Bend it like Bredt

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Naturally Occurring Anti-Bredt and Bridgehead Olefinic Systems

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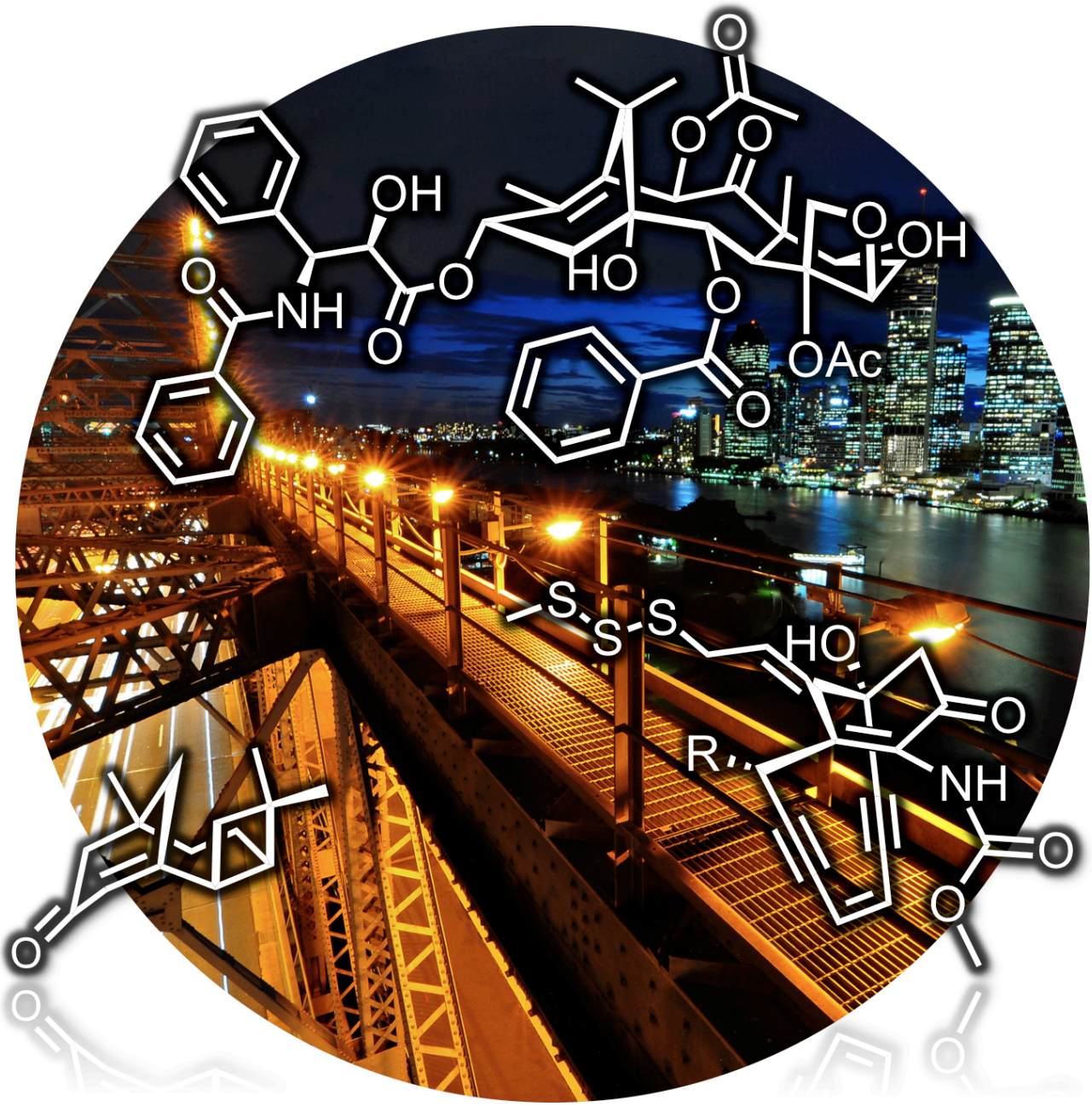
Bredt's rule · anti-Bredt · Bridgehead olefin (alkene / double bond) · strained double bonds · natural product

Dedicated to Prof. Dr. Armin de Meijere on the occasion of his 75th birthday



***W**ell over a hundred years ago, Professor Julius Bredt embarked on a career pursuing and critiquing bridged bicyclic systems that contained ring strain induced by the presence of a bridgehead olefin. These endeavors founded what we now know as Bredt's rule (Bredtsche regel). Physical, theoretical and synthetic organic chemists have intensely studied this premise, pushing the boundaries of such systems to arrive at a better-understood physical phenomenon. Mother nature has also seen fit to construct molecules containing bridgehead double bonds that encompass Bredt's rule and for the first time this topic is reviewed in a natural product context.*

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1. Introduction

Bredt's rule (Bredtsche regel),[1] as derived by Professor Julius Bredt (Technische Hochschule Aachen, Figure 1 Bottom) in the early part of last century,[2] simply states that the terminus of a double bond cannot exist at the bridgehead position (branching positions) of a bridged bicyclic system {i.e. bicyclo[m.n.o] **1**; Figure 1 top}. The premise of the rule is based solely on the overall strain imparted on the bridgehead double bond (*p*-orbitals) due to the distortion constraints imposed by the size of the bridging rings.[3] The term "anti-Bredt" system was later coined as examples that violated Bredt's rule started to emerge,[4] that is, bridged bicyclic systems that contained, or were proposed to contain, a double bond at a bridgehead position.[5]

1

Figure 1. Top: Generalized structure of a bridged bicyclo[m.n.o] system showing a bridgehead double bond (anti-Bredt system); Bottom: Prof. Julius Bredt, Technische Hochschule Aachen.

Fawcett proposed an empirical aspect to the rule to better predict violations of Bredt's rule,[5a] which culminated in the *S* value. The *S* value is the sum of atoms contained in all bridges of the bridged bicyclic system, for example, a bicyclo[3.2.1]octane has an *S* value of 6. Thus, according to Fawcett's generalization, bridged bicyclic systems with bridgehead double bonds with an *S* value $\geq$ 9 have the potential to be isolated, although a tentative upper limit value of 8 was conceivable. Systems with an *S* value of 7 could be observed but not isolated, whereas those with an *S* value 6 could be entertained as fleeting intermediates. Prelog,[6] concurrently proposed that only bicyclo[5.3.1] systems or larger ($S \geq 9$) could contain a stable bridgehead double bond. Wiseman subsequently developed a more rigid hypothesis (excuse the pun) by comparing the stability of *cis*- and *trans*-cycloalkenes and translating that to bicyclic bridgehead double bond systems.[7,8] Wiseman concluded that when the larger of the two rings containing the double bond (i.e. m and o in **1**; Figure 1 top) contained at least eight atoms (and in certain cases, seven), the bridged bicyclic system would be stable. The efforts of Fawcett, Prelog, and Wiseman were summarized by Köbrich as rules A, B and C in an attempt to better predict relative distortion energies.[5b]

Rule A. For homologs with different *S* values, the ring strain varies inversely with *S* value.

Rule B. For a given *S* value, the ring strain varies inversely with the size of the larger of the two rings with respect to which the bridgehead double bond is endocyclic.

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Rule C. For a given bicyclic ring skeleton, the ring strain varies inversely with the size of the bridge containing the bridgehead double bond.[5b]

The predictive rules were ultimately refined by Schleyer using MMI empirical force field calculations,[9] which provided the "olefin strain (OS)" energy (which is directly related to the heat of hydrogenation), as the predictive tool. It should be noted, that Burkert and Ermer had calculated this phenomena earlier, [10][11] but in a limited capacity. Schleyer's empirical rules, based on direct comparision of OS calculations to that of literature experimental data, facilitated classification of individual bridgehead olefins into three groups. 1) Isolable bridgehead olefins (OS ≤ 17 kcal/mol; e.g. bicyclo[3.3.3]undec-l-ene), 2) observable bridgehead olefins (17 kcal/mol ≤ OS ≤ 21 kcal/mol; e.g. bicyclo[4.2.l]non-l(9)-ene), and 3) unstable bridgehead olefins (OS ≥ 21 kcal/mol; e.g. bicyclo[2.2.2]oct-l -ene) (Figure 2). Further clarification of these catergories were provided by Schleyer, being roughly defined as: 1) "Isolable" olefins are kinetically stable at room temperature; 2) "Observable" olefins are not isolable at room temperature but may be detected at lower temperatures spectroscopically; and "Unstable" olefins are not spectroscopically observable at low temperatures, except perhaps in matrix isolation.[9]

With these predictive rules established, chemists continued to pursue anti-Bredt systems; 1) to further interrogate the proposed rules, 2) to use as versatile synthetic intermediates,[12,13] but to a much lesser extent, 3) evaluate them in the context of natural product structure.[12,14] It was this latter point that overlapped with our fascination of constructing natural products that contained bridged bicyclic moieties {i.e. bicyclo[m.n.o]}.[15] Furthermore, and perhaps more importantly however, we had recently isolated a novel natural product that contained a bridgehead double bond, and therefore wanted to better understand the application of Bredt's law to natural product systems.[16] In consideration of the above, and that it was Bredt's century old work on the camphene and pinane natural product series that resulted in the formulation of the rule, it seemed fitting to review this special class of natural products for the first time.

In order to provide a comprehensive survey of the field, the selection criteria for candidate inclusion within this article broadly include (with some exceptions) all natural products which contain a bridgehead olefin. Since Bredt's rule was first conceived, it quickly evolved through the work of Fawcett, Prelog, Wiseman, and Köbrich, finally culminating in Schleyer's system of bridgehead olefin stability (OS). Therefore, as understood within the context of this refined paradigm, Bredt's rule is applicable to stable (isolable), unstable (observable fleeting intermediates), and non-existent (Schelyer unstable) bridged bicyclic systems. Although stable and isolable bridgehead olefinic systems can now be quantitatively rationalized with this refined model, nonetheless, the term 'anti-Bredt' infers that a compound is unstable, and in the context of natural products, too unstable to be isolated. Therefore, by definition, it could be argued that most, if not all, isolated bridged bicyclic natural products containing a bridgehead olefin cannot be labeled anti-Bredt. That, is any natural product that appears in the literature must contain a degree of stability to exist in the natural environment, and to survive the manipulation process by the isolation chemist. Of course, Bredt himself was already aware towards the end of his career that examples containing larger rings would lead to violations of his rule.[4] On this premise many candidates are probably better viewed as containing bridgehead olefins rather than anti-Bredt systems. We have refrained at this point from presenting further views on whether the term anti-Bredt should even be entertained in the context of natural products. This will be further explained in section 6, giving the reader the opportunity to digest the material presented, before considering the subsequent analysis.

Lastly, the review does not include natural products containing the bicyclo[n.n.0] system (e.g. pteridanoside **2**),[17] only select examples of the cyclophane type (e.g. longithorone B **3**)[18] as this has been recently reviewed,[19] and not the rigid fused ring type (e.g. TG-2 **4**) (Figure 2).[20] Furthermore, it is beyond the scope of this review to comprehensively cover synthetic studies towards this group of natural products. However, brief reference is made to conquered total syntheses, much of which has already been reviewed elsewhere, and synthetic studies where pertinent.

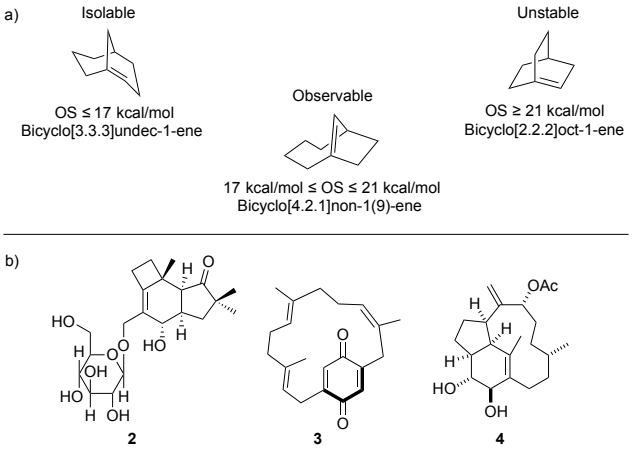

Figure 2. a) Examples that illustrate the 3 stability groups proposed by Schleyer. b) Examples of bridgehead olefin containing natural product systems not covered in this review i.e. bicyclo[n.n.0], cyclophane, and rigid fused ring type.

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2. Structural reassignments based on Bredt's rule

Following his initial publications, Bredt spent a considerable amount of his time correcting articles publishing clear violations of his rule, mostly however, on products proposed from the chemical treatment of many terpenes.[5] To the best of our knowledge, only on one occasion were natural product structures contested by Bredt,[1b, 21] and that was the case of an early proposal by Bartelt for two anti-Bredt fenchene isomers (**5** and **6**) (Figure 3).[22] Today there are 6 known fenchene isomers, α-(**7**), β-(**8**), γ-(**9**), δ-(**10**), ε-(**11**) and ζ-(**12**) (Figure 3), of which **5** and **6** do not feature.

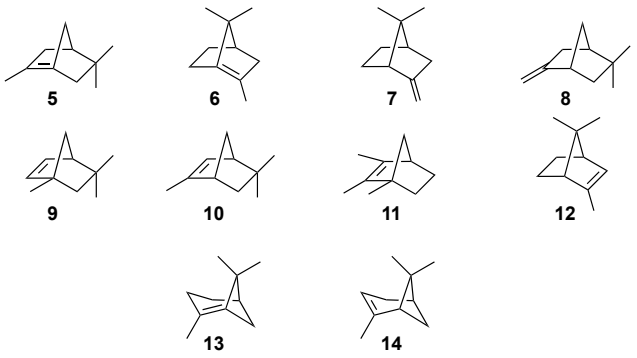

Figure 3. Top: Proposed anti-Bredt fenchene isomers by Bartelt and the 6 known fenchene isomers to-date (presented in the racemic form); Bottom: Wallach's proposal for α-pinene (**13**) and corrected α-pinene (**14**) shown as a racemate.

Wallach et al in 1907 suggested **13** as the chemical structure of α-pinene **14**,[23] however, this was identified by Richter and Anschütz as incorrect based on the Bredt premise (Figure 4).[24] It was almost 70 years later, however, that a natural product skeleton was questioned due to the presence of a double bond placed at a bridgehead position. In 2008, Fraga and co-workers,[25] argued convincingly that the chemical structure claimed by Chanudhuri et al as licamichauxiioic acid B (**15**),[26] which had considerable anti-cancer activity,[27] was incorrect. Although Fraga did not suggest a revised structure, the key to unmasking this error was the ^{1}H and ^{13}C NMR chemical shift comparison to licamichauxiioic acid A (**16**) (also proven to be incorrect) and known related systems (i.e. **17**). For example, the reported carbon chemical shifts of 35.7 ppm for C-9 and 33.9 ppm for C-11 were not consistent (i.e. significant downfield and upfield differences), and the ^{1}H NMR chemical shifts for **15** and **16** at positions H-9 and H-14 had disconcertingly similar values (i.e. 5.45 ppm and 5.44 ppm respectively) (Figure 4).[26]

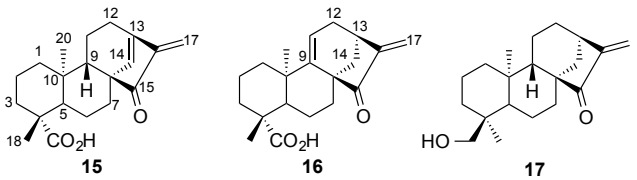

Figure 4. Licamichauxiioic acids A (**16**) and B (**15**) including the parent structure **17**.

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Craig M. Williams was born in Adelaide, Australia. He received his BSc(Hons) degree in chemistry in 1994 and in 1997 was awarded his PhD in organic chemistry from Flinders University under the supervision of Prof. Rolf H. Prager. He worked as an Alexander von Humboldt Postdoctoral Fellow with Prof. Armin de Meijere at the Georg-August-Universituat, Göttingen, Germany until 1999 and then took up a postdoctoral fellowship at the Australian National University with Prof. Lewis N. Mander. He has held an academic position, currently Assoc. Professor, at The University of Queensland since 2000 and during this time has won a number of awards including a Thieme Chemistry Journals Award in 2007. The primary research focus of the Williams group is the construction and isolation of biologically active complex natural products, and designing methodology to assist in this endeavour. The group also enjoys dabbling in medicinal, physical organic and computational chemistry.

Williams and Savchenko recently identified neoveratrenone **18**,[28] isolated from the roots and rhizomes of *Veratrum dahuricum* (Turcz.) Loes. f.,[29] as a suspiciously anti-Bredt candidate. Re-analysis of the spectroscopic data present by Cong *et al*.[29] suggested, even in the absence of some 2D NMR spectra (e.g. COSY), that the proposed anti-Bredt structure was incorrect as initially indicated by missing expected correlations in the NOESY spectra. A further clue en route to the likely structure was the fact that Cong *et al*. also reported the isolation of verapatuline (**19**), which on additional literature searching revealed the structurally related synthetic compound, **20**. Comparison of the ^{1}H and ^{13}C NMR very compellingly pointed to the reassigned structure **21** (Figure 5).

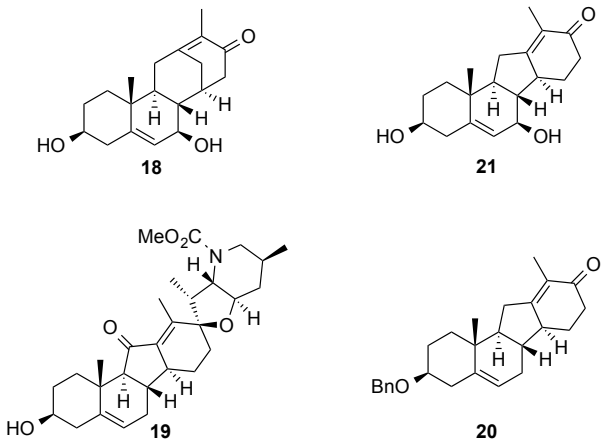


Figure 5. Neoveratrenone (**18**) and compounds **19** and **20** that led to the structural revision **21**.

Two further natural products, which fall into the same suspiciously anti-Bredt category have been reported. The first is hugonianene A **22**,[30] isolated from the cytotoxic root bark extract of *Hugonia busseana* (a shrub found in the southern parts of Tanzania), which has received attention for its high activity against *Anopheles gambiae* mosquito larvae causing complete larval mortality. In the second case Paridhavi et al reported the isolation of rosacedrenoic acid **23** from the flowers of *Rosa damascene* an Indian flowering plant.[31] No 2D NMR was undertaken in the elucidation process of **23** (Figure 6).

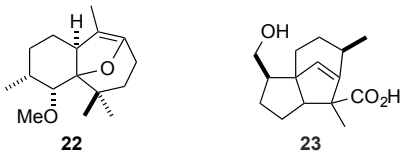


Figure 6. Proposed chemical structures for isolates from *Hugonia busseana* and *Rosa damascene*, respectively.

Williams et al utilised the ACDlabs NMR Structure Elucidator platform to aid in resolving the controversial proposals for hexacyclinol,[32] which agreed with the Rychnovsky proposal.[33] Although neither of the two structures qualifies for this review, in the course of formulating rules to limit impossible structure generation (as possible Structure Elucidator solutions to the analysis of inputted 2D NMR data), Bredt's rule was applied to the algorithm. Having had many successful outcomes with ACDLabs Structure Elucidator ourselves, when solving complex natural product structures,[34] we would caution against outright exclusion of potential solutions using Bredt's rule. Subsequent sections highlight the need for such caution.

3. All carbon containing bicyclic bridgehead olefinic systems

Note: for ease of bicyclic system classification within the all carbon, oxygen and nitrogen sections the smallest ring in each bridge has been selected.

3.1 Bicyclo[4.3.1] systems

The isolation of **24** by Munro and co-workers in 1988 represents the first reported example of a naturally-occurring bicyclo[4.3.1]decene system bearing the bridgehead double bond.[35] The cytotoxic sesquiterpene **24** was isolated from a methanol/toluene extract of a New Zealand *Eurypon* sp. sponge through bioassay-guided separation, and the structure was established with standard NMR spectroscopic techniques. Cambie and co-workers subsequently isolated the related compound **25** from the same species in 1990 (Figure 7).[36] The relative instability of **25** alludes to the reactivity of the bridgehead double bond in this instance, which is in agreement with the stability rules proposed by Prelog for the bicyclo[4.3.1]decene system.[6] Note that Schleyer predicted the bicyclo[4.3.1] to be completely stable.

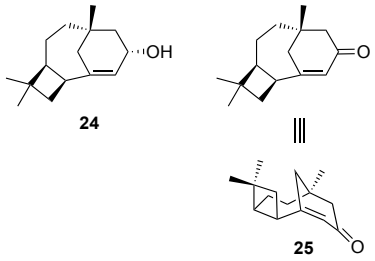
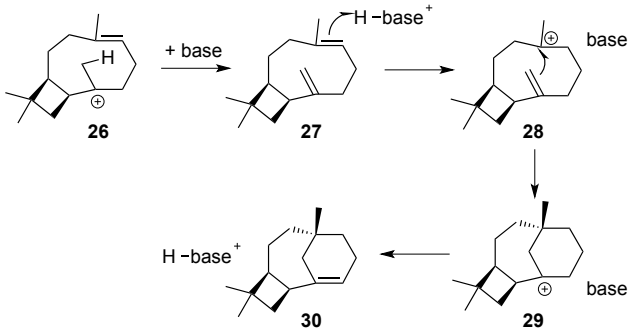


Figure 7. The New Zealand *Eurypon* sp. sponge isolates **24** and **25** (flat and three dimensional view) reported by Munro and Cambie.

In 2013, Tantillo and Nguyen published density functional theory (DFT) calculations probing the mechanism of formation of caryolene (**30**), a putative biosynthetic precursor to **24**.[37] Of the two proposed mechanisms, a base-catalysed sequence (via **26** to **29**) with a tertiary carbocation minimum was predicted to have a relatively low barrier for the formation of **30** (Scheme 1).



Scheme 1. The postulated mechanism of formation for caryolene (**30**) supported by DFT calculations.

The groups of Iwagawa and Duh have reported the isolation of structurally-related anti-Bredt bicyclo[4.3.1]decene xenia diterpenoids from soft corals belonging to the genus *Xenia*. Compound **31** was isolated from *Xenia florida*,[38] whereas umbellacins C (**32**) and E (**33**) were isolated from *Xenia umbellatta* Lamarck (Figure 8).[39] Strong correlation of NMR spectroscopic data for compounds **31**-**33** with that of related natural products with a saturated bicyclo[4.3.1]decene skeleton aided in the processes of structure elucidation. The configuration of the $\Delta^{4,12}$ alkene in **31** was assigned as *cis* on this basis.[38] However, for **33**, NOESY correlations from H-3 to H-12, and H-4a to H-13 established the geometry of the $\Delta^{4,12}$ alkene as *trans*. Umbellacin E (**33**) (Figure 8) was found to exhibit cytotoxicity against murine P-388 lymphocytic leukemia with an ED_{50} value of 3.8 μg/mL.[39]

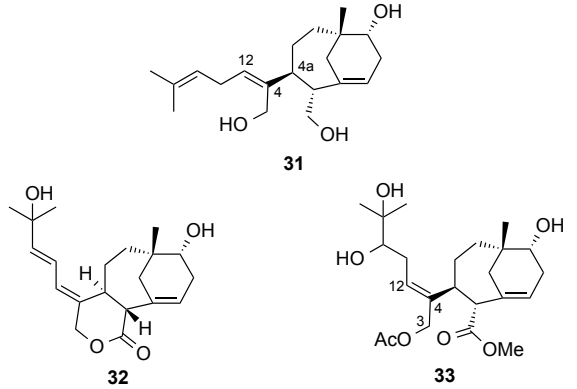
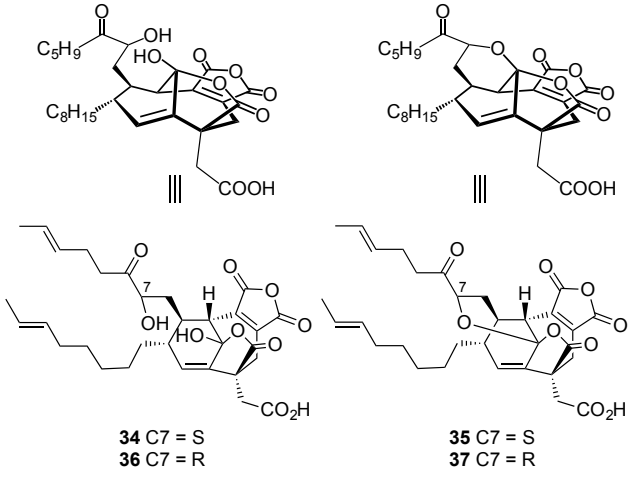


Figure 8. The umbellacins (**31**-**33**) isolated from the genus *Xenia*.

In a screening campaign aimed at the discovery of inhibitors of squalene synthase and protein farnesyl transferase, Kaneko and co-workers identified the novel bicyclo[4.3.1]deca-1,6-diene natural products phomoidride A (**34**) and B (**35**) (Figure 9).[40] Compounds **34** and **35** were isolated from the fermentation broth of an unidentified fungus, collected from a juniper twig in Texas. The C-7 epimeric compounds, phomoidride C (**36**) and D (**37**), were subsequently isolated by Danishefsky and Sulikowski (Figure 9).[41][42] While the bridgehead alkene skeleton of the phomoidrides is stable at room temperature, Kaneko and co-workers demonstrated that **34** is converted into **35** upon treatment with a catalytic amount of methanesulfonic acid, forming an internal acetal. Sulikowski and co-workers subsequently suggested that **35** is the biosynthetic precursor to the remaining three phomoidrides, where **36** and **37** are thermodynamic products.[42] Structure determination of the phomoidrides was achieved using NMR spectroscopy, and has since been confirmed through total synthesis of phomoidrides A (**34**) and B (**35**) [Nicolaou,[43a-c] Fukuyama,[43d] Shair,[43e] Danishefsky[43f]]. The biosynthesis, biological activity, total syntheses, and efforts towards the total synthesis of the phomoidrides have been reviewed previously by Wood et al.[43g] In this article an overview was put forward regarding which systems can be absolutely defined as anti-Bredt. The conclusion was that the phomoidrides could not be classed as anti-Bredt, as Kaneko stated, because the bicyclo[4.3.1]decene system is predicted to be stable according to Wiseman's assessment criteria (as well as Schleyer).



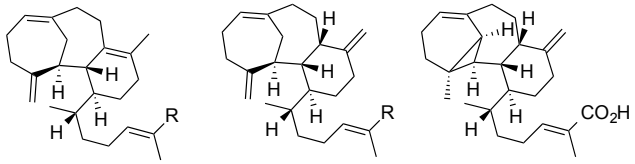
34 C7 = S
36 C7 = R

35 C7 = S
37 C7 = R

Figure 9. Phomoidrides A-D (**34**-**37**) (top and side view) originated from an unidentified Texan juniper twig fungus.

3.2 Bicyclo[4.4.1] systems

In 1983, Naya and co-workers presented the first example of a natural product containing a bicyclo[4.4.1]undec-1-ene skeleton.[44] Five novel sesterterpenoids, cerorubenic acid-I (**38**), cerorubenic acid-II (**39**), cerorubenic acid-III (**40**), cerorubenol-I (**41**), and cerorubenol-II (**42**) were isolated from the secretion of the scale insect *Ceroplastes rubens* Maskell (Figure 10). The structures of these compounds were determined by NMR spectroscopy. The bridgehead double bond of **38** was susceptible to slow oxidation in the air, reflecting the inherent strain of the system. In 1998 Paquette achieved the total synthesis of cerorubenic acid-III (**40**) in the form of its methyl ester.[45]



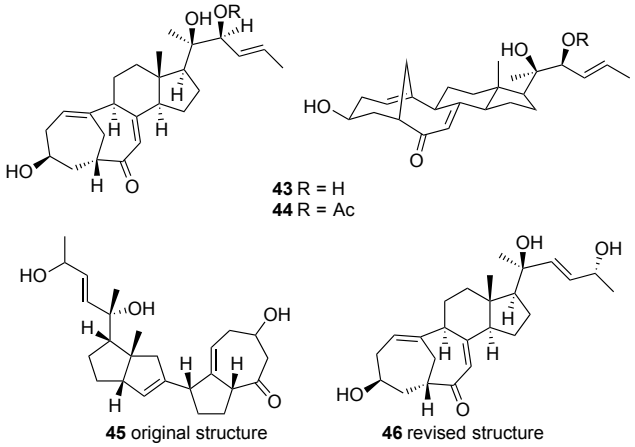
38 R = CO_2H
41 R = CH_2OH

39 R = CO_2H
42 R = CH_2OH

40

Figure 10. Cerorubenic acids and alcohols (**38**-**42**) from secretions of the scale insect.

From the culture broth of a marine isolate of *Penicillium citrinum*, Crews and co-workers isolated two novel steroids, isocyclocitrinol A (**43**) and 22-acetylisocyclocitrinol A (**44**).[46] An initial comparison of the spectroscopic data of **43** with that of the previously known compound cyclocitrinol (**45** – original structure) suggested that **43** was likely a new cyclocitrinol analogue.[47] However, upon extensive spectroscopic analysis, it was found that **43** and **44** did not resemble **45**, and in fact contained an entirely novel four-ring system including a bridgehead double bond. The structural assignment for **44** was confirmed by an X-ray crystal structure, and as a result, the structure of **45** was revised to that of **46**.[46,48] Compounds **43** and **44** were found to have weak antibacterial activity against *Staphylococcus epidermidis* and *Enterococcus durans* (Figure 11).[46]



43 R = H
44 R = Ac

45 original structure

46 revised structure

Figure 11. Top: Isocyclocitrinol A (**43**) and 22-acetylisocyclocitrinol A (**44**) (flat and three dimensional view); Bottom: Original and revised structure of cyclocitrinol **46** isolated from *Penicillium citrinum*.

In 2005, Rodrigues-Filho and co-workers reported the isolation of neocyclocitrinol, an epimeric mixture of novel bicyclo[4.4.1]undec-7,10-diene C25 steroids, akin to that reported by Crews, from the plant-derived fungus *Penicillium janthinellum*.[49] It was found that the isolated compounds showed strong spectroscopic similarities to **46**, differing only in the C-17 side-chain, which aided in the structure elucidation of neocyclocitrinol. Unfortunately, the configuration of the $\Delta^{20,22}$ alkene was not established, nor were the absolute configurations determined for C-23 and C-24 (Figure 11).

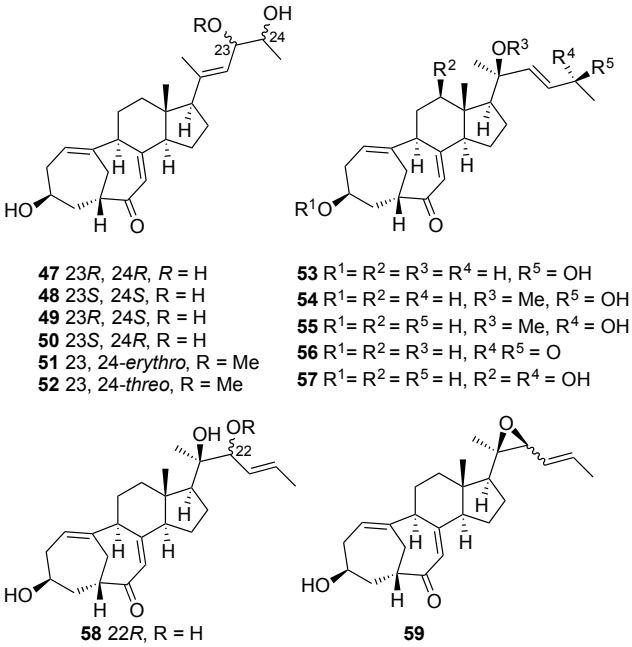
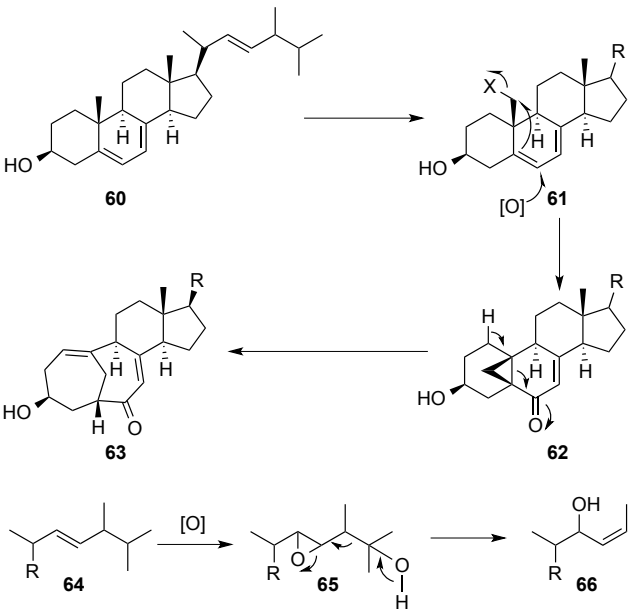


Figure 12. Additional cyclocitrinol family members isolated from *Penicillium citrinum* and *janthinellum*.

Zhu and co-workers subsequently re-isolated the neocyclocitrinols, isocyclocitrinol A (**43**) and 22-acetylisocyclocitrinol A (**44**), and a series of bicyclo[4.4.1]undec-7,10-diene analogues (**47**-**59**) from cultures of the volcanic ash-derived fungus *Penicillium citrinum* HGY1-5.[48] Extensive NMR analysis and X-ray crystallography allowed for the unambiguous assignment of structure and absolute configuration of these compounds. Comparison to the spectroscopic data reported by Rodrigues-Filho revealed that the reported epimeric mixture was composed of **47** and **49**. The authors furthermore demonstrated that **43**, **46**, **53**, and **58** are produced on exposure of **59** to acidic conditions, and that compounds **47**-**52**, **54** and **55** are artifacts of the acid hydrolysis of **46** and **53** (Figure 12).

Ergosterol (**60**), which was also found to be produced by both fungi,[49,48] is the proposed biosynthetic precursor to these unusual steroids. The proposed mechanism relies on the enzymatic activation of C-19 to generate an electrophilic center (**61**), which can react with the $\Delta^{5,6}$ alkene with concomitant oxidation of C-6 to produce cyclopropane intermediate **62**.[49] Subsequent fragmentation of the electron-deficient cyclopropane generates the bicyclo[4.4.1]undec-7,10-diene skeleton of the cyclocitrinols (**63**) (Scheme 2). The C-17 side-chain of the cyclocitrinols could be accessed through oxidation of the ergosterol side-chain (**64** to **65**), followed by elimination of acetone to produce intermediate **66**, which could undergo subsequent oxidations and rearrangements to produce the variety of observed functionality. Based on the proposed biosynthesis, the Zhu group undertook feeding studies of *P. citrinum* with [1,2-$^{13}C_2$]-acetate and [2-^{13}C]-acetate.[48] The resulting labeling patterns were consistent with Rodrigues-Filho's hypothesis (see Scheme 2).



Scheme 2. Top: The proposed biosynthetic pathway to the cyclocitrinols (**63**) starting from ergosterol (**60**); Bottom: Postulated oxidative transformation of the C-17 side-chain of the cyclocitrinols (**63**).

3.3 Bicyclo[5.3.1] systems

The taxanes [e.g. taxol (**67**), Figure 13] are perhaps the best-known class of natural products, which contain a bridgehead alkene, with in excess of 200 taxoids bearing this structural moiety isolated to date. The reader is referred to the existing reviews and articles, which discuss in depth the isolation, occurrence, synthesis, and biological activity of the taxanes.[50][51,52]

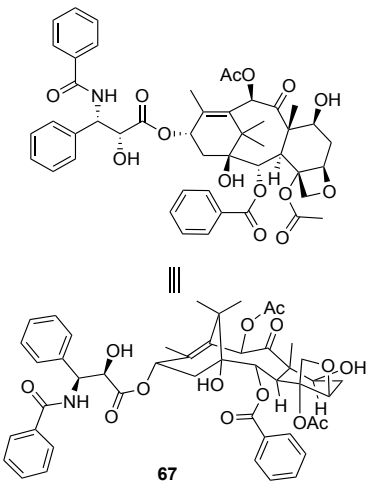
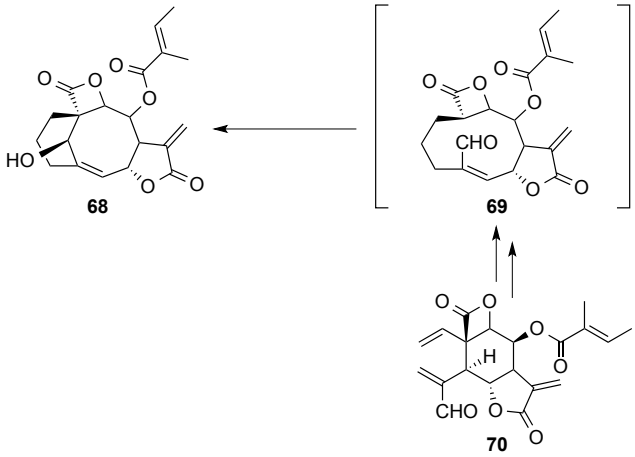


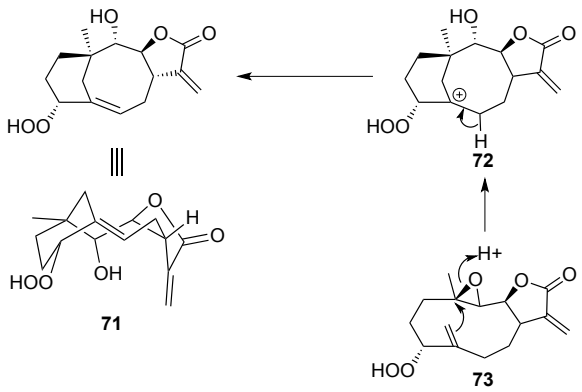
Figure 13. Taxol **67** (flat and three dimensional view), the best known taxane, used for the clinical treatment of various cancers.

Isolated from an extract of *Disynaphia halimifolia*, disyhamifolide (**68**), was reported by Bohlmann and co-workers in 1981.[53] The authors proposed that **68** results from a transannular aldol reaction of the medium-sized ring **69**, which could be derived from [3,3]-sigmatropic rearrangement and reduction of disnyaphiolide (**70**), which was also isolated from the same species (Scheme 3).



Scheme 3. Proposed transannular aldol reaction giving disyhamifolide (**68**).

Appendino found that chloroform extracts of *tanacetum vulgare* var. *crispum* and *T. vulgare* chemotypes tested positive for the presence of peroxides.[54] From these extracts was isolated crispolide (**71**), a hydroperoxysesquiterpene lactone bearing a bridgehead double bond. The structure of crispolide **71** was initially solved utilising NMR spectroscopy, and was subsequently confirmed by X-ray crystallography of the diacetate of the natural product.[55] The authors proposed a possible biogenetic route to crispolide (**71**), invoking an early introduction of the peroxyl moiety, followed by an acid catalyzed transannular cyclisation of known natural product peroxyparthenolide (**73**) (Scheme 4).



Scheme 4. Crispolide (**71**) (flat and three dimensional view); postulated to arise from an acid catalyzed transannular cyclisation originating from **73**.

A related structure, 1β,5β-dihydroxyeriocephaloide (**74**) was subsequently isolated by Zdero and co-workers from the aerial parts of *Eriocephalus kingesii* Merxm. Et Eberle (Figure 14), which was proposed to be biogenetically produced by an equivalent mechanism (see Scheme 4).[56]

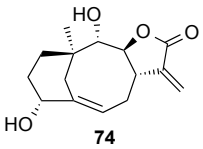


Figure 14. 1β,5β-Dihydroxyericocephaloide (**74**) isolated from the aerial parts of *Eriocephalus kingesii*.

3.4 Bicyclo[7.2.1] systems

Shikoccidin (**75**) (Figure 15), determined by X-ray crystallography in 1979, was isolated as the minor diterpenoid from the aerial parts of *Rabdosia shikokiana* (Makino) Hara *var. occidentalis* (Murata) Hara by Eiichi Fujita et al.[57] Upon treatment of shikoccidin (**75**) with acetic anhydride under basic conditions, a 8,9-secokaurane was produced which was found to be identical to the mono-acetate of the major diterpenoid isolated from the plant. Comparison of spectroscopic data led to the assignment of this structure as the bridgehead alkene containing shikoccin (**76**). The structure of shikoccin **76** was later confirmed by X-ray analysis of the mono-acetate derivative.[58] Although **76** was a potential Grob-type fragmentation product of **75**[57] (Figure 15), they subsequently confirmed that **76** was most likely not an artifact of the isolation. This conclusion was drawn based on the fact that conversion to **76** was not observed upon treatment of **75** with oxalic acid in methanol.[60] Eiichi Fujita and co-workers have also described the isolation and structure elucidation of *O*-methylshikoccin (**77**), which succumbed to total synthesis in 1996 by Paquette et al. (Figure 15).[59,60] Paquette went on to write that, "Although Bredt's rule is not at all violated in **77** [presumably as $S \geq 9$], sufficient ring strain evidently resides in its bridgehead double bond to endow this site with heightened reactivity."[60]

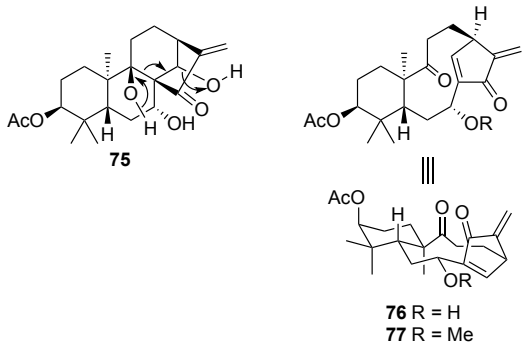


Figure 15. Shikoccidin (**75**), shown as a potential Grob-type fragmentation precursor of Shikoccin (**76**), and *O*-methylshikoccin (**77**) (flat and three dimensional view) isolated from *Rabdosia shikokiana var. occidentalis*.

Since the 1979 publication of Eiichi Fujita et al., the structures of a variety of compounds related to shikoccin (**76**) have been determined. Though the isolation of shikodomedin (**78**) was described in 1979 (Figure 16),[61] the structure determination of the major diterpenoid component of *Rabdosia shikokiana* (Makino) Hara var. *intermedia* (Kudo) Hara was not reported until some years later. In 1982 Tetsuro Fujita and co-workers documented the X-ray analysis of the structure arising from the mono-bromoacetate shikodomedin.[62] Shikodomedin (**78**) was found to have cytotoxic activity against the cultured rat mammary cancer FM 3A/B cell line.[62] The group also examined the diterpenoid chemistry of *Rabdosia umbros* var. *latifolia*, and isolated the new compound rabdolatifolin (**79**) (Figure 16), along with a number of known compounds.[63]

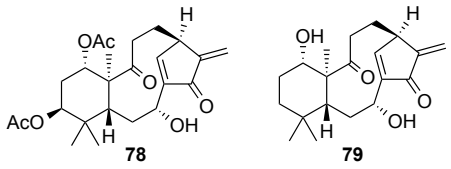


Figure 16. Shikodomedin (**78**) isolated from *Rabdosia shikokiana var. intermedia* and rabdolatifolin (**79**) *Rabdosia umbros* var. *latifolia*.

Takeda and co-workers isolated rabdoshikoccin A (**80**) and B (**81**) from *Rabdosia shikokiana var. occidentalis* (Murata) Hara (Figure 17).[64] Treatment of **81** with acetic anhydride in pyridine yielded the triacetate, which was found to be spectroscopically identical to peracetylated **78**, confirming the assigned structure. The Takeda research group also reported the isolation of rabdoumbrosanin (**82**) from *Rabdosia umbrosa* (Maxim.) Hara (Figure 17).[65]

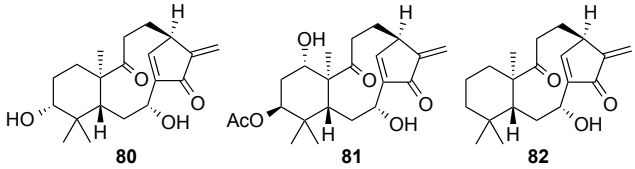


Figure 17. Rabdoshikoccin A (**80**) and B (**81**) isolated from *Rabdosia shikokiana var. occidentalis* and rabdoumbrosanin (**82**) from *Rabdosia umbrosa*.

From the liverwort *Lepidolaena taylorii*, Perry and co-workers re-isolated rabdoumbrosanin (**82**) along with **83**-**87** as minor components (Figure 18).[66, 67] The compounds were assessed for cytotoxic activity against mouse P388 leukemia cells, and compounds **82** and **87** were found to be the most potent. *Croton kongensis* has also proven to be a source of these 8,9-secokauranes, with the groups of Kittakoop and Li isolating new structures **88**-**90** from this plant (Figure 18).[68-70] Diterpenes **86** and **88** were found to have both antimycobacterial and antimalarial activity.[68]

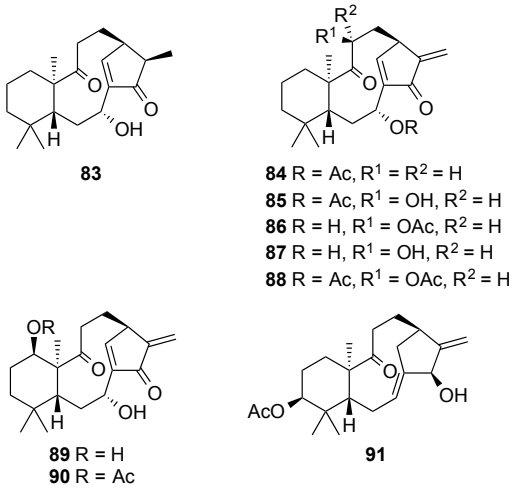
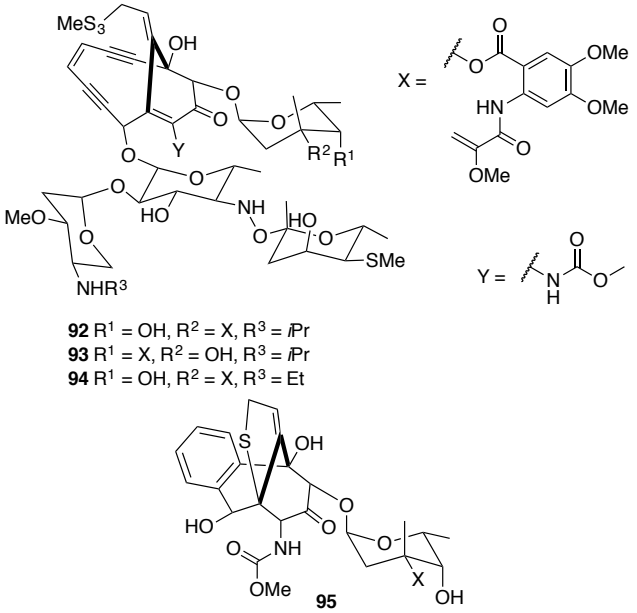


Figure 18. 8,9-Secokauranes extended family members **83**-**91**.

Kubo and co-workers presented an unusual member of this class of compounds with rabdohakusin (**91**) in which the bridgehead alkene is exocyclic to the five-membered ring (Figure 18). The structure of rabdohakusin (**91**) was initially established with the aid of NMR spectroscopy. Oxidation of the allylic alcohol with manganese dioxide produced a conjugated enone whose NMR spectra differed significantly from that of previously reported **76**, supporting the presence of the exocyclic alkene.[71]

3.5 Bicyclo[7.3.1] systems

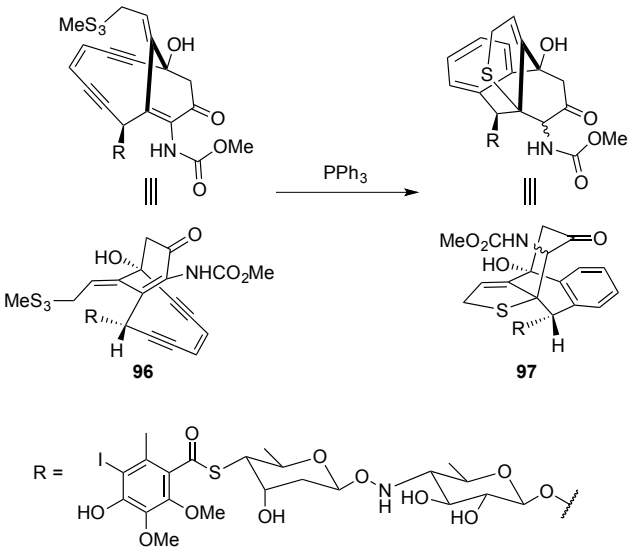
Four families of structurally related natural products belonging to this category include the esperamicins (Figure 19),[72] calicheamicins (Figure 20),[73] namenamicin,[74] and shishijimicins (Figure 21).[75a] In addition to possessing a bridgehead double bond, all of these compounds (except esperamicin X (**95**)[72]) possess a enediyne unit, which constitutes six of the seven carbons in the bicyclo[7.3.1] system, and a highly unusual allylic trisulfide unit. The main structural difference between the families is found in the sugars that decorate the bicyclic core. The two former families were derived from microbial fermentation; the esperamicins were produced by cultures of *Actinomadura verrucosospora*, collected from Pto Esperanza, Argentina, and the calicheamicins were isolated from *Micromonospora echinospora ssp. calichensis*. Namenamicin and the shishijimicins were isolated from the tunicates *Polysyncraton lithostrotum* on Namenalala Island and *Didemnum proliferum* in southern Japan respectively.



92 R^1 = OH, R^2 = X, R^3 = *i*Pr
93 R^1 = X, R^2 = OH, R^3 = *i*Pr
94 R^1 = OH, R^2 = X, R^3 = Et

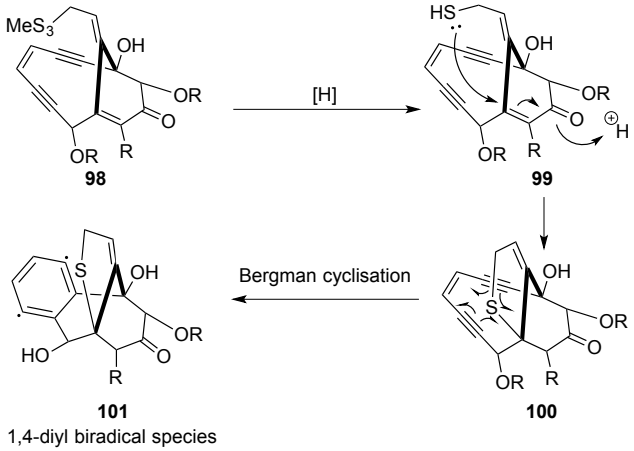
Figure 19. The esperamicins A_1, A_2, A_{1b} and X (**92**-**95)** isolated from *Actinomadura verrucosospora*, collected from Pto Esperanza, Argentina. The absolute configurations have not been determined, but are depicted as shown for the purpose of clarity and consistency.

Standard spectroscopic and spectrometric analysis of various chemical degradation products, in addition to the intact natural products, allowed for the structure determination of the esperamicins and the calicheamicins. The formation of dihydrothiophene **97** through reduction of pseudoaglycon **96** with excess triphenylphosphine was key to establishing the structure of the bicyclic core (Scheme 5).[73] Likewise, the discovery of esperamicin X (**95**) greatly aided the structure determination efforts of the esperamicins,[72] and also added further evidence for the proposed biological mechanism of action (more below).



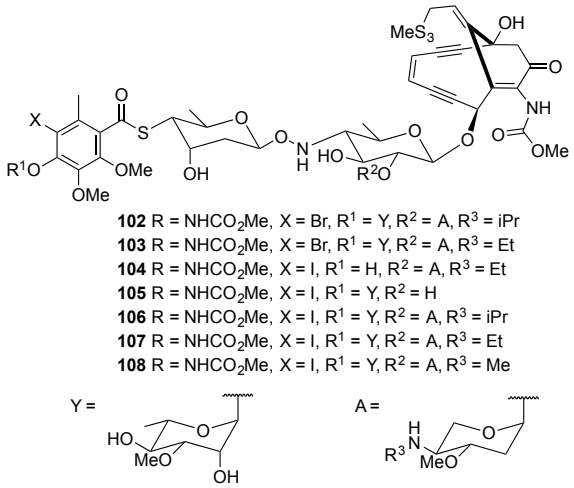
Scheme 5. Triphenylphosphine mediated reduction of aglycon **96** to give dihydrothiophene **97** (top and side views by 90° rotation) was instrumental in the elucidation of the calicheamicins' core.

The reactive bridgehead alkene of these natural products, in concert with the allylic trisulfide and enediyne unit, is key to their antitumour antibiotic properties (Scheme 6). Reduction of the allylic trisulfide **98** causes the corresponding sulfide (**99**) to undergo a 1,4-addition onto the bridgehead enamide. This allows the ends of the enedyne (**100**) (which were kept apart previously by the bridgehead double bond) to approach and undergo reductive aromatization (Bergman cyclisation) *via* a 1,4-diyl species (**101**).[75b] This biradical species is capable of hydrogen abstraction from the DNA backbone, leading to strand scission.



1,4-diyl biradical species

Scheme 6. Postulated chemical process that facilitates the mode of action of the enediyne-type anti-tumor antibiotics. Reduction of trisulfide **98** leads to conjugate addition of the resultant sulfide (**99**) to the bridgehead enamide, which allows a Bergman-type cyclisation on enediyne **100** to take place, leading to the formation of the active 1,4-diyl species **101**.

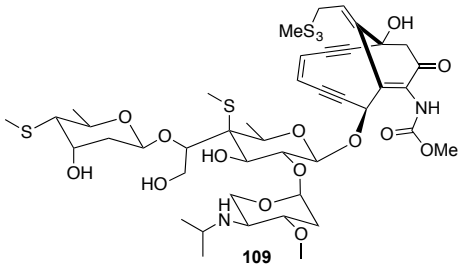


102 R = $NHCO_2Me$, X = Br, R^1 = Y, R^2 = A, R^3 = iPr
103 R = $NHCO_2Me$, X = Br, R^1 = Y, R^2 = A, R^3 = Et
104 R = $NHCO_2Me$, X = I, R^1 = H, R^2 = A, R^3 = Et
105 R = $NHCO_2Me$, X = I, R^1 = Y, R^2 = H
106 R = $NHCO_2Me$, X = I, R^1 = Y, R^2 = A, R^3 = iPr
107 R = $NHCO_2Me$, X = I, R^1 = Y, R^2 = A, R^3 = Et
108 R = $NHCO_2Me$, X = I, R^1 = Y, R^2 = A, R^3 = Me

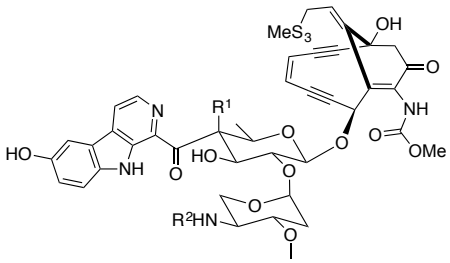
Figure 20. Calicheamicins β_1^{Br}, γ_1^{Br}, α_2^{I}, α_3^{I}, β_1^{I}, γ_1^{I}, δ_1^{I} (**102**-**108**) isolated from *Micromonospora echinospora ssp. Calichensis*.

Of the four families encompassing the esperamicins (Figure 19), calicheamicins (Figure 20), namenamicin and shishijimicins

(Figure 21), only calicheamicin γ_1^I (**107**) has succumb to total synthesis [Nicolaou 1992;[76] Danishefsky 1995[76f]].



109



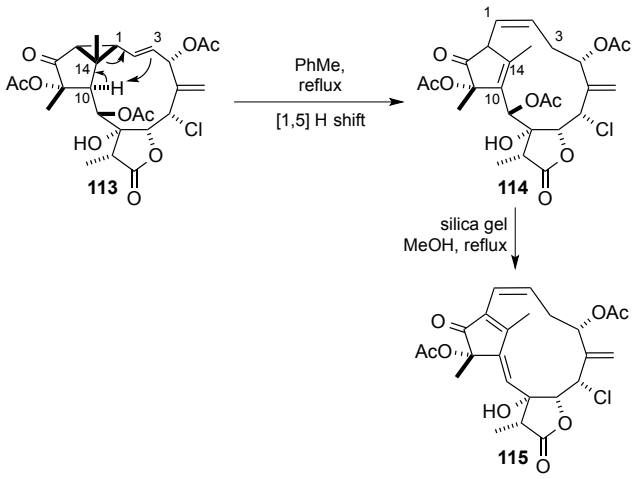
110 R^1 = SMe, R^2 = *i*Pr
111 R^1 = H, R^2 = *i*Pr
112 R^1 = SMe, R^2 = Et

Figure 21. Namenamicin **109** and shishijimicins A-C (**110**-**112**) isolated from *Polysyncraton lithostrotum* on Namenalala Island and *Didemnum proliferum* form southern Japan respectively.

3.6 Bicyclo[9.2.1] systems

The only representative within this class is the diterpene erythrolide K (**115**) (Scheme 7), isolated from a sample of the Caribbean gorgonian octocoral *Erythropodium caribaeorum* collected in Tobago, as disclosed by Mootoo in 1997.[77] Note that both bridgehead positions contain a double bond. The compound was characterized by NMR spectroscopy, with the unusual structure further secured by X-ray crystal structure analysis.

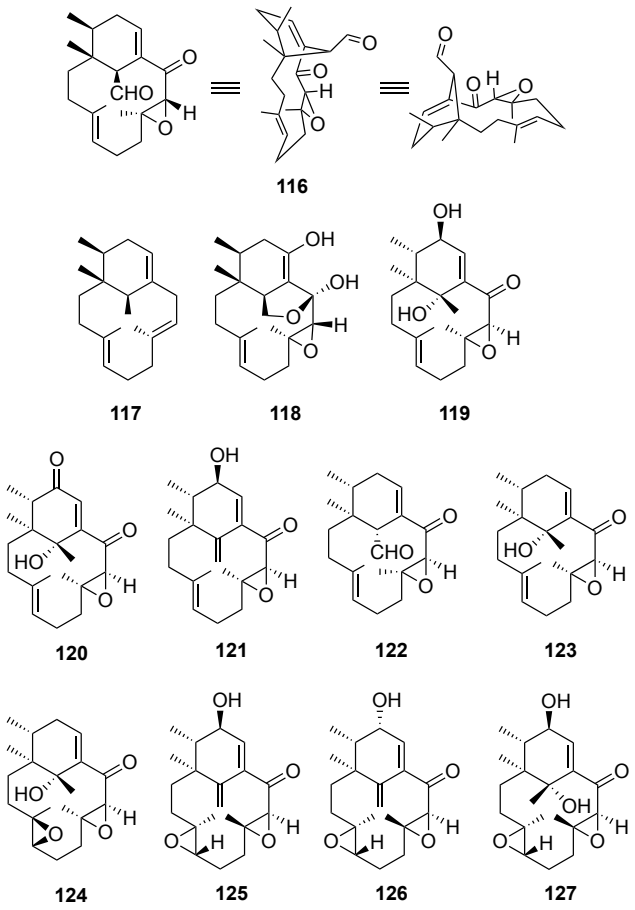
Based on the isolation of structurally related family members [*e.g.* erythrolide A (**113**)], it was postulated that erythrolide K (**115**) is biosynthetically derived from **113** *via* a [1,5]-sigmatropic hydrogen shift of the H-10 to C-3 with concomitant rupture of the cyclopropane unit (across the C-1 – C-14 bond). This transformation has been achieved in a synthetic setting (Scheme 7).



113 **114** **115**

Scheme 7. Erythrolide K (**115**) isolated from *Erythropodium caribaeorum*, and its postulated biosynthesis from erythrolide A (**113**).

3.7 Bicyclo[9.3.1] systems



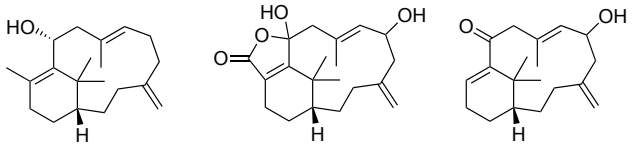
116 **117** **118** **119**
120 **121** **122** **123**
124 **125** **126** **127**

Figure 22. The phomactin and Sch bicyclo[9.3.1]pentadec-1-ene series, comprising of Sch 47918 (**116**) (flat and three dimensional view), Sch 49026 (**117**), Sch 49027 (**118**) and phomactins B (**119**), B1 (**120**), B2 (**121**), C (**122**), E (**123**), F (**124**), I (**125**; 13-*epi*, **126**) and J (**127**).

The phomactins (Figure 22),[78][79] isolated from the marine fungus *Phoma* sp., were found to be platelet activating factor antagonists, which are of potential benefit for the treatment of inflammatory disease states and ischemic disorders.[80] Not too surprisingly, the pharmaceutical companies Sankyo (Japan) and Schering-Plough (USA) showed considerable interests in these natural products, as did synthetic chemists.[81,82] The Goldring,[83] Hsung,[84] and Wulff[85] groups are amongst those who have been successful in the total synthesis of these compounds. The structures of Sch 47918 (**116**),[78c] E (**123**),[78e] I (**125**),[78g] and J (**127**)[78g] were all solved by X-ray crystallography (Figure 22).

Sch 49027 (**118**),[78c] is unique amongst this collection in that the double bond at the bridgehead could theoretically tautomerize to give the corresponding ketone. However, the oxygen bearing carbon of the enol had a chemical shift of 148.1 ppm, clearly indicating an olefinic carbon despite any perceived strain (Figure 22). The sp^2 hybridization at this bridgehead position, rather than inducing strain, is clearly energetically favourable for this system.

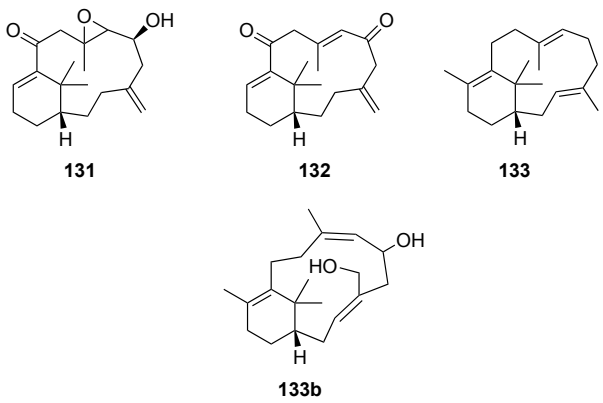
Duh, who contributed to the bicyclo[4.3.1]decene class in section **3.1** above, discovered the cespitularin family of diterpenes (Figure 23), isolated from the Formosan soft coral *Cespitularia hypotentaculata*.[86, 87] The structures were determined solely by NMR spectroscopy. Many of these compounds exhibited cytotoxicity against the cancer cell lines A549 (human lung adenocarcinoma), HT-29 (human colon adenocarcinoma) and P-388 (mouse lymphocytic leukemia).[88] However, cespitularin C (**128**) was particularly potent, exhibiting ED_{50} values of 0.12, 8.86 and 0.01 μg/mL against the aforementioned cell lines respectively.



128 **129** **130**

Figure 23. Cespitularins C (**128**), D (**129**) and E (**130**) isolated from the Formosan soft coral *Cespitularia hypotentaculata*.

Shen uncovered two further cespitularin-type natural products, cespihypotins C (**131**) and D (**132**), from *Cespitularia hypotentaculata* Roxas (Xeniidae) in Taiwan in 2006 (Figure 24).[89,90] Their structures were deduced by NMR spectroscopic methods. HMBC correlations between the gem-dimethyl protons and the bridgehead sp^2 carbon were important in identifying the bridgehead olefin of cespihypotins C (**131**) and D (**132**).



131 **132** **133** **133b**

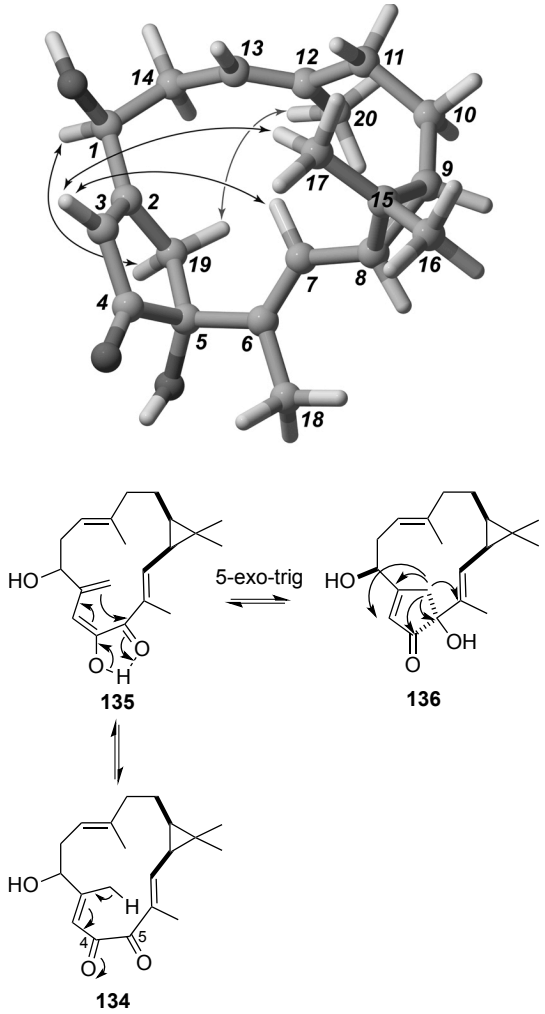
Figure 24. Cespihypotins C (**131**) and D (**132**) isolated from *Cespitularia hypotentaculata* Roxas (Xeniidae). The putative structure verticillene (**133**) is believed to be the biogenetic precursor of the cespitularins and cespihypotins, supported by **133b**.

Like the phomactins, the cespitularin-type structures have shared lineage with taxane natural products. Indeed, Shen and coworkers postulated that the cespitularins and cespihypotins all arise from verticillene (**133**) (Figure 24),[89,90] a putative structure that is proposed to be the biogenetic precursor of the taxane natural products. The recently reported compound 1 (**133b**), from *Trichoderma atroviridae* (UB-LMA), an endophytic fungus isolated from *Taxus baccata* trees, further supports this biosynthetic hypothesis (Figure 24).[90b]

3.8 Bicyclo[10.2.1] systems

The solitary entry in this section was discovered only very recently by Reddell, Parsons and Williams from the stems of *Croton insularis* (Baill) in a campaign aimed at discovering new anti-cancer agents from the Australian rainforest, in collaboration with EcoBiotics Ltd.[16] The bicyclo[10.2.1]pentadec-2,6,13-triene ring system of EBC-219 (**136**) was determined by NMR spectroscopy, specifically through the observation of key HMBC correlations. DFT calculations determined that four low-energy conformations could be adopted by the macrocyclic ring system. These featured either in-plane or perpendicular alignments of the alkene groups, with the perpendicular conformers giving 3D structures that are the most consistent with the NOESY NMR spectral data (Scheme 8, top). Calculations were also utilized to determine the absolute configuration of EBC-219 (**136**) by comparison of experimental and calculated CD spectra and found to be 1*S*, 5*R*, 8*S*, 9*R* (Scheme 8, middle).

The structurally related 1,2-dicarbonyl bearing EBC181 (**134**), which was also isolated from the same species, was proposed to be the biogenetic precursor of EBC-219 (**136**). It can be envisaged that the bridgehead double bond could arise from a 5-*exo*-trig cyclization of a γ-enol (of type **135**) of EBC181 (**134**) onto its C-5 ketone (Scheme 8, bottom).



Scheme 8. EBC-219 (**136**) isolated from *Croton insularis* (Baill). Top: Low-energy conformation with key NOEs. Bottom: Postulated biosynthetic conversion from EBC181 (**134**) *via* **135**, and key HMBC correlations assigning the bridgehead alkene shown on EBC-219 (**136**).

3.9. Bicyclo[13.3.1] systems

The longithorones,[18,91] and longithorols,[92] are exquisite natural products, owing to their curious polycyclic structure, the possibility of multiple atropisomers, and, significant to this review, multiple bridgehead alkenes [see also erythrolide K (**115**) (Scheme 7)] (Figure 25).[93] For instance, the archetypal compound in this family, longithorone A (**137**), possesses in the same molecule two bridgehead olefins within bicyclo[7.3.1] and [12.2.2] systems, and a greater bicyclo[13.3.1] system that contains three bridgehead alkenes. That is, five of the seven bridgehead positions contain a double bond!

The longithorones are farnesylated quinones isolated from the tunicate *Aplidium longithorax*. The structures of longithorones A (**137**) (the most complex member of the family),[91] B (**3**, Figure 2), and E (**138**) were all secured by X-ray crystallography,[18] while the others were determined through NMR spectroscopy. Longithorols A (**141**) and B (**143**) were unstable, presumably as the hydroquinone moieties were easily oxidized to the corresponding quinones; hence, the structures of the corresponding peracetylated derivatives **142** and **144** were elucidated instead.

Schmitz proposed that the key step in the biogenesis of these compounds was a [4+2] cycloaddition of farnesyl-quinone units **147** and **148** giving rise to the bicyclo[13.3.1] system.[91] In Shair's enantioselective total synthesis of (-)-longithorone A (**137**),[94] this [4+2] cycloaddition was successfully modeled using appropriately protected synthetic equivalents of **147** and **148** to furnish the bicyclic core, giving credence to the proposed biosynthetic pathway (Scheme 9).

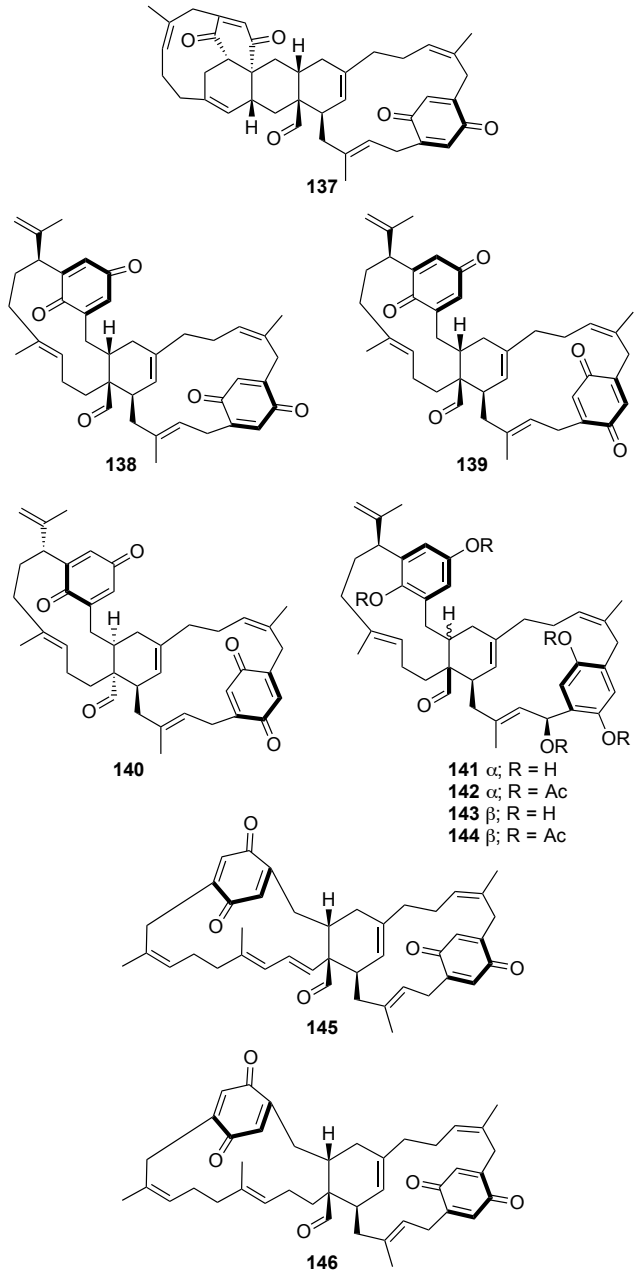
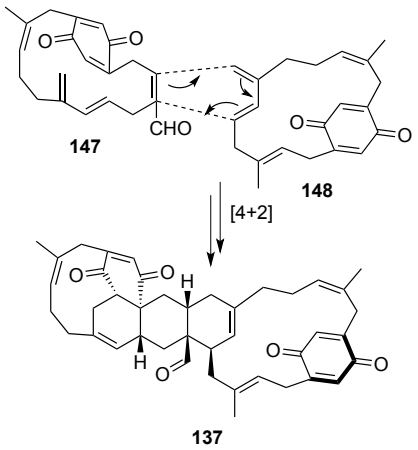


Figure 25. The longithorones A (**137**), E (**138**), F (**139**), G (**140**), H (**145**), I (**146**), and longithorols A (**141**; pentaacetate, **142**)[95] and B (**143**; pentaacetate, **144**) isolated from the tunicate *Aplidium longithorax*.



Scheme 9. The proposed key step in the biosynthesis of longithorone A (**137**) involving a [4+2] cycloaddition of quinone units **147** and **148** to furnish the polycyclic core.

4. Oxygen containing bicyclic bridgehead olefinic systems

4.1. 10-Oxabicyclo[4.3.1] systems

The oxygenated series are dominated by mono-oxygenated bicyclic ring systems and a good starting example is FR182877 (**149**) (Figure 26). In 1996 the Fujisawa Pharmaceutical Company patented a novel antimitotic agent isolated from a strain of Streptomyces sp. No.9885,[96] characterized by 2D NMR techniques and X-ray crystallography of a derivative as (+)-FR182877 (**149**) (Figure 26).[97] Synthetic chemists,[98] most notably Sorensen[99] and Evans,[100] were immediately attracted to this molecule, not only to the elegant structural architecture, but also to the striking anti-tumor activity. For example, FR182877 (**149**) displayed potent activity against both murine ascitic tumor P388 and Colon 38 solid tumors prolonging the life span of the tumor xenograph bearing mice, in addition, to other common cell lines.[97]

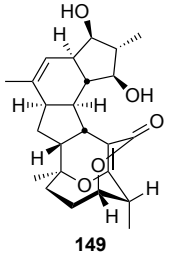


Figure 26. (–)-FR182877 (**149**) isolated from a strain of Streptomyces sp. No.9885. The work of Sorensen determined that the originally proposed (+)-enantiopode was incorrectly assigned.[97d,99]

The pinnacle attraction to this audience, however, was the fact that FR182877 (**149**) was found to be quite unstable due to the reactivity of the bridgehead double bond. It was found to react with molecular oxygen to form an epoxide,[97c] and with various nucleophiles in a Michael addition fashion.[99] These observations are unsurprising because the bridgehead double bond contained within FR182877 (**149**), whether considered as a 10-oxabicyclo[4.3.1]decene or a 2,7-dioxabicyclo[4.3.1]decene system, has Fawcett *S* = 8 and Wiseman *trans*-8 atom status, meaning it lies on the boundary of being classed as an anti-Bredt system.

4.2. 11-Oxabicyclo[4.4.1] systems

In 1991 Jereisterol A (**150**) (Figure 27) was isolated by Minale and co-workers from the pacific sponge *Jereicopsis graphidiophora* Lévi & Lévi in the north of New Caledonia at a depth of 225 m.[101] The structure of this rare 3-methoxy-8,9-secosteroid was deduced by comparing ^{13}C NMR data to that of known seco-steroids and those partially synthesized by the authors. Subsequent to the original discovery of this structural motif a number of reports later emerged in this area. The first from a second group in Napoli led by Costantino and co-workers who isolated compounds 4 (**152**) and 5 (**151**) from the Senegalese sponge *Microscleroderma spirophora* (Figure 27).[102] Tylopiol A (**153**) (solved by X-ray crystallography), and tylopiol B (**154**), reported by Wu *et al.*[103] were the only compounds of this class to be isolated from a terrestrial source. The source, namely *Tylopilus plumbeoviolaceus* (Snell. et Dick.) Sing., is an edible bitter fungus [family *Strobilomycetaceae* (Boletales)] widely distributed in the central area of Yunnan Province, China (Figure 27).

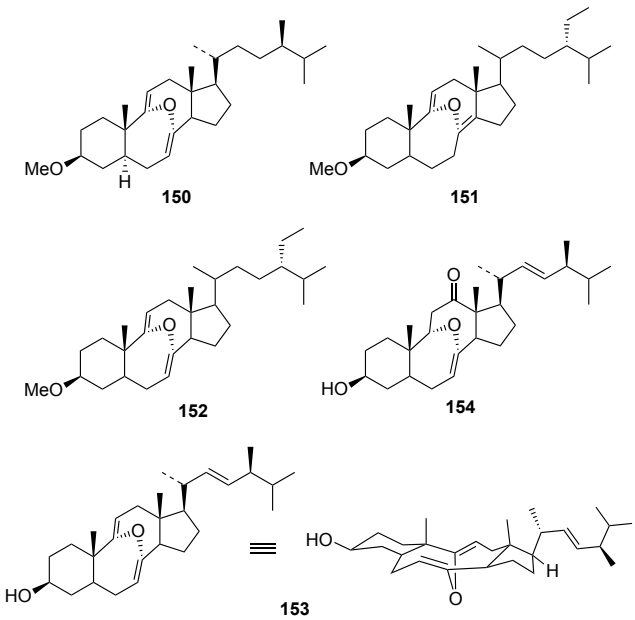


Figure 27. Jereisterol A (**150**), compounds 4 (**152**) and 5 (**151**), and tylopiol A (**153**) (flat and three dimensional view) and B (**154**).

A number of related structures bearing polysaccharide residues have also been isolated. Ebel and co-workers evaluated a sample of *Erylus lendenfeldi* (Geodiidae) collected off the Jordan coast in the gulf of Aqaba (Red Sea), discovering the steroidal saponin eryloside L (**155**) (Figure 28).[104] The same group later reported sarasinoside M (**156**) (Figure 28), isolated from the Indonesian sponge *Melophlus sarassinorum*.[105][106] Some 6 years later sarasinoside M (**156**) was isolated again, by a group

led by Oh and Shin, from the tropical sponge *Lipastrotethya sp.* collected from Chuuk, Micronesia, along with sarasinoside Q (**157**) (Figure 28).[107] Oh and Shin,[107] also demonstrated that sarasinoside M (**156**) and Q (**157**) display cytotoxicity against A549 and K562 cell lines, in addition to weak inhibitory activity against Na+ /K+ -ATPase.

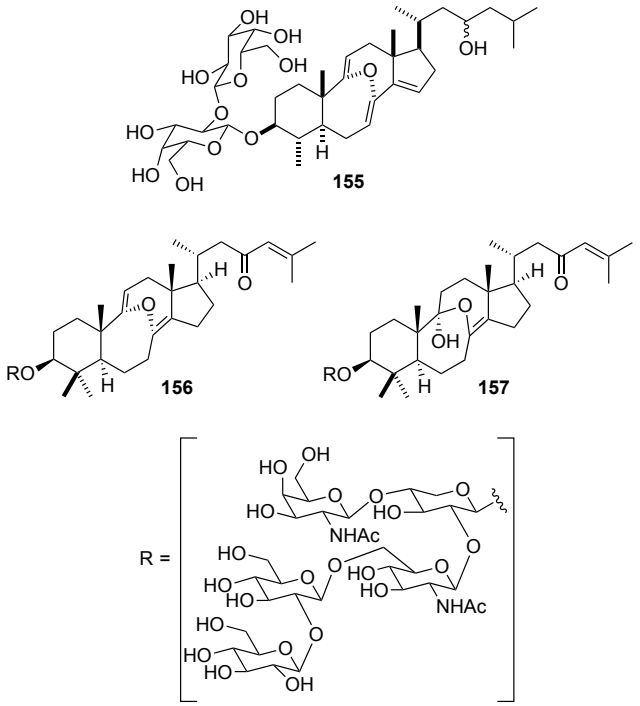


Figure 28. Eryloside L (**155**), and Sarasinosides M (**156**) and Q (**157**) isolated from *Erylus lendenfeldi*, *Melophlus sarassinorum* and *Lipastrotethya sp.*, respectively.

4.3. 11-Oxabicyclo[5.3.1] systems

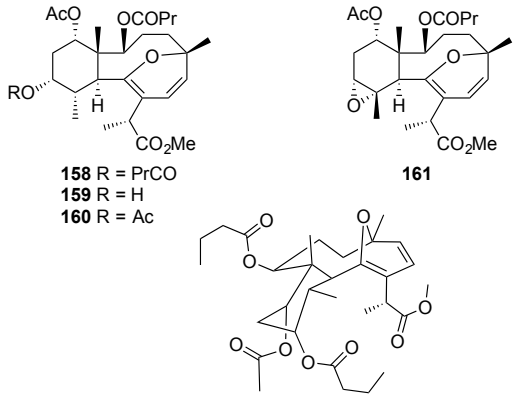


Figure 29. Briareolate esters A-C (**158-160**) and H (**161**) isolated from *Briareum asbestinum*. Flat and three dimensional view for **158** shown at bottom.

Extracts of Gorgonian octocorals (*Briareum asbestinum*), collected off the coast of Tobago, were investigated in a collaborative effort between the groups of Mootoo, McLean and Tinto. Using a combination of 2D NMR spectroscopy and X-ray crystal structure analysis, the structure of methyl briareolate (**158**) was elucidated (Figure 29).[108] A subsequent full paper disclosed two further family members (**159-160**),[109] and a later re-isolation paper reported **161**.[110] They were later renamed briareolate esters A (**158**), B (**159**), C (**160**) and H (**161**) (Figure 29).[110] No biological studies were reported.

4.4. 8-Oxabicyclo[5.4.1] systems

Francisco *et al.* disclosed that cystoseirol A (**162**) (Figure 30) was obtained from a brown alga (*Cystoseira mediterranea*) occurring along the Mediterranean coastline. It could also be isolated from *C. stricta* and *C. tamariscifolia*.[111] A subsidiary publication by this group announced cystoseirols B (**163**), C (**164**), D (**165**) and E (**166**) (Figure 30), also found in various sources of *Cystoseiraceae*, i.e. *C. mediterranea* (Banyuls sur Mer), *C. tamariscifolia* (Atlantic coasts), and *C. stricta* (Nice), around France.[112] The Francisco papers specifically commented that they had identified a natural product that "contains a bridge-head, *anti*-Bredt, double bond" "(in a large enough system to be accommodated)", but interestingly no citation to Bredt was provided.

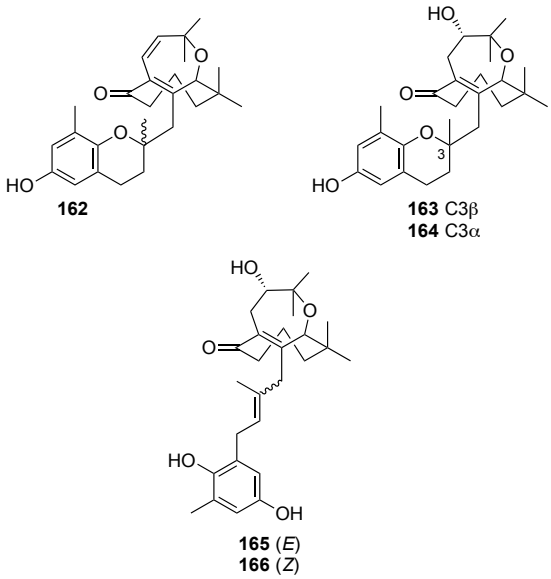


Figure 30. Cystoseirols A-E (**162-166**) isolated from *Cystoseira mediterranea*, *C. stricta* and *C. tamariscifolia*.

4.5. 11-Oxabicyclo[6.2.1] systems

de Vivar et al investigated the sesquiterpenoid constituents of members of the *Compositae* family isolating a new germacranolide, zexbrevin (**167**), from the aereal part of the schrub *Zexmenia breujfolia* (Figure 31).[113] Hydrogenation ($Pd/C/H_2$) of zexbrevin (**167**) afforded tetrahydrozexbrevin (**168**) (Figure 31), which surprisingly left the bridgehead double bond untouched. Some 15 years later a correction to the source of isolation was reported, where it was discovered that the actual natural source of zexbrevin (**167**) was *Viguiera greggi* (subgenus *Calanticaria*).[114] X-ray crystallographic confirmation of the elucidated structure was also reported, but well after the original elucidation.[115] Budlein-A (**169**), was also isolated by de Vivar from *Viguieru buddleiaeformis* (Figure 31).[116] Its epimer, lychnophorolide A (**170**), as confirmed by X-ray crystallography, was isolated from *Lychnophora affinis* by Le Quesne and

Raffauf,[117] as was lychnophorolide B (**171**) (Figure 31). Lychnophorolide A (**170**) showed significant cytotoxicity activity; a factor of ten greater than that of related eremantholide A (**172**) (Figure 31).[117,118] Total syntheses of eremantholide A (**172**) have been completed, notably by Hale,[119] Boeckman,[120] and Tadano.[121] Given that **171** was close in structure to that of atripliciolide tiglate (**173**), reported by Bohlmann (Figure 31),[122] and that of many other family members in this series,[123] led Le Quesne and Raffauf to suggest that a close relationship must exist between the genera *Eremanthus*, *Lychnophora*, *Piptolepis*, and *Vanillosmopsis* in the family *Vemoniae*.[117]

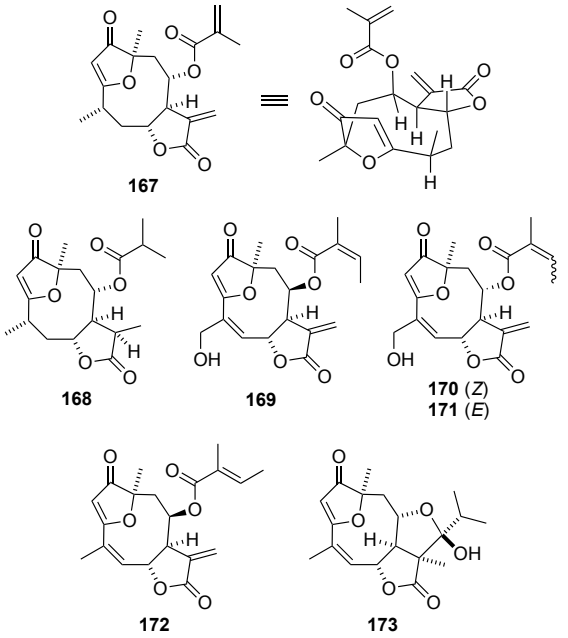


Figure 31. 11-Oxabicyclo[6.2.1] sesquiterpenoids (**167**-**173**) isolated form the genera *Eremanthus*, *Lychnophora*, *Piptolepis*, and *Vanillosmopsis* in the family *Vemoniae*. Zexbrevin (**167**); flat and three dimensional view.

4.6. 9-Oxabicyclo[6.2.2] systems

Two natural product groups fall into this ring size class, namely, the macquarimicins [A (**174**) and B (**175**)] and the cochleamycins [A (**176**) and A2 (**177**)] (Figure 32), which are closely related to FR182877 (**149**) discussed in section **4.1** {10-Oxabicyclo[4.3.1], Figure 26}. In 1984 Jackson *et al.*, working for Abbott Laboratories, reported the macquarimicins [A (**174**) solved by NMR and B (**175**) by X-ray crystallography] as low potency anti-anaerobic microbial metabolites from two soil fermentation broths (*Micromonospora chalcea*).[124] Around the same time, the cochleamycins [A (**176**) and A2 (**177**)] were reported by Shindo and Kawai from the Kirin Brewery Company,[125 126 127] having been isolated from a Japanese soil *Streptomyces sp.* (DTI36), and found to show antitumor antibiotic activity. Biosynthesis studies were undertaken using ^{13}C and ^{2}H labeled precursors, which assisted in proposing a plausible biosynthetic route involving an intramolecular Diels-Alder (IMDA) reaction.[128] It was this IMDA biosynthetic proposal that lured synthetic chemists to approach the synthesis of these captivating targets. Total syntheses were reported from the groups of Tadano [2004, Macquarimicins A and B (**174**-**176**)],[129] Tatsuta [2003, (+)-Cochleamycin A (**176**)],[130] Roush [2004, (+)-Cochleamycin A (**176**)],[131] and Lee [2009, (-)-Cochleamycin A (**176**) formal].[132]

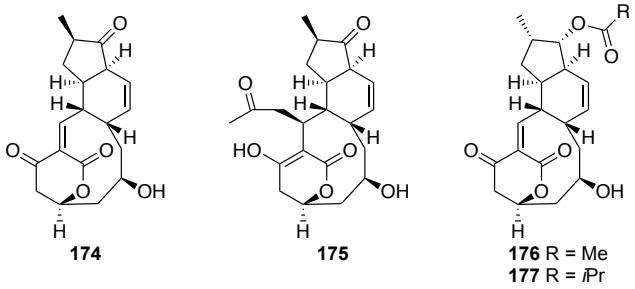


Figure 32. Macquarimicins [A (**174**) and B (**176**)] and the cochleamycins [A (**176**) and A2 (**177**)] isolated from soil bacteria.

4.7. 11-Oxabicyclo[8.2.1] systems

Jatrophones, are well known for their prevalent cancer biology,[123] and thus will not be extensively reviewed herein. Jatrophone (**178**) (Figure 33), was isolated from extracts of *Jatropha gossypiifolia L.* (*Euphorbiaceae*), in a search for tumor inhibitors by Kupchan and Bryan.[133] The structure of **178** was elucidated by X-ray crystallography. Notable total syntheses include Smith [1981, racemic Jatrophone],[134] Stille and Hegedus [1990, racemic Jatrophone],[135] and Wiemer [1992, (+)-Jatrophone][136].

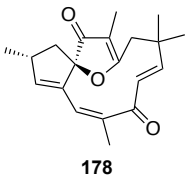


Figure 33. Jatrophone (**178**) isolated from *Jatropha gossypiifolia L.*

Other members of this class include the abyssomicins (Figure 34), which have attracted substantial attention from isolation and synthetic chemists alike. The initial isolation of abyssomicins B-D (**179**, **184**, **180**) was disclosed through a collaborative effort led by Fiedler and Süssmuth in 2004.[137] The attraction, beyond the structural beauty, to this suite of natural products was the potent antibiotic activity (inhibition of the *p*ABA biosynthetic pathway),[137] which in combination with the isolation from the "deep" [Japanese Sea, depth 289m, *Verrucosispora sp.* (AB-18-032)] gave inspiration for the name. In 2007 a subsequent collaborative report investigating the same species, spanning knowledge learned through synthesis, unveiled abyssomicins G (**187**) and H (**186**), and *atrop*-abyssomicin C (**185**).[138] Interestingly, within this time frame, it was discovered that this chemotype from the deep was not restricted to the marine environment. The first terrestrial isolations originated from Senegal and Mexico in the form of abyssomicin E (Sattler et al,[139] **181**) and abyssomicin I (Igarashi et al,[140] **188**), which were isolated from soil *Streptomyces sp.* This was followed by the isolation of *ent*-homoabyssomicin B (**189**) from a German soil sample, as reported by Laatsch and co-workers.[141] More recently, groups lead by Liu, Capon, and Zhang, driven by an anti-tuberculosis screening program, reported abyssomicins J

(**190**), K (**182**), and L (**183**), isolated from a sediment-derived actinomycete, *Verrucosispora sp* in the South China Sea (depth 2733m).[142] Total syntheses of this class have been prevalent, with syntheses completed by Sorensen [2005,[143] abyssomicin C (**184**)], Nicolaou [2006,[144] abyssomicin C (**184**) and *atrop*-C (**185**); 2007,[145] abyssomicin D (**180**)], and Bihelovic and Saicic [2012,[146] *atrop*-abyssomicin C (**185**)].

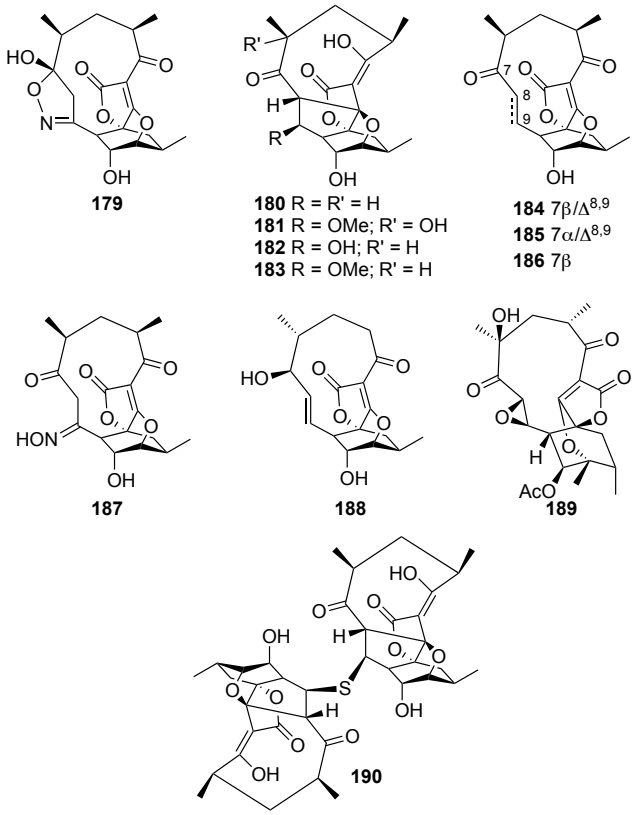


Figure 34. The abyssomicin antibiotics (**179**-**190**).

4.8. 12-Oxabicyclo[9.2.1] systems

The oxabicyclo[9.2.1] series are dominated by the pterolides [furancembranolides, e.g. kallolide A (**191a**)], which maintain a reasonable portion of diterpene families isolated from gorgonian, and other related corals {see also **4.3**. 11-oxabicyclo[5.3.1] systems}. This area has been extensively reviewed,[147] and thus the two structures presented here (Figure 35) are given with the sole purpose of presenting a class exemplar. Many of the furancembranolides, can be considered heterocyclophanes (see cyclophane review[19]),[148] which are outside the scope of this review, but are believed to be direct oxidative precursors to the furan opened members e.g. Kallolide C (**191b**). Kallolide C (**191b**) (Figure 35) was isolated in the Bahamas from *Pseudopterogorgia kallos*, a marine octocoral within the abundant genus of sea whips.[149]

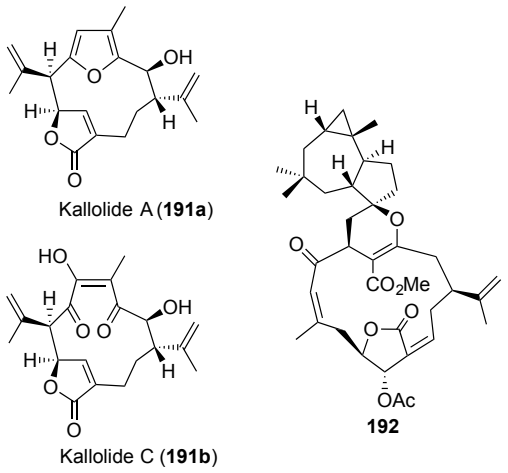


Figure 35. Kallolide A (**191a**) and Kallolide C (**191b**) isolated from *Pseudopterogorgia kallos*, and polymaxenolide (**192**) discovered in the hybrid soft coral species, *Sinularia maxima · Sinularia polydactyla*.

4.9. 14-Oxabicyclo[11.2.1] systems

Polymaxenolide (**192**), elucidated by X-ray crystallography, was isolated from a hybrid soft coral (*Sinularia maxima · Sinularia polydactyla*) (Figure 35). This natural product (**192**) is interesting from an evolutionary perspective. Not only is **192** obtained from a hybrid marine species, but the organism utilizes a hybrid biosynthetic pathway, producing a hybrid structure comprising cembrane-type diterpene and africanane-type sesquiterpene frameworks.[150]

4.10. 4,23-Dioxabicyclo[18.2.1] systems

The last representative in the oxygenated series is tuscolid A (**193**) (Figure 36), isolated from culture extracts of myxobacterium (*Sorangium cellulosum*, strains So ce1401 and So ce1383) as reported by Höfle. NMR spectroscopy was used to deduced the flat structure assisted by biosynthetic ^{13}C-labelled feeding studies.[151]

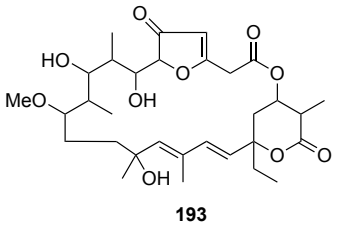
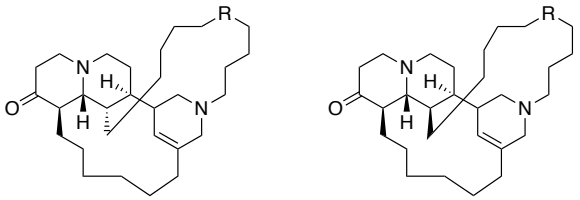


Figure 36. Tuscolid A (**193**) isolated from *Sorangium cellulosum*.

5. Nitrogen containing bicyclic bridgehead olefinic systems

Only a small number of alkaloids containing a bridgehead olefin were identified. These include the haliclamines A-F (**200**-**205**), halicyclamines A-B (**206**-**208**), saraines 1-3 (**194**-**196**) and isosaraines 1-3 (**197**-**199**), which, unsurprisingly, are all biogenically linked.[152]



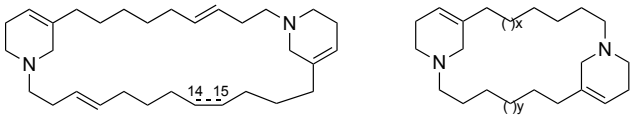
194 R = -CH=CH-
195 R = -CH_2-
196 R = -CH_2CH=CH-

197 R = -CH=CH-
198 R = -CH_2-
199 R = -CH_2CH=CH-

Figure 37. Saraines 1-3 (**194-196**) and Isosaraines 1-3 (**197-199**) isolated from *Reniera sarai*.

The saraines 1-3 (**194-196**) (Figure 37) ,[153] which bear a 3-azabicyclo[10.3.1]hexadec-1-ene core, were isolated from the Mediterranean sponge *Reniera sarai*, (order Haplosclerida) collected in the bay of Naples, Italy. Reduction of the carbonyl to the corresponding alcohols facilitated structure determination by subsequent conversion to Mosher esters, in conjunction with extensive 2D NMR spectroscopy. Approximately three years later diastereomers of the saraines, namely the isosaraines 1-2 (**197-198**), were isolated from the same marine sponge,[154] with saraine 3 and isosaraine 3 (**199**) discovered over a decade later.[153c]

Around the time the isosaraines (**197-199**) (Figure 37) were discovered, haliclamines A and B (**200-201**) (Figure 38) were isolated from a sponge of the genus *Haliclona* collected off the Japanese Island of Hiburi-jima in the Uwa Sea.[155] Both haliclamine A and B inhibited sea urchin (*Hemicentrotus pulcherrimus*) fertilized egg cell division, and more importantly inhibited the growth of leukemia cell lines L1210 (IC_{50} 0.9 ug/mL) and P388 (0.39 ug/mL).[155] More recently, haliclamines C (**202**), D (**203**), E (**204**) and F (**205**) were isolated by Köck *et al.* from the Arctic sponge *Haliclona viscosa*.[156, 157] The haliclamides are possibly the most intriguing examples in this class in that there are two bridgehead double bond systems contained within the same molecule, and furthermore, the nitrogen atom makes up one of the bridge junctions in each system (Figure 38). Of the haliclamines only A has succumb to total synthesis [1997, Morimoto].[158]

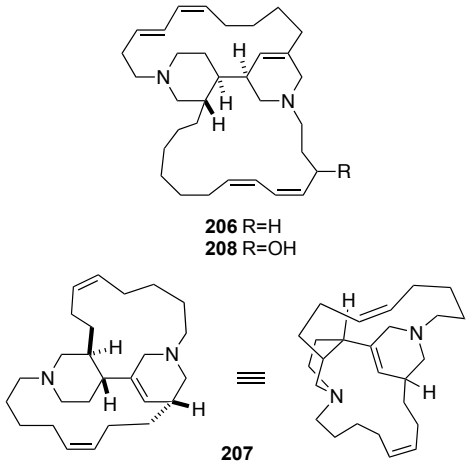


200
201 ($\Delta^{14,15}$)

202 x = 4, y = 6
203 x = 5, y = 6
204 x = 4, y = 5
205 x = 6, y = 6

Figure 38. Haliclamines A-F (**200**–**205**) isolated from *Haliclona viscosa*.

The last in this series are the halicyclamines A (**206**), B (**207**) and 22-hydroxyhalicyclamine A (**208**). Crews and co-workers reported the isolation of halicyclamine A (**206**) from *Haliclona sp.*; a massive, soft textured, olive green colored, tubular sponge, collected from Biak, Indonesia.[159] It showed good inhibition of inosine monophosphate dehydrogenase (IMPDH) (1 μg/mL), which is a potential cancer chemotherapy target. Much more recently, however, halicyclamine A (**206**) was found to be a lead anti-tuberculosis agent,[160] and an anti-dormant mycobacterial substance with the mechanism of action correlating to the DedA protein.[161] 22-Hydroxyhalicyclamine A (**208**) was later reported by Fusetani,[162] isolated from the marine sponge *Amphimedon sp*. To complete the set, halicyclamine B (**207**), elucidated by X-ray crystallography, was later reported by Crews and Clardy, isolated from the marine sponge *Xestospongia sp.* obtained from Sangihe Islands, Indonesia.[163] Structurally, halicyclamines A (**206**), B (**207**) and the hydroxyl derivative (**208**) are the only examples which contain two nitrogen atoms within the bicyclic core, giving rise to a 3,16-diazabicyclo[14.3.1]icos-1-ene system in the case of A (**206**) and hydroxy (**208**), and 3,9-diazabicyclo[12.3.1]heptdec-1-ene system in the case of B (**207**) (Figure 39).



206 R=H
208 R=OH

207

Figure 39. Halicyclamines A [**206**), B **207** flat and three dimensional view)] and 22-hydroxyhalicyclamine A (**208**).

6. Anti-Bredt or Bridgehead olefin?

Although it is somewhat ironic that Bredt's rule was developed through the study of simple terpenoid natural products, its application in this context remains uncertain. Should (or can) the term 'anti-Bredt' be applied to natural products containing a bridgehead olefin? In addition to the philosophical argument that a natural product is inherently stable for the purposes of isolation, the crux of the problem is that Bredt's rule (including the refinements of the last century) is based on investigations of fundamental and functionally unadorned parent bicyclic ring systems, unlike the plethora of functionalities and substitutions that are commonplace in natural products. The stability of bridgehead olefins can vary substantially depending on the presence or placement of these functional groups and additional architectural features.[9c]

These reasons compel us to propose that the anti-Bredt terminology is not directly applicable to natural products. Instead we feel that it is more instructive to evaluate the strain of naturally occurring bridgehead olefins quantitatively rather than qualitatively. Far from the natural product community abandoning Bredt's rule, it is this approach that strikes at the heart of the bridgehead olefin strain phenomenon first discovered by Bredt.

To this end, Schleyer's model of olefin strain (OS) energy is well poised to act as an important indicator, via computed OS values, of bridgehead olefin instability, rather than to attempt a classification as anti-Bredt or not. However, OS calculations of a suitable range of bridgehead olefins would lead to a prohibitively sizeable *in silico* study considering the number of natural products identified in this review.

Therefore, we herein suggest, and illustrate, two alternative methods based on *in vitro* data that allow the bridgehead olefin strain of natural products to be measured, or perhaps more importantly, better appreciated

Analysis 1: As elegantly described by Shea,[12a] in analogy to a *trans*-cycloalkene a bridgehead olefin is subject to torsional distortion. This distortion creates a twisting effect, bending the π bond out of co-planarity, sequentially diminishing p orbital overlap with decreasing ring size. Subsequently, the sp^2 centers rehybridize by incorporating s character into the p orbitals of the π bond, resulting in pyramidalization of both sp^2 centers. The degree of distortion and pyramidalization can be quantified by the angles τ and χ respectively (Figure 40). Although X-Ray crystallographic data cannot be used to determine τ, nor χ, directly, these angles can be determined by measuring either of the torsional angles YC_1C_2W (Φ_1) or ZC_1C_2X (Φ_2) (Figure 40). Due to the rehybridization, and ensuing pyramidalization however, Φ_1 and Φ_2 are now non-equivalent, and therefore, the torsional distortion τ is defined as an average [i.e. $\tau = (\phi_1 + \phi_2)/2$].

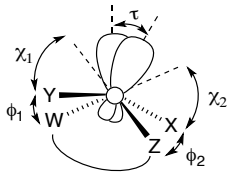


Figure 40. The projected view along a torsionally distorted double bond; distortional parameters χ and τ. Adapted from reference [12a].

Utilizing this mode of analysis, specifically concentrating on the degree of distortion (τ), select X-ray crystal structures of the all-carbon containing series (i.e. **44**, **71**, **76** and **116**; Figure 41) were examined, covering the bicyclo[4.4.1], [5.3.1], [7.2.1] and [9.3.1] systems.

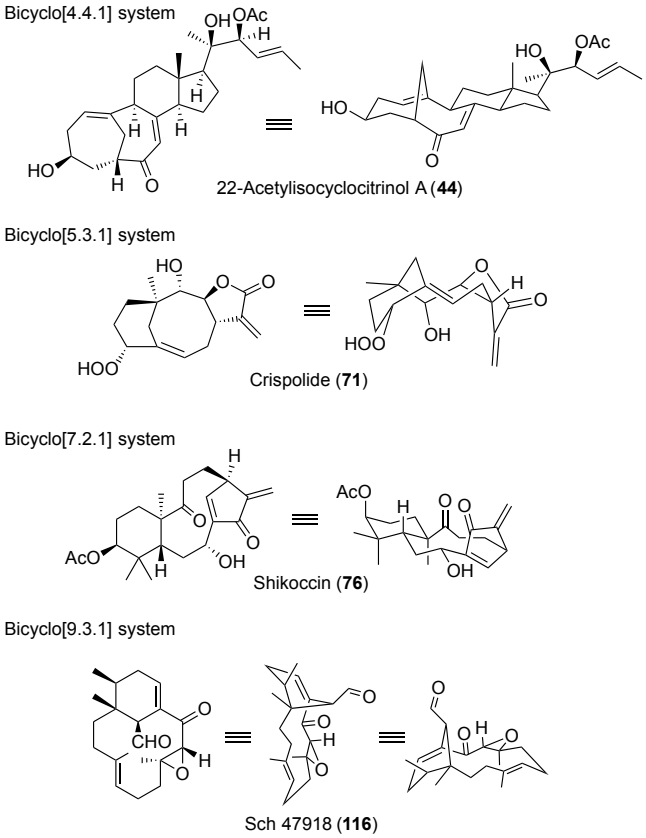


Figure 41. All carbon candidates **44**, **71**, **76** and **116**, solved by X-ray crystal structure analysis, used to evaluate bridgehead bond lengths and torsional values. Crispolide **71** solved as the diacetate, and Shikoccin **76** solved as the mono acetate.

Unfortunately, no examples of smaller ring systems have been solved by X-ray crystal structure analysis. However, in this instance, X-ray crystal structures of advanced synthetic intermediates towards the phomoidrides {bicyclo[4.3.1] system} were available from the work of Nicolaou,[43a] Wood[164] and Clive[165] et al. Thus, compounds **209** and **210** (Figure 42) were evaluated together with the above chosen natural products (i.e. **44**, **71**, **76** and **116**) (Figure 41 and Table 1).

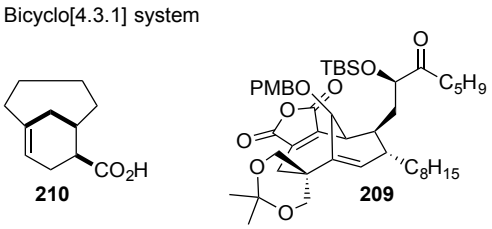


Figure 42. Shea's bridgehead olefin (**210**) and Nicolaou's intermediate (**209**).

Table 1. Bridgehead bond lengths and torsional (τ) values for compounds **44**, **67**, **71**, **76**, **116**, **209** and **210**.

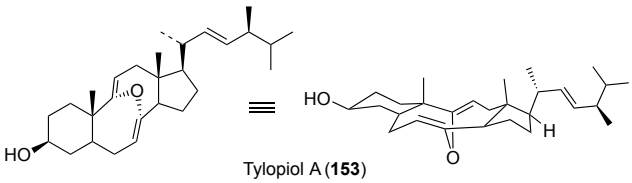
Entry [Ref]	Bridgehead Olefin length (Å)[a]	Bridgehead Olefin distortion (τ)[a][b][c]	Bicyclo[m.n.o] system
209[43a]	1.312	8.2°	[4.3.1]
210[12a, 166]	–	6.8°	
71[55]	1.328	3.4°	[5.3.1]
67[167]	1.351	3.6°	
44[46]	1.331	2.6°	[4.4.1]
76[58]	1.334	2.6°	[7.2.1]
116[78c]	1.326	0.4°	[9.3.1]

[a] See cited literature for standard deviations. [b] The value of τ was extracted from reported X-ray crystallographic data using the program Mercury.[168] [c] Variation in determining τ values can exist due to the accuracy of the calculated hydrogen positions, or the level of refinement obtained in the process of solving the X-ray crystal structure. For example, a structure measured at low temperature might be expected to have a lower refinement value providing a greater degree of hydrogen atom certainty or probability.

A clear trend is evident from the τ values listed in table 1 above, in that, on increasing ring size {i.e. [4.3.1] to [9.3.1]} the degree of bridgehead olefin twisting decreases. The most strained system is the phomoidride intermediate **209** within the bicyclo[4.3.1] series. The distortion angle of 8.2° is quite high compared to the value of 6.8° in **210**, which is more representative of an archetypal bicycle[4.3.1] system. This is most likely due to other skeletal strain features present in **209**,[9c] but nevertheless compares well with the parent system **210**.[12a,166] The vales of 3.4° and 3.6° for crispolide (**71**) and taxol (**67**), respectively, compare well for the [5.3.1] series, with decreasing values through to 0.4° for the [9.3.1] system [i.e. Sch 47918 (**116**)].

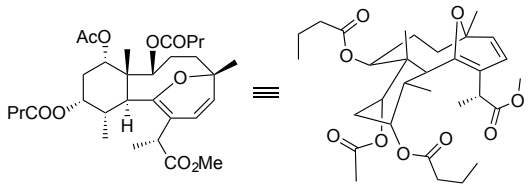
In the case of the oxygen containing bicyclic bridgehead olefinic systems, τ values were determined for tylopiol A (**153**), methyl briareolate (**158**) and tetrahydrozebrevin (**168**) (Figure 43, Table 2).

Oxobicyclo[4.4.1] system



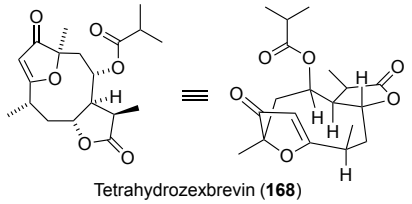
Tylopiol A (**153**)

Oxobicyclo[5.3.1] system



Methyl briareolate (**158**)

Oxobicyclo[6.2.1] system



Tetrahydrozexbrevin (**168**)

Figure 43. Oxygen bridged candidates (i.e. **153**, **158** and **168**) solved by X-ray crystal structure analysis, used to evaluate bridgehead bond lengths and torsional values.

Table 2. Bridgehead bond lengths and torsional (τ) values for compounds **153**, **158**, and **168**.

Entry [Ref]	Bridgehead Olefin length (Å)[a]	Bridgehead Olefin distortion (τ)[a][b][c]	Bicyclo[m.n.o] system
158[108]	1.348	0.5°	[5.3.1]
153[103]	1.218	7.6°	[4.4.1]
	1.389	4.3°	
168[115]	1.355	8.7°	[6.2.1]

[a] See cited literature for standard deviations. [b] The value of τ was extracted from reported X-ray crystallographic data using the program Mercury.[168] [c] Variation in determining τ values can exist due to the accuracy of the calculated hydrogen positions, or the level of refinement obtained in the process of solving the X-ray crystal structure. For example, a structure measured at low temperature might be expected to have a lower refinement value providing a greater degree of hydrogen atom certainty or probability.

The oxygen-bridged series are more difficult to analyze as the suggested trend is opposite to the all carbon series, in that, larger rings systems contain more strained bridgehead olefins. On closer inspection of these natural product candidates, however, it is apparent that skeletal structure is most likely a substantial contributor to the observed bridgehead olefin twisting. For

example, tylopiol A (**153**) (τ = 7.6° and 4.3°) contains two bridgehead olefins with significant differences between the two bridgehead bond lengths (Δ = 0.171Å). Meanwhile, with methyl briareolate (**158**) (τ = 0.5°) the bridgehead olefin is conjugated to a second alkene, which can potentially provide stability to the out of plane p orbital on the bridgehead olefin exo carbon through adjacent p orbital overlap. In the case of tetrahydrozebrevin (**168**) the torsional distortion value (τ = 8.7°) is unexpectedly high, matching more closely the value of the all-carbon bicyclo[4.3.1] systems. Contrary to this argument, however, is that the bridgehead olefin is conjugated to a carbonyl, and it has resisted hydrogenation. A similar observation is made in the nitrogen-bridged example, halicyclamine B (**207**). It might be expected that for such a large ring system {i.e. bicyclo[12.3.1]/[10.3.1] system} a very low or even negative τ value be found, but instead τ is relatively large (i.e. 3.7°) most likely due to the olefin residing in the smallest bridge (Figure 44).

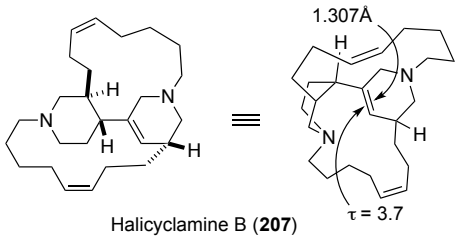
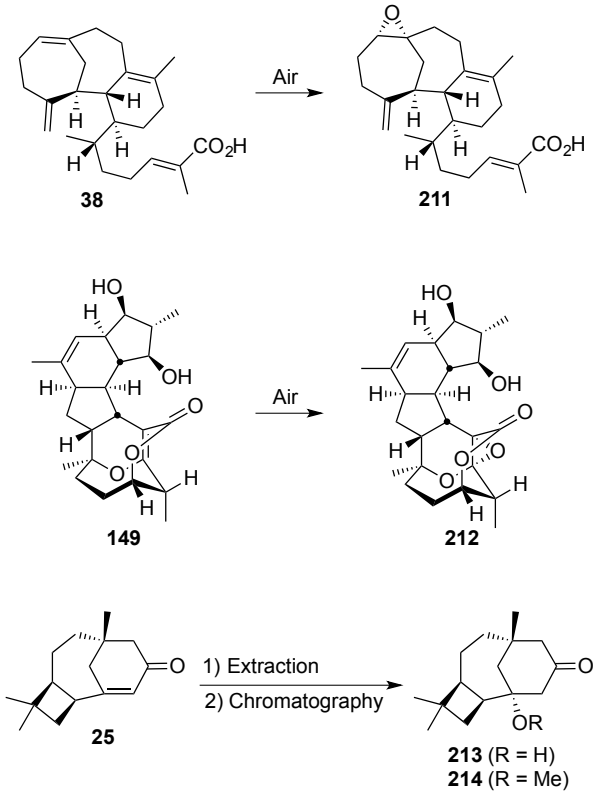


Figure 44. Halicyclamine B (**207**) bridgehead bond lengths and torsional values obtained from the reported X-ray crystal structure analysis.

Analysis 2: Another assessment criteria useful in the context of anti-Bredt natural product evaluation, is the chemical reactivity of the bridgehead olefin (which has been highlighted throughout, but not fully considered). In both the bicyclo[4.4.1] and the oxobicyclo[4.3.1] systems, cerorubenic acid-I (**38**)[44] and FR182877 (**149**)[97c] were observed to undergo slow aerial oxidation to give sp^3 bridgeheads in epoxides **211** and **212** (Scheme 10).[169] Sesquiterpene **25** was also reported to be unstable and the two co-isolates (**213** and **214**) were deemed to be artifacts of isolation arising from reaction at the bridgehead double bond. These observations suggest that **25**, **38** and **149** are members of Schleyer's "observable fleeting intermediates" class (i.e. unstable), but perhaps towards the more stable (long-lived) end of the spectrum. Indeed, although we urge discouragement of the 'anti-Bredt' terminology in relation to natural products, the observably unstable bridgehead olefins are very close to being naturally occurring violations of the classical Bredt's rule. By extension, natural products that have certain bridgehead functionality (e.g. epoxide or alcohol, i.e. **213**, Scheme 10) could potentially be extrapolated from a naturally occurring classical anti-Bredt reactive intermediate.



Scheme 10. Cerorubenic acid-I (**38**) and FR182877 (**149**) aerial oxidation to epoxides **211** and **212**, respectively. Sesquiterpene **25** artifacts of isolation **213** and **214**.

7. Summary and Outlook

It is of no wonder that the stability and classification of natural products containing bridgehead olefins was unclear. In the course of preparing this review we noticed that a significant proportion of canvassed articles did not refer to Bredt's rule, which strongly suggests anti-Bredt classification uncertainty. We hope this review brought clarification and indeed, introduced a helpful framework of evaluating bridgehead olefin containing natural products.

Lastly, we feel that Julius Bredt himself probably would never have imagined his legacy would continue into modernity, especially as he was already aware that violations of the rule were on the horizon. Nevertheless, the occurrence in nature of architecturally beautiful and biologically active candidates, unearthed by the isolation chemist, suggest that the field will continue to develop attracting the attention of biologists and chemists alike.

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