Hot off the Press

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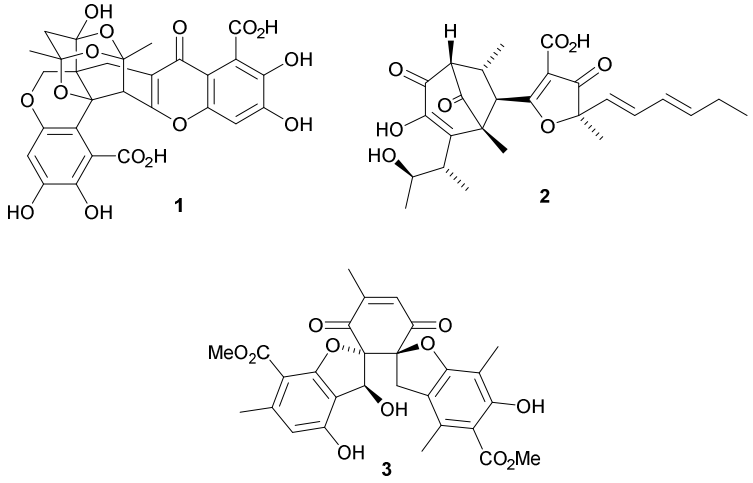
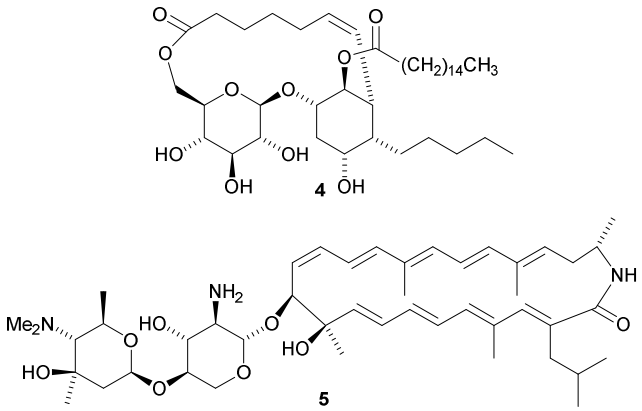
Abstract: A personal selection of 32 recent papers is presented covering various aspects of current developments in bioorganic chemistry and novel natural products such as huperphlegmine A from *Huperzia phlegmaria*.

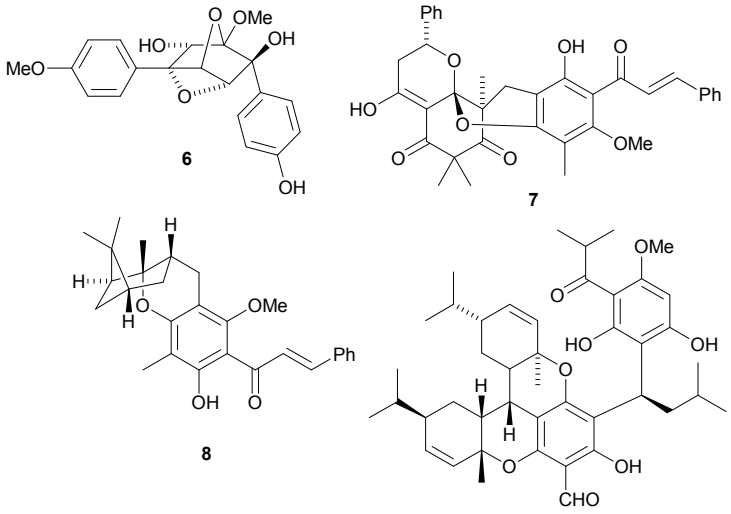
The structure of citrofulvicin **1**, a racemic metabolite from *Penicillium velutinum*, was confirmed by X-ray analysis.[1] It is proposed that the unprecedented framework of citrofulvicin **1** is formed by nonenzymatic Diels-Alder cycloaddition between heptaketide precursors. The structure of asperone A **2**, a metabolite of *Aspergillus* sp. AWG 1-15, was established by X-ray analysis of a methylated derivative.[2] A biosynthetic pathway to asperone A **2**, involving two polyketide precursors, has been suggested. The structure of tsavoenone A **3**, from the lichen *Parmotrema tsavoense*, was also established by X-ray anlysis.[3] A putative biosynthetic scheme for the formation of tsavoenone A **3** from a depsidone precursor, parmosidone D, has been presented.



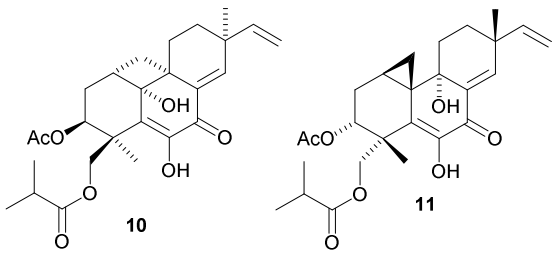
The insect-borne fungus *Mucor* sp. SNB-VECD13A produces mucorolactone **4** with a novel macrolactone skeleton that may be derived from linoleic acid.[4] Activation of a silent biosynthetic gene cluster in *Streptomyces roseosporus* produces a polyketide macrolactam, auroramycin **5**, that shows potent antibiotic activity.[5] Auroramycin **5** contains an unusual isobutyl extender unit and a novel disaccharide.

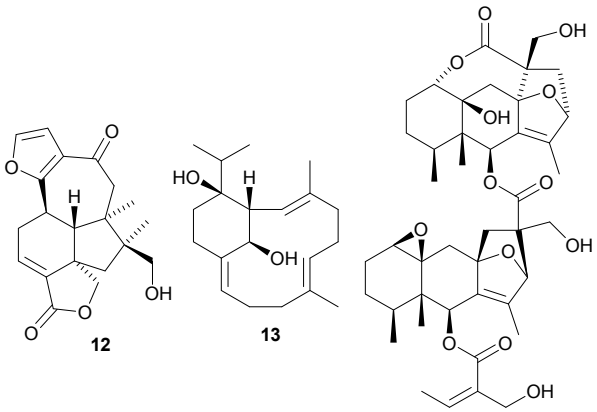


Four highly oxygenated *p*-terphenyl derivatives, including hawaiienol A **6**, have been identified as metabolites of the insect-associated fungus *Paraconiothyrium hawaiiense*.[6] Hawaiienol A **6** is the first example of a terphenyl with a 4,7-dioxatricyclo[3.2.1.$0^{3,6}$]octane unit and its structure and absolute configuration were determined by X-ray analysis. Further unusual natural products whose structures have been confirmed by X-ray analyses include cleistoperlones A **7** and C **8**, from *Cleistocalyx operculatus*,[7] and eucalyptusdimer A **9**, from *Eucalyptus robusta*.[8] Cleistoperlone A **7** is formed from two cinnamylphloroglucinol units and cleistoperlone C **8**, from a cinnamylphloroglucinol unit with α-pinene. Eucalyptusdimer A **9** has an unprecedented skeleton featuring two phelandrene and two acylphloroglucinol units. Biosynthetic pathways have been proposed for cleistoperlones A **7** and C **8** and eucalyptusdimer A **9**.



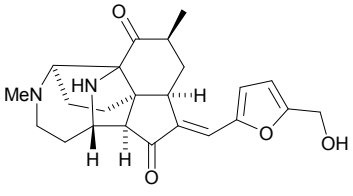
A rearranged isopimarane diterpenoid derivative featuring a fused cyclobutane ring, eutypellenone A **10**, is a metabolite of *Eutypella* sp. D-1.[9] The authors claim that eutypellenone A **10** belongs to the opposite entantiomeric series as the cometabolite libertellenone H **11**. Salvifarinin A **12**, from *Salvia farinacea*, has a cyclised and rearranged clerodane skeleton.[10] The authors propose a biosynthetic pathway to salvifarinin A **12** which is supported by a biomimetic synthesis. Mangelonoid A **13**, from *Croton mangelong*, has a novel 2,20-cyclocembrane diterpenoid skeleton.[11] The structures of salvifarinin A **12** and mangelonoid A **13** were confirmed by X-ray analyses. Four eremophilane sesquiterpenoid dimers and trimers, such as ligusaginoid A **14**, have been isolated from *Ligularia sagitta*.[12] A biosynthetic pathway to ligusaginoid A **14** has been proposed involving two Diels-Alder cycloadditions.





12 13 14

Huperphlegmine A **15**, from *Huperzia phlegmaria*,[13] and erchinine A **16**, from *Ervatamia chinensis*,[14] have new alkaloid skeletons. Biosynthetic pathways from obscurinine to huperphlegmine A **15** and from ibogaine to erchinine A **16** have been proposed. The structure of the racemic spirocyclic diketopiperazine valiecolortin A **17**, from the marine-derived fungus *Eurotium* sp. SCSIO F452, was established by X-ray analysis.[15] A biosynthetic pathway to the novel skeleton of valiecolortin A **17** has been suggested involving a hetero-Diels-Alder cyloaddition of a diketopiperazine with an anthraquinone and a Baeyer-Villiger oxidation as key steps. Isatindolignanoside A **18**, from roots of *Isatis indigotica*, is the first report of an indole linked to a lignan.[16] The authors propose a biosynthetic pathway to isatindolignanoside A **18**.



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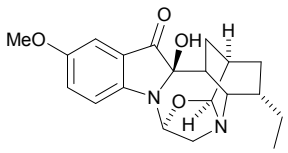

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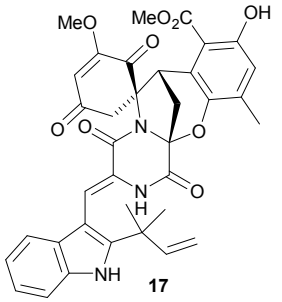

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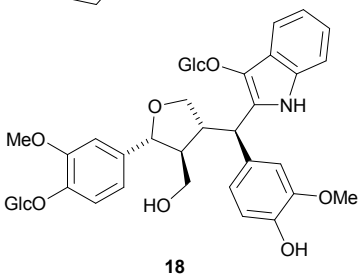

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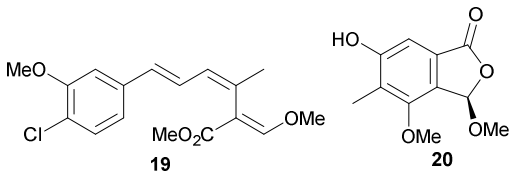
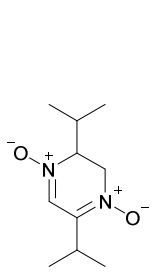
Feeding studies have been used to investigate the biosynthesis of strobilurins (e.g. strobilurin B **19**), antifungal metabolites isolated from various basidiomycetes.[17] These studies have shown that the stobilurins are formed from a linear tetraketide and a benzoate starter unit, which is produced from phenylalanine via cinnamate. The isolation of a novel biphenyl metabolite, pseudostrobilurin B confirmed the involvement of an epoxide intermediate during the formation of the β-methoxyacrylate moiety. Disruption of LaeB, a global regulator from *Aspergillus nidulans* has allowed activation of secondary metabolism and the isolation of eight cryptic compounds.[18] These include seven polyketides such as 3-methoxyporriolide **20**, an optically active phthalide.



19 **20**

Genome mining in *Pseudomonas* and overexpression of the *Pseudomonas virulence factor* (*pvf*) gene cluster has allowed the isolation of a family of pyrazine *N*-oxides, including the novel dihydropyrazine *N*,*N*'-dioxide **21**.[19] Following characterisation of the nonribosomal peptide synthetase (NRPS) responsible for the formation of these

compounds, a biosynthetic pathway from valine has been proposed. The biosynthetic gene cluster from the myxobacterium *Cystobacter violaceus* Cb vi35 that produces vioprolides (e.g. vioprolide C **22**), anticancer and antifungal compounds has been identified.[20] As well as the expression of the gene cluster in a stable heterologous host, which allowed high-titre production of these compounds, further studies revealed an *S*-adensoylmethionine (SAM)-dependent enzyme and a methyltransferase involved in the formation of the 4-methylazetidinecarboxylic acid moiety.



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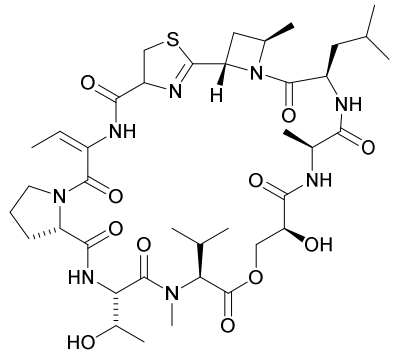

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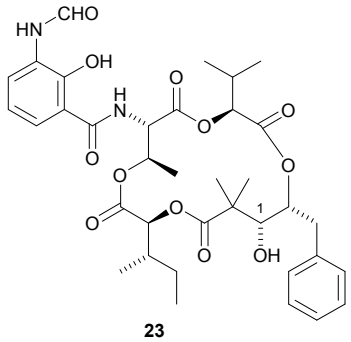
Genome sequencing and bioinformatics analysis has identified the biosynthetic gene cluster of antimycin-type depsipeptides from *Streptomyces conglobatus* such as neoantimycin A **23**, which have significant anticancer activities.[21] Heterologous expression of the partial gene cluster in *Streptomyces albus* J1074 led to the production of **23**, while bioengineering revealed an NADPH-dependent reductase responsible for formation of the C-1 hydroxyl. A unique NRPS-polyketide synthase hybrid gene cluster from *Sulfurospirillum barnesii* has been analysed and following gene expression and comparative metabolomics, led to the isolation of the lipo-dipeptide, barnesin A **24**.[22] The structure of barnesin A **24** was confirmed by total synthesis and the compound was found to have antimicrobial activity, as well as being a selective inhibitor of cathepsin B.



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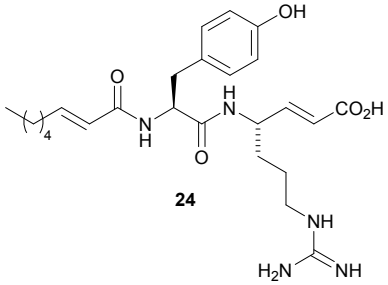

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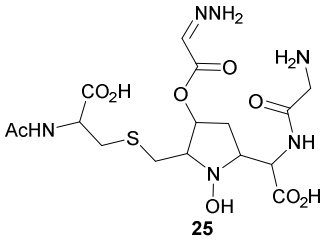
Further characterisation of the biosynthetic gene cluster from *Streptomyces* sp. SoC090715LN-17, that produces s56-p1 **25**, a dipeptide with a unique hydrazine unit has allowed the characterisation of three new enzymes.[23] A combination of in vivo and in vitro experiments has shown that these enzymes cooperate to form the hydrazinoacetic acid component of s56-p1. Genome mining and analysis of *Paraburkholderia graminis* has led to the characterisation of gramibactin **26**, an iron binding lipodepsipeptide.[24] NMR spectroscopy and in particular, complexation-induced chemical shifts were used to show that the *N*-nitrosohydroxylamine moieties are involved in metal binding.



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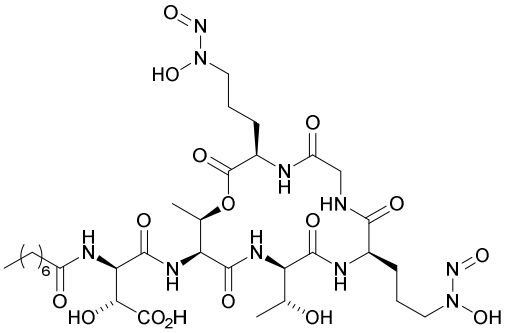

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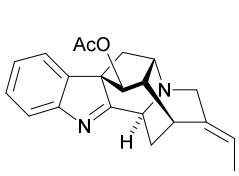
Three homologous cytochrome P450 enzymes from three indole alkaloid-producing plants have been discovered and shown to allow entry to two distinct classes of alkaloids, the sarpagans (e.g. vinorine **27**) and the β-carbolines.[25] These results reveal via a common mechanism, how distinct substrates lead to either a cyclisation or aromatisation process. The biosynthetic pathway of marinone and naphterpin natural products such as naphthgeranine A **28** have been shown to involve a cryptic halogenation, mediated by vanadium-dependent chloroperoxidase (VCPO) enzymes.[26] The VCPO-catalysed transformation involves a dearomatisation and dichlorination, followed by an α-hydroxyketone rearrangement and loss of chloride anion leaving groups, resulting in the highly oxidised naphthoquinone core.



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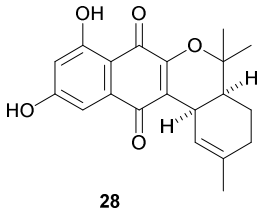

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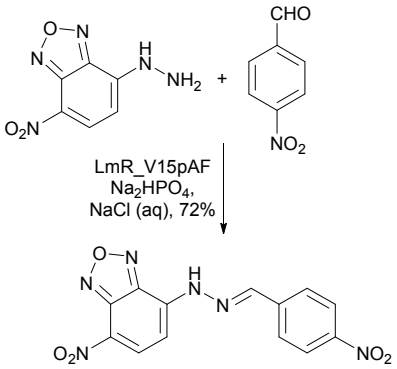
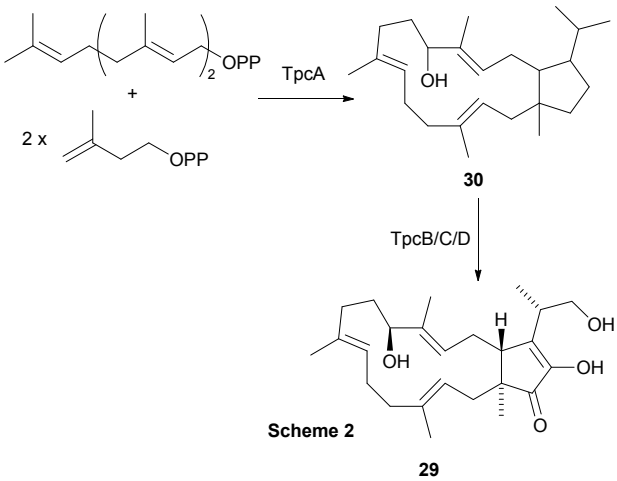
An artificial enzyme that has the ability to catalyse hydrazine (Scheme 1) and oxime formation has been created.[27] Introduction of the catalytically active *p*-aminophenylalanine into a promiscuous binding pocket of the multidrug transcriptional regulator from *Lactococcus lactis* results in a designer enzyme that can outperform other catalysts such as aniline. Heterologous expression of four enzymes (*tpcA–D*) in *Aspergillus oryzae* has allowed the total biosynthesis of the sesterterpene,

(–)-terpestacin **29**.[28] Following formation of preterpestacin I **30** by terpene synthase TpcA, three hydroxyl groups are introduced by two cytochrome P450 enzymes (TpcB/C) (Scheme 2). The process is then completed by the flavin-dependent oxidase TpcD, which catalyses oxidation of a diol unit to generate (–)-terpestacin **29**.



Scheme 1



Scheme 2

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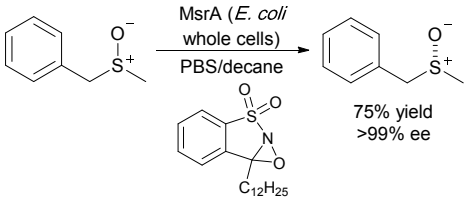
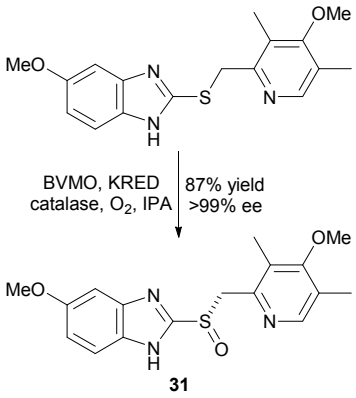
The first biocatalytic deracemisation of sulfoxides has been achieved using a combination of an oxaziridine-type oxidant and the highly enantioselective methionine sulfoxide reductase A (MsrA).[29] A biphasic system was used in which MSrA performs a kinetic resolution, forming a sulfide that is oxidised back to the sulfoxide by the oxaziridine-based lipophilic oxidant (Scheme 3). Overall, the process showed a wide substrate scope, producing optically active sulfoxides with excellent enantioselectivity. A combination of air as the terminal oxidant and an engineered Baeyer-Villiger monooxygenase (BVMO) has been used for the preparation of the

chiral sulfoxide, esomeprazole **31**, the *S*-enantiomer and active pharmaceutical ingredient of the blockbuster drug Nexium.[30] By directed evolution, the resulting engineered BVMO mediated-process provides an alternative to the Kagan chemocatalytic oxidation, producing esomeprazole in 87% yield and in >99% enantiomeric excess (Scheme 4).



Scheme 3



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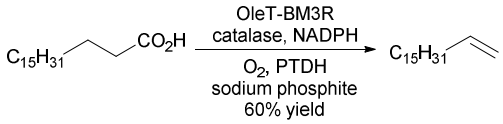
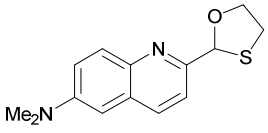
Scheme 4

A self-sufficient protein, OleT-BM3R, formed from the fusion of the decarboxylase $OleT_{JE}$ and the reductase domain of P450BM3 has been shown to catalyse the oxidative decarboxylation of carboxylic acids to form linear α-olefins.[31] The engineered fusion protein uses oxygen as the oxidant and NADPH as the electron donor, and in combination with a phosphite dehydrogenase-based NADPH regeneration system (Scheme 5), gave product titres of up to 2.51 g L^{-1}. A quinolone-based two-photon fluorescent probe **32** has been developed for the ratiometric detection and imaging of hypochlorous acid (HClO).[32] In response to HClO, the probe shows a decrease in blue emission with a concurrent increase of green emission and was used for detecting exogenous and endogenous HClO in living cells.



Scheme 5



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