Hot off the Press

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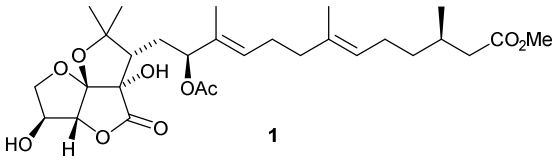
Abstract: A personal selection of 32 recent papers is presented covering various aspects of current developments in bioorganic chemistry and novel natural products such as tundrenone from *Methylobacter tundripaludum*.

Hongkonoid A **1**, from *Dysoxylum hongkongense*, has a diterpenoid skeleton linked to ascorbic acid.[1] A biosynthetic pathway for the formation of the tricyclic ring system of hongkonoid A **1** has been proposed. The same ring system is also present in pimentelamine A **2** isolated from *Flindersia pimenteliana* but with a different linkage to the prenyl group.[2]



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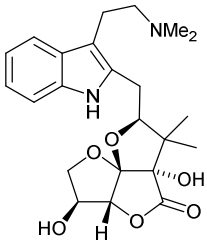
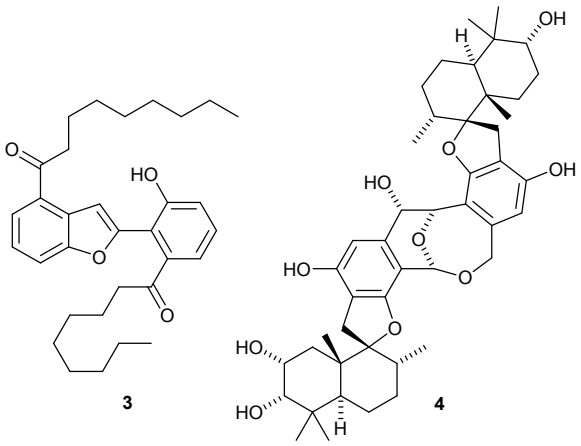
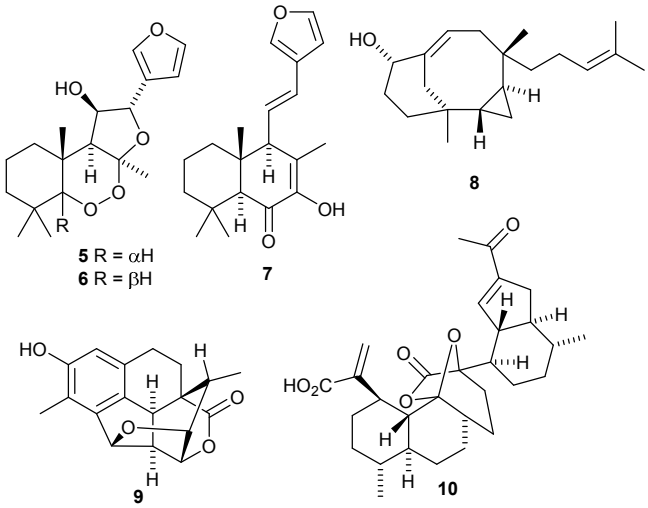


2

It is proposed that bysspectin A **3**, a metabolite of the endophytic fungus *Byssochlamys spectabilis* obtained from *Edgeworthia chrysantha*, is an octaketide dimer formed by a pinacol coupling.[3] A pinacol coupling is also proposed in the formation of the meroterpenoid dimer bistachybotrysin A **4** isolated from *Stachybotrys chartarum*.[4]

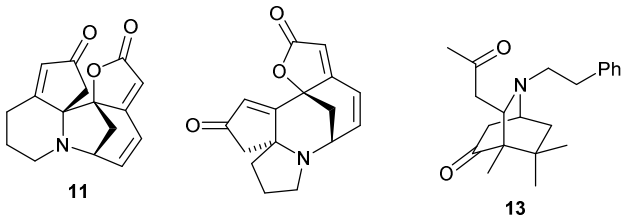


The structures of the dinorditerpenoids hedychins A **5** and B **6**, from *Hedychium forestii*, were established by X-ray analyses.[5] A biosynthetic route to the hedychins, from the co-occurring labdane 7-hydroxyhedychenone **7**, has been proposed. Chabrolin A **8**, from the soft coral *Nephthea chabroli*, has an unusual tricyclic diterpenoid skeleton.[6] The novel skeleton of the dinorditerpenoid cephanolide A **9**, from *Cephalotaxus sinensis*,[7] and the unusual dimeric cadinane sesquiterpenoid arteannoide A **10**, from *Artemisia annua*,[8] were both confirmed by X-ray analyses. Biosynthetic pathways to chabrolin A **8**, cephanolide A **9** and arteannoide A **10** have been proposed by the authors.

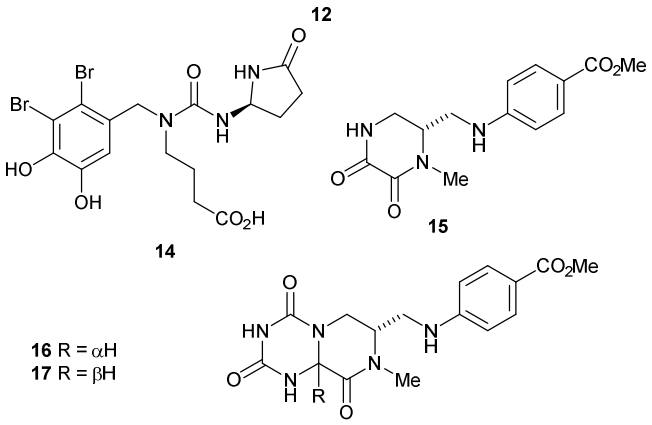


It is proposed that the additional cyclopentenone rings of the pentacyclic *Securinega* alkaloids fluvirosaones A **11** and B **12**, isolated from *Flueggea virosa*, are derived

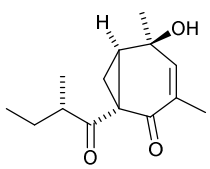
from acetoacetate.[9] The biosynthetic pathway to tectoricine **13**, from *Elaeocarpus tectorius*, is also thought to involve acetoacetate.[10]



The structure and absolute configuration of rhodomelin A **14**, from the red alga *Rhodomela confervoides*, was confirmed by synthesis.[11] Rhodomelin A **14** is an unusual ureidopyrrolidone alkaloid with a additional γ-aminobutyric acid unit. *Orychophragmus violaceus* is the source of orychophragines A **15**, B **16** and C **17** whose structures were determined by X-ray analyses.[12] Biosynthetic pathways to the novel skeletons of the orychophragines have been suggested.



Ophiosphaerellins A – I, such as A **18** whose structure was confirmed by X-ray analysis, are polyketide metabolites of the endolichenic fungus *Ophiospaerella korrae*.[13] The ophiosphaerellins are the first examples of bicyclo[4.1.0]heptenone polyketides. Hypoxylide **19** is a polyketide metabolite of the endophytic fungus *Annulohypoxylon* sp. obtained from *Rhizophora racemosa*.[14] Possible biosynthetic pathways involving aromatic and decalactone pentaketide precursors are discussed.



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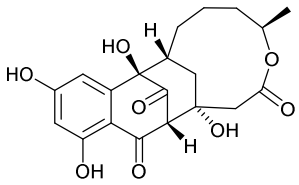

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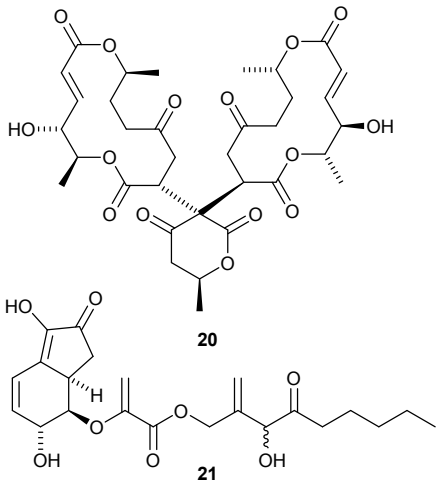
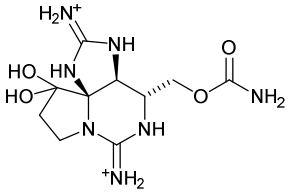
Acaulide **20** has been identified as a metabolite of the fungus *Acaulium* sp. associated with the isopod *Armadillidium vulgare* and its structure has been established by X-ray analysis.[15] A biosynthetic pathway to acaulide **20** has been proposed involving two Michael additions. Analysis of the genome of *Methylobacter tundripaludum* has identified the biosynthetic gene cluster for the unusual metabolite tundrenone **21**.[16] Tundrenone **21** incorporates a modified chorismate moiety that has not been identified before.



20 21

The first characterisation of an enzyme involved in the biosynthesis of saxitoxin **22**, a polyketide-like synthase, SxtA from the cyanobacteria *Cylindrospermopsis raciborskii T3* has been reported.[17] The megasynthase was shown to be comprised of four domains and performs two carbon-carbon bond forming reactions, two decarboxylations and a stereospecific protonation to generate a linear precursor of saxitoxin. Cloning of the biosynthetic gene clusters involved in the biosynthesis of anthrabenzoxocinones (ABXs) has allowed the characterisation of two promiscuous enzymes, a halogenase and a methyltransferase.[18] Engineering of these enzymes led to

the production of 14 novel ABX analogues (e.g. **23**), many of which had significantly improved antimicrobial activity.



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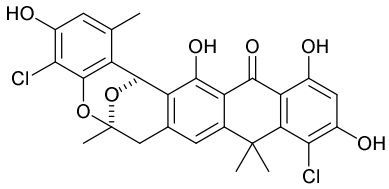

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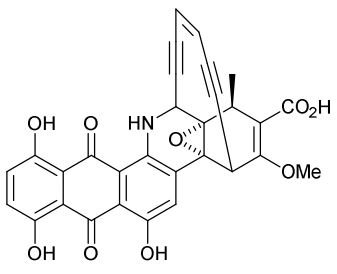
Investigation of the biosynthesis of dynemicin A **24**, by sequencing and analysing the genome of *Micromonospora chersina* has suggested that the dynemicin enediyne polyketide synthase (PKS), DynE8 may be responsible for the generation of both the enediyne and anthraquinone moieties.[19] Further evidence was provided by ^{18}O-labelling studies and has led to a working model of how DynE8 plays a dual role in generating the two halves of dynemicin A. Although type II PKSs are generally known for the production of aromatic compounds, a new subfamily, including ishigamide PKS, IgaPKS that produces ishigamide **25**, are able to synthesise polyene structures.[20] In vitro analysis of IgaPKS revealed the enzyme is able to form *trans*-alkenes, including tetraenes by a repeating cycle of condensation, keto-reduction and dehydration.



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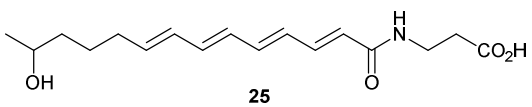
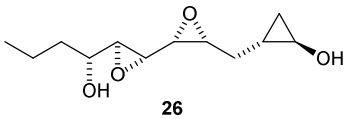


25

An in silico-based mining strategy of several bacteria has revealed an unusual *trans*-acyltransferase PKS in the model methylotroph *Methylobacterium extorquens AM1*, which produces the novel polyketides, toblerols (e.g. toblerol A, **26**).[21] Combined

gene disruption and labelling studies suggest that the cyclopropanol polyketide unit is formed by an oxidative chain-shortening process. Activation of the *mas* gene cluster of *Micromonospora* sp. HK160111 has allowed the isolation and characterisation of nine novel pentaketides such as microansamycin A **27**.[22] Retro-biosynthetic analysis revealed a diverse series of post-PKS modifications including hydroxylation, epoxidation, decarboxylation and *N*-acylation.



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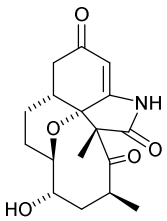

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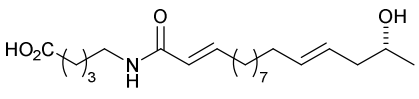
A genome mining strategy has been used to characterise a truncated iterative polyketide synthase-nonribosomal peptide synthetase (PKS-NRPS) hybrid from *Talaromyces wortmanii*.[23] As well as identify novel reduced long-chain polyketides coupled with 5-aminopentanoic acid (5PA) such as wortmanamide A **28**, the study revealed the role of the C-domain of the megasynthase in releasing the polyketide chain via amidation with 5PA. A new, fourth mechanism for β-lactam antibiotic biosynthesis, by a nonribosomal peptide synthetase has been reported.[24] During the biosynthesis of sulfazecin **29**, an assembled tripeptide is *N*-sulfonated *in trans* before β-lactam ring formation by a cysteine-containing thioesterase domain.



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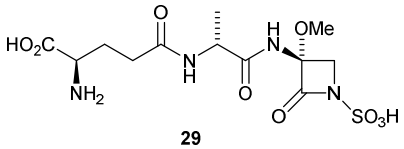

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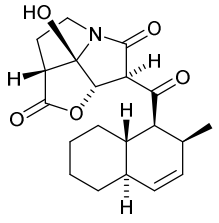
Genome mining of the thermophilic fungus *Myceliophthora thermophila* has shown that the biosynthesis of the fungal alkaloid UCS1025A **30**, a potent telomerase

inhibitor, is conducted by a PKS-NRPS.[25] Biochemical analysis of the PKS-NRPS assembly line has led to the proposed formation of the furopyrrolizidine ring system from (2*S*,3*S*)-3-methylproline. A combination of heterologous biotransformations and in vitro biochemical assays has allowed elucidation of the biosynthetic pathway of bicyclomycin **31**, a highly functionalised diketopiperazine alkaloid, used as a commercial antibiotic.[26] The pathway involves cyclodipeptide synthase heterodimerisation of leucine and isoleucine, followed by a six-oxidase cascade that results in the regio- and stereoselective functionalisation of eight unactivated C-H bonds.



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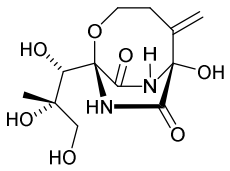

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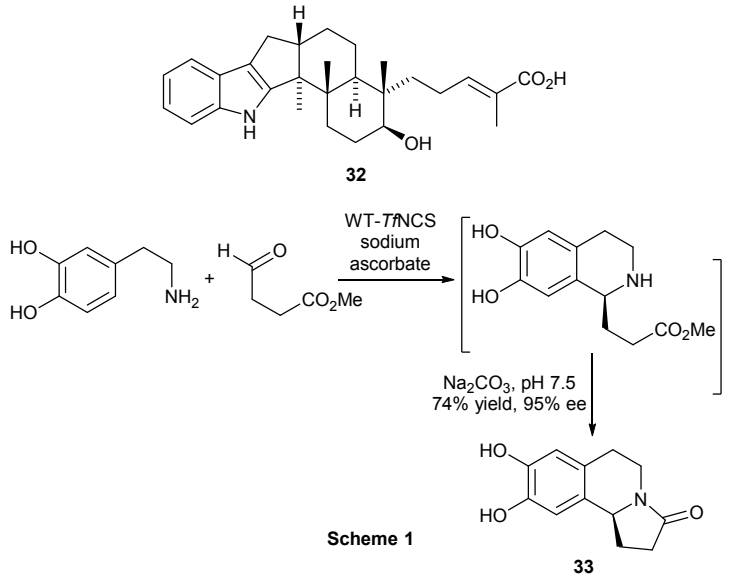
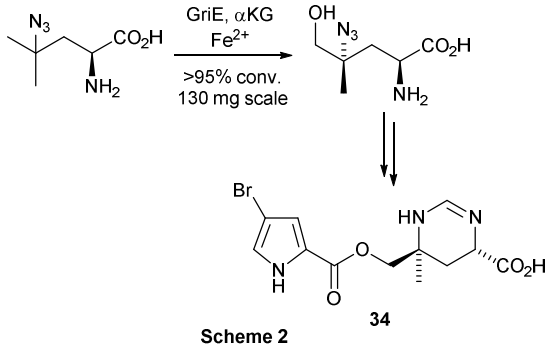
A gene cluster from the filamentous fungus *Hypoxylon pulicicidum*, responsible for the production of nodulisporic acids, indole terpenes that display insecticidal activity, has been characterised.[27] Reconstitution experiments have revealed the function of four of the genes that lead to core compound, nodulisporic acid F **32**, including two genes with novel functionality, such as a 3-geranylgeranylindole epoxidase. A one-pot chemoenzymatic synthesis of the alkaloid trolline **33** and other tetrahydroisoquinoline analogues has been developed using the Pictet-Spenglerase norcoclaurine synthase (NCS) (Scheme 1).[28] Enzyme catalysed reaction of dopamine with various aldehydes to give the tetrahydroisoquinolines was followed by addition of base and lactamisation. On a preparative scale, this gave (*S*)-trolline in 74% yield and 95% ee.

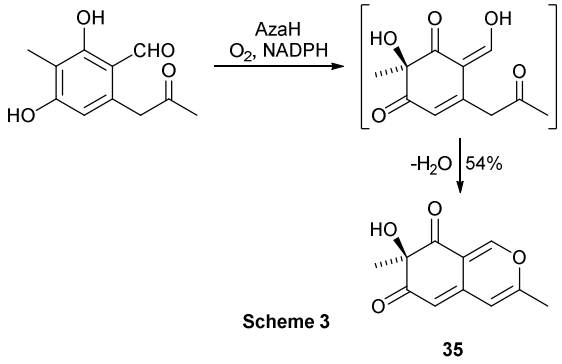


Scheme 1

Kinetic analysis and substrate profiling has allowed the evaluation of an α-ketoglutarate-dependent dioxygenase, leucine 5-hydroxylase (GriE), as a practical biocatalyst for remote C-H hydroxylation.[29] As well as the selective hydroxylation of the δ-position of a range of aliphatic amino acids, the biocatalyst was also used for an efficient synthesis of the alkaloid manzacidin C **34** (Scheme 2). The potential of a suite of complementary FAD-dependent monooxygenases for site- and stereoselective oxidative dearomatisation of phenols and rapid generation of molecular complexity has been demonstrated.[30] Biocatalysts from various biosynthetic pathways allowed the scalable and robust synthesis of a library of *ortho*-quinols, and rapid access to natural products such as the azaphilone, **35** (Scheme 3).



Scheme 2



Scheme 3

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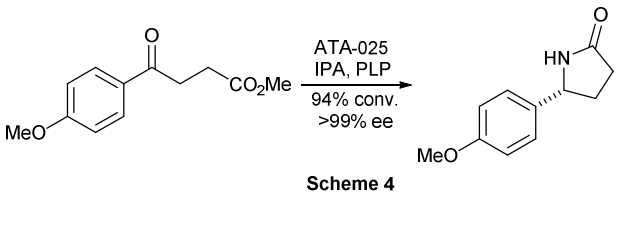
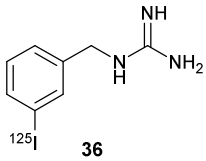
A one-pot two-step asymmetric chemoenzymatic synthesis of γ- and δ-lactams from the corresponding keto esters has been developed.[31] The strategy involves transaminase-mediated amination of the ketone, followed by spontaneous cyclisation to give the lactam (Scheme 4). A gold-catalysed iododeborination reaction has been developed for the radiolabeling of aromatic compounds and the generation of SPECT imaging agents.[32] The method was exemplified with the efficient preparation of *meta*-[^{125}I]iodobenzylguanidine **36**, a commercially available radiopharmaceutical used for the SPECT imaging of human norepinephrine transporter-expressing cancers.



Scheme 4



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