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

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

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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.

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,\(^5,^6\) sesterterpenes\(^\) and triterpenes). 

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.\(^7\) 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.\(^8\) Labdanes and related diterpenes (like clerodanes\(^9\)–\(^13\)) are included in this second group. According to Peters,\(^14\) halimanes are found within the labdane and clerodane group, as indicated in the general biogenetic scheme (Scheme 1). The halimane-type

Alejandro Martín Ronceró 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 alkylphosphocholines 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 (London), DIC 1991. She became Associate Professor in 1991 at the University of Salamanca and full Professor in 2008 at the same university. She 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.

**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 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.

**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.
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 $\Delta^{2}$ 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 series$^{17}$ in *Halimium viscosum* (Fig. 1). Previously in the literature, these compounds were known by generic
names, such as rearranged labdanes,\textsuperscript{18,19} isolabdanes\textsuperscript{20} or even friedolabdanes.\textsuperscript{21–25}

\textit{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. \textit{Ent}-halimic acid and acetoxy \textit{ent}-halimic acid are found in a 1 : 1 ratio in considerable amounts in \textit{Halimium viscosum} extracts (47%), 0.34% with respect of the dry plant weight. Nowadays, a cheap, quick and efficient methodology for the isolation of \textit{ent}-halimic acid has been achieved. The study of the components of \textit{Halimium viscosum} and the need for large amounts of \textit{ent}-halimic acid for the synthesis of biologically active compounds led us to search for \textit{Halimium viscosum} plants in new locations with better access. In this manner, we found several places for the study of the \textit{Halimium viscosum} components, such as Villarino de los Aires (Salamanca, Spain),\textsuperscript{17} La Fregeneda (Salamanca, Spain)\textsuperscript{26,27} and Valparaíso (Zamora, Spain),\textsuperscript{28} localities quite close together. To our surprise, in the first location rearranged \textit{ent}-labdanes (\textit{ent}-halimanes) with an unsaturated side chain were isolated, in the second \textit{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 \textit{Halimium viscosum} have been localized in Portugal near the border with Salamanca (Celorico da Beira\textsuperscript{29} and San João da Pesqueira\textsuperscript{30}).

In \textit{Halimium viscosum}, in addition to the referred \textit{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\textsuperscript{31–35} and valparolanes,\textsuperscript{36} bicyclic diterpenoids with tormesane skeleton (a new type of sphenolobanes),\textsuperscript{37,38} tormesolanes\textsuperscript{39} and new rearranged labdanes with an aromatized ring B, such as fregenedanes\textsuperscript{40,41} and isofregenedanes,\textsuperscript{42–43} are found. The biosynthesis of these new carbon skeletons, as valparanes and tormesanes, 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 \textit{ent}-labdane derivatives isolated in \textit{Halimium viscosum} and in order to simplify their nomenclature and to facilitate their classification, the name \textit{ent}-halimane was proposed for that carbon skeleton. Compounds of this class were isolated previously for the first time in the roots of \textit{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,\textsuperscript{44–48} anti-inflammatory,\textsuperscript{49} antimicrobial,\textsuperscript{50–52} antifungal,\textsuperscript{53} germination inhibitors\textsuperscript{54}) are being studied from different points of view. Compounds such as tuberculonol,\textsuperscript{55,56} isotuberculonol\textsuperscript{57–59} and analogues (Fig. 1) can be considered as virulence factors (VF) in \textit{Mycobacterium tuberculosis}, a microorganism that causes tuberculosis illness, a major source of morbidity and mortality worldwide.\textsuperscript{60} These compounds could be targets in a new route to anti-infective therapy.\textsuperscript{60,61} Recently, tuberculosinyl-adenosine derivatives have been tested as biomarkers for early diagnosis of tuberculosis.\textsuperscript{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.\textsuperscript{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 \textit{Cistus} studied until now, as can be observed in the reviews of diterpenes by Prof. Hanson,\textsuperscript{6} halimanes have only been found as minor compounds in one of them (\textit{Cistus laurifolius}). In contrast, the other studied plant of that family (\textit{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 tuberculonol adenosine derivatives isolated from \textit{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, antifouling 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 \textit{Mycobacterium tuberculosis}, is a major source of morbidity and mortality worldwide, with almost two million deaths annually.\textsuperscript{60} New drugs for the treatment of tuberculosis are necessary because of the worrying increase in the multidrug and extensively drug resistant...
strains. 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, 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.

It has been observed that tuberculosinol and isotuberculosinol (Fig. 1), produced in vivo by Mycobacterium tuberculosis (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. Thus, both tuberculosinol/isotuberculosinol biosynthetic proteins (Rv3377c and Rv3378c) are essential for the bacteria’s survival inside the macrophage. 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 6-TbAd and 1-TbAd) have been isolated from M. tuberculosis, 1-TbAd and N6-TBAd (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. 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). In fact, they are being evaluated as biomarkers for tuberculosis.
Natural Product Reports

2. Biosynthesis

2.1. Biosynthesis overview

Halimane skeleton diterpenoids are formed by cyclization of geranylgeranyl diphosphate (GGPP), catalyzed by class II diterpene cyclases (DTCs). 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 diphasphate ionization. Several studies have been carried out revealing that the ‘middle’ aspartate in the DXDD motif acts as an acid catalyst.

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 diphasphate 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). Anti-pode 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-13E-en-8-yl diphasphate intermediates (5, 6, 7 and 8) lead to the different copalyl diphasphate labdane precursors by reaction with a base: copalyl diphasphate (CPP, 9), syn-copalyl diphasphate (syn-CPP, 10), ent-copalyl diphasphate (ent-CPP, 11) and syn-ent-copalyl diphasphate (syn-ent-CPP, 12), respectively. Among labdanes, the major ones are ent-CPP 11 (9R,10R) derivatives, followed by the ‘normal’ labdane precursor CPP 9 (9S,10S) derivatives. A lot of class II DTCs that lead to these two precursors are known. However, syn-CPP 10 (9R,10S) derivatives are less common, and only a few syn-ent-CPP 12 (9S,10R) labdane derivatives have been reported. However, this is not the only way the intermediate carbocycles 5–8 can evolve. A rearrangement by sequential 1,2-hydrindene shifts (H–C9 to H–C8) and methyl group migration (C10 to C9) may occur instead of producing the stabilization of intermediate 5–8 (Scheme 2) by proton abstraction. In this way, the cationic halim-13E-en-10-yl diphasphate intermediates 13–16 are respectively produced, and they already contain the halimane backbone.

Those halimene diphasphate cations 13–16 can evolve by different ways (Scheme 3). Each one can lose a proton providing the halimadienyl diphasphates 17 or 18, or rearrangement by hydride shift to form the halimene diphasphate cation 19 followed by proton abstraction to give the halimadienyl diphasphate 20.

The different diastereoisomers forms (21–24), (25–28) and (29–32) correspond to the halimadienyl diphasphates 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 diphasphates 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 such as the dihydrohalimene 33, thus leading to formal
The designation of the relevant class II DTCs as hydratases. Otherwise, although 1,2-hydride and/or methyl shifts do not appear to be concerted, 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. The formation of 3-secohalimenyl derivatives, such as 35 (Scheme 4), can be explained by oxidation of the C3 position of a halimenyl derivative by some specific oxygenase, such as cytochrome P450 monooxygenase. It is notable that plants have vastly expanded numbers of cytochrome P450 monoxygenases in their genomes 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, 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, 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-secohalimenyl 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. 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 Δ5(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...
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.\textsuperscript{22}

### 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.\textsuperscript{16,55} Effectively, \textit{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/isotuberculosin synthase (Rv3378c) from \textit{Mycobacterium tuberculosis} has been reported.\textsuperscript{60} The biosynthesis of tuberculosins is catalyzed by two enzymes: Rv3377c, tuberculosinyldiphosphate (halima-5,13-dien-15-yl) diphosphate synthase, and Rv3378c, tuberculosinol/(R/S)-isotuberculosin synthase. Both proteins are essential for the bacteria survival inside the macrophage where tuberculosins inhibit phagolysosome maturation as well as macrophage phagocytosis.\textsuperscript{57,59,70}

Rv3377c is a DTC classified as class II that transforms GGPP into tuberculosinyldiphosphate (TPP) with a halimane core\textsuperscript{55,93} (Scheme 8), while Rv3378c is a diterpene synthase that converts
TPP into tuberculosinol or (R/S)-isotuberculosinols acting as a phosphatase/isomerase.\textsuperscript{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.\textsuperscript{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.\textsuperscript{71}

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

Recently the incubation of [16,16,16-\textsuperscript{2}H\textsubscript{3}]GGPP with tuberculosinyl diphosphate synthase (Rv3377c) from \textit{M. tuberculosis} allowed the stereochemical course of the cyclization reaction to
tuberculosinyl diphosphate via chair, chair transition state to be followed, confirming the cyclization pathway.95

New studies with class II DTCs have been carried out where the enzyme has been modified in order to check the fundamental role of the DXDD motif (Scheme 9).11 The high importance of that motif was confirmed and even a single residue modification in that motif can disrupt the normal activity of the enzyme. If the H501 residue is substituted in the rice (Oryza sativa) syn-copalyl diphosphate synthase OsCPS4 forming the mutant OsCPS4-H501D, the rearrangement of the initially formed bicycle is produced, obtaining the novel compound syn-HPP (Scheme 9), whose dephosphorylated derivative structure was characterized and its configuration established by NMR.85

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 of the labda-13E-en-8-yl\(^+\) intermediate, yielding the halimane skeleton instead of water capture giving the hydroxylabdane derivative.

Biomimetic rearrangements of simplified labdane diterpenoids have been carried out by treatment with a variety of Lewis and protic acids, demonstrating that those rearrangements involve a series of stereospecific 1,2-alkyl and hydride shifts, producing mainly halimanes or a mixture of different dehydration products depending on reaction conditions. However, further rearrangement to clerodane products was not observed, indicating a high degree of enzymatic control for the \textit{in vivo} formation of these natural products.97 In this work it was shown that the halimane skeleton appears to be inherently more stable than the clerodane structure, as Peters, Tantillo and co-workers demonstrated in their study of quantum chemical calculations.85,98

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 \textit{Halimium viscosum} ent-halimanes and labdanes coexist,17,26,28,99,100 in \textit{Cistus laurifolius} labdanes, ent-labdanes, cis-clerodanes and ent-
halimanes have been isolated,\textsuperscript{101-104} and in plants of genus \textit{Croton}\textsuperscript{44,105-107} (Euphorbiaceae) labdanes, halimanes and clerodanes coexist. In \textit{Haplopappus paucidentatus}\textsuperscript{25} and \textit{Nardophyllum lanatum}\textsuperscript{19} (Compositae) labdanes, halimanes and clerodanes coexist. It seems that in \textit{Halium viscosum} the biosynthetic route to clerodanes is enzymatically interrupted.

\section{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’, ‘anti-pode or enantiO’, 8-\textit{epi} and 8-\textit{epi-ent}. According to the biogenesis of each group, those derivatives in which methyls Me-17 and Me-20 are \textit{cis} to each other are denominated halimanes or \textit{ent}-halimanes, and those in which methyls Me-17 and Me-20 are \textit{trans} to each other are called 8-\textit{epi}-halimanes or 8-\textit{epi-ent}-halimanes (Fig. 3). Derivatives from all these groups of compounds are known, except for 8-\textit{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 ‘\textit{ent}’ series, except for four tetrnorhalimenes and three rearranged halimanes.

\section{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 ‘\textit{ent}’ series (ent-halimanes or 8-\textit{epi-ent}-halimanes) and the remaining 30\% are of the ‘normal’ series (halimanes or 8-\textit{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.

\subsection{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.

\subsubsection{ent-Halim-1(10)-enes.} Chetaphanin I (38), isolated from the roots of \textit{Adenochlaena siamensis}, was the first \textit{ent}-halimane to be discovered\textsuperscript{100} (Fig. 4, Table S1'). Its structure was spectroscopically determined in 1970; however, its absolute configuration remained unknown until 2003,\textsuperscript{109} when its synthesis was described starting from the methyl ester of \textit{ent}-halimic acid (39),\textsuperscript{17,110} a major component of \textit{Halium 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 \textit{Halium}.
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), La Fregeneda, (Salamanca, Spain), Valparaiso, (Zamora, Spain), Celorico da Beira, (Portugal) and San João da Pesqueira, (Portugal).
Fig. 4  ent-Halim-1(10)-enes.
In this group, the Euphorbiaceae, Cista-ceae, Leguminosae, Compositae, Jungermanniaceae, Velloziaceae and Annonaceae plant families have been studied together with marine organisms of genus Spurilla and Agelas. These two compounds were isolated from dichroism (CD) and the structure of (proved to be active as antitumour drugs.

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 polynuclearized 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.

Only eight compounds 79–86 do not have functionalized C18 or C19. Recently, spurullin 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. 8’-Oxo-agelasine C (86) is a novel purine diterpene that was recently isolated from Agelas nakamura and it is the only halimane purine presenting a carbonyl group at adenine C8. 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.

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) and crassin D (64), 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 and 84 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†). Charruoic acid (88) is the only halim-1(10)-ene showing a Δ2 in ring B and was isolated from Ophryosporus charua. The structure of the natural product agelasine C (89) was established by its enantiomer synthesis correcting, in this manner, the original structure proposed by Nakamura and co-workers. Agelasine C (89) was isolated from Okinawan sea sponge Agelas sp. and Agelas citrina and it exerts antifungal activity.

The structure of 87, halima-1(10),14-dien-13:ol, isolated from Plagiocilia barteri, was determined spectroscopically and by comparison with 79. 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 and 91–94 isolated from Vitex trifolia. Previously, vitextrifoloxide F was isolated from Vitex trifolia, but its C13 absolute configuration was not determined. We have noticed that vitextrifoloxide 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 Δ11(10)5. Vitextrifoloxide G (94) presents moderate cytotoxicity and topoisomerase I inhibition activity.

### 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. 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. 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. 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 8-epi-agelasine C (100) was isolated from the marine sponge Agelas mauritiana as an antifouling substance active against macroalgae. 128 The original structure proposed for 8-epi-agelasine C, a halim-1(10)-ene derivative, was corrected to the structure of 8-epi-ent-halim-1(10)-ene derivative for 100 (Fig. 7). Recently, the structure of isoagelasine C (101), isolated from Agelas nakamura, has been described and it shows potent antifungal and moderate antibacterial activity.
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. en-t-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) 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 en-t-halim-5(10)-enes are furo-en-t-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 en-t-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 (111) was corroborated by X-ray; however, its absolute configuration was not determined. As the crassifolins found in Croton crassifolius are included in the en-t-halim-5(10)-ene series, the same absolute configuration is proposed for crassifolin D (111) and it was included in this group. Crassin C (125) 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),143,144 118,158 cracrosin G (122),151 crassifolin M (123),44 and mallotucin B (127) show this functionalization.

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

Fig. 7 8-epi-en-t-Halim-1(10)-enes.
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 pendulifloroserin (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

Crolaeinoids 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

3α-Hydroxy-5(10)-didehydrochilolilide (139) was highly active against a human pancreatic adenocarcinoma cell line at micromolar concentrations76 and 140 shows antitumour activity.77 Formosin A–C (135–137) isolated from Excoecaria formosana were active as antimicrobials,147 and, in addition to crassifolin 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 crolaeinoid 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 densiflorum156 and 152 and 153 isolated from Amphichyris amoenae47 possess functionalization at C3. Allylic groups, as furan 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).51 Agelasine O (156), in which C18 is esterified with 2-carboxy-4-bromopyrrole, is biologically active as an antibacterial and antifungal.51 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 159160 and 162;160 V. trifolia 160161 and 162–166;27,132,162 V. rotundifolia 161–16281,163 and 167;164 Leonurus japonicus 168169 and Marrubium aschersonii 169170) except 158, which was isolated from Stevia gilliesii177 (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.
Compound 161 exerts moderate anti-hyperlipidemic activity and compounds 162 and 166 are cytotoxic against HCT 116 human colon carcinoma cell line.

4.2.4. **8-epi-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* (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. 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*, 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.

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, the first halimane isolated from plants of genus *Plectranthus*, have been synthesized and their antibacterial and antitumour activities have been studied.

The side chain can be saturated on 176 (isolated from *Haplopappus paucidentatus*), 177 and 178 (Relhania corymbosa and *R. squarrosa*), unsaturated on 175 (*Plectranthus ornatus*) and 179 (Baccharis salicifolia) or with furan on 180 (*Croton dichogamus*) and 181 (*Chiliotrichum rosmarinifolium* and *Nardophyllum bryoides*). 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.

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

4.3.2. **Halim-5-enes.** This is the biggest halimenes group 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) and isotuberculosinol (also known as nosyberkol; 183) are found among them. Nosyberkol was isolated for the first time in 2004 from the Nosy Be Islands (Madagascar) sponge *Raspailia* sp. as a single stereoisomer. 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*. None of the studies done detected the presence of 182 or 183 from the cultured cells of 12 nonpathogenic
It has been observed that tuberculinosol (182) and isotuberculinosol (183) (in a 1 : 1 ratio, with 183 being a mixture of the diastereomers 13R-isotuberculinosol (183R) and 13S-isotuberculinosol (183S) in a 1 : 3 ratio) inhibit phagolysosome maturation and macrophage phagocytosis in human-like cells. The structures of tuberculinosol (182) and isotuberculinosol (183) have been corroborated and their absolute configuration established by total synthesis. Recently, two new natural products derived from tuberculinosol have been isolated and characterized: 1-TbAd (200) and N6-TbAd (201). These two tuberculinosol 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. From Acalypha macrostachya the 7-oxo derivatives 193 and 194 were isolated. Micromonohalimanes A and B (198 and 199, from Micromonospora sp.), which present antibacterial activity, have been characterized. Micromonohalimane B (199) is the only halimane which includes a chlorine atom in its structure.

In this group, two plants of the Compositae family have been studied. From Koanophyllum conglobatum kaonophylic acids 185, 192, 196 and 197, with carboxylic function at C18, were isolated, and from Haplopappus pulchellus 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 ECD of their 3-p-bromobenzoate derivatives. This compound possesses antimicrobial activity. From Acalypha macrostachya the 7-oxo derivatives 193 and 194 were isolated.

Micromonohalimanes A and B (198 and 199, from Micromonospora sp.), 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†). Viteagusin A (202) and viterofolin C–E (203–205) 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.
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*), 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* and *Jungermannia truncata*, and *Baccharis salicifolia*, respectively), the most usual functionalization is the furan (210 and 211 from *Dysidea amblia*, 212 from *Croton crassifolius* and 213 and 214 from *Chiliotrichum rosmarinifolium*) or butanolide fragments (215 and 216 from *Heteroscyphus coalitus* and *Polyalthia longifolia* respectively). The stereoisomers ambliol B (210) and ambliol C (211) were isolated from *Dysidea amblia*, 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. Compound 209 is a germination inhibitor and the structure of compound 214 was corroborated by synthesis.

Fig. 13 Halim-5-enes.
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, 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 α₁ 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 that contains a butenolide in that chain. Frequently C20 is a carboxylic acid that lactonizes with a hydroxyl group at C12, 225–230, 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 (Δ⁴(18)) 231–232 or tetrasubstituted one (Δ⁴) 220–230.

These compounds are found in the plant families Leguminoseae (from Tessmannia densiflora 220–223), Compositae (Chiliotrichum rosmarinifolium 224–226, Nardophyllum lana-tum 224–228 and 232, and Nardophyllum bryoides 225–226 and 230) and Geocalycaceae (Heteroscyphus coalitus 231). Tessmannic acid (220) and its methyl ester (221) exhibit antibacterial and antifungal activity. Butanolides 225, 226 and 230 are biologically active as antitumour agents.

The known norhalimenes (233–245) can be mono-, di-, tri- and tetra-norhalimene derivatives (Fig. 16).
Compounds such as isoteucripin (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 jatrophaoides*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),17,18,192 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 euplectelloides*,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.

- Scopariusins A–C (246–248), isolated from *Isodon scoparius*,197,198 are characterized for ring B expansion, by incorporation of C11. The structure and absolute configuration of scopariusin A (246) were confirmed by biomimetic synthesis91 from isoscoparin 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...
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 ± 2.5 μM.

- Dytesins 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 1–J (261 and 262, from Raspailia sp.$^{9}$) are compounds that can be considered

Fig. 17 Rearranged halimanes.
rearranged halimanes or rearranged clerodanes because C19 is bonded to C4 and C5 forming a cyclopropane ring. Dytestinins 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 Δ2. 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 a consequence of a ring expansion. All of these compounds belong to the ‘enanti’ series except viterofolins A–B (253–254) and scapanalide B (283), which belong to the ‘normal’ series. Compounds 263 (Portulaca cv Jele199) and 264–269 (isolated from Portulaca pilosa200,201 and Portulaca grandiflora202) have an acyclic side chain, while 270–283 (isolated from Dodonaea viscosa203 Conyza scabrida272–273 and 277–282,204 Aparistium cordatum 274,205 Croton cortesianus 275206 and Scapania parva 283207) possess furan or butenolutes. 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, Δ11, and a hydroxyl group at C-15, a carboxyl group at C-18 and a double bond Δ16 in the decalin system. All of 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.211–214 (4) Sesterterpenolides and glycerophospholipids hybrid compounds.215 (5) Rearranged derivatives: ent-labdanes,216 abeicacinonas217 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)222 were synthesized from ent-halimic acid methyl ester (39) using methyl ketone 285 as an intermediate223,224 (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 chemo-selective oxidation and cleavage of the Δ13 double bond with m-CPP and periodic acid gives the required ketone 285 in very good yield (57% six steps).

Bestmann methodology225 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 silyleneether with OsO4 affords the hydroxyketone 286 in excellent yield. Reaction of the hydroxyketone 286 with Ph3P=O=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 $\Delta^{16(10)}$ 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 TBDMSI followed by reaction of the intermediate 2-triallylsilyloxyfuran with m-CPP 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)].223

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,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).14 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.
ent-Halic acid: versatile starting material for the synthesis of bioactive and other interesting compounds.
Oxidation of 288 with Na₃CrO₄ 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 acetylderivatives 295 and 296. The careful hydrolysis of 295 and 296 in acid medium leads to intermediate ketones that produce 297 and lactone 298 by alkalyne 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). Tetranorderivative 299 was obtained by Baeyer–Villiger reaction of intermediate 289 as the key step. Protection
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. 125 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-workers from the marine sponge Agelas mauritiana as an antifouling substance active against macroalgae.

Due to the interest of epi-Agelasine C as an antifouling agent125 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.

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

Scheme 13

| Reaction | Conditions |
|----------|------------|
| (a) OsO₄, NMO, t-BuOH/THF/H₂O (7 : 2 : 1); | (b) Pb(OAc)₄, C₆H₆ (94%, two steps); |
| (c) Na₂CrO₄, Ac₂O/AcOH, NaOAc, C₆H₆ (64%); | (d) UHP/TFAA (61%); |
| (e) ethylene glycol, p-TsOH, C₆H₆; | (f) 3% K₂CO₃ in MeOH; |
| (g) PDC, DMF (61%, three steps); | (h) 3-bromofuran, nBuLi, (1 : 1), −78 °C; |
| (i) TPAP/NMO, (99%, two steps); | (j) p-TsOH, acetone (72%); |
| (k) m-CPBA, CH₂Cl₂ (92%); | (m) p-TsOH, acetone or HClO₄, 30%. |

Scheme 14

| Reaction | Conditions |
|----------|------------|
| (a) DHP, p-TsOH, C₆H₆ (98%); | (b) LAH, Et₂O, 0 °C and then rt (99%); |
| (c) TPAP, NMO (94%); | (d) diethylene glycol, NH₂NH₂$\text{H}_2\text{O}$, KOH, 175–230 °C (81%); |
| (e) p-TsOH, MeOH (81%); | (f) CBr₄, PPh₃, DCM (76%); |
| (g) DMA, 50 °C; | (h) Zn, MeOH, H₂O, AcOH (13%, two steps). |
using Huang-Minlon methodology to give 305. Deprotection of the primary hydroxyl group followed by treatment with CBr₄ in the presence of PPh₃ gave the required bromodervative 306 (46%, six steps). Alkylation of methoxadenine 307 with the bromodervative 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-agelasime C, thus its proposed structure 304 (Fig. 19) should be revised. On the other hand, when the ¹H and ¹³C NMR spectra of 302 were compared with those for the proposed structure of (−)-agelasime C (303), the two pairs of spectra were identical. However, the optical rotatory power of 302 and natural (−)-agelasime C were similar in absolute value but had a different sign. So, it should be concluded that the structure of the natural product (−)-agelasime C should be corrected to structure 89 (Fig. 20), which is the enantiomer of the synthesized product (+)-agelasime C (302, Scheme 14).

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

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

The natural product structure of 3α-hydroxy-5β,10β-epoxychililolide (214) was corroborated by the synthesis of the racemic diterpene (Scheme 15). 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 BF₃·Et₂O 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 NaBH₄ 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 β3-hydroxy derivative 315c, so the natural product 214 is the 3α-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 (+)-agelasime A (217) and (+)-agelasime B (218)

Ohba and co-workers synthesized the diterpene-adenine derivatives (+)-agelasime A (217) and (+)-agelasime 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 (+)-agelasime A and (±)-agelasime B. In the asymmetric synthesis, the authors used (+)-trans-dihydrocarvone (317) as the starting material. Ozonolysis in methanol of 317 and subsequent treatment with FeSO₄·Cu(OAc)₂ (ref. 229 and 230) led to (+)-318, which was transformed into (+)-319 by MeLi treatment followed by PCC oxidation. Reaction of (+)-319 with vinylmagnesium bromide in the presence of CuBr and Me,SiCl 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. 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-
butenoic acid ethyl ester (323) afforded the \( \alpha,\beta \)-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 (+)-agelasiamine A. Reaction of (+)-326 with NaNH4 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). 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 BF₃·Et₂O leads mainly to a halimane derivative, which leads to the hydroxy acid 328 by hydrolysis with NaOH in MeOH. Esterification of 328 with Mel 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 Mel in KOH-acetone led to 246, whose properties were identical to those of the natural product scopariusin A. In this manner, the structures and absolute configurations of isoscoparin N (143) and rearranged *ent*-halimane scopariusin A (246) were confirmed.

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.

The tuberculosinols tuberculosinol (182) and isotuberculosinol (183; 13R and 13S) are VFs from *M. tuberculosis*. 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.

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
structure of nosyberkol (183; isolated from the Red Sea sponge Raspailia sp.72 extracts), also known as isotuberculosinol.

5.5.1. Snider’s synthesis of tuberculosinol (182) and isotuberculosinol (183). The synthesis by Snider and co-workers 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 NH₃/THF/EtOH, then by addition of vinylmagnesium bromide provides 183 as a mixture of stereoisomers. The spectroscopic data obtained from the synthetic compound 183 were identical with those reported for both natural nosyberkol and isotuberculosinol.

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.

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, the key step is an exo-selective Diels–Alder reaction. Cycloaddition of the known diene 329 and ethyl tiglate

Scheme 19  (a) Ethyl tiglate, neat, 160 °C, (71%) (2 : 1 exo/endo); (b) LAH, THF, (56%); (c) SO₂, pyridine, NE₃, CH₂Cl₂–DMSO (86%); (d) acetone, NaHMDS, THF (87%); (e) 10 mol% Rh(PPh₃)₃Cl, HSiEt₃, CH₂Cl₂ (83%); (f) vinylmagnesium bromide, THF (93%); (g) Ph₃PCH₂Br, KHMDS, THF (91%); (h) 9-BBN, THF; then 10 mol% PDCl₃(dpdpf), Ph₃As, CsCO₃, 338, DMF (73%); (i) 20 mol% CuCl₂, acetone (20%).

Scheme 20  (a) Me₂AlCl, CH₂Cl₂ (59%, ~10 : 1 exo/endo); (b) 1) n-BuLi, Et₂SH, THF; 2) LAH, THF; 3) TPAP, NMO, CH₂Cl₂ (87%); (c) 1) NaHMDS, acetone, THF; 2) RhCl(PPh₃)₃, Et₂SiH, CH₂Cl₂; 3) (EtO)₂POCH₂COOEt, NaH, THF; (d) DIBAL, CH₂Cl₂ (55%); (e) NCS, Me₂S, CH₂Cl₂ (quantitative); (f) NaI, DMF, rt (76%); (f) Me₂NH, H₂O, rt (quantitative).
followed by ester reduction and primary alcohols separation through purification by supercritical fluid chromatography provides the enantiopure material (>99% ee), that by Parikh and Doering oxidation conditions leads to \(\text{1-TbAd}^{32}\). An aldol condensation with acetone sodium enolate and conjugate reduction with Wilkinson’s catalyst allowed them to achieve ketone \(\text{336}\). Vinylmagnesium bromide addition provides \(\text{183}\) as a tertiary alcohol mixture. The spectroscopic data obtained from the synthetic compound \(\text{183}\) were identical with those reported for both natural nosyberkol and isotuberculosinol.

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

5.6. 1-Tuberculosinyl adenosine \((1-\text{TbAd}; \text{200})\) and \(\text{N}^6\)-tuberculosinyl adenosine \((\text{N}^6-\text{TbAd}; \text{201})\) syntheses

To date, there is no reliable and fast routine test for the diagnosis of infections caused by \(\text{M. tuberculosis}\), 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 \(1-\text{TbAd}; \text{200}\) and \(\text{N}^6\)-tuberculosinyl adenosine \((\text{N}^6-\text{TbAd}; \text{201})\), have been found. These tuberculosinol derivatives can be used as \(\text{Mycobacterium tuberculosis}\) (Mt) specific biomarkers. The \(\text{N}^6\)-\text{TbAd} \((\text{201})\) isomer appears that can be generated \textit{in vivo} by \(\text{M. tuberculosis}\), following a Dimroth rearrangement of \(1-\text{TbAd} \text{ (200)}\). Recently, \(1-\text{TbAd} \text{ (200)}\) and \(\text{N}^6\)-\text{TbAd} \((\text{201})\) syntheses have been carried out (10 and 11 steps, respectively) using as a key step a chiral auxiliary-aided Diels–Alder reaction \((\text{Scheme 20})\). This Diels–Alder reaction gives \(\text{339} \text{ (98% ee, 59%, ~10:1 exo/endo)}\), which is transformed into tuberculosinol \(\text{182}\) in seven steps. \(1-\text{TbAd} \text{ (200)}\) was obtained in two steps from \(\text{182}\) through the chloride derivative \(\text{340}\) and \(\text{N}^6\)-\text{TbAd} \((\text{201})\) was achieved later from \(\text{200}\) 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, \(\text{ent-HPP}\) and \(\text{syn-ent-HPP}\) 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 \(\text{182}\). The production of isotuberculosinol, tuberculosinol and analogues by \(\text{M. tuberculosis}\) 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 \textit{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 \(\text{ent-halimic acid}\) \((\text{39})\) and \(11\text{R}-\text{acetoxy-ent-halima-5,13E-dien-15-oic acid}\) \((\text{175})\), 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

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9. Notes and references

1 D. E. Cane and H. Ikeda, \textit{Acc. Chem. Res.}, 2012, \textit{45}, 463–472.
2 M. Jia and R. J. Peters, \textit{Org. Biomol. Chem.}, 2017, \textit{15}, 3158–3160.
3 J. W. Blunt, B. R. Copp, R. A. Keyzers, M. H. G. Munro and M. R. Prinsep, \textit{Nat. Prod. Rep.}, 2014, \textit{31}, 160–258.
4 B. M. Fraga, \textit{Nat. Prod. Rep.}, 2013, \textit{30}, 1226–1264.
5 J. R. Hanson, \textit{Nat. Prod. Rep.}, 2016, \textit{33}, 1227–1238.
6 J. R. Hanson, \textit{Nat. Prod. Rep.}, 2017, \textit{34}, 1233–1243.
7 L. Wang, B. Yang, X.-P. Lin, X.-F. Zhou and Y. Liu, \textit{Nat. Prod. Rep.}, 2013, \textit{30}, 455–473.
8 R. A. Hill and J. D. Connolly, \textit{Nat. Prod. Rep.}, 2015, \textit{32}, 273–327.
9 J. Buckingham, \textit{Dictionary of Natural Products on DVD, CRC, Boca Raton, FL}, 2007.
10 D. W. Christianson, \textit{Chem. Rev.}, 2017, \textit{117}, 11570–11648.
11 S. Prisic, J. Xu, R. M. Coates and R. J. Peters, \textit{ChemBioChem}, 2007, \textit{8}, 869–874.
12 K. U. Wendt and G. E. Schulz, \textit{Structure}, 1998, \textit{6}, 127–133.
13 J. MacMillan and M. H. Beale, \textit{Comprehensive Natural Products Chemistry: Isoprenoids Including Carotenoids and Steroids}, Elsevier, 1999, vol. 2.
14 A. T. Merritt and S. V. Ley, \textit{Nat. Prod. Rep.}, 1992, \textit{9}, 243–287.
15 R. Li, S. L. Morris-Natschke and K.-H. Lee, \textit{Nat. Prod. Rep.}, 2016, \textit{33}, 1166–1226.
| Reference                                                                 | Journal                                                                 | Year | Page Numbers   |
|--------------------------------------------------------------------------|-------------------------------------------------------------------------|------|----------------|
| 208 I. S. Marcos, J. L. Gonzalez, M. J. Sexmero, D. Diez, P. Basabe, D. J. Williams, M. S. J. Simmonds and J. G. Urones | *Tetrahedron Lett.*, 2000, 41, 2553–2557.                               | 2000 | 2553–2557      |
| 209 I. S. Marcos, F. A. Hernández, M. J. Sexmero, D. Diez, P. Basabe, A. B. Pedrero, N. García, F. Sanz and J. G. Urones | *Tetrahedron Lett.*, 2002, 43, 1243–1245.                               | 2002 | 1243–1245      |
| 210 I. S. Marcos, A. B. Pedrero, M. J. Sexmero, D. Diez, P. Basabe, F. A. Hernández, H. B. Broughton and J. G. Urones | *Synlett*, 2002, 105–109.                                              | 2002 | 105–109        |
| 211 I. S. Marcos, M. A. Escola, R. F. Moro, P. Basabe, D. Diez, F. Sanz, F. Mollinedo, J. de la Iglesia-Vicente, B. G. Sierra and J. G. Urones | *Bioorg. Med. Chem.*, 2007, 15, 5719–5737.                              | 2007 | 5719–5737      |
| 212 I. S. Marcos, A. B. Pedrero, M. J. Sexmero, D. Diez, P. Basabe, N. García, R. F. Moro, H. B. Broughton, F. Mollinedo and J. G. Urones | *J. Org. Chem.*, 2003, 68, 7496–7504.                                    | 2003 | 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.                                              | 2016 | 47             |
| 214 I. S. Marcos, M. J. Sexmero, F. Á. Hernández, M. Corrales, P. Basabe, D. Diez and J. G. Urones | *Molecules*, 2006, 11, 792–807.                                          | 2006 | 792–807        |
| 215 I. S. Marcos, N. García, M. J. Sexmero, F. A. Hernández, M. A. Escola, P. Basabe, D. Diez and J. G. Urones | *Tetrahedron*, 2007, 63, 2335–2350.                                     | 2007 | 2335–2350      |
| 216 I. S. Marcos, B. Martínez, M. J. Sexmero, D. Diez, P. Basabe and J. G. Urones | *Synthesis*, 2006, 3865–3873.                                           | 2006 | 3865–3873      |
| 217 I. S. Marcos, A. Conde, R. F. Moro, P. Basabe, D. Diez and J. G. Urones | *Tetrahedron*, 2010, 66, 8280–8290.                                     | 2010 | 8280–8290      |
| 218 I. S. Marcos, M. A. Escola, R. F. Moro, P. Basabe, D. Diez, F. Mollinedo and J. G. Urones | *Synlett*, 2007, 2017–2022.                                             | 2007 | 2017–2022      |
| 219 I. S. Marcos, R. F. Moro, I. Costales, P. Basabe, D. Diez, F. Mollinedo and J. G. Urones | *Tetrahedron*, 2012, 68, 7932–7940.                                     | 2012 | 7932–7940      |
| 220 I. S. Marcos, R. F. Moro, I. Costales, P. Basabe, D. Diez, F. Mollinedo and J. G. Urones | *Tetrahedron*, 2013, 69, 7285–7289.                                     | 2013 | 7285–7289      |
| 221 I. S. Marcos, R. F. Moro, I. Costales, M. A. Escola, P. Basabe, D. Diez and J. G. Urones | *Tetrahedron*, 2009, 65, 10235–10242.                                   | 2009 | 10235–10242    |
| 222 I. S. Marcos, R. F. Moro, I. Costales, P. Basabe, D. Diez, A. Gil, F. Mollinedo, F. Pérez-de la Rosa, E. Pérez-Roth and J. M. Padrón | *Eur. J. Med. Chem.*, 2014, 73, 265–279.                                | 2014 | 265–279        |
| 223 H. J. Bestmann | *Angew. Chem., Int. Ed.*, 1977, 16, 349–364.                            | 1977 | 349–364        |
| 224 J. Boukouvalas and N. Lachance | *Synlett*, 1998, 31–32.                                                | 1998 | 31–32          |
| 225 H. Rosemeyer | *Chem. Biodiversity*, 2004, 1, 361–401.                                 | 2004 | 361–401        |
| 226 M. Ohba, K. Iizuka, H. Ishibashi and T. Fujii | *Tetrahedron*, 1997, 53, 16977–16986.                                   | 1997 | 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.                              | 1995 | 6101–6104      |
| 228 M. Ohba, N. Kawase and T. Fujii | *J. Am. Chem. Soc.*, 1996, 118, 8250–8257.                              | 1996 | 8250–8257      |
| 229 S. L. Schreiber | *J. Am. Chem. Soc.*, 1980, 102, 6163–6165.                              | 1980 | 6163–6165      |
| 230 G. Solladie and J. Hutt | *J. Org. Chem.*, 1987, 52, 3560–3566.                                   | 1987 | 3560–3566      |
| 231 H. Iio, M. Monden, K. Okada and T. Tokoroyama | *J. Chem. Soc., Chem. Commun.*, 1987, 358–359.                           | 1987 | 358–359        |
| 232 J. R. Parikh and W. v. E. Doering | *J. Am. Chem. Soc.*, 1967, 89, 5505–5507.                               | 1967 | 5505–5507      |
| 233 I. Ojima and T. Kogure | *Tetrahedron Lett.*, 1972, 13, 5035–5038.                               | 1972 | 5035–5038      |