Hot off the Press

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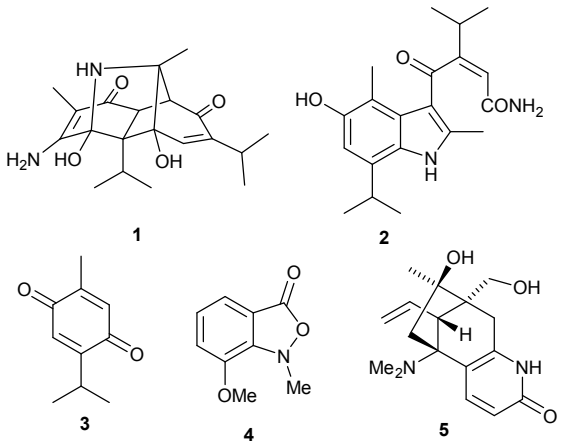
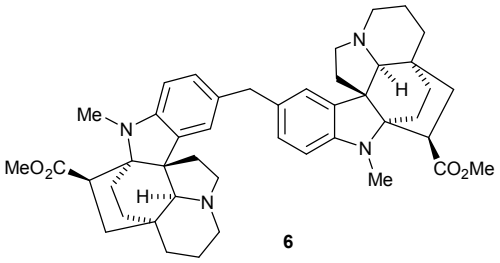
Abstract: A personal selection of 32 recent papers is presented covering various aspects of current developments in bioorganic chemistry and novel natural products such as illisimonin A from *Illicium simonsii*.

Nigegladines A **1** and B **2** have been isolated from *Nigella glandulifera*.[1] The tetracyclic system of nigegladine A **1** was confirmed by X-ray analysis. Biosynthetic pathways to nigegladines A **1** and B **2** from thymoquinone **3** have been proposed. The structure of oxazonigelladine **4**, from *Nigella damascena*,[2] and lycocasuarine A **5**, from *Lycopodiastrum casuarinoides*,[3] were also established by X-ray analysis. Oxazonigelladine **4** contains the unusual 2,1-benzisoxazo-3(1*H*)-one ring system. A biosynthetic pathway to the novel skeleton of lycocasuarine A **5** has been proposed.



Pleiokomenine A **6**, from the stem bark of *Pleiocarpa mutica*, is the first example of a dimeric aspidofractinine alkaloid linked through a methylene bridge.[4] The symmetrical dimeric isoindole alkaloid diaporisoindole C **7** is a metabolite of the

mangrove endophytic fungus *Diaporthe* sp. SYSU-HQ3 together with monomeric precursors.[5] Tengerensine **8** is a racemic dimeric benzopyrroloisoquinoline alkaloid from *Ficus fistulosa* var. *tengerensis*.[6] The structure and stereochemistry of tengerensine **8** was confirmed by X-ray analysis and this revealed that the cyclobutane stereochemistry is unsymmetrical and interestingly the alkaloid has opposite stereochemistry at C-11a and C-11'a.



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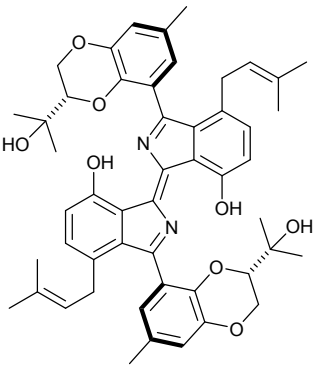

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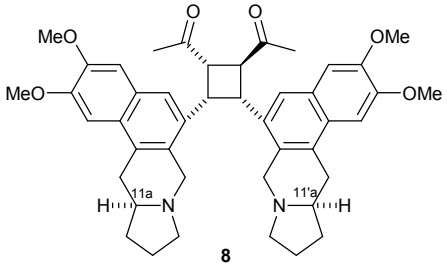

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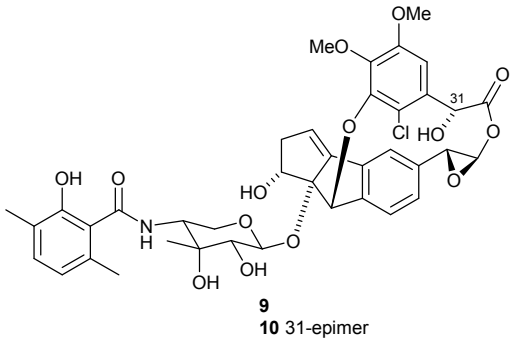
Amycolamycins A **9** and B **10** are metabolites of the locust-associated fungus *Amycolatopsis* sp. HCa4 with a novel ring system.[7] Sequencing and analysis of the *acm* gene cluster allowed the authors to propose a biosynthetic pathway to the amycolamycins involving an enediyne polyketide precursor. The mangrove-derived *Streptomyces* sp. 219807 produces the polyketide hainanmycin A **11** that has a skeleton involving an novel ring system.[8] The unusual structure of scopranone A **12** a

metabolite of *Streptomyces* sp. BYK-11038, was confirmed by synthesis.[9] Houttuynoid M **13**, from *Houttuynia cordata*, is the first example in this series with two polyketide chains tethered to a flavonoid core.[10] A biosynthetic pathway to houttuynoid M **13** has been proposed.



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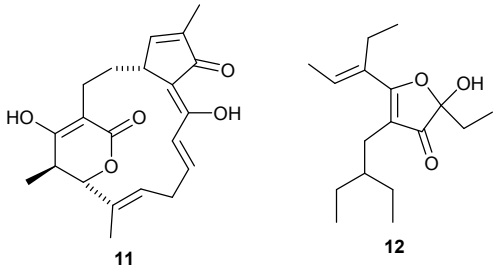

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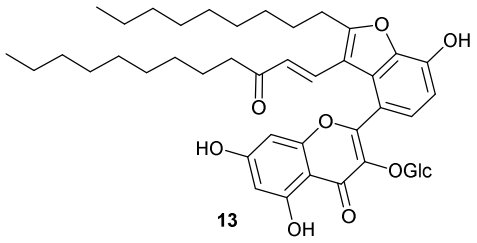

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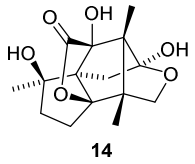
The rearranged sesquiternoid illisimonin A **14** has been identified in fruits of *Illicium simonsii*.[11] A biosynthetic pathway to the unusual ring-system of illisimonin A **14**, involving cedrane and allocedrane intermediates, has been proposed. The 8,10-cyclised bisabolane sesquiterpenoid phellilane L **15** has been isolated from the medicinal mushroom *Phellinus linteus*.[12] The structure and absolute configuration of phellilane L **15** were established by X-ray analysis and asymmetric synthesis. Feeding studies using labelled mevalonolactones have been used to propose a biosynthetic pathway to the diterpenoid harzianone **16** and related metabolites from *Trichoderma*

species.[13] The structure of aspterpenacid C **17**, a sesterterpenoid with a novel pentacyclic skeleton from *Swertia bimaculata*, was established by X-ray analysis.[14]



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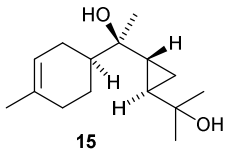

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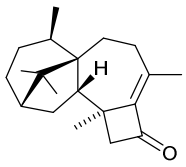

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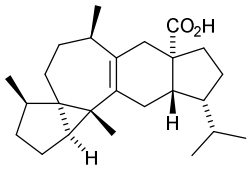

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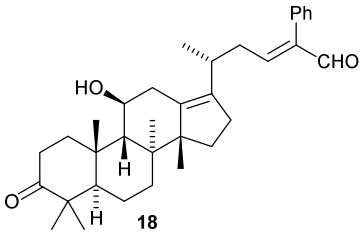
A biosynthetic pathway to the unusual triterpenoid alismanin A **18**, from *Alisma orientale*, has been proposed involving an aldol condensation of a degraded protostane triterpenoid with phenylpyruvic acid followed by decarboxylation.[15] The monoterpene-shikimate-conjugated meroterpenoids manginoids A – G with a variety of novel skeletons, such as manginoid C **19** whose structure was established by X-ray analysis, have been isolated from *Guignardia mangiferae*.[16] Biosynthetic pathways to the manginoids have been proposed.



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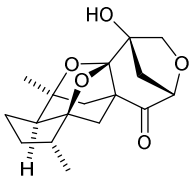

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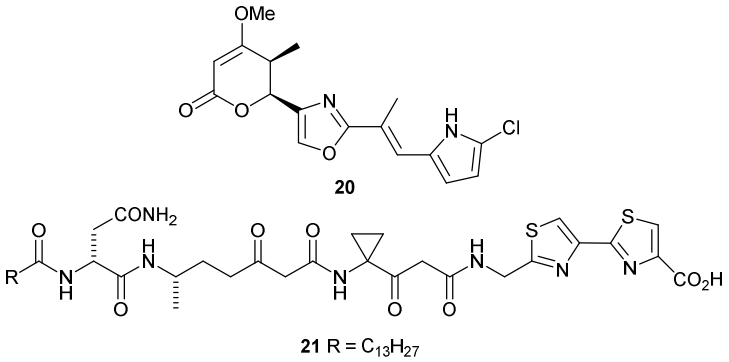
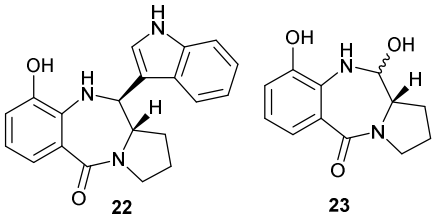
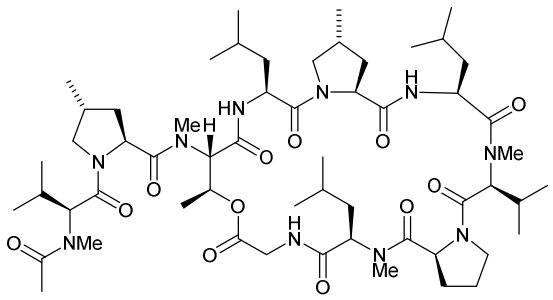
In silico analysis and feeding experiments have assisted in the identification of the nonribosomal peptide synthetase-polyketide synthase (NRPS-PKS) gene cluster of pyrronazol B **20** from the myxobacterial strain *Nannocystis pusilla* Ari7.[17] The proposed structure of pyrronazol B **20** was confirmed by the first stereoselective total synthesis of the natural product. The crystal structure and biochemical characterisation of ClbQ, a type II editing thioesterase from the colibactin NRPS-PKS

gene cluster has been reported.[18] Cocrystalisation of ClbQ with precolibactin derivatives (e.g. **21**) allowed insight into the unique structural features of the thioesterase and substrate specificity for precolibactin metabolites.



Investigation of the biosynthesis of tilivalline **22**, a indol-3-yl-substituted pyrrolobenzodiazepine produced by enteric bacterium *Klebsiella oxytoca* has shown that this nonribosomal peptide pathway initially forms tilimycin **23**.[19] Further studies revealed that tilimycin reacts with biogenetically generated indole via a non-enzymatic spontaneous reaction to form tilivalline. Sequencing, retrobiosynthetic analysis and inactivation experiments were used to identify the NRPS-containing biosynthetic gene cluster of griselimycin **24**, a depsidecapeptide with significant anti-tuberculosis activity.[20] Heterologous expression, gene inactivation and in vitro experiments showed that the 4-methylproline residues found in griselimycin are generated from leucine through a hydroxylation, oxidation and cyclisation sequence of transformations.





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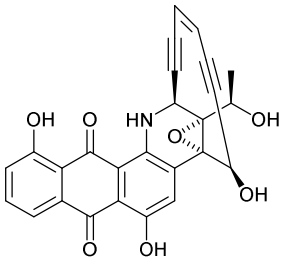
By surveying 11500 actinobacterial genomes from public genome databases and using proteins of the enediyne PKS cassette as probes, 137 distinct enediyne gene clusters have been identified.[21] Analysis of the enediyne clusters allowed the characterisation of *Micromonospora yangpuensis* DSM 45577 as a producer of yangpumicin A **25**, an anthraquinone-fused enediyne, which is active against a broad spectrum of human cancer cell lines. The biochemical function of two dehydratase domains from the PKS that forms fostriecin **26**, a selective protein phosphatase inhibitor has been elucidated.[22] Feeding studies with various acyl carrier protein (ACP) derivatives confirmed the predicted role of FosDH1 and FosDH2 in the formation of their respective *E*- and *Z*-disubstituted enoyl ACP products.



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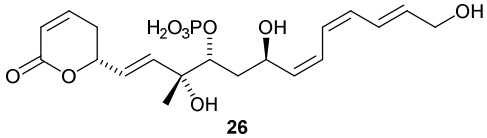

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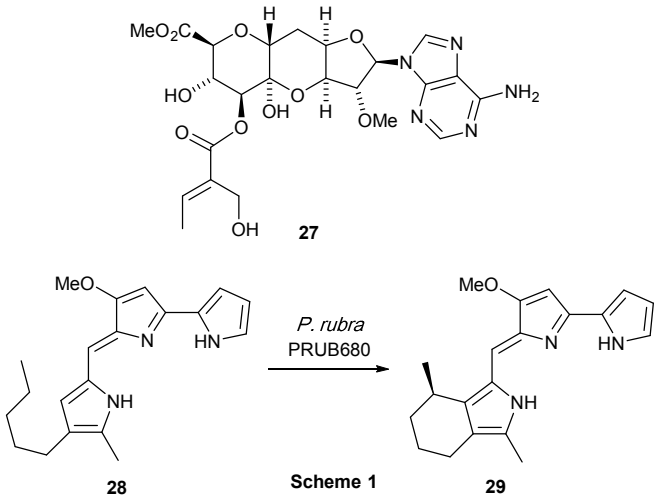
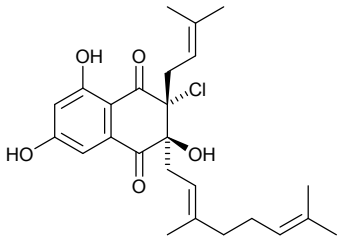
The gene cluster of herbicidin A **27**, an adenosine-based nucleoside with a tricyclic undecose core has been identified in *Streptomyces* sp. L-9-10.[23] This has allowed the characterisation of a carboxyl methyltransferase, Her8 involved in the biosynthesis of herbicidin A. Feeding studies have shown that the tricyclic undecose core is derived

from D-glucose and D-ribose, while the (5-hydroxyl)tiglyl moiety is from an intermediate of L-isoleucine. Discovery of an unclustered biosynthetic gene has allowed the identification of the enzyme that catalyses the regiospecific C-H activation and cyclisation of prodigiosin **28** to cycloprodigiosin **29** in *Pseudoalteromonas rubra* (Scheme 1).[24] The enzyme is a member of the fatty acid hydroxylase integral membrane di-iron oxygenase family that is predicted to use histidine-ligated nonheme iron centres.



Scheme 1

A vanadium-dependent haloperoxidase that performs a halogenation-induced α-hydroxyketone rearrangement has been discovered that accounts for the unusual substitution pattern in merochlorin and napyradiomycin meroterpenoid biosynthesis.[25] The α-hydroxyketone rearrangement was demonstrated in the total synthesis of naphthomevalin **30**, a key member of the napyradiomycin meroterpenes. A study of the scope of the biocatalytic Friedel-Crafts acylation with the acyltransferase from *Pseudomonas protegens* (*Pp*ATaseCH) has shown that various activated esters are suitable donors for this transformation.[26] For example, phenyl acetate was found to be very effective, giving the acetylated derivative of resorcinol in >99% yield (Scheme 2).



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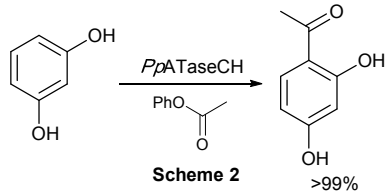
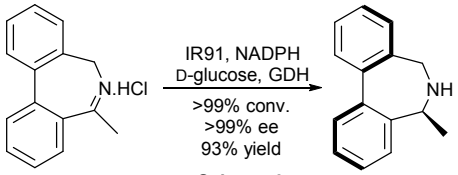
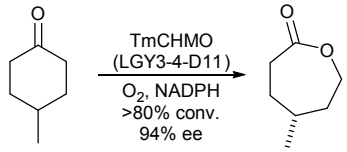


Scheme 2

Biocatalytic methods involving enantiocomplementary imine reductases have been developed for the asymmetric synthesis of dibenz[*c*,*e*]azepines, compounds found as structural units in drug molecules and organocatalysts.[27] Interestingly, the use of fungal imine reductases gave the *R*-configured product, while bacterial enzymes such as IR91 from *Kribbella flavida* gave the *S*-configured product (Scheme 3). Using directed evolution based on iterative saturation mutagenesis, the stereoselectivity of the thermostable Baeyer-Villiger monooxygenase from *Thermocrispum muncipale* (TmCHMO) was reversed.[28] The new mutants retained their thermostability relative to the wild type enzyme and gave the desymmetrised *R*-products with excellent enantioselectivity (Scheme 4).



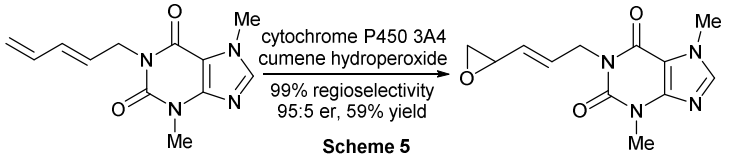
Scheme 3



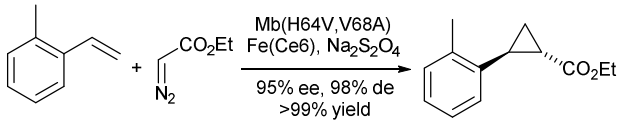
Scheme 4

A combination of a theobromine chemical auxiliary and a cytochrome P450 3A4 enzyme have been used to control the regioselectivity of biocatalytic epoxidation of

conjugated dienes.[29] The theobromine auxiliary was found to bind in the P450 3A4 active site, directly coordinating with the heme iron. This led to regioselective epoxidation of the C-4 position of the conjugated diene (Scheme 5), irrespective of electronic or steric factors. A stereoselective biocatalytic cyclopropanation under aerobic conditions has been developed using an artificial enzyme incorporating an iron-chlorin e6 cofactor [Fe(Ce6)] (Scheme 6).[30] As well as tolerance to oxygen and a broad substrate scope, the metalloenzyme can be recombinantly expressed in bacterial cells, allowing preparative-scale whole-cell cyclopropanation reactions.

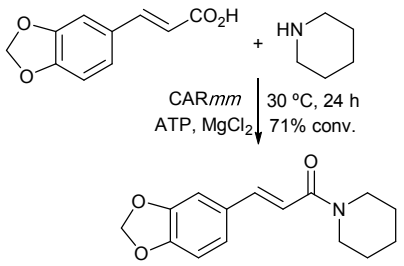


Scheme 5

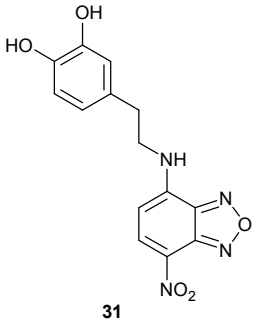


Scheme 6

A mechanistic understanding of carboxylic acid reductases has resulted in a new biotransformation for the synthesis of amides.[31] In the absence of the cofactor NADPH and using ATP as the driving force, a wide range of amides could be prepared, including the anticonvulsant ilepcimide (Scheme 7). A new fluorescent probe **31** containing a 4-nitrobenzo[1,2,5]oxadiazole and a dopamine moiety has been developed for the detection of hypochlorous acid (HOCl).[32] Due to the quenching effect of the dopamine moiety, the probe shows low fluorescence. However, on oxidation of the dopamine group by HOCl to the corresponding benzoquinone, fluorescence is turned on. As well as detecting the myeloperoxidase enzyme that produces HOCl, the probe could also be used to image HOCl in living cells.



Scheme 7



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