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**Title:** Fragment coupling reactions in total synthesis that form carbon—carbon bonds via carbanionic or free radical intermediates.

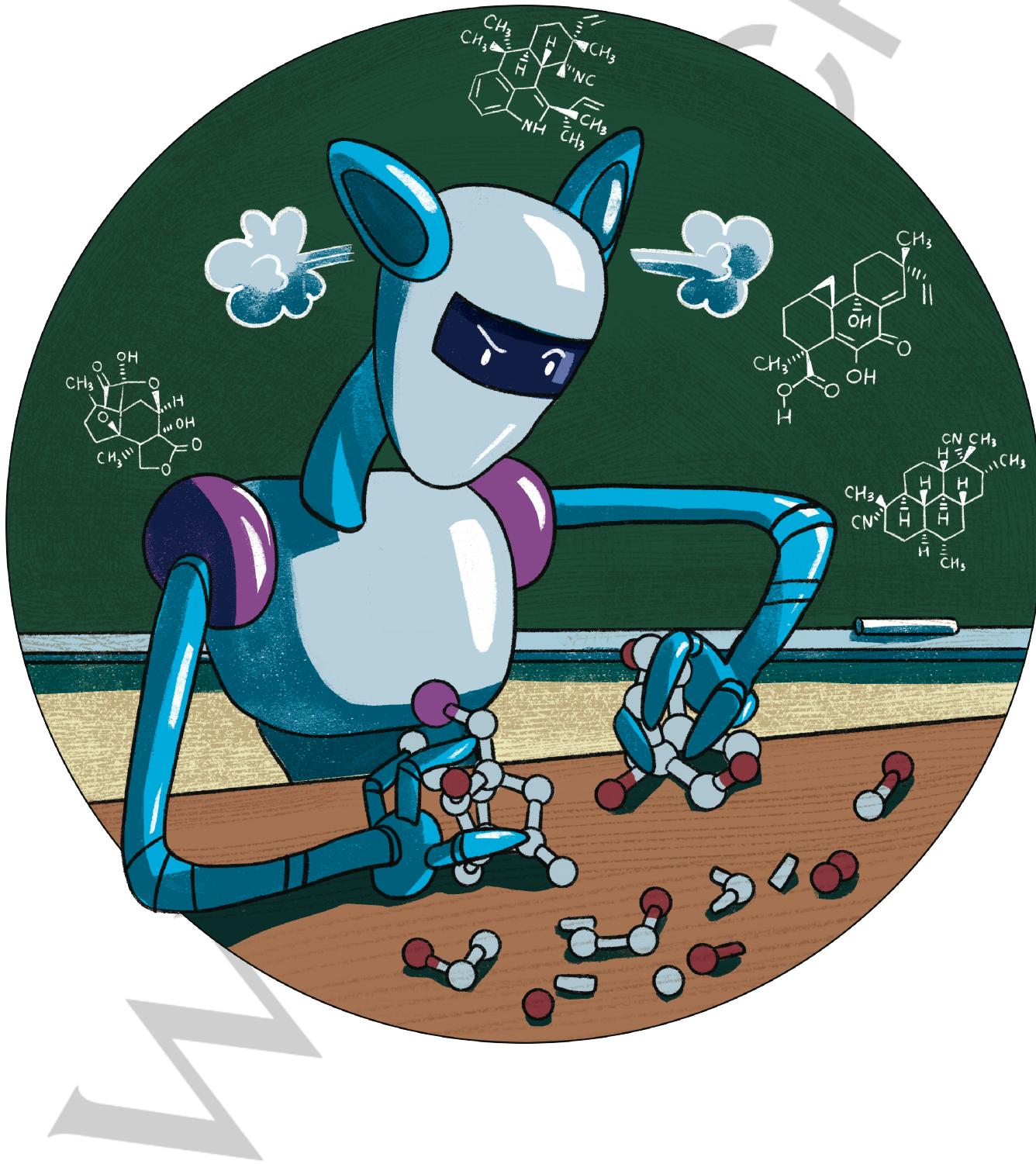
**Authors:** Martin Tomanik, Seth B. Herzon, and Ian Tingyung Hsu

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## REVIEW

**Fragment coupling reactions in total synthesis that form carbon–carbon bonds via carbanionic or free radical intermediates.**Martin Tomanik<sup>[a]+</sup>, Ian Tingyung Hsu<sup>[a]+</sup> and Seth B. Herzon<sup>\*[a][b]</sup>

Accepted Manuscript

## REVIEW

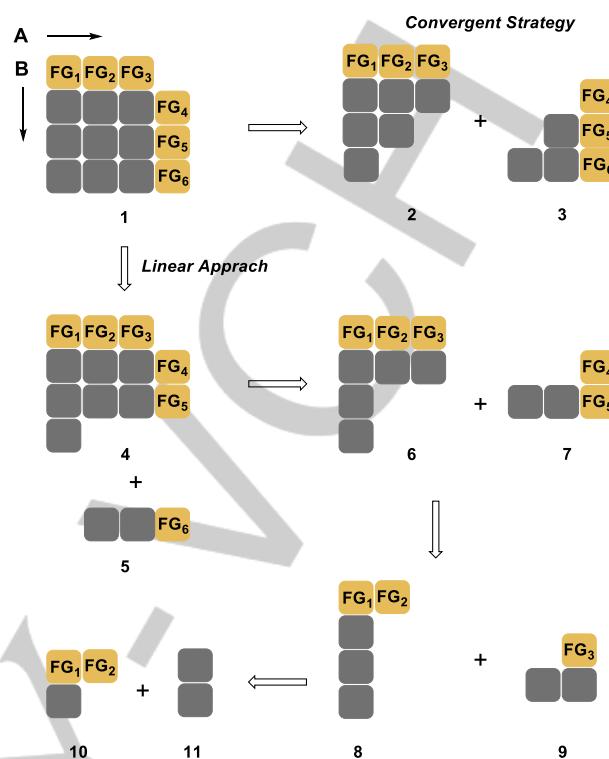
**Abstract:** Fragment coupling reactions that form carbon–carbon bonds are valuable transformations in synthetic design. Advances in metal-catalyzed cross-coupling reactions in the early 2000s brought a high level of predictability and reliability to carbon–carbon bond constructions involving the union of unsaturated fragments. By comparison, recent years have witnessed an increase in fragment couplings proceeding via carbanionic and open shell (free radical) intermediates. The latter has been driven by advances in methods to generate and utilize carbon-centered radicals under mild conditions. In this review, we survey a selection of recent syntheses that have implemented carbanion- or radical-based fragment couplings to form carbon–carbon bonds. We aim to highlight the strategic value of these disconnections in their respective settings and to identify extensible lessons from each example that might be instructive to students.

## 1. Introduction.

### 1.1. Convergence.

Convergence in synthesis<sup>[1]</sup> is a widely-accepted if loosely defined concept intimating the preparation of two synthetic intermediates of similar complexity, followed by their late-stage coupling. In-depth discussions are available,<sup>[2]</sup> and an abridged overview is provided. Pathway A in Figure 1 illustrates the retrosynthetic disconnection of the hypothetical target **1** to the fragments **2** and **3**. Here, the number of functional groups is used as a proxy for complexity; because fragments **2** and **3** possess similar complexity (as defined by their number of functional groups), the strategy that calls for synthesis of **1** via **2** and **3** is deemed convergent. Other proxies for complexity – such as topology, stereochemistry, or strain – are in some instances more significant.

In contrast, the stepwise retrosynthesis of **1** to **4** and **5**, followed by **6** and **7**, **8** and **9**, **10** and **11** reduces complexity via iterative removal of smaller building blocks (pathway B). Pathway B is characterized as less convergent than pathway A. Convergent strategies are desirable because: 1. They separate the target – here one that possesses six functional groups – into smaller subgoals – here, the synthesis of **2** and **3**. This reduces the potential for complications arising from competitive reactivity. 2. The independent synthesis of **2** and **3** imparts flexibility to the synthetic approach. Problems encountered en route to **2** do not influence the synthesis of **3**, and vice versa. 3. Convergent



**Figure 1.** Pathway A depicts the retrosynthetic disconnection of the hypothetical target **1** into the precursors **2** and **3**, which present similar levels of functional group complexity. Pathway B depicts the retrosynthetic disconnection of **1** via the iterative removal of small building blocks (**5**, **7**, **9**). Pathway A more rapidly decreases the overall complexity in the route and is deemed more convergent.

syntheses often (but not always) have a smaller number of overall linear steps, which increases throughput.

### 1.2. Convergent Fragment Coupling Reactions.

Fragment coupling reactions are required in order to realize the strategy **2** + **3** → **1** in Figure 1. Carbon–heteroatom bonds are logically disconnected into electrophilic carbon and nucleophilic heteroatomic intermediates. The formation of carbon–carbon bonds is more nuanced because of the absence of comparable bond polarization.

The syntheses of the polyether antibiotic (+)-monensin (**16**) by the Kishi<sup>[3]</sup> and Still<sup>[4]</sup> laboratories is a classic examples of fragment coupling by carbon–carbon bond formation (Scheme 1). Both laboratories synthesized (+)-monensin (**16**) using an aldol addition as the key step. The research groups arrived at similar conditions to achieve the coupling. Thus, the kinetic enolate derived from the methyl ketones **13a** or **13b** was generated [Kishi: diisopropylamido magnesium bromide; Still: lithium diisopropylamide (LDA), followed by transmetalation to magnesium]. Upon addition of the aldehydes **12a** or **12b**, the products **14** or **15** were produced with up to 8:1 diastereoselectivity, in favor of the Cram<sup>[5]</sup> addition product. This

[a] M. Tomanik<sup>[+]</sup>, I. T. Hsu<sup>[+]</sup>, Prof. S. B. Herzon

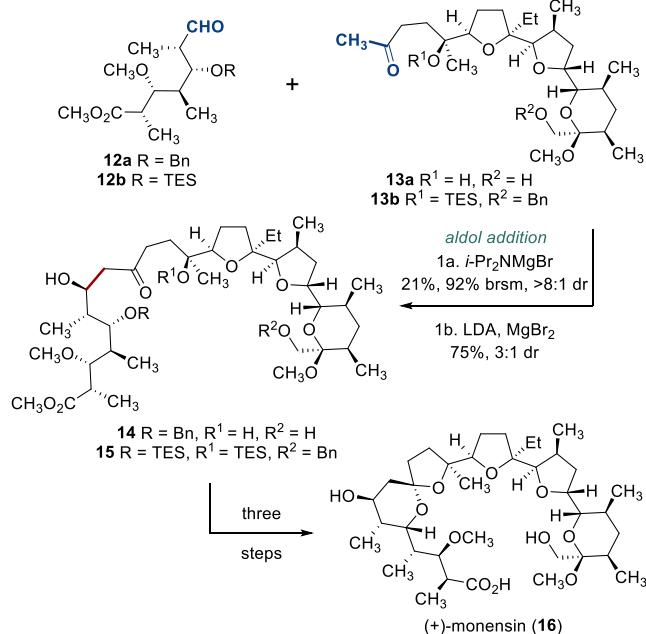
Department of Chemistry  
Yale University  
225 Prospect St, New Haven, CT (USA)  
E-mail: seth.herzon@yale.edu

[b] Prof. S. B. Herzon  
Department of Pharmacology  
Yale University  
333 Cedar St, New Haven, CT (USA)

[+] These authors contributed equally

## REVIEW

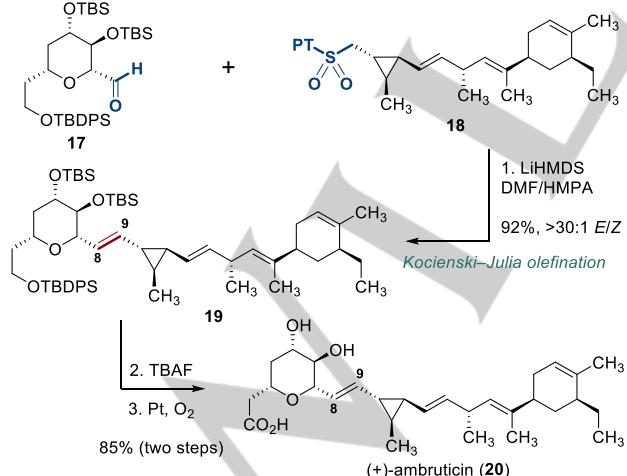
addition is notable because the two carbon atoms involved in the bond-forming step are  $sp^3$ -hybridized in the product. The



**Scheme 1.** Convergent synthesis of **14** and **15**, precursors to the antibiotic **(+)-monensin** (**16**). The fragment coupling products **14** and **16** were prepared by a stereoselective aldol addition employing the aldehydes **12a** or **12b** as electrophile, and the magnesium enolates derived from the methyl ketones **13a** or **13b** as nucleophile. BRSM = based on recovered starting material.

efficiency of this transformation owes much to a large amount of research in the 1970s, which brought the complex aldol additions to a point of high reliability and predictability.<sup>[6]</sup>

The development of mild methods for the stereodefined synthesis of alkenes marked a step forward in fragment coupling reactions. The synthesis of the antifungal agent **(+)-ambruticin** (**20**) by Liu and Jacobsen illustrates this point (Scheme 2).<sup>[7]</sup> These researchers employed a Kocieński–Julia olefination<sup>[8]</sup> to unite the fragments **17** and **18** and establish the C8–C9 *trans*-



**Scheme 2.** Synthesis of **(+)-ambruticin** (**20**) by Liu and Jacobsen. Fragment coupling of the aldehyde **17** and the sulfone **18** generated the key *E*-olefin intermediate **19**. PT = phenyltetrazolyl.

alkene in the target. Thus, the alkenylation product **19** was formed with >30:1 *E*:*Z* selectivity and in >90% yield by deprotection of the sulfone **18** with lithium bis(trimethylsilyl)amide (LiHMDS), followed by the addition of **17**.

In both the **(+)-ambruticin** (**20**) and **(+)-monensin** (**16**) syntheses, the fragment coupling was enabled by stabilization of a carbanionic intermediate. The introduction of anion-stabilizing functional groups allows for logical retrosynthetic disconnection of carbon–carbon bonds by polar pathways.

Since the mid-2000s, cross-coupling reactions have served as a lodestar in synthetic planning because they allow for further tempering of the nucleophilic component as a covalent organometallic intermediate.<sup>[9]</sup> The synthesis of **(−)-azaspiracid-1** (**24**) by Nicolaou and co-workers is illustrative.<sup>[10]</sup> Here, the vinyl stannane **21** and the allylic acetate **22** were united by a  $\pi$ -allyl

Martin Tomanik was born in Prerov, Czech Republic. He received his B.A. in chemistry cum laude from Dartmouth College (2015) and conducted research toward new three-component indole coupling reactions with Prof. Jimmy Wu. His interest in bioactive metabolites brought him to pursue graduate research work under the mentorship of Prof. Seth Herzon at Yale University, where he is currently devoting his attention to the total synthesis of terpenoid natural products.



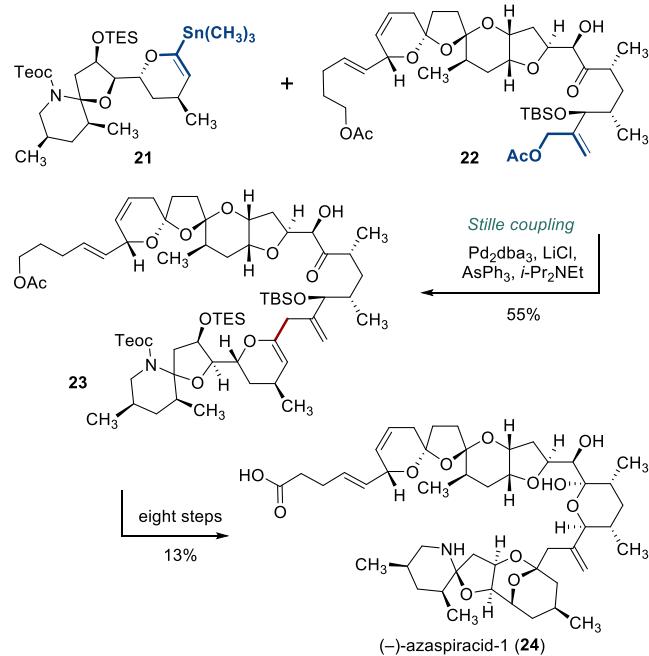
Ian Tingyung Hsu grew up in Taipei, Taiwan and Vancouver, Canada before obtaining his undergraduate degree from the University of Chicago under the supervision of Professor Scott A. Snyder. There, he worked on bromonium ion-induced ring expansion reactions and the total synthesis of cyclopiane diterpenes. In 2017, Ian began graduate studies in the lab of Prof. Seth Herzon at Yale University, where he is developing fragment coupling reactions for the synthesis of complex diterpenes.



Seth B. Herzon completed his undergraduate studies at Temple University, obtained a PhD from Harvard University under the guidance of Andrew G. Myers, and was an NIH postdoctoral fellow with John F. Hartwig at the University of Illinois, Urbana-Champaign. He began his independent career at Yale in 2008 and is currently the Milton Harris '29 Ph.D. Professor of Chemistry and a Professor of Pharmacology at the Yale School of Medicine. Herzon's research focuses on synthetic and translational studies of genotoxic natural products, human gut microbiome metabolites, and antibiotic development.



## REVIEW



**Scheme 3.** Synthesis of (*-*)-azaspiracid-1 (**24**) by Nicolaou et al. The vinyl stannane **21** and the allylic acetate ester **22** were employed in a  $\pi$ -allyl Stille fragment coupling.

Stille coupling (Scheme 3). Treatment of a mixture of **21** and **22** with tris(dibenzylideneacetone)dipalladium, triphenylarsine, lithium chloride, and Hünig's base provided the coupling product **23** in 55% yield. Notably, neither of the components **21** or **22** contain a classical anion stabilizing group. The complexity of the fragments **21** and **22** and the mild conditions of this coupling are especially noteworthy.

The reliability of cross-coupling reactions involving unsaturated carbon atoms has perhaps emboldened researchers to pursue ambitious disconnections that are less developed. In this review we have collected examples of fragment couplings that form carbon–carbon bonds by carbanionic or free radical intermediates. In the first half we focus on unstabilized and stabilized carbanions (such as enolates), and instances where the

carbon–carbon bond-forming step triggers a cascade reaction or forms a single bond of high strategic value. The latter section was assembled in response to the explosion of methods to generate and functionalize carbon-centered radical intermediates under mild conditions. Of course, many more examples remain beyond what is covered here, and we direct readers to additional related reviews.<sup>[11]</sup> The examples below illustrate specific points, which are enumerated following presentation of each work.

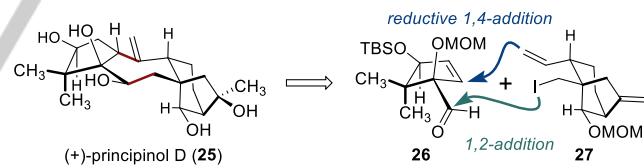
## 2. Convergent Two Electron Fragment Coupling.

Two electron fragment couplings typically rely on carbanion stabilizing elements. However, these anions are now being implemented in increasingly complex couplings and are more frequently serving as the initiators of two-electron cascades. Below we review recent examples of two electron fragment couplings and extensible lessons from each study.

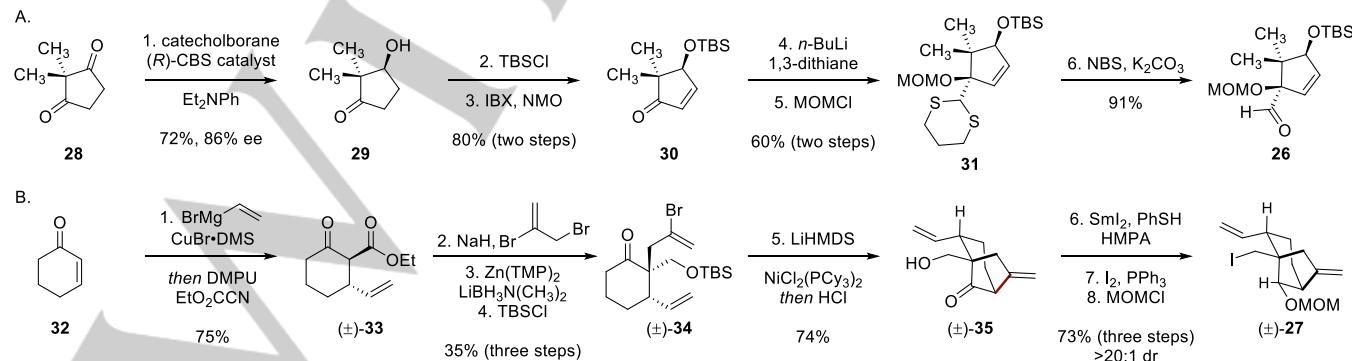
### 2.1. (+)-Principinol D: A bis(neopentylic) fragment coupling facilitates the synthesis of the central seven-membered ring in rearranged diterpenes.

Grayanane diterpenes contain a stereochemically-rich 5/7/6/5 skeleton derived biosynthetically from *ent*-kaurane structures. Many grayananes inhibit voltage-gated sodium ion channels.<sup>[12]</sup> While the kaurane diterpenes have been extensively studied,<sup>[13]</sup> fewer syntheses of grayanane natural products have been reported.<sup>[14]</sup> In 2019, Newhouse and co-workers<sup>[15]</sup> described a convergent route to the grayanane diterpene (+)-principinol D (**25**)<sup>[16]</sup>, as outlined below.

Retrosynthetically, the seven-membered ring of (+)-



**Scheme 4.** Retrosynthetic analysis of (+)-principinol D (**25**) by Turlik et al.



**Scheme 5. A.** Synthesis of the  $\beta,\gamma$ -unsaturated aldehyde **26**. **B.** Synthesis of the racemic alkyl iodide **27**.

## REVIEW

principinol D (**25**) was deconstructed to the aldehyde **26** and the iodide **27**. In the forward direction, it was envisioned that 1,2-addition of an organometal reagent derived from **27** to **26**, followed by a reductive coupling reaction, could be used to construct the seven-membered ring.

The synthesis of the aldehyde **26** began with enantioselective reduction of 2,2-dimethylcyclopenta-1,3-dione (**28**)<sup>[17]</sup> using the Corey–Bakshi–Shibata oxazaborolidine, which provided the  $\beta$ -hydroxyketone **29** (72%, 86% ee, Scheme 5A).<sup>[18]</sup> Silyl ether formation [*tert*-butyldimethylsilyl chloride (TBSCl)], followed by oxidation (2-iodoxybenzoic acid), then generated the cyclopentenone **30** (80%, two steps). Diastereoselective 1,2-addition of 2-lithio-1,3-dithiane and protection of the resulting alcohol [chloromethyl methyl ether (MOMCl)] provided the cyclopentene **31** (60%, two steps). Removal of the dithiane under oxidative conditions [*N*-bromosuccinimide (NBS)] formed the aldehyde **26** (91%).

The alkyl iodide **27** was prepared in racemic form from cyclohex-2-ene-1-one (**32**, Scheme 5B). Copper-catalyzed 1,4-addition of vinyl magnesium bromide, followed by enolate acylation (Mander's reagent),<sup>[19]</sup> provided the  $\beta$ -ketoester **33** (75%).<sup>[20]</sup> Diastereoselective alkylation of the  $\beta$ -ketoester **33** with 2,3-dibromopropene, protection of the ketone by deprotonation [zinc bis(2,2,6,6-tetramethylpiperamide)], reduction of the ester in situ (lithium dimethylaminoborohydride),<sup>[21]</sup> and silyl ether formation (TBSCl) provided **34** (35%, three steps).

The bicyclo[3.2.1]octane core of **27** was constructed by an intramolecular enolate vinylation [LiHMDS, bis(tricyclohexylphosphine)nickel dichloride]. Dilution of the reaction mixture with aqueous hydrochloric acid resulted in cleavage of the silyl ether to the alcohol **35** (74% overall). Diastereoselective reduction of the ketone was achieved using samarium diiodide and thiophenol<sup>[22]</sup> as a hydrogen atom source (>20:1 dr).<sup>[23]</sup> The use of hexamethylphosphoramide (HMPA) as solvent improved conversion.<sup>[24]</sup> An Appel reaction (triphenylphosphine, iodine), followed by protection of the secondary alcohol, then provided the racemic coupling partner **27** (73% overall).

The 1,2-addition product **36** was formed by treatment of the racemic iodide **27** with *tert*-butyllithium (*t*-BuLi), followed by addition of **26** (Scheme 6). Because the iodide was prepared in racemic form, four diastereomers are possible. The stereocenter

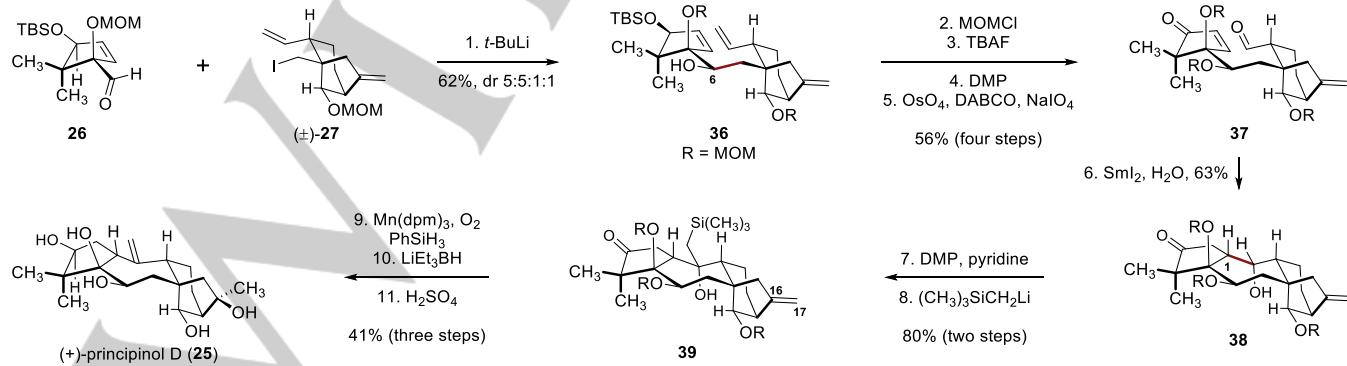
at C6 was generated with 5:1 selectivity, and no discrimination between either enantiomer of **27** was observed. Thus, the addition product **36** was produced as a 5.5:1:1 mixture of diastereomers in 62% combined yield. Following chromatographic separation, stereoisomerically pure **36** was obtained in 26% yield.

Protection of the secondary alcohol (MOMCl), removal of the silyl ether [tetra-*n*-butylammonium fluoride (TBAF)], oxidation of the allylic alcohol [Dess–Martin periodinane (DMP)], and regioselective oxidative cleavage of the  $\alpha$ -olefin (osmium tetroxide, sodium periodate) provided the cyclization precursor **37** (56% overall). The reductive cyclization product **38** was formed in 63% yield and as a single C1 diastereomer by treatment of **37** with samarium diiodide.<sup>[25]</sup> The secondary alcohol was oxidized (DMP) and the resulting ketone was treated with trimethylsilylmethylolithium<sup>[26]</sup> to provide the alcohol **39** (80%, two steps). Mukaiyama hydration<sup>[27]</sup> [tris(2,2,6,6-tetramethyl-3,5-heptanedionato)-manganese(III), phenylsilane, dioxygen] of the C16–C17 alkene provided a tertiary alcohol (not shown, diastereoselectivity not reported). The unpurified material was treated with lithium triethylborohydride and then heated with sulfuric acid to provide (+)-principinol D (**25**, 41%, three steps).

#### Summary and Strategic Lessons:

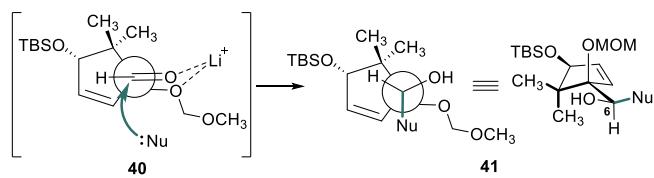
[1] The methoxymethyl ether protecting group in **26** was employed to enable chelate control in the coupling. The sense of addition is consistent with the Cram model,<sup>[5]</sup> as depicted in **40** (Scheme 7). Addition of the organolithium species (Nu in Scheme 7) to the face of the aldehyde opposite the *gem*-dimethyl substituent generates **41** (cooresponding to the major C6 diastereomer).

[2] The efficiency of the formal annulation relies on several subtle substituent effects. Neopentyllic centers, even when primary, are sterically-encumbered, and bond formation to these sites is often challenging. Here, the efficiency of the 1,2-addition to the neopentyllic aldehyde **26** to generate **36** (Scheme 6) may be attributed to 1) ground-state destabilization of the aldehyde via the inductive effects of the  $\alpha$ -alkoxyether, 2) use of the reactive alkylolithium species **43** (Scheme 8), and 3) pre-organization of the transition state via chelation. The ensuing 1,4-addition is promoted by polarity-matching between the electron-rich ketyl



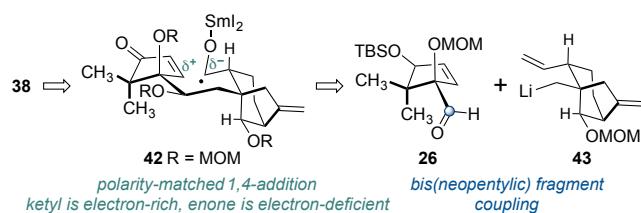
Scheme 6. Completion of the synthesis of (+)-principinol D (**25**).

## REVIEW



**Scheme 7.** The diastereoselectivity in the fragment coupling ( $26 + 27 \rightarrow 36$ , Scheme 6) is consistent with the Cram chelate model.<sup>[5]</sup>

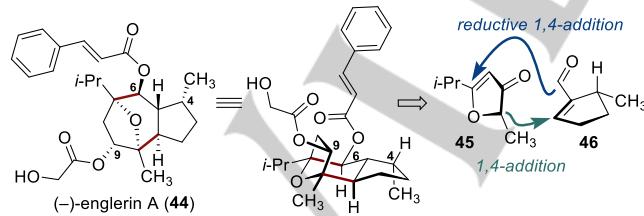
radical **42** and the electron-deficient enone (discussed further below).



**Scheme 8.** The intermediate **38** (Scheme 6) was accessed via an intramolecular, polarity-matched 1,4-addition between a neopentyl enone and ketyl radical. The vicinal diol **42** was further disassembled to a neopentyl 1,2-addition between the aldehyde **26** and the organolithium species **43**.

## 2.2. (-)-Englerin A: Successive 1,4-additions enable construction of an oxabicyclo[3.2.1]octane core containing five contiguous stereocenters.

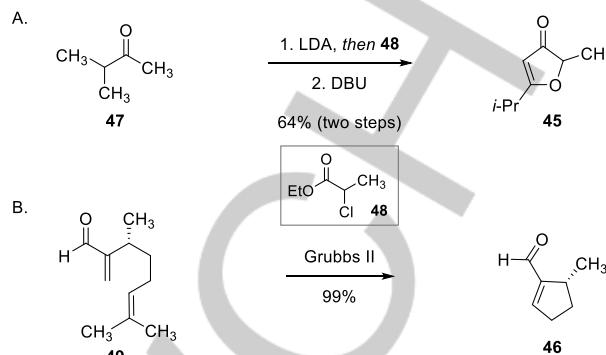
The guaiane sesquiterpene (-)-englerin A (**44**) was isolated in 2009 by Beutler and co-workers from the stem bark of *Phyllanthus engleri*.<sup>[28]</sup> The isolate possesses seven contiguous stereocenters and an 8-oxabicyclo[3.2.1]octane ring system fused to a five-membered ring. (-)-Englerin A (**44**) is cytostatic toward renal cell cancer lines ( $GI_{50} < 20 \text{ nM}$ ). To date, eighteen total and formal syntheses of (-)-englerin A (**44**) have been reported.<sup>[29]</sup> Selected strategies include ring-closing metathesis, gold-catalyzed cyclization cascades, and [5+2], [4+3], or [3+2] cycloaddition-based strategies.<sup>[30]</sup>



**Scheme 9.** Retrosynthetic analysis of (-)-englerin A (**44**) by Li et al.

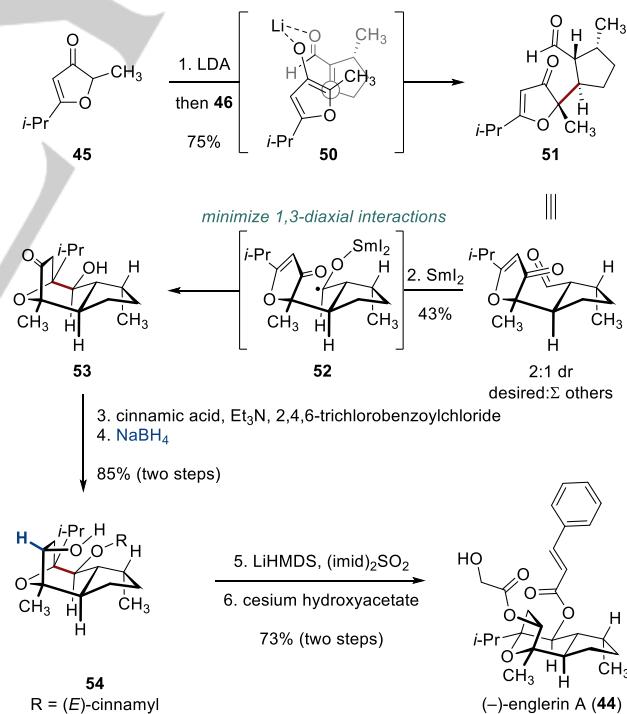
In 2011, the Chain laboratory disclosed a synthesis of (-)-englerin A (**44**) that employs the coupling of 5-isopropyl-2-methylfuran-3(2H)-one (**45**) and (*R*)-5-methylcyclopent-1-ene-1-

carbaldehyde (**46**) via an intermolecular Michael addition and a samarium-mediated reductive 1,4-addition (Scheme 9).<sup>[31]</sup>



**Scheme 10.** A. Synthesis of 5-isopropyl-2-methylfuran-3(2H)-one (**45**). B. (*R*)-5-methylcyclopent-1-ene-1-carbaldehyde (**46**).

5-Isopropyl-2-methylfuran-3(2H)-one (**45**) was prepared by a Claisen condensation between iso-propyl methyl ketone (**47**) and ethyl 2-chloropropionate (**48**), followed by an intramolecular etherification [1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 64% overall, Scheme 10A].<sup>[32]</sup> (*R*)-5-Methylcyclopent-1-ene-1-carbaldehyde (**46**) was synthesized from the  $\alpha,\beta$ -unsaturated aldehyde **49** (derived from citronellal) by a ring-closing metathesis (Grubbs' second-generation catalyst, 99%).<sup>[33]</sup>



**Scheme 11.** Synthesis of (-)-englerin A (**44**) from 5-isopropyl-2-methylfuran-3(2H)-one (**45**) and (*R*)-5-methylcyclopent-1-ene-1-carbaldehyde (**46**).

The Michael addition product **51** was formed in 75% yield by deprotonation of 5-isopropyl-2-methylfuran-3(2H)-one (**45**) (LDA),

## REVIEW

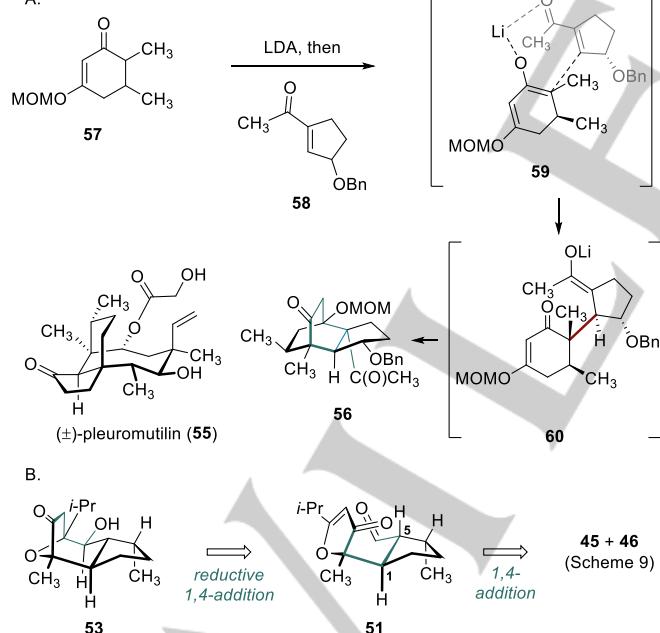
followed by the introduction of (*R*)-5-methylcyclopent-1-ene-1-carbaldehyde (**46**, Scheme 11). The ratio of the desired diastereomer **51** (shown) to all others was 2:1, though the diastereomers were not separable by flash-column chromatography. The major diastereomer **51** was proposed to derive from a closed, chair-like transition state involving chelation of the lithium ion of the enolate to the aldehyde (see **50**), with approach *anti* to the methyl substituent of (*R*)-5-methylcyclopent-1-ene-1-carbaldehyde (**46**).

Treatment of **51** with samarium diiodide generated the  $\gamma$ -hydroxyketone **53** (43%), via formation of a ketyl radical followed by 1,4-addition. The stereoselectivity is thought to arise from orientation of the bulky, samarium-coordinated radical anion in the pseudo-equatorial position, which minimizes 1,3-diaxial interactions (see **52**). The modest yield in the reductive cyclization is due in part to the presence of other diastereomers of **51** in the starting material.

Yamaguchi esterification<sup>[34]</sup> of the newly generated alcohol **53** (cinnamic acid, 2,4,6-trichlorobenzoylchloride, triethylamine) followed by reduction of the ketone (sodium borohydride) formed the alcohol **54** (85%, two steps). The glycolate was installed via activation of the alcohol (LHMDS, 1,1-sulfonyldimidazole), followed by *S*<sub>N</sub>2 displacement with cesium hydroxyacetate. The synthesis of (–)-englerin A (**44**) was completed in eight steps and 20% overall yield.

**Summary and Strategic Lessons:**

**[1]** The fragment coupling strategy employed here is reminiscent



**Scheme 12.** **A.** The tricycle **56**, an intermediate en route to pleuromutilin (**55**), bears two carbonyls in a 1,5-relationship that can be traced through two chains of bonds. This allowed for synthesis of **56** by a tandem Michael addition, as shown. **B.** The intermediate **53** contains a 1,4-ketoalcohol. Single electron reduction of **51** allows for construction of this intermediate by 1,4-addition. The carbonyl substituents in **51** are in a 1,5-relationship and properly disposed for synthesis by an intermolecular Michael addition.

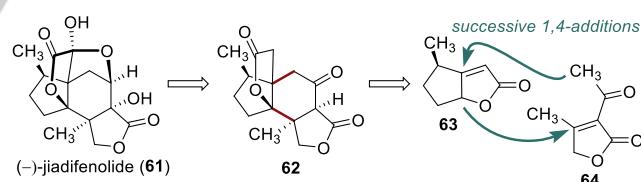
of a tandem Michael addition employed by Gibbons en route to the fungal metabolite (±)-pleuromutilin (**55**, Scheme 12A).<sup>[35]</sup> In Gibbons' work, the tricycle **56** was assembled by a double stereodifferentiating tandem Michael addition. The 1,5-relationship between the carbonyls in **56** allows for utilization of their natural polarization to construct the carbon–carbon bonds. In the present work, the 1,4-ketoalcohol in **53** is disconnected by a reductive 1,4-addition (Scheme 12B). This inverts the natural polarity of the aldehyde in **51**. The intermediate **51** contains two carbonyls in a 1,5-relationship, which is a retrone for a Michael addition. An additional tandem Michael addition strategy is discussed in Section 2.3.

**[2]** The predictable stereochemical outcome in conjugate additions involving cyclic unsaturated carbonyl compounds is utilized effectively in this work to establish three additional stereocenters in the first key carbon–carbon bond-forming reaction. The *anti*-relationship of the C1 and C5 hydrogens on the cyclopentane **51** (Scheme 12B) is consistent with bond formation to the less-hindered face of each fragment.

**2.3. (–)-Jiadifenolide: Formal [4+2] addition to establish a densely-substituted cyclohexane ring.**

The *Illicium* sesquiterpenes are neurotrophic metabolites that contain an oxidized hydrindane core. (–)-Jiadifenolide<sup>[36]</sup> (**61**) possesses seven stereocenters, five of which are contiguous and fully-substituted. Total and formal routes to **61** have been disclosed by Sorensen,<sup>[37]</sup> Theodorakis,<sup>[38]</sup> Paterson,<sup>[39]</sup> Zhang,<sup>[40]</sup> Gademann,<sup>[41]</sup> Maimone,<sup>[42]</sup> and Shenvi.<sup>[43]</sup> The approach by Shenvi and co-workers involving a fragment coupling between two butenolides is discussed here.

By strategic oxidation state adjustments, Shenvi and co-workers derived (–)-jiadifenolide (**61**) from the precursor **62** (Scheme 13). The researchers recognized that **62** could be formed by successive 1,4-additions between the two butenolides

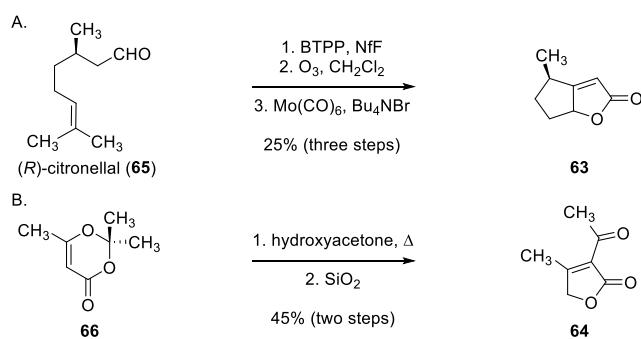


**Scheme 13.** Retrosynthetic analysis of (–)-jiadifenolide (**61**) by Lu et al.

**63** and **64**. The stereoselectivity in the coupling was expected to be controlled by the stereocenter in **63**.

The butenolide **63** was synthesized from (*R*)-citronellal **65** by a three-step process comprising enol nonaflate formation and *in situ* elimination [*tert*-butylimino-tri(pyrrolidino)phosphorane (BTPP), nonafluorobutanesulfonyl fluoride (NtF)],<sup>[44]</sup> ozonolysis alkene, and a hetero-Pauson–Khand reaction (25%, Scheme 14A).<sup>[45]</sup> The achiral butenolide **64** was obtained by the thermally-induced opening of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**66**) with hydroxyacetone, followed by an intramolecular aldol–dehydration promoted by silica gel (45% overall, Scheme 14B).<sup>[46]</sup>

## REVIEW



**Scheme 14.** A. Synthesis of the chiral butenolide **63** from (*R*)-citronellal (**65**). B. Synthesis of the butenolide **64**.

The fragment coupling began with deprotonation of **63** (LDA) to form an extended enolate, followed by addition of the achiral butenolide **64** (Scheme 15). The cyclic enol ether **67** could be isolated by arresting the reaction at this stage (see inset). This product forms by oxy-Michael cyclization of **69**. The stereoselectivity in this first addition may derive from an orientation that allows for secondary orbital overlap (see **68**), with approach of the electrophile **64** opposite to the face bearing the methyl substituent in **63**. To promote the second carbon–carbon bond-forming step *in situ*, the solution containing the initial addition product **69** was treated with excess LDA and titanium tetraisopropoxide. Under these conditions, the tandem 1,4-addition product **62** was obtained in 70% yield with >20:1 dr. The β-ketoester **62** was oxidized [*m*-chlorperoxybenzoic acid (*m*CPBA)]<sup>[47]</sup> and the resulting α-hydroxy-β-ketoester (not shown) was reduced (tetramethylammonium triacetoxyborohydride)<sup>[48]</sup> to provide the diol **71** (75%, 20:1 dr, two steps). Enolate formation (LDA) followed by addition of carbon tetrabromide provided **72**. Finally, enolization [sodium bis(trimethylsilyl)amide] (NaHMDS) and addition of the Davis oxaziridine **73**, generated the target.

#### Summary and Strategic Lessons:

[1] Similar to the (*–*)-englerin (**44**) synthesis, the fragment coupling relayed the configuration of the stereocenter in the

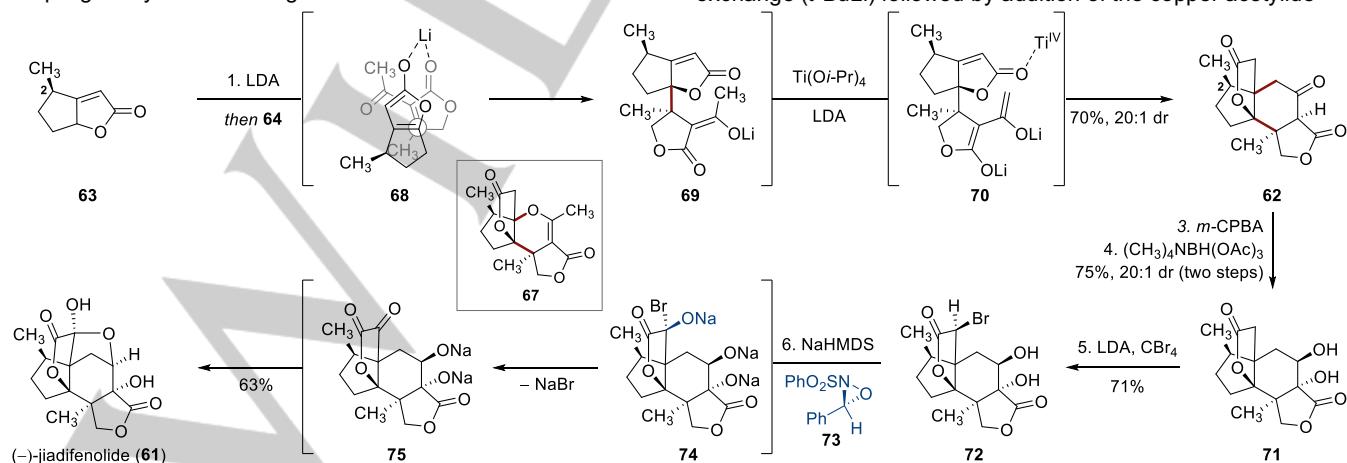
nucleophile **63** to four new stereocenters and provided the complete carbon framework of the target. By comparison, a single stereocenter in the electrophile was used to guide relative stereochemistry en route to (*–*)-englerin (**44**, Scheme 11). Both strategies reduce the synthesis of stereochemically complex (seven stereocenters each) and topologically complex [five rings for (*–*)-jiadifenolide (**61**), three for (*–*)-englerin (**44**)] molecules to the preparation of two fragments, one of which is achiral. The stereochemical outcome of the second carbon–carbon bond forming step in both instances is predictable based on consideration of non-bonded interactions.

[2] The fragment coupling partners employed in the (*–*)-englerin (**44**) and (*–*)-jiadifenolide (**61**) syntheses are accessible in three steps or less. This is advantageous because the optimization of the fragment coupling and modification of the coupling partners (if required) can be easily addressed.

#### 2.4. (+)-Fastigiatine: Formal [3+3]-cycloaddition and a biomimetic Mannich transformation facilitate assembly of the *Lycopodium* carbon skeleton.

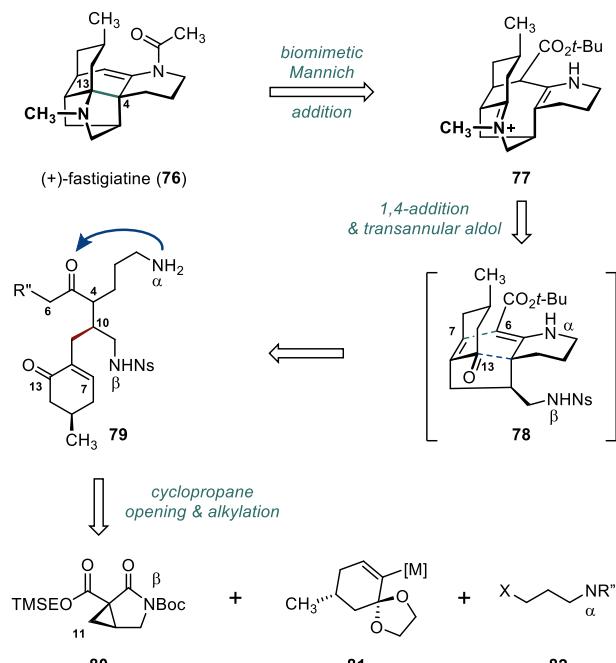
(+)-Fastigiatine (**76**) was isolated from the moss *Lycopodium fastigatum* by MacLean and co-workers.<sup>[49]</sup> (+)-Fastigiatine (**76**) belongs to the family of *Lycopodium* alkaloids.<sup>[50]</sup> Various *Lycopodium* alkaloids display cognitive enhancement effects, modulate the expression of neurotropic growth factor, and possess anticancer activity.<sup>[51]</sup> Many of these have attracted interest from the synthetic community, resulting in several completed syntheses.<sup>[52]</sup> The Shair and Rychnovsky laboratories have reported synthetic routes to **76**.<sup>[53]</sup> The Shair laboratory envisioned that the C4–C13 bond could be assembled via a transannular Mannich addition (Scheme 16). Intermediate **77** was anticipated to derive from the enamine **78** by a 1,4-addition–aldol reaction cascade. Retrosynthetic hydration of the enamine the diamine **79**, which could be simplified to the building blocks **80–82** by a cyclopropane-based fragment coupling and alkylation (vide infra).

The β-ketoester **80** was prepared in six steps starting from (*S*)-epichlorohydrin (**83**, Scheme 17A).<sup>[54]</sup> The mixed cuprate **88** was synthesized from the vinyl iodide **86** by a lithium-halogen exchange (*t*-BuLi) followed by addition of the copper acetyllide



**Scheme 15.** Synthesis of (*–*)-jiadifenolide (**61**) from the butenolides **63** and **64**.

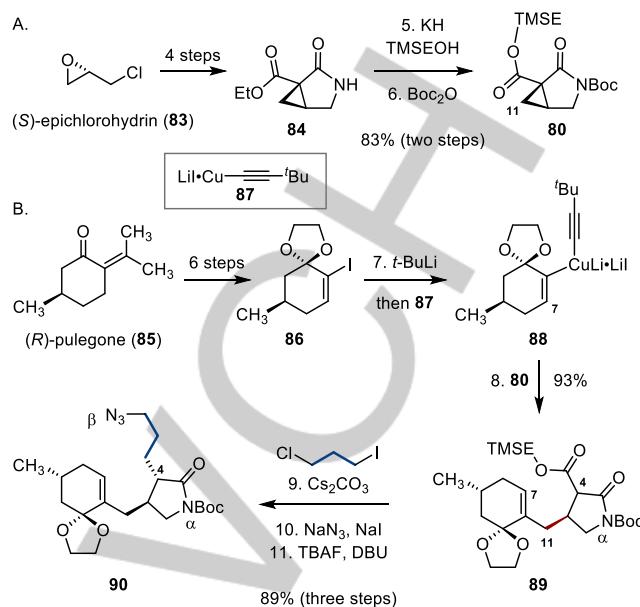
## REVIEW



Scheme 16. Synthetic strategy to (+)-fastigiatine (76) by Liu et al.

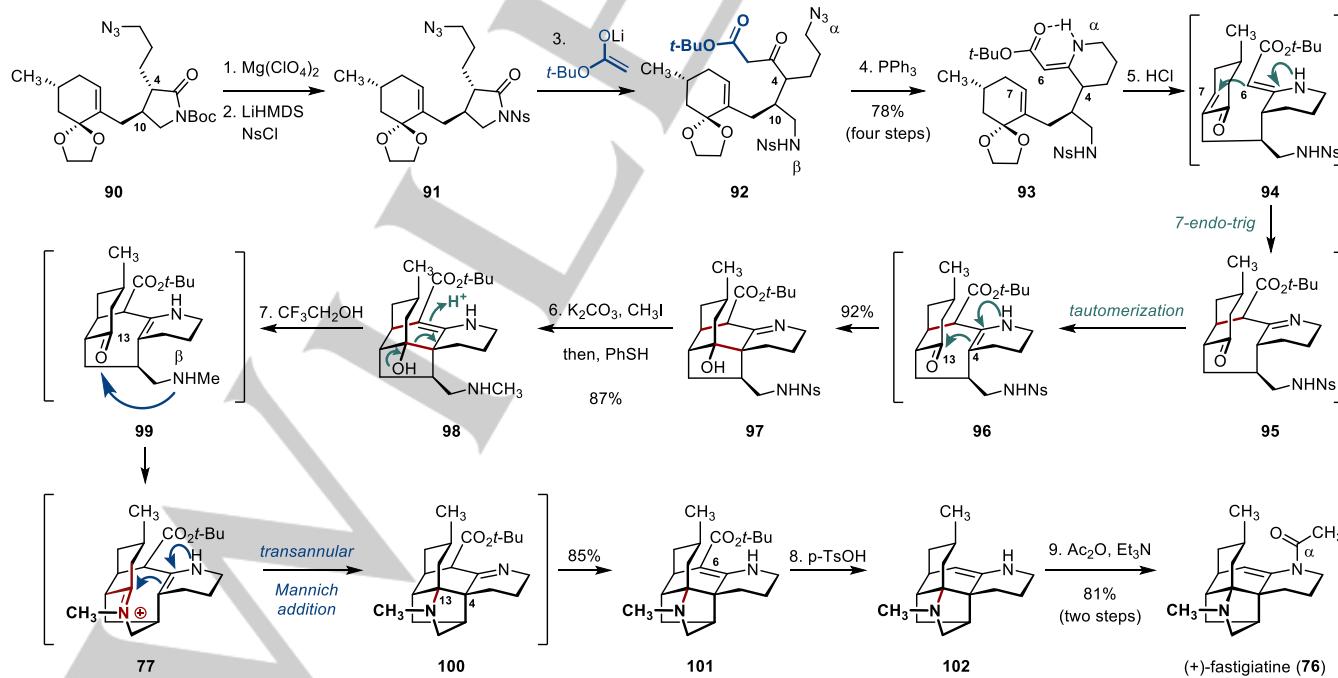
**87.**<sup>[55]</sup> Introduction of the  $\beta$ -ketoester 80 to the mixed cuprate resulted in ring-opening addition of the cyclopropane to furnish the fragment coupling product 89 (93%, Scheme 17B). In this transformation the acetylide functions as a nontransferable ligand.<sup>[56]</sup> The imide 89 was converted to the pyrrolidinone 90 in three steps (89% overall, Scheme 17B).

Following the fragment coupling, the *tert*-butyl carbamate



Scheme 17. A. Synthesis of cyclopropanes 80. B. Synthesis of 90 via diastereoselective cyclopropane ring-opening of 80 with mixed cuprate 88.

in 90 was exchanged for a sulfonamide (Scheme 18). Opening of the *N*-sulfonyl lactam 91 by the lithium enolate of *tert*-butyl acetate provided the  $\beta$ -keto ester 92. An intramolecularaza-Wittig reaction (triphenylphosphine) then provided the vinylogous urethane 93. Exposure of the linear precursor 93 to hydrochloric acid furnished the tetracycle 97 via a formal [3+3]-cycloaddition (92%). This transformation is believed to proceed by loss of the



Scheme 18. Completion of the synthesis of (+)-fastigiatine (76).

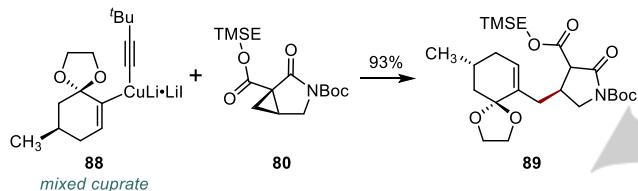
## REVIEW

ketal protecting group, 7-*endo*-trig cyclization (**94**→**95**), tautomerization (**95**→**96**), and transannular enamine addition (**96**→**97**).<sup>[57]</sup> The nitrogen atom was then methylated (potassium carbonate, iodomethane), and the sulfonyl substituent was removed by treatment with thiophenol and potassium carbonate to provide **98** (87%).

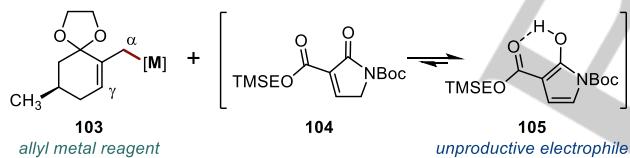
To complete the target, the tertiary alcohol at C13 needed to be formally substituted by N<sub>B</sub>. This transformation was achieved by heating **98** to 80 °C in trifluoroethanol (85%). A plausible pathway involves protonation of **98** with collapse of the tertiary alcohol to a ketone, leading to formation of **99**. Next, condensation of N<sub>B</sub> with the exposed ketone provided the iminium ion **77**. This iminium ion was poised to undergo a transannular Mannich addition forming the congested C4–C13 bond. Finally, tautomerization of **100** provided **101**. Removal of the *tert*-butyloxycarbonyl group [*p*-toluenesulfonic acid (PTSA)] followed by acylation of the resulting amine (acetic anhydride, Triethylamine) provided (+)-fastigiatine (**76**) in 15 steps and 30% overall yield from the cyclopropane **80**.

A.

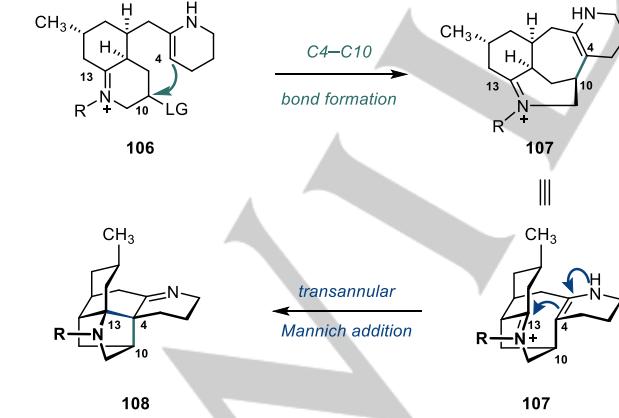
*Fragment coupling by cyclopropane opening:*



*Hypothetical coupling of an allyl metal reagent:*



B.



**Scheme 19.** A. Fragment coupling via addition to the cyclopropyl  $\beta$ -ketoester **80** addresses the challenges associated with addition of the allyl metal reagent **103** to the hypothetical electrophile **104** (see text). B. Biomimetic transannular enamine Mannich reaction.

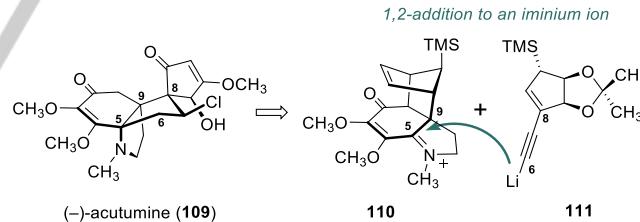
Summary and Strategic Lessons:

[1] The addition of the vinylmetal reagent **88** to the cyclopropyl  $\beta$ -ketoester **80** was employed to circumvent the more obvious but likely unfeasible approach involving addition of an allyl metal reagent to an alkylidene malonate (Scheme 19A). The latter coupling suffers from several challenges, including facile tautomerization of the electrophile **104** into the pyrrole **105** and  $\alpha$ -vs.  $\gamma$ -selectivity in the addition of the allyl metal reagent **103**. The use of a chiral cyclopropane electrophile circumvents the need to conduct a stereoselective 1,4-addition to an alkylidene malonate.

[2] While biosynthetic pathways are often difficult to fully recapitulate in the laboratory, recognition of these pathways can guide synthetic planning. In the present case, the identification of Mannich addition and aldol disconnections allows for rapid deconstruction of the carbon framework (Scheme 19B).

**2.5. (−)-Acutumine: Site-selective addition to a polyfunctional iminium ion to access propellane structures.**

(−)-Acutumine (**109**) is an alkaloid isolated from the roots of *Sinomenium acutum* in 1929.<sup>[58]</sup> (−)-Acutumine (**109**) displays a range of biological activities including inhibition of human T-cell proliferation and cognitive enhancement.<sup>[59]</sup> From a structural perspective, **109** possess unusual features including an oxidized spirocyclopentenone, three contiguous tetrasubstituted stereocenters, and a neopentyllic alkyl chloride (Scheme 20). The Castle and Herzon laboratories reported enantioselective synthetic routes to **109**, and studies toward the target have been disclosed.<sup>[60]</sup> Herzon and co-workers envisioned that (−)-acutumine (**109**) could be derived from the iminium ion **110** and the acetylidyne ion **111** (Scheme 20). Site and stereoselective addition of **111** to **110** would establish the tetra-substituted C5

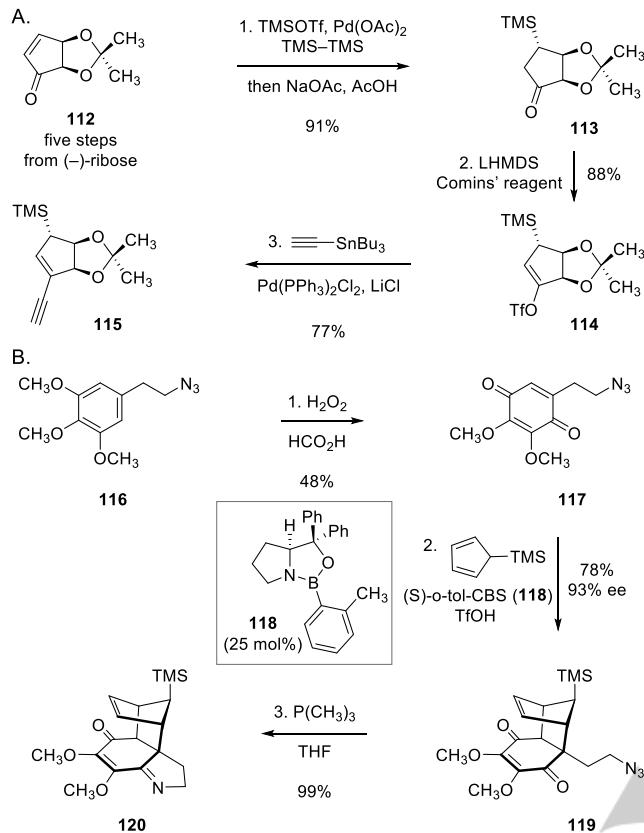


**Scheme 20.** Synthetic strategy toward (−)-acutumine (**109**) by King et al.

stereocenter while also introducing a synthon for the construction of the spirocyclopentenone residue in the target.

The synthesis began with the acetonide **112**,<sup>[61]</sup> which is accessible in five steps from (D)-ribose (Scheme 21A). Palladium-catalyzed 1,4-disilylation [palladium acetate, trimethylsilyl trifluoromethanesulfonate (TMSOTf), hexamethyldisilane] followed by cleavage of the resulting exoxysilane (not shown) provided the  $\beta$ -trimethylsilyl ketone **113**.<sup>[62]</sup> Deprotonation of **113** (LiHMDS) followed by the addition of Comins' reagent formed the vinyl triflate **114**. Stille coupling with ethynyl tributylstannane provided the enyne **115** (62% overall).

## REVIEW

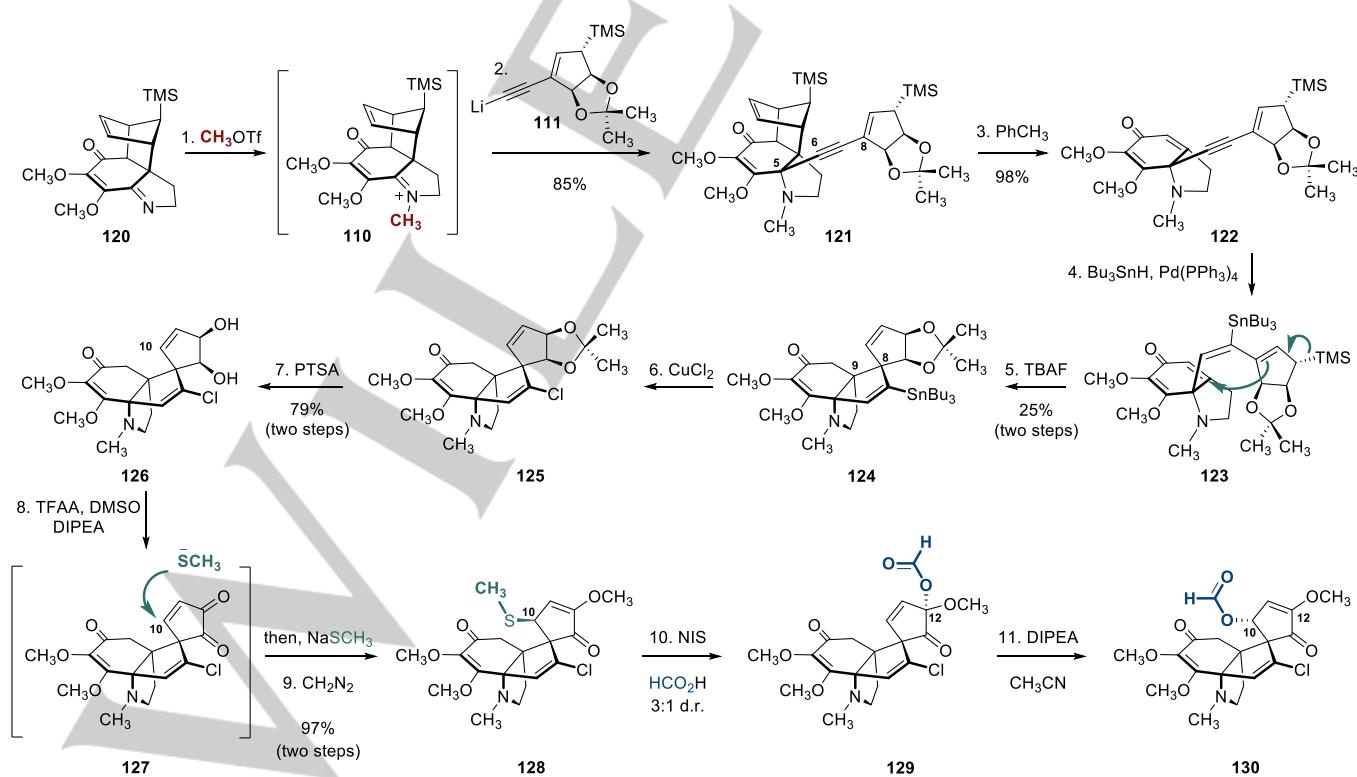


**Scheme 21.** A. Synthesis of the alkyne **115**. B. Preparation of the imine **120** via an enantioselective Diels–Alder reaction.

The synthesis of the imine **110** began with an oxidative dearomatization of the aryl azide **116**<sup>[63]</sup> (hydrogen peroxide–formic acid) to provide the quinone **117** (48%, Scheme 21B). A stereoselective Diels–Alder reaction between **117** and 5-trimethylsilylcyclpentadiene, promoted by the protonated form of the Corey–Bakshi–Shibata oxazaborolidine (**118**, 25 mol%), generated the tricyclic product **119** (87%, 93% ee). Staudinger reduction (trimethylphosphine) and *in situ* aza-Wittig reaction then formed the imine **120** (99%).

The addition of methyl triflate to a cold solution of the imine **120** generated the iminium ion **110** (Scheme 22). The acetylidy anion **111**, derived from the alkyne **115** by deprotonation with *n*-butyllithium (*n*-BuLi), was then added, to form the 1,2-addition product **121** as a single detectable diastereomer (85%). The stereoselectivity was attributed to the minimization of torsional strain in the transition state. Thermal extrusion of the silylcyclopentene residue (toluene, 135 °C, 98%), followed by a regioselective hydrostannylation [tributyltin hydride, tetrakis(triphenylphosphine)palladium, 67%], generated the dienyl stannane **123**. Fluoride-promoted 1,4-addition of the allyl silane provided the pentacycle **124** in 37% yield.<sup>[64]</sup> Copper-mediated chlorodestannylation [copper (II) chloride] and removal of the acetonide (PTSA) formed the vicinal diol **126** (79%, two steps).

The sulfide **128** was formed in 97% yield by oxidation of **126** using an excess of trifluoroacetic anhydride and methyl sulfoxide. 1,4-Addition of sodium methanethiolate to the enedione intermediate **127**, followed by O-methylation of the resulting enol (diazomethane) delivered **128**. Exposure of **128** to *N*-iodosuccinimide and formic acid triggered an oxidative elimination of the methanethiol substituent and a 1,2-addition of formate to a

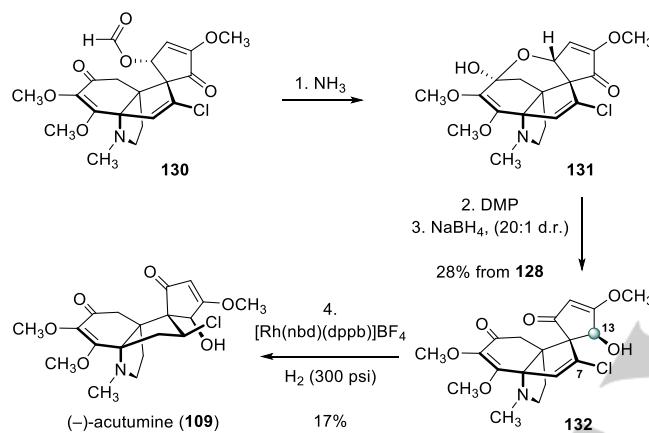


**Scheme 22.** Synthesis of **130** via addition of the acetylidy **111** to the *N*-methyl iminium ion **110**.

## REVIEW

putative oxycarbenium ion intermediate (not shown) to generate the methoxyformate **129** as a 3:1 mixture of C12 diastereomers. Thermally-induced [3,3]-sigmatropic rearrangement provided the formate ester **130** which possesses the desired oxidation at C10 of the spirocyclopentenone.

Removal of the formate substituent (ammonia, methanol) produced the hemiketal **131** (Scheme 23). The hemiketal **131** was oxidized to the corresponding vinylous  $\alpha$ -diketone (DMP), presumably via the chain intermediate. Site- and stereoselective reduction at C13 with sodium borohydride furnished (–)-dehydroacutumine (**132**) (28%, five steps, >20:1 dr at C13). Finally, reduction of the vinyl chloride ( $[\text{Rh}(\text{nbd})(\text{dpbb})]\text{BF}_4$ , 300 psi H<sub>2</sub>) formed (–)-acutumine (**109**, 17%) and (–)-dechloroacutumine (60%, not shown).



Scheme 23. Completion of the synthesis of (–)-acutumine (109).

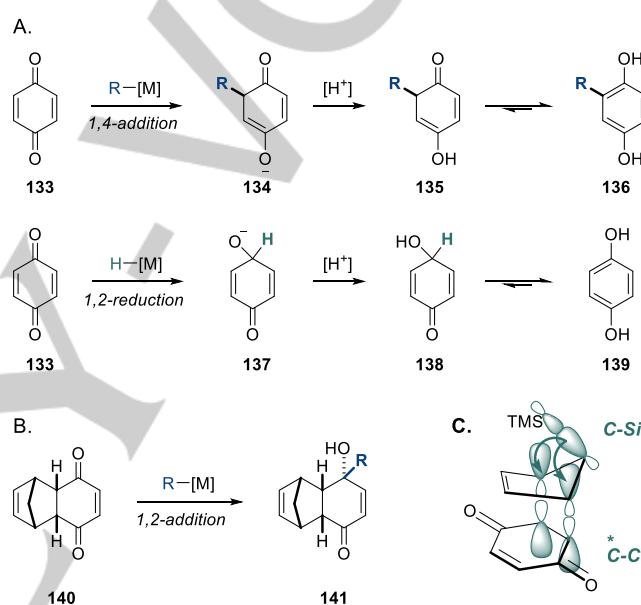
#### Summary and Strategic Lessons:

[1] The availability of substituted quinones renders them useful starting materials. However, methods to elaborate these to functionalized products are limited due to the presence of competing aromatization and electron transfer pathways. For example, the products of 1,2-reduction or 1,4-nucleophilic addition to quinones can readily aromatize (134→136 and 137→139) and strongly nucleophilic species are often oxidized by electron transfer (Scheme 24A). The Diels–Alder cycloaddition–functionalization–retrocycloaddition sequence outlined here is well-established and serves as a strategy to mask an otherwise reactive double bond, prevent aromatization, and introduce transient chirality.<sup>[65]</sup> For many years, the development of stereoselective quinone–diene cycloadditions stood as a prominent goal, and the Corey–Bakshi–Shibata oxazaborolidine is among the most general and effective promoters of this process. The resulting Diels–Alder adducts often undergo diastereoselective reactions (e.g., 140→141, Scheme 24B).<sup>[66]</sup>

[2] Functionalization of the Diels–Alder adducts is often accompanied by removal of one of the carbonyl substituents (deriving from the quinone). The resulting retrocycloadditions possess higher activation energies. In practice, this means that recourse to temperatures in excess of 200 °C or flash vacuum pyrolysis is required.<sup>[67]</sup> As first established by Magnus and

demonstrated here, Diels–Alder adducts of 5-trimethylsilylcyclopentadiene undergo retrocycloaddition at lower temperatures due to the donation of electron density from the carbon–silicon bonding orbital to the antibonding orbitals of the carbon–carbon bonds that cleave in the retrocycloaddition (essentially, an example of the  $\beta$ -silicon effect<sup>[68]</sup>, Scheme 24C).<sup>[69]</sup>

[3] 1,2-Additions to imines are well-established methods to generate chiral amines, and additions to Ellman *tert*-butane sulfinimines are arguably the most general approach to this bond construction.<sup>[70]</sup> Imines are less electrophilic than carbonyl groups, and the *tert*-butanesulfinyl substituent serves the dual role of rendering the imine more electrophilic while also providing



Scheme 24. A. Products resulting from 1,4-nucleophilic addition or 1,2-reduction of quinones readily aromatize. B. Example of stereochemical control in nucleophilic addition to the Diels–Alder cycloaddition adduct. C. The donation of electron density from the carbon–silicon bonding orbital to the carbon–carbon bonds that are breaking lowers the activation of the retrocycloaddition reaction of Diels–Alder adducts of 5-trimethylsilylcyclopentadiene.

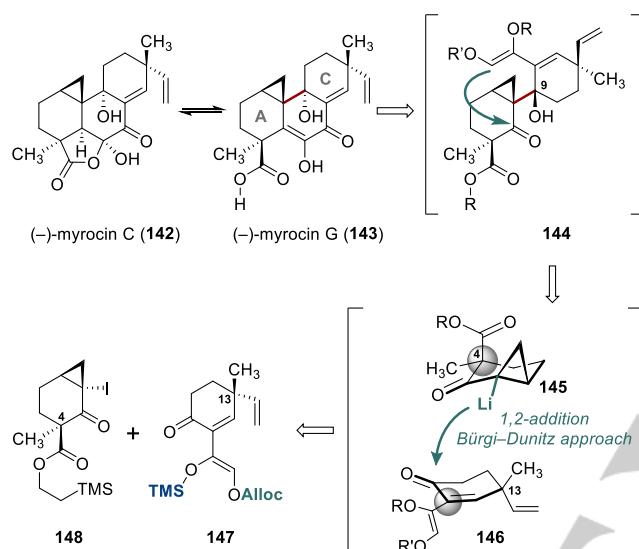
a handle for stereocontrol. The addition of strong nucleophiles to iminium ions is typically not high-yielding owing to their propensity to undergo proton transfer or hydrolysis. The iminium ion **110** employed here is stabilized by its cyclic structure and the absence of acidic protons. Selective *N*-methylation renders the iminium carbon more electrophilic than the carbonyl carbon allowing for site-selective 1,2-addition.

#### 2.6. (–)-Myrocin G: Single-step diosphenol synthesis enables a convergent approach to pimarane diterpenes.

The myrocins are pimarane diterpenes isolated from marine and soil fungi.<sup>[71]</sup> Various pimarane diterpenes possess antibiotic and antiproliferative activities, and myrocin C (**142**) has been proposed to cross-link DNA.<sup>[72]</sup> (±)-Myrocin C (**142**) was first synthesized by Chu-Moyer and Danishefsky in 1992.<sup>[73]</sup> The Chu-

## REVIEW

Moyer–Danishefsky approach established the core via sequential Diels–Alder cycloaddition reactions, followed oxidation state adjustments around the central ring. Myrocin C (**142**) contains a  $\gamma$ -hydroxylactone; related isolates deriving from opening of this ring have been characterized, and synthetic  $\gamma$ -hydroxylactones open under mildly acidic or basic conditions.<sup>[74]</sup> Accordingly, the Herzon laboratory targeted the chain isomer (–)-myrocin G (**143**), which they postulated as the biologically-active form of myrocin C (**142**).<sup>[75]</sup>

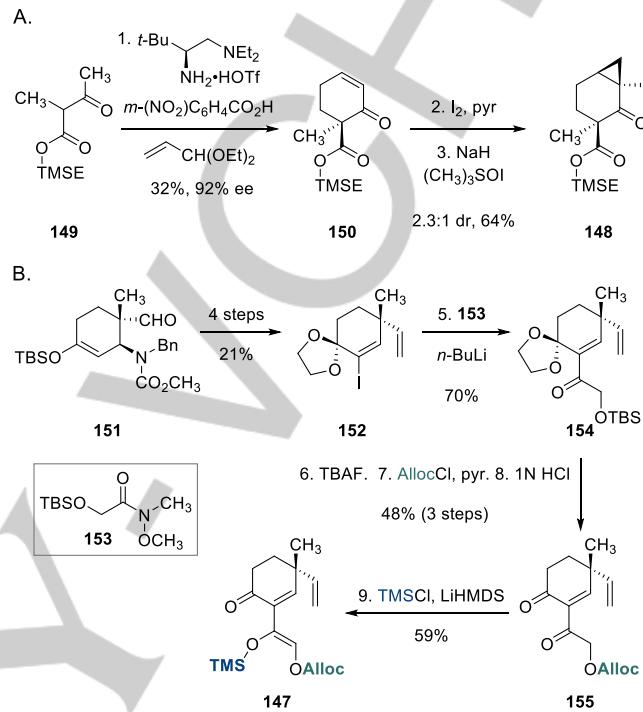


Scheme 25. Retrosynthetic analysis of (–)-myrocin G (**143**) by Economou et al.

The Herzon laboratory developed a fragment coupling–cyclization strategy to establish the C9 quaternary stereocenter and complete the central ring of (–)-myrocin G (**143**) (Scheme 25). This approach led to the cyclopropyl iodide **148** and the enoxysilane **147** synthetic precursors. The first step was envisioned to involve the addition of an organometallic intermediate derived from **148** to **147**. This addition was anticipated to provide the desired C9 stereochemistry, due to maximization of orbital overlap (Bürgi–Dunitz approach) and minimization of non-bonding interactions between the larger substituents (highlighted in grey spheres) in the transition state (Scheme 25).<sup>[76]</sup>

The synthesis of the  $\alpha$ -iodo- $\alpha$ , $\beta$ -cyclopropylketone **148** began with the  $\beta$ -ketoester **149**<sup>[77]</sup> (prepared in 2 steps from commercial reagents, Scheme 26). A stereoselective Robinson annulation<sup>[78]</sup> with acrolein diethyl acetal, followed by Johnson dehydroiodination<sup>[79]</sup> (iodine, pyridine), and Corey–Chaykovsky cyclopropanation<sup>[80]</sup> (trimethylsulfoxonium iodide, sodium hydride) provided **148** (Scheme 26A). The synthesis of **147** began with the known Diels–Alder adduct **151**<sup>[81]</sup> (prepared in four steps), which was advanced to the ketone **152** in four steps (21% overall). The addition of *n*-BuLi to **152**, followed by introduction of the Weinreb amide **153**, generated the  $\alpha'$ -silyloxy- $\alpha$ , $\beta$ -

unsaturated ketone **154** (70%). Protecting group manipulations followed by site-selective deprotonation of **155** with LiHMDS and trapping of the enolate with chlorotrimethylsilane provided the enoxysilane **147** (27%, four steps, Scheme 26B).



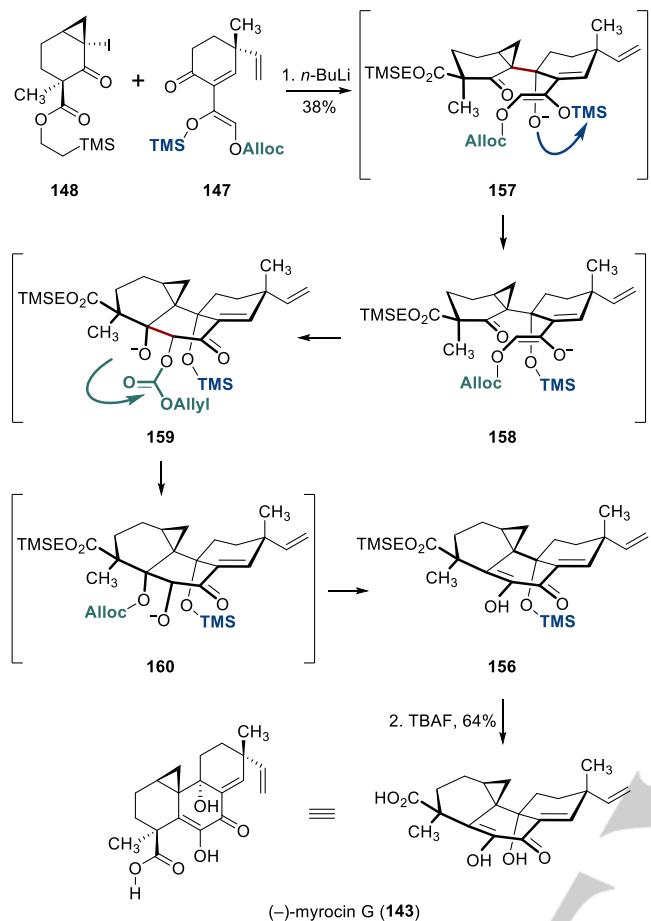
Scheme 26. Synthesis of the fragment coupling partners **147** and **148**.

With access to **147** and **148**, the fragment coupling was developed. Ultimately, it was found that treatment of the cyclopropyl iodide **148** with *n*-BuLi at –78 °C, followed by addition of the enoxysilane **147** and warming to 0 °C, provided the diosphenol **156** in 38% yield (Scheme 27). Based on the results of exploratory studies, this transformation was proposed to be initiated by diastereoselective 1,2-addition of **148** to the ketone of **147** (8.2:1 dr), followed by [1,5]-silyl migration (**157**→**158**). Intramolecular aldol addition (**158**→**159**), carbonate migration (**159**→**160**), and  $\beta$ -elimination (**160**→**156**), then provided the protected diosphenol **156**. Removal of the silyl protecting groups (TBAF) provided (–)-myrocin G (**143**, 64%).

#### Summary and Strategic Lessons:

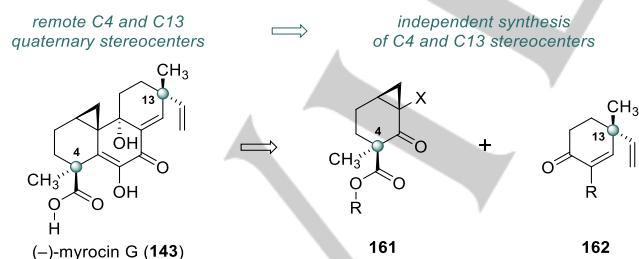
[1] The immediate retrosynthetic deconstruction of the core into two separate carbocyclic building blocks reduces the synthesis of (–)-myrocin G (**143**) to the smaller and independent goals of synthesizing **161** and **162** (Scheme 28). This approach allows for construction of the remote chiral centers at C4 and C13 independently. The diastereoselective synthesis of distant stereocenters is challenging; when possible, independent stereocontrolled introduction of these centers is often more efficient.

## REVIEW



**Scheme 27.** Single-step synthesis of the diosphenol **156** from the cyclopropyl iodide **148** and the enoxysilane **147**.

[2] Because the 1,2-addition, aldol addition, and dehydration are carried out under basic conditions, it was possible to relay the anionic charge in **157** throughout the molecule (Scheme 27). This strategy may be generally useful in designing cascade reactions wherein all steps involved are carried out under basic or acidic conditions.

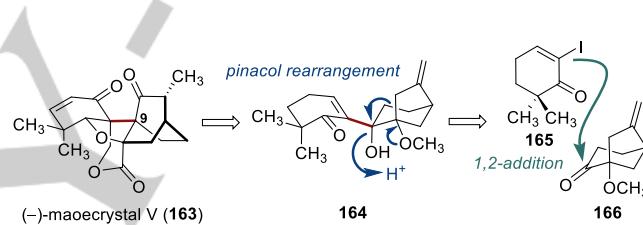


**Scheme 28.** The remote C4 and C13 stereocenters were identified as focal points for retrosynthetic deconstruction of (-)-myrocin G (**143**) to the fragments **161** and **162**.

[3] The sizes of the peripheral rings may be altered to allow access to other tricyclic scaffolds, for example, the [5-7-6] framework of the tigliane and daphnane diterpenoids.

### 2.7. (-)-Maoecrystal V: Pinacol rearrangement of a fragment coupling product provides access to a quaternary center in a complex bicyclo[2.2.2]octane.

The rearranged *ent*-kaurene diterpene (-)-maoecrystal V (**163**) was isolated from the leaves *Isodon eriocalyx* in 1994, and the structure was elucidated via X-ray crystallography in 2004.<sup>[82]</sup> The isolate was reported to be cytotoxic to HeLa cells with an IC<sub>50</sub> of 0.02 µg/mL. (-)-Maoecrystal V (**163**) contains three contiguous quaternary centers, two of which are embedded in a bicyclo[2.2.2]octane ring system. Enantioselective and racemic syntheses of maoecrystal V (**163**) have been reported by the Yang,<sup>[83]</sup> Danishefsky,<sup>[84]</sup> Zakarian/Davies,<sup>[85]</sup> and Thomson<sup>[86]</sup> research groups. A commonality of these syntheses involves construction of the bicyclo[2.2.2]octane ring system by a Diels–Alder cycloaddition. Baran and co-workers<sup>[87]</sup> devised a strategy that employs a biomimetic<sup>[88]</sup> pinacol rearrangement to construct the C9 quaternary stereocenter. A comprehensive review of synthetic approaches to maoecrystal V (**163**) has been disclosed.<sup>[89]</sup>

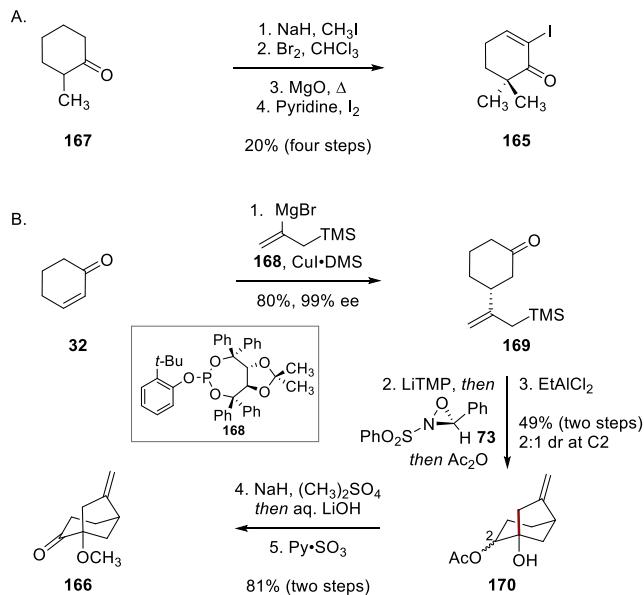


**Scheme 29.** Retrosynthetic analysis of (-)-maoecrystal V (**163**) by Cernienko et al.

Baran and co-workers envisioned that the bicyclo[2.2.2]octane ring system in (-)-maoecrystal V (**163**) could be constructed via a pinacol rearrangement of **164**. The 1,2-hydroxyether precursor **164** was anticipated to derive from fragment coupling of the α-iodoenone **165** and the bicyclo[3.2.1]octane **166**.

The construction of the α-iodoenone **165** began with methylation of 2-methylcyclohexane **167** (sodium hydride, iodomethane), followed by bromination (Br<sub>2</sub>, Scheme 30A). Elimination of hydrobromic acid (magnesium oxide) followed by Johnson dehydroiodination (pyridine, iodine) formed the α-iodoenone **165** (20% over four steps). The synthesis of **166** began with cyclohex-2-ene-1-one (**32**, Scheme 30B). Copper-catalyzed<sup>[90]</sup> 1,4-addition of 2-((3-trimethylsilyl)-1-propenyl) magnesium bromide, in the presence of the TADDOL-derived ligand<sup>[91]</sup> **168**, provided the ketone **169** (80%, 99% ee). α-Oxidation (lithium 2,2,6,6-tetramethylpiperidine, **73**) with in situ acetylation (acetic anhydride) followed by an intramolecular Sakurai reaction<sup>[92]</sup> promoted by ethylaluminum dichloride generated the alcohol **170** (49%, two steps). Methylation of the alcohol (dimethyl sulfate), in situ saponification of the ester (aqueous lithium hydroxide), and a Parikh–Doering oxidation (sulfur trioxide pyridine complex, triethylamine) provided the bicyclo[3.2.1]octane **166** (81%, two steps).

## REVIEW

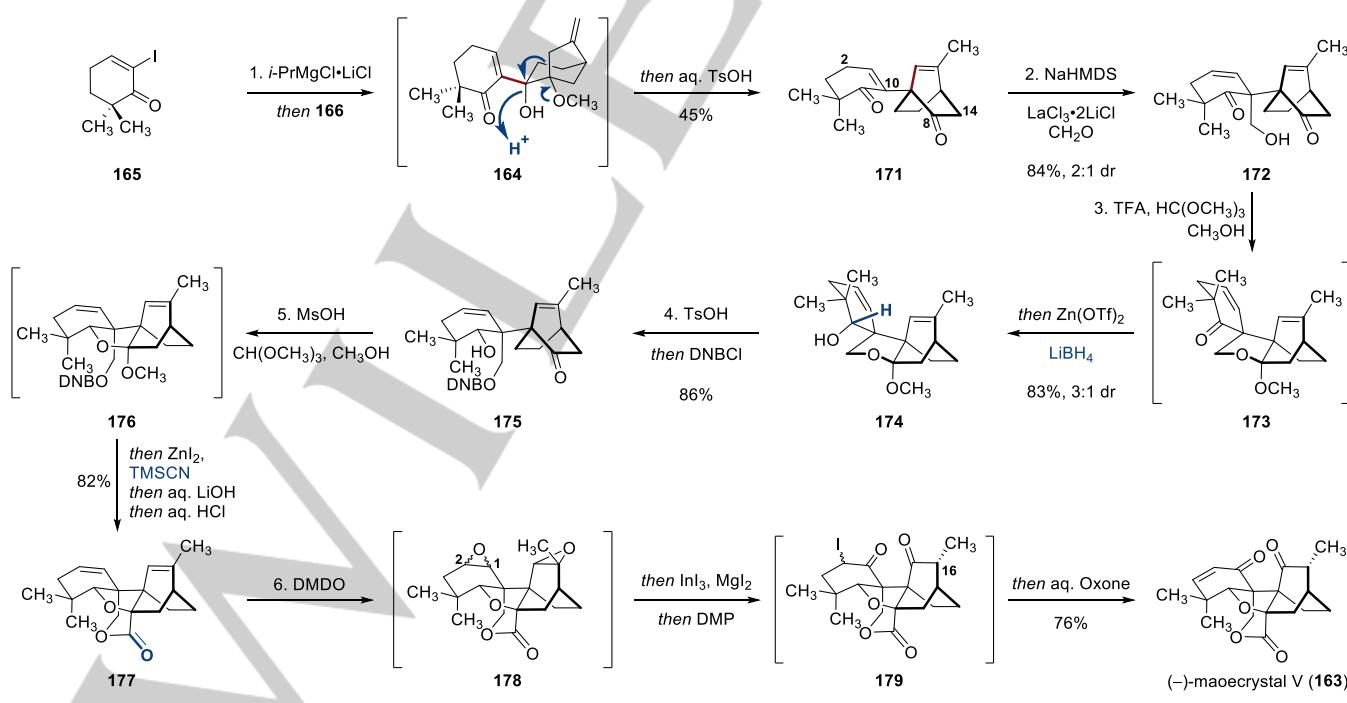


**Scheme 30.** A. Synthesis of the  $\alpha$ -idoenone 165. B. Synthesis of the bicyclo[3.2.1]octane 166.

Treatment of 165 with *i*-propyl magnesium chloride–lithium chloride complex,<sup>[93]</sup> followed by introduction of 166, provided the 1,2-addition product 164 (Scheme 31). This intermediate was not isolated but was treated directly with aqueous PTSA to induce a pinacol rearrangement, resulting in isolation of the rearranged bicyclo[2.2.2]octane 171 in 45% yield. Site-selective  $\gamma$ -deprotonation of the  $\alpha,\beta$ -unsaturated ketone within 171 (NaHMDS) in the presence of lanthanum chloride–

lithium chloride complex,<sup>[94]</sup> followed by the addition of paraformaldehyde, generated the  $\alpha$ -hydroxymethylketone 172 (84%, 2:1 dr). The site selectivity in the deprotonation was rationalized by poor alignment of the C14 C–H bonds with the C8 carbonyl and the ring strain that would result from planarization  $\alpha$  to this carbonyl substituent. The addition of lanthanum chloride–lithium chloride complex was found to promote  $\alpha$  (C10) rather than  $\gamma$  (C2) hydroxymethylation. The primary alcohol and less-hindered C8 ketone were protected as the acetal 173; reduction of the remaining carbonyl with the novel reagent combination of zinc triflate and lithium borohydride provided the secondary alcohol 174 (83%, 3:1 dr). Opening of the ketal and protection of the resulting primary alcohol was achieved in one flask by treatment with PTSA and dinitrobenzoyl chloride, to provide the ester 175 (86%). To form the last two rings of the target, a one-flask sequence comprising four transformations was developed. First, the ester 175 was treated with methanesulfonic acid in methanol to form the hemiketal 176. The addition of zinc iodide and trimethylsilylcyanide resulted in elimination of the methoxy substituent and diastereoselective addition of cyanide to the resulting oxocarbenium ion (not shown). Dilution of the reaction mixture with aqueous lithium hydroxide resulted in saponification of the dinitrobenzoyl group; the primary alcohol that was formed underwent 1,2-addition to the nitrile to form a cyclic amidate (not shown). Finally, hydrolysis of the amidate (aqueous hydrochloric acid) provided the lactone 177 (82%).

The synthesis was completed by a second four-step, one-flask sequence. Thus, diastereoselective diepoxydation of the lactone 177 with dimethyldioxirane (DMDO) provided the bis(epoxide) 178 as a 2:1 mixture of diastereomers at C1–C2



**Scheme 31.** Completion of the synthesis of ( $-$ )-maoecrystal V (163).

## REVIEW

(major diastereomer shown). The addition of indium iodide and magnesium iodide promoted ring-opening of the 1,2-disubstituted epoxide to an iodoalcohol and a stereospecific 1,2-hydride shift within the trisubstituted alkene, to establish the C16 methyl substituent in **179**. The iodoalcohol was oxidized by sequential treatment with DMP and aqueous oxone,<sup>[95]</sup> to provide (−)-maoecrystal V (**163**) in 76% yield.

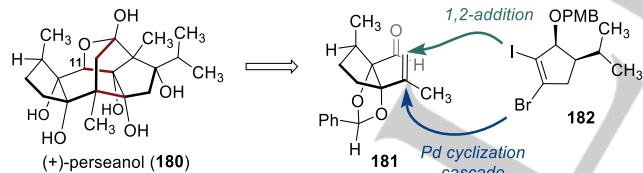
**Summary and Strategic Lessons:**

**[1]** Baran and co-workers' synthesis of (−)-maoecrystal V (**163**) was enabled by identification of a pinacol rearrangement to construct the C9 quaternary center and the bicyclo[2.2.2]octane ring system. The implementation of this transformation allowed the researchers to synthesize the target by the convergent coupling of the two fragments **165** and **166**. This fragment coupling establishes all but two carbon atoms in the target.

**[2]** The achiral nucleophile **165** enables the simplification of substrate preparation and reduction of the stereo-complexity involved in the coupling step. In addition, leveraging of the unique reactivity of the *iso*-propylmagnesium chloride–lithium chloride complex for metal–halogen exchange avoids extensive redox or protecting group manipulations of the enone in **165**.

**2.8. (+)-Perseanol: Two-step annulation strategy constructs the 5/6/5 isoryanodane core with a bridging lactone.**

(+)-Perseanol (**180**) is an isoryanodane diterpene isolated from the shrub *Persea indica*. The secondary metabolite possesses antifeedant activity against *Spodoptera litura*.<sup>[96]</sup> Characterized by a 5/6/5/7/5 pentacyclic carbon framework that bears ten contiguous stereocenters and a high degree of oxidation surrounding the central cyclohexane ring, (+)-perseanol (**180**) is structurally-related to the ryanodane class of natural products, which have been prepared by synthesis.<sup>[97]</sup>

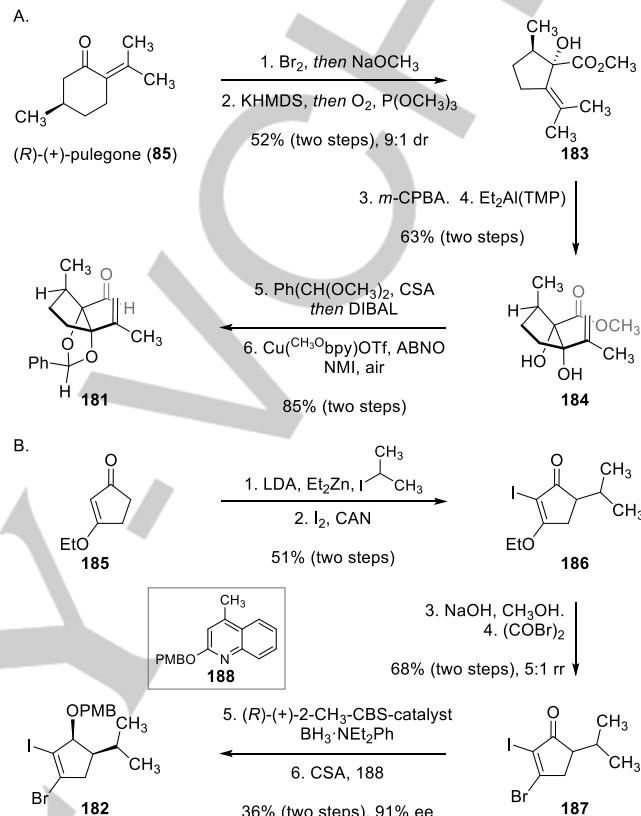


Scheme 32. Retrosynthetic analysis of (+)-perseanol (**180**) by Han et al.

The Reisman laboratory previously synthesized the related isolate (+)-ryanodol, and later developed a distinct approach to (+)-perseanol (**180**).<sup>[98]</sup> Retrosynthetically, they envisioned that the cyclohexane ring of (+)-perseanol (**180**) could be constructed from the aldehyde **181** and the dihaloalkene **182** (Scheme 32). Addition of an organometal reagent derived from **182** to the aldehyde in **181** would forge the C11 stereocenter. The remaining vinyl halide was anticipated to provide a handle for an intramolecular carbopalladation–carbonylation cascade to set the C5 quaternary center.

The synthesis of the alkenyl aldehyde **181** began with (*R*)-(−)-pulegone (**85**, Scheme 33). A one-flask bromination–

Favorskii rearrangement (bromine, sodium methoxide), followed by a diastereoselective hydroxylation of the resulting ester [potassium bis(trimethylsilyl)amide, dioxygen], provided the α-hydroxyester **183** (52%, 9:1 dr). Substrate-directed epoxidation

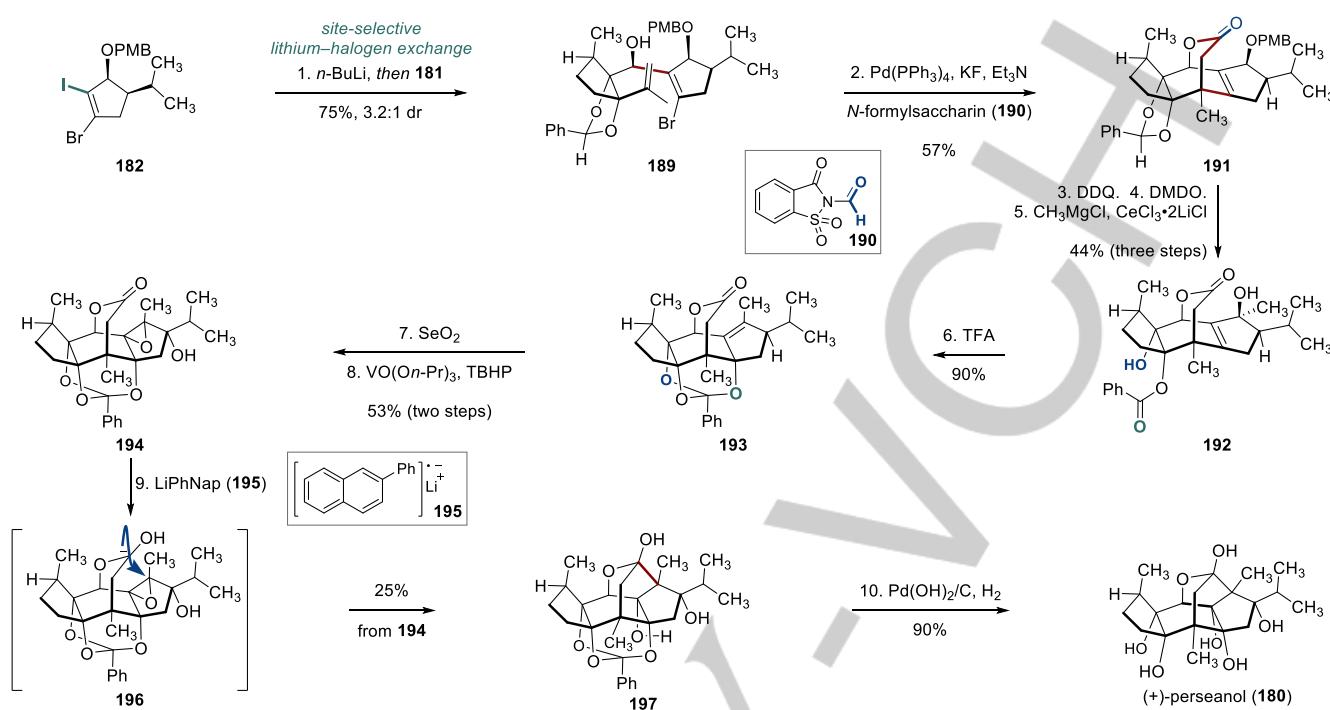


Scheme 33. A. Synthesis of alkenyl aldehyde **181**. B. Synthesis of the dihaloalkene **182**.

(*m*CPBA) and Lewis-acid promoted epoxide isomerization<sup>[99]</sup> generated the diol **184** (63%). The diol was protected as a benzylidene acetal [benzaldehyde dimethyl acetal, camphorsulfonic acid (CSA)], and the ester was reduced with di-*iso*-butylaluminum hydride (DIBAL-H). The resulting alcohol (not shown) was oxidized<sup>[100]</sup> to furnish the aldehyde **181** (85%, two steps).

The synthesis of the vicinal dihaloalkene **182** began with 3-ethoxy-cyclopent-2-ene-1-one (**185**). Zinc-mediated alkylation,<sup>[101]</sup> followed by dehydroiodination [iodine, ceric ammonium nitrate (CAN)] provided the α-iodoenone **186** (51%). Hydrolysis (sodium hydroxide, methanol) revealed a 1,3-diketone (not shown), that was converted to the vinylogous acyl bromide **187** by treatment with oxayl bromide (5:1 regioselectivity, 68% over two steps).<sup>[102]</sup> The racemic mixture of **187** was resolved by reduction with the Corey–Bakshi–Shibata oxazaborolidine. Protection of the secondary alcohol as the corresponding *p*-methoxybenzyl ether (CSA, **188**) provided the vicinal reduction with the Corey–Bakshi–Shibata oxazaborolidine. Protection of the secondary alcohol as the corresponding *p*-methoxybenzyl

## REVIEW



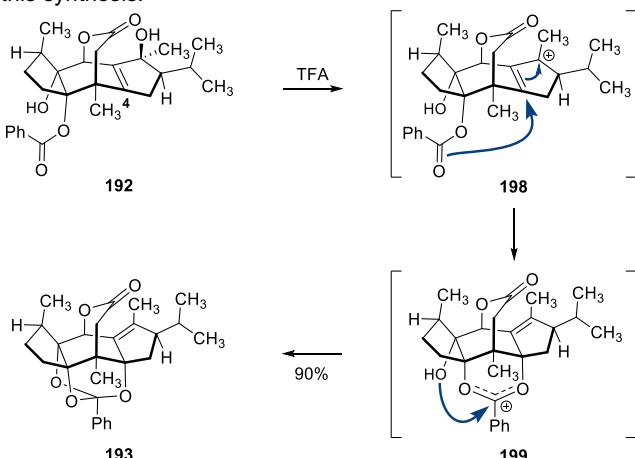
Scheme 34. Fragment coupling and the completion of the synthesis of (+)-perseanol (180)

ether (CSA, 188) provided the vicinal dihaloalkene **182** (36%, two steps, 91% ee).<sup>[103]</sup>

The 1,2-addition product **189** was formed in 75% yield and 3.2:1 diastereoselectivity by addition of *n*-BuLi to the vicinal dihaloalkene **182**, followed by introduction of the alkenyl aldehyde **181**. The carbopalladation–carbonylation cascade was achieved by heating solutions of the alcohol **189** with tetrakis(triphenylphosphine)palladium, *N*-formylsaccharin (**190**)<sup>[104]</sup> (as a source of carbon monoxide) and potassium fluoride in 1,4-dioxane, to give **191** (57%). Removal of the *p*-methoxybenzyl protecting group [2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)], oxidation of the benzylidene acetal and allylic alcohol functional groups (DMDO), and the addition of methyl magnesium bromide to the resulting enone provided the alcohol **192** (44%, three steps). Treatment with trifluoroacetic acid (TFA) resulted in Sn1' substitution of the allylic alcohol by the benzoate; trapping of the resulting cation by the neighboring tertiary alcohol then provided the orthoester **193** (90%, Scheme 35). Diastereoselective allylic oxidation (selenium dioxide) followed by hydroxyl-directed epoxidation [vanadium oxytripropoxide, *tert*-butylhydroperoxide (TBHP)] formed the epoxyalcohol **194** (53%, two steps). Lithium naphthalenide (**195**) reduction followed by a disfavored<sup>[105]</sup> 5-*endo*-tet opening of the epoxide by the carbanion intermediate **196** generated **197** (25%). Hydrogenolysis of the orthoester (Pearlman's catalyst) provided (+)-perseanol (**180**, 90%).

Summary and Strategic Lessons:

**[1]** Extensive protecting group manipulations are often necessary in the synthesis of highly oxidized molecules such as (+)-perseanol (**180**). Strategic introduction of the benzylidene acetal early in the synthesis and repurposing of this protecting group as a benzoate for stereospecific introduction of the C4 alcohol, through an S<sub>N</sub>1' substitution–oxocarbenium ion trapping cascade, served to greatly reduce the number of lateral manipulations in this synthesis.



Scheme 35. Strategic utilization of the benzoate protecting group to introduce the C4 alcohol.

## REVIEW

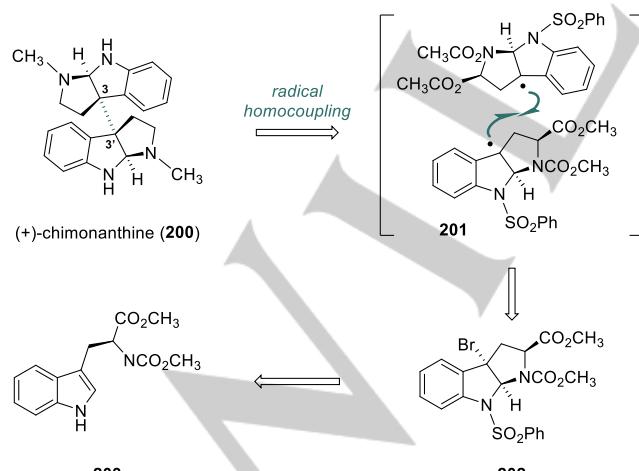
[2] The persistence of the palladium intermediate in the carbopalladation/carbonylation cascade is enforced by the lack of  $\beta$ -hydrogen after the initial insertion step, allowing further insertion into CO to formation of the seven-membered lactone. Altogether, this transformation sets one quaternary center, two C–C bonds, and two new rings.

### 3. Convergent Single-Electron Fragment Coupling

The following section provides examples of fragment couplings that proceed through open-shell intermediates.<sup>[106]</sup> Such couplings provide a strategic advantage when coupling sterically-hindered fragments. Because radicals are neutral, they are less susceptible to solvation effects, and because they are high in energy, bond formation occurs via early transition states. The surge in these types of couplings<sup>[107]</sup> has been driven by methods that allow the controlled generation of radical intermediates under mild conditions, such as photoredox catalysis.<sup>[108]</sup> As shown below, traditional strategies to generate carbon-centered radicals still find use, primarily for reasons related to the synthetic accessibility of the requisite precursors.

#### 3.1. (+)-Chimonanthine: Use of late stage radical homodimerization reaction enables rapid synthesis of a congested dimeric scaffold.

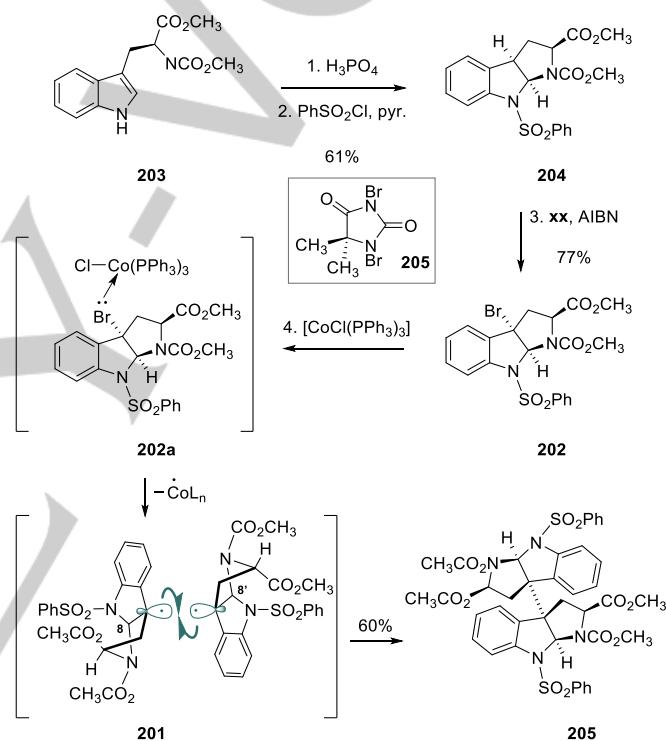
The dimeric alkaloid (+)-chimonanthine (**200**) is a member of the hexahydropyrroloidole family of natural products that biosynthetically originate from tryptophan.<sup>[109]</sup> (+)-Chimonanthine (**200**) was initially isolated in 1988 from the *Calycanthus glaucus* shrub by Eccles and co-workers; however, the correct chemical was elucidated almost seventy years after its original isolation by R. B. Woodward who employed a series of chemical degradation studies.<sup>[110]</sup> Structurally, this dimeric natural product is characterized by the presence of two sp<sup>3</sup>–sp<sup>3</sup> vicinal quaternary



**Scheme 36.** Retrosynthetic analysis of (+)-chimonanthine (**200**) by Schmidt et al.

stereocenters (C3–C3') that are adjacent to two aminals. A synthesis of **200** was reported by Overman<sup>[111]</sup> in 1999, and subsequently several additional routes have been disclosed.<sup>[112]</sup> The Movassaghi group developed a highly convergent radical homodimerization strategy to rapidly access **200**, and the approach will be discussed in detail in this review.<sup>[113]</sup>

Retrosynthetically, the Movassaghi group recognized the highly congested bridging bond could be accessed via a late stage reductive homodimerization of the two enantiomerically enriched free radicals **201** (Scheme 36) to obtain an intermediate that would contain all of the carbons present in the natural product. Furthermore, they envisioned that the key radical precursor **202** could be simplified to the commercially available N $\alpha$ -methoxycarbonyl-L-tryptophan methyl ester (**203**).



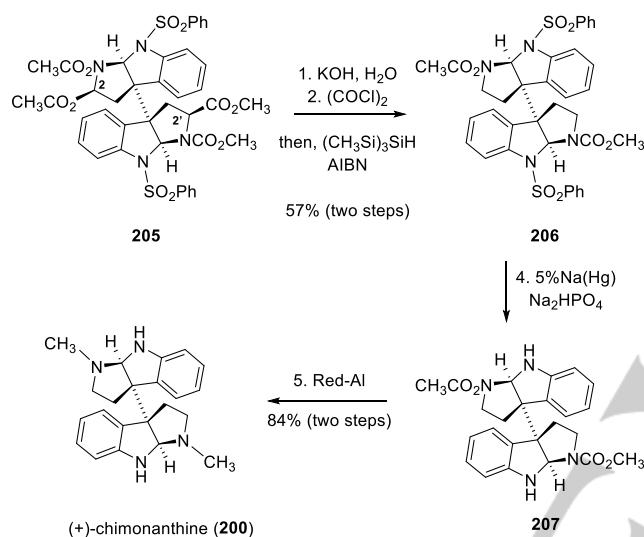
**Scheme 37.** Synthesis of **205** via a reductive homodimerization approach.

In the forward direction, the synthesis commenced with treatment of the building block **203** with neat phosphoric acid followed by nitrogen sulfonylation (benzenesulfonyl chloride, pyridine, 61% over two steps) to provide the hexahydropyrroloidole **204** (Scheme 37). To access the desired radical precursor, **204** was subjected to benzylic bromination [1,3-dibromo-5,5-dimethylhydantoin (**205**), AIBN] to deliver bromide **202** in 77% yield. The key reductive homodimerization was triggered by exposing **202** to tris(triphenylphosphine)cobalt(I) chloride as the stoichiometric reductant to provide the desired dimeric intermediate **205** in 60%.<sup>[114]</sup> The authors postulated that formation of **205** occurred via initial bromide abstraction (**202** → **202a**) to generate the short-lived, benzylic radical intermediate (**201**) that underwent a productive coupling reaction to yield the dimer product. The stereochemical outcome of this

## REVIEW

dimerization is rationalized by the orientation of the two radicals in a way that minimizes the non-bonding interaction with respect to the C8 and C8' position as shown in Scheme 37.

With a robust access to intermediate **205** possessing all of the carbon atoms as well as all of the stereochemistry present in the natural product, the completion of **200** was accomplished in four additional transformations (Scheme 38). The sequence starts with the hydrolysis of the two methyl ester groups at C2 and C2' (aqueous potassium hydroxide) to provide the corresponding dicarboxylic acid (not shown). Next, a double decarboxylation reaction was achieved by conversion of the two carboxylic acid groups to dicarboxylic acid chlorides (oxalyl chloride) followed by treatment with (trimethylsilyl)silane and AIBN to afford the



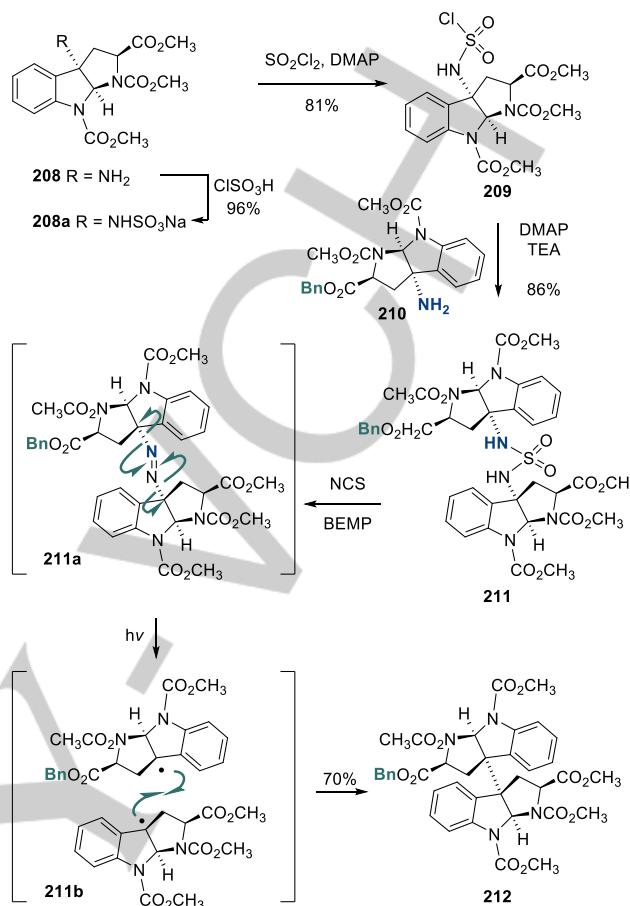
**Scheme 38.** Completion of the synthesis of (+)-chimonanthine (**200**).

hexacyclic intermediate **206** in 57% yield over two steps. Finally, removal of the benzenesulfonyl groups (sodium phosphate dibasic, sodium amalgam) provided the diamine **207** that was directly converted to (+)-chimonanthine (**200**) by a reduction with sodium bis(2-methoxyethoxy)aluminum hydride in 84% over two steps.

#### Summary and Strategic Lessons:

[1] Movassaghi and co-workers' synthesis of (+)-chimonanthine (**200**) was enabled by identification that dimeric bridging carbon–carbon bond could be constructed in a highly convergent manner via a radical homodimerization approach. This strategy significantly reduced the molecular complexity of the target and allowed for an exceedingly short synthesis, as the benzylic bromide fragment precursor **202** was accessed in three steps from a commercially available starting material. Moreover, to demonstrate the robustness of this approach, the Movassaghi lab has employed this strategy to synthesize several additional natural products, including (+)-WIN 64821<sup>[115]</sup>, (−)-ditryptophenaline<sup>[116]</sup>, and (+)-11,11'-dideoxyverticillin<sup>[117]</sup>.

[2] To access heterodimeric natural products, the Movassaghi lab has developed an alternative approach involving the generation and fragmentation of unsymmetrical dialkyl diazene intermediates



**Scheme 39.** Synthesis of the heterodimer **212** via a photolytic decomposition of the unsymmetrical diazine **211**.

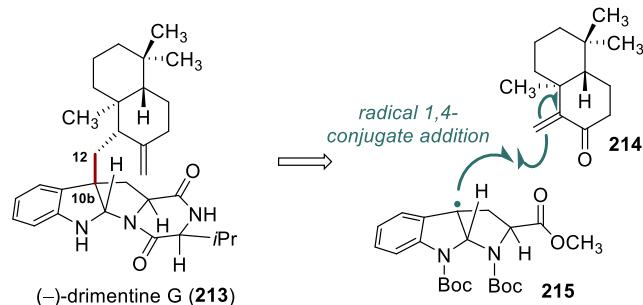
(Scheme 39).<sup>[118]</sup> For example, the heterodimeric sulfamide **211** was prepared by coupling of the sulfamoyl chloride **209** with the amine **210** (DMAP, triethylamine). Exposure of this intermediate to *N*-chlorosuccinimide in the presence of 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) generated the desired unsymmetrical diazine **211a**. Irradiation of this intermediate led to expulsion of dinitrogen and formation of the two tertiary radicals (**211b**) that underwent a heterodimerization to generate the coupling product **212** in 70% yield. This general strategy has been applied to the synthesis of numerous targets and is a powerful solution to the formation of the congested benzylic C<sub>sp3</sub>–C<sub>sp3</sub> bonds present in this class of alkaloids.<sup>[107a, 119]</sup>

#### 3.2. (−)-Drimentine G: Use of photoredox catalysis to enable fragment coupling by intermolecular diastereoselective conjugate addition.

(−)-Drimentine G (**213**) is an antiproliferative antimicrobial alkaloid containing a hexahydropyrrolo[2,3-*b*]indole core tethered to a sesquiterpene residue via a one-carbon bridge (Scheme 40).<sup>[109, 120]</sup> Many synthetic studies toward hexahydropyrrolo[2,3-*b*]indole alkaloids have been reported.<sup>[121]</sup> The Li group developed an

## REVIEW

enantioselective synthetic route to (*-*)-drimentine G (**213**) that employs a single electron fragment coupling to unite the

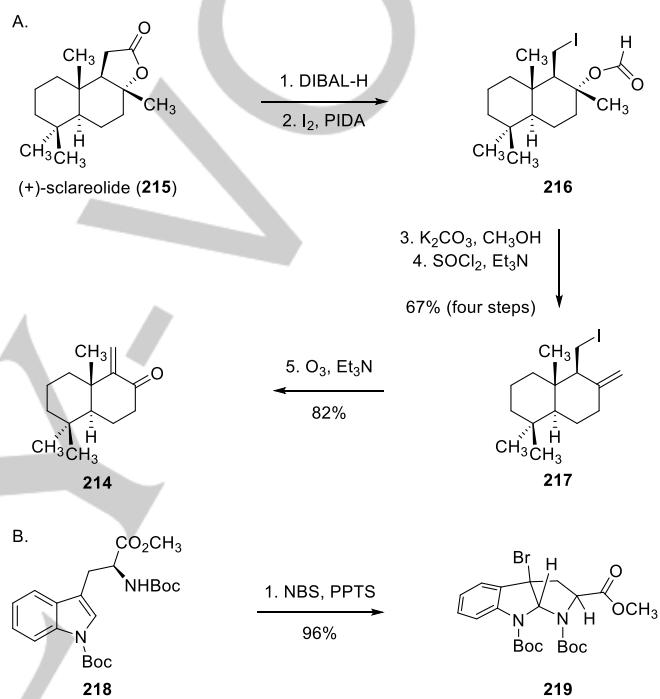


**Scheme 40.** Retrosynthetic analysis of (*-*)-drimentine G (**213**) by Sun et al.

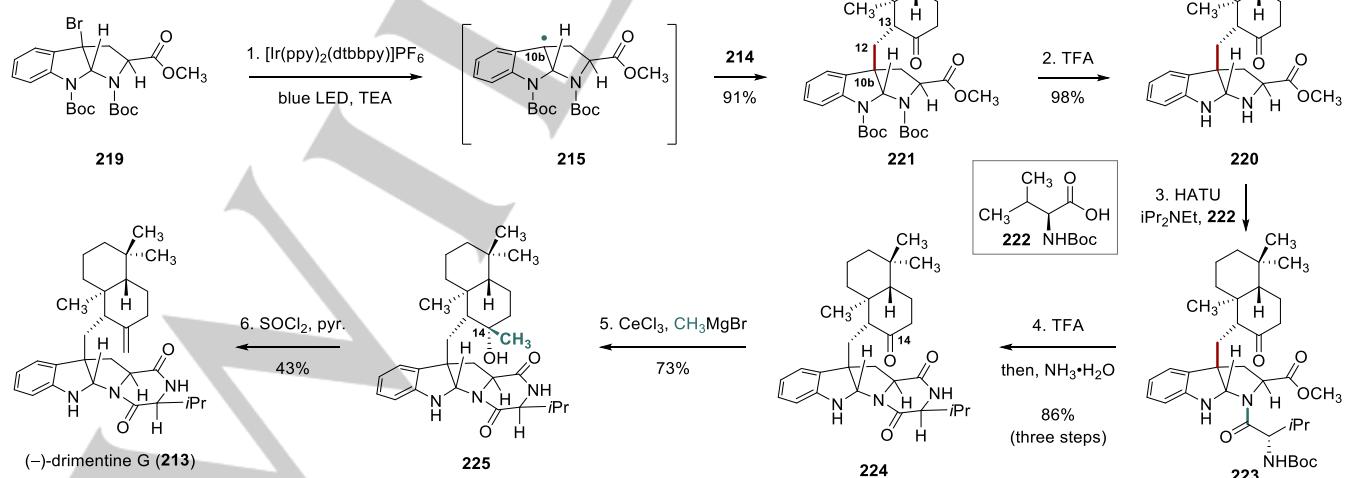
pyrroloindole and sesquiterpene residues (Scheme 40).<sup>[122]</sup> The enone **214** was synthesized in five steps from (+)-sclareolide (**215**) (Scheme 41A). The iodoformate **216** was prepared by reduction of **215** (DIBAL-H) and oxidative cleavage of the resulting lactol [iodine, (diacetoxymethoxy)benzene (PIDA)].<sup>[123]</sup> Removal of the formate (potassium carbonate, methanol) and elimination (thionyl chloride, triethylamine) furnished the exocyclic olefin **217** (67%, four steps). Ozonolysis of the alkene and base-catalyzed dehydrohalogenation provided the ketone **214** (83%). The bromopyrroloindoline **219** was prepared via an electrophilic bromocyclization of the L-tryptophan derivative **218** [NBS, pyridinium *p*-toluenesulfonate (PPTS), Scheme 41B].<sup>[124]</sup>

Irradiation of a mixture of the ketone **214** and the bromopyrroloindoline **219** in the presence of 2.5 mol% of the photocatalyst  $[(\text{Ir}(\text{ppy})_2(\text{dtbbpy}))\text{PF}_6]$  and triethylamine (Scheme 42) provided the fragment coupling product **221** in 91% yield (single diastereomer at C10b and C13). Conventional based procedures [2,2'-azobis(2-methylpropionitrile), tributyltin hydride or tris(trimethyl)silane] resulted in debromination. The mechanism advanced is shown in Scheme 43. Photoexcitation of the iridium complex followed by reduction of the

bromopyrroloindoline **219** and mesolytic cleavage of the carbon–bromine bond generated the alkyl radical **215**. 1,4-addition to the enone **214** provided the  $\alpha$ -keto radical **221a**. In parallel, the oxidized photocatalyst was proposed to undergo reduction by triethylamine; the resulting radical cation underwent hydrogen atom transfer to the  $\alpha$ -keto radical **221a** to give **221**.<sup>[125]</sup> This hydrogen atom transfer step is unexpected given the electron-deficient nature of **221a** and the amine radical cation. This fragment coupling could be carried out on gram-scale using 1.5 equiv of the bromopyrroloindoline fragment **219**.



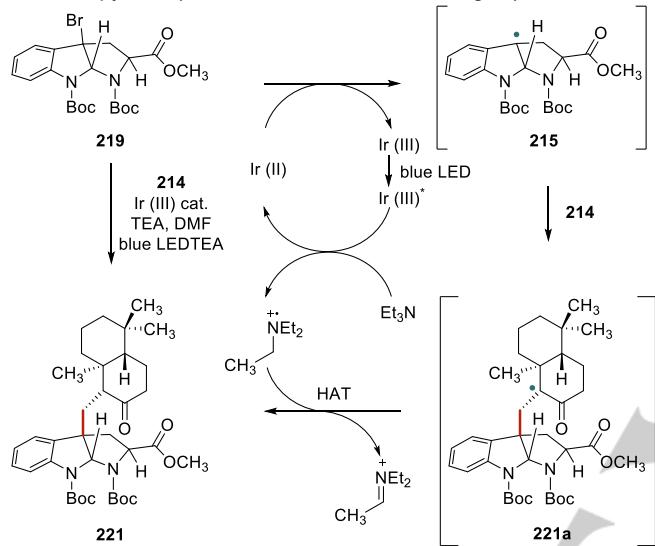
**Scheme 41.** A. Synthesis of the exo- $\alpha$ , $\beta$ -unsaturated ketone **214**. B. Synthesis of the bromopyrroloindoline **219**.



**Scheme 42.** Fragment coupling and completion of the synthesis of (*-*)-drimentine G (**213**).

## REVIEW

To complete the synthesis, the *tert*-butyloxycarbonyl substituents of **221** were removed by treatment with TFA to give **220** (96%, Scheme 42). Site-selective aminoacetylation with **222** [*HATU, N,N-diisopropylethylamine (DIPEA)*] provided the amide **223**. The diketopiperazine **224** was obtained by removal of the *tert*-butoxycarbonyl substituents (TFA) and neutralization of the resulting ammonium ion (aqueous ammonia) (86%, three steps). Direct methylation of the C14 ketone was unsuccessful, potentially due to the steric congestion surrounding this site. Therefore, a two-step procedure comprising the addition of methylmagnesium bromide, followed by dehydration (thionyl chloride, pyridine), was utilized to obtain the target (**213**, 31%, two



Scheme 43. Postulated mechanism of the intermolecular conjugate addition.

steps). Eleven synthetic transformations were required for the synthesis of **213**, underscoring the merits of this fragment coupling strategy.

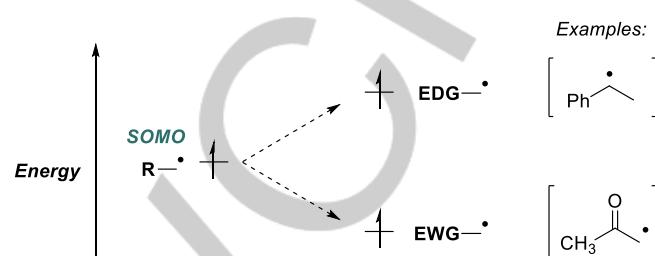
#### Summary and Strategic Lessons:

[1] The fragment coupling pursued here breaks the target into two fragments of comparable complexity at the methylene bridge. Each of these can be easily prepared from commercial simple materials [(+)-sclareolide (**215**) and the tryptophan derivative (**218**)].

[2] Radical based carbon–carbon bond forming reactions are especially valuable in sterically-hindered fragment coupling reactions. The SOMO orbital of the radical is diffuse. Consequently, radical-based fragment couplings are less sensitive to steric hindrance than two electron-based processes (e.g., nucleophilic displacement).

[3] Radical-based coupling reactions are subject to polar effects. Specifically, electron-rich (nucleophilic) radicals react efficiently with electron-deficient alkenes, while electron-poor (electrophilic) radicals react efficiently with electron-rich alkenes. The nucleophilicity or electrophilicity of a radical is determined by the substituents that interact with it. Here, the arene adjacent to the radical in **202** raises the energy of the SOMO by donation of

electron density, rendering the radical nucleophilic. By comparison,  $\alpha$ -keto radicals are illustrative electrophilic radicals. Because electron-rich radicals have a high energy SOMO, they react fastest with electron-deficient alkenes, which bear a low energy LUMO. By comparison, electron-deficient radicals react fastest with electron-rich alkenes, which bear a high-energy HOMO.

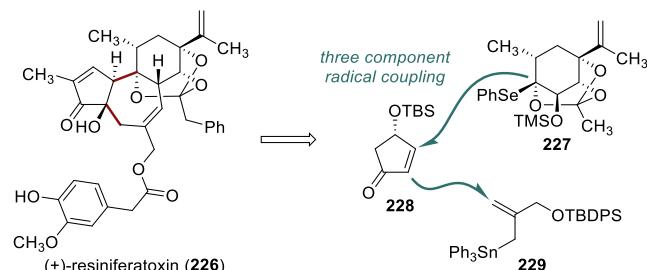


Note: EDG = electron-donating group; EWG = electron-withdrawing group  
Figure 2. The effects of substituents at the  $\alpha$ -carbon on the relative energy of the SOMO orbital.

Here the carbonyl removes electron density from the SOMO, lowering its energy. For a detailed discussion of radical nucleophilicity/electrophilicity and polar effects in radical couplings, see ref [126].

#### 3.3. (+)-Resiniferatoxin: Three component fragment coupling enables construction of a 5/7/6 tricyclic system from a bridgehead radical.

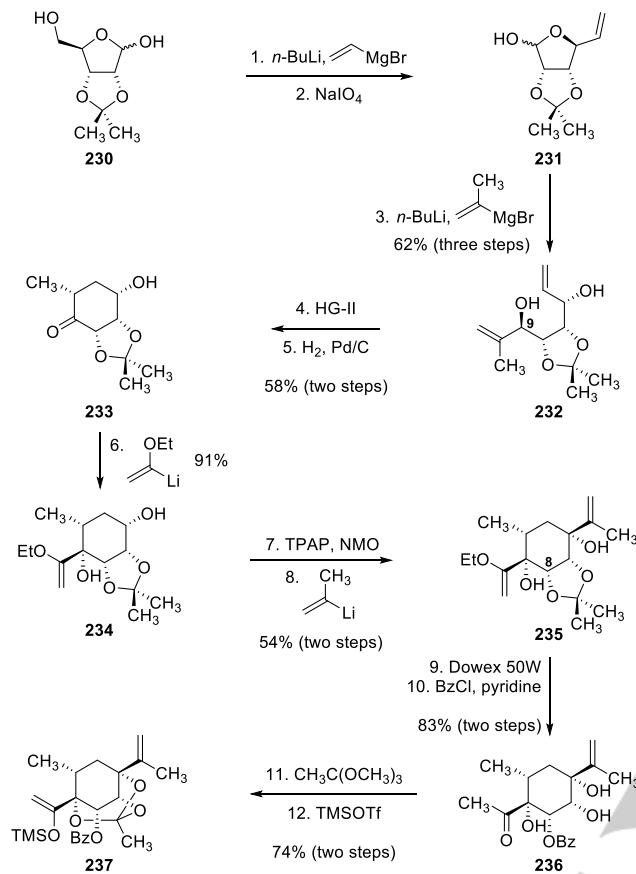
(+)-Resiniferatoxin (**226**) is a complex daphnane diterpenoid isolated from the latex of *Euphorbia resinifer*.<sup>[127]</sup> The structure of (+)-resiniferatoxin (**226**) was elucidated in 1982.<sup>[128]</sup> (+)-Resiniferatoxin (**226**) displays analgesic properties deriving from desensitization of nociceptive neurons. While daphnane terpenes have been known for decades,<sup>[129]</sup> the Wender<sup>[130]</sup> and Inoue<sup>[131]</sup> groups have reported the only complete routes to (+)-resiniferatoxin (**226**). The approach pursued by Inoue is discussed here.



Scheme 44. Retrosynthetic analysis of (+)-resiniferatoxin (**226**) by Hashimoto et al.

Retrosynthetically, Inoue and co-workers disassembled the target to **227**, **228**, and **229**. The researchers proposed that a tertiary radical derived from the selenide **227** would engage in a diastereoselective 1,4-addition to the enone **228**. Addition of the resulting  $\alpha$ -keto radical to the allylic stannane **229** (Keck allylation)<sup>[132]</sup> would then provide all of the carbon atoms found in the skeleton of the target.

## REVIEW

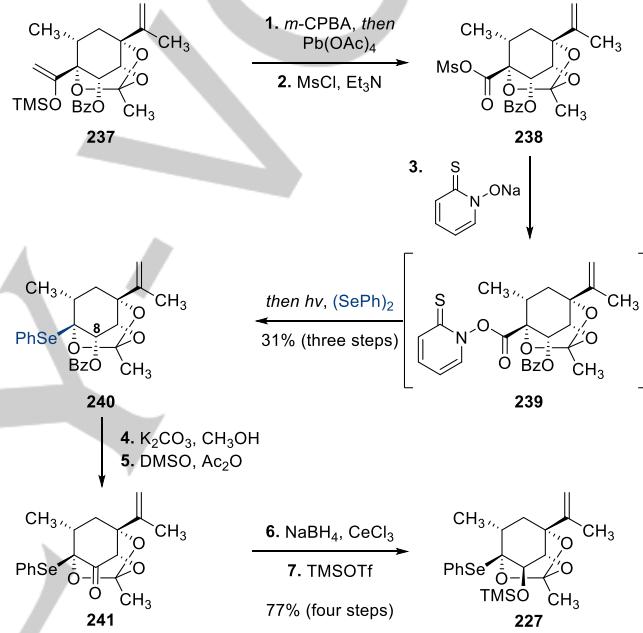
**Scheme 45.** Synthesis of the orthoester intermediate **237**.

The cyclohexane fragment **227** was prepared in enantiomerically pure form from the D-ribose derivative **230** (Scheme 45). The addition of vinyl magnesium bromide to the lactol **230**, followed by oxidative cleavage (sodium periodate), furnished the hemiacetal **231**. Deprotonation of the lactol (*n*-BuLi) followed by the addition of *iso*-propenylmagnesium bromide, provided the diol **232** (62%, three steps). Ring-closing metathesis (Hoveyda–Grubbs second-generation catalyst),<sup>[133]</sup> followed by isomerization of the allylic alcohol (not shown) generated the hydroxyketone **233** (58%, two steps). The addition of 1-ethoxy-1-lithioethylene to the ketone **233** formed the tertiary alcohol **234** (91%). Oxidation of the secondary alcohol [tetrapropylammonium perruthenate (TPAP), *N*-methylmorpholine *N*-oxide (NMO)]<sup>[134]</sup> followed by the addition of *iso*-propenyl lithium generated the diol **235** (54%, two steps). Removal of the acetonide (Dowex 50W), followed by selective benzoylation of the C8 hydroxyl group (benzoyl chloride, pyridine), provided the triol **236** (83%, two steps). To enforce structural rigidity, the triol **236** was protected as an orthoester (trimethyl orthoformate). Treatment with TMSOTf then provided the enoxysilane **237** (74%, two steps).

Rubottom oxidation (*m*CPBA), followed by oxidative cleavage of the resulting  $\alpha$ -hydroxyketone (lead tetraacetate) formed a carboxylic acid (not shown) that was sulfonated (methanesulfonyl chloride) to furnish the mesylate **238** (Scheme

46).<sup>[135]</sup> Barton ester formation (**239**),<sup>[136]</sup> followed by photoirradiation and trapping of the resulting bridgehead radical with diphenyl diselenide produced the selenide **240** (31%, three steps).<sup>[137]</sup> The C8 position was inverted by saponification of the ester (potassium carbonate, methanol), Swern oxidation (acetic anhydride, dimethyl sulfoxide),<sup>[138]</sup> and reduction (sodium borohydride, cerium trichloride).<sup>[139]</sup> Silylation of the resulting secondary alcohol (not shown, TMSOTf) formed the silyl ether **227** (77%, four steps). The cyclopentenone **228**<sup>[140]</sup> and allylic stannane **229**<sup>[141]</sup> were prepared by established procedures.

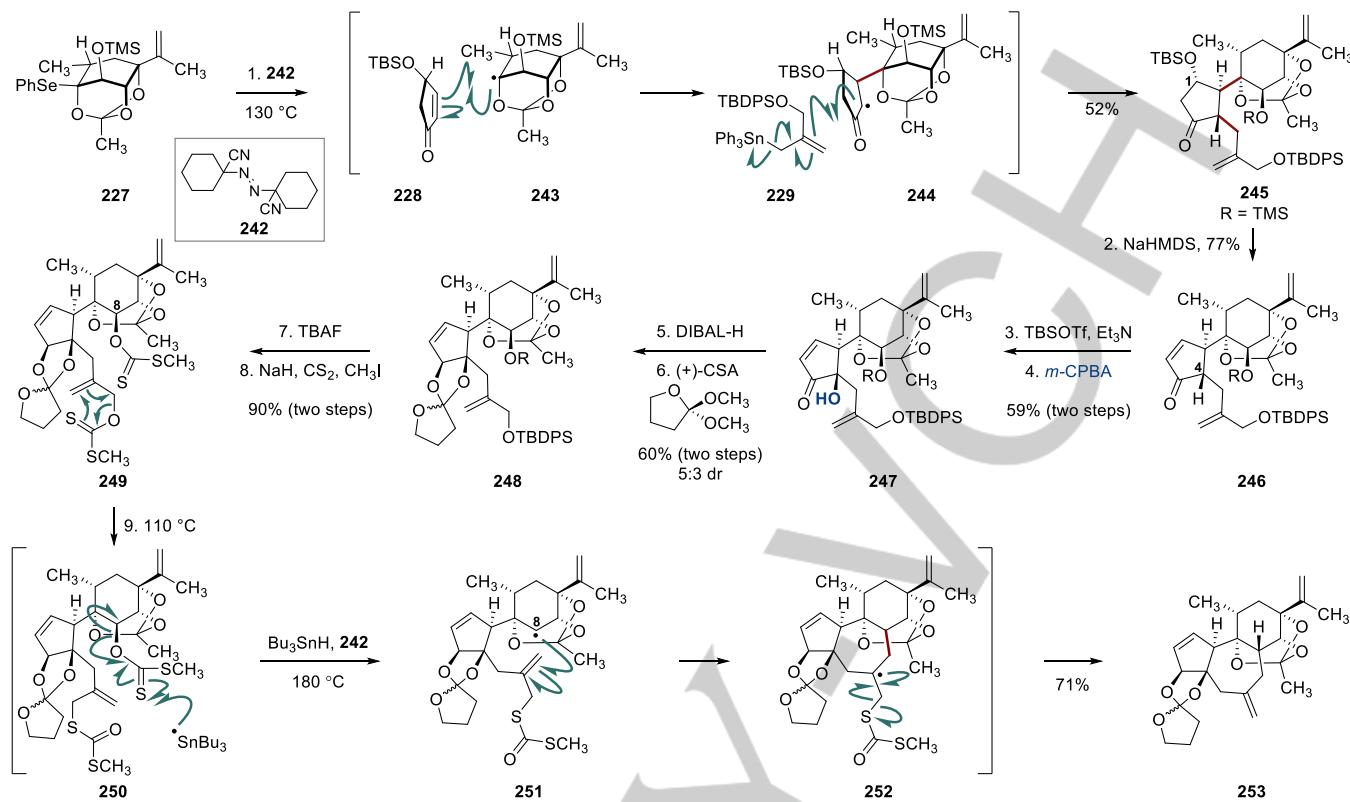
To effect the fragment coupling, a solution of the selenide **227**, the cyclopentenone **228**, and the allylic stannane **229** in chlorobenzene containing the initiator 1,1'-azobis(cyclohexane-

**Scheme 46.** Installation of the selenide substituent at the bridgehead position to provide the radical precursor **227**.

carbonitrile) (**242**) was heated to 130 °C (Scheme 47). The three-component coupling product **245** was formed in 52% yield. This transformation is believed to proceed by addition of the bridgehead radical **243** to the enone **228** (*anti* to the silyloxy substituent), addition of the resulting  $\alpha$ -ketoradical **244** to the allyl stannane **229**, and elimination of tributylstannyl radical. Overall, this transformation enabled stereocontrolled construction of two new chiral centers and introduction of all of the carbons in the 5/7/6 tricyclic core of (+)-resiniferatoxin (**226**).

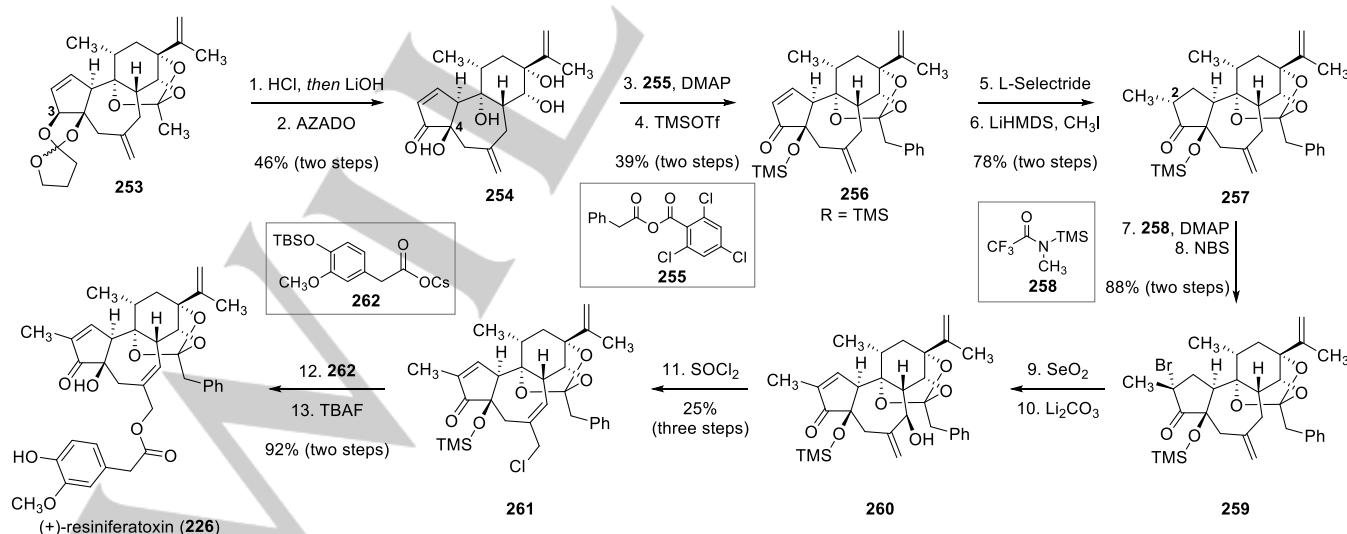
Treatment of the fragment coupling product **245** with NaHMDS resulted in elimination of the C1 silyloxy group to afford the  $\alpha,\beta$ -unsaturated ketone **246** (77%). Enoxysilane formation (*tert*-butyldimethylsilyl trifluoromethanesulfonate, triethylamine) followed by Rubottom oxidation (*m*CPBA) provided the  $\alpha$ -hydroxyketone **247** (59%, two steps). The ketone was reduced (DIBAL-H), and the resulting diol was protected as the cyclic ketal **248** (60%, two steps, 5:3 dr).<sup>[142]</sup> The silyl protecting groups were removed (TBAF), and the alcohols that were revealed were

## REVIEW

Scheme 47. Three-component radical coupling and ring closure to construct the advanced intermediate **253**.

converted to methyl xanthate esters (carbon disulfide, sodium hydride, iodomethane; 90%, two steps).<sup>[143]</sup> Thermolysis of the bis(xanthate ester) **249** induced a [3,3]-sigmatropic rearrangement of the unsaturated xanthate ester to give **250**.<sup>[144]</sup> The addition of tributyltin hydride and **242** to the reaction mixture then triggered generation of the C8 radical intermediate **251**; 7-*endo*-trig cyclization and elimination of sulfinyl radical from intermediate **252** formed the triene **253** (71%).<sup>[145]</sup>

To complete the synthesis, the ketal and orthoester substituents in **253** were removed by treatment with aqueous hydrochloric acid, followed by lithium hydroxide (Scheme 48). Nitroxyl radical-mediated oxidation<sup>[146]</sup> of the C3 alcohol (not shown) provided the α,β-unsaturated-ketone **254** (46%, two steps). Ortho phenylacetate formation (**255**, DMAP)<sup>[147]</sup> and protection of the C4 alcohol as a silyl ether (TMSOTf) generated **256**. 1,4-Reduction of the α,β-unsaturated ketone (lithium

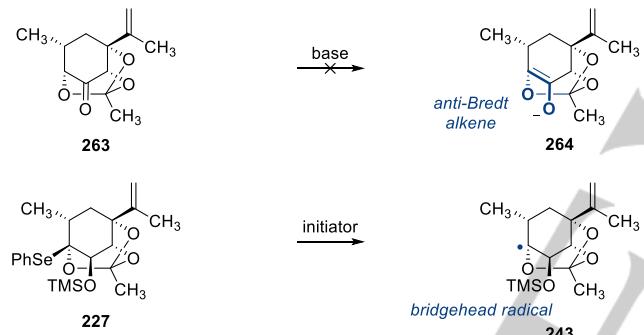
Scheme 48. Completion of the synthesis of **(+)-resiniferatoxin** (**226**).

## REVIEW

tri-sec-butylborohydride) followed by diastereoselective methylation (LiHMDS, iodomethane) provided the ketone **257** (78%, two steps, C2 configuration confirmed by NOESY analysis). Enoxysilane formation (**258**, DMAP)<sup>[148]</sup> followed by bromination (NBS) generated the  $\alpha$ -bromoketone **259** (88%, two steps). Site-selective allylic oxidation (selenium dioxide)<sup>[149]</sup> and base-mediated elimination of the bromide (lithium carbonate) formed the  $\alpha,\beta$ -unsaturated ketone **260**.  $S_N2'$  substitution of the allylic alcohol (thionyl chloride) then formed the allylic chloride **261** (25%, three steps). Finally, the chloride was displaced with cesium carboxylate **262**,<sup>[150]</sup> removal of the silyl ethers (TBAF) then formed (+)-resiniferatoxin (**226**, 92%, two steps).

Summary and Strategic Lessons:

[1] The radical disconnection in the three-component fragment coupling skillfully addresses a bond construction that could not be achieved using two-electron chemistry (Scheme 49). Whereas poor orbital overlap prohibits an enolate-mediated addition from the cyclohexane fragment **263** (the enolate would constitute an anti-Bredt alkene), the bridgehead radical **243** is generated in this transformation, without violating any stereochemical requirements.



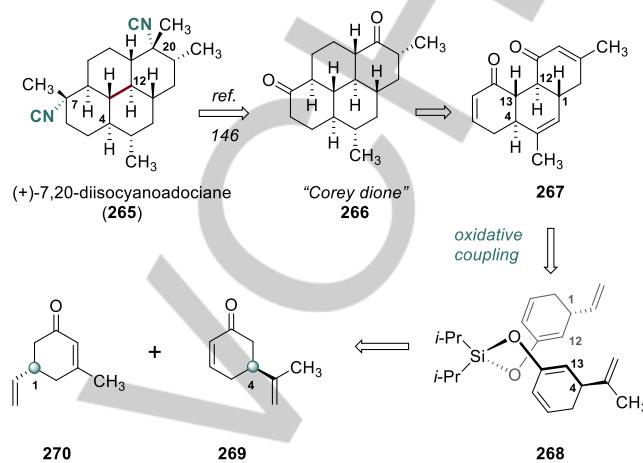
**Scheme 49.** Generation of a bridgehead enolate is not possible due to poor orbital overlap between the  $\alpha$ -carbon and the carbonyl (anti-Bredt alkene). The stereoelectronic requirements of single-electron intermediates allow bridgehead radical nucleophiles to participate in a multicomponent reaction.

[2] The scarcity of functional groups in the seven-membered ring limits the number of practical methods to close the ring that do not require lateral redox manipulations. The radical ring closure provides a terminal alkene, which after an allylic oxidation, allylic transposition, and displacement with the cesium carboxylate **262**, installed the required functional groups.

### 3.4. (+)-7,20-diisocyanoadociane: Convergent polycyclic cyclohexane synthesis via an oxidative coupling–ring-closing metathesis strategy.

(+)-7,20-Diisocyanoadociane (**265**) was isolated from a marine sponge found on the Great Barrier Reef in 1976.<sup>[151]</sup> (+)-7,20-Diisocyanoadociane (**265**) was shown to be a potent and selective antimalarial agent with IC<sub>50</sub> values of 4.7 and 4.3 ng/mL against two clones of the malaria parasite *Plasmodium falciparum* (D6 and W2) respectively.<sup>[152]</sup> (+)-7,20-Diisocyanoadociane (**265**)

contains ten contiguous stereocenters, two tertiary alkyl isonitriles (at C7 and C20), and an all-*trans*-perhydropyrene skeleton. The saturated carbon skeleton creates additional challenges as minimal functional group handles are in place for manipulations.



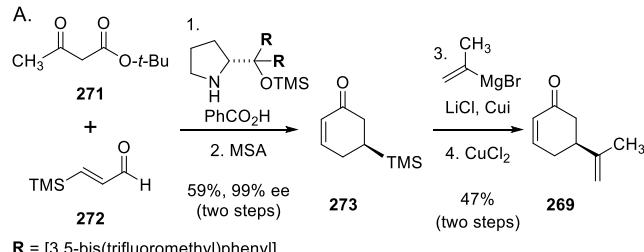
**Scheme 50.** Retrosynthetic analysis of (+)-7,20-diisocyanoadociane (**265**) by Robinson et al.

The first total synthesis of (+)-7,20-diisocyanoadociane (**265**) was reported by Corey and co-workers in 1987.<sup>[153]</sup> The tetracyclic diketone **266** was synthesized en route to the target; it is now referred to as the Corey dione. Subsequently, the Corey dione (**266**) has served as an intermediate in syntheses of (+)-7,20-diisocyanoadociane (**265**) developed by the Miyaoka, Vanderwal, and Thomson laboratories.<sup>[154]</sup> Additionally, the Shenvi and Mander groups developed enantioselective syntheses of 7,20-diisocyanoadociane (**265**).<sup>[155]</sup> The approach by Thomson and co-workers employs a stereoselective oxidative fragment coupling and is discussed herein.

The Thomson laboratory developed an oxidative coupling proceeding from two ketones of similar complexity (Scheme 50). This approach began with synthesis of the mixed bis(enoxysilane) **268** from the ketones **269** and **270**, followed by oxidative coupling using CAN, to generate a 1,4-diketone. A ring-closing metathesis reaction was employed to complete the framework of **267**. The stereochemical outcome of the oxidative coupling was anticipated based on orientation of the bis(enoxysilane) **268** in the conformation shown, which minimizes non-bonded interactions between the C1 and C4 substituents.

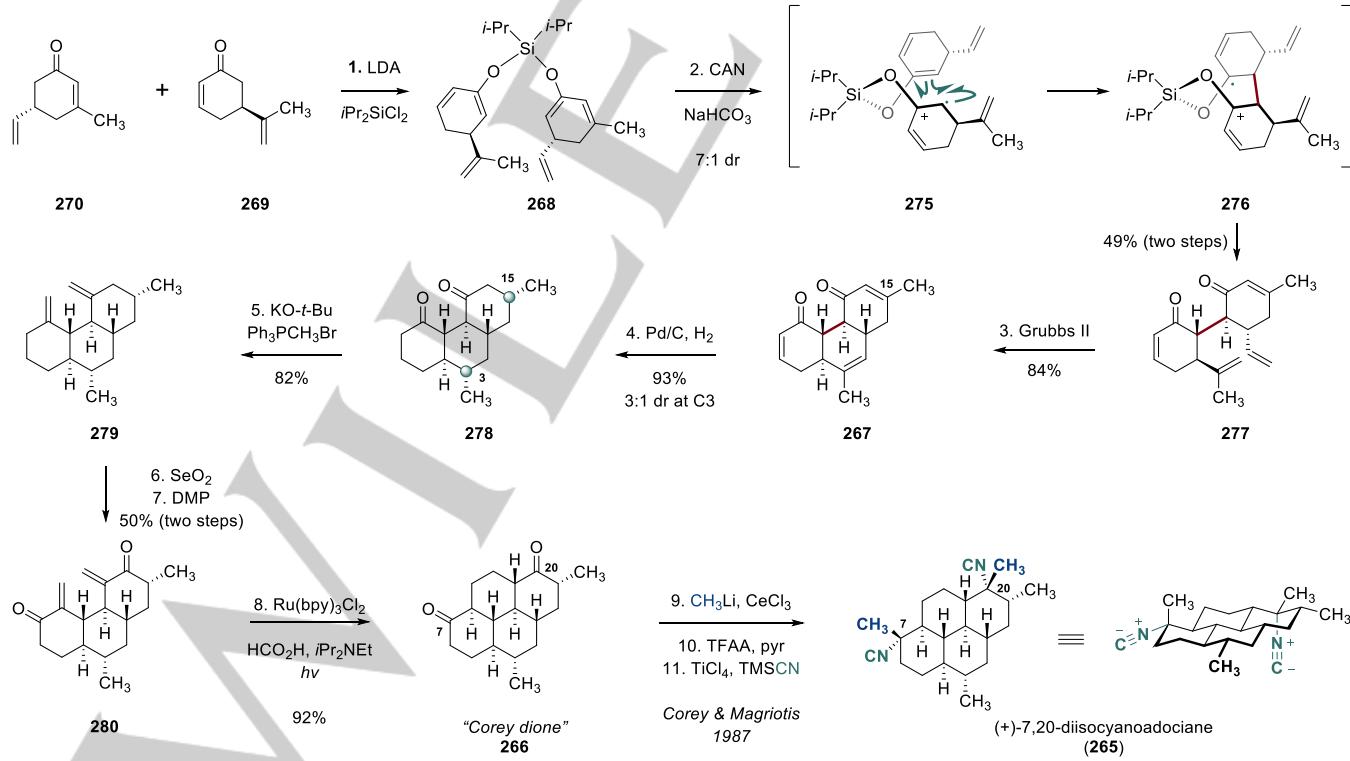
The synthesis of the enones **269** and **270** is shown in Scheme 51. Stereoselective Robinson annulation between *tert*-butyl acetoacetate (**271**) and the aldehyde **272**, followed by acid-catalyzed decarboxylation, provided the ketone **273** (59%, two steps, 99% ee, Scheme 51A).<sup>[156]</sup> Diastereoselective conjugate addition of iso-propenylmagnesium bromide, followed by oxidative elimination of the trimethylsilyl substituent [copper(II) chloride] provided the enone **269**.<sup>[157]</sup> The enone **270** was prepared from *ent*-**273**, which itself was accessed by an identical pathway but using the (S)-enantiomer of the proline-derived catalyst (Scheme 51B). Diastereoselective copper-catalyzed 1,4-

## REVIEW

Scheme 51. Synthesis of the oxidative coupling partners **269** and **270**.

addition of vinyl magnesium bromide (dr not reported), followed by oxidative elimination [copper(II) chloride] provided the unsaturated ketone **274** (66%, two steps). 1,2-Addition of methylolithium and oxidative transposition (pyridinium chlorochromate) then yielded the  $\alpha,\beta$ -unsaturated ketone **270**.

The mixed bis(enoxysilane) **268** was prepared by sequential addition of the lithium enolate of each enone to one-half equivalent of dichlorodiisopropylsilane (Scheme 52). Treatment of the resulting mixed bis(enoxysilane) **268** with cerium ammonium nitrate provided the 1,4-diketone **277** (49%). The diastereoselectivity (7:1 dr) was proposed to derive from the conformation shown in intermediate **268** (Scheme 52), which

Scheme 52. Completion of the formal synthesis of (+)-7,20-diisocyanoadociane (**265**) via an oxidative coupling strategy.

minimizes non-bonded interactions. Ring-closing metathesis (Grubbs' second-generation catalyst) provided the tricycle **267** (84%). Hydrogenation of **267** (palladium on carbon) proceeded with complete stereocontrol at C15 and with 3:1 diastereoselectivity at C3. Wittig olefination (potassium *tert*-butoxide, methyl triphenylphosphonium bromide) furnished the diene **269** (76% yield, two steps). A double allylic oxidation (selenium dioxide) followed by oxidation (DMP) provided the bis(enone) **280** (50%, two steps). Exposure of **280** to photoreductive cyclization conditions [ruthenium tris(bipyridine) dichloride, formic acid, DIPEA] formed the tetracyclic Corey dione **266** in 92% yield.<sup>[108a, 125]</sup> The target (+)-7,20-diisocyanoadociane (**265**) is accessible from **266** via a three-step sequence developed by Corey and Magriotis.<sup>[153]</sup>

**Summary and Strategic Lessons:**

[1] The oxidative coupling strategy pursued here reduces the stereochemical complexity of the tricyclic intermediate **267** into the two simpler unsaturated ketones **269** and **270**. Because the fragment coupling proceeds via a unimolecular process, the stereochemical outcome can be anticipated based on logical steric considerations.

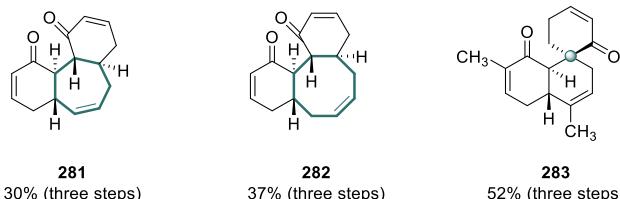
[2] Methods to achieve the enantioselective conjugate addition of vinyl nucleophiles to unsaturated ketones are limited.<sup>[158]</sup> The generation of the unsaturated ketones **269** and **270** via a diastereoselective conjugate addition to the  $\beta$ -silyl ketones **273** and *ent*-**273** addresses this shortcoming. In addition, this strategy addresses the issue of site-selectivity in reoxidation of the addition products. Although methods for the site-selective deprotonation

Accepted Manuscript

## REVIEW

of  $\beta$ -alkylcycloalkanones have been reported, selectivities are often modest.

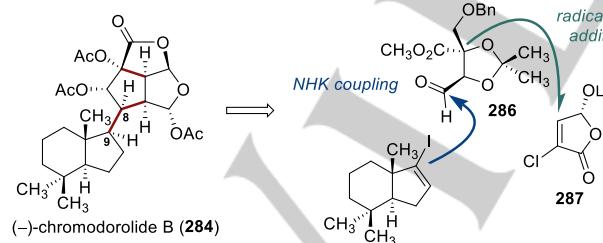
[3] A key feature of this strategy lies in the modularity. By varying the partners in the oxidative coupling step, different ring sizes can be prepared. The Thomson lab demonstrated that the tricyclic scaffold can be diversified to obtain [6-7-6] and [6-8-6] scaffolds (Scheme 53). One can also easily envision altering the remaining two ring sizes to prepare, for example, [5-6-5] or [5-6-6] cores present in other natural products.



**Scheme 53.** Polycyclic scaffolds accessible by Thomson's oxidative coupling–ring-closing metathesis sequence.

### 3.5. (-)-Chromodorolide B: Computationally-guided, photoredox radical cascade to construct highly oxidized dioxabicyclic rings.

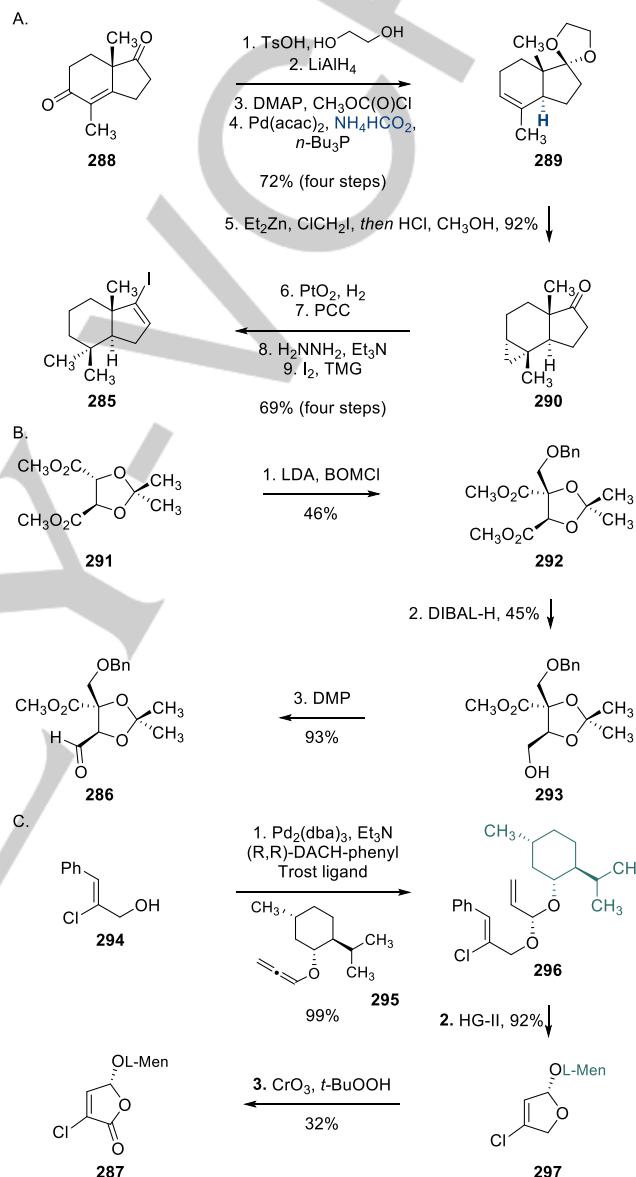
(-)Chromodorolide B (**284**) is a rearranged spongian diterpene first isolated from nudibranchs in the genus *Chromodoris*.<sup>[159]</sup> The isolate possesses antitumor, nematocidal, and antimicrobial activities. (–)-Chromodorolide B (**284**) contains two complex polycyclic fragments linked by a single carbon–carbon bond and ten contiguous stereocenters. The Overman laboratory developed a synthesis of **284** that leveraged both two-electron and single-electron fragment coupling processes, allowing the molecule to be disassembled into the three fragments **285**, **286**, and **287** (Scheme 54).<sup>[160]</sup> The Overman laboratory envisioned a diastereoselective Nozaki–Hiyama–Kishi addition<sup>[161]</sup> between the vinyl iodide **285** and the aldehyde **286** to construct the C8–C9 bond. Then, a computationally-guided reductive cyclization with **287** was developed to form the 3-oxabicyclo[3.3.0]octane system.



**Scheme 54.** Retrosynthetic analysis of (–)-chromodorolide B (**284**) by Tao et al.

The synthesis of the vinyl iodide **285** began with site-selective ketalization (ethylene glycol, PTSA) of the modified Hajos–Parrish ketone **288**,<sup>[162]</sup> followed by

diastereoselective 1,2-reduction [lithium aluminum hydride (LAH)] of the enone carbonyl (Scheme 55A). The resulting allylic alcohol (not shown) was acylated (methyl chloroformate). The resulting allylic carbonate underwent a reductive transposition on treatment with palladium bis(acetylacetone) and ammonium formate to provide **289** (72%, four steps).<sup>[163]</sup> Diastereoselective Simmons–



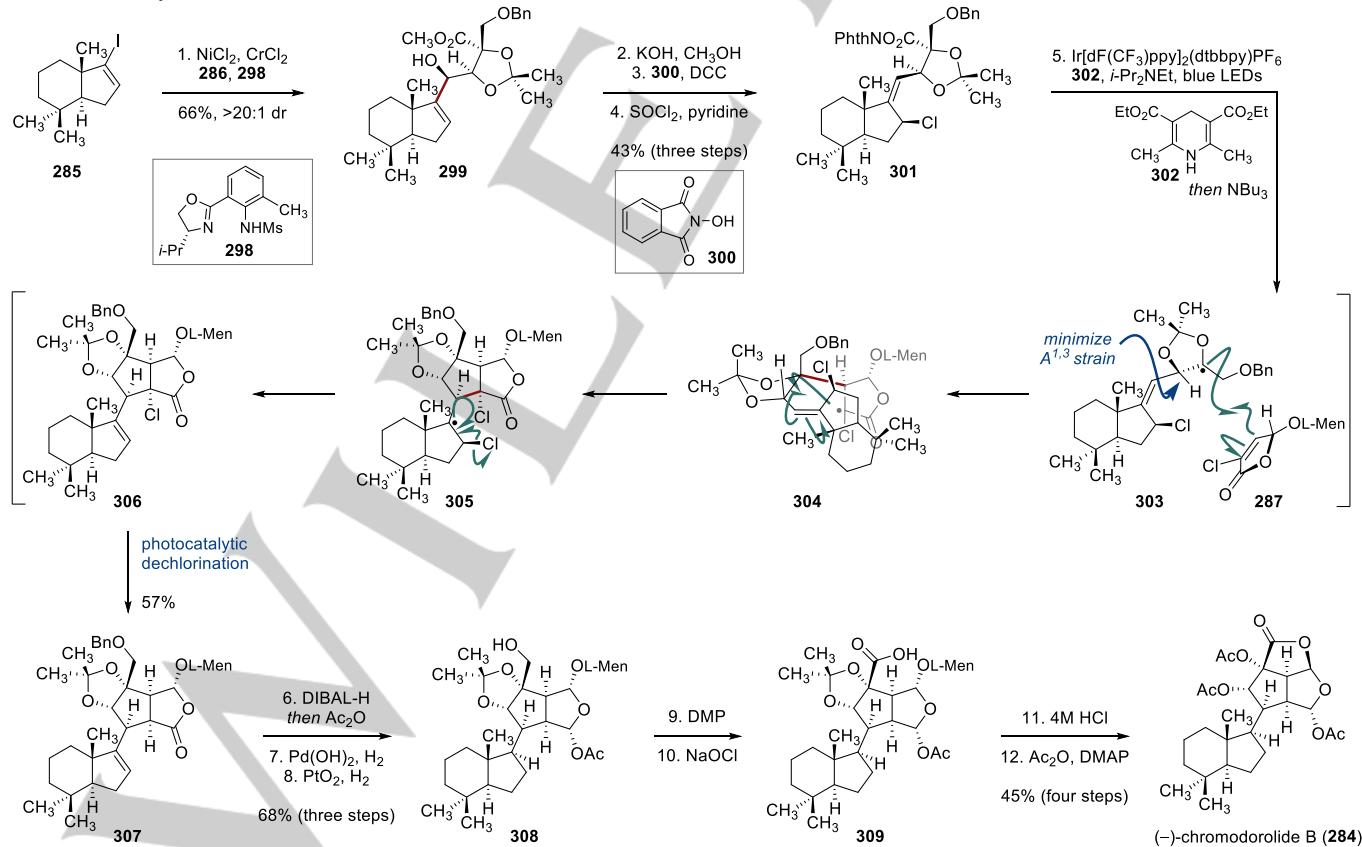
## REVIEW

followed by oxidation (iodine, tetramethylguanidine; 69%, four steps).

The aldehyde **286** was derived from the tartaric acid derivative **291** (Scheme 55B). Deprotonation of **291** (LDA) followed by alkylation with benzyl chloromethyl ether formed the ether **292** (46%).<sup>[167]</sup> Selective reduction of the less-hindered ester (DIBAL-H) followed by oxidation of the resulting alcohol (DMP) afforded the aldehyde **286** (42%, two steps).

The radical acceptor **287** was synthesized in three steps from the alcohol **294** (Scheme 55C). Enantioselective hydroalkoxylation using the L-menthol-derived allene **295** provided the acetal **296** as a single diastereomer and in quantitative yield.<sup>[168]</sup> Ring-closing metathesis (Hoveyda–Grubbs second-generation catalyst)<sup>[169]</sup> followed by allylic oxidation (chromium trioxide, TBHP)<sup>[170]</sup> generated the lactone **287** (29%, two steps).

The fragments **285** and **286** were joined by a diastereoselective Nozaki–Hiyama–Kishi reaction<sup>[171]</sup> in the presence of the ligand **298** to provide **299** (66%, >20:1 dr, Scheme 56).<sup>[172]</sup> The reductive cyclization precursor was prepared by a sequence comprising saponification (potassium hydroxide), esterification, and chlorination (thionyl chloride) with concomitant alkene transposition (43%, three steps).<sup>[173]</sup> The reductive cyclization was initiated by irradiation of a solution of the allylic chloride **301**, an iridium-based photocatalyst, and the Hantzsch ester **302**.<sup>[174]</sup> The pentacycle **307** was obtained as a single detectable diastereomer and in 57% yield. The stereoselectivity of the initial 1,4-addition in this cascade reaction



Scheme 56. Completion of the synthesis of (*-*)-chromodorolide B (284).

was rationalized as deriving from: 1. More favorable addition of the unsaturated lactone **287** to the less-hindered face of the acetonide ring (**303**→**304**) and 2. Minimization of A<sup>1,3</sup> strain in the addition of the radical intermediate **303** to the alkene (**303**→**304**). The intermediate **304** was then predisposed for a 5-exo-trig cyclization to generate **305**. Calculations performed by the authors suggested that the presence of a chloride or bromide substituent at the  $\alpha$ -carbon of the butenolide biased the desired *cis* fusion of the butenolide and cyclopentane ring by increasing destabilizing halogen–halogen interactions in the undesired transition state (not shown) and by pointing the chloride substituents away from each other to favor the desired transition state **304**. The intermediate radical **305** fragmented to generate the alkene **306**, which finally underwent photocatalytic dechlorination<sup>[175]</sup> to provide **307**.

The lactone was reduced (DIBAL-H) and the resulting lactol was acylated (acetic anhydride).<sup>[176]</sup> Hydrogenation provided **308** (68%, three steps). Oxidation of the primary alcohol (DMP, followed by sodium hypochlorite) formed the carboxylic acid **309**. Removal of the acetonide with concomitant lactonization (aqueous hydrochloric acid) and peracetylation (acetic anhydride, DMAP) provided (*-*)-chromodorolide B (**284**, 45% from **308**).

#### Summary and Strategic Lessons:

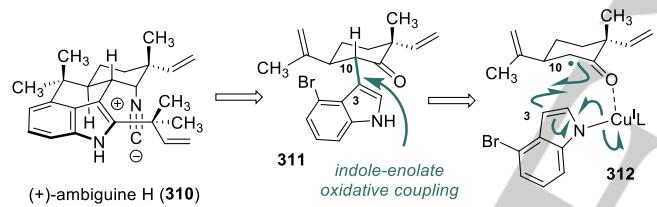
[1] The complimentary nature of two-electron and one-electron fragment coupling reactions is demonstrated in this synthesis. The Nozaki–Hiyama–Kishi addition allowed for a

## REVIEW

diastereoselective fragment coupling between the hydrindane **285** and the tartrate derivative **286**. This laid the foundation for the radical cascade reaction (**301**→**307**) to complete the carbon framework. [2] The high energy nature of the radical species allows for additional reactivity in the cascade cyclization. Matching the properties of a radical intermediate with the corresponding SOMOphile allows for propagation of intramolecular radical additions.

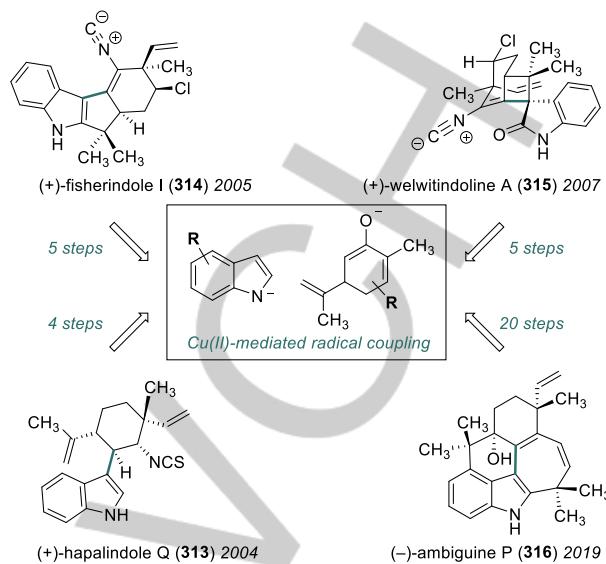
### 3.6. (+)-Ambiguine H: A Cu (II) mediated single-electron oxidative coupling enables the direct coupling of indole and carbonyl compounds.

The indole alkaloid (+)-ambiguine H (**310**) belongs to a diverse group of secondary metabolites produced by the *Stigonemataceae* family of cyanobacteria.<sup>[177]</sup> This large family of indole alkaloids is comprised of several structurally-related natural products including the hapalindole, fisherindole, welwitindolinone, and ambiguine families. Many of these isolates possess antifungal, antibacterial, or anticancer activities.<sup>[177b, 178]</sup> The hapalindole alkaloids have been popular targets for total syntheses and many laboratories have successfully accomplished racemic and enantioselective syntheses.<sup>[179]</sup> The Baran laboratory developed an efficient oxidative coupling strategy that established a streamlined entry to the hapalindole family of natural products. Their approach is discussed in detail.<sup>[180]</sup>



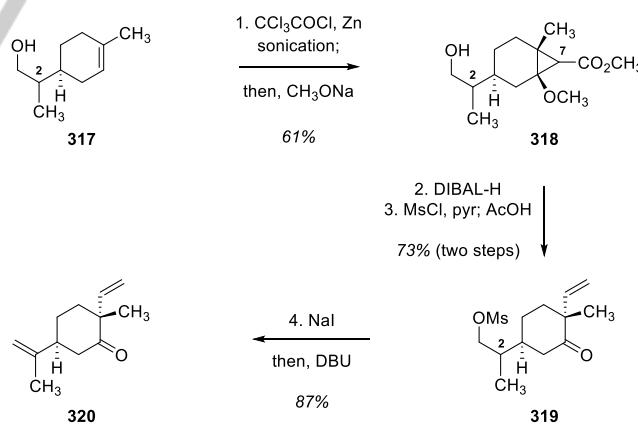
**Scheme 57.** Retrosynthetic analysis of (+)-ambiguine H (**310**) by Maimone et al.

Retrosynthetically, Baran and co-workers recognized that (+)-ambiguine H (**310**) could be assembled in a convergent fashion by coupling indole and terpenoid subunits as is shown in **312** (Scheme 57). To realize this approach, the authors developed an oxidative enolate coupling strategy to forge this bond in an efficient and diastereoselective manner.<sup>[181]</sup> In practice, this transformation was realized by treating a ketone enolate and the conjugate base of an indole derivative with a Cu(II) oxidant, to trigger a carbon–carbon bond forming reaction via a net two-electron oxidation. In the case of (+)-ambiguine H (**310**), the authors took advantage of this approach to forge the conjoining C3–C10 bond of the indole–terpene intermediate **311** with high diastereoselectivity (Scheme 57). The versatility of this direct indole–enolate coupling reaction has been demonstrated in the syntheses of several other natural complex products including (+)-hapalindole Q (**313**),<sup>[179a]</sup> (+)-fisherindole I (**314**),<sup>[179c]</sup> (+)-welwitindole A (**315**),<sup>[179c]</sup> and (-)-ambiguine P (**316**)<sup>[182]</sup> (Scheme 58).



**Scheme 58.** Selected examples of natural products synthesized via an indole–enolate oxidative coupling. The step count refers to the number of operations required to complete the synthesis following the oxidative fragment coupling.

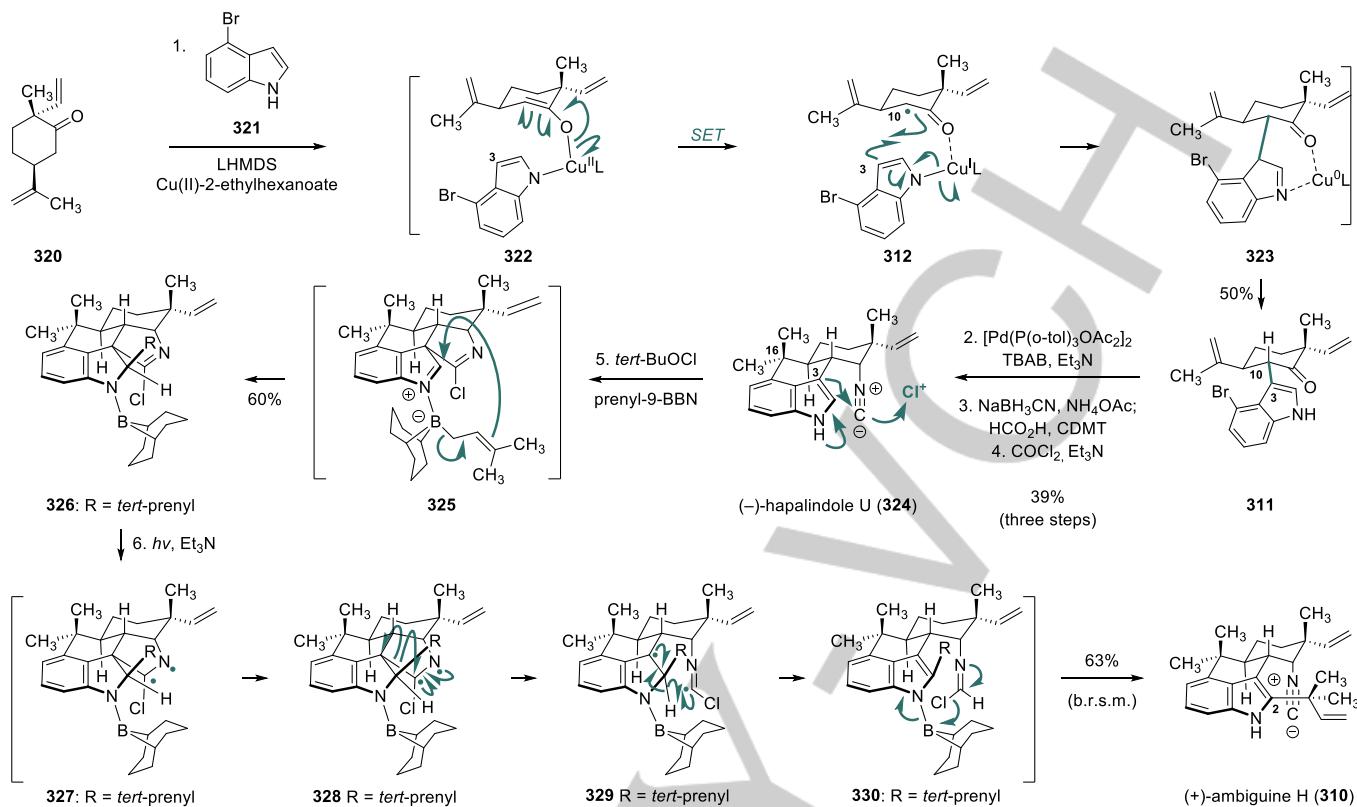
The synthesis of (+)-ambiguine H (**310**) began with preparation of the terpene subunit of the target (**320**), which was synthesized in four steps from the commercially available, chiral starting material **317** (note: **317** was obtained as an inconsequential mixture of C2 diastereomers; Scheme 59). A diastereoselective dichloroketene [2+2] cycloaddition inspired by Mehta (trichloroacetyl chloride, zinc), followed by the addition of sodium methoxide, formed the cyclopropane **318** (61%, inconsequential mixture of four diastereomers at C2 and C7).<sup>[183]</sup>



**Scheme 59.** Synthesis of terpene subunit (**320**).

Reduction (DIBAL-H), double mesylation (methanesulfonyl chloride, pyridine), and acid-induced fragmentation of the cyclopropane furnished the ketone **319**, (45% overall, inconsequential mixture of C2 diastereomers). Substitution of the

REVIEW



**Scheme 60.** Oxidative fragment coupling and completion of the synthesis of (+)-ambiguine H (310).

mesylate with iodide (sodium iodide) followed by elimination (DBU) delivered the coupling partner **320** (87%).

Deprotonation of **320** and 4-bromoindole **321** (LiHMDS), followed by the addition of copper bis(2-ethylhexanoate), provided the fragment coupling product **311** (50%, single diastereomer, Scheme 60). Mechanistically, it is believed that this transformation proceeded via formation of the copper(II) intermediate **322**, followed by a single-electron transfer to generate the coordinated  $\alpha$ -keto radical **312**.<sup>[181b]</sup> Addition of the electron-deficient  $\alpha$ -keto radical to the C3 position of the indole forms the C3–C10 bond with a concomitant electron transfer to the proximal copper(I) center provided the intermediate **323**. Tautomerization then generated the observed product **311**. (–)-Hapalindole U (**324**) was prepared by reductive cyclization (Herrmann’s catalyst, triethylamine, tetra-*n*-butylammonium bromide), diastereoselective reductive amination (sodium cyanoborohydride, ammonium acetate) with *in situ* formylation of the resulting amine (not shown), and dehydration to the isonitrile (phosgene, 39% overall).<sup>[184]</sup>

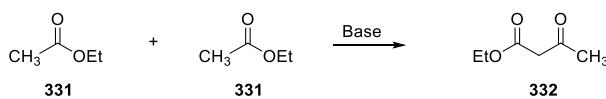
(+)-Ambiguine H (**310**) was prepared in two steps from (−)-haphalindole U (**324**). Treatment of (−)-haphalindole U (**324**) with *tert*-butyl hypochlorite and prenyl 9-BBN yielded the pentacyclic chloroimide **326** (60%).<sup>[185]</sup> This transformation is believed to proceed via C-chlorination of the isonitrile, addition of the C3 position of the indole, coordination of the boryl prenyl reagent to the nitrogen of the resulting imine, and prenyl transfer (**325**–**326**). Photoexcitation of the chloroimide **326** (**326**–**327**) followed by a type II Norrish cleavage and fragmentation cascade then completed the synthesis of (+)-ambiguine H (**310**) (63%.

based on recovered starting material, Scheme 60).<sup>[186]</sup> This enantioselective synthesis featured an efficient complexity-generating fragment-coupling reaction and constitutes a six-step route to the target from the readily available terpene subunit (**320**) without the use of any protecting groups.

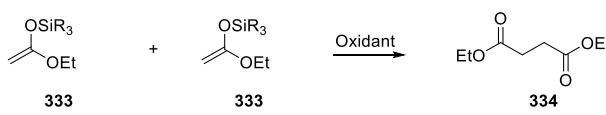
#### Summary and Strategic Lessons:

[1] The indole–ketone oxidative coupling is a reaction of broad utility, and has found applications in other contexts, such as the coupling of two carbonyl compounds. This transformation is

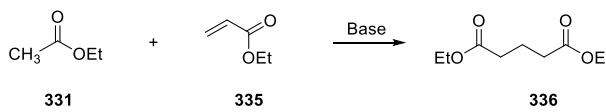
#### A. Claisen condensation to access 1,3-dicarbonyls



#### B. Enolate oxidative coupling to access 1,4-dicarbonyls



### C. Michael addition reaction coupling to access 1,5-dicarbonyls



**Scheme 61.** Common dicarbonyl building blocks and their corresponding synthetic precursors.

## REVIEW

powerful because it complements the polarity of enolate acylation and Michael addition reactions (Scheme 61).

[2] The fragment coupling allows for deconstruction of the natural product into two functionalized building blocks that are readily derived from commercial reagents. This avoids de novo construction of the cyclohexane and indole residues.

## 4. Conclusion.

In this review we have presented recent examples of fragment couplings that form carbon–carbon bonds via carbanionic and free radical intermediates. The syntheses presented were chosen to both illustrate the general utility of well-designed fragment coupling reactions, as well as more, potentially generalizable, lessons from each synthesis. The most efficient synthetic strategies are those that minimize the number of steps following the key fragment coupling strategy. Nonetheless, the introduction of additional steps as lateral manipulations is sometimes necessary to establish the requisite functionality to implement a fragment coupling reaction. It is our hope that this review will serve students in synthesis as they develop their synthetic planning skills and underscore the strategic value of fragment couplings that form carbon–carbon bonds.

## 5. Acknowledgements.

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## 6. References.

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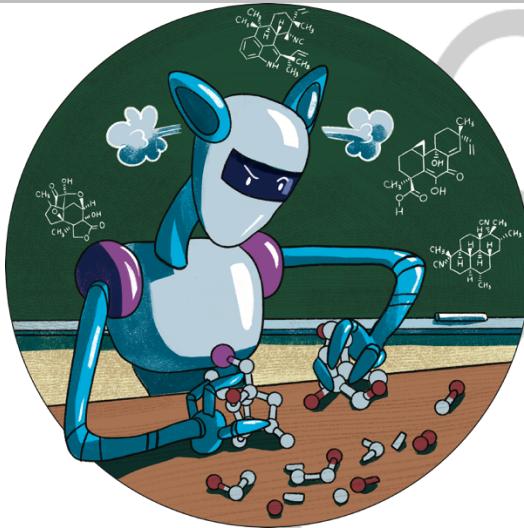
## REVIEW

## Entry for the Table of Contents (Please choose one layout)

Layout 1:

## REVIEW

**In this review** a survey of recent examples of fragment coupling reactions that form carbon–carbon bonds via carbanionic or free radical intermediates in total synthesis is presented. The review aims to identify extensible lessons from each example that might be useful to students in the field. The review highlights powerful advances in the generation and application of carbanionic and free radical intermediates in complex settings.



Martin Tomanik, Ian Tingyung Hsu,  
Seth B. Herzog\*

Page No. – Page No.

Fragment coupling reactions in total synthesis that form carbon–carbon bonds via carbanionic or free radical intermediates.

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