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Structural diversity and chemical synthesis of peroxide and peroxide-derived polyketide metabolites from marine sponges

Matthew D. Norris and Michael V. Perkins*

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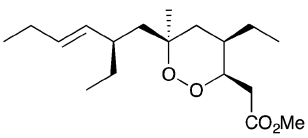
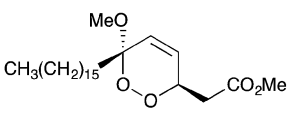
Marine sponges are widely known as a rich source of natural products, especially of polyketide origin, with a wealth of chemical diversity. Within this vast collection, peroxide and peroxide-derived secondary metabolites have attracted significant interest in the fields of natural product isolation and chemical synthesis for their structural distinction and promising *in vitro* antimicrobial and anticancer properties. In this review, peroxide and peroxide-derived polyketide metabolites isolated from marine sponges in the past 35 years are summarised. Efforts toward their synthesis are detailed with a focus on methods that utilise or attempt to elucidate the complex biosynthetic interrelationships of these compounds beyond enzymatic polyketide synthesis. Recent isolations, advances in synthetic methodology and theories of biogenesis are highlighted and critically evaluated.

1. Introduction

Organic extracts of marine sponges from all corners of the globe often exhibit promising *in vitro* antimicrobial and anticancer properties, prompting further exploration to identify and characterise the constituent metabolites. In 1978, Faulkner examined the crude ethanol extracts of *Plakortis halichondrioides* and attributed the sample's notable growth inhibition of *Staphylococcus aureus* and *Escherichia coli* to the major product isolated, plakortin.[1] Structural elucidation by spectroscopic methods and chemical degradation revealed 1,2-dioxane **1** as the identity of plakortin.[2] Near the same time, a novel peroxyketal metabolite, chondrillin (**2**), was isolated from a marine sponge of the genus *Chondrilla*.[3] Compound **2** and a number of natural analogues were shown to be cytotoxic against mouse leukaemia cells and were activators of sarcoplasmic reticulum Ca^{2+} ATPase.[4,5]



plakortin (**1**)



chondrillin (**2**)

With unique peroxyheterocyclic core structures and compelling therapeutic potential, compounds **1** and **2** have inspired numerous research programs in the fields of natural product isolation, chemical synthesis and medicinal chemistry since the late 1970s. The class has now expanded to include

School of Chemical and Physical Sciences, Flinders University, GPO Box 2100, Adelaide, SA 5001, Australia. E-mail: mike.perkins@flinders.edu.au

many new peroxide and peroxide-derived heterocycles and carbocycles with biological significance; and novel structural elements that have been targeted in the development of new synthetic methodology. A number of review articles on this topic have appeared in recent years. Most have focused on structural determination and biological analyses of marine endoperoxides;[6–13] and one, from 2004 focused on methods developed for their chemical synthesis.[14] However, none have detailed the complex biosynthetic interrelationships of these compounds beyond enzymatic polyketide synthesis. Now, we present a critical review discussing the structural elucidation, chemical synthesis and therapeutic potential of this important compound class, with special focus on their intriguing structural similarities and differences from a biogenetic perspective.

This review summarises the peroxide and peroxide-derived metabolites of polyketide origin reported since the discovery of **1** and **2**. Theories of biogenesis, both generally accepted and speculative; and examples of the use of chemical synthesis to demonstrate or utilise this understanding, are highlighted. Notably, it appears that the occurrence of many structurally novel polyketides in this family can be attributed to non-enzymatic modification or rearrangement of peroxide progenitors, which themselves are formed in enzymatic condensation and hydroperoxidation processes. This article is therefore presented in four parts: the first section summarises peroxide metabolites; the second section discusses related compounds most likely derived from base-mediated rearrangement; the third section details natural products that appear to arise from endoperoxide reduction; and the fourth section comments on the therapeutic potential of this compound class. Additionally, oxidative adducts are discussed where necessary.

2. Peroxide metabolites from marine sponges

Since the discovery of **1** and **2**, a suite of related metabolites have been isolated from marine sponges. These include plakorin (**3**),[4] xestins A (**4**), B (**5**),[5] manadoperoxides A–C, D (**6**), E–K,[15–17] manadodioxans A–E,[18] haterumadioxins A (**7**), B (**8**),[19] plakortenone (**9**),[20] plakortides E–O, P (**10**), Q–U, Z, AA,[20–32] plakorstatin **1** and **2** (**11**),[33] monotriajaponides B, C, D (**12**),[34] plakinic acids A (**13**), B–P,[32,35–43] plakortolides A–O, P (**14**), Q–W,[40–48] plakortoperoxides A1 (**15**), A2 (**16**), B–D,[48] capucinoate A (**17**),[49] plakortisinic acid (**18**),[50] andavadoic acid (**19**),[46] and related compounds (Fig. 1).[6,7,13,51–62] Following global interest in antimalarial peroxide natural products such as artemisinin,[63,64] compounds in this class are routinely screened for *in vitro* activity against strains of *Plasmodia* (Section 5.1).[11,12,65,66] Testing for cytotoxic action against cancer cell types is also commonplace (Section 5.2).[8–10] Despite many encouraging results, the availability of marine endoperoxides is usually very poor and methods for their chemical synthesis are still in development.

2.1 Peroxide biosynthesis

Importantly, all the above-mentioned endoperoxides are isolated as optically active compounds and are thus believed to arise from the enzymatic inclusion of molecular oxygen to an unsaturated polyketide scaffold. Capon first proposed a model for enzymatic hydroperoxidation of 2,5-dienoic acids to yield straight-chain peroxides (**20**), which then undergo oxa-Michael cyclisation to generate enantiomerically enriched 1,2-dioxanes (Scheme 1).[67] The model was initially developed to illustrate biosynthesis of the norterpene peroxide sigmosceptrellin D,[67,68] but has since been extended to rationalise the formation of other polyketide endoperoxides, including those related to plakortin.[47] Recently, metagenomic analyses of several marine sponges have provided insight to the complexity of the metabolic processes of these organisms and their symbiotic microbiome.[69,70]

2.2 Chemical synthesis of peroxide metabolites

Natural products of this family, characterised by highly substituted peroxyheterocyclic core structures with specific absolute configuration, present unique challenges as targets in the field of chemical synthesis. A variety of approaches have

Matthew Norris received his B.Sc. with first-class honours in Chemistry in 2011. He is currently completing his Ph.D. at the School of Chemical and Physical Sciences, Flinders University under the supervision of Michael Perkins. His research has focused on the synthesis of peroxide-derived secondary metabolites from marine sponges with a strong emphasis on developing a better understanding of their biosynthetic origin. He received the Australian Fulbright (WG Walker) Scholarship to work with Erik Sorensen at the Department of Chemistry, Princeton University in 2014.

Michael Perkins gained a Ph.D. from the University of Queensland in 1990 under the guidance of W. Kitching. He carried out post doctoral work on natural product synthesis with Ian Paterson at the University of Cambridge and then with Lew Mander at the Australian National University. He joined the Faculty of Flinders University in 1995. His main research interest is in the area of synthesis of natural products of polyketide origin.

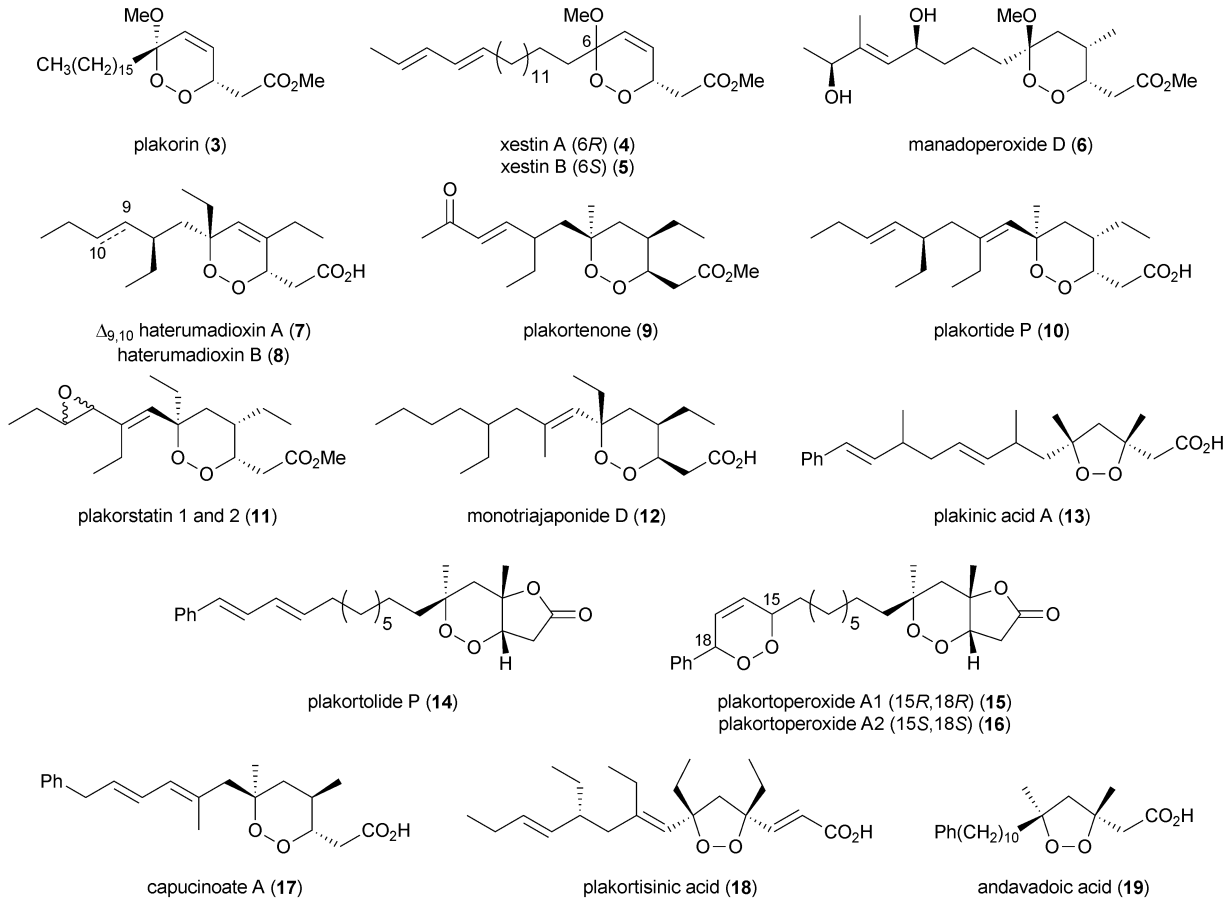
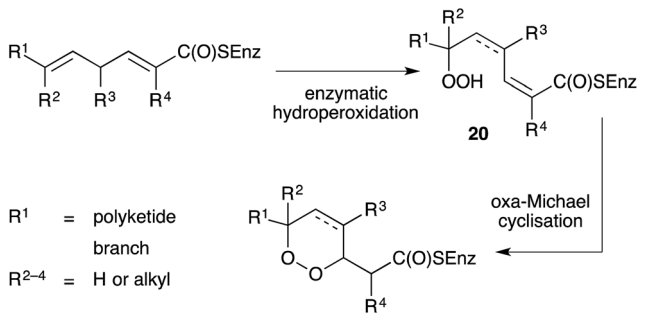


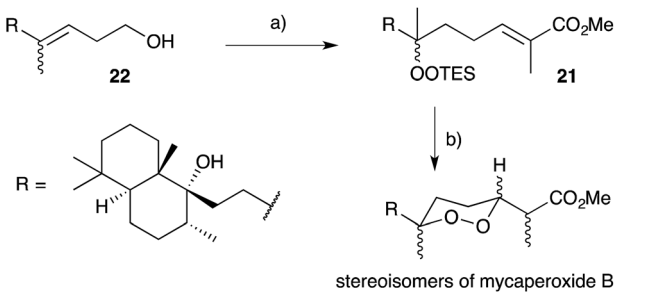
Fig. 1 Selected peroxide metabolites of polyketide origin isolated from marine sponges (absolute stereochemistry not implied).

been explored, most involving molecular oxygen or hydrogen peroxide as key reagents to construct the endoperoxide system.

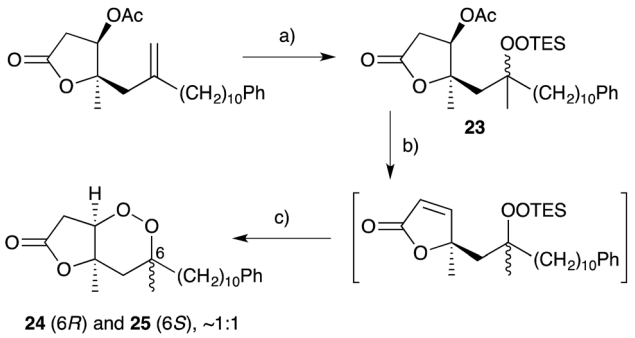
Cobalt(II)-catalysed peroxysilylation developed by Mukaiyama and Isayama[71,72] is used extensively to generate open hydroperoxide substrates, which are poised for cyclisation to 5- and 6-membered rings. Although the oxidation itself proceeds with little facial selectivity, stereocontrol in the subsequent cyclisation event has proven effective. Inspired by Capon's model (Section 2.1), Harwood accessed compound **21** by peroxysilylation of olefin **22** and effected oxa-Michael cyclisation to the pendant α,β-unsaturated ester yielding a number of stereoisomers related to mycaperoxide B (Scheme 2).[73,74] Similarly, Mukaiyama's method allowed the synthesis of lactone **23**, which underwent conjugate-base elimination and oxa-Michael cyclisation to construct both plakortolide E (**24**) and *ent*-plakortolide I (**25**) in 2012 (Scheme 3).[75] The asymmetric total synthesis of **24** and **25** prompted clarification of the relative and absolute configuration of the natural products.[47,75,76] Campiani and co-workers were able to obtain peroxysilane **26** by the same methodology, before initiating 6-*exo*-tet



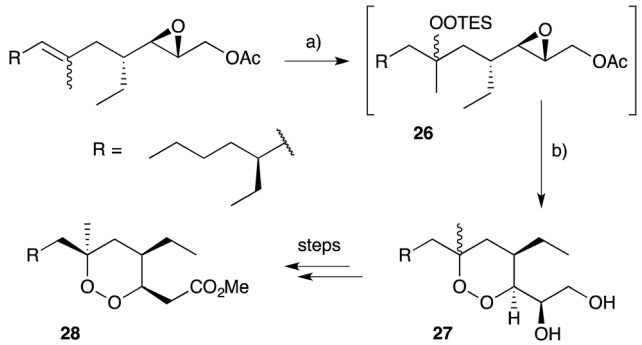
Scheme 1 Biosynthesis of polyketide endoperoxides based on Capon's model.



Scheme 2 Synthesis of mycaperoxide B diastereomers by Mukaiyama–Isayama peroxidation and cyclisation. (a) O_2, $Co(modp)_2$, Et_3SiH, DCE, r.t.; then DMP, CH_2Cl_2, r.t., 2 h; then $(CH_3)C(PPh_3)CO_2Me$, CH_2Cl_2, r.t., overnight, 21% over 3 steps; (b) PPTS, EtOH, r.t., 6 h; then Et_3N, MeOH, r.t., 2 d, 8% over 2 steps.



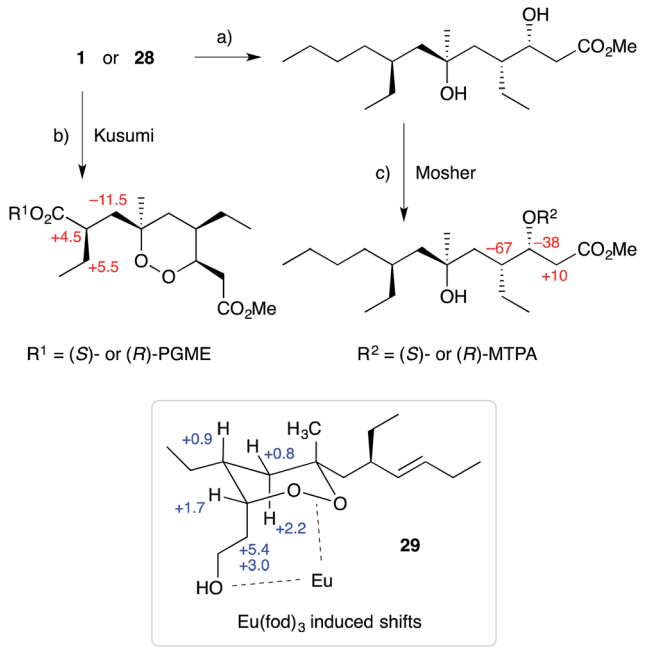
Scheme 3 Synthesis of plakortolide E (**24**) and *ent*-plakortolide I (**25**) by Mukaiyama–Isayama peroxidation and cyclisation. (a) O_2, $Co(thd)_2$, Et_3SiH, DCE, r.t., 2 h, 94%; (b) DBU, THF, 0 °C, 3 h; then (c) TFE, TBAF, 0 °C, 3 h, 75% over 2 steps.



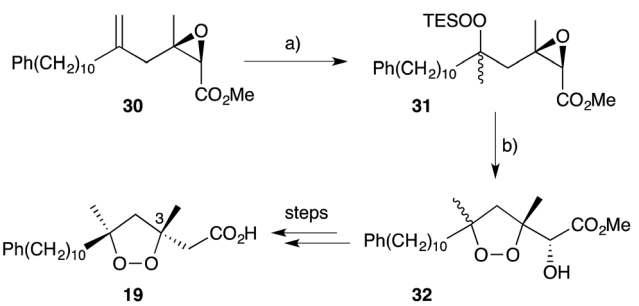
Scheme 4 Synthesis of 9,10-dihydroplakortin (**28**) by Mukaiyama–Isayama peroxidation and 6-*exo*-tet cyclisation. (a) O_2, $Co(thd)_2$, Et_3SiH, DCE, r.t., 5 h; then (b) Amberlyst, CH_2Cl_2, r.t., 18 h; then K_2CO_3, MeOH, 0 °C, 3 h, 78% over 3 steps.

hydroperoxide cyclisation to dioxane **27** (Scheme 4).[77–79] In a number of subsequent steps, the first total synthesis of 9,10-dihydroplakortin (**28**) was accomplished and its absolute configuration was confirmed.[77–79] Notably, the relative and absolute configuration of **28** and its dehydro analogue **1** were established from the natural material through application of Kusumi's and Mosher's methods to selected products of chemical degradation (Scheme 5).[2] Lanthanide-induced shift experiments of alcohol **29** with $Eu(fod)_3$ were also used to assign the relative stereochemistry of **1**.[1] Finally, Vatéle employed a similar hydroperoxide cyclisation approach toward the synthesis of andavadoic acid (**19**), effecting oxidation of olefin **30** to peroxysilyl ether **31**, which was followed by 5-*exo*-tet cyclisation to dioxolane intermediate **32** (Scheme 6).[80–82]

Wong and co-workers took a different approach to the synthesis of 1,2-dioxolanes *en route* to plakortide E (**33**), constructing a pivotal [3.2.1]-peroxybicycle intermediate (**34**) using Feldman's[83–85] method for vinyl cyclopropane oxygenation (Scheme 7).[86] Thus, irradiation of lactone *rac*-**35** with a 300 W sunlamp in the presence of catalytic Ph_2Se_2 and AIBN under an atmosphere of oxygen effected near quantitative oxidation to *rac*-**34**. Selective reduction of the lactone ester and lipase-mediated kinetic resolution gave TBS ether **36** in >99% ee,

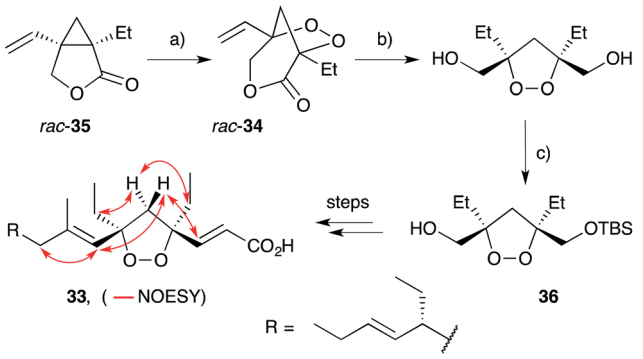


Scheme 5 Application of Kusumi's and Mosher's methods to determine the absolute configuration of plakortin (**1**) and dihydroplakortin (**28**); and $Eu(fod)_3$ induced shift data to determine relative configuration of **1**. Change in chemical shift due to Kusumi's and Mosher's method expressed as shift of (*R*)-PGME or (*R*)-MTPA compound subtracted from shift of (*S*)-PGME or (*S*)-MTPA compound (in Hz) and shown as red numbers. Change in shift due to incorporation of $Eu(fod)_3$ (in ppm) shown as blue numbers. (a) H_2 (1 atm), 10% Pd/C, EtOH, r.t., 5 h; (b) $KMnO_4$, $NaIO_4$, Na_2CO_3, ^tBuOH, H_2O, 37 °C, 20 h; then (*S*)- or (*R*)-PGME hydrochloride, PyBoP, HOBT, *N*-methylmorpholine, DMF, r.t., 3 h, 76% over 2 steps (for both (*S*)- and (*R*)-PGME amide); (c) (*S*)- or (*R*)-MTPA chloride, pyridine, r.t., overnight, 88% (for both (*S*)- and (*R*)-MTPA ester). PGME = phenylglycine methyl ester; PyBoP = benzotriazolyloxytri(pyrrolidinyl) phosphonium hexafluorophosphate; HOBT = 1-hydroxybenzotriazole; MTPA = methoxy(trifluoromethyl)phenylactate.

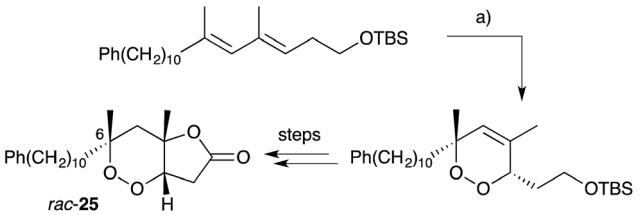


Scheme 6 Synthesis of andavadoic acid (**19**) by Mukaiyama–Isayama peroxidation and 5-*exo*-tet cyclisation. (a) O_2, $Co(thd)_2$, Et_3SiH, DCE, r.t., 3–4 h, 86%; (b) K_2CO_3, MeOH, 0 °C, 3 h, 64%.

before completing the synthesis over several steps. Using this approach, four stereoisomers of plakortide E were synthesised, establishing the relative and absolute configuration of the natural product as (4*S*,6*R*,10*R*)-**33** (selected NOESY correlations of the natural material shown in Scheme 7).[22] A similar method



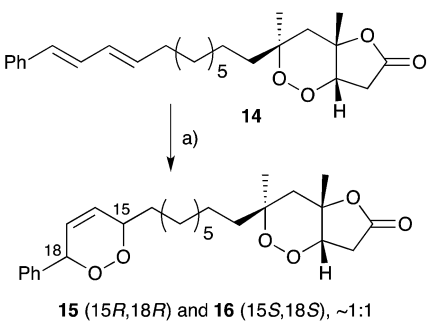
Scheme 7 Synthesis of plakortide E (**33**) by Feldman vinyl cyclopropane oxygenation. Selected NOESY correlations of natural **33** shown as red arrows. (a) O_2, Ph_2Se_2, AIBN, MeCN, 300 W lamp, r.t., 99%; (b) $LiBH_4$, THF, 0 °C; then $KO_2CN = NCO_2K$, AcOH, CH_2Cl_2, 0 °C (three cycles), 70% over 2 steps; (c) TBSCl, imidazole, DMAP, DMF, 0 °C to r.t.; then lipase, vinyl acetate, hexane, 29 h, 32% over 2 steps.



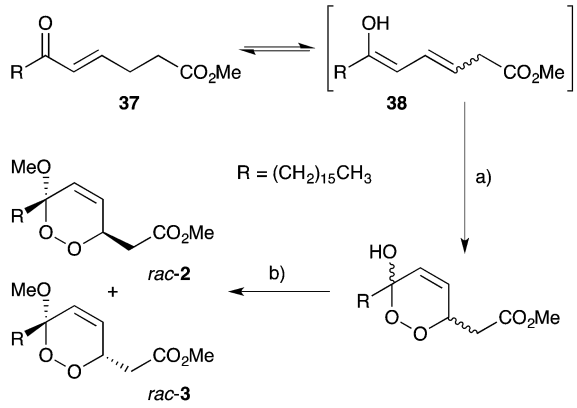
Scheme 8 Synthesis of 6-*epi*-plakortolide E (*rac*-**25**) by [4 + 2] cycloaddition of singlet oxygen. (a) O_2, rose bengal, CH_2Cl_2, MeOH, 500 W lamp, 0 °C, 6 h.

was later used to establish the first asymmetric total synthesis of epiplakinic acid F.[87]

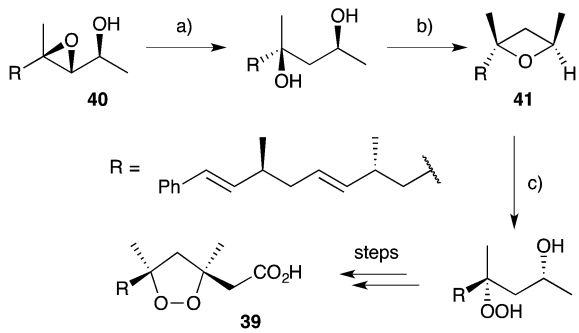
Endoperoxide substrates have also been successfully constructed from suitable straight-chain dienes by [4 + 2] cycloaddition with singlet oxygen.[88] Jung[89] and Taylor[90] have each prepared peroxylactone analogues from diene precursors and a racemic synthesis of 6-*epi*-plakortolide E (*rac*-**25**) was completed in 2002 (Scheme 8).[89] Steliou used a similar approach for the synthesis of two cytotoxic endoperoxides isolated from *Plakortis angulospiculatus* in 1990.[91,92] Garson effected photooxygenation of natural plakortolide P (**14**), yielding synthetic



Scheme 9 Conversion of natural plakortolide P (**14**) to plakortoperoxides A1 (**15**) and A2 (**16**) by [4 + 2] cycloaddition of singlet oxygen. (a) O_2, rose bengal bis(triethylammonium) salt, CH_2Cl_2, 500 W lamp, 5 °C, 3 h, 62%.



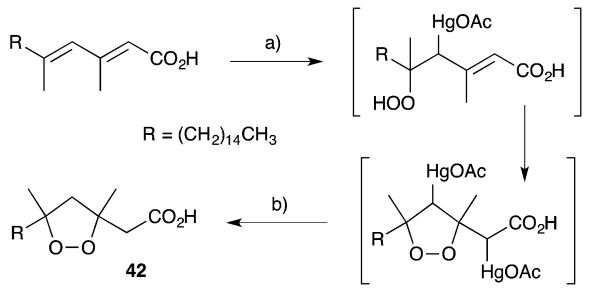
Scheme 10 Snider's racemic synthesis of chondrillin (**2**) and plakorin (**3**) by [4 + 2] oxygenation. (a) O_2, rose bengal lactone, 275 W lamp, CH_2Cl_2, MeOH, r.t., 12 h, 73%; (b) $TsOH \cdot H_2O$, MeOH, r.t., 80 h, 98%.



Scheme 11 Synthesis of an isomer (**39**) of plakinic acid A (**13**). (a) Red-Al, THF, 0 °C, overnight, 97%; (b) ^{t}BuOK, TsCl, THF, r.t., 3 h, then NaH, 0 °C, overnight, 72%; (c) H_2O_2, TMSOTf, Et_2O, THF, −78 °C, 45 min.

plakortoperoxide A1 (**15**) and A2 (**16**) as a 1 : 1 mixture (Scheme 9).[48] Snider constructed the peroxyketal diastereomers **2** and **3** by photooxygenation of ketone **37**, presumably *via* the enolic tautomer **38** (Scheme 10).[93–95] The first asymmetric synthesis of **2** and **3** was later achieved by photooxygenation of enantio-enriched allyl alcohols followed by hydroperoxide rearrangement.[96–98] Peroxyketal structures related to **1–3** were also synthesised by Fattorusso and co-workers using manganese(III) acetate catalysed addition of molecular oxygen to β-ketoester and olefin substrates.[99,100]

Other methods developed for the synthesis of peroxide scaffolds have involved the use of hydrogen peroxide rather than molecular oxygen.[101–103] Dussault completed the synthesis of a series of plakinic acid A (**13**) stereoisomers (including **39**) by advancing enantio-enriched α-hydroxyepoxides such as **40** (accessed by Sharpless asymmetric epoxidation of the corresponding allyl alcohol) to oxetane **41**, before stereoselective ring opening with hydrogen peroxide (Scheme 11).[104,105] Ring closure and acetate homologation were then achieved over a number of steps. Earlier, Bloodworth developed an effective double peroxymercuration–demercuration strategy for the synthesis of 1,2-dioxolanes, including a natural saturated analogue (**42**) of the plakinic acids (Scheme 12).[106] Most recently, Deng and co-workers developed an enantioselective and organocatalytic

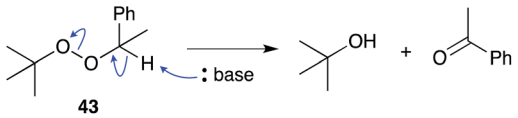


Scheme 12 Synthesis of a plakinic acid analogue (**42**) by peroxymercuration–demercuration. (a) H_2O_2, H_2O, $Hg(OAc)_2$, then (b) $NaBH_4$, NaOH.

method for the peroxidation of unsaturated ketones and aldehydes using cinchona alkaloid derivatives.[107–109]

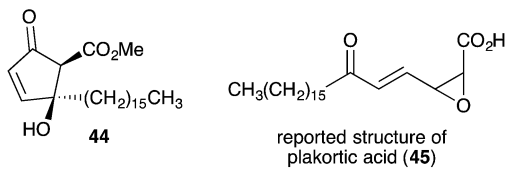
3. Metabolites derived from peroxide rearrangement

The base-catalysed rearrangement of dialkyl peroxides was first reported in the early 1950s when Kornblum and DeLaMare discovered that 1-phenylethyl *tert*-butylperoxide (**43**) decomposes in the presence of catalytic KOH, KOEt or piperidine to yield acetophenone and *tert*-butanol.[110,111] The reaction was rationalised by abstraction of hydrogen at the less substituted α-peroxy carbon, followed either by stepwise or concerted elimination across the C–O bond. The instability of peroxide scaffolds, including 1,2-dioxanes, to base-mediated rearrangement has lead to the occurrence and isolation of many rearranged endoperoxide metabolites related to **1–3**.

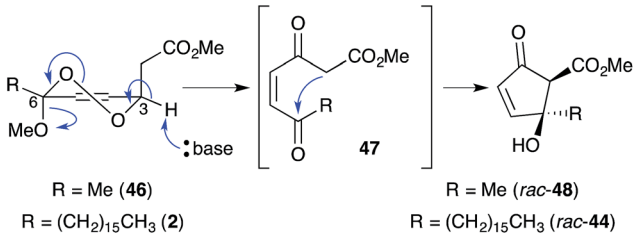


3.1 Untenone A and plakortic acid

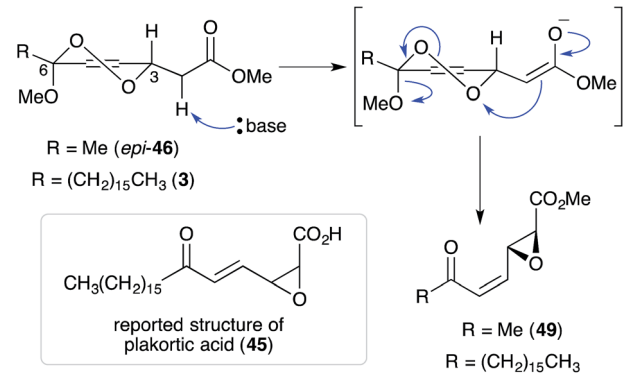
Untenone A (**44**)[112] and plakortic acid (**45**)[113] were each isolated from *Plakortis* marine sponges in 1993 and 2001, respectively. Although **44** and **45** appear to be quite different, both are closely related to chondrillin (**2**) and plakorin (**3**), sharing the same elemental composition and oxidation pattern of the central carbon chain. After completing a racemic total synthesis of **2** and **3** in the early 1990s (Section 2.2), Snider studied the base-catalysed structural rearrangements of the two diastereomers and found that they decompose *via* distinct pathways.[95] The findings of Snider's study have, in retrospect, provided insight to the biosynthesis of **44** and **45**.[114]



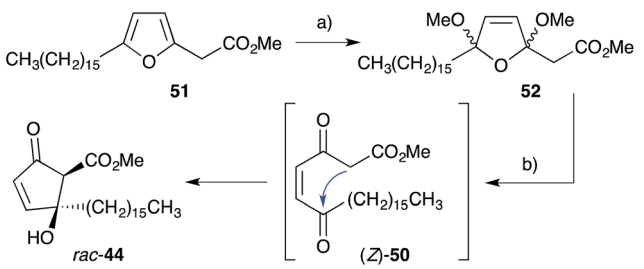
In a model system, Snider found that the rearrangement of peroxyketal heterocycles **46** and *epi*-**46** (analogues of **2** and **3**) is critically dependent on their relative stereochemistry. As shown in Scheme 13, the conformation in which the C6 alkyl substituent of **46** (a methyl analogue of **2**) is pseudoequatorial places the C3 dioxane hydrogen antiperiplanar to the adjacent 1,2-dioxane bond. This facilitates Kornblum–DeLaMare rearrangement to yield methyl ester **47** (R = Me) before rapid Dieckmann condensation to give cyclopentenone *rac*-**48**, a methyl analogue of untenone A (**44**). In contrast, the conformation in which the C6 alkyl substituent of *epi*-**46** (a methyl analogue of **3**) is pseudoequatorial places the C3 acetate group antiperiplanar to the O–O bond (Scheme 14). This allows nucleophilic attack of the α-keto acetate carbon to the peroxide yielding oxirane **49**, a structural analogue of plakortic acid (**45**).[115] It is therefore



Scheme 13 Kornblum–DeLaMare rearrangement and Dieckmann condensation of chondrillin (**2**) analogue **46**.



Scheme 14 Base-mediated decomposition of plakorin (**3**) analogue *epi*-**46**.



Scheme 15 Whitehead's biomimetic synthesis of untenone A (**44**). (a) Br_2, Na_2CO_3, MeOH, Et_2O, r.t., 1 h, 79%; (b) H_2SO_4, dioxane, H_2O, r.t., 1 h, then Na_2CO_3, H_2O, r.t., 30 min, 62%.

apparent that natural **44** and **45** are likely to be derived from the rearrangement of **2** and **3**, respectively. It is also important to note that **44** was isolated as a racemate[112,116,117] and **45** in enantio-enriched form,[113] which is consistent with the presented theory of biogenesis.

Inspired by Snider's work, Whitehead developed a synthesis of untenone A (**44**) by *in situ* generation of methyl ester (*Z*)-**50**, the postulated biosynthetic intermediate linking **2** and **44** (Scheme 15).[118–120] Thus, oxidation of synthetic plakorsin A (**51**, Section 4.4)[113] gave bismethyl acetal **52**, which on hydrolysis underwent Dieckmann condensation yielding *rac*-**44**, directly. After developing an efficient total synthesis, Whitehead's study into the reactivity of *rac*-**44** was pivotal in elucidating biosynthesis of the manzamenone family of oxylipin dimers (Section 3.2). Both racemic and asymmetric total syntheses of untenone A (**44**) were also accomplished by Takeda,[121] Asami[116] and Yamada;[117] with each approach targeting modification of 5-membered carbocycles introduced in the early stages of synthesis.

3.2 Manzamenones A–H, J–O and untenolide A

Manzamenones A–F (**53–58**)[122] and H (**59**)[123] were isolated by Kobayashi and co-workers from *Plakortis* sponges collected near Okinawa, Japan in 1992 and 1993 (Fig. 2). They share a common [4.3.0]-carbobicyclic structure differing only by the carboxy substituent at C5. Manzamenone A (**53**) was found to be a potent inhibitor of DNA polymerase β[124,125] and manzamenones B (**54**) and E (**57**) are inhibitors of T-cell protein tyrosine phosphatase.[126]

Initial speculation on the biosynthesis of **53–58** considered that the cyclohexene ring system may be constructed in a hetero-bimolecular [4 + 2] cycloaddition of untenone A (**44**)

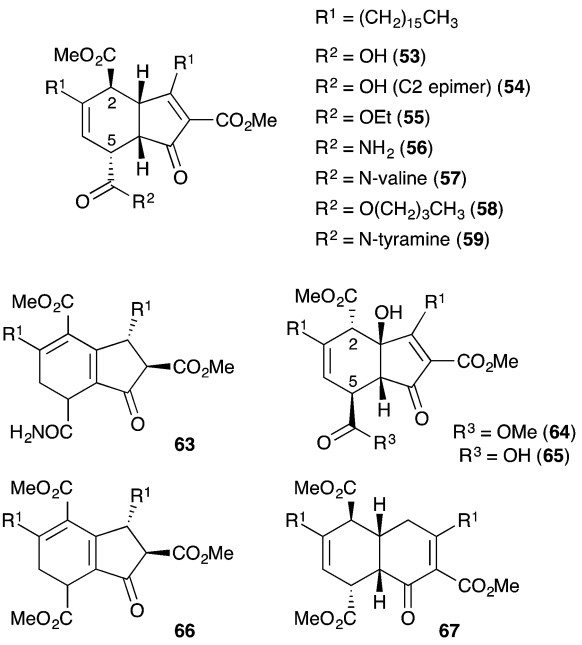
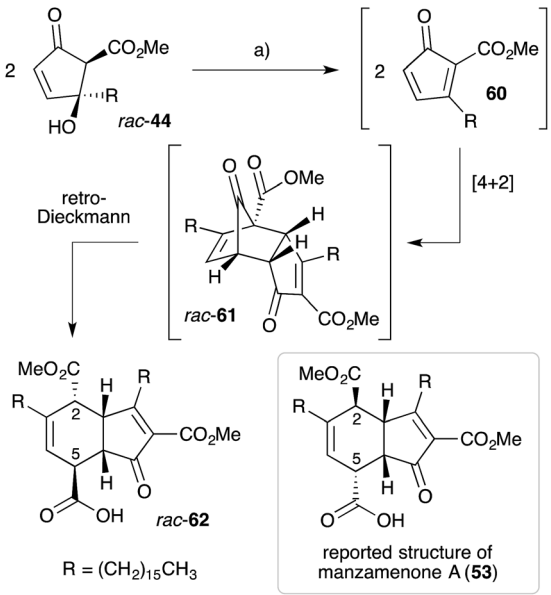


Fig. 2 Reported structures of manzamenone A–F (**53–58**), G (**67**), H (**59**), J (**63**) and L–N (**64–66**).

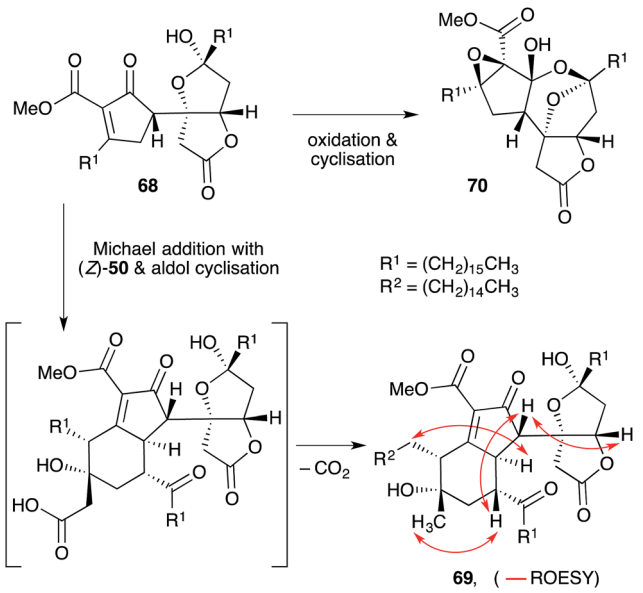


Scheme 16 Whitehead's biomimetic synthesis and structural elucidation of manzamenone A (**62**). (a) Neat, 72 °C, 24 h, 48%.

and a suitable diene counterpart.[122,123] However, Whitehead postulated that **53–58** are in fact homodimers of untenone A (**44**).[118–120,127] Heating a neat sample of synthetic *rac*-**44** (Section 3.1) to it's melting point (72 °C) caused dehydration to the anti-aromatic cyclopentadiene **60** followed by rapid [4 + 2] homodimerisation to give *endo*-adduct *rac*-**61** *in situ* (Scheme 16). Retro-Dieckmann fragmentation of the bridgehead carbonyl with uptake of water as an incident nucleophile yielded *rac*-**62**, whose relative stereochemistry was determined by X-ray crystallography and detailed NMR analysis.[120] The spectral data obtained for **62** matched that of natural manzamenone A, thus prompting stereochemical reassignment of the original structure (**53**) at C2 and C5. Whitehead also completed the synthesis of manzamenones C and F from *rac*-**62** resulting in a similar revision of the original structures **55** and **58**.[128] The apparent pre-disposition of **44** to undergo dehydrative dimerisation yielding **62** demonstrates beyond doubt that this process is responsible for the occurrence of **53–58** in the extracts of marine sponges.[129]

Manzamenones J (**63**)[130] and L–N (**64–66**),[131] also isolated from *Plakortis* sponges, were determined to have the same carbocyclic structure as **53–58** with a different oxidation pattern of the central core and thus, are likely to be directly related (Fig. 2). However, manzamenone G (**67**)[123] was reported as an unusual structural analogue with one carbon more than that expected for a dimer related to chondrillin (**2**). The structure of manzamenone G (**67**)[123] was only tentatively assigned and its biosynthetic origin remains unclear.

Manzamenone K (**68**),[130,132] O (**69**)[133] and untenolide A (**70**)[134] also appear to be related to **2** and **3**, yet are structurally distinct from **53–58** and **63–67** (Scheme 17). The central structure common to each natural product (**68–70**) was verified by X-ray crystallography[134] and ROE spectroscopy (selected ROESY correlations of compound **69** as shown in Scheme 17);[133] and



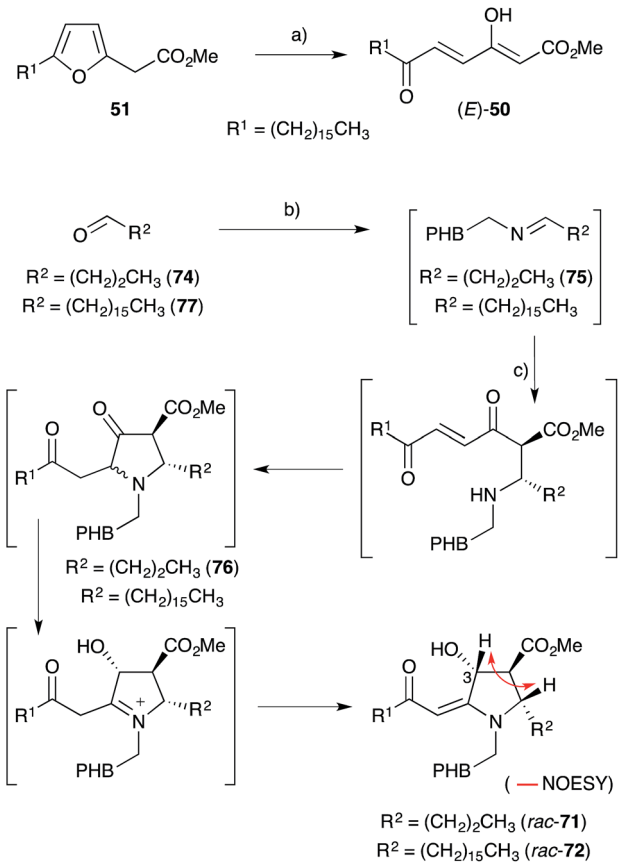
Scheme 17 Structures and postulated conversion of manzamenone K (**67**) to manzamenone O (**69**) and untenolide A (**70**). Selected ROESY correlations of compound **69** shown as red arrows.

found to consist of two structural elements that appear to be derived from **2** or **3** linked by a single C–C bond (most clearly seen in **68**). The compounds were isolated as racemic or presumably pseudo-racemic, suggesting that they may arise from non-enzymatic dimerisation of an achiral intermediate similar to manzamenones A–F (**53–58**) and H (**59**). However, if derived from **2** and **3** it appears that a single reduction event has occurred at some stage during construction of the central scaffold. Kobayashi reported that **70** is likely to be related to **68** by oxidation and cyclisation; and **69** is likely to be related to **68** *via* condensation with intermediate (*Z*)-**50** (derived from **2**).[133–135] Despite the complexity of these unique oxylipin natural products, no further studies have commented on the biosynthesis or attempted chemical synthesis of **68–70**.

3.3 Plakoridines A–C

Kobayashi and co-workers also isolated three fatty acid containing alkaloids from *Plakortis* marine sponges collected near Okinawa. Plakoridine A (**71**),[136] found to be an inhibitor of DNA polymerase,[124] and the less active compounds plakoridines B (**72**)[130] and C (**73**),[137] each contain a central carbon chain with a C16 aliphatic tail common to all peroxyketal-derived natural products related to chondrillin (**2**, Scheme 18).

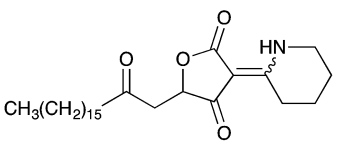
Whitehead postulated that **71** and **72** are biosynthetically related to (*E*)-**50**,[138] an intermediate derived from plakorsin A (**51**).[139] In a single experiment, tyramine and aldehyde **74** condensed to generate imine **75** *in situ* before addition of (*E*)-**50** (itself prepared by bromine-mediated oxidation of synthetic **51**) to give *rac*-**71** as a 3 : 1 mixture of C3 epimers (Scheme 18).[127,138,140] Over 11 days at room temperature, **75** and (*E*)-**50** were presumed to undergo an intermolecular Mannich reaction followed by Michael ring closure to afford heterocycle **76**. An internal redox process, resulting in reduction of the



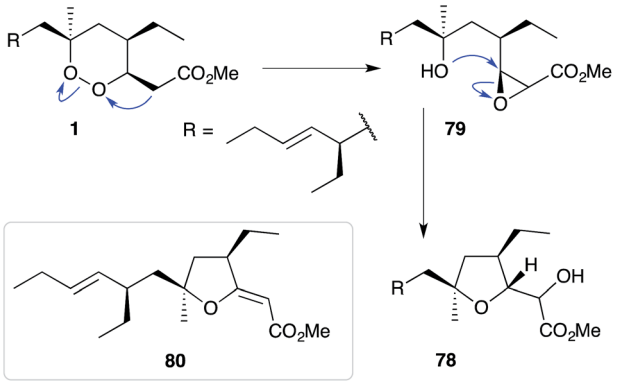
Scheme 18 Whitehead's biomimetic synthesis of plakoridine A (**71**) and B (**72**) from plakorsin A (**51**). Key NOESY correlation of compound *rac*-**71** shown as a red arrow. (a) Br_2, Me_2CO, H_2O, −20 °C to −10 °C, 6 h, 63%; (b) tyramine, $CDCl_3$, r.t., 3 h, then $MgSO_4$, r.t., 30 min, then (c) (*E*)-**50**, r.t., 11 d, 43% (beginning with **74**) and 36% (beginning with **77**). PHB = *p*-hydroxybenzyl.

cyclopentanone carbonyl and oxidation of the neighbouring α-amino methine, then followed to yield *rac*-**71**. Relative configuration of the pyrrolidine ring was established through the analysis of vicinal coupling constants and NOE spectroscopy (key NOESY correlation of compound *rac*-**71** shown in Scheme 18). Hexadecyl aldehyde (**77**) was also advanced to *rac*-**72** using this method, demonstrating that natural **71** and **72** are most likely related to **51**. Furthermore, Ma's asymmetric synthesis of (2*S*,3*S*,4*R*)-**71** in 2000 showed that natural plakoridine A (**71**) was isolated as a racemate,[141] which is consistent with Whitehead's theory of biogenesis. Stafford also reported a racemic synthesis of a plakoridine A lactam in 1995.[142]

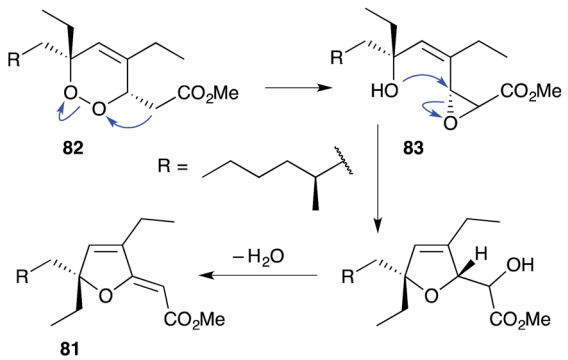
Plakoridine C (**73**) is structurally distinct from **71** and **72**; and appears to be derived from an intermediate related to **2** or **3** by addition of piperideine or δ-lactam.[137] To date, there is no published work on the synthesis of **73**.



73, ~1:1 (*E*:*Z*)



Scheme 19 An observed ring contraction of plakortin (**1**).

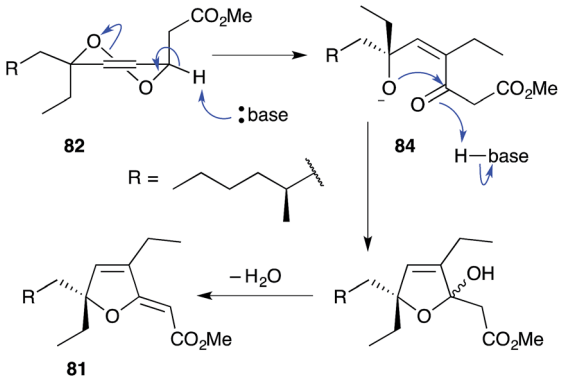


Scheme 20 Faulkner's hypothesis for ring contraction of peroxide **82** to furanylidene **81**.

3.4 Gracilioethers B–D, plakilactones A–H and related compounds

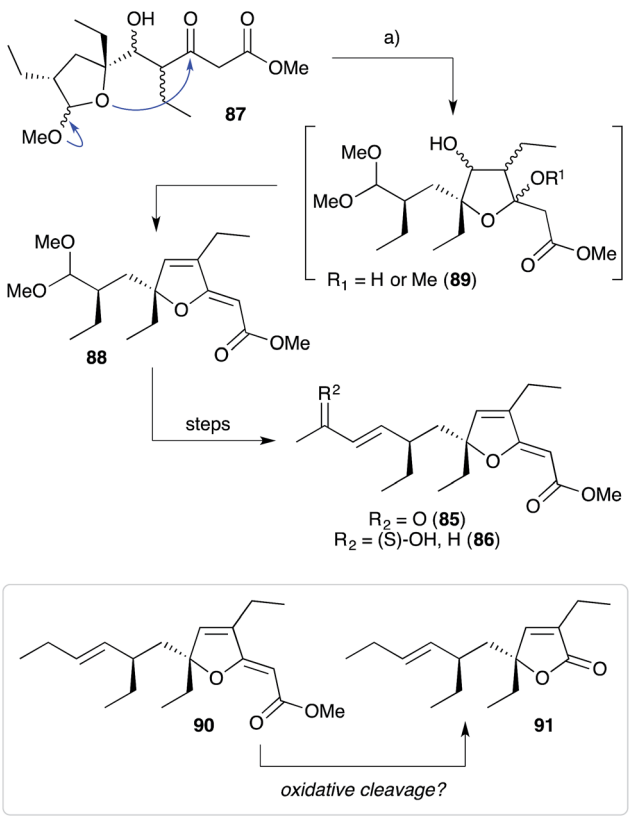
The base-catalysed rearrangements of dialkyl peroxides related to and including plakortin (**1**), which are structurally distinct from **2** and **3**, yield furan-containing polyketide metabolites by ring contraction of the 1,2-dioxane motif. Faulkner discovered that treating **1** with NaOMe in MeOH induced rearrangement to tetrahydrofuran **78**, presumably by ring closure of epoxide intermediate **79** (Scheme 19).[1] This general reaction of unsaturated dialkyl peroxides has been used in the synthesis of polyether tetrahydrofuran compounds;[143] and **78** has itself been linked to the sponge metabolite **80**, as a likely biogenetic precursor.[2] By extension, Faulkner rationalised biosynthesis of the [2(5*H*)-furanylidene]ethanoate (furanylidene) metabolite **81** from peroxide **82** through formation of epoxide **83** (Scheme 20).[144] However, Snider's work on the stereochemical dependence of base-catalysed rearrangements of 4,5-unsaturated-1,2-dioxane peroxyketals (Section 3.1) suggests that the conversion of **82** to **81** is likely to proceed by Kornblum–DeLaMare rearrangement *via* hydroxy-β-ketoester **84** (Scheme 21).[114] We believe a similar mechanistic course is most likely in the biosynthesis of gracilioethers B–D,[145,146] spongosoritin A,[147,148] spiroplakortone,[149] glanvillic acids A, B[49] and related compounds.[51,150–152]

Perkins has recently demonstrated the utility of targeting such hydroxy-β-ketoester intermediates in the synthesis of furanylidene



Scheme 21 Postulated Kornblum–DeLaMare rearrangement of peroxide **82** to furanylidene **81**.

compounds and has reported the total synthesis of gracilioethers B (**85**) and C (**86**) using this approach (Scheme 22).[153] Methyl acetal **87** (a synthetic analogue of **84**) was converted to furanylidene **88** by transacetalisation to intermediate **89** and dehydration to the conjugated system. **85** and **86** are known agonists of peroxisome proliferator-activated receptor γ (PPARγ);[146] and the related metabolite *des*-hydroxygracilioether C (**90**) was found to be cytotoxic against HCT-116 cells (human colon carcinoma).[31] Ohira and co-workers completed a racemic total synthesis of **90** in 2005 using reactions of alkylidenecarbenes.[154]

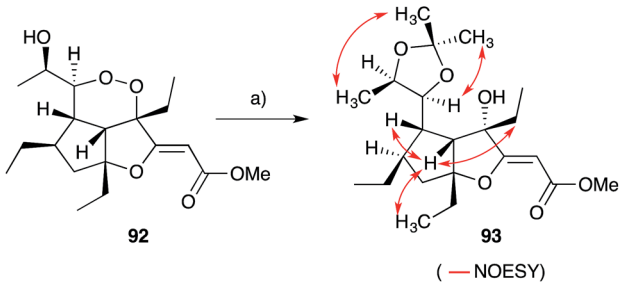


Scheme 22 Biomimetic total synthesis of gracilioethers B (**85**) and C (**86**); and a possible biogenetic link to the plakilactone metabolites *via* oxidative cleavage of the furanylidene heterocycle. (a) AcCl, MeOH, $CH(OMe)_3$, 20 °C, 15 h, 74% over 2 steps (first step not shown).

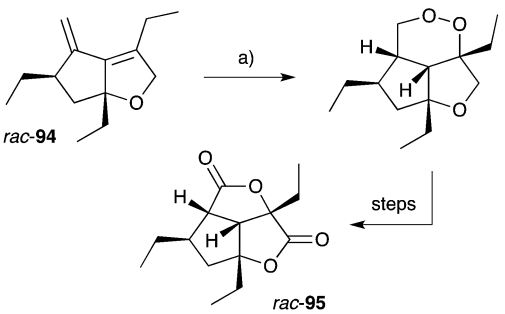
Plakilactones A–H[146] and *des*-hydroxyplakilactone B (**91**) were isolated from *Plakinastrella mamillaris* in 2012 along with a number of furanylidene natural products, including gracilioethers B (**85**), C (**86**) and *des*-hydroxygracilioether C (**90**). The structural similarity of the plakilactone butenolides and gracilioether furanylidenes would appear to suggest that they are related by oxidative cleavage of the furanylidene enol ether, although this possible relationship is yet to be demonstrated (Scheme 22).

3.5 Gracilioethers A, E–K and hippolachnin A

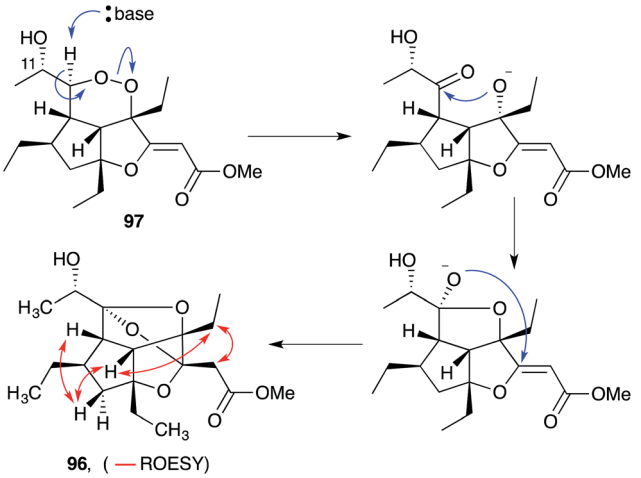
Gracilioethers A[145] and E–K[155,156] are complex polycyclic metabolites that also appear to be oxidative adducts of the furanylidene heterocycles, although the biosynthetic origins of these compounds remains unclear. The structure and absolute configuration of gracilioether A (**92**) was determined by chemical derivatisation and detailed NMR analysis of the resulting acetonide **93** (Scheme 23); and the structures of related natural products have been assigned accordingly. Wong recently demonstrated [4 + 2] addition of singlet oxygen to a reactive bicyclic diene (*rac*-**94**), forging the peroxy-tricyclic core of **92**, before completing total synthesis of gracilioether F (*rac*-**95**, Scheme 24).[157] Brown also completed a total synthesis of **95** in 2014 using a ketene–alkene [2 + 2] cycloaddition reaction and Baeyer–Villiger oxidation; and a carboxylic acid directed C–H oxidation to install each of the lactone rings.[158] The related



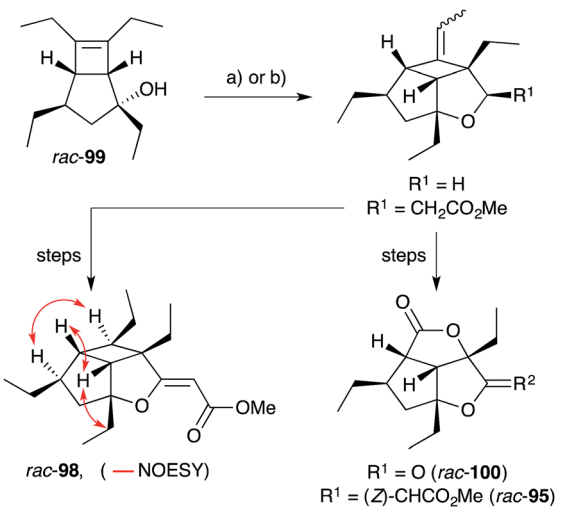
Scheme 23 Structural and stereochemical elucidation of gracilioether A (**92**) through chemical derivatisation and detailed NMR analysis. Selected NOESY correlations of compound **93** shown as red arrows. (a) Zn, Et_2O, AcOH, r.t., overnight; then $(CH_3)_2C(OCH_3)_2$, PPTS, CH_2Cl_2, r.t., overnight.



Scheme 24 Wong's synthesis of racemic gracilioether F (*rac*-**95**) by [4 + 2] oxygenation of diene *rac*-**94**. (a) O_2 (bubbled), methylene blue, CH_2Cl_2, sunlamp (200–300 W), 0–5 °C, 2 h.



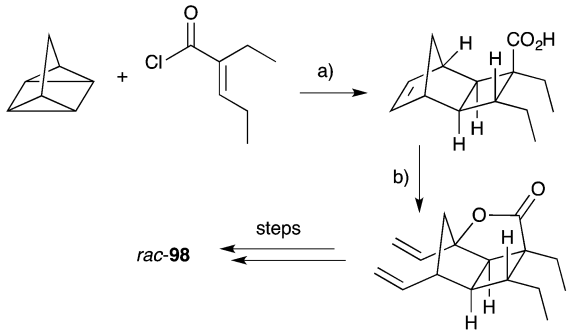
Scheme 25 Postulated base-catalysed rearrangement of (11*S*)-gracilioether A (**97**) to gracilioether K (**96**). Selected ROESY correlations of compound **96** shown as red arrows.



Scheme 26 Carreira's racemic synthesis of hippolachnin A (*rac*-**98**), gracilioether E (*rac*-**100**) and F (*rac*-**95**) from cyclobutene intermediate **99**. Selected NOESY correlations of natural **98** shown as red arrows. (a) $(CH_2O)_n$, $Sc(OTf)_3$, $CHCl_3$, −78 °C to r.t., 28 h, 61% brsm (for R^1 = H); (b) (*E*)-methyl-3-methoxyacrylate, PPTS, 80 °C, 4.5 days; then $BF_3{\cdot}2AcOH$, CH_2Cl_2, THF, r.t., 20 h, 62% over 2 steps (for R^1 = CH_2CO_2Me).

metabolite gracilioether K (**96**), whose structure was determined through detailed NMR analysis (selected ROESY correlations of compound **96** shown in Scheme 25) and by application of Mosher's method, is believed to arise from Kornblum–DeLaMare ring contraction and oxa-Michael cyclisation of (11*S*)-gracilioether A (**97**, Scheme 25),[156] which itself may be constructed from gracilioether C (**86**) by inclusion of molecular oxygen.

Hippolachnin A (**98**), isolated from *Hippospongia lachne* in 2013, also bears a unique tricyclic structure with a highly substituted cyclobutane ring (Scheme 26).[159] It appears that **98** arises biosynthetically from an intramolecular [2 + 2] cycloaddition of **90**, which itself was isolated from the same sponge

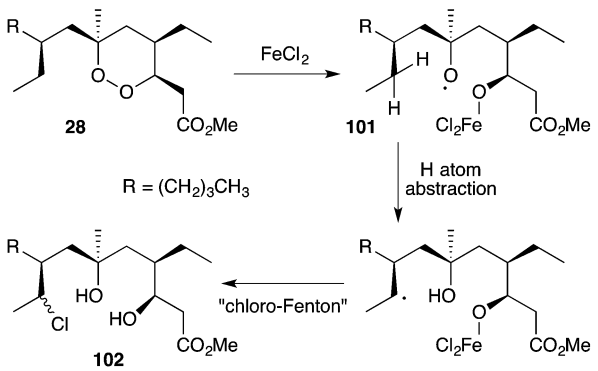


Scheme 27 Brown and Wood's synthesis of racemic hippolachnin A (*rac*-**98**) *via* quadricyclane cycloaddition and carboxylic acid directed C–H oxidation. (a) 140 °C (microwave irradiation), 4 h, then NaOH, r.t., 24 h, 50%; (b) ethylene (1 atm), Grubbs I, CH_2Cl_2, r.t., 7 h; then $PhSO(CH_2)_2SOPh{\cdot}Pd(OAc)_2$, Cr(salen)Cl, *p*-benzoquinone, dioxane, H_2O, 60 °C, 24 h, 64% over 2 steps.

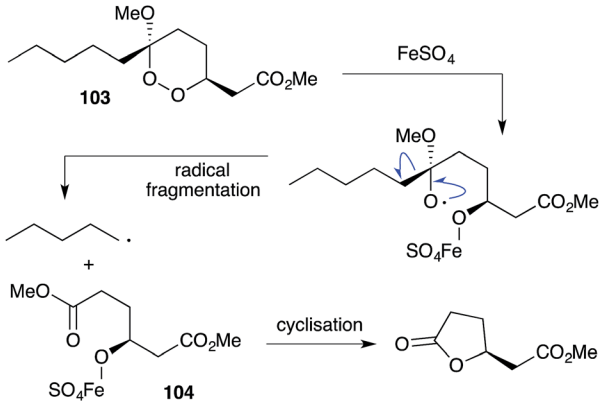
extract.[159] In turn, **90** is expected to arise from the dehydrative ring contraction of haterumadioxin A (7) methyl ester.[160] Carreira completed the first total synthesis of *rac*-**98** in 2015 constructing a pivotal cyclobutene intermediate **99** (Scheme 26)[161] *en route* to the natural product (selected NOESY correlations of natural **98** shown in Scheme 26);[159] and later extended the approach to achieve a racemic total synthesis of gracilioethers E (*rac*-**100**) and F (*rac*-**95**).[162] Brown and Wood recently published a collaborative project, which detailed the total synthesis of *rac*-**98** in only six steps through an enabling quadricyclane cycloaddition and late-stage carboxylic acid directed C–H oxidation, similar to that developed in Brown's earlier synthesis of *rac*-**95** (Scheme 27).[163] Ghosh has also been successful in accessing the central tricyclic core, effecting a [2 + 2] enone–alkene cycloaddition of a synthetic butenolide related to **90**.[164]

4. Metabolites derived from peroxide reduction

Iron(II)-mediated reduction has been identified as a likely biological mode of action of peroxide metabolites related to **1** and **2**. On treatment with $FeCl_2$, 9,10-dihydroplakortin (**28**) undergoes reductive cleavage of the 1,2-dioxane to give



Scheme 28 Reaction of 9,10-dihydroplakortin (**28**) with iron(II) chloride.

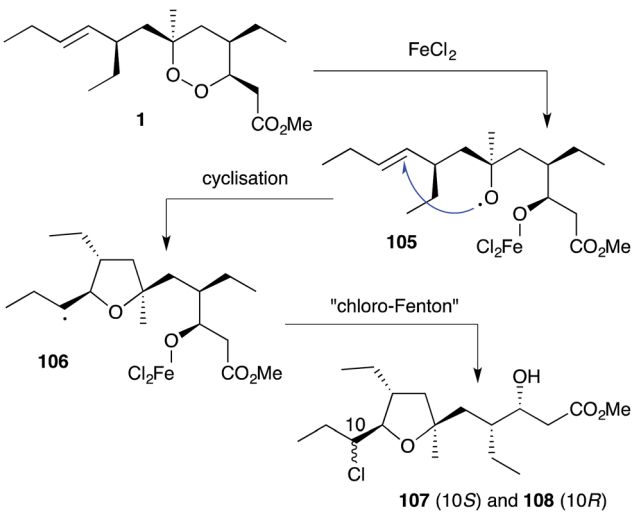


Scheme 29 Reaction of peroxyketal **103** with iron(II) sulfate and cyclisation.

oxyradical **101**, followed by H atom abstraction of the branched alkyl chain and "chloro-Fenton"[37,165] reaction yielding the isolated chlorides **102** (Scheme 28).[166] Peroxyketals such as **103** also undergo reduction with iron(II) followed by radical fragmentation with C–C bond scission to generate γ-hydroxyesters (by quenching of intermediate **104**) or the corresponding lactones (Scheme 29),[166] which themselves are isolated from marine sponge extracts.[5,113,167] In each case, it is the resultant carbon-centered radical that is believed to cause cell damage and the cytotoxic effect of these metabolites.[99,103,168]

4.1 Plakortethers A–G and simplakidine A

Plakortin (**1**) is known to undergo iron(II)-mediated reduction like dihydro-analogue **28**, with concomitant cyclisation of oxyradical **105** to the pendant olefin (Scheme 30).[166] When treated with $FeCl_2$, **106** is then presumed to undergo "chloro-Fenton" reaction yielding the isolated tetrahydrofuran adducts **107** and **108**, the latter isolated in 2002 from extracts of *Plakortis simplex* and named plakortether C (**108**).[169] A series of co-isolates,



Scheme 30 Reaction of plakortin (**1**) with iron(II) chloride yielding plakortether C (**108**).

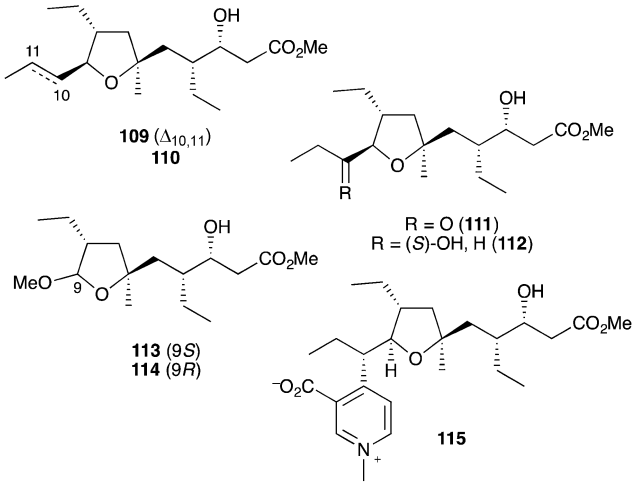
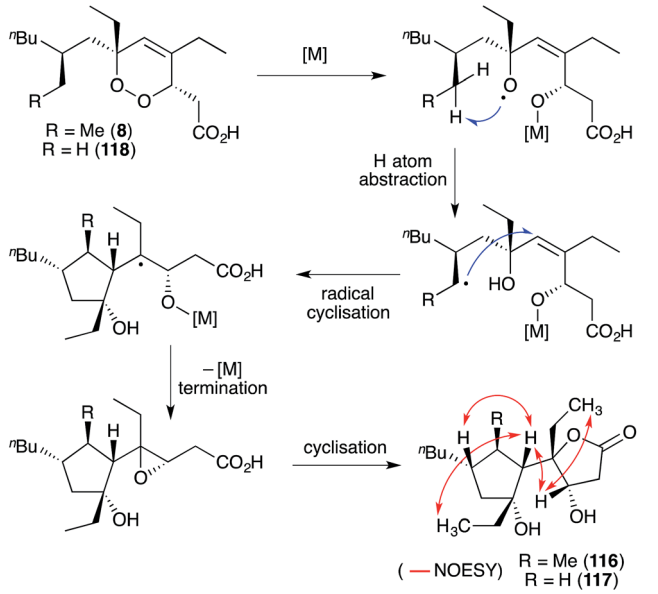
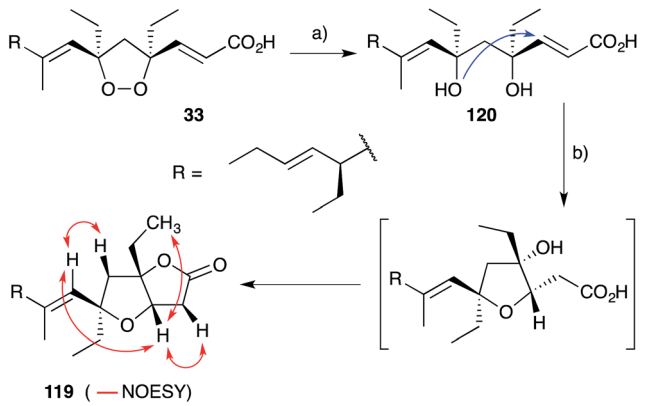


Fig. 3 Plakortethers A (**109**), B (**110**), D–G (**111–114**) and simplakidine A (**115**) from *Plakortis simplex*.



Scheme 31 Postulated biosynthesis of simplextones A (**116**) and B (**117**) from haterumadioxin B (**8**) and endoperoxide **118**, respectively. Selected NOESY correlations of compound **116** shown as red arrows. M = metal.



Scheme 32 Synthesis of plakortone B (**119**) from plakortide E (**33**). Selected NOESY correlations of natural **119** shown as red arrows. (a) Zn, AcOH, CH_2Cl_2, 0 °C to r.t., 2 h, 99%; (b) DBU, toluene, reflux, overnight, 90%.

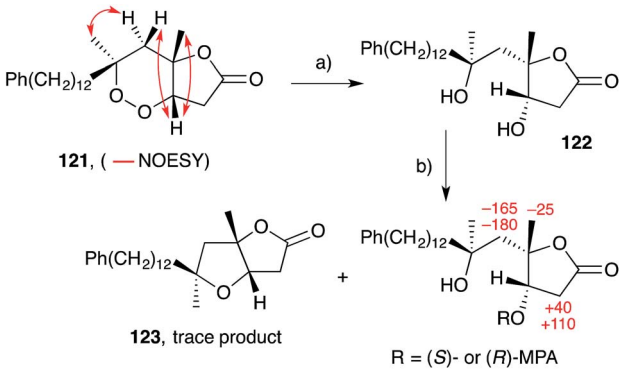
plakortethers A (**109**), B (**110**), D–G (**111–114**)[169] and simplakidine A (**115**)[170] are all reported to share a similar carbon framework, indicating that each analogue most likely arises from the reductive ring opening of **1**, with the termination of radical **106** taking a different mechanistic course in each case (Fig. 3). Plakortethers A (**109**), B (**110**), D (**111**) and E (**112**) are cytotoxic against the RAW 264-7 (murine macrophage) cell line in the range 7–12 μg mL^{-1};[169] and an asymmetric total synthesis of **113** and **114** was completed by Novikov and co-workers in 2009, exploiting symmetrical aspects of the central carbon frame.[171]

4.2 Simplextones A and B

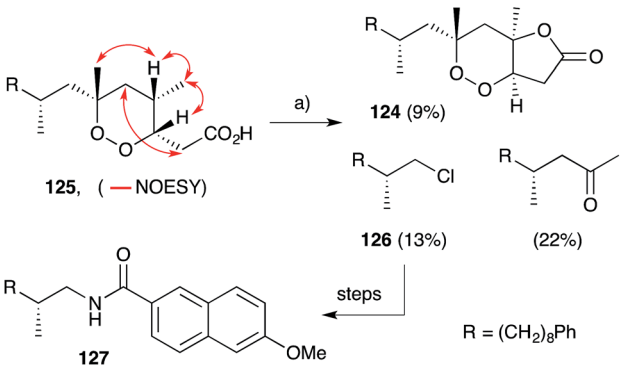
Simplextones A (**116**) and B (**117**),[172] recently isolated from *Plakortis simplex*, have an unprecedented skeletal arrangement with a substituted cyclopentane carbocycle connected to a γ-lactone motif by a single C–C bond (Scheme 31). Their structures and absolute configuration were determined by X-ray crystallography, application of Mosher's method, detailed NMR analysis (selected NOESY correlations of compound **116** shown in Scheme 31) and quantum calculation of the CD spectra.[172] The continuous carbon backbone of **116** and **117** is remarkably similar to that of **1** and hence, the plakortethers. We speculate that simplextones A (**116**) and B (**117**) may in fact result from reductive ring opening, radical cyclisation and lactonisation of the known endoperoxides haterumadioxin B (**8**)[19] and **118**,[143] respectively (Scheme 31).

4.3 Plakortones A–F, L, N, P and simplexolides A–E

Plakortones A–F, L, N and P[22,27,47,173] were isolated from marine sponges of the genera *Plakortis* and *Plakinastrella*. Each natural product is characterised by a common 2,6-dioxabicyclo[3.3.0] octan-3-one (furanolactone) motif, yet two distinct pathways of biogenesis have been identified. Following their synthesis of plakortide E (**33**, Section 2.2), Wong and co-workers[86] demonstrated the facile conversion of **33** to plakortone B (**119**) by reduction to diol **120**, itself related to a natural product isolated in 1993,[174] oxa-Michael cyclisation and lactonisation (Scheme 32). Impressively, this conversion was achieved with full stereocontrol for the desired bicyclic framework (NOESY correlations of natural **119** shown in Scheme 32)[22] providing strong evidence that natural **119** is derived from the reduction of **33**. In contrast, through application of Mosher's method to determine the absolute configuration of plakortolide L (**121**), Garson found that *seco*-anologue **122** undergoes dehydration and oxa-Michael cyclisation to yield plakortone L (**123**), directly (Scheme 33).[47] The relative structures and absolute configurations of plakortolide L and plakortone L were thus determined as (3*S*,4*S*,6*S*)-**121** and (3*S*,4*S*,6*S*)-**123**, respectively; and the biogenesis of **123** from **121** was implicated. Plakortones A–D are activators of cardiac



Scheme 33 Conversion of natural plakortolide L (**121**) to plakortone L (**123**). Change in chemical shift, expressed as shift of (*R*)-MPA compound subtracted from shift of (*S*)-MPA compound (in Hz) and shown as red numbers. (a) Zn, AcOH, Et_2O, r.t., 16 h, 83%; (b) (*S*)- or (*R*)-MPA, DCC, DMAP, CH_2Cl_2, r.t., overnight. MPA = methoxyphenylacetate.

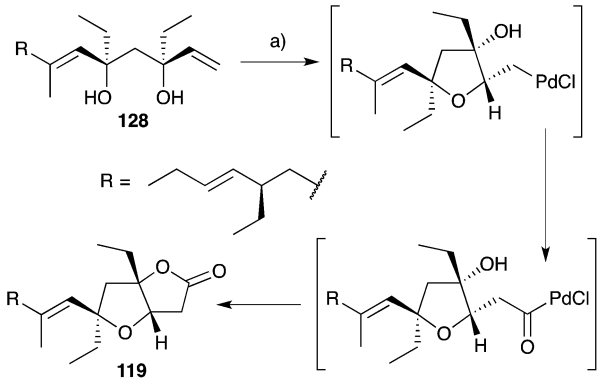


Scheme 34 Assigning the remote stereocenter of plakinic acid I (**125**) by chemical derivatisation and liposomal circular dichroism. Also, biomimetic conversion of plakinic acid I (**125**) to plakortolide B (**124**) through a complex "chloro-Fenton" reaction. Key NOESY correlations of compound **125** shown as red arrows. (a) $FeCl_2$, CH_3CN, H_2O, r.t., 45 min.

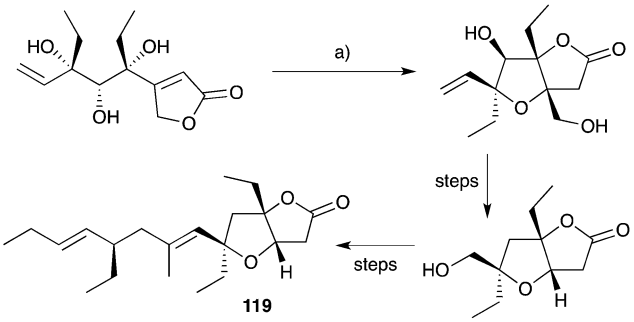
sarcoplasmic reticulum Ca^{2+} ATPase at micromolar concentrations[22] and plakortones B–F exhibit *in vitro* cytotoxicity against WEHI 164 murine fibrosarcoma cells.[173]

It is also interesting to note that plakortolide B (**124**), a structural homologue of **121**, has been accessed directly from plakinic acid I (**125**) on treatment with $FeCl_2$, presumably through a complex "chloro-Fenton" reaction (Scheme 34).[37] The conditions also gave rise to the expected chloride **126**, which was advanced to napthyl amide **127** and used to determine absolute configuration of the remaining stereocenter with a novel analytical technique, liposomal circular dichroism.[37]

Semmelhack[175,176] and Kitching[177–180] have independently developed palladium-mediated carbonylation reactions of diols such as **128** (which can be considered a structural analogue of **120**, the putative biosynthetic intermediate relating **33** and **119**) in the synthesis of plakortone natural products (Scheme 35).[176] Wong also completed the total synthesis of **119** independent to that of **33**, constructing the furanolactone system by oxa-



Scheme 35 Synthesis of plakortone B (**119**) by palladium(II)-mediated carbonylation. (a) $PdCl_2$, $CuCl_2$, NaOAc, AcOH, CO (1 atm), 23 °C, 24 h, 75%.



Scheme 36 Synthesis of plakortone B (**119**) by oxa-Michael cyclisation and transesterification. (a) DBU, toluene, reflux, 72 h, 90%.

Michael cyclisation and transesterification of a suitable butenolide (once again, drawing upon the intermediacy of a diol similar to **120**, Scheme 36).[181,182] In other works, Mehta constructed the core bicycle from simple Morita–Baylis–Hillman adducts;[183] Thornhill used an intramolecular Wittig reaction to build the furanolactone core;[184] Ohira successfully effected iodolactonisation of a dihydrofuran to construct plakortone E;[185] and most recently, Sugimura developed a [3 + 2] annulation strategy for the total synthesis of **123**.[186]

Simplexolides A–E (**129–133**, Fig. 4)[152] represent interesting structural analogues of the plakortone natural products, which

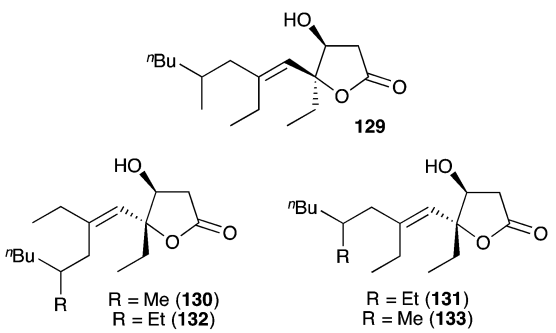
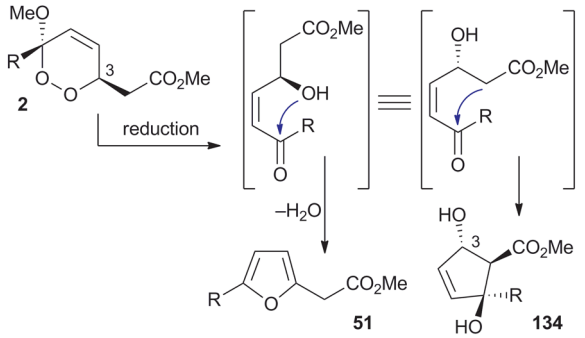


Fig. 4 Simplexolides A–E (**129–133**) from *Plakortis simplex*.



Scheme 37 Postulated reduction and cyclisation reactions of chondrillin (**2**) to give plakorsin A (**51**) and plakevulin A (**134**).

appear to arise from the tertiary alcohol dehydration of reduced peroxylactones analogous to compound **122** (Scheme 33).

4.4 Plakorsins A, B and plakevulin A

Plakorsins A (**51**), B[113] and plakevulin A (**134**)[187–190] were each isolated from *Plakortis* sponges and share a carbon framework that appears to be related to chondrillin (**2**, Scheme 37). While it is clear that plakorsin A (**51**) is likely to arise from the reduction of **2** itself, the biosynthetic origin of plakevulin A (**134**) is less certain. Due to their structural similarity, it has been suggested that **134** may arise by enzymatic reduction of untenone A (**44**).[187] However, we speculate that **134** may be generated from the reduction and Dieckmann condensation of **2** (Scheme 37), in a process analogous to the accepted biosynthesis of **44** (Section 3.1). Furthermore, the absolute configuration of plakevulin A (**134**) at C3, as determined by asymmetric synthesis,[189,190] matches that of chondrillin (**2**).

5. Therapeutic potential and biological activity

Continued interest in the isolation, structural elucidation and chemical synthesis of peroxide and peroxide-derived sponge metabolites is fuelled by their potential for development as therapeutic agents in the treatment of infectious diseases, cancers and physiological disorders. Many of the compounds presented in this review have promising activity for one or more therapeutic targets, and some exhibit selectivity for these targets against other microorganisms and non-tumour cells. However, the cytotoxicity of polyketide endoperoxides is often a factor that must be considered in the hope of producing desirable lead compounds. While a number of research groups have recently begun to address this challenge, managing the cytotoxicity of peroxide and peroxide-derived sponge metabolites remains an ongoing difficulty.

Potency has widely been attributed to the presence of 1,2-dioxane heterocycles, normally appended with a terminal acetate group, through their action as an oxidant. The rearranged congeners, where the peroxide functional group is lost, are typically less active for the desired target and also tend to have lower levels of cytotoxicity.[24,44,51,144] Endoperoxides appended with a free acid are normally more potent than their corresponding esters.[25,29,32,35,62] In some instances, the esterification of peroxyacids and their rearrangement to non-peroxide containing homologues has been attributed to prolonged storage in alcoholic solvents during specimen extraction.[29,51]

5.1 Infectious diseases

Since the discovery of peroxide metabolites as effective antimalarial agents, plakortin (**1**) and its related compounds have been routinely screened for antiplasmodial activity, especially against chloroquine-resistant strains. Although their mechanisms of action are still unclear, a number of studies have focused on understanding the structural requirements and limitations of plakortin-related 1,2-dioxanes as novel targets for treating malaria.

Plakortin (**1**) and its dihydro analogue **28** show good activity against the chloroquine sensitive D10 strain (IC_{50} 1.12–1.26 μM) and chloroquine resistant W2 strain (IC_{50} 0.74–0.76 μM) of *Plasmodium falciparum*.[65] Greater potency for the resistant strain follows the same trend as artemisinin and further demonstrates that polyketide endoperoxides do not share the same mechanism of resistance as chloroquine.[65] Recently, detailed studies on the structure–activity relationships (SARs) of plakortin (**1**) and plakortin-related scaffolds have shown that the formation of discrete carbon centered radicals plays a key role in their effect.[166,191] Other SAR studies on the dioxane scaffold have generated novel synthetic compounds, which maintain antiprotozoal activity and significantly reduce cytotoxicity.[88,99–101] Schwarzer recently discovered that plakortin (**1**) can induce lipid-peroxidation and a marked increase of the lipoperoxide breakdown product 4-hydroxynonenal, which conjugates to *P. falciparum* proteins critically involved in its cellular function.[66]

Manadoperoxides A–K were evaluated extensively for antitrypansomal activity. Most showed excellent activity against *Trypanosoma brucei rhodesiense* including manadoperoxide I (IC_{50} 0.062 μg mL^{-1}) and K (IC_{50} 0.087 μg mL^{-1}) with low levels of cytotoxicity against HMEC-1 (IC_{50} > 10 μg mL^{-1}).[15–17] Interestingly, Taglialatella–Scafati found that manadoperoxide B (**135**) had greater potency against *T. b. rhodesience* (IC_{50} 0.003 μg mL^{-1}) compared to *P. falciparum* (IC_{50} 2.30 μg mL^{-1}), whereas peroxyplakoric ester B_3 (**136**) had greater potency against *P. falciparum* (IC_{50} 0.040 μg mL^{-1}) compared to *T. b. rhodesience* (IC_{50} 3.61 μg mL^{-1}); and that notably, they only differ by the placement of methyl groups on an otherwise identical core structure (Fig. 5).[16] Furthermore, the isomeric compound **137** maintained activity against *T. b. rhodesience* (IC_{50} 0.011 μg mL^{-1}) but had increased cytotoxicity against L6 cells (IC_{50} 3.80 μg mL^{-1}).[17] Further SAR-based studies revealed the importance of the peroxyketal heterocycle and length of the lipophilic tether for antiprotozoal activity.[15–17]

Plakortide endoperoxides have similarly attracted interest as potential therapeutic agents for tropical diseases. Plakortide F was active against *P. falciparum* (IC_{50} 0.39–0.48 μg mL^{-1}) and cytotoxic against a number of cancer cell lines *in vitro*, but failed to prolong life expectancy when treating *Plasmodium* infected mice.[27] In the same study, plakortone G was found to be highly

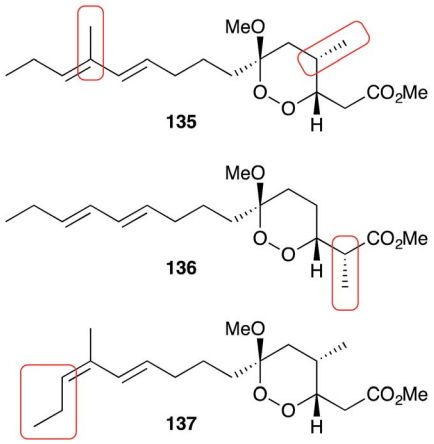


Fig. 5 The minor structural differences of manadoperoxide B (**135**), peroxyplakoric ester B_3 (**136**) and 12-isomanadoperoxide B (**137**), which greatly effect their antiprotozoal activity and cytotoxicity.

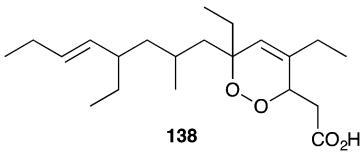
cytotoxic with no apparent selectivity. Plakortide P (**10**) had antiparasitic activity against *Leishmania chagasi* (IC_{50} 0.5–1.9 μg mL^{-1}) with low toxicity against human macrophages (IC_{50} 16.6 μg mL^{-1});[20] and plakortide I, possessing an unsaturated ketone, was effective when tested against *P. falciparum* (IC_{50} 0.57 μg mL^{-1}) but inactive against a panel of other pathogenic bacteria and fungi.[26] Plakortide E (**24**) was also found to be a non-competitive, slow-binding and reversible inhibitor of rhodesain from *T. B. rhodesience* (IC_{50} 5 μM) without cytotoxic effects against J774.1 macrophages at 100 μM.[30]

Recently, the novel endoperoxide metabolite gracilioether H was reported to be active against the chloroquine resistant FC29 strain (IC_{50} 3.3 μM) of *P. falciparum* with low cytotoxicity for vero cells (DT_{50} 324 μM).[160]

Other metabolites in this class have also been tested for activity against pathogenic fungi and bacteria with promising results. Plakinic acid M was active toward a number of *Cryptococcus* fungi (MIC_{90} 2.4–13 μM);[32] manzamenone O (**69**) was effective against *Micrococcus luteus* (MIC 4 μg mL^{-1}), *Apergillis niger* (IC_{50} 8 μg mL^{-1}) and *Trichophyton mentagrophytes* (IC_{50} 8 μg mL^{-1});[133] and hippolachnin A (**98**) was shown to have potent antifungal activity against *Cryptococcus neoformans*, *Trichophyton rubrum* and *Microsporum gypseum* (MIC 0.4 μM).[155]

5.2 Anticancer activity

The cytotoxic effects of many peroxide and peroxide-derived sponge metabolites have prompted numerous studies into their suitability as anticancer leads. Costa-Lotufo found that plakortide P (**14**) and a number of structural analogues were cytotoxic against HCT-116 cells, causing arrest at the G_2/M stage.[31] However, the co-isolated furanylidenes *des*-hydroxygracilioether C (**90**) and spongosoritin A induced arrest at the G_0/G_1 stage, indicating that the two structural subclasses have distinct modes of antimitotic action. Furthermore, while the peroxides showed low selectivity for tumour cells compared to non-tumour cells, compound **90** was more selective with IC_{50} 8.1 μM for HCT-116 and IC_{50} > 163 μM for MRC-5 cells.[31] Plakinic acids A–D and a number of structural analogues were found to be remarkably cytotoxic against L1210 murine leukemia (IC_{50} 0.003–0.052 μg mL^{-1});[39] and endoperoxide **138** showed significant *in vitro* cytotoxicity against P388 cells (IC_{50} 0.055 μg mL^{-1}), but failed to induce a response *in vivo*.[49,91]



Other work has specifically targeted the inhibition of DNA polymerase (pol) enzymes. Manzamenone A (**53**) showed inhibition of polα (IC_{50} 1.9 μM), β (IC_{50} 3.2 μM) and human terminal deoxynucleotidyltransferase (IC_{50} 2.5 μM).[124,125] Untenone A (**44**) demonstrated greater selectivity for polα (IC_{50} 4.3 μM);[125] plakevulin A (**134**) was a moderate inhibitor of polγ (IC_{50} 7.5 μg mL^{-1});[187] and a number of synthetic analogues of plakoridine A (**71**) and B (**72**) showed greater inhibition of polα and β than the natural products.[127]

5.3 Physiological disorders

Peroxide-derived sponge metabolites have also been reported as useful compounds for the investigation of a range of physiological disorders, including type II diabetes, heart failure and inflammation. Gracilioether B (**85**) and plakilactone C were recently shown to be selective covalent agonists of peroxisome proliferator-activated receptor γ (PPARγ, EC_{50} 2–5 μM), a known pharmacological target for the treatment of type II diabetes, undergoing thio-Michael addition of the lower binding domain cysteine residue to the unsaturated ketone of the natural products.[146] Both compounds were found to regulate the expression of PPARγ-dependent genes in the liver and inhibit the generation of inflammatory mediators.[146] In contrast, gracilioether C (**86**) was found to be a non-covalent agonist (EC_{50} 10 μM) and its *des*-hydroxy homologue (**90**) a non-covalent antagonist.[146] In a separate study, manzamenones B (**54**) and E (**57**) showed inhibition of T-cell protein tyrosine phosphatase (IC_{50} 2.5–3.2 μM) and protein tyrosine phosphatase-1B (IC_{50} 10.8–13.5 μM), also implicated in the treatment of type II diabetes.[126]

Plakortone D activated sarcoplasmic reticulum Ca^{2+} ATPase (EC_{50} 2.8 μM), a protein associated with cardiac muscle relaxation abnormalities, improving calcium uptake at a similar level to that reported for gingerol.[22] 3-*epi*-Plakortin was also found to be an activator, while the longer chain co-isolates plakortides F–H were less active.[23] Interestingly, the ability of polyketide endoperoxides to stimulate calcium uptake is also suggested to play a role in their antimitotic and antifungal activity.[31,192]

Finally, gracilioethers E (**100**), G and I–K were found to be agonists of pregnane-X-receptor, a novel pharmacological target for the treatment of various inflammatory and metabolic disorders, when administered in combination with rifaximin.[162]

6. Concluding remarks

Since their discovery in the late 1970s, plakortin (**1**) and chondrillin (**2**) have been the centerpiece of a global research effort to

uncover, elucidate and synthesise peroxide and peroxide-derived metabolites from marine sponges. Literature in the chemical sciences is now laced with novel polyketide substances related to **1** and **2** and synthetic methods to effectively construct and arrange their unique and often complex structural components. These efforts, especially those targeting the chemical synthesis of peroxide-derived natural products, have increasingly become inspired by a desire to understand the fascinating decomposition pathways and inherent structural rearrangements of these peroxide substrates. Their potential as therapeutic agents for a wide range of infectious diseases, cancers and physiological disorders adds further motivation for the investigation of this class of compound. Incredibly, investigations in the field to date places the sponge metabolites chondrillin (**2**) and plakorin (**3**) as sole non-enzymatic progenitors to the natural products untenone A (**44**), plakortic acid (**45**), plakorsin A (**51**), manzamenone A–F (**53–58**) and H (**59**) with many others expected. Furthermore, plakortin (**1**) and 4,5-unsaturated-1,2-dioxane analogues such as haterumadioxin A (**7**) and B (**8**), are thought to be directly responsible for the occurrence of plakortethers A–G (**108–114**), simplakidine A (**115**), gracilioethers B (**85**), C (**86**), D, hippolachnin A (**98**) and spiroplakortone plus many more.

However, efforts to elucidate the biosynthesis of peroxide-related metabolites have only begun. Understanding the assembly of complex polycyclic structures such as gracilioethers A (**92**), E (**100**), F (**95**), G–J, K (**96**), manzamenones K (**68**), O (**69**), untenolide A (**70**), simplextones A (**116**) and B (**117**) remains a challenge of significant novelty and interest. Feasible preparation of such intricate substrates on the scale required in a pharmaceutical context will undoubtedly be aided by consideration of how they are assembled in nature.

7. Acknowledgements

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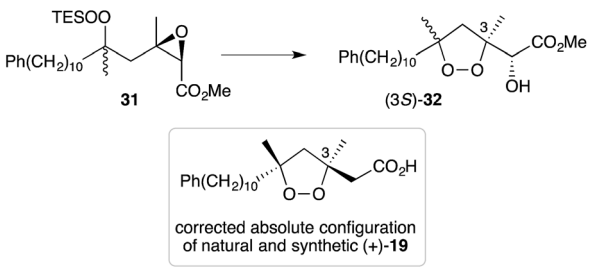

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