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Total Synthesis of Complex Terpenoids Employing Radical Cascade Processes

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Abstract

Radical cyclizations have a rich history in organic chemistry and have been particularly generous to the field of natural product synthesis. Owing to their ability to operate in highly congested molecular quarters, and with significant functional group compatibility, these transformations have enabled the synthesis of numerous polycyclic terpenoid natural products over the past several decades. Moreover, when programmed accordingly into a synthetic plan, radical cascade processes can be used to rapidly assemble molecular complexity, much in the same way nature rapidly constructs terpene frameworks through cationic cyclization pathways. This review highlights recent total syntheses of complex terpenoids (from 2011–2017) employing C–C bond-forming radical cascade sequences.

Introduction

Although once overlooked synthetically–or more likely feared–organic reactions proceeding via radical intermediates are now embraced and incorporated into nearly every facet of modern organic synthesis.[1–4] While the evolution from physical organic chemistry peculiarity to synthetic method required decades, by the 1980s the radical's time had come for inclusion into the ultimate synthetic methodology testing ground–natural product synthesis.[5] Accordingly, the last three decades have witnessed a profusion of total syntheses employing radical cyclization reactions. Owing to complex and stereochemically-rich polycyclic ring systems, terpene natural products in particular have proven to be ideal candidates for radical cyclization reactions. Figure 1A highlights an assortment of architecturally diverse terpene natural products that have employed radical cyclizations as key steps over the past thirty years.[6–19] Many of these natural products are some of the most synthetically challenging terpenoids ever assembled by synthetic chemists and in many cases, one could argue that radical chemistry *enabled* their chemical syntheses. In many instances, this was due to the ability of radicals to form highly congested C–C bonds with functional group tolerance toward polar functionality–conditions which cationic, anionic, and many metal-mediated methodologies often struggle with.

In addition to their potential in forming recalcitrant carbon-carbon bonds, one of the true powers of radicals lies in their ability to take part in cascade processes wherein multiple bonds are formed or broken.[20–23] Embodied by Curran's classic 1985 synthesis of hirsutene,

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[24] radical cascade sequences have featured prominently in terpene syntheses and notable examples are shown (Figure 1B).[24–31] Although not reviewed explicitly herein, modes of radical cyclization are diverse[1–5,32,33] and often complementary to nature's cyclase-mediated cationic processes.[34] Nevertheless, analogies exist between stages of abiotic radical cyclizations of polyprenyl-derived chains and those of terpene biosynthesis. Salient comparisons are shown in Figure 2 and an excellent 2011 review by Gansäuer and Cuerva discusses this topic in detail.[35] Nature's enzymes frequently initiate cationic cyclizations by protonation of an epoxide or alkene (see **1** and **2**) or by ionization of a pyrophosphate leaving group (see **3**). These processes can be mimicked by transition metal-mediated homolytic epoxide opening (see **4**), addition of an existing radical to an alkene (see **5**), or homolytic cleavage (C-X scission) to generate an allylic radical (see **6**). Breslow's early report on the benzoylative radical cyclization of geranyl acetate (**7**) to polycycle **8** serves as a historic example illustrating these aspects of radical terpene biomimicry (Figure 2B).[36]

In a second process, cyclase enzymes often promote the rearrangement of initially formed carbocyclic rings through series of hydride and alkyl migrations (see **9**→**10**).[34] While these processes do not have an exact radical equivalent, homoallylic rearrangements serve to formally migrate vinyl units in a 1,2-fashion (see **11**→**12**). A recent example in terpene synthesis comes from Nicolaou's synthesis of platencin wherein xanthate **13** was converted into [2.2.2] bicycle **14**, via the intermediacy of cyclopropane-containing radical **15** (Figure 2B);[37] an additional example can be found in the syntheses of andrastin D and terretonin L (Section 3.8).

Finally, cyclase-mediated cationic cascades often terminate with regiospecific proton loss (see **16**→**17–19**), a process which is often difficult to emulate in biomimetic synthesis wherein thermodynamic product ratios are often observed (i.e. **18** and **19** are formed in preference to **17**). Radical cyclization involving transitions metals, however, can terminate via a hydrogen atom transfer (HAT) process from less hindered methyl groups, thus affording 1,1-disubstituted alkene products (see **20**→**17**).[35,36,38] Breslow's conversion of **7** to **8** also highlights this process.

While biomimicry can often lead to expedient total syntheses,[39–40] radical transformations also open up a wealth of C–C bond disconnections nature does not have in its arsenal–as far as we are aware–and effort has been made to highlight such processes. The syntheses discussed have been selected from the period of 2011-present, a time range complementary to Gansäuer and Cuerva's insightful report.[35] In order to expand the breadth of chemistry discussed, we have also chosen to highlight select total syntheses of meroterpenes (polyketide/terpene hybrids) as well as terpene-derived alkaloids.

2. Ketyl Radical Initiated Cascade Processes

While not utilized by nature in terpene biosynthesis, ketyl radicals, typically formed via single-electron reduction of carbonyl groups, have proven to be highly valuable reactive intermediates in initiating radical cascades in natural product synthesis.[41–43] Moreover, since secondary and tertiary alcohols are directly produced during these transformations, such reactions have been particularly useful to the synthesis of hydroxylated terpene natural

products. Three representative syntheses employing ketyl radical cascades are discussed below.

2.1. Procter's synthesis of (+)-pleuromutilin (2013)

In 1951, Kavanagh and co-workers isolated the potent antibacterial fungal secondary metabolite (+)-pleuromutilin (**21**) from *Pleurotus mutilus* (Scheme 1).[44,45] Over a time-span of decades, analogues of this unique ribosome-targeting antibiotic entered the clinic, ultimately leading to marketed products for the treatment of veterinary diseases (Denegard® and Econor®) and more recently human skin infections (Altabax®). Two racemic total syntheses of **21** have been reported, the first by Gibbons in 1982,[46] and another by Boeckman in 1989.[47] Asymmetric routes to pleuromutilin have been slower to transpire, the first being Procter's 2013 synthesis,[48] and very recently, Herzon's 2017 report.[49,50] In addition, a number of approaches to the nucleus of **21** have been documented.[51–54] Herein we discuss Procter's 2013 synthesis which utilized an impressive SmI_2-mediated radical cascade to construct two of the three rings found in the target in a single step (Scheme 1).

Procter's synthesis commenced with known, two-step conversion of dihydrocarvone to (*R*)-*α*-methyl cyclohexenone (**22**).[55] Enone **22** underwent copper-mediated conjugate addition of Grignard reagent **23**, and following Saegusa-Ito oxidation, enone **24** was obtained in excellent yield. A second conjugate addition (CuI, **25**) followed by enolate trapping with Comin's reagent (**26**) produced a vinyl triflate that underwent Pd-catalyzed methoxycarbonylation ($Pd(OAc)_2$, PPh_3, CO, MeOH) to afford unsaturated methyl ester **27**. Subsequent Lewis acid-mediated allylation of this material with aldehyde **28** afforded **29**, and after a protection/deprotection/oxidation sequence, key cyclization precursor **30** was obtained.

Procter's key radical cascade sequence was initiated by treating dialdehyde **30** with 2.5 equivalents of SmI_2 in THF/*t*-BuOH. It was proposed that ketyl radical formation begins at C3 and that this species adds, in a conjugate sense, to the neighbouring unsaturated ester, possibly via the samarium chelate shown (see **30**→**31**→**32**, Figure 3). The resulting radical is then presumably reduced with another equivalent of SmI_2 to form samarium enolate **32**. Coordination of the samarium (III) center to the proximal aldehyde (see **33**) enforces a diastereoselective aldol cyclization furnishing **34** (C-5/C-15 bond formation), and ultimately **35**, after protonation. In addition to facile construction of a challenging 8-membered carbocycle in high yield (88%),[56] four new stereogenic centers were generated during this powerful cascade.

With the core structure of **21** in hand in only eleven steps, the remainder of the synthesis involved adding the final three carbon units as well as adjusting various oxidation states. Diol **35** was first silylated (TBSOTf, Et_3N), and then treated with $LiAlH_4$ to remove the pivalate protecting group (Scheme 1). A subsequent Dess-Martin periodinane oxidation and palladium-catalyzed hydrogenation afforded ketone **36** in 36% yield over 4 steps. Conversion of the methyl ester moiety to a requisite methyl group was then achieved in a six-step process. First, the ketone was protected as its ethylene glycol ketal (1,2-ethanediol, $HC(OMe)_3$, amberlyst), a process which also removed the C-3 hydroxyl protecting group.

The authors then found that the powerful reductant SmI_2/pyrrolidine/H_2O could reduce the sterically hindered methyl ester to a primary hydroxyl group in high yield (95% yield). Diol **37** could be mono *para*-methylbenzoylated at the C-3 hydroxyl position with LDA/*p*-MeBzCl; the small amount of material protected at the primary hydroxyl position (20%) could be recycled by basic hydrolysis (NaOMe, MeOH). The free primary alcohol was then converted to its corresponding thiocarbamate (1,1-thiocarbonyldiimidazole (TCDI), Δ) thus allowing for a subsequent Barton-McCombie deoxygenation (*n*-Bu_3SnH, AIBN, Δ). After removal of the ketal protecting group, ketone **38** was unveiled in 63% yield over 4 steps from diol **37**. The next task in the synthesis was to install the final secondary hydroxyl group found in **21**. Regioselective silyl enol ether formation (TMSI, HMDS) allowed for a Rubottom-type oxidation, and following protecting group manipulations, ketone **39** was obtained in 55% yield over 5 steps.

The remaining challenge in the synthesis of pleuromutilin was installation of the key all-carbon quaternary center bearing a vinyl and methyl group. (*Z*)-2-Ethoxyvinyl lithium was first added to ketone **39** and the resulting tertiary alcohol was dehydrated ($FeCl_3$•SiO_2) to reveal a conjugate aldehyde intermediate. 1,2-Reduction of this material with sodium borohydride followed by chlorination (NCS, Me_2S) afforded an allylic chloride intermediate. Inspired by Gibbons' and Boeckman's prior work,[46,47] a stereoselective, Cu-mediated S_N2' displacement with dimethyl zinc furnished the hallmark quaternary center as a single diastereomer. From this point, three more steps were needed to arrive at mutilin (**41**), which lacks the critical ester side chain found in **21**. Lithium aluminium hydride removed the *para*-methyl benzoate protecting group, allowing for a Dess-Martin oxidation of the resulting secondary hydroxyl group. Finally, the MOM protecting groups were cleaved with *in situ* generated hydrogen chloride (AcCl, EtOH). With **41** in hand, a two-pot process developed by SmithKline

Beecham researchers was utilized to convert **41** into **21**.[48] While approximately 35 steps were needed to ultimately furnish the full natural product, the Procter synthesis is a striking example of the power of radical cascades in forging synthetically challenging polycycles in rapid, high-yielding fashion. Not surprisingly this cascade has already been employed in the synthesis of diverse carbocyclic analogs of **21**.[57]

2.2. Reisman's synthesis of (−)-maoecrystal Z (2011) and (−)-longikaurin E (2013)

In 2006, Xu and coworkers isolated the diterpene natural product maoecrystal Z (**42**) from the flowering plant *Isodon eriocalyx*.[58] Owing to their longstanding use in traditional Chinese medicine, plants of the *Isodon* genus have been subject to intense natural product isolation efforts.[59] Maoecrystal Z in particular displayed moderate cytotoxicity against several human tumor cell lines (IC_{50} = 1–3 μg/mL). Moreover, the compact and densely functionalized 6,7-*seco*-*ent*-kauranoid skeleton of **42** makes it an attractive target for synthetic chemistry exploration.

In 2011, Reisman and coworkers reported the first total synthesis of **42**,[60] employing a powerful ketyl radical cascade transformation to assemble the 5,6-fused bicyclic ring system (Scheme 2). (−)-γ-cyclogeraniol (**43**) was identified as a key building block *en route* to **42**

and was assembled by a previously described route from ketone **44**.[61] First, treatment of ketone **44** with base (NaH) and dimethylcarbonate (**45**) furnished an intermediate β-ketoester which underwent smooth $SnCl_4$-mediated cyclization generating ester **46**. Methyl Wittig olefination and hydrolysis gave a carboxylic acid product, which could be resolved with chiral amine **47** thus furnishing enantioenriched carboxylate **48**. Esterification (MeI, K_2CO_3) and reduction with lithium aluminum hydride then afforded (−)-γ-cyclogeraniol (**43**). This material was subsequently silylated (TBSCl) and oxidized (*m*-CPBA), resulting in epoxide **49** (91%, 3:1 *dr*) and setting up one of two key radical couplings in the synthesis.

Treatment of epoxide **49** with Cp_2TiCl_2, Zn(0), and 2,4,6-collidine•HCl promoted homolytic epoxide opening forming a tertiary radical intermediate.[62,63] In analogy to RajanBabu's findings,[64] this species then underwent radical conjugate addition to 2,2,2-trifluoroethylacrylate (**50**) subsequently forming lactone **51** in excellent yield (74%) and as a single diastereomer. Notably, electron-deficient acrylate **50** proved to be an optimal radical acceptor for this transformation. Concurrently, iodide **52** was prepared in 4 steps by way of Myers' asymmetric alkylation and then reacted with the lithium enolate of **51**.[65] An α–selenation/oxidation sequence (KHMDS, PhSeBr; then H_2O_2) dehydrogenated the lactone moiety giving **53**, and following removal of TBS groups and DMP oxidation, dialdehyde **54** was obtained, setting the stage for the key radical cascade cyclization.

Reminiscent of Procter's radical cascade (Scheme 1),[48] treatment of **54** with SmI_2/LiBr triggered ketyl radical formation and subsequent addition to the α,β-unsaturated lactone, correctly setting the C-11 stereocenter in the process. Following radical reduction, a stereoselective aldol reaction ensued, also constructing both the C-7 and C-6 centers with the proper configurations. Overall, an impressive 54% yield of a single diastereomer was obtained in this cascade sequence; mono-cyclized products proved to be the major side products identified.

Diol **55** was then globally acetylated (Ac_2O, cat. TMSOTf) and the allyl fragment cleaved *via* ozonolysis. The resulting aldehyde (not shown) was α-methylenated using Eschenmoser's salt (**56**), and following deacetylation of the C-6 hydroxyl group with sodium hydroxide, maeocrystal Z (**42**) was obtained in 38% yield, along with fully deacetylated product (24%) and mono C-11 deacetylated product (24%). Overall, the synthesis of maeocrystal Z required only 18 steps from known ketone **44**. Notably, the Ti(III)-mediated spirolactonization and the ketyl radical cascade transformation swiftly built the carbon network of **42** in highly stereoselective and concise manner.[66]

In 2013, Reisman and coworkers also accomplished the total synthesis of longikaurin E (**57**),[67] a biosynthetically-related kaurane-type natural product (Scheme 2). Utilizing common intermediate **53** as a starting point, selective desilylation of the more accessible TBS ether (*p*-TsOH, *n*-Bu_4NHSO_4, MeOH) followed by DMP oxidation afforded cyclization precursor **58**. When aldehyde **58** was treated with the aformentioned SmI_2/LiBr system, smooth monocyclization ensued (57%) forging tricyclic lactone **59** after hydroxyl group protection. Diverging from their previous work, the authors developed a two-step sequence to construct the hallmark bicyclo[3.2.1]-octane motif characteristic of many *ent*-kaurenoids. The potassium enolate of ester **59** was first silylated (TBSCl) setting up an oxidative

palladium(II)-mediated, *5-exo-trig* cyclization. The combination of one equivalent of $Pd(OAc)_2$ and 0.5 equivalents of acetic acid in DMSO at 45 °C under air was found to be optimal in promoting this challenging transformation; under these conditions alkenylated tetracycle **60** was obtained in 48% yield over two steps. Treating **60** with strong protic acid cleaved both protecting groups and delivered diol **61** in good yield. Selective oxidation of the primary hydroxy group with TEMPO/PIDA and acetylation of secondary alcohol (Ac_2O) arrived at aldehyde **62**, setting the stage for a second essential Sm(II)-mediated reaction. Treating **62** with SmI_2 promoted a pinacol-type coupling furnishing the final ring of the target molecule in 55% yield, and importantly, with the correct stereochemistry at the newly-formed hydroxyl group. With the full *ent*-kaurenoid skeleton in hand, a final ozonolysis and α-methylenation using **64** smoothly produced longikaurin E (**57**) in only 12 steps from common building block **53**.

2.3. Carreira's synthesis of (+)-crotogoudin (2013)

In 2010, crotogoudin (**65**), a cytotoxic 3,4-*seco*-atisane diterpenoid, was isolated by Rasoanaivo and coworkers from the extraction of *Croton barorum* and *Croton goudotii*.[68] This structurally intriguing natural product quickly received attention from the synthetic community, and has already seen elegant total syntheses reported by the groups of Carreira (2013),[69] Liu (2015),[70] and recently Sarpong (2017).[71] Herein we highlight Carreira's 2013 pathway featuring a creative ketyl radical induced fragmentation/cyclization cascade.

The Carreira synthesis commenced with alkylation of the dianion derived from acetoacetate **66** with homoprenyl bromide (**67**), a subsequent Michael addition/aldol condensation with enal **68**, and a final Krapcho decarboxylation to generate cyclic enone **69** in 49% yield over 3 steps. Dissolving metal reduction of this material (Na, NH_3) simultaneously reduced the enone moiety as well as removed the benzyl protecting group giving aldehyde **70** after Swern oxidation. An acid-mediated aldol reaction then efficiently constructed the bicylo[2.2.2]octane core and following treatment with Dess-Martin Periodinane, *meso* dione **71** was generated in 54% yield over 4 steps. Employing a Baker's yeast-catalyzed asymmetric ketone reduction,[72] this material could be efficiently desymmetrized, and the remaining ketone subjected to a $LaCl_3$-promoted nucleophilic addition reaction with Grignard reagent **72**. Reagent approach occurred from the *exo* face in this transformation, resulting in the formation of **73** as both a single enantiomer and diastereomer. From this point, cyclopropane **75** was strategically assembled, via TBS protection of the less hindered secondary alcohol, rhodium-catalyzed cyclopropanation of the isopropenyl employing **74** (4.4:1 *dr*), and lactone formation under mildly basic conditions (aqueous $NaHCO_3$, methanol). Position selective allylic oxidation (SeO_2), aldehyde reduction, and pivaloylation afforded lactone **76** for use in the key radical cascade.

Treating cyclopropane **76** with 2.5 equivalents of SmI_2 in a THF/*N,N*′-dimethylpropyleneurea (DMPU) mixture generated a ketyl radical species via single-electron reduction of the lactone. This process then initiated radical cyclopropane cleavage (presumably generating **77**) and the newly-formed alkyl radical underwent clean *6-exo-trig* radical cyclization onto the pendant alkene chain. The final tertiary radical intermediate (not shown) is assumed to be reduced by additional Sm(II) to anion **78** which triggers elimination

of the pivalate leaving group and formation of tetracycle **79**. Notably this cascade occurred in high yield (80%), displayed good diastereocontrol, and completed construction of the entire carbocyclic skeleton of the natural product.

From polycycle **79**, a Krapcho decarboxylation, hydroxyl group deprotection, and DMP oxidation smoothly produced **80** (89% yield over 3 steps). To complete the total synthesis, the authors first protected the lactone as its silyl ketene acetal (TIPSOTf, Et_3N) thus allowing for three-step α-methylenation of the cyclic ketone which was found to be less reactive than the lactone otherwise. Ultimately crotogoudin (**65**) was realized in 54% yield over 4 steps. The Carreira synthesis nicely showcases the strategic incorporation and orchestration of a strained ring cleavage reaction within a radical cascade process.

3 Alkyl Radical Initiated Cascade Processes

Alkyl radicals have historically been the most heavily investigated radical species for use in natural product synthesis. While early studies typically generated these reactive intermediates from alkyl halide and xanthate ester precursors, a variety of more recent metal-mediated processes have greatly expanded the ability of other functional groups to serve as radical generators. Herein we further highlight processes exploiting olefins, epoxides, ketones, and carboxylic acid derivatives as initiators for radical cascade processes.

3.1 Pronin's synthesis of (±)-emindole SB (2015)

(±)-Emindole SB (**81**) belongs to the fungal-derived family of Paxilline indole diterpene alkaloids,[73] a class of natural products to which significant synthetic resources have been devoted.[74] Herein, we focus on the inaugural total synthesis of **81** by Pronin and co-workers which explored a radical-polar crossover polycyclization for rapid core assembly.[75]

Pronin's overarching strategy towards the construction of the key *trans*-hexahydroindene core relied upon a radical-polar cyclization cascade, which was initially investigated with model dialdehyde **82** (Scheme 4A). Easily accessible from 2-methylcyclopentenone, this dialdehyde (**82**) was found to exist as a *circa* 2:1 mixture favouring its conformationally rigid hemiacetal **83**. Under the action of iron(III) acetylacetonate and (isopropoxy)phenylsilane,[76] a tertiary radical was generated chemoselectively at the more electron-rich olefin via a hydrogen atom transfer (HAT) process and this species cyclized onto the pendant enal **π**-system via a *6-exo-trig* radical cyclization.[38] These events presumably formed radical intermediate **85** which underwent single-electron reduction by the Fe(II) formed after the initial HAT. The resulting enolate (**86**) then participated in an intramolecular aldol reaction generating products **87** and **88** (~7:1 mixture favouring **87**). The rigidifying element provided by the hemiacetal linkage in **83** was important in biasing the product ratio toward **87**; in its absence, near equal product ratios were observed.

With a blueprint identified for formation of the core structure in hand, the synthesis of (±)-emindole SB was completed in a concise fashion (Scheme 4B). Copper-mediated conjugate addition of Grignard **90** to 2-methylcyclopentenone (**89**) followed by silylative trapping generated silyl enol ether **91**. An indium (III)-mediated alkenylation process coupled **91** with the alkyne shown, resulting in the formation of one of the three challenging all-carbon

quaternary centers found in the target. Notably these researchers have further developed this chemistry into an efficient catalytic methodology.[77] Following *in situ* deprotection with hydrochloric acid, alcohol **92** was obtained and then converted to diol **93** by a selenium dioxide-mediated allylic oxidation. A Fischer indole synthesis then coupled phenylhydrazine with **93**, resulting in formation of indole **94** in good yield (68%). Parikh-Doering-type oxidation of this material generated an aldehyde intermediate which cyclized to hemiaminal **95**, setting the stage for the pivotal radical cyclization. Results from the model study (Scheme 4A) suggested that the hemiaminal locking element would be crucial in enforcing substrate rigidity and enhancing diastereoselectivity. Pleasingly, subjecting **95** to $Fe(acac)_3$/$PhSiH_2O$*i*-Pr promoted the formation of intermediate **96** which underwent an analogous cyclization to that of **83**. In this system, the stability of the cyclic template prevented final aldol cyclization from occurring in the same pot. Treating isolated product **97** with KHMDS, however, cleanly elicited this step in a stereoselective manner.

To finish the synthesis of (±)-emindole SB (**81**), a three-step procedure was developed to convert the aldehyde group into the requisite homoprenyl appendage. The addition of 2-ethoxyvinyllithium to **98** followed by acidic quench led to an enal intermediate which was subsequently hydrogenated ($Pd/CaCO_3$, H_2). Finally, Wittig olefination ($Ph_3P{=}CMe_2$) gave (±)-emindole SB (**81**), thus completing an efficient 11-step synthesis. As this synthesis clearly demonstrates, the ability to utilize simple olefins as radical precursors via HAT chemistry opens up a plethora of powerful bond-disconnections in natural product total synthesis.

3.2 Liu's synthesis of (−)-hispidanin A (2017)

Isolated in 2014 from the rhizomes of *Isodon hispida*, a plant native to southwest China and used in traditional herbal medicine, hispidanin A (**99**) is one of four dimeric diterpenoids comprised of a labdane (see **100**) and totarane (see **101**) diterpene scaffold.[79] Hispidanins exhibit significant cytotoxicity towards a number of cancer cell lines, and coupled with their obvious structural complexity, such molecules are compelling synthetic targets. Indeed, **99** has already seen two distinct total syntheses by the groups of Liu and the combined efforts of Lan, Gong, and Yang.[80,81] Of these, Liu's synthesis features a radical cascade for the assembly of the labdane-type diene (**100**) needed for downstream, biomimetic union with the totarane-derived fragment.

Forays into construction of diene **100** began with the nucleophilic opening of epoxide **102** with (ethoxyethynyl)lithium followed by hydroxyl group silylation (TBSCl) to yield **103**. Mild hydration of the alkyne moiety with $Au(PPh_3)Cl$ allowed for the preparation of ester **104** without formation of a γ-lactone, a side reaction observed when numerous other acids were employed.[82] Direct formylation of the lithium enolate of ester **104** with ethyl formate followed by stereoselective *(Z)*-enol tosylation (TsCl, *N*-methylimidazole) generated vinyl tosylate **105**.[83] An iron(III)-catalyzed cross-coupling smoothly merged **105** with Grignard reagent **106**, maintaining the olefin geometry in the process. Oxidation of the furan ring (HBr_3•pyr) followed by acid-mediated rearrangement afforded butenolide **107**, a requisite precursor for the key radical cascade cyclization.

Treating **107** with a similar reagent combination to those utilized by Pronin in the synthesis of **81** ($Fe(acac)_3/PhSiH_3$) generated a tertiary radical from the electron-rich alkene, and this species (see **108**) underwent a radical polycyclization event (*6-endo-trig*/*6-endo-trig* cyclization) leading to tricycle **109**. Notably manganese and cobalt-based catalysts proved ineffective for this transformation.[78] Four contiguous stereocenters were set during this process and a chair-like transition state was invoked to account for the stereochemistry of the major diastereomer.

The chiral secondary alcohol, which helped to orchestrate this cascade, was then removed via a three-step sequence involving desilylation (HF•pyr) and Barton-McCombie deoxygenation. Reduction of the lactone with diisobutylaluminum hydride and mesylation of the resulting lactol afforded a dihydrofuran intermediate (not shown) which was then oxidatively cleaved (K_2OsO_4•$2H_2O$/NMO, $NaIO_4$) and subjected to base-promoted elimination, ultimately affording enone **111**. Copper-mediated 1,4-addition of the anion derived from sulfone **112** to **111** followed by thermal, chelotropic extrusion of sulfur dioxide forged the requisite diene unit. Finally, addition of methyl lithium triggered a 1,2-addition/lactonization sequence thus completing the synthesis of the key labdane fragment (**100**). Reacting this material with exocyclic methylene lactone-containing totarane fragment **101** (prepared in 13 steps) led to a smooth [4+2] cycloaddition; this Diels-Alder reaction proceeded at room temperature and with good diastereocontrol (10:1), suggesting a similar process may be involved in the biogenesis of hispidanin A (**99**). A final reduction of the benzylic ketone and acetylation furnished **99** in 22 steps (longest linear sequence).

The HAT-induced radical cyclization of **107** again clearly showcased the power of this chemistry in stereocontrolled polycycle synthesis, in this case forging a ring system likely made in nature through a cationic cyclization process.[34]

3.3 Micalizio's synthesis of (−)-jiadifenin (2016)

Illicium sesquiterpenes are a moderately sized family of natural products exclusive to the *Illicium* genus of plants which includes the well-known "star anise" fruits and spices commonly found in Asian cuisine.[84] In recent years, newly isolated members bearing the *seco*-prezizaane core ring system, including (−)-jiadifenin (**113**) among others,[85,86] have displayed significant *in vitro* neurotrophic activity–a process thought to stem from modulation of the γ-aminobutyric acid (GABA) receptors.[87] Owing to their potential for treating neurodegenerative disease and their compact and highly oxygenated molecular frameworks, various *Illicium* sesquiterpenes have proven to be highly attractive synthetic targets. (−)-Jiadifenin in particular has already seen multiple syntheses reported to date;[88–93] herein we will examine Micalizio's radical-based route to **113** (Scheme 6).[94]

The pathway to **113** commenced with nucleophilic opening of chiral epoxide **114** with vinyl bromide **115** under the mediation of magnesium and copper. The resulting alcohol formed (see **116**) was then elaborated to enyne **117** via a four-step sequence consisting of: i) deprotection and mesylation of the primary hydroxyl group, ii) epoxide formation under basic conditions, and iii) subsequent epoxide opening with propynyl lithium. At this stage, assembly of the *seco*-prezizaane skeleton could be impressively accomplished via a low

valent, titanium-mediated [2+2+2] annulation of enyne **117** with the alkynyl stannane shown, demonstrating methodology previously developed by the group.[95] Impressively, **118** was formed as nearly a single regio- and diastereomer during this process which also forged a challenging all-carbon quaternary stereocenter. With bicycle **118** in hand, protecting group manipulations followed by lithium-tin exchange and quenching of the resulting lithiate with carbon dioxide accomplished formation of the full sesquiterpene carbon framework. Alkylation of the newly formed carboxylic acid with $PhSeCH_2Cl$ provided radical precursor **119** and a subsequent osmium-mediated dihydroxylation established compound **120**, setting the stage for the pivotal cyclization.

Subjecting **120** to standard tin-based radical initiation conditions (*n*-Bu_3SnH, AIBN, Δ) lead to formation of α-oxygen stabilized primary radical **121** which underwent a facile *5-exo-trig* cyclization onto the neighboring tetrasubstituted alkene; this process generated the hallmark γ-lactone system of jiadifenin. Typically, in many similar reactions the final radical is quenched via a hydrogen atom transfer (HAT) reaction with *n*-Bu_3SnH and indeed this occurs in this system as well, thus forming acetal **123**. Quite unexpectedly, however, a similar amount of ethyl ester **124** was also formed presumably by a process wherein the tertiary radical abstracts the weak C-H bond on the neighboring dioxolane ring (via 1,4-hydrogen atom abstraction) initiating ring fragmentation. A final HAT process with *n*-Bu_3SnH then forms the ethyl ester moiety. This process is notable in that the oxidation state of the dioxolane carbon is changed from formally an aldehyde to that of an ester–a process which is beneficial for the ensuing synthetic plan. While the 1:1 ratio of **124:123** could be altered to ~4.7:1 via switching to $(TMS)_3SiH$ as the H-atom donor, the efficiency of this process was lower, and for preparative purposes, routes were developed to process both **123** and **124**. Acetal **123** could be converted into δ-lactone **125** via a four-step sequence consisting of: i) Swern oxidation of the secondary alcohol, ii) acetonide deprotection and subsequent Pinnick oxidation to a carboxylic acid, iii) stereoselective reduction of the cyclic ketone, and iv) translactonization under acidic conditions. Gratifyingly, the route to **125** from ethyl ester **124** did not require the Pinnick step owing to the aforementioned oxidation state change at the dioxolane carbon.

With **125** in hand, the TBDPS protecting group was removed and the resulting secondary alcohol oxidized (IBX) generating cyclopentanone **126**. Saegusa-Ito oxidation of this material constructed the requisite enone system of the target, and following fluoride-mediated desilylation and stereoselective enolate oxidation with Davis' oxaziridine, the synthesis of the natural product (1*S*,10*R*)-2-oxo-3,4-dehydroneomajucin (**128**) was completed. Known Jones oxidation of this material followed by treatment with methanol rearranged the δ-lactone structure into the hallmark hemiketal motif, thereby completing a synthesis of jiadifenin (**113**).[88–92] While not shown, this work also allowed access to the related sesquiterpene natural product (2*S*)-hydroxy-3,4-dehydroneomajucin. The Micalizio route to **113** not only showcases the power of radical cyclizations in the construction of hindered, all-carbon quaternary stereocenters, but also nicely highlights the cascade capabilities of these reactive intermediates when weak C-H bonds are present in close spatial proximity.

3.4 Overman's synthesis of (−)-chromodorolide B (2016)

Marine nudibranches of the *Chromodoris* genus produce a collection of rearranged spongian diterpenes including the synthetically challenging metabolite (−)-chromodorolide B (**129**) which possesses ten contiguous stereogenic centers.[96] While the biological activities of constituents of this family are diverse, special interest has been placed on the Golgi modifying properties of related members and simplified analogues.[97] Herein we discuss the only synthetic route to a chromodorolide member, that of (−)-chromodorolide B by Overman and coworkers which employed a striking intermolecular radical addition/cyclization/fragmentation cascade as the key step.[98]

Beginning with enantioenriched enedione **130**, a five-step sequence was used to construct *trans*-hydrindanone cyclopropane **131** (Scheme 7). First, the cyclopentanone carbonyl was converted to its corresponding dioxolane thus allowing for 1,2-reduction of the nearby cyclohexenone group with $LiAlH_4$ and subsequent carbonate formation. This material then participated in a stereospecific, palladium-catalyzed reductive transposition ($Pd(acac)_2$, Bu_3P, HCO_2H) setting the key *trans*-fused 5,6-ring junction.[99] The resulting trisubstituted alkene formed was then cyclopropanated under Simmons-Smith conditions arriving at **131** after acidic removal of the dioxolane protecting group. Reductive cleavage of the strained cyclopropane was accomplished via hydrogenation with Adam's catalyst, and following PCC oxidation ketone **132** was formed. Conversion of this material to vinyl iodide **133** was conveniently accomplished using Barton's two-step hydrazone iodination protocol. In the first key C-C bond forming step in the synthesis, vinyl iodide **133** was coupled to aldehyde **135** using the venerable Nozaki-Hiyama-Kishi coupling, thus resulting in complex fragment **136**. The use of Kishi's chiral sulfonamide ligand (**134**) was crucial in obtaining exquisite levels of diastereocontrol during this process (>20:1 *dr*).[100] Ester **136** was hydrolyzed under basic conditions, revealing a hindered carboxylic acid which could be coupled to *N*-hydroxyphthalimide with *N,N´*-dicyclohexylcarbodiimide (DCC). Chlorination of the secondary allylic alcohol ($SOCl_2$) with concomitant allylic rearrangement gave activated ester **137** and set the stage for the key radical cascade.

Photoinduced fragmentation of the *N*-acyloxyphthalimide moiety mediated by the catalyst $Ru(bpy)_3(PF_6)_2$ generated hindered tertiary radical **138**, which added diastereoselectively to chiral butenolide fragment **139**.[101,102] The resulting α-carbonyl-stabilized radical **140** then underwent non-diastereoselective, intramolecular *5-exo-trig* radical cyclization onto the pendant alkene followed by β-fragmentation of the C–Cl bond to deliver pentacyclic products **141** and **142** (in 37% and 28% yields, respectively). Several other coupled, but not fully cyclized, products were also formed; their quantities, however, could be minimized by use of a deuterated Hantzsch ester (D_2-**HE**) additive, which presumably suppresses premature radical reduction. Moving forward, the minor product (lactone **142**) was converted to its corresponding lactol with DIBAL, acetylated *in situ*, and hydrogenated to afford alcohol **143.** The key stereocenter at the carbon linking the two complex halves of the rearranged spongian skeleton was then conveniently set by a simple heterogeneous hydrogenation (PtO_2/H_2). Two-step oxidation of the primary alcohol to a carboxylic acid gave compound **145**, and following treatment with acid, lactol **146** was readily formed. Exhaustive acetylation then furnished (−)-chromodorolide B (**129**) in 21 total steps. The

ability to couple complex, stereochemically-rich fragments with high efficiency via decarboxylative radical coupling has recently enabled the synthesis of many complex terpenes.[101] When combined with tandem radical cyclization processes, as demonstrated herein, such methodology is nearly unmatched in its power to rapidly generate molecular complexity.

3.5 Maimone's synthesis of (−)-6-*epi*-ophiobolin N (2016)

The ophiobolin sesterterpenes are a moderately sized family of natural products possessing complex, stereochemically-rich 5,8,5-fused tricyclic skeletons. While originally isolated and investigated for their phytotoxic effects which negatively impacted several agricultural crops,[103] ophiobolins have recently exhibited interesting anti-cancer effects against a number of cancer cell lines.[104] To date, only three ophiobolins have succumbed to total synthesis efforts: ophiobolin C by Kishi by 1989,[105] ophiobolin A by Nakada in 2011,[106] and 6-*epi*-ophiobolin N (**147**) by Maimone in 2016 which employed a radical cascade cyclization and is discussed below.[107]

Utilizing inexpensive (−)-linalool as a chiral pool building block,[108] ring-closing metathesis employing Hoveyda-Grubbs second generation catalyst (HG-II) provided alkene **148** after *in situ* silylation (Scheme 8). Ruthenium-catalyzed allylic oxidation then gave enone **149**. In a separate sequence (see lower insert, Scheme 8), *trans, trans* farnesol was subjected to Charette's asymmetric cyclopropanation protocol,[109] forging enantioenriched alcohol **150**. An Appel-type reaction then converted this material into iodide **151**. In the first key C–C bond-forming step of the synthesis, iodide **151** was treated with *tert*-butyllithium inducing anionic cyclopropane ring opening.[110] Treating this presumed lithiate intermediate with copper iodide, followed by enone **149** and finally trichloroacetyl chloride led to the formation of **152** via a 1,4-addition/trapping sequence (60%, *dr* = 3:1). Cyclopentanone carbonyl reduction of **152** (DIBAL/*n*-BuLi "ate" complex) followed by acetylation of the resulting secondary alcohol set the stage for the key radical cyclization.

Subjecting this material to conditions which promote reductive radical cyclizations ($(TMS)_3SiH$, Et_3B/O_2 as initiator) led to a tandem *8-endo-trig*/*5-exo-trig* radical cyclization cascade (see **153**), thus forging the entire ophiobolin skeleton. Key to the success of this process was the inclusion of bulky thiol **154** as a polarity reversal catalyst,[111] which influenced the final radical termination step (HAT process) at the C-15 position (shown in green) to favor the correct isomer. When simple, achiral thiols were utilized, the incorrect C-15 diastereomer predominated (*dr* ~ 3:2).

With compound **155** in hand, a Corey-Chaykovsky epoxidation completed the synthesis of the full C-25 carbon framework and following reductive, dehalogenative epoxide opening (promoted by lithium naphthalenide) diol **156** was obtained. Double Swern oxidation followed by acid-promoted E1cB elimination of the tertiary silyl ether group then completed a nine-step synthesis of (−)-6-*epi*-ophiobolin N. The Maimone synthesis of **147** is noteworthy in that it showcases not only the power of radical cascades to rapidly assemble complex terpene ring systems, but also the stereochemical challenges–and potential solutions–that can be encountered during their use.

3.6 Yamashita's synthesis of (±)-limonin (2015)

Limonoids are a series of triterpene derivatives commonly found in citrus fruit. Hundreds of congeners have been cataloged, including limonin (**157**), which was identified as early as 1841.[112] Due to their unique architectures and broad spectrum biological activities, various synthetic approaches have been detailed in the literature.[113] The first synthesis of limonin by Yamashita and co-workers featured a powerful tandem radical cascade polycyclization which will be examined below.[114]

The Yamashita synthesis commenced with conversion of geraniol into polyene **158** via a four-step sequence (Scheme 9). First, chlorination of the allylic alcohol and epoxidation of the terminal alkene afforded epoxygeranyl chloride. Next, a lithium acetylide displacement reaction and aluminum-mediated epoxide elimination gave rise to **158** in excellent yield. A second alcohol chlorination ($SOCl_2$) generated an allylic chloride which could be displaced by the dianion of β-ketoester **159** and following fluoride-mediated deprotection, polyene **160** was formed. Taking inspiration from the work of Snider,[115] treatment of **160** with $Mn(OAc)_3$ generated an α-keto radical (see **161**) which engaged the polyene system in a radical polycyclization. This cascade presumably terminated by reduction of the final vinyl radical with a hydrogen atom provided by ethanol.[115] It is worth noting that while the key all-carbon quaternary center at C-13 was set with 2.1:1 diasteroselectivity during this process, a related all alkene-based oxidative polycyclization employing a Mn(III)/Cu(II) system provided the undesired isomer almost exclusively.

Moving forward, reductive dechlorination of **162** and subsequent Robinson annulation established the androstane framework, and following a γ-deprotonation/methylation sequence, diene **163** was constructed. Global carbonyl reduction, selective silylation, and a final acetylation afforded acetate **164**. The exocyclic methylene carbon was expunged by epoxidation following by treatment with cyanide, a process presumably involving oxirane opening and subsequent ejection of acetonitrile. Reacetylation of this material furnished ketone **165**. A copper-catalyzed allylic oxidation then produced a B-ring enone intermediate which could be stereoselectively reduced *via* dissolving metal reduction, thus establishing the *trans*-fused A/B ring junction. These conditions also cleaved the acetate protecting group which allowed for Dess-Martin oxidation of the resulting secondary alcohol, and upon treatment with TBAF, cyclic hemiketal **166** was revealed. The hemiketal cage conveniently allowed for chemo- and stereoselective reduction of the B-ring ketone ($LiAlH(O\textit{t}\text{-}Bu)_3$) and the resulting alcohol product was immediately silylated. A Saegusa-Ito oxidation then provided enone **167**. Formation of a vinylogous enol triflate was accomplished by treating **167** with triflic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) which permitted a subsequent Pd-catalyzed Stille coupling to proceed with stannane **168**. The butenolide-containing product formed (**169**) then participated in a diastereoselective [4+2] cycloaddition reaction with singlet oxygen (O_2, methylene blue) and following conversion of the butenolide to a furan (DIBAL *then* Ac_2O) endoperoxide **170** was obtained. Isomerization of **170** under ruthenium(II) catalysis produced a bis(epoxide) intermediate (not shown), which rearranged to epoxyketone **171** by way of an acid-promoted 1,2-hydride shift. The diasteromeric ratio of **171** to its C-17 epimer could be enhanced by treatment with DBU whereby a 5.4:1 ratio favoring **171** could be established. Advanced intermediate **171** was

then converted into lactone **172** by way of a Baeyer-Villiger oxidation and selective deprotection.

In a second key radical-based step in the synthesis, **172** was subjected to Suárez's oxygen radical generating conditions ($PhI(OAc)_2$, I_2, *hν*) which cleaved the C-3/C-4 bond, resulting in a lactone ring and a carbon-centered radical on C-4. This radical was intercepted with molecular oxygen and postulated to ultimately form an alkoxy radical on C-4 which underwent intramolecular C-H abstraction from the C-1 position (i.e. 1,5 abstraction), iodination, and C–O bond formation leading to **173**. Finally, (±)-limonin (**157**) was obtained after a hydroxyl group deprotection and subsequent oxidation, thus completing a 35-step synthesis. As mentioned in the introduction, radical chemistry can provide orthogonal solutions to complex polycyclizations typically performed in nature using cationic chemistry;[34] Yamashita's route to limonin powerfully demonstrates this reaction dichotomy.

3.7 George's syntheses of (+)-garcibracteatone (2014)

Embodying a large array of intricate bicyclo[3.3.1]nonane-containing natural products from the plants of the Clusiaceae and Hypericaceae families,[116] polycyclic polyprenylated acylphloroglucinols (PPAPs) have garnered intense scrutiny from synthetic chemists over the past two decades, culminating in numerous completed syntheses.[117] Garcibracteatone (**174**) represents a particularly complex problem in PPAP synthesis owing to its compact caged architecture containing seven stereocenters, four of which are all-carbon quaternary centers (Scheme 10). In 2012, George and co-workers reported a shockingly short route to racemic **174** using an elegant, bio-inspired radical cascade.[118] Herein we will highlight the group's 2014 route to (+)-**174** which also secured the absolute configuration of the natural product.[119]

In order to access enantiopure lavandulyl iodide (**179**), a key fragment needed for their approach, an asymmetric synthesis was devised using chiral auxiliary methodology (Scheme 10).[120] The enolate of Evans oxazolidinone **176** was cleanly alkylated with prenyl bromide affording **177** and upon reduction and iodination, **179** was generated. In a separate sequence, Friedel-Crafts reaction of phloroglucinol with benzoyl chloride gave benzophenone **180** which could be diprenylated (prenylbromide, KOH) to give **181**. In the first key step in the synthesis, **179** and **181** were coupled by way of a dearomative phenolic *para*-alkylation reaction which produced **182** as a mixture of four compounds–two diastereomers each of which were vinylogous acid tautomers. In a single incredible step, (+)-garcibracteatone (**174**) and (−)-5-*epi*-garcibracteatone (**175**) were obtained in 22% combined yield via a Mn(III)-mediated oxidative cyclization cascade. In this process, the reaction of **182** with Mn(III) is believed to first form *α*-keto radical intermediate **183**, which then undergoes *7-endo-trig* cyclization onto the pendant lavandulyl chain (see blue arrows). The resulting tertiary radical then participated in two successive *5-exo-trig* cyclizations, first with the $\Delta_{7,8}$ enol double bond and then the $\Delta_{17,18}$ olefin (see red and green arrows, respectively). The cascade terminates with coupling of the C-18 carbon to the aromatic ring (see magenta arrows), a process which could involve radical addition to the arene and subsequent oxidation (as depicted) or possibly radical oxidation and a subsequent Friedel-Crafts alkylation. Incredibly, this total synthesis was only five linear steps owing to the ability of

the radical cascade to construct four C–C bonds in a single step. Moreover, George's work also clearly established the absolute configuration of natural garcibracteatone.

3.8 Maimone's synthesis of (±)-berkeleyone A (2016) and related meroterpenes (2017)

Extremophiles often possess unique metabolic capabilities and the ability to synthesize structurally and functionally interesting secondary metabolites. The Berkeley Pit (Butte, MT, USA), a former open copper mine turned toxic waste lake is home to the fungal strain *Penicillium rubrum* which has been found to produce a variety of meroterpene natural products derived from 3,5-dimethylorsellinic acid (DMOA) and farnesyl pyrophosphate, many of which possess anti-inflammatory effects.[121,122] Among these is berkeleyone A (**184**) which features a bicyclo[3.3.1]nonane-containing core skeleton and is likely a biosynthetic precursor to even more complex metabolites within this class (Scheme 11).[123] Berkeleyone A has recently succumbed to two unique syntheses by the groups of Maimone and Newhouse, works which also represent the first routes to any complex DMOA-derived meroterpenes.[124,125] Maimone's efforts feature a radical cascade for assembly of a key portion of the polycyclic scaffold and will be showcased below.

The synthesis of **184** began with the alkylation of the lithium anion derived from propionitrile with farnesyl bromide, and following regioselective epoxidation–via the intermediacy of a bromohydrin–terminal epoxide **185** was obtained (Scheme 11). Inspired by the work of Fernández-Mateos,[126] a titanocene-mediated reductive epoxide cyclization was envisioned to offer rapid access to three of the rings of **184** in a stereocontrolled manner.[35,127,128] Towards this end, treating **185** with *in situ* generated Ti(III) (formed from Cp_2TiCl_2, Zn^0) induced homolytic epoxide opening and cyclization onto the polyene system (see **186**). The radical cascade terminated with a *5-exo-dig* cyclization onto the nitrile followed by further reduction; following aqueous work-up, the intermediate imine was then hydrolyzed to a ketone resulting in polycycle **187**. Protection of **187** (TBSCl) then set the stage for a second key C–C bond-forming step wherein diketene underwent a formal [4+2] annulation reaction with the lithium enolate of protected-**187**. Methylation of the 1,3-diketone moiety with trimethylsilyldiazomethane afforded a stable vinylogous ester which underwent clean oxidative ring expansion to the bicyclo[3.3.1]nonane framework (see **189**) when treated with $PhI(OAc)_2$ under basic conditions.[129,130] An ensuing Wittig olefination and chlorination of the C-9 position yielded vinyl chloride **191** from **190**. Bridgehead (i.e. C-11) deprotonation of **191** was accomplished with lithium tetramethylpiperidide allowing for a remarkably hindered acylation reaction to occur with methylchloroformate. A Suzuki coupling installed the final carbon atom of the target and acidic hydrolysis of the *tert*-butyldimethylsilyl ether revealed advanced intermediate **192**. A final Krapcho demethylation and stereoselective hydroxylation of the vinylogous acid moiety completed a 13-step synthesis of racemic berkeleyone A.

Following disclosure of the synthesis of (±)-berkeleyone A (**184**), conditions were developed to convert advanced intermediate **192** into the related fungal meroterpenes andrastin D (**193**), preterrenoid (**194**), terrenoid (**195**), and terretonin L (**196**) (Scheme 12).[131] While the biosynthesis of **193**–**196** presumably involve similar initial steps to berkeleyone A, these metabolites possess a 5,6-fused diketone motif in place of the bicyclo[3.3.1]nonane

architecture. It was hypothesized that **197**, prepared via PCC oxidation of **192**, could be converted into this motif (i.e. **198**) *via* an acid-promoted quasi-biomimetic 1,2-ring shift. While the authors found no success realizing this rearrangement with acid, conditions reported by Shigehisa for cobalt-catalyzed oxidative hydrofunctionalization (cat. **199**, $PhSiH_3$, F^+ oxidant **200**) smoothly delivered **198** in high yield (90%) and as a single alkene isomer.[132] A simple demethylation then afforded andrastin D (**193**). Natural products **194–196** were envisioned to be more challenging to synthesize than **193** owing to the exocyclic olefin present. It was discovered that simply switching oxidant **200** for TsCl afforded **201** in moderate yield and with good selectivity for the less substituted alkene isomer (<5% of **198** was observed).[133] The authors hypothesized that these cobalt-catalyzed rearrangements may in fact be examples of the classic homoallyl rearrangement discussed earlier (Figure 2). In this scenario, radical intermediate **202** is initially generated via HAT and undergoes *3-exo-trig* cyclization onto the alkene of the vinylogous acid generating cyclopropane **203**. Fragmentation of **203** into radical **204** followed by formal loss of a hydrogen atom (HAT) from the less hindered methyl group then delivers **201**, the less stable alkene isomer. It is proposed that the more strongly oxidizing conditions containing **200** promote radical oxidation of **204** to a tertiary carbocation, and following proton loss, the more stable isomer (i.e **198**) is generated. With **201** in hand, Krapcho demethylation afforded preterrenoid (**194**) which could be oxidized stereoselectively to terrenoid (**195**) using magnesium monoperoxyphthalate (MMPP). Terrenoid is believed to be the biosynthetic precursor to the terretonin family and indeed it was found that simple treatment of **195** with NaOMe/MeOH afforded terretonin L (**196**), possibly by way of a retro-Claisen/intramolecular esterification cascade process.[134]

The route to berkeleyone A is yet further testament to the ability of radical cyclizations to mimic biosynthetic processes, in this case the opening of an epoxide followed by a polyene cyclization. Moreover, the pathways to **193–196** also highlight an instance where a mechanistically distinct radical reaction was capable of producing a product which biomimetic, cationic chemistry failed to prepare.

3.9 Inoue's synthesis of (+)-resiniferatoxin (2017)

The plant family Euphorbiaceae produces an extensive collection of biologically active natural products, most notably the complex tigliane,[135,136] and closely related daphnane diterpenes.[137] (+)-Resiniferatoxin (**205**), a potent irritant isolated from *Euphorbia resinifera* in 1975 is perhaps the flagship daphnane diterpene (Scheme 13).[138] Its synthetically challenging tricyclo[9.3.3.0]tetradecane skeleton coupled with potent modulatory properties toward the transient receptor potential vanilloid 1 (TRPV1) receptors have made **205** both a high profile synthetic target and chemical tool for studying pain.[139] Although intense effort has been devoted to the chemical synthesis of diterpenes from *Euphorbiaceae*,[136] resiniferatoxin remains the only daphnane natural product prepared by total synthesis; furthermore, Wender's historic 1997 synthesis[140] and Inoue's very recent 2017 report remain the only fully synthetic routes reported to **205**.[141] Herein, we explore Inoue's *de novo* synthesis of resiniferatoxin utilizing several powerful radical cascades to construct the stereochemically-rich and synthetically challenging polycyclic daphnane ring system.

The synthetic pathway to **205** utilized commercially available D-ribose derivative **206** as starting material (Scheme 13). Addition of *n*-BuLi (to deprotonate acidic functionality) allowed for addition of vinylmagnesium bromide to the unmasked aldehyde to take place. Oxidative diol cleavage ($NaIO_4$) then furnished a hemiacetal intermediate which was again treated with *n*-BuLi and a Grignard reagent, in this instance isopropenylmagnesium bromide. Finally, the cyclohexene ring was constructed via ring closing metathesis with Hoveyda-Grubbs second-generation catalyst in presence of 1,4-benzoquinone to prevent alkene migration thus forming **207**. Interestingly, subjecting **207** to hydrogenation conditions (H_2, Pd/C) led to stereoselective alkene isomerization giving a ketone at the C-9 position. Diastereoselective addition of 1-ethoxyvinyl lithium to this material followed by Ley oxidation of the remaining hydroxyl group generated ketone **208**. A fourth organometallic addition, this time utilizing 1-methylvinyl lithium, was employed to construct the isopropenyl group of the target. The acetonide group was then removed with acidic resin (Dowex 50W) which also conveniently furnished a methyl ketone from the preexisting vinyl ether group. The intermediate tetraol then underwent site-selective benzoylation, and following treatment with trimethylorthoformate, the three-remaining hydroxyl groups engaged in orthoester formation delivering **209**. Reacting methyl ketone **209** with TMSOTf/Et_3N afforded an enol ether which could be chemoselectively epoxidized to give an α-hydroxy ketone. Oxidative cleavage of this material with $Pb(OAc)_4$ generated an intermediate carboxylic which upon treatment with MsCl/pyridine formed acyl mesylate **210**. Conversion of **210** to Barton ester **211** was conveniently achieved using 2-mercaptopyridine *N*-oxide sodium salt and DMAP and the somewhat unstable intermediate formed was immediately irradiated with light in the presence of diphenyl diselenide inducing decarboxylative phenylselenation.[142] Selenide **212** was then taken through a four-step sequence consisting of desilylation, alcohol oxidation, stereoselective reduction, and protection to generate **213**, setting the stage for the key radical cascade.

When **213** was heated in the presence of the radical initiator V-40, deselenation occurred forming oxygen-stabilized bridgehead radical **214**. In the presence of the enone shown, a diastereoselective radical conjugate addition took place forging α-keto radical **215**. Finally, this radical species participated in a Keck-type radical allylation with stannane **216** delivering ketone **217**.[143] An impressive 52% overall yield was achieved in this remarkable 3-component radical coupling which forges several sterically hindered C–C linkages.

Several further synthetic manipulations were required in preparation for the 7-membered ring-forming event. From cyclopentanone **217**, E1cB elimination of the silyl ether group employing NaHMDS fashioned an enone which was subjected to two-step Rubottom oxidation (TBSOTf *then m*-CPBA). Stereoselective 1,2-reduction with DIBAL generated a *cis*-fused diol which could be masked as an oxacyclopentylidene orthoester when reacted with **218** under acidic conditions. Fluoride-mediated global desilylation followed by global xanthate formation (NaH, CS_2, MeI) afforded key radical precursor **219**.

In a single masterful stroke, simple heating of bisxanthate **219** at 110 °C promoted a clean [3,3]-sigmatropic rearrangement of the allylic xanthate into dithiocarbonate **220**. This maneuver was followed by further heating (180°C) in the presence of the radical initiator V-40 and Bu_3SnH which generated radical intermediate **221**. A diastereoselective *7-endo*-

trig cyclization subsequently ensued leading to **222** after ejection of the dithiocarbonate group. Given the plethora of intricate chemistry which occurs during this cascade, the 71% yield obtained is quite impressive.

With the daphnane 5,7,6-fused ring system in hand, the authors needed only to append one remaining carbon atom to the terpene framework and interconvert several functional groups to arrive at resiniferatoxin. To this end, global deprotection of **222** and chemoselective oxidation of the allylic alcohol provided enone **223**. A six-step sequence involving: i) formation of the hallmark orthoester group via Yamaguchi esterification with **224**, ii) TMS protection of the tertiary hydroxyl group, iii) enone 1,4-reduction using $LiBH(s\text{-}Bu)_3$, iv) enolate formation and alkylation with MeI, v) silyl enol ether formation using *N*-methyl-*N*-(trimethylsilyl)trifluoroacetamide, and vi) NBS-mediated bromination then afforded **225** in 27% over six steps. Next, the authors leveraged SeO_2 to install a hydroxyl group at C-7 *via* regioselective allylic oxidation. Heating this material in the presence of lithium carbonate and lithium bromide induced elimination of the tertiary bromine atom, thereby restoring the cyclopentenone system. Finally, chlorination ($SOCl_2$) of the allylic alcohol with concomitant transposition afforded C-20 allylic chloride **226**. To complete the synthesis, the allylic chloride was displaced with cesium carboxylate **227** and the silyl protecting group removed with TBAF. In the end, (+)-resiniferatoxin (**205**) was constructed in 41 steps. The two radical cascades employed in Inoue's work are particularly impressive when one considers both the complexity of the substrates utilized, as well as the high diastereoselectivities and yields obtained. It would be difficult to envision a significant number of polar bond-forming events which can craft such complexity so efficiently.

3.10 Gong and Yang's synthesis of (−)-pavidolide B (2017)

Marine cembranoids are a diverse group of macrocycle-derived diterpenes often produced by various species of coral.[144] The soft coral *Sinularia pavidai* in particular produces the tetracyclic 7,5,5,6-fused cembranoid (−)-pavidolide B (**228**) which possesses inhibitory activity against various human promyelocytic leukemia cell lines (Scheme 14).[145] Gong and Yang's inaugural 2017 route to this complex natural product featured an impressive radical cascade employing a vinyl cyclopropane cleavage/formal annulation process to forge an advanced tricyclic intermediate and ultimately delivering a short 10-step total synthesis of **228**.[146]

In order to assemble a key cyclopropane fragment, dimethyl bromomalonate (**229**) and dieneal **230** were merged via a domino Michael addition/alkylation using proline-derived catalyst **231** (Scheme 14).[147] The enantioenriched cyclopropane formed (**232**) was then subjected to acetal formation followed by mild ester monohydrolysis to arrive at carboxylic acid **233** as an inconsequential pair of diastereomers. Concurrently, (+)-carvone was regio- and stereoselectively oxidized to allylic alcohol **234** using copper-aluminum mixed oxide (Cu-Al Ox) in the presence of air and sodium *tert*-butoxide.[148] Hydrogenation of the isopropenyl group in **234** with Wilkinson's catalyst furnished alcohol **235**. The union of acid **233** and alcohol **235** was achieved under Mitsunobu conditions giving intermediate **236** in high yield and setting the stage for the critical radical cascade.

Visible light irradiation of the Ir(III) complex shown in the presence of *p*-toluidine and thiophenol resulted in the generation of the phenylthiyl radical which added to the alkene of **236** giving radical **237** after cyclopropane ring opening.[149–151] This species then underwent diastereoselective addition to the neighboring enone system generating α-keto radical (see **238**) which then cyclized back onto the alkene (*5-exo-trig* process) initially formed during the cyclopropane fragmentation. Finally, expulsion of the phenylthiyl radical delivered the annulated product (**239**) in 50% yield and impressively as a single diastereomer. With tricycle **239** in hand, the extraneous ester group was removed by hydrolysis to a carboxylic acid (Me_4NOH, *i*-PrOH/H_2O) and thermal decarboxylation, and following treatment with HCl to remove the acetal group, aldehyde **240** was generated. Next, a Nickel-catalyzed hydroacylation of **240** with isoprene followed by DMP-oxidation gave rise to olefin metathesis precursor **241** which was cyclized to **242** under the mediation of Grubbs' second generation catalyst. Finally, $RhCl_3$/*i*-PrOH isomerized the γ,δ-unsaturated enone into conjugation, thus completing the synthesis of (−)-pavidolide B (**228**). The Gong and Yang 10-step route to **228** is both elegant and efficient; without question its efficiency stems from both the judicious choice of chiral pool building blocks and the ability to form two rings and four contiguous stereocenters in a single operation via a diastereoselective radical cascade.

4. Alkenyl Radical Initiated Cascade Processes

Radical cyclizations originating at a sp^2-hybridized carbon center are less frequently encountered in natural product total synthesis perhaps owing to the rise of modern transition metal-catalyzed Heck and cross-coupling methodology. Nevertheless, notable examples of diverse aryl, alkenyl, and acyl radical cyclization permeate the literature.[152–164] As discussed previously with alkyl radicals, tin and silicon-based methods using AIBN decomposition have historically been employed to initiate radical generation, yet modern photoredox methods are increasingly offering new solutions to this problem.[149–151] In addition, radical additions to alkynes offer convenient entry into vinyl radicals, an example of which is discussed below.

4.1. Parker's synthesis of (±)-bisabosqual A (2013)

During efforts to discover new microsomal squalene synthase inhibitors, Minagawa and co-workers isolated the polycyclic meroterpene bisabosqual A (**243**) from a strain of *Stachybotrys* fungi.[165] This natural product features a compact, *cis*, *cis*-fused tetracyclic ring system with five contiguous stereogenic centers. The group of Parker reported an efficient 14-step total synthesis of **243** in 2013, in which an aryl radical-induced cascade transformation rapidly forged the core structure.[166]

Parker's synthesis began with a 2-step procedure to prepare known phenolic ester **245** which entailed silylation of **244** to produce a diene and a subsequent [4+2] cycloaddition with dimethyl acetylenedicarboxylate (DMAD) (Scheme 15).[167] Iodination of **245** followed by a DABCO-catalyzed 1,4-addition to the ynone shown afforded vinylogous ester **246** with high geometric purity. Coupling of **246** with allylic alcohol **247** was achieved under Mitsunobu conditions wherein **248** was produced in outstanding yield.

In the key step of the synthesis–which was inspired by previous synthetic work on morphine–aryl radical generation was initiated with *s*-Bu_3B/air producing an intermediate that underwent a tandem *5-exo-trig* cyclization onto the cyclohexene ring, followed by a *6-exo-trig* cyclization onto the vinylogous ester.[152] The final α-keto radical produced was then terminated via a hydrogen atom transfer reaction with supersilane ($(TMS)_3SiH$). Overall, the tetracyclic product (**249**) was isolated in 72% yield combined with its C-7 epimer (~3:2 mixture favouring **249**). Nevertheless, the creation of two rings and three stereogenic centers in a single step is quite impressive and the minor, unwanted diastereomer (7-*epi*-**249**) could be epimerized under basic conditions (1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), *then* $NaHCO_3$) to give 94% of a 2:1 mixture favouring **249**.

From this point, a three-step procedure was developed to remove the extraneous ketone group. Luche reduction and formation of an allylic acetate provided a suitable substrate for a palladium-catalyzed π-allyl reduction giving **250** in 86% overall yield. Subsequent removal of TBS protecting group (TBAF), DMP oxidation, and diastereoselective addition of trimethyl aluminium to the resulting ketone forged tertiary alcohol **251**. Finally, the dialdehyde motif was unveiled by global reduction and reoxidation, thus completing the first total synthesis of (±)-**243** in only 14 steps and further showcasing the power of radical cascade chemistry in a complex milieu.

4.2. Du Bois' synthesis of (−)-batrachotoxin (2016)

The steroidal alkaloid (−)-batrachotoxin (**252**) is the primary toxic constituent of Colombian poison dart frogs and acts as a potent agonist of voltage-gated sodium channels (Na_Vs). This acute toxin was first isolated by Witkop and co-workers from the skin extracts of *Phyllobates bicolor* in 1963,[168] and its structure was secured later in 1969 by X-Ray crystallographic analysis of a derivative.[169] Driven by its potent biological activity and intriguing chemical structure, Du Bois and co-workers completed a total synthesis of both **252** and its enantiomer in 2016,[170] work which represents only the second ever synthesis of this highly challenging target.[171] A remarkable tin radical-induced cyclization cascade serves as the cornerstone of this synthetic work, details of which are provided below.

Du Bois' and co-workers began by assembling key fragments **253** and **254** which would be later merged in convergent fashion (Scheme 16). First, ethyl diethylphosphonoacetate (**255**) was converted to enantioenriched allylic alcohol **256** by way of a Horner Emmons-type coupling with succinaldehyde and enzymatic resolution (lipase PS).[172] Protection of this material (TBSCl) and reduction with DIBAL afforded **257** which was taken through a four-step sequence to arrive at enone **253**. These steps entailed epoxidation of the allylic alcohol and Appel reaction, zinc-mediated reductive epoxide opening, and a final IBX oxidation of the resulting secondary alcohol. Using chemistry inspired by previous work from Parson,[173] the second key fragment, vinyl bromide **245**, was assembled from the Hajos-Parrish ketone. Ketalization and enol ether formation gave **258**, which when exposed to *in situ* generated dibromocarbene, underwent cyclopropanation and ring expansion producing vinyl bromide **259**. Addition of lithium (trimethylsilyl)acetylide to **259** followed by treatment with camphor sulfonic acid and methanol led to key bicycle **254**.

In a key coupling event, treatment of **254** with *t*-Buli produced a lithiate which underwent diastereoselective 1,2-addition to chiral cyclopentenone **253**. The TMS group was then removed with basic methanol and the tertiary alcohol coupled with the chlorosilane shown resulting in radical cascade precursor **260**. Under tributyltin radical generating condition (Et_3B, O_2, *n*-Bu_3SnH, 150 °C), the unprotected alkyne first reacted with $Bu_3Sn•$ leading to formation of a vinyl radical intermediate which participated in a *6-endo-trig/5-exo-dig* cyclization cascade (see **261**→**262**). Elevated reaction temperatures favored the desired initial *6-endo* process over the competing *5-exo* pathway. Finally, allylic hydrogen atom abstraction prior to the final HAT reaction with Bu_3SnH afforded isomerized product **263** from vinyl radical intermediate **262**.

With the batrachotoxin C-ring assembled, the authors turned toward construction of the homomorpholine E-ring. Global desilylation (TBAF), oxidation of secondary alcohol (IBX), and *in situ* oxidative cleavage of the mono-substituted alkene afforded aldehyde **264** in 54% yield from **263**. One-pot reductive amination of **264** with methylamine, acylation with chloroacetyl chloride, and intramolecular etherification then afforded lactam **265**. The D-ring ketone was converted to its corresponding vinyl triflate and in a somewhat unexpected finding, treating this compound with $CuCl_2$ under aerobic conditions afforded aldehyde **266** as opposed to the expected allylic chloride product. A sequence consisting of Pinnick oxidation, acyl azide formation, Curtius rearrangement, and acid-mediated hydrolysis then afforded **267**. It should be noted that the somewhat circuitous route to install the C-11 ketone (i.e **265**→**267**) was a result of difficulties encountered in trying to achieve the more direct protodestannylation/oxidative alkene cleavage pathway to this moiety. For purification purposes, the C-3 hemiketal was reprotected by condensing **267** with *p*-methoxyphenethyl alcohol, and following palladium-catalyzed Stille coupling and vinyl ether hydrolysis, methyl ketone **268** was generated. Treatment of **268** with freshly prepared alane (AlH_3) accomplished a remarkable, diasteroselective global carbonyl reduction which set two stereocenters and also forged the crucial cyclic amine. Finally, acid-mediated removal of ketal protecting group furnished batrachotoxinin A (**270**) which could be esterified at the C-20 position to afford (−)-batrachotoxin (**252**). Moroever, the authors also prepared (+)-batrachotoxin leading to the identification of this enantiomer as a fairly potent channel antagonist which likely shares some overlapping binding regions to the inner pore cavity as the natural antipode.

The Du Bois route to batrachotoxin is a testament to the power of chemical synthesis in addressing biological questions not answerable using naturally occurring substances alone. Moreover, the power of vinyl radical cyclization cascades to enable the rapid assembly of complex molecular complexity was on full display during this exercise in complex molecule total synthesis.

4.3. Barriault's formal synthesis of (±)-triptolide (2016)

Triptolide (**271**), a diterpene triepoxide, was isolated in 1972 by Kupchan and coworkers from the Chinese thunder god vine (*Tripterygium wilfordii*).[174] Due to its potent antitumor, anti-inflammatory, and immunosuppressive properties, this natural product has been extensively studied from both a chemical and biological perspective; derivatives of **271** have

even entered clinical trials for the treatment of pancreatic cancer.[175–177] In 2016, Barriault and co-workers reported a formal synthesis of racemic triptolide using a vinyl radical polycyclization initiated by gold photoredox catalysis.[178]

Barriault's synthesis began with allyl magnesium bromide addition to commercially available benzaldehyde derivative **272** and following *in situ* global methylation, anisole **273** was formed in 79% yield. A four-carbon extension of the homoallyl side chain was achieved via cross metathesis of **273** and methacrolein using Grubbs' second-generation catalyst followed by Wittig methylenation. The resulting diene (**274**) was then converted to aldehyde **275** by a hydroboration-oxidation sequence. Proline-catalyzed coupling of **275** with tetronic acid (**276**), and *in situ* reduction and triflation delivered a vinylogous acid triflate which could be converted into **277** with LiBr.

The key radical cyclization was initiated by irradiating a solution of **277** and the dimeric gold catalyst $[Au_2(dppm)_2]Cl_2$ (**278**) with ultraviolet light (365 nm). Under these conditions, vinyl radical **279** is presumably generated via reduction of the C–Br bond through a single electron transfer (SET) pathway involving the excited state gold complex. Vinyl radical **279** then undergoes a tandem radical cyclization cascade to give **280** after an oxidation event, presumably also mediated by the Au complex. The reaction mixture was then directly treated with sulfuric acid which furnished elimination product **281** in 64% yield overall yield from **277**. Finally, isomerization of the newly formed olefin (cat. $RuCl_2(PPh_3)_3$, DIPEA) into conjugation completed the synthesis of **282**, an intermediate which Berchtold had previously converted into triptolide by the seven-step synthetic sequence shown.[179]

At nine steps, Barriault's synthesis of **282** is quite concise owing to strategic incorporation of a redox neutral radical polycyclization cascade. Moreover, the use of photoredox catalysis to initiate such transformations offers both environmental and safety advantages over classic tin-based reagents and potentially dangerous radical initiators such as Et_3B/O_2 and AIBN.

Conclusions

The described works above give strong testament to the ability of radical cascades to rapidly assemble complex molecular frameworks. In particular, their ability to avoid falling under the influence of steric effects, which can plague many alternative reaction types, makes them particularly useful tools in the synthesis of complex, polycyclic molecules such as terpenes. Synthetic radical research of the past has established many of the "rules" governing the basic reactivity and cyclization modes of free radicals.[1–3,32,33] Modern day efforts seek to exploit more ubiquitous functional groups as radical progenitors, develop more environmentally benign radical reactions, and to merge radical chemistry with that of transition metal catalysis and organocatalysis.[180–192] *So what is left to explore?* While many of the aforementioned areas still offer many exciting avenues of inquiry, one could argue that stereocontrol over HAT processes which form stereogenic centers (both diastereocontrol and especially enantiocontrol) is very much an unsolved problem–especially in the realm of small molecule catalysis.[193,194] The synthesis of 6-*epi*-ophiobolin N (Section 3.5) highlights such challenges as the authors had to take a largely empirical approach to improving the reaction outcome, the results of which were far from ideal. Thus, there is much reason to

expect that the future of synthetic radical chemistry will feature many exciting areas of research, with the possibility of elevating the field of complex molecule synthesis to greater heights than is currently imaginable.

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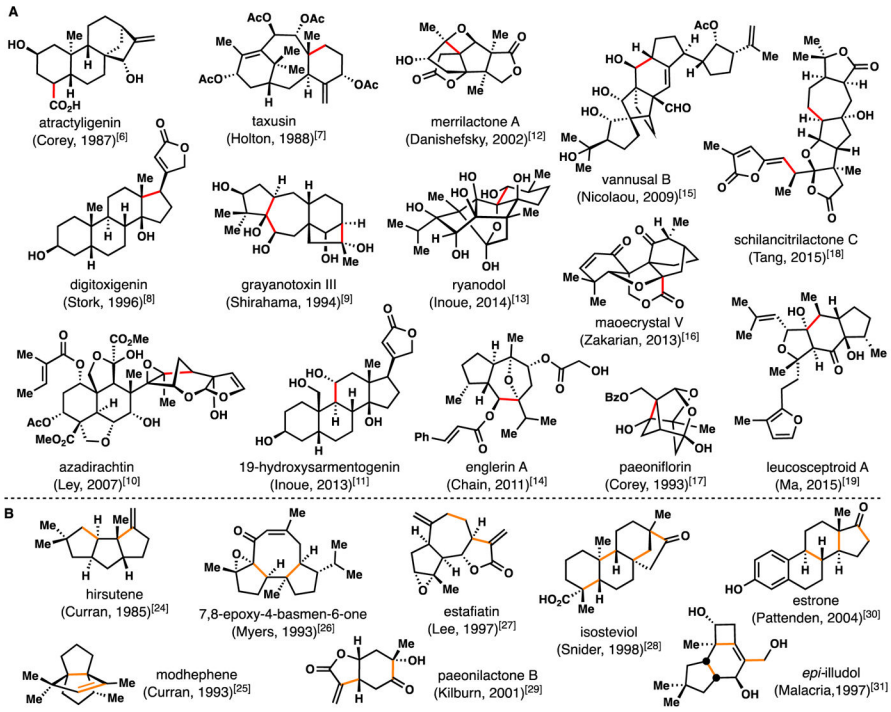


Figure 1.

Terpenoid natural products prepared using key radical C–C bond forming reactions. **A**) Selected total syntheses of highly complex targets which have employed a radical cyclization as a key step (C–C bond formed shown in red). **B**) Selected syntheses which have utilized radical cascade processes to form multiple carbon-carbon bonds in a single step (C–C bonds formed shown in orange.

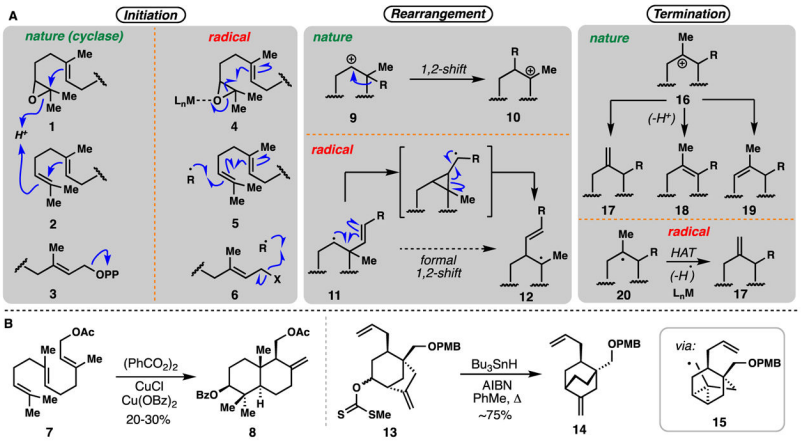


Figure 2.

Biosynthesis vs. radical synthesis. A) Key features of terpene biosynthesis that can be mimicked with radical chemistry. B) Selected examples in synthesis.

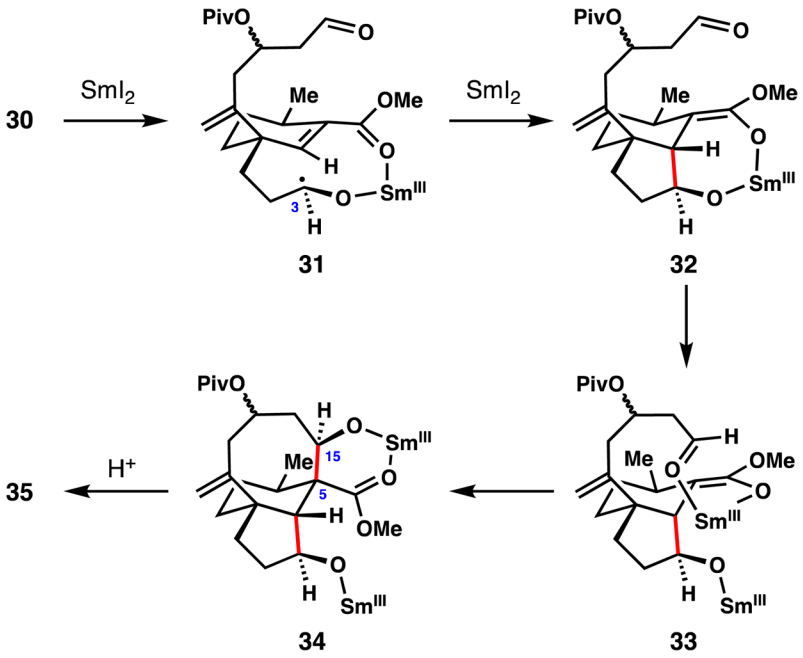
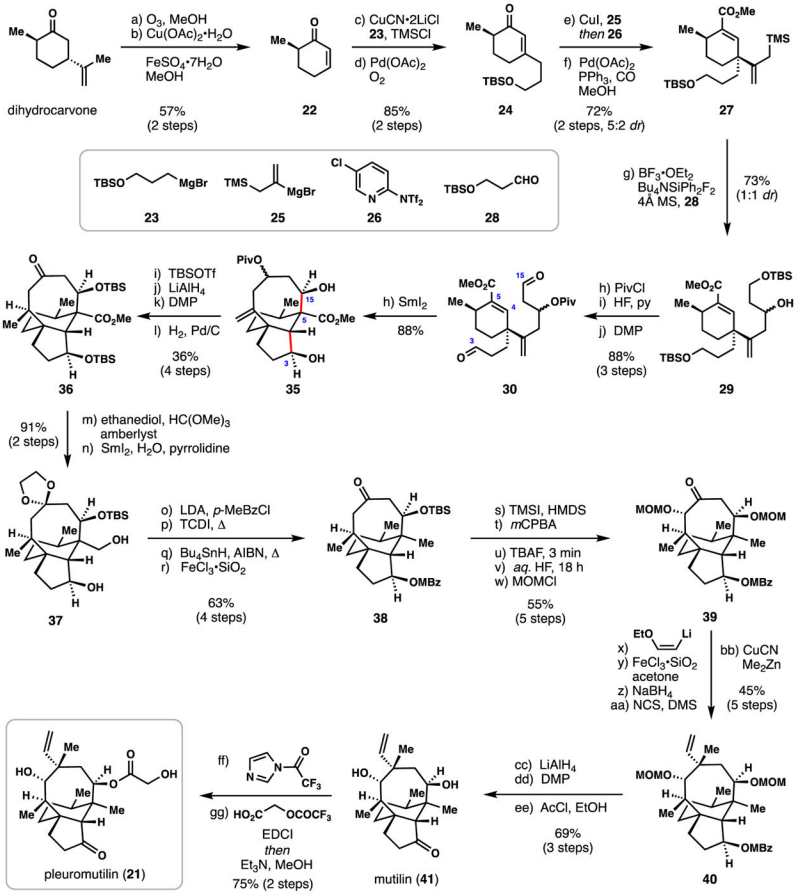
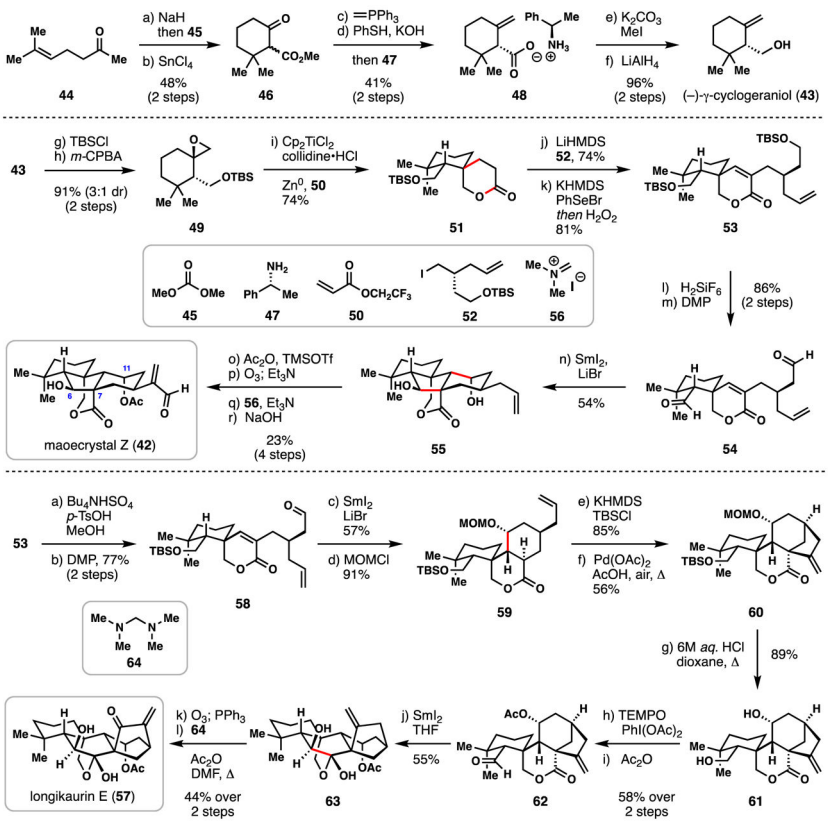


Figure 3.
Analysis of Procter's key cascade sequence.



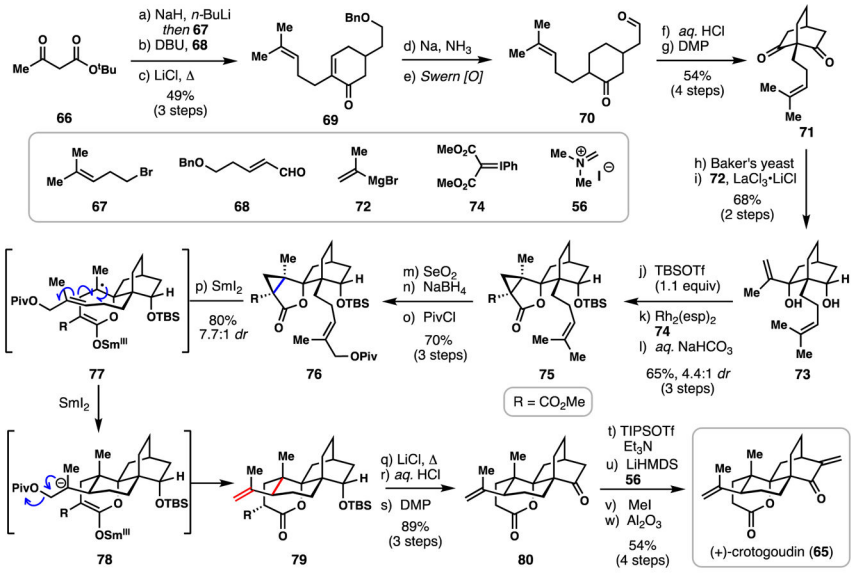
Scheme 1.

Procter's total synthesis of (+)-pleuromutilin (**21**).



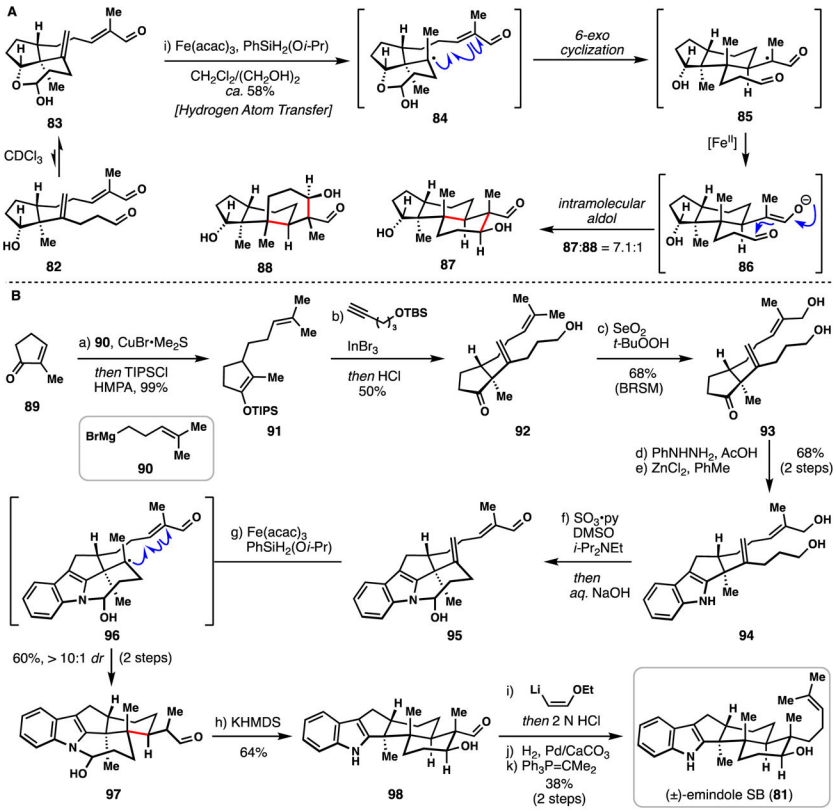
Scheme 2.

Reisman's syntheses of (−)-maoecrystal Z (**42**) and (−)-longikaurin E (**57**).



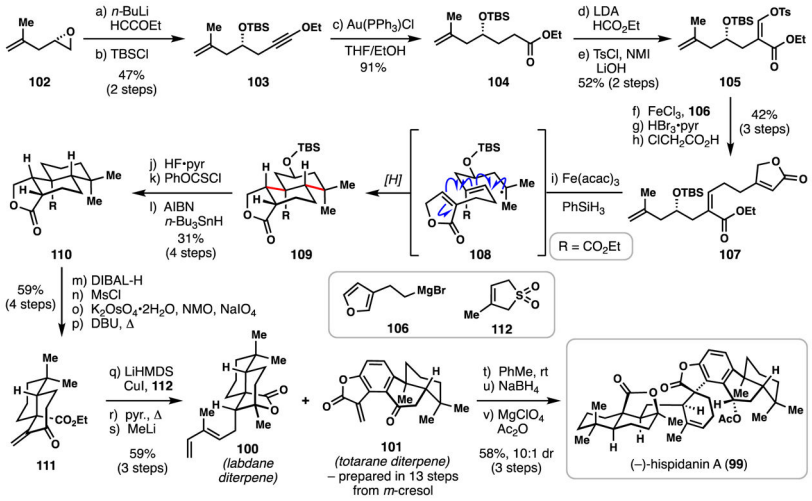
Scheme 3.

Carreira's synthesis of (+)-crotogoudin (**65**).



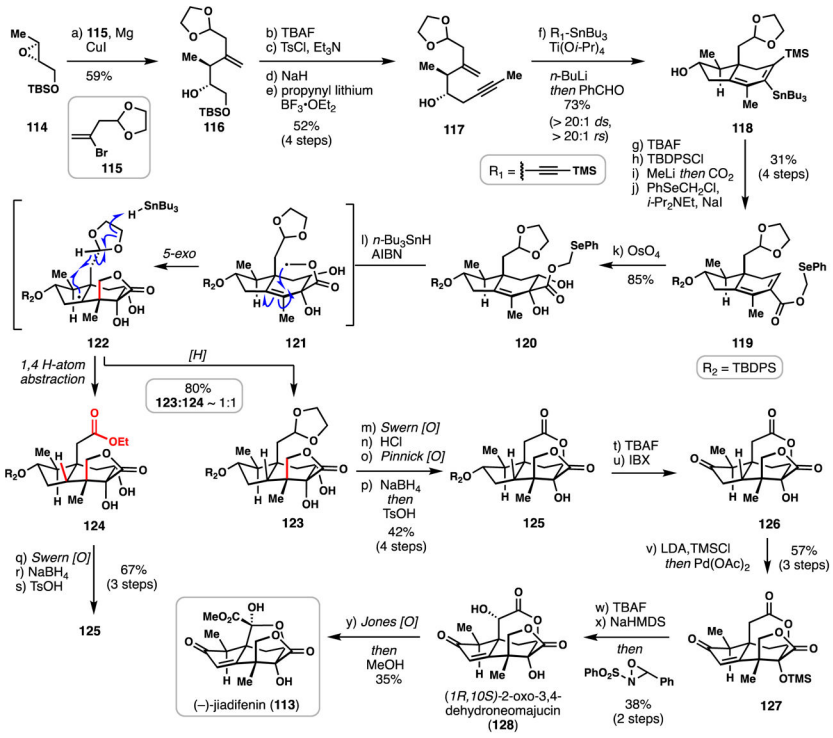
Scheme 4.

Pronins's synthesis of (±)-emindole SB (**81**)



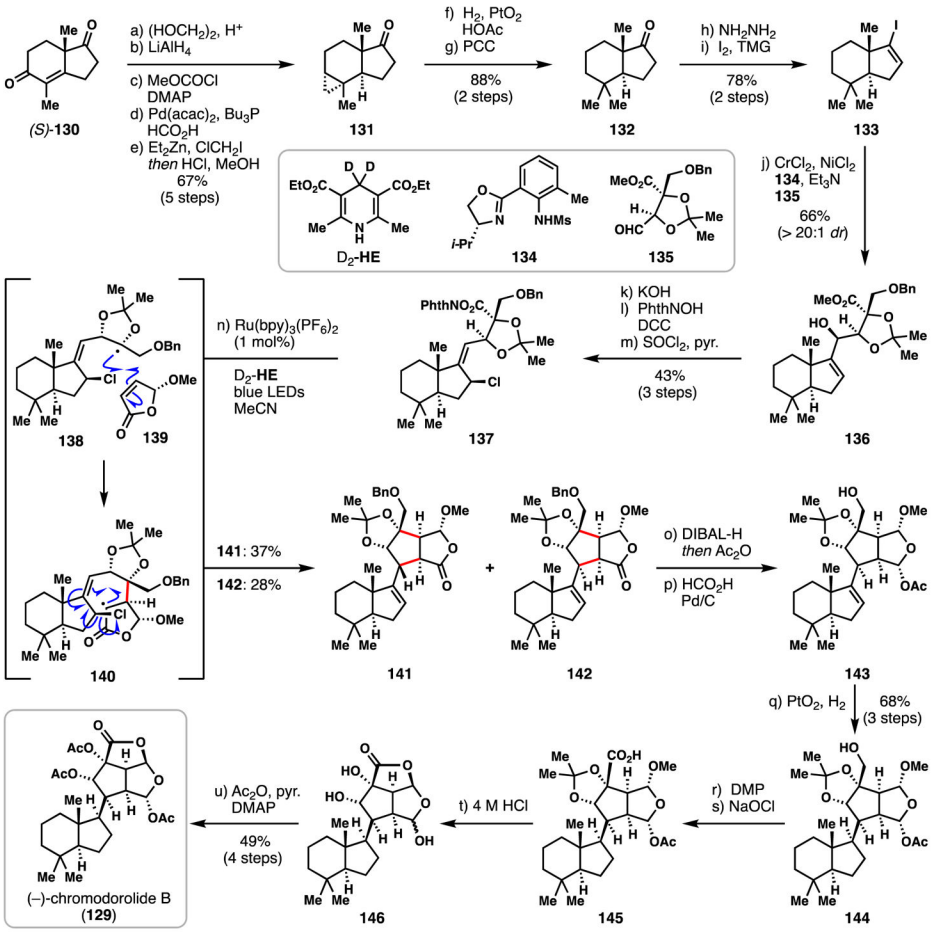
Scheme 5.

Liu's synthesis of (−)-hispidanin A (**99**).



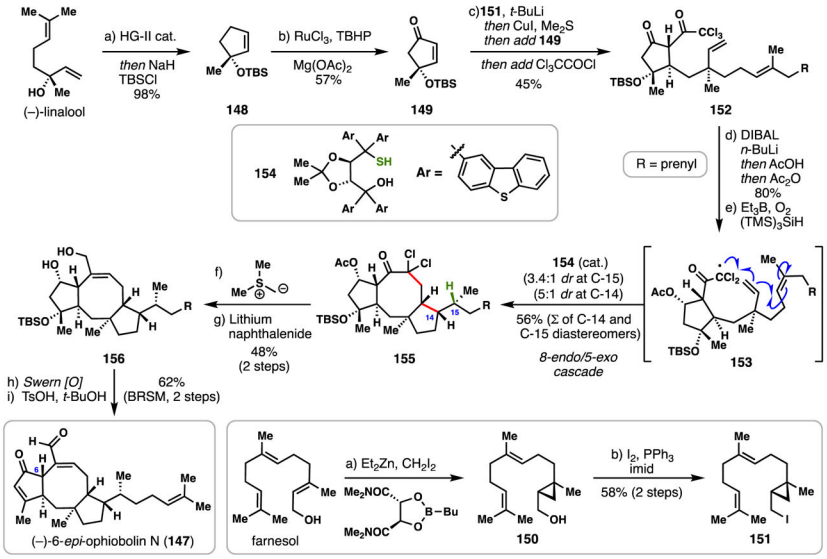
Scheme 6.

Micalizio's synthesis of (−)-jiadifenin (**113**).



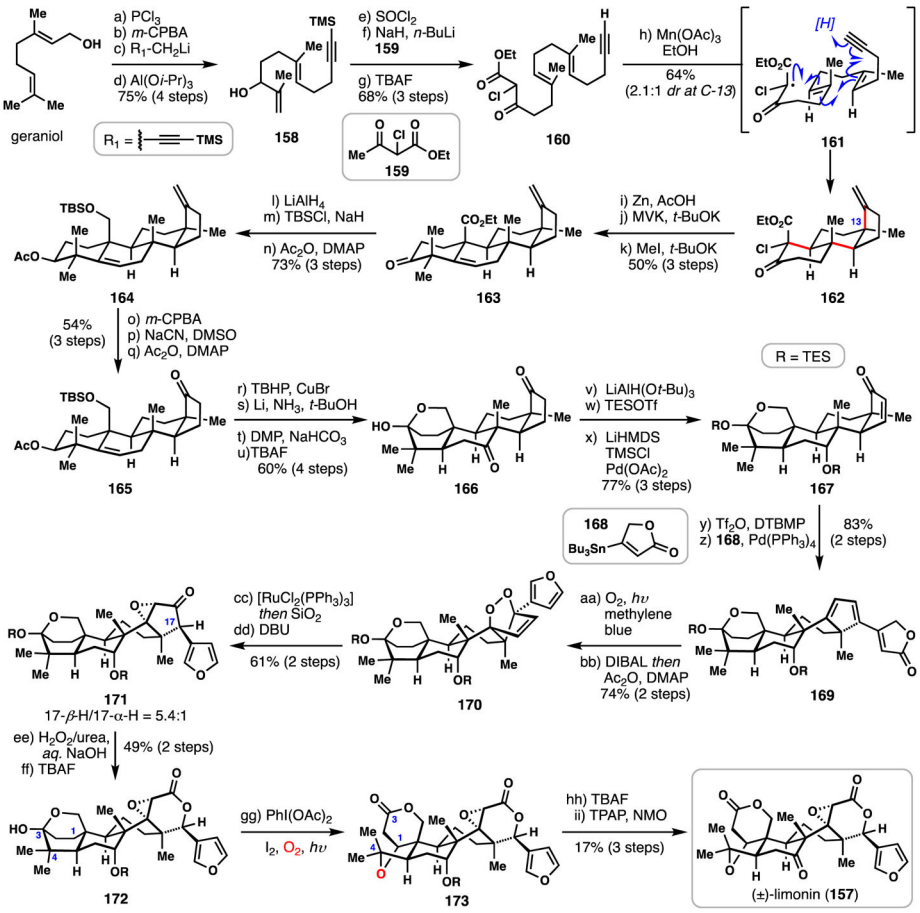
Scheme 7.

Overman's synthesis of (−)-chromodorolide B (**129**).



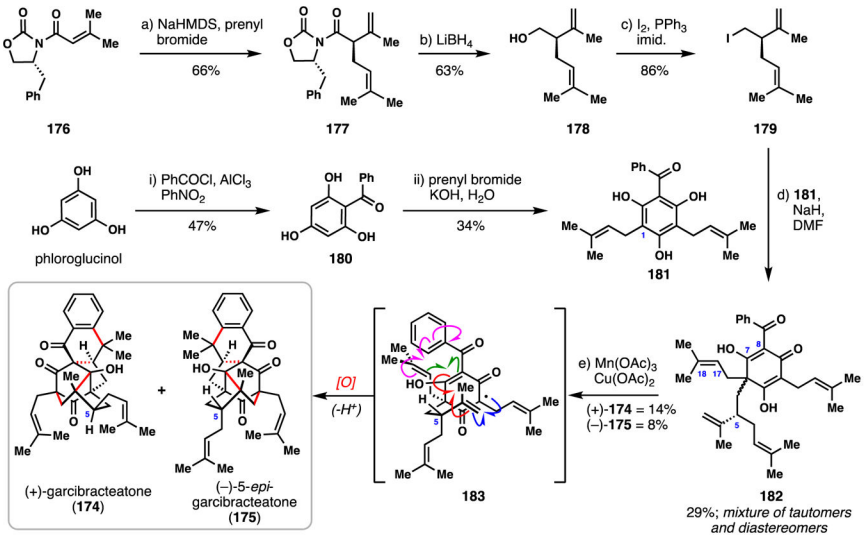
Scheme 8.

Maimone's synthesis of (−)-6-*epi*-ophiobolin N (**147**).



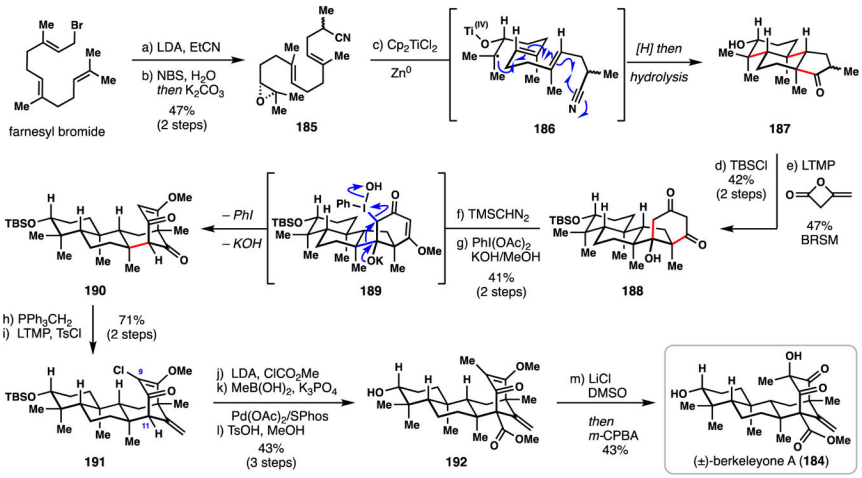
Scheme 9.

Yamashita's synthesis of (±)-limonin (**157**).



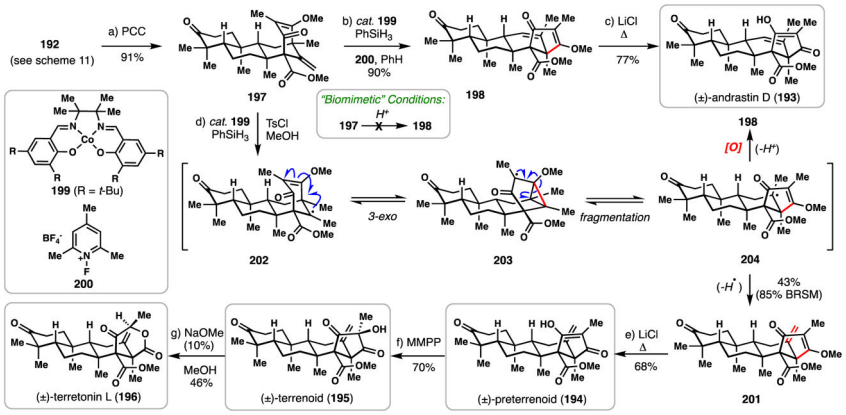
Scheme 10.

George's total synthesis of (+)-garcibracteatone (**174**) and (−)-5-*epi*-garcibracteatone (**175**).



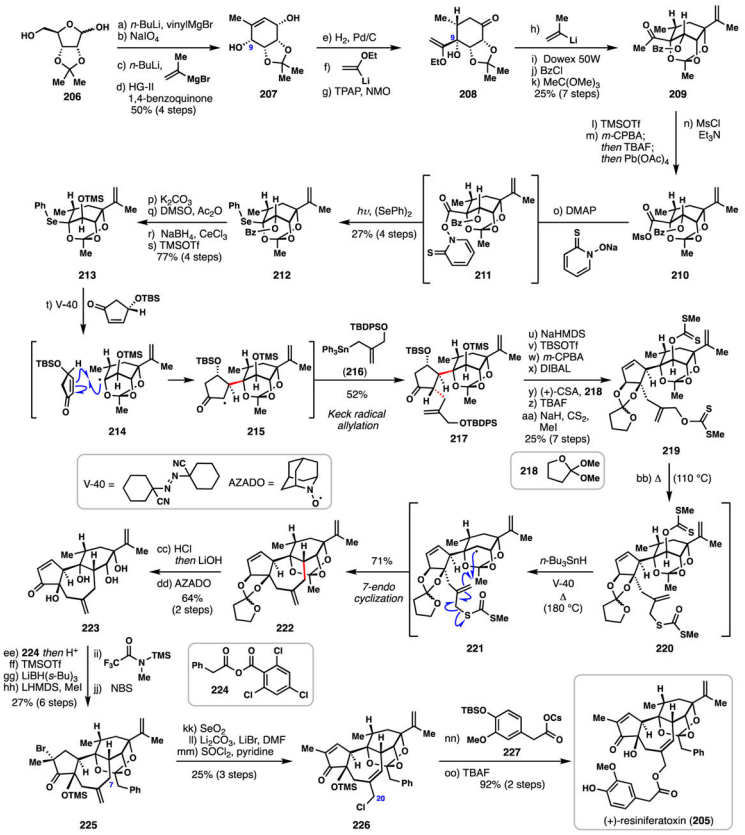
Scheme 11.

Maimone's total synthesis of (±)-berkeleyone A (**184**).



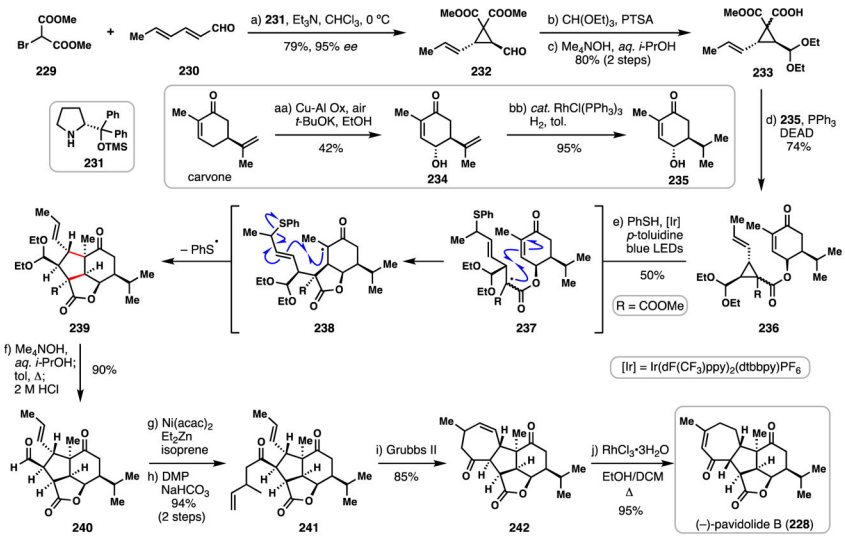
Scheme 12.

Radical-based conversion of berkeleyone congeners into andrastin and terretonin frameworks.



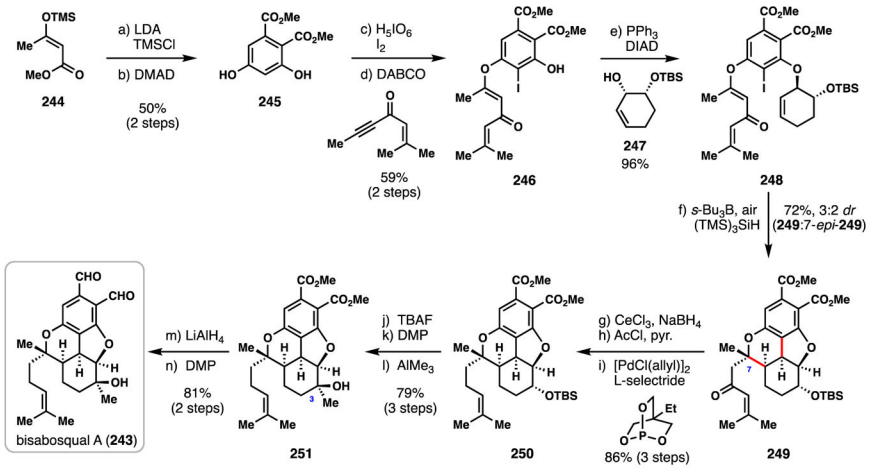
Scheme 13.

Inoue's synthesis of (+)-resiniferatoxin (**205**)



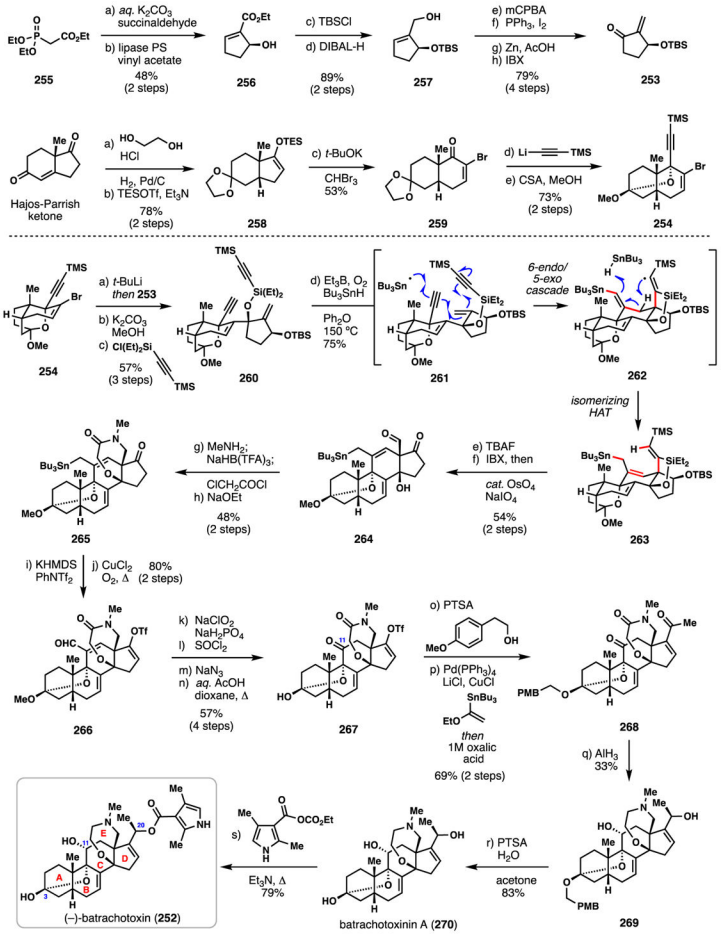
Scheme 14.

Gong and Yang's synthesis of (−)-pavidolide B (**228**).



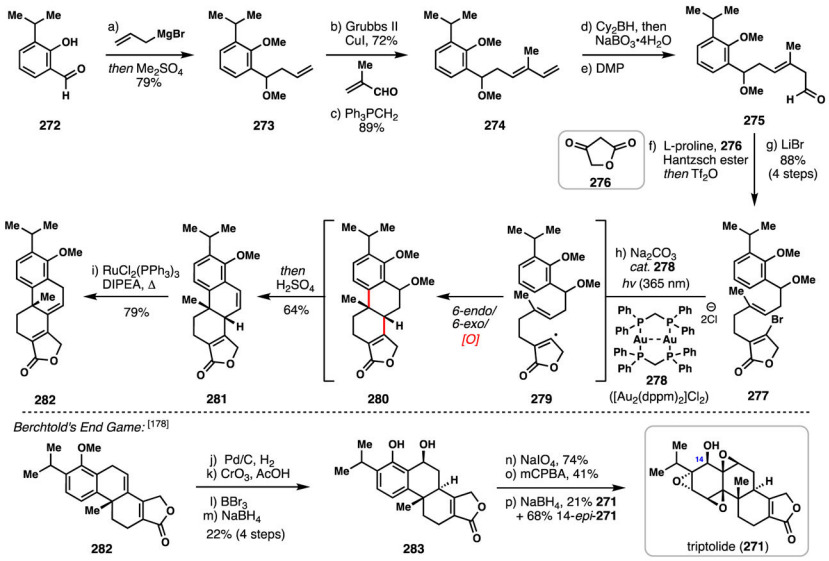
Scheme 15.

Parker's synthesis of (±)-bisabosqual A (**243**).



Scheme 16.

Total synthesis of (−)-batrachotoxin (**252**) by Du Bois and co-workers.



Scheme 17.

Barriault's formal synthesis of (±)-triptolide (**271**)