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Review

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The 2,11-Cyclized Cembranoids: Cladiellins, Asbestinins, and Briarellins (Period 1998−2010)

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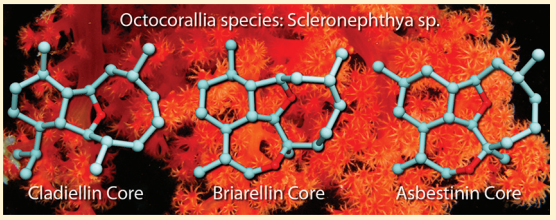
ABSTRACT: The 2,11-cyclized cembranoids are isolated from marine invertebrates of Octocorallia species. They are a very interesting class of natural products sharing a common oxatricyclo[6.6.1.0^{2,7}]pentadecane core and carrying a varied substituent pattern. This review presents their structural diversity along with the reported biological activities. The 2,11-cyclized cembranoids were comprehensively reviewed previously in 1998, and this contribution will serve as an update of that work. Since 1998 a number of structural assignments of the isolated products have been revised, some as a result of total synthesis efforts. The chemical reactivity of several of the natural compounds has been studied, and the relevance of these findings to the biosynthesis or the generation of isolation artifacts is discussed. The wide range of biological activities displayed by the 2,11-cyclized cembranoids justifies the interest shown within the synthetic chemistry community and suggests that this class of natural products remains a fruitful area for future synthetic and biological research.



The marine invertebrates of Octocorallia species have been the source of hundreds of structurally diverse and interesting natural products. This review focuses on a specific group of Octocorallia products, the 2,11-cyclized cembranoids, which fall into the related structural classes of cladiellins, asbestinins, and briarellins. The architecture of the 2,11-cyclized cembranoids and the range of biological activities observed for the compounds has prompted interest in these molecules from across the scientific community, and from synthetic chemists in particular.[1−17] This review presents the diverse structures and reported biological activities of this group of natural products. An extensive review written in 1998 by Bernardelli and Paquette detailed the 2,11-cyclized cembranoids known at that time and their biological activities.[18] Since 1998, a limited number of surveys of the literature on this class of compound have been published but have been restricted to the natural products associated with either a particular geographical area of origin[19] or a particular species of marine invertebrate.[20] It is therefore timely to review the reports published on cembranoids that fall into the aforementioned classes covering 1998−2010. In particular, this review seeks to annotate the natural products with their biological activities, concentrating on new activities reported since the last comprehensive survey,[18] and to examine the possibilities that these intriguing structures may present for drug discovery.

■ ECOLOGY

Cladiellins, asbestinins, and briarellins are diterpenoids isolated from certain marine invertebrates. These invertebrates all fall into the class of soft corals with 8-fold symmetry of their polyps and are hence known as Octocorallia. Octocorallia are representative of the phylum Cnidaria (previously known as Coelenterate) and the subclass Anthozoa. Octocorallia have an endosymbiotic relationship with zooxanthellae, single-celled algae, which provide energy for the coral to grow through photosynthesis, while the coral provides a protective environment. It is unclear whether the cembranoids are biosynthesized by the coral or the endosymbiotic zooxanthellae, and this has prompted much discussion in the literature.[21,22] It has been shown that lophotoxin, a furanocembranolide biosynthetically derived from the same C-20 terpenoid intermediate as the cembranoids, may be isolated from marine invertebrates without symbionts,[23] suggesting these diterpenoids are of animal origin. This hypothesis is supported by the observation that triterpenoid concentration levels remain constant between healthy and bleached corals.[22] However, it is also possible to isolate diterpenes from purified zooxanthellae,[24] which suggests that both the marine invertebrates and algae may play roles in the biosynthesis of the isolated natural products.

The 2,11-cyclized cembranoids are believed to originate from cembranes that are biosynthesized by the macrocyclization of geranylgeranyl diphosphate (Scheme 1). The cembrane scaffold then undergoes a carbon−carbon bond forming cyclization between C-2 and C-11, the exact mechanism of which is unknown. Ether formation between C-3 and C-10 yields the tricyclic cladiellin scaffold. Further ether formation between C-3 and C-20 (cladiellin scaffold numbering) gives the tetracyclic briarellin scaffold, which may be converted to the asbestinin scaffold through a 1,2-methyl shift.[25,26]

The presence of the cembranoid natural products may confer protective properties, on the basis of the activities the compounds have exhibited in biological assays. These include ichthyotoxic, molluscicidal, and gastropod-repellent activities, as well as lethality to brine shrimp and the ability to inhibit the cell division of starfish eggs at low concentrations.[18] The levels of the putative defensive natural products found within the corals have been shown to be related to the environment of the

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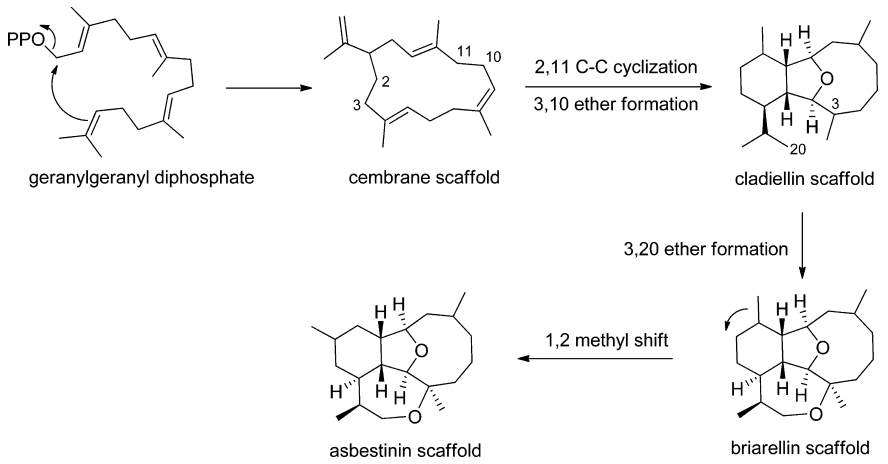
Scheme 1. Proposed Biosynthetic Pathway to 2,11-Cyclized Cembranoids



coral, with increased levels in deep water. This may be an advantage, since reduced photosynthesis and growth in deeper waters could lead to a higher metabolic cost for repairing predator damage in the lower resource environment.[27]

OXIDATION PATTERNS AND COMMON SUBSTITUENTS

Cladiellin, asbestinin, and briarellin natural products share a common core motif, an oxatricyclo[6.6.1.0^{2,7}]pentadecane core. The three structural families may be represented by their oxatricyclo[6.6.1.0^{2,7}]pentadecane scaffolds with multiple points of further elaboration by introduction of oxygen functionalities or unsaturation, as is common in other diterpenoid natural products.[28] The common scaffolds were first recognized by Bernadelli and Paquette,[18] but at that point sufficient numbers of briarellins had not been isolated to allow such a generalization. Currently, 23 briarellins are known, allowing the patterns of scaffold decoration to be summarized as shown in Figure 1. The atom numbering of the scaffolds shown in this

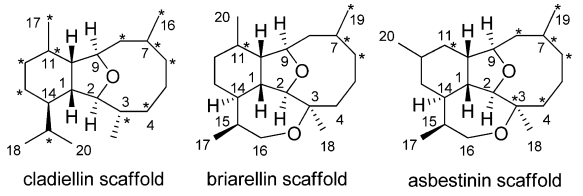


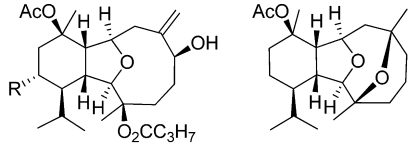
Figure 1. Core scaffolds of the cladiellins, briarellins, and asbestinins. Carbons bearing an asterisk are commonly oxygenated or unsaturated within the class.

figure will be referred to throughout this review. The majority of the functionalization of the scaffolds is observed in the form of unsaturation, hydroxylation, acetylation, butyroylation, or heptanoylation. Less commonly, functionalization can be found in the form of propenoylation, epoxide or peroxide formation, or methylsulfinyl substitution.

ABSOLUTE CONFIGURATION

The relative configurations of the 2,11-cyclized cembranoids have been assigned through various NMR techniques and X-ray crystallography as the compounds have been isolated. The 2,11-cyclized cembranoids have been depicted in the literature with either absolute or relative configuration throughout the last three decades. It is important to note that in the absence of firm data, some papers may inadvertently show an incorrect absolute configuration.

The earliest attempt to assign an absolute configuration was made in 1988[29] using circular dichroism methods. All subsequent experiments to confirm the absolute configuration of the series have shown that the compounds appear to have the same configurational properties.[18] For example, in 2009 the absolute configuration of simplexin A (**1**) was confirmed by making Mosher ester derivatives,[30] and the configuration of klysimplexin C (**2**) was also verified through Mosher methods.[31] The assignments of absolute configuration have been supported by several total syntheses.[2−10,12−17] These studies suggest all the 2,11-cyclized cembranoids are from the same enantiomeric series. One exception appears to be that of polyanthellin A (**3**). It was originally isolated in 1989, with a positive specific rotation ($[\alpha]^{25}_{D}$ = +8.9°, *c* 0.22, $CHCl_3$);[32] this correlates to a sample isolated in 2010 with a similar specific rotation ($[\alpha]^{25}_{D}$ = +8.0°, *c* 0.73, $CHCl_3$).[33] However, a spectroscopically identical sample was isolated in 2003 with a near-opposite specific rotation ($[\alpha]^{25}_{D}$ = −9.9°, *c* 1.0, $CHCl_3$).[34] The discrepancy in optical rotation suggests that polyanthellin A (**3**) may be biosynthesized as both enantiomers.



REACTIVITY

It has been reported that some examples of 2,11-cyclized cembranoids are formed with strained *E* double bonds between C-6 and C-7 and that these are capable of chemical reaction upon standing in solvents.[35] This is interesting, as it may allow some insight into the process by which substituents are introduced at these centers in a biological environment. It also serves as a caution that some of the compounds characterized may have been altered chemically during their isolation. Scheme 2 shows the change of 6(*E*) cladiellin diterpene (**4**)

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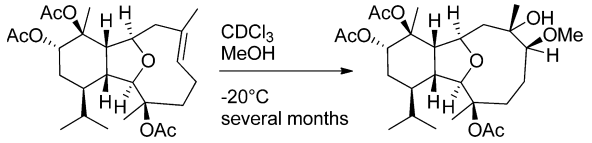
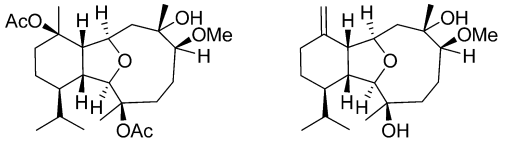
Scheme 2. Reaction of 6(*E*) Cladiellin Diterpene (4) on Standing in $CDCl_3$/MeOH



on storage in a chloroform−methanol mixture over several months, whereupon the formation of **5** was observed.[35]

The reactivity of **4** suggests that palmonine A[36] (**6**) and sclerophytin F methyl ether[37] (**7**) may also be artifacts of isolation, since they display the same substituent pattern at C-6 and C-7. It is also proposed that cladiellins that bear a β-oriented hydroxy at C-6 and an α-oriented hydroxy at C-7 may be derived from an epoxide precursor undergoing nucleophilic ring opening by water.[35] Examples of 2,11-cyclized compounds with a strained *E* double bond between C-6 and C-7 can also be found in the briarellin and asbestinin classes, and the capricious reactivity of the *E* double bond in the nine-membered ring of the asbestinins has been noted.[38]



CLADIELLINS

The cladiellins are the most numerous of the 2,11-cyclized cembranoids, with over 100 examples known and a wide range of biological activities demonstrated. A notable example is that of sclerophytin A (**8**).[39] Sclerophytin A (**8**) is cytotoxic to L1210 cells (mouse lymphocytic leukemia cells) in vitro with an IC_{50} value of 3 nM. The structural complexity and potent biological activity of this molecule has led to much interest in finding an efficient total synthesis.[2−5,17,40] The ambiguous depiction of sclerophytin A (**8**) as structure I (Figure 2)

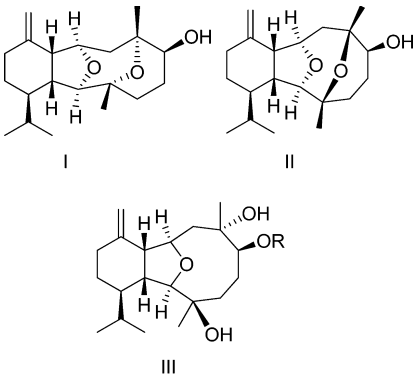
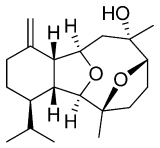


Figure 2. Structure of sclerophytin A (**8**) as initially presented by Sharma and Alam (I)[39] and as interpreted and synthesized (II)[2,4,40] and the authentic structure (III) as independently confirmed through total synthesis.[3−5,42]

presented by Sharma and Alam[39] following the isolation of the natural product was interpreted independently by the Overman and Paquette groups, and others, as the alternative, less strained arrangement of the second oxygen bridge (II).[2,40] The Overman and Paquette groups completed total syntheses of structure II,[2,4,40] which was shown not to replicate the spectroscopic features of the natural product. A re-examination of the spectroscopic data for the closely analogous natural product sclerophytin B (**9**) prompted the revision of the structures to those shown in III, without the presence of the second ether bridge.[41] Independent total syntheses by the Overman and Paquette groups demonstrated III to be the authentic structure of sclerophytin A (**8**).[3−5,42]

No further research has been reported on the biological activity of sclerophytin A (**8**) against the L1210 cell line, nor have any reported efforts been made to discover its mode of action. However, other biological activities have been reported. Thus, sclerophytin A (**8**) has been shown to inhibit the division of starfish eggs (complete arrest at 2 ppm concentration), which may represent a potential benefit to the coral of biosynthesizing the metabolite.[43] The compound has also demonstrated antiinvasive and antimetastatic activities toward PC-3 human prostate cancer cells in an in vitro assay.[33] Interestingly, the metabolite vigulariol (**10**), isolated from the sea pen *Vigularia juncea*,[44] was obtained initially as a side product in a total synthesis of sclerophytin A (**8**)[4] and has been shown to be cytotoxic to A549 human lung cancer cells in vitro (IC_{50} 57 μM).[44]



Ethyl acetate extracts from *Cladiella australis*, *Clavularia viridis*, and *Klyxum simplex* have been reported as cytotoxic to human oral squamous cell carcinoma cells (SCC4, SCC9, and SCC25), with apoptotic cell death accompanied by activation of caspase-3 expression.[45] Each of these extracts may be expected to contain numerous metabolites, including but not limited to 2,11-cyclized cembranoids. A number of isolated cladiellins have been assessed for their cytotoxic activities against various cancer cell lines (Table 1). The klysimplexins A (**11**), B (**12**), C (**2**), and D−H (**13**−**17**), isolated from *Klyxum simplex*, were all assessed against a panel of six carcinoma cell lines.[31] Klysimplexin B (**12**) and H (**17**) showed moderate cytotoxicity toward the majority of the cell lines tested (IC_{50} 3.9−15 μM), while the remaining six compounds showed no activity at the maximum dose (not specified).

A further nine compounds also isolated from *Klyxum simplex* have been named as simplexins A-I (**1**, **18**−**25**). Simplexins A (**1**) and B−F (**18**−**22**), and simplexin I (**25**) were assessed for cytotoxicity against four cancer cell lines.[30] Simplexins A (**1**), D (**20**), and E (**21**) showed some moderate cytotoxicities (IC_{50} 12−27 μM), while the remaining compounds exhibited no activity at the maximum doses tested. The MCF-7 breast cancer cell line was present in both panels used to assay the klysimplexins and symplexins, and the cytotoxicity assay formats were similar in the two studies; therefore, the independently determined activities for compounds **1**, **2**, and **11**−**25** are directly comparable. It is interesting to note that the only difference between klysimplexin C (**2**) and simplexin A

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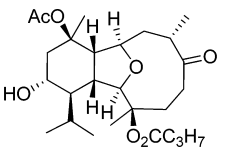
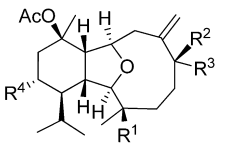
Table 1. Cytoxicity of Cladiellins to Human Cancer Cell Lines

	IC_{50}, μM[a]								
		liver		head and neck		breast			
compd	lung A549	Hep G2	Hep 3B	Ca9-22	Hep2	MDA-MB-231	MCF-7	brain Daoy	cervix HeLa
1[30]	*b*	*b*	*b*	*b*	27	*b*	27	23	>44
2[31]	na[c]	na	na	na	*b*	na	na	*b*	*b*
11[31]	na	na	na	na	*b*	na	na	*b*	*b*
12[31]	4.3	6.4	7.8	3.9	*b*	15	6.5	*b*	*b*
13[31]	na	na	na	na	*b*	na	na	*b*	*b*
14[31]	na	na	na	na	*b*	na	na	*b*	*b*
15[31]	na	na	na	na	*b*	na	na	*b*	*b*
16[31]	na	na	na	na	*b*	na[c]	na	*b*	*b*
17[31]	5.1	10	13	11	*b*	8.0	10	*b*	*b*
18[30]	*b*	*b*	*b*	*b*	>43	*b*	>43	>43	>43
19[30]	*b*	*b*	*b*	*b*	>33	*b*	>33	>33	>33
20[30]	*b*	*b*	*b*	*b*	>31	*b*	23	24	>31
21[30]	*b*	*b*	*b*	*b*	17	*b*	11	20	28
22[30]	*b*	*b*	*b*	*b*	>37	*b*	>37	>37	>37
25[30]	*b*	*b*	*b*	*b*	>40	*b*	>40	>40	>40
29[48]	*b*	5.4	*b*	*b*	*b*	14	19	*b*	*b*
42[51]	28	na	29	35	*b*	na	na	*b*	*b*
46[51]	34	4.7	14	34	*b*	41	35	*b*	*b*

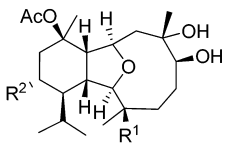
[a]Biological activities are expressed in micromolar units and have been recalculated from the reported units where necessary. [b]No reported result in this cell line. [c]na = not active in this assay (maximum concentration not specified).



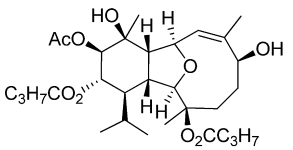
klysimplexin A (**11**)



klysimplexin B (**12**) $R^1 = O_2CC_3H_7$; R^2, R^3 = O; R^4 = OH
klysimplexin D (**13**) $R^1 = O_2CC_3H_7$; R^2 = OOH; R^3 = H; R^4 = OH
klysimplexin E (**14**) R^1 = OAc; $R^2 = R^4$ = OH; R^3 = H

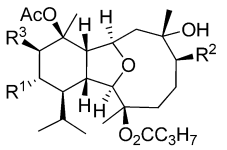


klysimplexin F (**15**) $R^1 = O_2CC_3H_7$; R^2 = OH
klysimplexin G (**16**) R^1=OAc; R^2 = H

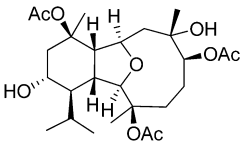


klysimplexin H (**17**)

(**1**) is the presence of a hydroxy group at C-13, and this seems to confer a difference in activity. Simplexin A (**1**) had an IC_{50} of 27 μM in MCF-7 cells, whereas klysimplexin C (**2**) was reported to be devoid of activity, although further information on the maximum dose at which compound **2** was tested would allow a more detailed comparison.



simplexin B (**18**) $R^1 = R^3$ = H; R^2 = OH
simplexin C (**19**) $R^1 = O_2CC_3H_7$; $R^2 = R^3$ = OAc
simplexin D (**20**) $R^1 = R^2 = O_2CC_3H_7$; R^3 = OAc
simplexin E (**21**) $R^1 = O_2CC_3H_7$; $R^2 = O_2CCHCH_2$; R^3 = OAc
simplexin F (**22**) R^1 = OH; $R^2 = R^3$ = OAc
simplexin G (**23**) $R^1 = R^3$ = OAc; R^2 = OH
simplexin H (**24**) R^1 = OH; R^2 = OAc; R^3 = H



simplexin I (**25**)

There are no clear systematic conclusions on structure–activity relationships that can be drawn from these results, other than it appears that subtle changes to the substituents in the molecules can lead to differences in activity. As an example of this, Kakonikos et al.[46] investigated the activity of the epimeric compounds labiatin C[47] (**26**) and labiatin E[46] (**28**). The compounds differ only in their configuration at C-6 yet showed some difference in their cytostatic effects against NSCLC-N6 human lung cancer cells (**26**, IC_{50} 16 μM; **28**, IC_{50} 73 μM).[46] Although the paper reporting the isolation of labiatin E[46] (**28**) discusses how the compound is a C-6 epimer of labiatin C (**26**) according to an analysis of spectroscopic data, the accompanying structure appears to have been drawn with the same C-6

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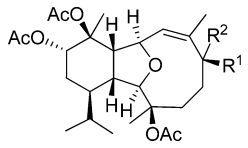
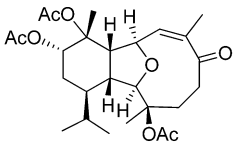
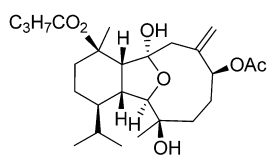
configuration as labiatin C (**26**). The structure **28** shown in this review shows the C-6 *R* epimer as discussed in the aforementioned paper. No biological activity data have been reported for the related labiatin D[46] (**27**). The australins B (**29**) and C (**30**) were isolated from the Taiwanese soft coral *Cladiella australis*, and australin B (**29**) showed moderate cytotoxicity toward three human cancer cell lines (Table 1).[48]



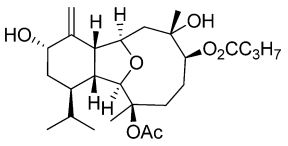
labiatin C (**26**) R^1 = OH; R^2 = H
labiatin E (**28**) R^1 = H; R^2 = OH



labiatin D (**27**)



australin B (**29**)



australin C (**30**)

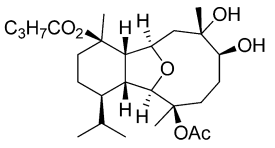
Fourteen cladiellins isolated from *Cladialla pachyclados* were assessed for their ability to inhibit the metastatic and invasive qualities of PC-3 prostate cancer cells (Table 2).[33] This included

Table 2. Inhibition of In Vitro Migration and Invasion of PC-3 Human Prostate Cancer Cells by Cladiellins[33]

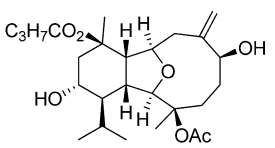
	inhibition at 50 μM, %[a]	
compd	migration[b]	invasion[c]
3	75	82
7	80	90
8	85	65
9	45	*d*
14	na[e]	*d*
16	70[f]	55[f]
31	72	98
32	40	*d*
33	45	*d*
34	70	*d*
35	5	*d*
36	70	*d*
37	65	*d*
38	50	*d*

[a]Data abstracted have been estimated from the published bar charts; for original graphical data, see ref 33. [b]Inhibition relative to DMSO control (0%), with positive control 4-hydroxyphenylmethylene hydantoin (200 μM, 75%). [c]Inhibition relative to DMSO control (0%), with positive control 4-mercaptoethylphenylmethylene hydantoin (50 μM, 50%). [d]No reported result. [e]Inactive. [f]Test concentration of 10 μM.

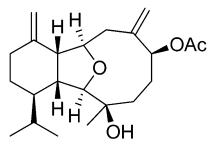
five new cladiellins, pachycladins A–E (**31**–**35**), as well as the previously known metabolites (+)-polyanthellin A (**3**), sclerophytin F methyl ether (**7**), sclerophytins A (**8**) and B (**9**), kysymplexins E (**14**) and G (**16**), 3-acetylcladiellisin (**36**), 3,6-diacetylcladiellisin (**37**), and (6*Z*)-cladiellin (**38**). Interestingly, a number of the compounds inhibited in vitro migration and/or invasion by these human cancer cells, but none were overtly cytotoxic (IC_{50} > 50 μM). Out of this small set of compounds, pachycladin A (**31**), sclerophytin F methyl ether (**7**), polyanthellin A (**3**), and sclerophytin A (**8**) were the most effective antiinvasive and antimetastatic agents at a 50 μM concentration. Klysymplexin G (**16**) was effective at 10 μM but caused notable change to cell morphology at higher doses. Examination of the structures of the cladiellins tested suggests that the presence of a butyrate or an exo methylene functionality at C-11 and an oxygenated quaternary carbon at C-7 led to the most potent activity in these assays.



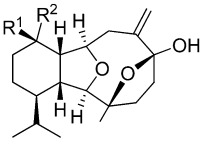
pachycladin A (**31**)



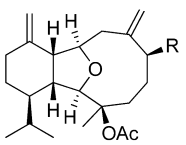
pachycladin B (**32**)



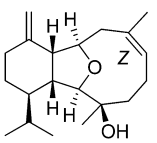
pachycladin C (**33**)



pachycladin D (**34**) R^1, R^2 = CH_2
pachycladin E (**35**) R^1 = OAc; R^2 = Me



3-acetylcladiellesin (**36**) R = OH
3,6-diacetylcladiellesin (**37**) R = OAc



(6*Z*)-cladiellin (**38**)

In 2010, the first examples of cladiellins containing sulfoxide substituents were isolated.[49] These compounds were extracted from cultured soft coral *Klyxum simplex* and were hence named klysimplexin sulfoxides A (**39**), B (**40**), and C (**41**). The klysimplexin sulfoxides demonstrated the ability to reduce the expression of iNOS protein in RAW264.7 macrophage cells. The iNOS protein is involved in the inflammatory immune response in cells. Klysimplexin sulfoxide C also reduced the levels of the pro-inflammatory enzyme COX-2, which has been implicated in the progression of certain cancers.[50] Several other cladiellins have shown similar activity, including simplexins A (**1**) and E (**21**)[30] and certain hirsutalins (**42**–**48**).[51] These findings indicate this compound class in general, and in particular klysimplexin sulfoxide C (**41**), may have anti-inflammatory properties (Table 3).

Hirsutalins A–E (**42**–**46**), G (**47**), and H (**48**) are a group of cladiellins published in 2010,[51] that show a previously unreported oxidation of the core scaffold. Hirsutalins A–D (**42**–**45**), G (**47**), and H (**48**) are all oxygenated at C-18. It is interesting to note that the desymmetrization of the isopropyl substituent in the hirsutalins resulting from this oxidation appears to be opposite to that found in the asbestinins and briarellins. Hirsutalins A (**42**) and E (**46**) have demonstrated moderate cytotoxicity against a small panel of cancer cell lines[51] (Table 1), and hirsutalin B (**43**), C(**44**), D (**45**) and H (**48**) have shown the ability to reduce the expression of iNOS protein in RAW264.7 macrophage cells,[51] indicative of anti-inflammatory activity (Table 3).

Some cladiellins have shown antibacterial properties assessed by the agar disk diffusion method.[52] Cladiellaperoxide (**49**) was tested against *Streptococcus pyogenes*, *Escherichia coli*, and *Pseudomonas aeruginosa* and appeared to be most active against

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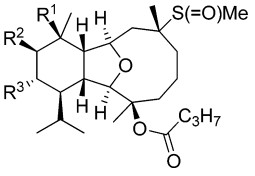
Table 3. Anti-Inflammatory Activities of Cladiellins in Human Macrophages

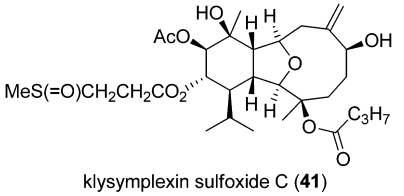
	protein expression, %[a]	
compd	iNOS[b]	COX-2[c]
1[30]	16	na[d]
18[30]	na	na
19[30]	na	na
20[30]	38	na
21[30]	4.8	38
22[30]	na	na
25[30]	na	na
39[49]	8.8	na
40[49]	18	na
41[49]	11	7.2
42[51]	na	na
43[51]	6.8	49
44[51]	44	na
45[51]	3.3	na
46[51]	na	na
47[51]	na	na
48[51]	33	na

[a]Expression of inflammatory proteins relative to control cells stimulated with LPS only (100%). [b]Reduction of LPS-induced iNOS protein expression in RAW264.7 cells at a 10 μM test concentration. [c]Reduction of LPS-induced COX-2 protein expression in RAW264.7 cells at a 10 μM test concentration. [d]na = no inhibition of protein expression observed at the test concentration used.



klysymplexin sulfoxide A (**39**) R^1 = OAc; $R^2 = R^3$ = H

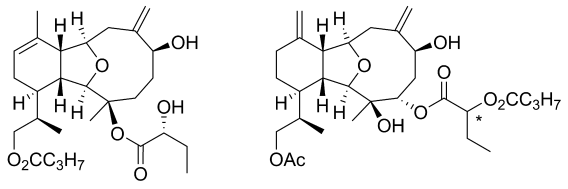
klysymplexin sulfoxide B (**40**) R^1 = OH; R^2 = OAc; $R^3 = O_2CC_3H_7$



klysymplexin sulfoxide C (**41**)

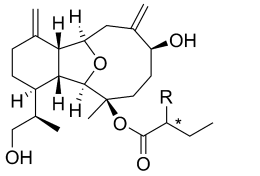
P. aeruginosa, a bacterium indicated in a number of hospital infections. In contrast, (6*E*)-2α,9α-epoxyeunicella-6,11(12)-dien-3β-ol (**50**) was most active against *E. coli*. These two compounds differ at three substituent positions, the acetylation at C-3, the position of the double bond at C-7, and in cladiellaperoxide the presence of a peroxide substituent at C-6, and these differences are sufficient to confer a degree of specificity in their antibacterial activity. Polyanthellin A (**3**), with a different scaffold, also showed antibacterial activity, but with *S. pyogenes* having the greatest sensitivity to this natural product.[52]

Epoxycladines A–D (**51**–**54**)[53] bear an unusual C-11–C-12 epoxide substituent that is known only in two other examples: calicophirin A[54] and 3,6-diacetoxy-11,12-epoxycladiellin-7-ol.[55] The reactivity of the epoxide led to compounds **51**–**54** decomposing rapidly; however, it was possible to collect adequate data to allow characterization. No biological activities have been reported, but the instability of the parent compounds would likely render any results difficult to interpret.

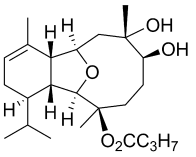


hirsutalin A (**42**)

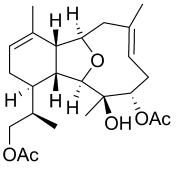
hirsutalin B (**43**)



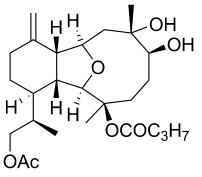
hirsutalin C (**44**) R = $O_2CC_3H_7$
hirsutalin D (**45**) R = OAc
* configuration unspecified



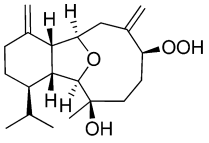
hirsutalin E (**46**)



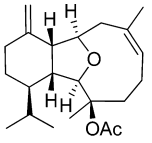
hirsutalin G (**47**)



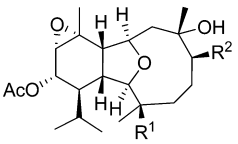
hirsutalin H (**48**)



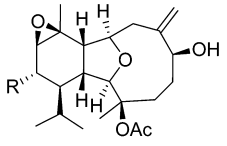
cladiellaperoxide (**49**)



(6*E*)-2α,9α-epoxy-eunicella-6,11(12)-dien-3β-ol (**50**)



epoxycladine A (**51**)
R^1 = OAc; R^2 = OH
epoxycladine B (**52**)
R^1 = OH; R^2 = OAc



epoxycladine C (**53**) R = OH
epoxycladine D (**54**) R = OAc

Klyxumines A[53] (**55**) and B[53] (**56**) are both oxygenated at C-8. This substitution pattern is unusual in the cladiellin family, and only four other cladiellins show this functionality: litophynol B,[56] sclerophytins C[57] and D,[57] and sclerophytin C-6 ethyl ether,[58] although this last compound is considered an artifact of isolation. Klyxumine A (**55**) is believed to have the same relative configuration at C-3, C-6, C-7, and C-8 as litophynol B[56] and sclerophytins C and D.[57] Comparison of the NMR data for sclerophytin C and klyxumine A showed a number of disparities in the multiplicities and coupling constants for the protons at important chiral centers, but this was rationalized as being due to the molecules adopting different conformations in the different NMR solvents used.[53]

Tandem mass spectrometry has been used to identify a homologous series of cladiellins that proved inseparable by chromatographic methods.[59] The authors were able to separate chromatographically and fully characterize two new compounds

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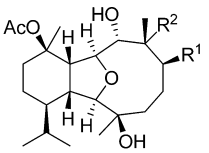
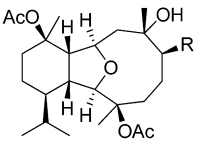
(**57** and **58**) but were unable to separate a mixture containing a closely related compound series. However, the mixture could be characterized with the application of precursor ion scanning mass spectrometry. Data from this technique suggested that the mixture contained a number of compounds **59** bearing different fatty acid chains in place of the C-6 acetate group. The approach



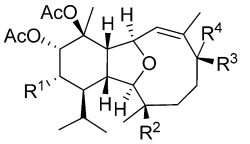
klyxumine A (**55**) R^1 = OAc; R^2 = OH
klyxumine B (**56**) R^1 = H; R^2 = OAc



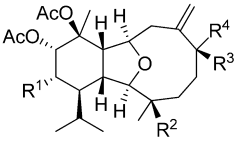
57 R = OAc
58 R = $O_2CC_5H_{11}$
59 R = $O_2C(CH_2)_nCH_3$; n = 5 - 20

may be useful to discover and characterize other such homologous series. Compounds **57** and **58** showed no cytotoxicity toward mouse colon adenocarcinoma C-38 cells.

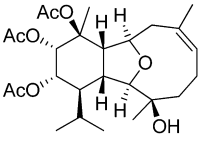
A number of unnamed new cladiellins (**60**–**69**) were isolated from *Eunicella cavolinii* and *Eunicella singularis* and contained an unusually high level of oxygenation of the cyclohexane ring.[35] No biological activity has been reported for these compounds as yet. The unnamed cladiellin **70** was found to be a potent inhibitor of the division of sea urchin eggs (complete arrest at 0.5 ppm) with a potency similar to that of sclerophytin A (**8**).[43]



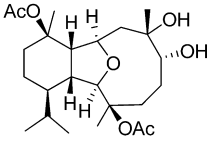
60 R^1 = R^2 = R^3 = OAc; R^4 = H
61 R^1 = R^3 = OAc; R^2 = OH; R^4 = H
62 R^1 = R^2 = OAc; R^3 = OH; R^4 = H
63 R^1 = R^2 = OAc; R^3, R^4 = O
64 R^1 = H; R^2 = R^3 = OAc; R^4 = H



65 R^1 = R^2 = R^3 = OAc; R^4 = H
66 R^1 = R^3 = OAc; R^2 = OH; R^4 = H
67 R^1 = R^2 = OAc; R^3, R^4 = O
68 R^1 = H; R^2 = OH; R^3 = OAc; R^4 = H



69

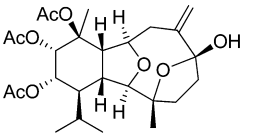


70

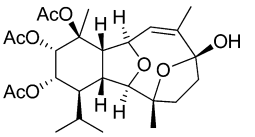
Massileunicellins A–C (**71**–**73**) were also isolated from *E. cavolinii* and showed a novel bridge between C-3 and C-6, corresponding to acetal formation between a C-3 β-hydroxy group and the C-6 carbonyl.[60] Compounds **71**–**73** showed no cytotoxicity toward two human tumor cell lines (KB and doxorubicin-resistant L1210).

BRIARELLINS

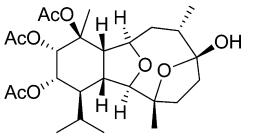
The briarellins differ from the cladiellins by the presence of an additional seven-membered ether or lactone ring between C-16 and C-3.[61] However, the general substitutions around the core



massileunicellin A (**71**)

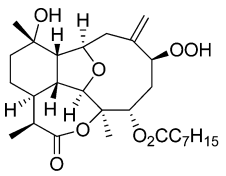


massileunicellin B (**72**)

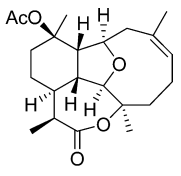


massileunicellin C (**73**)

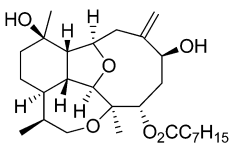
scaffold appear to be the same. Worthy of note is the configuration at C-11 of the proposed structures of the briarellins. Briarellins A–D[25] and J–P[34] have been assigned as having the opposite configuration to that of briarellins E–I.[62] Thus, the proposed structures of briarellin A (**74**) and briarellin J have a β-methyl group at C-11. The total synthesis of the proposed structure of briarellin J was published recently.[16] Detailed examination of the spectroscopic data reported suggested that a revision of the structure was required, specifically to the opposite configuration at C-11. Thus, the revised structure of briarellin J (**75**) has the same configuration at C-11 as that in the structures of briarellins E–I, with an α-methyl substituent. The structures of briarellins E (**76**) and F have been confirmed through total synthesis.[6,13] In light of the fact that all of the confirmed structures of the briarellins have the same stereochemical configuration at C-11, and since the proposed biosynthetic pathways to asbestinins from briarellins A–D and J–P would require an unlikely antarafacial methyl shift, it has been suggested that the structures of briarellins A (**74**), B–D (**77**), K (**79**), and L–P (**81**–**85**), and by implication the hydroperoxides **78** and **80**, and briarellins Q (**86**) and R (**87**) as currently proposed, may also require a reassignment of configuration at C-11.[16]



briarellin A (**74**)
(proposed)



briarellin J (**75**)
(revised)



briarellin E (**76**)
(verified)

Briarellins D (**77**), J (**75**), K (**79**) and L–P (**81**–**85**), along with the hydroperoxides **78** and **80** have been tested for activity

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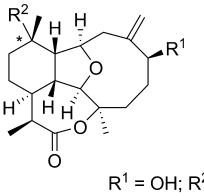
against *Plasmodium falciparum*,[34] a parasite responsible for malaria in humans (Table 4). The majority of the compounds showed some activity, with the most potent being briarellin D hydroperoxide (**78**), briarellin K hydroperoxide (**80**), and briarellin L (**81**). Although two of these compounds contain a hydroperoxide moiety, it does not appear to be essential for the activity, as briarellin L (**81**) lacks this moiety but has comparable activity. It appears that the motif of an exocyclic double bond at C-7 and oxygenation at C-6 is important for the antiparasitic effect, and the lack of activity in briarellin J (**75**) supports this hypothesis.[34] Briarellins Q (**86**), R (**87**), and seco-briarellin R (**88**) have been tested against *Plasmodium falciparum* (Table 4).[63] Briarellin Q (**86**) showed the most potent activity with IC_{50} 6.8 μM.

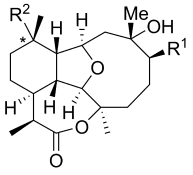
Table 4. Antiplasmodial Activity of Briarellins and Asbestinins

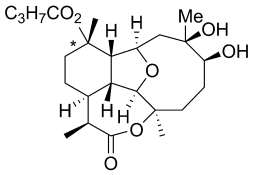
compd	IC_{50}[a], μM[b]	compd	IC_{50}, μM	compd	IC_{50}, μM
77[34]	32	**84**[34]	55	**91**[63]	45
78[34]	21	**85**[34]	31	**92**[63]	46
75[34]	>130	**86**[63]	6.8	**93**[63]	33
79[34]	38	**87**[63]	37	**95**[63]	39
80[34]	22	**88**[63]	44	**96**[63]	41
81[34]	17	**89**[63]	24	**97**[63]	>120
82[34]	54	**90**[63]	34	**98**[63]	48

[a]Inhibition of *Plasmodium falciparum* W2 growth. [b]Biological activities are expressed in micromolar units and have been recalculated from the reported units where necessary.



briarellin D (**77**) R^1 = OH; R^2 = $O_2CC_3H_7$
briarellin D hydroperoxide (**78**) R^1 = OOH; R^2 = $O_2CC_3H_7$
briarellin K (**79**) R^1 = OH; R^2 = OAc
briarellin K hydroperoxide (**80**) R^1 = OOH; R^2 = OAc
briarellin L (**81**) R^1 = OAc; R^2 = $O_2CC_3H_7$



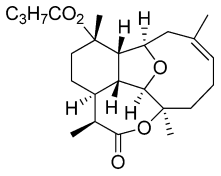


briarellin M (**82**) R^1 = OH; R^2 = OAc
briarellin N (**83**) R^1 = OMe; R^2 = OAc
briarellin O (**84**) R^1 = OH; R^2 = $O_2CC_3H_7$
briarellin P (**85**) R^1 = OMe; R^2 = $O_2CC_3H_7$

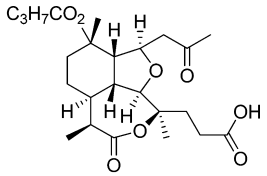
briarellin Q (**86**)

* These structures may require a revision of configuration at C-11; see discussion in text.

Briarellins Q (**86**) and R (**87**) demonstrated weak antibacterial activity against *Mycobacterium tuberculosis*, with 91% inhibition of growth at 290 μM and 43% inhibition of growth at 320 μM, respectively.[63] Briarellin R (**87**) was tested for antiviral effects against West Nile virus, HCV, influenza A (H1N1 and H3N2 strains), and influenza B, but no activity was observed.[63] However, briarellin R (**87**) was weakly cytotoxic to CCRF-CEM (human lymphoblastic leukemia) cells, with an IC_{50} value of 22 μM.[63] In contrast, briarellins D (**77**) and K (**79**) have been tested for cytotoxicity against three human cancer cell lines (MCF-7, NCI-H460, and SF-268), but showed IC_{50} values of >100 μM in all cases.[34]



briarellin R (**87**)

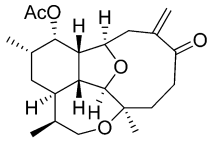


seco-briarellin R (**88**)

■ ASBESTININS

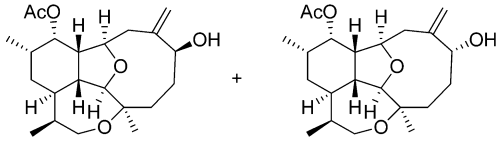
The asbestinins have a core structure similar to that of the briarellins but differ in the position of a methyl group on the cyclohexyl portion of the scaffold. The methyl is located on C-12 in the asbestinins, as opposed to C-11 in the briarellins. Since 1998, to the best of our knowledge, only five new asbestinins have been isolated. Asbestinin-10[64] (**89**), -20[65] (**90**), and -21[65] (**92**) and 11-acetoxy-4-deacetoxyasbestinin F[65] (**93**) were isolated previously, but a new analysis of the compounds has indicated that these structures required revision.[63] In asbestinin-10 (**89**) the carbonyl, previously assigned at C-4, is now thought to be at C-6, as shown by NMR HMBC correlations between the exocyclic methylene protons H-19 and the carbonyl carbon. The chemical reduction of this carbonyl moiety gave rise to a mixture of compounds **90** and **91** epimeric at C-6 (Scheme 3). Compound **90** was identical spectroscopically to asbestinin-20, indicating that the hydroxyl group in asbestinin-20 is at C-6, not C-4. Similarly, HMBC correlations of asbestinin-21 (**92**) were consistent with the presence of a carbonyl at C-6 and not at C-4.

Scheme 3. Chemical Conversion of Asbestinin-10 (89) to Asbestinin-20 (90)

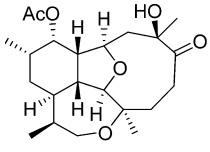


asbestinin-10 (**89**)

$NaBH_4$
MeOH



asbestinin-20 (**90**) **91**



asbestinin-21 (**92**)

11-Acetoxy-4-deacetoxyasbestinin F (**93**) has been reassigned as the hydroperoxide due to new HRFAB mass spectrometric data showing a mass ion consistent with the

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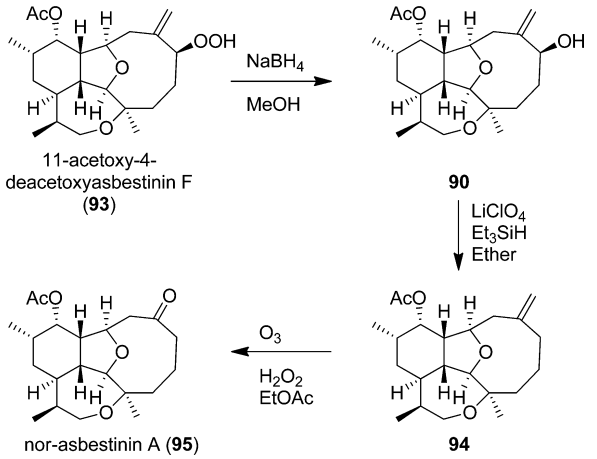
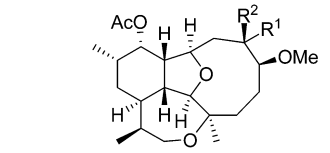
formula $C_{22}H_{34}O_6$.[63] The presence of the hydroperoxide moiety was confirmed through the conversion of 11-acetoxy-4-deacetoxyasbestinin F (**93**) to asbestinin-20 (**90**) using sodium borohydride in methanol (Scheme 4). The position

Scheme 4. Chemical Conversion of 11-Acetoxy-4-deacetoxyasbestinin F (93) to Nor-asbestinin A (95)

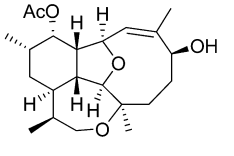


of the carbonyl in nor-asbestinin A (**95**) was confirmed by the chemical conversion of asbestinin 20 (**90**) to **94**, using $LiClO_4$ and Et_3SiH to remove the hydroxy group and ozonolysis of **94** to convert the exocyclic methylene to a carbonyl, generating asbestinin-20 (**95**).

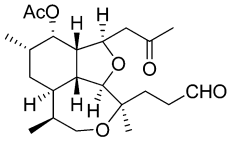
Asbestinin-10 (**89**), -20 (**90**), -21 (**92**), -24 (**96**), -25 (**97**), and -26 (**98**), 6-epi-asbestinin-20 (**91**), 11-acetoxy-4-deacetoxy-asbestinin F (**93**), and nor-asbestinin A (**95**) were tested against *Plasmodium falciparum*, and all showed moderate activity except for asbestinin-25 (**97**) (Table 4).[63] The same group of compounds and *seco*-asbestinin B (**99**) were shown to have no antibacterial activity against *Mycobacterium tuberculosis* H37 up to a concentration of 128 μg mL^{-1} [63] or antiviral activity against a panel of viruses (West Nile virus, HCV, influenzas A and B, VEE, Yellow fever, Dengue type 2, RSV A, HBV, and HBC).[63] However, asbestinin-10 (**89**) has now been shown to be a potent antiviral agent against the Epstein–Barr virus (IC_{50} 0.67 μM).[63] This may provide a starting point for efforts to discover additional clinically useful antiviral agents.



asbestinin-24 (**96**) R^1 = Me; R^2 = H
asbestinin-25 (**97**) R^1 = OH; R^2 = Me



asbestinin-26 (**98**)



seco-asbestinin B (**99**)

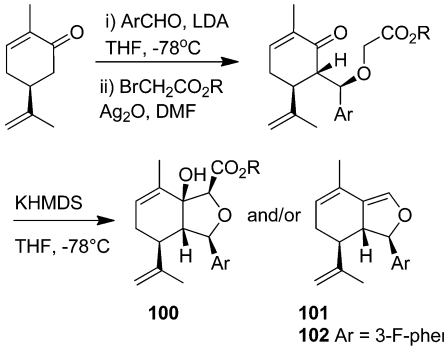
CONCLUSIONS

The cladiellins, asbestinins, and briarellins have been shown to be a structurally varied class of natural products with promising biological activities. The isolation and identification of new natural products in these structural classes have been aided by improvements in characterization technologies. This is well exemplified by the homologous cladiellin series identified using precursor ion scanning mass spectrometry.[59] In the future, computer-assisted structure elucidation[66] may facilitate correct structural assignments and further increase the rate at which new structures may be identified. A number of structures have been reassigned in recent years, such as asbestinins-10 (**89**) and -20 (**90**), and 11-acetoxy-4-deacetoxyasbestinin F (**93**).[63] Total syntheses continue to play an important role in the elucidation of the structures of these natural products, as illustrated by revision of the configuration at C-11 of briarellin J (**75**) and potentially other members of this structural subgroup.[16]

The wide range of biological activities detailed in this review suggests that the oxatricyclo[6.6.1.$0^{2,7}$]pentadecane core, or the embedded hexahydroisobenzofuran unit, may in the future have the status of a privileged structure. The term "privileged structure" was first used in 1988[67] and describes the propensity of a particular chemical scaffold to interact in a specific manner with a range of biological targets and thus form the basis for the development of multiple pharmacological agents. The benzodiazepine scaffold is a non-natural example,[67] and others have been identified from their frequent occurrence in biologically active natural products.[68] Privileged structures are differentiated from promiscuous inhibitors[69] by the specific nature of their interactions with biological macromolecular targets, which can be tuned by changes to the substituent patterns. The cembranoids have shown cytotoxic, anti-inflammatory, antiviral, and antibacterial properties, among others, and it is unlikely that these biological activities are due to interactions with the same biological target. Moreover, changes to the substituent patterns around the core scaffolds, often quite subtle, modulate the observed biological activities. A possible attractive feature of the cembranoid oxatricyclo-[6.6.1.$0^{2,7}$]pentadecane scaffold may lie in the diversity of accessible substitution vectors available from the fairly rigid polycycle, allowing the controlled positioning of substituents to occupy space around the core.

Many natural products represent exciting challenges to organic chemists who wish to devise synthetic routes to their formation. The 2,11-cyclized cembranoids are no exception, and several imaginative routes have been developed to these natural products or their precursors.[1−17] However, the total syntheses published often exceed 20 steps. Structural and synthetic complexity can be a major reason that such natural product skeletons are difficult to use in medicinal chemistry. McIntosh and colleagues have demonstrated that simplified versions of sclerophytin A may be more readily assembled and can retain some of the cytotoxic activity of the natural product.[70] A short aldol–cycloaldol sequence starting from (*S*)-carvone was used to generate analogues with a tetrahydroisobenzofuran core (**100**) and unsaturated derivatives (**101**) (Scheme 5). These have been assessed for anticancer activity through the Developmental Therapeutics Program of the United States National Cancer Institute (http://dtp.nci.nih.gov/, accessed on 12.08.2011), and one compound, in particular, showed good activity. The analogue **102** inhibited the proliferation of two human cancer cell lines at submicromolar concentrations (RPMI-8226, IC_{50} 0.15 μM; HOP-92, IC_{50} 0.55 μM). These results suggest it may be an effective and efficient strategy to target simplified core scaffolds

Scheme 5. Synthetic Route to Simplified Sclerophytin A Analogues



of this class of natural products for exploitation as therapeutic agents.

It is observed and accepted that natural products may occupy calculated physicochemical space outside that defined by Lipinski[71] and others[72] for non-natural compounds and yet still be orally bioavailable drugs.[73] Although the cembranoids have been assessed in various biochemical and cell-based assays, no reports have been made on their physicochemical properties. This information would be valuable if the 2,11-cyclized cembranoids or scaffolds derived from them are to become generally useful for drug discovery. The differences in biological activity observed for cembranoids such as simplexin A (**1**) and klysimplexin C (**2**), which only differ in the presence of a hydroxy group, also suggests selectivity in mechanism of action may be achieved through minimal structural changes.

Several total syntheses have been published that allow access to more than one cembranoid using the same key steps.[2,3,5,7−9,12,13,74,75] Overman and colleagues proposed that a range of cembranoids can be prepared from a common intermediate derived from the chiral pool materials carvone and glycidol.[3,5] The recent approach of Clark has demonstrated the use of different reaction conditions to vary the stereochemical outcome of a carbenoid insertion ring-closing step to prepare both *E* and *Z* isomers of the desired oxabicyclo[6.2.1]-undecenone.[74] It was possible to synthesize three cladiellins successfully using this approach. Kim et al. showed three cladiellins could be accessed from (−)-cladiella-6,11-dien-3-ol using various regio-, stereo-, and chemoselective reactions.[9] The ability to use a more "diversity oriented" approach[76] to the synthesis of such complicated natural products would doubtless ease the application of the compounds and related structures to drug discovery research. In the future, it will be interesting to see what further information will be learned from this class of natural products in terms of developing new synthetic methods and exploring the biological activities of complex structures.

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