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Marine diterpene glycosides

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ABSTRACT

Marine diterpene glycosides (MDGs) respresent a small but highly significant group of the much larger class of marine diterpenes. The three well-studied examples of MDGs are eleutherobins, pseudopterosins and fuscosides, all of which exhibit extremely promising biological activity. The eleutherobins are potent anti-mitotic agents, and the pseudopterosins and fuscosides are potent anti-inflammatory agents. This review discusses the structures and biological activities of these compounds, as well as their biosynthesis and synthesis.

1. Introduction

Terpene glycosides represent a large group of natural products dominated by compounds with a triterpene or sterol core. A small but highly significant subset of this class of natural products are the marine diterpene glycosides (MDGs). Interestingly, while there are large numbers of marine diterpenes with tremendous variation in the skeletal classes, there are very few glycosylated derivatives. Gorgonian corals are the most prolific source of diterpenes, and as described in our previous review,[1] there is substantial structural diversity of diterpenes isolated from gorgonians with 40 skeletal classes represented. Marine diterpene glycosides (MDGs) are unique to this group of invertebrates.

The three most thoroughly investigated examples of MDGs are the eleutherobins, pseudopterosins, and fuscosides. All such groups of compounds exhibit highly significant biological activity. The aim of this article is to review MDGs with a focus on these three intriguing families of natural products. Discussions will focus on structures, biological activities, biosynthesis as well as synthetic work. In addition to the three most significant examples of MDGs identified above, the structures and relevant chemical and biological studies of a small number of miscellaneous MDGs are also reviewed.

2. Eleutherobins

Eleutherobin and its derivatives belong to a small but highly significant family of diterpene glycosides. These are highly potent cytotoxic agents with activity comparable to the currently used cancer drug taxol. Unfortunately, the lack of supply has greatly limited the development of eleutherobin as a prospective anti-cancer agent and thus its full potential is unknown.

2.1. Isolation of eleutherobin and its derivatives

Eleutherobin (**1**) was originally isolated from the Western Australian Alcyonacean coral *Eleutherobia* sp. (possibly *Eleutherobia albiflora*) and shown to cause mitotic arrest by the stabilization of microtubules.[2–5] This mechanism of action associated with the observed cytotoxicity is only shared by a small group of natural products including the powerful anticancer drug taxol,[6,7] the myxobacterium metabolites epothilones A and B,[8] and the sponge metabolites laulimalide[9] and discodermolide.[10,11] Ojima et al. have proposed a common pharmacophore for these four structurally unique natural products that rationalizes extensive structure–activity relationship data. The three regions labeled A, B, and C indicated in Figure 1 are believed to play an important role in the binding of eleutherobin to tubilin.[12]

In 2000, Andersen enlarged this family of highly promising microtubule-stabilizing agents with the isolation of eleutherobin (**1**) with six new analogues (**2**–**7**) from the relatively common Caribbean gorgonian *Erythropodium caribaeorum*.[13] Desmethyleleutherobin (**2**) (IC_{50} 20 nM) and isoeleutherobin A (**4**) (IC_{50} 50 nM) were both slightly more potent than eleutherobin (**1**) (IC_{50} 100 nM). Some of these new analogues provided an opportunity to test the Ojima model. For example, caribaeoside (**6**, see Scheme 1) has a modified B region, with a tertiary alcohol in place of an alkene, and was found to be much less active (IC_{50} 20 μM) than eleutherobin. Clearly, this tri-substituted double bound is important for the antimitotic activity.[14]

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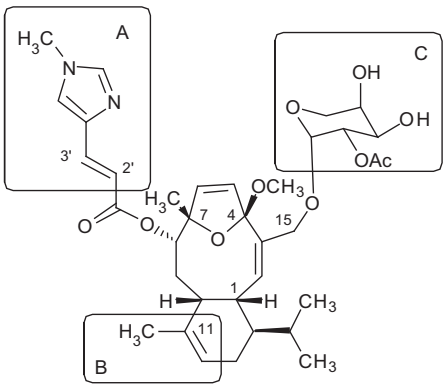
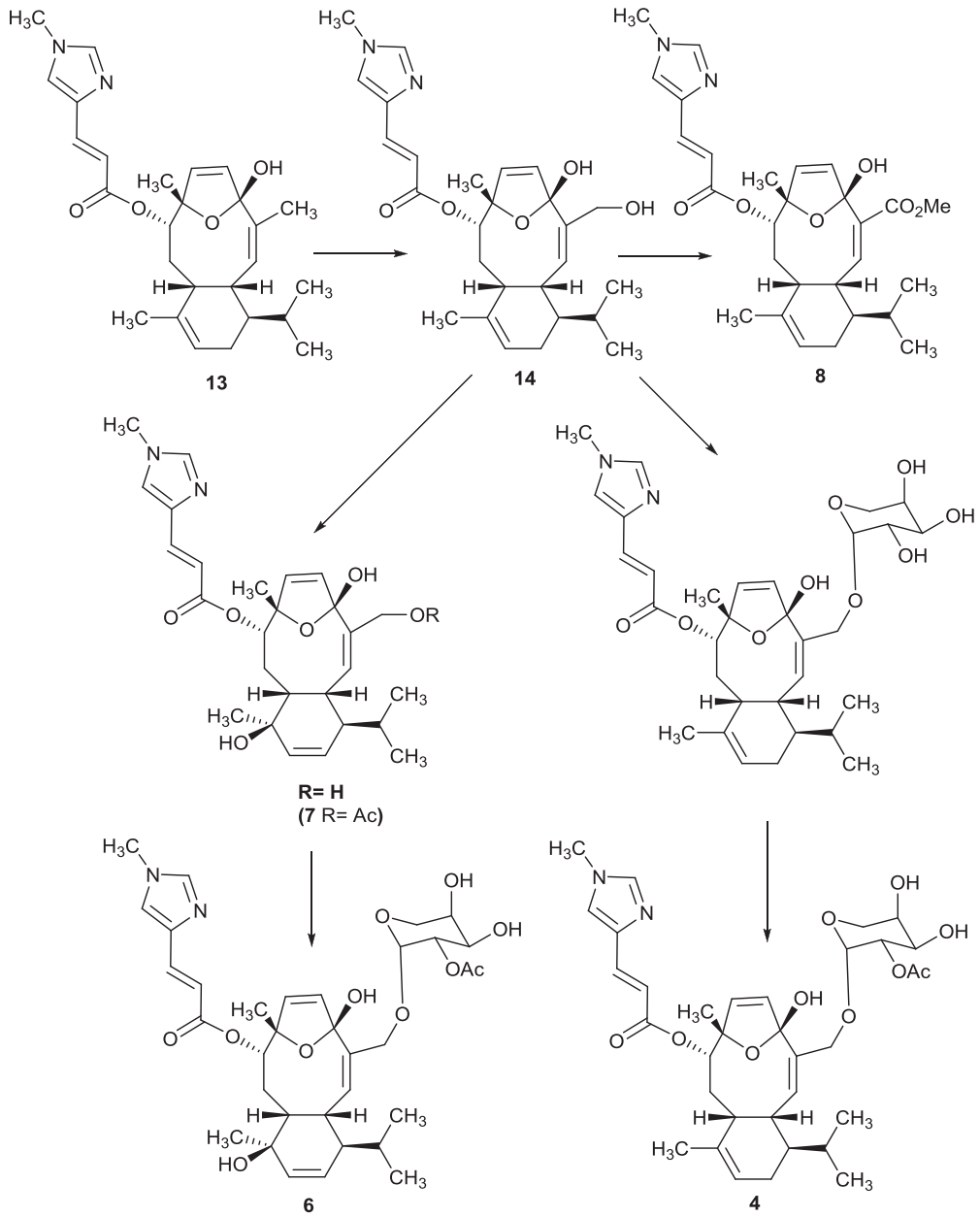


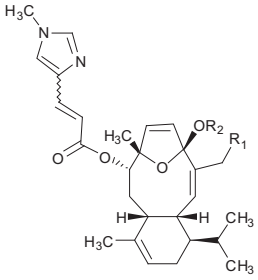
Figure 1. Eleutherobin (**1**) and proposed pharmacophore.

Sarcodictyins A–D (e.g., **8**) are not MDGs, but they are derivatives of the eleutherobin aglycone and their reduced biological activity highlights the importance of the sugar moiety in eleutherobin. The sarcodictyins represent the first examples of marine-derived eunicellanes that possess the unique C-4 to C-7 oxygen bridge; the sarcodictyins were isolated from the Mediterranean Stolonifer *Sarcodictyon roseum* prior to the isolation of eleutherobin.[15,16] As with eleutherobin, sarcodictyins possess *N*(6′)-methylurocanic acid esters at the C-8 position but they lack the glycosidic linkage at C-15. The significance of region C of Ojima's pharmacophore model is evident as the activity for sarcodictyin A (**8**) (IC_{50} 2 μM) is substantially less than that of eleutherobin.[17,18] More recently, (*Z*)-sarcodyctyin A was reported from the coral *Bellollena albiflora* collected off Shishi-jima Island in the Amakusa Islands (Japan).[19]



Scheme 1. Proposed biosynthetic pathway.

Eleuthoside A (**9**) and B (**10**) are two MDGs that were isolated in trace amounts, along with sarcodictyin A (**8**), from a South African sample of *Eleutherobia aurea* by Kashman in 1996.[20] Compounds **9** and **10** are closely related to desmethyleleutherobin (**2**) and differ only by the presence of an additional acetate group on the sugar moiety.



2 R_1= arabinose-(C2''-OAc); R_2= H; Δ (*E*)

3 R_1= arabinose; R_2= Me; Δ (*E*)

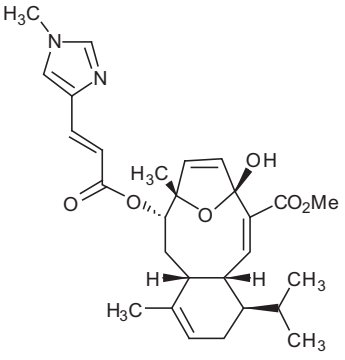
4 R_1= arabinose-(C3''-OAc); R_2= Me; Δ (*E*)

5 R_1= arabinose-(C2''-OAc); R_2= Me; Δ (*Z*)

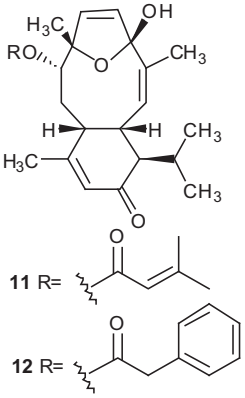
9 R_1= arabinose-(C2''&C3''-OAc); R_2= H, Δ (*E*)

10 R_1= arabinose-(C2''&C4''-OAc); R_2= H, Δ (*E*)

Valdivones A (**11**) and B (**12**) are diterpenes related to the eleutherobin aglycone, but in place of the urocanic acid moiety they possess a phenyl ester and an isopropyl ester, respectively. These compounds were isolated from the South African soft coral *Alcyonium valdivae* and inhibited chemically-induced inflammation in the mouse ear assay.[21]

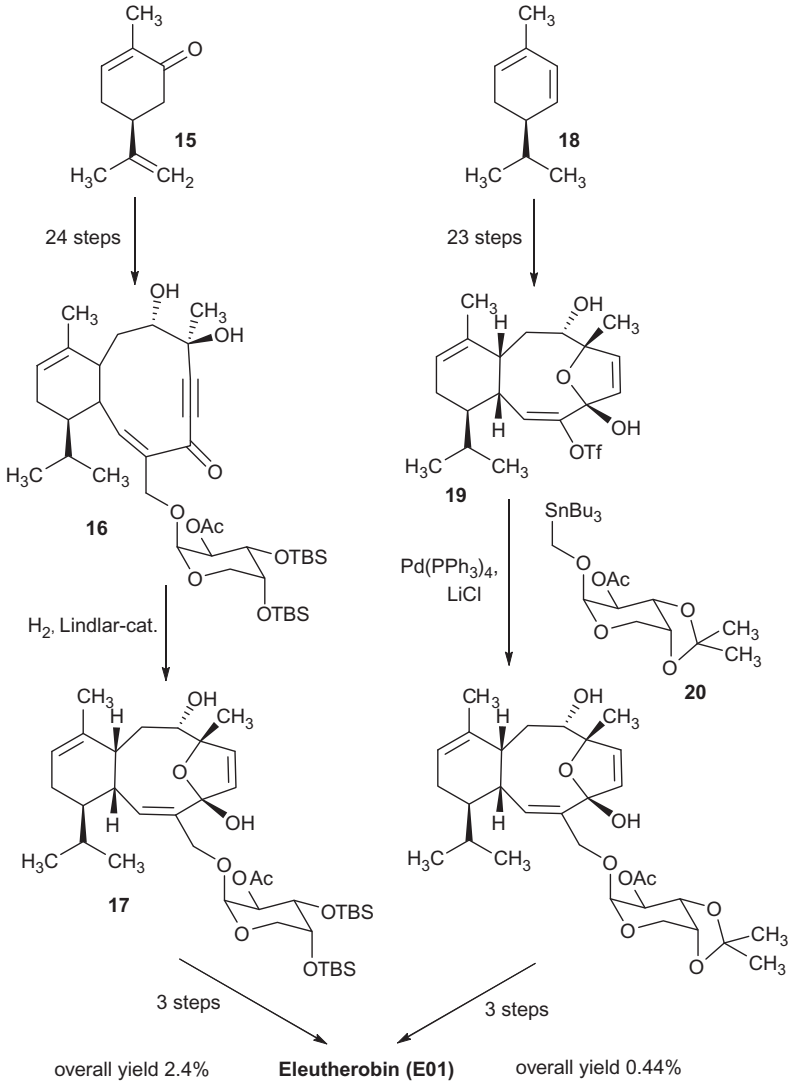


8



11 R=

12 R=



Scheme 2. Outline of the total syntheses of eleutherobin (**1**) by Nicolaou et al. and Danishefsky co-workers.

2.2. Biosynthesis and origin of eleutherobins

The eleutherobins are clearly products of mixed biosynthesis. A plausible biosynthetic pathway has been proposed by Andersen: the diterpenoid core is derived from geranylgeranyl diphosphate and is esterified to introduce the urocanic ester group yielding **13**. Subsequent oxidation gives the C-15 alcohol (**14**) which is then glycosylated (Scheme 1). This proposition was based on the isolation of the diterpenoids, caribaeorane (**13**) and 15-hydroxycaribaeorane (**14**) from the gorgonian *E. caribaeorum*. In this model **8** is a product of shunt metabolism[22]

The C-4 methylketals in eleutherobin and its derivatives are artifacts from the extraction of the coral biomass with methanol, as demonstrated by Andersen in 2001.[22] This issue was previously recognized with the isolation of valdivones A and B and their corresponding methylketals from a methanolic extract of *A. valdivae*.[18] Moreover, the presence of both the (*Z*) and (*E*) isomers of the *N*(6′)-methylurocanic acid moiety could be explained by the observation that urocanic acid is known to undergo photoisomerization from the naturally occurring *trans*-isomer to the *cis*-isomer on exposure to UV radiation.[23,24]

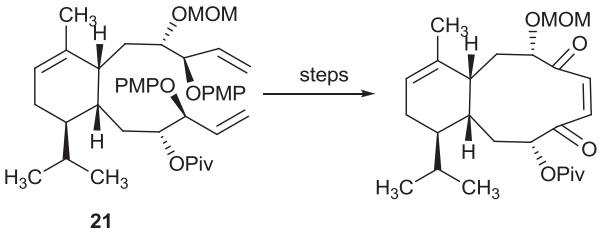
The obvious biosynthetic relatedness of the eleutherobins, sarcodictyins, valdivones, and the eleuthesides is remarkable when one considers the biological and geographic diversity of the source organisms. These compounds were isolated from corals of the genera *Eleutherobia, Erythropodium*, and *Sarcodictyon* and were collected from the Caribbean, the Mediterranean, South Africa and Western Australia. This raises the intriguing question of the identity of the true producer of the MDGs. Either there has been convergent evolution of very similar biosynthetic machinery in these different corals, or there is a common microbial symbiont that is responsible for the production of these MDGs. There is a growing recognition in the scientific community that microorganisms associated with marine invertebrates may play an important role in the biosynthesis of secondary metabolites; however, the producer of the eleutherobin family of MDGs in corals remains unknown.

2.3. Synthetic approaches to eleuthesides

The structural complexity and biological activity of eleutherobin has drawn considerable synthetic interest. Total syntheses of eleutherobin have been reported by the groups of Nicolaou[25,26] and Danishefsky,[27,28] and these facilitated the unambiguous assignment of the absolute stereochemistry of eleutherobin. Furthermore, these elegant syntheses have provided routes to analogues of this promising natural product: for example, Nicolaou's synthesis also yielded the non-natural α-glycoside of eleutherobin and an epothilone-inspired analogue which carries a thiazole-containing side chain instead of the *N*(6′)-methylurocanic acid residue.

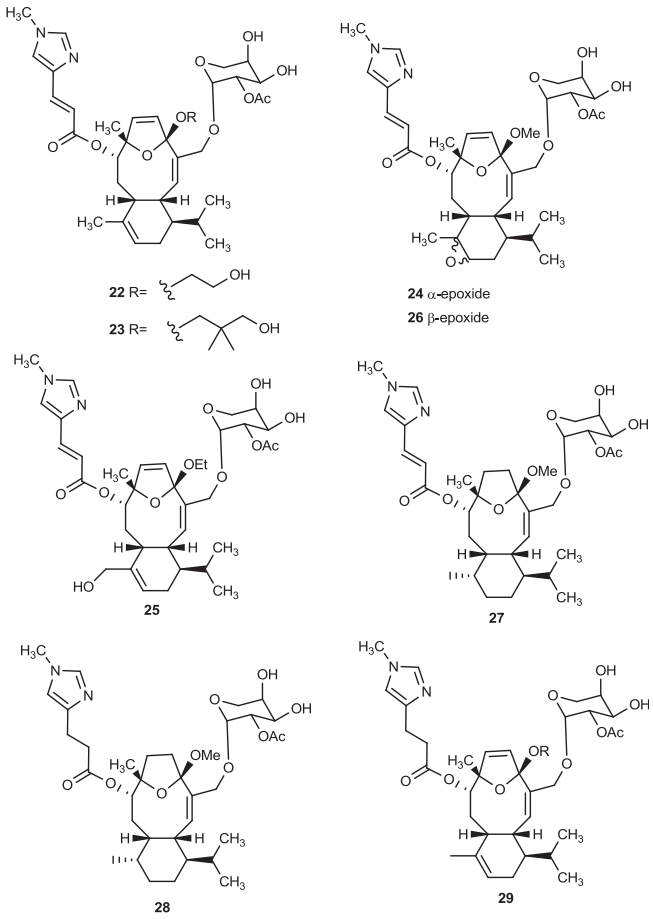
Nicolaou's and Danishefsky's syntheses each followed a linear synthetic approach with the longest sequences of 28 and 27 steps, respectively. Both syntheses utilized related monoterpenes as the starting chiral pools and built eleutherobin up from the cyclohexene portion of the molecule (Scheme 2). Nicolaou commenced with (+)-carvone (**15**), which was homologated over 24 steps to give **16**; an interesting stereoselective Lindlar reduction then provided an intermediate (*Z*)-olefin which spontaneously rearranged to the tricyclic dihydrofuran **17**. Danishefsky's synthesis built up the diterpene core **19** starting from (−)-α-phellandrene (**18**) and then elegantly introduced the carbohydrate moiety by exploiting the Stille coupling of the vinyl triflate (**19**) with the anomerically pure arabinosyloxymethyl stannane (**20**). Both total syntheses have been discussed in detail by different authors.[29–33]

In addition to the above total syntheses of eleutherobin, a number of synthetic approaches towards the eleutheside type of natural products and simplified analogues have been investigated by several groups including those of Gennari,[34–39] Mann,[40] Magnus,[41] Royer,[42] and Winkler.[43] Among these, Gennari et al. achieved a formal total synthesis of eleutherobin (**1**) through a controlled ring-closing metathesis reaction of the densely functionalized diene (**21**, Scheme 3).



Scheme 3. Gennari et al. controlled ring-closing metathesis reaction.

Busch and Kirschning, recently discussed the advantages and limitations of these synthetic routes, which are mostly linear rather than convergent.[33] In the laboratory the linear synthetic approach is very inefficient due to diminishing cumulative product yields. Syntheses of highly oxygenated polycyclic diterpenes, such as eleuthesides, remain a challenge.



Semi-synthetic derivatives of eleutherobin (**1**) have been prepared by Andersen's research group.[44] Transformation of the masked C-4 ketone in **1** yielded ketals that exhibited comparable antimitotic activities to eleutherobin: viz, **22** (IC_{50} 20 nM) and **23** (IC_{50} 80 nM). This demonstrated flexibility in the pharmacophore around the ketal. A series of modifications to the olefin moieties in eleutherobin yielded several additional analogs. Amongst this

series the semi-synthetic α-epoxide **24** (IC_{50} 30 nM) and 17-hydroxyeleutheside **25** (IC_{50} 20 nM) showed similar antimitotic potencies to **1**. In contrast the β-epoxide **26** (IC_{50} 300 nM) was 10 fold less active. Other less active analogs included tetrahydroeleutherobin **27** (IC_{50} 200 nM), and the partially hydrogenated derivatives **28** (IC_{50} >10 μM) and **29** (IC_{50} ~20 μM); the dramatically reduced activities revealed the importance of the $\Delta^{2',3'}$ olefin for the antimitotic activity. The above synthetic studies are significant as they reveal important features of eleuthesides for tubulin binding.

3. Pseudopterosins

The pseudopterosins (Figs. 2 and 3) are a notable class of MDGs with extant commercial applications in the market for skin care products. Since the initial isolation of the first members of this family from the gorgonian *Pseudoptergorgia elisabethae* (PE) in 1986,[45,46] the pseudopterosins have attracted significant attention due to their potent biological activities. Notably, pseudopterosins display more potent anti-inflammatory activity than the clinically used drug indomethacin,[45] and they may operate through a novel mechanism of action.[47] Importantly, the pseudopterosins show low acute toxicity in mice models.[48] While the pseudopterosins have undergone successful Phase I and II clinical trials, the development of this promising class of compounds as drugs has been limited in part due to supply issues. Based on biosynthetic studies we have previously proposed that the pseudopterosins are produced by a symbiotic microbe associated with PE,[49,50] and suggested that fermentation may be a possible route to addressing the supply of this natural product. Pseudopterosins might also be supplied by total synthesis, however, this is probably not an economically viable option due to the complexity of these natural products. Nonetheless, the pseudopterosin pharmacophore is incompletely understood, thus, it may not be necessary to synthesize the entire pseudopterosin structure: in an exciting recent development, a series of simplified synthetic analogs of pseudopterosins that retain biological activity have been developed by Fenical and co-workers.[51]

3.1. Isolation of pseudopterosins and derivatives

The pseudopterosins were discovered by Fenical and co-workers who initially reported pseudopterosins A–D (**30**–**33**, see Fig. 3)[67,80–82] which possessed an identical aglycone skeleton (**A1**) but differed in the nature of the sugar unit.[46] Subsequently, 27 other structurally unique pseudopterosins have been identified (Fig. 3) based around three isomeric aglycone structures (**A1**, **A2**, **A4**). These 31 pseudopterosins are structurally related to broader pseudopterosin-like compounds, namely the seco-pseudopterosins and the amphilectosins, embodied by seco-pseudopterosin A (**34**)[52] and amphilecotosin A (**35**),[53] respectively. To date 11 seco-pseudopterosin and two amphilectosins have been identified in nature. The pseudopterosins have been named sequentially as pseudopterosin A, B, C etc with the exception of the most recently reported pseudopterosin, iso-pseudopterosin E (**36**).[54] With regard to the 31 pseudopterosins, there is some confusion in the literature that arose relatively recently: in 2004 starting with 'pseudopterosin P' separate research groups used the same name for several different pseudopterosins and in three cases identical structures were assigned multiple names. While this issue has been noted previously,[55] Figure 3 summarizes all the known pseudopterosins and these ambiguities are noted as indicated. Fortunately, the nomenclature of the major members of the pseudopterosin family is not corrupted as the literature confusion applies to more recently isolated minor pseudopterosins.

All of the pseudopterosins and related natural products shown in Figure 3 were obtained from *P. elisabethae*, with the exception of seco-pseudopterosins A–D which were obtained from a gorgonian tentatively identified as *Pseudopterogorgia kallos*.[52] The geographic distribution of pseudopterosins is also indicated in Figure 3. Regions of the Caribbean have yielded different family members. The eponymous pseudopterosins are hexahydro-1*H*-phenalene derivatives of general structure **37** (Fig. 2). The aromatic A-ring is fully substituted and the glycoside sugar is directly attached to this ring at either positions C-9 or C-10, with a free phenol at the alternate position (see Fig. 3). In different pseudopterosins the sugar is a xylose, an arabinose or a fucose, and it may be acylated. The

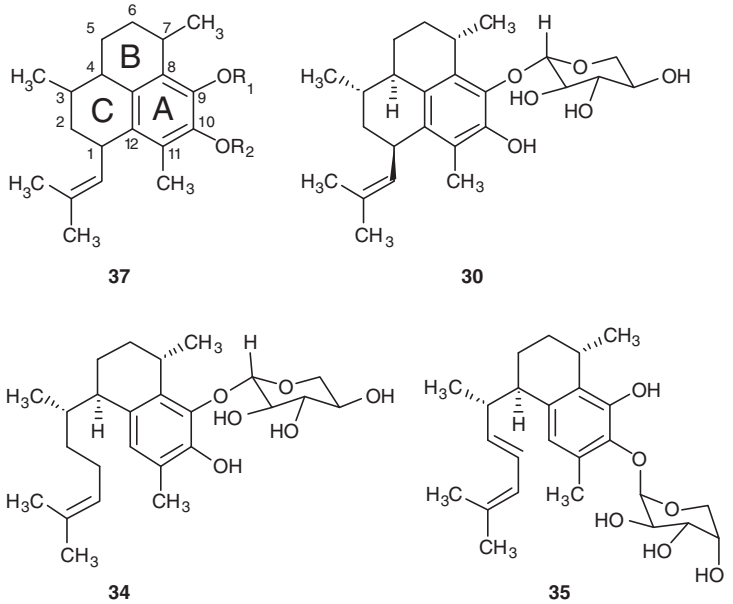
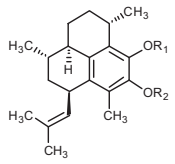


Figure 2. Pseudopterosins: general structure, representative pseudopterosins and related compounds.

Aglycone A1 ($R_1 = R_2 = H$)



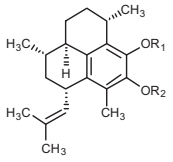
First reported isolation:

Bahamas (Fenical)[46]
Ps A (**30**): R_1 = β-D-xylose, R_2 = H
Ps B (**31**): R_1 = β-D-xylose-(C2'-OAc), R_2 = H
Ps C (**32**): R_1 = β-D-xylose-(C3'-OAc) , R_2 = H
Ps D (**33**): R_1 = β-D-xylose-(C4'-OAc) , R_2 = H
Bermuda (Fenical)[48]
Ps E (**55**): R_1 = H, R_2 = α-L-fucose
Ps F: R_1 = H, R_2 = α-D-arabinose
Bahamas[67]
Ps P: R_1 = Ac, R_2 = β-L-xylose
Ps Q: R_1 = Ac, R_2 = β-L-xylose-(C3'-OAc)
San Andres Island (Rodriguez)[68]
Ps Z: R_1 = H, R_2 = α-D-arabinose-(C3'&C4'-OAc)
Not reported (Little)[55]
Iso-Ps E (**36**): R_1 = L-fucose, R_2 = H

Syntheses:

Ps A-F aglycone syntheses:
Broka 1988[69]
Corey 1989,[70] 1990,[71] 1998[72]
McCombie 1990,[73] 1991[74]
Buszek 1995[75]
Schmalz 1997[76]
Kocienski 2001[77]
Harrowven 2004[78]

Aglycone A2 ($R_1 = R_2 = H$)



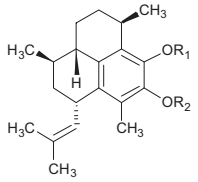
First reported isolation:

Bermuda (Fenical)[48]
Ps G: R_1 = α-L-fucose, R_2 = H
Ps H: R_1 = α-L-fucose-(C2'-OAc), R_2 = H
Ps I: R_1 = α-L-fucose-(C3'-OAc), R_2 = H
Ps J: R_1 = α-L-fucose-(C4'-OAc), R_2 = H
Florida Keys (Kerr)[80]
Ps M: R_1 = H, R_2 = D-arabinose-(C2'-OAc)
Ps N: R_1 = H, R_2 = D-arabinose-(C3'-OAc)
Ps O: R_1 = H, R_2 = D-arabinose-(C4'-OAc)
Providencia Island (Duque)[81]
Ps P: R_1 = H, R_2 = α-L-fucose[A]
Ps Q: R_1 = H, R_2 = α-L-fucose-(C4'-OAc)[B]
Ps R: R_1 = H, R_2 = α-L-fucose-(C3'-OAc)[C]
Ps S: R_1 = H, R_2 = α-L-fucose-(C2'-OAc)
Ps T: R_1 = H, R_2 = β - D-arabinose
Ps U: R_1 = H, R_2 = β - D-arabinose-(C4'-OAc)
Ps V: R_1 = H, R_2 = β - D-arabinose-(C3'-OAc)
San Andres Island (Rodriguez)[68]
Ps P: R_1 = H, R_2 = α-L-fucose-(C4'-OAc)[B]
Ps Q: R_1 = H, R_2 = α-L-fucose-(C3'-OAc)[C]
Ps R: R_1 = H, R_2 = α-L-fucose-(C3'&C4'-OAc)
Ps S: R_1 = H, R_2 = α-L-fucose-(C2'&C4'-OAc)
Ps T: R_1 = H, R_2 = α-L-fucose[A]
Ps U: R_1 = H, R_2 = α-D-arabinose-(C4'-OAc)
Ps V: R_1 = H, R_2 = α-D-arabinose-(C3'-OAc)
Ps W: R_1 = H, R_2 = α-D-arabinose-(C3'&C4'-OAc)
Ps X: R_1 = H, R_2 = α-D-arabinose-(C2'&C3'-OAc)
Ps Y: R_1 = H, R_2 = α- D-arabinose

Syntheses:

Ps G-J aglycone synthesis & structural revision:
Corey 1998,[72] 2000[57,82]

Aglycone A4 ($R_1 = R_2 = H$)



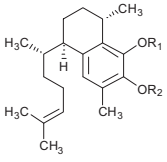
First reported isolation:

Bermuda (Fenical)[56]
Ps K: R_1 = α-L-fucose, R_2 = H
Ps L: R_1 = α-L-fucose-(C3'-OAc), R_2 = H

Syntheses:

Ps K-L aglycone syntheses:
Kocienski 2001[77]
Harrowven 2004[78]

Aglycone A5 ($R_1 = R_2 = H$)



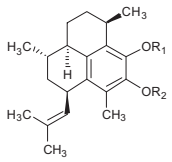
First reported isolation:

Florida Keys (Fenical)[52]
Seco-Ps A (**34**): R_1 = β-D-xylose, R_2 = H
Seco-Ps B: R_1 = β-D-xylose-(C2'-OAc), R_2 = H
Seco-Ps C: R_1 = β-D-xylose-(C3'-OAc) , R_2 = H
Seco-Ps D: R_1 = β-D-xylose-(C4'-OAc) , R_2 = H
Florida Keys (Kerr)[80]
Seco-Ps E: R_1 = H, R_2 = L-fucose-(C2'-OAc)
Seco-Ps F: R_1 = H, R_2 = L-fucose-(C3'-OAc)
Seco-Ps G: R_1 = H, R_2 = L-fucose-(C4'-OAc)
Providencia Island (Duque)[81]
Seco-Ps H: R_1 = H, R_2 = α-arabinose-(C4'-OAc)
Seco-Ps I: R_1 = H, R_2 = α-arabinose-(C3'-OAc)
Florida Keys (Kerr)[53]
Seco-Ps J: R_1 = H, R_2 = α-D-arabinose
San Andre´s & Providencia islands (Duque)[83]
Seco-Ps K: R_1 = H, R_2 = α-D-fucose

Syntheses:

Seco-Ps Aglycone synthesis:
McCombie [84]
Schmalz [76]

Aglycone A3 ($R_1 = R_2 = H$)

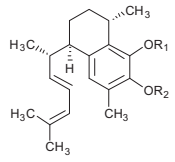


Syntheses:

Originally proposed Ps G-J aglycone:
Kocienski 2001[79]

KEY:
A,B,C Capitalized superscripts append compounds with identical structures but different names
Ps = pseudopterosin
Italicized names are indicative of duplicate usage of the same name, for different structures.
The numbering for the location of acetate substituents on sugars starts with C1' at the anomeric position

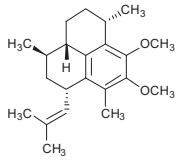
Amphilectosin A (35)



First reported isolation:

Florida Keys (Kerr)[53]
Amphilectosin A: R_1 = H, R_2 = α-D-arabinose

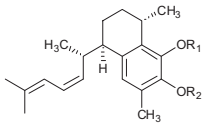
Aglycone A6 (dimethyl ether)



Syntheses:

Kocienski 1998[85]

Amphilectosin B



First reported isolation:

Florida Keys (Kerr)[53]
Amphilectosin B: R_1 = H, R_2 = α-D-arabinose

Figure 3. List of pseudopterosins and derivatives.

aliphatic B and C-rings are substituted with an isobutenyl group at C-1 and methyl groups at C-3 and C-7. Consequently, there are four stereocenters on the aglycone and 16 possible aglycone stereoisomers.

Only three of these aglycone stereoisomers are known in nature: the pseudopterosin A–F aglycone (**A1**), the G–J aglycone (**A2**), and the K–L aglycone (**A4**)[56]; **A1** and **A4** are enantiomeric with each other and diasteromeric with **A2**. Additionally, two pseudopterosin aglycone stereoisomers (**A3**, **A6**) that have not been identified in nature have been prepared synthetically. Compound **A3** was originally believed to represent the pseudopterosin G–J aglycone,[48] before a structural revision.[57]

3.2. Biosynthesis and origin of pseudopterosins

We have had a long-standing interest in pseudopterosin biosynthesis and have proposed a biosynthetic pathway based on a number of radioisotope labeling and NMR studies.[49,53,58–66] A simplified version of the proposed biosynthetic scheme is shown in Scheme 4. While details of this biosynthesis have been discussed in detail elsewhere,[1] we shall briefly recount the proposed key steps. An early stage metabolite elisabethatriene (**38**) is produced from geranylgeranyl diphosphate (**GGPP**) by a diterpence cyclase catalyzed transformation.

Subsequently, aromatization yields erogorgiaene (**39**), which is hydroxylated to the mono-hydroxylated (**40**) and then the dihydroxylated product (**A5**). Glycosylation then yields a seco-pseudopterosin, which undergoes cyclization to a pseudopterosin through a diene (**41**). The stereochemistry at C-1 in the pseudopterosin product is dependent on diene *E*/*Z* stereochemistry. This stereocontrol is based on the observation that treatment of amphiloctosin A and B with acid led to the production of the pseudopterosin G–J aglycone (**A2**) and A–F (**A1**) aglycones, respectively.[53]

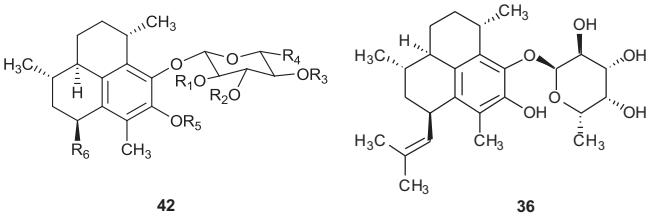
P. elisabethae is host to a rich and diverse microbial community. From a collaboration with the Jacobs group we reported that a preparation of the dinoflagellate symbionts of *P. elisabethae* was capable of pseudopterosin biosynthesis.[49] It is therefore possible that this family of MDGs could be produced through cell culture.

3.3. A synthesis of ideas: pseudopterosin biological activity and the development of pseudopterosin lead compounds

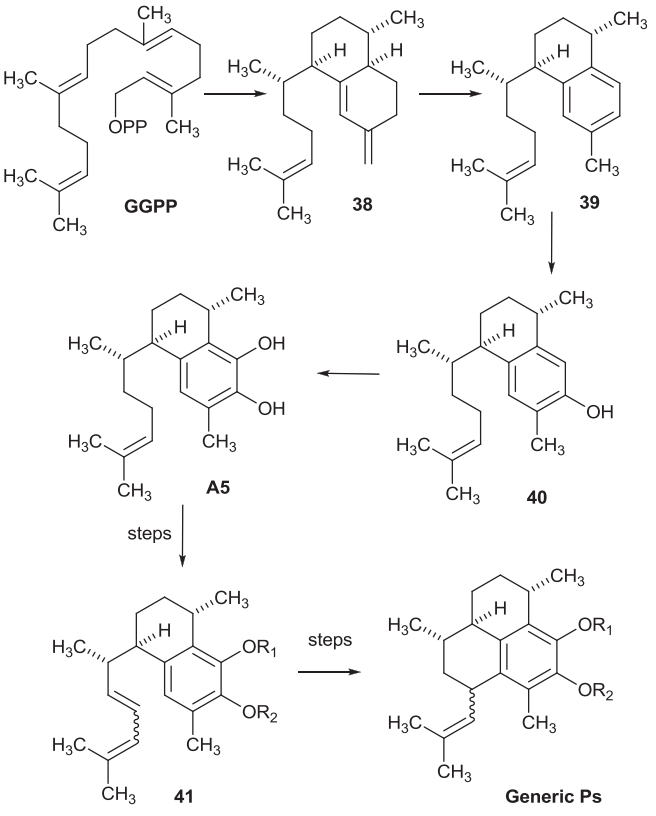
A major thesis of this review is that MDGs are biologically privileged molecules. It appears that the sugar moiety in pseudopterosins is necessary for the anti-inflammatory activity.[85,86] In addition to anti-inflammatory activity, various pseudopterosins have shown a remarkable range of other biological activities including the following: antiviral, anti-cancer, anti-mycobacterial activity and activity against gram-positive bacteria.[68] Details of various biological activities and evaluations of pseudopterosins are summarized in a recent article[51] and will not be repeated at length here. Instead, in this section we highlight the role that synthetic chemistry has played in helping to elucidate the anti-inflammatory mechanism of action of pseudopterosins. We shall also discuss synthetic and semi-synthetic pseudopterosins and their biological activities.

Both semi-synthetic pseudopterosin derivatives and synthetic pseudopterosin mimics have been prepared. Semi-synthetic pseudopterosins have shown useful anti-inflammatory properties. A number of patents describe pseudopterosins and semi-synthetic derivatives that possess anti-inflammatory or pain-reducing activity.[87–89] Compounds described in these patents are of general structure **42**, representing pseudopterosin A derivatives. The semi-synthetic derivatives described constitute products of standard alkoxy or phenoxy substitution such as ether and acetate derivatives. Another patent describes a use for semi-synthetic pseudopterosin A methyl ether to promote wound healing.[90]

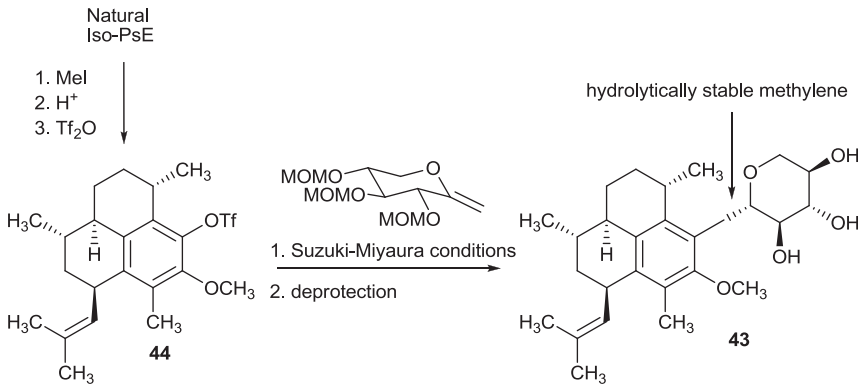
Recently, the research group of R. Daniel Little at UCSB has prepared and biologically evaluated a number of synthetic and semi-synthetic pseudopterosin derivatives whose biological activities have provided valuable information on the pharmacophore and mechanism of action of pseudopterosins. In an initial experiment they synthesized the hydrolytically stable pseudopterosin *C*-glycoside methyl ether (**43**). Given the *C*-glycoside will be resistant to hydrolysis by glycosidases, the aim here was to test the hypothesis that pseudopterosins are anti-inflammatory prodrugs, that is, is the aglycone the active species? Their semi-synthesis commenced with natural *iso*-pseudopterosin E (**36**), which possesses the pseudopterosin A–F aglycone core (**A1**). In a short number of steps the triflate **44** was obtained from the natural product and then cross coupled with a MOM-protected xylopyranoside under Suzuki–Miyaura conditions (Scheme 5).



In a mouse ear model the *C*-glycoside **43** displayed similar anti-inflammatory activity compared to pseudopterosin A methyl ether; similarly both methyl ethers inhibited phagocytosis in *Tetrahymena* cells. Finally, pseudopterosin A, iso-pseudopterosin E and the *C*-glycoside **43** were all shown to be competitive binders against two adenosine receptors (A_{2A} and A_3), which belong to the medicinally relevant G-protein coupled receptor class. From these results, the authors concluded that pseudoptersoins are not prodrugs.[85]

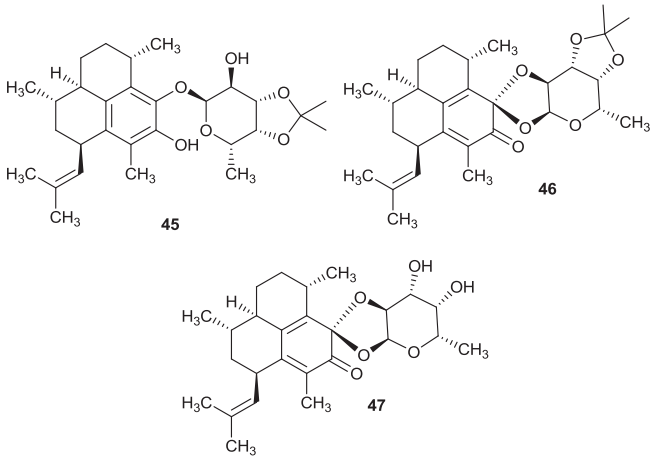


Scheme 4. Putative biosynthesis of pseudopterosins.



Scheme 5. Little's synthesis of the pseudopterosin A *C*-glycoside methyl ether.[85]

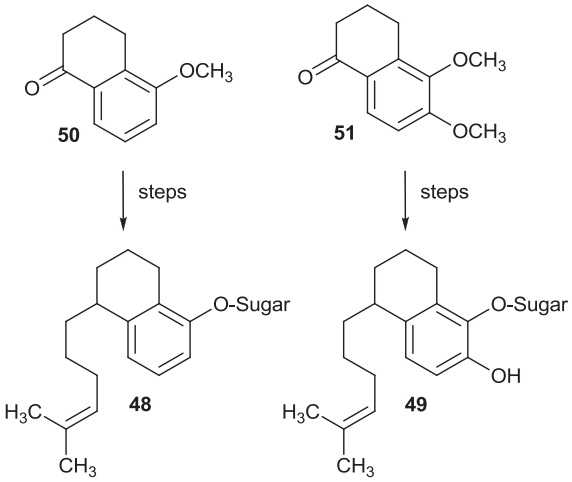
Based on the above results, the redox properties of pseudopterosins were subsequently investigated by the Little group. Cyclic voltammetry experiments utilizing the pseudopterosin E acetal derivative **45** revealed an irreversible redox curve suggesting a chemical transformation was occurring. To investigate this phenomenon, a preparative hypervalent iodine mediated oxidation of **45** was conducted which yielded the cyclic keto ketal **46**. Subsequently, the keto ketal **47** was also prepared and found to possess activity in a mouse ear edema assay. These results led the authors to postulate a possible mechanism for pseudopterosins' biological activity: they hypothesize that following binding to adenosine receptors, a conformational change induced by the keto ketal formation might lead to activation of these G-protein coupled receptors.[47]



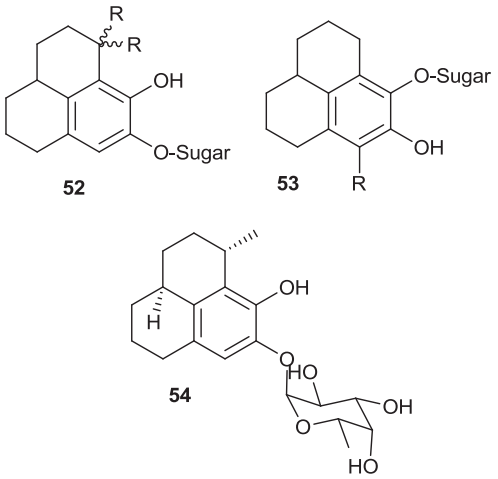
Synthetic mimics of pseudopterosin have the potential to be pharmacologically efficacious and commercially viable if they can be synthesized in an economically feasible fashion. Obviously a synthetic pseudopterosin mimic must retain its desirable biological activity (or have better activity), and not possess any deleterious activity (toxicity). Two sets of totally synthetic mimics are discussed below, one based on seco-pseudopterosin mimicry and the other on pseudopterosin mimicry. Two significant points are notable here. Firstly, one set provided mimics that possessed anti-inflammatory activity in a mouse ear model; the other set was not evaluated in this model. Secondly, if we compare the syntheses of the mimics with total syntheses of pseudopterosins (discussed in Section 3.4), the mimics are a lot more synthetically tractable: they were synthesized by simpler, shorter synthetic sequences.

Investigations into the minimum pseudopterosin pharmacophore by the Little group have revealed that simplified synthetic seco-pseudopterosin analogs can retain activity in models relevant to inflammation. Following a philosophy aiming to generate analogs by a practical synthetic approach, they prepared a series of simplified seco-pseudopterosin analogs; thus, they prepared compounds of general structure **48** and **49** (β-D-xylopyranoside, β-L-arabanopyranoside and β-L-fucopyranoside) from **50** and **51**, respectively (Scheme 6). It is notable that these syntheses provided hundreds of milligrams of seco-pseudopterosin mimics. Biological evaluation of these seco-pseudopterosin mimics (**48** and **49**) revealed they were inhibitors of phagocytosis, as are the pseudopterosins; interestingly two examples of the catechol based compounds (**49**) showed competitive binding against the adenosine receptor A_{2A} in a manner similar to that observed in natural pseudopterosin.[91] The activity of these seco-pseudopterosin mimics in an in vivo model, such as a mouse ear inflammation assay, has not been reported.

The Fenical group has recently described a series of synthetic pseudopterosin mimics that retained anti-inflammatory activity in a mouse ear assay. Nine out of ten compounds of general structure **52** and **53** (racemic) were active: the most potent mimic in this series **54** showed an ED_{50} of 24 μg/ear compared to an ED_{50} of 12 μg/ear displayed by pseudopterosin A. This synthesis, in which **54** was prepared in six steps from the tetralone **51**, represents a practical route to potentially useful pseudopterosin mimics. Indeed the aim of this study was to efficiently prepare pseudopterosin mimics that lacked C-1 and C-3 substituents to simplify the synthetic chemistry and reduce the number of possible stereoisomers.[51]



Scheme 6. Simplified seco-pseudopterosin mimics.[91]



3.4. Syntheses of pseudopterosins and seco-pseudopterosins

Synthesis plays an important role in natural products chemistry and may be used to (1) confirm the structure of a natural product, (2) revise the structure of a natural product, (3) provide natural product analogs for biological evaluation, and (4) supply a natural product. For the pseudopterosins, synthesis has unambiguously confirmed the structure of pseudopterosin A and E, in addition to facilitating a structural reassignment of the pseudopterosin G–J aglycone. Additionally, synthetic analogs and mimics of pseudopterosin are available and these have helped build up structure–activity relationships (as discussed above). Finally, while pseudopterosins have been prepared by some very elegant synthetic chemistry, it is doubtful that these will be commercially viable to provide large quantities of such compounds.

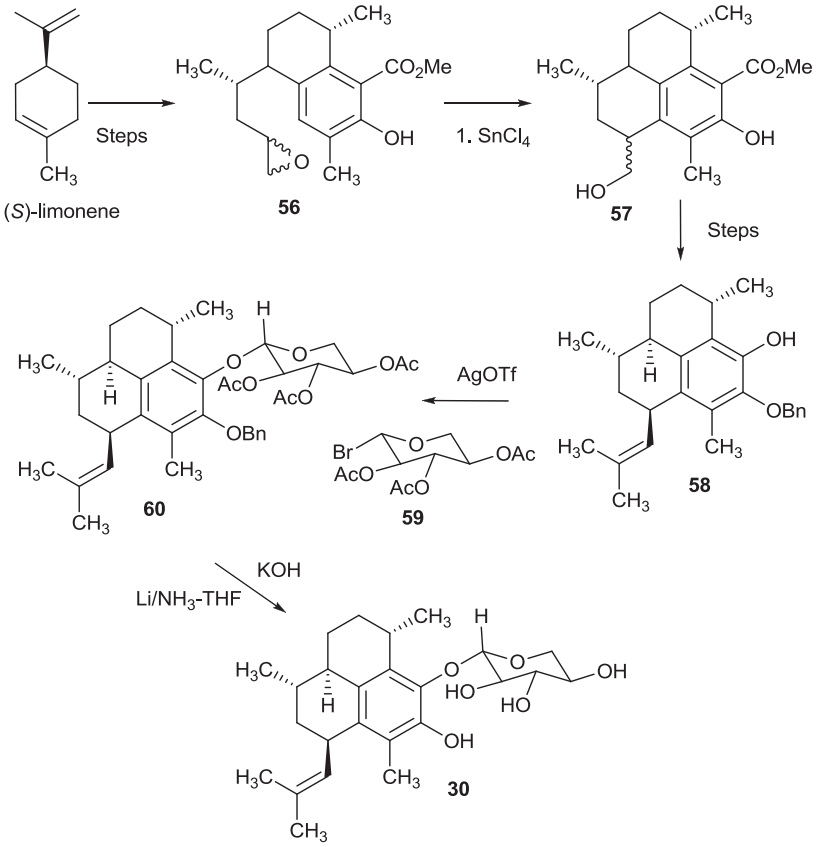
Two complete total syntheses of pseudopterosins are described in the literature. In the late 1980s Broka reported a total synthesis of pseudopterosin A[69]: shortly thereafter Corey reported enantioselective syntheses of pseudopterosin A (**30**) and E (**55**).[70] These pioneering syntheses necessarily incorporate formation of the glycoside from a pseudopterosin A–F aglycone (**A1**). All subsequently reported synthetic methodology has focused on alternative routes to the pseudopterosin A–F glycoside and stereoisomers (**A2**, **A3**, **A4**); references for all the syntheses of pseudopterosin aglycones are given in Figure 3. Furthermore, two syntheses of the seco-pseudopterosin aglycone (**A5**) have been reported, in both cases these are related to syntheses of pseudopterosin aglycones. No syntheses of seco-pseudopterosin glycosides are available.

The aims of this section are to highlight the synthetic methods available for syntheses of pseudopterosins, seco-pseudopterosins and their aglycones. A variety of strategies of varying degrees of enantioselectivity have been utilized in these syntheses and these have followed different approaches to the A, B, and C rings.[92] While not going into each synthesis in detail we aim to highlight the key ring forming steps. Thus all the complete syntheses of pseudopterosin aglycones are discussed below.

As discussed above the proposed biosynthesis of pseudopterosins follows an A→AB→ABC ring forming strategy. Several of the syntheses shown below follow this pattern; however, other cyclization strategies are also followed.

3.4.1. Total syntheses of pseudopterosins

The first publication of a pseudopterosin synthesis was a synthesis of pseudopterosin A by Broka et al. in 1988.[69] This synthesis commenced with (*S*)-(−)-limonene and proceeded through a non-stereoselective multistep route. In this sequence the A- and B-rings of pseudopterosin were prepared and then the tricyclic core of pseudopterosin was constructed by $SnCl_4$ mediated cyclization of

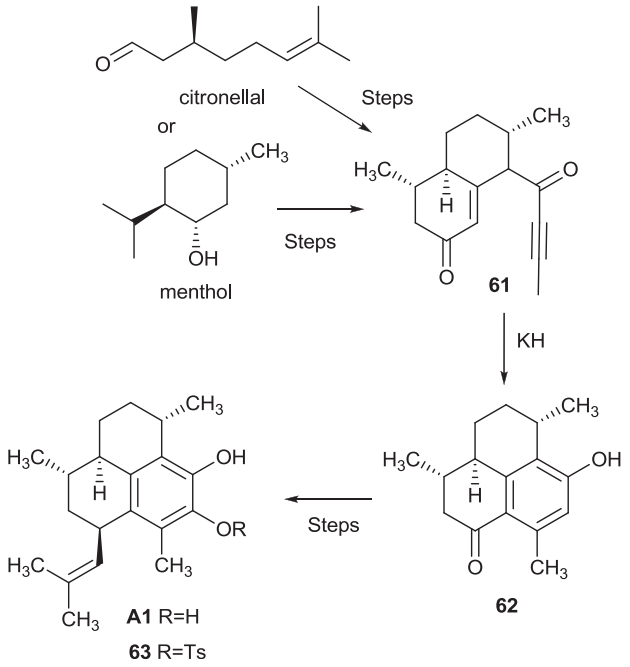


Scheme 7. Broka's synthesis of pseudopterosin A.[69]

the epoxide **56** to give the hexahydro-1*H*-phenalene derivative **57**. Further homologation yielded the pseudopterosin A aglycone benzyl ether **58** in approximately 1% overall yield (Scheme 7). The total synthesis of pseudopterosin A was completed by glycosylation of **58** with an excess of glycosyl donor **59**, to give the protected pseudopterosin **60**. Finally, deprotection of the acetate and benzyl groups gave pseudopterosin A in approximately 0.3% overall yield.

Shortly after Broka's synthesis was published, Corey's group reported a stereoselective total synthesis of pseudopterosin A and pseudopterosin E starting from (1*S*,2*R*,5*S*)-(+)-menthol.[70] In this strategy the B- and C-rings were prepared first to give the diketone **61**, and then a novel annulation methodology was used to generate the aromatic A ring yielding **62**. The tricyclic core of the pseudopterosin was then homologated to the aglycone **A1** (Scheme 8). A more efficient synthesis of **62** starting from (*S*)-citronellal was reported later.[71]

Corey's group carried the aglycone forward to pseudopterosin A (**30**) through a base promoted reaction between the tosylate **63** and 2,3,4-triacetyl-α-D-xylopyranosyl bromide followed by deprotection (not shown).



Scheme 8. Corey's first synthesis of pseudopterosin A aglycone.[70,71]

Pseudopterosin E (**55**) was synthesized from the aglycone **A1** and the glycosyl donor **64** (Scheme 9). Later, Corey developed an alternative route to pseudopterosins starting from (*S*)-(−)-limonene[72] (see below).

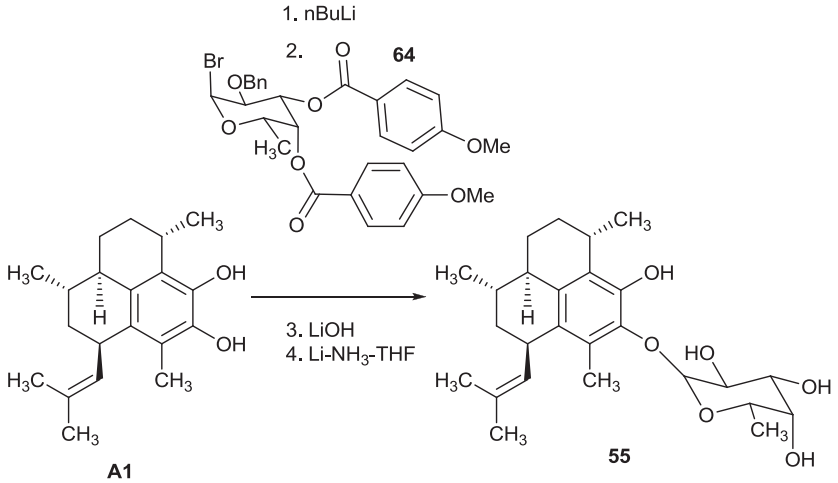
3.4.2. Total syntheses of pseudopterosin aglycones and seco-pseudopterosin aglycones

The above total syntheses are based around the pseudopterosin A–F aglycone (**A1**). A number of other elegant alternative syntheses of the pseudopterosin aglycones are available and are discussed below.

Following their initial synthesis of pseudopterosin A (**30**) and E (**55**), Corey's group developed a new elegant route to pseudopterosins starting from (*S*)-(−)-limonene (Scheme 10). This inexpensive starting material was used to efficiently and stereoselectively prepare the TBS protected hydronaphthalene **65** and its mesylate analogue **66**. Introduction of the C-ring by diastereoselective cyclization of **66** yielded **67**, the pseudopterosin A–F (**30**–**33**) aglycone derivative. Alternatively the TBS derivative **65** underwent cyclization to yield **68**, a pseudopterosin aglycone derivative that possessed the (*S*)-configuration at C-1, that is, the C-1 epimer of pseudopterosin.[72] This powerful methodology also proved useful in a structural revision of the pseudopterosin G–J aglycone from **A3** to the diastereomer **A2**. The revision was proven unequivocally[93] when **68** was converted to the monomethyl ether **69** which was identical to the ether derived from natural pseudopterosin I.[57,94] We note that the structural revision was not unexpected following a previous revision of a related natural product helioporin D, which is a benzodioxole that possesses the same carbon skeleton as the pseudopterosins.[95] It is notable that the cyclization of **65** and **66** to the aglycone is essentially biomimetic (see **41**), though in the synthetic case the stereochemistry is controlled by electronics, whereas for the natural product this is controlled by the diene stereochemistry (and is presumably enzyme mediated).

An alternative racemic route to **A1** starting from inexpensive 5-methoxytetralone (**50**) was disclosed by workers from Schering–Plough in the early 1990s (Scheme 11). In this synthesis, relative stereochemistry was controlled absolute stereochemistry was not. The A- and B-rings were derived from the starting tetralone: the central tricyclic core of the aglycone was then generated by homologation of the alcohol **70** to ketone **71**.

The synthesis was completed over several more steps to introduce the necessary trisubstituted alkene, and the aromatic methyl and catechol functionalities.[73,74] This route was also utilized to synthesize the seco-pseudopterosin aglycone (**A5**). In this case the common intermediate **70** was homologated to the prenylated

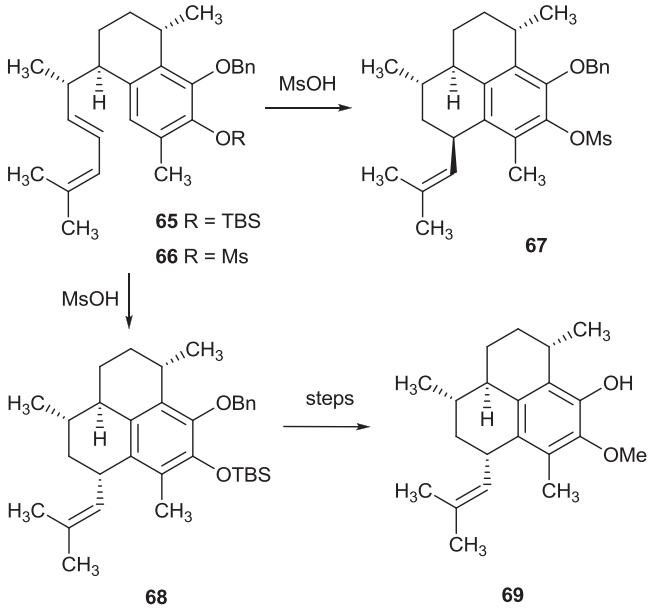


Scheme 9. Corey's synthesis of pseudopterosin E.[70]

derivative **72** before the aromatic methyl and catechol functionalities were installed.[83]

An elegant synthesis of **A1** that utilized benzyne Diels–Alder chemistry was reported by Buszek and Bixby in 1995 (Scheme 12).[75] The chiral phenylacetate **73** served as a starting material and was efficiently converted to diene **74**. Treatment of this key building block with LDA generated the benzyne intermediate which underwent an intramolecular Diels–Alder reaction to the ethylene-bridged compound **75** (plus the related diastereomer), which possessed the desired A-, B- and C-rings. The synthesis was completed by further homologation to **76**, which was an intermediate in Corey's pseudopterosin synthesis.

Schmalz and colleagues pursued an approach to pseudopterosins and seco-pseudopterosins starting with chiral η^6-arene-$Cr(CO)_3$ complexes.[96,97] This culminated in a synthesis of the pseudopterosin A–F aglycone (Scheme 13) and the seco-pseudopterosin aglycone.[76]



Scheme 10. Corey's diasteroeselective synthesis of the pseudopterosin A–F and G–J aglycone core structures.[57,94]

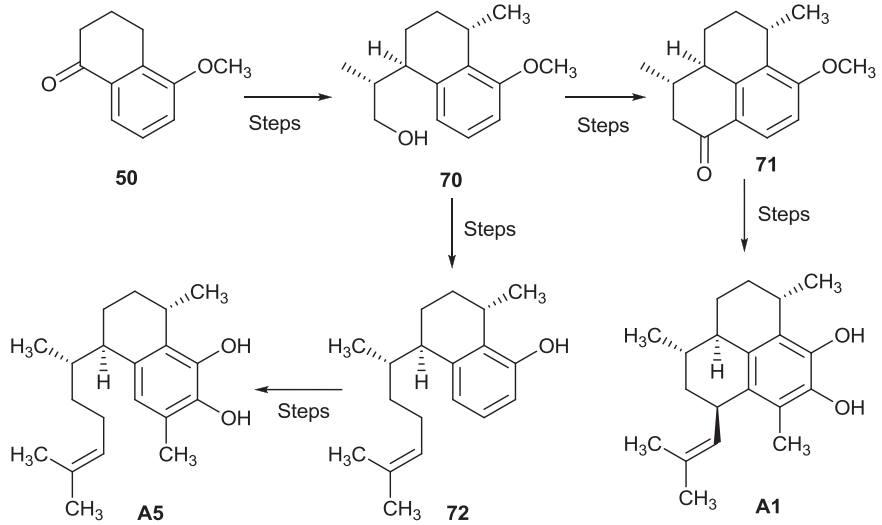
The chiral tetralone derivative **77** served as the starting material incorporating both the A- and B-rings and this was enantioselectively converted to the tosylate **78**. Nucleophilic substitution with the anion of (3-methylbut-2-enylsulfonyl)benzene yielded **79**, that was cyclized to yield the pseudopterosin A–F aglycone dimethyl ether **80**. Alternatively, **79** was selectively reduced to the seco-pseudopterosin aglycone dimethyl ether **81**. Around the same time, a simplified related methodology was used to synthesize 18-nor-seco-pseudopterosin aglycone (**82**) from **77** (see Fig. 4).[98]

Kocienski and co-workers have described two different synthetic strategies to pseudopterosin aglycones. The first 'A→AB→ABC annulation strategy' was used to prepare **83** corresponding to the methyl ether of the originally assigned structure of the pseudopterosin G–J aglycone (Scheme 14).[79] Here the starting chiral pool was ethyl (*S*)-lactate which was used to stereoselectively prepare the molybdenate complex **84**. Oxidative elimination of this species yielded **85**, a fragment comprising of the pseudopterosin A-ring with the correct stereochemistry at the benzylic position. The B-ring and another two stereocenters were then introduced resulting in **86**. This advanced intermediate was treated with $EtAlCl_2$, in a manner analogous to Schmalz's cyclization of **79**, to generate **83**.

In a related study, an alternative 'B→BA→BAC annulation strategy' was used to prepare both the pseudopterosin A–F (**A1**) and pseudopterosin K–L (**A4**) aglycones (Scheme 15).[77] Given **A1** and **A4** are enantiomeric, a common general strategy was utilized starting from either (+)-isopulegol or (−)-isopulegol respectively. In both cases, the isopulegol formed the B-ring of the final product. The aromatic A-ring was produced by an interesting annulation reaction of an α-oxoketene-*S*,*S*-acetal. Thus, for the A–F aglycone, (+)-isopulegol was converted to **87** and then annulated to **88**. From here the introduction of the C-ring follows a similar course to that seen in previous syntheses; compound **89** is obtained and cyclized following established methodology to ultimately arrive at **A1**. The K–L aglycone followed a similar but not identical pathway from (−)-isopulegol to the AB-ring containing intermediate **90**.

The most recent complete route to pseudopterosin aglycones is Harrowven's racemic synthesis of the aglycones of pseudopterosin A–F (**A1**) and its enantiomer K–L (**A4**) (Scheme 16).[78]

The starting coumarin **91**, which provided the A-ring in the final product, was transformed into the spirolactone **92** in six steps. After an additional five steps, the diene **93** was obtained and this underwent Lewis acid mediated cyclization and deprotection to give a racemic mixture of **A1** and **A4**.

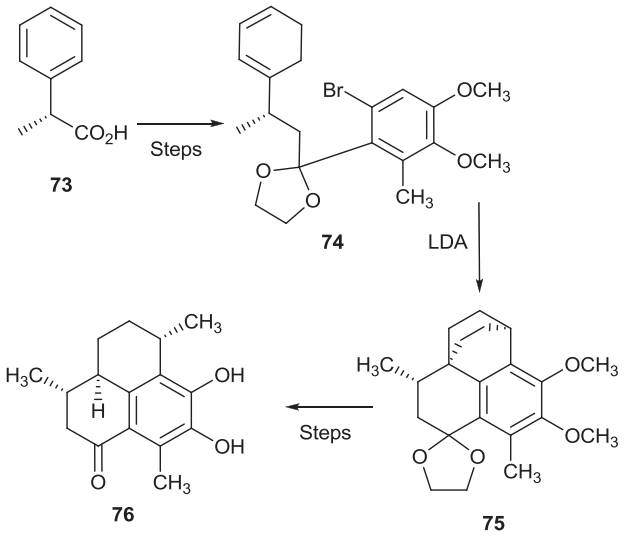


Scheme 11. McCombie's syntheses of the pseudopterosin A–F aglycone[73,74] and of the seco-pseudopterosin aglycone.[83]

3.4.3. Other approaches towards pseudopterosins

There are numerous syntheses towards pseudopterosins or pseudopterosin-like molecules[52,85,92,97–111]; thus, a variety of pseudopterosin-like molecules are known from these studies. Some of these analogs are structurally very close to pseudopterosin aglycones (Fig. 4). Notable examples include: **A6**,[84] which is a non-natural diastereomer; **94**,[106] an enantiomer of an intermediate used in McCombie's synthesis[74] of **A1**; **95**,[96] which represents an analog of the originally proposed structure of the pseudopterosin G–J aglycone, where the prenyl double bond is hydrogenated and **82**[98] a seco-pseudopterosin-like molecule. Other synthetic products contain the basic pseudopterosin ABC ring system but possess only limited ring substitution, examples include: **96**,[104] **97**,[111] **98**,[103] **99**,[47] and **100**[110] (Fig. 5). Another notable analog, **101**, was prepared semi-synthetically from the diterpene serrulantenol as part of a proposed semi-synthetic route to isomers of seco-pseudopterosins.[107] None of the above compounds were reported to possess any notable biological activity.

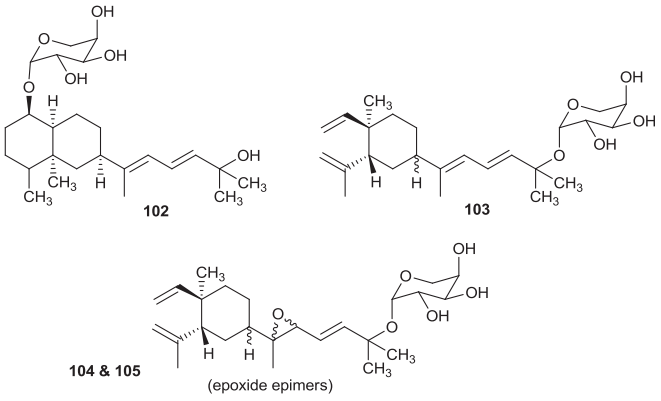
The seco-pseudopterosin aglycone has been used to prepare and reassign the structure of a related natural product, helioporin D.[95]

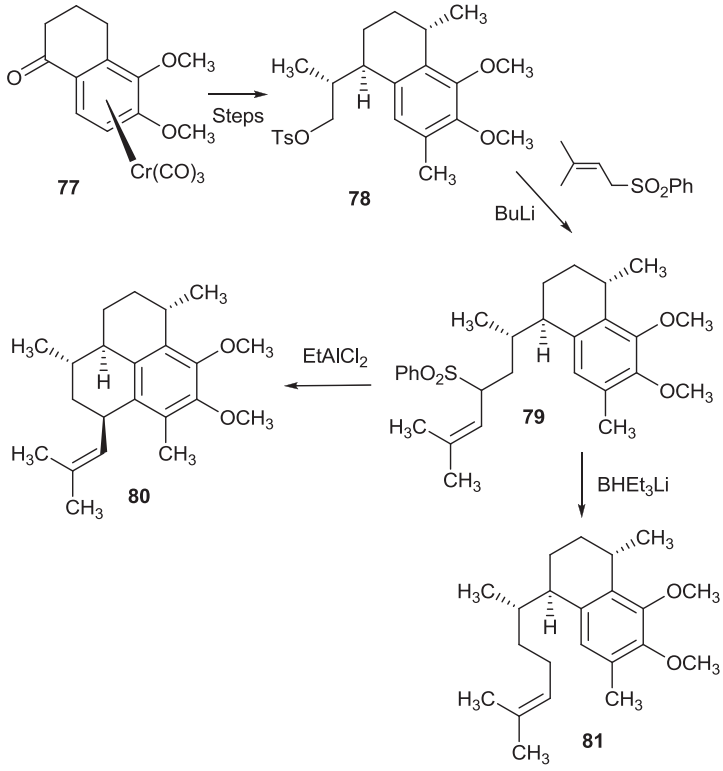


Scheme 12. Benzyne Diels–Alder approach to the pseudopterosin A–F aglycone.[75]

4. Fuscosides

The fuscosides are a class of biologically active MDGs isolated from *Eunicea fusca*. Four members of this family, fuscosides A–D (**102–105**), have been reported, and fuscosides A (**102**) and B (**103**) possess anti-inflammatory activity in mouse ear models superior to that of indomethacin.[112] They are believed to operate through selective inhibition of 5-lipoxygenase.[113]





Scheme 13. Schmalz's approach to the pseudopterosin A–F aglycone and the seco-pseudopterosin aglycone.[76]

While the aglycone of fuscoside B, fuscol (**106**), has been the subject of three different total syntheses (Fig. 6), none of the naturally occurring fuscosides have been synthesized. This likely reflects the difficulty of glycosylating a tertiary allylic alcohol.

The first synthesis of fuscol was reported by Yamada in 1992.[114] Notably, this stereoselective synthesis revealed the configuration of the C-4 stereocenter in fuscol, completing the structural assignment of this natural product. The synthesis utilized D-mannitol as the starting chiral pool and proceeded through 24 steps with an overall yield of about 6%. A key step in the synthesis was a sequential Michael addition of 3-methyl-2-cyclohexenone onto the α,β-unsaturated ester **107** (derived from D-mannitol) to stereoselectively generate the cyclohexane core of the target.

An alternative synthesis of fuscol was reported by E.J. Corey's group in 1995.[115] This was a relatively short and efficient synthesis, proceeding through 11 steps with an overall yield of about 32%. The synthesis made use of an enantioselective Ireland-Claisen reaction to efficiently convert the achiral ester **108** into a chiral rearranged product which possessed the core C-1 and C-2 stereocenters found in fuscol. The synthesis was completed by ring closure to give the cyclohexane moiety, followed by appendage of the hexadieneol based side chain.

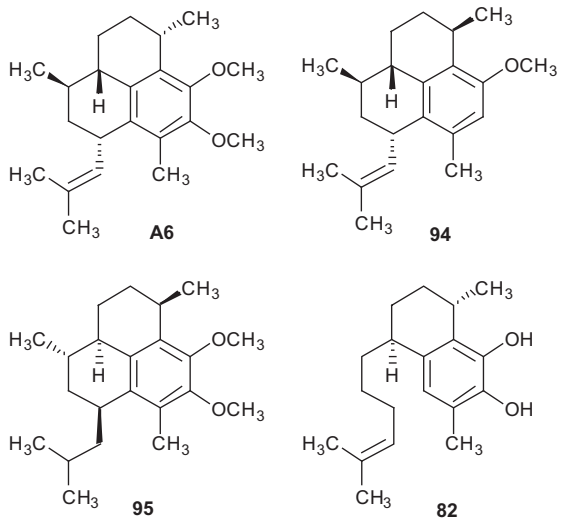


Figure 4. Pseudopterosin-like molecules closely related to the natural aglycones prepared in synthetic studies towards pseudopterosins.

The most recent synthesis of fuscol was reported by Kato and co-workers in 1998.[116] These authors had previously prepared the chiral cyclohexane derivative **109** from (+)-nopinone and recognized that **109** represented an obvious chiral starting material for the synthesis of fuscol. The strategy proceeded by removal of the unwanted keto group on the cyclohexane moiety, followed by several steps to install the hexadieneol based side chain. The synthesis was completed in 10 steps with an overall yield of about 20%.

Eunicol (**110**) was recently reported to co-occur with fuscol in *E. fusca*.[117] Both of these aglycones have been transformed to a small group of unnatural glycosides using a modified Koenigs–Knorr glycosylation.[118] This semisynthesis project provided access to the unnatural β-glycosides (e.g., **111** and **112**, Fig. 7) allowing for an evaluation of the effect of anomeric stereochemistry on the anti-inflammatory activity. Interestingly, all new derivatives were found to be either inactive or pro-inflammatory, highlighting the importance of the configuration of the glycosidic linkage of the natural products.

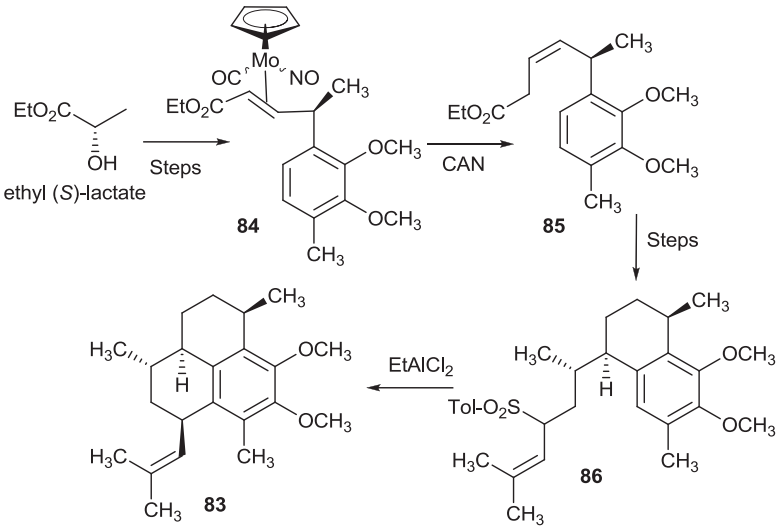
Biosynthetic studies using ^{3}H-labeled metabolites have led to the identification of the diterpene cyclase product formed en route to eunicol and fuscol.[117] The cyclase product has been assigned the trivial name eunicene A (**113**) and was demonstrated to undergo an oxidation to eunicol (**110**), which was shown to be subsequently transformed to fuscol (**106**), presumably via a Cope rearrangement (Fig. 8).

5. Miscellaneous

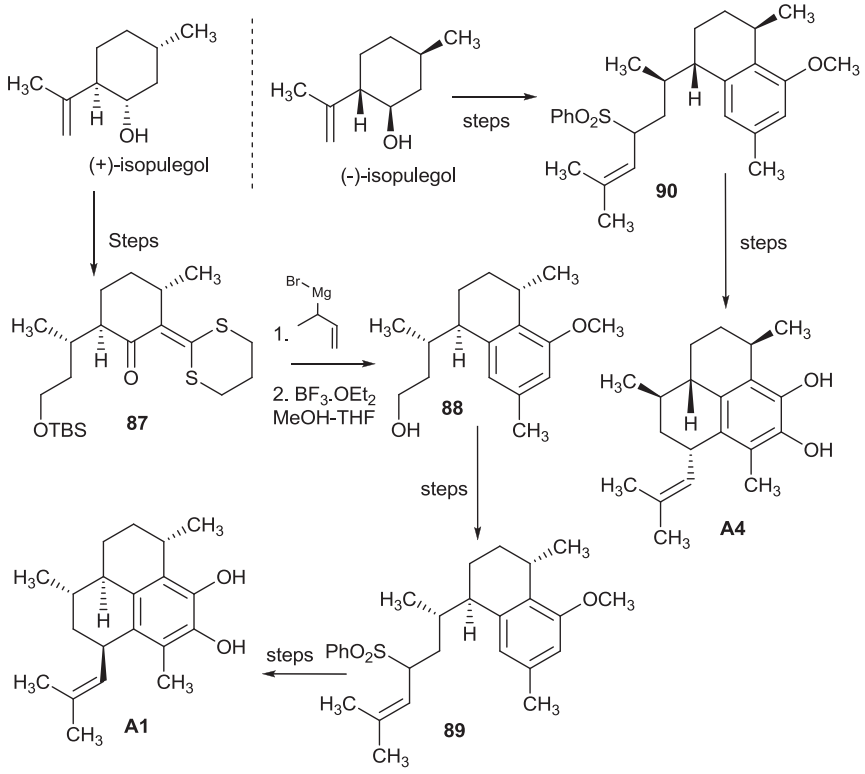
In addition to the extremely biologically interesting MDGs discussed above there are number of other known MDGs, several of which exhibit biological activity. The following miscellaneous MDGs have been obtained from either the gorgonian *Eunicea* sp. or from soft corals from the genus *Lemnalia*; furthermore, there is one report of a diterpene glycoside from a marine derived fungus.

5.1. *Eunicea* sp.

Calyculaglycosides A–E (**114**–**118**) are MDGs isolated from the gorgonian *Eunicea* sp. collected in Colombia and Puerto Rico.[119,120] The calyculaglycosides are derivatives of the same aglycone (**119**) and they differ from each other in the identity of the carbohydrate moieties. Compounds **114**–**116** were originally reported to possess

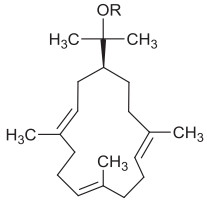


Scheme 14. Kocienski's 'A→AB→ABC annulation strategy' to the originally assigned structure of the pseudopterosin G–J aglycone.[79]



Scheme 15. Kocienski's 'B→BA→BAC annulation strategy' to the pseudopterosin A–F and pseudopterosin K–L aglycones.[77]

a dilophol skeleton; however, their structures were revised following the isolation of the parent aglycone **119**, which is an enantiomer of the known metabolite (−)-nephthenol. In the structural elucidation of the calyculagylcosides, the hexose residues were identified by chiral GC/MS analysis as mono- and di-acetylated D-galactose and D-glucose. The calyculaglycosides are the only MDGs that possess a cembrane aglycone.



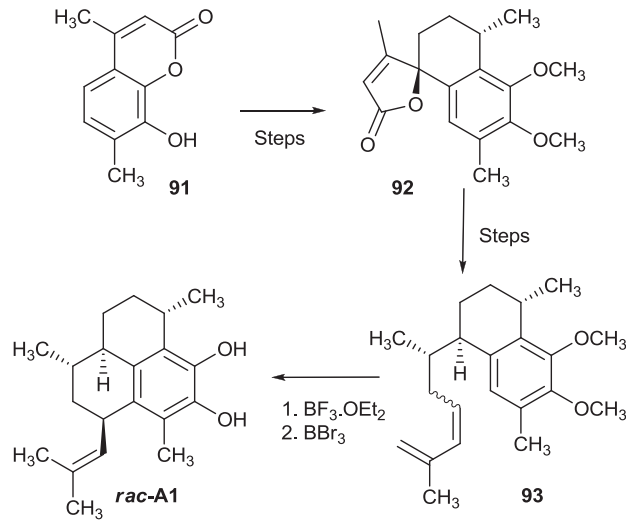
114 R= β-D-galactose-(C3'-OAc; C6'-OAc)
115 P= β-D-glucose-(C4'-OAc; C6'-OAc)
116 P= β-D-galactose-(C4'-OAc; C6'-OAc)
117 P= β-D-galactose-(X6 -OAc)
118 P= β-D-glucose-(X6 -OAc)
119 R= H

Notably, calyculaglycoside B (**115**) was shown to exhibit potent topical anti-inflammatory activity at a level comparable with indomethacin.[119] This preliminary study suggested that compound **115** is a nonselective inhibitor of the 5-lipoxygenase and cyclooxygenase pathways and its mechanism of action proceeds through mediation of arachidonic acid metabolism rather than by blocking the release the cytokine IL-1β and TNFα.

5.2. *Lemnalia* sp.

Eleven MDGs have been isolated from different *Lemnalia* sp. Lemnabourside (**120**) was isolated from the Chinese soft coral *Lemnalia bournei* near the Xisha Islands.[121] This MDG possesses an interesting acetal linkage between the D-glucose residue and the decalin-type bicyclic aglycone. A similar diterpene glycoside with an acetal linkage was previously isolated from *Lemnalia digitata*.[122] More recently, lemnabourides B (**121**) and C (**122**), acylated derivatives of compound **120**, were isolated from *L. bournei*. These exhibited weak cytotoxicity against hepatoma ascites cells (HepA), sarcoma 180 ascites cells (S_{180}A) and Ehrilich ascites carcinoma cells (EAC.[123] Lemnabourside (**120**) has also been reported from the closely related soft coral *Nephthae chabroli*, which belongs to the same family (Nephtheidae).[124] In addition to anti-proliferative activity against human prostate carcinoma LNCaP cells, lemnabourside was shown to inhibit 5α-reductase in vitro, using a rat prostate homogenate.[125]

Another series of related MDGs from *Lemnalia* sp. are lemnafl-avoside (**123**) and three minor monoactetate analogues



Scheme 16. Harrowven's racemic syntheses of the pseudopterosin A–F and K–L aglycones[78] (relative stereochemistry shown).

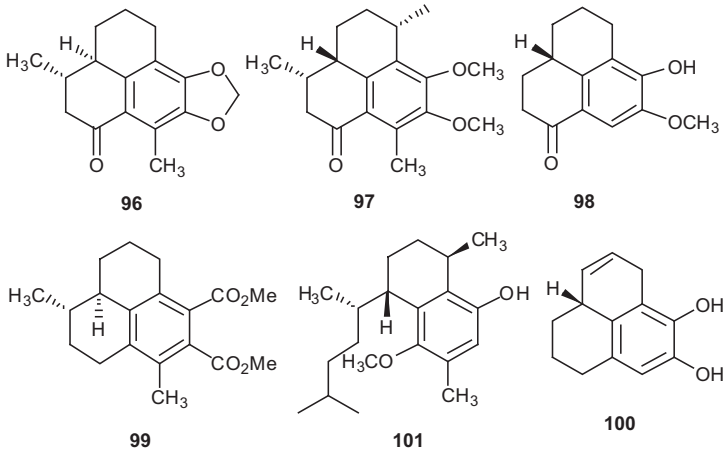


Figure 5. Selected examples of additional pseudopterosin-like molecules prepared in synthetic studies towards pseudopterosins.

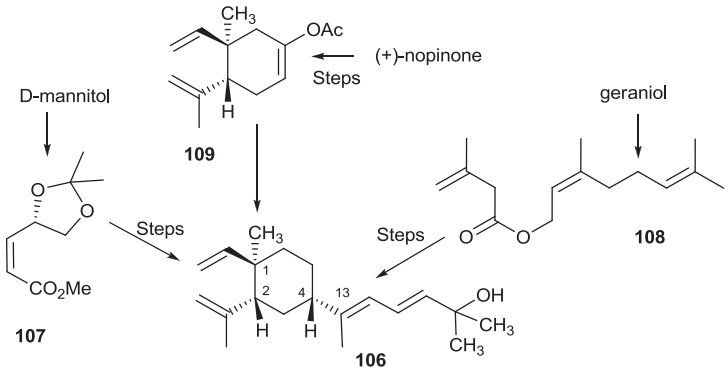


Figure 6. Synthetic approaches to fuscol (**106**).

(**124**–**126**), which were reported from the first chemical investigation of *Lemnalia flava* collected off Mombasa, Kenya.[126] Lemnaflavoside (**123**) was found to be cytotoxic to sea urchin embryos. More recently, similar diterpene glycosides, lemnalosides A–D (**127**–**130**) were reported along with lemnabourside (**120**) from an unidentified species of *Lemnalia* collected in the South China Sea, Malaysia.[127] Compounds **127** and **128** showed moderate activities in the hyphae formation inhibition (HFI) assay, a prokaryotic whole cell assay looking for protein kinase inhibition.[128]

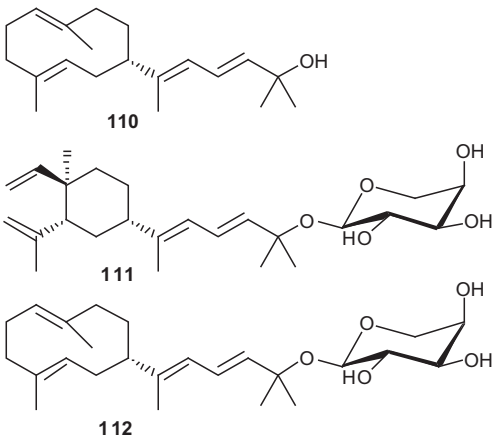
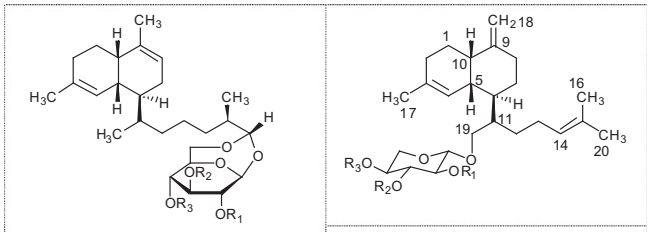


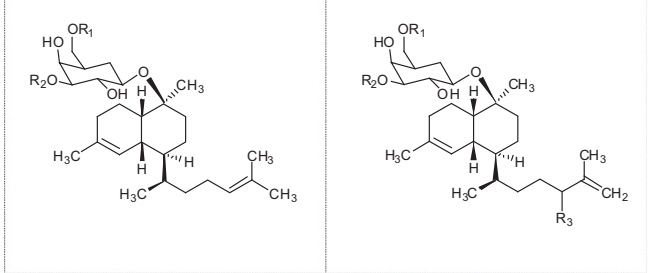
Figure 7. Eunicol and two unnatural β-glycosides.



123 R_1= R_2= R_3= H

120 R_1= R_2= R_3= H
121 R_1= R_3= H; R_2= Ac
122 R_1= R_2= H; R_3= Ac

124 R_2= R_3= H; R_1= Ac
125 R_1= R_3= H; R_2= Ac
126 R_1= R_2= H; R_3= Ac



127 R_2= H; R_1= Ac
128 R_1= H; R_2= Ac

129 R_2= H; R_1= Ac; R_3= OOH
130 R_1= R_2= H; R_3= O=

Lemnabour sides, lemnaflavoside, and lemnaloside are among the few diterpenes isolated from *Lemnalia* species; sesquiterpenes are the most abundant class of terpenoids isolated from this genus. These MDGs have not been synthesized. However, the diterpene skeleton of lemnaflavoside was previously obtained from the cyclization of obscuronatin (**131**), isolated from the soft coral *Xenia obscuronata*.[129] Moreover, Ishitsuka described a similar chemical transformation involving a transannular cyclization of **132** previously isolated from the brown algae *Dictyota dichotoma* (Fig. 9).[130] Treatment of (−)-obscuronatin (**131**) with acid in aqueous acetone yielded dictyoin B (**133**) in which the carbon skeleton is antipodal to another natural product, **134**, isolated from a termite.[131,132] It is notable that such diverse organisms may share similar secondary metabolite biosynthetic pathways.

5.3. *Acremonium striatisporum*

The sole case of the isolation of a MDG from an organism other than a coral is embodied in a series of reports of virescenosides from a strain of the fungus *A. striatisporum*. In 2000, the previously identified compounds virescenoside M (**135**) and virescenoside N (**136**) were reported from the marine fungus *A. striatisporum* associated with the superficial mycobiota of the Holothurian *Eupentacta fraudatrix*.[133] From this sea cucumber-associated fungus, the

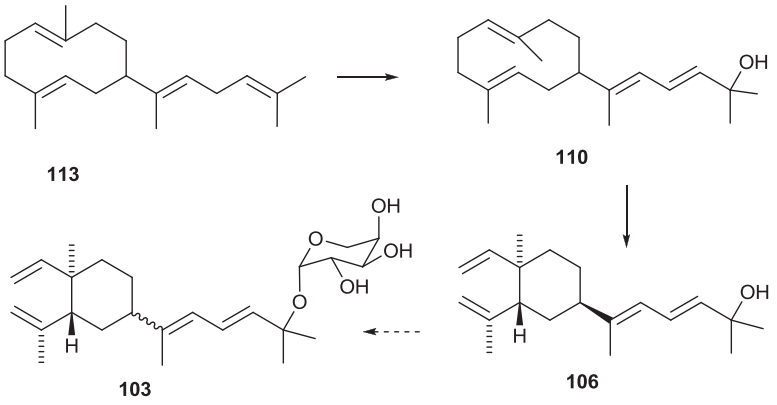


Figure 8. Proposed biosynthetic pathway leading to fuscoside B (**103**).

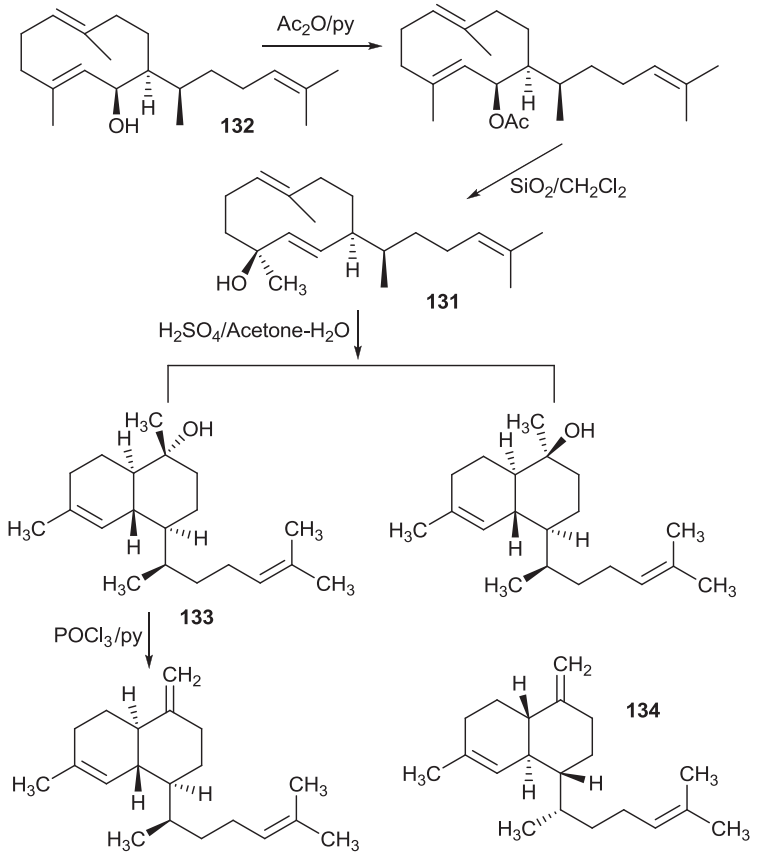
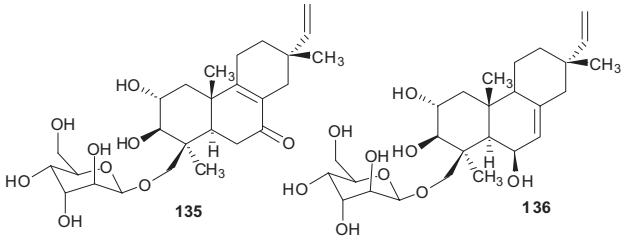


Figure 9. Ishitsuka et al. chemical transformation.

authors described the isolation of nine new isopimaradiene diterpene glycosides, virescenosides O–X.[134–138] Virescenosides were previously isolated from the terrestrial fungus *Acremonium luzulae* and shown to exhibit cytotoxic activity against developing eggs of the sea urchin and Ehrlich carcinoma cells. This class of compounds was recently reviewed.[139,140]



Marine fungi are still defined by the habitat from which they are isolated rather than being a physiologically or taxonomically defined group of microorganisms.[140] Consequently, it is uncertain whether or not the virescenosides should be considered to be marine metabolites.

6. Conclusion

Given the tremendous structural diversity of marine diterpenes together with the frequency of glycosylation of natural products, it is somewhat surprising to note the lack of glycosylation of marine diterpenes. However, while there are a small number of MDGs it is noteworthy that the three primary examples, eleutherobins, pseudopterosins, and fuscosides, display exceptional bioactivity. Desmethyleleutherobin has activity comparable to prominent natural products such as taxol, discodermolide, and epothilones. Pseudopterosins are potent anti-inflammatory agents with a commercial market in personal care products. Fuscosides are also potent anti-inflammatory agents exerting their effect by selective inhibition of 5-lipogygenase. This review summarizes data collectively suggesting that MDGs are privileged structures and highly worthy of tremendous attention by the scientific community.

It is apparent that the carbohydrate moiety of MDGs is required for optimal biological activity. The arabinose is important for the activity in the eleutherobin series. Andersen's data as well as the reported activity for the sarcodictyins clearly differentiates the glycosylated diterpenes as the most active. The aglycone of pseudopterosins is also much less active than the glycosides. Lastly, while fuscol has been shown to exhibit anti-inflammatory activity, it appears that its glycoside is more active.

The sole exception to corals as a source of MDGs is the virescenoside family from the fungus *A. striatisporum*. It is noteworthy that these belong to the copalyl diphosphate (CPP) class of diterpenes are thus are biosynthetically distinct from the MDGs isolated from corals.

Acknowledgments

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References and notes

1. Berrue, F.; Kerr, R. G. *Nat. Prod. Rep.* **2009**, *26*, 681.
2. Andersen, R. J.; Roberge, M.; Cinel, B. PCT Int. Appl. 2001, 2000-CA1395; 1999-2290316, 37.
3. Fenical, W. H.; Jensen, P. R.; Lindel, T. U.S. 1995, 1994-336518; 1994-336518, 10.
4. Lindel, T.; Jensen, P. R.; Fenical, W.; Long, B. H.; Casazza, A. M.; Carboni, J.; Fairchild, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 8744.
5. Long, B. H.; Carboni, J. M.; Wasserman, A. J.; Cornell, L. A.; Casazza, A. M.; Jensen, P. R.; Lindel, T.; Fenical, W.; Fairchild, C. R. *Cancer Res.* **1998**, *58*, 1111.
6. Schiff, P. B.; Fant, J.; Horwitz, S. B. *Nature* **1979**, *277*, 665.
7. Baum, S. G.; Wittner, M.; Nadler, J. P.; Horwitz, S. B.; Dennis, J. E.; Schiff, P. B.; Tanowitz, H. B. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 4571.
8. Bollag, D. M.; McQueney, P. A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazarides, E.; Woods, C. M. *Cancer Res.* **1995**, *55*, 2325.
9. Mooberry, S. L.; Tien, G.; Hernandez, A. H.; Plubrukarn, A.; Davidson, B. S. *Cancer Res.* **1999**, *59*, 653.
10. Ter Haar, E.; Kowalski, R. J.; Hamel, E.; Lin, C. M.; Longley, R. E.; Gunasekera, S. P.; Rosenkranz, H. S.; Day, B. W. *Biochemistry* **1996**, *35*, 243.
11. Von Angerer, E. *Curr. Opin. Drug Disc. Dev.* **2000**, *3*, 575.
12. Ojima, I.; Chakravarty, S.; Inoue, T.; Lin, S.; He, L.; Horwitz, S. B.; Kuduk, S. D.; Danishefsky, S. J. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 4256.
13. Cinel, B.; Roberge, M.; Behrisch, H.; van Ofwegen, L.; Castro, C. B.; Andersen, R. J. *Org. Lett.* **2000**, *2*, 257.
14. Roberge, M.; Cinel, B.; Anderson, H. J.; Lim, L.; Jiang, X.; Xu, L.; Bigg, C. M.; Kelly, M. T.; Andersen, R. J. *Cancer Res.* **2000**, *60*, 5052.
15. D'Ambrosio, M.; Guerriero, A.; Pietra, F. *Helv. Chim. Acta* **1987**, *70*, 2019.
16. D'Ambrosio, M.; Guerriero, A.; Pietra, F. *Helv. Chim. Acta* **1988**, *71*, 964.
17. Battistini, C.; Ciomei, M.; Pietra, F.; D'Ambrosio, M.; Guerriero, A. *PCT Int. Appl.* **1996**, 17.
18. Clomel, C.; Albanese, C.; Pastori, W.; Grandi, M.; Pietra, F.; D'Ambrosio, M.; Guerriero, A.; Battistini, C. *Proc. Am. Assoc. Cancer Res.* **1997**, 38. Abstract#30.
19. Nakao, Y.; Yoshida, S.; Matsunaga, S.; Fusetani, N. *J. Nat. Prod.* **2003**, *66*, 524.
20. Ketzinel, S.; Rudi, A.; Schleyer, M.; Benayahu, Y.; Kashman, Y. *J. Nat. Prod.* **1996**, *59*, 873.
21. Lin, Y.; Bewley, C. A.; Faulkner, D. J. *Tetrahedron* **1993**, *49*, 7977.
22. Britton, R.; Roberge, M.; Berisch, H.; Andersen, R. J. *Tetrahedron Lett.* **2001**, *42*, 2953.
23. Hanson, K. M.; Simon, J. D. *Photochem. Photobiol.* **1997**, *66*, 817.
24. Hug, D. H.; Dunkerson, D. D.; Hunter, J. K. *J. Photochem. Photobiol., B* **1999**, *50*, 66.
25. Nicolaou, K. C.; Ohshima, T.; Hosokawa, S.; Van Delft, F. L.; Vourloumis, D.; Xu, J. Y.; Pfefferkorn, J.; Kim, S. *J. Am. Chem. Soc.* **1998**, *120*, 8674.
26. Nicolaou, K. C.; van Delft, F.; Ohshima, T.; Vourloumis, D.; Xu, J.; Hosokawa, S.; Pfefferkorn, J.; Kim, S.; Li, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 2520.
27. Chen, X.; Zhou, B.; Bhattacharya, S. K.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 789.
28. Chen, X.; Bhattacharya, S. K.; Zhou, B.; Gutteridge, C. E.; Pettus, T. R. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 6563.
29. Nicolaou, K. C.; Chen, J. S.; Dalby, S. M. *Bioorg. Med. Chem.* **2009**, *17*, 2290.
30. Lindel, T. *Org. Synth. Highlights IV* **2000**, 268.
31. Lindel, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 774.
32. Diederichsen, U. *Org. Synth. Highlights V* **2003**, 317.
33. Busch, T.; Kirschning, A. *Nat. Prod. Rep.* **2008**, *25*, 318.
34. Ceccarelli, S.; Piarulli, U.; Gennari, C. *Tetrahedron Lett.* **1999**, *40*, 153.
35. Ceccarelli, S. M.; Piarulli, U.; Telser, J.; Gennari, C. *Tetrahedron Lett.* **2001**, *42*, 7421.
36. Ceccarelli, S. M.; Piarulli, U.; Gennari, C. *Tetrahedron* **2001**, *57*, 8531.
37. Beumer, R.; Bayon, P.; Bugada, P.; Ducki, S.; Mongelli, N.; Sirtori, F. R.; Telser, J.; Gennari, C. *Tetrahedron* **2003**, *59*, 8803.
38. Castoldi, D.; Caggiano, L.; Panigada, L.; Sharon, O.; Costa, A. M.; Gennari, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 588.
39. Castoldi, D.; Caggiano, L.; Panigada, L.; Sharon, O.; Costa, A. M.; Gennari, C. *Chem. Eur. J.* **2005**, *12*, 51.
40. Scalabrino, G.; Sun, X.; Mann, J.; Baron, A. *Org. Biomol. Chem.* **2003**, *1*, 318.
41. Carter, R.; Hodgetts, K.; McKenna, J.; Magnus, P.; Wren, S. *Tetrahedron* **2000**, *56*, 4367.
42. Bruyere, H.; Dos Reis, C.; Samaritani, S.; Ballereau, S.; Royer, J. *Synthesis* **2006**, 1673.
43. Winkler, J. D.; Quinn, K. J.; MacKinnon, C. H.; Hiscock, S. D.; McLaughlin, E. C. *Org. Lett.* **2003**, *5*, 1805.
44. Britton, R.; Dilip de Silva, E.; Bigg, C. M.; McHardy, L. M.; Roberge, M.; Andersen, R. J. *J. Am. Chem. Soc.* **2001**, *123*, 8632.
45. Look, S. A.; Fenical, W.; Jacobs, R. S.; Clardy, J. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 6238.
46. Look, S. A.; Fenical, W.; Matsumoto, G. K.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 5140.
47. Zhong, W.; Little, R. D. *Tetrahedron* **2009**, *65*, 10784.
48. Roussis, V.; Wu, Z.; Fenical, W.; Strobel, S. A.; Van Duyne, G. D.; Clardy, J. *J. Org. Chem.* **1990**, *55*, 4916.
49. Mydlarz, L. D.; Jacobs, R. S.; Boehnlein, J.; Kerr, R. G. *Chem. Biol.* **2003**, *10*, 1051.
50. Bunyajetpong, S.; Santiago-Vazquez, L. Z.; Kerr, R. U.S. Pat. Appl. Publ. 2008, 2008-111597; 2007-914856P, 11.
51. Flachsmann, F.; Schellhaas, K.; Moya, C. E.; Jacobs, R. S.; Fenical, W. *Bioorg. Med. Chem.* **2010**, *18*, 8324.
52. Look, S. A.; Fenical, W. *Tetrahedron* **1987**, *43*, 3363.
53. Ferns, T. A.; Kerr, R. G. *J. Org. Chem.* **2005**, *70*, 6152.
54. Hoarau, C.; Day, D.; Moya, C.; Wu, G.; Hackim, A.; Jacobs, R. S.; Little, R. D. *Tetrahedron Lett.* **2008**, *49*, 4604.
55. Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2006**, *23*, 26.

56. We are naming the aglycones according to the conventions followed in the literature.
57. Lazerwith, S. E.; Johnson, T. W.; Corey, E. J. *Org. Lett.* **2000**, *2*, 2389.
58. Brueck, T. B.; Kerr, R. G. *Comp. Biochem. Physiol., Part B: Biochem. Mol. Biol.* **2006**, *143B*, 269.
59. Newberger, N. C.; Ranzer, L. K.; Boehnlein, J. M.; Kerr, R. G. *Phytochemistry (Elsevier)* **2006**, *67*, 2133.
60. Ferns, T.; Kerr, R. G. *Tetrahedron* **2005**, *61*, 12358.
61. Kohl, A. C.; Kerr, R. G. *Arch. Biochem. Biophys.* **2004**, *424*, 97.
62. Kohl, A. C.; Ata, A.; Kerr, R. G. *J. Ind. Microbiol. Biotechnol.* **2003**, *30*, 495.
63. Kohl, A. C.; Kerr, R. G. *Mar. Drugs* **2003**, *1*, 54.
64. Thornton, R. S.; Kerr, R. G. *J. Chem. Ecol.* **2002**, *28*, 2083.
65. Coleman, A. C.; Kerr, R. G. *Tetrahedron* **2000**, *56*, 9569.
66. Coleman, A. C.; Mydlarz, L. D.; Kerr, R. G. *Org. Lett.* **1999**, *1*, 2173.
67. Ata, A.; Win, H. Y.; Holt, D.; Holloway, P.; Segstro, E. P.; Jayatilake, G. S. *Helv. Chim. Acta* **2004**, *87*, 1090.
68. Rodriguez, I. I.; Shi, Y.; Garcia, O. J.; Rodriguez, A. D.; Mayer, A. M. S.; Sanchez, J. A.; Ortega-Barria, E.; Gonzalez, J. *J. Nat. Prod.* **2004**, *67*, 1672.
69. Broka, C. A.; Chan, S.; Peterson, B. *J. Org. Chem.* **1988**, *53*, 1584.
70. Corey, E. J.; Carpino, P. *J. Am. Chem. Soc.* **1989**, *111*, 5472.
71. Corey, E. J.; Carpino, P. *Tetrahedron Lett.* **1990**, *31*, 3857.
72. Corey, E. J.; Lazerwith, S. E. *J. Am. Chem. Soc.* **1998**, *120*, 12777.
73. Ganguly, A. K.; McCombie, S. W.; Cox, B.; Lin, S.; McPhail, A. T. *Pure Appl. Chem.* **1990**, *62*, 1289.
74. McCombie, S. W.; Cox, B.; Ganguly, A. K. *Tetrahedron Lett.* **1991**, *32*, 2087.
75. Buszek, K. R.; Bixby, D. L. *Tetrahedron Lett.* **1995**, *36*, 9129.
76. Majdalani, A.; Schmalz, H. G. *Synlett* **1997**, 1303.
77. Kocienski, P. J.; Pontiroli, A.; Qun, L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2356.
78. Harrowven, D. C.; Tyte, M. J. *Tetrahedron Lett.* **2004**, *45*, 2089.
79. Chow, R.; Kocienski, P. J.; Kuhl, A.; LeBrazidec, J.; Muir, K.; Fish, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2344.
80. Ata, A.; Kerr, R. G.; Moya, C. E.; Jacobs, R. S. *Tetrahedron* **2003**, *59*, 4215.
81. Duque, C.; Puyana, M.; Narvaez, G.; Osorno, O.; Hara, N.; Fujimoto, Y. *Tetrahedron* **2004**, *60*, 10627.
82. Duque, C.; Puyana, M.; Castellanos, L.; Arias, A.; Correa, H.; Osorno, O.; Asai, T.; Hara, N.; Fujimoto, Y. *Tetrahedron* **2006**, *62*, 4205.
83. McCombie, S. W.; Cox, B.; Lin, S. I.; Ganguly, A. K.; McPhail, A. T. *Tetrahedron Lett.* **1991**, *32*, 2083.
84. LeBrazidec, J.; Kocienski, P. J.; Connolly, J. D.; Muir, K. W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2475.
85. Zhong, W.; Moya, C.; Jacobs, R. S.; Little, R. D. *J. Org. Chem.* **2008**, *73*, 7011.
86. Mayer, A. M. S.; Jacobson, P. B.; Fenical, W.; Jacobs, R. S.; Glaser, K. B. *Life Sci.* **1998**, 62. PL401.
87. Jacobs, R. S.; Fenical, W. H. *Eur. Pat. Appl.* **1986**, *1986-302711*; *1985-723214*, 31.
88. Jacobs, R. S.; Fenical, W. H. *PCT Int. Appl.* **1989,** *1988-US2695; 1987-85628*, 45.
89. Fenical, W. H.; Jacobs, R. S. *PCT Int. Appl.* **1996**, *1996-US9177*; *1995-487859*, 23.
90. Haimes, H. B.; Jimenez, P. A. *PCT Int. Appl.* **1996,** *1996-US9039; 1995-486359*, 60.
91. Tanis, V. M.; Moya, C.; Jacobs, R. S.; Little, R. D. *Tetrahedron* **2008**, *64*, 10649.
92. While syntheses of pseudopterosin aglycones have not been thoroughly reviewed excellent commentary summarizing different approaches is given in Ref. [79].
93. X-ray crystallographic data of a *p*-bromobenzoate derivative was an additional important aspect of this revision.
94. Corey, E. J. U.S. Pat. Appl. Publ. 2002, 2001-893333; 2000-712884, 13.
95. Geller, T.; Jakupovic, J.; Schmalz, H. *Tetrahedron Lett.* **1998**, *39*, 1541.
96. Schmalz, H.; Schwarz, A.; Duerner, G. *Tetrahedron Lett.* **1994**, *35*, 6861.
97. Schmalz, H.; Majdalani, A.; Geller, T.; Hollander, J.; Bats, J. W. *Tetrahedron Lett.* **1995**, *36*, 4777.
98. Majdalani, A.; Schmalz, H. *Tetrahedron Lett.* **1997**, *38*, 4545.
99. Jung, M. E.; Siedem, C. S. *J. Am. Chem. Soc.* **1993**, *115*, 3822.
100. Jung, M. E.; Lee, B. S. *J. Org. Chem.* **2000**, *65*, 9241.
101. Eklund, L.; Sarvary, I.; Frejd, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 303.
102. Harrowven, D. C.; Sibley, G. E. M. *Tetrahedron Lett.* **1999**, *40*, 8299.
103. Harrowven, D. C.; Dennison, S. T.; Howes, P. *Tetrahedron Lett.* **1994**, *35*, 4243.
104. Benoit-Marquie, F.; Csaky, A. G.; Esteban, G.; Martinez, M. E.; Plumet, J. *Tetrahedron Lett.* **2000**, *41*, 3355.
105. Schmalz, H.; Siegel, S.; Schwarz, A. *Tetrahedron Lett.* **1996**, *37*, 2947.
106. Gill, S.; Kocienski, P.; Kohler, A.; Pontiroli, A.; Qun, L. *Chem. Commun. (Cambridge)* **1996**, 1743.
107. Cowin, L. M.; Massy-Westropp, R. A. *J. Nat. Prod.* **1992**, *55*, 1790.
108. Esteban, G.; Rincon, R.; Csaky, A. G.; Plumet, J. *Nat. Prod. Commun.* **2008**, *3*, 495.
109. Kozikowski, A. P.; Wu, J. P. *Synlett* **1991**, 465.
110. Nicolaou, K. C.; Zhong, Y.; Baran, P. S.; Sugita, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 2145.
111. Harrowven, D. C.; Wilden, J. D.; Tyte, M. J.; Hursthouse, M. B.; Coles, S. J. *Tetrahedron Lett.* **2001**, *42*, 1193.
112. Shin, J.; Fenical, W. *J. Org. Chem.* **1991**, *56*, 3153.
113. Jacobson, P. B.; Jacobs, R. S. *J. Pharmacol. Exp. Ther.* **1992**, *262*, 866.
114. Iwashima, M.; Nagaoka, H.; Kobayashi, K.; Yamada, Y. *Tetrahedron Lett.* **1992**, *33*, 81.
115. Corey, E. J.; Roberts, B. E.; Dixon, B. R. *J. Am. Chem. Soc.* **1995**, *117*, 193.
116. Kosugi, H.; Yamabe, O.; Kato, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 217.
117. Saleh, M. B.; Kerr, R. G. *Aust. J. Chem.* **2010**, *63*, 901.
118. Marchbank, D. H.; Kerr, R. G. *Tetrahedron* **2011**, *67*, 3053.
119. Cobar, O. M.; Rodriguez, A. D.; Padilla, O. L.; Sanchez, J. A. *J. Org. Chem.* **1997**, *62*, 7183.
120. Shi, Y.; Rodriguez, A. D.; Padilla, O. L. *J. Nat. Prod.* **2001**, *64*, 1439.
121. Zhang, M.; Long, K.; Wu, H.; Ma, K. *J. Nat. Prod.* **1994**, *57*, 155.
122. Tursch, B. *Pure Appl. Chem.* **1976**, *48*, 1.
123. Zhang, M.; Huang, Z. *J. Nat. Prod.* **1998**, *61*, 1300.
124. Zhang, W.; Liu, W. K.; Che, C. *Chem. Pharm. Bull.* **2003**, *51*, 1009.
125. Liu, W. K.; Wong, N. L. Y.; Huang, H. M.; Ho, J. K. C.; Zhang, W. H.; Che, C. T. *Life Sci.* **2002**, *70*, 843.
126. Rudi, A.; Levi, S.; Benayahu, Y.; Kashman, Y. *J. Nat. Prod.* **2002**, *65*, 1672.
127. Yao, G.; Vidor, N. B.; Foss, A. P.; Chang, L. C. *J. Nat. Prod.* **2007**, *70*, 901.
128. Waters, B.; Saxena, G.; Wanggui, Y.; Kau, D.; Wrigley, S.; Stokes, R.; Davies, J. *J. Antibiot. (Tokyo)* **2002**, *55*, 407.
129. Kashman, Y.; Groweiss, A. *J. Org. Chem.* **1980**, *45*, 3814.
130. Ishitsuka, M. O.; Kusumi, T.; Ichikawa, A.; Kakisawa, H. *Phytochemistry* **1990**, *29*, 2605.
131. Wiemer, D. F.; Meinwald, J.; Prestwich, G. D.; Solheim, B. A.; Clardy, J. *J. Org. Chem.* **1980**, *45*, 191.
132. Mori, K.; Waku, M. *Tetrahedron* **1984**, *40*, 305.
133. Afiyatullov, S. S.; Kuznetsova, T. A.; Isakov, V. V.; Pivkin, M. V.; Prokof'eva, N. G.; Elyakov, G. B. *J. Nat. Prod.* **2000**, *63*, 848.
134. Afiyatullov, S. S.; Kalinovsky, A. I.; Kuznetsova, T. A.; Isakov, V. V.; Pivkin, M. V.; Dmitrenok, P. S.; Elyakov, G. B. *J. Nat. Prod.* **2002**, *65*, 641.
135. Afiyatullov, S. S.; Kalinovsky, A. I.; Kuznetsova, T. A.; Pivkin, M. V.; Prokof'eva, N. G.; Dmitrenok, P. S.; Elyakov, G. B. *J. Nat. Prod.* **2004**, *67*, 1047.
136. Afiyatullov, S. S.; Kuznetsova, T. A.; Isakov, V. V.; Pivkin, M. V.; Prokof'eva, N. G.; Elyakov, G. B. *J. Nat. Prod.* **2005**, *68*, 1308.
137. Afiyatullov, S. S.; Pivkin, M. V.; Kalinovsky, A. I.; Kuznetsova, T. A. *Recent Prog. Med. Plants* **2006**, *15*, 85.
138. Anisimov, M. M.; Chaikina, E. L.; Afiyatullov, S. S.; Kuznetsova, T. A. *Agrokhimiya* **2010**, 34.
139. Ebel, R. *Mar. Drugs* **2010**, *8*, 2340.
140. Rateb, M. E.; Ebel, R. *Nat. Prod. Rep.* **2011**, *28*, 290.