Merging Chemoenzymatic and Radical-Based Retrosynthetic Logic For Rapid and Modular Synthesis of Oxidized Meroterpenoids

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ABSTRACT: Here, we report a modular approach to access a suite of oxidized meroterpenoids using a novel hybrid synthetic strategy. By strategically incorporating chemoenzymatic and radical-based retrosynthetic logic in the design of the synthesis, we develop a concise route to prepare two versatile synthetic intermediates that can readily be converted to eight oxidized meroterpenoids (7–12 steps from commercial materials). Notable features of the synthesis include the use of regio- and stereoselective biocatalytic C–H hydroxylation on two terpenoid scaffolds, and the use of radical-based transformations to forge key bonds and stereocenters in the target molecules with orthogonal selectivity to traditional two-electron-based reactions. This work lays the foundation for efficient synthesis of a wide range of oxidized meroterpenoids by capitalizing on the interplay of two emerging synthetic paradigms.

Multistep chemical synthesis is predicated upon the use of retrosynthetic analysis.[1] Using this conceptual framework, a target molecule is disconnected through a series of reverse reactions to arrive finally at greatly simplified or commercial starting materials. As each disconnection needs to be sensible in the forward synthetic direction, the choice of bond(s) to disconnect is highly dependent on the contemporary synthetic transformations available at the practitioner's disposal. Throughout the history of organic chemistry, polar disconnections, due to their perceived robustness, permeate much of the discourse in the field. More recently, the emergence of new technologies in chemical synthesis has led to the formulation of alternative retrosynthetic paradigms. Biocatalytic retrosynthesis[2] has flourished into a highly powerful principle for multistep syntheses due to the unparalleled selectivity of enzymatic transformations and the ever-growing tools of protein engineering and directed evolution.[3] Similarly, radical-based retrosynthetic disconnections[4,5] have become increasingly popular, owing to the unique chemoselectivity and chemofidelity[6] of radicals. Despite their respective advantages, these emerging paradigms have largely developed as independent entities with minimal crosstalk. Here, we describe the development of a powerful strategy for meroterpenoid synthesis that combines the unparalleled site-selectivity of enzymatic hydroxylation with the unique reactivity profile of radical-based transformations. We show that the strategic merger of these largely disparate branches of synthetic chemistry dramatically streamlines synthetic access to meroterpenoid natural products (eight total), providing a compelling argument for more widespread pursuit of such a hybrid synthetic strategy in the preparation of complex molecular scaffolds.

Commonly isolated from fungi, meroterpenoids are a large family of hybrid terpene natural products possessing a wide range of structural diversity.[7] The α-pyrone meroterpenoids (e.g., **1**–**5**) constitute a prominent subset of this family and possess a common C3-oxidized drimane unit that is attached to various polyketide-derived pyrone fragments at C11.[8] Members of this family exhibit a broad range of bioactivity ranging from anti-cholinesterase activity to acyl-CoA/cholesterol acyltransferase (ACAT)

inhibition. While not as common, meroterpenoids bearing a diterpene unit have also been found in nature.[9] Members of this subset (e.g., **6**–**11**) typically share a common C3-oxidized *ent*-isocopalane fragment that occurs in combination with various aromatics and have been known to exhibit anti-mycobacterial, insecticidal, and cytotoxic properties. Notably, C3-oxidized *ent*-isocopalane fragment is also highly prevalent in many higher-order terpenes. C3-oxidized meroterpenoids commonly arise in nature[10] from the union of polyisoprene pyrophosphate with a polyketide-derived aromatic unit, followed by enantioselective epoxidation and polyene cyclization cascade. Two general synthetic approaches have been developed to stereoselectively access C3-oxidized meroterpenoids. The first aims to recapitulate the biosynthetic logic through the use of enantioselective dihydroxylation[11] on a polyisoprenyl unit (e.g., farnesyl or geranylgeranyl), followed by epoxide formation, and Lewis acid-catalyzed polyene cyclization. This approach is linear in nature, and is often beset by slow rates of dihydroxylation, variable levels of regio- and enantioselectivity, and varying degrees of success in the biomimetic cyclization step. For example, asymmetric dihydroxylation of farnesol derivatives is typically complicated by unwanted reaction at the internal double bond,[12] and polyene cyclization towards taondiol was reported to afford only 2% yield of the desired product.[13] The dearth of efficient methods for introducing additional oxygenation on the polyisoprenyl unit further hinders the synthetic versatility of this approach for accessing more oxidized meroterpenoids. An alternative strategy commencing from Wieland–Miescher ketone has also been developed. However, this approach is strategically inefficient as it requires multiple tailoring steps on the decalin skeleton and nontrivial C–C bond formation steps for subsequent ring construction.[14] For example, the use of organolithium addition to link the terpene and arene fragments of stypodiol resulted in a diastereomeric mixture of products,[15] and the use of Robinson annulation to form the tricyclic core of the decaturins was plagued by unexpected racemization.[16] Given these shortcomings, an orthogonal approach involving the use of alternative synthetic paradigms is warranted.

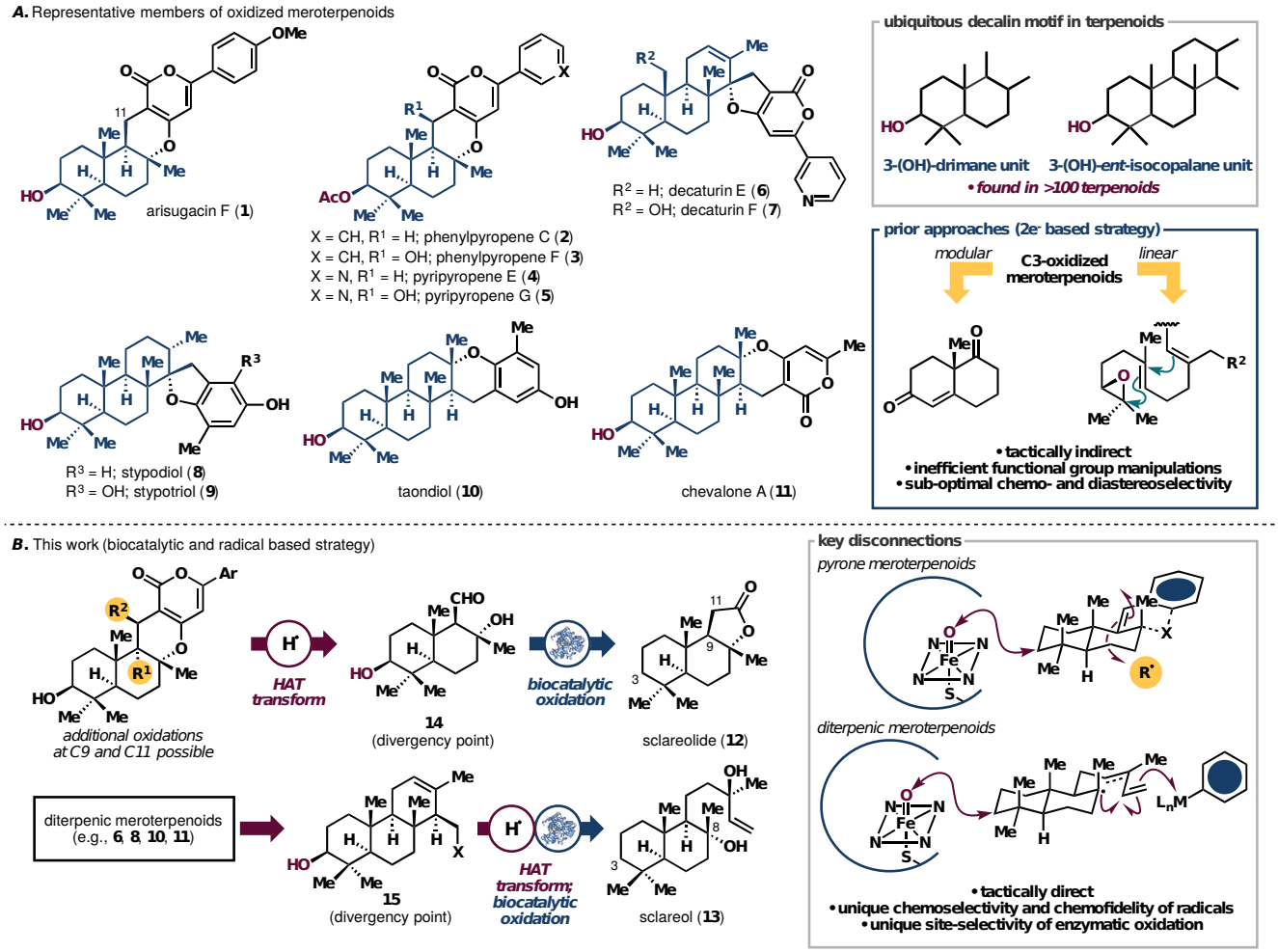

Figure 1. A. Representative examples of meroterpenoid natural products and higher order terpenes containing 3-(OH)-drimane or 3-(OH)-*ent*-isocopalane unit, and prior synthetic strategies employed to access C3-oxidized meroterpenoids. **B.** Retrosynthetic disconnection of C3-oxidized meroterpenoids using a combination of biocatalytic and radical-based transforms.

We envisioned a synthetic approach that is based on a site-selective oxidation of a simple drimane or isocopalane-like framework. Such unit is readily available in the form of sclareolide (**12**) and sclareol (**13**), common feedstocks in the perfume industry that can be accrued in kilogram quantities. With respect to α-pyrone meroterpenoids, a C3-selective hydroxylation of sclareolide will furnish the minimally-oxidized A/B ring of **1**–**5**. In turn, the lactone moiety could be readily manipulated to provide advanced intermediate **14** that would allow maximal divergency to access a wide range of α-pyrone meroterpenoids. A similar strategy for the synthesis of quinone sesquiterpenoids has previously been conceived through the intermediacy of boronosclareolide.[17] However, this approach suffers from the lack of ability to introduce additional oxygenations at C3, C9, and C11. To address these limitations, we envisioned the conversion of the aldehyde moiety of **14**, to the corresponding olefin, which would offer versatile installation[18] of various functionalities at C9 and C11. While this transform would lead to a retron containing multiple olefins, we reasoned that the abundance of options for olefin functionalization would allow the identification of a suitable method with the desired chemoselectivity. Similarly, a C3-selective hydroxylation of sclareol will generate a synthetic intermediate that not only possesses the correct oxidation state at C3, but also the requisite functional handles for the construction of the remaining rings of **6**–**11**. In the forward sense, a C–C bond formation event would afford advanced intermediate **15**, which acts as a divergency point to access a wide range of diterpenic meroterpenoids. It is worth noting that related tricyclic motifs

have previously been constructed from **13**. However, work in this area has been dominated by two electron-based transformations. For example, the only total synthesis of makassaric acid proceeded from **13** and enlisted the use of organolithium addition to an aldehyde, followed by Barton deoxygenation.[19] Adaptation of such transformation onto routes that feature 3-hydroxysclareol would necessitate undesired protecting group manipulations and functional group interconversions. In contrast, we believe that radical-based transformations, with their unique reactivity profile, would allow us to bypass such concession steps. From a medicinal chemistry perspective, this overall strategy provides an ideal synthetic blueprint to target a wide spectrum of meroterpenoids from just two common intermediates. Nevertheless, the realization of this strategy is not without its challenges. Numerous chemical methods have been reported for selective C–H functionalization of **12**.[20,21,22,23] However, they rely on the innate reactivity of the carbocyclic scaffold and result predominantly in C2 modification. While whole-cell fungal biotransformation of **12** has been reported to give C3-oxidized product, it is typically accompanied by over-oxidation to the ketone product and oxidation at other positions.[24] At the outset of our work, C3-selective enzymatic hydroxylation of **12** has been reported to take place with a $P450_{BM3}$ variant[25] II-H8 (15 mutations from wild type), or CYP101B1, a P450 monooxygenase from *N. aromaticivorans* DSM12444.[26] However, these bioconversions have only been carried out on up to 50 mg scale under high dilution conditions (1 mM substrate concentration with *ca.* 1000 total turnover number (TTN)), and their scalability remains to be addressed. Additionally, oxidation of sclareol has only been attempted with whole-cell fungal biotransformation and was reported to result in non-selective oxidation.[24,27]

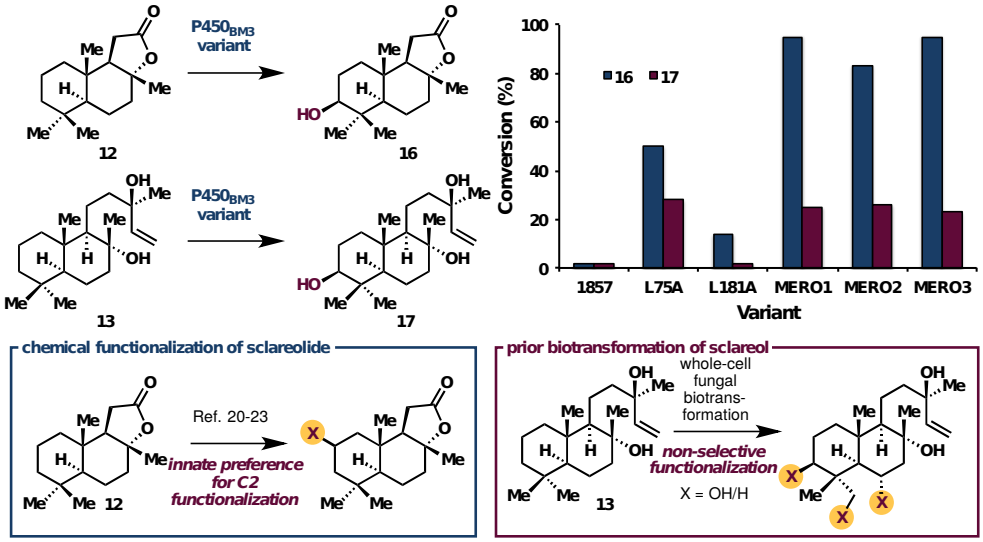

Figure 2. Optimization of $P450_{BM3}$ variant 1857 for practical and selective C3 hydroxylation of sclareolide and sclareol. The identities of the latter variants are as follows: BM3 MERO1 = 1857 V328A, BM3 MERO2 = 1857 T235A V328A R471A, BM3 MERO3 = 1857 C47R I94K V328A. Reaction conditions for terpene hydroxylation: **12** or **13** (5.0 mM), $NADP^+$ (1.0 mM), $NaHPO_3$ (100 mM), clarified lysate of *E. coli* BL21(DE3) expressing the appropriate $P450_{BM3}$ variant and Opt13 (suspension in 50 mM pH 8.0 kPi, pre-lysis OD_{600} = 15), 24 h at 20 ºC.

We began by conducting a brief survey of several $P450_{BM3}$ variants harboring similar mutations to II-H8 for the hydroxylation of sclareolide and sclareol. With an eye towards practical and inexpensive hydroxylation method, small-scale screening of these variants was performed with lysate of *E. coli* cells expressing both the $P450_{BM3}$ variant and a thermostabilized phosphate dehydrogenase (Opt13) for NADPH recycling.[28] Here, we chose to employ pET22b(+)- and pRSF-based vectors for overexpression of the $P450_{BM3}$ variant and Opt13 respectively, as they possess compatible origins of replication and allow the desired genes to be expressed under the control of strong

T7lac promoter. Alanine scanning[29] on variant 1857 (four amino acid substitutions from II-H8) revealed several mutants with varying levels of hydroxylation activity on **12**. Gratifyingly, variant 1857 V328A (BM3 MERO1) afforded >95% conversion to 3-(OH)-sclareolide (corresponding to *ca.* 5000 TTN), with no detectable presence of the undesired C2-hydroxylated product. Mutations T235A and R471A, previously reported to enhance the organic solvent tolerance of $P450_{BM3}$,[30] were introduced in an attempt to perform the biocatalytic oxidation at higher substrate concentration and amount of organic cosolvent. Unfortunately, this variant (BM3 MERO2) proved to be inferior to BM3 MERO1 for the hydroxylation of **12**. Reversion of thermostabilizing mutations C47R and I94K[29] resulted in variant BM3 MERO3, which showed comparable conversion to BM3 MERO1 on both small-scale and preparative-scale reactions, suggesting that the thermostabilizing mutations are not necessary for achieving high hydroxylation activity on **12**. The aforementioned variants were also tested for their ability to hydroxylate sclareol, revealing several variants with modest hydroxylation activity (*ca.* 30% conversion). Importantly, all variants examined proved selective for C3 hydroxylation and provided initial validation for our hybrid strategy in the synthesis of diterpenic meroterpenoids.

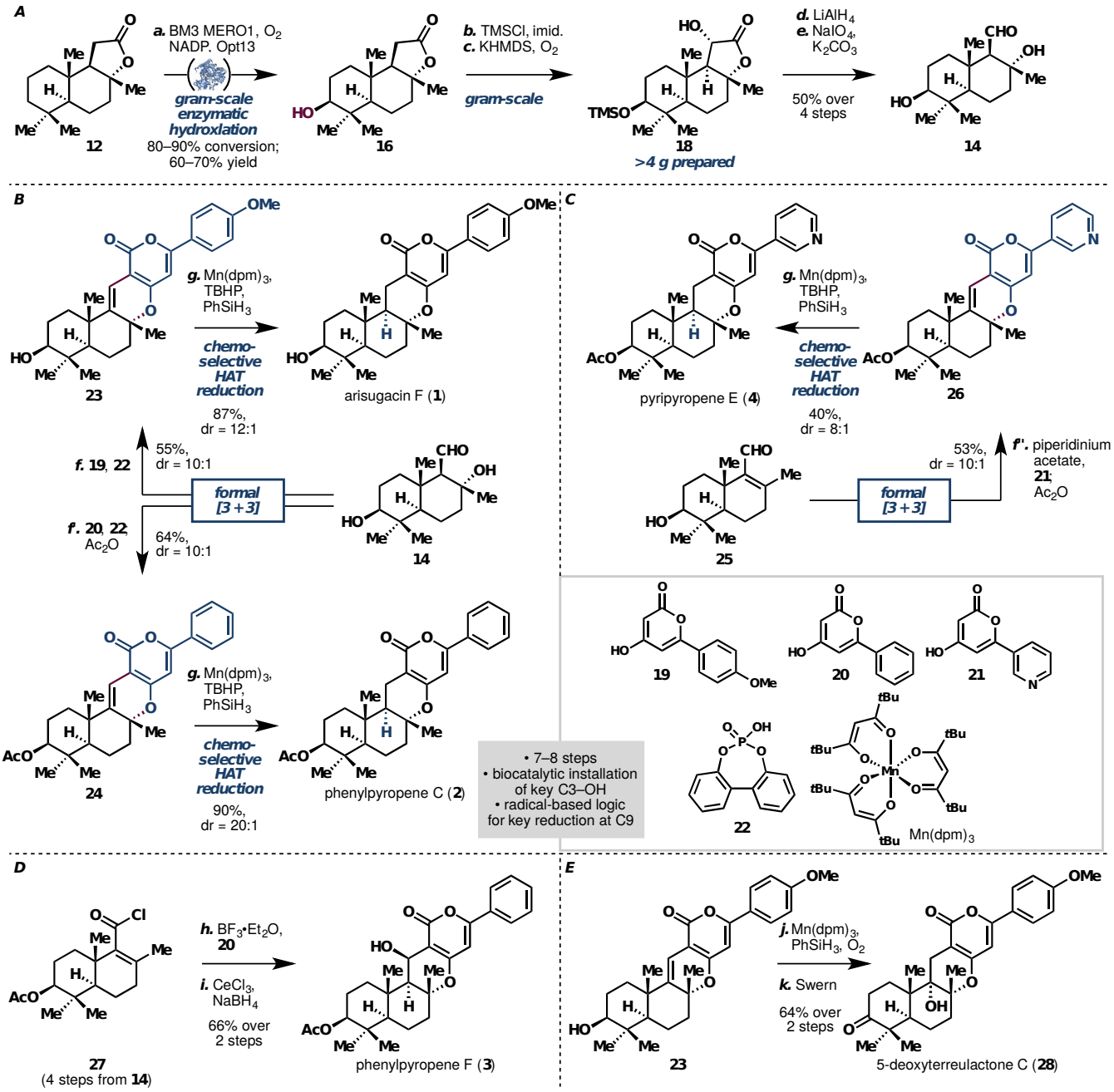

Figure 2. A. Preparation of key building block **14**, featuring a key biocatalytic hydroxylation of sclareolide (**12**) on gram scale. **B.** Completion of total syntheses of arisugacin F (**1**) and phenylpyropene C (**2**) via [3 + 3] coupling and HAT hydrogenation. **C.** Conversion of enal **25** to pyripyropene E (**4**) via [3 + 3] coupling and HAT hydrogenation. **D.** Conversion of **27** to phenylpyropene F (**3**), a pyrone meroterpenoid containing C11 oxidation. **E**. Synthesis of 5-deoxyterreulactone C (**28**) from **23** featuring a chemoselective Mukaiyama hydration of the C9–C11 olefin.

With optimized $P450_{BM3}$ variants for sclareolide hydroxylation in hand, we sought to establish a robust route to prepare a suitable precursor for fragment coupling with the pyrone unit. Enzymatic hydroxylation of sclareolide could be routinely conducted on gram scale with BM3 MERO1 with excellent conversion and isolated yield. The supplementation of Opt13 allowed for substoichiometric use of NADPH, lowering the overall cost of conducting large-scale reactions. As a testament to the scalability of the biotransformation, lactone **18** has been prepared in > 4g quantity to date. Intermediate **14** could be quickly accessed through tailoring of the C-ring lactone in 2 steps from **18**, setting the stage for the key coupling with pyrones **19**–**21**. In

contrast, preparation of **14** from Wieland-Miescher ketone is projected to require at least 8 steps, highlighting the tactical directness of our strategy. A brief survey of Brønsted and Lewis acids yielded phosphoric acid **22**[31] as an ideal catalyst for *in situ* alcohol dehydration and formal [3 + 3] union. Under these conditions, **23** and **24** were obtained in 55% and 62% yields, respectively. Coupling with pyrone **21** necessitated the use of enal **25** as a substrate, which readily underwent a formal [3 + 3] with **21** in the presence of piperidinium acetate.[32] With the carbon framework fully installed, attention turned to the reduction of the C9–C11 alkene. A gamut of hydrogenation conditions in the presence of Rh, Pt, and Pd catalysts was surveyed, only to yield reduction and/or over-reduction of the pyrone motif. We reasoned that hydrogen atom transfer-based (HAT-based) hydrogenation would provide a viable solution to this problem.[33,34] The steric bulk of the catalyst would suppress any undesired reactivity with the tetrasubstituted alkene, and between the two trisubstituted alkenes, reduction of $\Delta^{9,11}$ should be preferred due to the greater stability of the incipient radical at C9. Furthermore, HAT-based reduction is known to deliver the thermodynamic hydrogenation product, providing *trans*-decalin selectively from $\Delta^{9,10}$-octalin. Indeed, subjecting **23**, **24**, and **26** to Shenvi's[33] reduction conditions ($Mn(dpm)_3$, *tert*-butyl hydrogen peroxide (TBHP), and $PhSiH_3$) provided arisugacin F (**1**), phenylpyropene C (**2**), and pyripyropene E (**4**) in moderate to high yields and excellent diastereoselectivities. The modularity of the designed sequence was further underscored by the ability to obtain phenylpyropene F (**3**), a more oxidized member of the α-pyrone meroterpenoid family, in a concise manner. Here, aldehyde **14** was converted to acid chloride **27**, which was then subjected to a Friedel-Crafts acylation with pyrone **20**, followed by a cyclization/reduction sequence to complete the synthesis of **3** in 11 steps. The C9–C11 alkene proved to be a versatile functional handle, as Mukaiyama hydration[35] on this moiety proceeded in a highly selective fashion (>20:1 dr) to generate the corresponding 3º alcohol at C9. In contrast, previous approach to generate this alcohol required the intermediacy of the corresponding epoxide, which was then subjected to nucleophilic opening and alcohol reduction. In combination with C3 alcohol oxidation, this approach enabled rapid access to 5-deoxyterreulactone C (**28**) from **23** in 64% yield over 2 steps.

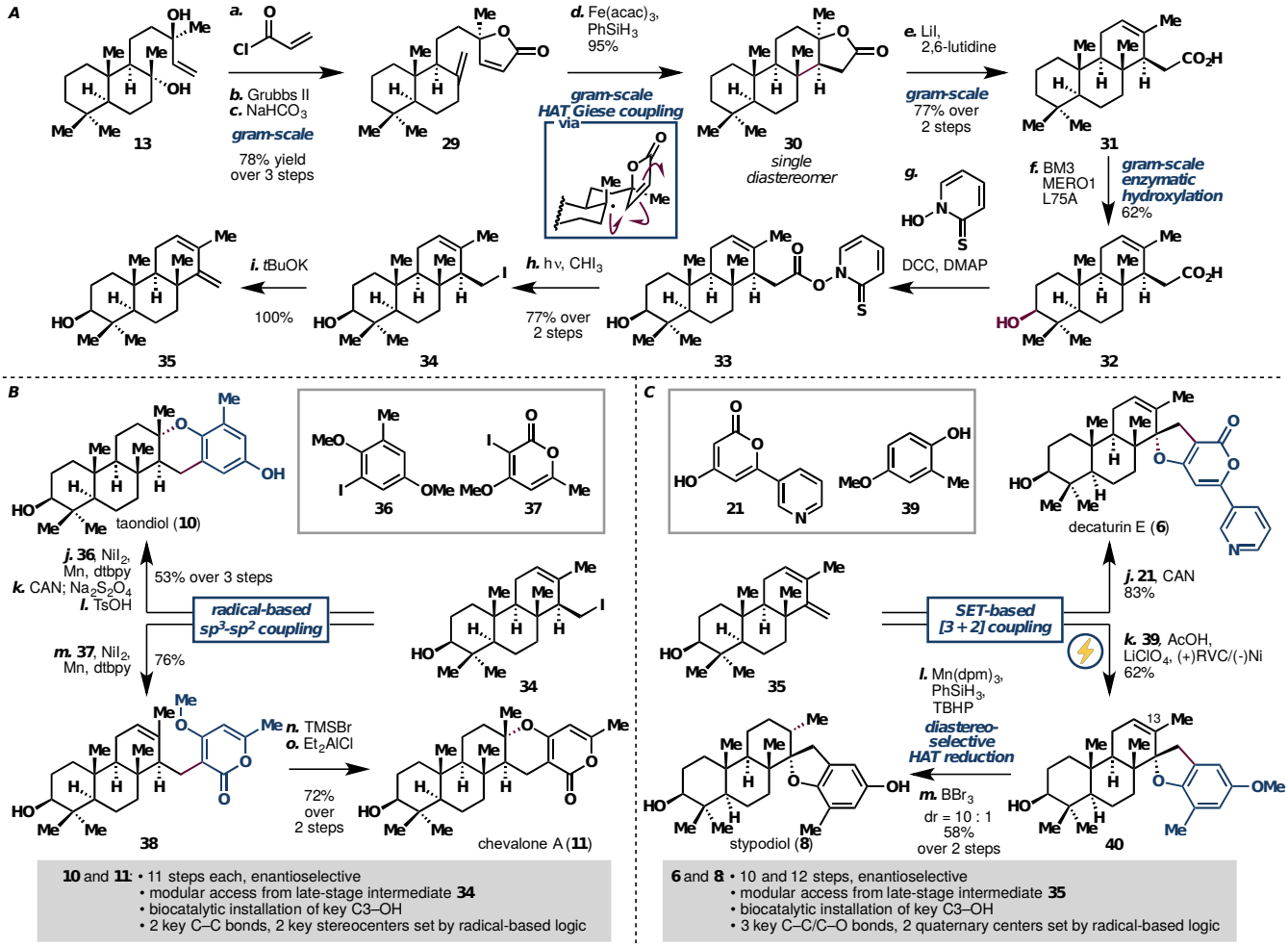

Figure 3. A. Concise synthesis of key building blocks **34** and **35** from sclareol (**13**), featuring a key biocatalytic hydroxylation of acid **31** with an engineered $P450_{BM3}$. **B.** Completion of the total syntheses of taondiol (**10**) and chevalone A (**11**) via Ni-catalyzed cross couplings. **C.** Completion of the total syntheses of decaturin E (**6**) and stypodiol (**8**) via SET-based [3 + 2] couplings.

In parallel, route scouting for efficient access to diterpenic meroterpenoids was undertaken, affording a five-step synthesis of tricycle **30** as a single diastereomer. Key to this success is the use of HAT-based intramolecular Giese coupling[36] to forge the C ring with complete diastereoselectivity and excellent yield. This outcome could be rationalized by invoking rapid pyramidalization of the incipient 3º radical and cyclic stereocontrol imposed by the rigid *trans*-decalin and butyrolactone moieties. In contrast, previous approach to construct methyl *ent*-isocopalate from sclareol using polar 2-electron-based transformations resulted only in 82% de of the desired isomer.[37] At this stage, intermediates **13**, **29**–**31** were tested for enzymatic hydroxylation with various $P450_{BM3}$ mutants. From this combinatorial experiment, the pairing of acid **31** and $P450_{BM3}$ variant BM3 MERO1 yielded the most promising outcome (33% yield). Further alanine scanning on MERO1 identified variant MERO1 L75A as a superior biocatalyst, providing the desired C3-oxidized product **32** in 62% yield with complete regio- and diastereoselectivity. At this stage, radical cross-coupling employing redox-active ester[38] derivatives of **32** was attempted to access taondiol and chevalone A. However, in both cases, no desired product formation was observed. As a workaround, **32** was first converted to the corresponding iodide (**34**), which was then subjected to nickel-catalyzed cross coupling using Weix's procedure[39] with **36** and **37**. Using this procedure, the desired coupling products could be obtained in great yields. Finally, acid-catalyzed cyclizations forged the final dihydropyran rings and completed the total syntheses of **10** and **11**. The versatility of

this synthetic approach is further highlighted by the ability to use the same iodo intermediate **34** to access decaturin E (**6**) and stypodiol (**8**) in a modular and efficient manner. Treatment of **34** with *t*BuOK afforded the corresponding diene (**35**) and set the stage for the final fragment coupling steps. The synthesis of **6** was realized by the use of a single electron transfer-based (SET-based) formal [3 + 2] coupling of **35** and pyrone **21**. Initial attempts to realize this transformation in the presence of ceric ammonium nitrate[40] were accompanied by competing oxidation of the C3 alcohol to the ketone. We hypothesized that increasing the equivalents of pyrone **21** would allow preferential single electron oxidation of this fragment and suppress undesired alcohol oxidation. Indeed, increasing the equivalents of pyrone **21** to 5 equivalents led to formation of **6** in 83% yield with no observable over-oxidation side product. Attempts to effect this CAN-mediated coupling with phenol **39** led to exclusive oxidation of **39** to the corresponding quinone. Hypothesizing that electrochemical methods[41] would allow a more controlled electron delivery to the phenol fragment, we subjected **35** and **39** to constant potential electrolysis. Gratifyingly, this approach was able to provide the desired [3 + 2] coupling product **40** in great yield and diastereoselectivity. At this stage, the C12–C13 olefin needed to be reduced to the thermodynamic product containing an equatorial methyl group at C13. Given its thermodynamic preference, we turned to Shenvi's HAT hydrogenation, which provided the correct stereochemical disposition at C13 with 10:1 dr. Once again, these radical-based conditions were found to be crucial as other reduction conditions led predominantly to the formation of the wrong diastereomer. Routine phenol demethylation finally completed the total synthesis of **8**. Stypodiol has been shown to undergo ready conversion to stypodione[42] and stypotriol.[43] Thus, our approach also constitutes a 13-step and 14-step formal synthesis of stypodione and stypotriol, respectively.

The collective synthesis of various meroterpenoids presented herein proceeded in 7–12 steps, comprising some of the most concise routes to the target molecules to date. By employing a judicious combination of biocatalytic[44] and radical-based approaches,[4,5] exquisite stereocontrol and chemoselectivity could be obtained in all of the key bond forming steps. Furthermore, the orthogonal selectivity[45,46] of biocatalytic C–H oxidation methods allowed the invention of a novel yet powerful disconnection for terpene synthesis. Such features represent a distinct departure from previous approaches to bioactive meroterpenoids and highlight the strategic benefits of combining these emerging paradigms in complex molecule synthesis. This work lays the foundation for a robust approach to more oxidized meroterpenoids, as well as other higher-order terpenes containing oxidized decalin motifs. Especially appealing is the recent discovery of various oxygenases from the fungal meroterpenoid biosynthesis,[47,48] which opens the possibility of developing highly concise chemoenzymatic syntheses featuring late-stage biocatalytic hydroxylation. Work in this area is underway and will be reported in due course.

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REFERENCES

1. E. J. Corey, X.-M. Cheng, *The Logic of Chemical Synthesis* (Wiley, New York, 1995).

2. N. J. Turner, E. O'Reilly, *Nat. Chem. Biol.* **2013**, *9*, 285–288.
3. N. J. Turner, *Nat. Chem. Biol.* **2009**, *5*, 567–573.
4. K. Hung, X. Hu, T. J. Maimone, *Nat. Prod. Rep.* **2018**, *35*, 174–202.
5. J. M. Smith, S. J. Harwood, P. S. Baran, *Acc. Chem. Res.* **2018**, *51*, 1807–1817.
6. S. A. Green, S. W. M. Crossley, J. L. M. Matos, S. Vasquez-Céspedes, S. L. Shevick, R. A. Shenvi, *Acc. Chem. Res.* **2018**, *51*, 2628–2640.
7. Y. Matsuda, I. Abe, *Nat. Prod. Rep.* **2016**, *33*, 26–53.
8. T. Sunazuka, S. Ōmura, *Chem. Rev.* **2005**, *105*, 4559–4580.
9. F. A. Macías, C. Carrera, J. C. G. Galindo, *Chem. Rev.* **2014**, *114*, 2717–2732.
10. T. Itoh, K. Tokunaga, Y. Matsuda, I. Fujii, I. Abe, Y. Ebizuka, T. Kushiro, *Nat. Chem.* **2010**, *2*, 858–864.
11. E. J. Corey, M. C. Noe, S. Lin, *Tetrahedron Lett.* **1995**, *36*, 8741–8744.
12. A. B. Smith, III, T. Kinso, T. Sunazuka, S. Ōmura, *Tetrahedron Lett.* **1996**, *37*, 6461–6464.
13. A. S. Kumanireng, T. Kato, Y. Kitahara, *Chem. Lett.* **1973**, 1045–1047.
14. T. Nagamitsu, T. Sunazuka, R. Obata, H. Tomoda, H. Tanaka, Y. Harigaya, S. Ōmura, A. B. Smith, III, *J. Org. Chem.* **1995**, *60*, 8126–8127.
15. A. Abad, C. Agulló, M. Arnó, A. C. Cuñat, B. Meseguer, R. J. Zaragozá, *J. Org. Chem.* **1998**, *63*, 5100–5106.
16. H. Takikawa, Y. Imamura, M. Sasaki, *Tetrahedron* **2006**, *62*, 39–48.
17. D. D. Dixon, J. W. Lockner, Q. Zhou, P. S. Baran, *J. Am. Chem. Soc.* **2012**, *134*, 8432–8435.
18. S. W. M. Crossley, C. Obradors, R. M. Martinez, R. A. Shenvi, *Chem. Rev.* **2016**, *116*, 8912–9000.
19. P. Basabe, M. Martín, O. Bodero, A. Blanco, I. S. Marcos, D. Díez, J. G. Urones, *Tetrahedron* **2010**, *66*, 6008–6012.
20. M. S. Chen, M. C. White, *Science* **2010**, *327*, 566–571.
21. R. K. Quinn, Z. A. Könst, S. E. Michalak, Y. Schmidt, A. R. Szklarski, A. R. Flores, S. Nam, D. A. Horne, C. D. Vanderwal, E. J. Alexanian, *J. Am. Chem. Soc.* **2016**, *138*, 696–702.
22. Y. Kawamata, M. Yan, Z. Liu, D.-H. Bao, J. Chen, J. T. Starr, P. S. Baran, *J. Am. Chem. Soc.* **2017**, *139*, 7448–7451.
23. N. D. Chiappini, J. B. C. Mack, J. Du Bois, *Angew. Chem. Int. Ed.* **2018**, *57*, 4956–4959.
24. L. M. T. Frija, R. F. M. Frade, C. A. M. Afonso, *Chem. Rev.* **2011**, *111*, 4418–4452.
25. K. Zhang, S. El Damaty, R. Fasan, *J. Am. Chem. Soc.* **2011**, *133*, 3242–3245.
26. E. A. Hall, M. R. Sarkar, J. H. Z. Lee, S. D. Munday, S. G. Bell, *ACS Catal.* **2016**, *6*, 6306–6317.
27. G. Aranda, M. S. El Kortbi, J. Lallemand, A. Neuman, A. Hammoumi, I. Facon, R. Azerad, *Tetrahedron* **1991**, *47*, 8339–8350.
28. M. J. McLachlan, T. W. Johannes, H. Zhao, *Biotechnol. Bioeng*. **2008**, *99*, 268–274.
29. J. C. Lewis, S. M. Mantovani, Y. Fu, C. D. Snow, R. S. Komor, C.-H. Wong, F. H. Arnold, *ChemBioChem* **2010**, *11*, 2502–2505.
30. T. S. Wong, F. H. Arnold, U. Schwaneberg, *Biotechnol. Bioeng.* **2004**, *85*, 351–358.
31. C. Hubert, J. Moreau, J. Batany, A. Duboc, J.-P. Hurvois, J.-L. Renaud, *Adv. Synth. Catal.* **2008**, *350*, 40–42.
32. R. P. Hsung, A. V. Kurdyumov, N. Sydorenko, *Eur. J. Org. Chem.* **2005**, 23–44.
33. K. Iwasaki, K. K. Wan, A. Oppedisano, S. W. M. Crossley, R. A. Shenvi, *J. Am. Chem. Soc.* **2014**, *136*, 1300–1303.
34. S. M. King, X. Ma, S. B. Herzon, *J. Am. Chem. Soc.* **2014**, *136*, 6884–6887.
35. S. Isayama, T. Mukaiyama, *Chem. Lett.* **1989**, *18*, 1071.
36. J. C. Lo, D. Kim, C.-M. Pan, J. T. Edwards, Y. Yabe, J. Gui, T. Qin, S. Gutíerrez, J. Giacoboni, M. W. Smith, P. L. Holland, P. S. Baran, *J. Am. Chem. Soc.* **2017**, *139*, 2484–2503.
37. S.-K. Hua, J. Wang, X.-B. Chen, Z.-Y. Xu, B.-B. Zeng, *Tetrahedron* **2011**, *67*, 1142–1144.
38. F. Sandfort, M. J. O'Neill, J. Cornella, L. Wimmer, P. S. Baran, *Angew. Chem. Int. Ed.* **2017**, *56*, 3319–3323.
39. D. A. Everson, R. Shrestha, D. J. Weix, *J. Am. Chem. Soc.* **2010**, *132*, 920–921.
40. H. Yokoe, C. Mitsuhashi, Y. Matsuoka, T. Yoshimura, M. Yoshida, K. Shishido, *J. Am. Chem. Soc.* **2011**, *133*, 8854–8857.
41. K. Chiba, M. Fukuda, S. Kim, Y. Kitano, M. Tada, *J. Org. Chem.* **1999**, *64*, 7654–7656.
42. J. R. Falck, S. Chandrasekhar, S. Manna, C. C. S. Chiu, C. Mioskowski, I. Wetzel, *J. Am. Chem. Soc.* **1993**, *115*, 11606–11607.
43. W. H. Gerwick, W. Fenical, *J. Org. Chem.* **1981**, *46*, 22–27.
44. E. King-Smith, C. R. Zwick, III, H. Renata, *Biochemistry* **2018**, *57*, 403–412.
45. S. A. Loskot, D. K. Romney, F. H. Arnold, B. M. Stoltz, *J. Am. Chem. Soc.* **2017**, *139*, 10196–10199.
46. A. N. Lowell, M. D. DeMars, II, S. T. Slocum, F. Yu, K. Anand, J. A. Chemler, N. Korakavi, J. K. Priessnitz, S. R. Park, A. A. Koch, P. J. Schultz, D. H. Sherman, *J. Am. Chem. Soc.* **2017**, *139*, 7913–7920.
47. J. Hu, H. Okawa, K. Yamamoto, K. Oyama, M. Mitomi, H. Anzai, *J. Antibiot.* **2011**, *64*, 221–227.
48. J. Yaegashi, J. Romsdahl, Y.-M. Chiang, C. C. C. Wang, *Chem. Sci.* **2015**, *6*, 6537–6544.