

Hot off the Press

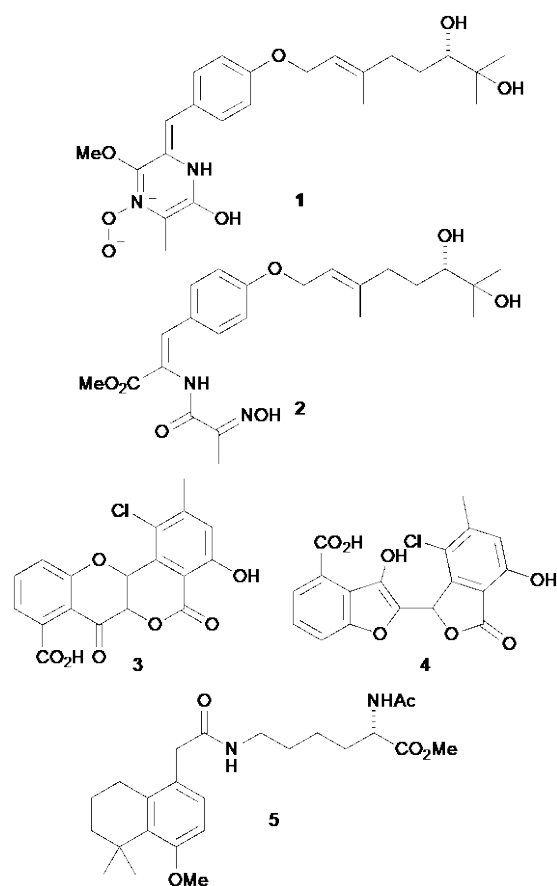
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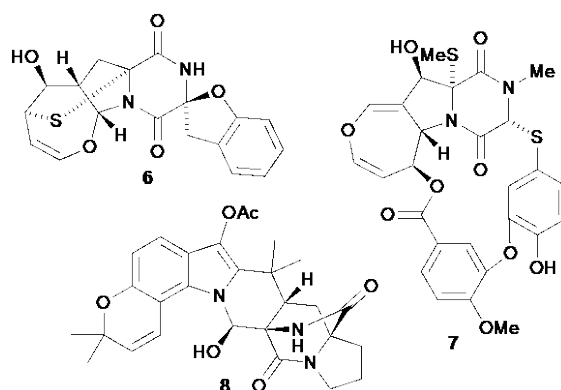
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Abstract: A personal selection of 32 recent papers is presented covering various aspects of current developments in bioorganic chemistry and novel natural products such as dcalycinumine A from *Daphniphyllum calycinum*.

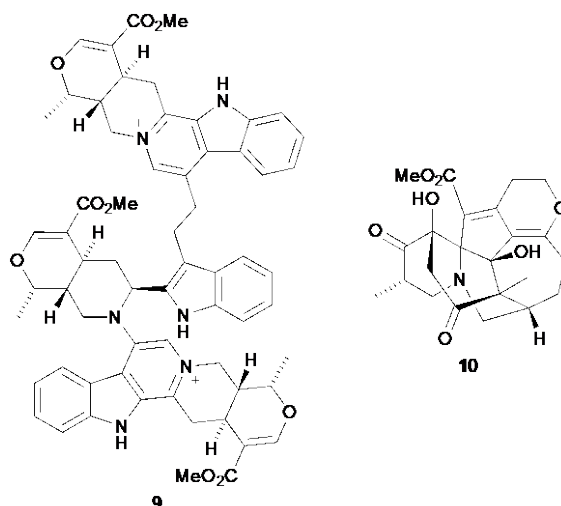
In 2006, the structure of janthinolide A, a metabolite of coral-derived *Penicillium janthinellum*, was assigned the unlikely structure **1** containing a zwitterionic *N*-peroxide.¹ Computational ¹³C NMR studies have been used to show that this structure is incorrect and that the compound described as janthinolide A is likely to be janthinolide C **2**.² Maduralactomycin A, a metabolite of *Actinomadura* sp. RB29, was assigned structure **3** in 2020.³ Biosynthetic considerations and computational ¹³C NMR data predictions have led to the revision of maduralactomycin A to **4**.⁴ Phragmunis A was isolated in 2021 from the poisonous mushroom *Trogia venenata* and shown to have interesting activity against glioblastoma multiforme.⁵ The proposed structure **5** for phragmunis A has been synthesised and the spectra do not agree with the natural product.⁶



Several thiodiketopiperazine alkaloids, including lecanicillium A **6**, are produced by mangrove sediment-derived *Lecanicillium kalimantanense*.⁷ Lecanicillium A **6** has a novel hexacyclic ring system. Noremestrin A **7**, produced by *Emericella* sp. 1454, has an unusual sulfur-bearing 15-membered macrocyclic lactone.⁸ The structure of asperinamide A **8**, from *Aspergillus* sp. TE-65L, was confirmed by X-ray analysis.⁹ Asperinamide A **8** has an unprecedented heptacyclic ring system. Biosynthetic pathways for the formation of lecanicillium A **6**, noremestrin A **7** and asperinamide A **8** have been proposed.

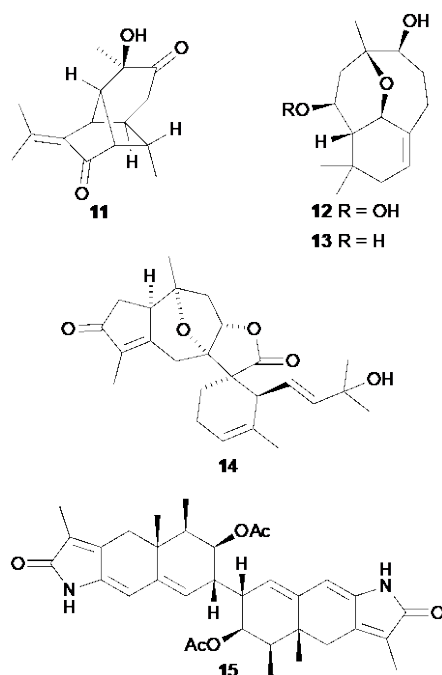


The first example of a trimeric ajmalicine-type alkaloid, trirosaline **9**, has been isolated from the well-studied *Catharanthus roseus*.¹⁰ A biosynthetic pathway to trirosaline **9** from ajmalicine has been suggested. Several polycyclic alkaloids have been isolated from *Daphniphyllum calycinum* including dcalcycinumine A **10** with a novel hexacyclic ring system.¹¹ The structure of dcalcycinumine A **10** was confirmed by X-ray analysis.

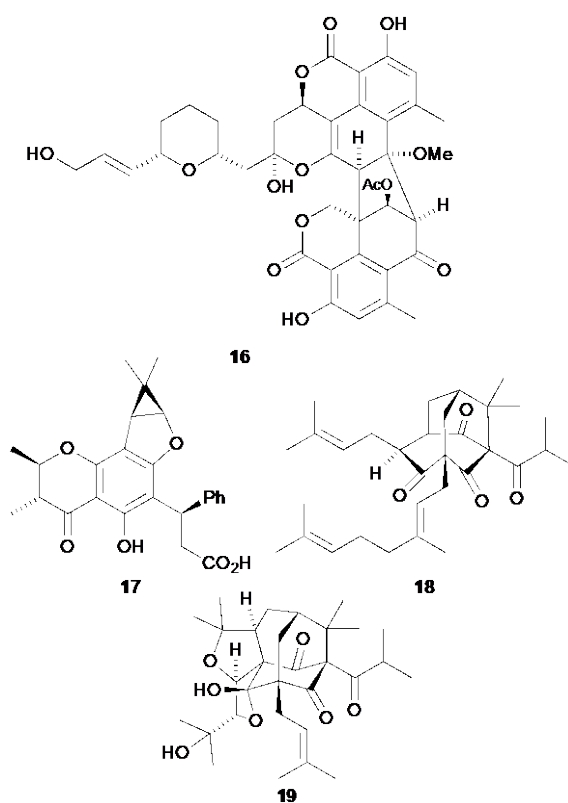


Eupatorione A **11**, from *Eupatorium adenophorum*, has an unreported tricyclic sesquiterpenoid skeleton.¹² Agarperoxinol A **12** and B **13**, from the agarwood of *Aquilaria malaccensis*, are tricyclic humulane sesquiterpenoids.¹³ A pathway for their formation from farnesyl diphosphate has been proposed. Orientanoid A **14**, from *Hedyosmum orientale*, is a Diels-Alder adduct between a guaiane sesquiterpenoid and an acyclic monoterpenoid.¹⁴ The structures of eupatorione A **11**, agarperoxinol A **12** and orientanoid A **14** were confirmed by X-ray analyses. The first dimeric

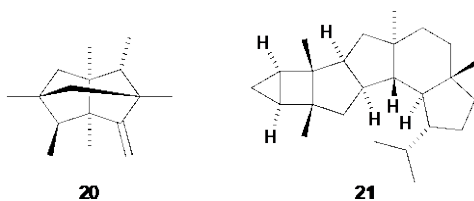
eremophilane lactam, dipeniroqueforin A **15**, has been identified as a metabolite of *Penicillium roqueforti*.¹⁵



Talaroclauxin B **16**, from *Talaromyces stipitatus*, has an unusual skeleton.¹⁶ Two possible biosynthetic pathways to talaclauxin B **16** from duclauxin and a polyketide precursor have been proposed. Membranaceumone A **17**, from leaves of *Calophyllum membranaceum*, has an unusual tetracyclic ring system.¹⁷ A biosynthetic pathway has also been proposed for membranaceumone A **17**. Several caged polycyclic polyprenylated acylphloroglucinol derivatives have been isolated from *Hypericum* species including hypseudohenone A **18** from *Hypericum pseudohenryi*¹⁸ and cumilcinol A **19** from *Hypericum wilsonii*.¹⁹ The structures of hypseudohenone A **18** and cumilcinol A **19** were confirmed by X-ray analyses. A biosynthetic pathway to hypseudohenone A **18** has been proposed.

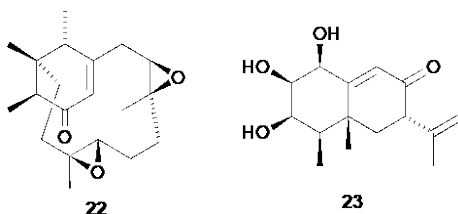


The use of genome mining and synthetic biology have been used to fully investigate the occurrence of C16 terpenoids in bacteria.²⁰ The study of 40 representative clusters from 739 sequenced bacterial genome candidates allowed the characterisation of 15 methyltransferases and 35 terpene synthases and their 16-carbon terpenoid product, such as aristotylene **20** from various *Pseudomonas* species. Genome mining of a terpene synthase from *Streptomyces subutilus* has led to the characterisation of the first saturated sesterterpene hydrocarbon, subrutilane **21**.²¹ Isotopic labelling studies and DFT calculations were used to study the cyclisation mechanism to subrutilane and its eight pentacyclic by-products.

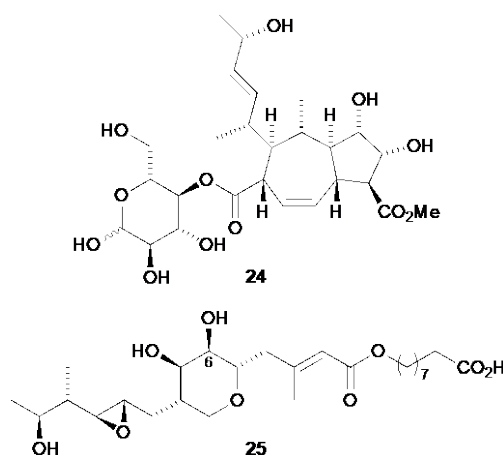


The gene cluster responsible for the biosynthesis of phomactin diterpenoids, which are platelet-activating factor antagonists, has been identified from the marine fungus,

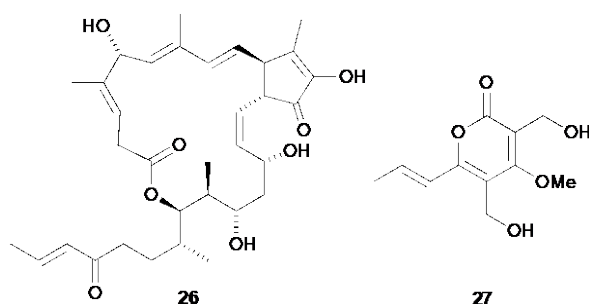
Phoma species ATCC 74077.²² Two key enzymes were shown to be responsible for the biosynthesis of phomactins. A type I diterpene cyclase PhmA produces phomactatriene from geranylgeranyl diphosphate, while a P450 monooxygenase PhmC performs various oxidations leading to products such as phomactin W **22**. The combination of genes from four different fungal pathways in the host organism *Aspergillus oryzae*, has allowed the total biosynthesis of twenty oxygenated aristolochene congeners.²³ As well as the production of the natural product hypoxylan A in a single process, more complex compounds such as the triol **23**, a C-1 epimer of the natural product guignaderemophilane C were also prepared.



Genome mining of agriculturally relevant fungi, such as the *Trichoderma* species has identified a conserved polyketide biosynthetic gene cluster that produces treconorin **24**, a glycosylated natural product, which contains a 5,7-bicyclic polyketide core.²⁴ Investigation of the key enzymes revealed that treconorin is formed via a novel glycosylation process, involving glycosidic cleavage of a trehalose ester precursor. An in vitro approach has been used to characterise the α -hydroxylation bimodule of the mupirocin biosynthetic pathway, responsible for the installation of the 6-hydroxy group of pseudomonic acid A **25**.²⁵ A combination of purified enzyme components, chemical synthesis and labelling studies revealed the precise timing of hydroxylation by MupA and the requirement of a FMN reductase, a complementary acyl carrier protein and a β -keto substrate.

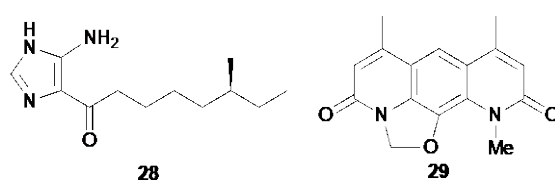


Systematic gene inactivation of the *sdl* biosynthetic gene cluster that generates macrocyclic polyketides, which possess rare internal 2-hydroxycyclopentenone moieties such as shaungdaolide D **26** has allowed the characterisation of several key enzymes and a proposed biosynthetic pathway.²⁶ The studies revealed the role of the multidomain protein, SdlR that catalyses 16,17-epoxidation during chain elongation and the tailoring oxidation enzymes, SdlB and SdlQ. Heterologous expression in the fungal host *Aspergillus oryzae* has been used to probe the biosynthesis of fungal tetraketide pyrones including multiforin I **27**.²⁷ As well as elucidating the biosynthetic pathway to these natural products, this approach yielded high titres of these pyrones, leading the authors to propose that this strategy could be used to rationally engineer the production of future novel members of this family.

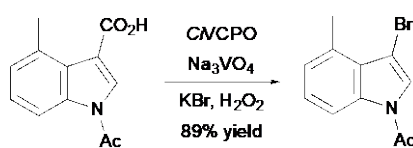
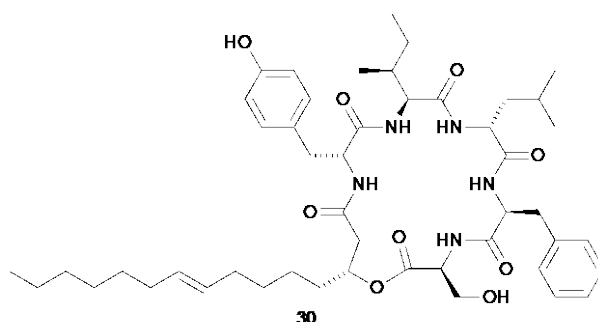


Bioinformatics, gene knockout and heterologous expression experiments have identified the biosynthetic gene cluster of 4-acyl-5-aminoimidazole alkaloids such as (+)-nocarimidazole C **28**, natural products from marine acintomycetes.²⁸ In vivo and in

vitro assays revealed the four genes essential for biosynthesis, including SmzB, a new Friedel-Crafts acyltransferase that catalyses the reaction between the acyl group and the 5-amino-imidazole-1-ribotide. Bioinformatics analysis has also been used to identify the biosynthetic gene cluster of antibacterial agents, deoxynybomycin **29** and nybomycin in *Embleya hyalina* NBRC 13850.²⁹ Various enzymes were characterised, including DnmT, a Fe(II)/ α -ketoglutarate-dependent dioxygenase that catalyses formation and decomposition of the angularly fused 4-oxazoline ring system.

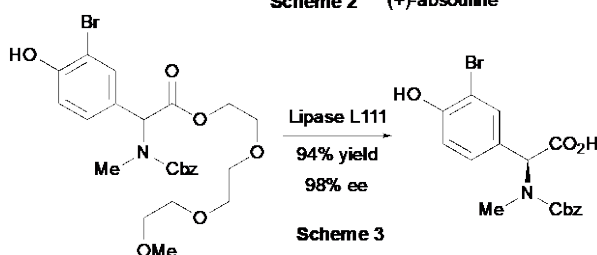
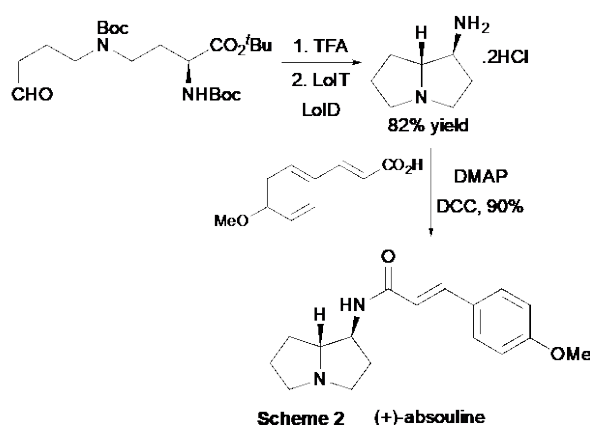


Heterologous expression of a multi-modular nonribosomal peptide synthetase from *Serratia fonticola* DSM 4576 in *E. coli* has led to the discovery of four novel lipodespsipeptides.³⁰ This included sefopeptide C **30**, which was found to possess cytotoxic activity against leukemia cells. A biocatalytic method for the preparation of 3-haloindoles has been developed by decarboxylative halogenation of 3-carboxyindoles.³¹ Vanadium chloroperoxidase from *Curvularia inaequalis* was amenable to decarboxylative chlorination, bromination (Scheme 1) and iodination and could be performed on gram scale quantities of substrates.



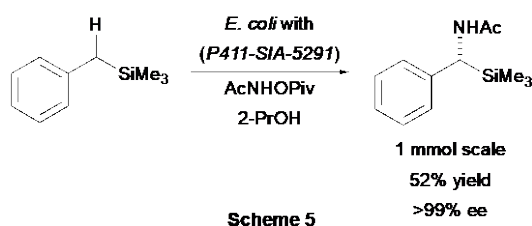
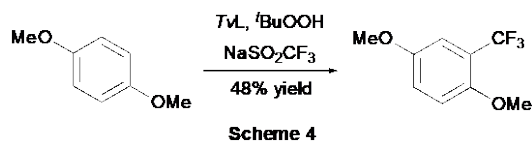
Scheme 1

The total synthesis of 1-aminopyrrolizidine alkaloids has been reported using a biocatalytic cascade process involving enzymes from the loline biosynthetic pathway.³² Acid mediated deprotection, stereoselective *5-endo-trig* cyclisation by the Mannich cyclase LoIT and a stereoretentive decarboxylation catalysed by LoID, allowed the efficient one-pot synthesis of the 1-aminopyrrolizidine core (Scheme 2). Subsequent acylation yielded natural products such as (+)-absouline and the first asymmetric synthesis of laburnamine. Dynamic kinetic resolution to access chiral *N*-alkyl amino acids has been achieved using lipase and substrates bearing PEGylated esters.³³ The PEGylated esters were found to have increased solubility in aqueous media compared to traditional ester substrates, resulting in more efficient access to chiral *N*-alkyl amino acid products (Scheme 3).



A novel biocatalytic approach for the C–H trifluoromethylation of arenes has been reported using the high redox potential fungal laccase from *Trametes versicolor* (TvL).³⁴ Combination of the arene radical cations generated by the laccase with in situ generated trifluoromethyl radicals gave the coupled products in moderate to high yields (Scheme 4). Site-saturation mutagenesis of a cytochrome P450 enzyme has produced a

biocatalyst capable of enantioselective nitrene transfer with benzylic Si–C–H bonds.³⁵ The reactions could be performed on preparative scale under aerobic conditions and allowed the asymmetric synthesis of α -aminosilanes with up to 125-fold higher yield than the original enzyme (Scheme 5).



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