Late-Stage Diversification: A Motivating Force in Organic Synthesis

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ABSTRACT: Interest in therapeutic discovery typically drives the preparation of natural product analogs, but these undertakings contribute significant advances for synthetic chemistry as well. The need for a highly efficient and scalable synthetic route to a complex molecular scaffold for diversification frequently inspires new methodological development or unique application of existing methods on structurally intricate systems. Additionally, synthetic planning with an aim toward late-stage diversification can provide access to otherwise unavailable compounds or facilitate preparation of complex molecules with diverse patterns of substitution around a shared carbon framework. For these reasons among others, programs dedicated to the diversification of natural product frameworks and other complex molecular scaffolds have been increasing in popularity, a trend likely to continue given their fruitfulness and breadth of impact. In this Perspective, we discuss our experience using late-stage diversification as a guiding principle for the synthesis of natural product analogs and reflect on the impact such efforts have on the future of complex molecule synthesis.

INTRODUCTION

Fine-tuned over thousands of centuries for specific biological roles,[1] natural products have long served therapeutic purposes and continue to play a central role in drug development in the modern world.[2] In addition to serving directly as pharmaceuticals, such as the analgesic morphine or the antimalarial artemisinin, natural products also provide inspiration for molecular design of many FDA-approved small molecule drugs.[2,3] Interest in natural products as scaffolds for therapeutic development has been fueled by the discovery that the biological activities of small molecules are influenced by structural attributes such as ring system complexity, percentage of sp^3-hybridized carbons, heteroatom content, and number of stereocenters.[4] This realization has facilitated the study of the relationship of molecular structure with biological function, enabling the design of relevant molecular targets.[5]

The past few decades have witnessed a surge in efforts to create structurally complex, diverse molecules resembling natural products.[6,7,8] In 2004, Danishefsky introduced the concept of "diverted total synthesis" (DTS),[9] in which a late-stage synthetic intermediate is used to access a suite of non-natural complex molecules inspired by a natural product family, somewhat similar to the unified or collective synthesis strategy for accessing multiple natural products from a common core.[10] This strategy is often preferable to direct modification of natural products because the synthetic scaffolds are often more accessible than the natural products themselves and can be designed for the purpose of diversification.[11] Employing DTS, Danishefsky and co-workers prepared vast libraries of natural product analogs, many of which exhibited superior therapeutic behavior compared to the naturally occurring substances.[12]

Various other approaches for analog synthesis based on bioactivity have emerged and have been described as "function-oriented synthesis" (FOS),[13] "biology-oriented synthesis" (BIOS),[14] or "complexity to diversity" (CtD)[15] based on the specifics of scaffold design and elaboration. An alternative strategy introduced by Schreiber called "diversity-oriented synthesis" (DOS)[16] aims to screen for a wide variety of biological activity by producing as many different complex scaffolds as possible through modular combination of simple building blocks.[17] Yet another approach involves the preparation of hybrid molecules that contain structural elements of two or more natural product families with the aim of enhancing bioactivity.[18] Despite the variations in these approaches, they all share a common goal: exploration of bioactive chemical space through synthesis and biological evaluation of novel complex organic compounds.

These strategies have been applied to the synthesis of vast libraries of natural product-inspired complex molecules, with notable examples arising from the research groups of Wender,[19] Boger,[20] Nicolaou,[21] Myers,[22] Carreira,[23] Burke,[24] Miller,[25] and Baran,[26] among others. These efforts have revealed important information about the mechanisms of activity among complex molecules, which in turn informs further synthetic design.[27,28] This Perspective is not intended as a comprehensive review of the field of complex molecule diversification or natural product analog synthesis; several excellent reviews of this extensive research area have been published within the last several years.[6–8] Instead, this piece describes our experiences with late-stage diversification as a guide for synthetic design and source of inspiration for methodological development.

To create libraries of diverse, structurally intricate compounds, many approaches involve the synthesis of a central molecular scaffold from which diversification can be achieved. This scaffold can be chosen strategically to maximize the number of useful functional handles available while retaining the structural framework of the natural product family and potentially associated bioactivity. Because the scaffold is intentionally designed for maximal synthetic accessibility, this strategy allows access to novel natural product analogs and proves more feasible than derivatizing the natural products themselves. The pathway to this critical synthetic intermediate often requires iterative refinement to generate derivatives efficiently. While this is also an important consideration in total synthesis efforts toward specific molecular targets, the amount of late-stage material required for a successful diversification project often exceeds what is needed for a typical total synthesis because the number of potential targets is essentially limitless.[9] As such, continual optimization of the synthetic route to the main scaffold is a hallmark of diversification programs and often inspires the development of new methodologies or improvement of existing processes for transformations of complex frameworks.

Overall, diversification programs offer a unique synthetic perspective complementary to those of pure total synthesis and methods development. While a prominent goal of diversification efforts is to discover new biologically active compounds, the concomitant synthetic aims also deserve thoughtful discussion. The synthesis of a vast array of complex organic molecules represents a significant feat, especially considering the structural complexity of the natural products that inspire target design. Furthermore, the continual optimization required to diversify a complex scaffold offers repeated opportunities to showcase the synthetic utility of newly developed methodologies and generates a steady flow of widely applicable findings. Considering these synthetic benefits alongside the contributions made to medicinal chemistry, it is no wonder that complex molecule diversification has become a significant driving force among research efforts in organic synthesis.

LATE-STAGE DIVERSIFICATION OF THE CYANTHIWIGIN NATURAL PRODUCT CORE

The cyanthiwigin natural products have captivated the synthetic community for decades due to their intricate molecular architectures and intriguing bioactivities.[29] Sharing a distinctive angularly fused 5–6–7 tricyclic framework with a larger family of more than 170 cyathane diterpenes, the cyanthiwigins feature a unique *syn* relative orientation of the two methyl substituents at the ring junctures instead of the *anti* configuration observed in most other cyathanes.[30] Since their initial isolation in the early 1990s, a number of elegant syntheses of various cyanthiwigins have been reported.[31] In 2008, our group disclosed a concise total synthesis of (–)-cyanthiwigin F (**1**) (Figure 1A).[32] Exploitation of symmetry in early synthetic intermediates and application of a powerful double asymmetric allylic alkylation enabled preparation of tricyclic intermediate **6** in only seven steps from succinic acid (**4**, Figure 1B). Cyanthiwigins B (**2**), F (**1**), and G (**3**) were accessed from tricyclic diketone **6**,[33] and a similar strategy was employed toward the core of the structurally similar gagunin natural products (Figure 1C).[34]

Noting the apparent influence of oxygenated substituents on the biological activity of the gagunins as reported by Shin and co-workers,[35] we sought to leverage our concise route to tricycle **6** to prepare a suite of oxygenated cyanthiwigin derivatives. Representing the framework of the cyanthiwigin natural products, tricycle **6** offered an ideal scaffold for this endeavor given the presence of multiple functional handles in the form of olefin and carbonyl moieties. We envisioned that installation of diverse oxygenated functionalities would give rise to cyanthiwigin–gagunin "hybrid" molecules possessing the carbocyclic framework characteristic of the cyanthiwigins and oxygenated substituents reminiscent of the gagunins. We anticipated that these efforts would generate novel complex molecules for biological study while contributing valuable synthetic insight into the reactivity of the cyanthiwigin framework under conventional strategies for oxidation and modern methods for C–H oxidation.

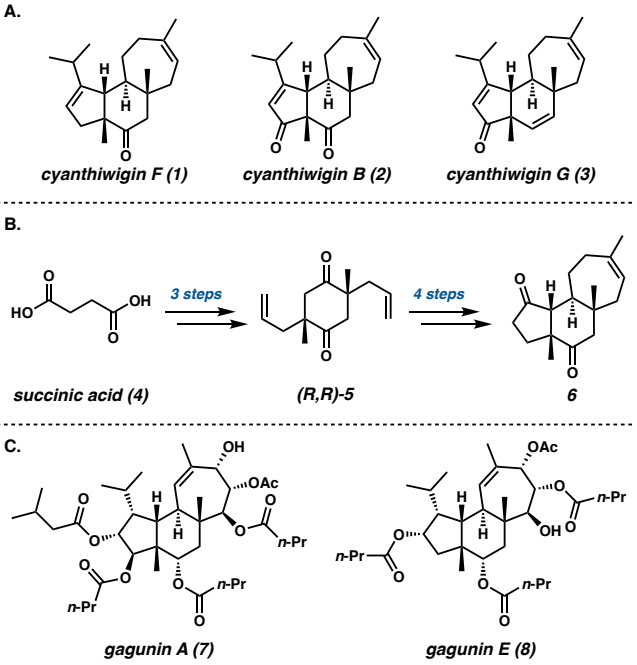
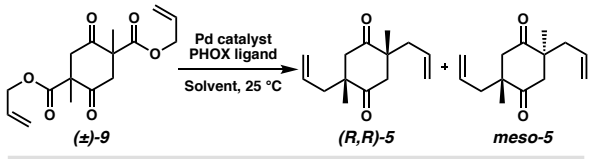


Figure 1. (A) Cyanthiwigin natural products accessible from **6**. (B) Synthetic approach toward tricycle **6** from succinic acid. (C) Structures of selected gagunin natural products.



Entry	Catalyst (mol %)	Ligand (mol %)	Solvent	Conc.	Yield	dr	ee
1	$Pd(dmdba)_2$ (5.0)	***L1*** (5.5)	Et_2O	0.01 M	78%	4.4:1	99%
2	$Pd(OAc)_2$ (0.25)	***L2*** (2.5)	PhMe	0.1 M	97%	4.9:1	99%

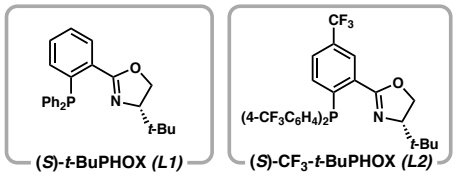
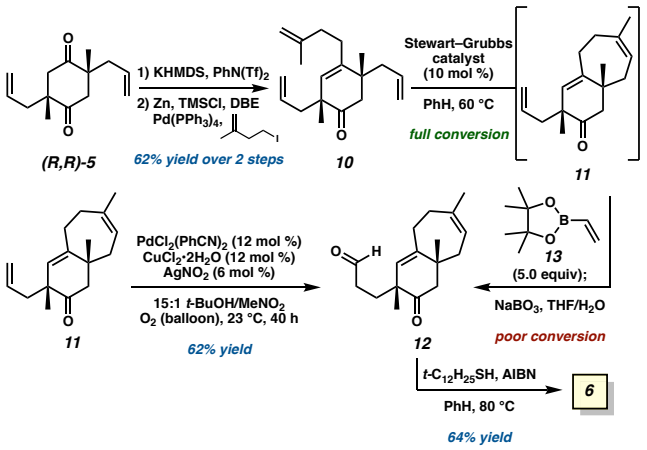


Table 1. Comparison of original (Entry 1) vs. modified conditions (Entry 2) for double enantioselective alkylation of **9**.

Because access to scaffold **6** was crucial for the success of our late-stage diversification plans, we began by critically re-examining our established synthesis of **6** despite its efficiency. We identified a few key transformations in need of further optimization for the large scale required for diversification

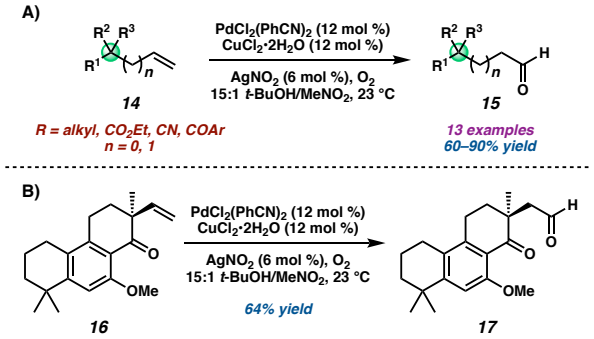
studies. The first synthetic challenge arose at the double catalytic enantioselective allylic alkylation to prepare diketone (*R*,*R*)-**5** from bis(β-ketoester) **9** and establish the requisite *syn* stereochemistry of the methyl substituents. This transformation required low reaction concentrations (0.01 M) and high loadings of $Pd(dmdba)_2$ and PHOX ligand **L1**, both only accessible through multistep preparation (Table 1, Entry 1). To address these limitations, we explored alternate conditions and ultimately discovered that commercially available $Pd(OAc)_2$ could be employed as a pre-catalyst with modified PHOX ligand **L2** in toluene at 10x concentration (0.1 M) to achieve the desired transformation. Moreover, these re-optimized conditions generated (*R*,*R*)-**5** in much higher yield and diastereoselectivity compared to the original conditions (Entry 2).[36] Importantly, these conditions were also effective on a 10-gram scale and required significantly less solvent, ligand, and Pd (by 20-fold) than the original protocol. This breakthrough streamlined the production of key enantioenriched diketone **5** on multi-gram scale, constituting an important advance in the synthesis of tricyclic scaffold **6**.



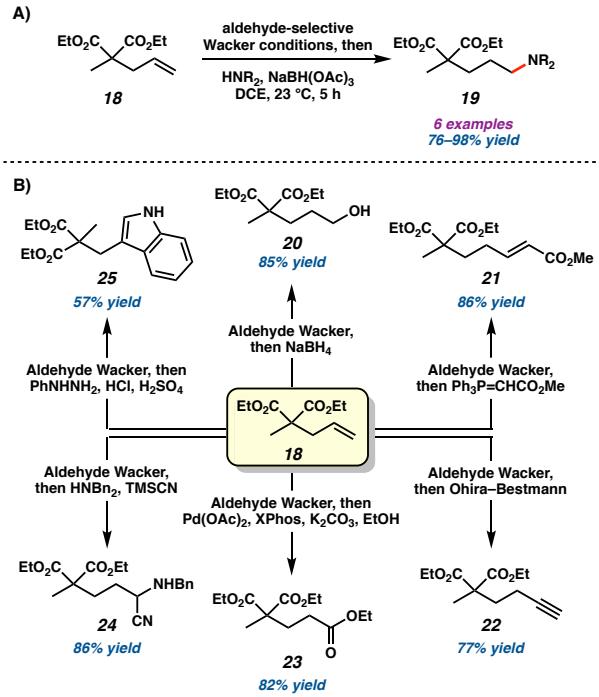
Scheme 1. Preparation of aldehyde **11**, facilitated by the aldehyde-selective Tsuji–Wacker oxidation, and completion of **5**.

After successful re-optimization of the critical stereodefining allylic alkylation, diketone **5** was converted to a vinyl triflate and subjected to Negishi coupling to afford tetraene **10** (Scheme 1). Ring-closing metathesis (RCM) to generate bicycle **11** proceeded smoothly, but the ensuing cross metathesis with vinylboronic acid pinacol ester (**13**) typically afforded aldehyde **12** in low yields after oxidative work-up. Eager to continue refining the synthesis using recently developed methodologies, we applied the aldehyde-selective Tsuji–Wacker oxidation protocol reported by Grubbs and co-workers in 2013 to RCM product **11**.[37] To our delight, **11** proved to be a competent substrate for the nitrite-modified Tsuji–Wacker oxidation, despite the presence of a sterically encumbered quaternary carbon at the homoallylic position. This discovery enabled productive use of the accrued quantities of bicycle **11**, thus increasing the amount of bicyclic aldehyde **12** available to undergo radical cyclization to generate the target cyanthiwigin natural product core (**6**).[38]

Considering the challenges of forming aldehydes proximal to sterically demanding quaternary carbons, we were intrigued by the successful oxidation of bicycle **11** and decided to investigate the synthetic potential of the nitrite-modified Tsuji–Wacker oxidation in more detail.[39] We began by examining its applicability to other sterically encumbered substrates given the ubiquity of such compounds as synthetic intermediates in the preparation of complex molecules. We were pleased to discover that terminal olefins bearing quaternary carbons at either the allylic or homoallylic position could be oxidized in high yields and aldehyde selectivity and with broad functional group tolerance (Scheme 2A). Considerably complex substrates were readily accommodated, as exemplified in the successful oxidation of aspewentin B derivative **16** (Scheme 2B), further underscoring the robustness of the nitrite-modified Tsuji–Wacker oxidation. Moreover, the aldehydes produced could be further transformed without purification to achieve direct conversion of terminal alkenes to a variety of functionalities. For instance, oxidation of alkene **18**, followed by reductive amination of the crude aldehyde enabled formal anti-Markovnikov hydroamination in good yields (Scheme 3A). Extension of this protocol facilitated other synthetic transformations, including carbon chain homologation and other anti-Markovnikov hydrofunctionalizations requiring only one purification step (Scheme 3B). This strategy has since been employed in various synthetic efforts.[40,41]



Scheme 2. (A) Aldehyde-selective Tsuji–Wacker oxidation of hindered terminal alkenes, (B) including aspewentin B derivative **16**.

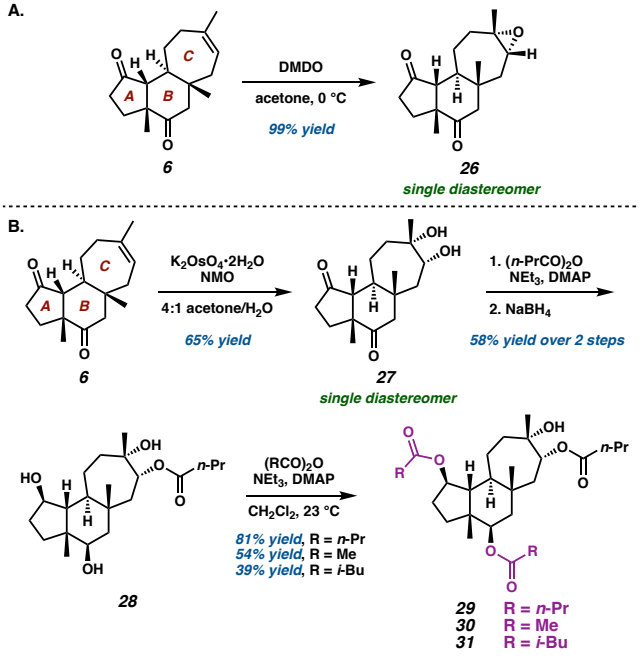


Scheme 3. (A) Formal anti-Markovnikov hydroamination of **18**. (B) Synthetic transformations of **18** enabled by aldehyde-selective Tsuji–Wacker oxidation.

With access to ample quantities of the cyanthiwigin core from the re-optimized synthetic route, we were well-equipped

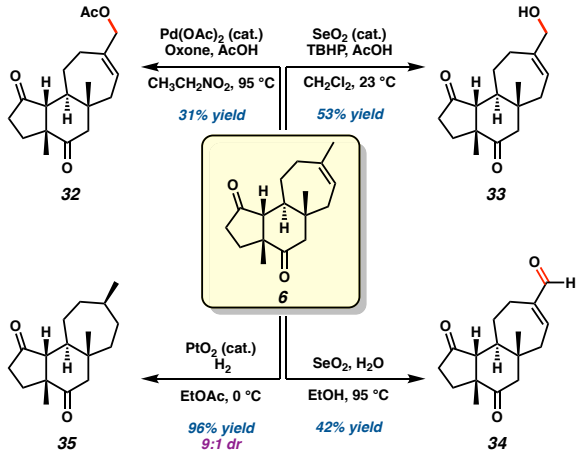
to prepare non-natural oxygenated cyanthiwigin analogs[42] and explore the reactivity of the cyanthiwigin core under various conditions for C–H oxidation.[43] Noting the potent anti-leukemia activity of gagunin E (**8**, Figure 1C) and the diverse biological activities of the cyanthiwigins,[29,30] we hypothesized that "hybrid" molecules possessing the core skeleton of the cyanthiwigins and the oxygenation pattern of the gagunins may exhibit heightened bioactivity.[44] To this end, the C-ring olefin and A- and B-ring carbonyls offered convenient handles for installing oxygenated functionalities onto the tricyclic core (**6**). Dimethyldioxirane (DMDO) epoxidation of the C-ring olefin proceeded with strong facial selectivity, forming epoxide **26** as a single diastereomer in 99% yield (Scheme 4A).[45] Although **26** was ultimately not employed as a synthetic precursor to cyanthiwigin–gagunin hybrids, the high stereoselectivity of the epoxidation indicated enhanced accessibility of the α-face of the C-ring of **6**.

In line with these findings, dihydroxylation of the C-ring olefin in **6** using catalytic dipotassium osmate in the presence of NMO occurred with the same facial selectivity, furnishing *syn*-diol **27** as a single diastereomer in good yield (Scheme 4B). Subsequent esterification using *n*-propyl anhydride followed by borohydride reduction of the A- and B-ring carbonyls with high facial selectivity afforded triol **28** in 80% yield (58% overall yield from **27**). Triol **28** was subsequently employed as a further point of diversification; esterification using various anhydrides readily generated cyanthiwigin–gagunin hybrid molecules **29**–**31**. Although these novel compounds did not exhibit significant anti-leukemia activity, these investigations revealed that tricycle **6** typically reacts preferentially at the α-face, as evidenced by the strong facial selectivity observed in epoxidation and dihydroxylation of the C-ring olefin in addition to hydride reduction of the A- and B-ring carbonyls. Given the concavity of the tricyclic framework, we were surprised to observe such strong preference for reactivity at the α-face. We surmised that the methyl substituents on the β-face of the cyanthiwigin core strongly influence reactivity, a conclusion supported by our C–H oxidation studies of the cyanthiwigin framework.



Scheme 4. (A) Stereoselective DMDO epoxidation of **6**. (B) Diversification of **6** to access cyanthiwigin–gagunin hybrids **29**–**31**.

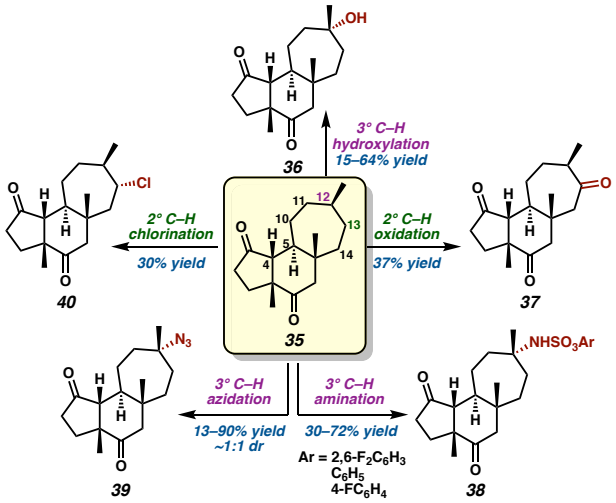
Considering the extensive interest in harnessing C–H functionalization as a robust strategy for complex molecule synthesis,[7,46] we sought to employ tricycle **6** in a comparative analysis of C–H oxidation methodologies. We began by examining allylic C–H acetoxylation of the cyanthiwigin core. Interestingly, **6** was unreactive under various conditions for Pd-catalyzed allylic C–H acetoxylation[47] and generated only low yields of acetoxylated product **32** in the presence of Oxone and $Pd(OAc)_2$ (Scheme 5).[48] In contrast, SeO_2 readily oxidized **6**, albeit in moderate yields. Allylic alcohol **33** was produced in the presence of catalytic selenium with *tert*-butyl hydroperoxide (TBHP) as the terminal oxidant whereas aldehyde **34** was the major product when stoichiometric selenium was employed at elevated temperatures. These findings suggest that usually robust Pd-catalyzed methods for allylic C–H oxidation have further room for optimization when applied to complex systems, although conventional strategies for allylic oxidation meet this synthetic need. To explore the fate of the cyanthiwigin framework under conditions for 3° C–H oxidation, saturated tricycle **35** was prepared via Pt-catalyzed hydrogenation of the C-ring olefin. As observed in the cyanthiwigin–gagunin hybrid synthesis, H_2 was added preferentially across the α-face of **6**, corroborating our previous conclusions about facial selectivity in reactions of **6**.



Scheme 5. Allylic C–H oxidation and hydrogenation of the cyanthiwigin framework (**6**).

With substrate **35** in hand, we carried out a comparative study of 3° C–H hydroxylation, amination, and azidation reactions. Significant discrepancies in efficacy of 3° C–H hydroxylation[49] were observed, with yields of tertiary alcohol **36** ranging from 15–64% (Scheme 6). Similarly varying results were observed in 3° amination[50] and 3° azidation[51] studies. While yields of tertiary azide **39** as high as 90% were achievable, most methods generated **39** in nearly 1:1 dr, an outcome with important implications for employing 3° C–H azidation in complex molecule synthesis. In all cases, **35** reacted exclusively at C12, indicating potential electronic deactivation of C4 and C5 by the proximal electron-withdrawing carbonyls. Oxidation of 2° C–H bonds was also achievable, albeit in lower yields. Investigation of 2° C–H oxygenation[52] and C–H chlorination[53] methods furnished ketone **37** and chloride **40**, respectively, in modest yields. In both cases oxidation was observed only at C13, likely due to steric and electronic deactivation at C10, C12, and C14. Notably, chlorination occurred preferentially on the α-face of **35**, mirroring the facial selectivity observed in the reactivity of tricycle **6**. Together, these findings showcase the influence of electronics, sterics,

and intrinsic reactivities of C–H bonds in C–H oxidation reactions, highlighting the importance of methods that offer alternate regioselectivities.



Scheme 6. 2° and 3° C–H oxidation of hydrogenated tricycle **35**.

Conditions for 3° C–H hydroxylation: a) $RuCl_3$•xH_2O (5 mol %), $KBrO_3$, pyridine, MeCN, 60 °C, 42% yield; b) $(Me_3tacn)RuCl_3$ (2 mol %), CAN, $AgClO_4$, *t*-BuOH/H_2O, 23 °C, 64% yield; c) 6-chloro-4-trifluoromethyl-1,2,3-benzoxathiazine-2,2-dioxide (20 mol %), Oxone, HFIP/H_2O, 70 °C, 21% yield; d) DMDO, acetone, 23 °C, 15% yield; e) Fe(*S,S*-PDP) (15 mol %), H_2O_2, AcOH, MeCN, 23 °C, 22% yield; f) $Mn(OTf)_2$ (0.1 mol %), AcOOH, bipy, AcOH/H_2O, 23 °C, 20% yield. ***Conditions for 3° C–H amination:*** g) $(2,6\text{-}F_2C_6H_3)OSO_2NH_2$, $[Rh_2(esp)_2]$ (10 mol %), $PhI(OAc)_2$, $PhMe_2CCO_2H$, MgO, 5Å MS, *i*-PrOAc, 30% yield; h) $PhOSO_2NH_2$, $[Rh_2(esp)_2]$ (10 mol %), $PhI(OPiv)_2$, Al_2O_3, *t*-BuCN, 70% yield; i) $(4\text{-}FC_6H_4)OSO_2NH_2$, $[Rh_2(esp)_2]$ (10 mol %), $PhI(OPiv)_2$, Al_2O_3, *t*-BuCN, 72% yield. ***Conditions for 3° C–H azidation:*** j) methyl 2-(azidosulfonyl)benzoate, $K_2S_2O_8$, $NaHCO_3$, MeCN/H_2O, 85 °C, 90% yield, 1.0:1.9 d.r.; k) 1-azido-1,2-benziodoxol-3-(1*H*)-one, $Fe(OAc)_2$, *i*-Pr-Pybox, MeCN, 35→50 °C, 86% yield, 1.2:1.0 d.r.; l) 1-azido-1,2-benziodoxol-3-(1*H*)-one, BzOOBz, ABCN, DCE, 84 °C, 13% yield. ***Conditions for 2° C–H oxidation:*** m) Fe(*R,R*-CF_3-PDP) (15 mol %), H_2O_2/H_2O, MeCN, AcOH, 23 °C, 37% yield. ***Conditions for 2° C–H chlorination:*** n) ArCON(Cl)(*t*-Bu), Ar = $3,5\text{-}(CF_3)_2C_6H_3$, Cs_2CO_3, hν (23W), PhH, 55 °C, 30% yield.

Overall, these investigations illustrate how pursuing a goal of diversifying a complex molecular scaffold can precipitate broadly applicable synthetic discoveries. In our quest to explore the reactivity of the cyanthiwigin core (**6**) and prepare structurally diverse analogs, we developed a revised synthetic route to **6** employing state-of-the-art methodologies. Beyond facilitating production of **6** on large scale, these efforts showcase the synthetic applicability of recently developed methodologies, expanding the known utility of powerful transformations by offering fresh contexts for their application.

SYNTHESES OF JORUNNAMYCIN A, JORUMYCIN, AND ANALOGS

The bis-tetrahydroisoquinoline (bis-THIQ) alkaloids have been extensively studied over the past 40 years due to their unique chemical structures and potent biological activities as antitumor antibiotics.[54] Among these, jorumycin (**41**) and jorunnamycin A (**42**) feature a pentacyclic carbon skeleton, highly oxygenated ring termini, and a central pro-iminium ion that serves as an alkylating agent in vivo, resulting in covalent modification of DNA that ultimately leads to cell death (Figure 2).[55] The potent bioactivity of these natural products yields promise as anticancer agents, such as Et 743 (**43**) (Yondelis, trabectedin) which has been approved for the treatment of advanced soft-tissue sarcoma and ovarian cancer in the United States and Europe.

The highly electron-rich functional groups embedded in these natural products are key structural features in the biosynthetic pathways of the bis-THIQ alkaloids, which are forged by Pictet-Spenglerase enzymes.[56] Previously reported chemical syntheses of jorumycin (**41**) and jorunnamycin A (**42**) feature biomimetic applications of electrophilic aromatic substitution (EAS) chemistry for the construction of one or more of the tetrahydroisoquinoline (THIQ) motifs (Figure 3).[57] However, this approach is only limited to electron-rich groups appended to the phenyl ring, inhibiting the synthesis of non-natural analogs with substituents of differing electronic effects. Moreover, analogs possessing electron-withdrawing groups on these rings are inaccessible using biomimetic approaches, which is a commonly employed strategy to improve a drug molecule's metabolic stability.[58] Thus, to overcome the limitations of the current state of the art with respect to analog diversity, we implemented an alternative, nonbiomimetic route to access these natural products and their analogs.

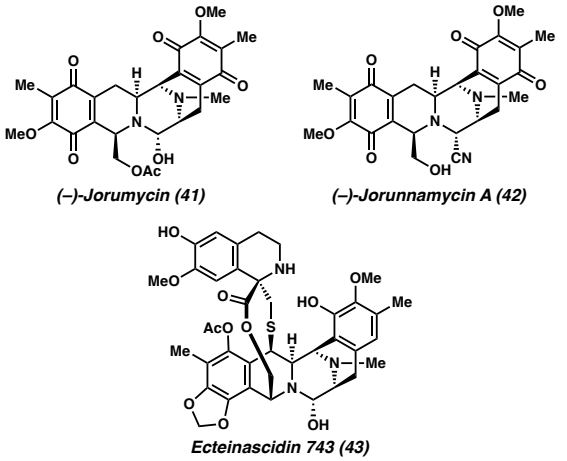


Figure 2. Bis-Tetrahydroisoquinoline (bis-THIQ) Alkaloids

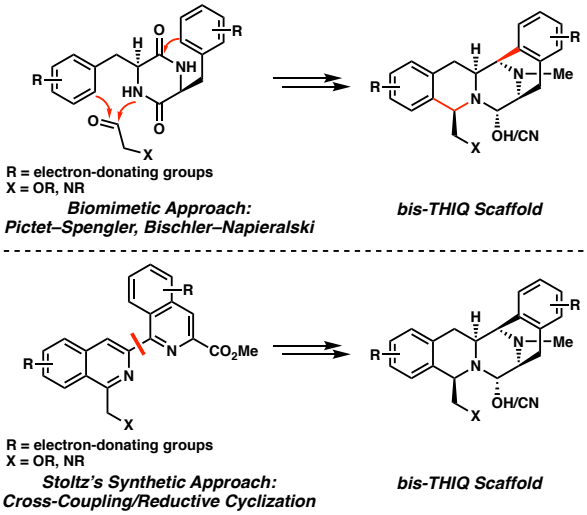
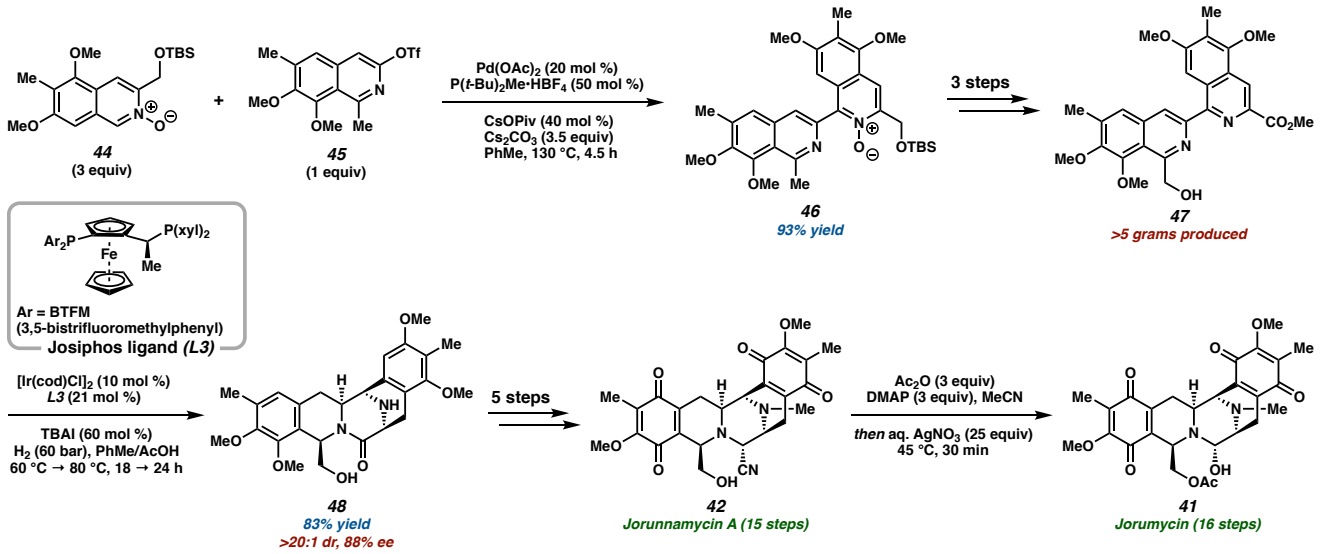


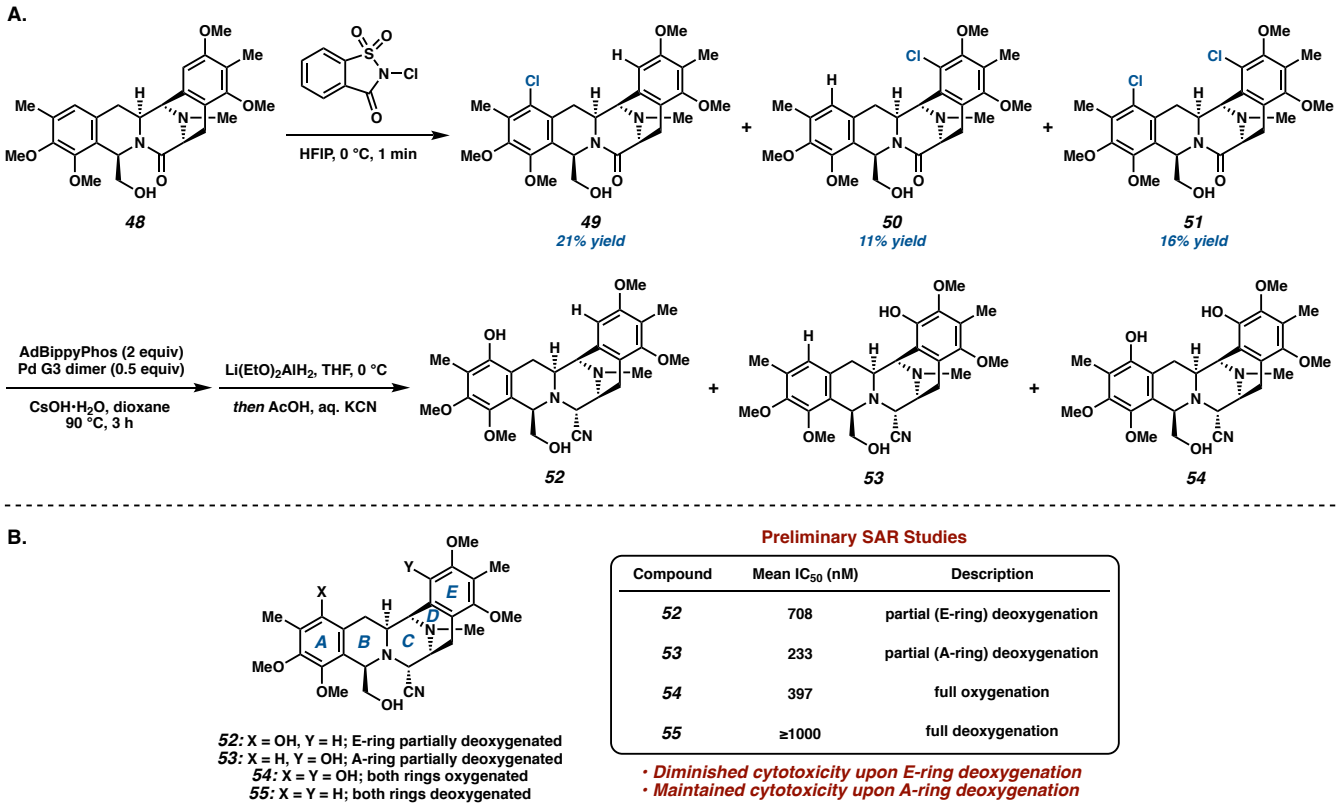
Figure 3. Conventional biomimetic approaches toward the bis-THIQ natural products versus our synthetic approach

Toward diversification efforts of natural product analogs, we designed a nonbiomimetic route for the total syntheses of (–)-jorumycin (**41**) and (–)-jorunnamycin A (**42**) (Scheme 7).[59] This unprecedented synthetic approach harnesses transition-metal catalysis to forge the two functionalized isoquinoline monomers **44** and **45** through a Pd-catalyzed cross-coupling reaction developed by Fagnou and coworkers, accessing bis-isoquinoline **46** in 93% yield on a 7-gram scale.[60] After installing the required oxidation levels of the natural product scaffold, an Ir-catalyzed enantioselective hydrogenation was performed to undergo reduction and subsequent cyclization to install pentacyclic intermediate **48**. Inspired by the asymmetric ether-directed imine reduction using a chiral Ir catalyst developed by scientists at Ciba-Geigy (Syngenta) for the preparation of the herbicide metolachlor, we utilized the appended hydroxymethyl group as a directing group for hydrogenation.[61] Using chiral Josiphos ligand **L3**, we initially observed reduction of the isoquinoline with the C1-appended hydroxy functionality, confirming the accelerating effects of the directing group under the hydrogenation conditions. Further optimization established the natural product scaffold **48** in 83% yield with >20:1 dr and 88% ee on greater than 1-mmol scale. Finally, late-stage C–H oxidation of the arenes enabled access to both (–)-jorunnamycin A (**42**) and (–)-jorumycin (**41**). The convergent coupling strategy allows for the preparation of a diverse set of isoquinoline monomers, wherein different permutations of partial and full oxygenations of the arene ring can be installed to explore structure-activity relationships of novel analogs.

This non-biomimetic synthetic route not only strategically leverages modern catalysis for the construction of the bis-THIQ natural products with high efficiency, but also advances late-stage diversification with key intermediate **48** for the production of several jorunnamycin A analogs inaccessible through conventional EAS approaches. Using bis-THIQ **48** as a branching point for derivative synthesis, we sought to synthesize permutations of partial and full oxygenation patterns on the quinone rings to explore structure-activity relationships, which have previously been synthetically inaccessible. A late-stage C–H oxidation of **48** with 1.1 equivalents of *N*-chlorosaccharine established the mono-chlorinated products **49** and **50**, and dichlorinated product **51** in comparable yields (Scheme 8A). Hydroxylation of the aryl halides then established different oxygenation patterns on the western and eastern fragments of the molecule, furnishing analogs **52**–**54**.



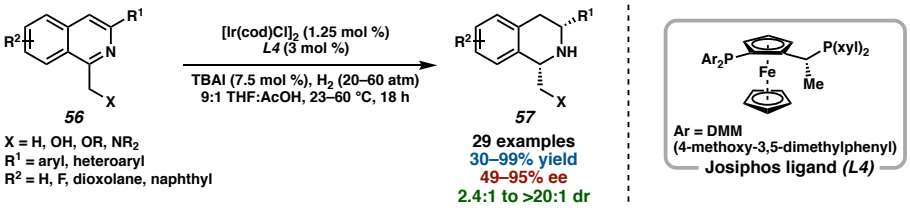
Scheme 7. Total synthesis of (–)-jorumycin (**41**) and (–)-jorunnamycin A (**42**).



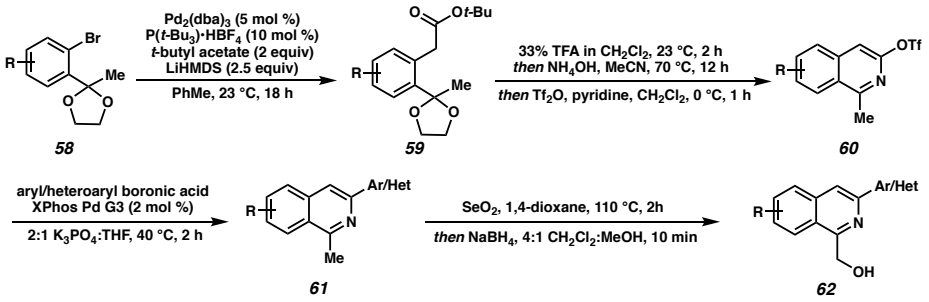
Scheme 8. (A) Synthesis of bis-THIQ analogs and (B) Biological evaluation of non-natural analogs **52**–**55**.

Preliminary biological evaluations of these analogs were then conducted to probe the relative cytotoxicity against cancer cell lines (Scheme 8B). Interestingly, mono-hydroxylated products **52** and **53** show considerably different activity profiles depending on the relative location of oxygenation. Featuring only E-ring oxygenation, compound **53** displayed similar levels of cytotoxicity to fully oxygenated **54** while molecule **52** with A-ring oxygenation showed significantly diminished activity.[59] Though further studies are needed to determine actual efficacy, comparing the activity of the series **52**–**55** highlights the significance of the location and degree of oxygenation on the A- versus E- rings.

In addition to creating a diverse library of non-natural analogs, this novel synthetic approach toward jorumycin and jorunnamycin A also inspired reaction development for further transformations of complex heterocyclic frameworks. Considering the limited reports on the asymmetric hydrogenation of isoquinolines,[62] we drew inspiration from the hydrogenation of **47** in the total synthesis of jorumycin to develop a general method for the hydrogenation of 1,3-disubstituted isoquinolines. Using the hydroxymethyl group at the C1-position as a directing group, this synthetic method enabled access to a wide variety of enantioenriched tetrahydroisoquinolines (THIQs) and amino alcohols, both highly valuable pharmacophores.[63] Using 1.25 mol % of $[Ir(cod)Cl]_2$ and 3 mol % of Josiphos ligand **L4**, a broad scope of differentially substituted isoquinolines were well tolerated (Scheme 9).



Scheme 9. The general asymmetric hydrogenation of 1,3-disubstituted isoquinolines inspired by the total synthesis of jorumycin.



Scheme 10. Diversified synthetic approach toward a wide variety of 1,3-disubstituted isoquinolines.

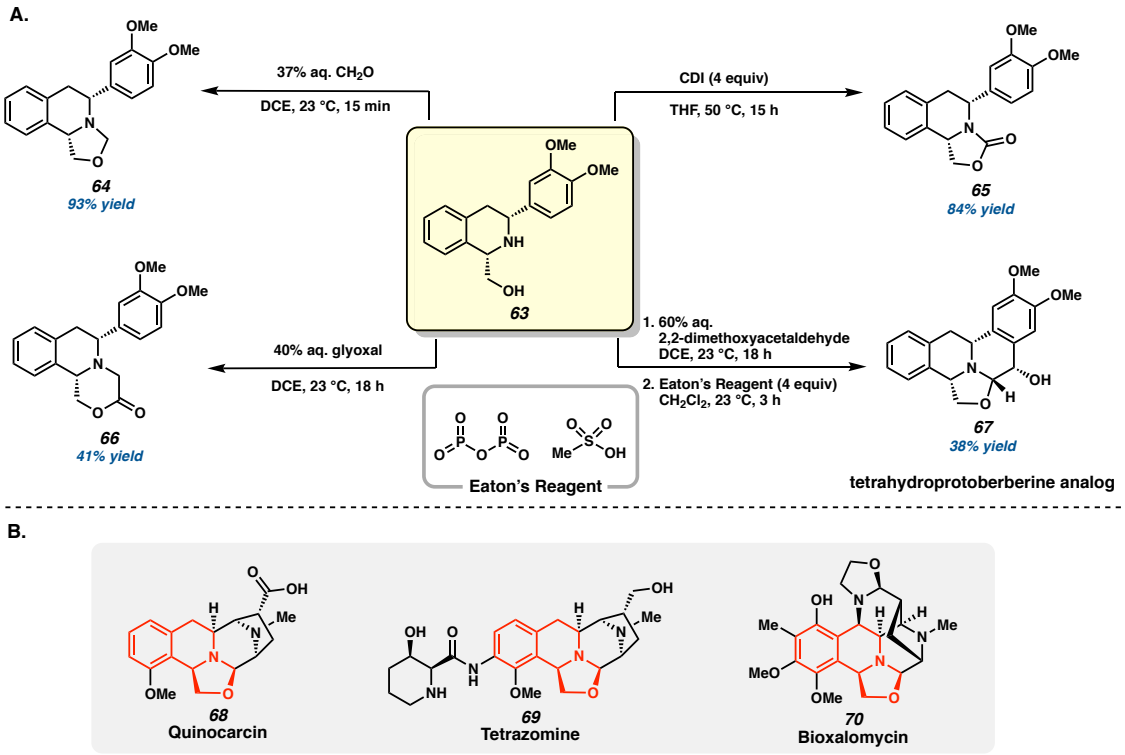


Figure 4. (A) Synthetic derivatizations of hydrogenated THIQ product **63** to complex THIQ scaffolds and (B) Select examples of natural products with fused 6,6,5-tricyclic THIQ systems.

Investigation of the hydrogenation methodology for a variety of 1,3-disubstituted isoquinolines required a simple and divergent synthetic route to access a wide range of 1-(hydroxymethyl)-3-arylisoquinoline substrates. To expand on the limited number of general methods for the synthesis of substituted isoquinolines, we developed an efficient synthetic approach toward isoquinoline diversification by accessing isoquinoline triflate **60** from a Pd-catalyzed enolate arylation and subsequent annulation and alcohol triflation (Scheme 10).[64] At this stage, different aryl or heteroaryl groups could be coupled with intermediate **60** to deliver a wide range of 1,3-disubstituted isoquinolines, highlighting the divergent synthesis of this sequence. Finally, SeO_2 oxidation to afford the aldehyde and subsequent $NaBH_4$ reduction provided the desired isoquinoline substrate **62** to investigate the hydroxy-directed asymmetric hydrogenation.

Ultimately, the development of this hydrogenation method provides access to a range of decorated THIQ analogs that are difficult to synthesize via biomimetic approaches. Furthermore, the hydroxymethyl directing group can also serve as a functional handle toward the synthesis of complex scaffolds from the hydrogenated products. The synthetic utility of this functionality was demonstrated by subjecting THIQ **63** to one-step protocols, accessing fused 6,6,5- and 6,6,6-tricyclic systems **64**–**66** (Figure 4A). Notably, scaffolds **64**–**65** are conserved structural motifs in a number of natural products such as quinocarcin, tetrazomine, and bioxalomycin (**68**–**70**, Figure 4B).[65] Additionally, non-natural analog **67** of the tetrahydroprotoberberine alkaloids, a family of natural products with a tetracyclic bis-THIQ core, was synthesized via a 2-step sequence. After the reaction of **63** with glyoxal dimethyl acetal to access an oxazolidine-fused intermediate, a Pomeranz-Fritsch reaction using Eaton's Reagent (7.7 wt. % phosphorus pentoxide in methanesulfonic acid) delivers the fused pentacyclic THIQ scaffold **67** in 38% yield as a single diastereomer (Figure 4A). Overall, the application of this asymmetric hydrogenation technology toward the synthesis of complex THIQ structural motifs of several biologically active natural products represents an expansion of synthetic utility from the seminal hydrogenation sequence of the jorumycin synthesis.

CONCLUDING REMARKS

The contributions of diversification studies to chemical synthesis are plentiful. Designing a synthesis to access an array of natural product analogs not only enables a concise, efficient synthetic route but also inspires new methodological development and motivates creative application of established methods in previously untested contexts. Once prepared, the diversification scaffold serves as a platform for creating libraries of structurally diverse complex molecules, a process which frequently reveals intriguing and unexpected patterns of reactivity. The outcomes of these investigations are broadly applicable, offering important synthetic insights and providing access to biosynthetically unavailable natural product analogs. In turn, the preparation of molecular libraries facilitates study of structure–activity relationships of privileged scaffolds with the potential to inform drug development. Given these considerable motivating factors, future synthetic endeavors will undoubtedly continue to feature diversification as a prominent aim, whether in the form of analog preparation or the demonstration of potential for access to derivatives. Distinct from traditional natural product total synthesis, the targeting of analog libraries reflects the modern age of chemical synthesis and increasingly calls on practitioners to address new research questions. Essentially, ruminations on whether or how a complex molecule can be synthesized are giving way to considerations of how the synthesis of a molecule can be designed for maximum impact. Interest in natural products as synthetic targets remains robust, but having cultivated the ability to prepare any molecule of interest with enough creativity and determination, synthetic chemists are re-conceptualizing complex molecule synthesis. As evidenced by the last few decades, diversification will likely be a mainstay of organic synthesis research programs for many years to come.

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Notes

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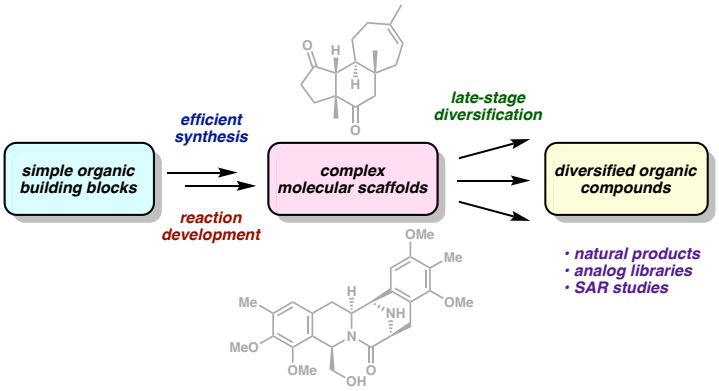
TOC Graphic: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