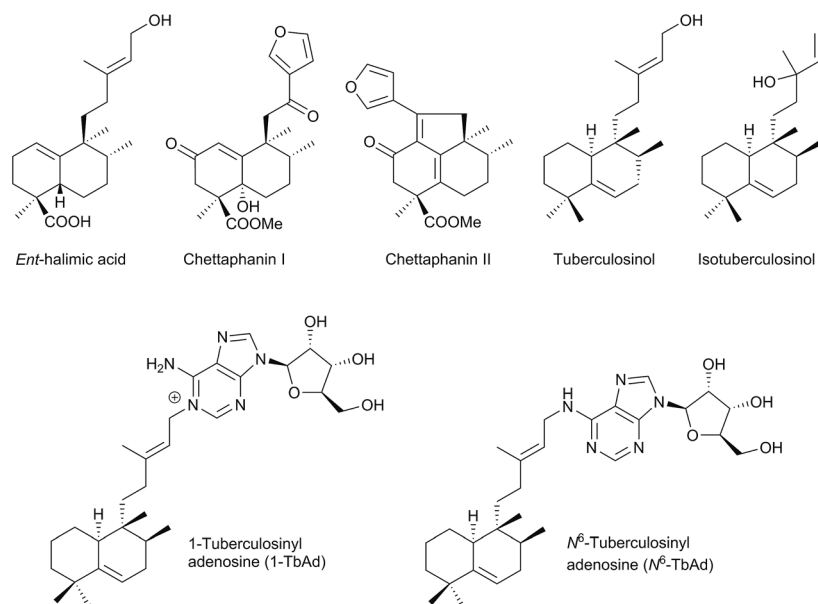


Fig. 1 Relevant halimane diterpenoids.



names, such as rearranged labdanes,^{18,19} isolabdanes²⁰ or even friedolabdanes.^{21–25}

Halimium viscosum is a plant of the Cistaceae family that shows a Hispano–Mauritanian distribution and is abundant in the west of the Iberian Peninsula. *Ent*-halimic acid and acetoxy *ent*-halimic acid are found in a 1 : 1 ratio in considerable amounts in *Halimium viscosum* extracts (47%), 0.34% with respect of the dry plant weight. Nowadays, a cheap, quick and efficient methodology for the isolation of *ent*-halimic acid has been achieved. The study of the components of *Halimium viscosum* and the need for large amounts of *ent*-halimic acid for the synthesis of biologically active compounds led us to search for *Halimium viscosum* plants in new locations with better access. In this manner, we found several places for the study of the *Halimium viscosum* components, such as Villarino de los Aires (Salamanca, Spain),¹⁷ La Fregeneda (Salamanca, Spain)^{26,27} and Valparaíso (Zamora, Spain),²⁸ localities quite close together. To our surprise, in the first location rearranged *ent*-labdanes (*ent*-halimanes) with an unsaturated side chain were isolated, in the second *ent*-halimanes with a saturated side chain were found, and, from the plants of Valparaíso, labdanes with the structural strangeness of having a carboxyl function at C-17 were only isolated. At the time of these studies, to find different chemotypes of the same plant was a novelty. Furthermore, two other chemotypes of *Halimium viscosum* have been localized in Portugal near the border with Salamanca (Celorico da Beira²⁹ and San João da Pesqueira³⁰).

In *Halimium viscosum*, in addition to the referred *ent*-halimanes and labdanes, a series of compounds that show new carbon skeletons has been isolated, characterized and then synthesized. Among them, tricyclic diterpenoids such as valparanes^{31–35} and valparolanes,³⁶ bicyclic diterpenoids with torsesane skeleton (a new type of spenolobanes),^{37,38} torsesolanes³⁹ and new rearranged labdanes with an aromatized ring B, such as fregenedanes^{40,41} and isofregenedanes,^{42,43} are found. The biosynthesis of these new carbon skeletons, as valparanes and torsesanes, contrary to the halimane diterpenoids, starts with a cyclization involving the pyrophosphate, so in this plant two different classes of diterpene cyclases should be present.

Owing to the high number of rearranged *ent*-labdane derivatives isolated in *Halimium viscosum* and in order to simplify their nomenclature and to facilitate their classification, the name *ent*-halimane was proposed for that carbon skeleton. Compounds of this class were isolated previously for the first time in the roots of *Adenochlaena siamensis*, chettaphanin I and chettaphanin II (Fig. 1), with unknown absolute configuration.

To the best of our knowledge, there are no reviews of known halimanes. Owing to the important biological properties that some of them show, and their novelty and structural diversity, we considered it to be very interesting to establish a classification and write a review on these compounds.

Nowadays, the biological activities of these compounds (such as antitumour,^{44–48} anti-inflammatory,⁴⁹ antimicrobial,^{50–52} antifungal,⁵³ germination inhibitors⁵⁴) are being studied from different points of view. Compounds such as tuberculosinol,^{55,56} isotuberculosinol^{57–59} and analogues (Fig. 1) can be considered as virulence factors (VF) in *Mycobacterium*

tuberculosis, a microorganism that causes tuberculosis illness, a major source of morbidity and mortality worldwide.⁶⁰ These compounds could be targets in a new route to anti-infective therapy.^{60,61} Recently, tuberculosinyl-adenosine derivatives have been tested as biomarkers for early diagnosis of tuberculosis.^{62,63}

1.1. Sources of halimane diterpenoids

Halimane diterpenoids form a group of secondary metabolites that can be found in different plant species of several families and in other taxonomic group, such as marine organisms and microorganisms (Table 1).

The majority of known halimanes have been isolated from Magnoliophyta (Dicotyledon) plants and among them halimanes can be found in nine orders and curiously only in eleven families. It looks like, as occurs in the clerodane diterpenoid family, that the orders and families that contain halimanes are not very numerous. That is, they do not follow the usual taxonomic tendency in which a pyramidal form will be found when going from order to genus.¹⁴

Among the families that possess halimane diterpenoids, we can highlight the Compositae, Lamiaceae and Euphorbiaceae families owing to the number of studied species and the number of halimanes found in them. In Cistaceae, it is noteworthy that all the *Cistus* studied until now, as can be observed in the reviews of diterpenes by Prof. Hanson,⁶ halimanes have only been found as minor compounds in one of them (*Cistus laurifolius*). In contrast, the other studied plant of that family (*Halimium viscosum*) is the species that has provided a major number of halimanes.

The occurrence of halimanes in non-dicotyledon plants (with only seven species studied), in eleven marine organisms (highlighting the sponges), and in three strains of bacteria is much reduced. However, the interest in halimane diterpenoids is definitively much greater because of the presence of halimane purines with important biological activities among them. Besides the mentioned tuberculosinyl adenosine derivatives isolated from *Mycobacterium tuberculosis*, eleven other halimane purines, mainly isolated from marine sponges, have been characterized. They could constitute a very interesting area for further biological and chemical research owing to their biological activities.

Herein, an up-to-date review of the 246 isolated and characterized natural halimanes is shown.

1.2. Biological activities of halimanes

The halimane purine derivatives present the most relevant biological activities related to tuberculosis biomarkers, anti-fouling and antimicrobial activities.

1.2.1. Biomarkers for tuberculosis. Another illness closely related with some halimane type compounds is tuberculosis. Tuberculosis, which is mainly caused by *Mycobacterium tuberculosis*, is a major source of morbidity and mortality worldwide, with almost two million deaths annually.⁶⁰ New drugs for the treatment of tuberculosis are necessary because of the worrying increase in the multidrug and extensively drug resistant



Table 1 Sources of halimane diterpenoids

Kingdom	Phylum	Class	Order	Family	Genus	No of species		
Plantae	Magnoliophyta	Dicotyledon	Asterales	Asteraceae	<i>Ageratum</i> , <i>Conyza</i>	2		
				Compositae	<i>Amphiachyris</i> , <i>Baccharis</i> , <i>Chiliotrichum</i> , <i>Chromolaena</i> , <i>Haplopappus</i> , <i>Koanophyllon</i> , <i>Nardophyllum</i> , <i>Oedera</i> , <i>Ophryosporus</i> , <i>Relhania</i> , <i>Stevia</i>	15		
			Caryophyllales	Portulacaceae	<i>Portulaca</i>	3		
			Fabales	Leguminosae	<i>Colophospermum</i> , <i>Hymenaea</i> , <i>Tessmania</i>	4		
			Lamiales	Lamiaceae	<i>Callicarpa</i> , <i>Isodon</i> , <i>Leonurus</i> , <i>Leucas</i> , <i>Marrubium</i> , <i>Plectranthus</i> , <i>Salvia</i> , <i>Teucrium</i> , <i>Vitex</i>	13		
					<i>Polyalthia</i>	1		
			Magnoliales	Annonaceae	<i>Acalypha</i> , <i>Aparisthmium</i> , <i>Chrozophora</i> , <i>Cladogynos</i> , <i>Croton</i> , <i>Excoecaria</i> , <i>Mallotus</i>	17		
			Malpighiales	Euphorbiaceae				
			Malvales	Cistaceae	<i>Cistus</i> , <i>Halimium</i>	2		
			Pandanales	Velloziaceae	<i>Vellozia</i>	3		
			Sapindales	Meliaceae	<i>Aglaia</i> , <i>Dysoxylum</i>	2		
				Dodonaeaceae	<i>Dodonaea</i>	1		
			Marchantiophyta	Jungermanniopsida	Jungermanniales	Geocalycaceae	<i>Heteroscyphus</i>	1
						Jungermanniaceae	<i>Jungermannia</i>	3
						Plagiochilaceae	<i>Plagiochila</i>	1
	Scapaniaceae	<i>Scapania</i>				1		
	Pleuroziales	Pleuroziaceae				<i>Pleurozia</i>	1	
	Animalia	Chordata	Ascidiacea	Aplousobranchia	Polycitoridae	<i>Cystodytes</i>	1	
		Cnidaria	Anthozoa	Alcyonacea	Plexauridae	<i>Echinomuricea</i>	1	
		Mollusca	Gastropoda	Nudibranchia	Aeolidiidae	<i>Spurilla</i>	1	
Dorididae					<i>Doris</i>	1		
Agelasidae					<i>Agelas</i>	4		
Porifera		Demospongiae	Axiniellida	Raspailiidae	<i>Raspailia</i>	1		
			Dictyoceratida	Dysideidae	<i>Dysidea</i>	1		
			Poecilosclerida	Mycalidae	<i>Mycale</i>	1		
Bacteria		Actinobacteria	Actinobacteria	Actinomycetales	Micromonosporaceae	<i>Micromonospora</i>	1	
				Mycobacteriaceae	<i>Mycobacterium</i>	1		
	Streptomycetales			Streptomycetaceae	<i>Kitasatospora</i>	1		

strains.^{60,64} Nowadays, maximum interest is focused on the development of new therapies that target virulence factor (VF) formation. VFs by definition are not essential for bacterial growth outside the host cell but are involved in processes such as invasion, persistence, lysis and evasion of innate immune system responses. Compounds such as tuberculosinol and isotuberculosinol can be considered VF in *M. tuberculosis*.^{60,61}

Currently, two genes (*Rv3377c* and *Rv3378c*) found only in virulent species of genus *Mycobacterium* (such as *M. tuberculosis* and *M. bovis*) are known and they are involved in tuberculosinol and isotuberculosinol biosynthesis. Interestingly, these genes could not be found in avirulent species of genus *Mycobacterium* (such as *M. smegmatis* and *M. avium*),^{59,65} so they may be involved in the infection processes of these bacteria. However, these genes only seem to be functional in *M. tuberculosis* and not in *M. bovis*, so that may explain the lower virulence of *M. bovis* in comparison with *M. tuberculosis*.^{66,67}

It has been observed that tuberculosinol and isotuberculosinol (Fig. 1), produced *in vivo* by *Mycobacterium tuberculosis*^{68,69} (in a 1:1 ratio), inhibit phagolysosome

maturation as well as macrophage phagocytosis, plus a synergistic effect increased by the coexistence of both compounds has been observed. Decrease of the phagocytic capacity could help to explain the pathogenicity of *M. tuberculosis*.⁵⁹ Thus, both tuberculosinol/isotuberculosinol biosynthetic proteins (*Rv3377c* and *Rv3378c*) are essential for the bacteria's survival inside the macrophage.^{57,59,70} Because of that, both enzymes are likely to be new potential targets for the development of new drugs.

Recently, two new natural tuberculosinol derivatives (having an adenosine unit attached at diterpene C15) have been isolated from *M. tuberculosis*, 1-TbAd⁷¹ and N⁶-TbAd⁶² (Fig. 1). In a comparative lipidomics assay between *M. tuberculosis* and *M. bovis*, it has been observed that these two compounds appear in higher amounts in *M. tuberculosis* and they accumulate to comprise >1% of all *M. tuberculosis* lipids, so they could serve as an abundant chemical marker of *M. tuberculosis*.^{62,71} In addition, in this study it has been proved that the *Rv3378c* enzyme is responsible for 1-TbAd formation, so this protein appears to be a tuberculosinyl transferase (prenyl transferase).⁷¹ In fact, they are being evaluated as biomarkers for tuberculosis.⁶²



Owing to all mentioned above, Rv3377c and Rv3378c are new targets for anti-infective therapies against tuberculosis that block virulence factor (tuberculosinols) formation.⁶⁰

1.2.2. Halimane purines bioactivity. The halimane diterpenoids found in marine organisms, such as Porifera, sponges of the genus *Agelas* and *Raspailia*, are characterized as halimane purines. Several of these compounds show antibacterial activity. It is interesting to point out that these compounds are structurally similar to the diterpene purines isolated from *Mycobacterium tuberculosis* (1-TbAd and N⁶-TbAd) although in these ones the purine appears glycosylated and the union with the diterpene is different. It is probable that the biosynthesis of these compounds follows a similar path to 1-TbAd and N⁶-TbAd, in which enzyme homologs to Rv3378c could be involved, probably expressed in the genome of the surrounding microbiome around the macroorganism.

Nosyberkol (isotuberculosinol) was isolated for the first time from *Raspailia* sp. and the sponge contains halimane purines too.⁷² Recently there has been enormous interest in the bioactivities of diterpenyl purines.⁷³

From *Agelas* sp.,⁷⁴ nine halimane purines have been isolated that show antibacterial, antifungal, antimalarial, cytotoxic activities, inhibition of adenosine transfer rabbit erythrocytes and Ca²⁺ channel antagonistic action and α_1 adrenergic blockade, among others. Some of these compounds possess antifouling activity against macroalgae. Natural products with this activity are very useful in the fishing industry as an alternative to the antiadherent mixtures that include metals with toxic effects on the marine environment. For this reason, antifouling substances with no or reduced toxicity must be discovered or developed.⁷⁵

1.2.3. Other bioactivities. Antitumour halimane diterpenoids against several cell lines^{45,48,52,76} (pancreatic adenocarcinoma, human colon carcinoma, bladder, lung and cervix cancer) have been isolated from plants and marine organisms of genus *Echinomuricea*, *Agelas* and *Raspailia*. Several halimane derivatives with antiangiogenic⁴⁴ activity and a topoisomerase inhibitor⁷⁷ have been described.

Other halimanes show interesting biological activities, such as antibacterial,⁵⁰ antiviral,⁷⁸ antifungal,⁵³ and antimalarial.⁷⁹ Others exert anti-inflammatory,⁴⁵ anti-ulcerogenic,⁸⁰ anti-hyperlipidemic⁸¹ or hepatogenic activities. Some halimane diterpenoids act as allelochemicals, regulating the growth of monocotyledon seeds.⁵⁴ Others behave as allomones acting against insects as repellents or mosquitocidals.⁸² From the Antarctic nudibranch a series of allomones has been isolated, including diterpene glycerides, which seem to be involved in the defense of those nudibranchs.⁸³

Many of the known halimane diterpenoids have not been biologically evaluated.

2. Biosynthesis

2.1. Biosynthesis overview

Halimane skeleton diterpenoids are formed by cyclization of geranylgeranyl diphosphate (GGPP), catalyzed by class II diterpene cyclases (DTCs).^{12,13,16} These enzymes are characterized by having an aspartate-rich DXDD motif and are differentiated

between class I terpene synthases (TPS) enzymes by not having the characteristic aspartate-rich DDXXD motif that binds divalent metal ions required for catalysis of diphosphate ionization¹¹ (Scheme 2). Several studies have been carried out revealing that the 'middle' aspartate in the DXDD motif acts as an acid catalyst.^{11,84}

The DTCs catalyze GGPP bicyclization by a general acid-base mechanism. The process starts by 14,15 double bond protonation of *E,E,E*-GGPP followed by carbon-carbon double bond anti addition (C10 on C15, then C6 on C11) to give four possible bicyclic products. Effectively, depending on the different prochiral substrate conformer (**1**, **2**, **3** or **4**) operating in the cyclization, the corresponding stereoisomer of labda-13-en-8-yl diphosphate intermediate will appear (**5**, **6**, **7** or **8**).

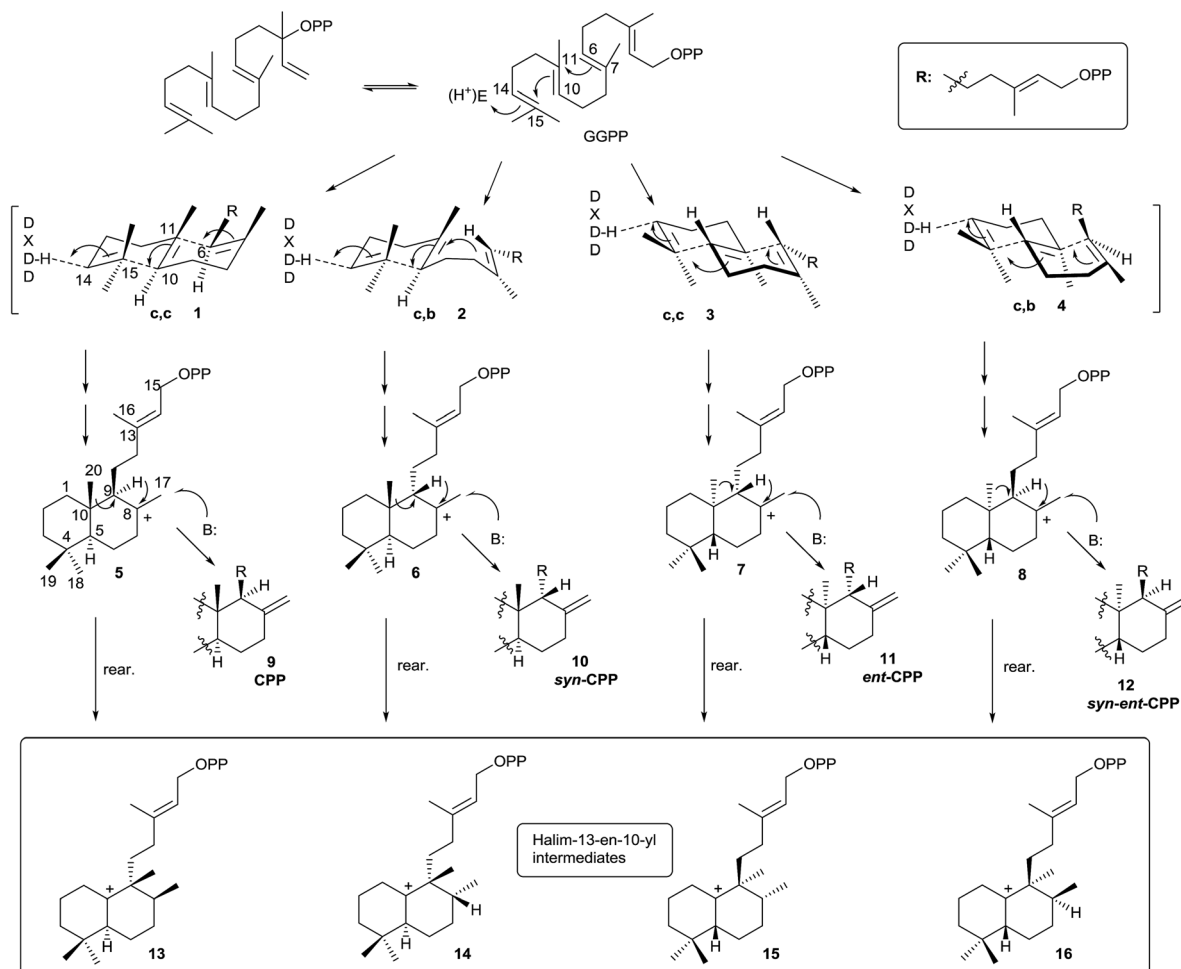
In this manner, chair-chair (c,c) conformer **1** leads to 8-carbonium ion **5**, which possesses the 'normal' *anti,anti* absolute stereochemistry (between H9-C20-H5). Chair-boat conformer (c,b) **2** leads to carbocation **6** with the 'normal' *syn,anti* absolute stereochemistry (between H9-C20-H5). Antipode conformers of the preceding ones, the chair-chair (c,c) **3** and chair-boat (c,b) **4**, lead to the 8-carbonium ions **7** and **8** with *anti,anti* and *syn,anti* absolute stereochemistry (between H9-C20-H5), respectively.

Labda-13*E*-en-8-yl diphosphate intermediates (**5**, **6**, **7** and **8**) lead to the different copalyl diphosphate labdane precursors by reaction with a base: copalyl diphosphate (CPP, **9**), *syn*-copalyl diphosphate (*syn*-CPP, **10**), *ent*-copalyl diphosphate (*ent*-CPP, **11**) and *syn-ent*-copalyl diphosphate (*syn-ent*-CPP, **12**), respectively.¹⁶ Among labdanes, the major ones are *ent*-CPP **11** (9*R*,10*R*) derivatives, followed by the 'normal' labdane precursor CPP **9** (9*S*,10*S*) derivatives. A lot of class II DTCs that lead to these two precursors are known. However, *syn*-CPP **10** (9*R*,10*S*) derivatives are less common, and only a few *syn-ent*-CPP **12** (9*S*,10*R*) labdane derivatives have been reported.¹⁶

However, this is not the only way the intermediate carbocations **5**–**8** can evolve. A rearrangement by sequential 1,2-hydride shifts (H-C9 to H-C8) and methyl group migration (C10 to C9 methyl migration) can occur instead of producing the stabilization of intermediates **5**–**8** (Scheme 2) by proton abstraction. In this way, the cationic halim-13*E*-en-10-yl diphosphate intermediates **13**–**16** are respectively produced, and they already contain the halimane backbone.

Those halimenyl diphosphate cations **13**–**16** can evolve by different ways (Scheme 3). Each one can lose a proton providing the halimadienyl diphosphates **17** or **18**, or rearrange by hydride shift to form the halimenyl diphosphate cation **19** followed by proton abstraction to give the halimadienyl diphosphate **20**. The different diastereoisomer forms (**21**–**24**), (**25**–**28**) and (**29**–**32**) correspond to the halimadienyl diphosphates **17**, **18** and **20**, respectively (HPP, *syn*-HPP, *ent*-HPP, and *syn-ent*-HPP; where *syn* prefix refers to *cis* configuration between H8 and C20). These diphosphates are the precursors of nearly all known halimanes. As has been indicated previously, the final cations **19** usually evolve by deprotonation yielding halimadiene skeleton compounds. However, water addition to the previously cited cations can occur, producing hydroxylated derivatives,^{85,86} such as the dihydrohalimene **33**, thus leading to formal





Scheme 2

designation of the relevant class II DTCs as hydratases.⁸⁶ Otherwise, although 1,2-hydride and/or methyl shifts do not appear to be concerted,¹⁶ the clerodane skeleton is formed from intermediate **19** by methyl group migration (C4 to C5 methyl migration giving *trans* and *cis* clerodanes) and later stabilization, thus generating the more than 1300 compounds that make up the clerodane diterpenoids family.^{14,15}

The formation of 3-secohalimanyl derivatives, such as **35** (Scheme 4), can be explained by oxidation of the C3 position of a halimanyl derivative by some specific oxygenase, such as cytochrome P450 monooxygenase.⁸⁷ It is notable that plants have vastly expanded numbers of cytochrome P450 monooxygenases in their genomes⁸⁸ providing a ready source of potential downstream acting enzymes. Studies have proved that cytochrome P450 takes part in the biogenesis of a considerable number of tricyclic and tetracyclic diterpenes,^{16,89} oxidizing these compounds at C3. So, we cannot discard the oxidation of any biogenetic intermediates of **35**, achieving a hydroxy derivative like **34**. For the formation of intermediates such as **34**, in other families of compounds, it has been speculated with the epoxy derivative participation,⁹⁰ as the GGPP oxide, although in diterpene biosynthesis that intermediate has not been detected until now in nature.

Finally, oxidation with rupture of the C3–C4 bond leads to the wide group of 3-secohalimanyl derivatives.

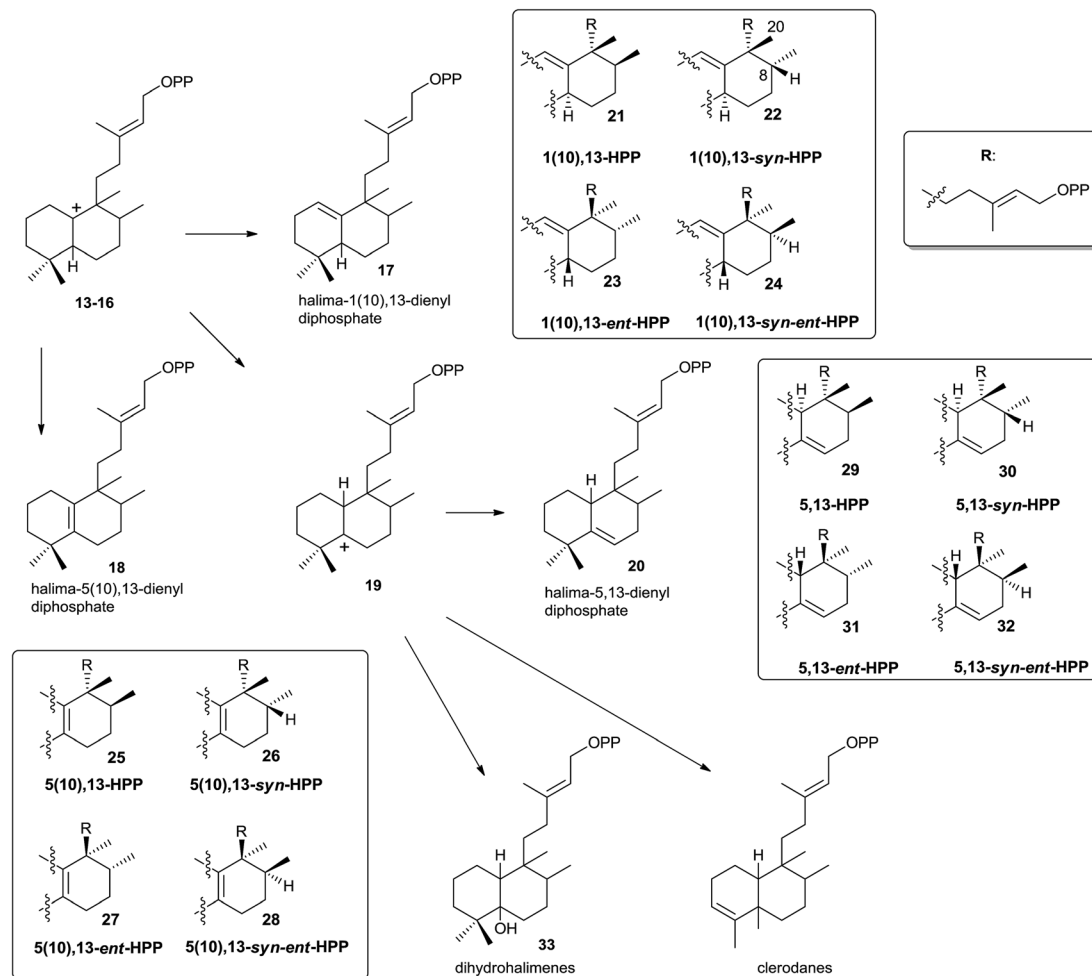
Rearranged halimanes of different types (I–V) are known (Fig. 2). Each one can be formed by rearrangement of some intermediate cations of other halimanes. In fact, rearranged halimanes have been obtained through biomimetic synthesis starting from natural halimanes.⁹¹

Type I rearranged compounds should be formed by ring B expansion (Scheme 5). Oxidation of **27** (5(10),13-*ent*-HPP) at C11 gives **36**, the precursor of an intermediate carbocation **36a** that facilitates ring B expansion through an intermediate such as **36b**, which finally could be stabilized by double bond formation between C9 and C11.

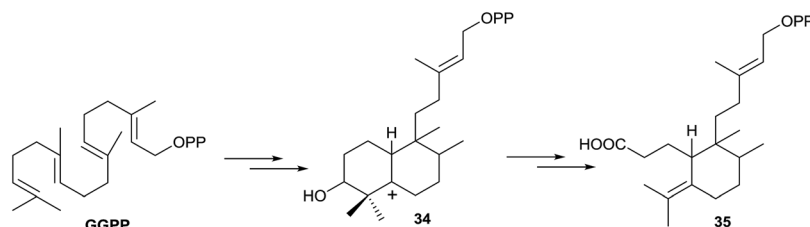
Type II and III derivatives could be formed by expansion/contraction of the decaline annular system that arises from an intermediate diketone **37a**, which will be formed by oxidation of the double bond $\Delta^{5(10)}$ through the intermediate **37**, as it is shown in Scheme 6.

Type IV derivatives are compounds that can be considered as rearranged halimanes or rearranged clerodanes because C19 is bonded to C4 and C5 forming a cyclopropane ring, and type V derivatives can also be considered rearranged halimanes or clerodanes because C19 has been included in ring A as





Scheme 3



Scheme 4

a consequence of a ring expansion, while other biosynthetic pathways cannot be discarded (Scheme 7). Possibly, the relevant class II diterpene cyclase might promote the cyclopropanation or the ring A expansion as it occurs with the ring contractions in the biosynthesis of permutilin.⁹²

2.2. Enzymatic and genetic experimental studies

A bacterial class II (B type) DTC that produces halima-5,13-dienyl diphosphate (29) has been identified.^{16,55} Effectively, *Mycobacterium tuberculosis* Rv3377c gene has been identified, and the encoded diterpene cyclase has been proved to be responsible for the production of the halimane skeleton (Scheme 8).

Recently the structure of the diterpene tuberculosinol/isotuberculosinol synthase (Rv3378c) from *Mycobacterium tuberculosis* has been reported.⁶⁰ The biosynthesis of tuberculosinols is catalyzed by two enzymes: Rv3377c, tuberculosinyl (halima-5,13-dien-15-yl) diphosphate synthase, and Rv3378c, tuberculosinol/(R/S)-isotuberculosinol synthase. Both proteins are essential for the bacteria survival inside the macrophage where tuberculosinols inhibit phagolysosome maturation as well as macrophage phagocytosis.^{57,59,70}

Rv3377c is a DTC classified as class II that transforms GGPP into tuberculosinyl diphosphate (TPP) with a halimane core^{55,93} (Scheme 8), while Rv3378c is a diterpene synthase that converts



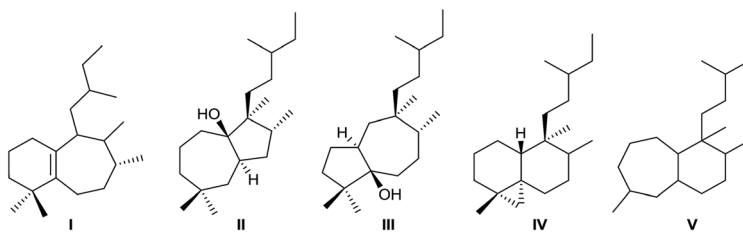
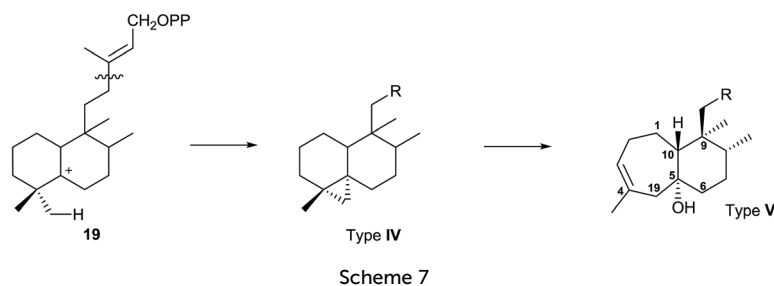
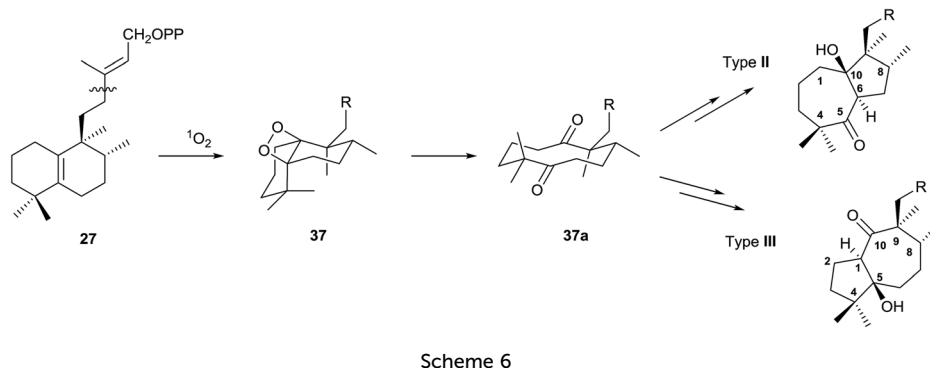
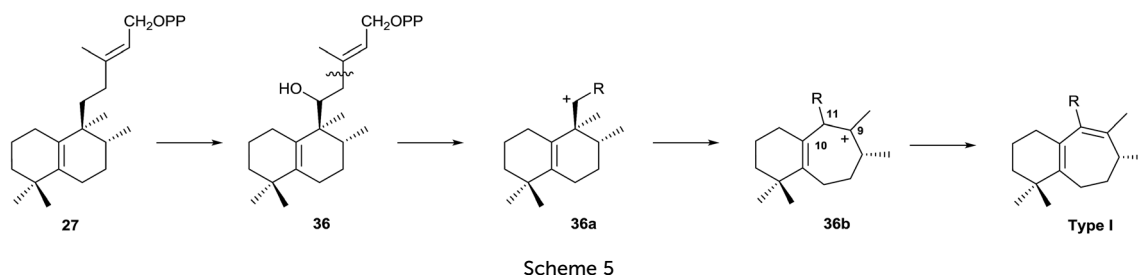


Fig. 2 Types of rearranged halimanes.



TPP into tuberculosinol or (*R/S*)-isotuberculosinols acting as a phosphatase/isomerase.^{57,59} However, although these two enzymes are sufficient to generate tuberculosinol and isotuberculosinol from GGPP, some studies on the evolution and functional characterization of the biosynthetic operon where these two genes are found have been carried out.⁹⁴ Recently, a previously unknown type of diterpene-nucleoside, 1-tuberculosinyl adenosine (1-TbAd), was isolated and characterized (Scheme 8). This discovery leads us to consider a reviewed biosynthetic model in which the Rv3378c protein is not a simple phosphatase as currently believed, but that the enzyme acts

with combined phosphatase and tuberculosinyl transferase functions by using adenosine as nucleophilic substrate.⁷¹

Interestingly, the Rv3377c and Rv3378c genes are found only in virulent *Mycobacterium* species, and not in avirulent ones.^{59,66} Another work reported that these genes are only functional in *M. tuberculosis*, despite being present in other less virulent species, such as *M. bovis*.⁶⁷

Recently the incubation of [16,16,16-²H₃]GGPP with tuberculosinyl diphosphate synthase (Rv3377c) from *M. tuberculosis* allowed the stereochemical course of the cyclization reaction to



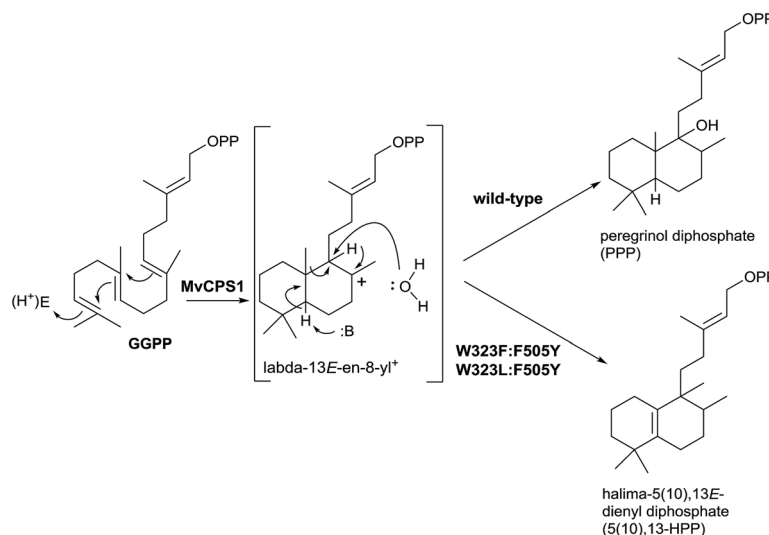


Scheme 8

Recently, Zerbe and co-workers,⁹⁶ in a work guided to achieve bioactive natural products harnessing the plasticity of these class II diTPS, have realized mutagenic experiments with the horehound (*Marrubium vulgare*) class II diTPS peregrinol diphosphate synthase (MvCPS1) (Scheme 10). Two double mutants based on the combination of F505 and W323 (W323L : F505Y and W323F : F505Y) produce the rearrangement

In many of these plants that contain halimanes, labdanes have also been isolated and in other plants they coexist with clerodanes. For example, in a Cistaceae such as *Halimium viscosum* *ent*-halimanes and labdanes coexist,^{17,26,28,99,100} in *Cistus laurifolius* labdanes, *ent*-labdanes, *cis*-clerodanes and *ent*-





Scheme 10

halimanes have been isolated,^{101–104} and in plants of genus *Croton*^{44,105–107} (Euphorbiaceae) labdanes, halimanes and clerodanes coexist. In *Haplopappus paucidentatus*²⁵ and *Nardophyllum lanatum*¹⁹ (Compositae) labdanes, halimanes and clerodanes coexist. It seems that in *Halimium viscosum* the biosynthetic route to clerodanes is enzymatically interrupted.

3. Classification

In this review, halimane diterpenoids have been classified according to the endocyclic double bond position and to their corresponding dihydro derivatives. Seco-, nor- and rearranged halimanes have been considered too (Fig. 3).

In this manner, we have divided the halimanes into six different groups: (1) halim-1(10)-enes, (2) halim-5(10)-enes, (3) halim-5-enes, (4) dihydrohalimenes, (5) seco- and norhalimenes and (6) rearranged halimanes. As can be seen in Fig. 2, the first four groups could be divided into four series: 'normal', 'antipode or entantio', 8-*epi* and 8-*epi-entantio*. According to the biogenesis of each group, those derivatives in which methyls Me-17 and Me-20 are *cis* to each other are denominated halimanes or *ent*-halimanes, and those in which methyls Me-17 and Me-20 are *trans* to each other are called 8-*epi*-halimanes or 8-*epi-ent*-halimanes (Fig. 3). Derivatives from all these groups of compounds are known, except for 8-*epi-ent*-halim-5-ene.

To the best of our knowledge, all examples of seco-, nor-, and rearranged halimanes (groups 5 and 6) known nowadays belong to the 'enantio' series, except for four tetranorhalimenes and three rearranged halimanes.

4. Natural halimanes

In this section the structures of natural halimanes can be observed; each one is numbered and accompanied by its trivial name. In addition, we summarize the information in tables that appear in the S.I., including the source of isolation, the plant

part or organism from which they were isolated, the biological activities and references (Tables S1–S6†).

Approximately 70% of the natural halimanes known are of the 'enantio' series (*ent*-halimanes or 8-*epi-ent*-halimanes) and the remaining 30% are of the 'normal' series (halimanes or 8-*epi*-halimanes).

The halimane structure elucidation has been carried out by extensive spectroscopic techniques, mainly NMR and chemical correlation. X-ray structural analysis has been carried out for several of them, as indicated in the comments of the diverse groups that appear afterwards. The absolute configuration has been established by circular dichroism. However, in some cases, mainly due to the scarcity of natural product, it has not been possible to determine the stereochemistry.

The figures and tables will show the natural products as they have been described and characterized; in most cases the carboxylic acids appear as their respective methyl ester derivatives.

4.1. Halim-1(10)-enes group

The first known halimanes are found in the group of halim-1(10)-enes, which is the most numerous class so we start the classification from them.

4.1.1. *ent*-Halim-1(10)-enes. Chettaphanin I (38), isolated from the roots of *Adenochlaena siamensis*, was the first *ent*-halimane to be discovered¹⁰⁸ (Fig. 4, Table S1†). Its structure was spectroscopically determined in 1970; however, its absolute configuration remained unknown until 2003,¹⁰⁹ when its synthesis was described starting from the methyl ester of *ent*-halimic acid (39),^{17,110} a major component of *Halimium viscosum* (Villarino de los Aires), whose structure and absolute configuration are known.

In literature, the first halimanes were designated as rearranged labdanes, isolabdanes or friedolabdanes, but in order to classify them in a diterpene group, it was decided to name them as halimanes due to the high number of these compounds that appear in plants of genus *Halimium*.¹⁷



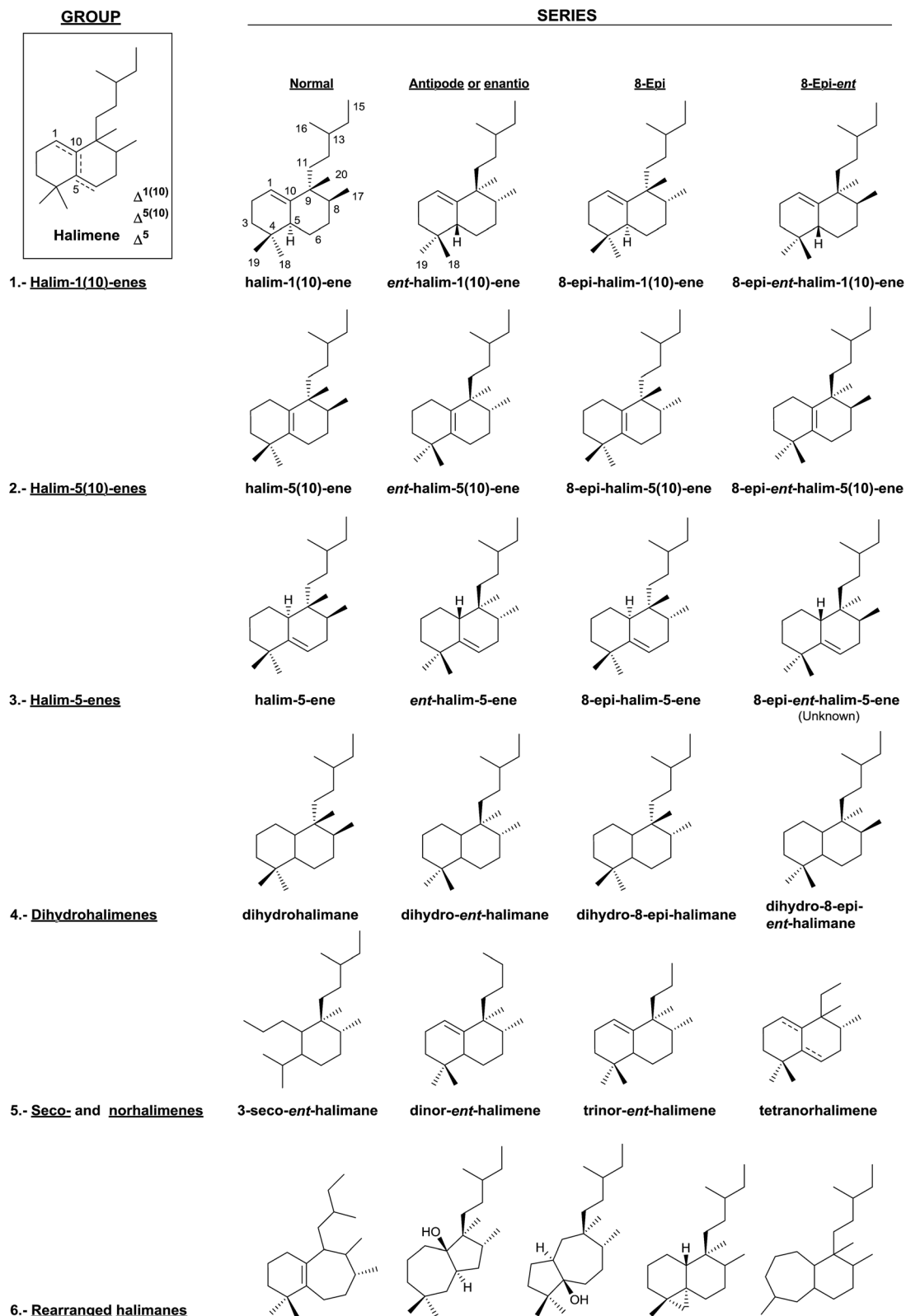
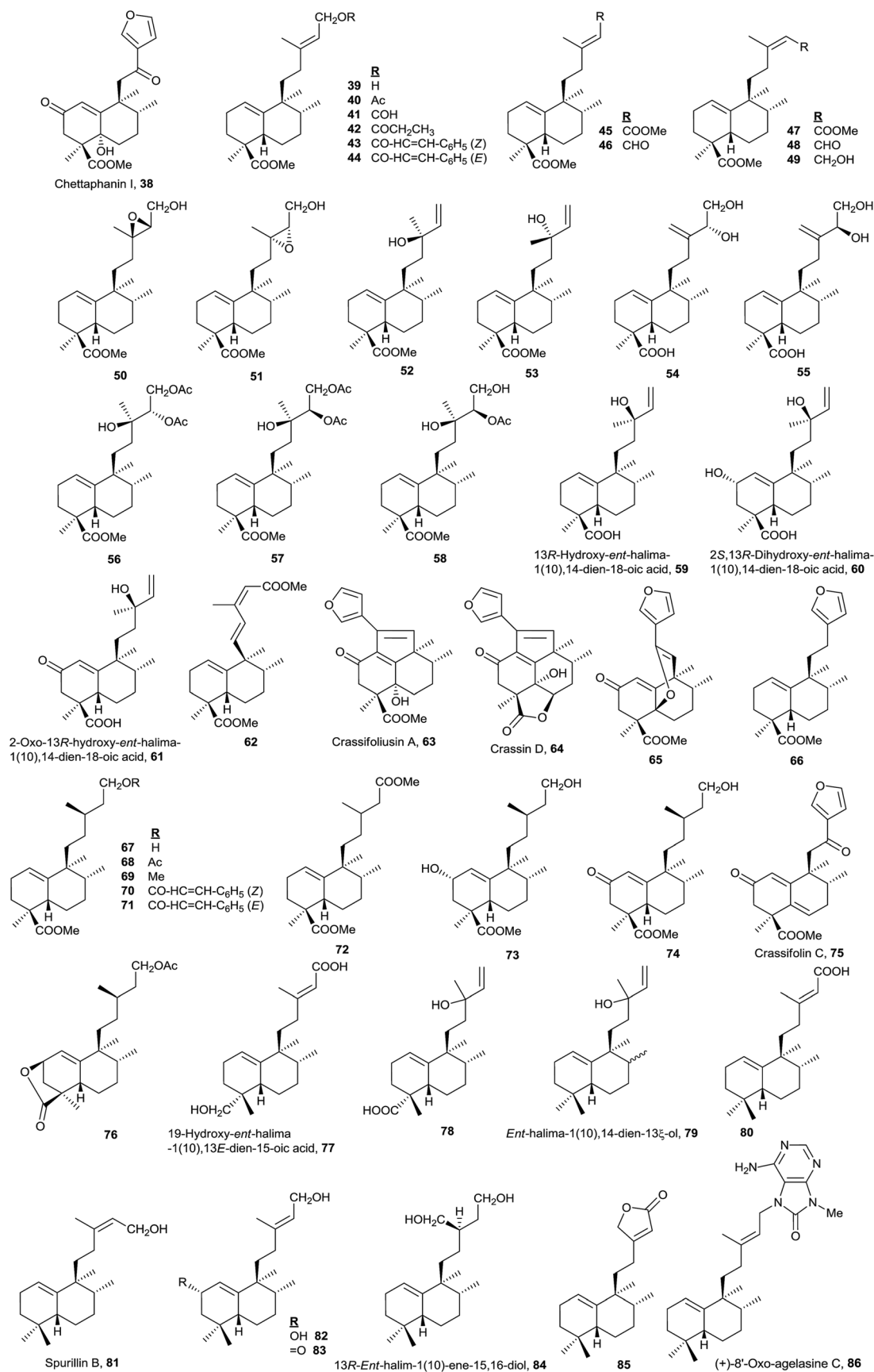


Fig. 3 Classification of halimanes.

The study of genus *Halimium* plants has made possible to determine the presence of five chemotypes of *Halimium viscosum*, known in accordance with the harvesting place: Villarino de los

Aires, (Salamanca, Spain),¹⁷ La Fregeneda, (Salamanca, Spain),^{26,27} Valparaíso, (Zamora, Spain),²⁸ Celorico da Beira, (Portugal)²⁹ and San João da Pesqueira, (Portugal).³⁰



Fig. 4 *ent*-Halim-1(10)-enes.

In this group, the Euphorbiaceae,^{78,108,109,111–114} Cistaceae,^{17,26,27,29,30,110,115–118} Leguminosae,^{48,119,120} Compositae,^{21,24} Jungermanniaceae,¹²¹ Velloziaceae⁵² and Annonaceae^{122,123} plant families have been studied together with marine organisms of genus *Spurilla*¹²⁴ and *Agelas*.^{74,125}

The most numerous compounds of this group (Fig. 4) are those that show a carboxylic function at C18 and among them the most frequent possess an unsaturated or polyfunctionalized side chain. However, compounds **77** and **78** are the only ones that have an oxygenated function at C19. Compounds with the saturated side chain are abundant too, finding among them those oxidized at C2.

The absolute configuration of **61** was determined by circular dichroism (CD) and the structure of **59** was corroborated by X-ray. These two compounds were isolated from *Hymenaea courbaril*.⁴⁸

Only eight compounds **79–86** do not have functionalized C18 or C19. Recently, spurillin B (**81**), isolated from *Spurilla* sp (Nudibranchia), has been described, and it is one of the few *ent*-halimanes with a *cis* double bond in their side chain.¹²⁴ 8'-Oxo-agelasine C (**86**) is a novel purine diterpene that was recently isolated from *Agelas nakamurai* and it is the only halimane purine presenting a carbonyl group at adenine C8.¹²⁵ Compounds of this type, usually known as agelasines, have been isolated from genus *Agelas* sponges and are very interesting owing to their antimicrobial and antispasmodic activities and their action as Na,K-ATPase enzyme inhibitors.¹²⁶

Although this group is quite numerous, only six furo-halimane derivatives (**38**, **63–66** and **75**) and a halimanolide (**85**) are known. These functionalizations are most frequent in the *ent*-halim-5(10)-enes, as we will explain later. Crassifoliusin A (**63**)¹¹³ and crassin D (**64**),¹¹⁴ isolated from *Croton crassifolius*, have a tricyclic system formed by cyclization of C1 with C12 of the halimane side chain.

A lot of these compounds have been isolated from plants used in folk medicine, but the biological activity of many of them has not been determined yet. Only **59**⁴⁸ and **84**⁵² have proved to be active as antitumour drugs.

4.1.2. Halim-1(10)-enes. Only three compounds of this kind are known: **87**, **88** and **89** (Fig. 5, Table S1†). Charruic acid (**88**) is the only halim-1(10)-ene showing a Δ^7 in ring B and was isolated from *Ophryosporus charua*.¹²⁷

The structure of the natural product agelasine C (**89**) was established by its enantiomer synthesis¹²⁸ correcting, in this

manner, the original structure proposed by Nakamura and co-workers.¹²⁶ Agelasine C (**89**) was isolated from Okinawan sea sponge *Agelas* sp. and *Agelas citrina*¹²⁹ and it exerts antifungal activity.

The structure of **87**, halima-1(10),14-dien-13 ξ -ol, isolated from *Plagiochila barteri*, was determined spectroscopically and by comparison with **79**.¹³⁰ In any case, the configuration at C13 has not been determined yet.

4.1.3. 8-*epi*-Halim-1(10)-enes. Until now, only five natural products (**90–94**) have been described within 8-*epi*-halim-1(10)-ene series (Fig. 6, Table S1†), **90** isolated from *Relhania acerosa*¹³¹ and **91–94** isolated from *Vitex trifolia*^{77,132} or *Vitex rotundifolia*.⁸¹ Previously, vitextrifloxiolide F was isolated from *Vitex trifolia*, but its C13 absolute configuration was not determined.⁷⁷ We have noticed that vitextrifloxiolide F's spectroscopic properties are the same as those of viterofolin F, so we have numbered them as a single compound, **92**. Compounds **91–94** are, together with **75**, the only halimanes showing a trans-annular dienic system $\Delta^{1(10),5}$. Vitextrifloxiolide G (**94**) presents moderate cytotoxicity and topoisomerase I inhibition activity.⁷⁷

4.1.4. 8-*epi-ent*-Halim-1(10)-enes. 8-*epi-ent*-Halim-1(10)-ene skeleton compounds are not too numerous (Fig. 7, Table S1†); all of them were isolated from marine organisms.^{46,47,75,83,128,133–135} A series of diterpene glycerides involved in chemical defense of nudibranchs has been isolated from the Antarctic nudibranch *Austrodoris kerguelensis*. Among them **95**, **97** and **98** are included.^{83,133,134} Austrodorin (**95**) was characterized as its diacetyl derivative diacetyl-austrodorin (**96**). Palmadorin R (**97**) and palmadorin S (**98**) possess a conjugated carbonyl at C2.

Echinohalimane A (**99**), which shows a γ -hydroxybutenolide in the side chain, was isolated from a gorgonian identified as *Echinomuricea* sp.^{46,47} It is the first halimane isolated from a marine organism belonging to the phylum Cnidaria. This compound was found to exhibit cytotoxicity towards various tumour cell lines and displays an inhibitory effect on the release of elastase by human neutrophils.

The new diterpene alkaloid *epi*-agelasine C (**100**) was isolated from the marine sponge *Agelas mauritiana* as an antifouling substance active against macroalgae.^{75,128} The original structure proposed for *epi*-agelasine C, a halim-1(10)-en derivative,⁷⁵ was corrected to the structure of 8-*epi-ent*-halim-1(10)-ene derivative for **100**¹²⁸ (Fig. 7). Recently, the structure of isoagelasine C (**101**), isolated from *Agelas nakamurai*, has been described and it shows potent antifungal and moderate antibacterial activity.¹³⁵

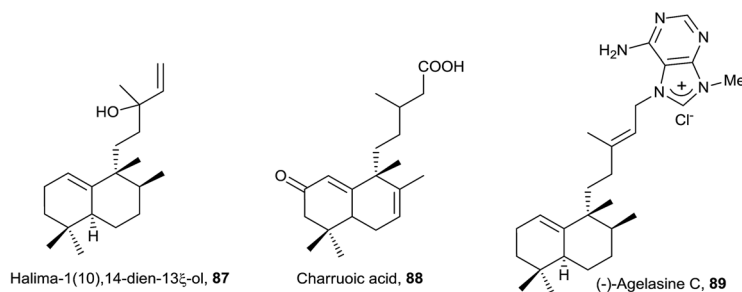


Fig. 5 Halim-1(10)-enes.



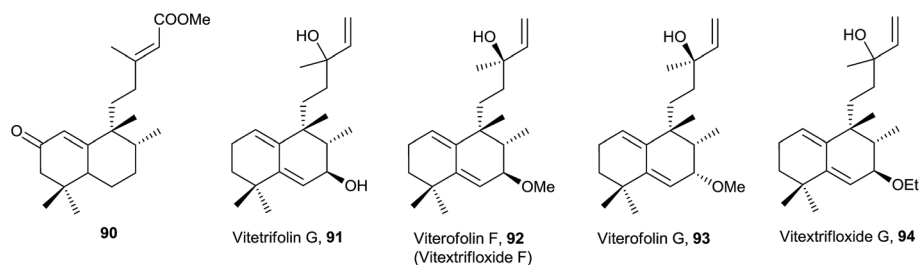


Fig. 6 8-epi-Halim-1(10)-enes.

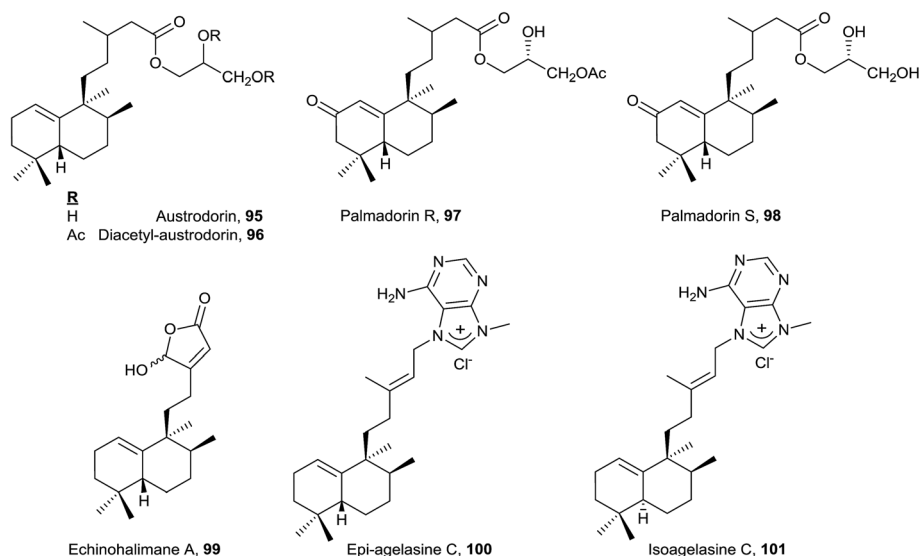


Fig. 7 8-epi-ent-Halim-1(10)-enes.

4.2. Halim-5(10)-enes group

Together with the halim-1(10)-enes, these compounds form the two largest groups of halimanes.

4.2.1. ent-Halim-5(10)-enes. It is the most numerous class within the halim-5(10)-enes group (Fig. 8, Table S2†). Compounds of this type have been isolated from plants of the families Euphorbiaceae,^{44,78,105,107,109,111–114,136–151} Compositae,⁴⁵ Annonaceae,¹²² Lamiaceae,⁹¹ Jungermanniaceae,^{152,153} Asteraceae,⁷⁶ and Meliaceae,¹⁵⁴ and in sponges of genus *Agelas*.^{79,135} Among them, chettaphanin II (**102**)¹¹¹ is found. It was isolated from *Adenochlaena siamensis*, which, along with chettaphanin I (**38**), are the two first known halimanes. Chettaphanin II (**102**) synthesis enabled its structure to be confirmed and its absolute configuration to be established.¹⁰⁹ Chettaphanin II (**102**) shows a tricyclic system resulted of a bond between C1–C12.

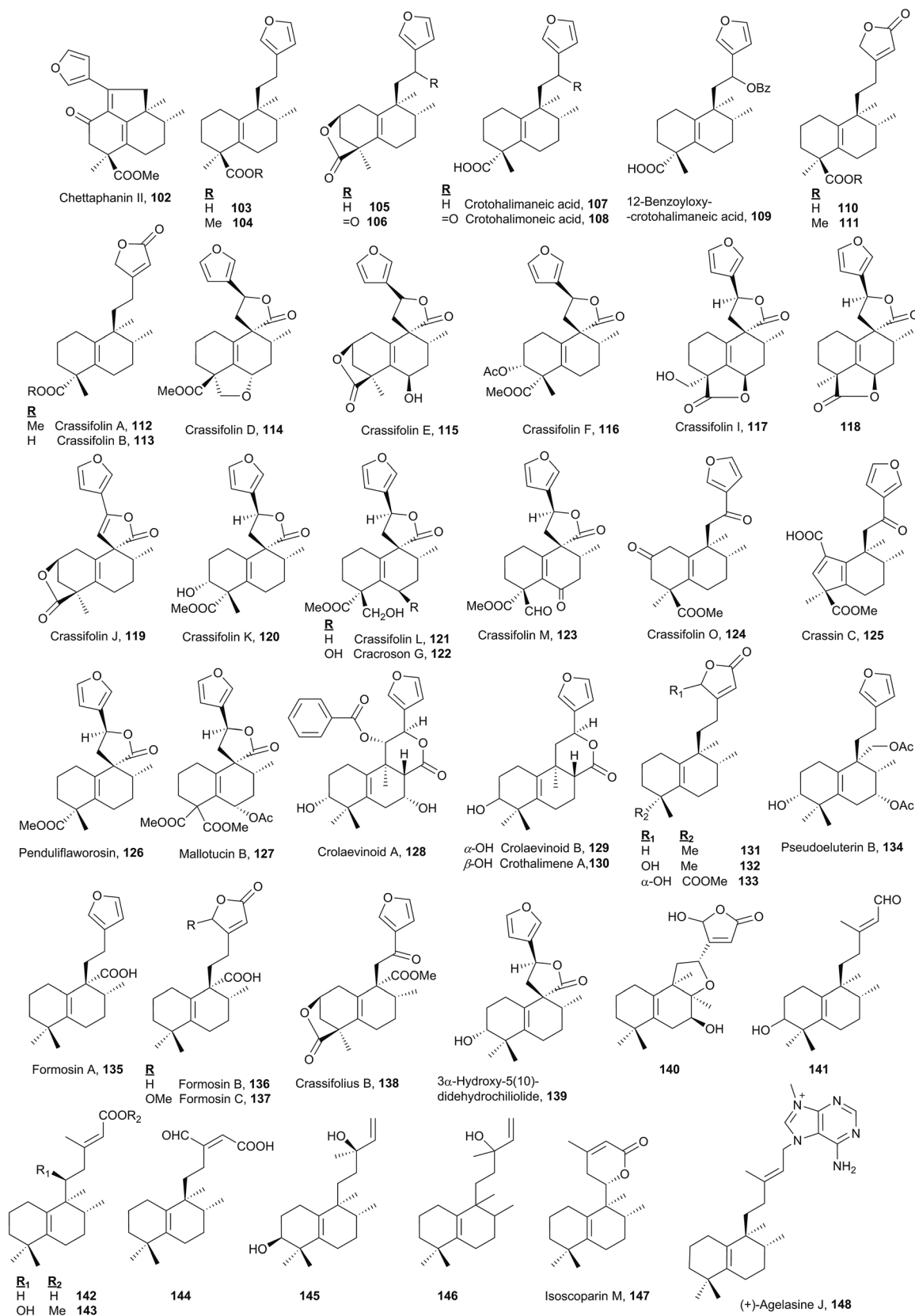
As chettaphanin II (**102**), the majority of known *ent*-halim-5(10)-enes are furo-*ent*-halimanes. In some of them the furan fragment appears oxidized in the form of 15,16-butenolide. The lactone group can be observed in other positions, for example 20,12-olides. It is usual to find derivatives of this kind with a carboxylic function at C18 or C19. The side chain C12 position usually appears functionalized and ring A can be oxygenated at C2 or C3.

The structure and absolute configuration of lactone **106** were corroborated by synthesis and it shows a moderate activity against HeLa cells.^{44,78,112,141} Crotohalimaneic acid (**107**) and crotohalimoneic acid (**108**) show activity against several human cancer cell lines.¹⁴⁰ The structure of crotohalimoneic acid (**108**) was corroborated by X-ray.

A series of *ent*-halim-5(10)-enes known as crassifolins **112–117**, **119–121**, **123–124** and crassin C (**125**) has been isolated from *Croton crassifolius*.^{44,78,144} The absolute configuration of several of them was confirmed by CD. The structure of crassifolin D (**114**) was corroborated by X-ray; however, its absolute configuration was not determined. As the crassifolins found in *Croton crassifolius* are included in the *ent*-halim-5(10)-ene series, the same absolute configuration is proposed for crassifolin D (**114**) and it was included in this group. Crassin C (**125**)¹⁴⁴ is characterized by its ring A contraction, showing a carboxylic function at C1. This compound could be the result of an oxidation followed by condensation, of any compound that coexists in that plant with functionalization at C2, forming in this manner a [5.6] ring system.

Compounds of this kind functionalized at C6 in ring B are not frequent, only crassifolin D (**114**), crassifolin E (**115**), crassifolin I (**117**),^{143,144} **118**,¹³⁸ cracroson G (**122**),¹⁵¹ crassifolin M (**123**),⁴⁴ and mallotucin B (**127**)¹³⁶ show this functionalization.



Fig. 8 *ent*-Halim-5(10)-enes.

Functionalization at C7 is seen in compounds **128**, **134** and **140** and at C8 only on compound **140**.⁷⁶

Crassifolin A (**112**), crassifolin B (**113**), and penduliflorosin (**126**) showed anti-angiogenic activity using a wild-type zebrafish *in vivo* model,^{44,78} and crassifolin D (**114**) shows antiviral and anti-angiogenic activities.⁴⁴

Crolaevinoids A–B (**128**–**129**) and crothalimene A (**130**) were recently isolated from *Croton laevigatus* and *Croton dichogamus*, respectively.^{105,148} They are the only C17 functionalized derivatives known in this class forming a δ -lactone with carbon C12. The absolute configuration of compounds **128** and **129** was determined by electronic circular dichroism (ECD). These compounds exhibit pronounced inhibition of nitric oxide (NO) production.¹⁰⁵

3 α -Hydroxy-5(10)-didehydrochiliolide (**139**) was highly active against a human pancreatic adenocarcinoma cell line at micromolar concentrations⁴⁵ and **140** shows antitumour activity.⁷⁶ Formosin A–C (**135**–**137**) isolated from *Excoecaria formosana* were active as antimicrobials,¹⁴⁷ and, in addition to crassifolius B (**138**),¹⁵⁰ they are the only compounds that possess a carboxylic acid or methyl ester functionality at C20.

In six of the known *ent*-halim-5(10)-enes **141**–**146**, no furanic or lactone systems appear in the side chain. Isoscoparin N (**143**) and isoscoparin M (**147**),^{91,155} together with crolaevinoid A (**128**), are the only ones that show oxygenated functions at C11. The structure of compound **146** has been proposed but its absolute configuration has not been solved.¹⁵³ Compound **145** shows antitumour activity.¹⁵⁴

In this group, the halimane purine agelasine J (**148**) is included. Agelasine J was isolated from the Solomon Islands marine sponge *Agelas cf. mauritiana*. It shows antimalarial and antimicrobial activity and MCF7 cell cytotoxicity.^{79,135}

4.2.2. Halim-5(10)-enes. Only nine halimanes of this type are known (**149**–**157**, Fig. 9, Table S2†). Compounds **150** and **151**

isolated from *Dysoxylum densiflorum*¹⁵⁶ and **152** and **153** isolated from *Amphiachyris amoena*¹⁵⁷ possess functionalization at C3. Allylic groups, as furyl or butenolide derivatives, appear in the unsaturated side chain, except **149**, isolated from a Dominican amber,¹⁵⁸ which shows a saturated side chain with a carboxyl group at C15. Derivatives with oxygenated functions at C19 appear esterified with *p*-hydroxyphenylpropionic acid, amoenolide L (**152**) and amoenolide M (**153**).¹⁵⁷ These last compounds include oxygenated functions on ring B at C6. Recently, crassifolius A (**154**) and crassifolius C (**155**), from *Croton crassifolius*, have been characterized and their absolute configurations established by ECD.¹⁵⁰

In this class, two halimane purines isolated from an Okinawan marine sponge *Agelas* sp. can be found: agelasine O (**156**) and agelasine S (**157**).⁵³ Agelasine O (**156**), in which C18 is esterified with 2-carboxy-4-bromopyrrole, is biologically active as an antibacterial and antifungal.⁵³ Agelasine S (**157**) exerts antibacterial and antifungal activities and is the only derivative of this type difunctionalized at C1 and C3.

4.2.3. 8-*epi*-Halim-5(10)-enes. Compounds of this group (Fig. 10, Table S2†) have been isolated from plants of the Lamiaceae family (*Vitex agnus-castus* **159**¹⁵⁹ and **162**;¹⁶⁰ *V. trifolia* **160**¹⁶¹ and **162**–**166**;^{77,132,162} *V. rotundifolia* **161**–**162**^{81,163} and **167**;¹⁶⁴ *Leonorus japonicus* **168**¹⁶⁵ and *Marrubium aschersonii* **169**¹⁶⁶) except **158**, which was isolated from *Stevia gilliesii*¹⁶⁷ (Compositae). The most usual derivatives in this series are those that present oxygenated functions on ring B, normally on carbons C6 and C7 (Fig. 9, Table S3†). Only two compounds do not have oxygenated functions on ring B: **158** and **159**. In the side chain, only isoleojaponin (**168**) shows a furan ring and all the rest possess allylic groups. Functionalized compounds on ring A are less usual, having found only **159**, **161** and **169**. Only one of them, marrubasch C (**169**), shows functionalization at C19.¹⁶⁶

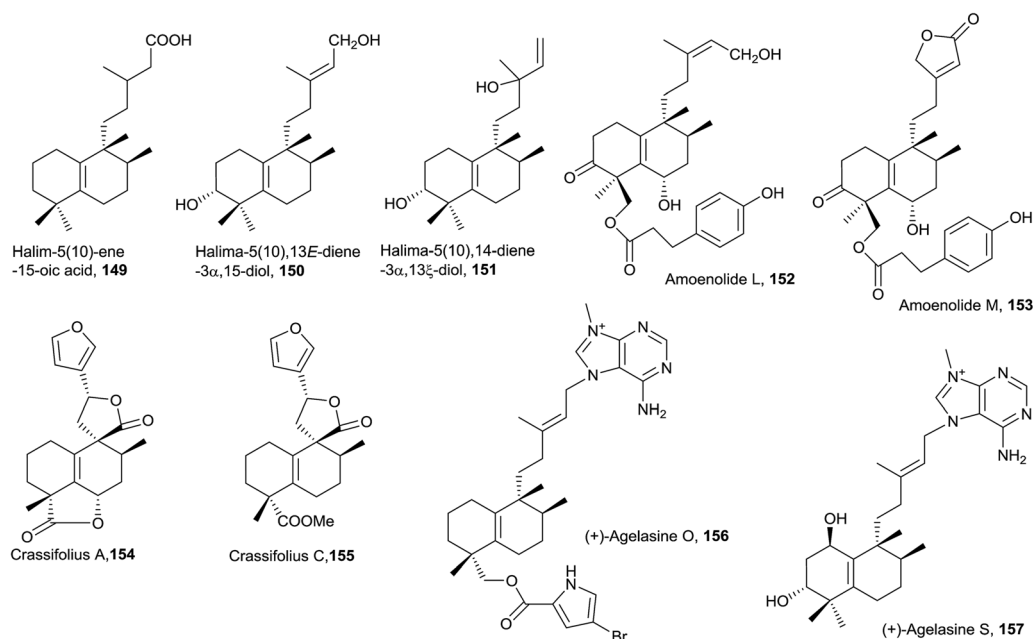
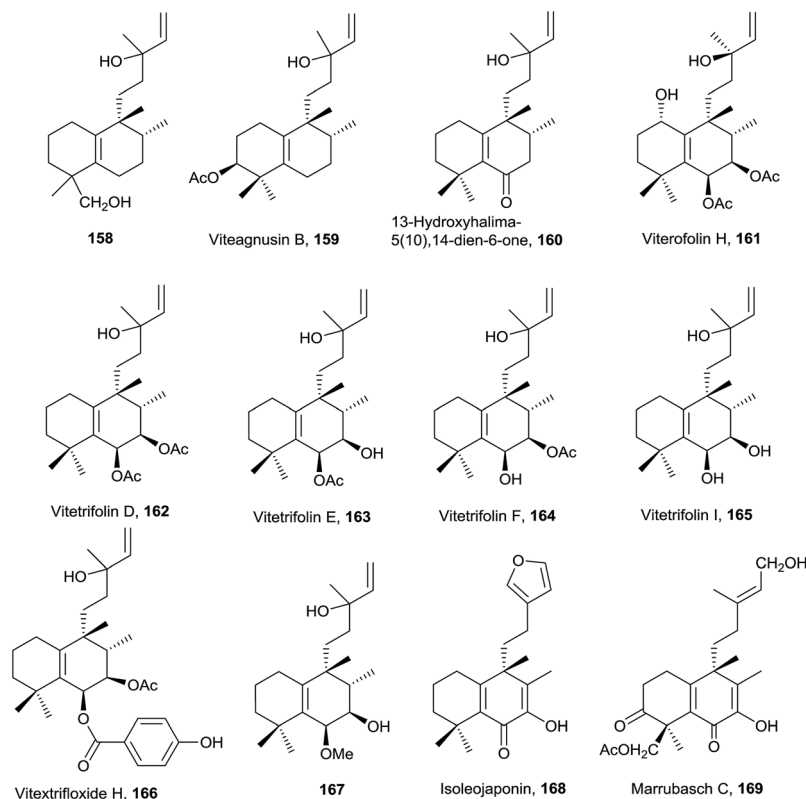


Fig. 9 Halim-5(10)-enes.



Fig. 10 8-*epi*-Halim-5(10)-enes.

Compound **161** exerts moderate anti-hyperlipidemic activity⁸¹ and compounds **162** and **166** are cytotoxic against HCT 116 human colon carcinoma cell line.^{77,162}

4.2.4. 8-*epi-ent*-Halim-5(10)-enes. The first known halim-5(10)-enes appear within this series: salmantic acid (**170**), its methyl ester (**171**) and salmantidiol (**172**), isolated from *Cistus laurifolius*¹⁰² (Fig. 11, Table S2†). Their structures were spectroscopically determined and their absolute configurations assigned by chemical correlation by comparison with rearranged products of labdanolic, populifolic or *ent*-halimic acid.^{102,168}

The five compounds of this type are functionalized at C3. Salmantic acid (**170**), its methyl ester (**171**) and salmantidiol (**172**) have the side chain saturated, while leucasperone A (**173**) and leucasperone B (**174**), isolated from *Leucas aspera*,¹⁶⁹ show a double bond at C14 and have oxygenated functions at C11 and C13. Leucasperones A and B (**173** and **174**) possess acetoxy groups at C6 and C18. Leucasperone A (**173**) inhibits prostaglandin-induced contractions.¹⁶⁹

4.3. Halim-5-enes group

This group of halimanes, having a double bond in ring B, is the most interesting owing to the biological activities that some of them show.

4.3.1. *ent*-Halim-5-enes. The *ent*-halim-5-ene class is not very extensive (Fig. 12, Table S3†). All of them show oxygenated functions in ring A except for **175** and **176**. A great number of derivatives of compound **175**,¹⁷⁰ the first halimane isolated from

plants of genus *Plectranthus*, have been synthesized and their antibacterial and antitumour activities have been studied.^{171,172}

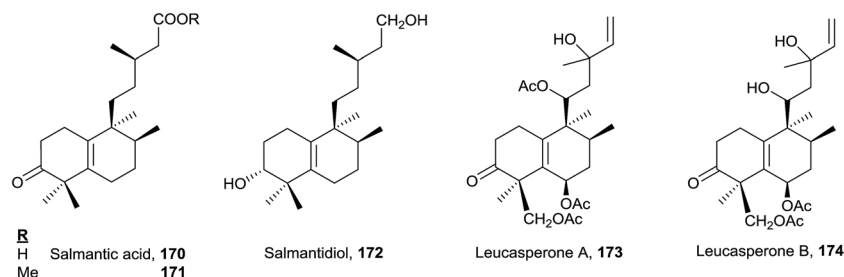
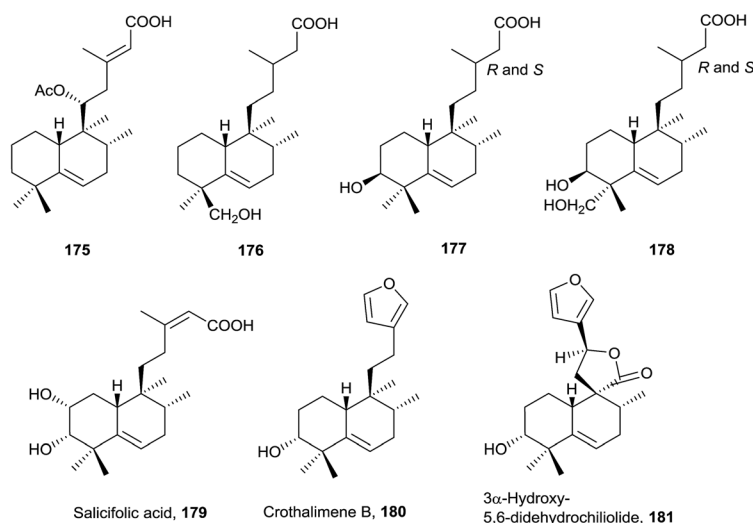
The side chain can be saturated on **176** (isolated from *Haplopappus paucidentatus*²⁵), **177** and **178** (*Relhania corymbosa* and *R. squarrosa*²⁰), unsaturated on **175** (*Plectranthus ornatus*¹⁷¹) and **179** (*Baccharis salicifolia*⁵⁴) or with furan on **180** (*Croton dichogamius*¹⁴⁸) and **181** (*Chiliotrichum rosmarinifolium*¹⁹ and *Nardophyllum bryoides*⁴⁵). Acids **177** and **178** were isolated as their methyl esters and their epimers at C-13 separated, although assignment of their stereochemistry at C-13 was not possible.²⁰

Salicifolic acid (**179**) regulates the growth of *Panicum miliaceum* (monocotyledon) seedlings⁵⁴ and 3 α -hydroxy-5,6-didehydrochililide (**181**) was highly active against a human pancreatic adenocarcinoma cell line at micromolar concentrations.⁴⁵

4.3.2. Halim-5-enes. This is the biggest halimenes group (**182–201**) with a double bond at C5 (Fig. 13, Table S3†) and perhaps the most interesting group considering the bioactivity of its derivatives, because tuberculosinol (**182**)⁵⁵ and isotuberculosinol (also known as nosyberkol; **183**) are found among them.^{56–58,72} Nosyberkol was isolated for the first time in 2004 from the Nosy Be Islands (Madagascar) sponge *Raspailia* sp. as a single stereoisomer.⁷² However, the stereochemistry at C-13 of natural nosyberkol has not been determined.

It has been proved that compounds tuberculosinol (**182**) and isotuberculosinol (**183**) are produced by *Mycobacterium tuberculosis*.^{68,69} None of the studies done detected the presence of **182** or **183** from the cultured cells of 12 nonpathogenic



Fig. 11 8-*epi-ent*-Halim-5(10)-enes.Fig. 12 *ent*-Halim-5-enes.

Mycobacterium species.⁶⁵ It has been observed that tuberculosinol (**182**) and isotuberculosinol (**183**) (in a 1 : 1 ratio, with **183** being a mixture of the diastereomers 13*R*-isotuberculosinol (**183R**) and 13*S*-isotuberculosinol (**183S**) in a 1 : 3 ratio) inhibit phagolysosome maturation and macrophage phagocytosis in human-like cells.³⁹ The structures of tuberculosinol (**182**) and isotuberculosinol (**183**) have been corroborated and their absolute configuration established by total synthesis.^{56,58}

Recently, two new natural products derived from tuberculosinol have been isolated and characterized: 1-TbAd (**200**)⁷¹ and *N*⁶-TbAd (**201**).⁶² These two tuberculosinol derivatives possess an adenosine unit bonded at C15 by N1' or by the nitrogen at C6' of the adenosine (Fig. 13). Recently it has been observed that compounds **200** and **201** accumulate to comprise >1% of all *M. tuberculosis* lipids. These diterpene nucleoside compounds are being investigated as biomarkers for tuberculosis.⁶² The structures of 1-TbAd (**200**) and *N*⁶-TbAd (**201**) have been corroborated by total synthesis.⁶³

In the halim-5-enes series (Fig. 13), the side chain can be saturated or unsaturated and furans or functionalized butanolides can be found on it.

Tuberculosene (**184**) has been obtained by enzymatic reaction from a mixture of GGPP with tuberculosinyl diphosphate synthase and CYC2 enzyme from the bacteria *Kitasatospora griseola*.^{173,174}

In this group, two plants of the Compositae family have been studied. From *Koanophyllon conglobatum*¹⁷⁵ koanophyllic acids **185**, **192**, **196** and **197**, with carboxylic function at C18, were isolated, and from *Haplopappus pulchellus*²³ **186**–**191** were isolated, all of them with a saturated side chain. The structure of **195** was spectroscopically determined and its absolute configuration established by ECD⁵¹ of their 3-*p*-bromobenzoate derivatives. This compound possesses antimicrobial activity. From *Acalypha macrostachya* the 7-oxo derivatives **193** and **194** were isolated.²²

Micromonohalimanes A and B (**198** and **199**, from *Micromonospora* sp.⁵⁰), which present antibacterial activity, have been characterized. Micromonohalimane B (**199**) is the only halimane which includes a chlorine atom in its structure.

4.3.3. 8-*epi*-Halim-5-enes. Only six compounds of this class are known: **202**–**207** (Fig. 14, Table S3†). Viteagnusin A (**202**)¹⁵⁹ and viterofolin C–E (**203**–**205**)⁸¹ were isolated from *Vitex agnus-castus* and *Vitex rotundifolia*, respectively. Although compounds **206** and **207** have not been found until now as natural products, they have been obtained by enzymatic reaction from a mixture of 5,13-*syn*-HPP (**30**) with SsSS enzyme from *Salvia sclarea* and with KgTS enzyme from *Kitasatospora griseola*, respectively.¹⁷⁴



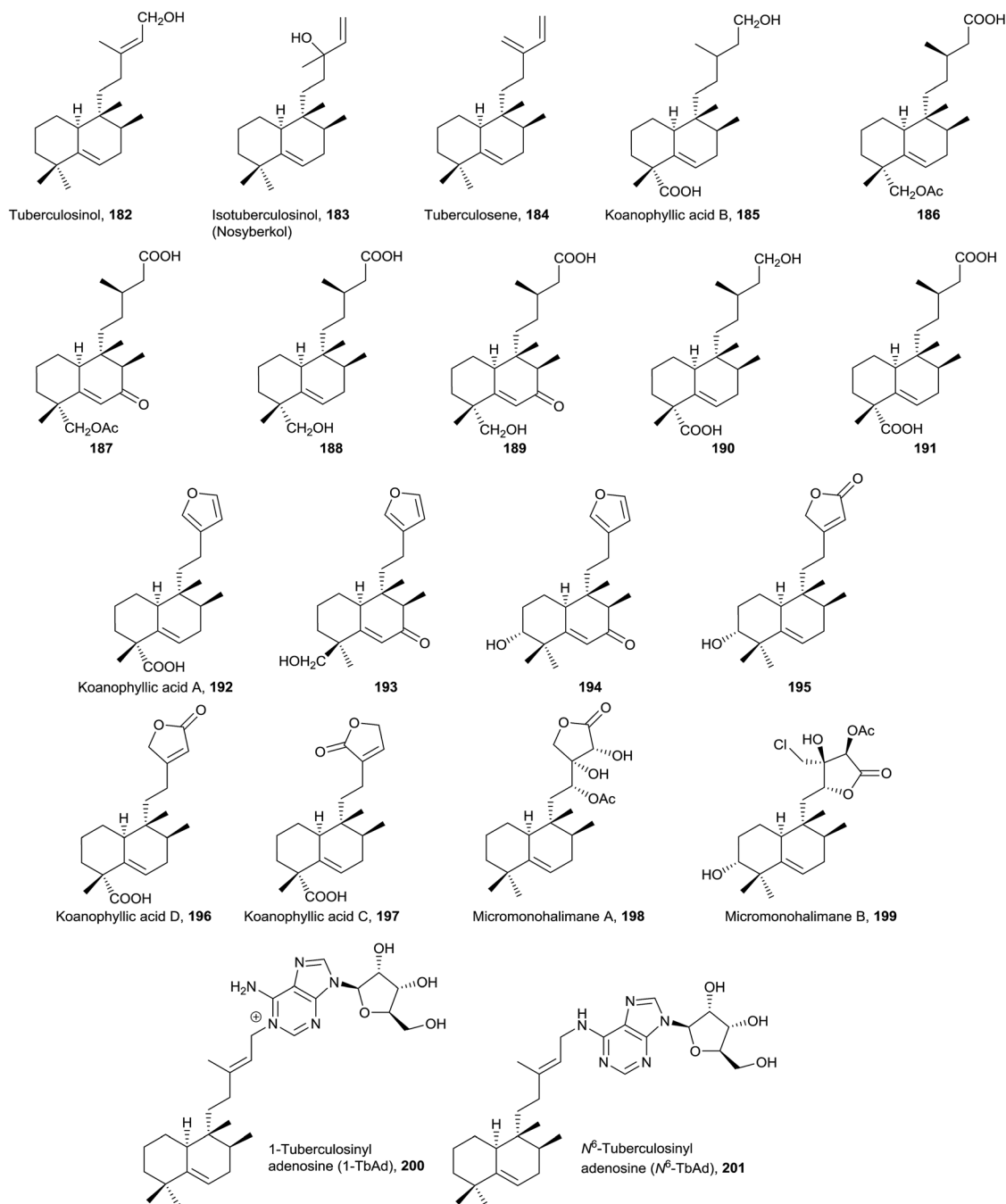


Fig. 13 Halim-5-enes.

4.4. Dihydrohalimenes group

A structural characteristic of this group of compounds (**208–219**) is that all of them show oxygenated functions at C5, except diasin (**219**, from *Croton diasii*),¹⁷⁶ which we include in this group precisely for not having any unsaturation in the decalin system (Fig. 15, Table S4†). Although some members possess acyclic chains (**208** and **209**, isolated from *Pleurozia gigantea*¹⁸ and *Jungermannia truncata*,¹⁷⁷ and *Baccharis salicifolia*,⁵⁴ respectively), the most usual functionalization is the furan (**210** and **211** from *Dysidea ambliia*,¹⁷⁸ **212** from *Croton crassifolius*¹⁵¹

and **213** and **214** from *Chilietrichum rosmarinifolium*¹⁹) or butanolide fragments (**215** and **216** from *Heteroscyphus coalitus*¹⁷⁹ and *Polyalthia longifolia*,¹⁸⁰ respectively). The stereoisomers ambliol B (**210**) and ambliol C (**211**) were isolated from *Dysidea ambliia*,¹⁷⁸ being the only occasion that halimanes and 8-*epi*-halimanes coexist in the same organism. Originally, a *cis*-fused bicyclic ring system was assigned to ambliol B (**210**), but finally the structure was revised by X-ray analysis.^{178,181} Compound **209** is a germination inhibitor⁵⁴ and the structure of compound **214** was corroborated by synthesis.¹⁸²



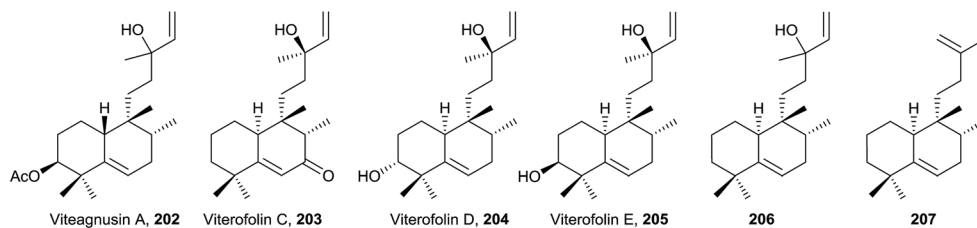
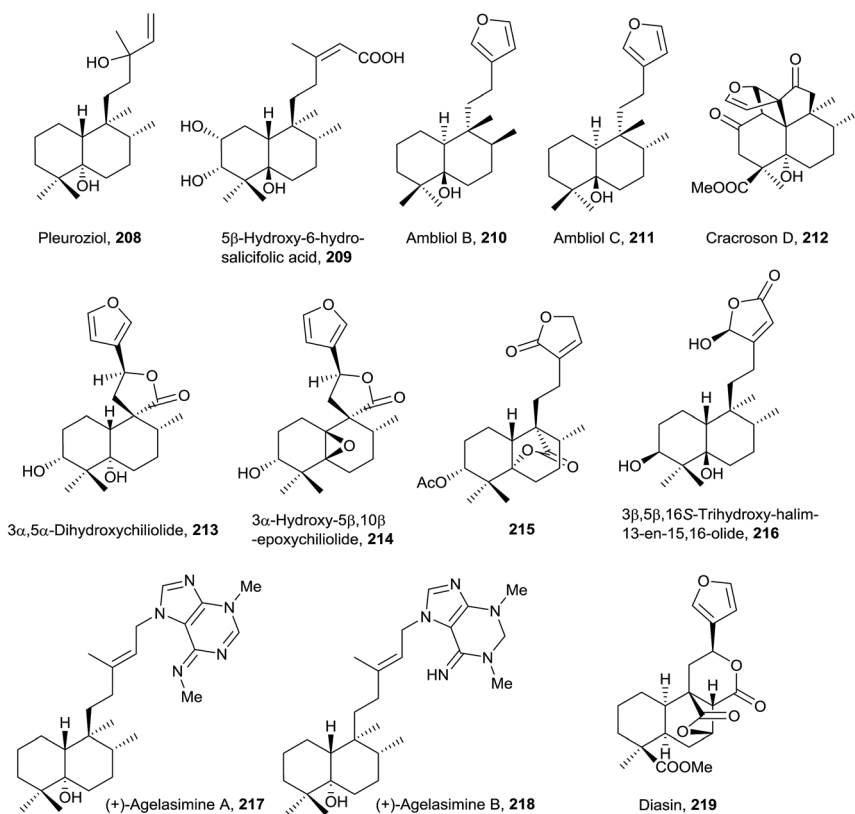
Fig. 14 8-*epi*-Halim-5-enes.

Fig. 15 Dihydrohalimenes.

Cracroson D (**212**) shows a new pentacyclic scaffold. It is chemically related to chettaphanin I (**38**) because **212** is generated from **38** by an intramolecular [2 + 2]-photocycloaddition. The existence of this compound in the extract as a natural product is confirmed by HPLC-MS. Cracroson D (**212**) exerts moderate cytotoxicity against T24 and A549 cell lines (bladder and lung cancer respectively).

In this group, halimane-purines such as agelasimines A and B (**217** and **218**, respectively), isolated from *Agelas mauritiana*,¹⁸³ are included. In this case, halimane C15 is bonded to purine N7. Both compounds show a wide range of interesting biological activities, such as cytotoxicity, inhibition of adenosine transfer into rabbit erythrocytes, Ca²⁺ channel antagonistic action and α_1 adrenergic blockade.

4.5. Secohalimenes and norhalimenes group

All secohalimenes known **220–232** (Fig. 16, Table S5†) are included in the *ent*-halimenes series, and are formed by

cleavage of the C3–C4 bond. All of them show a furan unit in the side chain, except for **231**¹⁷⁹ that contains a butenolide in that chain. Frequently C20 is a carboxylic acid that lactonize with a hydroxyl group at C12, **225–230**,^{19,45} or with a hydroxyl group at C5, **231**. C3 is always a carboxylic acid (free, lactonized or esterified) except for **229** and **230**. C4 is part of a disubstituted olefin ($\Delta^{4(18)}$) **231–232** or tetrasubstituted one (Δ^4) **220–230**.

These compounds are found in the plant families Leguminosae (from *Tessmannia densiflora* **220–223**⁸²), Compositae (*Chiliotrichum rosmarinifolium* **224–226**,¹⁹ *Nardophyllum lanatum* **224–228** and **232**,¹⁹ and *Nardophyllum bryoides* **225–226** and **230**⁴⁵) and Geocalycaceae (*Heteroscyphus coalitus* **231**¹⁷⁹).

Tessmannic acid (**220**) and its methyl ester (**221**) exhibit antibacterial and antifungal activity.^{82,184} Butanolides **225**, **226** and **230** are biologically active as antitumour agents.⁴⁵

The known norhalimenes (**233–245**) can be mono-, di-, tri- and tetra-norhalimene derivatives (Fig. 16).



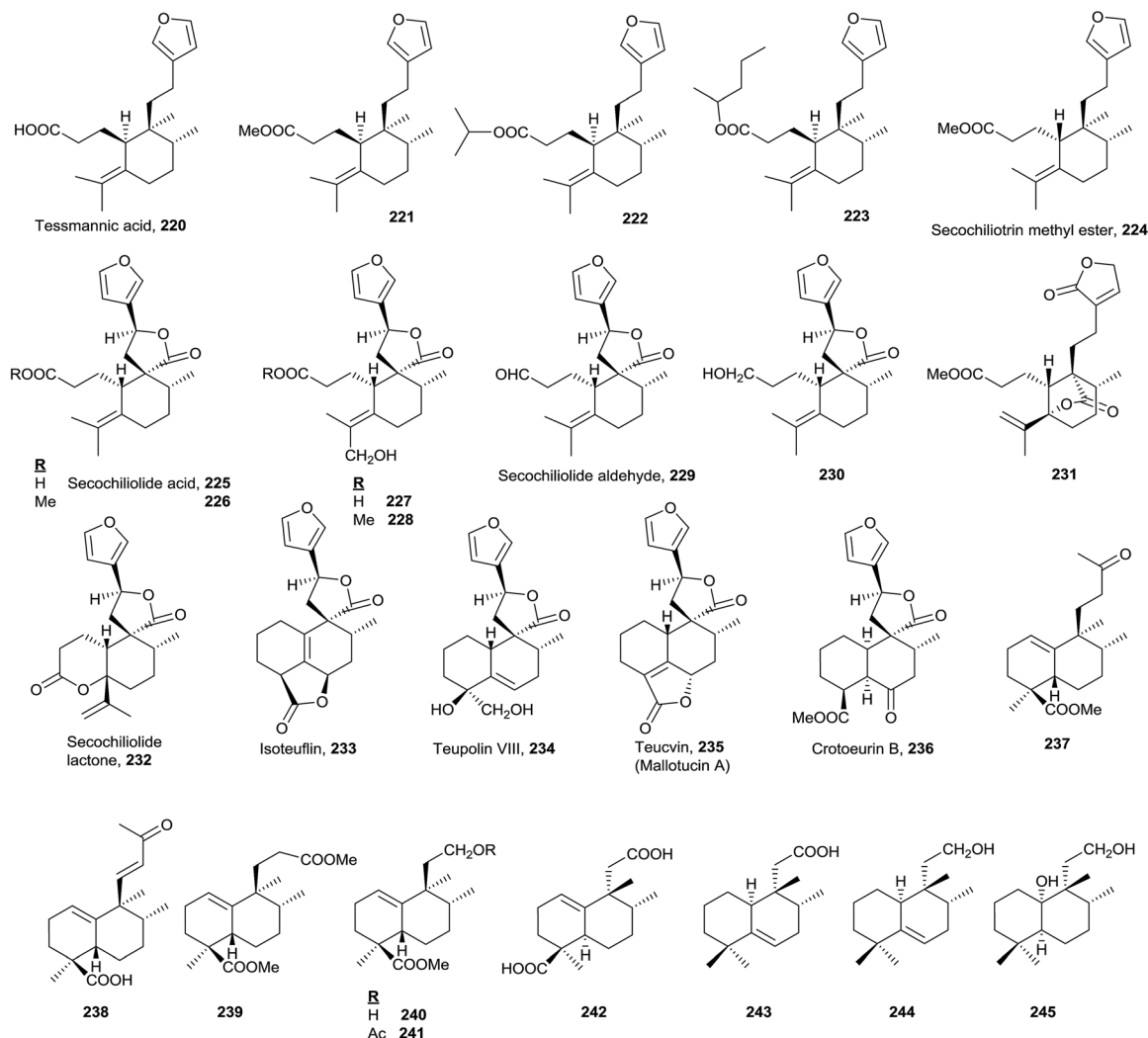


Fig. 16 Secohalimenes and norhalimenes.

Compounds such as isoteuflin (233; isolated from *Croton crassifolius*¹⁴⁴ and *Teucrium canadense*¹⁸⁵), teupolin VIII (234; *Teucrium polium*¹⁸⁶), teucvin (mallotucin A; 235; *Teucrium viscidum*,^{187,188} *Mallotus repandus*,¹³⁶ *Teucrium chamaedrys*,¹⁸⁹ and *Croton jatrophoides*¹⁹⁰) and crotoeurin B (236; *Croton euryphyllus*¹⁹¹) belong to a norderivatives group and have always been considered as clerodanes. However, these compounds could be considered norhalimanes as well, since up to now there is no biosynthetic evidence regarding the exact moment at which C19 (or C18) is lost. In any case, a table collecting all norclerodanes (norhalimanes) known to date has been elaborated as a ESI† (Fig. S15–S16, Table S7†). In the table the natural sources of these compounds are presented, as well as their bioactivities and the concerning references.

Among the nine known di-, tri- and tetra-norderivative (237–245), five are *ent*-halim-1(10)-enes (237–241),^{17,118,192} all of which are isolated from *Halimium viscosum*. The other four are 8-*epi*-halim-1(10)-ene (242; *Vellozia stipitata*¹⁹³), 8-*epi*-halim-5-ene (243 and 244; *V. flavicans*¹⁹⁴) and 8-*epi*-dihydrohalimene (245; *Mycale euplecteloides*,¹⁹⁵ Porifera). From all of these, the only

ones that do not present a carboxylic acid function at C18 are 243, 244 and 245.

4.6. Rearranged halimane group

The known rearranged halimanes are shown in Fig. 17 (Table S6†). They can be classified into four different groups.

- Scopariisins A–C (246–248), isolated from *Isodon scoparius*,^{91,155} are characterized for ring B expansion, by incorporation of C11. The structure and absolute configuration of scopariisin A (246) were confirmed by biomimetic synthesis⁹¹ from isoscaparin N (143). These compounds were not active as anti-tumour agents.

- Randainins A–D (249–252;⁴⁹ from *Callicarpa randaiensis*) and viterofolins A–B (253–254;⁸¹ *Vitex rotundifolia*) are rearranged compounds having a *trans*-7/5 ring system or a *trans*-5/7 ring scaffold in randainins A–B (249 and 250) or randainins C–D (251 and 252) and viterofolins A–B (253–254), respectively, instead of the classic bicyclo[4.4.0]decane system. This is a consequence of contraction-expansion ring processes. Anti-inflammatory activity and cytotoxicity were tested and



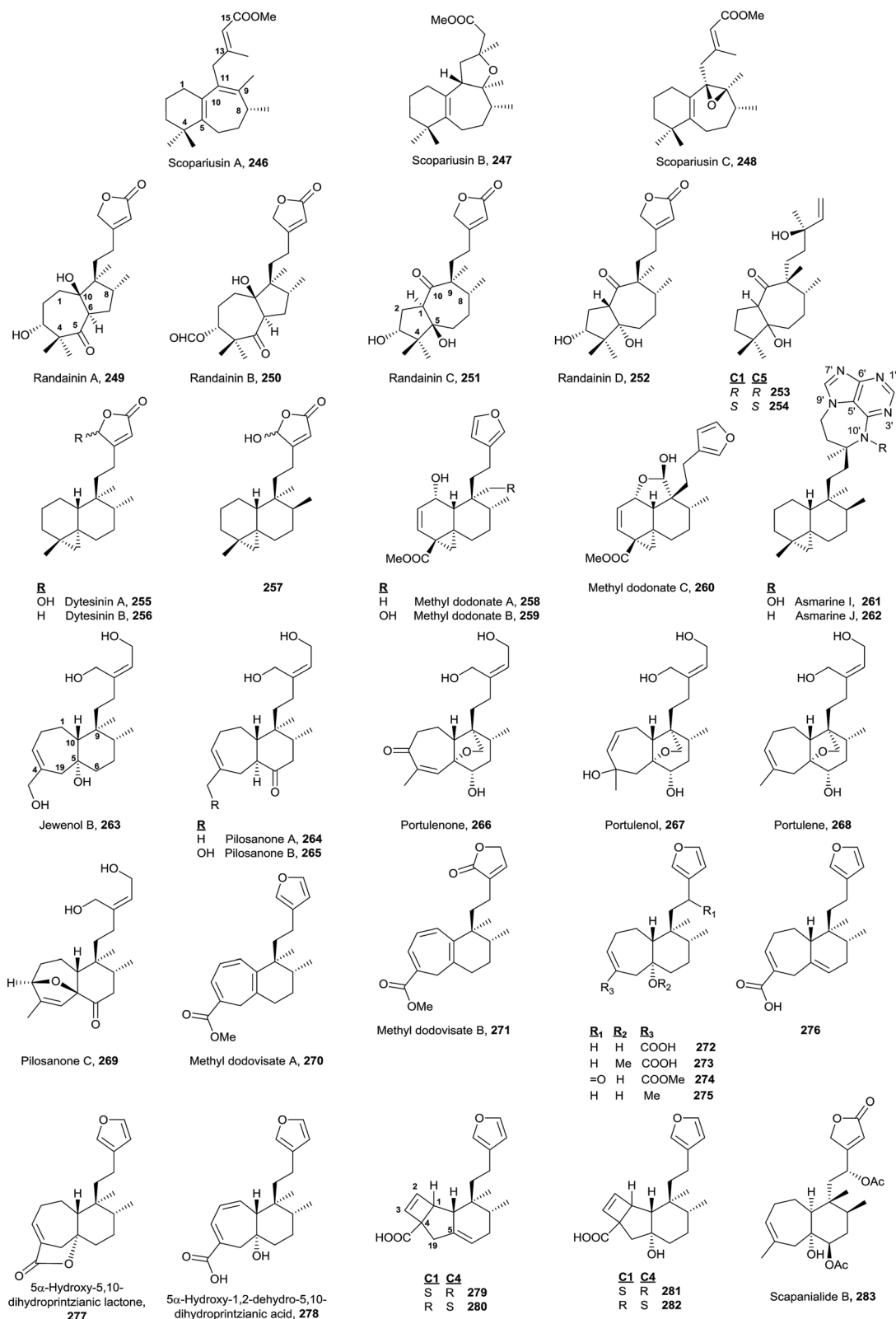


Fig. 17 Rearranged halimanes.

evaluated for randainins A–D (249–252), and anti-hyperlipidemic activity for viterofolins A–B (253–254). Compound 252 exhibits moderate superoxide anion generation inhibition with an IC_{50} value of $21.5 \pm 2.5 \mu\text{M}$.

• Dytesinins A–B (255 and 256, from *Cystodytes* sp.¹⁹⁶), 257 (from *Echinomuricea* sp.¹⁹⁷), methyl dodonates A–C (258–260, from *Dodonaea viscosa*¹⁹⁸), and asmarines I–J (261 and 262, from *Raspailia* sp.⁷²) are compounds that can be considered



rearranged halimanes or rearranged clerodanes because C19 is bonded to C4 and C5 forming a cyclopropane ring. Dytesinins A and B (255 and 256) are *ent*-halimanes and 257 is an 8-*epi-ent*-halimane that shows cytotoxic and anti-inflammatory activities. Compounds 255–257 have butenolides or hydroxybutenolides in the side chain. Methyl dodonates A–C (258–260) have C18 functionalized with a methoxycarbonyl group, and they show a furan at the side chain, plus a double bond Δ^2 . Asmarines I–J (261 and 262) are diterpene-adenine compounds with an 8-*epi-ent*-halimane skeleton bonded by C15 and C13 to adenine nitrogens N9 and N10. These compounds show cytotoxic activity.

• Compounds 263–283 can also be considered rearranged halimanes or clerodanes because C19 has been included in ring A as consequence of a ring expansion. All of these compounds belong to the ‘enantio’ series except viterofolins A–B (253–254) and scapanialide B (283), which belong to the ‘normal’ series. Compounds 263 (*Portulaca* cv Jewel¹⁹⁹) and 264–269 (isolated from *Portulaca pilosa*^{200,201} and *Portulaca grandiflora*²⁰²) have an acyclic side chain, while 270–283 (isolated from *Dodonaea viscosa* 270–271,²⁰³ *Conyza scabrida* 272–273 and 277–282,²⁰⁴ *Aparisthium cordatum* 274,⁸⁰ *Croton cortesianus* 275²⁰⁵ and *Scapania parva* 283²⁰⁶) possess furan or butenolides. All of them show double bonds in different positions of ring A. Compounds 279–282 show a tricyclic skeleton as a consequence of an electrocyclic reaction in ring A.

5. Halimane diterpenoids: synthesis and transformation into bioactive compounds

In the following paragraphs, several natural halimane diterpenoids synthesis and transformations of some of them into bioactive compounds are described.

5.1. *ent*-Halimic acid as precursor of biologically active compounds and other derivatives of interest

ent-Halimic acid, characterized as its methyl ester (39), is very abundant in *Halimium viscosum* extract (0.34% with respect to the dry plant weight). We have developed a very quick and efficient method to isolate the natural product in multigram quantities by chromatographic separation of the ethyl acetate extract. This compound has an unsaturated side chain, Δ^{13} , and a hydroxyl group at C-15, a carboxyl group at C-18 and a double bond $\Delta^{1(10)}$ in the decalin system. All these functionalities make *ent*-halimic acid a versatile molecule and a very appropriate starting material for the synthesis of natural halimanes, biologically active compounds and other interesting compounds. In Fig. 18 some of the compounds obtained from *ent*-halimic acid are shown: (1) *ent*-Halimanolides.^{123,141,207,208} (2) Chettaphanin I and II.^{109,209} (3) Bioactive sesterterpenolides.^{123,210–212} (4) Sesterterpenolides and glycerophospholipids hybrid compounds.²¹³ (5) Rearranged derivatives: *ent*-labdanes,²¹⁴ abeopicrasanes²¹⁵ and propellanes.²¹⁶ (6) Sesquiterpene-quinone/hydroquinone.²¹⁷ (7) Sesqui- and diterpene-alkaloids.^{128,218–222}

Synthesis from *ent*-halimic acid methyl ester (39) of several natural halimanes, such as *ent*-halimanolides, chettaphanin I and II and agelasine C (a diterpene-purine derivative), will be commented on in the following points. These syntheses have made it possible to corroborate their structures.

5.1.1. *ent*-Halimanolides synthesis. The first three known natural *ent*-halimanolides (85, 131 and 132)¹²² were synthesized from *ent*-halimic acid methyl ester (39) using methyl ketone 285 as an intermediate^{123,207} (Scheme 11).

The synthesis of intermediate 285 requires the reduction of the C18 methoxycarbonyl to a methyl and two carbon degradation of the side chain. First of all, the C15 hydroxy group is protected as its methoxy derivative and the resulting compound is treated with LAH followed by TPAP oxidation to obtain 284. Huang-Minlon reduction, followed by chemoselective oxidation and cleavage of the Δ^{13} double bond with *m*-CPBA and periodic acid gives the required ketone 285 in very good yield (57% six steps).

Bestmann methodology²²³ has been used for the synthesis of butenolides in similar systems. In order to apply it, functionalization of C16 as a hydroxy group is necessary. Treatment of 285 with LDA in the presence of TMSCl followed by oxidation of the intermediate silylenolether with OsO₄ affords the hydroxyketone 286 in excellent yield. Reaction of the hydroxyketone 286 with Ph₃P=C=O gives an intermediate ylide, which cyclizes by intramolecular Wittig reaction with formation of a double bond to give butenolide 85. Isomerization reaction of the double bond $\Delta^{1(10)}$ to $\Delta^{5(10)}$, with I₂ in C₆H₆, gives butenolide 131 in quantitative yield. The physical properties of the synthesized compounds 85 and 131 are identical to those described for the natural products *ent*-halima-1(10),13E-dien-15,16-olide and *ent*-halima-5(10),13E-dien-15,16-olide, respectively.

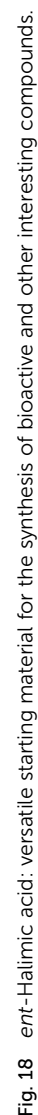
The synthesis of the γ -hydroxybutenolide 132 has been done by Boukouvalas methodology.²²⁴ Treatment of 85 with LDA and TBDMSTf followed by reaction of the intermediate 2-tri-alkylsilyloxyfuran with *m*-CPBA afforded 287 in good yield, after column chromatography. Compound 132 was obtained in quantitative yield by acidic isomerization of 287 using HI in benzene at 85 °C. The physical and spectroscopic data of the synthetic product 132 are identical with those reported for the natural product 16-hydroxy-*ent*-halima-5(10),13-dien-15,16-olide. This synthesis confirms the structures and absolute configurations of the natural products obtained.

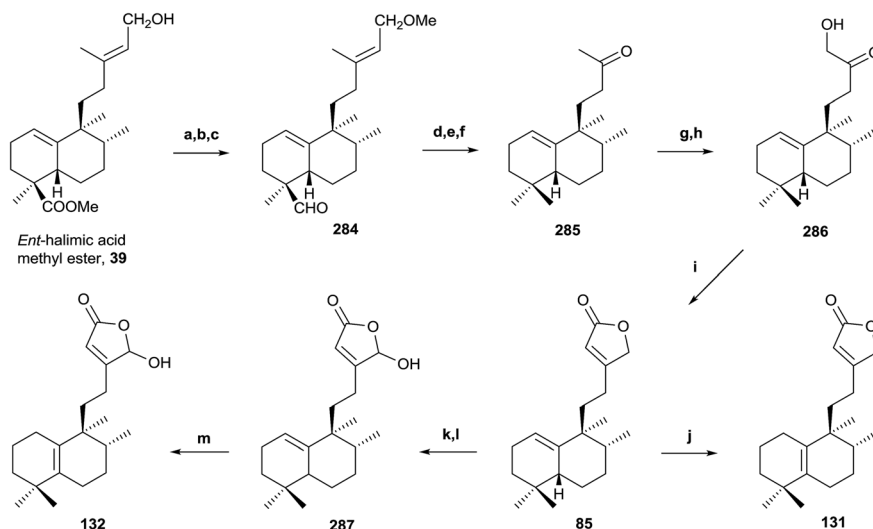
Biological assays have been carried out on these compounds and confirmed that compound 85 exhibits cytotoxic and antiviral activity [HeLaM cells (IC₅₀ = 5.0), MDCK (IC₅₀ = 5.1) and influenza virus (IC₅₀ = 6.8)].¹²³

In the same way, an efficient synthesis of *ent*-halimanolide 106 (15,16-epoxy-12-oxo-*ent*-halima-5(10),13(16),14-trien-18,2 β -olide) has been achieved from *ent*-halimic acid methyl ester 39, corroborating the structure of the natural compound and establishing its absolute configuration (Scheme 12).¹⁴¹ A new route employing the dinorderivatives 289 and 291 as intermediates allowed the tetranorderivative 292 to be obtained in multigram scale (53% from 39).

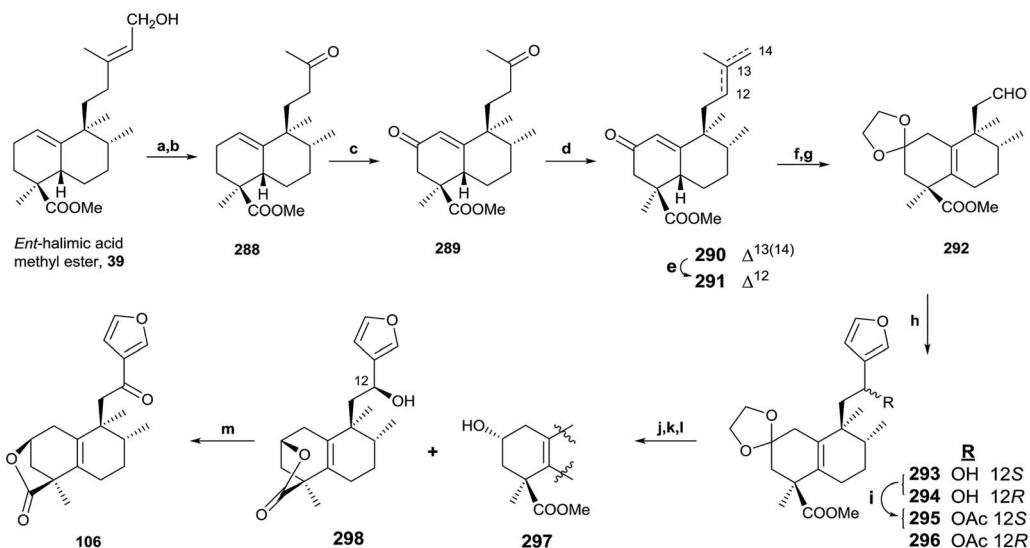
ent-Halimic acid methyl ester (39) oxidation with OsO₄ was regioselective. The resulting triol was oxidized with Pb(OAc)₄, giving ketone 288 in a 94% global yield for the two steps.







Scheme 11 (a) NaH, MeI, THF (92%); (b) LAH, Et₂O (96%); (c) TPAP, NMO (91%); (d) diethylene glycol, NH₂NH₂·H₂O, KOH, 175–230 °C, 23 h (85%); (e) *m*-CPBA (92%); (f) H₅IO₆, THF, H₂O (91%); (g) LDA, TMSCL, THF, –78 °C (97%); (h) OsO₄, NMO, *t*BuOH/THF/H₂O (7 : 2 : 1) (96%); (i) Ph₃P=C=O, C₆H₆ (91%); (j) I₂/C₆H₆ (10^{–2} M) (99%); (k) LDA, TBDMSf, THF, –78 °C (94%); (l) *m*-CPBA (77%); (m) HI/C₆H₆ (5 × 10^{–2} M) (99%).



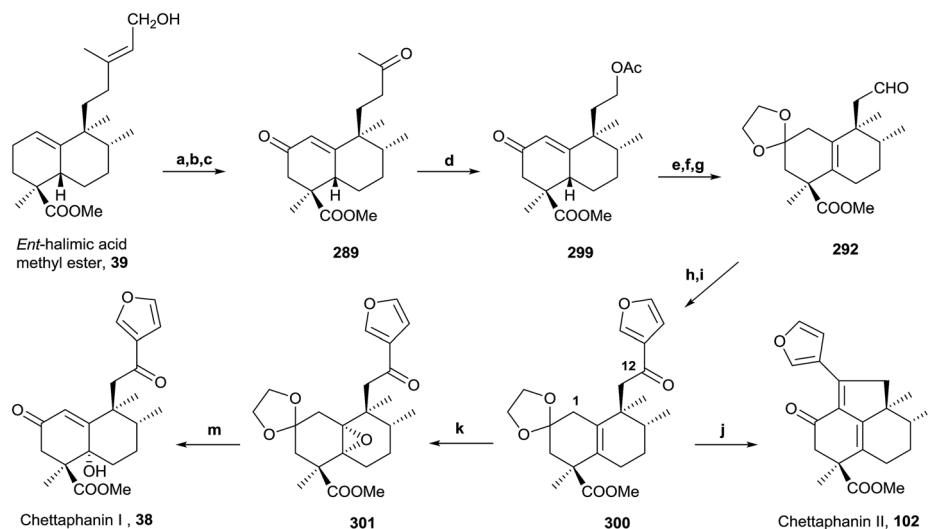
Scheme 12 (a) OsO₄, NMO, *t*-BuOH/THF/H₂O (7 : 2 : 1); (b) Pb(AcO)₄, C₆H₆, 20 min, (94%, two steps); (c) Na₂CrO₄, Ac₂O/AcOH, NaOAc, C₆H₆, (64%); (d) MePPh₃Br, NaHMDS, THF, –78 °C (94%); (e) *p*-TsOH, C₆H₆, 60 °C (96%); (f) (CH₂OH)₂, *p*-TsOH, C₆H₆, Dean Stark (97%); (g) (1) OsO₄, NMO, *t*-BuOH, THF, H₂O; (2) Pb(AcO)₄, C₆H₆ (96%, two steps); (h) 3-bromofuran, *n*-BuLi, THF (**293**: 54%, **294**: 39%); (i) Ac₂O, pyridine (98%); (j) HCl 2 M, EtOH (96%); (k) Na₂CO₃, MeOH, 2 h, (96%); (l) NaBH₄, EtOH (**298**: 38%, **297**: 43%); (m) TPAP, NMO, DCM, rt, 50 min (92%).

Oxidation of **288** with Na₂CrO₄ gives the α,β-unsaturated ketone **289** (64%). Compound **290** was obtained by chemoselective Wittig reaction of **289**. Treatment of **290** in very mild acidic conditions produces double bond isomerization to give **291** in quantitative yield. The synthesis of **292** was achieved in three steps. First, dioxolane carbonyl group protection of **291** gives not only the protection of the carbonyl function, but the double bond isomerization in the bicyclic system to the tetrasubstituted position; and then, OsO₄ oxidation and Pb(OAc)₄ treatment lead to aldehyde **292**. Reaction of **292** with 3-furyllithium gives **293** and **294**, which are separated and characterized as their acetyl derivatives **295** and **296**. The careful

hydrolysis of **295** and **296** in acid medium leads to intermediate ketones that produce **297** and lactone **298** by alkylne hydrolysis and reduction with NaBH₄. Oxidation of **298** gives the desired *ent*-halimanolide **106** in good yield, which is moderately active against HeLa cells (human cervical cancer).

5.1.2. Chettaphanins synthesis. An efficient synthesis of the first known *ent*-halimanes, chettaphanin I (**38**) and II (**102**), has been achieved from *ent*-halimic acid methyl ester **39** (Scheme 13). The absolute configuration of the natural products was established by nOe and X-ray analysis of chettaphanin II (**102**).^{109,209} Tetranorderivative **299** was obtained by Baeyer–Villiger reaction of intermediate **289** as the key step. Protection





Scheme 13 (a) OsO_4 , NMO, $t\text{-BuOH/THF/H}_2\text{O}$ (7 : 2:1); (b) $\text{Pb}(\text{AcO})_4$, C_6H_6 (94%, two steps); (c) Na_2CrO_4 , $\text{Ac}_2\text{O/AcOH}$, NaOAc , C_6H_6 (64%); (d) UHP/TFAA (61%); (e) ethylene glycol, $p\text{-TsOH}$, C_6H_6 ; (f) 3% K_2CO_3 in MeOH; (g) PDC, DMF (61%, three steps); (h) 3-bromofuran, $n\text{BuLi}$, (1 : 1), -78°C ; (i) TPAP/NMO, (99%, two steps); (j) $p\text{-TsOH}$, acetone (72%); (k) $m\text{-CPBA}$, CH_2Cl_2 (92%); (m) $p\text{-TsOH}$, acetone or HClO_4 , 30%.

reaction of **299** in acidic media led to isomerization of the double bond to the tetrasubstituted position, which, followed by deprotection of the primary hydroxyl group and oxidation gave **292** in three steps. Reaction of **292** with 3-furyllithium followed by oxidation gave the key intermediate **300** (36%, global). Chettaphanin II (**102**) was obtained by reaction of **300** in acidic media (92%) and chettaphanin I (**38**) was synthesized from **300** in two steps: epoxidation followed by reaction in acidic media (28%, two steps).

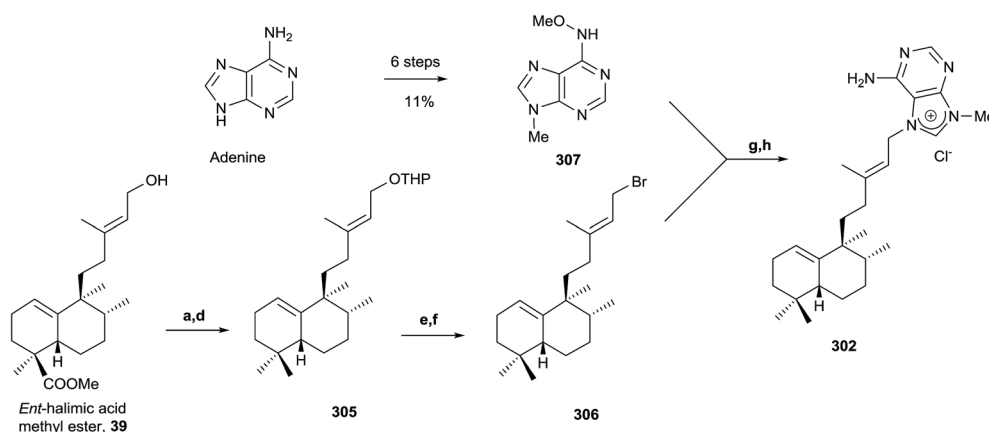
5.1.3. Halimane purine synthesis: (+)-agelasine C. *ent*-Halimic acid methyl ester (**39**) has been used for the synthesis of different terpene alkaloids. In this section, the preparation of the 7,9-dialkylpurine (+)-agelasine C (**302**) is reported (Scheme 14).

Agelasines are diterpene alkaloid 7,9-dialkylpurine salts, isolated from marine sponges of the genus *Agelas*.²²⁵ Agelasine C is one of the first four agelasines to be isolated by Nakamura and co-workers in 1984¹²⁶ from the Okinawan sea sponge *Agelas* sp. (–)-agelasine C showed powerful inhibitory effects

on Na,K-ATPase and antimicrobial activities (Fig. 19). In their work, Nakamura and co-workers proposed the structural formula **303** for (–)-agelasine C. *epi*-Agelasine C (**304**) was isolated in 1997 by Hattori and co-workers⁷⁵ from the marine sponge *Agelas mauritiana* as an antifouling substance active against macroalgae.

Due to the interest of *epi*-Agelasine C as an antifouling agent⁷⁵ and to establish the absolute configuration of this compound, the synthesis of **302** (Scheme 14) was carried out.¹²⁸ The synthesis of **302** was planned following an analogue design for other agelasines, which consists of coupling the terpenic fragment **306** with a purine derivative such as **307**.¹²⁸

The synthesis of the bromoderivative **306** was achieved in six steps starting from *ent*-halimic acid methyl ester (**39**) using the tetrahydropyranyl derivative **305** as an intermediate (Scheme 14) (46%, six steps). Reaction of **39** with DHP in $p\text{-TsOH}$ followed by reduction with LAH leads to a hydroxy derivative that was oxidized with TPAP to the carbonyl function and reduced



Scheme 14 (a) DHP, $p\text{-TsOH}$, C_6H_6 (98%); (b) LAH, Et_2O , 0°C and then rt (99%); (c) TPAP, NMO (94%); (d) diethylene glycol, $\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}$, KOH, $175\text{--}230^\circ\text{C}$ (81%); (e) $p\text{-TsOH}$, MeOH (81%); (f) CBr_4 , PPh_3 , DCM (76%); (g) DMA, 50°C ; (h) Zn, MeOH, H_2O , AcOH (13%, two steps).



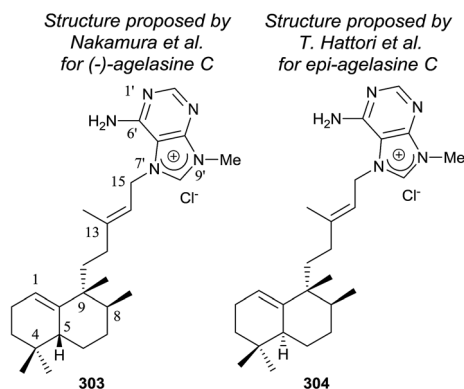


Fig. 19 Proposed structures for (–)-agelasine C and *epi*-agelasine C.

using Huang-Minlon methodology to give **305**. Deprotection of the primary hydroxyl group followed by treatment with CBr_4 in the presence of PPh_3 gave the required bromoderivative **306** (46%, six steps). Alkylation of methoxyadenine **307** with the bromoderivative **306** by heating in dimethylacetamide and subsequent reduction with Zn/AcOH gave compound **302** (13%, two steps).

The physical properties of the synthesized product **302** were very different to those of the natural product *epi*-agelasine C, thus its proposed structure **304** (Fig. 19) should be revised. On the other hand, when the ^1H and ^{13}C NMR spectra of **302** were compared with those for the proposed structure of (–)-agelasine C (**303**), the two pairs of spectra were identical. However, the optical rotatory power of **302** and natural (–)-agelasine C were similar in absolute value but had a different sign. So, it should be concluded that the structure of the natural product (–)-agelasine C should be corrected to structure **89** (Fig. 20), which is the enantiomer of the synthesized product (+)-agelasine C (**302**, Scheme 14).

Spectroscopic considerations made when comparing the spectra of **302** with those of *epi*-agelasine C and their specific rotations permitted structure **100** to be suggested for the natural *epi*-agelasine C, as shown in Fig. 20.

5.2. Synthesis of 3 α -hydroxy-5 β ,10 β -epoxychiliolide (**214**)

The natural product structure of 3 α -hydroxy-5 β ,10 β -epoxychiliolide (**214**) was corroborated by the synthesis of the

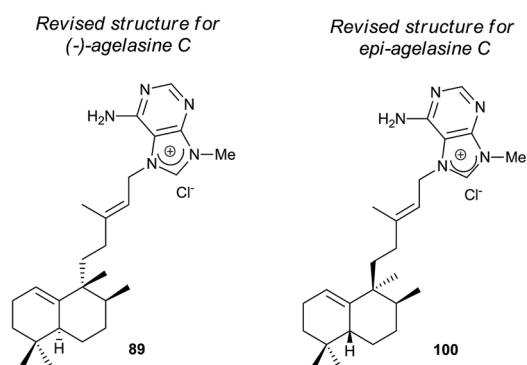


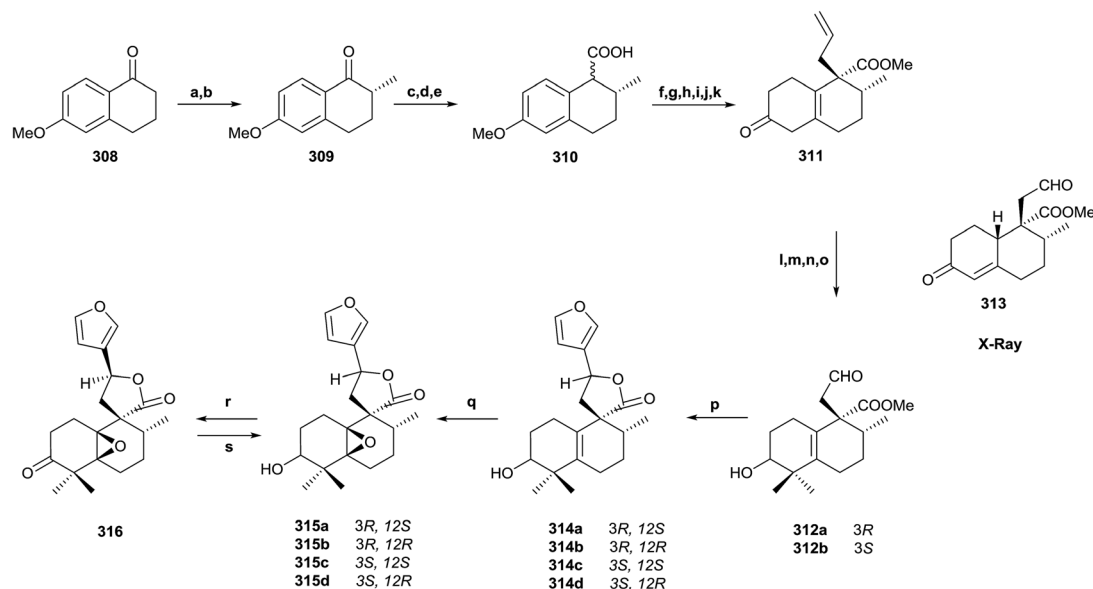
Fig. 20 Revised structures for (–)-agelasine C and *epi*-agelasine C.

racemic diterpene (Scheme 15).¹⁸² The synthesis starts with the available tetralone **308**. Intermediate **309** was obtained in high yield by Mannich reaction, followed by hydrogenation of the resulting *exo*-methylene bond. In order to introduce the carboxyl group and achieve **310**, an epoxidation followed by epoxide isomerization with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ was done. In this manner the corresponding aldehydes, epimers at C9, were obtained, which *via* Jones oxidation led to **310**. Birch reduction of **310** followed by hydrolysis, esterification and protection as 1,3-dioxolane, alkylation with LDA and allyl bromide and deprotection with diluted sulfuric acid on silica gel gave ketone **311** in 72% overall yield. Reduction of **311** with NaBH_4 followed by oxidation with osmium tetroxide/*N*-methyl morpholine-*N*-oxide and cleavage with sodium periodate gave aldehydes **312a** and **312b**, which were separated by column chromatography. From ketone **311**, the derivative **313** was also obtained by oxidative degradation. Its X-ray analysis allowed the configuration of C8 and C9, quaternary centres, to be established for all compounds. Reaction of epimer **312** with 3-lithiofuran and subsequent lactonization afforded the intermediates **314a–d**, and the epoxidation of each led to the isomeric diterpenes **315a–d**. Configuration at C12 was established by nOe experiments, but the relative stereochemistry at C3, C5, and C10 still had to be solved. The NMR spectra for **315a** was identical to the natural product one. Only one epoxide was obtained with both isomers, so a β -orientation of the epoxy group was more likely. PCC oxidation of **315a** gives ketone **316**, which gave one isomer by reduction with sodium borohydride, the 3 β -hydroxy derivative **315c**, so the natural product **214** is the 3 α -hydroxy derivative **315a**. Through inspection of a model, it was determined that the most favorable entry of the hydride is by the α -face of the molecule, so the relative configuration of all compounds was established in this manner.

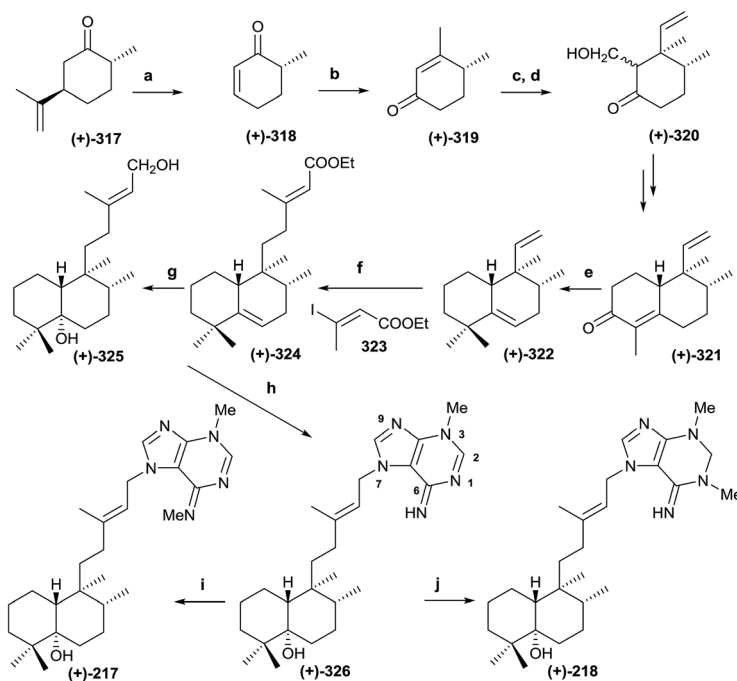
5.3. Synthesis of (+)-agelasimine A (**217**) and (+)-agelasimine B (**218**)

Ohba and co-workers²²⁶ synthesized the diterpene-adenine derivatives (+)-agelasimine A (**217**) and (+)-agelasimine B (**218**) from (+)-*trans*-dihydrocarvone and, in this manner, they established the absolute configuration of the natural products isolated from the orange sponge *Agelas mauritiana* (Scheme 16). Previously, Ohba and co-workers followed a similar reaction sequence when they communicated the racemic synthesis of (\pm)-agelasimine A and (\pm)-agelasimine B.^{227,228} In the asymmetric synthesis, the authors used (+)-*trans*-dihydrocarvone (**317**) as the starting material. Ozonolysis in methanol of **317** and subsequent treatment with $\text{FeSO}_4\text{--Cu}(\text{OAc})_2$ (ref. 229 and 230) led to (+)-**318**, which was transformed into (+)-**319** by MeLi treatment followed by PCC oxidation.²³¹ Reaction of (+)-**319** with vinylmagnesium bromide in the presence of CuBr and Me_3SiCl gave stereoselectively a silylenol ether that reacts with formaldehyde to give **320** as a diastereoisomeric mixture. Cyclohexanone **320** was transformed into **321** following the previously described procedure.²³¹ Methylation of **321** and subsequent Huang-Minlon reduction led to **322**. Reaction of **322** with 9-BBN followed by Suzuki cross-coupling reaction with *E*-3-iodo-2-





Scheme 15 (a) *p*-Formaldehyde, *N*-methyl-anilinium-trifluoro acetate; (b) H₂, RANEY® nickel; (c) trimethylsulfonium iodide, DMSO, NaH; (d) BF₃·Et₂O; (e) Jones reagent; (f) Li, NH₃; (g) HCl 10%, MeOH, H₂O; (h) CH₂N₂; (i) ethyleneglycol, TMSCL, CH₂Cl₂; (j) LDA, allyl bromide; (k) SiO₂, H₂SO₄; (l) MeI, *t*-BuOK, *t*-BuOH; (m) NaBH₄, EtOH; (n) OsO₄, NMO; (o) NaIO₄, H₂O; (p) 3-bromofuran, *n*BuLi, (1 : 1), −78 °C; (q) *m*-CPBA, CH₂Cl₂; (r) PCC, CH₂Cl₂; (s) NaBH₄, EtOH.



Scheme 16 (a) (1) O₃, MeOH, (2) FeSO₄, Cu(OAc)₂ (44%); (b) (1) MeLi, (2) PCC (94%); (c) (1) CH₂=CHMgBr, CuBr·Me₂S, Me₃SiCl; (d) aq. HCHO, Yb(OTf)₃ (75%); (e) (1) MeI, *t*-BuOK, *t*-BuOH, (2) NH₂NH₂·H₂O, KOH, diethylene glycol 130 °C 1 h, 190 °C 3 h (72%); (f) (1) 9-BBN, (2) **323**, PdCl(dppf), CsCO₃, Ph₃As (67%); (g) (1) *m*-CPBA; (2) DIBAL, −78 °C; (3) LAH, THF reflux (51%); (h) (1) PBr₃, (2) 3-methyladenine, AcNMe₂; (3) aq. NaOH (60%); (i) (1) MeI, AcNMe₂; (2) aq. NaOH (61%); (j) (1) NaBH₄, (2) MeI, AcNMe₂; (3) aq. NaOH (41%).

butenoic acid ethyl ester (**323**) afforded the α,β -unsaturated ester (**324**). Treatment of **324** with *m*-CPBA, DIBAL reduction and subsequent treatment with LAH in boiling THF for epoxide reduction led to **325**. Reaction of **325** with PBr₃ achieved bromination of the primary hydroxy group and subsequent

alkylation with 3-methyladenine led to compound **326** after neutralizing the hydrobromide salt. Methylation of (+)-**326** with MeI followed by neutralization gave the desired compound (+)-**217**, which was identical to the natural product (+)-agelastimine A. Reaction of (+)-**326** with NaBH₄ followed by methylation



and neutralization led to (+)-**218**, which was identical to the natural product agelasimine B. In this manner, the two structures (**217** and **218**) were corroborated and their absolute configurations established.

5.4. Biomimetic synthesis of scopariusin A (**246**) and isoscoparin N (**143**)

Scopariusin A (**246**) was isolated from *Isodon scoparius*. Its structure was spectroscopically determined and confirmed by biomimetic synthesis from the clerodane isoscoparin O (**327**) found in the same plant (Scheme 17).⁹¹ The structure and absolute configuration of isoscoparin O (**327**) has been confirmed previously by X-ray analysis and for scopariusin A (**246**).

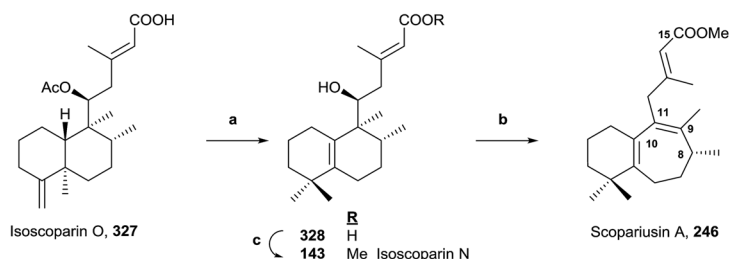
Treatment of **327** with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ leads mainly to a halimane derivative, which leads to the hydroxy acid **328** by hydrolysis with NaOH in MeOH. Esterification of **328** with MeI in the presence of potassium carbonate gives **143**, whose properties were identical to isoscoparin N isolated from the same extract of *Isodon scoparius*. Reaction of **328** with *p*-toluenesulfonic acid (PTSA) in toluene and posterior methylation with MeI in KOH-acetone led to **246**, whose properties were identical to those of the natural product scopariusin A. In this manner, the

5.5. Synthesis of tuberculosinol (**182**) and isotuberculosinol (**183**)

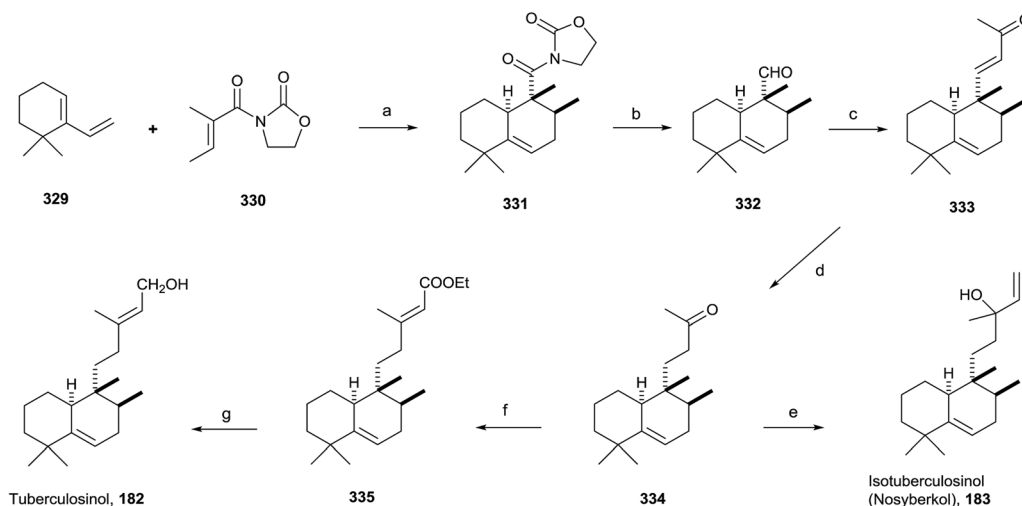
Tuberculosis, caused by *Mycobacterium tuberculosis*, is one of the biggest causes of morbidity and mortality worldwide. Developing new drugs effective against those bacteria and new therapies directed to inhibit virulence factor (VF) formation have a great interest.^{60,63}

The tuberculosinols tuberculosinol (**182**) and isotuberculosinol (**183**; *13R* and *13S*) are VFs from *M. tuberculosis*.^{57,59,93} However, without any doubt the most interesting and promising halimane is tuberculosinol (**182**). The original proposed structures have been confirmed by synthesis, as can be seen in the following points.^{56,58}

Snider and co-workers' and Sorensen and co-workers' syntheses of tuberculosinol and isotuberculosinol (Schemes 18 and 19, respectively) were published simultaneously and made possible a structural revision of the diterpene obtained from *M. tuberculosis*, to which the edaxadiene structure was originally assigned, and finally it was revised and reassigned to the same

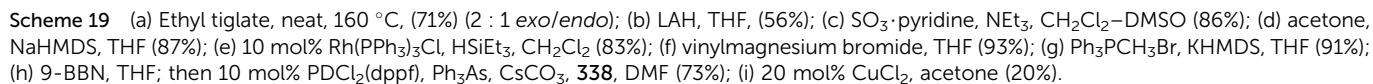


Scheme 17 (a) (1) $\text{BF}_3 \cdot \text{Et}_2\text{O}$, (2) NaOH, MeOH (67%); (b) (1) PTSA, PhCH_3 , 85 °C, (2) MeI, KOH (64%); (c) MeI, K_2CO_3 (95%).



Scheme 18 (a) Me_2AlCl , CH_2Cl_2 (54%, ~10 : 1 *exo/endo*); (b) (1) LiBH_4 , THF/ H_2O ; (2) DM periodinane, CH_2Cl_2 (77%); (c) acetone/MeOH, NaOMe (60%); (d) (1) Li, NH_3 , EtOH; (2) Jones oxidation (90%); (e) $\text{CH}_2=\text{CHMgBr}$, THF (88%); (f) $(\text{EtO})_2\text{POCH}_2\text{COOEt}$, NaH, THF (84%); (g) DIBAL, CH_2Cl_2 (92%).

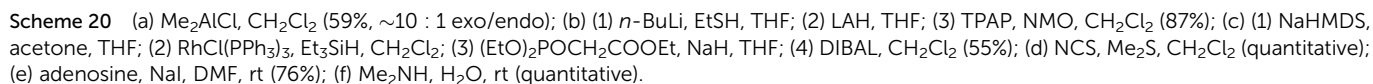




5.5.1. Snider's synthesis of tuberculosinol (182) and isotuberculosinol (183). The synthesis by Snider and co-workers⁵⁶ uses an *exo*-cycloaddition as a key step in the syntheses of isotuberculosinol (**183**) and tuberculosinol (**182**; Scheme 18). In this case, the cycloaddition step was done with **329** in the presence of *N*-tigloylisoxazolidinone (**330**) and Me₂AlCl to afford a mixture of the desired *exo* Diels–Alder adduct **331** and the *endo* adduct (54%, ~10 : 1 *exo/endo*). Reduction of **331** followed by oxidation with Dess–Martin periodinane gives *exo* aldehyde **332**. Reaction of **332** with acetone in the presence of NaOMe leads to **333**, which gives ketone **334** by reduction with Li in

Reaction of ketone **334** with triethylphosphonoacetate in the presence of NaH leads to **335** in good yield. DIBAL reduction of **335** leads to **182**, which is identical to the natural tuberculosinol.⁵⁵

5.5.2. Sorensen's synthesis of tuberculosinol (182) and isotuberculosinol (183). In the synthesis of tuberculosinol (182) and isotuberculosinol (183; Scheme 19) achieved by Sorensen and co-workers,⁵⁸ the key step is an *exo*-selective Diels-Alder reaction. Cycloaddition of the known diene **329** and ethyl tiglate



followed by ester reduction and primary alcohols separation through purification by supercritical fluid chromatography provides the enantioenriched material (>99% ee), that by Parikh and Doering²³² oxidation conditions leads to **332a**. An aldol condensation with acetone sodium enolate and conjugate reduction with Wilkinson's catalyst²³³ allowed them to achieve ketone **336**. Vinylmagnesium bromide addition provides **183** as a tertiary alcohol mixture. The spectroscopic data obtained from the synthetic compound **183** were identical with those reported for both natural nosyberkol and isotuberculosinol.

Tuberculosinol (**182**) was also synthesized from aldehyde **332a**. Methylenation of **332a** gives diene **337**, which by 9-BBN hydroboration and palladium-mediated cross-coupling with (*E*)-3-iodobut-2-en-1-ol **338** provides tuberculosinol (**182**). Isotuberculosinol (nosyberkol; **183**) was achieved by treatment of **182** with catalytic copper(II) chloride.

5.6. 1-Tuberculosinyl adenosine (1-TbAd; **200**) and *N*⁶-tuberculosinyl adenosine (*N*⁶-TbAd; **201**) syntheses

To date, there is no reliable and fast routine test for the diagnosis of infections caused by *M. tuberculosis*, in spite of it being one of the more prevalent and fatal causes of infection in the world. Recently, two natural compounds, 1-tuberculosinyl adenosine (1-TbAd; **200**) and *N*⁶-tuberculosinyl adenosine (*N*⁶-TbAd; **201**), have been found.^{62,71} These tuberculosinol derivatives can be used as *Mycobacterium tuberculosis* (Mtb) specific biomarkers. The *N*⁶-TbAd (**201**) isomer appears that can be generated *in vivo* by *M. tuberculosis*, following a Dimroth rearrangement of 1-TbAd (**200**).⁶² Recently, 1-TbAd (**200**) and *N*⁶-TbAd (**201**) syntheses have been carried out (10 and 11 steps, respectively) using as a key step a chiral auxiliary-aided Diels–Alder reaction⁶³ (Scheme 20). This Diels–Alder reaction gives **339** (98% ee, 59%, ~10 : 1 *exo/endo*), which is transformed into tuberculosinol (**182**) in seven steps. 1-TbAd (**200**) was obtained in two steps from (**182**) through the chloride derivative **340** and *N*⁶-TbAd (**201**) was achieved later from **200** by a Dimroth rearrangement.

6. Conclusion

In this article, the first natural halimane skeleton diterpenoids review is reported. We have classified them into six different groups according to their biogenetic origin. Herein, 246 natural halimanes have been collected, summarizing their structure, natural source and bioactivity.

Among the halimane family, the major group corresponds to the 'antipode or enantio' series, as also happens in the labdane skeleton diterpenoids. In this manner, *ent*-HPP and *syn-ent*-HPP derivatives represent 70% (taking into account nor-, seco-, dihydro-, and rearranged halimanes of these series too) of all known halimanes.

The most interesting reported halimane with the most potential is tuberculosinol (**182**). The production of isotuberculosinol, tuberculosinol and analogues by *M. tuberculosis* inhibits the phagocytosis of human macrophage-like cells, thus they can be considered virulence factors (VFs). Recently, two

tuberculosinyl adenosines have been isolated. These two natural halimanes, derived from tuberculosinol and isotuberculosinol, are being evaluated as possible biomarkers for early diagnosis of tuberculosis.

Some nor- and rearranged halimanes can be considered as 19-norclerodanes or rearranged clerodanes, respectively, and *vice versa*. These structures can be classified indistinctly as clerodanes or halimanes without further information on their biosynthetic origin. For this reason, halimanes with a 19-norclerodane structure have been also reviewed and included in the ESI.†

Different halimanes, such as *ent*-halimic acid (**39**) and 11*R*-acetoxy-*ent*-halima-5,13*E*-dien-15-oic acid (**175**), have been used as starting materials for the syntheses of bioactive compounds, for example antibacterial or antitumoral compounds.

7. Conflicts of interest

There are no conflicts to declare.

8. Acknowledgements

The authors would like to thank the Spanish Ministry of Economy and Competitiveness, MINECO (SAF2014-59716-R, CTQ2015-68175-R), European Funds for Regional Development, FEDER and Junta de Castilla y León (BIO/SA59/15, UIC21) and Universidad de Salamanca for financial support. AMR and IET are grateful for their fellowships from the FSE (European Social Fund), MINECO and Junta de Castilla y León, respectively. The authors thank Profs. J. G. Urones and P. Basabe for their dedication as teachers, and their guidance and friendship over many years.

9. Notes and references

- 1 D. E. Cane and H. Ikeda, *Acc. Chem. Res.*, 2012, **45**, 463–472.
- 2 M. Jia and R. J. Peters, *Org. Biomol. Chem.*, 2017, **15**, 3158–3160.
- 3 J. W. Blunt, B. R. Copp, R. A. Keyzers, M. H. G. Munro and M. R. Prinsep, *Nat. Prod. Rep.*, 2014, **31**, 160–258.
- 4 B. M. Fraga, *Nat. Prod. Rep.*, 2013, **30**, 1226–1264.
- 5 J. R. Hanson, *Nat. Prod. Rep.*, 2016, **33**, 1227–1238.
- 6 J. R. Hanson, *Nat. Prod. Rep.*, 2017, **34**, 1233–1243.
- 7 L. Wang, B. Yang, X.-P. Lin, X.-F. Zhou and Y. Liu, *Nat. Prod. Rep.*, 2013, **30**, 455–473.
- 8 R. A. Hill and J. D. Connolly, *Nat. Prod. Rep.*, 2015, **32**, 273–327.
- 9 J. Buckingham, *Dictionary of Natural Products on DVD*, CRC, Boca Raton, FL, 2007.
- 10 D. W. Christianson, *Chem. Rev.*, 2017, **117**, 11570–11648.
- 11 S. Prisic, J. Xu, R. M. Coates and R. J. Peters, *ChemBioChem*, 2007, **8**, 869–874.
- 12 K. U. Wendt and G. E. Schulz, *Structure*, 1998, **6**, 127–133.
- 13 J. MacMillan and M. H. Beale, *Comprehensive Natural Products Chemistry: Isoprenoids Including Carotenoids and Steroids*, Elsevier, 1999, vol. 2.
- 14 A. T. Merritt and S. V. Ley, *Nat. Prod. Rep.*, 1992, **9**, 243–287.
- 15 R. Li, S. L. Morris-Natschke and K.-H. Lee, *Nat. Prod. Rep.*, 2016, **33**, 1166–1226.



- 16 R. J. Peters, *Nat. Prod. Rep.*, 2010, **27**, 1521–1530.
- 17 J. G. Urones, J. De Pascual Teresa, I. S. Marcos, D. Díez Martín, N. Martín Garrido and R. A. Guerra, *Phytochemistry*, 1987, **26**, 1077–1079.
- 18 Y. Asakawa, X. Lin, M. Tori and K. Kondo, *Phytochemistry*, 1990, **29**, 2597–2603.
- 19 J. Jakupovic, S. Banerjee, F. Bohlmann, R. M. King and H. Robinson, *Tetrahedron*, 1986, **42**, 1305–1313.
- 20 F. Tschritzis and J. Jakupovic, *Phytochemistry*, 1990, **29**, 3173–3187.
- 21 C. Zdero, F. Bohlmann, R. M. King and H. Robinson, *Phytochemistry*, 1986, **25**, 2841–2855.
- 22 K. Siems, J. Jakupovic, V. Castro and L. Poveda, *Phytochemistry*, 1996, **41**, 851–853.
- 23 C. Zdero, F. Bohlmann and H. M. Niemeyer, *Phytochemistry*, 1991, **30**, 3669–3677.
- 24 J. Jakupovic, E. Ellmauerer, F. Bohlmann, A. Whitemori and D. Gage, *Phytochemistry*, 1986, **25**, 2677–2678.
- 25 J. Jakupovic, R. N. Baruah, C. Zdero, F. Eid, V. P. Pathak, T. V. Chau-thi, F. Bohlmann, R. M. King and H. Robinson, *Phytochemistry*, 1986, **25**, 1873–1881.
- 26 J. De Pascual Teresa, J. G. Urones, P. Basabe, H. Carrillo, M. A. G. Muñoz and I. S. Marcos, *Phytochemistry*, 1985, **24**, 791–794.
- 27 J. De Pascual Teresa, J. G. Urones, H. Carrillo and M. A. G. Muñoz, *An. Quim.*, 1979, **75**, 140–143.
- 28 J. De Pascual Teresa, J. G. Urones, I. S. Marcos, D. D. Martín and V. M. Alvarez, *Phytochemistry*, 1986, **25**, 711–713.
- 29 J. M. L. Rodilla, D. I. M. De Mendonça, J. G. Urones and R. F. Moro, *Phytochemistry*, 1998, **49**, 817–822.
- 30 J. M. L. Rodilla, D. I. D. Mendonça, M. I. G. Ismael, J. A. Figueiredo, M. L. A. Silva and E. Lopes, *Nat. Prod. Lett.*, 2001, **15**, 401–409.
- 31 J. G. Urones, I. S. Marcos, P. Basabe, C. A. Alonso, D. Díez, N. M. Garrido, I. M. Oliva, J. S. Rodilla, A. M. Z. Slawin and D. J. Williams, *Tetrahedron Lett.*, 1990, **31**, 4501–4504.
- 32 J. G. Urones, P. Basabe, I. S. Marcos, C. Alonso, I. M. Oliva, N. M. Garrido, D. D. Martín and A. M. Lithgow, *Tetrahedron Lett.*, 1992, **33**, 5269–5272.
- 33 J. G. Urones, I. S. Marcos, P. Basabe, C. Alonso, I. M. Oliva, N. M. Garrido, D. D. Martín and A. M. Lithgow, *Tetrahedron*, 1993, **49**, 4051–4062.
- 34 J. G. Urones, I. S. Marcos, P. Basabe, C. Alonso, I. M. Oliva, N. M. Garrido, D. D. Martín and A. M. Lithgow, *Phytochemistry*, 1993, **34**, 747–750.
- 35 I. S. Marcos, R. F. Moro, A. Gil-Mesón and D. Díez, in *Studies in Natural Products Chemistry*, ed. R. Atta ur, Elsevier, 2016, vol. 48, pp. 137–207.
- 36 J. G. Urones, I. S. Marcos, P. Basabe, C. A. Alonso, D. Díez-Martin, N. M. Garrido and I. M. Oliva, *Tetrahedron Lett.*, 1990, **31**, 5665–5668.
- 37 J. G. Urones, I. S. Marcos, N. M. Garrido, J. de Pascual Teresa and A. S. Feliciano Martín, *Phytochemistry*, 1989, **28**, 183–187.
- 38 J. G. Urones, I. S. Marcos and N. M. Garrido, *Phytochemistry*, 1990, **29**, 3243–3246.
- 39 J. G. Urones, I. S. Marcos and N. M. Garrido, *Phytochemistry*, 1990, **29**, 2585–2589.
- 40 J. G. Urones, I. S. Marcos, N. M. Garrido and R. F. Moro, *Phytochemistry*, 1990, **29**, 3042–3044.
- 41 J. G. Urones, I. S. Marcos, P. Basabe, N. M. Garrido, A. Jorge, R. F. Moro and A. M. Lithgow, *Tetrahedron*, 1993, **49**, 6079–6088.
- 42 J. G. Urones, A. Jorge, I. S. Marcos, P. Basabe, D. Díez, N. M. Garrido, A. M. Lithgow, M. O. C. F. da Fonseca and J. M. L. Rodilla, *Tetrahedron Lett.*, 1996, **37**, 1659–1662.
- 43 I. S. Marcos, A. Jorge, D. Díez, P. Basabe, A. M. Lithgow, M. J. Sexmero, N. M. Garrido and J. G. Urones, *Phytochemistry*, 1996, **41**, 1155–1157.
- 44 J.-J. Wang, H. Y. Chung, Y.-B. Zhang, G.-Q. Li, Y.-L. Li, W.-H. Huang and G.-C. Wang, *Phytochemistry*, 2016, **122**, 270–275.
- 45 M. Sánchez, M. Mazzuca, M. J. Veloso, L. R. Fernández, G. Siless, L. Puricelli and J. A. Palermo, *Phytochemistry*, 2010, **71**, 1395–1399.
- 46 H.-M. Chung, L.-C. Hu, W.-H. Yen, J.-H. Su, M.-C. Lu, T.-L. Hwang, W.-H. Wang and P.-J. Sung, *Mar. Drugs*, 2012, **10**, 2246.
- 47 H. Lei, *Chem. Biodiversity*, 2016, **13**, 345–365.
- 48 M. Abdel-Kader, J. M. Berger, C. Slebodnick, J. Hoch, S. Malone, J. H. Wisse, M. C. M. Werkhoven, S. Mamber and D. G. I. Kingston, *J. Nat. Prod.*, 2002, **65**, 11–15.
- 49 H.-H. Cheng, Y.-B. Cheng, T.-L. Hwang, Y.-H. Kuo, C.-H. Chen and Y.-C. Shen, *J. Nat. Prod.*, 2015, **78**, 1823–1828.
- 50 Y. Zhang, N. Adnani, D. R. Braun, G. A. Ellis, K. J. Barns, S. Parker-Nance, I. A. Guzei and T. S. Bugni, *J. Nat. Prod.*, 2016, **79**, 2968–2972.
- 51 K. Du, M. De Mieri, M. Neuburger, P. C. Zietsman, A. Marston, S. F. van Vuuren, D. Ferreira, M. Hamburger and J. H. van der Westhuizen, *J. Nat. Prod.*, 2015, **78**, 2494–2504.
- 52 C. G. Silva, H. M. Santos Júnior, J. P. Barbosa, G. L. Costa, F. A. R. Rodrigues, D. F. Oliveira, L. V. Costa-Lotufo, R. J. V. Alves, E. C. A. Eleutherio and C. M. Rezende, *Chem. Biodiversity*, 2015, **12**, 1891–1901.
- 53 T. Kubota, T. Iwai, A. Takahashi-Nakaguchi, J. Fromont, T. Gonoï and J. i. Kobayashi, *Tetrahedron*, 2012, **68**, 9738–9744.
- 54 S. del Corral, S. L. Cuffini, S. G. Cardoso, A. J. Bortoluzzid and S. M. Palacios, *Phytochem. Lett.*, 2012, **5**, 280–283.
- 55 C. Nakano, T. Okamura, T. Sato, T. Dairi and T. Hoshino, *Chem. Commun.*, 2005, 1016–1018.
- 56 N. Mangel, F. M. Mann, M. L. Hillwig, R. J. Peters and B. B. Snider, *Org. Lett.*, 2010, **12**, 2626–2629.
- 57 C. Nakano, T. Ootsuka, K. Takayama, T. Mitsui, T. Sato and T. Hoshino, *Biosci., Biotechnol., Biochem.*, 2011, **75**, 75–81.
- 58 J. E. Spangler, C. A. Carson and E. J. Sorensen, *Chem. Sci.*, 2010, **1**, 202–205.
- 59 T. Hoshino, C. Nakano, T. Ootsuka, Y. Shinohara and T. Hara, *Org. Biomol. Chem.*, 2011, **9**, 2156–2165.
- 60 H.-C. Chan, X. Feng, T.-P. Ko, C.-H. Huang, Y. Hu, Y. Zheng, S. Bogue, C. Nakano, T. Hoshino, L. Zhang, P. Lv, W. Liu,



- D. C. Crick, P.-H. Liang, A. H. J. Wang, E. Oldfield and R.-T. Guo, *J. Am. Chem. Soc.*, 2014, **136**, 2892–2896.
- 61 C.-I. Liu, G. Y. Liu, Y. Song, F. Yin, M. E. Hensler, W.-Y. Jeng, V. Nizet, A. H.-J. Wang and E. Oldfield, *Science*, 2008, **319**, 1391–1394.
- 62 D. C. Young, E. Layre, S.-J. Pan, A. Tapley, J. Adamson, C. Seshadri, Z. Wu, J. Buter, A. J. Minnaard, M. Coscolla, S. Gagneux, R. Copin, J. D. Ernst, W. R. Bishai, B. B. Snider and D. B. Moody, *Chem. Biol.*, 2015, **22**, 516–526.
- 63 J. Buter, D. Heijnen, I. C. Wan, F. M. Bickelhaupt, D. C. Young, E. Otten, D. B. Moody and A. J. Minnaard, *J. Org. Chem.*, 2016, **81**, 6686–6696.
- 64 A. Koul, E. Arnoult, N. Lounis, J. Guillemont and K. Andries, *Nature*, 2011, **469**, 483–490.
- 65 T. Sato, A. Kigawa, R. Takagi, T. Adachi and T. Hoshino, *Org. Biomol. Chem.*, 2008, **6**, 3788–3794.
- 66 C. Nakano, M. Oshima, N. Kurashima and T. Hoshino, *ChemBioChem*, 2015, **16**, 772–781.
- 67 F. M. Mann, S. Pristic, H. Hu, M. Xu, R. M. Coates and R. J. Peters, *J. Biol. Chem.*, 2009, **284**, 23574–23579.
- 68 F. M. Mann, B. C. VanderVen and R. J. Peters, *Mol. Microbiol.*, 2011, **79**, 1594–1601.
- 69 L. Prach, J. Kirby, J. D. Keasling and T. Alber, *FEBS J.*, 2010, **277**, 3588–3595.
- 70 F. M. Mann, M. Xu, X. Chen, D. B. Fulton, D. G. Russell and R. J. Peters, *J. Am. Chem. Soc.*, 2009, **131**, 17526–17527.
- 71 E. Layre, H. J. Lee, D. C. Young, A. Jezek Martinot, J. Buter, A. J. Minnaard, J. W. Annand, S. M. Fortune, B. B. Snider, I. Matsunaga, E. J. Rubin, T. Alber and D. B. Moody, *Proc. Natl. Acad. Sci.*, 2014, **111**, 2978–2983.
- 72 A. Rudi, M. Akin, E. Gaydou and Y. Kashman, *J. Nat. Prod.*, 2004, **67**, 1932–1935.
- 73 K. K. Wan and R. A. Shenvi, *Synlett*, 2016, **27**, 1145–1164.
- 74 H. Zhang, M. Dong, J. Chen, H. Wang, K. Tenney and P. Crews, *Mar. Drugs*, 2017, **15**, 351.
- 75 T. Hattori, K. Adachi and Y. Shizuri, *J. Nat. Prod.*, 1997, **60**, 411–413.
- 76 E. Scio, A. Ribeiro, T. M. A. Alves, A. J. Romanha, J. D. de Souza Filho, G. A. Cordell and C. L. Zani, *Phytochemistry*, 2003, **64**, 1125–1131.
- 77 P. Luo, Q. Yu, S.-N. Liu, W.-J. Xia, Y.-Y. Fang, L.-K. An, Q. Gu and J. Xu, *Fitoterapia*, 2017, **120**, 108–116.
- 78 G.-C. Wang, J.-G. Li, G.-Q. Li, J.-J. Xu, X. Wu, W.-C. Ye and Y.-L. Li, *J. Nat. Prod.*, 2012, **75**, 2188–2192.
- 79 J. Appenzeller, G. Mihci, M.-T. Martin, J.-F. Gallard, J.-L. Menou, N. Boury-Esnault, J. Hooper, S. Petek, S. Chevalley, A. Valentin, A. Zaparucha, A. Al-Mourabit and C. Debitus, *J. Nat. Prod.*, 2008, **71**, 1451–1454.
- 80 C. A. Hiruma-Lima, J. S. Gracioso, W. Toma, A. B. Almeida, A. C. Paula, D. S. B. Brasil, A. H. Muller, A. R. M. Souza Brito and A. R. M. Souza Brito, *Phytomedicine*, 2001, **8**, 94–100.
- 81 W.-q. Wang, Y.-p. Yin, L. Jun and L.-j. Xuan, *Phytochemistry*, 2018, **146**, 56–62.
- 82 C. Kihampa, M. H. H. Nkunya, C. C. Joseph, S. M. Magesa, A. Hassanali, M. Heydenreich and E. Kleinpeter, *Phytochemistry*, 2009, **70**, 1233–1238.
- 83 M. Gavagnin, E. Trivellone, F. Castelluccio, G. Cimino and R. Cattaneo-Vietti, *Tetrahedron Lett.*, 1995, **36**, 7319–7322.
- 84 K. U. Wendt, K. Poralla and G. E. Schulz, *Science*, 1997, **277**, 1811–1815.
- 85 K. C. Potter, M. Jia, Y. J. Hong, D. Tantillo and R. J. Peters, *Org. Lett.*, 2016, **18**, 1060–1063.
- 86 K. Potter, J. Criswell, J. Zi, A. Stubbs and R. J. Peters, *Angew. Chem., Int. Ed.*, 2014, **53**, 7198–7202.
- 87 R. J. Peters, *Phytochemistry*, 2006, **67**, 2307–2317.
- 88 P. R. Wilderman and R. J. Peters, *J. Am. Chem. Soc.*, 2007, **129**, 15736–15737.
- 89 Q. Wang, M. L. Hillwig, Y. Wu and R. J. Peters, *Plant Physiol.*, 2012, **158**, 1418.
- 90 Y. Matsuda and I. Abe, *Nat. Prod. Rep.*, 2016, **33**, 26–53.
- 91 M. Zhou, H.-C. Geng, H.-B. Zhang, K. Dong, W.-G. Wang, X. Du, X.-N. Li, F. He, H.-B. Qin, Y. Li, J.-X. Pu and H.-D. Sun, *Org. Lett.*, 2013, **15**, 314–317.
- 92 M. Xu, M. Jia, Y. J. Hong, X. Yin, D. J. Tantillo, P. J. Proteau and R. J. Peters, *Org. Lett.*, 2018, **20**, 1200–1202.
- 93 C. Nakano and T. Hoshino, *ChemBioChem*, 2009, **10**, 2060–2071.
- 94 R. Peters, F. Mann, M. Xu and E. Davenport, *Front Microbiol.*, 2012, **3**, 368.
- 95 C. A. Citron, P. Rabe, L. Barra, C. Nakano, T. Hoshino and J. S. Dickschat, *Eur. J. Org. Chem.*, 2014, 7684–7691.
- 96 S. Mafu, E. Fischer, J. B. Addison, I. Riberio Barbosana and P. Zerbe, *ChemBioChem*, 2016, **17**, 2304–2307.
- 97 J. H. George, M. McArdle, J. E. Baldwin and R. M. Adlington, *Tetrahedron*, 2010, **66**, 6321–6330.
- 98 K. C. Potter, J. Zi, Y. J. Hong, S. Schulte, B. Malchow, D. J. Tantillo and R. J. Peters, *Angew. Chem., Int. Ed.*, 2016, **55**, 634–638.
- 99 J. G. Urones, I. S. Marcos, P. B. Barcala and N. M. Garrido, *Phytochemistry*, 1988, **27**, 501–504.
- 100 J. G. Urones, I. S. Marcos, D. D. Martin, F. M. S. B. Palma and J. M. Rodilla, *Phytochemistry*, 1987, **26**, 3037–3040.
- 101 J. De Pascual Teresa, J. G. Urones, I. S. Marcos, P. B. Barcala and N. M. Garrido, *Phytochemistry*, 1986, **25**, 1185–1187.
- 102 J. De Pascual Teresa, J. G. Urones, I. S. Marcos, F. Bermejo and P. Basabe, *Phytochemistry*, 1983, **22**, 2783–2785.
- 103 J. De Pascual Teresa, P. Basabe, I. S. Marcos, F. Bermejo and J. G. Urones, *An. Quim.*, 1981, **77C**, 184–188.
- 104 J. De Pascual Teresa, J. G. Urones, P. Basabe, F. Bermejo and I. S. Marcos, *An. Quim.*, 1981, **77C**, 290–295.
- 105 J.-S. Zhang, Y.-Q. Tang, J.-L. Huang, W. Li, Y.-H. Zou, G.-H. Tang, B. Liu and S. Yin, *Phytochemistry*, 2017, **144**, 151–158.
- 106 A. Aldhaher, M. Langat, B. Ndunda, D. Chirchir, J. O. Midiwo, A. Njue, S. Schwikkard, M. Carew and D. Mulholland, *Phytochemistry*, 2017, **144**, 1–8.
- 107 A. Salatino, M. L. F. Salatino and G. Negri, *J. Braz. Chem. Soc.*, 2007, **18**, 11–33.
- 108 A. Sato, M. Kurabayashi, H. Nagahori, A. Ogiso and H. Mishima, *Tetrahedron Lett.*, 1970, **11**, 1095–1098.
- 109 I. S. Marcos, F. A. Hernández, M. J. Sexmero, D. Díez, P. Basabe, A. B. Pedrero, N. García and J. G. Urones, *Tetrahedron*, 2003, **59**, 685–694.



- 110 J. G. Urones, I. S. Marcos, P. Basabe, M. J. Sexmero, H. Carrillo and M. J. Melchor, *Phytochemistry*, 1994, **37**, 1359–1361.
- 111 A. Sato, M. Kurabayashi, A. Ogiso and H. Mishima, *Tetrahedron Lett.*, 1971, **12**, 839–842.
- 112 M. Kanlayavattanukul, N. Ruangrunsi, T. Watanabe, M. Kawahata, B. Therrien, K. Yamaguchi and T. Ishikawa, *J. Nat. Prod.*, 2005, **68**, 7–10.
- 113 Z.-X. Zhang, H.-H. Li, F.-M. Qi, H.-Y. Xiong, L.-L. Dong, G.-X. Fan and D.-Q. Fei, *Bull. Korean Chem. Soc.*, 2014, **35**, 1556–1558.
- 114 Q.-Q. Yuan, S. Tang, W.-B. Song, W.-Q. Wang, M. Huang and L.-J. Xuan, *J. Nat. Prod.*, 2017, **80**, 254–260.
- 115 J. De Pascual Teresa, J. G. Urones and H. Carrillo, *An. Quim.*, 1978, **74**, 488–493.
- 116 J. G. Urones, I. S. Marcos, M. J. Sexmero, P. Basabe and A. M. Lithgow, *Phytochemistry*, 1990, **29**, 1247–1251.
- 117 D. I. M. D. de Mendonça, J. M. L. Rodilla, A. M. Lithgow and I. S. Marcos, *Phytochemistry*, 1997, **44**, 1301–1307.
- 118 J. G. Urones, M. J. Sexmero, F. A. Hernandez, P. Basabe, A. B. Pedrero, D. Diez and I. S. Marcos, *Nat. Prod. Lett.*, 2001, **15**, 387–391.
- 119 S. F. Khoo, A. C. Oehlschlager and G. Ourisson, *Tetrahedron*, 1973, **29**, 3379–3388.
- 120 A. F. Monteiro, J. M. Batista, M. A. Machado, R. P. Severino, E. W. Blanch, V. S. Bolzani, P. C. Vieira and V. G. P. Severino, *J. Nat. Prod.*, 2015, **78**, 1451–1455.
- 121 F. Nagashima, M. Suzuki and Y. Asakawa, *Fitoterapia*, 2001, **72**, 83–85.
- 122 N. Hara, H. Asaki, Y. Fujimoto, Y. K. Gupta, A. K. Singh and M. Sahai, *Phytochemistry*, 1995, **38**, 189–194.
- 123 I. S. Marcos, A. B. Pedrero, M. J. Sexmero, D. Diez, P. Basabe, F. A. Hernández and J. G. Urones, *Tetrahedron Lett.*, 2003, **44**, 369–372.
- 124 M. L. Ciavatta, S. García-Matucheski, M. Carbone, G. Villani, M. R. Nicotera, C. Muniain and M. Gavagnin, *Chem. Biodiversity*, 2017, **14**, e1700125.
- 125 L.-L. Hong, J.-B. Sun, F. Yang, M. Liu, J. Tang, F. Sun, W.-H. Jiao, S.-P. Wang, W. Zhang and H.-W. Lin, *RSC Adv.*, 2017, **7**, 23970–23976.
- 126 H. Nakamura, H. Wu, Y. Ohizumi and Y. Hirata, *Tetrahedron Lett.*, 1984, **25**, 2989–2992.
- 127 L. S. Favier, M. Nieto, O. S. Giordano and C. E. Tonn, *Phytochemistry*, 1997, **45**, 1469–1474.
- 128 I. S. Marcos, N. García, M. J. Sexmero, P. Basabe, D. Díez and J. G. Urones, *Tetrahedron*, 2005, **61**, 11672–11678.
- 129 E. P. Stout, L. C. Yu and T. F. Molinski, *Eur. J. Org. Chem.*, 2012, 5131–5135.
- 130 L. Harinantenaina, S. Kida and Y. Asakawa, *ARKIVOC*, 2007, **8**, 22–29.
- 131 F. Bohlmann and J. Jakupovic, *Phytochemistry*, 1979, **18**, 631–635.
- 132 M. Ono, Y. Ito and T. Nohara, *Chem. Pharm. Bull.*, 2001, **49**, 1220–1222.
- 133 J. A. Maschek, E. Mevers, T. Diyabalanage, L. Chen, Y. Ren, J. B. McClintock, C. D. Amsler, J. Wu and B. J. Baker, *Tetrahedron*, 2012, **68**, 9095–9104.
- 134 S. Soldatou and B. J. Baker, *Nat. Prod. Rep.*, 2017, **34**, 585–626.
- 135 M.-J. Chu, X.-L. Tang, G.-F. Qin, Y.-T. Sun, L. Li, N. J. de Voogd, P.-L. Li and G.-Q. Li, *Chem. Biodiversity*, 2017, **14**, e1600446.
- 136 T. Kawashima, T. Nakatsu, Y. Fukazawa and S. Itô, *Heterocycles*, 1976, **5**, 227–232.
- 137 E. K. Adesogan, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1151–1153.
- 138 M. C. Kapingu, D. Guillaume, Z. H. Mbwambo, M. J. Moshi, F. C. Uliso and R. L. A. Mahunnah, *Phytochemistry*, 2000, **54**, 767–770.
- 139 G. Appendino, F. Borrelli, R. Capasso, C. Campagnuolo, E. Fattorusso, F. Petrucci and O. Tagliatela-Scafati, *J. Agric. Food Chem.*, 2003, **51**, 6970–6974.
- 140 S. Roengsumran, S. Pornpakakul, N. Muangsins, P. Sangvanich, T. Nhujak, P. Singtothong, N. Chaichit, S. Puthong and A. Petsom, *Planta Med.*, 2004, **70**, 87–89.
- 141 I. S. Marcos, A. Conde, R. F. Moro, P. Basabe, D. Diez, F. Mollinedo and J. G. Urones, *Molecules*, 2008, **13**, 1120.
- 142 Y. Hu, L. Zhang, X.-Q. Wen, X.-J. Zeng, W. Rui and Y.-Z. Cen, *J. Asian Nat. Prod. Res.*, 2012, **14**, 785–788.
- 143 W.-H. Huang, G.-Q. Li and J.-G. Li, *Heterocycles*, 2014, **89**, 1585–1593.
- 144 M. Qiu, D. Cao, Y. Gao, S. Li, J. Zhu, B. Yang, L. Zhou, Y. Zhou, J. Jin and Z. Zhao, *Fitoterapia*, 2016, **108**, 81–86.
- 145 B. Ndunda, M. K. Langat, J. O. Midiwo and L. K. Omosa, *Nat. Prod. Commun.*, 2015, **10**, 557–558.
- 146 J.-T. Song, Y. Han, X.-L. Wang, T. Shen, H.-X. Lou and X.-N. Wang, *Fitoterapia*, 2015, **107**, 54–59.
- 147 B.-D. Lin, B. Zhou, L. Dong, Y. Wu and J.-M. Yue, *Nat. Prod. Bioprospect.*, 2016, **6**, 57–61.
- 148 A. Aldhaher, M. Langat, B. Ndunda, D. Chirchir, J. O. Midiwo, A. Njue, S. Schwikkard, M. Carew and D. Mulholland, *Phytochemistry*, 2017, **144**, 1–8.
- 149 Y. Liang, Y. Zhang, G. Wang, Y. Li and W. Huang, *Molecules*, 2017, **22**, 126.
- 150 J.-L. Tian, G.-D. Yao, Y.-X. Wang, P.-Y. Gao, D. Wang, L.-Z. Li, B. Lin, X.-X. Huang and S.-J. Song, *Bioorg. Med. Chem. Lett.*, 2017, **27**, 1237–1242.
- 151 M. Qiu, J. Jin, L. Zhou, W. Zhou, Y. Liu, Q. Tan, D. Cao and Z. Zhao, *Phytochemistry*, 2018, **145**, 103–110.
- 152 F. Nagashima, H. Tanaka, Y. Kan, S. Huneck and Y. Asakawa, *Phytochemistry*, 1995, **40**, 209–212.
- 153 F. Nagashima, M. Suzuki, S. Takaoka and Y. Asakawa, *J. Nat. Prod.*, 2001, **64**, 1309–1317.
- 154 S.-M. Yang, D.-G. Wu and X.-K. Liu, *Z. Naturforsch. C Bio. Sci.*, 2010, **65**, 39–42.
- 155 M. Liu, W.-G. Wang, H.-D. Sun and J.-X. Pu, *Nat. Prod. Rep.*, 2017, **34**, 1090–1140.
- 156 J. Gu, S.-Y. Qian, G.-G. Cheng, Y. Li, Y.-P. Liu and X.-D. Luo, *Nat. Prod. Bioprospect.*, 2013, **3**, 66–69.
- 157 M. J. Pcolinski, D. P. O'Mathúna and R. W. Doskotch, *J. Nat. Prod.*, 1995, **58**, 209–216.
- 158 T. Abe, M. Kobayashi, Y. Okawa, T. Inui, J. Yoshida, H. Higashio, H. Shinden, S. Uesugi, H. Koshino and K.-i. Kimura, *Fitoterapia*, 2016, **113**, 188–194.



- 159 M. Ono, T. Yamasaki, M. Konoshita, T. Ikeda, M. Okawa, J. Kinjo, H. Yoshimitsu and T. Nohara, *Chem. Pharm. Bull.*, 2008, **56**, 1621–1624.
- 160 M. Ono, K. Eguchi, M. Konoshita, C. Furusawa, J. Sakamoto, S. Yasuda, T. Ikeda, M. Okawa, J. Kinjo, H. Yoshimitsu and T. Nohara, *Chem. Pharm. Bull.*, 2011, **59**, 392–396.
- 161 N. Tiwari, J. Thakur, D. Saikia and M. M. Gupta, *Phytomedicine*, 2013, **20**, 605–610.
- 162 J. Wu, T. Zhou, S.-w. Zhang, X.-h. Zhang and L.-j. Xuan, *Planta Med.*, 2009, **75**, 367–370.
- 163 M. Ono, T. Yanaka, M. Yamamoto, Y. Ito and T. Nohara, *J. Nat. Prod.*, 2002, **65**, 537–541.
- 164 C. Lee, J. W. Lee, Q. Jin, H. J. Lee, S.-J. Lee, D. Lee, M. K. Lee, C. K. Lee, J. T. Hong, M. K. Lee and B. Y. Hwang, *Bioorg. Med. Chem. Lett.*, 2013, **23**, 6010–6014.
- 165 H. Wu, S. Wang, Z. Xu, S. Sun, H. Liu, J. Wang, Y. E, Y. Lv, X. Dong, G. Li, L. Zhang and Y. Shi, *Molecules*, 2015, **20**, 839.
- 166 J.-S. Zhang, Y.-H. Zou, J.-J. Zhao, Y. Chen, J.-M. Bao and G.-H. Tang, *Phytochem. Lett.*, 2016, **16**, 241–244.
- 167 T. L. Meragelman, D. S. Pedrosa and R. R. Gil, *Biochem. Syst. Ecol.*, 2004, **32**, 45–53.
- 168 J. De Pascual Teresa, J. G. Urones, I. S. Marcos, F. Bermejo, P. Basabe and P. Queimadelos, *An. Quim. C.*, 1983, **79**, 451–453.
- 169 S. K. Sadhu, E. Okuyama, H. Fujimoto and M. Ishibashi, *J. Nat. Prod.*, 2006, **69**, 988–994.
- 170 P. Rijo, C. Gaspar-Marques, M. F. Simões, M. L. Jimeno and B. Rodríguez, *Biochem. Syst. Ecol.*, 2007, **35**, 215–221.
- 171 P. Rijo, B. Rodríguez, A. Duarte and M. F. Simoes, *Nat. Prod. J.*, 2011, **1**, 57–64.
- 172 O. Burmistrova, M. F. Simões, P. Rijo, J. Quintana, J. Bermejo and F. Estévez, *J. Nat. Prod.*, 2013, **76**, 1413–1423.
- 173 C. Nakano, T. Hoshino, T. Sato, T. Toyomasu, T. Dairi and T. Sassa, *Tetrahedron Lett.*, 2010, **51**, 125–128.
- 174 M. Jia, K. C. Potter and R. J. Peters, *Metab. Eng.*, 2016, **37**, 24–34.
- 175 F. Bohlmann, W.-R. Abraham, R. M. King and H. Robinson, *Phytochemistry*, 1981, **20**, 1903–1906.
- 176 M. A. de Alvarenga, H. E. Gottlieb, O. R. Gottlieb, M. T. Magalhães and V. O. da Silva, *Phytochemistry*, 1978, **17**, 1773–1776.
- 177 M. S. Buchanan, J. D. Connolly, A. A. Kadir and D. S. Rycroft, *Phytochemistry*, 1996, **42**, 1641–1646.
- 178 R. P. Walker, R. M. Rosser, D. J. Faulkner, L. S. Bass, C. H. He and J. Clardy, *J. Org. Chem.*, 1984, **49**, 5160–5163.
- 179 M. Toyota, I. Nakamura, S. Takaoka, Y. Kan and Y. Asakawa, *Phytochemistry*, 1996, **41**, 575–580.
- 180 C.-Y. Chen, F.-R. Chang, Y.-C. Shih, T.-J. Hsieh, Y.-C. Chia, H.-Y. Tseng, H.-C. Chen, S.-J. Chen, M.-C. Hsu and Y.-C. Wu, *J. Nat. Prod.*, 2000, **63**, 1475–1478.
- 181 R. P. Walker and D. J. Faulkner, *J. Org. Chem.*, 1981, **46**, 1098–1102.
- 182 C. Harde and F. Bohlmann, *Tetrahedron*, 1988, **44**, 81–90.
- 183 R. Fathi-Afshar and T. M. Allen, *Can. J. Chem.*, 1988, **66**, 45–50.
- 184 S. S. Nyandoro, *J. Pharmacogn. Phytochem.*, 2014, **3**, 147–157.
- 185 M. Bruno, F. Piozzi, G. Savona, M. C. De La Torre and B. Rodríguez, *Phytochemistry*, 1989, **28**, 3539–3541.
- 186 A. Fiorentino, B. D'Abrosca, S. Pacifico, M. Scognamiglio, G. D'Angelo, M. Gallicchio, A. Chambery and P. Monaco, *Phytochemistry*, 2011, **72**, 2037–2044.
- 187 E. Fujita, I. Uchida, T. Fujita, N. Masaki and K. Osaki, *J. Chem. Soc., Chem. Commun.*, 1973, 793–794.
- 188 E. Fujita, I. Uchida and T. Fujita, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1547–1555.
- 189 F. Fernández-Gadea, C. Pascual, B. Rodríguez and G. Savona, *Phytochemistry*, 1983, **22**, 723–725.
- 190 Z. H. Mbwaambo, K. Foubert, M. Chacha, M. C. Kapingu, J. J. Magadula, M. M. Moshi, F. Lemièrre, K. Goubitz, J. Fraanje, R. Peschar, A. Vlietinck, S. Apers and L. Pieters, *Planta Med.*, 2009, **75**, 262–267.
- 191 Z. Pan, D. Ning, X. Wu, S. Huang, D. Li and S. Lv, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 1329–1332.
- 192 J. G. Urones, I. S. Marcos, M. J. Sexmero, P. Basabe and A. M. Lithgow, *Phytochemistry*, 1990, **29**, 3597–3600.
- 193 Â. C. Pinto, O. A. C. Antunes, M. G. Pizzolatti and V. M. Rumjanek, *Phytochemistry*, 1996, **42**, 771–774.
- 194 A. C. Pinto, O. A. C. Antunes, C. M. Rezende and C. R. D. Correia, *Phytochemistry*, 1995, **38**, 1269–1271.
- 195 M. Salmoun, J. C. Braekman, J. Dewelle, F. Darro, R. Kiss, N. J. De Voogd and R. W. M. Van Soest, *Nat. Prod. Res.*, 2007, **21**, 149–155.
- 196 K. Shimbo, M. Tsuda, E. Fukushima, J. Kawabata and J. Kobayashi, *Tetrahedron*, 2000, **56**, 7923–7926.
- 197 C.-H. Cheng, H.-M. Chung, T.-L. Hwang, M.-C. Lu, Z.-H. Wen, Y.-H. Kuo, W.-H. Wang and P.-J. Sung, *Molecules*, 2012, **17**, 9443.
- 198 A. Ortega, P. E. García, J. Cárdenas, C. Mancera, S. Marquina, M. L. d. Carmen Garduño and E. Maldonado, *Tetrahedron*, 2001, **57**, 2981–2989.
- 199 A. Ohsaki, N. Ohno, K. Shibata, T. Tokoroyama, T. Kubota, K. Hirotsu and T. Higuchi, *Phytochemistry*, 1988, **27**, 2171–2173.
- 200 A. Ohsaki, K. Shibata, T. Tokoroyama and T. Kubota, *J. Chem. Soc., Chem. Commun.*, 1987, 151–153.
- 201 A. Ohsaki, Y. Kasetani, Y. Asaka, K. Shibata, T. Tokoroyama and T. Kubota, *Phytochemistry*, 1995, **40**, 205–207.
- 202 O. Ayumi, S. Kozo, T. Takashi, K. Takashi and N. Hideo, *Chem. Lett.*, 1986, **15**, 1585–1588.
- 203 H.-M. Niu, D.-Q. Zeng, C.-L. Long, Y.-H. Peng, Y.-H. Wang, J.-F. Luo, H.-S. Wang, Y.-N. Shi, G.-H. Tang and F.-W. Zhao, *J. Asian Nat. Prod. Res.*, 2010, **12**, 7–14.
- 204 F. Bohlmann, M. Grenz, P. Wegner and J. Jakupovic, *Liebigs Ann. Chem.*, 1983, 2008–2020.
- 205 K. Siems, X. A. Dominguez and J. Jakupovic, *Phytochemistry*, 1992, **31**, 4363–4365.
- 206 D.-X. Guo, X.-N. Wang, R.-X. Zhu, N. Liu, J.-C. Zhou, W.-T. Yu and H.-X. Lou, *Phytochem. Lett.*, 2012, **5**, 535–540.
- 207 I. S. Marcos, A. B. Pedrero, M. J. Sexmero, D. Diez, N. García, M. A. Escola, P. Basabe, A. Conde, R. F. Moro and J. G. Urones, *Synthesis*, 2005, 3301–3310.



- 208 I. S. Marcos, J. L. Gonzalez, M. J. Sexmero, D. Díez, P. Basabe, D. J. Williams, M. S. J. Simmonds and J. G. Urones, *Tetrahedron Lett.*, 2000, **41**, 2553–2557.
- 209 I. S. Marcos, F. A. Hernández, M. J. Sexmero, D. Díez, P. Basabe, A. B. Pedrero, N. García, F. Sanz and J. G. Urones, *Tetrahedron Lett.*, 2002, **43**, 1243–1245.
- 210 I. S. Marcos, A. B. Pedrero, M. J. Sexmero, D. Díez, P. Basabe, F. A. Hernández, H. B. Broughton and J. G. Urones, *Synlett*, 2002, 105–109.
- 211 I. S. Marcos, M. A. Escola, R. F. Moro, P. Basabe, D. Díez, F. Sanz, F. Mollinedo, J. de la Iglesia-Vicente, B. G. Sierra and J. G. Urones, *Bioorg. Med. Chem.*, 2007, **15**, 5719–5737.
- 212 I. S. Marcos, A. B. Pedrero, M. J. Sexmero, D. Díez, P. Basabe, N. García, R. F. Moro, H. B. Broughton, F. Mollinedo and J. G. Urones, *J. Org. Chem.*, 2003, **68**, 7496–7504.
- 213 A. Gil-Mesón, A. M. Roncero, I. E. Tobal, P. Basabe, D. Díez, F. Mollinedo and I. S. Marcos, *Molecules*, 2016, **21**, 47.
- 214 I. S. Marcos, M. J. Sexmero, F. Á. Hernández, M. Corrales, P. Basabe, D. Díez and J. G. Urones, *Molecules*, 2006, **11**, 792–807.
- 215 I. S. Marcos, N. García, M. J. Sexmero, F. A. Hernández, M. A. Escola, P. Basabe, D. Díez and J. G. Urones, *Tetrahedron*, 2007, **63**, 2335–2350.
- 216 I. S. Marcos, B. Martínez, M. J. Sexmero, D. Díez, P. Basabe and J. G. Urones, *Synthesis*, 2006, 3865–3873.
- 217 I. S. Marcos, A. Conde, R. F. Moro, P. Basabe, D. Díez and J. G. Urones, *Tetrahedron*, 2010, **66**, 8280–8290.
- 218 I. S. Marcos, M. A. Escola, R. F. Moro, P. Basabe, D. Díez, F. Mollinedo and J. G. Urones, *Synlett*, 2007, 2017–2022.
- 219 I. S. Marcos, R. F. Moro, I. Costales, P. Basabe, D. Díez, F. Mollinedo and J. G. Urones, *Tetrahedron*, 2012, **68**, 7932–7940.
- 220 I. S. Marcos, R. F. Moro, I. Costales, P. Basabe, D. Díez, F. Mollinedo and J. G. Urones, *Tetrahedron*, 2013, **69**, 7285–7289.
- 221 I. S. Marcos, R. F. Moro, I. Costales, M. A. Escola, P. Basabe, D. Díez and J. G. Urones, *Tetrahedron*, 2009, **65**, 10235–10242.
- 222 I. S. Marcos, R. F. Moro, I. Costales, P. Basabe, D. Díez, A. Gil, F. Mollinedo, F. Pérez-de la Rosa, E. Pérez-Roth and J. M. Padrón, *Eur. J. Med. Chem.*, 2014, **73**, 265–279.
- 223 H. J. Bestmann, *Angew. Chem., Int. Ed.*, 1977, **16**, 349–364.
- 224 J. Boukouvalas and N. Lachance, *Synlett*, 1998, 31–32.
- 225 H. Rosemeyer, *Chem. Biodiversity*, 2004, **1**, 361–401.
- 226 M. Ohba, K. Iizuka, H. Ishibashi and T. Fujii, *Tetrahedron*, 1997, **53**, 16977–16986.
- 227 M. Ohba, N. Kawase, T. Fujii, K. Aoe, K. Okamura, R. Fathi-Afshar and T. M. Allen, *Tetrahedron Lett.*, 1995, **36**, 6101–6104.
- 228 M. Ohba, N. Kawase and T. Fujii, *J. Am. Chem. Soc.*, 1996, **118**, 8250–8257.
- 229 S. L. Schreiber, *J. Am. Chem. Soc.*, 1980, **102**, 6163–6165.
- 230 G. Solladie and J. Hutt, *J. Org. Chem.*, 1987, **52**, 3560–3566.
- 231 H. Iio, M. Monden, K. Okada and T. Tokoroyama, *J. Chem. Soc., Chem. Commun.*, 1987, 358–359.
- 232 J. R. Parikh and W. v. E. Doering, *J. Am. Chem. Soc.*, 1967, **89**, 5505–5507.
- 233 I. Ojima and T. Kogure, *Tetrahedron Lett.*, 1972, **13**, 5035–5038.

