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Contemporary Synthetic Strategies Toward Seco-Prezizaane Sesquiterpenes from *Illicium* sp.

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Abstract

Since the elucidation of the structure of anisatin in the late 1960's, sesquiterpene lactones from various *Illicium* species of plants have captivated synthetic chemists worldwide resulting in a large body of synthetic work. In particular, *Illicium* sesquiterpenes containing the *seco*-prezizaane carbon framework have seen immense interest in recent years owing to both desirable structural and medicinal attributes. This synopsis will focus on recently developed synthetic strategies to access these compact, highly oxidized terpenoids.

Graphical Abstract

In 1968, Yamada and co-workers disclosed the X-ray crystal structure of the unusual β -lactone-containing toxin anisatin (**1**), thus ushering in an exciting new chapter in natural products chemistry.^{1,2} Over the next 50 years, over 100 natural products with apparent biosynthetic connections to **1** have been isolated from various *Illicium* species of plants, a family of short shrubs and trees indigenous to the Southeastern United States, Australasia, and certain regions of Asia.³ Among these natural products are a large proportion of sesquiterpenes which feature the 5,6-fused “*seco*-prezizaane” terpene skeleton shown and are endowed, in many cases, with exceedingly high levels of oxidation (Figure 1A). Majucin (**2**), jiadifenin (**3**), jiadifenolide (**4**), minwanenone (**5**), and pseudoanisatin (**6**), are all representative of this series and have served as attractive synthetic targets.

The first reported synthetic work toward an *Illicium* family member was Woodward's posthumous 1982 communication detailing a clever intramolecular glyoxylate ene reaction to construct an anisatin model system.⁴ This work was followed up several years later (1985) by Kende's remarkably efficient synthesis of ($\pm$)-8-deoxyanisatin (10-deoxyanisatin, by modern numbering conventions).⁵ In 1990, the first *seco*-prezizaane natural product, namely anisatin itself, succumbed to total synthesis via a heroic synthetic effort by the group of

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Yamada.⁶ While the ensuing decade proved quiet, the 21st century witnessed a sharp increase in synthetic efforts toward this family of compounds and the majority of work has appeared after 2011. To date, almost twenty total syntheses of *seco*-prezizaane-containing *Illicium* sesquiterpenes have been reported as well as a swath of studies toward publications.^{7–10} In this synopsis, we will highlight recent synthetic efforts towards *seco*-prezizaane-containing *Illicium* sesquiterpenes aiming to complement Inoue's review which covers up to 2009.^{11,12} Due to space constraints, syntheses of related *allo*-cedrane and anislactone-type sesquiterpenes, typified by 11-*O*-debenzoyltashironin (**7**) and merrilactone A (**8**) respectively, are not covered despite also being popular synthetic targets (Figure 1B).^{13–15}

JIADIFENIN

In 2002, Fukuyama reported the isolation and neurotrophic activity of jiadifenin (**3**), a compact *seco*-prezizaane sesquiterpene from *I. jiadifengpi*.¹⁶ Unlike **1**, **3** belongs to a subgroup of *Illicium* natural products which do not have reported convulsant properties but instead promote neurite outgrowth.^{16,17} The biochemical effects of *Illicium* sesquiterpenes have been the subject of considerable study as well and a major driving force behind their syntheses in general.¹⁷ The group of Danishefsky reported the first synthetic route to (±)-**3** in 2004,^{7a} an exercise which also provided some of the first pharmacophore mapping of the neurotrophic *Illicium* sesquiterpenes.^{7b}

In 2011, Theodorakis reported the first asymmetric route to **3**, a task facilitated by the availability of enantiopure Hajos-Parrish-like diketone building block **12**, prepared in 3 straightforward steps from 1,3-cyclopentadione (**9**) (Scheme 1).^{7c} Of note, the Robinson annulation, first utilized by Kende,⁵ serves as a recurring disconnection in *Illicium* sesquiterpene syntheses. From **12**, cyclopentanone reduction and protection afforded an enone which was subjected to a Stiles-type α -carboxylation reaction with magnesium methyl carbonate (**13**). Following γ -deprotonation and alkylation with methyl iodide, bicycle **14** was generated. Global reduction of this material with lithium aluminum hydride, protection of the primary hydroxy group, oxidation of the secondary hydroxyl group and enolate triflation afforded **15** setting the stage for construction of the ubiquitous δ -valerolactone motif.

Subjecting **15** to Pd-catalyzed methoxycarbonylation conditions (*cat.* Pd(PPh₃)₄, CO, MeOH) afforded the expected methyl ester **16** (60%) along with substantial amounts of cyclized product **17** (22%) which contains the requisite lactone. Moreover, **16** was easily converted to **17** upon exposure to trifluoroacetic acid. The electrophilic α,β -unsaturated lactone of **17** underwent clean basic epoxidation and following a similar oxidative cyclization to Danishefsky's work,^{7a} the crucial δ -valerolactone sector was installed. Following treatment with tetrabutylammonium fluoride, key tetracycle **18** was furnished; notably this material will also serve as a precursor to jiadifenolide (**4**) (*vide infra*). To advance **18** to (1*R*,10*S*)-2-oxo-3,4-dehydroxyneomajucin (ODNM) (**22**)—and ultimately **3**—only five additional steps were required. First the secondary alcohol was eliminated with Martin sulfurane (**19**) and the resulting alkene hydrogenated to generate **20**. Next Mn(III)-mediated allylic oxidation generated the required cyclopentenone. Finally, α -hydroxylation of the ester with **21** and α -methylation of the cyclopentenone gave **22**. Utilizing

Danishefsky's protocol,^{7a} **22** could also be converted into **3** in one step using the Jones reagent followed by treatment with methanol. Following up on Danishefsky's work, a number of differentially oxidized congeners were evaluated for their neurite outgrowth thus greatly expanding the *Illicium* pharmacophore map.^{7e}

In 2012, a conceptually disparate strategy toward ODNM (**22**) and jiadifenin (**3**) was reported by the group of Zhai (Scheme 2).^{7d} Notably this work introduced the Pauson-Khand disconnection into the *seco-Prezizaane* synthetic field—a strategy which will be revisited again. Allylic bromide **23** was first converted into protected, enantioenriched diol **25** via a three-step procedure consisting of coupling with a lithium acetylide generated from **24**, Sharpless asymmetric dihydroxylation (in 93% *ee*), and dioxolane formation. From alkyne **25**, the PMP group was removed under oxidative conditions and the resulting alcohol oxidized to an acid via Jones conditions. Following the coupling of this acid with (*Z*)-configured allylic alcohol **26**, ester **27** was generated setting the stage for the first key C–C bond-forming step. Enolization of **27** and trapping with TMSCl generated the depicted silyl ketene acetal which upon warming underwent a diastereoselective Ireland-Claisen rearrangement, presumably via the chair-like transition state shown (see **28**). Upon treating the reaction mixture with *para*-toluenesulfonic acid, lactone **29** was generated in good yield and with reasonable selectivity.

With enyne **29** in hand, work began on construction of the cyclopentenone ring. Following dioxolane removal and protection of the secondary alcohol as its TBS ether, a diastereoselective Pauson-Khand reaction ensued under the mediation of [Co₂(CO)₈] generating tricycle **30** in good yield (67%). To install the remaining carbon atoms of the target, the Zhai lab utilized a clever photochemical enone/allene [2+2] reaction to construct **31** in 72% yield—a small amount of diastereomer **32** was also generated in this reaction. Oxidative scission of the exocyclic alkene via ozonolysis followed by sodium methoxide-mediated cleavage of the resulting strained cyclobutanone led to ester **33**. To complete the synthesis of ODNM (**22**), and therefore also **3**, four additional transformations were required. A two-step Saegusa oxidation accomplished desaturation of the cyclopentanone ring and upon treatment of this compound with TBAF, the δ -valerolactone ring was generated. Finally, α -oxidation according to Theodorakis (NaHMDS *then* oxaziridine **21**) furnished **22** and ultimately **3**.

In 2015, a formal synthesis of **3** was reported by Y. Fukuyama and co-workers via Theodorakis' advanced intermediate **20** (Scheme 3).^{7f} Vinyl bromide **34**, prepared in five steps, underwent a high-yielding Heck cyclization to furnish **35**. After twelve additional manipulations, β -keto ester **36** was prepared and this material served as a substrate for an intramolecular palladium-mediated Tsuji-Trost allylation/lactonization cascade leading to tricycle **37** in an impressive 65% yield. Deprotection of this material and subjection to Grieco's elimination sequence afforded **38** after hydroxylation of the β -ketoester with *m*-CPBA. Finally, diastereoselective ketone reduction and two-step oxidative cyclization (OsO₄/NaIO₄ *then* Ag(I)) arrived at **20**, completing the formal synthesis.

Recently, Micalizio and co-workers reported a distinct route to both **22** and **3** as well as the related *Illicium* member (2*S*)-hydroxy-3,4-dehydro-neomajucin (**52**) (Scheme 4).^{7g} Key to

the success of this route was a complex application of the hydroxyl-directed metallacycle-mediated formal [2+2+2] annulation of enynes with alkynes.¹⁸ The synthesis commenced with the preparation of key fragment **42**. Beginning with enantiopure epoxide **39**, copper-mediated oxirane opening with the Grignard reagent derived from vinylbromide **40** afforded alcohol **41**. TBAF-mediated deprotection of this material, activation of the primary alcohol as its tosylate, and cyclization under basic conditions (NaH) formed a second epoxide which could be opened with propynyl lithium to give **42**.

In the first key step of the synthesis, the lithium alkoxide of enyne **42** was reacted with stannyl-substituted TMS-acetylene **43** and a reduced titanium complex prepared by mixing $\text{Ti}(\text{O}i\text{-Pr})_4$ and *n*-BuLi, inducing a formal [2+2+2] annulation. Notably the product formed (i.e., diene **44**) was generated as essentially a single regioisomer—and diastereomer—in excellent yield. Compound **44** was next treated with tetrabutylammonium fluoride, cleaving the carbon-silicon bond. The secondary hydroxyl group was protected as TBDPS ether. A tin-lithium exchange followed by lithiate quench with carbon dioxide appended a carboxylic acid which could be alkylated with chloromethyl phenylselenide to deliver **45**. Following chemo- and diastereoselective osmium tetroxide-mediated dihydroxylation, selenophenyl methyl ester **46** was secured.

In a second key C–C bond-forming step in the synthesis, a 5-*exo* radical cyclization was envisioned to generate the butyrolactone ring, and thus the entire *seco*-prezizaane skeleton.¹⁹ Subjecting **46** to classic tin-mediated reductive radical cyclization conditions led to the expected product **48** in a diastereoselective fashion. Interestingly, however, this material was accompanied by an almost equimolar quantity of ethyl ester **47**, which was believed to be formed by a process involving intramolecular radical C–H abstraction of the weak dioxolane C–H bond followed by fragmentation. Product formation could be biased toward **47** by replacing Bu_3SnH with TMS_3SiH . This finding was welcome as the ester oxidation state found in **47** was more ideal for conversion into **49**—only a Swern oxidation, stereoselective reduction, and acid-mediated lactonization were required. In contrast, five steps were needed to advance **48** into **49**. Tricycle **49** could be converted into enone **50** via a sequence consisting of fluoride-mediated desilylation, IBX oxidation, and desaturation via Saegusa's protocol. Advanced intermediate **50** served as an entry point into several *seco*-prezizaane natural products. First, ODNM (**22**) could be prepared by deprotection (TBAF) and α -oxidation of the lactone under basic conditions, which also correctly epimerized the methyl-bearing stereocenter. As demonstrated before, **22** could be converted into **3**. The authors also utilized **50** in the construction of (2*S*)-hydroxy-3,4-dehydro-neomajucin (**52**), a neurotrophic family member which had not been previously synthesized. Diastereoselective ketone reduction of **50** followed by lactone α -hydroxylation fashioned **51**. Finally, a four-step double hydroxyl inversion sequence generated **52**. This work attests to the power of both modern metal-mediated and classic radical-based cascades to forge challenging carbon-carbon bonds in the context of complex molecule synthesis.

JIADIFENOLIDE

Fukuyama's 2009 disclosure of jiadifenolide (**4**), a compact *seco*-prezizaane with a propellane core and very high neurotrophic activity set off a frenzy within the synthetic

community.²⁰ **4** was demonstrated to induce neurite outgrowth of rat cortical neurons at concentrations as low as 10 nM, and more recently, a similar effect has been seen in human induced pluripotent stem cells.²¹ While isolated less than a decade ago, **4** has seen a multitude of total and formal syntheses which will be discussed below.

In addition to their previously reviewed route to ODNM and jiadifenin, the group of Theodorakis reported the first total synthesis of **4** in 2011 (Scheme 5).^{8a} Utilizing previously disclosed bislactone **18**, a clever sequence was described to construct the hallmark propellane system. First, the trisubstituted olefin was epoxidized with *m*-CPBA. Then, oxidation of the secondary alcohol triggered an epoxide elimination/trans-lactonization cascade, smoothly affording propellane **55**. Hydrogenation of the enone followed by silyl protection of the secondary alcohol prepared **56**, a suitable substrate for late-stage installation of the final methyl group. By opting for a palladium-catalyzed cross-coupling sequence from a vinyl triflate intermediate, **57** was rapidly assembled. Hydrogenation and sequential lactone oxidations of **57** then completed the first synthesis of **4**.

Following that seminal work, Sorensen disclosed his group's efforts towards the same target, featuring the first example of a C(sp³)-H bond activation in the context of *Illicium* terpene synthesis (Scheme 6).^{8b} Beginning from pulegone-derived building block **58**, the venerable Robinson annulation was once again called on to construct the 5,6-fused ring system seen in **59**. Straightforward functionalization of this intermediate, including double methylation, dioxolane protection, ester reduction, and oxidation afforded **61**. An intriguing use of TosMIC (**62**), a reagent typically reserved for heterocycle synthesis,²² led to aldehyde chain extension and nitrile formation. Acidic methanolysis both instigated propellane formation by nitrile hydrolysis and cleavage of dioxolane protecting group, unveiling **63**, the key entry point for an ambitious C-H oxidation.

Taking inspiration from Sanford's methodology,^{23,24} ketone **63** was converted to an intermediate oxime, which served as a directing group for a palladium-catalyzed C-H acetoxylation reaction. Remarkably, synthetically useful amounts of the desired acetoxylated product **64** could be isolated after oxime cleavage. Unfortunately, differentiation of the *gem*-dimethyl group was not perfect – oxidation of the other methyl group was observed, along with a small amount of doubly-oxidized product – speaking to the challenges associated with planning late stage C-H activation reactions in synthesis. Palladium-catalyzed carbonylation of the vinyl triflate of **64** installed the final carbon atom for the synthesis, giving **66** which was well-suited for a lactonization/epoxidation sequence leading to **67**. Similar to Theodorakis's endgame, double oxidation of the propellane lactone was now required. A creative iodination/iodoso-Pummerer rearrangement sequence installed that requisite oxidation, which completed the synthesis of **4** after basic hydrolysis.

Shortly after Sorensen's work, Paterson reported a conceptually distinct approach to constructing the polycyclic ring system of **4** (Scheme 7).^{8c} Rather than planning a Robinson annulation, a key samarium(II) iodide-mediated reductive cyclization was envisioned.

A four-step sequence from simple 3-methyl-cyclopentenone (**68**) quickly prepared building block **69**, which underwent facile intermolecular Horner-Wadsworth-Emmons (HWE)

olefination with phosphonate **70**. Reduction of the intermediate ester (LiAlH_4) and acetate protection provided ample amounts of **71**. Silyl ketene acetal synthesis followed by heating initiated a highly diastereoselective Ireland-Claisen rearrangement, cleanly setting one of the challenging quaternary centers. Reduction of the resulting material, silyl-group cleavage, and oxidation produced aldehyde **72**. Fittingly, a boron enolate of butenolide **73** was prepared and reacted with **72** to furnish **74** after silyl protection of the secondary alcohol. In the key step of the synthesis, samarium(II) iodide reduced the ketone in **74** with concomitant ketyl radical addition into the pendant butenolide moiety, generating **75** as a single diastereomer after straightforward functional group manipulations. This impressive transformation set adjacent stereocenters with high fidelity and completed the 5,6-fused ring system in a single operation. Two-step Rubottom-type oxidation of **75** installed a tertiary alcohol, which was then used to direct reduction of the adjacent ketone, delivering **76** after silyl protection. Finally, dihydroxylation of the monosubstituted alkene and oxidative lactonization gave an intermediate keto-lactone from which **4** was prepared after desilylation.

Possibly inspired by Paterson's key samarium(II) iodide-mediated cyclization, Zhang and Gademann both emulated that disconnection in their own total and formal syntheses of **4** (Scheme 8). Zhang's total synthesis began from pulegone-derivative **77**, which was allylated and oxidatively cleaved to yield aldehyde **78**, a compound parallel to Paterson's **72**.^{8e} As such, it was also treated with the boron enolate of **73**, giving rise to **79**, which was advanced to cyclization precursor **80** after straightforward functional group manipulations. Once again, samarium(II) iodide was employed to construct the strategic bond, and key aldehyde **81** was isolated after subsequent oxidation. **81** was then poised to undergo a novel [4+1] annulation reaction with TMS-diazomethane. In this step, the anion of TMS-diazomethane is thought to add into the aldehyde, triggering a Brook rearrangement and subsequent O–H insertion into the adjacent tertiary alcohol. The authors also provided a substrate scope for this transformation to demonstrate its utility for tetrahydrofuran synthesis. A sequence of three consecutive oxidations and basic hydrolysis then completed the synthesis of **4**.

Gademann's formal synthesis of **4** was disclosed as part of a larger collection of *seco*-prezizaane synthetic studies and targeted aldehyde **81** as the formal synthesis endpoint.^{8f} Beginning from aldehyde **83**, prepared in the same way as Zhang's **78**, a proline-catalyzed aldol/dehydration reaction with tetronic acid afforded a highly electrophilic enone which was reduced in the same operation with a Hantzsch ester. Triflation followed by iron-catalyzed cross-coupling reaction cleanly appended an additional methyl group onto the structure to provide **84**, the key cyclization precursor. Though somewhat less diastereoselective than the other substrates with stronger biasing elements, cyclization of **84** with samarium(II) iodide nevertheless proceeded efficiently and the intermediate ester could be reduced to aldehyde **81**, completing the formal synthesis of **4**.

In 2015, Shenvi reported an impressive gram-scale synthesis of **4** (Scheme 9).^{8d} Like many previous works, this synthesis had planned a key annulation reaction to construct the 5,6-fused ring system; specifically, a butenolide heterodimerization between **87** and **88** was envisioned. **87** could be prepared in only three steps from (+)-citronellal by dehydration

(BTPP, NfF), oxidative alkene cleavage (O_3 ; DMS), and a hetero-Pauson Khand reaction ($Mo(CO)_6$) of enyne **85**. A four-step route traversing intermediate dibromide **86** was also developed to ensure greater material throughput. Likewise, **88** was synthesized rapidly – in only two steps, diketene acetone adduct (**89**) was condensed with hydroxyacetone to afford butenolide **88** in good yield on multi-gram scales. In the key step, the lithium enolate of **87** was joined with **88** with exquisite diastereoselectivity to forge **92** via **90**, presumably due to the intermediacy of a chelated intermediate, like **91**. With **92** in hand, completion of the synthesis of **4** was straightforward: enol hydroxylation and directed reduction converted **92** to *trans*-diol **93**. A further two-step oxidation sequence, involving sequential bromination and hydroxylation events, advanced **93** on to **4**, completing the synthesis in just eight steps. In a subsequent publication, **92** was also shown to go on to **7**, speaking to the power of this route in also accessing *allo*-cedrane members.

ANISATINOIDS & PSEUDOANISATINOIDS

In contrast to the prolific work seen toward majucinoid synthesis, studies on anisatinoids and pseudoanisatinoids have been somewhat less frequent in the 21st century. Since Yamada's groundbreaking work, only a single additional synthesis of **1** has been completed and will be presented in this section. Additionally, Mehta's 2007 synthesis of *ent*-minwanenone (*ent*-**5**) stood as the only synthesized member of the latter category for nearly a decade.^{9a,b}

T. Fukuyama's synthesis of **1** relied on a very non-obvious dearomatization sequence for key bond formations (Scheme 10).^{9c} Beginning with compound **94** (prepared in four steps from commercial materials), propargylation of the primary alcohol followed by functional group manipulations afforded alkyne **95**. Dearomatization of the electron-rich aromatic core ($PhI(OAc)_2$, MeOH) of **95** generated an intermediate protected *ortho*-quinone which then underwent smooth intramolecular Diels-Alder reaction with the pendant alkyne upon heating. HWE olefination of the remaining ketone with phosphonate **96** followed by reduction cleanly led to primary alcohol **97**. This compound was alkylated with Bu_3SnCH_2I , a cuing element for a [2,3]-sigmatropic rearrangement. Indeed, lithium-tin exchange initiated that transformation, setting the second *seco*-prezizaane quaternary center with high fidelity. Benzylation and strained olefin cleavage afforded intermediate **98** in short order.

Unfortunately, while this opening sequence offered rapid access to a highly-substituted cyclohexane ring a further 11 steps were required to close the five-membered ring and complete the *seco*-prezizaane ring system. First, primary iodide **99** was prepared in six steps from **98**; then, lithium-halogen exchange created an organometallic nucleophile that added into the pendant ketone. Further functional group manipulations advanced that intermediate on to **101**. Although the *seco*-prezizaane skeleton was now in place, extraneous oxidation at C12 and C15 were also present and required an additional 8 steps to address, proceeding through **102**. From **103**, the terminal alkene was exhaustively oxidized to carboxylic acid **104**, and the signature *spiro*- β -lactone of **1** was formed by employing anhydride **105** as an activating reagent. Protecting group cleavages and olefin dihydroxylation finally arrived at **1** completing a synthesis that truly exemplifies the diversity of insight possible for creating any given structure.

Our own group's work in both the pseudoanisatinoid and majucinoid areas represents a significant departure from the previously discussed syntheses. We focused on utilizing a semisynthetic approach, predicated on the ability to convert a pre-existing 15-carbon sesquiterpene into various *Illiciums* via sequential C–C bond reorganization and site-selective C(sp³)–H bond activation (Scheme 11).^{9d,e}

Owing to both availability and biosynthetic considerations, (+)-cedrol was chosen as starting material and converted into a cyclic ether via Suarez's hypoiodite-mediated C–H functionalization (Scheme 11).²⁵ The strained tetrahydrofuran ring formed could then be smoothly eliminated under the alkylative action of methyl Meerwein's salt to provide alkene **106**. Further oxidations were introduced by cleavage of the trisubstituted olefin with *in situ* generated RuO₄, giving keto-acid **107** in good yield. A challenging intramolecular oxidative lactonization was found to proceed under the action of CuBr₂ giving lactone **108**. At this point, the 5,5-fused cedrane system needed to be converted to the 5,6-fused *seco*-prezizaane one, and an abiotic α -ketol rearrangement was chosen for this task.²⁶ Thus, treating **108** with strong base (KOH, KO*t*-Bu) effected lactone hydrolysis with concomitant ring shift, giving *seco*-prezizaane core **109** after silylation. In a key step of this synthesis, the exceptionally hindered C4 methine position was successfully oxidized by carboxylic acid-directed non-heme iron(oxo)-catalysis.^{27,28} Although this step was not perfect – a designer pinene-derived ligand architecture was required for sufficient catalyst activity and multiple products of excessive C–H oxidation were isolated (see **111** and **112**) – it nevertheless provided lactone **110** in serviceable enough yield for the completion of the synthesis. The lactone of **110** could be eliminated by the action of ethyl Meerwein's salt, giving rise to ethyl ester **113**. Two-step deprotection of the methyl ether (*in situ* TMSI) and silyl ether (TBAF, AcOH) led to an intermediate ϵ -lactone, which could undergo directed, diastereoselective dihydroxylation using conditions developed by Donohoe.²⁹ Following inversion of the secondary alcohol by activation of it as the mesylate and subsequent displacement–by a presumed intramolecular carboxylate nucleophile–the first synthesis of pseudoanisatin (**6**) was completed.

To gain synthetic entry into majucinoids even further oxidation was required (Scheme 12). In order to circumvent previous challenges encountered in acid-directed methine C–H oxidation, substrate **116** was prepared in three straightforward steps from (+)-cedrol, by way of alkene **115**. Subjecting **116** to hypoiodite photolysis conditions smoothly oxidized the same methine position, and **117** could be isolated in excellent yield. Inspired by Waegell's work on simpler substrates,³⁰ we treated **117** with *in situ* generated RuO₄ in order to perform a double C–H activation/C–C oxidation cascade and arrive at keto-lactone **118** in a single step. Additional oxidations required for the majucinoids were installed by treating **118** with selenium(IV) oxide. Remarkably, all C–H bonds next to the ketone in **119** were oxidized. Reduction and an acetate cleavage/isomerization cascade took this material (i.e. **119**) on to enol lactone **120**. Once again, an α -ketol rearrangement was desired to isomerize the 5,5-fused ring system to the 5,6-fused one. This time, while oxidation to the α -hydroxy ketone was more facile (DMDO), that intermediate was far more labile and would only undergo ring shift under thermal conditions, providing diol **93** after directed reduction. As diol **93** was prepared in both Shenvi's and Theodorakis's routes to **4**, isolation of that

intermediate constituted a formal synthesis. As we were interested in also accessing compounds that had not previously been synthesized, we advanced **93** to alkene **121** by an intramolecular transactonization/dehydration sequence. **121** was reported by Theodorakis to go on to **3** and **22**. Finally, a three-step sequence of hydroxylation, ruthenium-catalyzed epimerization, and dihydroxylation completed the synthesis of **2**, conclusively demonstrating the viability of an oxidative route to accessing multiple family members including highly oxidized majucinoids.

In summary, a host of different strategies have been explored for *seco*-prezizaane *Illicium* sesquiterpene synthesis. From strategic annulations and radical cyclization cascades, to elaborate dearomatizations, transition metal couplings, and creative use of the chiral pool, *Illicium* syntheses truly showcase a wide variety of synthetic strategies and tactics, making their study inherently valuable for the synthetic practitioner. It is reasonable to speculate at this point where the future of *Illicium* sesquiterpene chemistry lies – what questions are there left to answer? We note from a synthetic chemistry perspective that routes to anisatinoids and pseudoanisatinoids are still comparably underdeveloped relative to majucinoid synthesis and perhaps future success will be seen in that area. Nevertheless, we are confident that future syntheses will doubtlessly provide fertile ground for new, inspiring chemistries. From a medicinal and biological perspective many questions still remain with regard to the (poly)pharmacology of these compounds, atomic level descriptions of their binding, and ultimately whether they, or designed derivatives, are effective agents to treat human neurological disease. Many of these questions can be greatly aided by the advances in synthetic chemistry described herein.

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BIOGRAPHIES

Matthew Condakes received his A.B. and A.M. degrees in chemistry summa cum laude from Harvard University in 2014. While there, he conducted research on the synthesis of novel macrolide antibiotic analogues under the guidance of Prof. Andrew Myers. His passion for complex molecule synthesis then led him to pursue graduate work with Prof. Tom Maimone at the University of California, Berkeley, as an NSF predoctoral fellow. He earned his Ph.D. in 2018 for work on developing new synthetic strategies and methodologies, particularly those seen in the context of *Illicium* sesquiterpene syntheses.

Luiz Novaes received his B.S. (2013) and M.S. (2015) degrees in Chemistry from University of Campinas under the supervision of Prof. Ronaldo Pilli. In 2015, he joined the group of Prof. Julio Pastre (University of Campinas) for his Ph.D. studies on the total synthesis of natural terpenes. In March of 2018, Luiz moved to UC Berkeley as a visiting Ph.D. student in the Maimone research group.

Tom Maimone was born and raised in Warsaw, NY. He completed his B.S. degree in chemistry at UC-Berkeley in 2004 and his Ph.D. at The Scripps Research Institute in 2009. During these periods, he conducted total synthesis research in the labs of Prof. Dirk Trauner and Phil Baran respectively. From 2009-2012 he was an NIH post-doctoral fellow at MIT under the tutelage of Prof. Stephen Buchwald. In 2012 Tom joined the faculty at UC-Berkeley where his group works in the area of natural products chemistry.

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Figure 1.
(A) The *seco*-prezizaane skeleton and chemical structures of many highly-oxidized *Illicium* sesquiterpenes possessing it. (B) Other major *Illicium* sesquiterpene scaffolds, with representative example members.

Scheme 1.
Theodorakis's 2011 Total Synthesis of (-)-Jiadifenin (3)

Scheme 3.

Y. Fukuyama's 2015 Formal Synthesis of (±)-Jiadifenin (3)

Scheme 4.

Micalizio's 2016 Total Synthesis of (–)-Jiadifenin (3) and Related Majucinoids

Scheme 5.
Theodorakis's 2011 Total Synthesis of (–)-Jiadifenolide (4)

Scheme 6.
Sorensen's 2014 Synthesis of (-)-Jiadifenolide (4).

Scheme 7.
Paterson's 2014 Total Synthesis of (±)-Jiadifenolide (4)

Scheme 8.

Zhang's 2015 Total Synthesis and Gademann's 2016 Formal Synthesis of (-)-Jiadifenolide (4)

Scheme 9.
Shenvi's 2015 Gram-Scale Total Synthesis of (-)-Jiadifenolide (4)

Scheme 10.

T. Fukuyama's 2012 Total Synthesis of (–)-Anisatin

Scheme 11.
 Maimone's 2016 Synthesis of (+)-Pseudoanisatin (6) from (+)-Cedrol

Scheme 12.

Maimone's 2017 Synthesis of (-)-Majucin (2) and Related Majucinoids