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Hot off the Press

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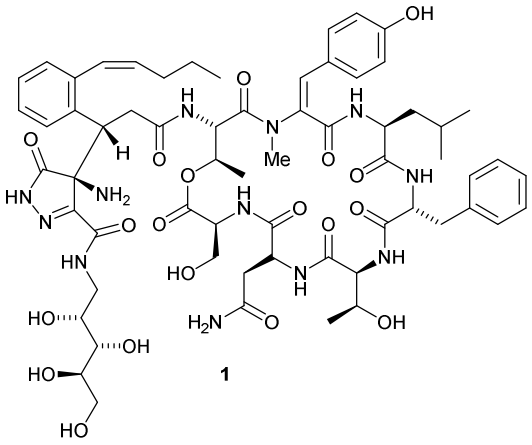
Abstract: A personal selection of 32 recent papers is presented covering various aspects of current developments in bioorganic chemistry and novel natural products such as mollebenzylanol A from *Rhododendron molle.*

The metabolite of an intertidal mudflat-derived *Streptomyces* species, WS9326H **1**, is a cyclic peptide containing an unprecedented pyrazolone ring connected to a D-arabinitol via an amide bond.[1] The tryptophan-linked polyketide georatusin **2** has been isolated from the soil-fungus *Geomyces auratus*.[2] Georatusin **2** shows interesting antiparasitic properties and a biosynthetic pathway for its formation has been proposed. A biosynthetic pathway, involving two Michael additions, has been suggested for the trimeric macrodiolide acaulin A **3**, a metabolite of an *Acaulium* species.[3]



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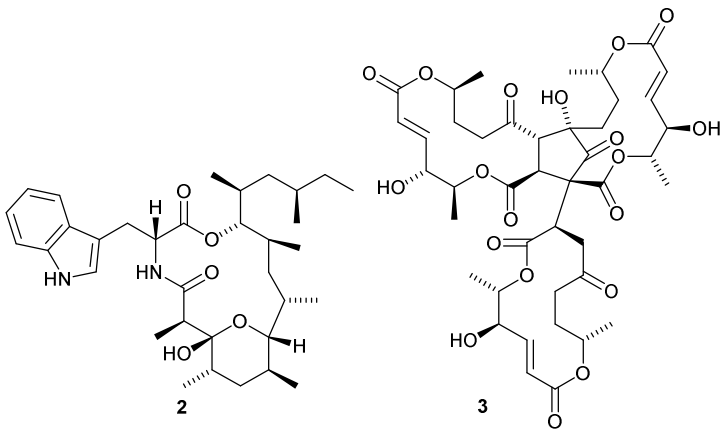
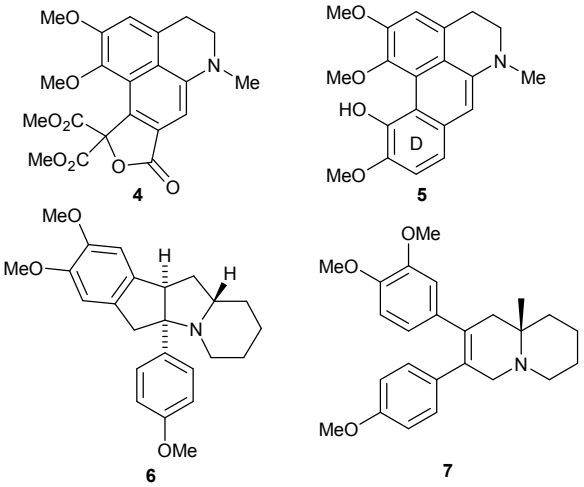


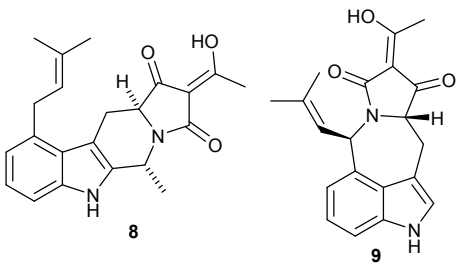
2 **3**

The structure of dactyllactone A **4**, from *Dactylicapnos scandens*, was established by X-ray analysis.[4] The authors propose that dactyllactone A **4** is formed from the co-occurring isocorydione **5** involving oxidation, rearrangement and ring cleavage of ring D. Pileamartine A **6**, from *Pilea* aff. *martinii*, has a new skeleton.[5] It is suggested that pileamartine A **6** is formed by rearrangement of the co-occurring julandine **7**.

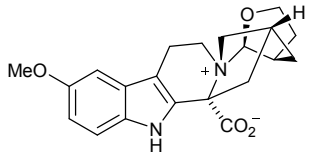


4 **5** **6** **7**

Griseofamines A **8** and B **9**, metabolites of *Penicillium griseofulvum*, have new indole alkaloid skeletons.[6] The structure of griseofamine A **8** was confirmed by X-ray analysis. Voacafricine A **10**, from *Voacanga Africana*, also has a new indole alkaloid skeleton.[7] Biosynthetic pathways to griseofamines A **8** and B **9** and voacafricine A **10** have been proposed.

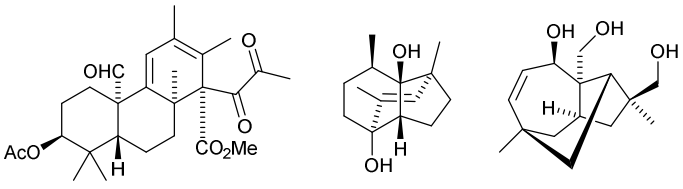


8 **9**



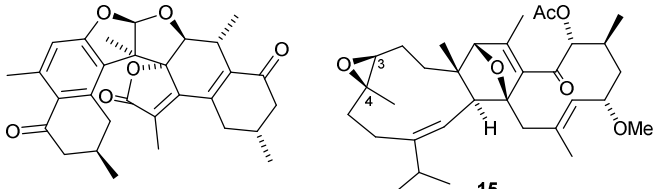
10

The structures of the highly rearranged meroterpenoid simpterpenoid A **11**, a metabolite of *Penicillium simplicissimum*,[8] and the rearranged sesquiterpenoid longifodiol **12**, from the root of *Leontopodium longifolium*,[9] were confirmed by X-ray analyses. A further rearranged sesquiterpenoid, pestalustaine A **13**, has been found as a metabolite of *Pestalotiopsis adusta*.[10] Biosynthetic pathways to the novel skeletons of simpterpenoid A **11**, longifodiol **12** and pestalustaine A **13** have been proposed by the authors.



11 **12** **13**

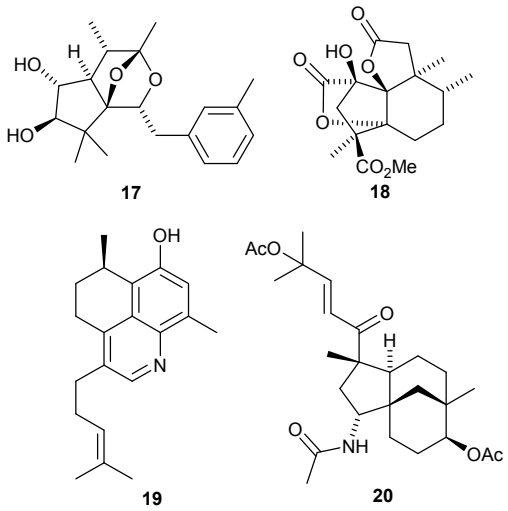
Resina commiphora is the source of several dimeric sesquiterpenoids with novel skeletons including commiphoratone A **14**[11] and commiphoroids A **15** and B **16**[12] whose structures were confirmed by X-ray analyses. The authors suggest possible pathways to these dimeric sesquiterpenoids.



14

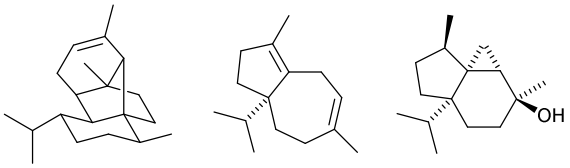
15
16 3,4-diepimer

Mollebenzylanol A **17**, from *Rhododendron molle*, has a novel diterpenoid skeleton that is proposed to be derived from a grayanane precursor involving a rearrangement to produce the aromatic ring.[13] The structure or norcrassin A **18**, from *Croton crassifolius*, was established by X-ray analysis.[14] A biosynthetic pathway to the novel skeleton of norcrassin A **18** from a clerodane precursor has been proposed. The first quinolone-containing serrulatane diterpenoid, microthecaline A **19**, has been obtained from the roots of *Eremophila microtheca*.[15] Sarinfacetamide A **20**, from the soft coral *Sarcophyton infundibuliforme*, has a novel diterepenoid skeleton that is proposed to be derived by rearrangement of a xeniaphyllane precursor.[16]



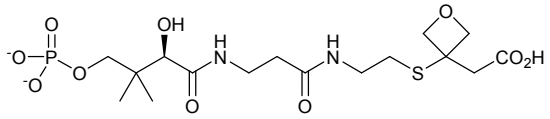
The gene for a terpene synthase from the tropical soil isolate *Allokutzneria albata* DSM 44149 has been cloned and then expressed in *E. coli*, resulting in an enzyme that has produced spiroalbatene **21**, a novel spirotetracyclic diterpene.[17] From a detailed mechanistic study of the terpene synthase by isotope labelling experiments, site-directed mutagenesis and variation of metal co-factors, the authors propose that such insight may assist in generating predicative approaches to access new terpene scaffolds. Metabolic engineering has been used to characterise the function of FgJ03939, a novel sesquiterpene synthase from *Fusarium graminearum*.[18] Overexpression of FgJ03939 in a *Saccharomyces cerevisiae* platform led to the

production of novel sesquiterpenes with 5/7 and 5/6/3 ring systems, including fusariumdiene **22** and fusagramineol **23**.



21 **22** **23**

An oxetane-based polyketide synthase substrate mimic has been prepared and used as a carbonyl isostere to investigate the mechanism of DpsC, the priming ketosynthase for daunorubicin biosynthesis.[19] Co-crystallisation of **24** with DpsC led to the first structural determination of a ketosynthase-inert mimic complex, revealing the substrate orientation for DpsC-catalysed decarboxylation-Claisen condensation of malonyl-CoA. Gene knockout experiments of a fungus that produces okaramines (e.g. okaramine B **25**), prenylated indole alkaloids that are highly selective insecticides, allowed access to structurally diverse okaramine metabolites.[20] Biological testing of these compounds showed that the 1,4-dihydroazocine and *N*-aliphatic group attached to the indole ring are essential for activity.



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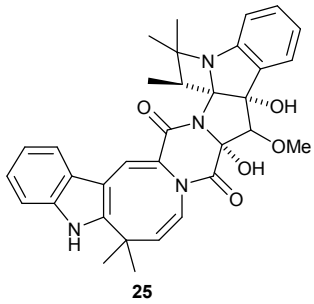
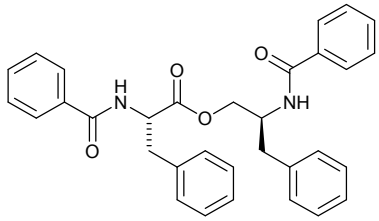


25

Targeted gene disruption in *Penicillium brevicompactum* and heterologous expression in *Aspergillus nidulans* has allowed the characterisation of two nonribosomal peptide synthetases (NRPSs) responsible for the synthesis of the amino ester, asperphenamate

26.[21] The NRPS enzyme ApmA that has a reductase domain produced the alcohol side-chain, while the NRPS enzyme ApmB catalysed intermolecular ester bond formation. Metabologenomics, which combines genomic and metabolomic data has been used for the discovery of novel nonribosomal peptides, the tyrobetaines (e.g. tyrobetaine **27**).[22] The biosynthetic gene cluster was identified by heterologous expression and suggested an unusual mechanism for trimethylation of the N-terminal amine by a novel-type of NRPS *N*-methyltransferase.



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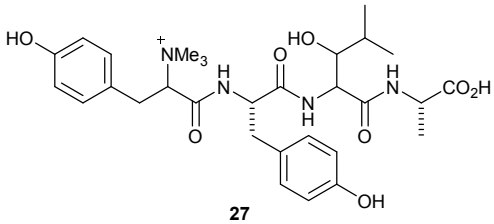
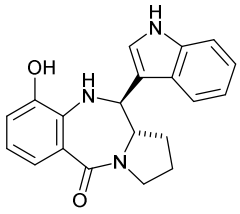


27

The biosynthesis of tilivalline **28**, a pyrrolo[4,2]benzodiazepine produced by the pathobiont *Klebsiella oxytoca* has been investigated by heterologous expression of the gene cluster in *E. coli*.[23] Reconstitution of the NRPS revealed indole incorporation via a nonenzymatic Friedel-Crafts-like alkylation. Novel tilivalline derivatives were also generated by incubation of anthraniliate and indole precursors with the heterologous system. Structure guided engineering of 5-(hydroxymethyl)furfural oxidase (HMFO) has created biocatalysts capable of performing oxidative kinetic resolution of 1-phenylethanethiols (Scheme 1).[24] The engineering strategy for these studies involved enlarging the active site by additional hydrogen bonding, as verified by crystal structure analysis.



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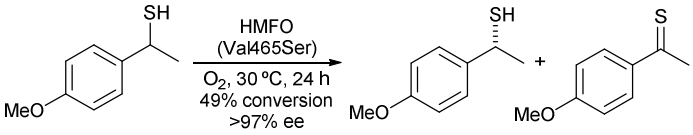
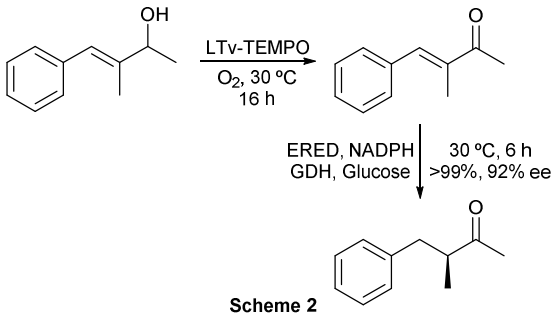
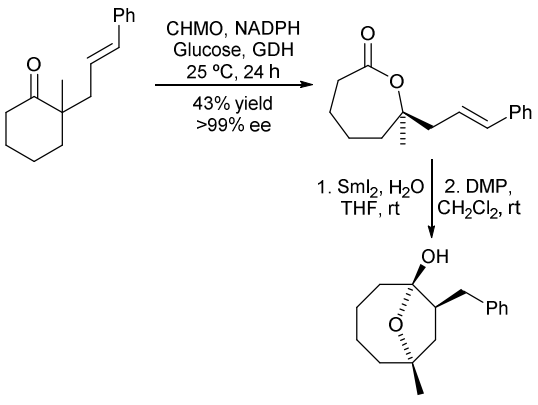


Scheme 1

A one-pot bi-enzymatic strategy has been developed for the conversion of racemic allylic alcohols to enantiomerically enriched saturated ketones (Scheme 2).[25] The laccase from *Trametes versicolor* (LTv) and TEMPO were shown to oxidise a series of allylic *sec*-alcohols, and when combined with commercially available ene-reductases, resulted in an overall redox isomerisation process. Cyclohexanone monooxygenase (CHMO) from *Acinetobacter calcoaceticus* has been used for the kinetic resolution of cyclic ketones bearing quaternary stereocentres. (Scheme 3).[26] Samarium iodide mediated cyclisation of the resulting lactones and oxidation allowed access to enantiomerically enriched carbocyclic scaffolds.

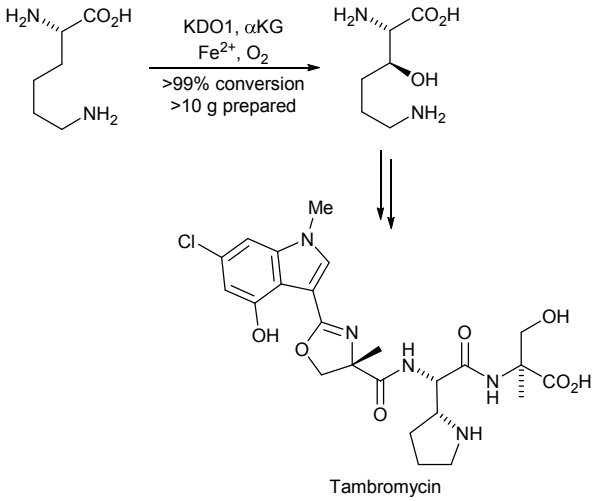


Scheme 2



Scheme 3

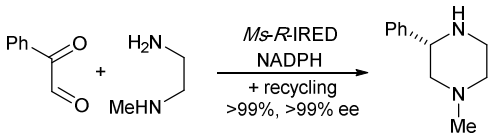
The first total synthesis of tambromycin, a nonribosomal peptide natural product from various *Streptomyces* strains has been achieved using a biocatalytic C-H functionalisation as the key step.[27] An iron and α-ketoglutarate-dependent dioyxgenase, lysine hydroxylase KDO1 was overexpressed and used for the regio- and stereoselective C3-hydroxylation of lysine, on a multigram scale (Scheme 4). 3-Hydroxylysine was then used as a key intermediate for the rapid synthesis of tambroline, the pyrrolidine-containing amino acid in the core of tambromycin.



Scheme 4

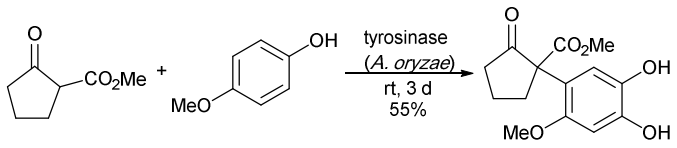
A direct approach for the synthesis of piperazines from 1,2-dicarbonyls and 1,2-diamines has been reported using a *R*-selective imine reductase from *Myxococcus stipitatus*.[28] This double reductive amination approach tolerated a wide range of aryl

and alkyl substrates, generating a diverse series of chiral piperazine building blocks (Scheme 5).

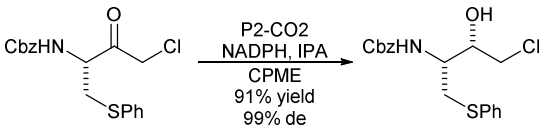


Scheme 5

A tyrosinase from *Aspergillus oryzae* has been shown to be a useful biocatalyst for the α-arylation of β-dicarbonyl compounds and the generation of quaternary carbon centres.[29] The process involves the enzymatic oxidation of phenols to the corresponding quinones that then undergo a 1,4-addition reaction with the β-dicarbonyl compound. An examination of the substrate scope showed that electron-rich phenols are preferred (Scheme 6). A commercially available engineered ketoreductase, P2-CO2 has been used to conduct a highly *erthyro* selective synthesis of a chlorohydrin product, a key intermediate for the synthesis of the HIV-protease inhibitor nelfinavir.[30] On screening a set of ketoreductases, P2-CO2 was found to be the most active and in combination with the green solvent, cyclopentyl methyl ether (CPME) allowed the scalable synthesis of the chlorohydrin in 99% de (Scheme 7).



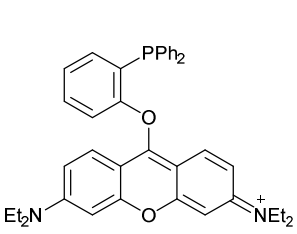
Scheme 6



Scheme 7

A dual-channel fluorescent agent based on a 2-(diphenylphosphino)phenol-functionalised pyronin structure **29** has been developed for the diagnosis of cancer cell-types and tissues.[31] The agent is selectively taken up into cancer cells by the organic anion transporting polypeptide transporters that are overexpressed in many

cancer cell types before being activated by cysteine and glutathione to produce either green or red-emitting species. A long wavelength fluorescent probe **30** has been designed as a high affinity imaging agent of estrogen receptor β (ERβ), a pharmaceutical target in hormone replacement therapy for breast cancers.[32] As well as being highly selective for ERβ over estrogen receptor α, the probe was used to monitor ERβ expression in prostate cancer and triple-negative breast cancer cells.



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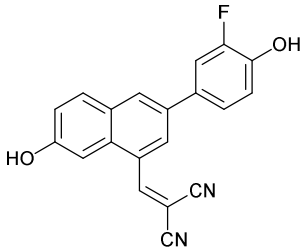

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