Hot off the Press

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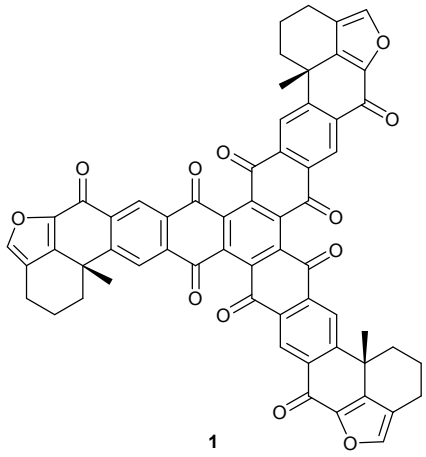
Abstract: A personal selection of 32 recent papers is presented covering various aspects of current developments in bioorganic chemistry and novel natural products such as chrysamide A from a deep-sea fungus *Penicillium chrysogenum*.

The marine sponge *Petrosia alfiani* is a rich source of the xestoquinone derivatives, petroquinones A – L, including the trimeric petroquinone A **1**.[1] Biosynthetic pathways to some of the petroquinones have been proposed. The first example of a trimeric phthalide derivative, angesinenolide A **2** has been isolated from roots of *Angelica sinensis* together with the dimeric derivative angesinenolide B **3**.[2] The structures of both angesinenolides A **2** and B **3** were confirmed by X-ray analyses. The angesinenolides show interesting anticoagulation activities.



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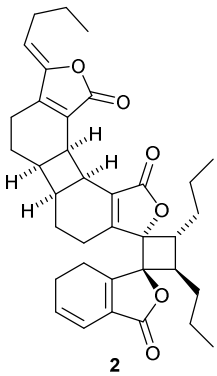

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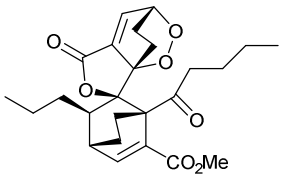
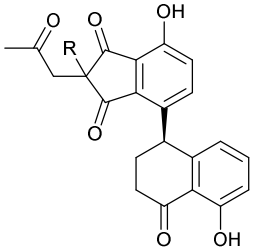
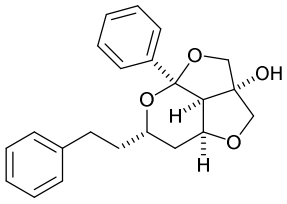


3

Clindanones A **4** and B **5** are metabolites of a deep-sea derived fungus *Cladosporium cladosporioides*.[3] It is proposed that the clindanones are formed from two polyketide precursors and that the biosynthesis involves a ring contraction step. The structure of diocollettines A **6**, from rhizomes of *Dioscorea collettii*, was established by X-ray analysis.[4] Diocollettines A **6** appears to be formed from a diarylheptanoid together with a 3-carbon unit.



4 R = αOH
5 R = βOH



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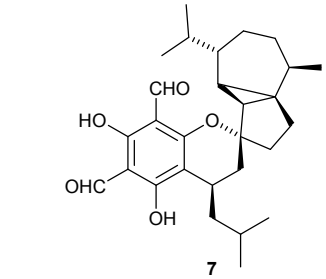
Nine phloroglucinol meroterpenoids, eucalrobusones A – I have been isolated from the leaves of *Eucalyptus robusta* including the first examples of phloroglucinol meroterpenoids with cubebane sesquiterpenoid components, such as eucalrobusone G **7**.[5] The modified bisabolane sesquiterpenoids artaboterpenoids A **8** and B **9** have been found in the roots of *Artabotrys hexapetalus*.[6] Artaboterpenoid A **8** has a 2,8-cyclised structure and the racemic artaboterpenoid B **9** is the first example of a 2,3-cleaved bisabolane derivative. Caesalpinone A **10**, from pods of *Caesalpinia spinosa*, is the first example of a 1,15-cyclised gorgonane sesquiterpenoid.[7] A terpene cyclase from *Streptomyces pristinaespiralis* produces a sesquiterpenoid with a novel framework,

pristinol **11**.[8] The structure of pristinol **11** was confirmed by X-ray analysis. A biosynthetic pathway to this regular sesquiterpenoid involving cyclisation of a humulyl cation has been proposed.



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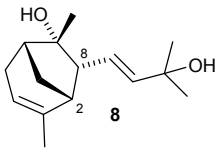

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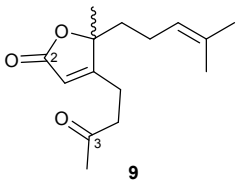

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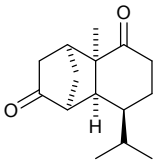

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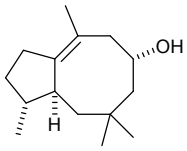

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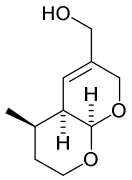
The structure of secoarguterin **12**, from the roots of *Incarvillea argute*, was confirmed by synthesis.[9] Secoarguterin **12** is the first example of a 5,6-secoiridoid. Delavatine A **13** has a new alkaloid skeleton from *Incarvillea delavayi*.[10] The authors propose a biosynthetic pathway to delavatine A **13** from two iridoid precursors.



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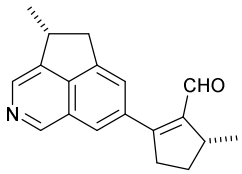

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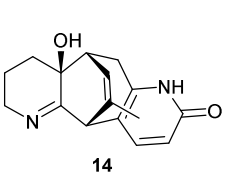
The *lycopodium* alkaloid phlefargesiine A **14**, from the club moss *Phlegmariurus fargesii*, has a new skeleton.[11] Two biosynthetic pathways to phlefargesiine A **14** have been suggested. Flavesine A **15** is a member of a novel group of dimeric matrine alkaloids from roots of *Sophora flavescens*.[12] The structure of flavesine A **15** was confirmed by X-ray analysis. Biosynthetic pathways to the flavesines have been proposed.



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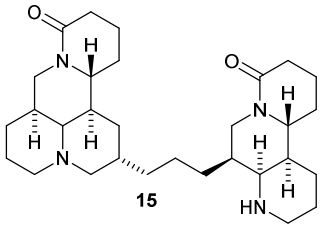

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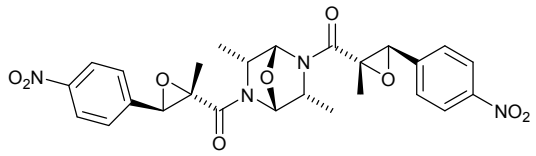
Chrysamides A **16**, B and C are dimeric 4-nitrocinnamoyl amides from a deep-sea fungus *Penicillium chrysogenum*.[13] The structure of chrysamide A **16**, with a novel 2,5-diaza-7-oxabicyclo[2.2.1]heptane ring system, was confirmed by X-ray analysis. Proposed biosynthetic pathways to the chrysamides, from phenylalanine and glycine, have been presented. A termite-associated fungus *Pseudoxylaria* species produces a group of cyclic tetrapeptides such as pseudoxylallemycin B **17** which has interesting allene moieties.[14]



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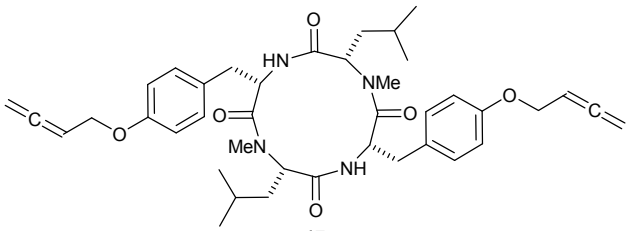
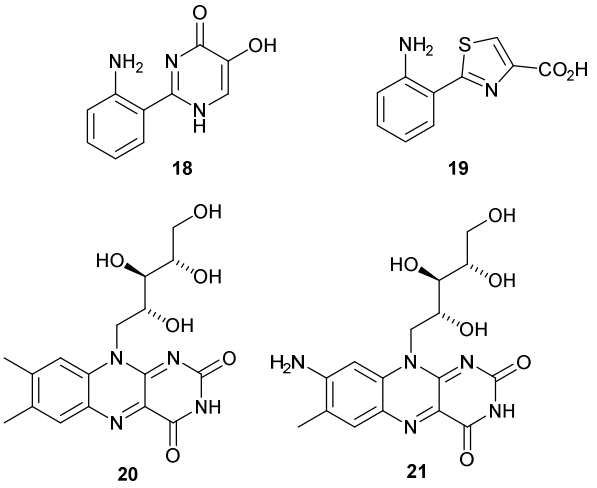
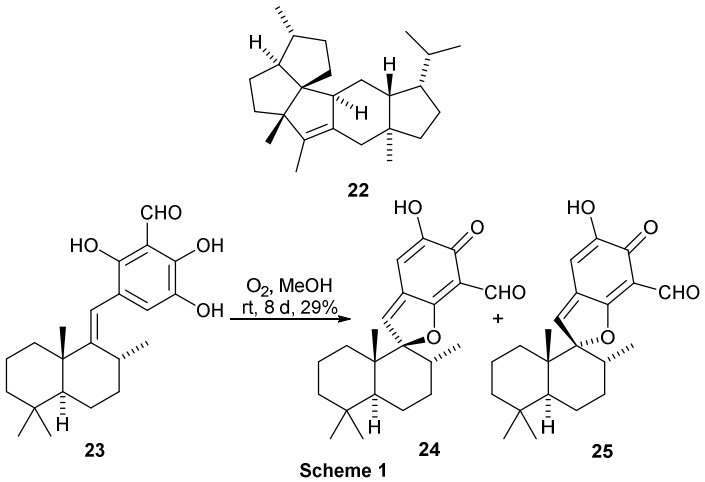


17

The original structure **18** proposed for thiasporine A, a metabolite of a marine-derived *Actinomycetospora chlora*, has been shown to be incorrect by synthesis.[15] The revised structure **19** for thiasporine A has also been synthesised. An enzyme, involved in the biosynthetic pathway to roseoflavin, has been identified that converts the C8 methyl group of riboflavin **20** into an amino group in **21** using glutamate as a nitrogen donor.[16]

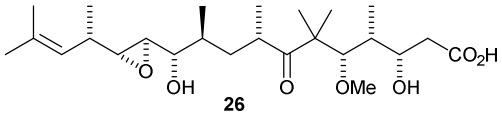


A bifunctional sesterterpene synthase EvQS from *Emericella variecolor* NBRC 32302 has been characterised and shown to produce quiannulatene **22**, which has a novel, highly congested carbon skeleton.[17] In vitro and in vivo labelling experiments have identified the mechanism of cyclisation of the precursor, geranylfarnesyl pyrophosphate to quiannulatene **22** through various hydride shifts and C–C bond migrations. Siphonodictyal B **23**, a meroterpenoid from the tropical marine sponge *Aka coralliphagum* has been shown to undergo spontaneous aerobic oxidation to give natural products corallidictyals A **24** and B **25** (Scheme 1).[18] The ease of cyclisation and the ratio of diastereomeric products produced during this process strongly suggests that corallidictyals A **24** and B **25** are artefacts of the isolation process.



Scheme 1

To elucidate the timing of how C-methyltransferases (MT) install α-methyl groups into nascent polyketide backbones, five monomethylating MTs and one gem-dimethylating MT, from the biosynthesis of gephyronic acid **26**, have been studied.[19] All six MTs were active against β-ketoacylthioester substrates but inactive with the corresponding malonyl thioester substrates, which suggests that MT-catalysed methylation occurs directly after ketosynthase-mediated condensation. A new secondary metabolite, haprolid **27**, comprising of four modified amino acids and a polyketide fragment has been isolated from myxobacteria.[20] Bioinformatic analysis of the biosynthetic gene cluster and total synthesis was required to establish the stereochemical assignments. Haprolid **27** also showed selective, nanomolar cytotoxicity against various cell lines.



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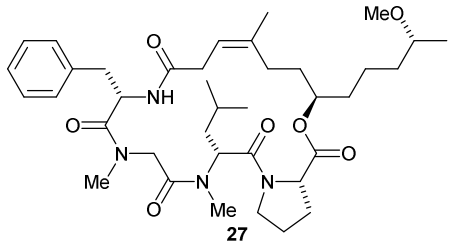

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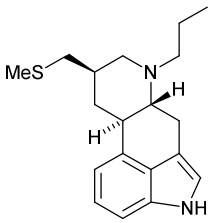
McCabe and Wipf have reviewed the biosynthesis and total synthesis of the clavine subfamily of ergot alkaloids, highlighting pharmaceutical applications such as that of the semi-synthetic clavine alkaloid pergolide **28**, which is used to treat Parkinson's disease.[21] The isolation, characterisation and biosynthesis of the prodiginine bacterial alkaloids such as prodigiosin **29** have also been reviewed.[22] The review describes how total synthesis has been used for structural elucidation and structural revision of the prodiginines.



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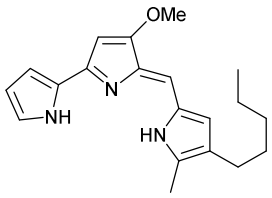

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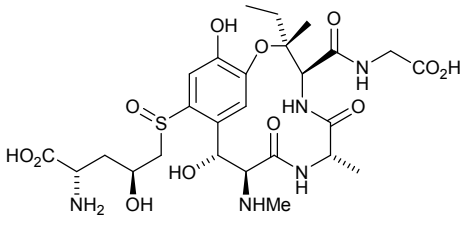
Gene inactivation and heterologous expression studies have revealed the biosynthetic pathway of the ribosomally synthesised and post-translationally modified peptide ustiloxin B **30** in fungi.[23] The key role of the enzymes UstA/Q/Ya/Yb in macrocyclic ring formation has been elucidated as well the involvement of two homologous flavin adenine dinucleotide-dependent enzymes and a pyridoxal 5'-phosphate-dependent enzyme in side-chain modifications. The key transformations in the biosynthesis of bottromycin A_2 **31**, another ribosomally synthesised and post-translationally modified peptide have been identified using an untargeted metabolomics approach.[24] In particular, a YcaO domain and a partner protein were shown to catalyse together macrocyclisation resulting in formation of the structurally unique amidine ring system.



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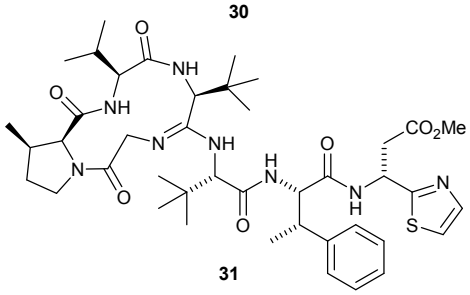

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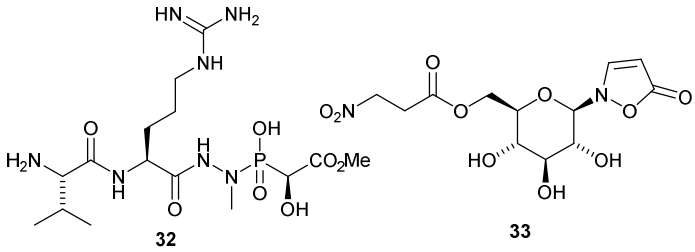
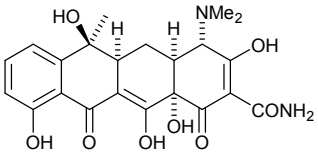
Analysis of the biosynthetic pathway of the phosphonate natural product fosfazinomycin A **32** has revealed the activities of five proteins from its gene cluster.[25] Two of these enzymes, a flavin-dependent oxygenase FzmM and a 3-

carboxymuconate cycloisomerase FzmL were shown to convert L-aspartic acid to fumarate and nitrous acid. Further studies using metabolic labelling experiments showed that at least one of the nitrogens in the hydrazide moiety of fosfazinomycin A is derived from L-aspartic acid. Isotopic labelling studies have also been used to establish the biosynthesis of an isoxazolin-5-one glucoside **33** from β-alanine in Chrysomelina larvae.[26] Both the 3-nitropropanoate and isoxazolinone moieties are formed from β-alanine by successive oxidations of the amino group.



32 **33**

The commercially available tetracycline antibiotics have been shown to be substrates for the marine derived fungus *Paecilomyces* species.[27] For example, tetracycline **34** was converted to *seco*-cycline A **35** (Scheme 2), while compounds such as oxytetracycline were transformed to the corresponding *hemi*-cyclines. The authors comment on the potential threat of tetracycline antibiotic-degrading fungi. An enzymatic cascade process involving a dynamic reductive kinetic resolution by ketoreductases, coupled with a nitrile hydratase and amidase from whole cells of *Rhodococcus rhodochrous* has been developed for the stereoselective synthesis of cyclic β-hydroxyacids.[28] The combination of a fast racemisation process before ketoreduction and then hydrolysis of the β-hydroxynitrile rather than the starting β-ketonitrile resulted in a highly efficient process for a range of substrates (e.g. Scheme 3).



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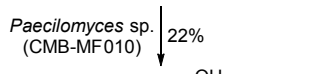

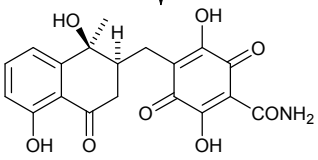

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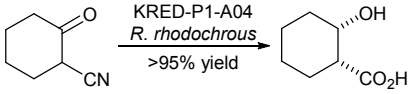
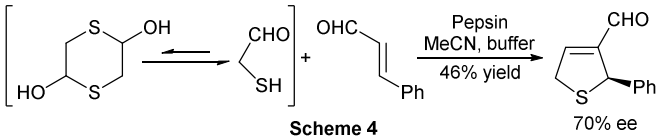
Scheme 2



Scheme 3

>99:1 dr
>99% ee

Optically active dihydrothiophenes have been prepared from 1,4-dithiane-2,5-diol and a range of α,β-unsaturated aldehydes using a pepsin-catalysed domino thia-Michael/aldol condensation cascade process (Scheme 4).[29] Site-directed mutagenesis showed that the reaction took place in the active site of pepsin and involved two aspartate residues. Directed evolution of tryptophan synthase from *Pyrococcus furiosus* has generated an engineered biocatalyst that will accept L-threonine as a substrate, producing (2*S*,3*S*)-β-methyltryptophan with excellent stereoselectivity (Scheme 5).[30] Various indole analogues were found to be accepted as the nucleophile by the enzyme, resulting in the asymmetric synthesis of a wide range of β-methyltryptophan scaffolds.



Scheme 4

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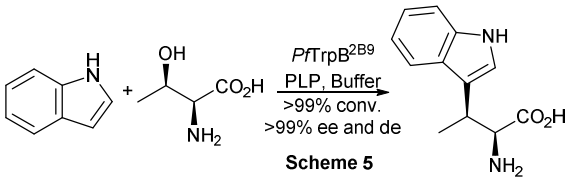
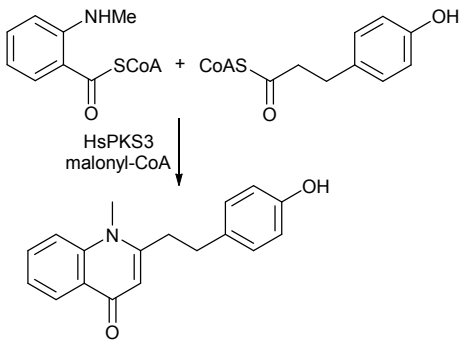
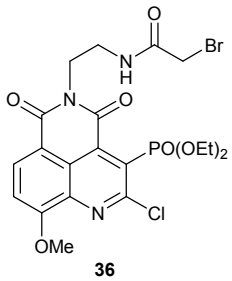


Scheme 5

A new type III polyketide synthase (PKS) from *Huperzia serrata*, which produces curcuminoids, benzalacetone and quinolone was also shown to form 2-substituted quinolones and 1,3-diketones via head to head condensation of two different substrates.[31] For example, reaction of *N*-methylanthraniloyl-CoA with *p*-hydroxypropinoyl-CoA in the presence of HsPKS3 and malonyl-CoA gave the corresponding quinolone alkaloid (Scheme 6). A series of solvatochromic naphthalimide-quinoline hybrid fluorophores that display large Stokes shift and photostability have been incorporated into amino acids and peptides as new tools for biological imaging.[32] For example, incorporation of **36** into a CDK5 kinase derived peptide allowed detection of its regulatory partner, endogenous p25 in living glioblastoma cells.



Scheme 6



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