Enantioselective synthesis of an ophiobolin sesterterpene via a programmed radical cascade

Zachary G. Brill, Huck K. Grover, Thomas J. Maimone*

Cyclase enzymes weave simple polyprenyl chains into the elaborate polycyclic ring systems of terpenes, a sequence that is often difficult to emulate under abiotic conditions. Here we report a disparate synthetic approach to complex terpenes whereby simple polyprenyl-derived chains are cyclized using radical, rather than cationic, reaction pathways. This strategy allowed us to efficiently forge the intricate 5,8,5- fused ring systems found in numerous complex natural product classes and also enabled a nine-step total synthesis of (–)-6-epi-ophiobolin N, a member of the large family of cytotoxic ophiobolin sesterterpenes. A small-molecule thiol catalyst was found to override the inherent diastereoselectivity observed during a reductive radical cascade cyclization process. This work lays the foundation for efficient synthesis of terpenoid ring systems of interest in medicinal research, particularly those that have been historically challenging to access.

terpenes represent a highly diverse class of natural products whose derivatives have been developed into numerous medical applications approved by the U.S. Food and Drug Administration for the treatment of cancer, bacterial infection, malaria, and various other human diseases (1, 2). Despite these successes, terpenes can pose distinct challenges for medicinal research because of their often-limited commercial availability, resistance to deep-seated structural modifications, and incompletely elucidated biosynthetic pathways. Owing to their non-molecular chemical structures, a unifying strategy for the chemical synthesis of terpenes does not exist, further exacerbating the difficulties of working with these compounds (3). Terpenes arise via the enzymatic conversion of simple polyprenyl chains into highly intricate polycyclic carbon networks of extraordinary diversity (4). Biomimetic synthesis, the act of emulating nature’s bond construction process, would be an ideal synthetic tool in this context (5, 6). Indeed, cationic polycyclic terpene cyclizations are perhaps the best studied of all biomimetic cyclization reactions (7). To date, however, a very limited subset of terpenoid carbocycle diversity can be accessed in this manner in a laboratory setting, and the synthesis of many medium and larger terpene ring frameworks has proven especially problematic. In contrast, shape-restricted enzyme cavities in terpene cyclases have evolved with appropriately placed amino acid residues to stabilize selective transition states and, in concert, dictate cyclization pathways. As a result of modulating this environment, the formation of myriad terpene skeletons, elaborate rearrangement processes, and various termination modes all become chemically possible (4). Here we describe a disparate approach, in which simple polyprenyl-derived chains are cyclized via radical-based (as opposed to cationic-based) methods. Through the use of different reagent combinations, we show that the termination modes of these cyclizations can be controlled and, with a chiral small-molecule thiol catalyst, their inherent stereocchemical preferences altered.

Complex 5,8,5-b fused ring systems (n = 5 or 6) are found in numerous di- and sesterterpenes that possess notable antibiotic (8), cytotoxic (9), and immunosuppressant properties, among others (10) (Fig. 1). Central to this structural type is the continually expanding family of ophiobolin sesterterpenes featuring a stereochemically rich and synthetically formidable 5,8,5 fused ring system (Fig. 1A). Though compounds in this family were initially investigated for their phytotoxic effects, which negatively influence agricultural production, ophiobolin A (1) was later discovered to be a powerful inhibitor of calmodulin and remains an important tool for studying this calcium signaling protein (11). Most recently, these fungal metabolites have attracted much attention for their potent cytotoxic effects against multiple cancer cell lines, including the highly drug-resistant human brain tumor glioblastoma multiforme (12–14). Although more than 30 distinct members have been identified to date, often in minute and varying quantities, ophiobolin A (1), ophiobolin C (2), and 6-epi-ophiobolin N (3) highlight the major structural variations found in this terpenoid family, including (i) hydroxylation at carbon-3 or dehydration to an enone system; (ii) epimeric stereochemistry at carbon-6 for nearly all members; and (iii) myriad side-chain oxidation motifs, sometimes resulting in tetrahydrofuran (THF) ring formation (see Fig. 1, for example) (11, 15). Notwithstanding decades of research by numerous laboratories (16–22), only Rowley et al. (23) and, more recently, Tsuna et al. (24) have charted fully synthetic routes to various ophiobolin members. Despite these achievements, the long step
counts required (38 steps to 2, 47 steps to 1, respectively) are limitations for accessing numerous family members, conducting in-depth structure activity studies, and ultimately producing superior derivatives. Undoubtedly, these limitations are a direct consequence of the challenges posed by the carbogenic complexity of the ophiobolins.

In analyzing previous syntheses of ophiobolins, the lengthy, stepwise construction of the 5-8-5 fused ring system stands in marked contrast to the concise cyclase-mediated biosynthetic pathway (Fig. 2A). Chiba et al. proposed that the biosynthesis of the ophiobolins involves a cationic cyclization of geranylfarnesyl pyrophosphate to carbocation 4, which—through a hydride shift, transannular cyclization, and hydration process—is then converted into the 5-8-5 fused skeleton of 5 (the process is shown in one step for simplicity) (25). In developing a retrosynthesis of ophiobolins, we were inspired by hypothetical carbon-centered radical 6 and considered its formation by the 8-endo/5-exo-cascade cyclization process shown (see 7–6, Fig. 2B). Further disconnection, via the illustrated hypothetical four-component coupling sequence, led to the identification of linalool (C-10) and farnesol (C-15) as suitable materials wherein the carbons labeled in red are incorporated into the final target. Thus, the central tenet of our synthetic strategy was a desire to use the biochemical building blocks but to forge the bonds in an abiotic fashion—a strategy that we have previously found to facilitate the synthesis of simpler terpenoids (26).

Seeking to realize aspects of this synthetic blueprint, we prepared cyclopentene 9 via a short sequence from the abundant monoterpene (-)-linalool (Fig. 3). A solvent-free ring closing metathesis reaction catalyzed by 0.1 mole percent of the Hoveyda-Grubbs second-generation catalyst (HG-II) was first used to construct the cyclopentenone (27), and upon complete consumption of linalool, the reaction mixture was diluted with THF and silylated in situ [NaH, tert-butyldimethylsilyl chloride (TBSCI)], affording chiral cyclopentene 8 in near-quantitative yield (>95%). After examining a variety of allylic oxidation conditions, we found that modifications to a ruthenium-catalyzed procedure developed by Miller et al. (28) smoothly furnished 9 in reasonable yield and on a multigram scale (57% isolated). In a separate vessel, we used Charette's asymmetric cyclopropanation methodology (29) in conjunction with a modified Appel procedure to prepare highly sensitive alkyl iodide 10 from geraniol. With two-step access to chiral fragments 9 and 10, we developed and optimized a challenging three-component coupling reaction, bearing strong analogy to our retrosynthetic blueprint (Fig. 2B) but with the methylene (–CH2) unit already incorporated. Treating 10 with tert-butyllithium induced lithium-halogen exchange and subsequent anionic cyclopropane fragmentation (30). After transmetallation with a copper iodide dimethylsulfide complex, an intermediate organocopper species (12) was formed, which cleanly added to cyclopentene 9. This 1,4-addition occurred in a diastereoselective fashion (diastereomeric ratio [dr] = 3:1), with the nucleophile approaching opposite the bulky OTBS group. After quenching with trichloroacetyl chloride, cyclopentene 13 could be isolated via column chromatography. Even though this reaction proved sensitive to temperature and mixing efficiency, it was highly reproducible on half-gram scales.

Our efforts to effect the key radical cyclization of trichloroketone 13 were initially focused on copper-mediated atom-transfer radical cyclization processes to construct the 5-8-5 fused ring system. Though molecular models gave credence to the feasibility of this cascade process, both 8-endo and 7-exo cyclization pathways have been observed previously (31, 32). Therefore, the outcome of this transformation, especially with

Fig. 1. Complex terpenoids containing 5-8-n fused carbocyclic skeletons. (A) Members of the ophiobolin sesterterpenes. Me, methyl. (B) Di- and sesterterpene classes of relevance to multiple therapeutic areas.

Fig. 2. Synthetic approaches to access complex ophiobolin ring systems. (A) Pathway for cyclase-mediated carbocationic cascades (25). (B) Retrosynthetic analysis with a strategic radical cascade involving simple polypropenyl building blocks.
regard to stereochemistry, was by no means certain (33). However, when 13 was heated with copper(I) chloride and bipyridine, polycycle 14, which contains the desired trans 5-8 ring junction, was formed in 43% yield. The stereochemistry of this alkenes in this sector (Fig. 1B). With respect to the ophiobolin synthetic problem, this termi-nation mode is not ideal, as a key stereocenter is lost, as will be shown below.

Fig. 3. Four-step entry into complex 5-8-5 fused ring systems. Reagents and conditions: (Step a) HG-II (0.1 mol %), THF, 0°C, 5 min; then add AcOH (1.0 equiv), MeOH/THF, 0°C, 1 hour, 60%. (Step f) NaBH₄ (2 equiv), MeOH/THF, 0°C, 2 hours, 60%, dr = 3:1. (Step i) Ir(ppy)₃ (1 mol %), Et₃N (1.5 equiv), THF, 0°C, 78°C, 2 hours, 60%, dr = 3:1. HG-II, (1,3-Bis-(2,4,6-trimethylphenyl)-2-(3,5-dimethyl-1-cyclohexylmethylidene)dichloro(1H-imidazolidinylidene)dichloro(2,5-diisobutyl-2H-pyrrol-1-ylidene) ruthenium; OAc, acetate; Bu, butyl; Et, ethyl; ppy, 2-phenylpyridinato; bipy, 2,2′-bipyridine; DMSO, dimethyl sulfoxide; TMS, trimethylsilyl.

After surveying a variety of options, we perceived two notable solutions. First, we found that through examination of the synthetic pathway, it was possible to construct the basic ophiobolin scaffold in its correct oxidation state directly, which con-tributed to the overall enantiomeric purity of the product. This was achieved through the use of a chiral thiol as a catalyst (25 mol %), we obtained a 1.6:1 mixture favoring 15-aldehyde (Fig. 4B). Given that the thiol is believed to donate the final hydrogen atom under these conditions (35), we examined the effect of thiol structure on the diastereoselectivity of the process 18 → 20 (Fig. 4B). All achiral aromatic and aliphatic thiols tested favored the incorrect isomer with slightly varying preferences (1.4:1 to 1.6:1 dr in favor of 15-aldehyde).

In an attempt to translate these results into the synthesis of full ophiobolin natural products, we subjected farnesol to an analogous four-step se-quence previously described for geraniol (Fig. 4). After the final hydride reduction step, either free alcohol 18 or its acetylated variant 19 could be isolated in one pot. Subjecting 18 to the previously discovered conditions for reductive radical cyclization afforded tri cyclic 20 featuring the complete eastern sector of all minimally oxidized ophiobolins. Although we were pleased to find that the diastereoselectivity at the cyclopentane stereocenter (C-14) was slightly improved relative to the geraniol-based system (dr = 1:1, T = 5°C), our excitement was quickly diminished when we determined that the major product of the cas-tle possessed the incorrect stereochemistry at the neighboring C-15 methyl stereocenter. In par-ticular, when using previously employed 3,5-CF₃PhSH as a catalyst (25 mol %), we obtained a 1.6:1 mixture favoring 15-epi 20 (Fig. 4B). Given that the thiol is believed to donate the final hydrogen atom under these conditions (35), we examined the effect of thiol structure on the diastereoselectivity of the process 18 → 20 (Fig. 4B). All achiral aromatic and aliphatic thiols tested favored the incorrect isomer with slightly varying preferences (1.4:1 to 1.6:1 dr in favor of 15-epi 20). Taking inspiration from Cai et al. ’s work on enantioselective radical hydroxylation (36), we began to examine the potential of chiral thiol catalysts to override the inherent substrate bias of this terminating hydrogen atom abstraction event (37). Although known glucose-based thiol 24 and 1,1′-bi-2-naphth di thiol 25 led
Fig. 4. Total synthesis of an ophiobolin sesterterpene. (A) Nine-step asymmetric synthesis of (−)-6-epi-ophiobolin N (3) (yields reported for synthetic steps e to h are for the diastereomeric mixture). (B) Evaluation of thiol catalysts for the transformation of 18–20 (yields and selectivity determined by 1H nuclear magnetic resonance analysis; dr at C-14 was 4:1). Reagents and conditions: (Steps a to d) See Fig. 3 for analogous conditions. (Step e) 1.0 equiv. TMS3SiH, Et3B (1.0 M solution in THF, 10°C, 12 hours, air, cyclopentane (0.009 M), 78% combined yield of reductively cyclized material [the reported dr values at C-14 (5.3:1) and C-15 (3.4:1) were determined after synthetic step h (see supplementary materials)]. (Step f) Me3Si (24.0 equiv), DMSO (15.0 equiv), Et3N (20.0 equiv), CH2Cl2, 40°C, 24 hours, 59% plus 19% recovered starting material. (Step g) p-TsOH (3.0 equiv), t-BuOH/CH2Cl2, 40°C, 24 hours, 59% plus 19% recovered starting material, p-TsOH, para-toluenesulfonic acid: py, pyridine; DMAP, 4-dimethylaminopyridine; BRSM, based on recovered starting material.

Tricycle 21, accessible in only five steps from readily abundant farnesol, requires only one carbon to complete the full C-25 skeleton of the target. This task was readily accomplished via the Corey-Chaykovsky epoxidation reaction (38), which fortuitously also removed the acetate group in the process (Fig. 4A). A second reductive cascade process was then designed to convert this spiro-epoxide intermediate (not shown) into the requisite ophiobolin cyclooctene ring system. Thus, treatment with excess lithium naphthalenide (1.0 M solution in THF, 0°C) afforded 21 in 77% yield, followed by treatment with para-toluenesulfonic acid under slightly elevated temperatures, forged (−)-6-epi-ophiobolin N (3), thus completing a nine-step enantioselective total synthesis in 2% overall yield. To date, we have used this sequence to prepare 15 mg of (−)-3. The described synthesis of 6-epi-ophiobolin N (3) lays the foundation for the efficient synthesis of other complex 5-8 fused terpenes for which no simple chemical or synthetic biological solutions exist. Moreover, this work also represents one of the shortest total syntheses of any known sesterterpene natural product (40). In addition, this strategy represents a departure from biomimetic, cationic cascade processes in that the chiral reagent exerts its influence during the termination of the cascade, rather than its initiation (7); combinations of both may prove even more powerful. Nevertheless, the synthesis described here is not without flaw: a lack of complete diastereoccontrol is noted in several steps. Finally, myriad reductive radical cyclizations terminate...
POLYMER CHEMISTRY

Organocatalyzed atom transfer radical polymerization driven by visible light

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ATOM TRANSFER RADICAL POLYMERIZATION (ATRP) has become one of the most implemented methods for polymer synthesis, owing to impressive control over polymer composition and associated properties. However, contamination of the polymer by the metal catalyst remains a major limitation. Organic ATRP photoredox catalysts have been sought to address this difficult challenge but have not achieved the precision performance of metal catalysts. Here, we introduce diaryl dihydrophenazines, identified through computationally directed discovery, as a class of strongly reducing photoredox catalysts. These catalysts achieve high initiator efficiencies through activation by visible light to synthesize polymers with tunable molecular weights and low dispersities.

Over the past two decades, atom transfer radical polymerization (ATRP) (1−4) has matured into one of the most powerful methodologies for precision polymer synthesis (5). Strict control over the equilibrium between a dormant alkyl halide and an active propagating radical dictates a low concentration of radicals and minimizes bimolecular termination to achieve controlled polymer chain growth (6). ATRP has historically relied on transition-metal catalysts to mediate this equilibrium and polymerize monomers with diverse functionality into macromolecules with controlled molecular weight (MW), low MW dispersity (D), defined chemical composition, and complex architecture (7).

The caveat of traditional ATRP has been that the transition-metal catalysts present purification challenges for the polymer products and impede their use in biomedical and electronic applications (8). Despite substantial strides in lowering catalyst loading (9, 10) and facilitating purification (11), organocatalyzed methods remain highly desirable for circumventing the need for metal removal, reducing toxicity concerns, and avoiding interference with electronic systems. Organocatalyzed variants of ATRP by use of alkyl iodide initiators have been established, although they are not a broadly applicable replacement for metal-catalyzed ATRP (12–14).

Our interest in this field originated in 2013 with the discovery that perylene could serve as an organic-visible-light photoredox catalyst (PC) to mediate an ATRP mechanism with alkyl bromide initiators, albeit with less control over the polymerization than has become the benchmark for traditional metal-catalyzed ATRP (15–17). Our ongoing work has striven to establish organocatalyzed ATRP (O-ATRP) for the synthesis of polymers with the precision of traditional ATRP, using visible-light PCs to realize energy-efficient polymerization methods that eliminate a major limitation of ATRP. Although photoredox catalysis has been established for decades, visible-light photoredox catalysis has drawn increasing attention by presenting the opportunity to harness solar energy to mediate chemical transformations under mild conditions (18, 19). Phenyl phenothiazine derivatives have since also proven effective as PCs for the ATRP of methacrylates (20) and acrylonitrile (21) but require irradiation by ultraviolet light and leave much room for improvement for generating polymers with higher molecular weights and lower dispersities coupled with increased initiator efficiency.

Our proposed mechanism of photoredox O-ATRP posits reversible electron transfer (ET) from with systems. Organocatalyzed variants of ATRP by use of alkyl iodide initiators have been established, although they are not a broadly applicable replacement for metal-catalyzed ATRP (12–14).

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A radical route to ophiobolin rings
Chemical ring-closing cascades resemble molecular yoga. One reactive site on a linear precursor can pull the whole molecule into a remarkably complex polycyclic arrangement. Cyclase enzymes rely on substantial internal scaffolding to guide this process during the biosynthesis of the ophiobolin sesterterpene frameworks, which comprise two pentagons sharing edges with an octagon. Brill et al. now show that the same motif is accessible abiotically by tweaking the cascade mechanism to rely on neutral radical intermediates in place of the positively charged activated sites in the biosynthetic pathways.
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