Biosynthetic interrelationships within polycyclic cembranoids isolated from corals. Conjecture, biomimetic synthesis and reality.

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Abstract: Macrocyclic furanobutenolide-based cembranoids are precursors to a wide variety of complex ring-fused diterpene structures in corals, implicating a wide variety of oxidation and photochemical processes, cyclisation and transannulation reactions, and skeletal rearrangements from a variety of reactive intermediates and pericyclic processes. This article gives an up to date personal perspective on the speculations that underpin these interesting biosynthetic interrelationships, and summarises biomimetic synthesis and interconversions that would seem to vindicate some of these speculations.

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1. Introduction and scope†

Furanobutenolide-based cembranoids (FBCs) are a large family of 14-membered ring diterpenes derived from gerany geranyl pyrophosphate which accommodate furan rings between C3-C6 and butenolide ring systems encompassing C10-C12 in their structures.[1-4] They have been isolated exclusively from corals and all are related to the core rubifolide structure **1**. The first of their number to be characterised however was pukalide **2**, from the soft coral *Sinularia abrupta* by Scheuer *et al.* in 1975 . Other representative members are bipinnatin J (**3**), and the muscular neurotoxin lophotoxin **4** (Fig.1) The many oxy-substituted FBCs in Nature are either products of biological epoxidations at C7-C8 and C11-C12 (also C15-C17) or oxidations at C13, C14, C16 and C18, or both, in the core structure **1**. Although most FBCs have *Z*-configurations at their C7-C8 alkene bonds a few, like acerosolide **5**, show the alternative *E*-configuration at the same alkene bond.[1] Enedione-based cembranoids, *e.g.* coralloidolide E (**6**) resulting from oxidative cleavage of the furan rings in FBCs,[5] and isomeric structures with 12-membered rings known as pseudopterolides or kallolides,[6] *e.g.* kallolide B (**7**) are also commonly found alongside FBCs in corals.

By far the most exciting FBC-related metabolites to be found in corals however are a variety of highly oxygenated and complex

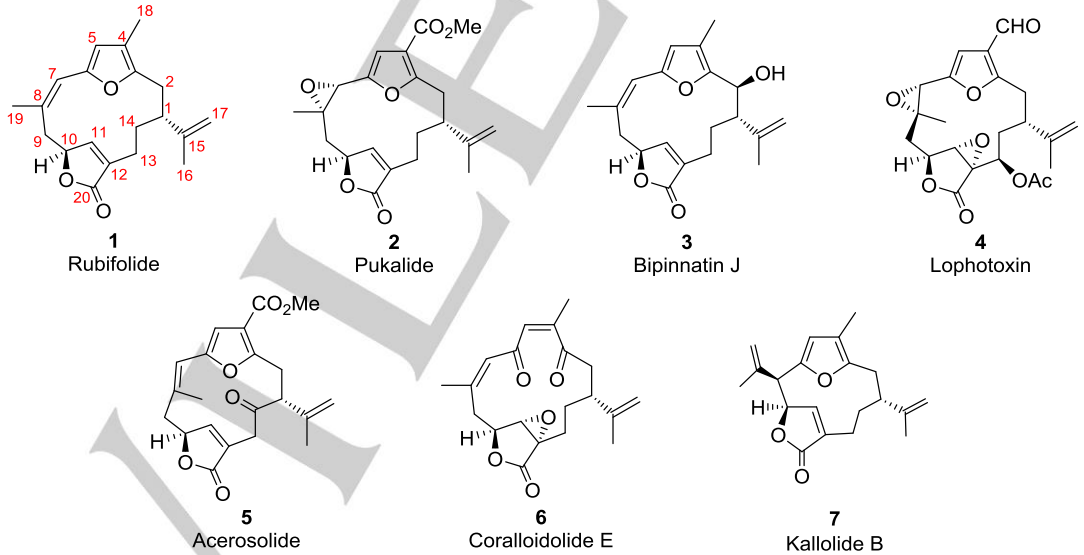

Figure 1. Some furanobutenolide-based cembranoids, (FBCs), and oxidised relatives isolated from corals**.**

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†**Footnote:** Gerry Pattenden lectured at the Bristol Synthesis Meeting during 2008, and on that occasion he presented the total synthesis of three widely different natural products, i.e. ulapualide A, salinosporamide A and intricarene. Over the ensuing recent years his research group has investigated biomimetic synthetic approaches to a range of complex polycyclic natural diterpenoids found in corals. This personal Perspective summarises the progress his group has made in this area, alongside contemporaneous studies of others.

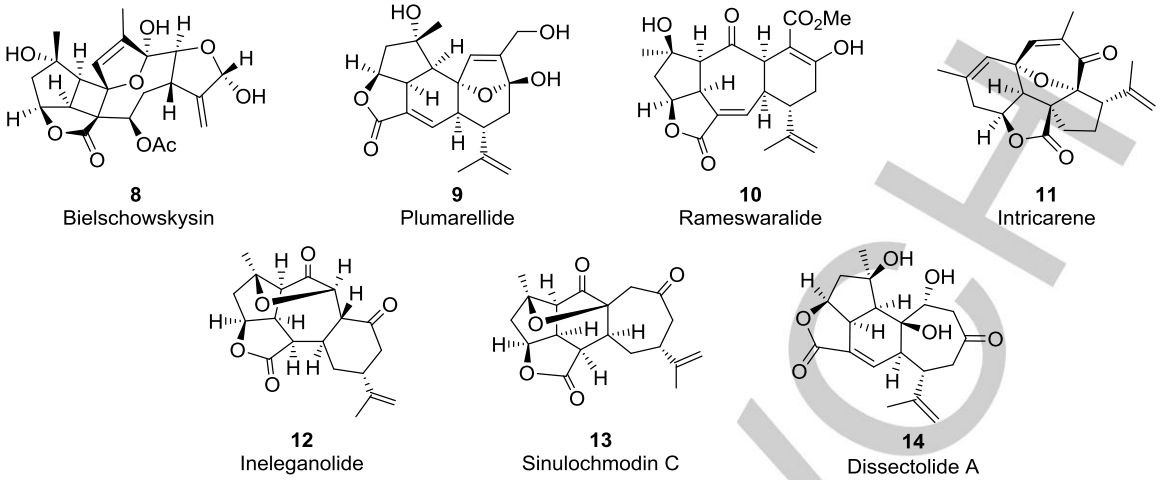


Figure 2. Examples of polycyclic cembranoids and related norcembranoids isolated from corals.

ring-fused diterpene metabolites, represented by bielschowskysin **8**,[7] plumarellide **9**,[8] rameswaralide **10**,[9] and intricarene **11**.[10] In addition, a number of related C19 *nor*diterpenes, which also have highly complex ring-fused systems, *e.g.* ineleganolide **12**,[11] sinulochromodin C (**13**)[12] and dissectolide **14**,[13] have been isolated from corals and clearly have their origins in FBC precursors.The aristocratic nature, combined with the unusual fusion of rings with complex oxy-substitution patterns and stereochemistry in the polycyclic structures **8**-**14** have enticed and seduced a number of synthetic chemists to take up the challenge of their synthesis in the lab. A recent review has summarised a variety of synthetic approaches that have been made towards members of the polycyclic structures **8-14**, especially towards bielschowsksin **8** and ineleganolide **12**.[14] In this Perspective we focus on speculations that have been made, by us and others, over the past decade on the most likely biosynthesis pathways to the aforementioned polycycles and some of their relatives, and then summarise the progress that has been made to vindicate some of these speculations in the lab., *i.e.* by biomimetic syntheses.

In needs to be mentioned that the marine milieu is not the ideal environment to conduct studies of the biosynthesis of polycyclic structures like **8**-**14** and indeed few have been published. Nevertheless, the marine milieu does have oxygen and water, and contains metals and salts for triggering a variety of oxidations, hydrolyses and C→C bond forming reactions and, of course' there is sunlight for catalysing an array of novel photochemical rearrangements and other bond-forming reactions. All of these "opportunities" for the possible elaboration of the polycyclic structures **8**-**14** and their relatives from macrocyclic FBC starting materials will be discussed and evaluated in this Perspective.

Earlier, in 2011, we presented our speculations on some of these events in two reviews published in *Natural Product Reports*. Since that time several new polycyclic cembranoid secondary metabolites have been found in corals, and more

Gerry Pattenden is Emeritus Professor in the School of Chemistry at The University of Nottingham. He was Sir Jesse Boot Professor of Organic Chemistry until 2005 and then Research Professor until his supposed retirement in 2009. However, Gerry has continued to do research and publish, and his most recent publications (with Matthew Palframan) describe the structure and chemistry of a new and exciting insect pheromone, named sobralene, isolated from males of the Brazilian sand fly. Sobralene has a close biosynthetic relationship with its co-metabolite taxadiene which he is now studying further. Over his career Gerry's research has been driven largely by his curiosity of biosynthetic interrelationships within several families of natural products. Alongside studies of these relationships, largely through synthesis, he also discovered and developed a wide range of cascade radical reactions leading to steroids and polycyclic terpenes, and synthesised a wide variety of natural products including complex polyene and azole-based macrocyclic compounds.

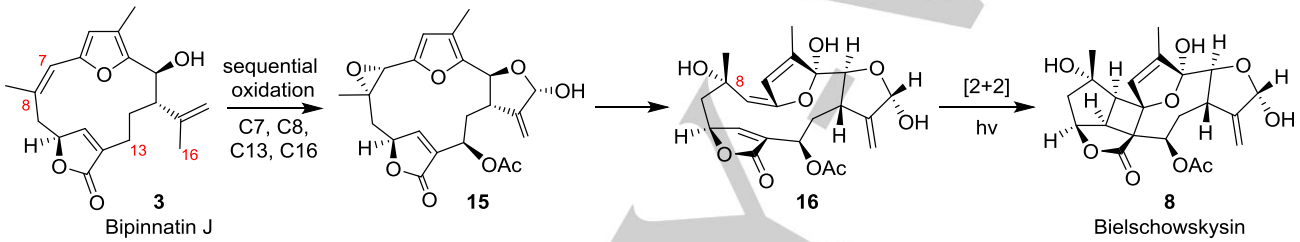
Matthew Palframan graduated from Oxford University with an MChem, and then carried out research with Professor Andy Parsons at the University of York on the synthesis of alkaloids leading to a PhD in 2010. After post-doctoral research exploiting the products of microbial oxidations in synthesis with Dr Simon Lewis at the University of Bath, Matthew joined the research group of Professor Pattenden in Nottingham where he explored biomimetic intramolecular cycloaddition reactions for the construction of complex ring systems found in diterpenes, such a rameswaralide and plumarellide isolated from corals. Subsequently Matthew conducted research as a medicinal chemist in the labs of Prof. Chris Hayes in Nottingham. He is now a Lecturer in Medicinal Chemistry in the School of Pharmacy at The University of Wolverhampton.

biosynthesis speculations as to their possible origins have been forthcoming. To provide a coherent survey and Perspective on this recent progress it has been necessary to summarise some of the ideas we have reviewed previously. We apologies for this and hope that we have not missed any important earlier work or, indeed offended any colleagues who may feel that some of their studies have not been considered in sufficient detail or even overlooked.

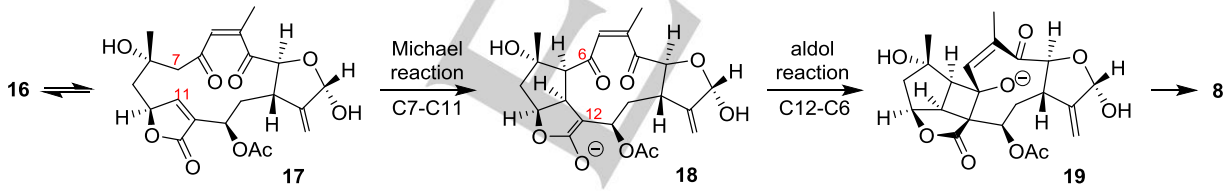
2. Bielschowsyksin

Bielschowskysin **8** accommodates a rare substituted-cyclobutane ring embedded within its unique and complex polycyclic structure. It is also reported to exhibit cytotoxicity against non-small lung cancer cells and renal cancer cells. Its challenging structure and interesting biological properties have combined to make bielschowskysin one of the most revered targets amongst synthetic chemists in recent years.[14]

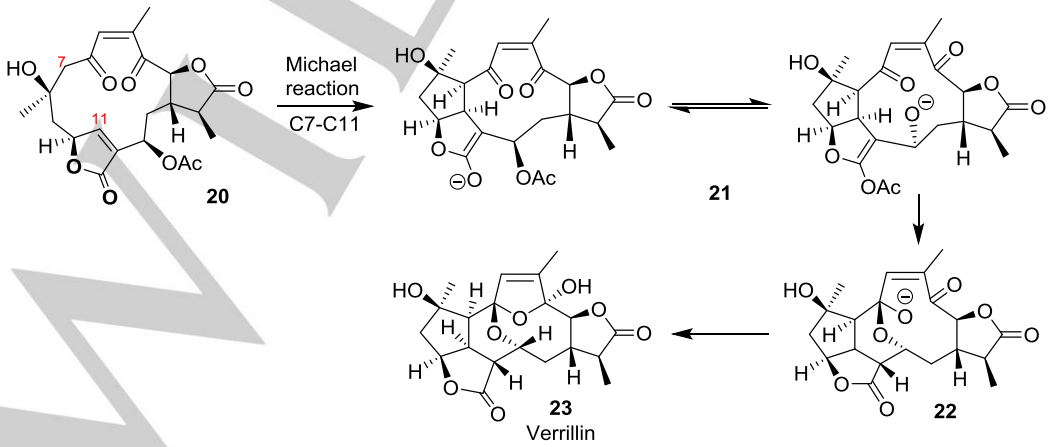
The complex fused ring system in bielschowskysin **8** is thought to originate *in vivo* from the FBC structure bipinnatin J (**3**) after a sequence of regio- and stereo-selective oxidations, which first lead to the epoxide **15**, followed by acid-catalysed hydration producing the exocyclic enol ether cyclic hemiketal **16** as key intermediate (Scheme 1).[1,2] Intramolecular [2+2] photocycloaddition involving the butenolide and enol ether alkene bonds in **16** would then lead to the natural product. The enol ether cyclic hemiketal unit in **16** is the tautomer of the cyclic enedione **17** and an alternative ionic pathway to bielschowskysin from the enolate produced from **17,** involving sequential Michael and aldol reactions between C7 and C11, and between C12 and C6 in **17**, *viz*, **17→18→19** (Scheme 2), has also been suggested.[1]



Scheme 1 Proposal for the biosynthesis of bielschowskysin **8** from bipinatin J (**3**) featuring an intramolecular [2+2] photocycloaddition in the enol ether cyclic hemiketal intermediate **16**



Scheme 2. An alternative proposal for the biosynthesis of bielschowskysin **8** from the enedione intermediate **17** *via* anionic intermediates.



Scheme 3. Proposal for the biosynthesis of verrillin **23** *via* the enedione intermediates **20** and **21**.

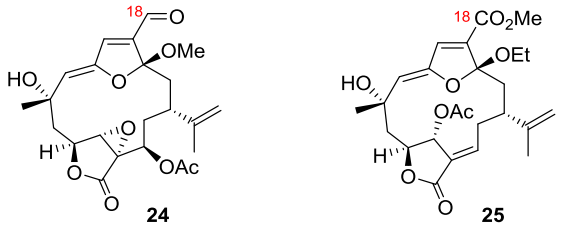
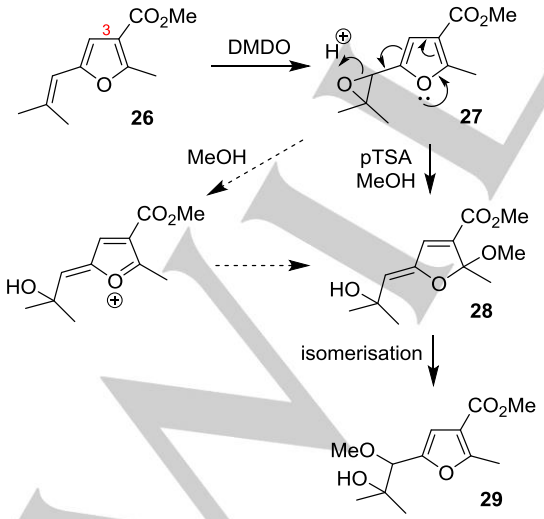


Figure 3. Some enol ether cyclic ketal metabolites isolated from corals.

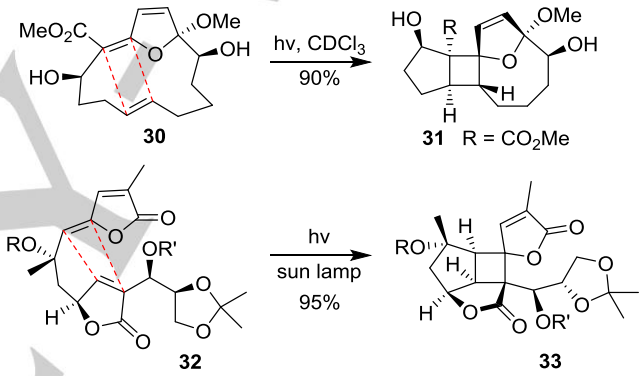
Verrillin **23** co-occurs with bipinnatin J (**3**) in *P. bipinnata*[15] and even though it has a different oxidation pattern at C17 and is epimeric at C8 with beilschowskysin **8** , it is likely that it is also derived from an enedione intermediate similar to **17**, *viz* **20** which, after an intramolecular Michael reaction to **21** followed by transacetalisation to **22** would cascade to verrillin (Scheme 3). Interestingly, Theodorakis *et al.*[16] have recently synthesised a macrocyclic structure which accommodates the important fused cyclopentane-butyrolactone unit in **21** but with the enedione unit masked as a furan ring. However this biosynthesis inspired synthesis approach to verrillin has not been progressed.

Secondary metabolites which accommodate the interesting enol ether cyclic hemiketal unit in the penultimate intermediate **16** in the proposed biosynthesis of bielschowskysin **8** (see Scheme 1) have been isolated from corals, often alongside their likely C7,C8 vicinal diol and epoxide precursors. Significantly however these natural products, *e.g*. **24** and **25**, have only been characterised with CO_2Me or CHO groups at C18 (*i.e*. not Me as in bielschowskysin), and only as C3 methyl or ethyl ethers. In early model studies of the oxidation of vinyfurans, *e.g.* **26**, to enol ether cyclic ketals **28**, *cf.* **24**, *via* the epoxide intermediate **27** it was demonstrated[17] how crucial it was to have an ester group at C3 in the furan ring and how sensitive the enol ether cyclic ketal product **28** was to rearrangement /re-aromatisation



Scheme 4. A model study of the synthesis of enol ether cyclic ketals **28** from epoxy furans **27** in the presence of protic acids.

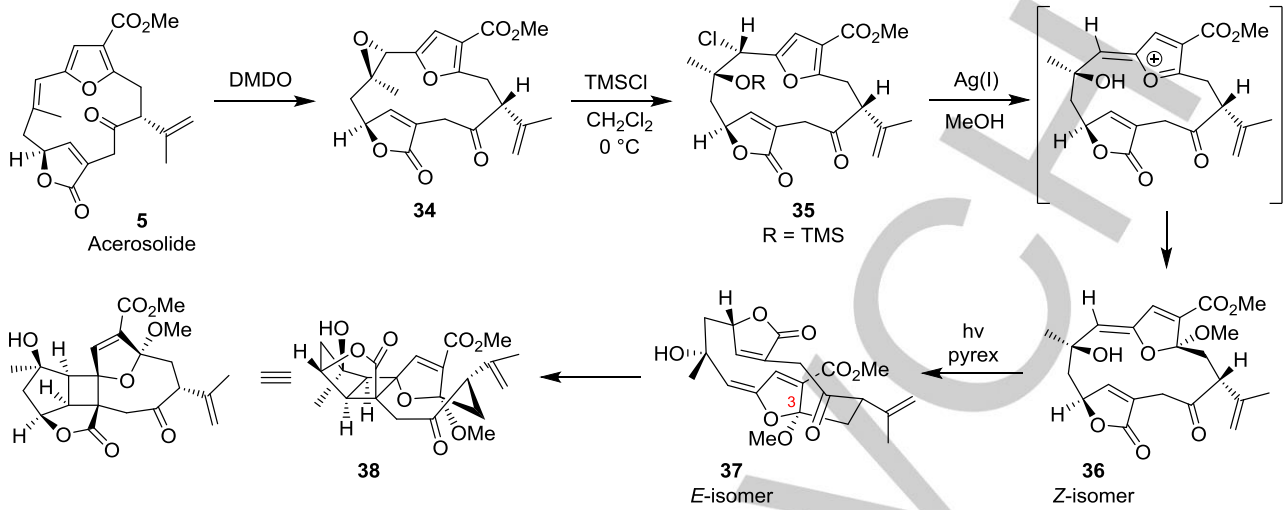
to the more stable furan isomer, *viz* **29** (Scheme 4). Indeed, the enol ether cyclic ketal **28** was only observed and characterised by ^{1}H NMR spectroscopy before it rearranged to **29**, thus precluding any study of its [2+2] photocycloaddition chemistry. However, in parallel investigations Nicolaou *et al.*[18] were able to achieve a synthesis of the macrocyclic ester-stabilised enol ether cyclic ketal compound **30** and then showed that it underwent facile intramolecular [2+2] photocycloaddition to produce the cyclobutane ring-fused structure **31** in high yield. Furthermore, some pioneering intramolecular [2+2] photochemical studies by Sullikowski *et al.*[19] with substituted ylidene butenolide precursors, *e.g.* **32** resulted in the elaboration of several of the critical elements of the cyclobutane ring-fused system **33** in bielshowskysin. Each of the aforementioned investigations therefore combined to give some credence to the earlier biosynthetic proposal to bielschowskysin **8** involving enol ether intermediates and [2+2] photocycloaddition (see Scheme 1)



Scheme 5. Model photochemical studies towards the cyclobutane ring-fused system in bielschowskysin **8**

Nevertheless, throughout the past decade synthetic chemists have concentrated their efforts towards bielschowskysin using non-biomimetic approaches, where both thermal and photochemical approaches to cyclobutane ring intermediates have all been carried out early-on in the synthetic designs. Most of these synthetic approaches to bielschowskysin, which are summarised elsewhere,[14] were thwarted however by the difficulties in achieving satisfactory macrocyclisation procedures from substituted cylcobutane ring-containing precursors. Interestingly, in some complementary investigations of the formation of the cyclobutane ring in bielschowskysin using quantum chemical calculations Tang *et al.*[20] concluded that whilst the photochemical pathway is computed to be highly efficient an alternative thermal process is also feasible in water *via* an unusual concerted ring-forming transition state without the intervention of an enzyme.

Moving forward from our own early model work, Roche *et al.*[21] took up the challenge of establishing the earlier described biosynthetic proposal to bielschowskysin **8** by examining a synthesis of the enol ether cyclic ketal **37** produced from the natural product acerosolide **5** and then studying its



Scheme 6. Synthesis of the macrocyclic *Z*-enol ether cyclic ketal **36** from acerosolide **5** followed by its isomerisation to **37** and intramolecular photochemical [2+2] photocycloaddition to the bielschowskysin analogue **38**.

intramolecular [2+2] photocycloaddition to the cyclobutane ring in the analogue **38** of bielschowskysin. Key to their success was the conversion of the epoxide **34** derived from acerosolide into the labile chlorohydrin **35** following treatment with TMSCl (Scheme 6). Halogen abstraction from the chlorohydrin **35** mediated by a Ag(I) salt, next led to the furanoxonium ion intermediate shown, which was intercepted under kinetic control at -78 °C by methanol to give the *Z*- enol ether cyclic ketal **36** (46% from the epoxide **34**). The *Z*-enol ether cyclic ketal **36** was found to be stable for three days in the dark, but when a solution in chloroform was irradiated at 254 nm through Pyrex it was isomerised to the *E*-isomer **37** which underwent intramolecular [2+2] cycloaddition leading to the polycycle **38** containing the bielschowsksin ring system. None of the synthetic steps to **38** were trivial, and the stereochemistry at the ketal C3 centre in **37** was shown to be critical to realise the final intramolecular [2+2] photochemical cycloaddition. Unlike bipinnatin J (**3**), the proposed biosynthetic precursor to bielschowsksin, acerosolide **5** has a CO_2Me rather than a Me group at C4, together with an *E*-rather than *Z*- double bond at C7,C8 and an additional carbonyl group at C14. Nevertheless, the study by Roche *et al.*[21] provides a significant blueprint for the biosynthesis of bielschowsksin **8** *via* an intramolecular [2+2] cycloaddition from an enol ether cyclic ketal intermediate as key step. We await further developments of this exciting biomimetic synthetic approach to bielschowskysin **8**.

3. Plumarellide and rameswaralide

Plumarellide **9** was isolated from the gorgonian coral *Plumarella* sp which inhabits the Kuri Island region of the Pacific ocean, in 2002.[8] It is characterised by having a central cyclohexene ring which is conjoint with a substituted cyclopentane and an oxy-bridged cycloheptene. The metabolite is structurally related to the earlier isolated mandapamates **39**[22] and **40**[23] found in soft corals of the genus *Sinularia* which are epimeric at C8 and have a CO_2Me group instead of a CH_2OH at C18 in their structures (Fig 4). Rameswaralide **10,** by contrast, has a central cycloheptene ring flanked by substituted cyclopentane and cyclohexene rings.[9] It co-occurs with the mandapamates **39** and **40** in *Sinularia dissecta,* and it was earlier suggested that rameswaralide could be derived *via* ring expansion of the 6-membered ring in a mandapamate *via* a novel vinylogous α-ketol rearrangement.[1] The four metabolites **9**, **10**, **39** and **40**, show subtle variations in the orientations of the C7 and C8 centres in their structures. Thus, whereas plumarellide **9** has an α-orientated OH group at C8, the same OH group in the

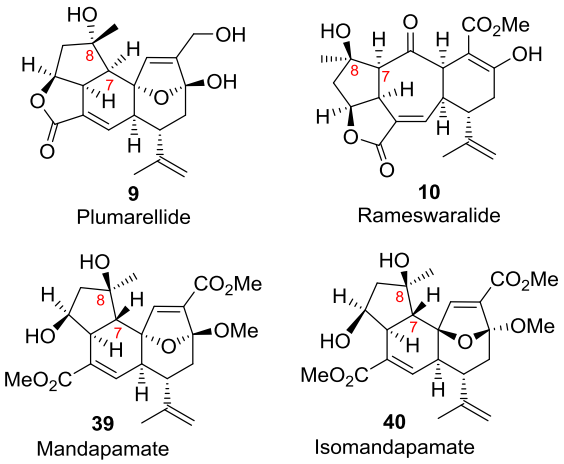
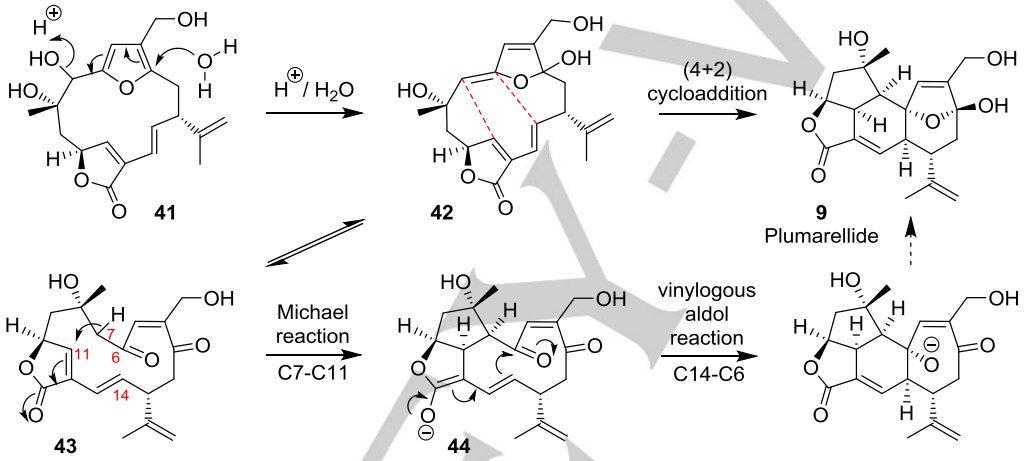


Figure 4. Natural products plumarellide **9,** rameswaralide **10** and the mandapamates **39** and **40**

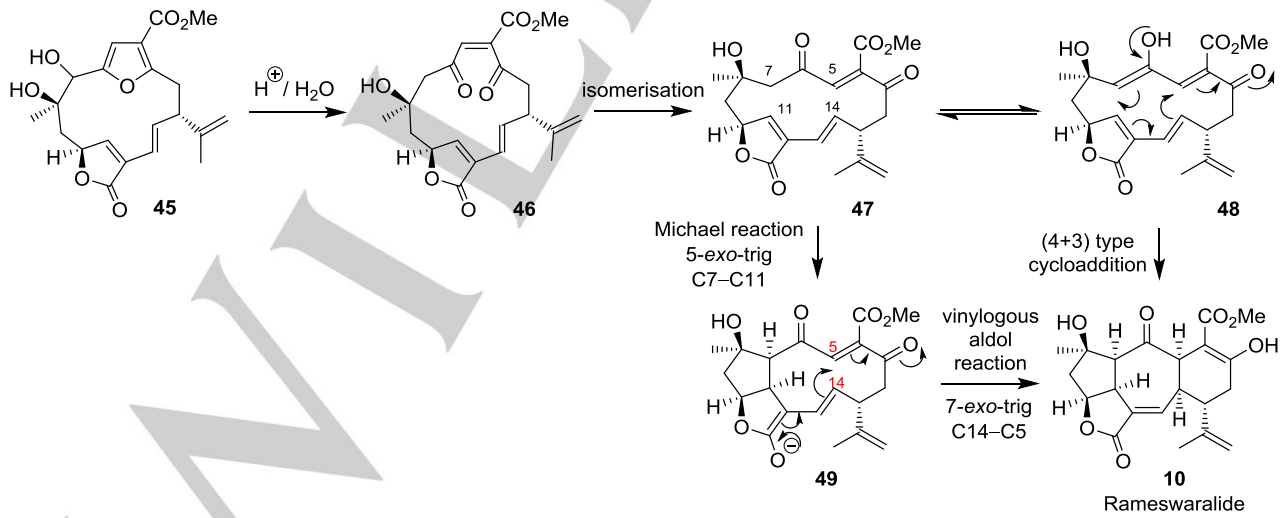
metabolites **10**, **39**, and **40** is orientated β instead. Also, whereas the bridged C7-H centre in **9** and **10** is α-orientated, the same centre in the mandapamates **39** and **40** has the alternative β-H stereochemistry. These differences clearly have significanceregarding the biosynthetic origins of the four metabolites.

It has been proposed that the fused ring systems in plumarellide **9** and rameswaralide **10** have their origins in FBC precursors, *viz* **41** and **45** which have unsaturation at C13-C14, by way of conversion into enol ether cyclic hemiketal intermediates, *e.g* **42** (*cf* bielshowsksin biosynthesis earlier) and/or enedone intermediates, *viz* **46**, followed by transannular (4+2) and (4+3) type cycloaddition reactions respectively, *viz* **42**→plumarellide **9**, and **48**→rameswaralide **10** (Schemes 7 and 8).[1,2] Alternative two-step ionic pathways to the same metabolites have also been proposed involving 5-*exo* trig cyclisation between C7 and C11 in the enedione tautomers **43** (for plumarellide) and **47** (for rameswaralide) (Schemes 7 and 8) followed by intramolecular vinylogous aldol reactions from the enolate intermediates **44** and **48** respectively.[1] The cyclohexene rings in the mandapamates **39** and **40** are thought to arise by way of a similar intramolecular (4+2) processes to that shown for plumarellide.

More recently, in 2016, Chitturi *et al.*[24] described the "pambanolide" structures **50** and **51** which were isolated alongside rameswaralide **10** and mandapamate **39** from the soft coral *Sinularia inelegans*. The authors suggested that pambanolide A (**50**) could be derived from mandapamate **39** *in vivo* following a reverse vinylogous aldol reaction leading to the same intermediate **49** proposed in Scheme 8 to ramesawaralide **10**. It seems more likely however that the natural product is



Scheme 7. Proposals for the biosynthesis of plumarellide **9** from the macrocyclic enol ether cyclic hemiketal **42** *via* intramolecular (4+2) type cycloaddition or *via* a two-step ionic process from the enedione **43** , *viz.* **43**→**44**→**9**



Scheme 8. Proposals for the biosynthesis of rameswaralide **10** from the macrocyclic polyene dione **47** *via* intramolecular (4+3) type cycloaddition or *via* a two-step ionic process, *viz*. **47**→**49**→**10**.

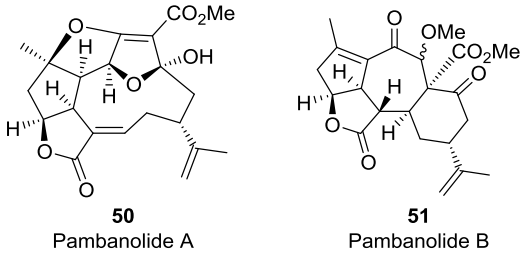


Figure 5. Structures of the pambanolides **51** and **52** from *Sinularia inelegans*.

derived from the FBC **45** *via* **49** followed by isomerisation to the *E*- enedione **52** and cyclisation to the bridged ether intermediate **54** (Scheme 9). Cyclic hemiketal formation from **54** would next lead to **53,** the positional isomer of pambanolide A (**50**). The intermediate **52** is also the likely precursor to pambanolide B (**51**) in *S. elegans* by addition of methanol at C5 triggering a Michael cyclisation across C4 and C13 leading to **55** which then eliminates water producing **51** (Scheme 10). Up until very recently a perplexing issue with the aforementioned biosynthetic proposals for plumarellide, rameswaralide and the mandapamates was that no FBC epoxide or similar precursor having 1,3-diene functionality between C11 and C14 had been described in corals. This changed in 2018 when Baker *et al.*[25] uncovered the keikipukalides **56** and **57**, displaying such unsaturation, in the deep sea octocoral *Plumarella delicatissima* collected from the "Plateau of Fascination" north east of Stanley, Falkland Islands in the Southern Ocean. The characterisation of the keikipukalides has given some credence to, and confidence in the broad proposals put forward in Schemes 7 and 8 to plumarellide **9** and rameswaralide **10.**

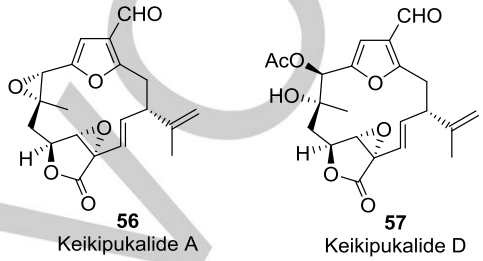
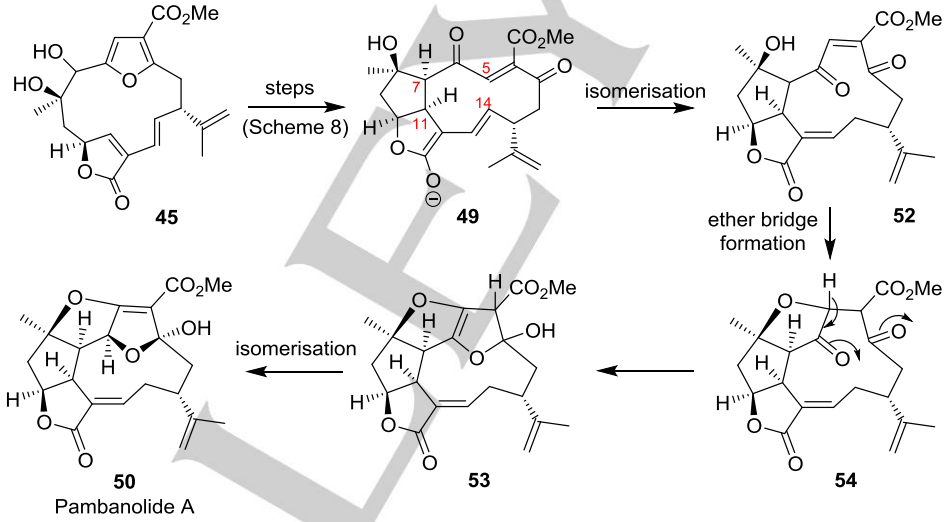
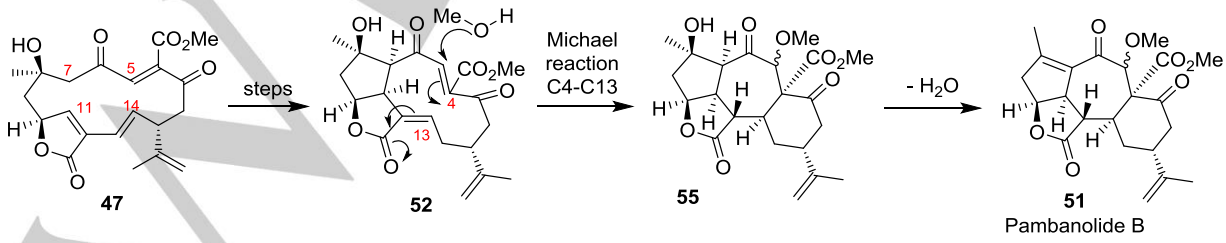


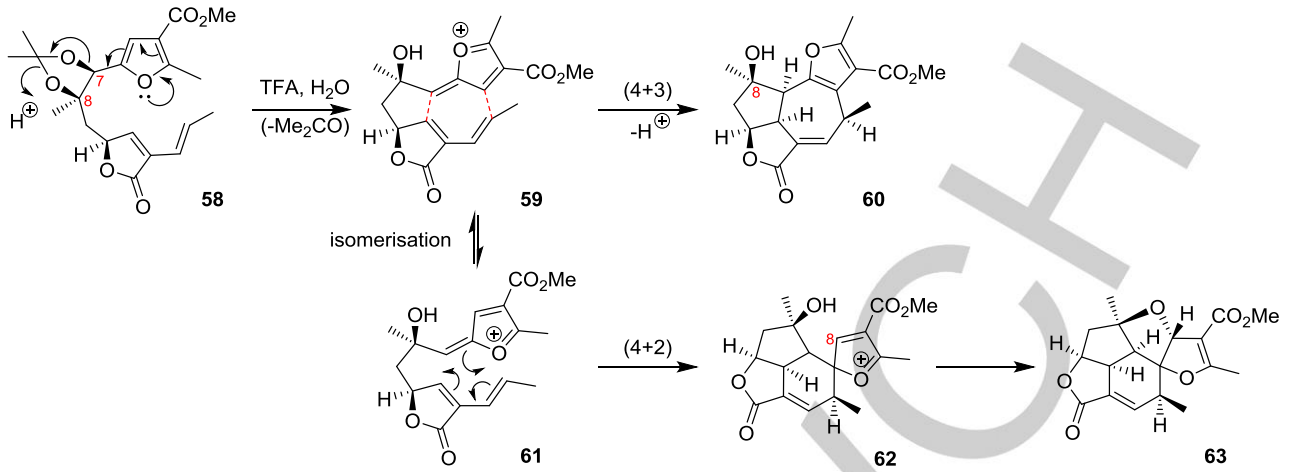
Figure 6. Structures of the keikipukalides **56** and **57** found in *Plumarella delicatissima*.



Scheme 9. Proposal for the biosynthesis of pambanolide A (**50**) from the FBC **45** *via* the enedione **52** and the cyclic ether **54** intermediates.

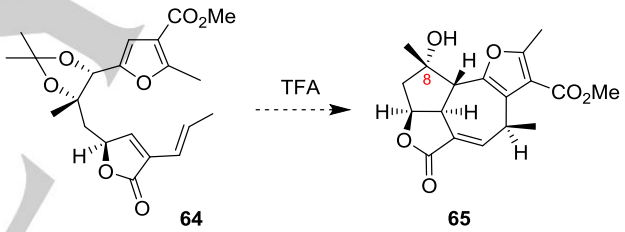


Scheme 10. Proposal for the biosynthesis of pambanolide B (**51**) from the enedione **47** *via* the tricylic intermediate **55** implicating concerted methanol addition and an intramolecular Michael reaction.

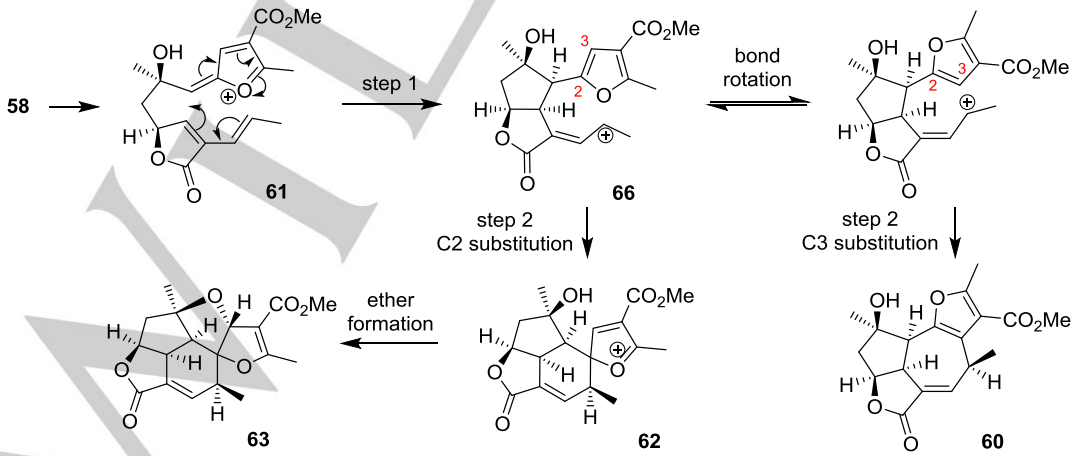


Scheme 11. Formation of the rameswaralide and plumarellide ring systems **60** and **63** respectively from acid treatment of the model furanobutenolide **58** implicating (4+3) and (4+2) type cycloadditions.

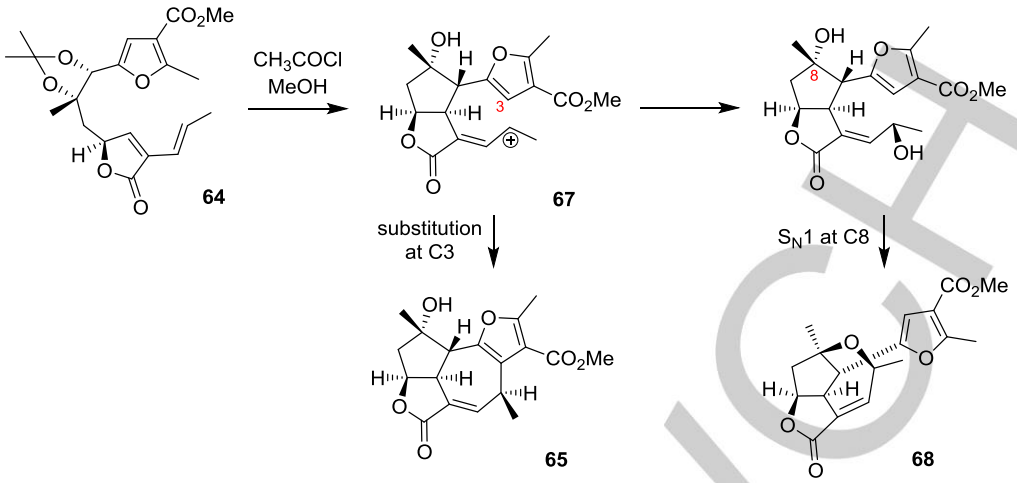
In pursuit of a unified biosynthetic approach to plumarellide and rameswaralide based on the proposals in Schemes 7 and 8, Pattenden and his group[26-28, 30-31] made an extensive study of the acid-catalysed transformations of the model C8 OH diastereoisomeric furanobutenolide acetonide isomers **58** and **64**. When the β-orientated C8 OH diastereoisomer **58** was treated with TFA in DCM it was hydrolysed to the *E*-and *Z*-isomeric furanoxonium ion intermediates **59** and **61** which then underwent separate transannular cyclisations producing a 7:5 mixture of the polycycles **60** and **63** containing the rameswaralide and plumarellide ring systems respectively in a combined 60% yield (Scheme 11). Perhaps not too surprisingly, treatment of the diastereoisomer **64** of **58**, having the alternative α-orientated OH at C8, under similar conditions gave only the C8 epimer **65** of the rameswaralide ring system **60** (with no plumarellide ring- containing by-product) (Scheme 12). It was proposed that formation of the diastereoisomeric rameswaralide ring-containing compounds **60** and **65** resulted from unprecedented (4+3) type cycloaddition reactions from furanoxonium ion intermediates, *viz* **59**. At the time these studies were carried out they were the first demonstrations of



Scheme 12. Formation of the rameswaralide ring system **65** from acid treatment of the model furanobutenolide **64**.



Scheme 13. Two-step carbonium ion cyclisation pathways for the conversion of the furanobutenolide **58** into the rameswaralide and plumarellide ring systems **60** and **63** respectively.

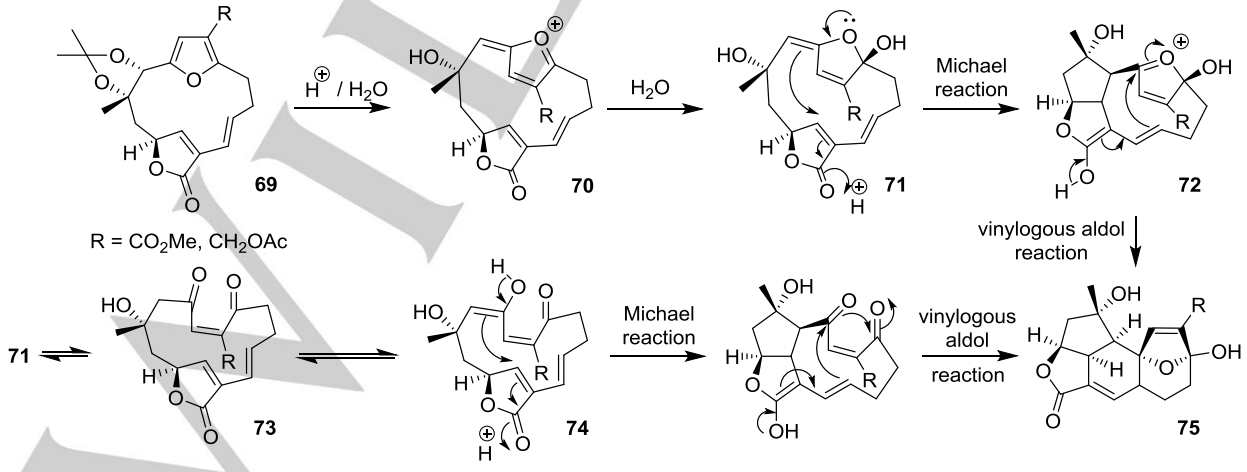


Scheme 14. Rationale for the formation of the 7-ring cyclic ether by-product **68** following treatment of the acetonide **64** with HCl.

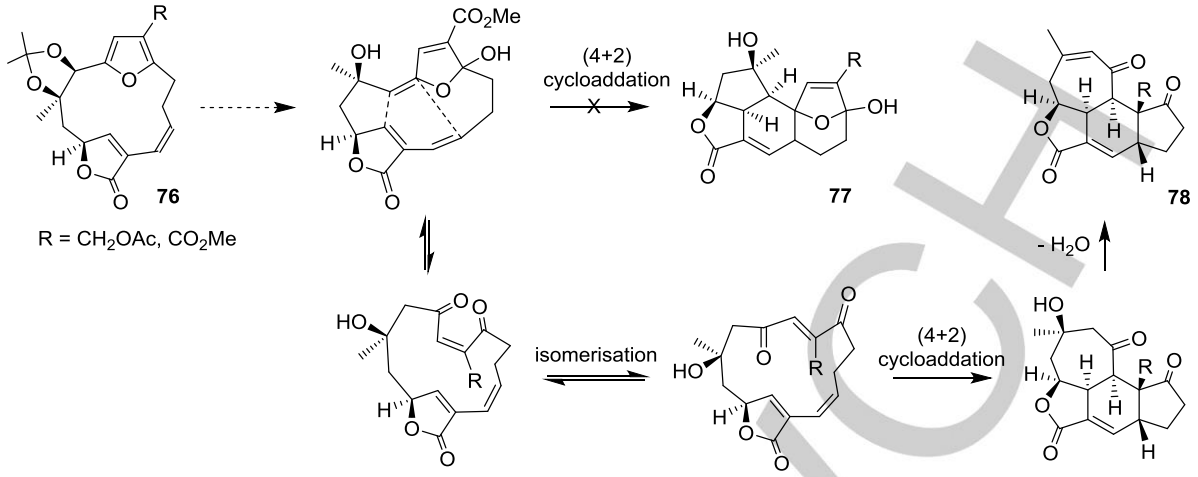
furanoxonium ions taking part in (4+3) cycloadditions. Later, Johan Winne *et al.* and other researchers greatly expanded the scope of this novel (4+3) cycloaddition process to the synthesis of different, related ring systems.[29,30]

The isolation of the cyclohexene plumarellide ring-containing compound **63**, (albeit "strapped" *via* an ether bridge), from acid treatment of the model furanobutenolide acetonide **58** gave some support to the (4+2) cycloaddition biosynthetic rational towards plumarellide put forward in Scheme 7. However it was also suggested that the conversion **58**→**63** might proceed by an alternative stepwise carbocation ion cyclisation sequence, *i.e.* **61**→**66** followed by **66**→**62** as shown in Scheme 13.[28] Likewise, the conversion of **58** into the rameswaralide ring-containing system **60** could also be represented as a two-step carbonium ion cyclisation sequence, *i.e.* **61**→**66** followed by **66**→**60**, rather than a (4+3) type cyclisation (Scheme 13). In an experiment, which gave some credence to this proposal, the diastereoisomeric acetonide **64** was treated with acetyl chloride–methanol (to generate HCl) in DCM and the presumed first-formed allylic carbocation intermediate **67** [*cf.* **66** Scheme 13] was intercepted leading to the interesting 7-ring ether **68** in 20% yield (Scheme 14) in addition to the expected rameswaralide ring-containing polycycle **65**.[27,31]

In complementary DFT calculation studies,[32] aimed at probing (4+2) and (4+3) intramolecular cycloadditions involving furanoxonium ion intermediates, the suggested alternative stepwise carbonium ion cyclisation reactions shown above, to plumarellide and to rameswaralide models **63** and **60** (Scheme 13), were shown to be highly probable, and indeed favour the products formed. DFT calculations were also made to compare the stepwise cyclisation pathway with the [4+2] cyclisation of the furanoxonium ion intermediate **70** produced from the macrocyclic FBC **69** leading to the tetracyclic ring system **75** present in plumarellide **9** (Scheme 15). In addition, since the cyclisation **70**→**75** could also take place by stepwise acid-catalysed cyclisation from the enedione tautomer **73** of **71** *via*



Scheme 15. DFT calculations on the alternative transannulation pathways from the FBC **69** to the polycycle **75** favouring the stepwise pathway **71**→**72**→**75**.



Scheme 16. Formation of the polycyclic structure **78** in preference to the plumarellide ring system **77** following acid-catalysed rearrangement of the C13, C14 unsaturated furanobutenolide-based acetonide **76**.

the enol **74**, these alternative cyclisation possibilities were also investigated. Overall, the DFT calculation studies predicted that the acid-catalysed stepwise carbonium ion pathway **71**→**72**→**75** was more favourable than the thermal [4+2] cycloaddition. Furthermore, the enedione **73** was found to be relatively more stable than its cyclic hemiacetal tautomer **71** which is relatively more stable than its enol tautomer **74**.

In other studies which were designed to achieve a biomimetic-type synthesis of the plumarellide ring system **77,** the *Z*-olefin isomer of the macrocycle **76** corresponding to **69** was synthesised and then treated with TFA.[33] Disappointingly, this experiment gave none of the plumarellide structure **77** and instead produced the interesting polycyclic structure **78** in 82% yield. The structure **78** is thought to arise from **76** by hydrolysis leading to an enol ether cyclic hemiketal intermediate followed by an intramolecular (4+2) cycloaddition process from its enedione tautomer, as shown in Scheme 16.[33]

The aforementioned studies, inspired by biosynthesis speculation, clearly provided a wealth of new synthesis and mechanistic knowledge on the complex pathways to the ring systems in plumarellide and rameswaralide implicating furanoxonium ions and their derivatives as central intermediates. Nevertheless, the studies are incomplete and further work by those who are excited by the challenge of designing and then evaluating biomimetic synthesis must come forward.

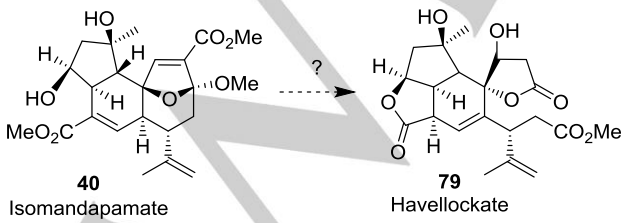


Figure 7. Proposed origin of havellockate **79** form isomandapamate **40**.

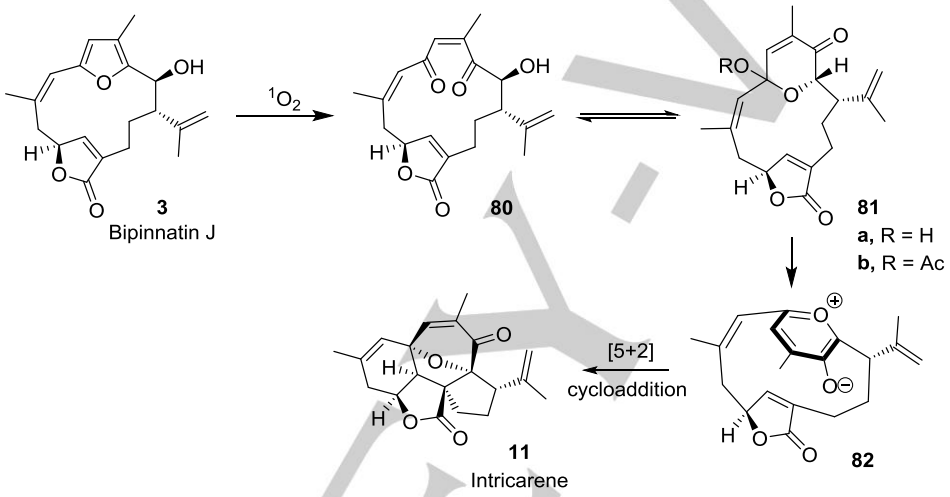
Over the past two decades a number of complementary *in vitro* approaches have been made towards the synthesis of the ring systems in the natural products **9, 10, 39** and **40**, and also to the related seco-cembranoid structure havellockate **79**,[34] which is likely to be derived from isomandapamate in *Sinularia granosa.* (Figure 7) Interested readers should study a recent comprehensive review of these synthetic approaches.[14]

4. Intricarene

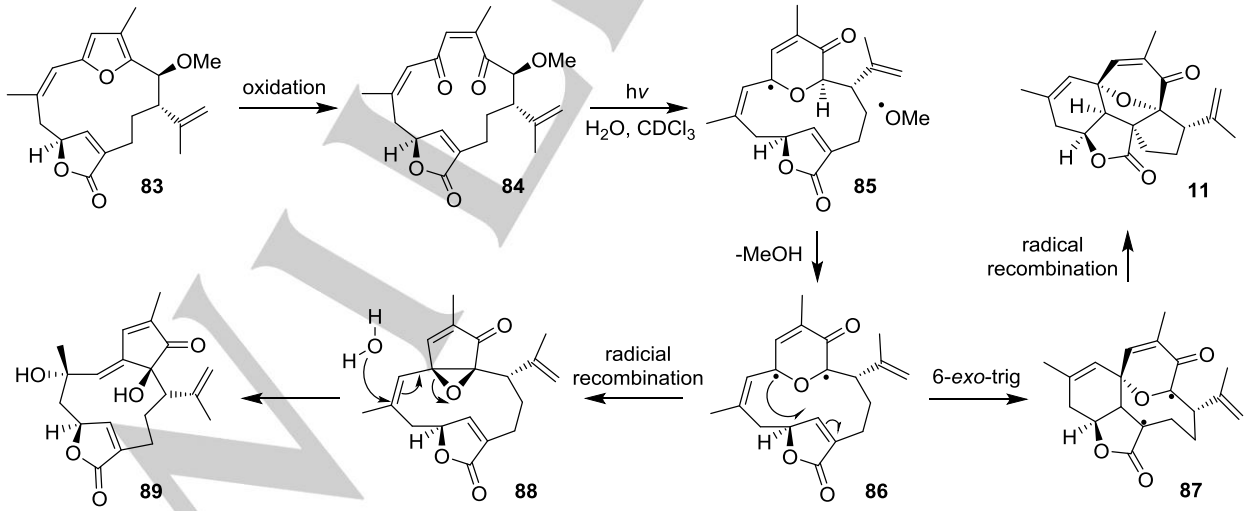
Intricarene **11** was isolated alongside bielschowskysin **8 f**rom the coral *Pseudopterogorgia kallos* by Rodrigues *et al.* in 2005.[10] An hypothesis for its biosynthesis from bipinnatin J (**3**) was put forward simultaneously by Trauner[35] and by Pattenden[36] which envisaged oxidative cleavage of the furan ring in bipinnatin J leading to the enedione **80** which should exist as the hydroxypyranone tautomer **81a**. Elimination of water from **81a** would next lead to the oxidopyrylium intermediate **82** which would be expected to undergo intramolecular dipolar [5+2] cycloaddition leading to intricarene **11** (Scheme 17). This proposed biosynthetic pathway was mimicked *in vitro* by the groups of both Trauner and Pattenden in almost identical fashion, and published in 2006.[35,36] Both research groups developed asymmetric syntheses of bipinnatin J (**3**) which they next oxidised using different oxidants to the hydroxyl pyranone **81a**, characterised as its acetate **81b.** Exposure of the acetate **81b** to DBU in refluxing acetonitrile (Pattenden) or to TMP in DMSO at 150 °C (Trauner) then produced intricarene in 10-26% yield. Tantillo *et al.*[37] later provided computational evidence that the key cycloaddition step **82**→**11** was feasible thermally with an activation barrier of approx. 20 kcal/mol^{-1}. On this basis therefore the aforementioned *in vitro* syntheses of intricarene, in hot refluxing solvents, could hardly be presented as “biomimetic”.

Later, in 2014 Trauner and colleagues,[38] made some interesting studies of the photochemistry of the enedione **84** which they produced from oxidation of the O-methyl ether **83** of bipinnatin J (**3**). Irradiation of a solution of **84** in 1:1 H_2O-deuterochloroform using ultraviolet light from a common reptile lamp remarkably led to intricarene **11** (25%) alongside the hydroxyl cyclopentenone **89**. Quantum chemical calculations provided an insight into the likely photochemical pathway from bipinnatin J methyl ether to intricarene and implicated the biradical intermediates **85, 86** and **87** (Scheme 18). Furthermore, they showed that the formation of the diradical pyrone intermediate **86** and the cycloaddition occur *via* a triplet state implicating a stepwise 1,3-dipolar cycloaddition. The formation of the by-product **89** is thought to arise from **86** through a radical recombination to the epoxycyclopentenone **88** which, by vinylogous nucleophilic addition of water leads to **89**. These interesting photochemical studies raised the question whether or not intricarene **11** is an actual natural product biosynthesised in the coral or whether it might be an artefact formed during the isolation procedure. To add to the debate, the O-methyl ether **83** of bipinnatin J has been isolated from *P. bipinnatis* and is the only C2 methyl ether of a furanocembranoid to be described. Perhaps this methyl ether is also an artefact, produced by methanolysis of bipinnatin J during isolation?

The total synthesis of intricarene described independently by Trauner and by Pattenden in 2006 was the first demonstration of the scope for biomimetic synthesis amongst the complex polycyclic cembranoids represented by structures **8**-**14**, and has remained a significant milestone in this area.



Scheme 17. Proposal for the biosynthesis of intricarene **11** involving an intramolecular dipolar [5+2] cycloaddition from the oxidopyrylium intermediate **82**



Scheme 18. A photochemical pathway to intricarene **11** from the methyl ether **83** of bipinnatin J implicating the biradical intermediates **85**-**87**

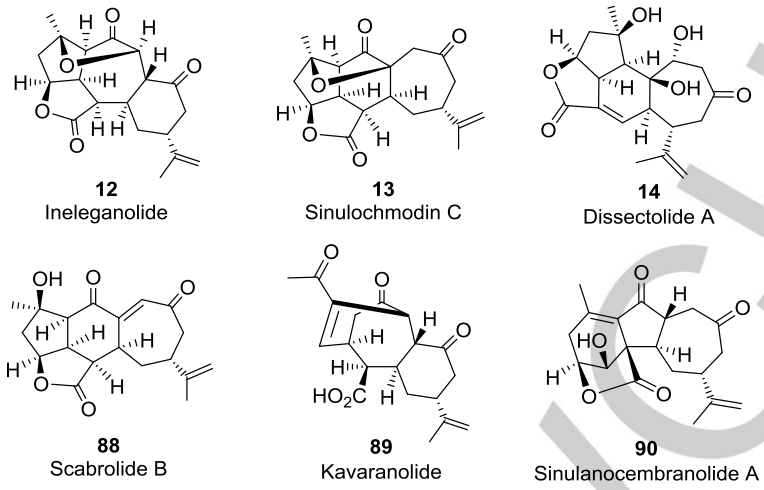
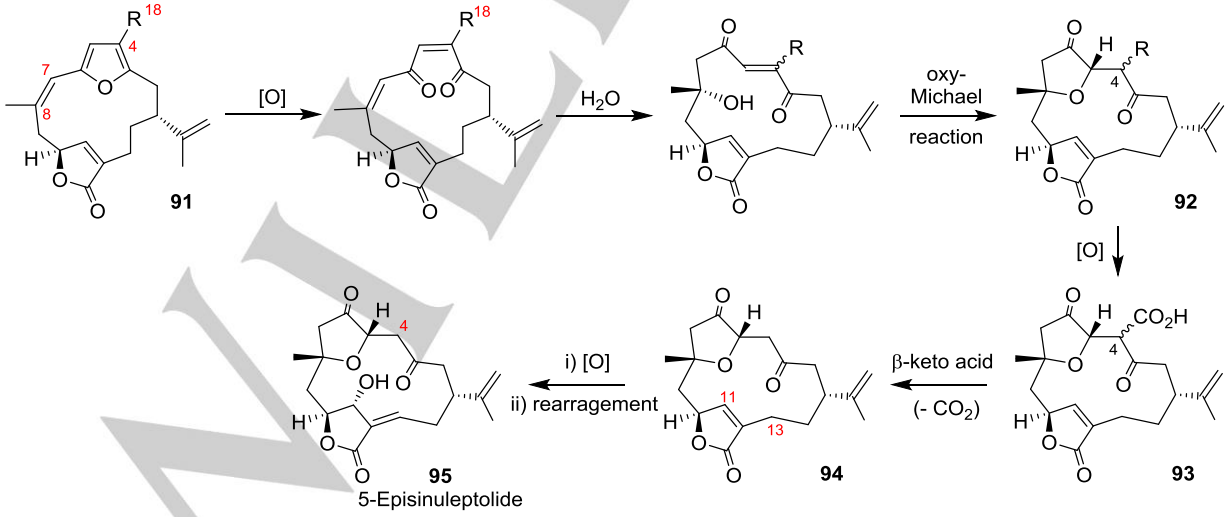


Figure 8. Some polycyclic C19 norcembranoids from soft corals of the genus *Sinularia*

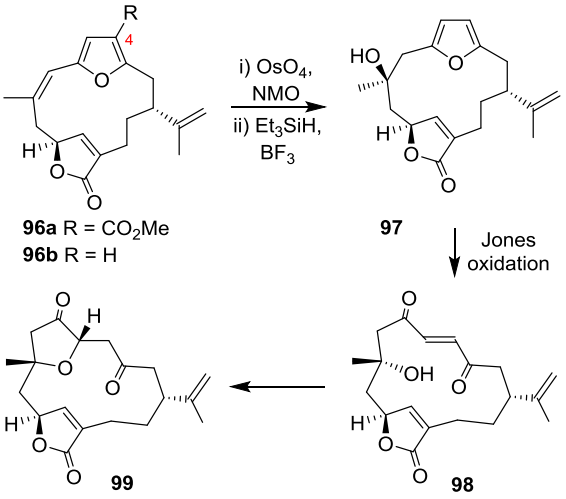
5. Ineleganolide and related norcembranoids

Polycyclic C_{19}-norcembranoids, represented by ineleganolide **12**,[11] sinulochmodin C (**13**),[12] dissectolide A (**14**),[13] scabrolide B (**88**),[39] kavaranolide **89**[40] and sinulanocembranolide A (**90**),[41] are found exclusively in soft corals of the genus *Sinularia*. Dissectolide A (**14**) and the antileukemic ineleganolide **12** were amongst the first members of this family to be characterised, during the 1990s, and in the early 2000s sinulochmodin C (**13**) and scabrolide B (**88**) were isolated from *S.lochmodes* and *S. scabria* respectively. Kavaranolide **89** and sinulanocembranolide A (**90**) are examples of more recently isolated norcembranoids from corals.

The polycycles in Figure 8 show several structural features in common with the C_{20}-polycyclic cembranoids discussed earlier, and they are often found in corals alongside C19 macrocyclic 3(2H)-furanone-based norcembranoids, particularly 5-episinuleptolide **95**, which lack a carbon constituent, (*i.e.* C18) at C4 in their structures. The 3(2H)-furanone ring in 5-episinuleptolide, and other norcembranoids, has its origins in oxidative cleavage of the furan ring in an FBC precursor, *e.g.* **91** followed by hydration and oxy-Michael cyclisation which first lead to **92** (Scheme 19).[6] The C18 group R in **92** is then lost, probably following decarboxylation from the β-keto acid intermediate **93** leading to **94**. Further oxidation and rearrangement involving C11-C13 in **94** would then produce 5-episinuleptolide **95**.[42] It is no coincidence that all FBCs that



Scheme 19. Proposal for the origin of the norditerpene 5-episinuleptolide **95** from the FBC **91** involving loss of the C18 substituent in the furanone intermediate **93**.

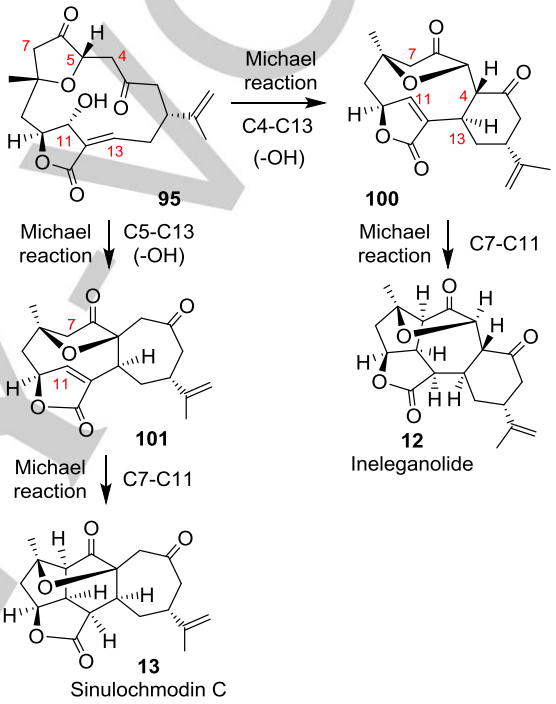


Scheme 20. A biogenetically patterned synthesis of norcembrenolide B (**99**) from norrubifolide **96b**.

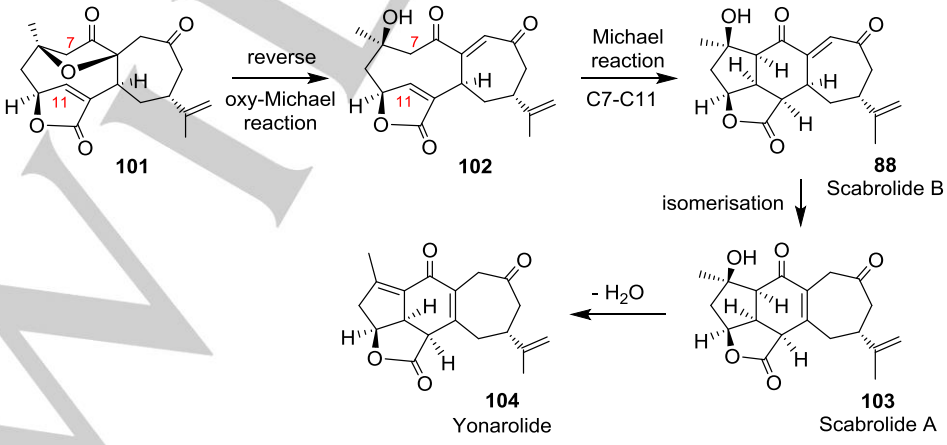
have been isolated from *Sinularia* accommodate a CO_2Me substituent at C4 in their structure. Although this biosynthesis proposal, in its entirety, has not been mimicked in the lab, *i.e.* from for example deoxypukalide **96a**, inspired by the speculated relationship between FBCs and furanone-based sinuleptolides, Theodorakis *et al.*[43] synthesised norrubifolide **96b**, R=H and showed that after its conversion into the C8 alcohol furanobutenolide **97**, oxidative cleavage of the furan ring led to the corresponding enedione **98** which cyclised spontaneously to the furanonebutenolide-based natural product norcembrenolide B (**99**) (Scheme 20).

Ineleganolide **12** and sinulochmodin C (**13**) occur with 5-episinuleptolide **95** in *Sinularia* and it has been proposed that the two polycyclic metabolites **12** and **13** come from the same furanone-based macrocyle **95** *in vivo* by successive transannular Michael reactions involving C4-C13 and C7-C1 for ineleganolide **12** and involving C5-C13 and C7-C11 for sinulochmodin C (**13**) (Scheme 21).[6]

It is likely that scabrolide B (**88**) is produced in *S. scabria* by way of a reverse oxy-Michael reaction and cleavage of the ether bridge in the cycloheptanone intermediate (**101**) to sinulochmodin C (or indeed the latter itself), leading to **102**, followed by a transannular Michael reaction (Scheme 22). The biosynthesis of the related metabolites scabrolide A (**103**) and yonarolide **104** follow from sequential isomerisation of scabrolide B (**88**) to scabrolide A (**103**), and dehydration of **103** to yonarolide (**104**).[6]



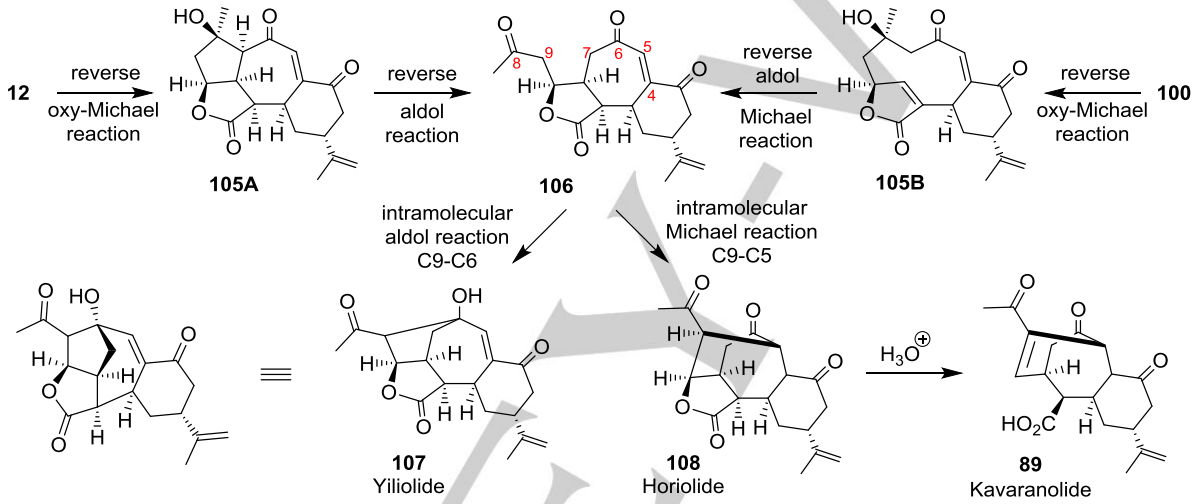
Scheme 21. Proposals for the biosynthesis of ineleganolide **12** and sinulochmodin A (**13**) from 5-episinuleptolide **95**



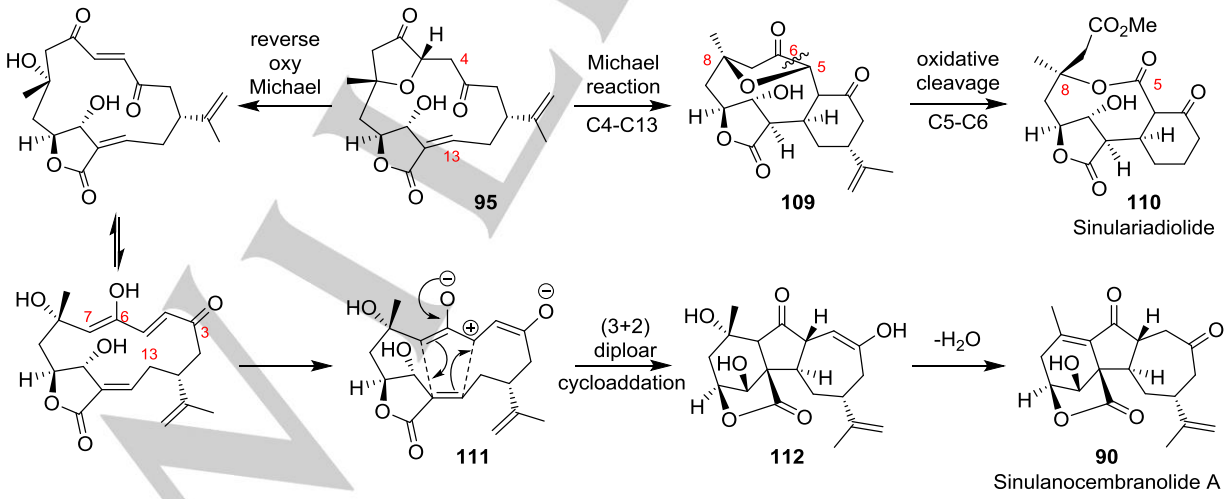
Scheme 22. Proposed biosynthesis of the scabrolides **88** and **103,** and of yonarolide **104**.

Kavaranolide **89**, which was isolated recently alongside ineleganolide **12** from *S. kavarattiensis*,[40] is probably produced *in vivo* from ineleganolide or its proposed biosynthetic intermediate **100**. Thus, a reverse oxy-Michael reaction in ineleganolide **12** or **100** would first lead to **105A** and **105B** respectively. Reverse aldol reactions from **105A** and **105B** would then give the key trione intermediate **106** (Scheme 23). An intramolecular Michael reaction from **106** would produce horiolide **108**, which has been isolated from an Indian ocean collection of *Sinularia* sp., and an acid-catalysed opening of the butyrolactone ring in **108** would then lead to kavaranolide **89** (Scheme 23). Interestingly, a competing intramolecular aldol reaction from **106** could produce the novel polycycle **107**, which has not yet been reported in Nature (see later discussion).

Several years before the discovery of ineleganolide the unusual metabolite sinulariadiolide **110** had been isolated together with 5-episinuleptolide **95** and yonarolide **104** from an Okinawan *Sinularia* species.[44] It seems likely that sinulariadiolide is derived from 5-episinuleptolide *via* oxidative cleavage of the cyclohexanone-based intermediate **109** which would be produced after Michael reaction between C4 and C13 in 5-episinuleptolide (Scheme 24).[45] It has also been proposed that the novel norcembranoid sinulanocembranolide A (**90**) found in *S. gaweli*,[41] is also derived from 5-episinuleptolide **95** by way of a reverse oxy Michael reaction followed by a novel intramolecular dipolar (3+2) cycloaddition, *viz* **111**→**112**, as the key step (Scheme 24).[46]



Scheme 23. Proposal for the biosynthesis of kavaranolide **89** and horiolide **108** from ineleganolide **12** or its precursor **100** *via* the key intermediate **106**.



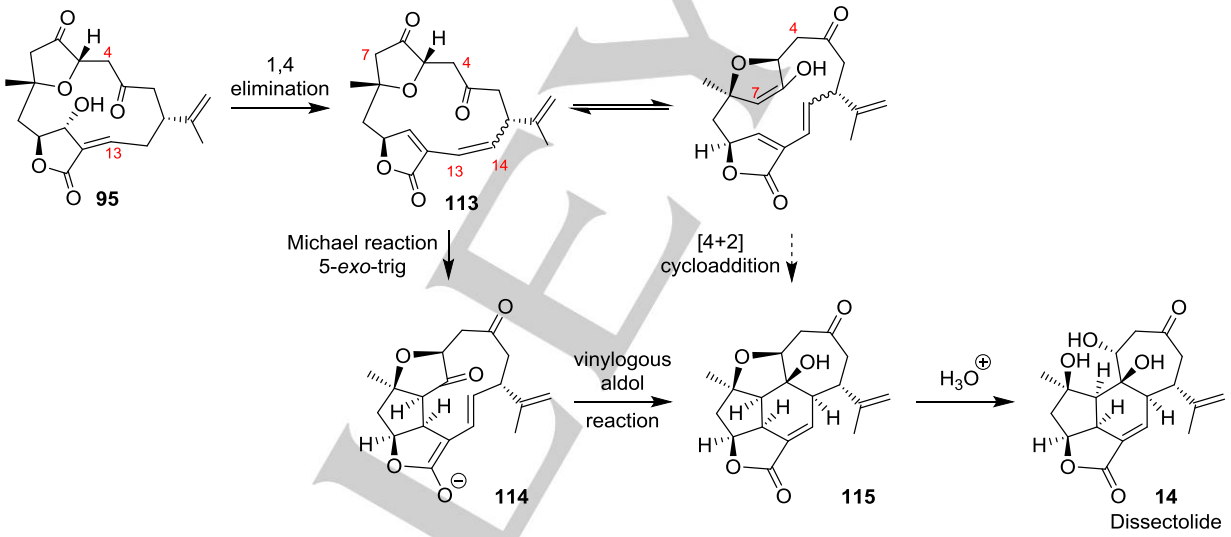
Scheme 24. Proposed origins of sinulariadiolide **110** and sinulnocembranolide **90** from episinuleptolide **95** featuring oxidative cleavage, **109**→**110**, and an intramolecular dipolar [3+2] cycloaddition, *viz* **111**→**112**.

An interesting biosynthetic route to dissectolide **14**, also from 5-episinuleptolide **95**, implicating either an intramolecular (4+2) cycloaddition from the diene intermediate **113** or a Michael cyclisation / vinylogous aldol process, **113**→**114**→**115**, has been put forward (Scheme 25).

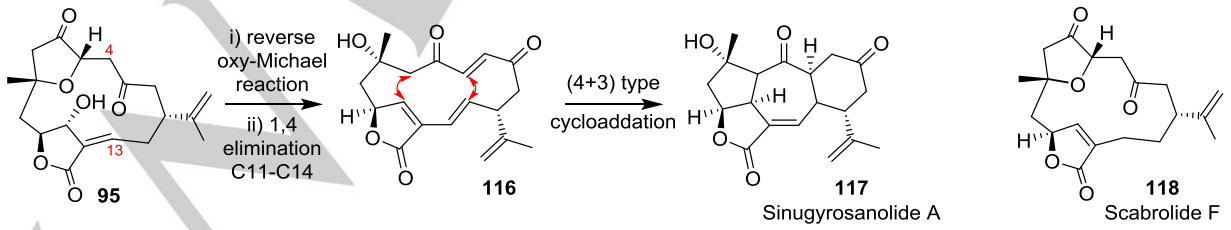
Sinugyrosanolide A (**117**) is yet another interesting 5,7,6 ring-fused norcembranoid which was isolated from the Formosan soft coral *S. gyrosa* in 2014.[47] This metabolite is also likely to be derived from 5-episinuleptolide **95** following a reverse oxy Michael reaction and concomitant 1,4-elimination between C11 and C14 in **95** leading to the intermediate **116** (Scheme 26). The macrocyclic trienedione **116** is nicely predisposed to take part in an intramolecular (4+3) type cycloaddition reaction leading directly to the natural product. The (4+3) cycloaddition **116**→**117** is similar to one of the proposals put forward for rameswaralide **10** discussed earlier. Sinugyrosanolide A (**117**) corresponds to C4 descarboxyrameswaralide and the authors who isolated the natural product have suggested that it might be derived *in vivo* from rameswaralide; the same authors have also put forward a more circuitous biosynthetic proposal to **117** from scabrolide F (**118**).

Over the past decade a number of chemists have made huge efforts to achieve a total synthesis of the highly oxygenated polycyclic norcembranoid ineleganolide **12**. Disappointingly, all of these synthetic efforts, although getting very close to the target, have so far been unsuccessful.[14]

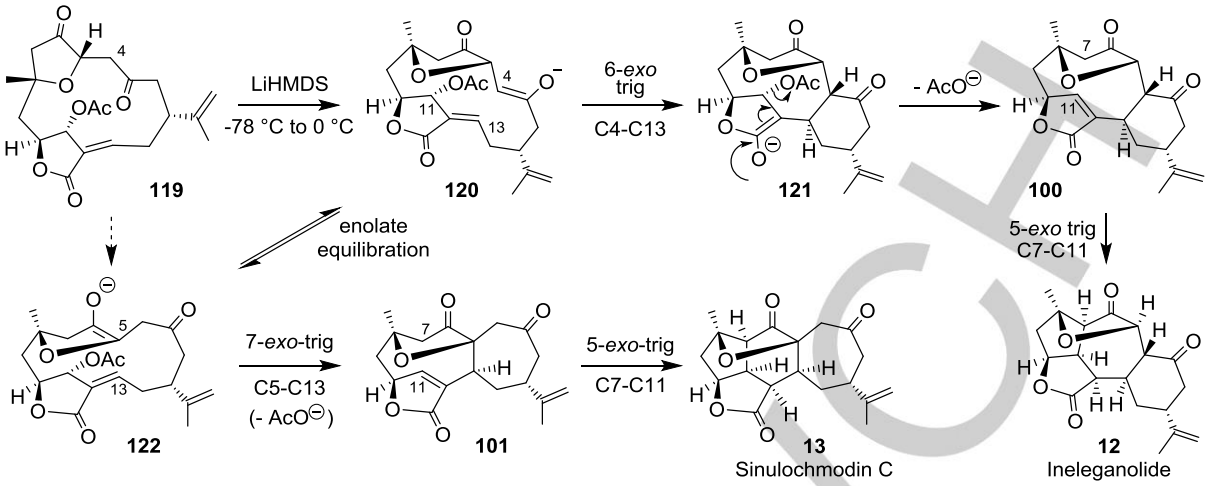
In 2011, very soon after its structure was published, Pattenden *et al.* rationalised the biosynthesis of ineleganolide **12** occurring from 5-episinuleptolide **95**.[6] Thus, we suggested that the 5,7,6 angular tricyclic ring system in ineleganolide was produced from the fourteen-membered ring system in 5-episinuleptolide **95** by way of successive transannular Michael reactions between the C4,C13 and C7,C11 centres in its structure. Furthermore, since sinulochmodin C (**13**) co-occurs with ineleganolide and 5-episinuleptolide in *Sinularia* it seemed probable that the corresponding 5,6,7 linear tricyclic ring system in sinulochmodin C (**13**) was also derived from 5-episinuleptolide by an alternative sequence of transannular Michael reactions involving the C5,C13 and C7,C11 centres in the latter. These proposals were set out earlier in Scheme 21. With a view to vindicating our proposals we obtained a small sample of natural 5-episinuleptolide which had been isolated from *Sinularia* sp, through the generosity of Professor J-H. Sheu, National Sun Yat-sen University, Taiwan). In the lab we found that 5-episinuleptolide **95** remained unchanged on treatment with bases and hence we prepared the corresponding acetate **119**



Scheme 25. Proposal for the origin of dissectolide **14** from 5-episinuleptolide **95** implicating the vinybutenolide intermediate **113**.



Scheme 26. Proposals for the biosynthesis of sinugyrosanolide A (**11**) from 5-episinuleptolide **95**.



Scheme 27. Biomimetic synthesis of ineleganolide **12** and sinulochmodin C(**13**) from 5-episinuleptolide acetate **119** in the presence of lithium HMDS.

To our satisfaction when a solution of the acetate **119** in THF was treated with lithium hexamethydisilazide (LiHMDS) at -78 °C to 0 °C, work-up gave a mixture of ineleganolide **12** and sinulochmodin C (**13**) (*ca.* 80% crude) which was cleanly separated by chromatography.[48] The straightforward one-pot conversion of 5-episinuleptolide into ineleganolide and sinulochmodin C in the presence of LiHMDS seems quite remarkable and provided convincing support for the biosynthesis proposals we made earlier to these novel structures. Interestingly, several months after this work was published, Yen *et al*.[49] isolated 5-episinuleptolide acetate **119** from a soft coral *Sinularia* sp collected off the coast of Taiwan.

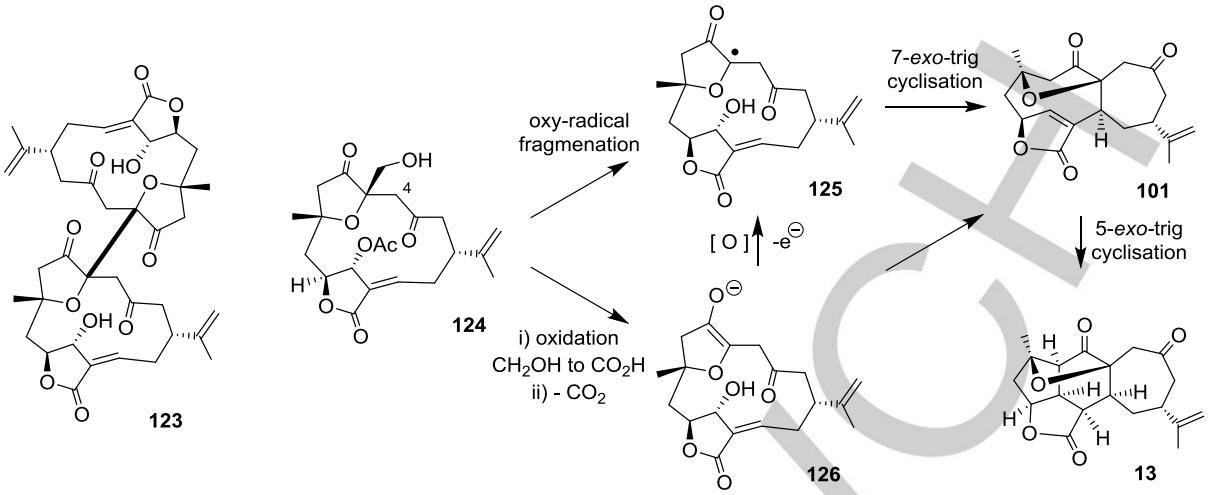
It seems likely that, as proposed, the angular 5,7,6-ring fused system in ineleganolide **12** is produced by initial deprotonation of the more sterically accessible C4 centre in the acetate **119** leading to the enolate **120** which then undergoes 6-*exo* trig cyclisation producing intermediate **121** (Scheme 27). Displacement of the acetate in **121** next leads to **100** which undergoes deprotonation at C7 followed by 5-*exo* trig cyclisation providing ineleganolide **12**. The isomeric linear 5,6,7-ring fused system in sinulochmodin C (**13**) most likely arises from the enolate **122** produced from equilibration with **120** [or directly from the acetate **119**] by 7-*exo* trig cyclisation between C5 and C13 accompanied by displacement of the OAc group at C11 leading to **101** followed by 5-*exo* trig cyclisation between C7 and C11 in the latter (Scheme 27).

Intriguingly, when 5-episinuleptolide acetate **123** was treated with *sodium* instead of lithium HMDS at higher temperature, *i.e.* -40 °C to -10 °C a clean reaction gave the new polycyclic norcembranoid **107** in 75% yield.[48] The new structure **107,** which we have named yiliolide, has not yet been reported as a natural product but it clearly has features in common with horiolide **108** and kavaranolide **89** found in *Sinularia.* As we have discussed earlier in Scheme 23 we suggest that similar to its isomers **108** and **89**, yiliolide is produced from ineleganolide by way of a competitive aldolisation reaction from the key intermediate **106** which leads to horiolide and kavaranolide *in vivo*.

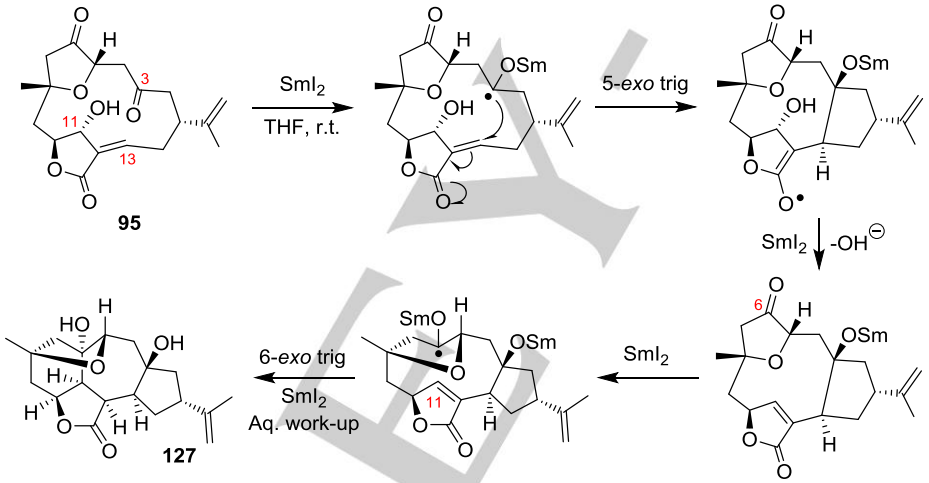
It is interesting that the biosynthetic speculations presented above, leading to the formation of polycyclic norcembranoids in soft corals of the genus *Sinularia*, all start from the same 3(2*H*)-furanone ring-based macrocycle 5-episinuleptolide **95**. This metabolite was first reported in 1978 but since then a number of related furanone structures with different oxidation patterns between C11-C13 and stereochemistry at C5 and C8 have been described.[6]

More interestingly, Sheu *et al.*[50] have isolated the C20 isocembranoid **124** and the episinuleptolide dimer **123** alongside 5-episinuleptolide **95** and sinulochmodin C (**13**) from *S. lochmodes* (Scheme 28) which has raised the question whether or not carbon centre radicals, *e.g* the furanone radical **125** rather than the enolate **126** (*cf*. **122** in Scheme 27) might be involved in the biosynthesis of sinulochmodin C and, indeed, other polycyclic norcembranoids.[6]

Carbon centred radicals are often suggested as intermediates in biosynthetic pathways and can be produced *in vivo* in a variety of ways, including photochemical excitation, electron transfer and oxidation reactions. The particular captodative radical **125** is relatively stable and it is not surprising that it dimerises to **123** *in vivo*. However, efforts to synthesise sinulochmodin C (**13**) *via* **125** from treatment of 5-episinuleptolide **95** with a number of radical-initiating conditions have not been successful.[46] Albeit interesting, treatment of **95** with samarium diiodide instead led to the 6,7,5-ring fused polycyclic structure **127** in 62% yield (Scheme 29) instead of to sinulochmodin C (**13**).[46] The jury remains out therefore as to whether radical intermediates might be involved in any of the biosynthetic sequences presented here leading to polycyclic norcembranoids from episinuleptolide.



Scheme 28. Proposal for the biosythesis of sinulochmodin C (**13**) implicating the radical intermedate **125**.

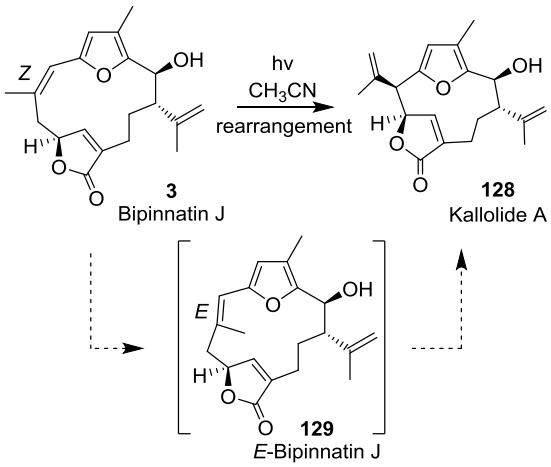


Scheme 29. Proposal for the origin of the polycycle **127** resulting from treatment of 5-episinuleptolide **95** with samarium diiodide in THF.

6. Other cembranoid-derived secondary metabolites

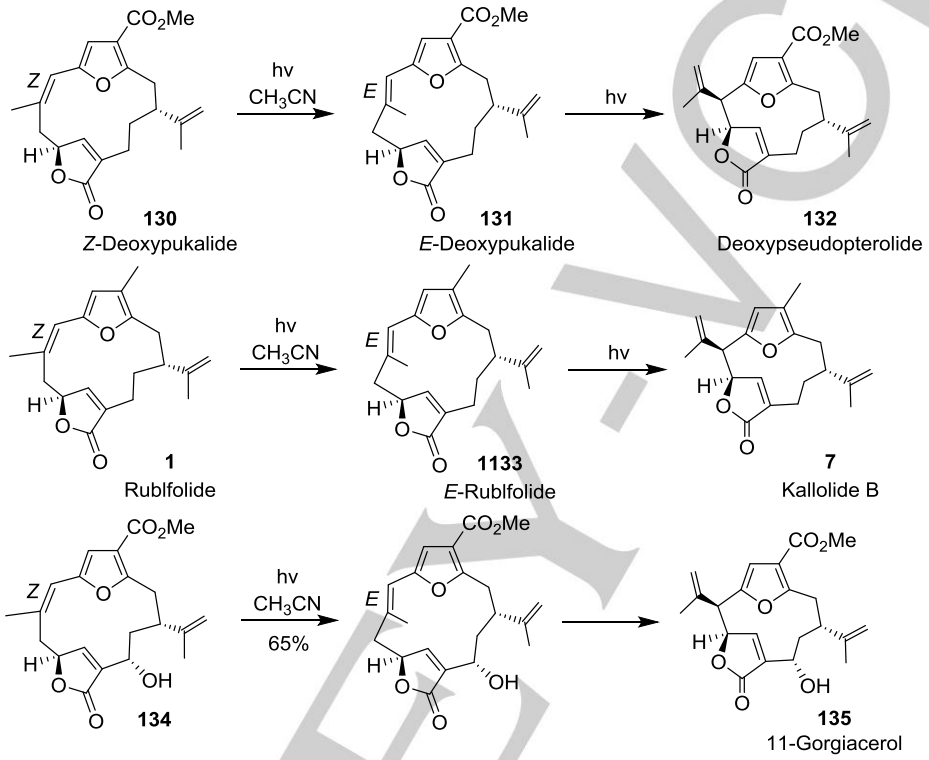
Pseudopteranes (also known as kallolides) are macrocyclic 12-membered ring furanobutenolide-based cembranoids which were first isolated from *Pseudopterogorgia* sp during the 1980s.[51,52] In 1998 Rodrigues *et al.*[53] isolated kallolide A (**128**) alongside bipinnatin J (**3**) from *P. bipinnata* and found that when they irradiated a solution of bipinnatin J in acetonitrile with a medium pressure Hg lamp through Pyrex it underwent facile ring contraction to kallolide A (Scheme 30). This single photochemical (biomimetic) reaction, for the first time, established the biogenetic relationship between a 14-membered furanobutenolide-based cembranoid and its 12-membered ring isomer.

More recently, following the characterisation of *Z*-and *E*-isomers, **130** and **131** respectively, of deoxypukalide in the Pacific coral

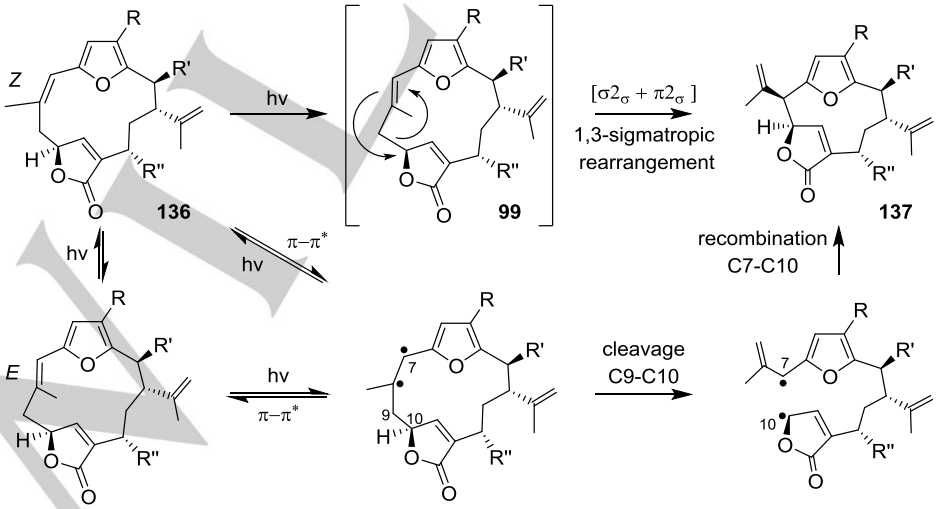


Scheme 30. Photochemical ring contraction of bipinnatin J (**3**) to the 12-membered ring-containing kallolide A (**128**).

Leptogorgia Pattenden *et al*.[54] examined the photochemical behaviour of (*Z*)-bipinnatin J (**3**) in more detail alongside that of naturally occurring *Z*-deoxypukalide **130** and *Z*-rubifolide **1**. In each study it was found that short irradiation times resulted only in isomerisations of the *Z*- alkene bonds in **3**, **130** and **1** leadingto the corresponding *E*-isomers **129**, **131** and **133** respectively. However, when the same irradiations were continued for longer periods of time the anticipated ring contractions occurred from the intermediate *E*-isomers leading to kallolide A (**128**), deoxypseudopterolide **132** and kallolide B (**7**) respectively (Scheme 31). Deoxypseudopterolide **132** was first described alongside acerosolide **5** in *Pseudopterogorgia* corals during the 1980s. The closely related 11-gorgiacerol **135** and its C11 epimer were later found in the coral *P. acerosa,*



Scheme 31. Photochemical *Z*→*E* isomerisations of *Z*- FBCs followed by 14→12-membered ring contractions leading to pseudopteranes and kallolides..

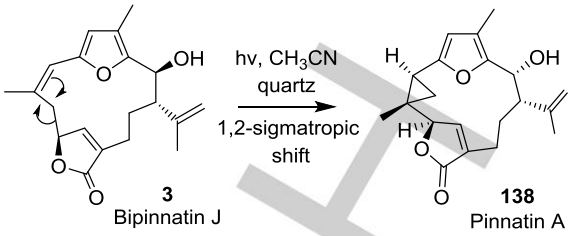


Scheme 32. Proposed 1,3-sigmatropic rearrangement and radical mechanisms for the photo-induced ring contractions of FBCs to pseudopteranes/kallolides.

and Mulzer *et al.*[55] have described a biomimetic synthesis of **135** and also its C11 epimer following irradiation and ring contraction of the *Z*-configured C11 epimeric FBC **134**.

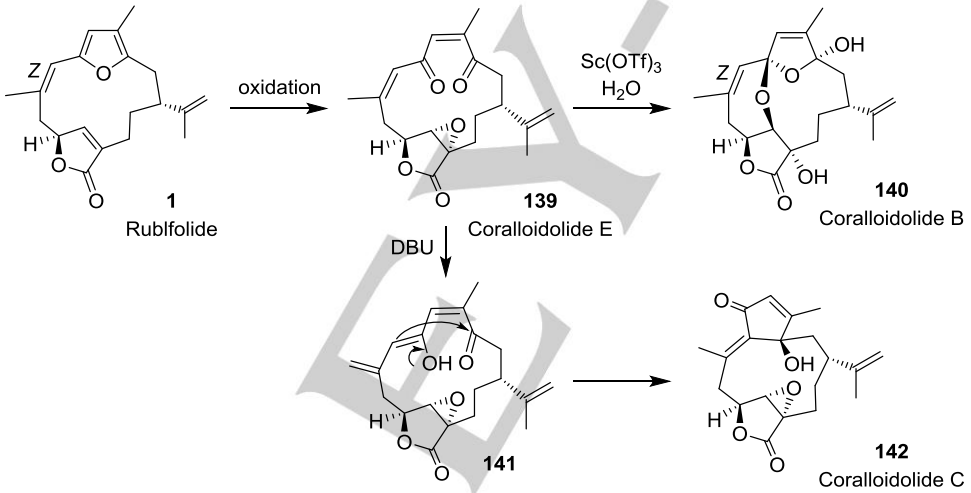
The 14→12-membered ring contractions shown in Schemes 30 and 31 are stereospecific 1,3-sigmatropic rearrangements, *i.e.* **136**→**137** (Scheme 32), which are allowed photochemically. The isomerisations of the *Z*-FBCs to the corresponding *E*-isomers, which seem necessary prior to ring contraction, are initiated by π-π* excitation of the C7,C8 alkene bonds in **136**. It is also possible therefore to represent the same 14→12-membered ring contractions proceeding *via* the radical pathway shown in Scheme 32.[56]

Interestingly, Rodrigues *et al.*[53] also found the novel cyclopropane ring-containing pinnatin A (**138**) (<0.5% yield) alongside kallolide A (**129**) after irradiation of bipinnatin J (**3**) through quartz instead of Pyrex. Furthermore, pinnatin A has been found with kallolide A and bipinnatin J in *P.bipinnata*. The "biomimetic" isomerisation of bipinnatin J (**3**) into pinnatin A (**138**) is accompanied by complete epimerisation of the OH group at C2, and has been represented as a [$\alpha 2_s+\pi 2_s$] cycloaddition reaction (Scheme 33).

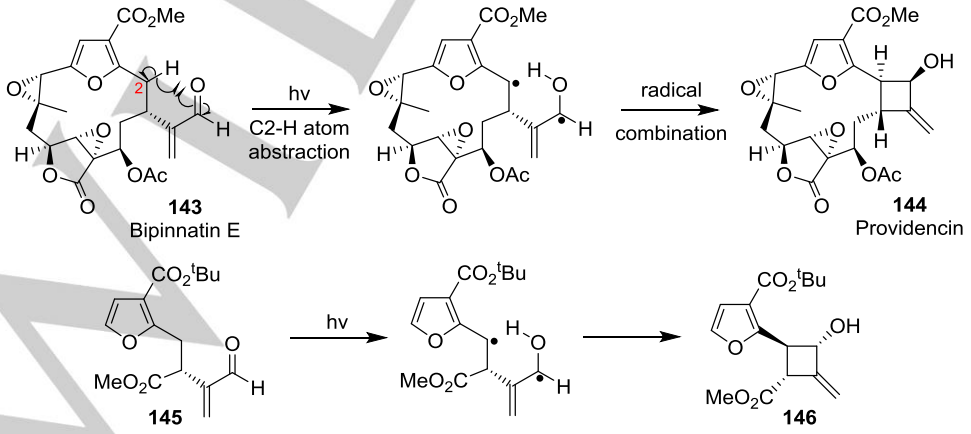


Scheme 33. Photochemical 1,2-sigmatropic rearrangement, accompanied by epimerisation at C2, of bipinnatin J (**3**) leading to pinnatin A (**138**).

Coralloidolides B (**140**) and C (**142**), found in the Mediterranean coral *Alcyonium coralloides,* are examples of another family of natural products whose biosynthesis Trauner[57] and others[5] proposed to be from the FBC rubifolide **1** by oxidation and oxidative cleavage to the epoxy enedione **139** (coralloidolide E)



Scheme 34. Biomimetic syntheses of coralloidolides from rubifolide **1** following oxidation cleavage and skeletal rearrangement.



Scheme 35. A proposed C-H insertion reaction leading to the methylenecyclobutanol unit in the biosynthesis of providencin **144** from bipinnatin E (**143**)

followed by skeletal rearrangement. Trauner and his group later synthesised coralloidolide E (**135**) from rubifolide **1** which, after extensive experimentation, they were able to convert into coralloidolide B (**140**) on treatment with hydrated scandium triflate (Scheme 34).[57] In other biomimetic experiments, treatment of **139** with DBU was shown to lead to coralloidolide C (**142**) presumably *via* an intramolecular aldol reaction from the enol intermediate **141**.

This Perspective would not be complete without a brief mention of the unique cyclobutane-ring containing metabolite providencin **144** isolated from *P. kallos*, if only to acknowledge the considerable amount of effort that has been committed to its synthesis in the lab. over the past decade.[58] The biosynthesis of the methyleneyclobutanol ring in providencin is most likely produced *in vivo* from bipinnatin E (**143**) by a photochemical route implicating an intramolecular insertion reaction (Norrish-Yang type) of the CHO functionality at C16 into the C-H bond at C2 in **143** (Scheme 35).[59] Indeed this novel C-H insertion reaction, which was unprecedented, has been modelled successfully using the furan substrate **145** which on irradiation was shown to lead to the substituted methylenecyclobutanol **146** in acceptable yield.[59]

An alternative proposal to the cyclobutane ring in providencin implicating initial cyclisation of a carbocation at C2 into a propenyl residue at C1 followed by further specific oxidation seems less attractive.[58a] Nevertheless, a non-biomimetic route has been developed to 17-deoxyprovidencin which allows at least the final part of this alternative biomimetic proposal to be evaluated. In addition, Tang and Paton,[60] have recently used DFT calculations to assess the C-H insertion proposal to providencin and they show that not only is the cyclisation possible but the stereochemical outcome of the cyclisation is consistent with that found in providencin.

7. Concluding remarks

In the absence of any biosynthesis studies, speculations on the likely origins of secondary metabolites will always be considered by some as “an interesting paper exercise”. Nevertheless, the speculations presented in this personal Perspective, have led to plausible biomimetic syntheses of the marine natural products intricarene **11**, ineleganolide **12** and sinulochmodin C (**13**), in particular, and also to the pseudopteranes / kallolides, *e.g.* **7** and coralloidolides, *e.g.* **137**. In addition, other biomimetic studies have provided a wealth of new synthetic and mechanistic knowledge particularly on the complex pathways to the ring systems in beilschowskysin **8**, plumarellide **9** and rameswaralide **10** involving novel furanoxonium ions as key intermediates.

It goes without saying that the isolation of similar secondary metabolites from the same organism does not always signal that one is the actual precursor of another. Indeed there is evidence that some metabolites isolated from corals are actually biosynthesised by the symbiotic microorganisms that the coral frequently shelters. There is also the issue that some of the compounds isolated from corals are not natural products at all, but in fact artefacts of the isolation procedures formed during work up, *i.e* by oxidation and /or photochemical processes.

A range of oxidation processes have been invoked in the speculated biosynthetic pathways to polycyclic cembranoids from FBCs in corals described here, and although we know little about the enzymes that are involved those based on P450 monoxygenases are surely implicated. Other oxidations triggered by light are also rife. The photon is also the “reagent” in a number of biosynthetic C-C bond forming reactions and rearrangements, and it is not possible to avoid implicating radical intermediates in many of these processes, *cf.* intricarene and the pseudopteranes.

An arsenal of common ionic reactions, particularly Michael reactions and aldol processes (and their reverse processes), and cycloaddition (including dipolar) reactions are implicated in the speculations presented in this Perspective. Indeed the subtle balance of competing aldol and Michael reactions which lead from 5-episinuleptolide **95** to ineleganolide **12**, sinulochmodin C (**13**) and yiliolide (**107**) is really quite mind-boggling !

Similar to designing a synthetic route to a complex natural product structure, there is nothing more satisfying than speculating on the likely biosynthesis of the same complex structure and then vindicating your proposal in the lab. You feel you have not only accomplished a challenging target but that you have also uncovered some of Nature’s secrets.

This will probably be the final contribution that Gerry Pattenden will make to this area, and I hope that the beauty and complexity of the structures of polycyclic cembranoids found in corals, alongside the variety of biological properties they display, will continue to entice and challenge the next generation of chemists to further explore their total synthesis and biomimetic synthesis for several years to come.

Acknowledgments

We are greatly indebted to the ever-diminishing number of creative natural product isolation scientists who have delivered a wide variety of intriguing structures over the past decades to excite and challenge the imaginations of we mere synthetic chemists.

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Keywords: Biomimetic synthesis • Cycloaddition • Natural products • Macrocycles • Furanobutenolide-cembranoids

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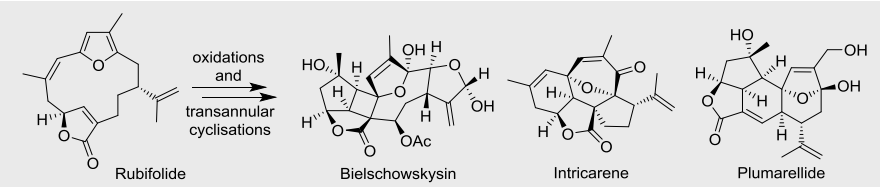

Macrocyclic furanobutenolide-based cembranoids are precursors to a wide variety of complex ring-fused diterpene structures in corals, implicating a wide variety of oxidation and transannlar cyclisations. This article gives a personal perspective on the speculations that underpin these biosynthetic interrelationships and summarises biomimetic synthesis studies designed to probe these speculations.

Biomimetic synthesis • Natural products •

*Matthew J. Palframan[a] and Gerald Pattenden**

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Biosynthetic interrelationships within polycyclic cembranoids isolated from corals. Conjecture, biomimetic synthesis and reality.