Hill, R. A., and Sutherland, A. (2017) Hot off the press. *Natural Product Reports*, 34(2), pp. 130-134.

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/135103/>

Deposited on: 28 April 2017

Enlighten – Research publications by members of the University of Glasgow
<http://eprints.gla.ac.uk>

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 hitorin A from *Chloranthus japonicus*.

Selesconol **1**¹ and spirodalesol **2**² are polyketide metabolites from *Daldinia eschscholzii* with new carbon frameworks. Both selesconol **1** and spirodalesol **2** were isolated as racemic mixtures and their structures were confirmed by X-ray analyses. The authors propose that they are formed from a common intermediate. The structure of trichotoxin, a metabolite from *Trichodesmium thiebautii*, has been revised from **3** to **4** after careful examination of the NMR data.³

Two alkaloids with new skeletons, stemona-amines F **5** and G **6**, have been isolated from *Stemona tuberosa*.⁴ The structure of stemona-amine F **5** was confirmed by X-ray analysis. The structure of eudustidine C **7**, from a marine ascidian of the genus

Eudistoma, was established using a new NMR pulse sequence (LR-HSQMBC) which is optimised to detect four- and five-bond heteronuclear correlations together with computer-assisted structure elucidative software.⁵ The structure of eudustidine C **7** was also confirmed by synthesis. A *Theonella* sponge is the source of lanesoic acid **8** which has an unusual tetrahydropyrimidine cation stabilised by a carboxylate.⁶

Hypericum species are a rich source of prenylated acylphloroglucinols with diverse structures. Further interesting examples include hypatulins A **9** and B **10**, with highly substituted caged structures, from *Hypericum patulum*⁷ and the sabinene and pinene derivatives, hyperjaponines F **10** and H **11**, from *Hypericum japonicum*.⁸ Garmultin A **13**, from *Garcinia multiflora*, is a polycyclic caged acylphloroglucinol whose structure was established by X-ray analysis.⁹ Biosynthetic pathways to all of these acylphloroglucinol derivatives have been proposed.

Lentinulactam **14**, a metabolite of *Lentinus* cf. *fasciatus*, has a new skeleton that is proposed to be formed by rearrangement of a hirsutane sesquiterpenoid.¹⁰ The structure of the rearranged norditerpenoid scrodentoid F **15**, from *Scrophularia dentata*, was established by X-ray crystallography.¹¹ The authors propose that scrodentoid F **15** is formed from a pimarane precursor. The structures of dodovisnoid A **16** from *Dodonaea viscosa*¹² and hypophyllin A **17** from *Hypoestes phyllostachya*¹³ were also established by X-ray analyses. The authors propose biosynthetic pathways to dodovisnoid A **16** and hypophyllin A **17** from clerodane and labdane diterpenoid precursors, respectively.

Anvilone A **18**, from a *Phorbas* sponge, has a new sesterterpenoid skeleton that the authors name as anvilane.¹⁴ It is proposed that the C₂₅ terpenoid hitorin A **19**, from *Chloranthus japonicus*, is formed from eudesmane sesquiterpenoid and thujane monoterpene precursors.¹⁵ The structure of teuviscin A **20**, from *Teucrium viscidum*, was established as a 7(8→9)-abeofernane triterpenoid by X-ray analysis.¹⁶

A combination of genome mining and expression studies has led to the discovery of the biosynthetic gene cluster responsible for the production of the antiparasitic natural product siphonazole **21** in *Herpetosiphon* sp. B060.¹⁷ The pathway involves a shikimate starter unit extended by polyketide synthases and nonribosomal peptide synthetases, as well as an unusual termination mechanism that forms the diene terminus of siphonazole. The olefin shift process that occurs during the biosynthesis of the 3-methyl-1,4-pentadiene fragment of ambruticins (e.g. ambruticin VS3 **22**) has been delineated.¹⁸ The process initially involves a multifunctional domain AmbDH4 that catalyses a dehydration, epimerisation and enoyl isomerisation sequence. The unfavourable equilibrium of this process is then trapped by a C-methyltransferase catalysed α -methylation leading to the pentadiene fragment of the ambruticins.

Using ^{13}C -labelling and NMR analysis, the mechanism of B-ring contraction during gibberellin biosynthesis in bacteria has been elucidated.¹⁹ A combination of the cytochrome P450 monooxygenase CYP114 and the ferredoxin Fd_{GA} results in oxidative extrusion of C-7 likely via a semipinacol-type rearrangement guided by the 4α -carboxylate (Scheme 1). Genome sequencing has shown that *Streptomyces* sp. SANK 60404 uses amino-group carrier proteins (AmCP) for the biosynthesis of the novel nonproteinogenic amino acid (2*S*,5*R*,6*R*)-2,6-diamino-5,7-dihydroxyheptanoic acid (**DADH**).²⁰ It was also discovered that a combination of nonribosomal peptide synthetases and other modification enzymes convert **DADH** into the peptide metabolite vazabotide A (**Vaza**), an unstable 1-azabicyclo[3.1.0]hexane ring system.

A heterologous expression system using *Aspergillus oryzae* has allowed the elucidation of the late-stage biosynthetic pathway of the indole diterpene shearinine D **25**.²¹ In particular, a flavoprotein oxidase, JanO was shown to be responsible for formation of the A/B bicyclic shearinine core from a diprenylated intermediate via hydroxylation and a hydride transfer mechanism. A novel prenyltransferase KgpF, which transfers dimethylallyl groups to tryptophan residues during the biosynthesis of kawaguchipectin A **26**, a cyanobactin, has been characterised.²² The stereo-configuration of the modified tryptophan residues by KgpF was determined using in vitro dimethylallylation experiments of Fmoc-tryptophan. The authors have suggested that the relaxed substrate specificity of KgpF may allow enzyme engineering for the preparation of novel prenylated tryptophan derivatives.

An investigation of the enzyme GLligase involved in lipoinitiation of pneumocandins (e.g. **27**) in *Glarea lozoyensis* has resulted in new side-chain analogues.²³ Mutasynthesis experiments showed that GLligase can shuttle various acyl side chains to the nonribosomal peptide synthetase yielding new pneumocandins, some of which

showed antifungal activity. The biosynthetic pathway of herquiline A **28**, a highly strained fungal piperazine alkaloid has been characterised.²⁴ Following nonribosomal peptide synthetase generation of a dityrosine piperazine intermediate and enzymatic reduction of a cross-linked dicyclohexadienone, *N*10'-methylation initiates a stereoselective cascade process resulting in the multicyclic core of herquiline A.

The Turner group has reported two new biocatalytic approaches for the synthesis of α -amino acids. A one-pot Knoevenagel-Doebner condensation of heteroaromatic derived aldehydes with malonic acid, followed by a phenylalanine ammonia lyase biocatalysed hydroamination has allowed the asymmetric synthesis of L-heteroarylalanines (Scheme 2).²⁵ In the second approach, a recombinant whole cell system containing an engineered dehydrogenase has been used for the preparation of D-amino acids.²⁶ Extensive directed evolution of the highly stereoselective *meso*-diaminopimelate dehydrogenase from *Corynebacterium glutamicum* produced a biocatalyst that was able to perform reductive amination on a range of aryl derived α -keto acids, forming the corresponding D-amino acids in excellent enantiomeric excess and high yields (Scheme 3).

A recent issue of *Tetrahedron* (2016, **72**, issue 46) has been dedicated to “modern developments in biotransformations” and contain a range of articles on biocatalyst development, including the one-pot preparation of L-dihalotryptophans and L-alkynyltryptophans (Scheme 4) from L-serine and indoles using tryptophan synthase.²⁷ Extensive protein engineering of the transaminase from *Ruegeria* sp. TM1040 has produced a biocatalyst with 8900-fold higher activity than the starting enzyme.²⁸ The biocatalyst was able to accept particularly bulky substrates, producing pharmaceutically relevant amines with excellent conversions and enantiomeric excess (Scheme 5).

A fungal carboxylate-reducing enzyme (CAR) from *Neurospora crassa* OR74A has been expressed in *E. coli* and shown to have broad substrate specificity for a range of aromatic, aliphatic and alkenyl derived carboxylic acids.²⁹ Application of this whole-

cell system was demonstrated with the highly efficient gram-scale synthesis of piperonal from piperonylic acid (Scheme 6). Mutation of a single amino acid residue of *p*-hydroxyphenylacetate 3-hydroxylase (HPAH) from *Acinetobacter baumannii* has produced a biocatalyst with a wider substrate scope than the wild-type enzyme.³⁰ Substitution of serine-146, a residue close to the phenolic group binding site for an alanine has allowed the efficient hydroxylation of an aniline substrate with similar activity as the natural phenolic substrate (Scheme 7).

An iron-catalysed dehydrogenation-hydrogenation reaction has been combined with a lipase mediated esterification for the dynamic kinetic resolution of various benzylic, aliphatic and heteroaromatic secondary alcohols (Scheme 8).³¹ The dual catalytic process was also used to invert the configuration of an optically pure secondary alcohol and generated the enantiomeric acetate in excellent yield. The enzymatic decarboxylation of cinnamic acids by phenolic acid decarboxylase from *Bacillus subtilis* (*bsPAD*) has been combined with a ruthenium catalysed cross metathesis reaction for the one-pot synthesis of stilbenes.³² The incompatibility of the enzyme reaction that is normally performed under aqueous conditions with the metathesis reaction that requires anhydrous conditions was solved by encapsulation of the decarboxylase in a cryogel. This allowed both steps to be done in methyl *tert*-butyl ether (MTBE) producing the antioxidant 4,4'-dihydroxystilbene in 90% yield (Scheme 9).

Scheme 8

Scheme 9

References

- 1 A. H. Zhang, R. Tan, N. Jiang, K. Yusupu, G. Wang, X. L. Wang and R. X. Tan, *Org. Lett.*, 2016, **18**, 5488.
- 2 A. H. Zhang, W. Liu, N. Jiang, Q. Xu and R. X. Tan, *Org. Lett.*, 2016, **18**, 6496.
- 3 M. J. Bertin, P. V. Zimba, H. He and P. D. R. Moeller, *Tetrahedron Lett.*, 2016, **57**, 5864.
- 4 Y. Hitotsuyanagi, Y. Sekiya, H. Fukaya, H. S. Park, S. Zhu and K. Komatsu, *Tetrahedron Lett.*, 2016, **57**, 5746.
- 5 S. T. S. Chan, R. R. Nani, E. A. Schauer, G. E. Martin, R. T. Williamson, J. Sauri, A. V. Buevich, W. A. Schafer, L. A. Joyce, A. K. L. Goey, W. D. Figg, T. T. Ransom, C. J. Henrich, T. C. McKee, A. Moser, S. A. MacDonald, S. Khan, J. B. McMahon, M. J. Schnermann and K. R. Gustafson, *J. Org. Chem.*, 2016, **81**, 10631.
- 6 J. Rodríguez, C. Jiménez, M. Blanco, G. Tarazona, R. Fernández and C. Cuevas, *Org. Lett.*, 2016, **18**, 5832.
- 7 N. Tanaka, Y. Yano, Y. Tatano and Y. Kashiwada, *Org. Lett.*, 2016, **18**, 5360.

- 8 Y.-P. Li, X.-W. Yang, F. Xia, H. Yan, W.-G. Ma and G. Xu, *Tetrahedron Lett.*, 2016, **57**, 5868.
- 9 D. S. Tian, P. Yi, L. Xia, X. Xiao, Y. M. Fan, W. Gu, L. J. Huang, Y. Ben-David, Y. T. Di, C. M. Yuan and X. J. Hao, *Org. Lett.*, 2016, **18**, 5904.
- 10 S. E. Helaly, C. Richter, B. Thongbai, K. D. Hyde and M. Stadler, *Tetrahedron Lett.*, 2016, **57**, 5911.
- 11 L.-q. Zhang, Y.-y. Zhao, C. Huang, K.-x. Chen and Y.-m. Li, *Tetrahedron*, 2016, **72**, 8031.
- 12 L.-B. Zhang, H.-B. Liao, H.-Y. Zhu, M.-H. Yu, C. Lei and A.-J. Hou, *Tetrahedron*, 2016, **72**, 8036.
- 13 X.-D. Wu, D. Luo, W.-C. Tu, Z.-T. Deng, X.-J. Chen, J. Su, X. Ji and Q.-S. Zhao, *Org. Lett.*, 2016, **18**, 6484.
- 14 M. Wang, I. Tietjen, M. Chen, D. E. Williams, J. Daoust, M. A. Brockman and R. J. Andersen, *J. Org. Chem.*, 2016, **81**, 11324.
- 15 S.-Y. Kim, H. Nagashima, N. Tanaka, Y. Kashiwada, J. Kobayashi and M. Kojoma, *Org. Lett.*, 2016, **18**, 5420.
- 16 Z.-Y. Li, F.-M. Qi, D.-J. Zhi, Q.-L. Hu, Y.-H. Liu, Z.-X. Zhang and D.-Q. Fei, *Org. Chem. Front.* 2017, **4**, 42.
- 17 M. M. Mohseni, T. Höver, L. Barra, M. Kaiser, P. C. Dorrestein, J. S. Dickschat and T. F. Schäberle, *Angew. Chem. Int. Ed.*, 2016, **55**, 13611.
- 18 G. Berkhan, C. Merten, C. Holec and F. Hahn, *Angew. Chem. Int. Ed.*, 2016, **55**, 13589.
- 19 R. S. Nett, J. S. Dickschat and R. J. Peters, *Org. Lett.*, 2016, **18**, 5974.

- 20 F. Hasebe, K. Matsuda, T. Shiraishi, Y. Futamura, T. Nakano, T. Tomita, K. Ishigami, H. Taka, R. Mineki, T. Fujimura, H. Osada, T. Kuzuyama and M. Nishiyama, *Nat. Chem. Biol.*, 2016, **12**, 967.
- 21 C. Liu, A. Minami, T. Dairi, K. Gomi, B. Scott and H. Oikawa, *Org. Lett.*, 2016, **18**, 5026.
- 22 M. Okada, T. Sugita, K. Akita, Y. Nakashima, T. Tian, C. Li, T. Mori and I. Abe, *Org. Biomol. Chem.*, 2016, **14**, 9639.
- 23 L. Chen, Y. Li, Q. Yue, A. Loksztajn, K. Yokoyama, E. A. Felix, X. Liu, N. Zhang, Z. An and G. F. Bills, *ACS Chem. Biol.*, 2016, **11**, 2724.
- 24 X. Yu, F. Liu, Y. Zou, M.-C. Tang, L. Hang, K. N. Houk and Y. Tang, *J. Am. Chem. Soc.*, 2016, **138**, 13529.
- 25 S. T. Ahmed, F. Parmeggiani, N. J. Weise, S. L. Flitsch and N. J. Turner, *Org. Lett.*, 2016, **18**, 5468.
- 26 F. Parmeggiani, S. T. Ahmed, M. P. Thompson, N. J. Weise, J. L. Galman, D. Gahloth, M. S. Dunstan, D. Leys and N. J. Turner, *Adv. Synth. Catal.*, 2016, **358**, 3298.
- 27 M. J. Corr, D. R. M. Smith and R. J. M. Goss, *Tetrahedron*, 2016, **72**, 7306.
- 28 I. V. Pavlidis, M. S. Weiß, M. Genz, P. Spurr, S. P. Hanlon, B. Wirz, H. Iding and U. T. Bornscheuer, *Nat. Chem.*, 2016, **8**, 1076.
- 29 D. Schwendenwein, G. Fiume, H. Weber, F. Rudroff and M. Winkler, *Adv. Synth. Catal.*, 2016, **358**, 3414.
- 30 T. Dhammaraj, C. Pinthong, S. Visitsatthawong, C. Tongsook, P. Surawatanawong and P. Chaiyen, *ACS Chem. Biol.*, 2016, **11**, 2889.

31 O. El-Sepelgy, N. Alandini and M. Rueping, *Angew. Chem. Int. Ed.*, 2016, **55**, 13602.

32 Á. G. Baraibar, D. Reichert, C. Mügge, S. Seger, H. Gröger and R. Kourist, *Angew. Chem. Int. Ed.*, 2016, **55**, 14823.