
This is the author’s final accepted version.

There may be differences between this version and the published version. You are advised to consult the publisher’s version if you wish to cite from it.

http://eprints.gla.ac.uk/152570/

Deposited on: 07 December 2017
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 euphorikanin A from Euphorbia kansui.

Darwinolide 1, from the Antarctic sponge Dendrilla membranosa, shows interesting activity against methicillin-resistant Staphylococcus aureus. The novel diterpenoid structure of darwinolide 1 was confirmed by X-ray analysis. A biosynthetic pathway for darwinolide 1, from a spongiane precursor, has been proposed. The structure of euphorikanin A 2, from Euphorbia kansui, was also confirmed by X-ray analysis. The authors suggest that the new skeleton of euphorikanin A 2 is formed from an ingenane diterpenoid precursor. Perovskiaol 3, from Perovskia atriplicifolia, may be formed by condensation of acetoacetyl CoA with a 20-norabietane diterpenoid.
Genome mining of a terpene synthase gene from *Emericella variecolor* and its functional expression in *Aspergillus oryzae* led to the isolation of the sesterterpenoid astellifadiene 4 which has a new skeleton.\(^4\) The structure and absolute configuration of astellifadiene 4, which exists as an oil, were established by the crystalline sponge method. A biosynthetic pathway to astellifadiene 4 has been proposed based on the results of acetate labelling studies. Phomarol 5, with a novel 1(10→19)abeo steroid skeleton, is a metabolite of a *Phoma* species isolated from the giant jellyfish *Nemopilema nomurai*.\(^5\)

![Chemical structure of astellifadiene and phomarol]

The meroterpenoid verrubenzospirolactone 6, from the soft coral *Sinularia verruca*, has a new carbon skeleton.\(^6\) Applanatumols A 7 and B 8, from *Ganoderma applanatum*, are further meroterpenoids with new skeletons.\(^7\) Biosynthetic pathways to applanatumols A 7 and B 8 have been proposed.

![Chemical structures of applanatumols]

The structural diversity of the limonoid family, or the tetranortriterpenoids, is enormous. Two additional examples with unusual structures are ciliatonoid A 9, from *Toona ciliata*,\(^8\) and perforanoid A 10, from *Harrisonia perforata*.\(^9\) The structure of
ciliatonoid A 9, was confirmed by X-ray analysis whereas the structure of perforanoid A 10, including the stereochemistry at C-10, was confirmed by total synthesis.

Myritonine A 11, from *Myrioneuron tonkinensis*, has a novel heterohexacyclic ring system. The structure of myritonine A was confirmed by X-ray analysis. Another new ring system is present in palcernuine 12 which has been isolated from *Palhinhaea cernua f. sikkimensis*. A biosynthetic pathway for the formation of the five-membered ring of palcernuine 12 from a cernuane alkaloid precursor has been proposed. The symmetrical pyrazine grizeusrazin A 13, a metabolite of marine-derived *Streptomyces griseus* ssp. *griseus*, shows interesting anti-inflammatory properties.

Outovirins A – C are epipolythiodiketopiperazines isolated from *Penicillium raciborskii*, an endophytic fungus isolated from *Rhododendron tomentosum*. Outovirin C 14 is the first reported trisulfide of the gliovirin family of alkaloids. The first cyclopentachromone with a sulfide chain, chromosulfine 15, has been isolated from a marine-derived *Penicillium purpurogenum*. Chromosulfine 15 is produced by
a silent biosynthetic pathway that was induced after the introduction of neomycin resistance.

Callyazepin 16, from a sponge of the genus *Callyspongia*, has a new skeleton and includes a chiral quaternary nitrogen. Callyazepin 16 is of mixed biogenetic origin and appears to be derived from a polyketide and alanine. Antalid 17, a metabolite of a *Polyangium* species, is also of mixed biosynthetic origin. In *silico* analysis of the biosynthetic gene cluster for antalid 17 has established the biosynthetic origin of this PKS-NRPS hybrid natural product. The structure of antalid 17 was confirmed by crystal structure analysis and total synthesis.

Cox and co-workers have recreated the biosynthesis of maleidrides such as byssochlamic acid 18 in a heterologous host. Gene disruption and heterologous expression experiments identified two proteins with homology to ketosteroid isomerases involved in the key stage of C9-maleic anhydride monomer dimerisation.
The Cox group have also reported the elucidation of the gene cluster responsible for the biosynthesis of squalestatin S1 19, a lead compound in the 1990s for the treatment of hypercholesteremia. An acyltransferase gene from the cluster was expressed in *E. coli*, with the resulting protein MfM4 found to be responsible for loading acyl groups from coenzyme A (CoA) onto the squalestatin core. The broad substrate specificity of MfM4 for acyl CoA substrates allowed the *in vitro* preparation of novel squalestatins.

In *in vitro* and *in vivo* studies of the biosynthesis of SF2575 20, a tetracycline antibiotic produced by *Streptomyces* sp. SF2575 have identified an ATP-dependent acyl-CoA ligase responsible for the Claisen cyclisation of the A-ring. The authors propose that the reaction proceeds by the ligase-mediated adenylation of a tricyclic carboxylic acid substrate followed by Claisen cyclisation. The spirotetronate cyclase AbyU, a key enzyme for the biosynthesis of the antibiotic abyssomicin C 21 has been fully characterised and shown to be a cofactor-independent Diels-Alderase. A combination of enzyme assays, X-ray crystallography and molecular modelling has established the binding mode of the linear substrate as well as the catalytic mechanism of the [4+2] cycloaddition.
Comparative metabolomics of the human pathogen *Aspergillus fumigatus* have revealed the *fsq* gene cluster which features a non-ribosomal peptide synthetase gene (*fsqF*) that lacks a condensation domain. The *fsqF* gene is responsible for the production of a series of novel isoquinoline alkaloids (e.g. fumisoquin A) that are formed via a carbon-carbon bond forming reaction between L-serine and L-tyrosine.

The late stage biosynthesis of sesterterpenes such as ophiobolin F have been investigated by the heterologous expression of four candidate genes from ophiobolin gene clusters in *Aspergillus oryzae*. The resulting transformant was shown to catalyse a four-step oxidative process, converting ophiobolin F to ophiobolin C. One of the enzymes OblB, a cytochrome P450 was found to be responsible for the introduction of oxygen functionality at C-5 and C-21.

A combination of systematic gene deletion, heterologous gene expression and biochemical studies have revealed the key enzyme involved in the biosynthesis of roseoflavin, the only known natural riboflavin analogue with antibiotic activity. This key enzyme produced from gene BN159_7989 from *Streptomyces davawensis* was shown to convert riboflavin-5’-phosphate via a series of reactions to 8-demethyl-8-aminoriboflavin-5’-phosphate, an advanced intermediate of roseoflavin biosynthesis. Six phenazine antibiotics including four N-oxides (e.g. myxin) have been isolated from *Lysobacter antibioticus OH13*. Identification of the phenazine gene cluster has led to the characterisation of the enzyme LaPhzNO1, which although homologous to Baeyer-Villiger flavoproteins performs the N-oxidation of phenazines.
A chemoenzymatic synthesis of α-fluoro β-hydroxy carboxylic esters has been developed using a trans-o-hydroxybenzylidene pyruvate aldolase catalysed reaction between fluoropyruvate and various aromatic aldehydes (Scheme 1). Following the aldolase reaction, hydrogen peroxide was used to facilitate decarboxylation, yielding the target compounds after esterification with excellent yields and enantioselectivity. Deuterium-substituted probe substrates in combination with mass spectrometry have been used to discover variants of rebeccamycin halogenase for the chlorination of indoles. This evolution strategy identified enzymes that could selectivity produce ortho-, meta- or para-substituted products in high yields (Scheme 2).
A one-pot chemoenzymatic oxidative aza-Friedel-Crafts reaction for the α-functionalisation of pyrrolidines has been developed.\textsuperscript{27} Oxidation of meso-pyrrolidines by an engineered monoamine oxidase, followed by reaction with a range of C-nucleophiles gave the substitution products as single diastereomers with high enantioselectivity (Scheme 3). Experimental and computation work have identified a single mutation in the F/G loop of the nitrating cytochrome P450 TxtE enzyme that alters the regioselectivity of the reaction.\textsuperscript{28} Rather than forming the wild-type C-4 nitration product with L-tyrosine, mutation of this single residue which interacts with the substrate and contributes to active site organisation produced instead the C-5 product (Scheme 4).

Lavandera and co-workers have shown that cis- and trans-but-2-ene-1,4-diamines can be used as sacrificial co-substrates in enzymatic transamination reactions.\textsuperscript{29} Following amino group transfer, the resulting ω-amino aldehyde intermediate undergoes an intramolecular cyclisation, providing the driving force for the efficient production of optically active amines with excellent enantioselectivity (Scheme 5). The recombinant
ketoreductase KRED1-Pglu isolated from the yeast *Pichia glucozyma* CBS 5766 has been shown to be an effective biocatalyst for the asymmetric reduction of β-hydroxynitriles (Scheme 6) and α-haloketones.\(^{30}\) Using a glucose/glucose dehydrogenase recycling system for the NADP\(^+\) cofactor gave chiral synthetic building blocks in excellent yields.

Baker’s yeast has been shown to catalyse the highly regioselective 1,4-conjugate addition reaction of indoles with nitroalkenes.\(^{31}\) The operationally simple procedure was found to be tolerant of a wide range of substitution patterns for both substrates, giving the addition products in high yields (Scheme 7). A two-photon fluorescent probe 26 has been reported that has the potential to act as a visual tool in the real-time dynamic imaging of DNA damage.\(^{32}\) The probe operates through sequential intramolecular charge transfer (ICT) processes and allows in vivo visualisation of DNA damage in cancer cells either by one/two photon microscopic imaging or using a hand-held UV lamp.
References


