The Methylene-Cycloalkylacetate (MCA) Scaffold in Terpenyl Compounds with Potential Pharmacological Activities

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

Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad de Salamanca. Plaza de los Caídos 1-5, 37008 Salamanca, Spain; ignaciotobal@usal.es (I.E.T.); alexmaron@usal.es (A.M.R.); rfm@usal.es (R.F.M.); ddm@usal.es (D.D.)

* Correspondence: ismarcos@usal.es; Tel.: +34-923-294-482

† These authors have contributed equally to this work.

Abstract: Recently, the methylene-cycloalkylacetate (MCA) scaffold has been reported as a potential pharmacophore for neurite outgrowth activity. In this work, natural diterpenes that embed MCA fragments are reviewed, as they are major components of Halimium viscosum: ent-halimic acid, the prototype for these bioactive compounds. Herein, structures, sources, and activities for the natural diterpenes, as well as their synthetic derivatives of interest, are reviewed.

Keywords: methylene-cycloalkylacetate; MCA; ent-halimic acid; halimanes; neurotrophic

1. Halimanes Containing the MCA Fragment

Recently, molecules containing methylene-cycloalkylacetate (MCA) fragments (Figure 1) have been reported to show very interesting neurotrophic properties [1]. The MCA scaffold can be observed in many easily available terpenes of natural origin and synthetic derivatives, many of which show interesting pharmacological activities [2–6].

Figure 1. The methylene-cycloalkylacetate (MCA) scaffold for novel neurotrophic agents and ent-halimic acid, the halimane reference compound.
Although different terpenoids containing the MCA scaffold have been reported, in this work only the natural diterpenoids will be reviewed. Among diterpenoids containing the MCA fragment, halimane is the most structurally diverse and numerous family.

As the MCA moiety can be considered as a pharmacophore for neurotrophic activity, these natural diterpenoids could be understood as novel neurotrophic lead compounds, but show other interesting biological (e.g., antitumor and antifeedant) activities [7,8].

Firstly, halimane diterpenoids, with an MCA fragment embedded, with eventually potential neurotrophic activity and other biological activities are discussed. They have been classified into three groups according to the annular double bond found: in Ring A, Group I (Figure 2), in Ring B, Group II (Figure 3), or, as secoderivatives, in Group III (Figure 4). The compounds of each group have been included in Tables 1–3, respectively, where the natural source, the biological activity (if studied), and references are given. As can be observed in Group I (Table 1), nearly all are ent-halimanes and degraded compounds such as di-, tri-, and tetranorderivatives. Group II contains halimanes from the normal and enantiomeric series. All the secoderivatives, the Group III compounds, correspond to the enantiomeric series. All compounds have been isolated from plants of different families, and only two of them have been found in microorganisms—bacteria of the genus Micromonospora.
Table 1. Halim-1(10)-enes.

| Halim-1(10)-enes                                                                 | Natural Source                                                                 | Activity                                                                 | Ref. |
|---------------------------------------------------------------------------------|-------------------------------------------------------------------------------|------------------------------------------------------------------------|------|
| Chettaphanin I, 1                                                               | Adenochlaena siamensis (Syn. of Cladogynos orientalis)                        | H. viscosum (V.A.)                                                     | [5,9–13]|
| Ent-halimic acid methyl ester, 2                                                 | Croton crassifolius                                                          | H. viscosum (V.A.)                                                     | [14,15]|
| 3                                                                               | Halimium viscosum (Villarino de los Aires, V.A.)                             | H. viscosum (V.A.)                                                     | [14,15]|
| 4                                                                               |                                                                                | H. viscosum (V.A.)                                                     | [14]  |
| 5                                                                               |                                                                                | H. viscosum (V.A.)                                                     | [14]  |
| 6                                                                               |                                                                                | H. viscosum (V.A.)                                                     | [14]  |
| 7                                                                               |                                                                                | H. viscosum (V.A.)                                                     | [14]  |
| 8                                                                               | Hymenaea courbaril                                                           | H. viscosum (V.A.)                                                     | [14]  |
| 9                                                                               |                                                                                | H. viscosum (V.A.)                                                     | [14]  |
| 10                                                                              |                                                                                | H. viscosum (V.A.)                                                     | [15]  |
| 11                                                                              |                                                                                | H. viscosum (V.A.)                                                     | [15]  |
| 12                                                                              |                                                                                | H. viscosum (V.A.)                                                     | [17]  |
| 13                                                                              |                                                                                | H. viscosum (V.A.)                                                     | [18]  |
| 14                                                                              |                                                                                | H. viscosum (V.A.)                                                     | [18]  |
| 15                                                                              |                                                                                | H. viscosum (V.A.)                                                     | [14]  |
| 16                                                                              |                                                                                | H. viscosum (V.A.)                                                     | [14]  |
| 17                                                                              |                                                                                | H. viscosum (V.A.)                                                     | [18,19]|
| 18                                                                              |                                                                                | H. viscosum (V.A.)                                                     | [18,19]|
| 19                                                                              |                                                                                | H. viscosum (V.A.)                                                     | [18]  |
| 20                                                                              |                                                                                | H. viscosum (V.A.)                                                     | [18]  |
| 21                                                                              |                                                                                | H. viscosum (V.A.)                                                     | [18]  |
| 13R-Hydroxy-ent-halima-1(10),14-dien-18-oic acid, 22                             | Hymenaea courbaril                                                           | A2780 human ovarian cell line (IC_{50} > 40 µg/mL)                     | [20]  |
| 25,13R-Dihydroxy-ent-halima-1(10),14-dien-18-oic acid, 23                        | H. courbaril                                                                 | Not cytotoxic (HepG2, SGC-7901 and K562)                                | [12]  |
| 2-Oxo-13R-hydroxy-ent-halima-1(10),14-dien-18-oic acid, 24                        | H. courbaril                                                                 | Not cytotoxic (HL-60, and A549)                                       | [22]  |
| Crassifoliusin A, 26                                                             | H. viscosum (Celorico da Beira, C.B.)                                       | Not cytotoxic (NCI-H187), not antitubercular (Mycobacterium tuberculosis H_{37}Ra) | [13]  |
| Crassin D, 27                                                                    | Crassifolius                                                                 |                                                                          |      |
| 28                                                                               | Cladogynos orientalis                                                         |                                                                          |      |
| 29                                                                               | Hymenaea courbaril                                                           |                                                                          | [16]  |
| 30                                                                               | Halimium viscosum (La Fregeneda, L.F.)                                       |                                                                          | [23]  |
| 31                                                                               | H. viscosum (V.A. and L.F.)                                                   |                                                                          | [14,23]|
| 13R-Methyl-15-methoxy-ent-halim-1(10)-en-18-oate, 32                             | H. viscosum (L.F. and C.B.)                                                  |                                                                          | [23,24]|
Table 1. Cont.

| Natural Source                  | Activity                                      | Ref.     |
|--------------------------------|-----------------------------------------------|----------|
| Halim-1(10)-enes               |                                               |          |
| 33                             | H. viscosum (L.F. and C.B.)                   | [24,25]  |
| 34                             | H. viscosum (L.F. and C.B.)                   | [24]     |
| 35                             | Hymenaea courbaril                            | [16]     |
| 36                             | H. viscosum (C.B.)                            | [24]     |
| 37                             | H. viscosum (C.B.)                            | [24]     |
| Crassifolin C, 38              |                                               | [11]     |
| 39                             | H. viscosum (L.F. and C.B.)                   | [23,26]  |
| 18-Hydroxy-ent-halima-1(10),13E-dien-15-oic acid, 40 | Hymenaea stigonocarpa                  | [27]     |
| 41                             | Eupatorium turbinatum (Syn. of Chromolaena bigelovii) | [28]     |
| 42                             | Halimium viscosum                             | [15,29]  |
| 43                             | H. viscosum                                   | [17]     |
| 44                             | H. viscosum                                   | [15,29]  |
| 45                             | H. viscosum                                   | [29]     |
| 46                             | H. viscosum                                   | [29]     |
| 47                             | Vellozia stipitata                            | [30]     |

Table 2. Halim-5-enes.

| Natural Source                  | Activity                                      | Ref.     |
|--------------------------------|-----------------------------------------------|----------|
| Ent-halim-5-enes                |                                               |          |
| 11R-Acetoxy-ent-halima-5,13E-dien-15-oic acid, 48 | Plectranthus ornatus                  | Enterococcus faecalis ATCC 51,299 MIC 15.63 | [31,32] |
| 49                             | Haploppus paucidentatus (Syn. of H. glutinosus) |              | [33]     |
| 50                             | R. squarrosa (Syn. of Oedera squarrosa)       | Germination inhibition of Panicum miliaceum (EC50 1.9/mM) and Raphanus sativum (EC50 4.6/mM) | [34]     |
| 51                             | R. corymbosa                                  | Murine lung adenocarcinoma cells (MLAC) LM3 (ID50 40 µM) | [34]     |
| Salicifolic acid, 52            | Baccharis salicifolia (Syn. of B. salicina)   | Germination inhibition of P. miliaceum (EC50 1.9/mM) and R. sativum (EC50 4.6/mM) | [34]     |
| Crothalimene B, 53             | Croton dichogamus                             | Murine lung adenocarcinoma cells (MLAC) LM3 (ID50 40 µM) | [34]     |
| 3α-Hydroxy-5,6-didehydrochiliolide, 54 | Chliostichum rosmarinifolium | Human ductal pancreatic carcinoma (HDPC) PANC1 (ID50 0.34µM) | [37,38]  |
| Teupolin VIII, 55              | Teucrium polium                               | Human hepatoblastoma cells HepG2 (cell viability inhibition, 6.86% 100mM) | [39,40]  |
| Teupolin VII, 56               | T. polium                                     | HPC HepG2, CVI, 6.35% 100mM | [39]     |
Table 2. Cont.

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|--------------------------|---------|

| **Halim-5-enes** | **Natural Source** | **Activity** | **Ref.** |
|------------------|--------------------|--------------|---------|
| Koanophyllonic acid B, 57 | Koanophyllon conglobatum | | [41] |
| 58               | Haplopappus pulchellus | | [42] |
| 59               | H. pulchellus        | | [42] |
| 60               | H. pulchellus        | | [42] |
| 61               | H. pulchellus        | | [42] |
| 62               | H. pulchellus        | | [42] |
| 63               | H. pulchellus        | | [42] |
| Koanophyllonic acid A, 64 | Koanophyllon conglobatum | | [41] |
| 65               | Acalypha macrostachya | | [43] |
| 66               | A. macrostachya      | | [43] |

| 67               | Colophospermum mopane | | [44] |

| Koanophyllonic acid D, 68 | Koanophyllon conglobatum | | [41] |
| Koanophyllonic acid C, 69 | K. conglobatum | | [41] |
| Micromonohalimane A, 70 | Micromonospora sp. | | [45] |
| Micromonohalimane B, 71 | Micromonospora sp. | | [45] |

| **8-Epi-halim-5-enes** | **Natural Source** | **Activity** | **Ref.** |
|------------------------|--------------------|--------------|---------|
| Viteagnusin A 72       | Vitex agnus-castus | | [46] |
| Viterofolin D, 73      | V. rotundifolia    | | [47] |
| Viterofolin E, 74      | V. rotundifolia    | | [47] |
| 75                     | Vellezia stipitata | | [48] |
| 76                     | V. flavicans (Syn. of V. squamata) | | [48] |
| 77                     | V. flavicans       | | [48] |

Klebsiella pneumoniae ATCC 13,883 (MIC 62.5 µg/mL)  
Escherichia coli ATCC 8739 (MIC 125 µg/mL)  
Enterococcus faecalis ATCC 29,212 (MIC 62.5 µg/mL)  
Staphylococcus aureus ATCC 25,923 (MIC 93.7 µg/mL)  
Methicillin-resistant Staphylococcus aureus (MRSA) ATCC 33,591 (MIC > 200 µg/mL)  
(MRSA) ATCC 33,591 (MIC 40 µg/mL)
Table 3. Secohalimanes and 4-enes.

| Secohalimanes                              | Natural Source                        | Activity                                                                 | Ref.        |
|--------------------------------------------|---------------------------------------|--------------------------------------------------------------------------|-------------|
| Tessmannic acid, 78                         | *Tessmannia densiflora*               | Larvicidal activity *Anopheles gambiae* (LC₅₀ 48 h, 34 ppm)             | [49,50]     |
| Tessmannic acid methyl ester, 79            | *T. densiflora*                       | Larvicidal activity *Anopheles gambiae* (LC₅₀ 48 h, 92 ppm)             | [49,50]     |
|                                            |                                       |                                                                          | [49,50]     |
| Secochiliotrin methyl ester, 82             | *Chiliotrichum rosmarinifolium*       |                                                                          | [37]        |
|                                            |                                       |                                                                          |             |
| Secochiliolide acid, 83                     | *Nardophyllum lanatum*                | (MLAC) LM3 (ID₅₀ 14.1 µM)                                               | [37,38]     |
|                                            |                                       | (HDPC) PANC1 (ID₅₀ 31.6 µM)                                              |             |
| Secochiliolide acid methyl ester, 84        | *Chiliotrichum rosmarinifolium*       |                                                                          | [37]        |
| 19-Hydroxysecochiliolide acid, 85           | *Nardophyllum bryoides*               |                                                                          | [37]        |
| 19-Hydroxysecochiliolide acid methyl ester, 86| *Teucrium viscidum*                   | (MLAC) LM3 (ID₅₀ 20.0 µM)                                               | [38]        |
| Secochiliolide aldehyde, 87                 | *Mallotus repandus*                   | (HDPC) PANC1 (ID₅₀ 25.1 µM)                                              |             |
|                                            |                                       |                                                                          |             |
| Teucvin (Mallotucin A), 89                  | *Teucrium chamaedrys*                 |                                                                          | [51–55]     |
1.1. Group I: The Halim-1(10)-Enes Group

This group is composed of 46 ent-halimanes 1–46 and a halimane 47 (Figure 2). All of them have a carboxylic function at C18, except 40 and 41 where the function appears at C19 as a hydroxyl group or a carbocyclic acid. This group contains compounds such as chettaphanin I, 1, the first halimane known, and ent-halimic acid, characterized as its methyl ester, 2, from which the group attains its name, and which has been used as a starting material to establish the absolute configuration of chettaphanin I, 1, and for the synthesis of many ent-halimanes, as will be discussed later on.

1.2. Group II: The Halim-5-Enes Group

This group contains 30 compounds (Figure 3). Nine of them (48–56) belong to the enantiomeric series called ent-halimanes, two of which are nor-ent-halimanes, and the rest of the halimanes belong...
to the normal series (57–77), among which six 8-epi-halimanes (72–77) can be found, where three are
tetranorderivatives (75–77).

Figure 3. Halimane diterpenoids with the annular double bond in Ring B.
1.3. Group III: Secohalimanes and 4-Enes Derivatives

All secohalimanes (78–89) that contain the MCA fragment are 3-seco derivatives (Figure 4). All of them contain a furan fragment in the side chain and four present a butan-20,12-olide. The only halim-4-en derivative is a norderivative known as teucvin or mallotucin A, 89.

![Figure 4. Secohalimanes and 4-enes derivatives.](image-url)

2. Ent-Halimic Acid as a Precursor of Biologically Active Compounds and Other Derivatives of Interest

Ent-halimic acid is very abundant in the Halimium viscosum extract, and its methyl ester 2 has been used as a starting material for the synthesis of a series of natural halimanes corroborating their structures, biologically active derivatives and the preparation of other interesting compounds. Figure 5 shows some of the diterpene or sesquiterpene derivatives synthesized from ent-halimic acid: 1. ent-halimanolides [2,56–58]; 2. chettaphanin I and II [4,5]; 3. sesterterpenolides [6,59,60]. Figure 6 shows other groups of compounds prepared from 2, among which are as follows: 4. hybrid compounds: sesterterpenolide bioconjugates and glycerophospholipids [61]; 5. rearranged derivatives: ent-labdanes [62], abepicrasanes [63], and a propellane [64]; 6. sequiterpene-quinone/hidroquinones [65]; 7. terpene alkaloids: sesqui- and diterpene-alkaloids [7,8,66–69].
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**Figure 5.** Ent-halimanolides, chettaphanins, and sesterterpenolides obtained from 2.

**Figure 6.** Hybrid and rearranged compounds, sesquiterpene-quinones/hydroquinone, and terpene alkaloids obtained from 2.
3. Synthetic Transformations of Ent-halimic Acid Methyl Ester, 2

In this section, the synthesis of these compounds is discussed. The synthetic routes starting from ent-halimic acid methyl ester 2 have made it possible to establish or corroborate the structure of different natural ent-halimanes and access other interesting derivatives due to their rearranged structures or to their biological activities. Many of the synthesized intermediates possess the MCA fragment in their structures.

3.1. Synthesis of Ent-Halimanolides

The first three natural ent-halimanolides 90, 91 and 92 were synthesized from ent-halimic acid using the methyl ketone 94 as intermediate [2,56] (Scheme 1). This methyl ketone 94 was obtained from ent-halimic acid methyl ester 2 by a six-step procedure that includes reduction of the methoxycarbonyl at C18. Bestmann methodology was used for the synthesis of butenolide 96 [70], the key intermediate in the synthesis of ent-halimanolides 90, 91, and 92. The decalin double bond isomerization of 96 to the tetrasubstituted position permits the synthesis of 90. The γ-hydroxybutenolides 91 and 92 can be obtained using Boukouvalas methodology [71]. Biological testing has been carried out on these compounds. The compound 96 shows cytotoxic and antiviral activity [HELAM cells (IC_{50} = 5.0), MDCK (IC_{50} = 5.1) and influenza virus (IC_{50} = 6.8)] [56].

![Scheme 1. Synthesis of ent-halimanolides 90–92 from 2.](image)

Due to the biological (antifeedant, anti-inflammatory, antitumor, and antimicrobial) activity related to diterpenoids and sesterterpenoids containing the hydroxybutenolide scaffold, a synthesis of ent-halimanolides, structurally related to natural occurring lactones, was designed, starting from ent-halimic acid (α and β-hydroxybutenolides: 15,16-olides 97–100 and 16,15-olides 101–104) [58]. The key intermediate, triol 106 (Scheme 2), was obtained by selective photooxygenation and ulterior hydroboration. The selective protection of 106 as 1,3-dioxolane or 1,3-dioxane led to the hydroxyderivatives 107 and 108, respectively, after oxidation and deprotection of which produced the β-hydroxybutanolides 97–100 (in a ratio 27:33:20:20) and the α-hydroxybutanolides 101–104 (in a ratio 22:22:28:28), respectively. The relative configuration of these compounds was established by 1H NMR, and the absolute configuration achieved by CD spectroscopy. The structures of 100 and 103 were confirmed via X-ray. Lactone 109 was synthesized by a 5-step sequence using methylketone 110 as an intermediate [29]. Using Reformatsky methodology [72,73], β-hydroxybutanolides 109 was
obtained. Antifeedant testing has been carried out on these compounds. The α-hydroxybutanolides 103 and 104 are weakly active, and β-hydroxybutanolides 109 are moderately active [58].

In the same manner, an efficient synthesis of the ent-halimanolide 112 (15,16-epoxy-12-oxo-ent-halima-5(10),13(16),14-trien-18,2β-olide), from ent-halimic acid, has been achieved, corroborating the structure of the natural compound and establishing its absolute configuration [57] (Scheme 3).

By using the dinorderivatives 113 and 114 as intermediates, the tetranorderivative 116 was accessed by a new route at the multigram scale. From 116, by a six-step sequence, the natural lactone 112, moderately active against HeLa (human cervix cancer), was obtained [57].
3.2. Chettaphanin Synthesis

Chettaphanins I, 1, and II, 123, isolated from Adenochlaena siamensis Ridl (Euphorbiaceae) in 1970 [9] and 1971 [10] are the first two ent-halimanes discovered. Both compounds are the main components of “chettaphangki,” a digestive remedy used in folk medicine in Thailand. Their structures have been determined by chemical and spectroscopic correlations. The chettaphanin II structure was corroborated by X-ray crystallography of a chettaphanin II derivative. The absolute configuration that remained undetermined was established by synthesis using ent-halimic acid as a starting material [4,5] (Scheme 4). The key intermediate 125 was accessed from ent-halimic acid methyl ester 2 by a seven-step sequence, with good global yield. This sequence includes, side chain degradation to the corresponding dinorderivative followed by C2 functionalization and Baeyer–Villiger oxidation until the corresponding tetrannorderivative 124 was obtained. The protection of enone 124 was followed by hydrolysis of the acetoxy group and oxidation, leading to aldehyde 125. During the enone protection with ethylene glycol, the dioxygen formed, and the isomerization of the double bond to the decalin tetratactsubstituted position took place at the same time. Furyllithium addition to 125 followed by oxidation led to intermediate 126. Chettaphanin II, 123, was obtained by a simple treatment in acidic media of 126, and chettaphanin I, 1, was obtained by epoxidation of 126, followed by treatment in acidic media.

Scheme 4. Synthesis of chettaphanins I and II from 2. (a) OsO4, NMO, t-BuOH/THF/H2O (7:2:1), 24 h (99%); (b) LTA, C6H6, 20 min (95%); (c) Na2CrO4, Ac2O/AcOH, NaOAc, benzene, 55°C, 15 h (64%); (d) UHP/TFFA, CH2Cl2, 60 min (61%); (e) ethylene glycol, p-TsOH, benzene, reflux, 8 h (76%); (f) K2CO3, MeOH, 3%, 60 min (99%); (g) PDC, DMF, 3 h (98%); (h) 3-bromofuran, n-BuLi, THF, −78°C, 20 min (90%); (i) TPAP, NMO, CH2Cl2, 45 min (93%); (j) p-TsOH, acetone, 5 h (72%); (k) m-CPBA, Cl2CH2, 12 h, rt; (m) p-TsOH, acetone, 5 h, rt or HClO4, 3 h, rt.

3.3. Sesterterpenolide Synthesis

Several sesterterpenoids isolated from marine natural sources contain a residue of glyhydroxybutenolide as a characteristic structural fragment. This fragment is responsible in many cases for the bioactivity of the corresponding sesterterpenolides.

Cladocorans A and B, isolated from the mediterranean coral Cladocora cespitosa (L) by Fontana et al. [74] (Figure 7), are sesterterpenolides, and their structures, 127 and 128, were established according to their spectroscopic properties. These sesterterpenolides are structural analogues of the natural dysidiolide [75,76], an inhibitor of protein phosphatases cdc25A (IC50 = 9.4 µM) and cdc25B (IC50 = 87 µM), which are essential for cell proliferation. Dysidiolide inhibits the growth of A-549 human lung carcinoma and P388 murine leukaemia cell lines at low micromolar concentrations [77–81]. These important physiological activities of the dysidiolide attract the attention of chemists, biologists, and pharmacologists. Compounds 127 and 128 can be considered as isoprenyl-halimanes and their
potential biological activities inspired us to synthesize them with some analogues using the methyl ester of ent-halimic acid 2 as a starting material. The synthesis by our group of compounds 127 and 128 and their epimers at C18 (129 and 130) demonstrate that the structures proposed by Fontana et al. for cladocorans A and B (127 and 128) should be revised. The natural product structures for cladocorans A and B were finally revised by Miyaoka and colleagues [3] (Figure 7), and the correct structures of these natural products appear in Figure 7. It was found that cladocoran B is an olefinic regioisomer of dysidiolide, and cladocoran A is its acetate.

Figure 7. Chemical structures for sesterterpenolides and ent-halimic acid.

The synthesis of bioactive sesterterpenoid γ-hydroxybutenolides 15,18-bisepi-ent-cladocoran A and B, 127 and 128 (Scheme 5), and the epimers of these compounds at C18, 15-epi-ent-cladocoran A and B, 129 and 130, using ent-halimic acid methyl ester 2 as a starting material was achieved (Figure 7). Starting from ent-halimic acid methyl ester 2, the key intermediate 131 was accessed by a degradation sequence of the side chain of four carbon atoms and elongation of C18 by introduction of the south chain. The furosesterterpenoid 132 was obtained by introducing the furan fragment by the addition of furyllithium, and the isoprenic unit of the south chain was completed by coupling the adequate Grignard reagent with the iododerivative or the tosyl derivative of 131. The corresponding epimers at C18 of 132 were separated by column chromatography. In each of them, the γ-hydroxybutenolide unit was finally obtained using Faulkner methodology [82], obtaining in each case 127, 128, 129, and 130. The synthesized sesterterpenolides 127, 128, 129, and 130 inhibited cellular proliferation (IC50 ≈ 2 μM) of a number of human leukaemic and solid tumor cell lines [60].

Scheme 5. Synthesis of sesterterpenolides from 2.

The promising biological activities showed that, in some cases, sesterterpenolides 127, 128, 129, and 130, dysidiolide analogues, are more active than the compound of reference dysidiolide and boost the search for new analogues. In this manner, several sesterterpenolide analogues of dysidiolides 135–139 (Scheme 6) have been synthesized from ent-halimic acid methyl ester 2, according
The main structural change with the previous cladocoran derivatives is the situation of the γ-hydroxybutenolide in the south side chain of the molecule. The antitumoral activity in vitro against human HeLa, A549, HT-29, and HL-60 carcinoma cells was achieved. The proliferation inhibition data showed significant antitumor activity in the compounds 135–139, inhibiting proliferation of distinct cancer cell types with an IC₅₀ in the low micromolar range (Scheme 6) [59].

Scheme 6. Synthesis of sesterterpenolides analogues 135–138 from 2.

### 3.4. Synthesis of Hybrid Compounds of Sesterterpenolides with Glycerols

One of the sesterterpenolides, 135, obtained from ent-halimic acid methyl ester 2 was used in the synthesis of a series of bioconjugated sesterterpenoid with phospholipids and polyunsaturated fatty acids (PUFAs) such as 141 and 142 (Figure 8), potentially bioactive compounds and antiproliferative agents in several cancer cell lines [61]. Each of the compounds that participate in these bioconjugates show antitumor activities, and a synergistic effect was expected to result from their conjugation [83–85]. Different substituted analogues of the original lipidic ether edelfosine [86] (1-O-octadecyl-2-O-methyl-rac-glycero-3-phosphocholine) were obtained while varying the sesterterpenoid in position 1 or 2 of the glycerol or a phosphocholine or PUFA unit in position 3. Simple bioconjugates of sesterterpenoids and eicosapentaenoic acid (EPA) have also been obtained. All synthetic derivatives were tested against human tumor cell lines HeLa (cervix) and MCF-7 (breast). Some compounds showed good IC₅₀ (0.3 and 0.2 μM) values against these cell lines [61].

![Figure 8. Synthesized sesterterpenolides hybrid compounds.](image)

### 3.5. Synthesis of Rearranged Compounds

Due to its functionality, ent-halimic acid methyl ester 2 can be considered as an excellent synthon for the synthesis of new natural products and as a starting material in the synthesis of rearranged compounds and compounds of interest in perfumery.

#### 3.5.1. Synthesis of Ent-Labdanes from Ent-Halimanes.

Scheme 7 shows the 1,2-shift of Me-20 of ent-halimanes (143) that leads to ent-labdanes (144). This rearrangement will be the opposite to the biosynthetic route in which the ent-labdanes are the
precursors of \textit{ent}-halimanes. For the first time, \textit{ent}-labdanes have been synthesized starting from \textit{ent}-halimic acid methyl ester 2, following a route that is the reverse of the biosynthetic one leading to the former compounds \cite{62} (Scheme 7). Effectively, the \textit{ent}-halimane epoxyderivative 143, formed in three steps from 2, led to the \textit{ent}-labdane tetranorderivative 144 by treatment with Lewis acid. The rearrangement allowed the 1(10)-halimanes to be used as starting materials for the synthesis of bioactive labdanes, so this rearrangement could be used for the transformation of compounds in picrasanes with an abeopicrasane skeleton obtained from \textit{ent}-halimic methyl ester 2, as will be described in the following.

![Scheme 7. Tetrnorlabdanes synthesized from 2.](image)

3.5.2. Synthesis of Abeopicrasanes from \textit{ent}-Halimanes.

Picrasanes are quassinoids and degraded triterpenes and are interesting for their antitumoral properties, bruceantin being one of the best known \cite{87}. An advanced intermediate 147 (Scheme 8) with the ABC ring of the picrasane quassinoid skeleton 148 has been synthesized from \textit{ent}-halimic acid methyl ester 2. The rearrangement from \textit{ent}-halimanes to \textit{ent}-labdanes previously described (Scheme 7) was thought to apply to the transformation of abeopicrasanes into picrasanes \cite{63}. The bicyclic system of the starting material, \textit{ent}-halimic acid methyl ester 2, has been incorporated as the BC part of the ABC system. To date, no diterpenes of the antipode series have been used in this kind of approach for the quassinoids with a picrasane skeleton. The tricyclic system was elaborated using the tetranorderivative 145 as an intermediate, performing the allylic oxidation and incorporating on C18 the four carbon atoms necessary to access the 4,5-secoabeopicrasane 146. The quaternary carbon C-4 was incorporated as C-10, and carbon C-5 incorporated as C-9, with the right configuration. Annulation of dione 146 led to the adequate abeopicrasane 147, exploiting the rearrangement described before.

![Scheme 8. Synthesis of abeopicrasane 147 from 2.](image)
3.5.3. Synthesis of [4.3.3] Propellanes from Ent-Halimanes.

*Ent*-halimic acid methyl ester 2 was used as the starting material for an efficient synthesis of a series of tetranorderivatives 149–151, functionalized at C-18 (Scheme 9). These compounds could be used to synthesize the [4.3.3] propellane 154, the oxide 152, and the lactone 153 similar to ambreinolide, all of which may be of interest to those in the perfume industry [64].

![Scheme 9. Synthesis of propellane terpenoids from 2.](image)

3.6. Quinone/Hydroquinone Sesquiterpenes

The quinone/hydroquinone sesquiterpenes are compounds mainly of marine origin and are interesting for their structural variety and biological activities [88]. *Ent*-halimic acid methyl ester 2 has been used in the synthesis of the quinone/hydroquinone sesquiterpene (-)-aureol 155, the (-)-smenoqualone 157, and the (-)-neomamanuthaquinone 156 and in the formal synthesis of the (-)-cyclosmenospongine 158 (Scheme 10) with, for example, antiinflammatory, antimicrobial, antitumor, or antiviral activities.

![Scheme 10. Synthesis of quinones/hydroquinones sesquiterpenes from 2.](image)
The syntheses of those quinone/hydroquinone sesquiterpenes 155–158 from ent-halimic acid methyl ester 2 were planned according to the synthetic sequence in Scheme 10, which was developed by the AB/ABD/ABCD approach. Effectively starting from ent-halimic acid methyl ester 2, the tetranoderivative intermediate 159 was prepared, and from this, key intermediate 160, which incorporates Ring D, was synthesized, which included a Barton decarboxylation reaction in the presence of benzoquinone [89]. The reduction of 160 and ulterior cyclization of hidroquinone 161 yielded (-)-aureol 154. The cyclization to obtain the tetracyclic compound was achieved with p-TsOH and in a stereoselective manner with F₃B·Et₂O. With 160 in hand, (-)-neomamanuthaquinone 156 (Scheme 10) can be obtained by the addition of NaOMe to the quinone ring, according to the procedure of Theodorakis and co-workers for the synthesis of ilimaquinone [90]. This tricyclic sesquiterpene quinone/hydroquinone, 156, give access to (-)-smenoqualone 157 and (-)-cyclosmenospongine 158.

3.7. Sesqui- and Diterpene-Alkaloids

Ent-halimic methyl ester 2 has also been used in the synthesis of terpene-alkaloids, in particular in the preparation of 7,9-dialkylpurines ((+)-agelasine C) and other diterpene- and sesquiterpene-indoles.

3.7.1. Synthesis of Diterpene-alkaloid, (+)-agelasine C [7]

Agelasines are a family of diterpene-alkaloids isolated from marine sponges of genus Agelas [91]. Agelasine C is one of the first four known agelasines, shows powerful inhibitory effects on Na and K-ATPase, and shows antimicrobial activities (Figure 9). Nakamura et al. in 1994 presented the structural formula 162 for agelasine C determined by spectroscopic methods [92]. Epi-agelasine C, 163, is an antifouling substance active against macroalgae and was isolated in 1997 by Hattori et al. [93] from the marine sponge Agelas mauritiana, whose structure was proposed by spectroscopic methods (Figure 9).

Figure 9. First proposed structures for agelasine C (162) and epi-agelasine C (163).

The interest in epi-agelasine C as an antifouling agent [93] and the necessity of establishing the absolute configuration led to the decision to synthesize 164 (Scheme 11). This synthesis was carried out according the synthetic strategy shown in Scheme 11, analogue to the ones developed for other agelasines, consisting in coupling the adequate terpenic fragment (165) with a purine (166) [7].
The synthesized tumor cell lines with an IC50 in the range of 10−5 M showed antitumor activity against a number of several human tumor cell lines with an IC50 in the range of 10−5 M [8].

The physical properties of the synthesized product 164 are very different from the natural product epi-agelasine C, whose proposed structure of 163 (Figure 9) should be revised. On the contrary, comparing the 13C NMR spectra of 164 with agelasine C, with the proposed structure of 162, showed that they were identical to their 1H NMR spectra. Although the specific rotation for 164 and agelasine C have a similar absolute value, they have a different sign. It should be concluded that the structure for (-)-agelasine C should be corrected to the structure of 165, an enantiomer of the synthetic product 164 (+)-agelasine C (Figure 10).

Spectroscopic considerations that arose by comparison of the spectroscopic data of 164 with those of epi-agelasine C and by the specific rotation of both compounds suggested the structure that appears in Figure 10 [7] for the natural product epi-agelasine C 166.

3.7.2. Synthesis of the Indole Diterpene-alkaloid (+)-thiersindole C

The indole diterpene-alkaloid (+)-thiersindole C 167 was synthesized from ent-halimic acid methyl ester 2 [8] (Scheme 12). Firstly, the bicyclic system was elaborated by the adequate functionalization of C3, preparing intermediates 168 and 169. Secondly, a Fischer indolization was used in order to obtain the north side chain in intermediate 170, and the elongation of the south side chain with an isoprene unit was finally afforded in two steps through 171, leading to (+)-thiersindole C 167. The synthesis of (+)-thiersindole C 167 corroborated the absolute configuration of the natural product (+)-thiersindole C. The synthesized (+)-thiersindole C 167 showed antitumor activity against a number of several human tumor cell lines with an IC50 in the range of 10−5 M [8].
3.7.3. Synthesis of Sesquiterpenil-Indoles

The synthesis of 12-epi-ent-polyalthenol 172 and 12-epi-ent-pentacyclindole 174 from ent-halimic acid methyl ester 2 as starting material was carried out using the following as intermediates: the trinorderivative 175 and the trinorderivatives functionalized in C3 176-177 [66,67] (Scheme 13). The synthesis of the pentacyclic compounds can be considered biomimetic, as our group performed a cyclization of 3-(but-3-enyl) indole derivatives that produce polycyclic compounds with a hexahydrocarbazole structure. In this reaction, three stereogenic centers are generated in one step [69]. The structure of the natural product polyalthenol 178 and pentacyclindole 179 (Figure 11) were confirmed in this way.
Several of the sesquiterpene-indoles synthesized show cellular proliferation inhibition of a number of human leukaemic and solid tumor cell lines [66,67].

A series of sesquiterpene-indole (180–203 and 204–221) analogues of polyalthenol 178 and pentacyclindole 179, respectively, were synthesized (Figure 12) starting from ent-halimic acid methyl ester 2 in order to test their biological activity [68]. These 42 analogues include diverse oxidation levels at the sesquiterpenyl moiety and different functionalization on the indole ring. All derivatives were tested against a representative panel of Gram-positive and Gram-negative bacterial strains, and the human solid tumor cell lines A549 (non-small cell lung), HBL-100 (breast), HeLa (cervix), SW1573 (non-small cell lung), T-47D (breast), and WiDr (colon). Overall, the compounds presented activity against the cancer cell lines. The resulting lead, displaying a polyalthenol scaffold, showed GI50 values in the range 1.2–5.7 μM against all cell lines tested [68].

![Figure 11. Polyalthenol and pentacyclindole structures.](image)

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![Figure 12. Sesquiterpenylindoles synthesized from 2.](image)
4. Conclusions

Among natural terpenoids, bicyclic diterpenes with a halimane skeleton constitute the family that most often shows the methylene-cycloalkylacetate (MCA) fragment with potential application as neurotrophic agents. *Ent*-halimic acid, a major constituent of *Halimium viscosum*, is the prototype for this MCA-containing diterpene, which has been proven to be an excellent starting material for the synthesis of a variety of biological active compounds and therefore for potentially neurotrophic diterpenes.

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