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Allylative Approaches to the Synthesis of Complex Guaianolide Sesquiterpenes from *Apiaceae* and *Asteraceae*

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Abstract

With hundreds of unique members isolated to date, guaianolide lactones represent a particularly prolific class of terpene natural products. Given their extensive documented therapeutic properties and fascinating chemical structures, these metabolites have captivated the synthetic chemistry community for many decades. As a result of divergent biosynthetic pathways, which produce a wide array of stereochemical and oxidative permutations, a unifying synthetic pathway to this broad family of natural products is challenging. Herein we document the evolution of a chiral pool-based synthetic program aimed at accessing an assortment of guaianolides, particularly those from the plant family *Apiaceae* as well as *Asteraceae*, members of which possess distinct chemical substructures and necessitate deviating synthetic platforms. An initial route employing the linear monoterpene linalool generated a lower oxidation state guaianolide, but was not compatible with the majority of family members. A double allylation disconnection using a carvone-derived fragment was then developed to access first an *Asteraceae*-type guaianolide and then various *Apiaceae* congeners. Finally, using these findings in conjunction with a tandem polyoxygenation cascade, we developed a pathway to highly-oxygenated nortrilobolide. A variety of interesting observations in metal-mediated aldehyde allylation and alkene polyoxygenation are reported and discussed.

Graphical Abstract

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ASSOCIATED CONTENT

Supporting Information

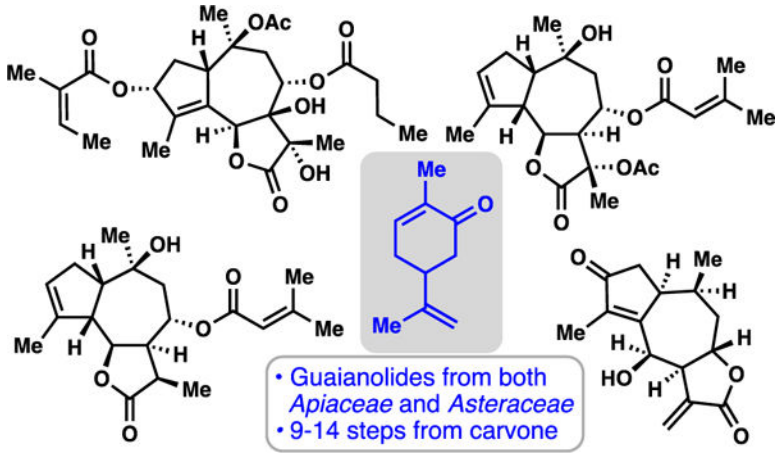
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b08001.

X-ray crystallographic data for **F1** (CIF)

X-ray crystallographic data for **80** (CIF)

Experimental procedures and spectroscopic data (PDF)

The authors declare no competing financial interests.



Introduction

Humans have experimented with plant-derived sesquiterpenes as medicine, poison, flavoring, and fragrance for several millenia.[1] Amongst such natural products, the large family of guaianolide lactones represents a particularly diverse and important source of bioactive metabolites.[2] Notably, such compounds have been heavily investigated for the treatment of inflammation and cancer among other ailments; certain derivatives have even advanced into human clinical trials.[1–3]

Although detailed biosynthetic blueprints are missing for most guaianolide members, it is generally assumed that an oxidized germacrene-type macrocycle (see **1**) serves as the precursor to guaianolides (Figure 1).[4] Of critical importance is the stereochemistry surrounding the lactone ring, particularly the configuration of the proton labelled H_a in orange. In the plant family *Asteraceae*, guaianolides produced (see **2**) typically have a β-configured proton at this center (guaianolide C6 position) with the 5,7-fused lactone being *trans* configured and thus costunolide (**1** where R = H and H_a is β) appears to be a biosynthetic precursor. Notably terpene cyclases in this family forge products with *cis* stereochemistry at the 5,7-fused carbocycle ring junction with α-configurations of the protons at the newly-formed C1 and C5 positions. Also, present in many members is a $\Delta_{11,13}$ alkene, thus making many *Asteraceae* guaianolides potentially protein reactive via *hetero*-Michael reactions with reactive cysteine residues,[5,6] a theme that presumably underpins much of their significant documented bioactivity.[1–2]

Guaianolides obtained from plants of the *Apiaceae* family (aka slovanolides, see **3**) generally feature the opposite configuration at C6 (see H_a) and possess *cis* stereochemistry at the 5,7-fused lactone ring junction. Upon enzymatic cyclization of **1**, a *cis*-fused 5,7 ring system is also made, but with the opposite configurations at C1 and C5 relative to *Asteraceae* guaianolides. These differences can have important ramifications when using chiral pool starting materials available in only one enantiomeric series (*vide infra*). *Apiaceae* guaianolides typically do not possess $\Delta_{11,13}$ unsaturation and thus are not likely covalent modifiers of cysteine residues in proteins in most cases. Finally, **2** and **3** are both 6,12-guaianolides owing to the position of the lactone, but when a free hydroxyl group is present

at C8, an isomeric 8,12-guaianolide (see **4**) can arise; this process has been noted in a variety of saponification studies of guaianolides and is presumably more favorable for the *Apiaceae*-derived systems.

The stereochemical divergence of these pathways combined with extensive late-stage C-H oxidation leads to a truly incredible array of highly complex sesquiterpenes (Figures 2 and 3). Figure 2 highlights a small sampling of *Asteraceae* members (**5**–**11**) showcasing various oxidation patterns. Notable is the 8,12-guaianolide mikanokryptin (**8**) which features unusual, inverted C6 stereochemistry. Absinthin (**10**) and ainsliatrimer (**11**) highlight the occurrence of higher order *Asteraceae* members which are often formed via pericyclic reactions amenable to biomimetic synthesis.[6c,7]

The complexity found in slovanolides can exceed that of the *Asteraceae* guaianolides from a stereochemical and oxidative perspective (Figure 3).[2b] In analogy to *Asteraceae* members, the simplest congeners (see **12**–**17**) do not possess oxidation at the C8 position, but can range from lowly oxidized sinodielide A (**12**) to the more heavily oxidized ferulide (**17**). The majority of *Apiaceae* members, however, do possess oxidation at C8 although many are unoxidized at the C11 position (see **18**–**22**). Of note, ferulidin (**22**) is an example of an 8,12-guaianolide from *Apiaceae*. The most highly oxidized guaianolides possess hydroxyl groups at C8, C11, and often elsewhere (**23**–**30**). From an oxidation state perspective, the ferupennin (see **25**–**27**) and trilobolide/thapsigargin (see **28**–**30**) members represent the pinnacle of complexity in this series. Unlike most guaianolides, these structures can be found with oxidation at the C5, C7, C14, and C15 positions.

Given the structural complexity and medicinal properties of guaianolide lactones it is not surprising that such natural products have served as popular synthetic targets for decades resulting in over 50 syntheses.[8,9] The stereochemical and oxidative diversity found in the guaianolides makes a unifying synthetic strategy challenging. Most synthetic work has focused on the syntheses of a small subset of the *Asteraceae* guaianolides, while the trilobolide/thapsigargin subtypes represent the only *Apiaceae* members chemically synthesized. Herein we detail the evolution of a synthetic program aimed at synthesizing multiple, diverse guaianolide members, work that has resulted in syntheses of mikanokryptin (**8**), sinodielide A (**12**), slovanolide **18**, montanolide (**23**), and nortrilobolide (**29**).

Results and Discussion

Synthetic Planning.

The chiral pool of terpenes has been featured prominently in past syntheses of guaianolides,[9] and given our laboratories interest in this area,[10] we also began our investigations there. In analyzing past chiral pool approaches to guaianolide skeletons (see **31**) two major strategies have been employed (Figure 4). In the first, the abundant sesquiterpene lactone (–)-α-santonin has been utilized,[11] often employing classic dienone photochemical rearrangements.[12] Remarkably, over 30 unique guaianolides have been assembled from this chiral pool building block.[11] This work is best applied to *Asteraceae* members owing to the absolute configuration of natural (–)-α-santonin. The second major disconnection involves the use of a ring-contracted cyclic monoterpene as a surrogate for the guaianolide

cyclopentane ring system.[9] The availability of many cyclic monoterpenes in either enantiomeric form makes this route potentially applicable to a wide array of members. In this work, we further investigated this structural disconnection as well as a third route which traces the guaianolide skeleton back to a *linear* monoterpene building block.

Initial Linalool-Based Design: Total Synthesis of Sinodielide A.

The linear monoterpene linalool, which possesses an asymmetric tertiary alcohol stereocenter evocative of the C10 position of many guaianolides, was chosen as a starting point (Scheme 1). We envisioned that the cyclopentane ring system could be constructed rapidly via a Pauson-Khand reaction and the 7-membered ring closed by exploiting the nucleophilic terminal prenyl group.[13,14] Thus (–)-linalool was converted into ester **32** via deprotonation and reaction with the mixed anhydride of 2-butynoic acid. This material underwent smooth Pauson-Khand (PK) reaction using dicobalt octacarbonyl resulting in strained bicyclic lactone **33** (65% yield, 5:2 *dr*) which was rapidly reduced with DIBAL to afford triol **34**.[15] The major isomer formed in the PK reaction was found to have a *cis* relationship between the C1 proton and C10 methyl group which is unusual for most guaianolides. Nevertheless, this stereochemical pattern is found in absinthin (**10**) and thus we viewed this outcome at the time as potentially amenable to the preparation of *ent*-**10** via Diels-Alder dimerization of **35** (See inset, Scheme 1).[16] Notably, a past route to **10**, which relies on the α-santonin photorearrangement, has to invert this center via a multi-step procedure.[7a]

We envisioned closing the seven-membered ring, via Barbier-type coupling of an allylic chloride in analogy to our work on chatancin.[17] Thus **34** was converted into aldehyde **37** via one-pot silylation (TESOTf, collidine) and allylic chlorination (SO_2Cl_2) to give **36** followed by a chemoselective chromium-mediated oxidation. Allylic chloride **37** smoothly participated in an intramolecular NHK-type coupling generating **38** in 57% yield and with good diastereoselectivity. We note that we were unable to directly forge the same corresponding C–C bond from a similar allylic chloride formed from ester **33** despite the apparent strain in the lactone ring.[18] Unfortunately, the relative stereochemistry in **38** does not correspond to that found in *Asteraceae*-type guaianolides, such as **10**, but instead has the correct relative configuration for *Apiaceae* members. We decided therefore to advance this material to lower oxidation state slovanolides featuring $\Delta_{1,10}$ unsaturation (Scheme 1). The hallmark *cis*-fused 6,12-lactone was assembled through straightforward means involving hydroboration and oxidation giving **39** which could be converted to isomerically pure **40** via deprotonation and kinetic proton quench. Notably the combination of TBAF and AcOH served as a both a proton source as well as desilylating reagent in this reaction. Following one-pot transpositive allylic reduction (DIAD, PPh_3, IPNBSH)[19,20] tertiary alcohol **41** was generated which could be cleanly dehydrated to give the simple, apoptosis-inducing guaianolide sinodielide A (**12**).[21]

While this initial route was successful in accessing a lower oxidation state guaianolide, the scope of natural products obtainable is lacking. Although the formation of a *cis*-lactone is desirable in many contexts, and not accessible by many guaianolide synthetic strategies, the

need to install C-8 oxygenation–which is present in the majority of slovanolides–facilitated a new approach.

A Double Allylation Disconnection: Total Synthesis of Mikanokryptin, an *Asteraceae* Guaianolide.

Our second-generation retrosynthesis of guaianolides targeted structural motif **42** via a double allylation disconnection of a ten-carbon fragment (see **43**) with that of a 5-carbon piece (see **44**) (Figure 5). This strategy was expected to offer considerable flexibility as: *i*) the C-1 stereocenter is available in either enantiomeric form from the chiral pool of cyclic monoterpenes, *ii*) the $\Delta_{10,14}$ alkene could be reduced or hydrated to afford motifs common to many guaianolides, and *iii*) the C6–8 stereocenters could potentially be controlled by various allylation conditions.

We began our investigations by preparing aldehyde **47**, the requisite ten-carbon fragment (Scheme 2).[9n] A three-step route to this piece was developed from carvone involving: *i*) one-pot allylic chlorination/Luche reduction, *ii*) hydroxyl silylation, and *iii*) one-pot chemoselective ozonolysis/aldol condensation. This chemistry was robust and allowed for multi-gram procurement of aldehyde **47**. We then merged **47** with allylic bromide **48** under indium-mediated allylation conditions generating **49** (67%, 2:1 *dr* at C-6) on multigram scale. Notably, the inclusion of one equivalent of water both aided in the diastereoselectivity of this transformation as well as reduced formation of the corresponding 6,12-lactone framework. The stereochemical relationship between the C6 and C7 centers in **49** meant that we would inevitably again (as in the case of **38**) form a *cis*-fused 6,12-lactone system upon ring closure, however, the relationship relative to C1 is incorrect for *Apiaceae* members. This finding though presented a unique opportunity to access mikanokryptin (**8**), which, while a member of the *Asteraceae*-type guaianolides, possesses inverted C6 stereochemistry. Notably, such members cannot be prepared in a straightforward manner from α-santonin.

With large quantities of **49** we proceeded toward mikanokryptin (**8**) (Scheme 2). Mild deacetalization with concomitant silylation according to Fujioka and Kita's protocol (TESOTf, collidine)[22] generated **50** and set the stage for the second key intramolecular allylation. Treating **50** with $SnCl_2$ in the presence of NaI lead to a remarkably clean and diastereoselective allylation reaction presumably via an *in-situ* generated allylic iodide. This reaction provided multi-gram batches of **51** which additionally possesses the desired 8,12-guaianolide lactone system.

The efficient conversion of **50** to **51** was the result of extensive optimization efforts involving a variety of known aldehyde/allyl halide coupling procedures (Table 1). Initial investigations involving the Nozaki–Hiyama–Kishi (NHK) coupling afforded the desired product (**51**), but with diminished yield (10%) and diastereoselectivity (2:1 *dr* at C8) (Entry 1). Interestingly, the major product produced under these conditions was cyclooctane **53**, formed as a mixture of diastereomers. Competition between the formation of 7- and 8-membered ring–the latter of which we attribute to a radical process–was also observed in samarium iodide-mediated (entry 2) and zinc-mediated (entry 3) conditions.[23] Indium-mediated allylation conditions of an *in-situ* generated allylic iodide were selective for

formation of **51**, but inefficient overall (entry 4). Finally, tin(II) chloride proved to be a superior reductant in this system, giving high yields of **51** even on multi-gram scales.

To complete the synthesis of mikanokryptin (**8**), a chemoselective reduction of the $\Delta_{10,14}$ alkene was required. While we were unable to perform such a reaction directly,[9n] the *exo*-methylene lactone was easily protected as its methanol adduct (*cat.* NaOMe, MeOH) allowing for clean olefin hydrogenation (*cat.* PtO_2/H_2) in the same vessel generating **52**. Upon deprotecting **52**, we gratifyingly found that TBAF was sufficiently basic to promote the retro conjugate addition reaction of methanol giving a 5:2 mixture of *exo*-methylene lactone:methanol adduct, both with concomitant deprotection of the secondary hydroxyl group. On larger scales, we elected to utilize DBU as base for the E1cB reaction, which was somewhat higher yielding. Finally, a near quantitative yielding allylic oxidation with manganese dioxide generated mikanokryptin. The robustness of this route allowed for the preparation of substantial quantities of material (>1g) which in turn helped fuel target identification studies of this unexplored cytotoxic natural product.[24]

Reversing Allylation Stereochemistry for Entry into Complex Slovanolides.

Given our success in forging stereochemical motifs needed for *cis*-fused 6,12-lactones, the complex slovanolides produced by the *Apiaceae* plant family (see Figure 3) were logically the next targets using the double allylation strategy. Many of these natural products, particularly those with *cis*-fused lactones, have remained inaccessible by synthesis, and the most complex members (*i.e.* trilobolide/thapsigargin-type) have served as grand challenges to the field of total synthesis for nearly two decades.[9b,9c,9d,9m,9o,25] In order to gain access to slovanolides such as **18** and montanolide (**23**), a disparate stereochemical outcome in the initial allylation of aldehyde **47** (or more precisely *ent*-**47** for these targets) was needed (Figure 6). Specifically, the configurations at C6 and C7 (relative to C1) requires inversion compared to the mikanokryptin allylation outcome (i.e *ent*-**47** needs to produce *diast*-**49** and not *ent*-**49**). Nucleophilic additions to aldehydes that are quite similar to **47** have been studied,[26] and a variety of stereochemical outcomes at C6 have been reported depending on the nucleophile and conditions. We were therefore hopeful that alternative allylation conditions and/or reagents could provide us with the desired configuation.

It was discovered that *ent*-**47** could be merged with allylic bromide **54** under Zn^0-mediated allylation conditions to give lactone **55** in good yield and with the correct C6 configuration in the major diastereomer (Scheme 3A).[27] While the diastereoselectivity of this transformation was not high, this reaction was robust and enabled the procurement of gram-quantities of material. Worth noting, indium-mediated allylations employing **54** slightly favored the undesired diastereomer in analogy to the mikanokryptin work.[9n] The presence of catalytic Zn(II) chloride was necessary to promote cyclization to the requisite lactone. Sodium borohydride in methanol cleanly reduced the reactive exocyclic methylene lactone in nearly quantitative yield giving alcohol **56** after removal of the *para*-methoxybenzyl group. A Dess-Martin periodinane oxidation of **56** then generated the somewhat sensitive aldehyde **57** thus setting up another key 7-membered ring forming allylation.

A reductive, titanocene-mediated allylation ($TiCp_2Cl_2$, Zn^0) generated tricycle **58**,[28] largely as a single isomer and with the correct configuration at the C-8 stereocenter as found in slovanolides. Significant experimentation went into achieving this stereochemical outcome which was crucial as we were unable to invert this center in one-step via Mitsunobu reaction of 8-*epi*-**58** (*i.e.* **64**) with a carboxylic acid side-chain found in slovanolides (Scheme 3B). Furthermore, our previously employed Sn^{II}-mediated conditions give exclusively the wrong stereochemical outcome at C8 both with and without exogenous transition metals (see entries 1–4). NHK coupling conditions afforded a small amount of desired **58**, but were still dominated by formation of **64** (entry 5). We found that samarium (II) iodide, both with and without additives, was selective in the formation of **58**, but ultimately low yielding (entries 6 and 7). Under these conditions chloride **66** was also formed, presumably via a *6-exo-trig* ketyl radical cyclization. It is noteworthy that with only simple changes to the reductant employed, a near complete reversal in selectivity could be achieved (entry 1 vs. 8). With the *5,7,5*-fused ring system in place, the senecioyl ester was attached via straightforward DCC-coupling giving **59** (Scheme 3A). This material was then subjected to Mukaiyama-type hydration employing cobalt catalyst **60**.[29,30] In accordance with Evans' findings on a related scaffold containing a *β*-configured hydroxyl group at C-7,[9o] the C10 stereocenter was set correctly during this process, albeit with diminished diastereoselectivity in this system; the topological differences imparted by the configuration of the C-7 stereocenter likely influence the radical coupling event. Finally, ester **61** could be converted into slovanolide **18** via a two-step sequence involving removal of the *tert*-Butyldiphenylsilyl protecting group (TBAF/HOAc) and one-pot reductive allylic transposition (DIAD, IPNBSH, PPh_3).[31]

Using a slightly modified route, key intermediate **59** could also be advanced to the more heavily oxidized slovanolide montanolide (**23**).[32] Enolate oxidation of **59** with Davis' oxaziridine followed by acetylation generated **62** in a stereoselective manner and with high yield. A similar endgame of formal radical hydration, deprotection, and reductive allylic transposition, resulted in the synthesis of **23**. The routes to **18** and **23** proceeded in only 12- and 14-steps respectively from carvone. Moreover, it is easy to envision expanding this chemistry to include allylic oxidation products **24**-**27** (Figure 3).

An Oxygen Stitching Strategy for the Synthesis of Heavily Oxidized *Apiaceae* Members.

While our studies so far had realized syntheses of a variety of guaianolides, our strategy did not easily lend itself to the preparation of the most heavily oxidized subtypes, namely the trilobolide (**28**) and thapsigargin (**30**) members. In particular, the presence of hydroxylation at C7 is troublesome synthetically given the chemistry developed so far (*vide supra*). Taking note of the relative spatial orientations of the oxygen atoms at C10, C7, and C11, however, we wondered if a polyoxygenation cascade using molecular oxygen could construct this motif in analogy to our work on the antimalarial cardamom peroxide (**67**) (Figure 7).[33] In this scenario, the complexity of trilobolide (**29**) can be reduced to that of butenolide **69** by way of a metal-catalyzed radical hydroperoxidation cascade.[34] If successful, much of the stereochemical complexity of the target could be installed in a single operation.

Our efforts began by retooling our prior slovanolide synthesis to access butenolide **69** (Scheme 4). Starting from lactone **55**, the PMB group was removed with DDQ and the

exocyclic olefin isomerized into the lactone ring using catalytic quantities of RuHCl(CO)$(PPh_3)_3$ in refluxing DCE.[35] Under optimized conditions this step could be telescoped with a mild, buffered TEMPO/bleach oxidation delivering sensitive aldehyde **70**. With this material in hand, yet another seven-membered ring-forming allylation was investigated. We found that our previously utilized $SnCl_2$/NaI-mediated conditions were quite effective in this setting, yet unlike in the cases of substrates **50** (Scheme 2) and **57** (Scheme 3), this reaction afforded a near equimolar mixture of alcohol diastereomers at C8 (Scheme 4). The lack of stereochemistry at C7 and C11 may contribute to this outcome. Inspired by reports on the use of exogenous transition-metals in combination with $SnCl_2$ as catalysts for allylation chemistry,[36] we found that addition of catalytic quantities of $PdCl_2$ afforded **71** as essentially a single diastereomer.[37] Moreover, this chemistry was easily scaled without a depression in yield. While the C8 hydroxyl group was set with an incorrect β-configuration during this process, it underwent facile Mitsunobu inversion with butyric acid to give **69**, a result in stark contrast to the reactivity of **64** (*vide supra*).

With **69** now secure, we were poised to examine the key polyoxygenation cascade. Subjecting **69** to classic Mukaiyama hydroperoxidation conditions ($Co(acac)_2$, Et_3SiH, O_2) lead to desired triol **72** after reductive workup in 15% yield and as a single diastereomer. While the yield of this transformation is low, three tertiary alcohols are formed in a single step and the stereochemical outcome at C7 and C11 was remotely controlled by the initial hydroperoxidation at C10 via the strategic peroxide handle. The successful reactivity window for this transformation was exceedingly small – nearly any variation to these conditions led to no desired product (Table 2). Only $Co(acac)_2$-based systems formed any product (entries 1 and 2). The major competing pathways were premature reduction of the peroxy radical intermediate forming alcohol **77**, and formation of an unstable peroxide tentatively assigned as **75**.[38] The prolonged exposure of these reactions to oxygen led to significant oxidative degradation resulting in mass balances of only ~50%. Notably, while manganese and iron-based catalysts afforded none of these products (entries 5 and 6), cobalt catalyst **60** was reasonably efficient in producing peroxide **76**, again the result of premature reduction of the radical intermediate (entry 4).[39] Finally, acetylation of **72** followed by desilylation with hydrofluoric acid intercepted triol **73**, thus marking the completion of a 12-step formal synthesis of **29**.[9m,9o,40]

A major challenge in the polyoxygenation cascade is presumably the addition of a peroxy radical to an electron-deficient π-system in combination with the ring flip in the 7-membered carbocycle necessary to accommodate this *6-exo* cyclization geometry.[41] These requirements presumably compete with simple reduction of the reactive intermediates. We wondered, however, if the oxygen stitching cascade could be a useful tool in other terpene settings, particularly those in which the cyclization requirements are more accommodating.

To this end, we targeted the eudesmane sesquiterpene boariol (**80**) as a way to examine the efficiency of this strategy in an alternative environment (Scheme 5).[42,43] Carvone Robinson annulation product **78**, prepared in one-step, was chosen as the starting material. Subjecting this enone to the tandem peroxidation conditions formed triol **79** after reductive work-up, presumably via the *bis*-peroxide intermediate shown. This transformation, which like **69**, also involves peroxy radical addition to an electron deficient π-system and *6-exo*

cyclization, proceeded in a respectable 50% isolated yield. Finally, lithium aluminum hydride induced stereoselective reduction of **79**, producing a tetraol which cyclized to boariol in 73% yield overall yield after treatment with protic acid (HCl). Overall, these results suggest the oxygen stitching strategy has utility in the rapid synthesis of polyol natural products. Moreover, in terms of efficiency, this 3-step route compares quite favorably to terpene synthetic strategies targeting similar molecules, yet assembling them via the oxidation of C-H bonds rather than the polyoxygenation of alkenes.[44]

Conclusion

In this report, we have detailed the evolution of an allylative approach to five complex guaianolide natural products from both the *Apiaceae* and *Asteraceae* plant families in 9–14 synthetic steps. Seeking to leverage abundant chiral pool building blocks, several strategies were explored. First, we examined the annulation and cyclization of the linear monoterpene linalool, ultimately finding a pathway toward the simple, stereochemical complexity-deficient *Apiaceae* members sinodielide A (**12**). Several oxidative and stereochemical challenges, however, limited the utility of this route in broader guaianolide contexts. A double allylation strategy employing a carvone-derived fragment proved more general and led to syntheses of several more complex guaianolides (see **8**, **18**, **23**), not accessible by previous strategies. Key to the success of this overarching blueprint were five distinct metal-mediated allylation events, each of which presented their own unique reactivity and stereochemical challenges. It is noteworthy that many of the stereocenters forged during these processes could be influenced by very simple changes to reagents and conditions utilized–in no instance were chiral reagents employed. Finally, we extended a previous polyoxygenation cascade strategy for endoperoxide synthesis to the formation of complex hydroxylated terpenes, namely nortrilobolide (**29**) and the eudesmane sesquiterpene boariol (**80**). In cases where peroxyradical addition is geometrically favorable, this reaction can quite efficiently and rapidly increase hydroxyl complexity. While significant interest has recently been placed on C-H activation routes to complex natural products, particularly terpenes, these results suggest polyoxygenation-based cascades could serve as alternative tools in the retrosynthetic planning stages. Further work in this area is underway and will be reported in due course.

Supplementary Material

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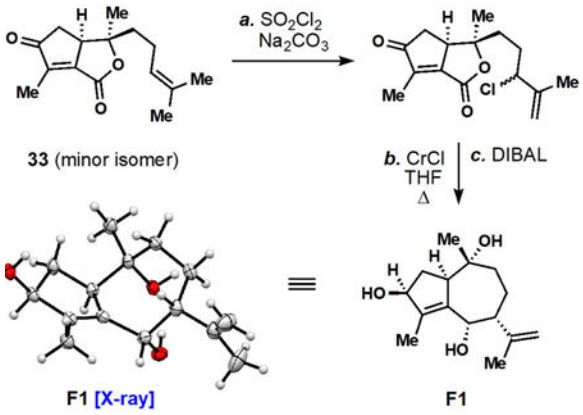

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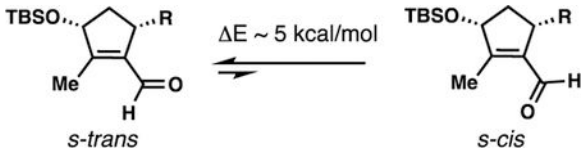

s-trans *s-cis*

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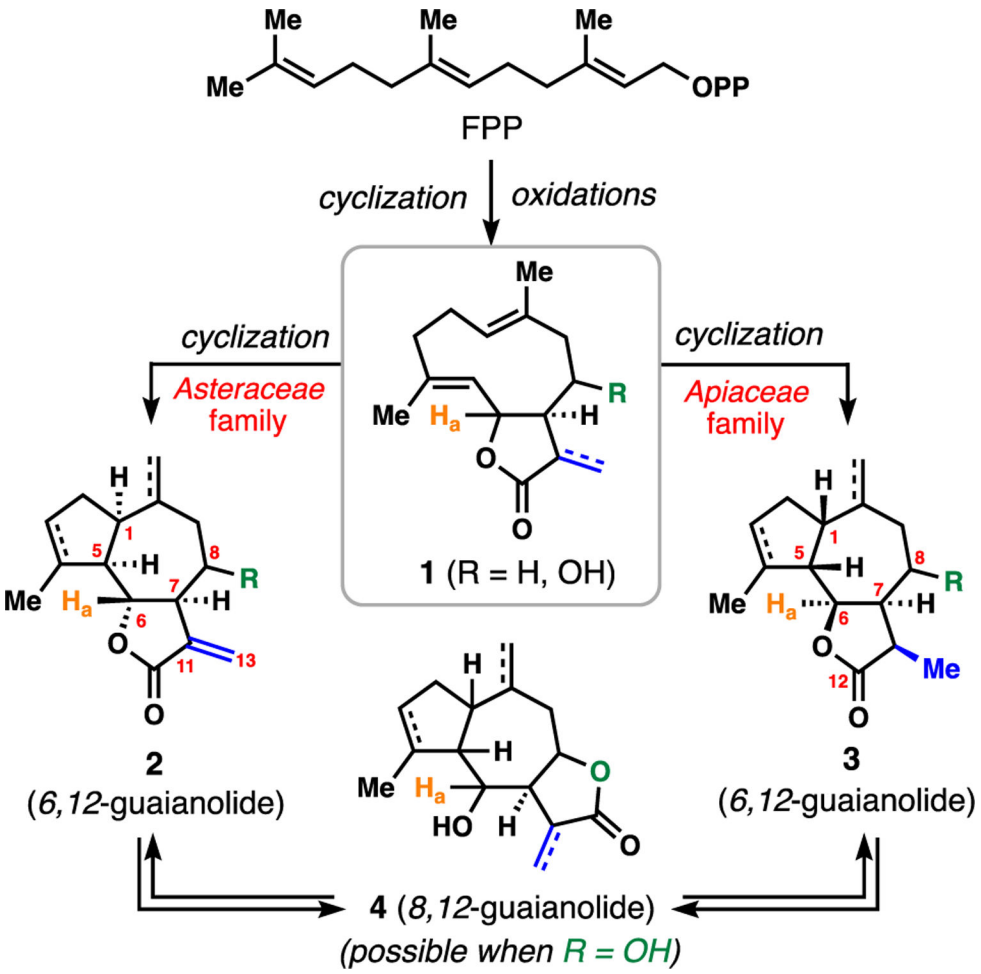


Figure 1.
General overview of guaianolide lactone biosynthesis in *Asteraceae* and *Apiacea*e.

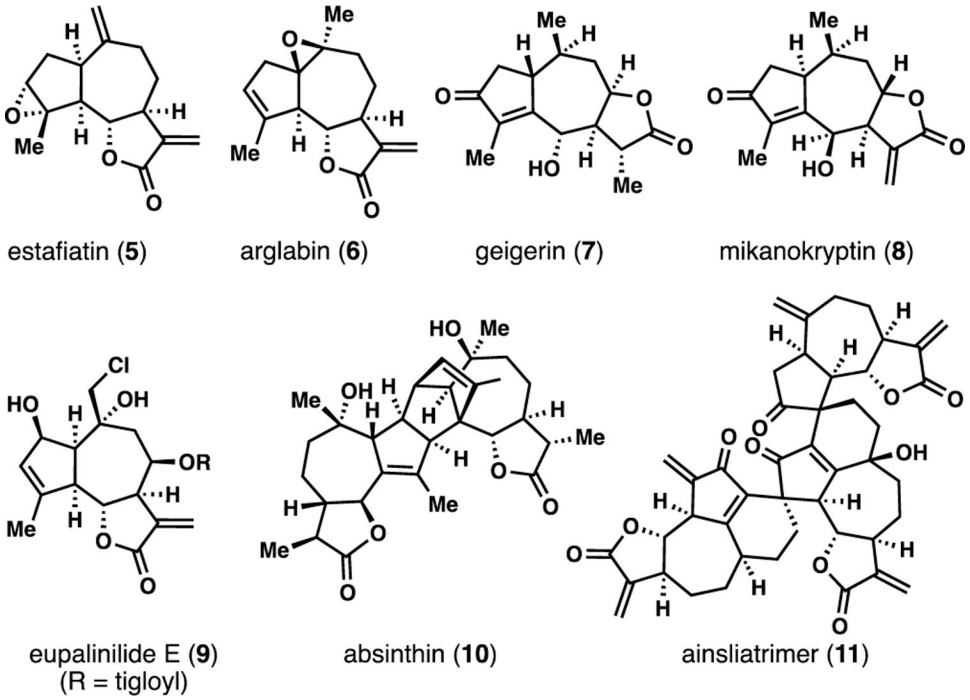


Figure 2.
Select guaianolide natural products from the plant family *Asteraceae*.

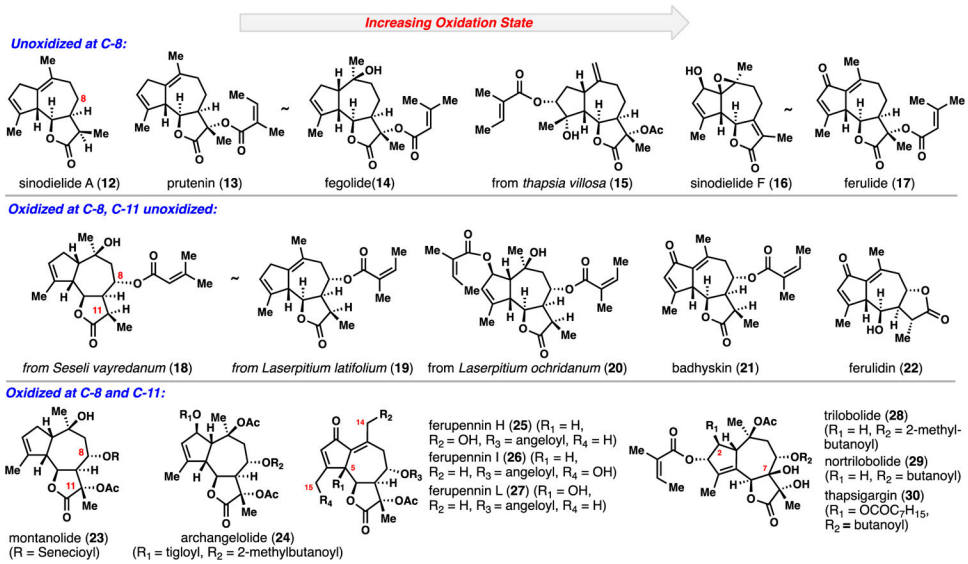


Figure 3.
Select, complex guaianolide lactones from *Apiaceae* (slovanolides).

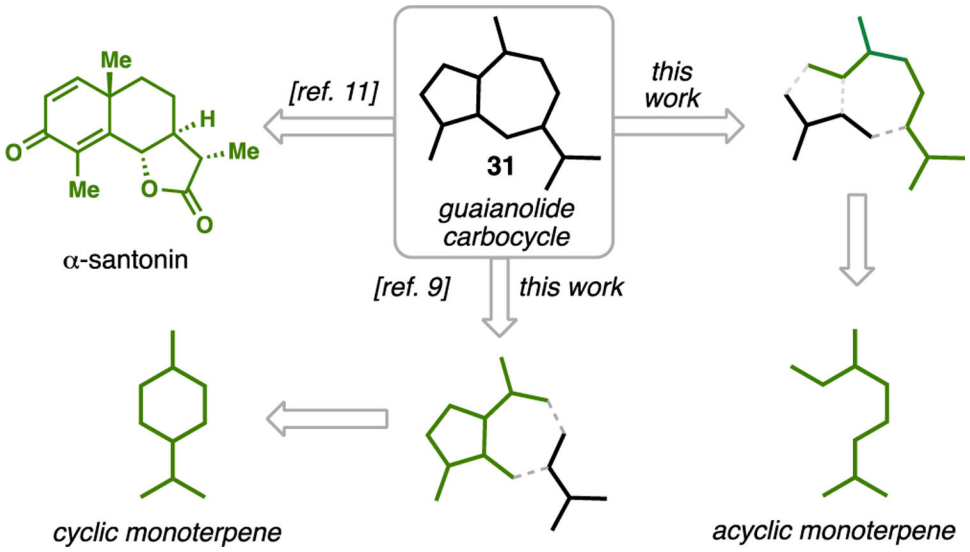


Figure 4.
Chiral pool-based disconnections of the guaianolide skeleton.

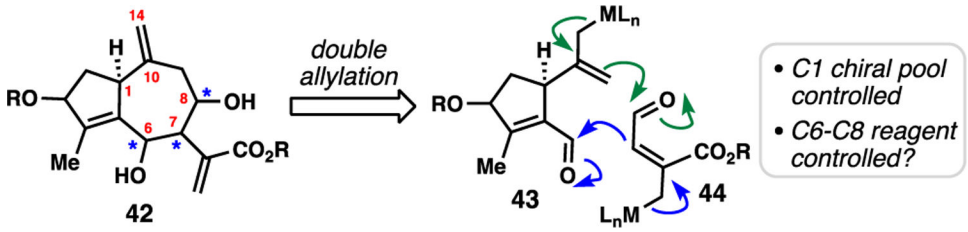


Figure 5.
Revised double allylation retrosynthesis

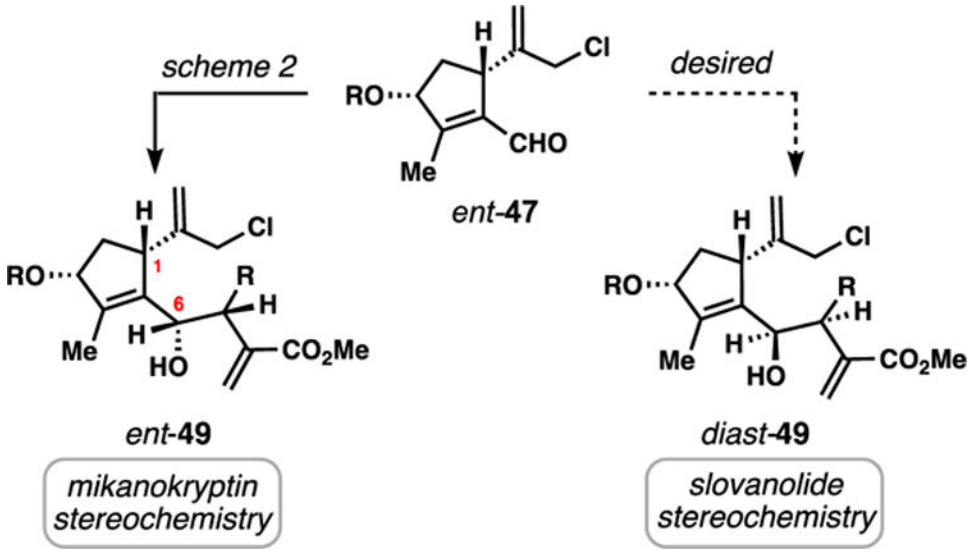


Figure 6.
Stereochemical considerations for an allylative synthesis of slovanolides.

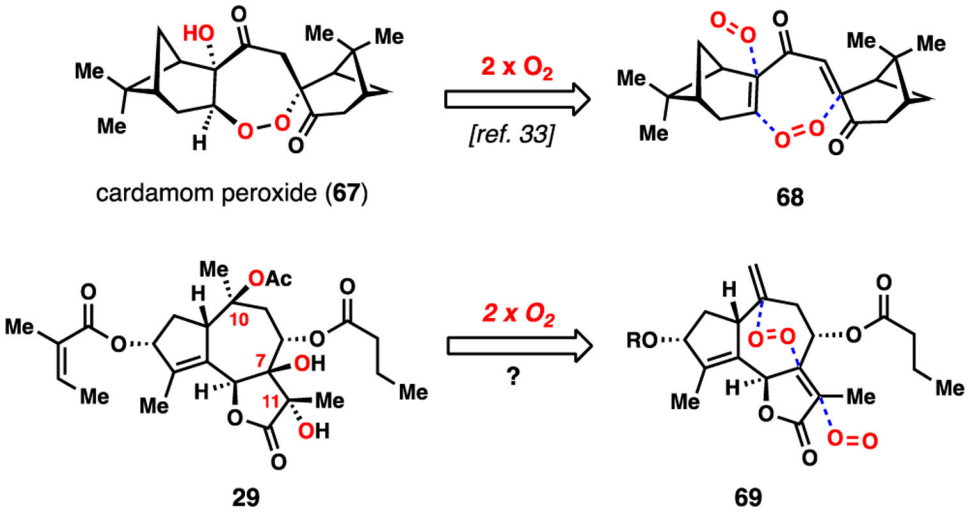
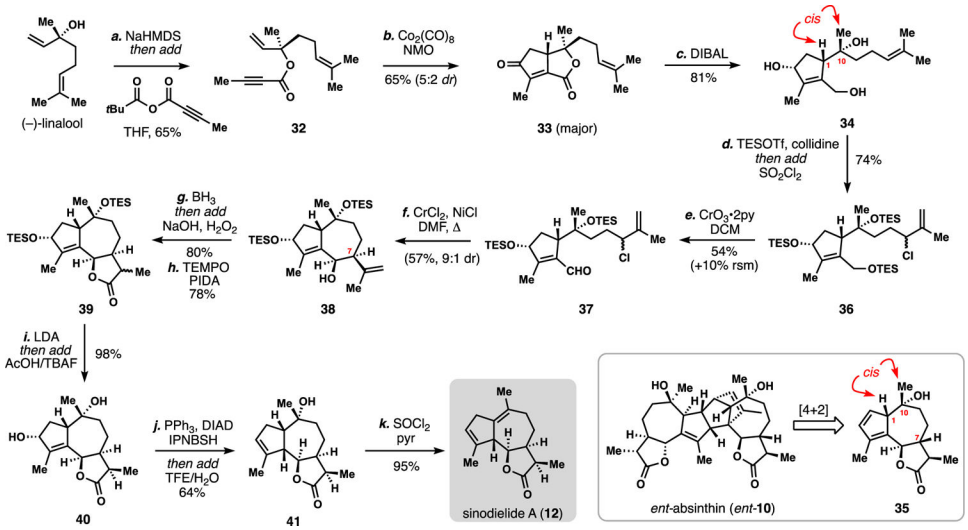


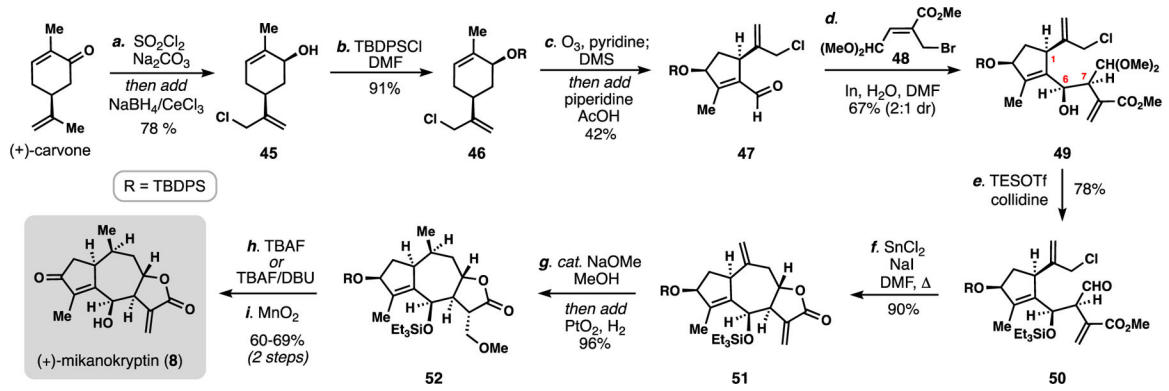
Figure 7.
Oxygen stitching retrosynthesis of nortrilobolide (**29**).



Scheme 1.

Total synthesis of sinodielide A (**12**) from (–)-linalool.

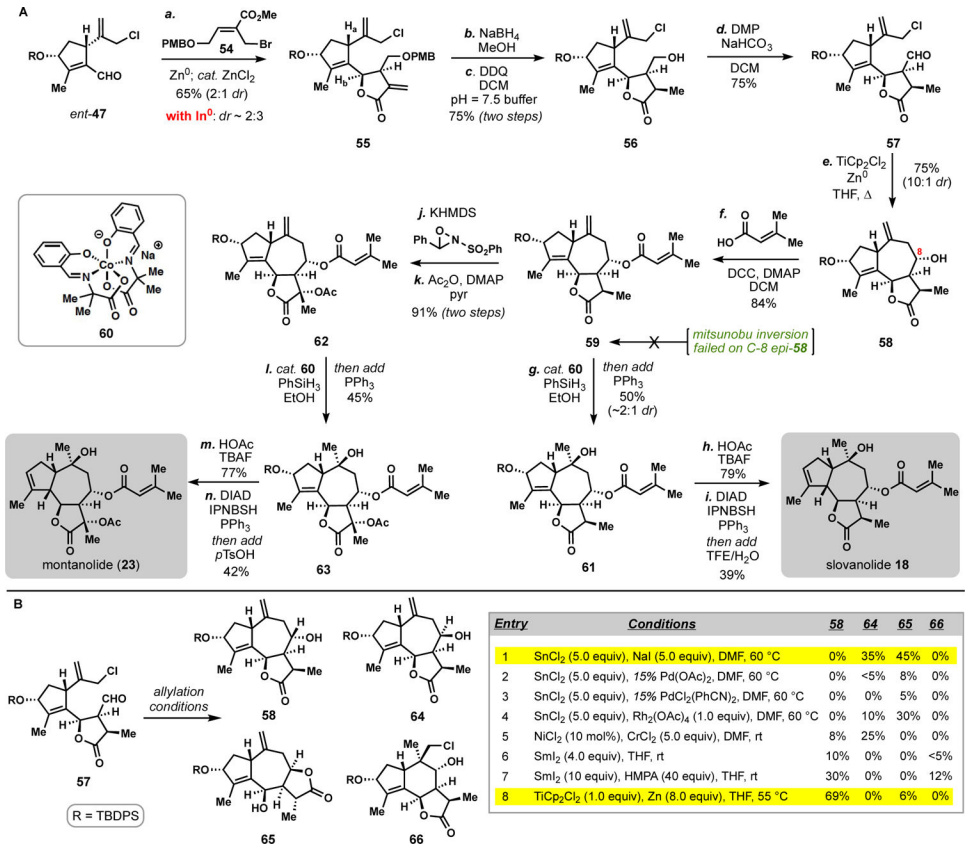
[a]Reagents and conditions: (a) (–)-linalool (1.0 equiv), NaHMDS (2.0 equiv), but-2-ynoic pivalic anhydride (2.5 equiv), THF, −45 °C to 23 °C, 11 h, 65%; (b) $Co_2(CO)_8$ (1.1 equiv), NMO (9.5 equiv), DCM, 2 h, 65% (*dr* = 5:2); (c) DIBAL (4.0 equiv), DCM, −78 ºC to rt, 16 h, 81%; (d) 2,4,6-Colldine (10.0 equiv), TESOTf (5.0 eq.), SO_2Cl_2 (1.2 eq.), DCM, −78 ºC to 23 °C, 74%; (e) CrO_3•2pyr (3.0 equiv), DCM, 0 ºC, 54%; (f) $CrCl_2$ (5.0 equiv), $NiCl_2$ (0.1 equiv), DMF, 60 ºC, 1 h, 57% (*dr* = 9:1); (g) BH_3• THF (1.8 equiv), THF, 0 ºC, *then add* $NaOH/H_2O_2$, 1.5 h, 80% (*dr* = 5:4); (h) TEMPO (1 equiv), PIDA (10 equiv), DCM, 8 h, 76%; (i) LDA (2 equiv), 1 h, −78 ºC to −40 ºC, *then* AcOH (5 equiv), TBAF (6 equiv), −78 ºC to 23 °C, 8 h, 98%; (j) IPNBSH (3 equiv), DIAD (3 equiv), PPh_3 (3 equiv), THF, 0 ºC, 1 h, *then* 23 °C, 4 h, *then add* TFE:H_2O (*v*:*v* = 1:1), 0 ºC, 14 h, 64%; (k) $SOCl_2$ (5 equiv), pyridine (8 equiv), DCM, −40 ºC to 23 °C, 95%; NaHMDS = sodium 1,1,1-trimethyl-N-(trimethylsilyl)silanaminide, NMO = *N*-methylmorpholine *N*-oxide, TESOTf = Triethylsilyl trifluoromethanesulfonate, PIDA = (Diacetoxyiodo)benzene, TEMPO = (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl, LDA = lithium diisopropylamide, TBAF = tetrabutylammonium fluoride, DIAD = Diisopropyl azodicarboxylate, IPNBSH = *N*-Isopropylidene-*N*′−2-nitrobenzenesulfonyl hydrazine.



Scheme 2.

Nine-step total synthesis of the unusual *Asteraceae* member mikanokryptin (**8**).[a]

[a]Reagents and conditions: (a) SO_2Cl_2 (1.2 equiv), Na_2CO_3 (3.0 equiv), DCM, 0 ºC, 2 h, *then add* $CeCl_3$•$7H_2O$ (1.1 equiv), $NaBH_4$ (3.0 equiv), MeOH, 0 ºC, 1 h, 78%; (b) TBDPSCl (1.2 equiv), imidazole (3.0 equiv), DMAP (0.05 equiv), DMF, 23 °C, 8 h, 91%; (c) O_3, pyridine (0.3 equiv), DCM, −78 ºC, 20–40 min, *then add* DMS (2.0 equiv), 25 °C, 8 h, *then add* piperidine (0.15 equiv), AcOH (0.2 equiv), 40 ºC, 16 h, 42%; (d) In^0 (1.5 equiv), **48** (1.2 equiv), H_2O (1 equiv), DMF, 23 °C, 1 h, 67% (*dr* = 2:1); (e) TESOTf (4 equiv), 2,4,6-collidine (6 equiv), DCM, 0 ºC, 24 h, 78%; (f) $SnCl_2$ (4.5 equiv), NaI (9 equiv), DMF, 60 ºC, 12 h, 90%; (g) NaOMe (0.1 equiv), MeOH, 16 h, *then add* AcOH (0.1 equiv), PtO_2 (0.1 equiv), H_2 (1 atm), 6 h, 96%; (h) TBAF (3.0 equiv), THF, 23 °C, 60%; (i) MnO_2 (30.0 equiv), DCM, 23 °C, 16 h, 97%; TBDPSCl = *tert*-butyldiphenylsilyl chloride, DMS = dimethylsulfide, DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene.

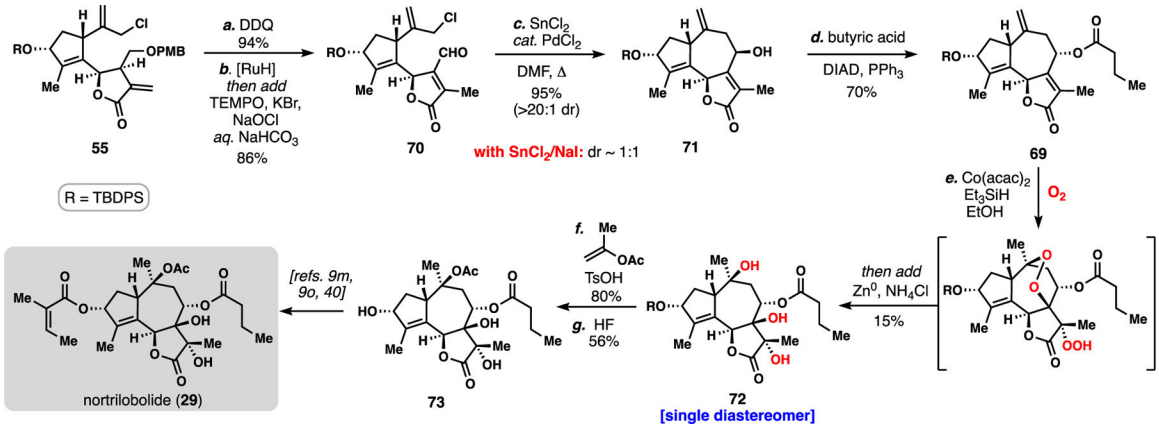


Entry	Conditions	58	64	65	66
1	$SnCl_2$ (5.0 equiv), NaI (5.0 equiv), DMF, 60 °C	0%	35%	45%	0%
2	$SnCl_2$ (5.0 equiv), *15%* $Pd(OAc)_2$, DMF, 60 °C	0%	<5%	8%	0%
3	$SnCl_2$ (5.0 equiv), *15%* $PdCl_2(PhCN)_2$, DMF, 60 °C	0%	0%	5%	0%
4	$SnCl_2$ (5.0 equiv), $Rh_2(OAc)_4$ (1.0 equiv), DMF, 60 °C	0%	10%	30%	0%
5	$NiCl_2$ (10 mol%), $CrCl_2$ (5.0 equiv), DMF, rt	8%	25%	0%	0%
6	SmI_2 (4.0 equiv), THF, rt	10%	0%	0%	<5%
7	SmI_2 (10 equiv), HMPA (40 equiv), THF, rt	30%	0%	0%	12%
8	$TiCp_2Cl_2$ (1.0 equiv), Zn (8.0 equiv), THF, 55 °C	69%	0%	6%	0%

Scheme 3.

Total synthesis of slovanolide **18** and montanolide (**23**).[a]

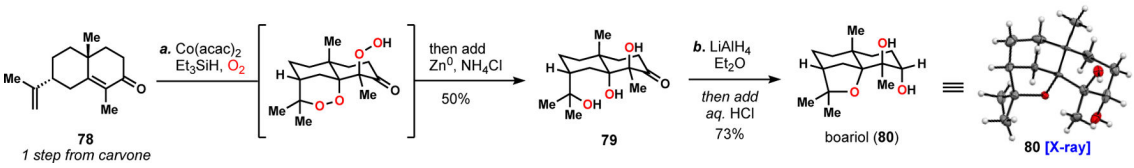
[a]Reagents and conditions: (a) *ent*-**47** (1.0 equiv), Zn^0 (1.5 equiv), $ZnCl_2$ (0.06 equiv), **54** (1.5 equiv), NMF, 23 °C, 65% (*dr* = 2:1); (b) $NaBH_4$ (1.5 equiv), MeOH, 23 °C; (c) DDQ (3.0 equiv), pH = 7.5 buffer, DCM, 23 °C, 1 h, 75% *(two steps)*; (d) DMP (1.5 equiv), $NaHCO_3$ (1.5 equiv) DCM, 23 °C, 1 h, 75%; (e) $TiCp_2Cl_2$ (1.0 equiv), Zn^0 (3.0 equiv), THF, 55 ºC, 2 h, 75% (*dr* = 10:1) (*two steps*); (f) 3,3-dimethylacrylic acid (2.0 equiv), DMAP (2.0 equiv), DCC (2.0 equiv) DCM, 23 °C, 84%; (g) **60** (0.2 equiv), $PhSiH_3$ (2.5 equiv), EtOH, 23 °C, 2 h, *then add* PPh_3 (2.0 eq.), 30 min, 50% (*dr* = 1.9:1); (h) TBAF (16.0 equiv), AcOH (10.0 equiv), 23 °C, 48 h, 79%; (i) IPNBSH (3 equiv), DIAD (3 equiv), PPh_3 (3 equiv), THF, 0 ºC, 1 h, *then add* TFE/H_2O (*v*:*v* = 1:1), 23 °C, 14 h, 39%; (j) NaHMDS (1.1 equiv), Davis' oxaziridine (1.2 equiv), −78 ºC, 0.5 h, 92%; (k) Ac_2O (1.5 equiv), DMAP (0.1 equiv), pyridine (3.0 equiv), 23 °C, 3 h, 99%; (l) **60** (0.2 equiv), $PhSiH_3$ (2.5 equiv), EtOH, 23 °C, 2 h, *then add* PPh_3 (2.0 equiv), 30 mins, 45%; (m) TBAF (16.0 equiv), AcOH (10.0 equiv), 48 h, 23 °C, 77%; (n) IPNBSH (3 equiv), DIAD (3 equiv), PPh_3 (3 equiv), THF, 0 ºC, 8 h, *then add p*-TsOH (0.5 equiv), 55 ºC, 1 h, 42%; PMB = 4-methoxybenzyl, DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone, DMP = Dess-Martin periodinane, DCC = *N,N'*-Dicyclohexylcarbodiimide, DMAP = 4-Dimethylaminopyridine, KHMDS = potassium 1,1,1-trimethyl-*N*-(trimethylsilyl)silanaminide, DIAD = Diisopropyl azodicarboxylate, IPNBSH = *N*-Isopropylidene-*N*′−2-nitrobenzenesulfonyl hydrazine.



Scheme 4.

12-Step formal synthesis of nortrilobolide (**29**).[a]

[a]Reagents and conditions: (a) **55** (1.0 equiv), DDQ (3.0 equiv), pH = 7.5 buffer, DCM, 23 °C, 1 h, 94%; (b) $RuHCl(CO)(PPh_3)_3$ (0.1 equiv), DCE, 60 ºC, 16 h, *then add* TEMPO (0.1 equiv), KBr (1.0 equiv), *aq.* NaOCl, pH = 8.6 buffer, 23°C, 1 h, 86%; (c) $SnCl_2$ (5.0 equiv), $PdCl_2(PhCN)_2$ (0.15 equiv), DMF, 60 ºC, 8 h, 95%; (d) butyric acid (3.0 equiv) DIAD (3.0 equiv), 0 ºC to 23 °C, 8 h, 70%. (e) $Co(acac)_2$ (0.2 equiv), Et_3SiH (5.0 equiv), O_2 (1 atm), EtOH 24 h, 23 °C, *then add* Zn (3.0 equiv), *aq.* NH_4Cl (5 equiv), 15%; (f) *p*TSA (1.2 equiv), isopropenyl acetate, 23 °C, 80%; (g) HF/MeCN (1:5 = *v*/*v*), 23 °C, 56%; DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone [RuH] = $RuHCl(CO)(PPh_3)_3$, acac = acetylacetone.



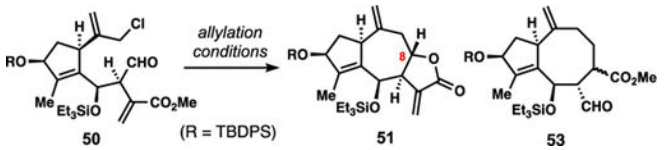
Scheme 5.

Three-step synthesis of the eudesmane sesquiterpene boariol (**80**).

[a]Reagents and conditions: (a) **78** (1 equiv), $Co(acac)_2$ (0.2 equiv), Et_3SiH (2.4 equiv.), O_2 (1 atm), EtOH, *then add* Zn^0 (2.0 equiv), NH_4Cl EtOH, 50%; (b) $LiAlH_4$ (1.5 equiv), Et_2O, 0 ºC, 45 mins, *then add aq.* 1N HCl, 0 ºC to 23 °C, 73%. acac = acetylacetone.

Table 1.

Intramolecular allylation of aldehyde **50**: Key findings.



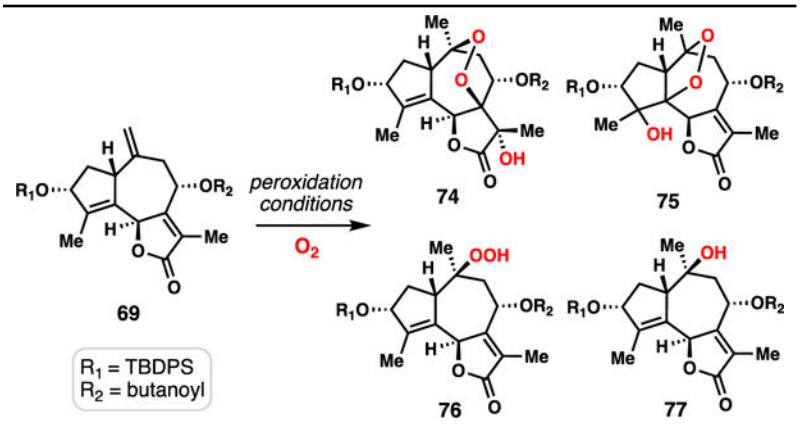
Entry	Conditions	yield of 51	yield of 53
1	$CrCl_2$, cat. $NiCl_2$, DMF, 60 °C	10% (2:1 *dr*)	17%
2	NaI, SmI_2 THF/HMPA, −78 °C	27% (2:1 *dr*)	17%
3	NaI, Zn^0, *aq.* NH_4Cl, THF, rt	–	51%
4	In^0, NaI, DMF, 60 °C	13%	–
5	NaI, $SnCl_2$, DMF, 60 °C[b]	90%	–

[a] reactions performed on a 30 mg scale, isolated yields are shown.

[b] yield on 7-gram scale

Table 2.

Catalyst evaluation in the key polyoxygenation Step.



Entry	Conditions	74	75	76	77
1	25 mol% $Co(acac)_2$, Et_3SiH, EtOH	16%	10%	–	19%
2	25 mol% $Co(acac)_2$, $PhSiH_3$, *i*-PrOH/DCM	13%	18%	–	15%
3	30 mol% $Co(modp)_2$, Et_3SiH,DCE	–	–	–	–
4	30 mol% **60**, Et_3SiH, EtOH	–	–	63%	–
5	30 mol% $Mn(dpm)_3$, $PhSiH_3$, *i*-PrOH/DCM	–		–	–
6	30 mol% $Fe(acac)_3$, $PhSiH_3$ or Et_3SiH, EtOH	–		–	–