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A radical approach to diverse meroterpenoids

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Natural products provide rich inspiration in the discovery of bioactive small molecules, and have played a dominant role in shaping early-stage drug discovery.[1] Indeed, of the 1211 small-molecule drugs that were approved between 1981 and 2014, 6% were unaltered natural products and 26% were natural product derivatives.[1] Yet, the structural complexity of natural products means that the development of viable total syntheses is usually time-consuming and resource-intensive. In most cases, total syntheses are bespoke, although divergent syntheses have also been developed to access natural products based on the same, or several closely-related, scaffolds.[2] In contrast, families of biosynthetic enzymes, such a terpenoid cyclases,[3] can enable common intermediates to be converted into many diverse molecular scaffolds. How, then, can synthetic chemists best harness[4] the chiral pool to drive both the discovery, and the subsequent supply, of natural product-inspired drugs? This challenge is likely to require chemists to harness a wide reaction toolkit[5] that integrates both bio- and chemocatalysis.[6] On page XX, Li *et al* report that a toolkit of radical-based chemistries could be harnessed to yield nine distinct meroterpenoid natural products.[7]

Retrosynthetic analysis revealed that two key intermediates (**3** and **7**) might be exploited in the synthesis of all nine natural product targets (Figure 1). It was recognised that these intermediates might be prepared from two readily-available starting materials, sclareolide **1** and sclareol **4**, provided that chemoselective oxidation was possible. However, it was noted that oxidations of sclareolide are generally selective for the C2 position rather than for the required C3 position. To address this challenge, a range of $P450_{BM3}$ variants was screened, leading to the identification of a variant, BM3 MERO1, that enabled chemoselective oxidation of sclareolide **1** to yield **2** in 60-70% yield. This biotransformation was possible on a gram scale, contrasting with previous examples that had been performed at high dilution on, at most, a 50 mg scale. It is interesting to contrast this early-stage oxidation, which needed to be performed on a relatively large scale, with a total synthesis of Nigelladine A in which a late-stage oxidation was catalysed by an engineered P450 enzyme.[8] The hydroxylated product **2** was converted into the key intermediate **3** in four further steps.

The synthesis of the key intermediate **7** was achieved in seven steps from sclareol **4**. Here, a key step was a hydrogen atom transfer (HAT) based Giese coupling which enabled introduction of the third

fused ring with excellent diastereoselectivity. Crucially, this coupling proceeded in excellent yield on a gram scale, enabling it to be harnessed at an early stage in the divergent synthesis. Alanine scanning on BM3 MERO1 enabled the identification of a point mutant (L75A) that was superior for the chemoselective oxidation step: with this mutant, hydroxylation was possible in 62% yield on a gram scale (compared to 33% for MERO1), and with excellent chemo- and diastereoselectivity.

A reaction toolkit was then developed to append the additional rings found in the natural product targets, and to control the oxidation level of specific carbon atoms. For example, dehydration of the β-hydroxy aldehyde **3** could be followed by condensation with an appropriate 4-hydroxy pyrone to yield the fused ring system found in the α-pyrone meroterpenoids **8**-**12**. In the case of **9**, **10** and **12**, a HAT-based reduction enabled hydrogenation of an intermediate alkene with high diastereoselectivity; in contrast, hydrogenation under many other conditions resulted in over-reduction of the pyrone motif.

Radical-based chemistry was also used to fuse additional rings to the key intermediate **7**. Nickel-catalysed cross-couplings involving the alkyl iodide **7** enabled introduction of appropriate (het)aryl rings; subsequent acid-catalysed cyclisation onto the alkene yielded the fused ring systems found in chevalone A **13** and taondiol **14**. The possibility of reducing the number of synthetic steps may serve as a spur for the development of new methods that would enable earlier intermediates to be exploited in place of the iodide **7**. Nonetheless, exploitation of the iodide **7** allowed elimination to give a useful 1,3-diene intermediate; efficient electrochemical coupling with a phenol or a 4-hydroxy pyrone then yielded the spiro-fused ring systems found in stypodiol **15** and decaturin E **16**. It is notable that the exploitation of a toolkit of radical reactions enabled the use of protecting groups to be largely avoided. Whilst focus was placed on the synthesis of natural products, exploitation of these methods to prepare additional related scaffolds could have demonstrated their wider value.

This work demonstrates that it is possible to harness abundant chiral feedstocks effectively provided that an expanded underpinning reaction toolkit is in place. Here, bio- and chemo-catalytic radical-based chemistries were used in combination to prepare nine meroterpenoids from two readily-available starting materials. This study complements the use of halogenases to functionalise diverse substrates.[9] Wider adoption of an integrated toolkit of bio- and chemo-catalysed methods may broaden the natural product-inspired chemical space that is available for discovery. Such methods may enable the derivatisation of natural products in new ways,[1] the synthesis of new natural product-inspired scaffolds,[10] and the fusion of natural product sub-structures to yield pseudo-natural products with novel functions![11]

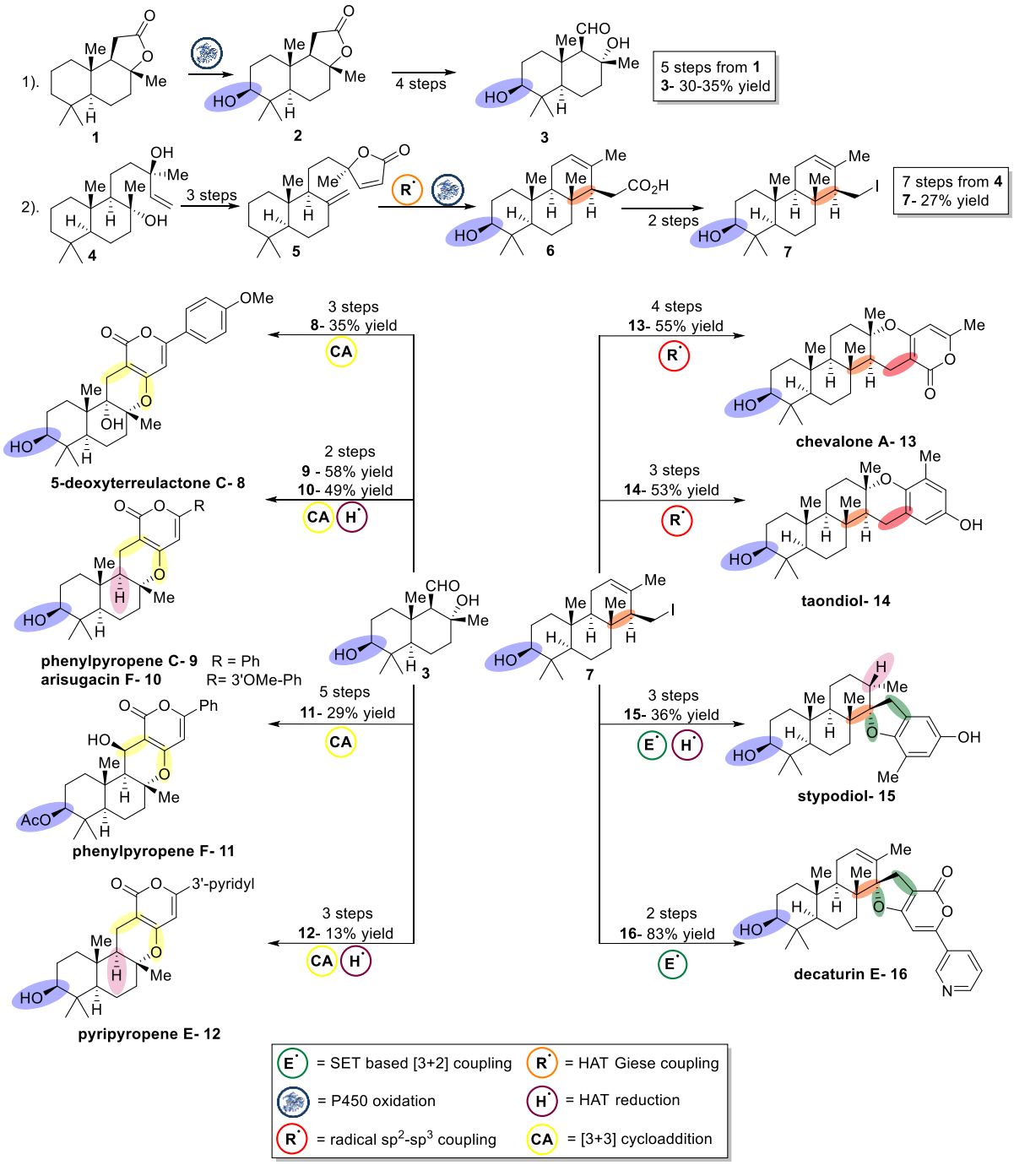

Figure legend: Divergent synthesis of nine meroterpenoid natural products. The synthesis of two key intermediates (top) enabled the synthesis of the natural product targets (bottom).

1. Newman, D. J. & Cragg, G. M. *J. Nat. Prod*. **79,** 629−661 (2016).

2. Li, L., Chen, Z., Zhang, X. & Jia, Y. Divergent Strategy in Natural Product Total Synthesis. *Chem. Rev.* **118**, 3752-3832 (2018).

3. Christianson, D. W. Structural and Chemical Biology of Terpenoid Cyclases. *Chem. Rev.* **117**, 11570-11648 (2017).

4. Brill, Z. G., Condakes, M. L., Ting, C. P. & Maimone, T. J. Navigating the Chiral Pool in the Total Synthesis of Complex Terpene Natural Products. *Chem. Rev.* **117**, 11753-11795 (2017).

5. Boström, J., Brown, D. G., Young, R. J. & Keserü, G. M. Expanding the medicinal chemistry synthetic toolbox. *Nat. Rev. Drug. Discov.* **17**, 709-727 (2018).

6. Hönig, M., Sondermann, P., Turner, N. J. & Carreira, E. M. Enantioselective Chemo- and Biocatalysis: Partners in Retrosynthesis. *Angew. Chem. Int. Ed.* **56**, 8942-8973 (2017).

7. Li, J. Li, F. King-Smith, E. & Renata, H. Merging Chemoenzymatic and Radical-Based Retrosynthetic Logic For Rapid and Modular Synthesis of Oxidised Meroterpenoids. *Nat. Chem.* **11**, pages (2019).

8. Loskot, S. A., Romney, D. K., Arnold, F. H. & Stoltz, B. M. Enantioselective Total Synthesis of Nigelladine A via Late-Stage C–H Oxidation Enabled by an Engineered P450 Enzyme. *J. Am. Chem. Soc.* **139**,10196-10199 (2017).

9. (a) Gkotsi, D. S. *et al.* A marine viral halogenase that iodinates diverse substrates. *Nature Chem.* DOI: 10.1038/s41557-019-0349-z (2019); (b) Latham, J., Henry, J.-M., Sharif, H. H., Menon, B. R. K., Shepherd, S. A., Greaney, M. F. & Micklefield, J. *Nature Commun.* **7**, 11873 (2016).

10. van Hattum, H. & Waldmann, H. Biology-oriented synthesis: harnessing the power of evolution. *J. Am. Chem. Soc.* **136**, 11853–11859 (2014).

11. Karageorgis, G., Reckzeh, E. S., Ceballos, J., Schwalfenberg, M., Sievers, S., Ostermann, C., Pahl, A., Ziegler, S. & Waldmann, H. Chromopynones are pseudo natural product glucose uptake inhibitors targeting glucose transporters GLUT-1 and -3. *Nat. Chem.* **10**, 1103-1111 (2018).