Annulative Methods in the Synthesis of Complex Meroterpene Natural Products

Xingyu Shen,[a] *Danny Q. Thach,*[a] *Chi P. Ting,*[a,b] *and Thomas J. Maimone*[a]*

[a] Department of Chemistry, 826 Latimer Hall, University of California–Berkeley, Berkeley, CA 94720

[b] current address: Department of Chemistry, Edison-Lecks Laboratory, 415 South St., Brandeis University, Waltham, MA 02453

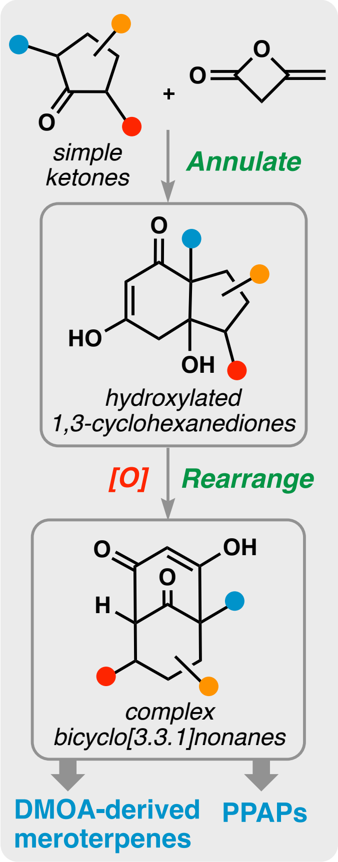
CONSPECTUS. From the venerable Robinson annulation to the irreplaceable Diels-Alder cycloaddition, annulation reactions have fueled the progression of the field of natural product synthesis throughout the past century. In broader terms, the ability to form a cyclic molecule directly from two or more simpler fragments has transformed virtually every aspect of the chemical sciences from the synthesis of organic materials to bioconjugation chemistry and drug discovery. In this Account, we describe the evolution of our meroterpene synthetic program over the past five years, enabled largely by the development of a tailored anionic annulation process for the synthesis of hydroxylated 1,3-cyclohexanediones from lithium enolates and the reactive β-lactone-containing feedstock chemical diketene.

First, we provide details on short total syntheses of the prototypical polycyclic polyprenylated acylphloroglucinol (PPAP) natural products hyperforin and garsubellin A which possess complex

bicyclo[3.3.1]nonane architectures. Notably, these molecules have served as compelling synthetic targets for several decades and induce a number of biological effects of relevance to neuroscience and medicine. By merging our diketene annulation process with a hypervalent iodine-mediated oxidative ring expansion, bicyclo[3.3.1]nonane architectures can be easily prepared from simple 5,6-fused bicyclic diketones in only two chemical operations. Leveraging these two key chemical reactions in combination with various other stereoselective transformations allowed for these biologically active targets to be prepared in racemic form in only 10-steps.

Next, we extend this strategy to the synthesis of complex fungal-derived meroterpenes generated biosynthetically from the coupling of 3,5-dimethylorsellinic acid (DMOA) and farnesyl pyrophosphate. A Ti(III)-mediated radical cyclization of a terminal epoxide was used to rapidly prepare a 6,6,5-fused tricyclic ketone which served as an input for our annulation/rearrangement process, ultimately enabling a total synthesis of protoaustinoid A, an important biosynthetic intermediate in DMOA-derived meroterpene synthesis, and its oxidation product berkeleyone A. Through a radical-based, abiotic rearrangement process, the bicyclo[3.3.1]nonane cores of these natural products could again be isomerized, resulting in the 6,5-fused ring systems of the andrastin family and ultimately delivering a total synthesis of andrastin D and preterrenoid. Notably, these isomerization transformations proved challenging when employing classic, acid-induced conditions for carbocation generation, thus highlighting the power of radical biomimicry in total synthesis. Finally, further oxidation and rearrangement allowed for access to terrenoid and the lactone-containing metabolite terretonin L.

Overall, the merger of annulative diketene methodology with an oxidative rearrangement transformation has proven to be a broadly applicable strategy to synthesize bicyclo[3.3.1]nonane-containing natural products, a class of small molecules with over 1000 known members.



KEY REFERENCES

- Ting, C. P.; Maimone, T. J. Total Synthesis of Hyperforin. *J. Am. Chem. Soc.* **2015**, *137*, 10516–10519.[1] Initial discovery of an annulation reaction between lithium enolates and diketene and its application to a short total synthesis of the polycyclic polyprenylated acylphloroglucinol (PPAP) natural product hyperforin.

- Shen, X.; Ting, C. P.; Xu, G.; Maimone, T. J. Programmable Meroterpene Synthesis. *Nat. Commun*. **2020**, *11,* 508.[2] This work reported an extended substrate scope of the diketene annulation process and disclosed a 10-step total synthesis of the PPAP natural product garsubellin A.

- Ting, C. P.; Xu, G.; Zeng, X.; Maimone, T. J. Annulative Methods Enable a Total Synthesis of the Complex Meroterpene Berkeleyone A. *J. Am. Chem. Soc.* **2016**, *138,* 14868–14871.[3] This manuscript describes a total synthesis of Berkeleyone A, the first bicyclo[3.3.1]nonane-containing meroterpene derived from dimethylorsellinic acid (DMOA) to be prepared through total synthesis.
- Xu, G.; Elkin, M.; Tantillo, D. J.; Newhouse, T. R.; Maimone, T. J. Traversing Biosynthetic Carbocation Landscapes in the Synthesis of Andrastin and Terretonin Meroterpenes. *Angew. Chem. Int. Ed.* **2017**, *56,* 12498–12502.[4] In this work, we studied the interconversion of bicyclo[3.3.1]nonane-containing DMOA-derived meroterpenes into the andrastin and terretonin natural product families.

INTRODUCTION Transformations wherein two molecular units are merged and two new bonds created – annulation reactions – remain some of the most powerful tools in the synthetic organic chemistry repertoire.[5] Given the assortment of polycyclic ring systems found in natural products, annulations have had a particularly meaningful impact on the field of total synthesis. Equally, natural product structures themselves have likewise served as inspiration for the development of new annulative processes. Throughout the 20th century, a variety of powerful annulation reactions, particularly those forming two C–C bonds, have been strategically employed on problems in total synthesis including Robinson's classic synthesis of cholesterol employing a polar, anionic annulation,[6,7] Stork's synthesis of cantharidin featuring an early application of the Diels-Alder reaction,[8,9] Curran's radical annulation-based synthesis of albene,[10,11] and Trost's transition metal-mediated synthesis of loganin aglycone leveraging a transition metal-catalyzed annulation (Figure

1).[12,13] While these annulations all serve the general goal of forming a new ring, the diversity of the reaction mechanisms and reactive intermediates involved is both distinct and notable.

Over the past five years, our laboratory has initiated a program in the synthesis of biologically active polyketide/terpenoid hybrids (i.e. meroterpenes) featuring bicyclo [3.3.1]nonane-containing scaffolds.[1-4,14] Beginning with the popular polycyclic polyprenylated acylphloroglucinol (PPAP) family and then advancing to meroterpenes derived from dimethylorsellinic acid (DMOA) and farnesyl pyrophosphate, we devised synthetic routes to these natural products which required the invention of a new annulation process at the retrosynthetic planning stages. Specifically, we developed a polar, anionic annulation reaction between diketene and lithium enolates derived from substituted cyclopentanones resulting in cyclic 1,3-diketone motifs amenable to further rearrangement into bicyclo[3.3.1]nonanes (see inset, Figure 1). Herein, we detail the evolution of this program resulting in concise and modular routes to a variety of complex meroterpenes including hyperforin, garsubellin A, berkeleyone A, andrastin D, and terretonin L.

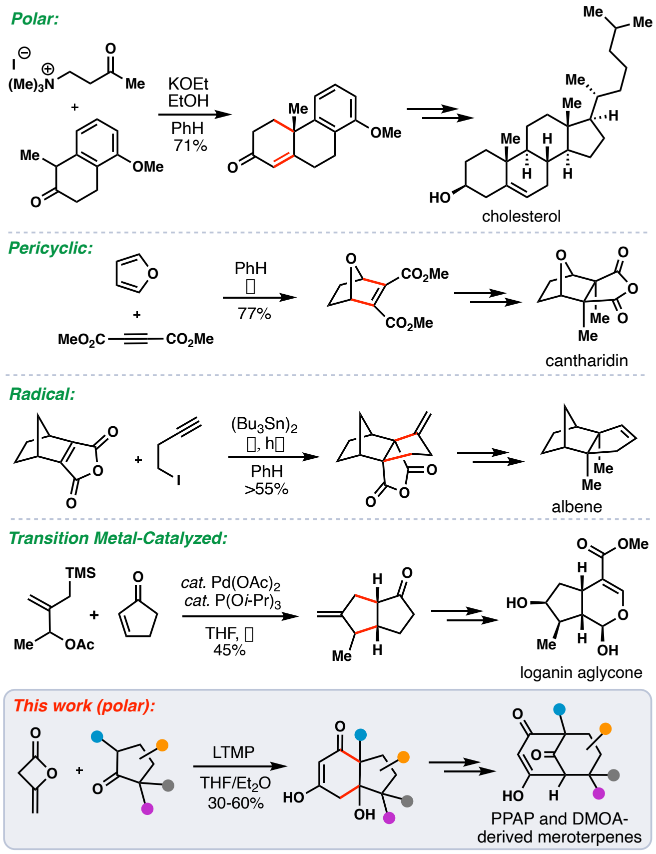


Figure 1. Selected annulation processes used in the assembly of polycyclic natural products during the 20th century.

POLYCYCLIC POLYPRENYLATED ACYLPHLOROGLUCINOLS (PPAPs): INSPIRATION FOR A NEW ANNULATION PROCESS

Owing to both their structural diversity and biological activity, which include antiproliferative, antidepressant, antibacterial, and antiviral effects, the large family of bicyclo [3.3.1] nonane-containing polycyclic polyprenylated acylphloroglucinols (PPAPs) remain the most well-studied family of meroterpenes from a synthetic chemistry perspective (Figure 2). To date, a large number of PPAP natural products have been prepared through total synthesis via a variety of highly creative approaches.[15]

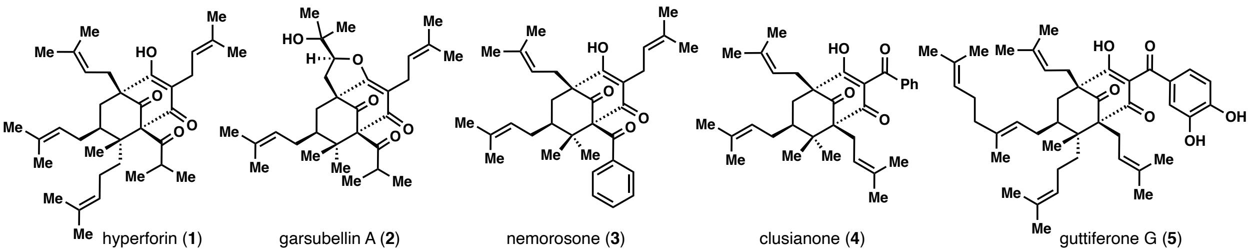

hyperforin (**1**) garsubellin A (**2**) nemorosone (**3**) clusianone (**4**) guttiferone G (**5**)

Figure 2. Selected members of the large family of bicyclo[3.3.1]nonane-containing polycyclic polyprenylated acylphloroglucinols (PPAPs).

The bicyclo[3.3.1]nonane 2,4,9-trione motif of the PPAPs is formed in nature through a multi-step, dearomative process involving the three-component coupling of a trisubstituted phloroglucinol derivatives and two units of either prenyl or geranyl-based electrophiles in most cases (abbreviated in Figure 3). Through this process, not only is molecular complexity rapidly generated from simple achiral precursors, but the substituents surrounding the PPAP core can be easily “mixed and matched” by varying the chemical inputs (see colored balls, Figure 3) and enzyme cyclization modes. While direct annulation to forge the PPAP bicyclo[3.3.1]nonane polycycle has proven to be a popular synthetic disconnections,[16] we traced this motif (see **6**, Figure 3) back to 5,6-fused bicycle **7** via a rearrangement process involving carbonyl α-oxidation and 1,2-alkyl shift. Bicycle **7** could then be viewed as the product of a higher oxidation state Robinson-type annulation between hypothetical intermediate **9** and a highly-substituted cyclopentanone-derived enolate. At the outset of our studies, we recognized that the merger of these two disconnections could serve as a powerful strategy to access complex bicyclo[3.3.1]nonane architectures (see **6**) from readily accessible substituted cyclopentanones. Importantly, we believed that a concerted 1,2-shift could smoothly transfer the stereochemical information of structurally diverse cyclopentanone building blocks, and in analogy to the biosynthesis, would enable highly modular syntheses of conserved structural types. Key to the success of this proposal though would be the identification of an annulation reagent capable of mimicking the reactivity of hypothetical intermediate **9** and its subsequent inclusion into a diastereoselective synthesis of **7**.

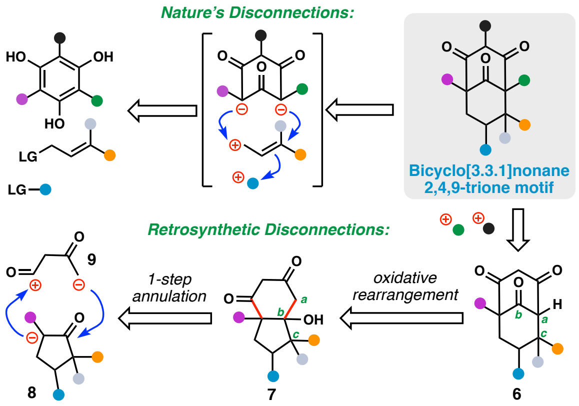
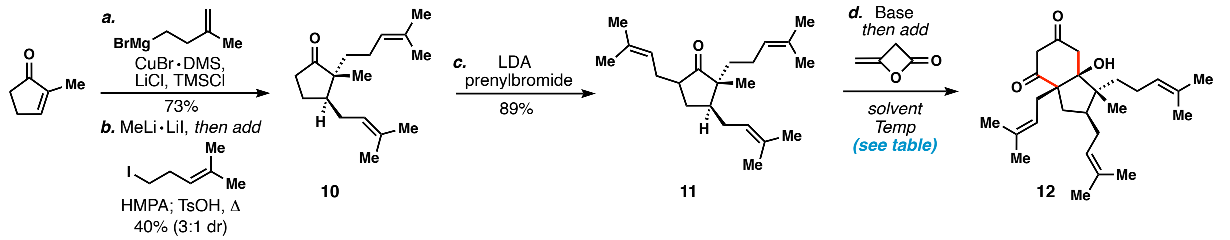


Figure 3. A comparison of Nature's modular blueprint for PPAP construction and our abiotic synthetic approach. LG = leaving group

We began our investigation by preparing highly-substituted cyclopentanone **11** in three steps from methylcyclopentenone (Figure 4).[1] Copper-mediated conjugate addition of (3-methylbut-3-en-1-yl) magnesium bromide followed by lithium enolate generation and enolate alkylation with homoprenyl iodide furnished **10** after acid-catalyzed isomerization of the exocyclic olefin using *p*-toluenesulfonic acid. Formally, this sequence accomplished linear-selective prenyl conjugate addition to a cyclopentenone. A second alkylation (LDA, prenylbromide) then converted **10** into tetrasubstituted cyclopentanone **11** allowing for the examination of the key annulation reaction. While a variety of 4-carbon annulation reagents were examined to replicate the reactivity of hypothetical intermediate **9** (see Figure 3), only the reactive β-lactone diketene furnished any annulation product (see inset, Figure 4).[17] Using LDA as base, an 11% yield of diketone **12** was attained along with *C*-acylated product **13** (3%) and *O*-acylated product **14** (30%); similar results were also attained with Lithium bis(trimethylsilyl)amide (LHMDS) as base (entries 1 & 2). Given the ability of diketene to react with diisopropylamine, *tert*-butyllithium (*t*-BuLi) and lithium tetramethylpiperidine (LTMP) were examined as bases and both improved the amount of annulated product formed (entries 3 & 4). In an effort to reduce the *O*-acylation product, studies were conducted using ethereal solvents of varying polarity (entries 5-7), and ultimately identified THF/Et_2O mixtures as optimal for this substrate. After further temperature optimization, we were able to produce **12** in 35% isolated yield (45% BRSM) and as a single diastereomer (entry 8).



Entry	Base	Solvent	Temp (°C)	**12** (%)^a	**13** (%)^a	**14** (%)^a	**11** (%)^a
1	LDA	THF	–78 → 0	11	3	17	30
2	LHMDS	THF	–78 → 0	9	2	5	23
3	*t*-BuLi	THF	–78 → 0	17	11	24	42
4	LTMP	THF	–78 → 0	21	6	8	24
5	LTMP	Et_2O	–78 → 0	9	9	0	25
6	LTMP	THF/CPME	–78 → 0	15	10	14	19
7	LTMP	THF/*i*-Pr_2O	–78 → 0	19	17	11	20
8	LTMP	THF/Et_2O	–40	35^b	6	14	22^b

^{a} yields determined by ^1H NMR. ^{b} isolated yields

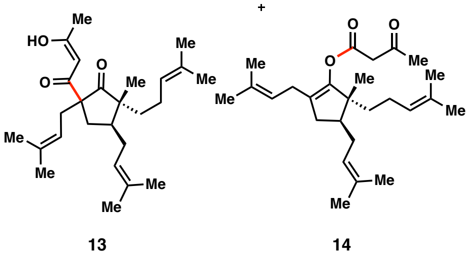


Figure 4. A lithium enolate annulation with diketene: Discovery and optimization.

To date, we have prepared over 20 previously unknown 1,3-cyclohexanediones using this annulation reaction (Figure 5).[1-3] 5,6-Fused bicycles similar to **12**, but with differing substituents and stereochemistry could be prepared (see **15-18**). A notable strength of this methodology is its ability to forge motifs with highly sterically congested C–C bond linkages as typified by adducts **19-21**. An array of aryl-containing adducts derived from substituted propiophenone derivatives (see **22-30**) could also be prepared in good yields as could both 7,6- and 6,6-fused ring systems (see **31** and **32**). Finally, enone-containing natural products such as carvone and nootkatone could be annulated generating adducts **33** and **34**, respectively. It is worth noting that many of these hydroxylated 1,3-cyclohexanedione products are only a simple water loss removed from aromatization to diphenols thus highlighting the mild nature of the annulation process.

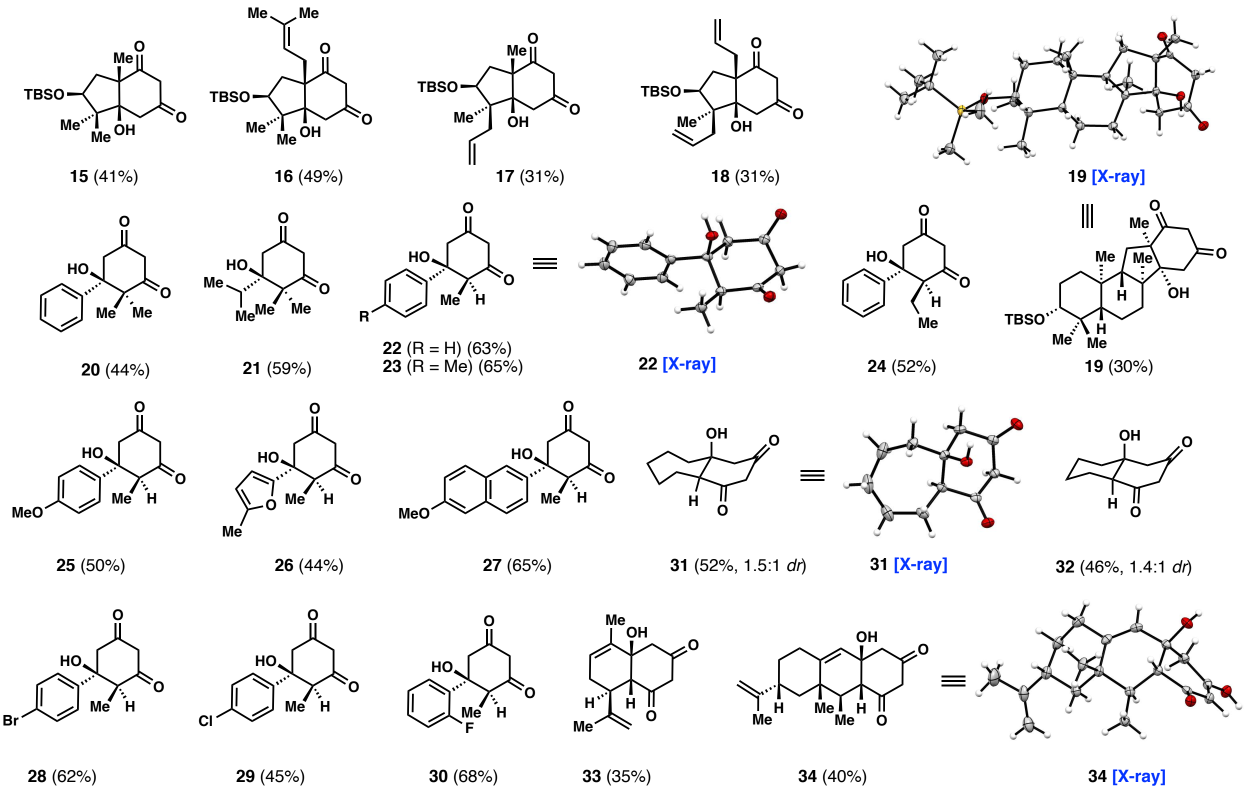


Figure 5. Hydroxylated 1,3-cyclohexanediones successfully prepared by a diketene–enolate annulation.

TOTAL SYNTHESIS OF HYPERFORIN

With a significant hurdle crossed in our blueprint toward PPAPs, we targeted the flagship PPAP hyperforin (**1**) for chemical synthesis (Scheme 1). Isolated in 1975 by Bystrov and co-workers,[18] hyperforin possesses marked anticancer, antibiotic, antidepressant, and procognitive effects among others;[19] moreover, as an active constituent of St. John's wort, it has seen centuries of documented human use. To date, the synthetic challenges of **1** have been met by the groups of

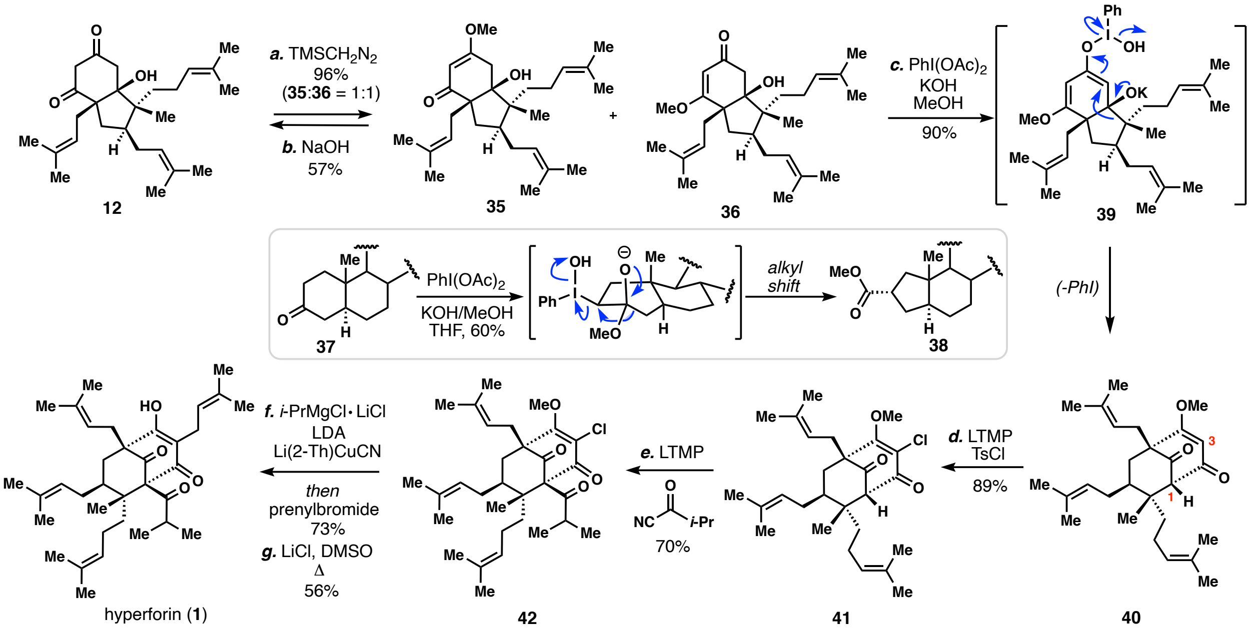
Shibasaki,[20] Shair,[21] Nakada,[22] Barriault,[23] as well as our own lab;[1,14] in each case, distinct tactics were employed to generate the key bicyclo[3.3.1]nonane substructure.[14]

Annulated bicycle **12** could be methylated with trimethylsilyldiazomethane generating vinylogous ester isomers **35** and **36** in near quantitative yield, but with no regioselectivity. Notably, canonical basic methylation conditions (Me_2SO_4, K_2CO_3, acetone) or acid methanolysis (MeOH, $HC(OMe)_3$, TsOH) both favored isomer **35** which unfortunately failed in later chemistry (*vide infra*). As a small consolation, **35** could be hydrolyzed back to **12** for enhanced material throughput. With **36** in hand, we evaluated the second step in our synthetic plan, namely the oxidative rearrangement of the 5,6-fused bicycle to the bicylo[3.3.1]nonane ring system. Inspired by oxidative rearrangements of cholestanone derivatives (see **37→ 38**), wherein a mechanistically related C–C bond shift presumably occurs,[24] we found that under similar conditions ($PhI(OAc)_2$, MeOH/KOH) compound **36** very cleanly isomerizes to **40**, possibly via intermediate **39**.[25]

With compound **40** prepared, only the functionalization of C-1 and C-3 was required to complete the total synthesis of **1**. The C-3 position could be deprotonated with LTMP, allowing for a subsequent chlorination to take place upon exposure to toluenesulfonyl chloride. With C-3 blocked, a critical bridgehead (C-1) deprotonation and functionalization occurred cleanly according to Shair's protocol (LTMP, then isobutyryl cyanide),[21] generating **42** in 70% yield. Finally, treating **42** with excess *i*-PrMgCl•LiCl and LDA regenerated the C-3 anion which could be converted into the corresponding cuprate (lithium 2-thienylcyanocuprate) and alkylated with prenylbromide. Finally, demethylation (LiCl, DMSO, Δ) afforded hyperforin in seven steps from annulation product **12**.

The described route to **1**, albeit racemic, significantly reduced the number of steps needed to access this prized PPAP. Moreover, all of the substituents surrounding the bicyclo[3.3.1]nonane core were installed using simple anionic chemistry, a feature we viewed as ideal for accessing analogs and other PPAP members in a highly modular fashion. Importantly, this study laid the groundwork for exploring the diketene annulation/rearrangement strategy for other bioactive meroterpenes.

Scheme 1. Total synthesis of hyperforin from diketene annulation product **12**.



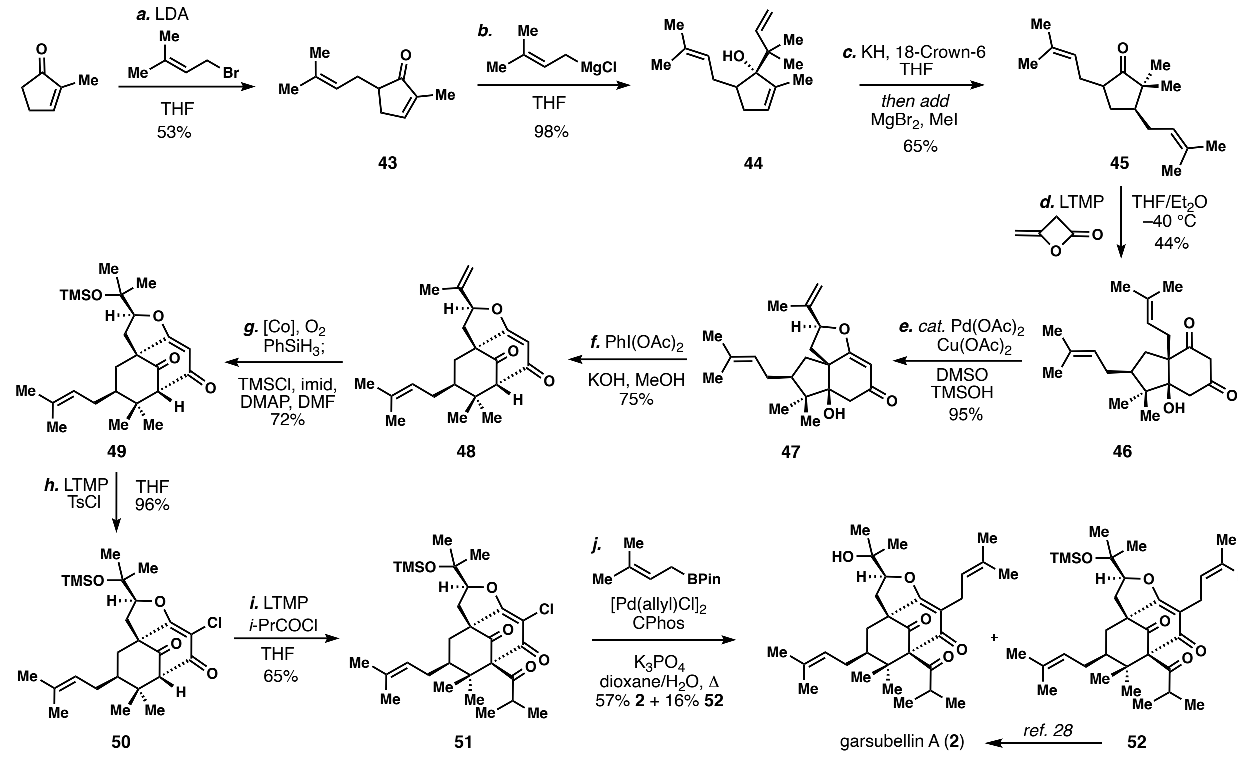
TOTAL SYNTHESIS OF GARSUBELLIN A

With a route to hyperforin developed, we turned our attention to the total synthesis of garsubellin A (**2**) which does not possess the challenging adjacent all-carbon quaternary stereocenters present in **1**, but instead presents a complex cyclic ether motif as a result of chemo- and stereoselective oxidation of a prenyl side-chain (Scheme 2). Fukuyama and co-workers, who isolated **2** from the wood of *Garcinia subelliptica*, found that this small molecule increased choline acetyltransferase (ChAT) levels in P10 rat septal neurons 154% relative to control suggesting, like with other PPAPs, possible applications in the treatment of neurodegenerative diseases.[26]

Garsubellin A has attracted substantial synthetic interest worldwide, with the groups of Shibasaki,[27] Danishefsky,[28] Nakada,[29] and our own group reporting full solutions to this intriguing problem in PPAP synthesis.[2]

We began our investigations toward **2** by preparing diprenylated cyclopentanone building block **45**, but modified our initial route to allow for the use of intact dimethylallyl-containing building blocks (Scheme 2). Thus, the kinetic enolate of methylcyclopentenone was alkylated with prenylbromide to generate **43** and this material converted to allylic alcohol **44** by the addition of prenylmagnesium chloride. Finally, the reverse prenyl group underwent anionic oxy-Cope rearrangement to generate an enolate, which after addition of $MgBr_2$, could be alkylated with methyl iodide.

Scheme 2. Short total synthesis of garsubellin A (**2**).



The crucial diketene annulation of **45** proceeded to generate **46** in analogy to the hyperforin series, but with slightly higher isolated yield. With the rigid 5,6-fused bicycle in hand we turned toward construction of the key tetrahydrofuran unit of garsubellin A cognizant that cyclic ether motifs found in the PPAPs have at times proven challenging to access by prenyl side chain epoxidation and acid-promoted cyclization. After significant experimentation we found that catalytic quantities of palladium acetate in the presence of a stoichiometric copper (II) acetate led to the formation of tricycle **47** as a single diastereomer in very high yield (95%), presumably via an unusual Wacker-type cyclization of a vinylogous acid. Additionally, from a strategic perspective, installation of the THF ring at this stage allowed us to avoid the unselective vinylogous acid methylation that plagued the synthesis of hyperforin (see **12** → **35** + **36**, Scheme 1).

With a five-step route to tricycle **47**, we were positioned to evaluate our key I(III)-mediated oxidative ring expansion. Despite the presence of the additional rigidifying ether ring, treatment of this substrate with (diacetoxyiodo)benzene under basic conditions again smoothly forged the PPAP bicyclo[3.3.1]nonane skeleton in good yield (75% of **48**). Next, a cobalt-catalyzed Mukaiyama hydration of **48** chemoselectively furnished the tertiary alcohol motif, which conveniently could be silylated in the same pot with trimethylsilyl chloride. Tricycle **49** could again be taken through a two-step procedure consisting of vinylic deprotonation and chlorination (LTMP, TsCl) to form **50**, and bridgehead acylation (LTMP, *i*-PrCOCl) to generate **51** in analogy to the hyperforin synthesis. Finally, we were able to elicit linear-selective prenylation of the vinyl chloride under Pd-catalysis,[30] a process which could be telescoped with desilylation to arrive at garsubellin A (**2**) in 10 steps from commercially available methylcyclopentenone along with a small amount of **52** which can also be converted into **2**.[28] This short route to **2**, highlights how simply switching the cyclopentanone input into our annulation/rearrangement-based synthetic platform produces a different PPAP member with similar yields and efficiency.

DMOA-DERIVED MEROTERPENES

Members of the fungal kingdom are proficient at assembling highly complex meroterpene natural products with numerous biological activities.[31] Specifically, over one hundred ornate and structurally distinct natural products can be assembled via the union of the polyketide-derived fragment 3,5-dimethylorsellinic acid (DMOA) with the C-15 isoprenoid farnesyl pyrophosphate (FPP) (see **54**-**60**, Figure 6).[32] In analogy to the biosynthesis of PPAPs, dearomative coupling between these two building blocks generates intermediate **53**, and a subsequent polyene cyclization forges complex bicyclo[3.3.1]nonane architectures typified by berkeleyone A (**54**), preaustinoid A (**55**), and berkeleytrione (**56**). Further rearrangement and oxidation of this core then leads to the scaffolds found in **57-60** thus highlighting the significance of the bicyclo[3.3.1]nonane architecture as a potential gateway into multiple DMOA-derived meroterpene skeletal types. Given our success in synthesizing the PPAPs hyperforin and garsubellin A, we wondered if our general annulation/rearrangement strategy could be exploited in these even more complex and demanding molecular settings.

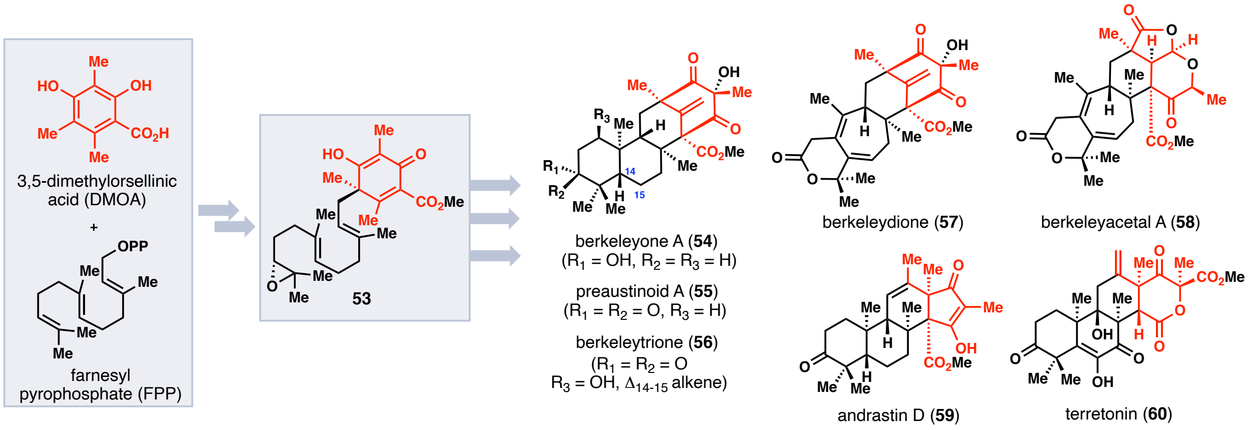
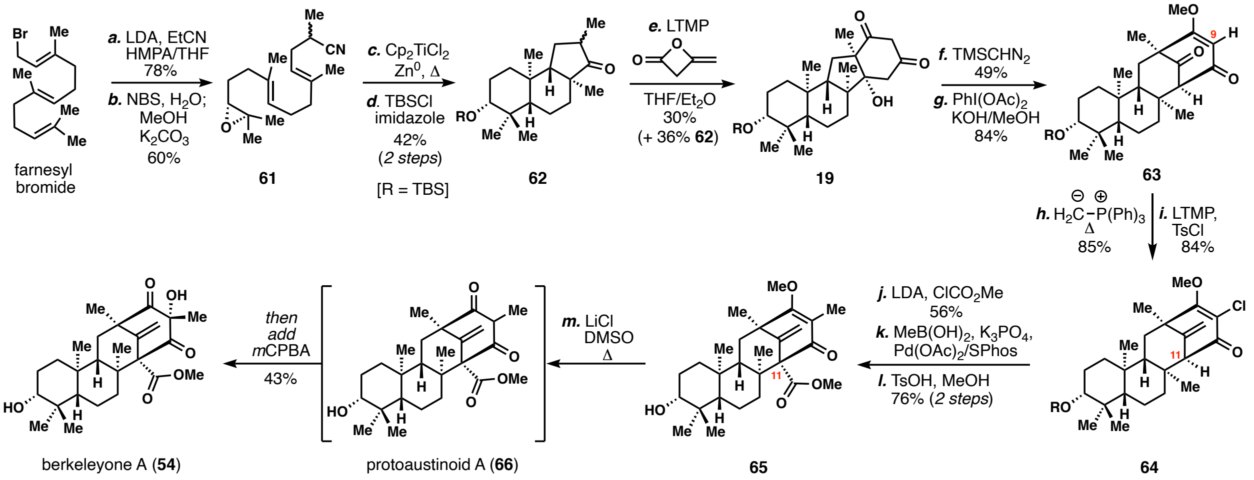


Figure 6. Selected meroterpene families biosynthesized from 3,5-dimethylorsellinic acid (DMOA) and farnesyl pyrophosphate (FPP).

TOTAL SYNTHESIS OF BERKELEYONE A

Berkeleyone A (**54**), an anti-inflammatory meroterpene isolated from *Penicillium rubrum* found growing in the toxic Berkeley Pit, a former copper mine turned waste lake of pH ~ 2.5, was chosen as our initial DMOA-derived target.[33] To date, only our lab and the Newhouse group have reported total syntheses of this meroterpene natural product;[3,34] moreover, despite interest from the enzymatic synthesis communities,[32,35] these works represent the only completed total syntheses of any complex DMOA-derived members.

Scheme 3. Total synthesis of berkeleyone A (**54**).



Farnesyl bromide was first reacted with the anion of propionitrile and this alkylation product was converted to epoxide **61** via one-pot bromohydrin formation/cyclization sequence (Scheme 3). While nature employs a cationic polyene cyclization in the formation of berkeleyone A, we elected to employ a reductive, epoxide-opening radical cyclization to construct the *trans*-fused decalin core of **54**.[36] Under slightly modified conditions reported by Fernández-Mateos (Cp_2TiCl_2, Zn^0, Δ),[37] **61** cyclized to tricyclic ketone **62** in 42% isolated yield after silylation of the secondary alcohol.

With gram-scale access to **62**, the key diketene annulation was evaluated and found to produce 1,3-diketone **19** in 30% isolated yield (36% of recovered **62** was also isolated). Notably, this bond-forming step constructs a hindered tetracyclic compound possessing four methyl groups in nearly axial orientations. Next we proceeded to evaluate the second pivotal transformation in the synthetic pathway–conversion of the 5,6-fused ring system into the bicyclo[3.3.1]nonane skeleton. Following high-yielding, but unselective *O*-methylation of the 1,3-diketone with trimethylsilyldiazomethane, our previously developed I(III)-mediated oxidative ring expansion ($PhI(OAc)_2$, KOH/MeOH) performed well in this non-PPAP setting, affording **63** in 84% isolated yield.[1,2] A high-yielding Wittig olefination of the hindered ketone followed by chlorination of the C-9 position (LTMP then TsCl) led to polycycle **64** in excellent yield.

We envisioned that deprotonation of the bridgehead position (C-11) of **64** and reaction with methylchloroformate could forge the final, challenging all-carbon quaternary stereocenter of the target, but in contrast to the bicyclo[3.3.1]nonane trione system found in the PPAPs, the C-11 proton in **64** is much less acidic as a result of one, not two, neighboring carbonyl groups. To our delight however, deprotonation of this material with LDA, followed by quenching with methylchloroformate led to the desired functionalization in 56% isolated yield. Akin to our synthesis of garsubellin, the vinyl chloride participated in an efficient Suzuki coupling ($MeB(OH)_2$, $Pd(OAc)_2$/SPhos) to install the final requisite alkyl group in excellent yield. Acidic cleavage of the *tert*-butyldimethylsilyl ether then afforded **65** in 76% yield (two steps). Chloride-mediated demethylation (LiCl, DMSO, Δ) of **65** proceeded smoothly to generate the previously isolated DMOA-derived metabolite protoaustinoid A (**66**), a biosynthetic precursor to berkeleyone A. Gratifyingly, we were able to telescope the demethylation reaction with a diastereoselective hydroxylation of the 1,3-dicarbonyl motif using *meta*-chloroperbenzoic acid. Under such conditions, berkeleyone A (**54**) was isolated in 43% yield thus completing a thirteen-step route to this significant DMOA-derived metabolite.

Our total synthesis of **54** provided the first laboratory route to a complex DMOA-derived meroterpene and validated the diketene annulation/rearrangement platform outside of the PPAP space. Additionally, this chemistry proved scalable, and allowed for gram quantities of bicyclo[3.3.1]nonane-containing polycycles to be prepared for further biomimetic investigations.

TOTAL SYNTHESES OF ANDRASTIN D AND TERRETONIN L

With a synthetic pathway to protoaustinoid A and berkeleyone A secured, we had the unique opportunity to study the biosynthetic relationships between various DMOA-derived meroterpene skeletons. In particular, we were keen to explore the interconversion of the bicyclo[3.3.1]nonane skeletons of these compounds into the 6,5-fused rings systems found in the andrastins (see **69**) and preterretonins (see **70**) (Figure 7). The protoaustinoid A carbocation (**67**), an intermediate generated by the cyclase-mediated polyene cyclization of **53** is believed to be involved in the biosynthesis of the majority of members. Importantly, **67** can undergo a 1,2-acyl shift to generate alternative carbocation **68**.[32] Selective loss of a proton from **67** or **68** then leads to **66**, **69**, or **70**. While these processes are controlled by various cyclases in fungi,[38] DFT calculations hinted to the feasibility of replicating the **67**→**68** rearrangement in the laboratory.[4]

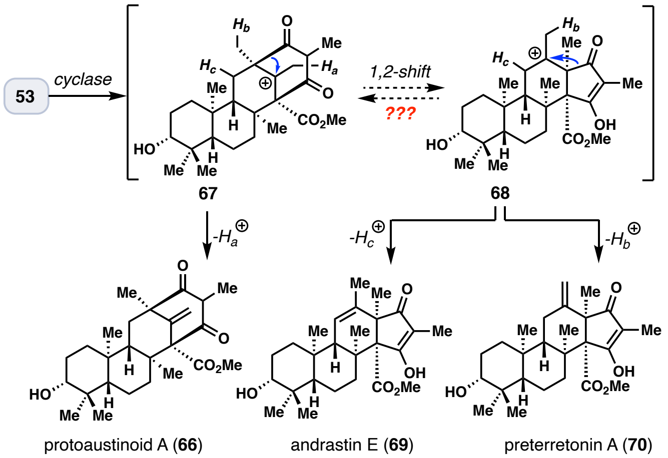
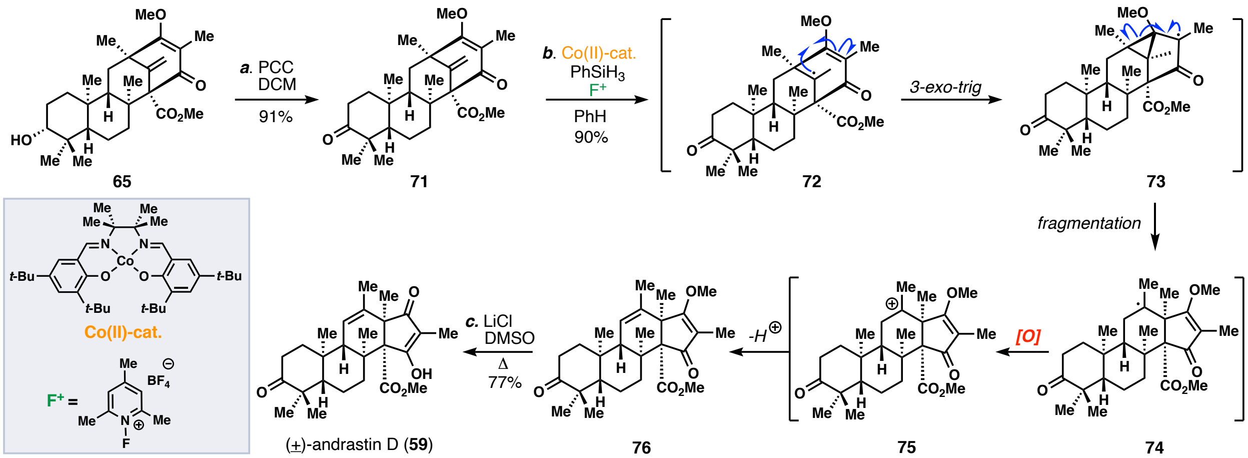


Figure 7. Biosynthetic connection between bicyclo[3.3.1]nonane-containing DMOA-derived meroterpenes and those featuring a 6,5-fused bicyclic motif.

Previously prepared polycycle **65** was oxidized to ketone **71**, affording a robust substrate from which to commence skeletal rearrangement studies (Scheme 4). Despite surveying a number of acidic conditions, which could conceivably generate the key carbocation found in **67**, we were never able to isomerize **71** to the andrastin ring system via classical alkene protonation methods. Seeking alternative methods for carbocation generation, we were drawn to Shigehisa's exceedingly mild, Co-catalyzed hydroalkoxylation reaction via an oxidative variant of the classic Mukaiyama radical hydration/hydroperoxidation.[39] Subjecting **71** to modified Shigehisa conditions (*cat.* Co(II), $PhSiH_3$, *N*-fluoropyridinium salt (F^+) oxidant) yet omitting the alcohol trapping agent cleanly promoted the desired rearrangement in a remarkable 90% isolated yield. We suspect that the initially formed radical in this process (**72**) likely reacts in a 3-*exo*-trig cyclization with the neighboring alkene owing to its very close proximity thus producing cyclopropane-containing radical **73** which fragments to **74** completing a homoallylic rearrangement process.[40] Oxidation of **74** to **75** followed by proton loss then forms the andrastin skeleton; a final, lithium chloride-mediated demethylation then completes a total synthesis of andrastin D (**59**), the first andrastin meroterpene to be prepared synthetically.[41]

While this approach offers selective entry into the andrastin family, it presents clear challenges for the synthesis of terretonin-type metabolites (see **60** Figure 6, **78-80** Scheme 5) which possess an *exocyclic* 1,1-disubstituted alkene rather than the thermodynamically more stable trisubstituted olefin isomer. Recognizing that loss of a proton and loss of a hydrogen atom (i.e. HAT process) can lead to distinct alkene isomers,[42] we wondered if a purely radical-based homoallyl-type rearrangement/HAT process could be leveraged to solve this problem.

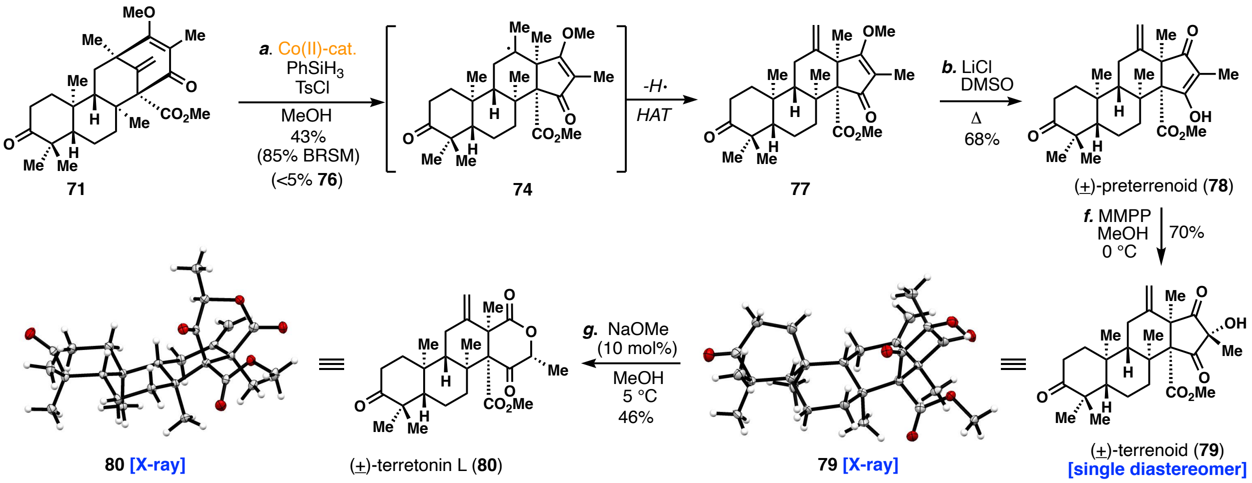
Scheme 4. Total synthesis of andrastin D (**59**) via an abiotic radical rearrangement.



Subjecting tetracycle **71** to modified alkene hydrochlorination conditions reported by Carreira (*cat.* Co(II), $PhSiH_3$, TsCl) lead to the formation of **77** in 43% yield (85% BRSM) and with minimal formation of isomer **76** (Scheme 5).[43] We suspect that steric congestion surrounding radical **74** precludes efficient trapping with TsCl and that a final hydrogen atom transfer (HAT) from the less-hindered methyl position ensues instead, forming **77**. With a route to the exocyclic olefin in place, we demethylated **77** (LiCl, DMSO, Δ) generating the natural product preterrenoid (**78**) and setting the stage for exploration of the late-stage oxidative chemistry of this scaffold. Stereoselective α-oxidation of the 1,3-diketone group with magnesium monoperoxyphthalate (MMPP) afforded terrenoid (**79**) as a single diastereomer in analogy to the oxidation of protoaustinoid A to berkeleyone A (*vide supra*); the stereochemistry of the hydroxylation was confirmed by single crystal X-ray crystallography. With **79** secured we proceeded to evaluate the key biomimetic ring expansion linking the andrastin-type 1,3-cyclopentanedione motif and the distinct 6-membered ketolactone found in terretonin metabolites.[44] Under carefully optimized conditions, we found that treatment of cold, methanolic solutions of **79** with catalytic quantities of NaOMe afforded terretonin L (**80**) in reasonable yield (46%) presumably via a retro-Claisen/esterification cascade. Notably, a single diastereomer – confirmed by X-ray analysis – was obtained, likely due to a preference for the newly-formed methyl stereocenter to occupy a pseudoequatorial position away from the *β*-face of the polycyclic ring system.

Our work in the andrastin and terretonin area importantly showed that simple chemical reagents could "revert" the berkeleyone scaffold to other DMOA-derived meroterpene frameworks without the need to exactly generate the same presumed biosynthetic intermediate. Key to the success of these interconversions, was the use of abiotic radical-based chemistry which provided distinct, but similarly efficient solutions to nature's carbocation-based chemistry.[42,45]

Scheme 5. Divergent synthetic entry into the terretonin meroterpenes.



CONCLUSION

In this account we provide insight into both reaction design and discovery for annulative methodology employing diketene as well as the incorporation of this transformation into broader synthetic strategies for bicyclo[3.3.1]nonane-containing natural products. The chemistry developed herein largely reduces the complexity of complex bicyclo[3.3.1]nonanes to that of highly substituted cyclopentanones, motifs with numerous synthetic preparation options that continue to grow.[46] In the case of PPAPs, simple anionic chemistry (i.e. cuprate conjugate addition, Grignard 1,2-addition, and enolate α-alkylation) provided the requisite annulation precursors; alternatively, a straightforward radical polyene cyclization was employed for DMOA-derived meroterpenes. For PPAP synthesis in particular, we estimate that only a small panel of cyclopentanones are needed to access a large percentage of family members;[2] moreover, this strategy easily renders itself amenable to flexibly incorporating side chains not found in natural PPAPs.

While our own contributions are modest, annulation reactions continue to advance the science of complex molecule synthesis, and a survey of modern-day total syntheses finds such processes alive and well (Figure 8). Morken's double allylation in the asymmetric synthesis of pumilaside aglycon,[47] Carreira's cyclohexyne-based annulation *en route* to guanacastepenes,[48] Pronin's forskolin synthesis leveraging a radical/polar cross-over annulation,[49] and Dong's enantioselective annulation by C–C bond activation to access the alkaloid cycloclavine all beautifully leverage annulative processes as key steps.[50] Many of these tandem processes have been made possible through advances in asymmetric synthesis, contemporary radical chemistry, and methods for inert bond functionalization – all cutting-edge synthetic areas with annulative potential.[7,9,11,13,51] We fully suspect this trend of advancement to continue, heralding powerful new annulations and ultimately improved synthetic pathways to complex polycyclic natural products.

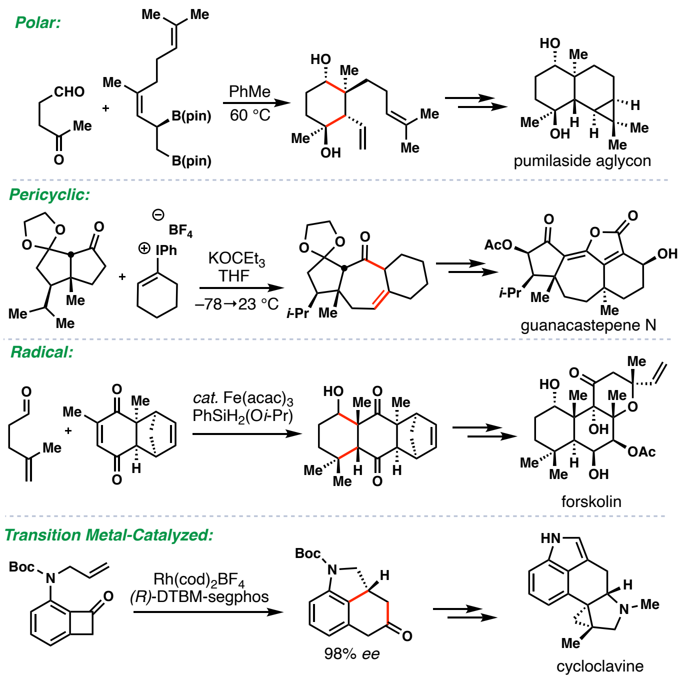


Figure 8. Annulative C–C bond construction in contemporary total syntheses.

AUTHOR INFORMATION

Corresponding Author

*maimone@berkeley.edu

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Acknowledgements

We are grateful to all past and present Maimone laboratory members for their contributions to these and other projects. We are appreciative to the NSF for funding our meroterpene synthetic program (CAREER Award #1554544 to T. J. M.) as well as for providing pre-doctoral fellowships to D.Q.T. and C. P. T. (DGE-1106400). Bristol Myers Squibb is also acknowledged for providing graduate fellowship support to D.Q.T. and C.P.T.

Notes

The authors declare no competing financial interest.

Biographies

Xingyu (Linus) Shen received his B.S. in chemistry from Purdue University in 2016 wherein he conducted research under the guidance of Prof. Mingji Dai. In the same year, he joined the Maimone lab for his graduate studies which have focused on the total synthesis of a variety of complex terpene and meroterpenes.

Danny Thach received his B.S. in chemistry from The University of Texas at Austin in 2016, wherein he conducted research in the lab of Prof. Guangbin Dong. In 2016, he began his graduate studies in the Maimone lab working on the total synthesis of various terpenoid natural products.

Chi Ting received a B.S. degree in Chemistry at the University of Illinois at Urbana-Champaign, where he worked under the direction of Prof. Steven Zimmerman. From 2012-2017 he was a member of the Maimone group, working on the synthesis of complex meroterpenes. From 2017-2020, he was an NIH post-doctoral fellow in the lab of Wilfred van der Donk. In 2020, Chi began his independent career as an assistant professor at Brandeis University.

Tom Maimone received a B.S. degree in chemistry from UC-Berkeley in 2004 where he conducted Prof. Dirk Trauner. From 2005-2009 he was a member of Prof. Phil Baran's research group at Scripps, and from 2009-2012, an NIH postdoctoral fellow in Prof. Steve Buchwald's lab at MIT. In 2012, he began his independent career at UC-Berkeley where he is currently an associate professor engaged in the study of natural products chemistry and biology.

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