Natural Products with Anti-Bredt and Bridgehead Double Bonds

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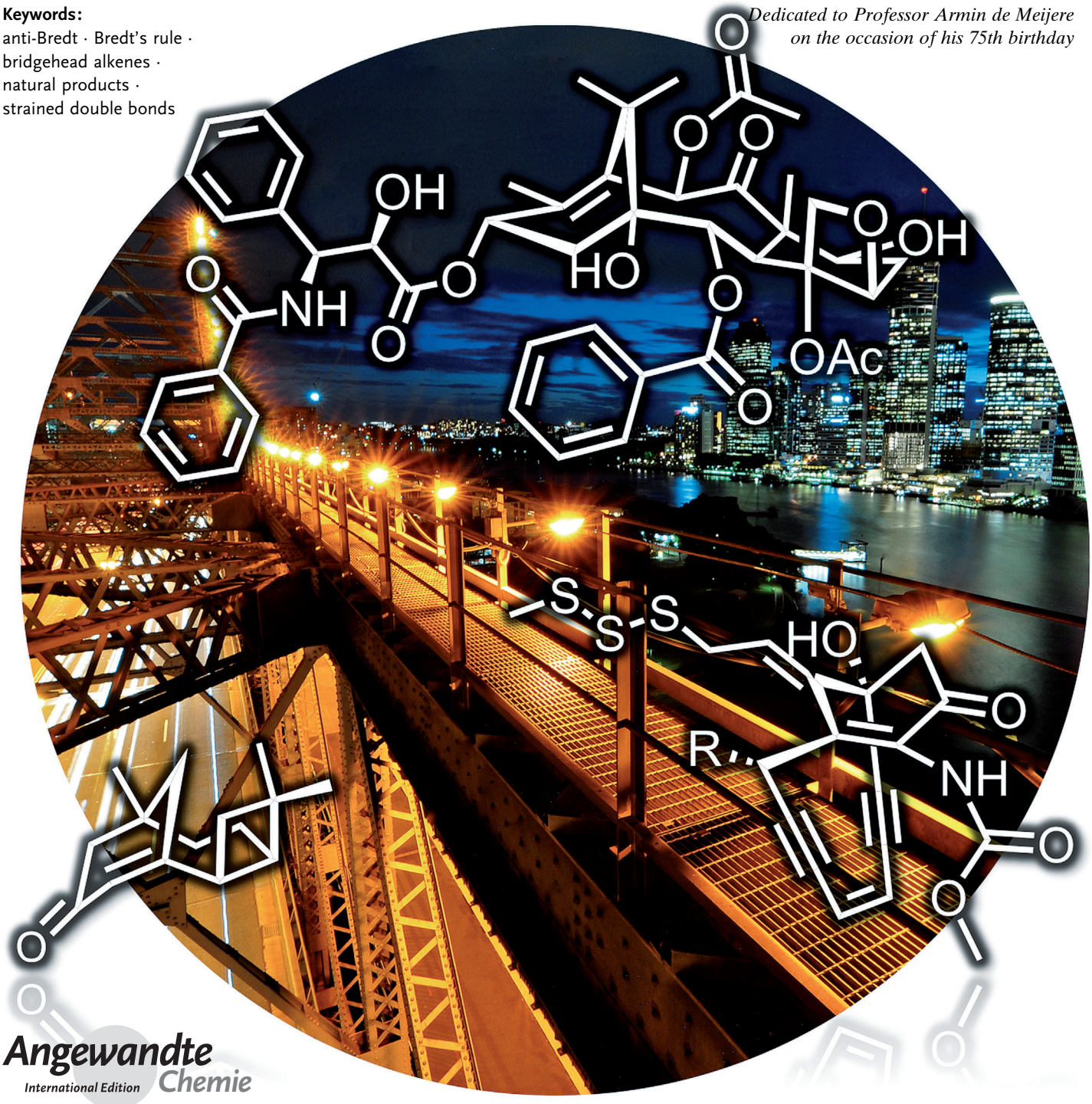
Anti-Bredt Olefins

Natural Products with Anti-Bredt and Bridgehead Double Bonds

*Jeffrey Y. W. Mak, Rebecca H. Pouwer, and Craig M. Williams**

Keywords:
anti-Bredt · Bredt's rule · bridgehead alkenes · natural products · strained double bonds

Dedicated to Professor Armin de Meijere on the occasion of his 75th birthday



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Well 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. For the first time, this topic is reviewed in a natural product context.

From the Contents

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 the last century,[2] simply states that the terminus of a double bond cannot exist at the bridgehead position (branching position) of a bridged bicyclic system (that is, 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), which is 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]

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 the bridges of the 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 ≥ 9 have the potential to be isolated, although a tentative upper limit value of 8 was conceivable. Systems with $S=7$ could be observed but not isolated, whereas those with $S=6$ could be entertained as fleeting intermediates. Prelog[6] concurrently proposed that only bicyclo[5.3.1] or larger systems ($S\geq 9$) could contain a stable bridgehead double bond. Wiseman subsequently developed a more rigid hypothesis 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 (see below) in an attempt to better predict relative distortion energies.[5b]

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

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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.

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]

These predictive rules were ultimately refined by Schleyer using MMI empirical force field calculations,[9] which provided the "olefin strain" (OS) energy (a value 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] albeit in a limited capacity. Schleyer's empirical rules,[9] based on the direct comparison of OS calculations to experimental data from the literature, facilitated the classification of individual bridgehead olefins into three groups (Figure 2):

1) Isolable bridgehead olefins ($OS \leq 17$ kcal mol^{-1}; for example, bicyclo[3.3.3]undec-l-ene). These are expected to be kinetically stable at room temperature.
2) Observable bridgehead olefins (17 kcal mol$^{-1} \leq OS \leq 21$ kcal mol^{-1}; for example, bicyclo[4.2.1]non-l(9)-ene). These are not isolable at room temperature, but may be spectroscopically detected at lower temperatures.
3) Unstable bridgehead olefins ($OS \geq 21$ kcal mol^{-1}; for example, bicyclo[2.2.2]oct-l-ene). These are not spectroscopically observable at low temperatures, except perhaps through a matrix isolation process.

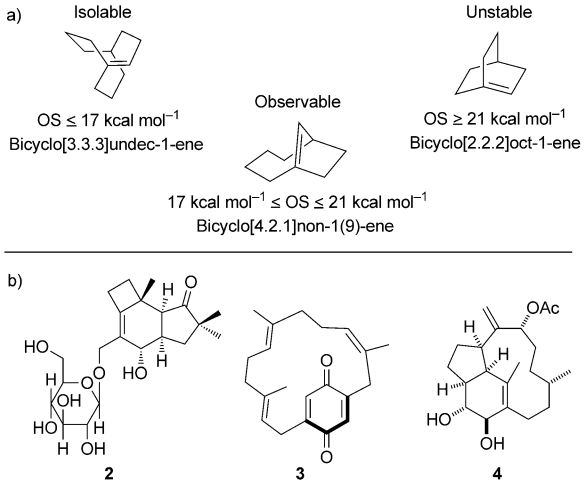

Figure 2. a) Examples that illustrate the three stability groups proposed by Schleyer. b) Examples of bridgehead-olefin-containing natural product systems that are not covered in this Review, that is, bicyclo-[n.n.0], cyclophane, and rigid fused-ring-type systems.

With these predictive rules established, chemists continued to pursue anti-Bredt systems, 1) to further interrogate the proposed rules, 2) to use such systems as versatile synthetic intermediates,[12,13] and, albeit to a much lesser extent, 3) to evaluate them in the context of natural product structures.[12,14] It was this latter point that overlapped with our fascination with constructing natural products that contained bridged bicyclic moieties (that is, bicyclo[m.n.o]).[15] Furthermore, and perhaps even more importantly, 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 rule to natural product systems.[16] In consideration of the above and the fact 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.

To provide a comprehensive survey of the field, we chose to broadly include (with some exceptions) all natural products that contain a bridgehead olefin within this Review. 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 strain (OS). Therefore, within the context of these refinements, Bredt's rule is applicable to stable (isolable), unstable (observable fleeting intermediates), and non-existent (Schleyer 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 as anti-

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Bredt systems. 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 processes during isolation. Of course, towards the end of his career, Bredt himself was already aware of the fact 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 as 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 an 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 [for example, pteridanoside (**2**)],[17] only select examples of the cyclophane type [for example, longithorone B (**3**)][18] as these systems have been recently reviewed,[19] and no rigid fused-ring systems [for example, 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 successful total syntheses, many of which have already been reviewed elsewhere, and synthetic studies where pertinent.

2. Structural Reassignments Based on Bredt's Rule

Following his initial publications, Bredt spent a considerable amount of his time correcting clear violations of his rule, which however mostly concerned products proposed to be obtained through the chemical treatment of terpenes.[5] To the best of our knowledge, only on one occasion was a natural product structure contested by Bredt,[1b,21] and that was the case for 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-fenchene (**12**; Figure 3), whereas **5** and **6** do not exist.

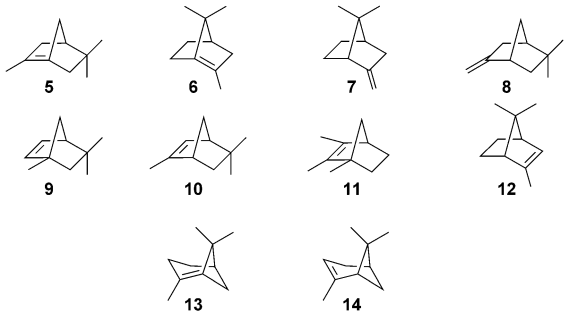


Figure 3. Anti-Bredt fenchene isomers proposed by Bartelt, the six fenchene isomers known to date (presented in the racemic form), and Wallach's proposal for α-pinene (**13**) and corrected α-pinene (**14**), shown as a racemate.

In 1907, Wallach and Blumann suggested **13** as the chemical structure of α-pinene **14**;[23] however, this was identified by Richter and Anschütz as incorrect based on Bredt's premise (Figure 3).[24] It was almost 70 years later that a natural product skeleton was questioned because of the presence of a double bond placed at a bridgehead position. In 2008, Fraga and co-workers[25] argued convincingly that the chemical structure proposed 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 a comparison of the ^{1}H and ^{13}C NMR chemical shifts to those of licamichauxiioic acid A (**16**; also shown to be incorrect) and known related systems (i.e., **17**). For example, the reported carbon chemical shifts of $\delta = 35.7$ ppm for C9 and $\delta = 33.9$ ppm for C11 were not consistent (i.e., significant downfield and upfield differences), and the ^{1}H NMR chemical shifts for the H9 and H14 atoms of **15** and **16** had disconcertingly similar values (i.e., 5.45 ppm and 5.44 ppm, respectively; Figure 4).[26]

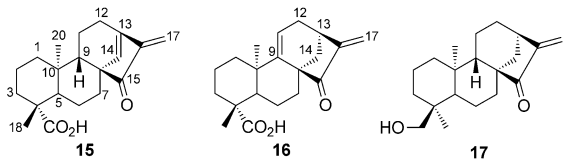


Figure 4. Licamichauxiioic acids A (**16**) and B (**15**) including the parent structure **17**.

Williams and Savchenko recently identified neoveratrenone (**18**),[28] which was isolated from the roots and rhizomes of *Veratrum dahuricum* (Turcz.) Loes. f.,[29] as a possible anti-Bredt candidate. Re-analysis of the spectroscopic data presented by Cong et al.[29] suggested, even in the absence of further 2D NMR spectra (e.g., COSY), that the proposed anti-Bredt structure was incorrect as initially indicated by the absence of expected correlations in the NOESY spectra. A

Craig M. Williams was born in Adelaide, Australia. He received his B.Sc.(Hons) degree in chemistry in 1994 and in 1997 was awarded his Ph.D. 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-Universität 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, he 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.

further clue en route to the likely structure was the fact that Cong et al. had also reported the isolation of verapatuline (**19**). A further literature search revealed the structurally related synthetic compound **20**. Comparison of the ^{1}H and ^{13}C NMR spectra very compellingly pointed to the reassigned structure **21** (Figure 5).

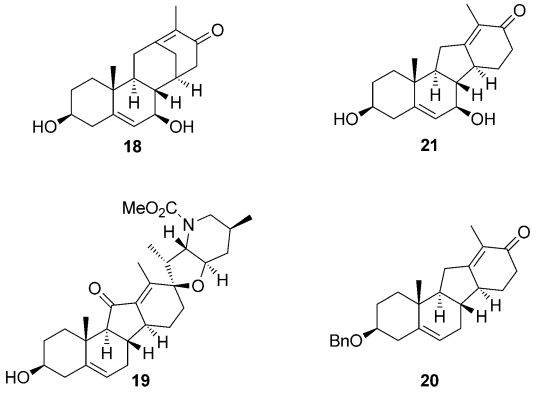


Figure 5. Neoveratrenone (**18**) and compounds **19** and **20**, which led to structural revision **21**. Bn = benzyl.

Two further natural products that 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. The second natural product is rosacedrenoic acid (**23**), which was isolated from the flowers of *Rosa damascene*, an Indian flowering plant, by Paridhavi and co-workers.[31] No 2D NMR spectral analysis was undertaken in the elucidation process of **23** (Figure 6).

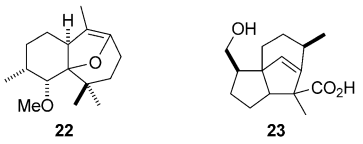


Figure 6. Proposed chemical structures for isolates from *Hugonia busseana* and *Rosa damascene*.

Williams et al. utilized the ACDlabs NMR Structure Elucidator platform to aid in resolving the controversial proposals for hexacyclinol,[32] which agreed with Rychnovsky's proposal.[33] Although neither of the two structures qualifies for this review, in the course of formulating rules to avoid the generation of impossible structures (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 the ACDLabs Structure Elucidator ourselves when solving the structures of complex natural products,[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 Bicyclic Bridgehead-Olefinic Systems

Note: For ease of bicyclic-system classification (i.e., bicyclo[m.n.o]) within the all-carbon, oxygen, and nitrogen sections, the smallest ring in each bridge has been selected. For example, in the bicyclo[4.3.1] system below, the fused four-membered ring has been ignored.

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 a bridgehead double bond.[35] The cytotoxic sesquiterpene **24** was isolated from a methanol/toluene extract of a New Zealand *Eurypon* sp. sponge through a 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

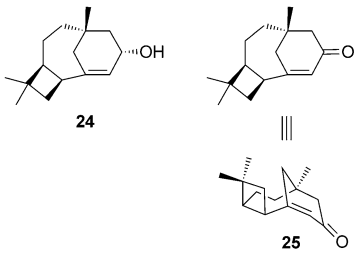
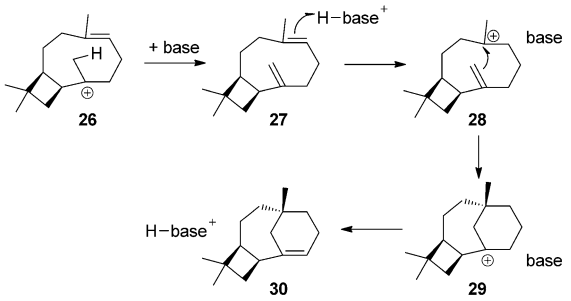


Figure 7. The New Zealand *Eurypon* sp. sponge isolates **24** and **25** (flat and three-dimensional views) reported by Munro as well as Cambie and Kernan.

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]decene system to be completely stable.

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-catalyzed 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).

The groups of Iwagawa and Duh have reported the isolation of structurally related 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 the



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

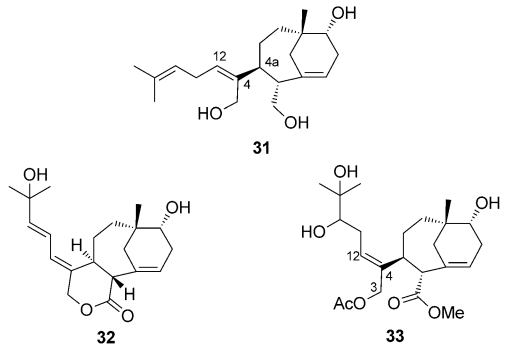


Figure 8. The umbellacins (**31**–**33**) isolated from the genus Xenia.

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 H3 to H12, and H4a to H13 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 $\mu g\,mL^{-1}$.[39]

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 C7 epimeric compounds, phomoidride C (**36**) and D (**37**), were subsequently isolated by the groups of Danishefsky and Sulikowski (Figure 9).[41,42] Whereas 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, whereas **36** and **37** are the thermodynamic products.[42] Structure determination of the phomoidrides was achieved using NMR spectroscopy, and has since been confirmed through the total syntheses of

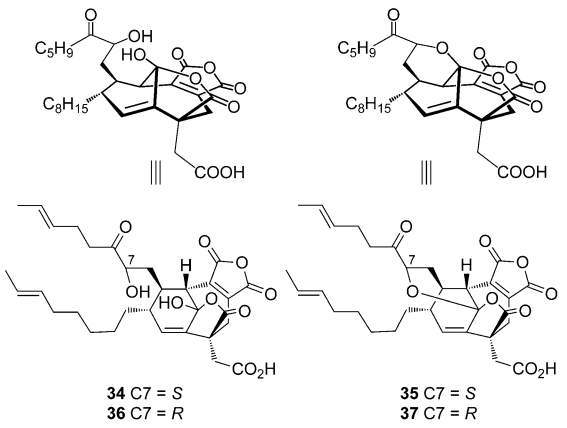


Figure 9. Phomoidrides A–D (**34**–**37**; top and side view) originating from an unidentified Texan juniper twig fungus.

phomoidrides A (**34**) and B (**35**) by the groups of Nicolaou,[43a–c] Fukuyama,[43d] Shair,[43e] and 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] The article concluded that despite Kaneko's initial assertions, the phomoidrides could not be classed as anti-Bredt systems because the bicyclo[4.3.1]decene system is predicted to be stable according to Wiseman's (as well as Schleyer's) assessment criteria.

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

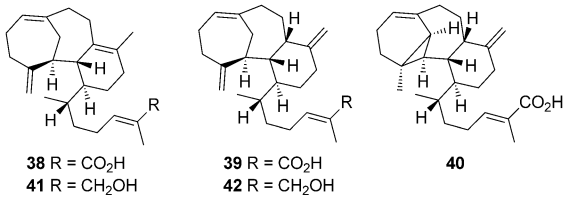


Figure 10. Cerorubenic acids and alcohols (**38**–**42**) from secretions of the scale insect.

determined by NMR spectroscopy. The bridgehead double bond of **38** was susceptible to slow oxidation in air, reflecting the inherent strain of the system. In 1998, Paquette and Dyck achieved the total synthesis of cerorubenic acid-III (**40**) in the form of its methyl ester.[45]

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]

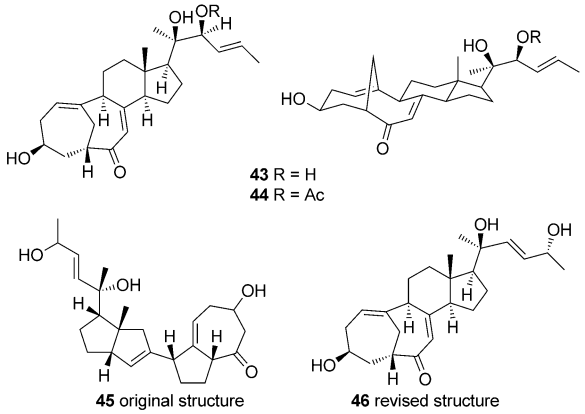


Figure 11. Top: Isocyclocitrinol A (**43**) and 22-acetylisocyclocitrinol A (**44**; flat and three-dimensional views). Bottom: Original and revised structure of cyclocitrinol (**46**) isolated from *Penicillium citrinum*.

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 C_{25} steroids, akin to the compounds reported by Crews, from the plant-derived fungus *Penicillium janthinellum*.[49] The isolated compounds showed strong spectroscopic similarities to **46**, differing only in the C17 side chain, which aided in the structural elucidation of neocyclocitrinol. Unfortunately, the configuration of the $\Delta^{20,22}$ alkene was not established, nor were the absolute configurations determined for the C23 and C24 centers (Figure 11).

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 spectral analysis and X-ray crystallography allowed for the unambiguous assignment of the 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 found to be produced by the fungi,[48,49] is the proposed biosynthetic precursor to these

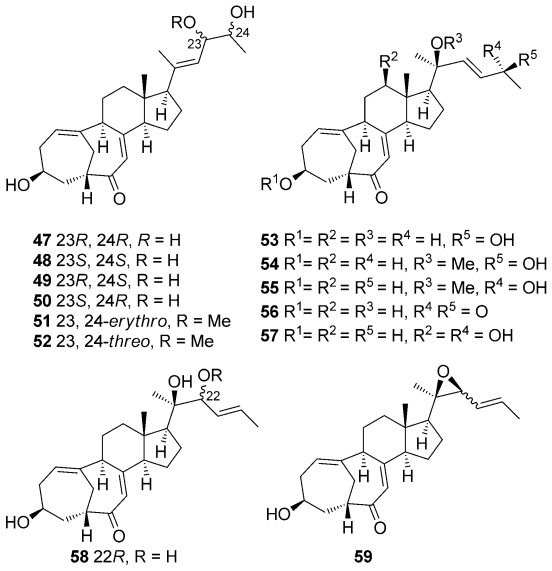
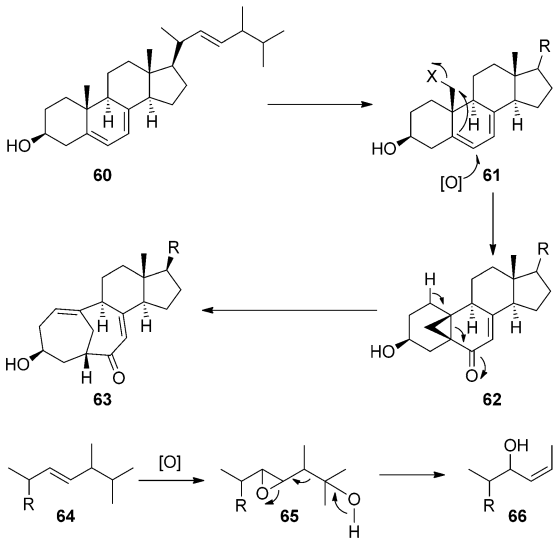


Figure 12. Additional cyclocitrinol family members isolated from *Penicillium citrinum* and *P. janthinellum*.

unusual steroids. The proposed mechanism relies on the enzymatic activation of the C19 position to generate an electrophilic center (**61**), which can react with the $\Delta^{5,6}$ alkene with concomitant oxidation of the C6 carbon atom 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 C17 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 various observed functionalities. Based on the proposed biosynthesis, the Zhu group



Scheme 2. Top: The proposed biosynthetic pathway to the cyclocitrinols (**63**) starting from ergosterol (**60**). Bottom: Postulated oxidative transformation of the C17 side chain of the cyclocitrinols.

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 the hypothesis of Rodrigues-Filho et al. (see Scheme 2).

3.3. Bicyclo[5.3.1] Systems

The taxanes [for example, taxol (**67**), Figure 13] are perhaps the best-known class of natural products that 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 that discuss in depth the isolation, occurrence, synthesis, and biological activity of the taxanes.[50–52]

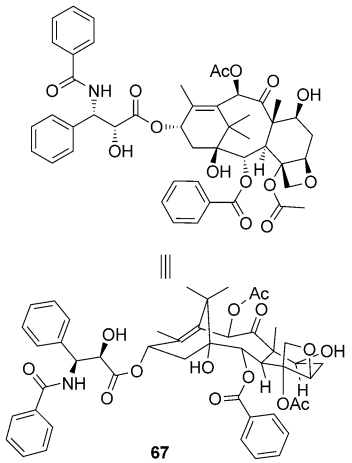
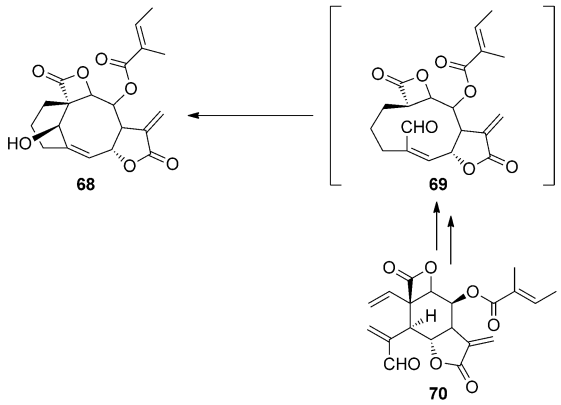


Figure 13. Taxol (**67**; flat and three-dimensional view), the best known taxane, is used for the clinical treatment of various cancers.

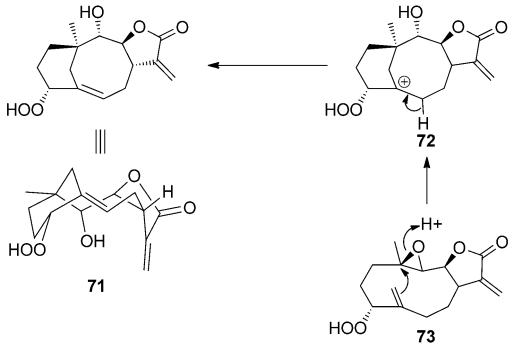
Isolated from an extract of *Disynaphia halimifolia*, disyhamifolide (**68**), was reported by Bohlmann and co-workers in 1981.[53] The authors proposed that **68** results from a transannular aldol reaction of the medium-sized ring **69**, which could be derived from a [3,3] sigmatropic rearrangement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

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

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



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



Scheme 4. Crispolide (**71**; flat and three-dimensional view), which is postulated to arise from an acid-catalyzed transannular cyclization from **73**.

(Figure 14), which was proposed to be biogenetically produced by an equivalent mechanism (see Scheme 4).[56]

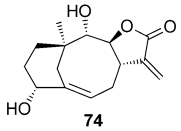


Figure 14. 1β,5β-Dihydroxyeriocephaloide (**74**) isolated from the aerial parts of *Eriocephalus kingesii*.

3.4. Bicyclo[7.2.1] Systems

Shikoccidin (**75**; Figure 15), the structure of which was determined by

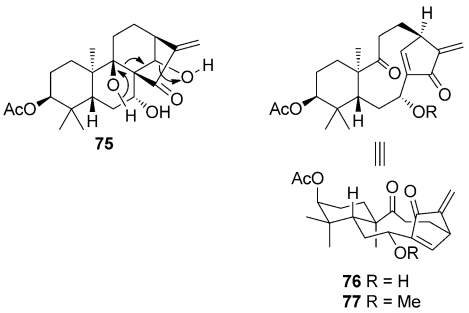


Figure 15. Shikoccidin (**75**), shown as a potential Grob-type fragmentation precursor of shikoccin (**76**), and *O*-methylshikoccin (**77**; flat and three-dimensional view) isolated from *Rabdosia shikokiana* var. *occidentalis*.

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 Fujita and co-workers.[57] Upon treatment of **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 bridgehead-alkene-containing shikoccin (**76**). The structure of **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), the authors subsequently confirmed that **76** was most likely not an artifact of the isolation. This conclusion was drawn based on the fact that conversion into **76** was not observed upon treatment of **75** with oxalic acid in methanol. 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]

Since the 1979 publication of Fujita et al., the structures of a variety of compounds related to shikoccin (**76**) have been determined. Although the isolation of shikodomedin (**78**) was described in 1979 (Figure 16),[61] the structural determination

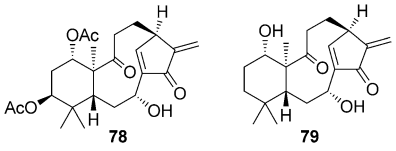


Figure 16. Shikodomedin (**78**) isolated from *Rabdosia shikokiana* var. *intermedia* and rabdolatifolin (**79**) isolated from *Rabdosia umbros* var. *latifolia*.

of the major diterpenoid component of *Rabdosia shikokiana* (Makino) Hara var. *intermedia* (Kudo) Hara was not reported until several years later. In 1982, 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 cell line FM 3A/B.[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]

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]

From the liverwort *Lepidolaena taylorii*, Perry and co-workers re-isolated rabdoumbrosanin (**82**) along with **83**–**87**

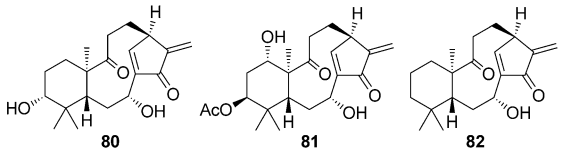


Figure 17. Rabdoshikoccin A (**80**) and B (**81**) isolated from *Rabdosia shikokiana* var. *occidentalis* and rabdoumbrosanin (**82**) from *Rabdosia umbrosa*.

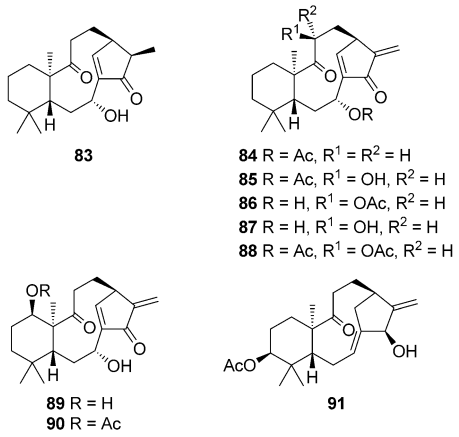


Figure 18. 8,9-Secokauranes extended family members **83**–**91**.

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 the new compounds **88**-**90** from this plant (Figure 18).[68–70] Diterpenes **86** and **88** were found to have both antimycobacterial and antimalarial activity.[68]

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 those of previously reported **76**, supporting the presence of the exocyclic alkene.[71]

3.5. Bicyclo[7.3.1] Systems

The 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).[75] In addition to possessing a bridgehead double bond, all of these compounds [except esperamicin X (**95**)][72] possess an enediyne unit, which constitutes six of the seven carbon atoms 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

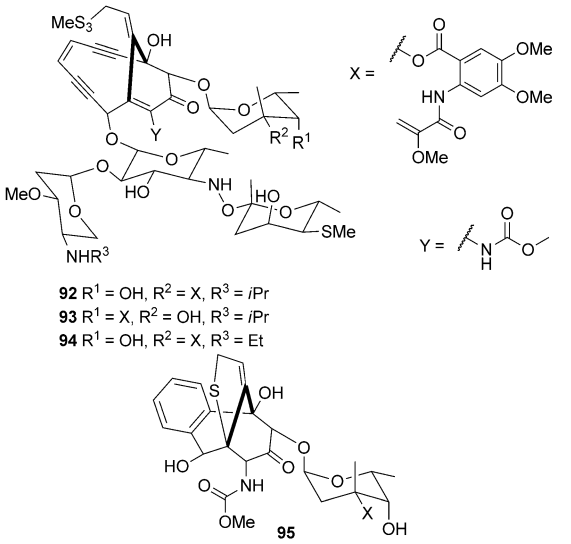


Figure 19. The esperamicins A_1, A_2, A_{1b}, and X (**92**–**95**), isolated from *Actinomadura verrucosospora*, collected from Puerto Esperanza, Argentina. The absolute configurations have not been determined, but are depicted as shown for the purpose of clarity and consistency.

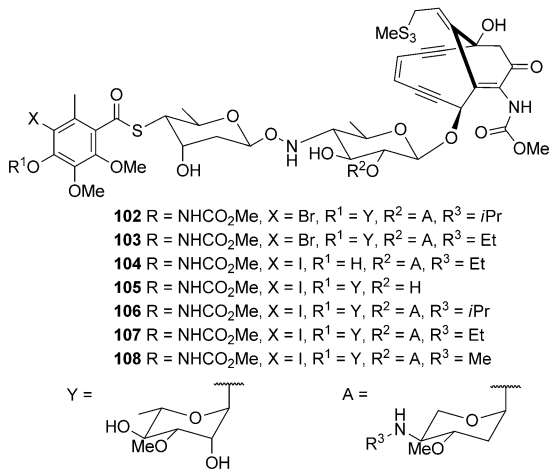


Figure 20. Calicheamicins β_1^{Br}, γ_1^{Br}, α_2^I, α_3^I, β_1^I, γ_1^I, and δ_1^I (**102**–**108**), isolated from *Micromonospora echinospora* ssp. *Calichensis*.

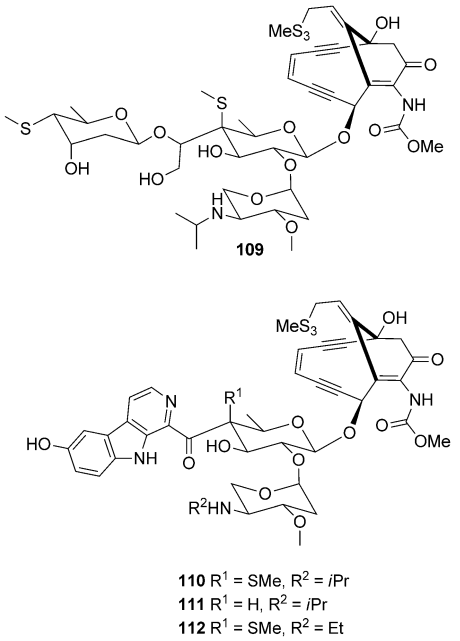
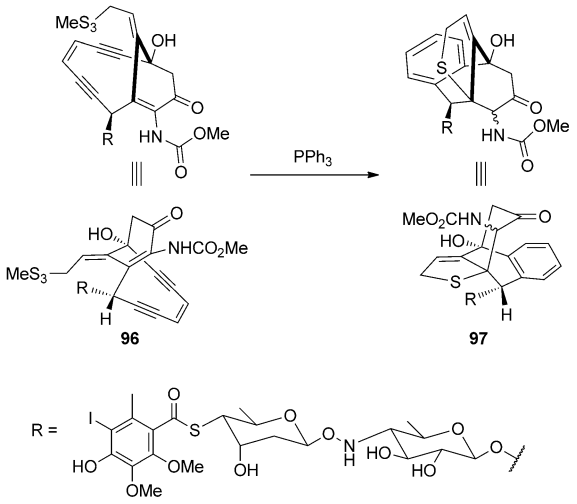


Figure 21. Namenamicin **109** and shishijimicins A–C (**110**–**112**), isolated from *Polysyncraton lithostrotum* on Namenalala Island and *Didemnum proliferum* from southern Japan, respectively.

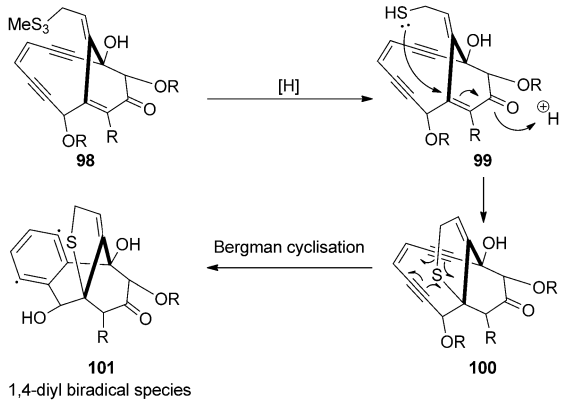


Scheme 5. Triphenylphosphine-mediated reduction of aglycon **96** to give dihydrothiophene **97** (top and side views by 90° rotation) was instrumental in the elucidation of the core structure of the calicheamicins.

were derived from microbial fermentation; the esperamicins were produced by cultures of *Actinomadura verrucosospora*, collected from Puerto 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.

Standard spectroscopic and spectrometric analysis of various chemical degradation products, aside from analysis of 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 efforts towards structure determination of the esperamicins,[72] and also added further evidence for the proposed biological mechanism of action (see Scheme 6).

The reactive bridgehead alkene of these natural products, in concert with the allylic trisulfide and enediyne unit, is key to their antitumor and 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 enediyne **100** (which



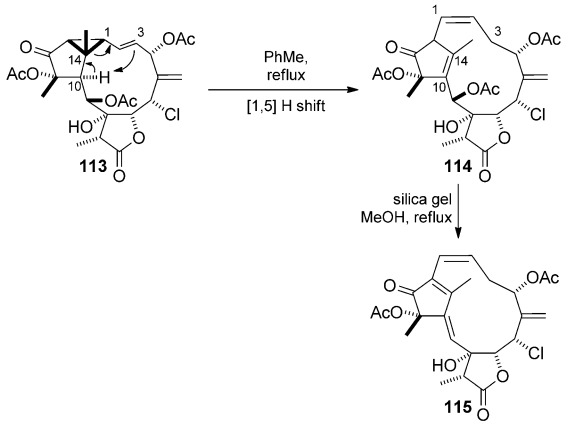
Scheme 6. Postulated chemical process that facilitates the mode of action of the enediyne-type anti-tumor antibiotics. Reduction of trisulfide **98** leads to the conjugate addition of the resultant sulfide **99** to the bridgehead enamide. This in turn triggers a Bergman-type cyclization on enediyne **100**, leading to the formation of the active 1,4-diyl species **101**.

were previously kept apart by the bridgehead double bond) to approach and undergo reductive aromatization (Bergman cyclization) via a 1,4-diyl species (**101**).[76] This biradical species is capable of hydrogen abstraction from the DNA backbone, leading to strand scission.

Of the four families encompassing the esperamicins (Figure 19), calicheamicins (Figure 20), namenamicin, and shishijimicins (Figure 21), only calicheamicin γ_1^I (**107**) has succumbed to total synthesis [Nicolaou et al. in 1992;[77] Danishefsky et al. in 1995].[78]

3.6. Bicyclo[9.2.1] Systems

The only representative within this class is the diterpene erythrolide K (**115**; Scheme 7), which was isolated from a sample of the Caribbean gorgonian octocoral *Erythropodium caribaeorum* collected in Tobago, as disclosed by Mootoo et al. in 1997.[79] It is noteworthy 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.



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

Based on the isolation of structurally related compounds [for example, erythrolide A (**113**)], it was postulated that erythrolide K (**115**) is biosynthetically derived from **113** through a [1,5] sigmatropic hydrogen shift of the H10 hydrogen atom to the C3 carbon atom with concomitant rupture of the cyclopropane unit (across the C1–C14 bond). This transformation has been achieved in a synthetic setting (Scheme 7).

3.7. Bicyclo[9.3.1] Systems

The phomactins (Figure 22),[80,81] 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.[82] Not too surprisingly, synthetic chemists and pharmaceutical companies, such as Sankyo (Japan) and Schering–Plough (USA), have shown considerable interest in these natural products.[83,84] The Goldring,[85] Hsung,[86] and Wulff[87] groups are amongst those who have been successful in the total synthesis of these compounds. The structures of Sch 47918 (**116**)[80c] and phomactins E (**123**),[80e] I (**125**),[80g] and J (**127**)[80g] were all solved by X-ray crystallography (Figure 22).

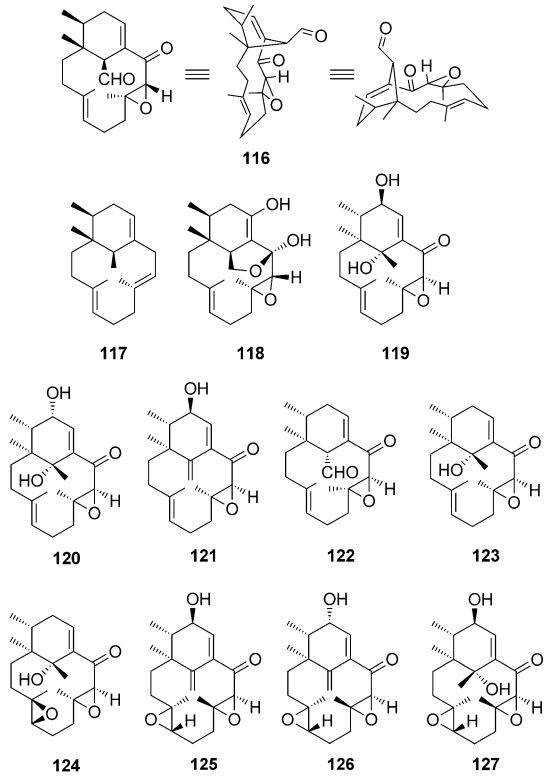


Figure 22. The phomactin and Sch bicyclo[9.3.1]pentadec-1-ene series, comprising Sch 47918 (**116**; flat and three-dimensional views), Sch 49026 (**117**), Sch 49027 (**118**), and phomactins B (**119**), B1 (**120**), B2 (**121**), C (**122**), E (**123**), F (**124**), I (**125**; 13-*epi*, **126**),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

Sch 49027 (**118**)[80c] 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 atom of the enol had a chemical shift of 148.1 ppm, clearly indicating an olefinic carbon atom despite any perceived strain (Figure 22). The sp^2 hybridization at this bridgehead position is clearly energetically favorable for this system.

Duh and co-workers, who already contributed to the bicyclo[4.3.1]decene class described in Section 3.1 above, discovered the cespitularin family of diterpenes (Figure 23),

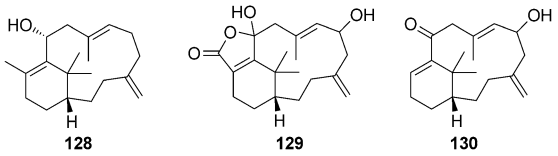


Figure 23. Cespitularins C (**128**), D (**129**), and E (**130**), isolated from the Formosan soft coral *Cespitularia hypotentaculata*.

which were isolated from the Formosan soft coral *Cespitularia hypotentaculata*.[88,89] 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).[90] However, cespitularin C (**128**) was particularly potent, exhibiting ED_{50} values of 0.12, 8.86, and 0.01 $\mu g\,mL^{-1}$ against the aforementioned cell lines, respectively.

Shen et al. uncovered two further cespitularin-type natural products, cespihypotins C (**131**) and D (**132**), from *Cespitularia hypotentaculata* Roxas (Xeniidae) in Taiwan in 2006 (Figure 24).[91,92] Their structures were deduced by NMR spectroscopic methods. HMBC correlations between the *gem*-dimethyl protons and the bridgehead sp^2 carbon atom were important in identifying the bridgehead olefin of **131** and **132**.

Like the phomactins, the cespitularin-type structures have shared lineage with the taxane natural products. Indeed, Shen and co-workers postulated that the cespitularins and cespihypotins all arise from verticillene (**133**; Figure 24),[91,92]

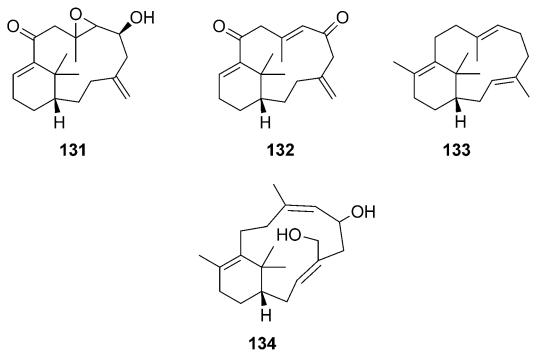
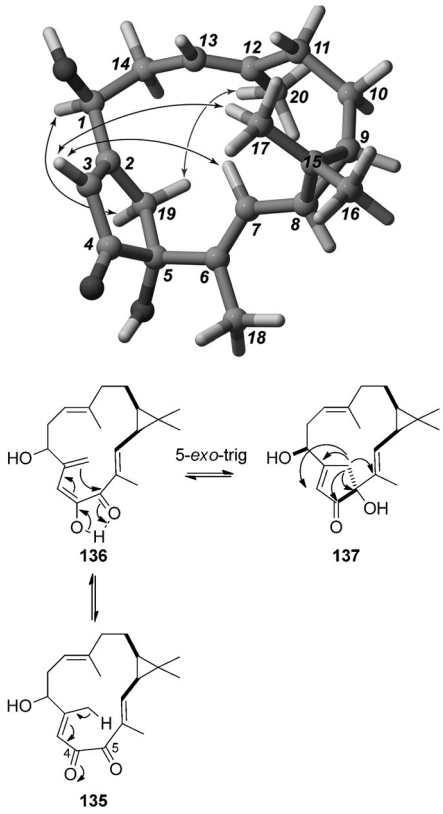


Figure 24. Cespihypotins C (**131**) and D (**132**), isolated from *Cespitularia hypotentaculata* Roxas (Xeniidae). The putative structure verticillene (**133**) is believed to be the biogenetic precursor of the cespitularins and cespihypotins, as further supported by compound **134**.

a putative structure that has been proposed to be the biogenetic precursor of the taxane natural products. The recently reported compound **134**, from *Trichoderma atroviridae* (UB-LMA), an endophytic fungus isolated from *Taxus baccata* trees, further supports this biosynthetic hypothesis (Figure 24).[92b]

3.8. Bicyclo[10.2.1] Systems

The solitary entry in this section was discovered only very recently by Reddell, Parsons, and Williams in 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 structure of the bicyclo[10.2.1]pentadec-2,6,13-triene ring system of EBC-219 (**137**; Scheme 8) was determined by NMR spectroscopy, specifically through the observation of key HMBC correlations. DFT calculations indicated 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). The absolute configuration of EBC-219 (**137**) was also determined by comparison of experimental and calculated CD spectra and was found to be 1*S*,5*R*,8*S*,9*R*.



Scheme 8. EBC-219 (**137**) isolated from *Croton insularis* (Baill). Top: Low-energy conformation with key NOEs. Bottom: Postulated biosynthetic conversion from EBC-181 (**135**) via **136**, and key HMBC correlations assigning the bridgehead alkene shown for **137**.

The structurally related 1,2-dicarbonyl-bearing compound EBC-181 (**135**), which was also isolated from the same species, was proposed to be the biogenetic precursor of EBC-219 (**137**). It can be envisaged that the bridgehead double bond could arise from a 5-*exo*-trig cyclization of a γ-enol (of type **136**) of EBC-181 (**135**) onto its C5 ketone (Scheme 8, bottom).[16b]

3.9. Bicyclo[13.3.1] Systems

The longithorones[18,93] and longithorols[94] 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].[95] For instance, the archetypal compound in this family, longithorone A (**138**), 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 feature a double bond!

The longithorones are farnesylated quinones isolated from the tunicate *Aplidium longithorax*. The structures of longithorones A (**138**; the most complex member of the family),[93] B (**3**; Figure 2), and E (**139**) were all secured by X-ray crystallography,[18] whereas the others were determined through NMR spectroscopy. Longithorols A (**142**) and B (**144**) were unstable, presumably as the hydroquinone moieties were easily oxidized to the corresponding quinones; hence, the structures of the corresponding peracetylated derivatives **143** and **145** were elucidated instead.

Schmitz and co-workers proposed that the key step in the biogenesis of these compounds was a [4+2] cycloaddition of **148** with **149** giving rise to the bicyclo[13.3.1] system.[93] In the total synthesis of (−)-longithorone A (**138**) published by Shair and co-workers,[96] this [4+2] cycloaddition was successfully modeled using appropriately protected synthetic equivalents of **148** and **149** to furnish the bicyclic core, giving credence to the proposed biosynthetic pathway (Scheme 9).

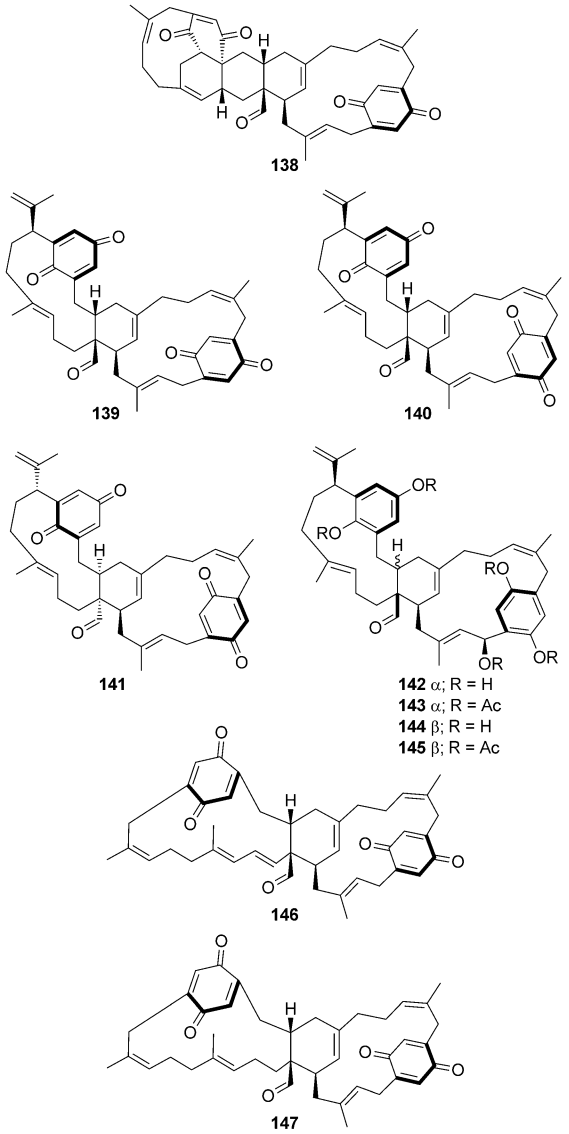
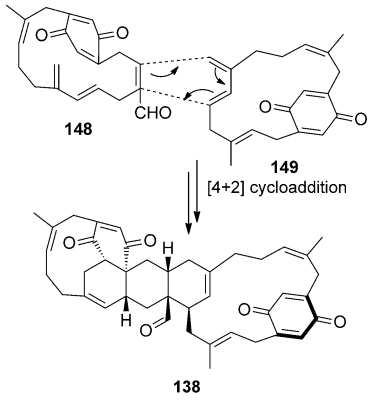


Figure 25. The longithorones A (**138**), E (**139**), F (**140**), G (**141**), H (**146**), and I (**147**) and the longithorols A (**142**; pentaacetate, **143**)[97] and B (**144**; pentaacetate, **145**), isolated from the tunicate *Aplidium longithorax*.

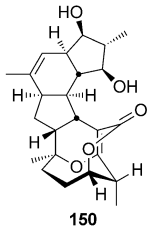


Scheme 9. Proposed key step of the biosynthesis of longithorone A (**138**) involving a [4+2] cycloaddition of quinone units **148** and **149** to furnish the polycyclic core.

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 (**150**; Figure 26). In 1996 the Fujisawa Pharmaceutical Company patented a novel antimitotic agent isolated from a strain of *Streptomyces* sp. No. 9885;[98] its structure was determined by 2D NMR analysis and X-ray crystallography of a derivative to be the one shown for FR182877 (**150**) in Figure 26.[99] Synthetic chemists,[100] most notably the groups of Sorensen[101] and Evans,[102] were immediately attracted to this molecule, not only to the elegant structural architecture,



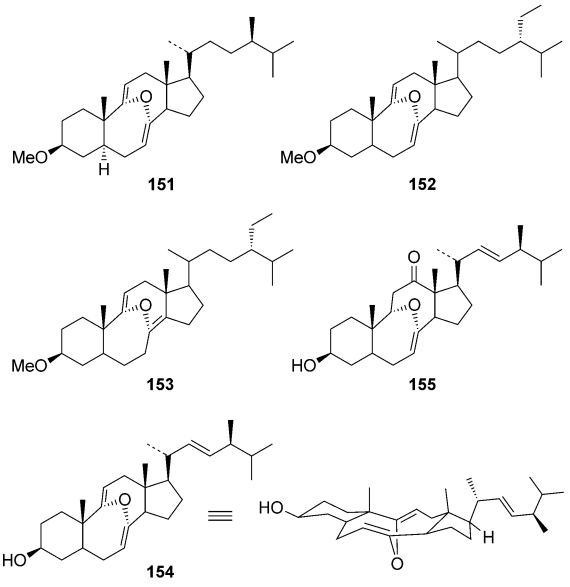
150

Figure 26. (−)-FR182877 (**150**), isolated from a strain of *Streptomyces* sp. No. 9885. Sorensen and co-workers determined that the originally proposed (+)-enantiopode was incorrectly assigned.[99d,101]

but also to the striking anti-tumor activity. For example, **150** displayed potent activity against both murine ascitic tumor P388 and Colon 38 solid tumors, prolonging the life span of the tumor-xenograft-bearing mice; the compound was also active against other common cell lines.[99] The pinnacle attraction to this audience, however, is the fact that **150** was found to be quite unstable owing to the reactivity of the bridgehead double bond. It was found to react with molecular oxygen to form an epoxide[99c] and with various nucleophiles in a Michael addition fashion.[101] These observations are unsurprising because the bridgehead double bond contained within **150**, 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

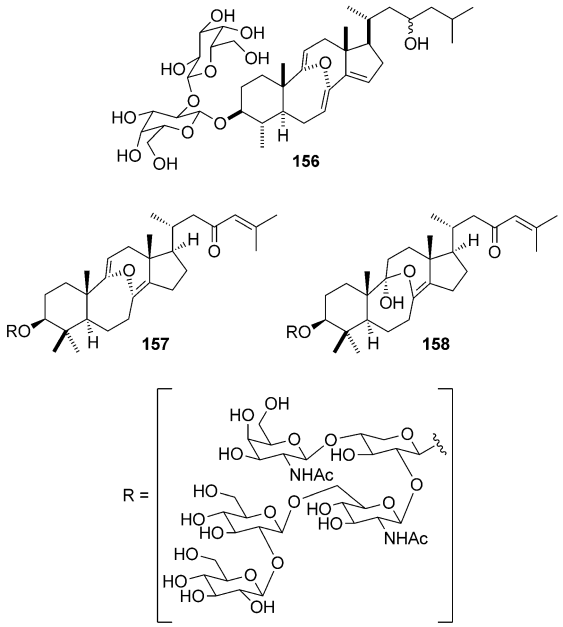
In 1991 jereisterol A (**151**; Figure 27) was isolated by Minale and co-workers from the pacific sponge *Jereicopsis graphidiophora* Lévi & Lévi in the north of New Caledonia at a depth of 225 m.[103] The structure of this rare 3-methoxy-8,9-secosteroid was deduced by comparing ^{13}C NMR data to those of known secosteroids 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 of these came from another group in Napoli led by Costantino and co-workers who isolated compounds 4 (**152**) and 5 (**153**) from the Senegalese sponge *Microsclerderma spirophora* (Figure 27).[104] Tylopiol A (**154**; solved by X-ray crystallography) and tylopiol B (**155**), reported by Wu et al.,[105] were the only compounds of this class to be isolated from a terrestrial source, *Tylopilus plumbeoviolaceus* (Snell. et Dick.) Sing., an edible, bitter fungus from the family *Strobilomycetaceae* (Boletales), which is widely distributed in the central area of Yunnan Province, China (Figure 27).



151 152 153 155 154

Figure 27. Jereisterol A (**151**), compounds 4 (**152**) and 5 (**153**), and tylopiol A (**154**; flat and three-dimensional view) and B (**155**).

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 (**156**; Figure 28).[106] The same group later reported sarasinoside M



156 157 158

Figure 28. Eryloside L (**156**) and sarasinosides M (**157**) and Q (**158**), isolated from *Erylus lendenfeldi*, *Melophlus sarassinorum*, and *Lipastrotethya* sp., respectively.

(**157**; Figure 28), isolated from the Indonesian sponge *Melophlus sarassinorum*.[107,108] Six years later, sarasinoside M (**157**) was isolated again by a group led by Oh and Shin from the tropical sponge *Lipastrotethya* sp. collected in Chuuk, Micronesia, along with sarasinoside Q (**158**; Figure 28).[109] They also demonstrated that **157** and **158** display cytotoxicity against the A549 and K562 cell lines, in addition to weak inhibitory activity against Na^+/K^+-ATPase.[109]

4.3. 11-Oxabicyclo[5.3.1] Systems

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 (**159**) was elucidated

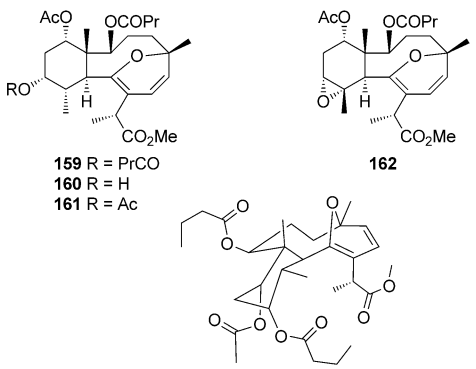


Figure 29. Briareolate esters A–C (**159**–**161**) and H (**162**), isolated from *Briareum asbestinum*. Flat and three-dimensional views of **159** shown at the bottom.

(Figure 29).[110] A subsequent full paper disclosed two further family members (**160** and **161**),[111] and a later re-isolation paper reported **162**.[112] These compounds were later renamed briareolate esters A (**159**), B (**160**), C (**161**), and H (**162**; Figure 29).[112] No biological studies were reported.

4.4. 8-Oxabicyclo[5.4.1] Systems

Francisco et al. disclosed that cystoseirol A (**163**; Figure 30) was obtained from a brown alga (*Cystoseira mediterranea*) occurring along the Mediterranean coastline. It was also isolated from *C. stricta* and *C. tamariscifolia*.[113] A subsidiary publication by this group disclosed cystoseirols B (**164**), C (**165**), D (**166**), and E (**167**; Figure 30), which are also found in various sources of *Cystoseiraceae*, that is, *C. mediterranea* (Banyuls sur Mer), *C. tamariscifolia* (Atlantic coasts), and *C. stricta* (Nice), around France.[114] Francisco and co-workers specifically commented that they had identified a natural product that "*contains a bridge-head, anti-Bredt, double bond*", which was (paradoxically) "*in a large enough system to be accommodated*", but interestingly no citation to the work of Bredt was provided.

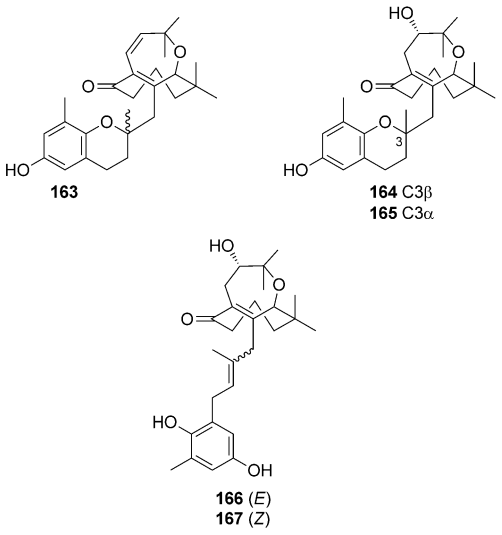


Figure 30. Cystoseirols A–E (**163**–**167**), isolated from *Cystoseira mediterranea*, *C. stricta*, and *C. tamariscifolia*.

4.5. 11-Oxabicyclo[6.2.1] Systems

The group of de Vivar investigated the sesquiterpenoid members of the *Compositae* family, resulting in the isolation of a new germacranolide, zexbrevin (**168**), from the aerial part of the schrub *Zexmenia breujfolia* (Figure 31).[115] Hydrogenation (Pd/C/H_2) of **168** afforded tetrahydrozexbrevin (**169**; Figure 31) and surprisingly left the bridgehead double bond

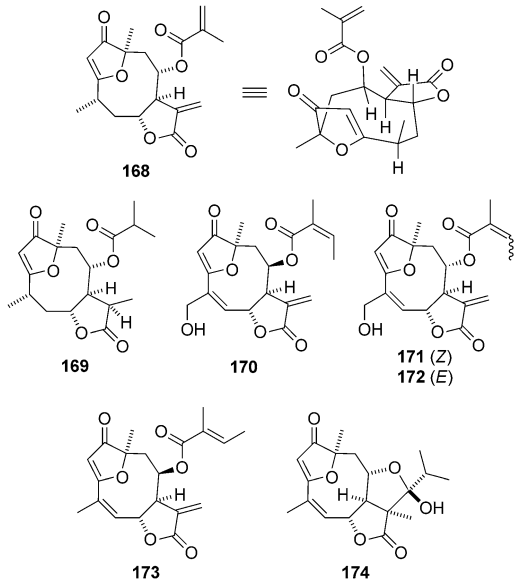


Figure 31. 11-Oxabicyclo[6.2.1] sesquiterpenoids (**168**–**174**), isolated form the genera *Eremanthus*, *Lychnophora*, *Piptolepis*, and *Vanillosmopsis* in the family Vemoniae. Zexbrevin (**168**) is shown in both flat and three-dimensional views.

untouched. Fifteen years later, a correction to the source of isolation was reported, as it was discovered that the actual natural source of **168** was *Viguiera greggi* (subgenus *Calanticaria*).[116] X-ray crystallographic confirmation of the elucidated structure was also reported, but well after the original elucidation.[117] Budlein-A (**170**) was also isolated by de Vivar from *Viguiera buddleiaeformis* (Figure 31).[118] Its epimer, lychnophorolide A (**171**), whose structure was confirmed by X-ray crystallography, was isolated from *Lychnophora affinis* by Le Quesne and co-workers,[119] as was lychnophorolide B (**172**; Figure 31). Lychnophorolide A (**171**) showed significant cytotoxicity activity, which was a factor of ten greater than that of related eremantholide A (**173**; Figure 31).[119,120] Total syntheses of **173** have been completed, notably by the groups of Hale,[121] Boeckman,[122] and Tadano.[123] Given that **172** is close in structure to atripliciolide tiglate (**174**), which was reported by Bohlmann et al. (Figure 31),[124] and to many other family members in this series,[125] Le Quesne and Raffauf suggested that a close relationship must exist between

the genera *Eremanthus*, *Lychnophora*, *Piptolepis*, and *Vanillosmopsis* in the family *Vemoniae*.[119]

4.6. 9-Oxabicyclo[6.2.2] Systems

Two natural product groups fall into this ring-size class, namely, the macquarimicins A (**175**) and B (**176**) and the cochleamycins A (**177**) and A2 (**178**; Figure 32), which are

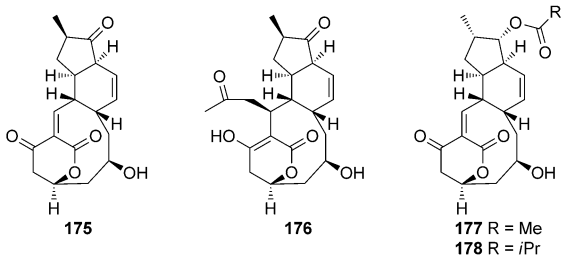


Figure 32. Macquarimicins A (**175**) and B (**176**) and the cochleamycins A (**177**) and A2 (**178**), isolated from soil bacteria.

closely related to FR182877 (**150**) discussed in Section 4.1 (10-oxabicyclo[4.3.1] systems, Figure 26). In 1984 Jackson et al., working for Abbott Laboratories, reported the macquarimicins (the structure of **175** was solved by NMR spectroscopy and that of **176** by X-ray crystallography) as low-potency anti-anaerobic microbial metabolites from two soil fermentation broths (*Micromonospora chalcea*).[126] Around the same time, Shindo et al. from the Kirin Brewery Company[127–129] described the cochleamycins A (**177**) and A2 (**178**), which were isolated from a Japanese soil *Streptomyces* sp. (DTI36) and found to exhibit antitumor and antibiotic activity. Biosynthetic 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.[130] It was this IMDA biosynthetic proposal that lured synthetic chemists to approach the synthesis of these captivating targets. Total syntheses were reported by the groups of Tadano [2004, macquarimicins A (**175**) and B (**176**)],[131] Tatsuta [2003, (+)-cochleamycin A (**177**)],[132] Roush [2004, (+)-cochleamycin A (**177**)],[133] and Lee [2009, (−)-cochleamycin A (**177**), formal].[134]

4.7. 11-Oxabicyclo[8.2.1] Systems

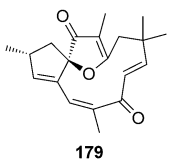


Figure 33. Jatrophone (**179**), isolated from *Jatropha gossypiifolia* L.

Jatrophones are well known for their prevalent cancer biology[125] and thus will not be extensively reviewed herein. Jatrophone (**179**; Figure 33) was isolated from extracts of *Jatropha gossypiifolia* L. (Euphorbiaceae) in a search for tumor inhibitors by Kupchan and co-workers.[135] The structure of **179** was elucidated by X-ray crystallography. Notable total syntheses include those by the groups of Smith

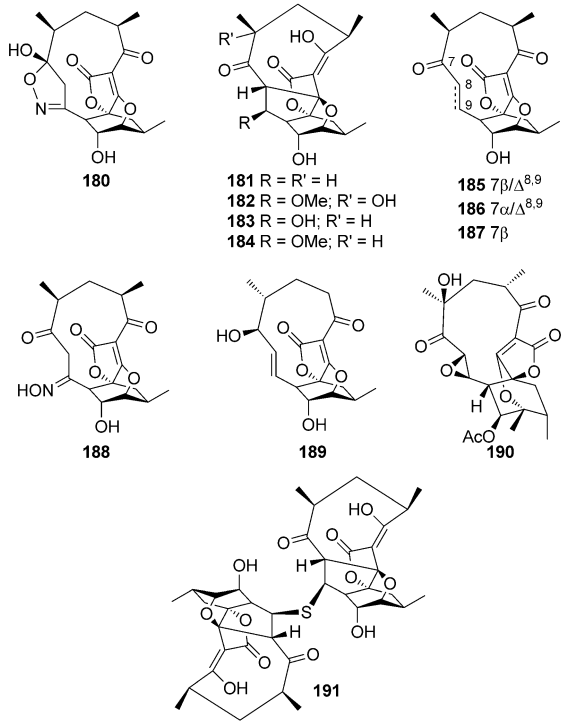


Figure 34. The abyssomicin antibiotics (**180**–**191**).

[1981, racemic jatrophone],[136] Stille and Hegedus [1990, racemic jatrophone],[137] and Wiemer [1992, (+)-jatrophone].[138]

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 (**180**, **185**, **181**) was disclosed through a collaborative effort led by Fiedler and Süssmuth in 2004.[139] Beyond the structural beauty, the attraction to this suite of natural products was the potent antibiotic activity (inhibition of the *p*ABA biosynthetic pathway),[139] which in combination with their isolation from the "deep" [Japanese Sea, depth 289 m, *Verrucosispora* sp. (AB-18-032)] provided the inspiration for the name. In 2007 a subsequent collaborative report investigating the same species unveiled abyssomicins G (**188**) and H (**187**), and *atrop*-abyssomicin C (**186**).[140] 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.,[141] **182**) and abyssomicin I (Igarashi et al.,[142] **189**), which were isolated from soil *Streptomyces* sp. This was followed by the isolation of *ent*-homoabyssomicin B (**190**) from a German soil sample, as reported by Laatsch and co-workers.[143] More recently, groups lead by Liu, Capon, and Zhang, driven by an anti-tuberculosis screening program, reported abyssomicins J (**191**), K (**183**), and L (**184**), which were isolated from a sediment-derived actinomycete, *Verrucosispora* sp., in the South China Sea (depth: 2733 m).[144] Total syntheses of this class of compounds have been prevalent, with syntheses completed by the groups of Sorensen [2005,[145] abyssomicin C (**185**)], Nicolaou [2006,[146] abyssomicin C (**185**) and *atrop*-

abyssomicin C (**186**); 2007,[147] abyssomicin D (**181**)], and Bihelovic and Saicic [2012,[148] *atrop*-abyssomicin C (**186**)].

4.8. 12-Oxabicyclo[9.2.1] Systems

The oxabicyclo[9.2.1] series are dominated by the pterolides [furancembranolides, for example, kallolide A (**192**)], which encompass a reasonable portion of the diterpene families isolated from gorgonian and other related corals (see also Section 4.3 on 11-oxabicyclo[5.3.1] systems). This area has been extensively reviewed,[149] and thus the two structures presented here (Figure 35) are given with the sole purpose of

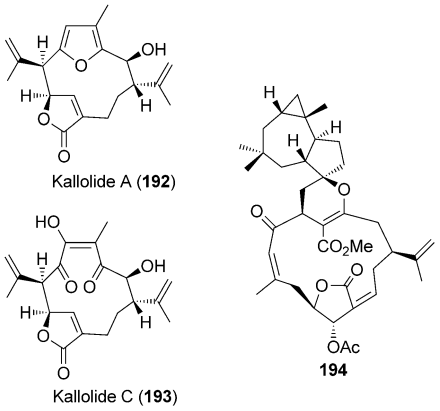


Figure 35. Kallolides A (**192**) and C (**193**), isolated from *Pseudopterogorgia kallos*, and polymaxenolide (**194**), discovered in the hybrid soft coral species *Sinularia maxima* · *Sinularia polydactyla*.

presenting a class exemplar. Many of the furancembranolides can be considered as heterocyclophanes (see a cyclophane review),[19,150] which are outside the scope of this review, but are believed to be direct oxidative precursors to the furan-opened members, for example, kallolide C (**193**). **193** (Figure 35) was isolated in the Bahamas from *Pseudopterogorgia kallos*, a marine octocoral within the abundant genus of sea whips.[151]

4.9. 14-Oxabicyclo[11.2.1] Systems

Polymaxenolide (**194**), whose structure was elucidated by X-ray crystallography, was isolated from a hybrid soft coral (*Sinularia maxima* · *Sinularia polydactyla*; Figure 35). This natural product is interesting from an evolutionary perspective. Not only is **194** 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.[152]

4.10. 4,23-Dioxabicyclo[18.2.1] Systems

The last representative in the oxygenated series is tuscolid A (**195**; Figure 36), which was isolated from culture

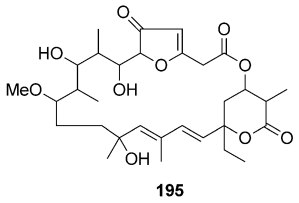


Figure 36. Tuscolid A (**195**), isolated from *Sorangium cellulosum*.

extracts of myxobacterium (*Sorangium cellulosum*, strains So ce1401 and So ce1383) by Höfle and co-workers. NMR spectroscopy, assisted by biosynthetic feeding studies with ^{13}C-labelled precursors, was used to deduce the flat structure.[153]

5. Nitrogen-Containing Bicyclic Bridgehead-Olefinic Systems

Only a small number of alkaloids containing a bridgehead olefin have been identified. These include the saraines 1–3 (**196**–**198**), isosaraines 1–3 (**199**–**201**), haliclamines A–F (**202**–**207**), and halicyclamines A–B (**208**–**210**), which, unsurprisingly, are all biogenically linked.[154]

The saraines 1–3 (**196**–**198**; Figure 37),[155] 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. In conjunction with

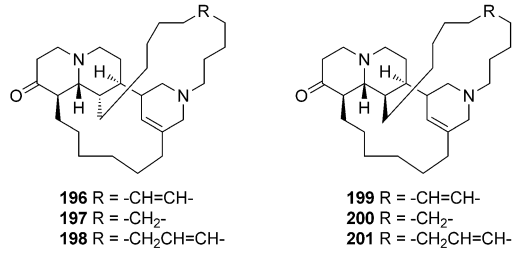


Figure 37. Saraines 1–3 (**196**–**198**) and ososaraines 1–3 (**199**–**201**), isolated from *Reniera sarai*.

extensive 2D NMR spectroscopy, reduction of the carbonyl moiety to the corresponding alcohols, followed by conversion into the Mosher esters facilitated structure determination. Approximately three years later, diastereoisomers of the saraines, namely the isosaraines 1 (**199**) and 2 (**200**), were isolated from the same marine sponge,[156] with saraine 3 and isosaraine 3 (**201**) discovered over a decade later.[155c]

Around the time the isosaraines (**199**–**201**; Figure 37) were discovered, haliclamines A and B (**202** and **203**; Figure 38) were isolated from a sponge of the genus Haliclona collected off the Japanese Island of Hiburi-jima in the Uwa Sea.[157] Both haliclamine A and B inhibited the division of fertilized egg cells of the sea urchin (*Hemicentrotus pulcherrimus*), and more importantly inhibited the growth of leukemia cell lines L1210 ($IC_{50} = 0.9\ \mu g\,mL^{-1}$) and P388 ($IC_{50} = 0.39\ \mu g\,mL^{-1}$).[157] More recently, haliclamines C

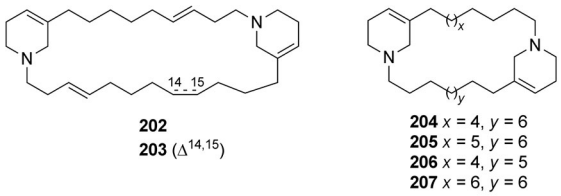


Figure 38. Haliclamines A–F (**202**–**207**), isolated from *Haliclona viscosa*.

(**204**), D (**205**), E (**206**), and F (**207**) were isolated by Köck et al. from the Arctic sponge *Haliclona viscosa*.[158,159] 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 atoms make up one of the bridge junctions in each system (Figure 38). Only haliclamine A (**202**) has succumbed to total synthesis [1997, Morimoto].[160]

The last in this series are the halicyclamines A (**208**), B (**209**), and 22-hydroxyhalicyclamine A (**210**). Crews and co-workers reported the isolation of halicyclamine A (**208**) from *Haliclona* sp., a massive, soft-textured, olive-green-colored tubular sponge collected from Biak, Indonesia.[161] It showed good inhibition of inosine monophosphate dehydrogenase (IMPDH; 1 $\mu g\,mL^{-1}$), which is a potential cancer chemotherapy target. Much more recently, however, halicyclamine A (**208**) was found to act as an anti-tuberculosis agent,[162] in addition to displaying anti-dormant mycobacterial activity, with a mechanism of action linked to the DedA protein.[163] 22-Hydroxyhalicyclamine A (**210**) was later isolated from the marine sponge *Amphimedon* sp. by Fusetani and co-workers.[164] To complete the set, halicyclamine B (**209**), whose structure was elucidated by X-ray crystallography, was later reported by Crews and co-workers; it was isolated from the marine sponge *Xestospongia* sp., obtained from Sangihe Islands, Indonesia.[165] Only the structures of halicyclamines A (**208**), B (**209**), and the hydroxy derivative **210** 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 **208** and **210**, and a 3,9-diazabicyclo[12.3.1]heptdec-1-ene system in the case of **209** (Figure 39).

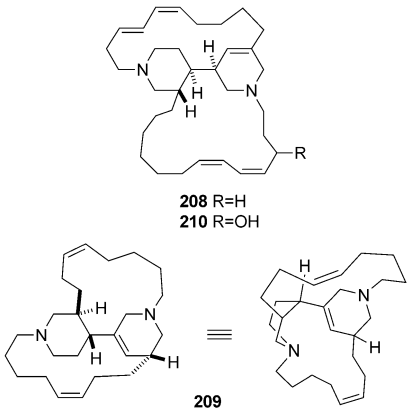


Figure 39. Halicyclamines A (**208**) and B (**209**; flat and three-dimensional views) and 22-hydroxyhalicyclamine A (**210**).

6. Anti-Bredt System or Bridgehead Olefin?

It is somewhat ironic that Bredt's rule was developed through the study of simple terpenoid natural products, as its application in this context remains uncertain. Should (or can) the term "anti-Bredt" be applied to natural products containing a bridgehead olefin? Aside from 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 functional groups 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 of bridgehead olefin instability through calculated OS values.

We wish to conclude the Review by providing the reader with an appreciation of the strain present in the bridgehead alkenes of the natural products presented above. However, calculating Schleyer's OS even for a representative sample of the 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 appreciated.

Analysis 1: As elegantly described by Shea and co-workers[12a] through an 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-hybridized 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 YC1C2W (Φ_1) or ZC1C2X (Φ_2; Figure 40). Owing to the rehybridization and ensuing pyramidalization, however, Φ_1 and Φ_2 are now non-equivalent, and therefore, the torsional

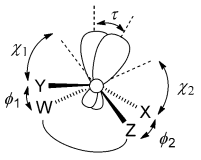


Figure 40. The projected view along a torsionally distorted double bond; distortional parameters χ and τ. Adapted from Ref. [12a].

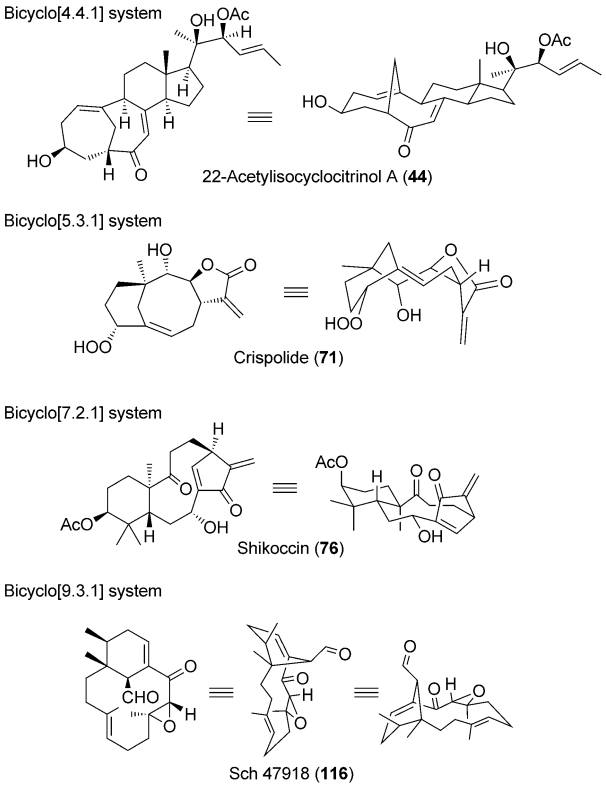


Figure 41. All-carbon candidates **44**, **71**, **76**, and **116**, solved by X-ray crystal-structure analysis and used to evaluate bridgehead bond lengths and torsional values. Crispolide (**71**) was solved as the diacetate, and shikoccin **76** solved as the mono-acetate.

distortion τ is defined as an average [that is, $\tau = (\Phi_1 + \Phi_2)/2$].

Utilizing this mode of analysis, specifically concentrating on the degree of distortion (τ), selected X-ray crystal structures of the all-carbon 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.

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 the groups of Nicolaou,[43a] Wood[166] and Clive.[167] Thus compounds **211** and **212** (Figure 42) were evaluated together with the above chosen natural products (Figure 41 and Table 1). A clear trend is evident from the τ values listed in Table 1. On

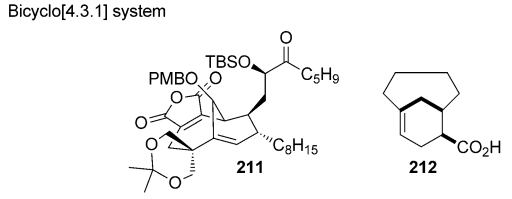


Figure 42. Intermediate reported by Nicolaou et al. (**211**) and bridgehead olefin reported by Shea and co-workers (**212**). PMB = *para*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl.

Table 1: Bridgehead bond lengths and torsional (τ) values for compounds **44**, **67**, **71**, **76**, **116**, **211**, and **212**.

Entry[Ref]	Bridgehead olefin length [Å][a]	Bridgehead olefin distortion [τ][a,b,c]	Bicyclo[m.n.o] system
211[43a]	1.312	8.2°	[4.3.1]
212[12a,168]	–	6.8°	
71[55]	1.328	3.4°	[5.3.1]
67[169]	1.351	3.6°	
44[46]	1.331	2.6°	[4.4.1]
76[58]	1.334	2.6°	[7.2.1]
116[80c]	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.[170] [c] Variations in determining τ values can exist owing 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, thus providing a greater degree of hydrogen atom certainty or probability.

increasing ring size (that is, [4.3.1] to [9.3.1]), the degree of bridgehead olefin twisting decreases. The most strained system is the phomoidride intermediate **211** within the bicyclo[4.3.1] series. The distortion angle of 8.2° is quite high compared to the value of 6.8° in **212**, the structure of which is more representative of an archetypal bicyclo[4.3.1] system. This is most likely due to other skeletal strain features present in **211**,[9c] but nevertheless still compares well with the parent system **212**.[12a,168] 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 [for Sch 47918 (**116**)].

In the case of the oxygen-containing bicyclic bridgehead-olefinic systems, τ values were determined for tylopiol A (**154**), methyl briareolate (**159**), and tetrahydrozexbrevin (**169**; Figure 43, Table 2).

The oxygen-bridged series are more difficult to analyze as the suggested trend is opposite to that of 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 the skeletal structure is most likely a substantial contributor to the observed

Table 2: Bridgehead bond lengths and torsional (τ) values for compounds **154**, **159**, and **169**.

Entry[Ref]	Bridgehead olefin length [Å][a]	Bridgehead olefin distortion [τ][a,b,c]	Bicyclo[m.n.o] system
159[110]	1.348	0.5°	[5.3.1]
154[105]	1.218	7.6°	[4.4.1]
	1.389	4.3°	
169[117]	1.355	8.7°	[6.2.1]

[a] See the cited literature for standard deviations. [b] The value of τ was extracted from reported X-ray crystallographic data using the program Mercury.[170] [c] Variations in determining τ values can exist owing 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, thus providing a greater degree of hydrogen atom certainty or probability.

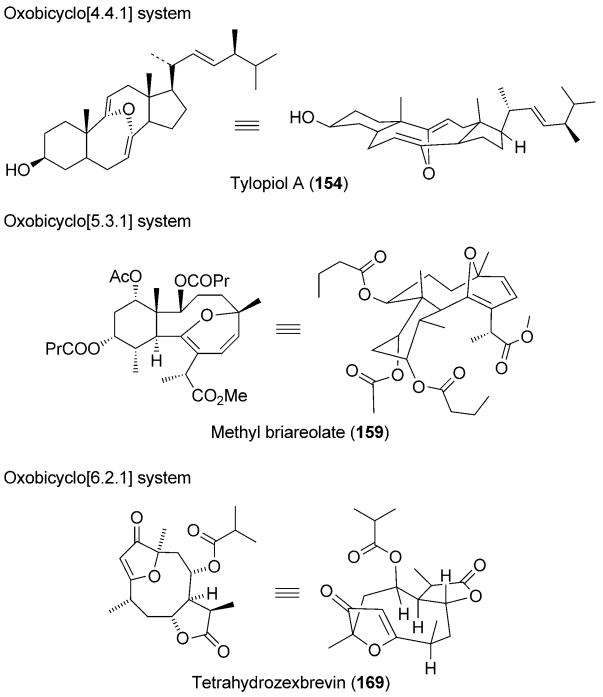


Figure 43. Oxygen-bridged candidates (i.e., **154**, **159**, and **169**), solved by X-ray crystal-structure analysis and used to evaluate bridgehead bond lengths and torsional values.

bridgehead olefin twisting. For example, tylopiol A (**154**; $\tau =$ 7.6° and 4.3°) contains two bridgehead olefins with significant differences between the two bridgehead bond lengths ($\Delta =$ 0.171 Å). Meanwhile, in methyl briareolate (**159**; $\tau = 0.5°$), 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 atom through adjacent p orbital overlap. In the case of tetrahydrozexbrevin (**169**), the torsional distortion value ($\tau = 8.7°$) is unexpectedly high, matching more closely the values of the all-carbon bicyclo-[4.3.1] systems. Despite this relatively high value for torsional strain, the bridgehead olefin, which is conjugated to a carbonyl group, is resistant to hydrogenation. A similar observation is made for the nitrogen-bridged example halicyclamine B (**209**). It might be expected that for such a large ring system (a bicyclo[12.3.1]/[10.3.1] system), a very low or even negative τ value is found, but instead the τ value is relatively large (3.7°), which is most likely due to the olefin residing in the smallest bridge (Figure 44).

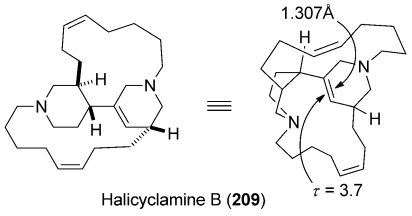
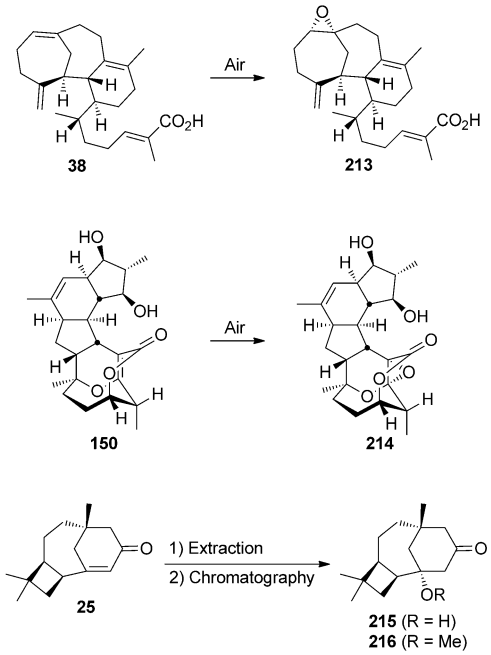


Figure 44. Bridgehead bond lengths and torsional values of halicyclamine B (**209**) obtained from the reported X-ray crystal structure.

Analysis 2: Another useful measure of bridgehead alkene strain in the context of natural products 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 (**150**)[99c] were observed to undergo slow aerial oxidation to give sp^3-hybridized bridgeheads in epoxides **213** and **214** (Scheme 10).[171] Sesquiterpene



Scheme 10. Aerial oxidation of cerorubenic acid-I (**38**) and FR182877 (**150**) to epoxides **213** and **214**, respectively. **215** and **216** are artifacts of the isolation of sesquiterpene **25**.

25 was also reported to be unstable and the two co-isolates **215** and **216** were deemed to be artifacts of isolation arising from reactions at the bridgehead double bond. These observations suggest that **25**, **38**, and **150** 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, these 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, that is, **215**, Scheme 10) could potentially be extrapolated from a naturally occurring classical anti-Bredt reactive intermediate.

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 uncertainty with respect to the anti-Bredt classification. We hope that this Review brought clarification and indeed introduced a helpful framework for evaluating bridgehead olefin containing natural products.

Lastly, we feel that Julius Bredt himself probably would never have imagined that his legacy would continue into modernity, especially as he was already aware that violations of the rule were on the horizon. Nevertheless, the natural occurrence 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.[172]

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[172] During the revision process of this Review, two new oxygen-containing bicyclic bridgehead-olefinic systems were reported; for an oxabicyclo[6.3.2] system, see: a) L.-F. Liang, T. Kurtán, A. Mándi, L.-X. Gao, J. Li, W. Zhang, Y.-W. Guo, *Eur. J. Org. Chem.* **2014**, 1841 – 1847; for an oxabicyclo[9.3.2] system, see: b) K.-H. Lin, Y.-J. Tseng, B.-W. Chen, T.-L. Hwang, H.-Y. Chen, C.-F. Dai, J.-H. Sheu, *Org. Lett.* **2014**, *16*, 1314 – 1317.