Hot off the Press

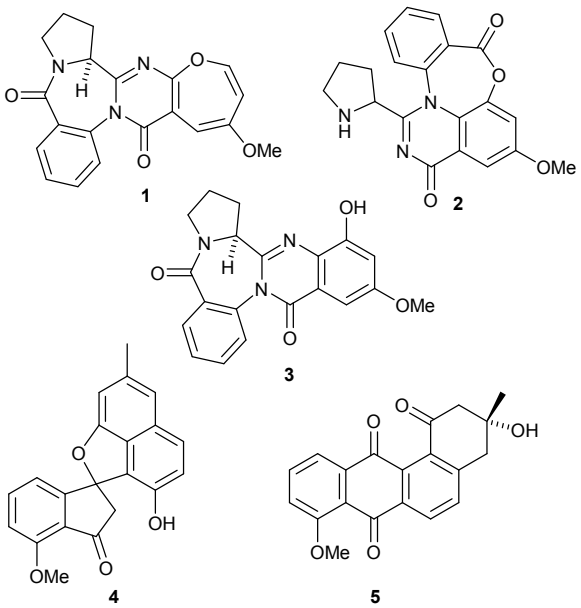
Robert A. Hill and Andrew Sutherland

School of Chemistry, Glasgow University, Glasgow, UK, G12 8QQ.

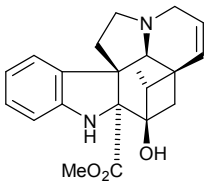
E-mail: Bob.Hill@ glasgow.ac.uk, Andrew.Sutherland@glasgow.ac.uk

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 tryptorubin A isolated from a *Streptomyces* species.

The structure of aspergicine **1**, a metabolite obtained from the co-culture of two *Aspergillus* species isolated from the fruit of *Avicennia marina*, was established by X-ray analysis.[1] This work prompted the revision of the structure of the co-metabolite aspergicin from **2** to **3**. Three racemic spiro indolinone-naphthofuran alkaloids, such as pratensilin A **4**, have been isolated from cultures of a marine *Streptomyces* species.[2] The authors propose biosynthetic pathways to the pratensilins from the angucyclinone co-metabolite 8-*O*-methylrabelomycin **5**.



Melodinus yunnanensis is the source of the monoterpenoid indole alkaloid meloyine A **6** that has a novel hexacyclic skeleton.[3] Clausoxamine **7**, from seeds of *Clausena lansium*, also has a novel skeleton.[4] The authors propose that clausoxamine **7** is formed from co-occurring lansiumamide B **8**. A *Streptomyces* species, isolated from the bracket fungus *Hymenochaete rubiginosa*, produced the polycyclic peptide tryptorubin A **9**.[5] Genome sequencing identified the likely genes for the production of the linear hexapeptide backbone of trytorubin A **9** which is then modified with three side-chain linkages to give a rigid globular structure.



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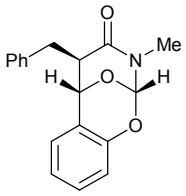

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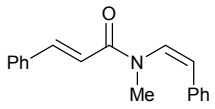

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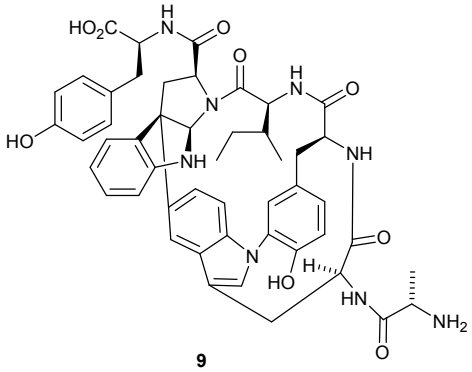

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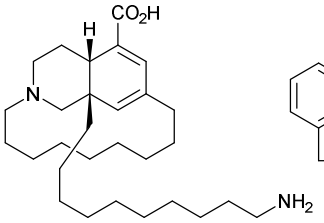
Lissodendoric acid A **10**, from the sponge *Lissodendoryx florida*, has a novel manzamine-related alkaloid structure.[6] A biosynthetic route from cyclostellettamine N **11** to lissodendoric acid A **10** has been proposed. The polyketide trichothiazole A **12**, a metabolite of a *Trichodesmium* cyanobacterium, features a thiazole ring, a terminal alkyne and two vinyl chlorides.[7] The authors discuss possible biosynthetic routes to trichothiazole A **12**.



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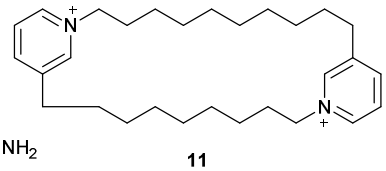

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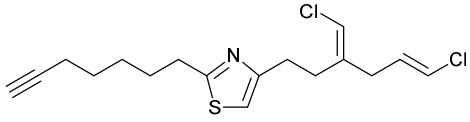
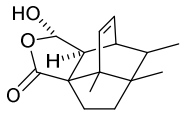


12

The marine sponge *Lamellodysidea herbacea* produces several sesquiterpenoids including lamellodysidine A **13** that has a new skeleton.[8] A biosynthetic pathway to lamellodysidine A **13** from dendrolasin **14** has been proposed. The new skeleton of daphnauranin A **15**, from the roots of *Daphne aurantiaca*, is suggested to be formed from a guaiane sesquiterpenoid precursor.[9] The structure of nicotabin A **16**, from *Nicotiana tabacum*, was confirmed by X-ray analysis.[10] Nicotabin A **16** is a sesquiterpenoid linked to a 6-carbon unit that is possibly derived from citric acid. A biosynthetic pathway has been proposed.



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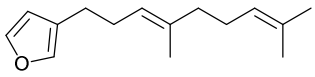

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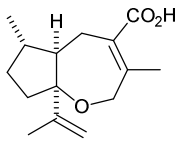

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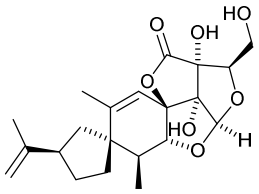

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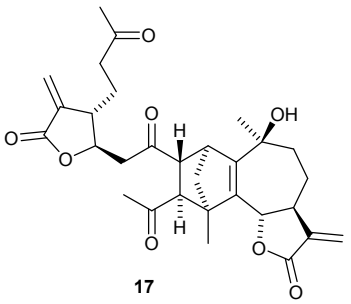
Four closely-related dimeric sesquiterpenoids, including artemisian A **17**, have been isolated from *Artemisia argyi*.[11] The artemisians appear to be formed by a Diels-Alder cyclisation of guaiadiene and 1,10:4,5-disecoguaiene precursors. A Diels-Alder cyclisation is also thought to be involved in the formation of the dimeric clerodane diterpenoid bistinospinoside A **18** from *Tinospora sagittata*.[12]



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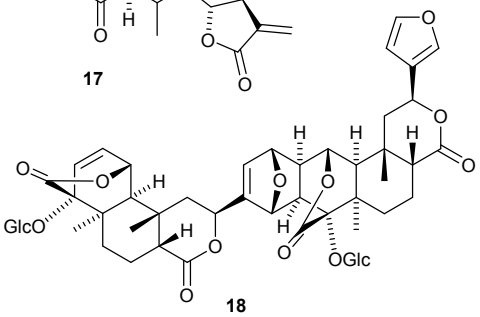

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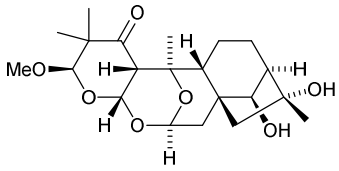
Rhododendron molle is a rich source of grayanane diterpenoids. New examples include novel 2,3:5,6-diseco-derivatives such as rhodomollacetal A **19** whose structure was confirmed by X-ray analysis.[13] The authors propose a biosynthetic pathway to rhodomollacetal A **19**. The structure of pleurocin A **20**, from fruiting bodies of *Pleurotus eryngii*, was also confrmed by X-ray analysis.[14] Pleurocin A **20** is a novel 11(9→7)-abeo-ergostane steroid and a biosynthetic pathway for its formation has been suggested.



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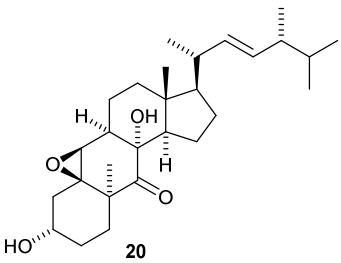

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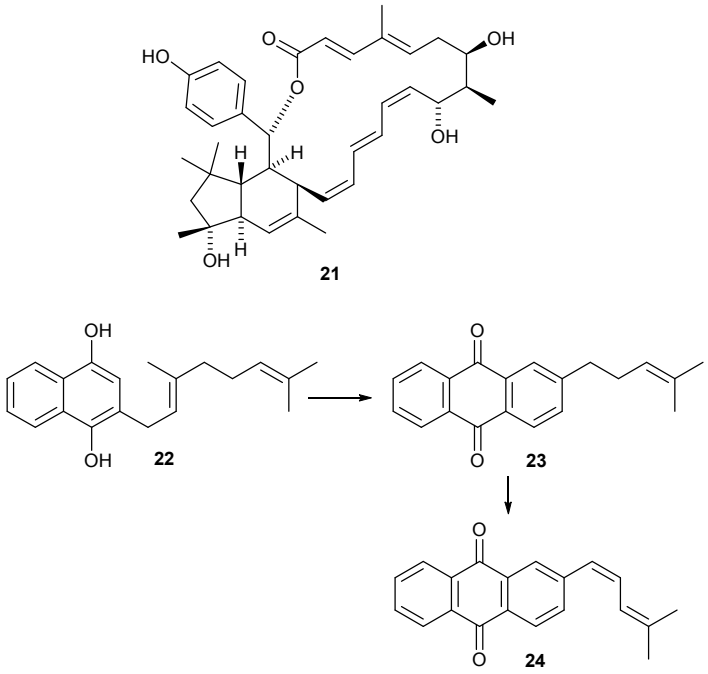
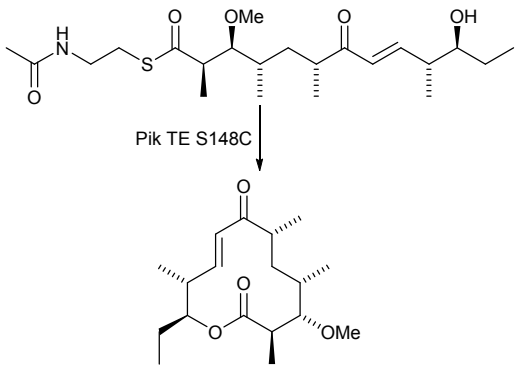
Synthetic studies have been used to support the hypothesis that an intramolecular Diels-Alder cycloaddition is involved in the biosynthesis of the elansolids (such as A1/A2 **21**) from the gliding bacterium *Chitinophaga sancti*.[15] Precursor labelling studies have demonstrated that 2-geranyl-1,4-naphthohydroquinone **22** is efficiently converted to 2-(4-methyl-3-penten-1-yl)anthraquinone **23** in *Sesamum indicum* and that **23** is also efficiently converted into 2-(4-methyl-1*Z*,3-pentadien-1-

yl)anthraquinone **24** but not into more highly oxygenated anthraquinone derivatives (Scheme 1).[16]

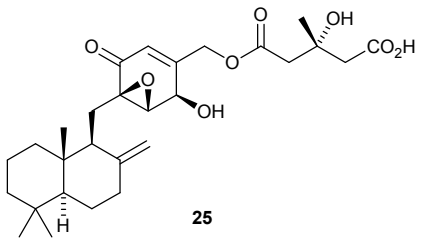


Scheme 1

To improve substrate scope and reaction rates, molecular dynamic simulations have been used to study the recently identified thioesterase from the pikromycin biosynthetic pathway.[17] This work has shown that a single active site mutation (S148C) that increases substrate flexibility can produce a more effective macrolactonisation catalyst, allowing the production of novel diastereomeric macrolactones (Scheme 2). The biosynthetic gene cluster of the epoxycyclohexenone macrophorins (e.g. macrophorin D **25**) has been isolated and characterised from *Penicillium terrestris*.[18] From this cluster, MacJ, a membrane-bound type-II terpene cyclase has been shown to cyclise meroterpenoids through direct olefinic bond protonation.



Scheme 2



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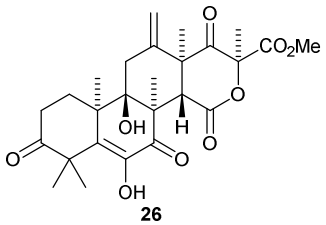
Biochemical and crystallographic analyses have revealed the role of the multifunctional enzyme, Trt14 from *Aspergillus terreus*, in the biosynthesis of the fungal meroterpenoid terretonin **26**.[19] As well as catalysing the D-ring expansion via intramolecular methoxy rearrangement, the enzyme is also involved in hydrolysis of the expanded D-ring. Activation of a cryptic gene cluster in *Lysobacter enzymogenes* that contains three nonribosomal peptide synthetases (NRPS) has led to the production of novel pyrrolopyrazines (e.g. **27**).[20] Targeted gene inactivation showed that these pyrrolopyrazines are synthesised by the NRPS via a module-domain portable mechanism.



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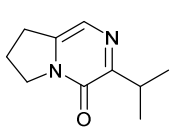

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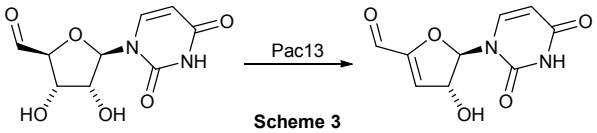
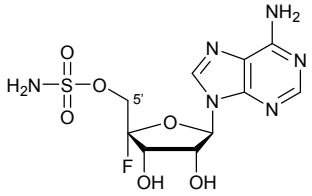
The dehydratase enzyme, Pac13 responsible for the conversion of uridine-5'-aldehyde to 3'-deoxy-3',4'-didehydrouridine-5'-aldehyde (Scheme 3) during the biosynthesis of uridyl peptide antibiotics has been characterised.[21] Studies have shown that an

active site residue, histidine-42 is crucial for enzyme activity and that dehydration likely proceeds via an $E1_{cB}$ mechanism. Feeding studies with deuterium-labelled glycerols in *Streptomyces calvus* have provided insight into the biosynthesis of the antibiotic nucleocidin **28**.[22] In particular, deuterium incorporations from various glycerol isotopomers at the C-5' site of nucleocidin indicate that there is no oxidation of the *pro*-R hydroxymethyl group of glycerol during the biosynthesis of the antibiotic.

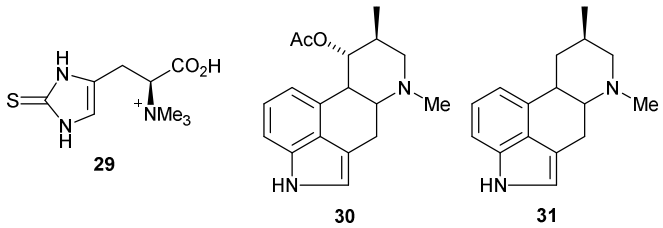


Scheme 3



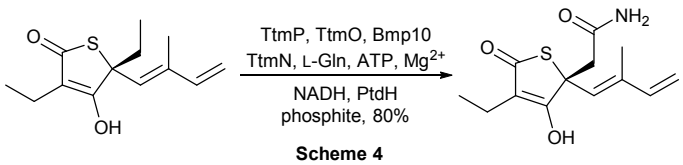
28

An entirely novel biosynthetic pathway of the sulfur metabolite, ergothioneine **29** from the anaerobic green sulfur bacterium *Chlorobium limicola* has been reported.[23] From this pathway, a sulfur transferase, EanB has been characterised and shown to convert *N*-α-trimethylhistidine to ergothioneine by transfer of sulfur to a non-activated carbon. Characterisation of the biosynthetic pathway of the ergot alkaloid isofumigaclavine A **30** from the blue cheese-making fungus *Penicillium roqueforti* has led to the identification of a bifunctional old yellow enzyme (OYE) homologue involved in the production of the intermediate, festuclavine **31**.[24] Further studies showed that the OYE homologue also enhances the production of the preceding biosynthetic intermediate, chanoclavine-I aldehyde via activation of short-chain dehydrogenase/reductases.

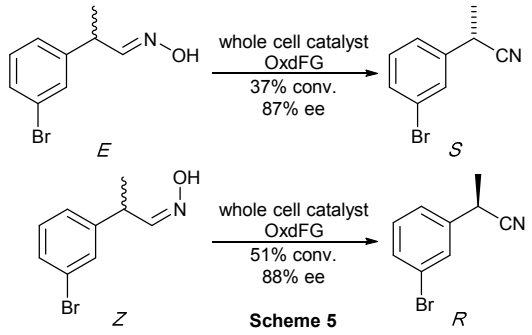


29 **30** **31**

The two-step biosynthetic conversion of thiotetromycin to thiotetramide C by tandem oxidation and amidation of a chemically inert alkyl group has been reported.[25] The transformation which is mediated by a cytochrome P450-amidotransferase enzyme pair could be conducted as an *in vitro* chemoenzymatic reaction, resulting in the efficient preparation of thiotetroamide C (Scheme 4) and other unnatural bioactive analogues. The use of efficient recombinant *E. coli* whole-cells overexpressing aldoxamine dehydratases have been used as a new general approach for the synthesis of chiral nitriles.[26] The study also discovered that the use of the *E* or *Z* isomer of a racemic aldoxamine substrate gave preferentially one or the other enantiomer with a particular enzyme (Scheme 5).



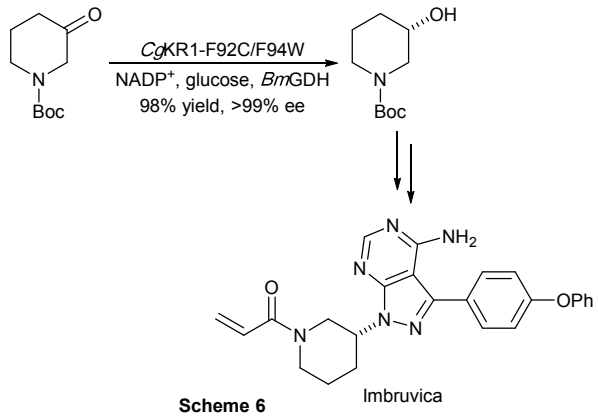
Scheme 4



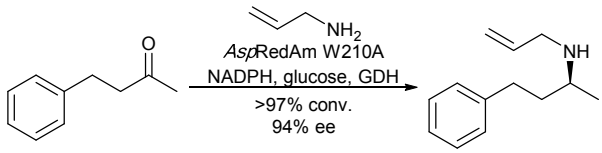
Scheme 5

Computational analysis has allowed the engineering of a ketoreductase *Cg*KR1 from *Candida glabrata*, resulting in a high activity biocatalyst (*Cg*KR1-F92C/F94W).[27] The engineered biocatalyst was used for the large scale synthesis of various chiral alcohols, such as (*S*)-*N*-Boc-3-hydroxypiperidine (Scheme 6), a key intermediate for

the preparation of imbruvica, used in the treatment of lymphoma. A NADPH-dependent reductive aminase from *Aspergillus oryzae* has been discovered that has particularly high activity for the reductive amination of ketones.[28] X-Ray crystallography of the enzyme was used to inform mutagenesis studies, resulting in variant biocatalysts with a switch in stereoselectivity compared to the wild-type enzyme (Scheme 7). The wild-type enzyme and mutant variants were also used for the preparative-scale synthesis of various optically active amines.

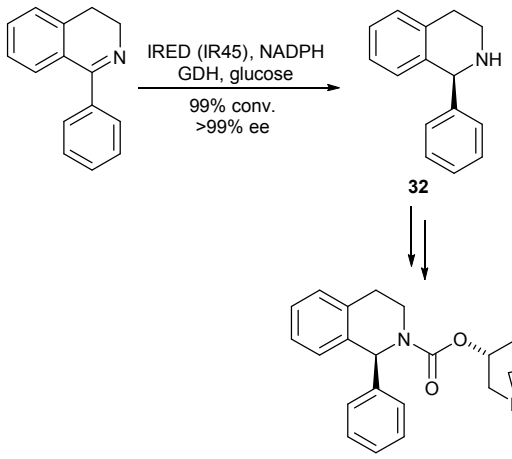


Scheme 6

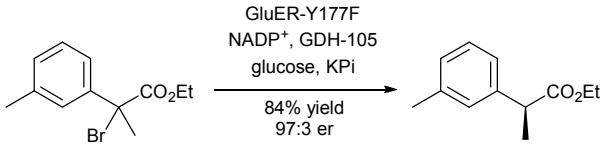


Scheme 7

Extensive analysis of a large number of imine reductases has identified various biocatalysts that are able to convert 1-aryl substituted dihydroisoquinolines to the corresponding *R*- or *S*-tetrahydroisoquinolines (THIQ) with high conversion and enantioselectivity.[29] The potential of these biocatalysts was demonstrated with the synthesis of THIQs such as **32**, used as a key intermediate for the preparation solifenacin (Scheme 8). Flavin-dependent ene-reductases have been discovered that can perform enantioselective radical dehalogenation reactions of α-bromo-α-aryl esters (Scheme 9).[30] Mechanistic studies confirmed the role of flavin hydroquinone as the single electron reductant.

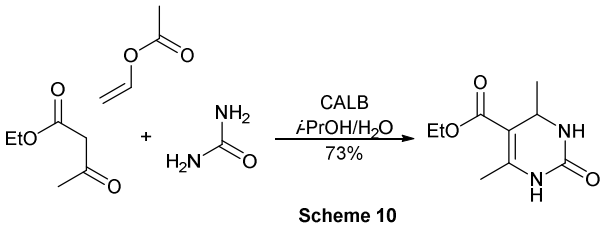


Scheme 8 Solifenacin

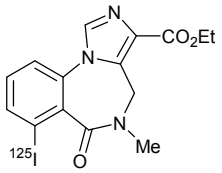


Scheme 9

A tandem multi-component reaction catalysed by *Candida antarctica* lipase B for the preparation of 3,4-dihydropyrimidin-2(1*H*)-ones has been developed (Scheme 10).[31] The two-step process involves the lipase generation of acetaldehyde from vinyl acetate, followed by an enzyme-mediated Biginelli reaction with urea and a β-dicarbonyl compound. A new tandem method for the preparation of ^{125}I-labelled aryl compounds from anilines via stable diazonium salts has been reported.[32] The resulting radioiodinated compounds can be used as single-photon emission computed tomography (SPECT) imaging agents, such as iomazenil **33**, a SPECT tracer of central-type benzodiazepine receptors in brain tissue.



Scheme 10



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