



Published in final edited form as:

J Org Chem. 2015 October 2; 80(19): 9740–9766. doi:10.1021/acs.joc.5b01844.

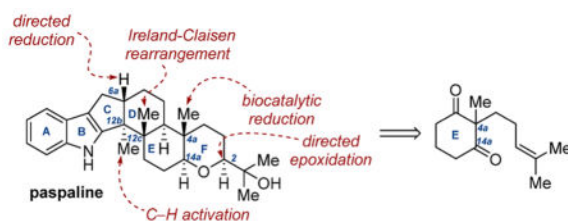
Asymmetric Total Synthesis of the Indole Diterpene Alkaloid Paspaline

Robert J. Sharpe and Jeffrey S. Johnson*

Department of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3290, United States

Abstract

An enantioselective synthesis of the indole diterpenoid natural product paspaline is disclosed. Critical to this approach was the implementation of stereoselective desymmetrization reactions to assemble key stereocenters of the molecule. The design and execution of these tactics are described in detail, and a thorough analysis of observed outcomes is presented, ultimately providing the title compound in high stereopurity. This synthesis provides a novel template for preparing key stereocenters in this family of molecules, and the reactions developed en route to paspaline present a series of new synthetic disconnections in preparing steroidal natural products.



INTRODUCTION

Production of novel metabolites by the ergot fungus has been well-documented.¹ Most notably, those produced by *Claviceps purpurea* have long been implicated in the contamination of various grains.² *Claviceps paspali*, another species in this genus, has been linked to “paspalum stagger” poisoning in livestock,³ and it was from this fungus that Arigoni and co-workers isolated paspaline (**1**, Figure 1) and paspalicine (**4**), the first of a now extensive family of indole diterpene alkaloid natural products.⁴ A diverse range of

*Corresponding Author: jsj@unc.edu.

The authors declare no competing financial interest.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01844.

NMR spectra, X-ray crystallographic data (x1504008, x1405008, x1501005, and x1502014), and computational details (PDF)

X-ray data for **32** (CIF)

X-ray data for **54** (CIF)

X-ray data for **91** (CIF)

X-ray data for **1** (CIF)

related structures have since been reported including paspaline B (**2**),⁵ paspalinine (**3**),⁶ JBIR-03 (**5**),⁷ and paxilline (**6**).⁸

The varied biological profiles of these compounds have rendered them particularly attractive to the chemical industry. The recently discovered JBIR-03 has displayed significant inhibition of *Valsa ceratosperma* (MIC = 128 $\mu\text{g/mL}$) while showing no cytotoxic effects to the human fibrosarcoma cell line HT-1080 at 100 μM .⁷ Moreover, paspalinine and its derivatives have demonstrated marked activity as Maxi-K channel antagonists and, as a result, are under examination as treatments for Alzheimer's disease and other neurological disorders.⁹ Paxilline is currently under study for its properties as a BK channel antagonist toward the suppression of seizures in postnatal mammals.¹⁰ From a standpoint of structure–activity, prior work by Cole has underscored the significance of the axial *tert*-hydroxyl functionality (C4b, paspaline numbering) as an important source of activity for these structures, evidenced by the lack of tremorgenicity demonstrated by paspaline and paspalicine.¹¹

The absolute structure of **1** was confirmed in 1980 by Springer and Clardy on the basis of X-ray diffraction studies.^{11a} Paspaline and its related compounds are characterized by their unique indole and tetrahydropyran (or derivatives thereof) ring fusions. Furthermore, grafted onto the D/E decalin core, three all-carbon quaternary atoms are encountered (C4a, C12b, C12c). These salient features necessitate careful planning for endeavors in total synthesis. These challenges were first addressed by the Smith laboratory,¹² whose body of work in this area has defined the state of the art for the synthesis of paspaline and its related structures. Subsequent partial¹³ and total¹⁴ synthetic studies of these molecules have since been disclosed, building on these advances. As an extension to previous work in our laboratory in developing total synthesis platforms for complex molecular frameworks,¹⁵ we sought to develop an expedient synthesis of **1**, particularly of the key C4a, C12b, and C12c stereocenters, which could serve as a template for assembly of the remaining structures in this family. Our work toward this goal culminated in a highly stereocontrolled total synthesis of paspaline.¹⁶ Herein, we disclose the entirety of our efforts, ultimately leading to the conception and implementation of two critical stereoselective desymmetrization reactions for facile target assembly. These studies have laid the groundwork for future investigations in this family of natural products.

Our preliminary synthetic plan for **1** began with translation to hydroxyalkene **7** (Scheme 1). The decalin functionality (D and E rings) in **7** would be constructed via a transannular ketone addition/Friedel–Crafts alkylation cascade arising from cyclodecenone **8**,¹⁷ establishing the vicinal C12b and C12c quaternary centers in a single operation. The tetrasubstituted (*E*)-alkene in **8** would be prepared via intramolecular coupling of the corresponding diene **9** or dicarbonyl **10** via a metathesis¹⁸ or McMurry process.¹⁹ Synthesis of this ketone would rely on the union of fragments **11** and **12** to assemble the C6a, C6, and C5 carbon–carbon bonds. Access to the tetrahydropyran **12** was envisioned via an alkylation/Michael addition cascade between dimethylmalonate and **13** inspired by methodology developed by Gharpure.²⁰

RESULTS AND DISCUSSION

In accordance with the above strategy, initial focus was placed on synthesizing the tetrahydropyranyl F ring and C2/C14a stereodiad in **1** (Scheme 2). In a forward sense, tosylation of the previously reported diol **14** followed by oxy-Michael addition and iodination furnished the requisite iodoalkene **13** in 62% yield over three steps,²¹ setting the stage for the proposed annulation. Thus, treatment of **13** with CH₂(CO₂Me)₂ and Cs₂CO₃ in DMF provided exclusively the desired 2,6-*cis*-pyran in 99% yield and >20:1 dr. Selective reduction of the ethyl ester in **17** proceeded smoothly to give alcohol **18** in 72% yield, and subsequent iodination and alkylation installed the requisite alkene in **12**. With this compound in hand, we turned our attention to desymmetrization of the C4a *gem*-diester in **12** via nucleophilic addition. Experiments with this compound revealed a strong diastereotopic group bias for the equatorial ester, giving the desired relative stereochemistry at C4a.²² To enable maximum flexibility in the downstream strategy, the corresponding carboxylic acid **19**, methyl ketone **20**, and enone **21** were prepared.

With the pyran subunit in place, the next challenge became introduction of the indole fragment bearing the atoms necessary for cyclodecenone synthesis (Scheme 3); however, we found this union to be significantly more challenging than first expected. In the first iteration, Michael addition of the enolate of **20** to the indole-derived enone **22**²³ using a variety of bases (LDA, LHMDS, NaOMe) showed no productive reactivity, presumably due to low reactivity of enone **22**. Mukaiyama Michael addition to **22** using the enolsilane derived from **20** resulted in rapid desilylation prior to engaging **22** under all conditions examined. Methyl vinyl ketone also failed to react with **20** under these conditions. An alternative strategy explored reversal of the nucleophile/electrophile identities via the reaction of enolsilane **24** and pyranyl enone **21**. However, exposure of these compounds to Lewis acidic conditions (BF₃·OEt₂, TiCl₄, Cu(OTf)₂, etc.) resulted only in desilylation of **24** and decomposition of enone **21**. Finally, a Lewis acid promoted ene reaction was examined as a method for the union of enone **21** and nucleophilic alkene **25**; unfortunately, the inherent instability of enone **21** remained problematic in this approach. These failed efforts led us to conclude that direct intermolecular coupling methodologies of these fragments to **1** from the C4a functionality were prohibitively challenging, and as a result, this approach was abandoned.

In an effort to circumvent the issues associated with the above strategy, we postulated that an intramolecular approach to the critical bond disconnection might be more facile (Scheme 4). This process would be enabled via appendage of the appropriate functionality to the iodide **27** (which had been synthesized previously in the described route to alkene **12**). We selected 2-methyl-1,3-cyclohexanedione **28** as this nucleophile, anticipating that Krapcho decarboxylation of the corresponding alkylation product **29** might initiate an intramolecular aldol addition process to assemble the D,E ring decalin moiety as well as the C12c and C4b stereocenters (**33**). In practice, alkylation of iodide **27** with **28** gave a ~1:2 mixture of diketone **29** and the undesired O-alkylation product **30** in 34 and 56% yields, respectively.²³ While this issue of regiochemistry rendered material throughput challenging, we carried on in the interest of validating the proposed downstream reactivity. Operating first on small

scale (15 mg), treatment of diketone **29** with NaCl in DMSO afforded a ~1:1 ratio of the Krapcho adduct **31** and the cyclization product **32** as a single diastereomer. However, a single-crystal X-ray diffraction study revealed **32** to be the undesired *cis*-decalinone product (e.g., epimeric at C12c). Fortunately, formation of **32** was suppressed when the reaction was further scaled (70 mg), giving exclusively the Krapcho adduct **31** in 43% yield. In hopes that a stepwise Krapcho/aldol process might proceed with selectivity orthogonal to **32**, we began screening conditions for the conversion of **31** to **33**. Toward this aim, treatment of **31** with Brønsted or Lewis acidic conditions gave either no reaction or starting material decomposition upon heating. Alternatively, exposure to basic conditions resulted in no reaction or retro-Dieckmann decomposition of the dione functionality.

Having arrived at another critical impasse, we began to question the viability of this route in providing access to **1**. While the alkylation/Michael cascade sequence (**13** → **17**) provided expedient access to the F ring tetrahydropyran stereochemistry and desymmetrization of the C4a stereocenter proceeded as planned, further elaboration of this material to **1** seemed an unlikely venture. At this critical stage in our studies, we began to examine alternative points of initiation for our synthesis (Scheme 5).

Guided by our previous work in developing symmetry-breaking processes to enable rapid construction of complex natural products,^{15g,h} we surmised that a synthesis beginning from desymmetrization of a paspaline E ring precursor might circumvent the problems associated with our initial strategy. It is important to note at this juncture that Smith's synthesis of **1** also commences via a symmetry-breaking process;^{12a} namely, the Wieland–Miescher ketone synthesis (**28** → **34**) assembles the D–E ring fusion of **1** concomitant with the C12c quaternary stereocenter. While this reaction is a classic “single stereocenter” desymmetrization, we envisioned an alternative E ring desymmetrization arising from stereoselective monoreduction of functionalized diketone **35**. Reduction of this compound would establish the stereochemical identity of C4a and C14a in **36** in a single operation while supplying the needed functional handles for tetrahydropyran assembly and synthesis completion. Armed with this new hypothesis, we refocused our efforts in the synthesis of **1** via this approach.

The first challenge in our revised synthesis plan was preparation of the desymmetrization precursor **35** via alkylation of dione **28** or its derivatives (Scheme 6). In the event, deprotonation of **28** with NaH followed by addition of iodide **37** provided the desired cycloalkanone **35** in 7% yield along with 26% of the undesired O-alkylation product **38**. This result was not entirely unexpected: challenges associated with regioselective C-alkylation of cyclic α -dicarbonyls have been well-documented.²⁴ In hopes of enhancing C-nucleophilicity of this structure, we prepared hydrazone **39**.²⁴ Screening of conditions revealed that enolization with KH followed by addition of iodide **37** provided exclusively the corresponding C-alkylation adduct which, following hydrazone deprotection, afforded functionalized diketone **35** in 76% yield over two steps. Of particular importance is the scalability of this process: diketone **35** can be prepared in >10 g scale in a single batch. This reaction represents a useful advance over prior art in preparing this compound,²⁵ and the scope of this method is currently under study.

With the critical desymmetrization precursor in our possession, we began investigating selective monoreduction of **35** to access the C4a–C14a stereodiad. Treatment of **35** with NaBH₄ provided the racemic monoreduction product **40** with excellent yield and diastereoselectivity (19:1), albeit the opposite diastereomer to that desired. It is reasonable to expect formation of this diastereomer under strictly substrate-controlled conditions, although we were surprised by the magnitude of selectivity for this diastereomer. We were encouraged, however, by the recent reports of Nakada²⁶ and Node²⁷ which demonstrated access to the diastereomer needed for our synthesis on similar cyclic diketones using biocatalytic reducing conditions. In experimenting with our compound, we were pleased to find that monoreduction of **35** with yeast from *Saccharomyces cerevisiae* type 2 (YSC-2) proceeded with virtually complete reagent control, giving the desired alcohol diastereomer **36** in 65% yield, 10:1 dr, and >99:1 er. The success of this transformation provided encouragement to the viability of our revised synthesis plan and set the stage for further manipulation to **1**.

From hydroxy olefin **36**, we anticipated assembly of the tetrahydropyranyl F ring via an oxidative cyclization sequence. With this goal in mind, treating the alkene in **36** with *m*-CPBA provided the corresponding epoxide **41** in 93% yield and poor diastereoselectivity (2:1). While any number of asymmetric epoxidation methods could likely enhance this selectivity, of greater concern was that treatment of this diastereomeric mixture **41** with conditions requisite for ring closure (PPTS) gave an inseparable 5:1 mixture of products with the desired tetrahydropyran **42** as the minor product. The major material was identified as alcohol **43**, the result of epoxide trapping by the enol tautomer of the ketone in **41**. To circumvent this issue, we envisaged that masking the ketone in **36** would preclude this undesired mode of ring closure. Since it translated well to our downstream strategy for D ring construction, **36** was converted to the corresponding tosyl hydrazone **44** in 97% yield. To our surprise, the reaction of this compound with *m*-CPBA followed by PPTS initiated an epoxidation/cyclization cascade, providing the desired tetrahydropyran **45** directly in 77% yield and >20:1 dr. This reaction gave expedient preparation of the paspaline F ring in a single operation.

We were unaware of any previously reported directing effects of tosyl hydrazones on analogous systems (Scheme 7). To provide understanding to this difference in reactivity between hydroxyketone **36** and hydrazone **44**, we carried out the following experiments. First, the alkene in hydrazone **44** was removed via hydrogenation to give alcohol **46**. Treatment of **46** with the exact reaction conditions used in the epoxidation of **44** resulted in quantitative starting material recovery. This datum excluded the possibility of intramolecular oxygen delivery in the reaction via a transient oxaziridine such as **47**. Concluding that the reactivity may be a consequence of underlying conformational differences between **36** and **44**, we calculated both structures using density functional theory (DFT) at the level of B3LYP/6-311G(d).²⁸ Interestingly, the optimized structures of **36** and **44** showed a significant difference in the dihedral angle about the C14a C–OH bond and the C4a C–CH₂R bond (69° for **36** and 85° for **44**). On the basis of these facts, we hypothesize that the observed selectivity is a consequence of the hydrazone in **44** imposing a favorable reactive conformation (**48**) on the cyclohexane such that the C14a hydroxyl is in close proximity to

the alkene during the oxidation. It follows that this would enhance transfer of the substrate's chiral information to C2 during the oxidation, giving the observed pyran **45** following ring closure. To the best of our knowledge, this reaction is the first example of an alkene epoxidation stereoselectivity being influenced by the presence of a tosyl hydrazone.²⁹

With assembly of the E and F rings complete, attention was directed to construction of the sterically congested D ring and C12c stereocenter (Scheme 8). We believed that the tosyl hydrazone in **45** would be engaged via the Shapiro reaction to produce a transient vinylolithium which, upon trapping with the appropriate electrophile, would provide the functionality required to meet these synthetic challenges.³⁰

Thus, TBS protection of the *tert*-alcohol in **45** proceeded to give silyl ether **49** in 77% yield. Shapiro reaction of **49** followed by DMF trapping furnished unsaturated aldehyde **50** in 62% yield which, upon olefination, gave diene **51** poised for a Diels–Alder cycloaddition. Nitroethylene proved to be an effective dienophile in this reaction, giving the annulation product **52** in 94% yield and with complete regioselectivity under thermal conditions. Subsequent Nef reaction and alkene isomerization afforded the ketone **53**, from which we envisioned manipulation of the alkene would complete D ring assembly to give **58**. Accordingly, Birch reduction of **53** followed by electrophilic trapping with MeI furnished decalinone **54** in 67% yield and high stereoselectivity (>20:1). Unfortunately, this compound was identified as the undesired *cis*-decalinone (bearing the desired C4b stereochemistry and undesired C12c stereochemistry) via X-ray diffraction analysis of a derivative.³¹ After a screen of reducing metals, solvents, and addition methods showed no promise for overriding this selectivity, we began exploring auxiliary methods for stereoselective introduction of the C12c methyl group. In the first iteration, Birch reduction of **53** followed by protic quenching and epimerization with DBU gave the *trans*-decalinone **55** as a single diastereomer. However, all attempts at thermodynamic methylation of this compound proved fruitless, giving either polymethylated products or starting material decomposition. We next examined whether the C12c methyl group could be introduced stereospecifically via an epoxidation/semipinacol reaction sequence. While epoxidation of **53** was achieved upon treatment with *p*-NPBA³² to give the desired oxirane **56** as a single diastereomer in 46% yield, the subsequent ketone methylation requisite for rearrangement consistently gave starting material recovery or decomposition under more forcing conditions. In a final case, the ketone in **53** was reduced upon treatment with LiAl(O*t*Bu)₃H to give alcohol **57** in 95% yield and 10:1 dr. From this compound, we pursued radical delivery of the C12c methyl group via tethering from the secondary hydroxyl.³³ However, this approach also proved unsuccessful, as the alkene in **57** failed to engage all radical precursors bound to the alcohol.

Collectively, these reactions indicated that the inherent bias of enone **53** for the α -face of the D–E ring fusion (presumably influenced by the C4a angular methyl group) would preclude all attempts at late-stage introduction of the C12c methyl group. At this key juncture in our studies, we determined that if D ring assembly was preceded by introduction of this methyl group, then the subsequent annulation step might also proceed with α -face selectivity to give the requisite *syn*-diaxial methyl group relationship (Scheme 9). Thus, methylation of hydrazone **49** upon treatment with *n*-BuLi and MeI proceeded smoothly to give the

monomethylated product **59** in excellent yield. In accordance with our Diels–Alder strategy, Shapiro reaction of **59** followed by trapping with DMF afforded aldehyde **60** in 61% yield, giving the diene **61** upon olefination. While we at first anticipated that the [4 + 2] annulation of **61** with nitroethylene would proceed in a manner similar to the previously described desmethyl cycloaddition (**51** → **52**), we quickly found the steric impact of the newly introduced methyl group to be much greater than expected. In our initial trials, the reaction of **61** with nitroethylene failed to produce cycloadduct **62** under both thermal and Lewis acidic conditions. An extensive screen of Diels–Alder dienophiles and promoters ensued, showing no further promise for D ring construction via this method. We then turned our attention to alternative annulation methods, making use of the flexibility of electrophile choice in the Shapiro reaction step and its subsequent intermediates. To bypass an intermolecular cycloaddition, we pursued an electrocyclization pathway to form the requisite D ring. Olefination of aldehyde **60** with the ylide derived from allyltriphenylphosphonium bromide gave the simplified triene **63** in 36% yield, and irradiation of **63** (Hg vapor lamp) gave complete conversion to a single product after 1 h. Unfortunately, this material was identified as the sigmatropic rearrangement product **65** and not the desired cyclization product **64**. Suspecting that this rearrangement might predominate using any analogue of this triene, we abandoned this pathway in favor of alternative cyclization modes. Toward these aims, substrates **66–68** were prepared via modification of the electrophilic trap (and subsequent product manipulation) in the Shapiro reaction and examined for their viability in D ring synthesis. Electron-rich Diels–Alder diene **66** and Nazarov substrate **67** failed to participate in any productive reactivity, either giving no reaction or decomposing to complex mixtures. Iodide **68** was synthesized with the goal of completing D ring synthesis via cross-coupling; however, this approach also proved fruitless.

Our options diminishing, we prepared primary alcohol **69** via trapping the Shapiro intermediate of **59** with (HCHO)_n (Table 1). We surmised that the appropriately selected ester of **69** would participate in an Ireland–Claisen rearrangement,³⁴ influenced by the C4a stereocenter, to install the C12c (and potentially C12b) quaternary methyl group(s) while providing functional handles for D ring construction. We then began screening esters of **69** compatible with our synthetic manifold. In the simplest cases, acetate **70a** (entry 1) and propionate **70b** (entry 2) did not undergo rearrangement as the corresponding silyl ketene acetals were labile at elevated reaction temperatures. Isobutyrate **70c** (entry 3) performed exceptionally to give **71a** (80% yield, 6:1 dr, 4 g scale), although a downstream C–H activation at C12b would be required for this product to be a viable intermediate toward **1**. With the reaction's viability demonstrated, functionalized esters **70d–h** were probed. Indole ester **70d** or protected analogues thereof failed to rearrange, presumably due to a steric impact of the indole on silyl ketene acetal generation. Esters **70e–g** (entries 5–7) likewise suffered from the same issue. We were excited to find promising reactivity, however, in the case of silyl-functionalized isobutyrate **70h** (entry 8, 52% yield, 6.6:1.1:1 dr). The stereochemistry at C12c of this compound was assigned by analogy to rearrangement product **71a** (vide infra). The identity of the C12b stereocenter could not be identified.

The next portion of our strategy involved conversion of the rearrangement product to its methyl ketone for subsequent ring closure (Scheme 10). After first reoptimizing the Shapiro

reaction step to facilitate one-pot conversion of desmethylhydrazone **49** to alcohol **69**, we moved forward in this approach. Unfortunately, conversion of silyl-functionalized isobutyrate product **71b** to its derived methyl ketone proved unfeasible due to a significant steric impact at the α -position. In contrast, early returns on the simpler isobutyrate rearrangement product **71a** showed that the methyl ketone synthesis worked well, and as a result, we moved forward in our synthesis with this compound. Thus, esterification of acid **71a** with TMSCHN₂ followed by treatment with MeLi furnished ketone **72** in 84% yield. The C4b stereocenter was established via hydroboration/oxidation of **72** to give diol **73** in 74% yield and >20:1 dr. After some experimentation, bisoxidation of **73** was accomplished via Swern conditions to give ketoaldehyde **74** poised for intramolecular condensation. Exposure of **74** to basic conditions cleanly afforded enone **75** in 74% yield over two steps, thereby completing D ring synthesis. The resultant alkene was removed via hydrogenation to give the corresponding ketone, which was converted to oxime **76** in 82% yield.

With D ring synthesis concluded, desymmetrization of the nonstereogenic C12b dimethyl group in **76** became compulsory for synthesis completion. The success of this transformation would require a selective functionalization of the equatorial methyl group at C12b over its axial counterpart to provide the diastereomer needed; we were aware that the lowest energy conformer of **76** places the oxime C–N double bond in the same plane as the equatorial methyl group and anticipated that the appropriate catalytic system would operate on **76** using the oxime as a directing group. We selected the catalytic C–H oxidation reaction developed by Sanford and co-workers,³⁵ which had demonstrated applicability to substituted cyclohexanone oximes. In the event, treatment of oxime **76** with Sanford's conditions provided acetate **78** in 79% yield (via **77**) with complete diastereoselection, establishing the stereochemistry of the final quaternary center in **1** and providing the necessary functional handle for synthesis completion.

The yield and selectivity of this transformation are noteworthy; examples for the successful execution of this reaction as a platform for desymmetrization of achiral quaternary centers are scarce in recent literature (Scheme 11). In 2008, Yu and co-workers reported a stoichiometric desymmetrization of dimethyl oxime **79**, proceeding in 72% yield and complete selectivity (assisted by the conformational rigidity of **79**) en route to the synthesis of lobatoside E.³⁶ Six years later, the Sorenson laboratory described the first symmetry-breaking implementation of Sanford's catalytic reaction in their synthesis of jiadifenolide.³⁷ In this reaction, treating oxime **81** with Pd(OAc)₂ and PhI(OAc)₂ afforded the desired acetate **82** in 22% yield and 1:1 dr. The poor selectivity in this transformation may be attributed to the oxime in **81** bisecting the two methyl groups. In our case, exposure of oxime **76** to Sanford's conditions provided the desired acetate diastereomer **78** in 79% yield and >20:1 dr (presumably aided by the coplanar oxime and equatorial methyl group). That this reaction (**76** → **78**) provided the desired product diastereomer in such high yield illustrates the viability of this and related transformations in the late-stage pursuit of challenging quaternary stereocenters, particularly scenarios in which inherent structural biases may lend a degree of stereochemical predictability.

With acetate **78** in hand, we faced the remaining challenges of C ring installation, C6a reduction, and indolization to complete our synthesis (Scheme 12). Acetate **78** was subjected to global hydrolysis to remove the acetate, oxime, and silyl ether functionalities. The resulting primary alcohol was oxidized with Dess-Martin periodinane (DMP) to give ketoaldehyde **83** in 70% yield over two steps. From **83**, we envisioned that bisvinylation followed by ring-closing metathesis (RCM) would install the needed carbon skeleton. Unfortunately, treatment of **83** with vinylmagnesium bromide at $-78\text{ }^{\circ}\text{C}$ gave predominantly retro-aldol decomposition products with only small amounts of **84**. After some experimentation, we found that the $\text{CeCl}_3\cdot 2\text{LiCl}$ complex recently reported by Knochel aided in suppressing the retro-aldol product completely,³⁸ giving diol **84** in 95% yield. Treatment of **84** with Grubb's second generation catalyst provided allylic alcohol **85** in 71% yield. While an alcohol oxidation/hydroxyl elimination pathway was first pursued for the conversion of diol **85** to enone **86**, we found that simply subjecting **85** to acidic conditions (TFA) resulted in direct elimination of the *tert*-hydroxyl to give nonconjugated enone **86** in 71% yield. This set the stage for hydrogenation of the resultant alkene to install the final stereocenter found in **1**. In the event, catalytic hydrogenation of alkene **86** with Pd/C provided ketone **87** in 87% yield and >20:1 dr. However, ^1H NMR spectral data of this compound were not consistent with that of the desired compound previously synthesized by Smith and co-workers,^{12d} leading to the conclusion that this hydrogenation had delivered the opposite diastereomer to that required. In order to rationalize this result, we calculated the structure of nonconjugated enone **86**. As anticipated, the DFT-optimized structure of **86** revealed a marked puckering of the C–D ring fusion; catalytic hydrogenation of this alkene to give the desired diastereomer at C6a would necessitate approach of H_2 to the concave *Re* face of **86**. This result is in accord with prior studies on similar steroidal systems³⁹ which also describe convex surface hydrogenation on related enones.

Upon assessing our available functional handles, we surmised that selective reduction of the ketone in **86** might alter the outcome of the ensuing alkene hydrogenation by virtue of the hydroxyl's function as a directing group (Scheme 13). The use of Crabtree's catalyst in alcohol-directed alkene hydrogenations has been well-documented⁴⁰ and would presumably engage the alkene on the same face as the hydroxyl. To this end, treatment of ketone **86** with LiAlH_4 afforded the desired (*S*)-alcohol **88** in 60% yield and >20:1 dr over two steps from diol **85**. The steric impact of the C12c methyl group on the outcome of this reaction cannot be overstated; ketone reduction in analogous steroidal systems not bearing this methyl group generally proceed with the opposite sense of selectivity.^{39,41}

With this alcohol in hand, catalytic hydrogenation of **88** using Crabtree's catalyst completely over-rode the inherent substrate bias, giving the corresponding alcohol **90** (via **89**) in >20:1 dr and subsequently the ketone **91** in 86% over two steps after reoxidation of the alcohol. The stereochemistry of **91** was confirmed via ^1H NMR comparison with Smith's intermediate and an X-ray diffraction study.^{12d} This left only indolization to complete our total synthesis of **1**. The Gassman indolization utilized previously by Smith proved to be the method of choice in affording paspaline (**1**) in 46% yield from **91**.^{12a,42} Synthetic **1** matched the reported analytical data for paspaline, and single-crystal X-ray analysis of this sample was in agreement with the reported structure.^{11a}

CONCLUSIONS

In conclusion, we have described the entirety of our efforts toward the synthesis of paspaline. The final route totals 28 steps from commercially available **28** in 0.4% yield (Smith synthesis: 24 steps from **28**, 0.2% yield).^{12a} Of particular note is the stereoselectivity of the described route: the least stereoselective reactions in our synthesis are the Ireland–Claisen rearrangement (**70c** → **71a**, 6:1 dr) and the biocatalytic reduction (**35** → **36**, >99:1 er, 10:1 dr). All other stereodetermining transformations occur in >20:1 dr (Scheme 14). After initial approaches for the assembly of **1** via a cationic transannular cyclization were unsuccessful, a symmetry-breaking approach to paspaline was developed to complete construction of the E,F ring fusion within the first four steps of the synthesis. A novel tosyl hydrazone influenced epoxidation enabled excellent control of the C2 stereocenter (>20:1), and the Ireland–Claisen rearrangement provided access to the D ring and C12c stereocenter of **1**. A substrate-directed symmetry-breaking C–H acetoxylation inspired by Sanford and co-workers provided control of the C12b stereocenter (>20:1). To override the inherent facial bias in the hydrogenation of enone **86**, stereoselective reduction of the ketone followed by hydrogenation with Crabtree’s catalyst provided the final stereocenter in **1** with excellent selectivity (>20:1). Emphasis was placed throughout on expedient assembly of the critical C4a, C12b, and C12c quaternary methyl groups toward facile preparation of the remaining structures in this family of molecules. The route and methods described in this work present a number of complementary conceptual disconnections in the preparation of “steroid-like” natural products. Work in our laboratory in preparing these and related compounds is ongoing and will be reported in due course.

EXPERIMENTAL SECTION

Materials and Methods

General—Tetrahydrofuran (THF), diethyl ether (Et₂O), dichloromethane (CH₂Cl₂), and toluene (C₇H₈) were dried by passage through a column of neutral alumina under nitrogen prior to use. Aniline, hexamethylphosphoramide (HMPA), and diisopropylamine were freshly distilled from calcium hydride prior to use. Compounds **14**,⁴³ **37**,⁴⁴ and **39**²⁴ were prepared according to known procedures. All other reagents were purchased from commercial sources and were used as received unless otherwise noted. Proton and carbon magnetic resonance spectra (¹H NMR and ¹³C NMR) were recorded with solvent resonance as the internal standard (¹H NMR: CDCl₃ at 7.26 ppm and C₆D₆ at 7.16 ppm; ¹³C NMR: CDCl₃ at 77.0 ppm). ¹H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, br d = broad doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Mass spectra were obtained via Fourier transform mass spectrometry (FTMS) with electrospray introduction (ESI) and external calibration in positive ion mode. All samples were prepared in methanol. Visualization for thin layer chromatography (TLC) was accomplished with UV light, KMnO₄, and/or Seebach’s stain followed by heating. Purification of the reaction products was carried out by flash chromatography on silica gel. Unless otherwise noted, all reactions were carried out under an atmosphere of dry nitrogen in flame-dried glassware with magnetic stirring. Yield refers to isolated yield of analytically pure material unless otherwise noted. Yields are

reported for a specific experiment and as a result may differ slightly from those found in figures, which are averages of at least two experiments.

Computation Analysis—High-level DFT calculations using the B3LYP^{28a,b} approximate exchange-correlation energy density functional were performed with the standard Pople triple- ζ basis set 6-311G(d)^{28c,d} for all elements when stable structures are optimized. Calculations were performed in the gas phase at 0 K with tight SCF convergence and ultrafine integration grids. All calculations were performed with the package of Gaussian 09 version D01.⁴⁵ Cartesian coordinates of the studied systems are provided in the Supporting Information.

3-Hydroxy-4-methylpent-4-en-1-yl 4-Methylbenzenesulfonate (15): A flame-dried, 1000 mL round-bottomed flask was charged with diol **14** (4.67 g, 40.2 mmol, 1.00 equiv) and CH₂Cl₂ (300 mL) under an atmosphere of N₂. The solution was cooled to 0 °C, and NEt₃ (14.0 mL, 100.5 mmol, 2.50 equiv), DMAP (0.49 g, 4.00 mmol, 0.10 equiv), and TsCl (8.43 g, 44.2 mmol, 1.10 equiv) were added sequentially. The resulting mixture was allowed to stir at this temperature until complete conversion of the starting material was observed by TLC analysis, typically 12 h. The mixture was then diluted with H₂O (150 mL) and partitioned in a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (3 × 40 mL). The combined organic extracts were dried with sodium sulfate and concentrated in vacuo. The product was purified via flash chromatography (70:30 to 60:40 hexanes/EtOAc) to afford the tosylate **15** (8.75 g, 81% yield) as a pale yellow oil. Analytical data: ¹H NMR (600 MHz, CDCl₃) δ 7.79 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 4.91 (s, 1H), 4.82 (s, 1H), 4.22 (m, 1H), 4.16 (m, 1H), 4.09 (m, 1H), 2.44 (s, 3H), 1.91 (m, 1H), 1.79 (m, 1H), 1.75 (br s, 1H), 1.68 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 146.4, 144.8, 132.9, 129.8, 127.9, 111.4, 71.5, 67.6, 34.1, 21.6, 17.6; HRMS (ESI⁺) calcd for C₁₃H₁₈O₄S+Na, 293.0824; found 293.0815; IR (thin film, cm⁻¹) 3545, 3055, 2984, 2686, 1652, 1616, 1456, 1360, 1266, 1189; TLC (80:20 hexanes/EtOAc) R_f = 0.14.

Ethyl (E)-3-((2-Methyl-5-(tosyloxy)pent-1-en-3-yl)oxy)acrylate (16): A flame-dried, 500 mL round-bottomed flask was charged with alcohol **15** (8.75 g, 32.0 mmol, 1.00 equiv) and CH₂Cl₂ (160 mL) under an atmosphere of N₂ at rt. *N*-Methylmorpholine (3.60 mL, 35.7 mmol, 1.10 equiv) and ethyl propiolate (3.92 mL, 35.7 mmol, 1.10 equiv) were added sequentially, and the mixture was allowed to stir until complete conversion of the starting material was observed by TLC analysis, typically 4 h. The reaction mixture was concentrated on a rotary evaporator, and the crude product was purified via flash chromatography (80:20 to 70:30 hexanes/EtOAc) to give the vinyl ether **16** (11.4 g, 97% yield) as a clear oil. Analytical data: ¹H NMR (600 MHz, CDCl₃) δ 7.77 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 12.6 Hz, 1H), 5.14 (d, J = 12.6 Hz, 1H), 4.97 (s, 1H), 4.93 (s, 1H), 4.31 (dd, J = 4.8, 4.2 Hz, 1H), 4.16–4.06 (m, 4H), 2.43 (s, 3H), 1.97 (m, 2H), 1.61 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 167.6, 160.5, 145.0, 141.5, 132.6, 129.9, 127.9, 115.4, 98.6, 81.5, 66.2, 59.8, 32.7, 21.6, 16.7, 14.3; HRMS (ESI⁺) calcd for C₁₈H₂₄O₆S+Na, 391.1191; found 391.1181; IR (thin film, cm⁻¹) 2980,

2916, 2849, 1706, 1644, 1488, 1362, 1189, 1097, 923; TLC (80:20 hexanes/EtOAc) R_f = 0.32.

Ethyl (E)-3-((5-Iodo-2-methylpent-1-en-3-yl)oxy)acrylate (13): To a solution of tosylate **16** (11.4 g, 30.8 mmol, 1.00 equiv) in acetone (300 mL) at rt was added NaI (40.0 g, 308.0 mmol, 10.0 equiv) portionwise with vigorous stirring. The resulting suspension was allowed to stir 12 h at which point TLC analysis confirmed complete consumption of the starting material. The reaction mixture was diluted with brine (150 mL) and transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (3 × 60 mL), and the combined organic extracts were dried with magnesium sulfate and concentrated in vacuo. The product was purified via flash chromatography (90:10 to 80:20 hexanes/EtOAc) to afford the alkyl iodide **13** (8.67 g, 87% yield) as a pale yellow oil. Analytical data: ^1H NMR (600 MHz, CDCl_3) δ 7.46 (d, J = 12.6 Hz, 1H), 5.27 (d, J = 12.6 Hz, 1H), 5.05 (s, 1H), 5.04 (s, 1H), 4.39 (dd, J = 4.8, 3.0 Hz, 1H), 4.14 (m, 2H), 3.17 (m, 2H), 2.21 (m, 1H), 2.07 (m, 1H), 1.67 (s, 3H), 1.25 (t, J = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 167.7, 160.8, 141.5, 115.3, 98.6, 85.5, 59.8, 36.7, 17.0, 14.3, 0.9; HRMS (ESI⁺) calcd for $\text{C}_{11}\text{H}_{17}\text{IO}_3+\text{Na}$, 347.0120; found 347.0111; IR (thin film, cm^{-1}) 3078, 2978, 2916, 1707, 1644, 1456, 1322, 1171, 1006, 834; TLC (80:20 hexanes/EtOAc) R_f = 0.64.

Dimethyl 2-(2-Ethoxy-2-oxoethyl)-6-(prop-1-en-2-yl)dihydro-2Hpyran-3,3(4H)-dicarboxylate (17): A 500 mL round-bottomed flask was charged with the iodide **13** (8.75 g, 27.00 mmol, 1.00 equiv) and DMF (130 mL) at rt. Dimethyl malonate (6.20 mL, 54.0 mmol, 2.00 equiv) and Cs_2CO_3 (26.4 g, 81.0 mmol, 3.00 equiv) were added sequentially, whereupon a bright orange color was observed. The resulting mixture was allowed to stir for 14 h and was subsequently diluted with H_2O (50 mL) and Et_2O (50 mL). The layers were partitioned in a separatory funnel, and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with brine (40 mL), dried with magnesium sulfate, and concentrated in vacuo to give the crude pyran as a single diastereomer (as determined by ^1H NMR spectroscopic analysis of the crude mixture, which revealed a single compound). The product was purified via flash chromatography (90:10 to 80:20 hexanes/EtOAc) to afford tetrahydropyran **17** (8.85 g, 99% yield) as a clear, viscous oil. Analytical data: ^1H NMR (600 MHz, CDCl_3) δ 4.86 (s, 1H), 4.75 (s, 1H), 4.31 (dd, J = 9.0, 6.0 Hz, 1H), 4.11 (m, 2H), 3.83 (d, J = 12.0 Hz, 1H), 3.72 (s, 3H), 3.67 (s, 3H), 2.77 (m, 2H), 2.54 (m, 1H), 1.92 (m, 1H), 1.82 (m, 1H), 1.67 (br s, 1H), 1.65 (s, 3H), 1.20 (t, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 171.4, 170.7, 169.0, 144.6, 110.7, 81.1, 77.3, 60.3, 55.8, 52.5, 52.2, 38.0, 31.7, 26.0, 18.8, 14.1; HRMS (ESI⁺) calcd for $\text{C}_{16}\text{H}_{24}\text{O}_7+\text{Na}$, 351.1420; found 351.1409; IR (thin film, cm^{-1}) 3446, 2955, 2849, 1733, 1652, 1455, 1267, 1186, 1072, 904; TLC (80:20 hexanes/EtOAc) R_f = 0.43.

Dimethyl-2-(2-hydroxyethyl)-6-(prop-1-en-2-yl)dihydro-2Hpyran-3,3(4H)-dicarboxylate (18): A flame-dried, 500 mL roundbottomed flask was charged with ester **17** (6.00 g, 18.3 mmol, 1.00 equiv) and THF (150 mL) under an atmosphere of N_2 . The solution was cooled to 0 °C, and DIBAL-H (1 M solution in hexane, 18.3 mL, 18.3 mmol, 1.00 equiv) was added slowly. The reaction was then analyzed for reaction completion via TLC analysis, which indicated incomplete starting material conversion. Another 1.00 equiv of

DIBAL-H was added, whereupon TLC analysis indicated complete conversion of the starting material. The reaction mixture was quenched via addition of acetone (30 mL), and the mixture was stirred 5 min at 0 °C. Saturated Rochelle's salt_(aq) (40 mL) was then added, and the mixture was transferred to a separatory funnel. The aqueous layer was extracted with Et₂O (3 × 40 mL), and the combined organic extracts were washed with 1 M HCl_(aq) (40 mL) and brine (40 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (60:40 to 50:50 to 40:60 hexanes/EtOAc) to afford alcohol **18** (3.78 g, 72% yield) as a clear, viscous oil. Analytical data: ¹H NMR (600 MHz, CDCl₃) δ 4.92 (s, 1H), 4.81 (s, 1H), 4.01 (dd, *J* = 8.4, 1.8 Hz, 1H), 3.88 (m, 1H), 3.79–3.76 (m, 5H), 3.71 (s, 3H), 2.54 (m, 1H), 2.42 (d, *J* = 5.4 Hz, 1H), 2.14 (m, 1H), 1.93–1.88 (m, 3H), 1.70 (s, 3H), 1.67 (m, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 171.2, 169.3, 144.7, 111.1, 81.5, 81.1, 62.1, 56.2, 52.6, 52.1, 34.7, 31.9, 26.6, 18.7; HRMS (ESI⁺) calcd for C₁₄H₂₂O₆+Na, 309.1314; found 309.1305; IR (thin film, cm⁻¹) 3446, 3055, 2954, 2883, 1731, 1455, 1266, 1078, 906, 737; TLC (75:25 hexanes/EtOAc) *R*_f = 0.05.

Dimethyl-2-(2-iodoethyl)-6-(prop-1-en-2-yl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (27): A 500 mL round-bottomed flask was charged with CH₂Cl₂ (96 mL), and the solution was cooled to 0 °C. Imidazole (3.22 g, 47.4 mmol, 4.96 equiv) and PPh₃ (5.14 g, 19.0 mmol, 2.05 equiv) were added followed by I₂ (4.83 g, 19.0 mmol, 2.00 equiv). The mixture was allowed to stir at 0 °C for 10 min, whereupon a pale yellow suspension was observed. The alcohol **18** (2.73 g, 9.55 mmol, 1.00 equiv) was then added as a solution in CH₂Cl₂ (20 mL), and the mixture was allowed to warm to rt and stirred until complete consumption of the starting material was observed by TLC analysis, typically 12 h. The mixture was then quenched via addition of saturated Na₂S₂O_{3(aq)} (50 mL) and transferred to a separatory funnel. The aqueous layer was extracted with CH₂Cl₂ (3 × 30 mL), and the combined organic extracts were washed with brine (30 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (95:5 to 90:10 hexanes/EtOAc) to afford primary iodide **27** (2.64 g, 70% yield) as a white solid. Analytical data: mp 61–65 °C; ¹H NMR (600 MHz, CDCl₃) δ 4.93 (s, 1H), 4.83 (s, 1H), 3.88 (d, *J* = 10.2 Hz, 1H), 3.84 (d, *J* = 11.4 Hz, 1H), 3.75 (s, 3H), 3.72 (s, 3H), 3.36 (m, 1H), 3.28 (m, 1H), 2.56 (dt, *J* = 6.6, 3.0 Hz, 1H), 2.37 (m, 1H), 2.13 (m, 1H), 1.95 (m, 1H), 1.84 (m, 1H), 1.73 (s, 3H), 1.69 (m, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 171.0, 169.3, 144.8, 110.9, 81.4, 80.9, 56.4, 52.6, 52.2, 35.8, 32.0, 26.3, 19.0, 4.3; HRMS (ESI⁺) calcd for C₁₄H₂₁IO₅+Na, 419.0326; found 419.0320; IR (thin film, cm⁻¹) 2917, 2849, 1731, 1652, 1540, 1455, 1265, 1083, 905; TLC (75:25 hexanes/EtOAc) *R*_f = 0.50.

Dimethyl-2-(3-methylbut-3-en-1-yl)-6-(prop-1-en-2-yl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (12): A flame-dried, 50 mL roundbottomed flask was charged with 2-bromopropene (0.67 mL, 7.57 mmol, 3.00 equiv) and Et₂O (13 mL) under an atmosphere of N₂. The mixture was cooled to –78 °C, and ^tBuLi (1.70 M solution in pentane, 8.91 mL, 15.14 mmol, 6.00 equiv) was added dropwise. The reaction mixture was allowed to stir 30 min at –78 °C, then warmed to rt and stirred for 1 h. During this time period, a second flame-dried, 100 mL round-bottomed flask was charged with CuI (0.72 g, 3.79 mmol, 1.50 equiv) and Et₂O (12 mL) and was cooled to –78 °C. The isopropenyllithium solution was then cooled to –78 °C and transferred via cannula to the CuI suspension over a period of ~1

min. The resulting suspension was then warmed to $-45\text{ }^{\circ}\text{C}$ and stirred 1 h, upon which a color change from pale brown to dark gray to dark yellow-green was observed. The mixture was cooled to $-78\text{ }^{\circ}\text{C}$, and a solution of iodide **27** (1.00 g, 2.52 mmol, 1.00 equiv) in Et_2O (5 mL) was added. The reaction was then warmed to $0\text{ }^{\circ}\text{C}$ and stirred until complete conversion of the starting material was observed by TLC analysis, typically 30 min. The reaction was then quenched via addition of saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (20 mL), and the mixture was transferred to a separatory funnel. The aqueous layer was extracted with Et_2O ($3 \times 20\text{ mL}$), and the combined organic extracts were washed with saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (20 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (100:0 to 95:5 to 90:10 hexanes/ EtOAc) to afford the alkene **12** (0.77 g, 99% yield) as a clear oil. Analytical data: ^1H NMR (600 MHz, CDCl_3) δ 4.93 (s, 1H), 4.81 (s, 1H), 4.72 (s, 1H), 4.69 (s, 1H), 3.75 (br s, 4H), 3.70 (br s, 4H), 2.53 (m, 1H), 2.21 (m, 1H), 2.12 (m, 1H), 1.94–1.78 (m, 4H), 1.74 (s, 3H), 1.72 (s, 3H), 1.67 (m, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 171.6, 169.7, 154.4, 145.1, 110.6, 110.3, 81.0, 80.5, 56.6, 52.4, 52.0, 34.9, 32.2, 30.1, 26.2, 22.2, 19.2; HRMS (ESI⁺) calcd for $\text{C}_{17}\text{H}_{26}\text{O}_5+\text{Na}$, 333.1678; found 333.1669; IR (thin film, cm^{-1}) 3446, 3056, 2953, 2849, 1731, 1669, 1636, 1520, 1455, 1203, 1266; TLC (75:25 hexanes/ EtOAc) R_f = 0.52.

3-(Methoxycarbonyl)-2-(3-methylbut-3-en-1-yl)-6-(prop-1-en-2-yl)tetrahydro-2H-pyran-3-carboxylic Acid (19): A 20 mL scintillation vial was charged with diester **12** (0.10 g, 0.32 mmol, 1.00 equiv) and THF (3 mL) with stirring at rt. KOH (1 M in MeOH, 1.70 mL, 1.70 mmol, 5.27 equiv) was added, and the resulting mixture was allowed to stir at rt until complete consumption of the starting material was observed by TLC analysis. This time period varied widely for each experiment (from 12 h to 6 days dependent on scale; in this iteration, 5 days were required to reach complete conversion). Once complete, the reaction mixture was concentrated on a rotary evaporator. The residue was diluted with H_2O (10 mL), transferred to a separatory funnel, and extracted with Et_2O ($2 \times 5\text{ mL}$). The aqueous layer was acidified to pH = 1 with 1 M $\text{HCl}_{(\text{aq})}$ and extracted with EtOAc ($3 \times 5\text{ mL}$). The combined EtOAc extracts were dried with magnesium sulfate and concentrated in vacuo to afford the crude monoacid **19** (0.094 g, >99% crude yield) as a pale yellow, viscous oil. The diastereomeric ratio was determined via ^1H NMR spectroscopic analysis of this crude material, which revealed a single compound. Analytical data: ^1H NMR (600 MHz, C_6D_6) δ 10.56 (br s, 1H), 5.02 (s, 1H), 4.90 (s, 1H), 4.84 (s, 1H), 4.80 (s, 1H), 3.84 (dd, J = 7.2, 1.8 Hz, 1H), 3.58 (d, J = 11.4 Hz, 1H), 3.31 (s, 3H), 2.56 (d, J = 13.2 Hz, 1H), 2.33 (m, 2H), 2.17 (m, 2H), 2.08 (m, 1H), 1.71 (s, 3H), 1.68–1.67 (m, 4H), 1.34 (d, J = 1.8 Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 177.1, 169.6, 145.3, 145.0, 110.8, 110.4, 81.1, 80.3, 56.6, 52.2, 34.8, 32.2, 30.1, 26.1, 22.2, 19.2; HRMS (ESI⁺) calcd for $\text{C}_{16}\text{H}_{24}\text{O}_5+\text{Na}$, 319.1521; found 319.1513; IR (thin film, cm^{-1}) 3566, 3074, 2952, 2857, 2633, 1732, 1650, 1438, 1268, 1080, 891; TLC (75:25 hexanes/ EtOAc) R_f = 0.32.

Methyl-3-acetyl-2-(3-methylbut-3-en-1-yl)-6-(prop-1-en-2-yl)-tetrahydro-2H-pyran-3-carboxylate (20): A flame-dried, 25 mL round-bottomed flask was charged with diester **12** (0.35 g, 1.13 mmol, 1.00 equiv) and THF (11 mL) under an atmosphere of N_2 . The solution was cooled to $-78\text{ }^{\circ}\text{C}$, and MeLi (1.60 M in Et_2O , 0.6 mL, 0.97 mmol, 2.00 equiv) was added over 5 s. The reaction was then checked via TLC analysis, which showed incomplete

conversion of the starting material. Another 1.00 equiv of MeLi was added, whereupon TLC analysis showed complete conversion of the starting material. The reaction mixture was then quenched via addition of saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (5 mL) and subsequently warmed to rt. The mixture was transferred to a separatory funnel, and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo to give the crude ketone as a single diastereomer (as determined via ^1H NMR spectroscopic analysis of the crude product residue, which revealed a single stereoisomer in combination with overaddition products). The product was purified via flash chromatography (100:0 to 98:2 to 95:5 to 90:10 hexanes/EtOAc) to afford ketone **20** (0.22 g, 65% yield) as a clear, viscous oil. Analytical data: ^1H NMR (600 MHz, CDCl_3) δ 4.94 (s, 1H), 4.82 (s, 1H), 4.71 (s, 1H), 4.69 (s, 1H), 3.78–3.75 (m, 4H), 3.71 (d, $J = 11.4$ Hz, 1H), 2.45 (m, 1H), 2.22 (m, 1H), 2.12 (br s, 4H), 1.99 (m, 1H), 1.75 (br s, 4H), 1.73 (br s, 4H), 1.68 (m, 2H); ^{13}C NMR (150 MHz, CDCl_3) δ 205.1, 171.0, 145.6, 145.2, 110.6, 110.3, 80.8, 80.3, 62.3, 52.0, 34.9, 31.4, 30.2, 27.1, 26.4, 22.3, 19.3; HRMS (ESI⁺) calcd for $\text{C}_{17}\text{H}_{26}\text{O}_4+\text{Na}$, 317.1729; found 317.1720; IR (thin film, cm^{-1}) 3445, 3072, 2969, 2857, 1708, 1649, 1436, 1356, 1221, 1081; TLC (75:25 hexanes/EtOAc) $R_f = 0.45$.

Synthesis of Unsaturated Ketone 21

Methyl-2-(3-methylbut-3-en-1-yl)-6-(prop-1-en-2-yl)-3-propionyltetrahydro-2H-pyran-3-carboxylate (S1): A flame-dried, 20 mL scintillation vial was charged with bromoethane (0.13 mL, 1.69 mmol, 3.50 equiv) and THF (5 mL) under an atmosphere of N_2 . The solution was cooled to -78 °C, and $t\text{BuLi}$ (1.70 M in pentane, 1.99 mL, 3.38 mmol, 7.00 equiv) was added dropwise. The mixture was allowed to stir 30 min at -78 °C, whereupon a solution of the diester **12** (0.15 g, 0.48 mmol, 1.00 equiv) was added over ~ 10 s. The reaction progress was immediately checked via TLC analysis, which confirmed complete consumption of the starting material. The reaction was then quenched via addition of saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (5 mL) and warmed to rt. The mixture was transferred to a separatory funnel, and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo to afford the crude ketone as a single diastereomer (as determined via ^1H NMR spectroscopic analysis of the crude product residue, which revealed a single stereoisomer in combination with overaddition products). The product was purified via flash chromatography (100:0 to 98:2 to 95:5 to 90:10 hexanes/EtOAc) to afford ketone **S1** (0.13 g, 89% yield) as a clear, viscous oil. Analytical data: ^1H NMR (600 MHz, CDCl_3) δ 4.93 (s, 1H), 4.82 (s, 1H), 4.71 (s, 1H), 4.68 (s, 1H), 3.79–3.77 (m, 4H), 3.71 (d, $J = 3.6$ Hz, 1H), 2.42 (m, 3H), 2.21 (m, 1H), 2.12 (m, 1H), 1.95 (m, 1H), 1.78 (m, 1H), 1.74 (s, 3H), 1.73 (s, 3H), 1.69 (m, 2H), 1.60 (br s, 1H), 1.03 (t, $J = 7.2$ Hz, H); ^{13}C NMR (150 MHz, CDCl_3) δ 208.0, 171.2, 145.6, 145.2, 110.6, 110.3, 80.8, 80.5, 62.4, 51.9, 34.9, 32.6, 31.7, 30.2, 26.4, 22.3, 19.3, 7.9; HRMS (ESI⁺) calcd for $\text{C}_{18}\text{H}_{28}\text{O}_4+\text{Na}$, 331.1885; found 331.1876; IR (thin film, cm^{-1}) 3446, 3073, 2970, 2855, 1739, 1650, 1455, 1342, 1159, 892; TLC (75:25 hexanes/EtOAc) $R_f = 0.47$.

Methyl 3-Acryloyl-2-(3-methylbut-3-en-1-yl)-6-(prop-1-en-2-yl)-tetrahydro-2H-pyran-3-carboxylate (21): A flame-dried, 20 mL scintillation vial was charged with THF (4 mL) and diisopropylamine (0.08 mL, 0.55 mmol, 1.30 equiv) under an atmosphere of N_2 . The mixture was cooled to 0 °C, and $n\text{BuLi}$ (1.74 M in hexanes, 0.32 mL, 0.55 mmol, 1.30

equiv) was added dropwise. After being stirred 30 min, the mixture was cooled to $-78\text{ }^{\circ}\text{C}$, and a solution of ketone **S1** (0.13 g, 0.42 mmol, 1.00 equiv) in THF (1 mL) was added. After being stirred 45 min at $-78\text{ }^{\circ}\text{C}$, PhSeBr (0.11 g, 0.51 mmol, 1.10 equiv) was added, and the mixture was allowed to stir until complete consumption of the starting material was observed by TLC analysis, typically 45 min. The reaction mixture was diluted with H_2O (10 mL), warmed to rt, and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et_2O ($3 \times 10\text{ mL}$). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo to give the crude α -selenide, which was used in the next step without further purification.

The intermediate selenide was dissolved in CH_2Cl_2 (2 mL), and the mixture was cooled to $0\text{ }^{\circ}\text{C}$. H_2O_2 (30% w/w in H_2O , 0.80 mL) was added dropwise, and the mixture was stirred at $0\text{ }^{\circ}\text{C}$ until complete consumption of the starting material was observed by TLC analysis, typically 15 min. The reaction mixture was diluted with H_2O (7 mL) and transferred to a separatory funnel. The aqueous layer was extracted with EtOAc ($3 \times 7\text{ mL}$), and the combined organic extracts were dried with magnesium sulfate and concentrated in vacuo. The product was purified via flash chromatography (100:0 to 98:2 to 95:5 hexanes/EtOAc) to afford unsaturated ketone **21** (0.079 g, 56%) as a pale yellow, viscous oil. Analytical data: $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 6.39 (d, $J = 3.0\text{ Hz}$, 1H), 6.38 (s, 1H), 5.71 (dd, $J = 4.2, 3.0\text{ Hz}$, 1H), 4.95 (s, 1H), 4.84 (s, 1H), 4.72 (s, 1H), 4.70 (s, 1H), 3.84 (d, $J = 10.2\text{ Hz}$, 1H), 3.76 (s, 3H), 3.72 (d, $J = 11.4\text{ Hz}$, 1H), 2.43 (m, 1H), 2.22 (m, 1H), 2.17 (m, 1H), 2.08 (m, 1H), 1.81 (m, 1H), 1.77 (s, 3H), 1.74 (s, 3H), 1.72–1.66 (m, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 195.6, 170.9, 145.6, 145.2, 131.7, 129.7, 110.7, 110.4, 80.7, 79.9, 60.8, 52.0, 34.8, 31.0, 30.2, 26.2, 22.3, 19.4; HRMS (ESI⁺) calcd for $\text{C}_{18}\text{H}_{26}\text{O}_4+\text{Na}$, 329.1729; found 329.1720; IR (thin film, cm^{-1}) 3420, 3054, 2952, 2852, 1740, 1636, 1455, 1265, 1049, 894; TLC (75:25 hexanes/EtOAc) $R_f = 0.63$.

Synthesis of Unsaturated Ketone 22

tert-Butyl 3-(3-oxopropyl)-1H-indole-1-carboxylate (S2): A flame-dried, 50 mL round-bottomed flask was charged with 3-(1*H*-indol-3-yl)propanal⁴⁶ (0.37 g, 2.10 mmol, 1.00 equiv), CH_2Cl_2 (14 mL), NEt_3 (0.44 mL, 3.15 mmol, 1.50 equiv), and DMAP (0.005 g, 0.21 mmol, 0.10 equiv) at rt under an atmosphere of N_2 . Boc_2O (0.55 g, 2.52 mmol, 1.20 equiv) was added in one portion, and the resulting mixture was allowed to stir until complete consumption of the starting material was observed by TLC analysis, typically 5 h. The mixture was then diluted with H_2O (10 mL) and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 ($3 \times 10\text{ mL}$). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo. The product was purified via flash chromatography (100:0 to 90:10 to 80:20 hexanes/EtOAc) to afford the protected indole **S2** (0.24 g, 42% yield) as a clear, viscous oil. Analytical data: $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 9.87 (s, 1H), 8.13 (br s, 1H), 7.51 (d, $J = 7.8\text{ Hz}$, 1H), 7.38 (br s, 1H), 7.33 (t, $J = 7.2\text{ Hz}$, 1H), 7.25 (t, $J = 7.2\text{ Hz}$, 1H), 3.04 (t, $J = 7.2\text{ Hz}$, 2H), 2.87 (t, $J = 7.8\text{ Hz}$, 2H), 1.67 (s, 9H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 201.5, 124.5, 122.6, 122.4, 119.1, 118.7, 115.3, 43.1, 28.2, 17.4; HRMS (ESI⁺) calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_3+\text{Na}$, 296.1263; found 296.1256; IR (thin film, cm^{-1}) 3446, 2977, 2916, 1731, 1670, 1636, 1455, 1373, 1256, 1158, 1018, 746; TLC (80:20 hexanes/EtOAc) $R_f = 0.53$.

tert-Butyl 3-(2-formylallyl)-1H-indole-1-carboxylate (S3): A flame-dried, 50 mL round-bottomed flask was charged with aldehyde **S2** (0.16 g, 0.60 mmol, 1.00 equiv) and CH₂Cl₂ (12 mL) at rt under an atmosphere of N₂. NEt₃ (0.84 mL, 6.00 mmol, 10.0 equiv) was added followed last by dimethylmethylenimine iodide (0.33 g, 1.8 mmol, 3.00 equiv). The mixture was allowed to stir at rt until complete conversion of the starting material was observed by TLC analysis, typically 12 h. The reaction was then concentrated on a rotary evaporator and purified via flash chromatography (95:5 to 90:10 hexanes/EtOAc) to afford unsaturated aldehyde **S3** (0.08 g, 45% yield) as a yellow, viscous oil. Analytical data: ¹H NMR (600 MHz, CDCl₃) δ 9.67 (s, 1H), 8.13 (br s, 1H), 7.42 (br s, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 8.4 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 1H), 3.65 (s, 2H), 1.67 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 194.0, 149.7, 147.9, 135.3, 130.1, 124.4, 124.1, 122.5, 119.1, 116.8, 115.3, 83.6, 28.2, 23.3; HRMS (ESI⁺) calcd for C₁₇H₁₉NO₃+Na, 308.1263; found 308.1255; IR (thin film, cm⁻¹) 3446, 2916, 1732, 1685, 1488, 1455, 1370, 1255, 1158, 1083, 959; TLC (80:20 hexanes/EtOAc) *R*_f = 0.60.

tert-Butyl 3-(2-methylene-3-oxobutyl)-1H-indole-1-carboxylate (22): A flame-dried, 20 mL scintillation vial was charged with aldehyde **S3** (0.04 g, 0.12 mmol, 1.00 equiv) and THF (2 mL) under an atmosphere of N₂. The solution was cooled to 0 °C, and MeMgBr (3 M in Et₂O, 0.12 mL, 0.37 mmol, 3.00 equiv) was added over a period of ~1 min. The mixture was allowed to stir until complete consumption of the starting material was observed by TLC analysis, typically 30 min. The reaction was then quenched via addition of saturated NH₄Cl_(aq) (5 mL), and the mixture was transferred to a separatory funnel. The aqueous layer was extracted with Et₂O (3 × 10 mL), and the combined organic extracts were dried with magnesium sulfate and concentrated in vacuo to give the crude alcohol, which was used in the next step without further purification.

The crude residue was dissolved in CH₂Cl₂ (2 mL) and transferred to a 20 mL scintillation vial. Dess-Martin periodinane (0.10 g, 0.25 mmol, 2.00 equiv) was added to the vial, and the resulting mixture was allowed to stir until complete consumption of the starting material was observed by TLC analysis, typically 20 min. The reaction mixture was then quenched via a 1:1 mixture of saturated NaHCO_{3(aq)} and saturated Na₂S₂O_{3(aq)} (5 mL) and allowed to stir 5 min. The mixture was then transferred to a separatory funnel, and the aqueous layer was extracted with Et₂O (3 × 5 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo. The product was purified via flash chromatography (95:5 to 90:10 hexanes/EtOAc) to afford enone **22** (0.026 g, 71% yield) as a yellow viscous oil. Analytical data: ¹H NMR (600 MHz, CDCl₃) δ 8.12 (br s, 1H), 7.41 (d, *J* = 9.0 Hz, 1H), 7.39 (br s, 1H), 7.31 (t, *J* = 9.0 Hz, 1H), 7.21 (t, *J* = 9.0 Hz, 1H), 6.10 (s, 1H), 5.72 (s, 1H), 3.67 (s, 2H), 2.39 (s, 3H), 1.67 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 199.4, 146.8, 126.5, 124.3, 124.0, 122.4, 119.2, 117.8, 115.2, 36.6, 28.2, 25.9; HRMS (ESI⁺) calcd for C₁₈H₂₁NO₃+Na, 322.1419; found 322.1411; IR (thin film, cm⁻¹) 3445, 3054, 2980, 2930, 1731, 1680, 1628, 1454, 1368, 1256, 1158, 1082; TLC (80:20 hexanes/EtOAc) *R*_f = 0.60.

Synthesis of Enol Silane 24

4-(1-(2,2,2-Trifluoroacetyl)-1H-indol-3-yl)butan-2-one (S4): A flame-dried, 100 mL round-bottomed flask was charged with TFAA (1.51 mL, 10.7 mmol, 4.00 equiv) and

CH₂Cl₂ (25 mL) under an atmosphere of N₂. 4-(1*H*-Indol-3-yl)butan-2-one⁴⁷ (0.50 g, 2.67 mmol, 1.00 equiv) was dissolved in CH₂Cl₂ (2 mL) and added dropwise to the TFAA solution. Once the addition was complete, the mixture was allowed to stir at rt until complete consumption of the starting material was observed by TLC analysis, typically 12 h. The reaction was quenched via addition of saturated NaHCO_{3(aq)} (10 mL) and transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were dried with sodium sulfate and concentrated in vacuo. The product was purified via flash chromatography (90:10 to 80:20 hexanes/EtOAc) to afford TFAprotected indole **S4** (0.54 g, 71% yield) as a pale yellow solid. Analytical data: mp 55–58 °C; ¹H NMR (600 MHz, CDCl₃) δ 8.43 (d, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.42 (m, 2H), 7.25 (br s, 1H), 2.99 (t, *J* = 7.8 Hz, 2H), 2.87 (t, *J* = 7.8 Hz, 2H), 2.20 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 207.0, 136.2, 130.5, 126.4, 125.5, 125.2, 120.3, 120.2, 119.2, 117.0, 42.2, 30.0, 18.6; HRMS (ESI⁺) calcd for C₁₄H₁₂F₃NO₂+Na, 306.0718; found 306.0709; IR (thin film, cm⁻¹) 2917, 1717, 1459, 1419, 1292, 1207, 1155, 880; TLC (80:20 hexanes/ EtOAc) *R*_f = 0.48.

2,2,2-Trifluoro-1-(3-(3-((trimethylsilyloxy)but-2-en-1-yl)-1Hindol-1-yl)ethan-1-one

(24): A flame-dried, 20 mL scintillation vial was charged with ketone **S4** (0.05 g, 0.267 mmol, 1.00 equiv) and CH₂Cl₂ (3 mL) under an atmosphere of N₂. The mixture was cooled to –10 °C, and HMDS (0.17 mL, 0.801 mmol, 3.00 equiv) was added followed by TMSI (0.02 mL, 0.267 mmol, 1.00 equiv) dropwise. The reaction mixture was warmed to rt and stirred until TLC analysis confirmed complete consumption of the starting material, typically 45 min. The reaction mixture was then quenched via addition of saturated NaHCO_{3(aq)} (5 mL) and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (3 × 5 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo to afford the crude enol silane as a ~3:1 mixture of alkene isomers as determined by ¹H NMR analysis. This material was unstable to further purification and was used directly in reaction screenings. The crude ¹H NMR spectrum is included in the Supporting Information.

tert-Butyl 3-(3-Methylbut-2-en-1-yl)-1H-indole-1-carboxylate (25): A flame-dried, 20 mL scintillation vial was charged with 3-(3-methylbut-2-en-1-yl)-1*H*-indole⁴⁸ (0.05 g, 0.27 mmol, 1.00 equiv), NEt₃ (0.06 mL, 0.41 mmol, 1.50 equiv), DMAP (0.003 g, 0.027 mmol, 0.10 equiv), and CH₂Cl₂ (3 mL) at rt under an atmosphere of N₂. Boc₂O (0.07 mL, 0.32 mmol, 1.20 equiv) was added, and the mixture was allowed to stir at rt until TLC analysis confirmed complete consumption of the starting material, typically 12 h. The mixture was diluted with H₂O (5 mL) and transferred to a separatory funnel. The aqueous layer was extracted with CH₂Cl₂ (3 × 5 mL), and the combined organic extracts were washed with H₂O (5 mL), dried with sodium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (100:0 to 98:2 hexanes/EtOAc) to afford protected indole **25** (0.06 g, 73% yield) as a yellow viscous oil. Analytical data: ¹H NMR (600 MHz, CDCl₃) δ 8.11 (d, *J* = 9.0 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.35–7.31 (m, 2H), 7.25 (t, *J* = 7.8 Hz, 1H), 5.41 (t, *J* = 7.2 Hz, 1H), 3.39 (d, *J* = 7.2 Hz, 2H), 1.78 (br s, 6H), 1.68 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 133.0, 124.2, 123.1, 122.3, 122.2, 121.5, 120.6, 120.5, 119.1, 115.2, 107.1, 28.2, 25.7, 23.9, 17.8; HRMS (ESI⁺) calcd for C₁₈H₂₃NO₂+Na, 308.1626; found

308.1619; IR (thin film, cm^{-1}) 3421, 3053, 2980, 2931, 1730, 1454, 1371, 1265, 1158, 855; TLC (80:20 hexanes/EtOAc) $R_f = 0.95$.

Dimethyl 2-(2-(1-Methyl-2,6-dioxocyclohexyl)ethyl)-6-(prop-1-en-2-yl)dihydro-2H-pyran-3,3(4H)-dicarboxylate (29): A flame-dried, 20 mL scintillation vial was charged with iodide **27** (0.60 g, 1.51 mmol, 1.00 equiv), 2-methyl-1,3-cyclohexanedione (0.27 g, 2.12 mmol, 1.4 equiv), and DMF (3 mL) at rt under an atmosphere of N_2 . Cs_2CO_3 (0.74 g, 2.27 mmol, 1.50 equiv) was added, and the mixture was warmed to 65 °C. The reaction was allowed to stir at this temperature until complete consumption of the starting material was observed by TLC analysis, typically 5 h. The reaction mixture was cooled to rt, diluted with H_2O (6 mL) and Et_2O (5 mL), and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic extracts were washed with brine (10 mL), dried with magnesium sulfate, and concentrated in vacuo. The mixture was purified via flash chromatography (70:30 to 60:40 to 50:50 hexanes/ EtOAc) to afford diketone **29** (0.20 g, 34% yield) as a clear, viscous oil and enol ether **30** (0.34 g, 56% yield) as a clear, viscous oil. Analytical data: O-alkylation product **30**: ^1H NMR (600 MHz, CDCl_3) δ 4.90 (s, 1H), 4.79 (s, 1H), 4.09 (m, 2H), 3.92 (d, $J = 10.8$ Hz, 1H), 3.77 (d, $J = 11.4$ Hz, 1H), 3.74 (s, 3H), 3.69 (s, 3H), 2.55–2.51 (m, 3H), 2.31 (t, $J = 6.6$ Hz, 2H), 2.21 (m, 1H), 2.09 (m, 1H), 1.96–1.90 (m, 3H), 1.79 (m, 1H), 1.70 (s, 3H), 1.68 (s, 3H), 1.66 (m, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ 198.8, 171.5, 110.9, 169.3, 144.8, 115.0, 110.8, 81.3, 77.1, 64.6, 56.4, 52.6, 52.1, 36.2, 32.7, 31.9, 26.4, 25.3, 20.9, 18.8, 7.3; HRMS (ESI⁺) calcd for $\text{C}_{21}\text{H}_{30}\text{O}_7 + \text{Na}$, 417.1889; found 417.1879; IR (thin film, cm^{-1}) 2953, 1731, 1635, 1455, 1377, 1355, 1262, 1095, 921; TLC (75:25 hexanes/ EtOAc) $R_f = 0.10$. C-alkylation product **29**: ^1H NMR (600 MHz, CDCl_3) δ 4.90 (s, 1H), 4.79 (s, 1H), 3.73–3.70 (m, 4H), 3.68 (s, 3H), 3.61 (m, 1H), 2.76 (m, 2H), 2.56–2.48 (m, 3H), 2.12 (m, 1H), 2.04 (m, 1H), 1.85–1.74 (m, 4H), 1.69 (s, 3H), 1.63 (m, 1H), 1.59 (m, 2H), 1.18 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 210.0, 209.8, 171.3, 169.2, 145.0, 110.6, 81.1, 80.9, 66.1, 56.2, 52.5, 52.0, 37.5, 35.5, 32.0, 27.6, 26.4, 18.8, 17.8, 17.0; HRMS (ESI⁺) calcd for $\text{C}_{21}\text{H}_{30}\text{O}_7 + \text{Na}$, 417.1889; found 417.1879; IR (thin film, cm^{-1}) 3403, 3057, 2954, 2872, 1729, 1696, 1455, 1266, 1084, 905; TLC (75:25 hexanes/EtOAc) $R_f = 0.13$.

Methyl 10a-Hydroxy-6a-methyl-7-oxo-3-(prop-1-en-2-yl)-decahydro-1H-benzof[chromene-10b(4aH)-carboxylate (32): A 5 mL dram vial was charged with diketone **29** (0.015 g, 0.04 mmol, 1.00 equiv) and DMSO (2 mL), and NaCl (0.02 g, 0.38 mmol, 10.0 equiv) was added in one portion. The vial was sealed with a screw-cap, and the mixture was warmed to 150 °C and stirred 9 h. The mixture was cooled to rt, diluted with Et_2O (2 mL), and transferred to a separatory funnel containing H_2O (10 mL). The aqueous layer was extracted with Et_2O (3×5 mL), and the combined organic extracts were washed with brine (5 mL), dried with magnesium sulfate, and concentrated in vacuo. Crude ^1H NMR analysis revealed a ~1:1 mixture of the diastereomeric decarboxylation product **31** and annulation product **32**. This mixture was purified via flash chromatography (70:30 to 60:40 hexanes/EtOAc) to afford annulation product **32** (0.006 g, 47% yield) as a clear, viscous oil and Krapcho adduct **31** (0.005 g, 39% yield) as a clear, viscous oil. Slow evaporation of **32** from acetone and hexanes provided crystals suitable for X-ray crystallographic analysis. (Note: when this reaction was conducted on 0.07 g, scale, only the Krapcho adduct **31** was

isolated in 43% yield. No cyclization product **32** was detected on this scale.) Analytical data: Decarboxylation product **31**: ^1H NMR (600 MHz, CDCl_3) δ 4.94 (s, 2H), 4.82–4.81 (m, 2H), 3.73–3.70 (m, 2H), 3.68–6.67 (m, 3H), 3.47–3.41 (m, 2H), 2.80–2.69 (m, 4H), 2.60–2.54 (m, 4H), 2.24 (m, 1H), 2.14–2.12 (m, 2H), 2.07–1.98 (m, 5H), 1.85–1.77 (m, 3H), 1.74–1.73 (m, 5H), 1.51–1.39 (m, 5H), 1.21 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 210.3, 210.1, 210.0, 209.9, 174.3, 172.8, 145.8, 145.5, 110.6, 110.2, 81.5, 80.0, 78.0, 77.3, 66.1, 65.5, 51.7, 51.3, 46.7, 37.8, 37.7, 37.5, 34.0, 33.5, 29.7, 29.1, 28.9, 28.8, 27.7, 26.2, 25.7, 19.0, 18.8, 18.3, 17.9, 17.7, 16.4; HRMS (ESI⁺) calcd for $\text{C}_{19}\text{H}_{28}\text{O}_5+\text{Na}$, 359.1834; found 359.1825; IR (thin film, cm^{-1}) 3446, 2917, 2849, 1731, 1652, 1540, 1456, 1200, 901; TLC (75:25 hexanes/EtOAc) R_f = 0.17. Annulation product **32**: ^1H NMR (600 MHz, CDCl_3) δ 4.91 (s, 1H), 4.78 (s, 1H), 3.86 (d, J = 12.0 Hz, 1H), 3.66 (dd, J = 7.8, 4.8 Hz, 1H), 3.59 (s, 3H), 2.47 (m, 2H), 2.31 (m, 2H), 2.16 (dd, J = 10.8, 6.0 Hz, 1H), 2.10–2.00 (m, 3H), 1.77 (m, 2H), 1.68 (s, 3H), 1.62 (m, 1H), 1.52 (br s, 1H), 1.45 (m, 1H), 1.35 (m, 1H), 1.18 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 210.0, 172.5, 145.7, 110.9, 82.0, 80.0, 78.2, 53.5, 53.2, 50.5, 34.1, 29.1, 28.1, 27.5, 26.9, 25.9, 25.4, 18.4, 18.1; HRMS (ESI⁺) calcd for $\text{C}_{19}\text{H}_{28}\text{O}_5+\text{Na}$, 359.1834; found 359.1825; IR (thin film, cm^{-1}) 3446, 3055, 2950, 1718, 1456, 1339, 1265, 1073, 899; TLC (75:25 hexanes/EtOAc) R_f = 0.07.

2-Methyl-3-((4-methylpent-3-en-1-yl)oxy)cyclohex-2-en-1-one (38): A flame-dried, 25 mL round-bottomed flask was charged with 2-methyl-1,3-cyclohexanedione (1.00 g, 7.93 mmol, 100 equiv) and DMF (8 mL) under an atmosphere of N_2 . The mixture was cooled to 0 °C, and NaH (60% dispersion in oil, 0.39 g, 10.3 mmol, 1.30 equiv) was added portionwise. The mixture was warmed to rt and stirred 10 min, whereupon the iodide **37** (2.16 g, 10.3 mmol, 1.30 equiv) was added. The mixture was allowed to stir 12 h, and the reaction mixture was poured into a separatory funnel containing H_2O (20 mL). CH_2Cl_2 (20 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried with magnesium sulfate, and concentrated in vacuo. The products were purified via flash chromatography (90:10 to 80:20 to 60:40 hexanes/EtOAc) to afford cycloalkanedione **35** (0.12 g, 7% yield) as a yellow oil and vinyl ether **38** (0.43 g, 26% yield) as a clear, viscous oil. Analytical data: ^1H NMR (600 MHz, CDCl_3) δ 5.11 (m, 1H), 3.93 (t, J = 6.6 Hz, 2H), 2.51 (m, 2H), 2.36 (q, J = 7.2 Hz, 2H), 2.30 (t, J = 6.6 Hz, 2H), 1.93 (m, 2H), 1.68 (s, 3H), 1.66 (t, J = 1.2 Hz, 3H), 1.61 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 198.8, 171.4, 134.8, 118.9, 115.0, 67.4, 36.2, 28.7, 25.7, 25.4, 20.9, 17.7, 7.29; HRMS (ESI⁺) calcd for $\text{C}_{13}\text{H}_{20}\text{O}_2+\text{Na}$, 231.1361; found 231.1354; IR (thin film, cm^{-1}) 3446, 2926, 1732, 1646, 1472, 1376, 1238, 1096; TLC (70:30 hexanes/EtOAc) R_f = 0.26.

(E)-3-(2,2-Dimethylhydrazono)-2-methylcyclohexan-1-one (39): A 250 mL round-bottomed flask was charged with 2-methyl-1,3-cyclohexanedione (12.0 g, 95.1 mmol, 1.00 equiv), C_6H_6 (150 mL), H_2NNMe_2 (8.70 mL, 114.2 mmol, 1.20 equiv), and TsOH (0.50 g, 2.63 mmol, 0.03 equiv). A Dean–Stark apparatus was connected to the flask, and the mixture was heated to 100 °C with vigorous stirring for 6 h. The mixture was cooled to rt and concentrated on a rotary evaporator. The crude residue was then recrystallized from C_7H_8 to afford ketohydrazone **39** (16.00 g, 99% yield) as a yellow powder. Analytical data for this compound matched that reported in the literature:²⁴ ^1H NMR (600 MHz, CDCl_3) δ

5.05 (br s, 1H), 2.64 (m, 2H), 2.53 (s, 6H), 2.32 (t, $J = 7.2$ Hz, 2H), 1.90 (m, 2H), 1.66 (s, 3H).

2-Methyl-2-(4-methylpent-3-en-1-yl)cyclohexane-1,3-dione(35): A flame-dried, 500 mL round-bottomed flask was charged with THF (250 mL) under an atmosphere of N_2 . KH (10.40 g, 30% dispersion in oil, 78.50 mmol, 1.20 equiv) was washed free of oil three times with petroleum ether, suspended in THF (20 mL), and added to the flask with stirring. The reaction mixture was cooled to -78 °C, and a solution of ketohydrazone **39** (11.00 g, 65.42 mmol, 1.00 equiv) in THF (25 mL) was slowly added. The reaction was warmed to 0 °C and allowed to stir 4.5 h. The resulting dark-brown mixture was recooled to -78 °C, and iodide **S2** (17.3 g, 78.50 mmol, 1.20 equiv) was added. The reaction mixture was allowed to stir while slowly warming to rt overnight, producing a cream-white suspension. The reaction was then quenched with saturated $NH_4Cl_{(aq)}$ (50 mL), and the resulting mixture was partitioned in a separatory funnel. The aqueous layer was extracted with Et_2O (3×50 mL), and the combined organic extracts were washed with brine (40 mL), dried with magnesium sulfate, and concentrated in vacuo to give the intermediate alkylation product, which was used in the next step without further purification.

$Cu(OAc)_2 \cdot H_2O$ (26.00 g, 130.9 mmol, 2.00 equiv) was dissolved in H_2O (300 mL) in a 1000 mL round-bottomed flask with vigorous stirring. The crude hydrazone was then dissolved in THF (300 mL) and added to the $Cu(OAc)_2 \cdot H_2O$ solution, and the reaction mixture was allowed to stir until TLC analysis confirmed complete conversion of the starting material, typically 12 h. The resulting mixture was concentrated on a rotary evaporator to remove the THF, and the solution was then diluted with saturated $NH_4Cl_{(aq)}$ (100 mL) and CH_2Cl_2 (100 mL). This mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were washed with brine (2×50 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (90:10 to 80:20 hexanes/ $EtOAc$) to afford diketone **35** (10.34 g, 76% yield) as an orange, viscous oil. Analytical data: 1H NMR (600 MHz, $CDCl_3$) δ 4.99 (br s, 1H), 2.70 (m, 2H), 2.60 (m, 2H), 2.01 (m, 1H), 1.86–1.80 (m, 5H), 1.64 (s, 3H), 1.55 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 210.3, 132.9, 122.9, 65.6, 37.9, 37.5, 25.6, 23.3, 18.9, 17.7, 17.6; HRMS (ESI⁺) calcd for $C_{13}H_{20}O_2 + H$, 209.1542; found 209.1537; IR (thin film, cm^{-1}) 3400, 2967, 2929, 1725, 1695, 1602, 1451, 1280, 1169, 1026; TLC (80:20 hexanes/ $EtOAc$) $R_f = 0.40$.

3-Hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)cyclohexan-1-one (40): A 20 mL scintillation vial was charged with diketone **35** (0.1 g, 0.48 mmol, 1.00 equiv) and MeOH (10 mL), and the solution was cooled to 0 °C. $NaBH_4$ (0.005 g, 0.12 mmol, 0.25 equiv) was added, and the mixture was allowed to stir at this temperature until complete consumption of the starting material was observed by TLC analysis, typically 10 min. The reaction was diluted with brine (5 mL) and CH_2Cl_2 (5 mL), and the mixture was transferred to a separatory funnel. The aqueous layer was extracted with CH_2Cl_2 (3×5 mL), and the combined organic extracts were dried with sodium sulfate and concentrated in vacuo to give the crude alcohol as a 19.4:1 mixture of diastereomers. The diastereomeric ratio was determined by 1H NMR spectroscopic analysis of the crude reaction mixture by comparison

of the integration of the resonances at δ 1.14 (major diastereomer) and δ 1.09 (minor diastereomer). The product was purified via flash chromatography (80:20 to 70:30 hexanes/EtOAc) to afford hydroxyketone **40** (0.093 g, 93% yield) as a clear, viscous oil. Analytical data: ^1H NMR (600 MHz, CDCl_3) δ 5.05 (t, $J = 6.0$ Hz, 1H), 3.65 (d, $J = 7.8$ Hz, 1H), 2.39 (m, 1H), 2.32 (m, 1H), 1.99–1.88 (m, 5H), 1.73 (m, 1H), 1.66–1.63 (m, 4H), 1.55 (br s, 4H), 1.15 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 214.1, 132.1, 123.9, 77.5, 54.7, 37.6, 31.5, 28.7, 25.6, 21.9, 20.7, 18.7, 17.6; HRMS (ESI⁺) calcd for $\text{C}_{13}\text{H}_{22}\text{O}_2+\text{Na}$, 233.1518; found 233.1510; IR (thin film, cm^{-1}) 3420, 2939, 2871, 1698, 1455, 1375, 1161, 1059, 993, 831; TLC (70:30 hexanes/EtOAc) $R_f = 0.32$.

(2R,3S)-3-Hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)-cyclohexan-1-one (36): A 1000 mL round-bottomed flask was charged with H_2O (320 mL), and YSC-2 (77 g, purchased from Sigma-Aldrich) was added portionwise with vigorous stirring. Diketone **35** (2.00 g, 9.60 mmol, 1.00 equiv) was dissolved in DMSO (32 mL) and added to the YSC-2 suspension, and the mixture was warmed to 30 °C and vigorously stirred for 24 h. The reaction mixture was then cooled to rt, diluted with Et_2O (50 mL), and Celite (10 g) was added. The stirring was stopped, and the mixture was allowed to let stand at rt for 12 h. The resulting mixture was then filtered through a pad of Celite in a Buchner funnel. Once the filter cake was dry, the Celite pad was then washed with Et_2O (100 mL), CH_2Cl_2 (100 mL), acetone (100 mL), Et_2O (100 mL), and EtOAc (100 mL), ensuring that the filter cake was loosened with a spatula between each wash. The filtrate was transferred to a separatory funnel, and the organic layer was separated. The aqueous layer was extracted with EtOAc (50 mL), and the combined organic extracts were dried with sodium sulfate and concentrated in vacuo, giving crude alcohol **36** as a 10:1 mixture of diastereomers. The diastereomeric ratio was determined by ^1H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 1.15 (minor diastereomer) and δ 1.10 (major diastereomer). The product was purified via flash chromatography (80:20 to 70:30 hexanes/EtOAc) to afford alcohol **36** (1.32 g, 67% yield) as a yellow, viscous oil. (Note: for purposes of material throughput, the crude residue may be stored indefinitely with no deleterious effects to yield. In practice, up to 8 iterations of this procedure were carried out, and the crude residues were combined and purified simultaneously.) The enantioselectivity (>99:1) was determined via ^{19}F NMR analysis of the resulting Mosher ester **S8** (vide infra). Analytical data: $[\alpha]_{\text{D}}^{28} -74.7$ ($c = 0.30$, CHCl_3); ^1H NMR (600 MHz, CDCl_3) δ 5.04 (m, 1H), 3.89 (dd, $J = 3.0, 2.4$ Hz, 1H), 2.41 (m, 1H), 2.31 (m, 1H), 2.08 (m, 1H), 2.02 (m, 1H), 1.93 (m, 1H), 1.87–1.79 (m, 4H), 1.65 (br s, 4H), 1.56 (s, 3H), 1.53 (m, 1H), 1.10 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 214.4, 132.2, 123.7, 76.3, 54.3, 37.8, 36.2, 28.1, 25.6, 22.6, 20.7, 17.6, 17.3; HRMS (ESI⁺) calcd for $\text{C}_{13}\text{H}_{22}\text{O}_2+\text{Na}$, 233.1518; found 233.1514; IR (thin film, cm^{-1}) 3434, 3054, 2985, 2305, 1703, 1630, 1442, 1265, 738; TLC (80:20 hexanes/EtOAc) $R_f = 0.23$.

(1S,2R)-2-Methyl-2-(4-methylpent-3-en-1-yl)-3-oxocyclohexyl-(R)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (Mosher Ester of 36): A flame-dried, 20 mL scintillation vial was charged with (*R*)-(+)- α -methoxy- α -trifluoromethylphenylacetic acid (0.45 g, 1.90 mmol, 2.00 equiv) and CH_2Cl_2 (8 mL) with magnetic stirring at rt under an atmosphere of N_2 . DCC (0.39 g, 1.90 mmol, 2.00 equiv) was added followed by DMAP (0.01 g, 0.10

mmol, 0.10 equiv) and a 10:1 diastereomeric mixture of alcohol **36** (0.20 g, 0.95 mmol, 1.00 equiv) in CH₂Cl₂ (2 mL). The reaction mixture was allowed to stir at rt until complete conversion of the starting material was observed by TLC analysis, typically 12 h. The resulting mixture was filtered through cotton and concentrated in vacuo. The product was purified via flash chromatography (95:5 to 90:10 hexanes/EtOAc) to provide the Mosher ester (0.40 g, 99% yield) as an inseparable 10:1 mixture of diastereomers (as determined by integration of the resonances at δ 5.33 (major diastereomer) and δ 5.06 (minor diastereomer)). ¹⁹F NMR analysis revealed only a 10:1 mixture of diastereomers at δ -71.1 ppm (minor diastereomer) and δ -71.2 ppm (major diastereomer). Analytical data: [α]_D²⁸ +22.6 (*c* = 0.50, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 7.50 (m, 2H), 7.39 (m, 3H), 5.33 (dd, *J* = 3.0, 3.0 Hz, 1H), 3.50 (s, 3H), 2.45 (m, 1H), 2.35 (m, 1H), 2.22 (m, 1H), 1.96–1.74 (m, 5H), 1.66 (s, 3H), 1.57 (s, 3H), 1.54 (m, 2H), 0.96 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 211.5, 165.8, 132.5, 131.9, 129.6, 128.4, 127.2, 123.2, 80.3, 55.3, 52.6, 37.4, 35.9, 25.6, 25.5, 22.4, 20.4, 17.8, 17.6; HRMS (ESI⁺) calcd for C₂₃H₂₉F₃O₄+Na, 449.1916; found 449.1923; IR (thin film, cm⁻¹) 3423, 2949, 2855, 1746, 1713, 1451, 1270, 1168, 1019, 807, 721; TLC (80:20 hexanes/ EtOAc) *R*_f = 0.51.

(2R,3S)-2-(2-(3,3-Dimethyloxiran-2-yl)ethyl)-3-hydroxy-2-methylcyclohexan-1-one (41): A 20 mL scintillation vial was charged with hydroxyketone **36** (0.10 g, 0.48 mmol, 1.00 equiv) and CH₂Cl₂ (5 mL), and the mixture was cooled to 0 °C. *m*-CPBA (70% dispersion in H₂O, 0.19 g, 0.76 mmol, 1.60 equiv) was added in one portion, and the mixture was stirred until complete consumption of the starting material was observed by TLC analysis, typically 20 min. The reaction was quenched via saturated Na₂S₂O₃ (5 mL), and the mixture was transferred to a separatory funnel. The aqueous layer was extracted with CH₂Cl₂ (3 × 5 mL), and the combined organic extracts were dried with sodium sulfate and concentrated in vacuo to give the crude epoxide as a 2:1 mixture of diastereomers. The diastereomeric ratio was determined by ¹H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 1.13 (major diastereomer) and δ 1.12 (minor diastereomer). The product was purified via flash chromatography (60:40 to 50:50 to 40:60 hexanes/EtOAc) to afford epoxide **41** (0.10 g, 93% yield) as a clear oil in an inseparable mixture of diastereomers. Analytical data: [α]_D²⁵ +1.9 (*c* = 1.25, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 3.83 (dd, *J* = 4.2, 3.0 Hz, 1H), 2.68 (m, 1H), 2.33 (m, 2H), 2.01 (m, 2H), 1.84–1.54 (m, 5H), 1.48–1.40 (m, 1H), 1.27 (m, 3H), 1.23 (m, 3H), 1.09 (m, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 214.2, 214.1, 75.6, 74.4, 64.7, 64.3, 59.1, 58.7, 54.3, 54.0, 37.6, 37.5, 32.0, 31.7, 28.4, 28.3, 24.8, 23.6, 23.5, 20.4, 20.3, 18.6, 18.5, 18.0, 17.1; HRMS (ESI⁺) calcd for C₁₃H₂₂O₃+Na, 249.1467; found 249.1459; IR (thin film, cm⁻¹) 3446, 3054, 2982, 2874, 1732, 1702, 1497, 1422, 1266, 1156, 1016, 895; TLC (80:20 hexanes/EtOAc) *R*_f = 0.07.

(4aR,8aS)-2-(2-Hydroxypropan-2-yl)-4a-methyloctahydro-5Hchromen-5-one (42) and (4aR,5S)-2-(2-hydroxypropan-2-yl)-4amethyloctahydro-2H-chromen-5-ol (43): A 20 mL scintillation vial was charged with keto-epoxide **41** (0.05 g, 0.22 mmol, 1.00 equiv) and CH₂Cl₂ (2 mL), and PPTS (0.01 g, 0.04 mmol, 0.20 equiv) was added. The mixture was allowed to stir at rt until TLC analysis indicated complete consumption of the starting material, typically 30 min. The reaction mixture was diluted with saturated NaHCO_{3(aq)} (5

mL) and transferred to a separatory funnel. The aqueous layer was extracted with CH₂Cl₂ (3 × 5 mL), and the combined organic extracts were dried with sodium sulfate and concentrated in vacuo. Crude ¹H NMR analysis revealed an inseparable ~1:5 mixture of diastereomeric tetrahydropyrans **42** and diastereomeric vinyl ethers **43**. The crude ¹H NMR spectrum is included in the Supporting Information: HRMS (ESI⁺) calcd for +Na, 249.1467; found 249.1459.

N'-(2S,3S,E)-3-Hydroxy-2-methyl-2-(4-methylpent-3-en-1-yl)-cyclohexylidene)-4-

methylbenzenesulfonylhydrazide (44): The alcohol **40** (8.20 g, 38.99 mmol, 1.00 equiv) was dissolved in wet C₇H₈ (195 mL) in a 500 mL round-bottomed flask, and *p*-toluenesulfonylhydrazine (8.71 g, 46.79 mmol, 1.20 equiv) was added with magnetic stirring. The mixture was placed in a preheated oil bath at 70 °C and allowed to stir for 50 min. (Note: product decomposition was observed if the reaction was allowed to stir for longer than this time period.) The resulting mixture was cooled to rt and concentrated on a rotary evaporator. The product was purified via flash chromatography (70:30 to 60:40 to 50:50 hexanes/EtOAc) to provide the hydrazone **44** (14.75 g, > 99% yield) as a pale yellow, viscous foam. Analytical data: [α]_D²⁸ -144.6 (*c* = 0.50, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 7.82 (d, *J* = 8.4 Hz, 2H), 7.64 (br s, 1H), 7.28 (d, *J* = 7.8 Hz, 2H), 4.93 (t, *J* = 6.6 Hz, 1H), 3.63 (dd, *J* = 3.0, 2.4 Hz, 1H), 2.39 (s, 3H), 2.35 (m, 1H), 2.00 (m, 1H), 1.90 (m, 1H), 1.75–1.66 (m, 3H), 1.64 (s, 3H), 1.57–1.49 (m, 2H), 1.46 (s, 3H), 1.37 (m, 2H), 1.04 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 163.3, 143.9, 135.1, 131.5, 129.3, 128.2, 124.1, 75.4, 47.6, 36.5, 25.6, 22.0, 21.5, 19.8, 19.1, 17.5; HRMS (ESI⁺) calcd for C₂₀H₃₀N₂O₃S+Na, 401.1875; found 401.1892; IR (thin film, cm⁻¹) 3516, 3212, 2933, 2872, 1914, 1725, 1598, 1447, 1329, 1185, 1165, 1091, 736; TLC (80:20 hexanes/EtOAc) *R*_f = 0.17.

N'-(2S,4aS,8aS,E)-2-(2-Hydroxypropan-2-yl)-4a-methyloctahydro-5H-chromen-5-

ylidene)-4-methylbenzenesulfonylhydrazide(45): Hydrazone **44** (14.76 g, 38.99 mmol, 1.00 equiv) was dissolved in CH₂Cl₂ (320 mL) in a 1000 mL round-bottomed flask with stirring. The mixture was cooled to 0 °C, and *m*-CPBA (14.42 g, 70% dispersion in H₂O, 58.49 mmol, 1.50 equiv) was added. The reaction was allowed to stir at this temperature until TLC analysis showed full conversion of the starting material, typically 10 min. The reaction was quenched via addition of saturated Na₂S₂O_{3(aq)} (70 mL), and the mixture was partitioned in a separatory funnel. The mixture was extracted with CH₂Cl₂ (3 × 50 mL), and the combined organic extracts were washed with brine (50 mL), dried with magnesium sulfate, and concentrated to a volume of ~300 mL on a rotary evaporator. A stir bar was added followed by PPTS (0.98 g, 3.90 mmol, 0.10 equiv), and the mixture was allowed to stir 12 h at rt. The reaction mixture was then concentrated in vacuo to give the crude tetrahydropyran **45** as a single diastereomer (as determined by ¹H NMR spectroscopic analysis of the crude reaction mixture, which revealed a single stereoisomer). The product was purified via flash chromatography (60:40 to 50:50 to 40:60 hexanes/EtOAc) to afford pyran **45** (11.63 g, 76% yield) as a pale yellow, viscous foam. Analytical data: [α]_D²⁸ -63.2 (*c* = 0.40, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 7.82 (d, *J* = 7.8 Hz, 2H), 7.73 (br s, 1H), 7.30 (d, *J* = 7.8 Hz, 2H), 3.11 (t, *J* = 3.6 Hz, 1H), 3.09 (t, *J* = 2.4 Hz, 1H), 2.52 (dd, *J* = 12.0, 3.0 Hz, 1H), 2.45–2.40 (m, 4H), 1.94 (m, 1H), 1.82 (m, 2H), 1.67 (m, 2H), 1.59–1.50 (m, 3H), 1.33–1.26 (m, 2H), 1.15 (s, 3H), 1.14 (s, 3H), 0.96 (s, 3H); ¹³C NMR (150 MHz,

CDCl₃) δ 164.5, 143.9, 135.1, 129.3, 128.1, 84.5, 82.0, 71.8, 42.4, 32.1, 26.3, 21.6, 17.2; HRMS (ESI⁺) calcd for C₂₀H₃₀N₂O₄S+Na, 417.1824; found 417.1840; IR (thin film, cm⁻¹) 3451, 3216, 2946, 2870, 1630, 1598, 1450, 1333, 1166, 1089, 925; TLC (80:20 hexanes/EtOAc) *R_f* = 0.11.

N'-((2S,3S,E)-3-Hydroxy-2-methyl-2-(4-methylpentyl)-cyclohexylidene)-4-

methylbenzenesulfonylhydrazide (46): A 20 mL scintillation vial was charged with alkene **44** (0.05 g, 0.13 mmol, 1.00 equiv) and MeOH (4 mL). Pd/C (0.025 g, 0.50 mass equiv) was added, and the resulting suspension was placed under 1 atm H₂ (balloon) and allowed to stir 1 h, whereupon TLC analysis indicated complete consumption of the starting material. The suspension was filtered through a pad of Celite and concentrated on a rotary evaporator to afford hydrazone **46** (0.05 g, > 99% crude yield) as a single diastereomer (as determined by ¹H NMR analysis of the crude mixture, which revealed a single stereoisomer). When this material was subjected to the reaction conditions used in the conversion of **44** to **45**, no reaction was observed, and the starting material was recovered quantitatively. Analytical data: [*a*]_D²⁸ -51.9 (*c* = 1.25, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 7.83 (d, *J* = 8.2 Hz, 2H), 7.65 (br s, 1H), 7.28 (d, *J* = 7.8 Hz, 2H), 3.63 (dd, *J* = 3.0, 1.8 Hz, 1H), 2.40 (s, 3H), 2.36 (m, 1H), 1.93 (m, 2H), 1.79–1.64 (m, 3H), 1.56 (m, 1H), 1.46 (m, 1H), 1.34 (m, 1H), 1.27 (m, 1H), 1.02 (s, 3H), 1.00–0.98 (m, 3H), 0.77 (d, *J* = 6.6 Hz, 3H), 0.76 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 163.5, 143.8, 135.2, 129.3, 128.2, 75.6, 47.6, 39.5, 36.8, 27.7, 27.6, 22.6, 22.5, 21.5, 21.1, 19.7, 19.2; HRMS (ESI⁺) calcd for C₂₀H₃₂N₂O₃S +Na, 403.2031; found 403.2022; IR (thin film, cm⁻¹) 3503, 3214, 2951, 2868, 1670, 1470, 1329, 1165, 1092, 1001, 924; TLC (80:20 hexanes/EtOAc) *R_f* = 0.07.

N'-((2S,4aS,8aS,E)-2-(2-((tert-Butyldimethylsilyloxy)propan-2-yl)-4a-

methyloctahydro-5H-chromen-5-ylidene)-4-methylbenzenesulfonylhydrazide(49): A flame-dried, 150 mL round-bottomed flask was charged with pyran **45** (9.41 g, 23.88 mmol, 1.00 equiv) and CH₂Cl₂ (120 mL) under an atmosphere of N₂. The reaction mixture was cooled to -50 °C (CO₂(s)/acetonitrile bath), and 2,6-lutidine (5.50 mL, 47.46 mmol, 2.00 equiv) and TBSOTf (9.87 mL, 42.99 mmol, 1.8 equiv) were added sequentially. The reaction was allowed to stir at this temperature until TLC analysis confirmed complete consumption of the starting material, typically 30 min. The reaction was quenched via addition of saturated NaHCO₃(aq) (40 mL), and the mixture was warmed to rt and partitioned in a separatory funnel. The aqueous layer was extracted with EtOAc (3 × 30 mL), and the combined organic extracts were washed with brine (40 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (100:0 to 95:5 to 90:10 to 80:20 hexanes/EtOAc) to remove silanol byproducts then purified a second time (90:10 to 80:20 hexanes/EtOAc) to afford silyl ether **49** (9.46 g, 79% yield) as a pale yellow, viscous foam. Analytical data: [*a*]_D²⁸ -75.5 (*c* = 0.35, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 7.84 (d, *J* = 8.4 Hz, 2H), 7.57 (br s, 1H), 7.31 (d, *J* = 7.8 Hz, 2H), 3.04 (dd, *J* = 7.8, 3.6 Hz, 1H), 2.99 (d, *J* = 11.4 Hz, 1H), 2.50 (d, *J* = 14.4 Hz, 1H), 2.43 (s, 3H), 1.93 (m, 1H), 1.83–1.76 (m, 2H), 1.68–1.50 (m, 6H), 1.19 (s, 3H), 1.15 (s, 3H), 0.95 (s, 3H), 0.84 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 165.0, 143.8, 135.2, 129.3, 128.1, 85.3, 82.0, 76.8, 74.7, 42.5, 32.4, 27.2, 25.1, 21.6, 21.3, 17.3, -2.1, -2.2; HRMS (ESI⁺) calcd for C₂₆H₄₄N₂O₄SSi+Na, 531.2689; found

531.2704; IR (thin film, cm^{-1}) 3433, 3054, 2985, 2855, 2305, 1630, 1422, 1167, 1092, 835, 739; TLC (80:20 hexanes/EtOAc) R_f = 0.37.

(2S,4aS,8aS)-2-(2-((tert-Butyldimethylsilyloxy)propan-2-yl)-4a-methyl-3,4,4a,7,8,8a-hexahydro-2H-chromene-5-carbaldehyde (50): A flame-dried, 100 mL round-bottomed flask was charged with hydrazone **49** (2.00 g, 3.93 mmol, 1.00 equiv) and THF (39 mL) under an atmosphere of N_2 . The mixture was cooled to $-50\text{ }^\circ\text{C}$, and $^n\text{BuLi}$ (1.64 M in hexane, 12.0 mL, 19.7 mmol, 5.00 equiv) was added dropwise, producing a dark orange color. The mixture was allowed to stir 30 min at $-50\text{ }^\circ\text{C}$. The flask was fitted with a venting needle, and the mixture was warmed to $0\text{ }^\circ\text{C}$ and stirred 5 min, then warmed to rt and stirred until complete consumption of the starting material was observed by TLC analysis, typically 20 min (scale dependent). The venting needle was removed, and DMF (3.02 mL, 39.3 mmol, 10.0 equiv) was added. Following this addition, the reaction was stirred 20 min, diluted with H_2O (20 mL) and Et_2O (20 mL) and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et_2O ($3 \times 20\text{ mL}$). The combined organic extracts were washed with brine (20 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (100:0 to 95:5 to 90:10 hexanes/EtOAc) to afford unsaturated aldehyde **50** (0.92 g, 66% yield) as a yellow, viscous oil. Analytical data: $[\alpha]_{\text{D}}^{28} -138.0$ ($c = 0.55$, CHCl_3); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 9.38 (s, 1H), 6.55 (t, $J = 3.0\text{ Hz}$, 1H), 3.22 (dd, $J = 8.4, 3.6\text{ Hz}$, 1H), 3.15 (dd, $J = 9.0, 3.0\text{ Hz}$, 1H), 2.70 (m, 1H), 2.46 (m, 2H), 1.68 (m, 2H), 1.57 (m, 2H), 1.28 (m, 1H), 1.23 (s, 3H), 1.18 (s, 3H), 1.14 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 193.8, 151.0, 148.3, 85.9, 80.9, 74.9, 35.4, 32.6, 27.2, 26.4, 25.8, 25.1, 23.2, 21.3, 17.9, -2.2 ; HRMS (ESI⁺) calcd for $\text{C}_{20}\text{H}_{36}\text{O}_3\text{Si}+\text{Na}$, 375.2331; found 375.2323; IR (thin film, cm^{-1}) 3435, 2955, 2855, 1692, 1635, 1472, 1376, 1251, 1173, 1042; TLC (90:10 hexanes/EtOAc) R_f = 0.49.

tert-Butyldimethyl-((2-((2S,4aS,8aS)-4a-methyl-5-vinyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-2-yl)propan-2-yl)oxy)silane (51): A flame-dried, 100 mL round-bottomed flask was charged with methyltriphenylphosphonium bromide (4.90 g, 13.7 mmol, 6.00 equiv) and THF (20 mL) under an atmosphere of N_2 . The mixture was cooled to $0\text{ }^\circ\text{C}$ and $^n\text{BuLi}$ (1.65 M in hexanes, 7.63 mL, 12.6 mmol, 5.50 equiv) was added dropwise. The deep yellow mixture was allowed to stir 1 h at $0\text{ }^\circ\text{C}$ upon which the aldehyde **50** (0.81 g, 2.29 mmol, 1.00 equiv) was added as a solution in THF (3 mL). The reaction was allowed to stir until complete consumption of the starting material was observed by TLC analysis, typically 15 min. The reaction was diluted with H_2O (15 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with Et_2O ($3 \times 15\text{ mL}$). The combined organic extracts were washed with brine (15 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (100:0 to 99:1 to 97.5:2.5 hexanes/EtOAc) to afford diene **51** (0.69 g, 86% yield) as a clear oil. Analytical data: $[\alpha]_{\text{D}}^{28} -167.4$ ($c = 0.35$, CHCl_3); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 6.24 (dd, $J = 10.8, 6.0\text{ Hz}$, 1H), 5.61 (t, $J = 3.6\text{ Hz}$, 1H), 5.26 (d, $J = 17.4\text{ Hz}$, 1H), 4.93 (d, $J = 10.8\text{ Hz}$, 1H), 3.23 (dd, $J = 5.4, 4.8\text{ Hz}$, 1H), 3.12 (m, 1H), 2.20 (m, 1H), 1.93 (dt, $J = 6.0, 3.0\text{ Hz}$, 1H), 1.66 (m, 2H), 1.60 (m, 2H), 1.35 (m, 1H), 1.24 (s, 3H), 1.18 (s, 3H), 1.07 (s, 3H), 0.85 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 144.5, 135.4, 121.6,

113.5, 85.5, 81.5, 74.9, 36.1, 34.3, 27.4, 25.9, 25.0, 23.8, 21.8, 18.9, 18.2, -2.1, -2.2; HRMS (ESI⁺) calcd for C₂₁H₃₈O₂Si+Na, 373.2539; found 373.2529; IR (thin film, cm⁻¹) 3053, 2985, 2956, 2854, 2685, 1716, 1636, 1456, 1265, 1143; TLC (90:10 hexanes/EtOAc) *R*_f = 0.91.

tert-Butyldimethyl-((2-((3S,4aS,10bS)-10b-methyl-7-nitro-2,3,4a,5,6,6a,7,8,9,10b-decahydro-1H-benzof[chromen-3-yl]-propan-2-yl)oxy)silane (52): A 20 mL scintillation vial was charged with diene **51** (0.66 g, 1.88 mmol, 1.00 equiv) and CH₂Cl₂ (9 mL). Nitroethylene⁴⁹ (10 M solution in CH₂Cl₂, 0.75 mL, 7.50 mmol, 4.00 equiv) was added, and the vial was sealed with a screw-cap. The mixture was heated to 65 °C and stirred until complete conversion of the starting material was observed by TLC analysis, typically 12 h. The mixture was cooled to rt and concentrated on a rotary evaporator. The product was purified via flash chromatography (100:0 to 97.5:2.5 to 95:5 to 90:10 hexanes/EtOAc) to afford alkene **52** (0.75 g, 95% yield) as a clear, viscous oil in an inseparable mixture of diastereomers. Analytical data: [*α*]_D²⁸ -4.7 (*c* = 0.75, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 5.51 (br s, 1H), 5.45 (d, *J* = 4.8 Hz, 1H), 4.79–4.66 (m, 1H), 4.32–4.20 (m, 1H), 3.45 (dd, *J* = 7.8, 3.0 Hz, 1H), 3.06–3.01 (m, 4H), 2.96–2.87 (m, 3H), 2.27–1.89 (m, 13H), 1.76–1.72 (m, 3H), 1.66–1.37 (m, 17H), 1.25 (m, 2H), 1.21–1.19 (m, 8H), 1.17–1.15 (m, 3H), 1.05–1.03 (m, 8H), 0.84 (br s, 25H), 0.07 (s, 8H), 0.05 (s, 8H); ¹³C NMR (150 MHz, CDCl₃) δ 144.8, 143.9, 143.2, 118.4, 117.9, 117.7, 90.6, 89.8, 85.6, 85.4, 85.1, 84.9, 83.4, 82.2, 74.8, 39.6, 37.5, 36.8, 36.4, 36.1, 34.4, 28.0, 27.3, 27.1, 27.0, 25.5, 25.2, 25.0, 24.4, 24.0, 23.0, 22.7, 21.9, 21.8, 21.6, 21.5, 18.1, 17.0, -2.2; HRMS (ESI⁺) calcd for C₂₃H₄₁NO₄Si+Na, 446.2703; found 446.2692; IR (thin film, cm⁻¹) 3054, 2954, 2930, 2855, 1732, 1670, 1546, 1488, 1362, 1265, 1167, 1046; TLC (90:10 hexanes/EtOAc) *R*_f = 0.66.

(3S,4aS,10bS)-3-(2-((tert-Butyldimethylsilyl)oxy)propan-2-yl)-10b-methyl-1,2,3,4a,5,6,8,9,10,10b-decahydro-7H-benzo[f]-chromen-7-one (53): A 100 mL round-bottomed flask was charged with alkene **52** (0.753 g, 1.78 mmol, 1.00 equiv) and a 1:1 mixture of THF/MeOH (35 mL). The solution was cooled to 0 °C, and KOH (1 M in H₂O, 5.34 mL, 5.34 mmol, 3.00 equiv) was added dropwise, subsequently warming to rt. The mixture was stirred until complete conversion of the starting material was observed by TLC analysis, typically 45 min. The mixture was cooled to 0 °C, and MsOH was added drop-by-drop until the reaction pH reached <1 (scaledependent, ~2 mL was required in this iteration), resulting in the formation of a white suspension. The resulting mixture was warmed to rt and stirred vigorously for 1 h, whereupon the mixture was neutralized with saturated NaHCO_{3(aq)} (20 mL). The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with Et₂O (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried with magnesium sulfate, and concentrated in vacuo to give the crude nonconjugated enone, which was used in the next step without further purification.

The crude ketone was transferred to a flame-dried, 50 mL roundbottomed flask and dissolved in CH₂Cl₂ (18 mL) under an atmosphere of N₂. DBU (0.52 mL, 3.60 mmol, 2.00 equiv) was added, and the mixture was allowed to stir at rt until complete conversion of the starting material was observed by TLC analysis, typically 3 h. The reaction was diluted with

H₂O (15 mL) and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were dried with sodium sulfate and concentrated in vacuo. The product was purified via flash chromatography (100:0 to 97.5:2.5 to 95:5 to 90:10 hexanes/EtOAc) to afford conjugated enone **53** (0.38 g, 54% yield) as a yellow solid. Analytical data: mp 85–89 °C; [α]_D²⁸ –118.8 (*c* = 0.85, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 3.19 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.08 (dd, *J* = 4.2, 4.2 Hz, 1H), 2.44 (m, 2H), 2.34–2.20 (m, 4H), 2.01 (m, 1H), 1.93 (dt, *J* = 6.0, 3.0 Hz, 1H), 1.84 (m, 1H), 1.76 (m, 1H), 1.65–1.59 (m, 3H), 1.40 (m, 1H), 1.24 (s, 3H), 1.19 (s, 3H), 1.10 (s, 3H), 0.84 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 199.8, 162.7, 129.8, 85.1, 80.4, 74.8, 38.0, 37.7, 33.3, 27.5, 25.8, 25.2, 24.9, 23.3, 22.9, 22.4, 21.4, 18.1, 18.0, –2.1, –2.2; HRMS (ESI⁺) calcd for C₂₃H₄₀O₃Si+Na, 415.2644; found 415.2636; IR (thin film, cm^{–1}) 3053, 2954, 2887, 2855, 1683, 1616, 1576, 1472, 1362, 1265, 1172, 1045; TLC (90:10 hexanes/EtOAc) *R*_f = 0.34.

(3S,4aS,6aR,10aS,10bS)-3-(2-((tert-Butyldimethylsilyl)oxy)-propan-2-yl)-6a,10b-dimethyldodecahydro-7H-benzof[chromen]-7-one (54): An oven-dried, 50 mL two-neck round-bottomed flask was fitted with a stir bar and an oven-dried coldfinger condenser and placed under an atmosphere of Ar. The flask and condenser were cooled to –78 °C, and liq. NH₃ (5 mL) was allowed to condense into the flask. Freshly cut Li⁰ (0.01 g, 1.43 mmol, 14.3 equiv) was washed with hexanes and added to the flask, resulting in the formation of a dark blue color. After being stirred 5 min at –78 °C, a solution of ketone **53** (0.04 g, 0.10 mmol, 1.00 equiv) in THF (3 mL) was added, and the reaction was warmed to –33 °C and stirred 15 min. The reaction was cooled to –78 °C, diluted with THF (5 mL), and a solution of MeI (0.38 mL, 6.0 mmol, 60.0 equiv) in THF (2 mL) was added dropwise. The mixture was allowed to warm to rt and stirred until liq. NH₃ had completely evaporated. The residue was quenched with saturated NH₄Cl_(aq) (10 mL), diluted with Et₂O (10 mL) and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo to give the crude ketone **54** as a single diastereomer (as determined by ¹H NMR spectroscopic analysis of the crude reaction mixture, which revealed a single compound). The product was purified via flash chromatography (100:0 to 98:2 to 95:5 to 90:10 hexanes/EtOAc) to afford ketone **54** (0.025 g, 61% yield) as a clear, viscous oil. Analytical data: [α]_D²⁸ –38.2 (*c* = 0.75, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 2.98 (dd, *J* = 8.4, 3.0 Hz, 1H), 2.84 (dd, *J* = 7.8, 3.6 Hz, 1H), 2.64 (m, 1H), 2.44 (dt, *J* = 7.2, 3.0 Hz, 1H), 2.25 (dd, *J* = 10.2, 6.0 Hz, 1H), 2.08 (m, 2H), 1.95–1.87 (m, 3H), 1.52–1.44 (m, 5H), 1.25 (m, 1H), 1.24 (s, 3H), 1.20 (s, 3H), 1.14 (s, 3H), 1.06 (m, 1H), 0.83 (s, 9H), 0.82 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 216.0, 84.9, 84.3, 74.8, 54.4, 47.9, 37.9, 37.3, 36.4, 32.6, 29.9, 27.3, 25.8, 25.1, 25.1, 23.8, 21.5, 19.1, 18.2, 16.0, –2.1, –2.2; HRMS (ESI⁺) calcd for C₂₄H₄₄O₃Si+Na, 431.2957; found 431.2949; IR (thin film, cm^{–1}) 3421, 2954, 2855, 1792, 1698, 1377, 1265, 1215, 1058; TLC (90:10 hexanes/EtOAc) *R*_f = 0.54.

(3S,4aS,6aS,10aR,10bS)-3-(2-((tert-Butyldimethylsilyl)oxy)-propan-2-yl)-10b-methyldodecahydro-7H-benzof[chromen]-7-one (55): An oven-dried, 50 mL two-neck round-bottomed flask was fitted with a stir bar and an oven-dried coldfinger condenser and

placed under an atmosphere of Ar. The flask and condenser were cooled to $-78\text{ }^{\circ}\text{C}$, and liq. NH_3 (5 mL) was allowed to condense into the flask. Freshly cut Li^0 (0.005 g, 0.714 mmol, 14.3 equiv) was washed with hexanes and added to the flask, resulting in the formation of a dark blue color. After being stirred 5 min at $-78\text{ }^{\circ}\text{C}$, a solution of ketone **53** (0.02 g, 0.05 mmol, 1.00 equiv) in THF (2 mL) was added, and the reaction was warmed to $-33\text{ }^{\circ}\text{C}$ and stirred 15 min. The reaction was carefully quenched via portionwise addition of $\text{NH}_4\text{Cl}_{(s)}$, and the mixture was allowed to warm to rt and stirred until liq. NH_3 had completely evaporated. The residue was diluted with H_2O (10 mL) and Et_2O (10 mL) and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo to afford the crude ketone as a 1:1 mixture of diastereomers, which was taken on directly to the next step without further purification. A crude ^1H NMR spectrum of this reaction is included in the Supporting Information.

This crude residue was transferred to a flame-dried, 20 mL scintillation vial and dissolved in C_7H_8 under an atmosphere of N_2 . DBU (0.01 mL, 0.05 mmol, 1.00 equiv) was added, and the mixture was warmed to $65\text{ }^{\circ}\text{C}$ and stirred 12 h. The reaction was cooled to rt, diluted with H_2O (10 mL) and CH_2Cl_2 (5 mL) and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo. At this juncture, crude ^1H NMR analysis revealed complete epimerization to a single diastereomer. The product was purified via flash chromatography (100:0 to 97.5:2.5 to 90:10 hexanes/EtOAc) to afford ketone **55** (0.015 g, 75% yield) as a clear, viscous oil. Analytical data: $[\alpha]_{\text{D}}^{28} -72.0$ ($c = 0.75$, CHCl_3); ^1H NMR (600 MHz, CDCl_3) δ 3.03 (dd, $J = 7.2, 3.6$ Hz, 1H), 2.87 (dd, $J = 7.8, 3.6$ Hz, 1H), 2.36 (m, 1H), 2.26 (m, 2H), 2.10 (m, 1H), 1.91–1.83 (m, 3H), 1.63 (m, 1H), 1.57–1.52 (m, 4H), 1.43–1.36 (m, 3H), 1.21 (s, 3H), 1.16 (br s, 4H), 0.91 (s, 3H), 0.84 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 213.2, 85.1, 83.2, 74.8, 52.3, 49.2, 41.8, 36.7, 36.6, 27.4, 26.5, 26.2, 25.8, 24.9, 24.3, 23.6, 21.8, 18.1, 12.1, $-2.1, -2.2$; HRMS (ESI $^+$) calcd for $\text{C}_{23}\text{H}_{42}\text{O}_3\text{Si}+\text{Na}$, 417.2801; found 417.2793; IR (thin film, cm^{-1}) 3420, 2951, 2854, 1715, 1652, 1472, 1376, 1251, 1155, 1051, 835; TLC (90:10 hexanes/EtOAc) $R_f = 0.40$.

(3S,4aS,6aS,10aR,10bR)-3-(2-((Butyldimethylsilyl)oxy)propan-2-yl)-10b-methyloctahydro-1H-6a,10a-epoxybenzof[chromen-7(8H)-one (56):

A 20 mL scintillation vial was charged with enone **53** (0.10 g, 0.26 mmol, 1.00 equiv) and $(\text{CH}_2\text{Cl})_2$ (5 mL). *p*-NPBA³² (0.19 g, 0.89 mmol, 3.50 equiv) was added, and the vial was sealed with a screw-cap. The mixture was warmed to $65\text{ }^{\circ}\text{C}$ and stirred until complete consumption of the starting material was observed by TLC analysis, typically 3 h. The reaction mixture was warmed to rt, quenched via saturated $\text{Na}_2\text{S}_2\text{O}_3(\text{aq})$ (5 mL), and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3×7 mL). The combined organic extracts were dried with sodium sulfate and concentrated in vacuo to afford the crude epoxide as a single diastereomer (as determined by ^1H NMR spectroscopic analysis of the crude reaction mixture, which revealed a single compound). The product was purified via flash chromatography (100:0 to 97.5:2.5 to 95:5 hexanes/EtOAc) to afford keto-epoxide **56** (0.05 g, 47% yield) as a clear, viscous oil. Slow

evaporation of **56** from HPLC grade methanol afforded crystals suitable for X-ray crystallographic analysis. Analytical data: $[\alpha]_{\text{D}}^{28} -105.2$ ($c = 0.70$, CHCl_3); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 3.43 (dd, $J = 8.4, 4.2$ Hz, 1H), 3.06 (m, 1H), 2.58 (m, 1H), 2.08 (m, 2H), 1.91–1.85 (m, 3H), 1.64 (m, 3H), 1.55–1.49 (m, 3H), 1.37 (m, 1H), 1.20 (s, 3H), 1.15 (s, 3H), 1.03 (s, 3H), 0.84 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 207.2, 84.8, 75.4, 74.7, 64.3, 36.4, 36.2, 32.0, 27.4, 25.8, 24.9, 22.3, 21.6, 21.3, 18.9, 18.8, 18.1, 15.9, –2.1, –2.2; HRMS (ESI⁺) calcd for $\text{C}_{23}\text{H}_{40}\text{O}_4\text{Si}+\text{Na}$, 431.2594; found 431.2585; IR (thin film, cm^{-1}) 3420, 2955, 2856, 1704, 1646, 1488, 1396, 1265, 1173, 1072, 835, 739; TLC (90:10 hexanes/EtOAc) $R_f = 0.25$.

(3S,4aS,7S,10bS)-3-(2-((tert-Butyldimethylsilyl)oxy)propan-2-yl)-10b-methyl-2,3,4a,5,6,7,8,9,10,10b-decahydro-1H-benzo[fl]-chromen-7-ol (57):

A flame-dried, 20 mL scintillation vial was charged with ketone **53** (0.06 g, 0.15 mmol, 1.0 equiv) and THF (2 mL) under an atmosphere of N_2 . The reaction mixture was cooled to -78 °C, and $\text{LiAl}(\text{O}^t\text{Bu})_3\text{H}$ (1 M solution in THF, 0.31 mL, 0.31 mmol, 2.00 equiv) was added in one portion. The reaction mixture was allowed to stir for 12 h, slowly warming to rt during this time period at which point TLC analysis confirmed complete consumption of the starting material. The reaction was quenched via saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (5 mL) and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3×7 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo to give the crude alcohol as a 10:1 mixture of diastereomers. The diastereomeric ratio was determined by $^1\text{H NMR}$ spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 3.99 (major diastereomer) and δ 3.82 (minor diastereomer). The product was purified via flash chromatography (90:10 to 80:20 hexanes/EtOAc) to afford alcohol **57** (0.054 g, 90% yield) as a clear, viscous oil. Analytical data: $[\alpha]_{\text{D}}^{28} -92.7$ ($c = 1.00$, CHCl_3); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 3.99 (m, 1H), 3.20 (dd, $J = 8.4, 3.6$ Hz, 1H), 3.08 (dd, $J = 7.2, 3.6$ Hz, 1H), 2.49 (m, 1H), 1.98 (m, 2H), 1.88 (m, 2H), 1.82 (m, 1H), 1.71 (m, 2H), 1.65 (m, 2H), 1.57 (m, 2H), 1.52 (m, 2H), 1.29 (m, 1H), 1.23 (s, 3H), 1.17 (s, 3H), 0.99 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 139.7, 128.2, 85.1, 81.2, 74.9, 70.6, 34.5, 34.0, 32.6, 27.3, 26.8, 25.9, 25.1, 24.0, 23.8, 21.8, 19.8, 18.4, 18.2, –2.1, –2.2; HRMS (ESI⁺) calcd for $\text{C}_{23}\text{H}_{42}\text{O}_3\text{Si}+\text{Na}$, 417.2801; found 417.2791; IR (thin film, cm^{-1}) 3420, 2930, 2855, 1683, 1636, 1507, 1456, 1361, 1264, 1046, 835; TLC (90:10 hexanes/EtOAc) $R_f = 0.25$.

N'-((2S,4aS,8aS,E)-2-(2-((tert-Butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyloctahydro-5H-chromen-5-ylidene)-4-methylbenzene-sulfonohydrazide (59):

A flame-dried, 500 mL round-bottomed flask was charged with hydrazone **49** (6.21 g, 12.2 mmol, 1.00 equiv) and THF (122 mL) under an atmosphere of N_2 . The mixture was cooled to -50 °C, and $^n\text{BuLi}$ (2.60 M in hexanes, 16.4 mL, 42.7 mmol, 3.50 equiv) was added over a period of ~2 min, producing a dark orange color. The reaction mixture was allowed to stir 40 min, whereupon MeI (1.90 mL, 30.5 mmol, 2.50 equiv) was added, resulting in a color change from orange to yellow. The reaction was allowed to stir until complete consumption of the starting material was observed by TLC analysis, typically 20 min. The reaction was quenched via saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (40 mL) and allowed to warm to rt. The mixture was

transferred to a separatory funnel, the organic layer was separated, and the aqueous layer was extracted with Et₂O (3 × 40 mL). The combined organic extracts were washed with brine (40 mL), dried with magnesium sulfate and concentrated in vacuo. The product was purified via flash chromatography (90:10 to 80:20 hexanes/EtOAc) to afford hydrazone **59** (6.37 g, 98% yield) as a white foam in a 7:1 diastereomeric ratio. Analytical data: $[\alpha]_{\text{D}}^{28}$ -121.0 (*c* = 0.60, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 7.83 (d, *J* = 7.2 Hz, 2H), 7.72 (br s, 1H), 7.30 (d, *J* = 7.8 Hz, 2H), 3.05 (m, 1H), 3.00 (s, 1H), 2.73 (q, *J* = 7.8 Hz, 1H), 2.43 (s, 3H), 2.01 (d, *J* = 13.2 Hz, 1H), 1.69 (m, 1H), 1.57–1.54 (m, 5H), 1.45 (m, 1H), 1.34 (m, 1H), 1.20 (s, 3H), 1.15 (s, 3H), 1.07 (d, *J* = 7.2 Hz, 3H), 0.95 (s, 3H), 0.84 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 167.1, 143.8, 135.3, 129.3, 128.0, 127.9, 85.2, 82.0, 74.7, 41.9, 33.3, 28.3, 27.7, 27.2, 25.8, 25.0, 22.8, 21.6, 21.2, 19.1, 18.3, 18.1, -2.1, -2.2; HRMS (ESI⁺) calcd for C₂₇H₄₆N₂O₄SSi+Na, 545.2845; found 545.2840; IR (thin film, cm⁻¹) 3225, 2954, 2855, 1472, 1396, 1265, 1168, 1090, 1038, 812, 773; TLC (90:10 hexanes/EtOAc) *R_f* = 0.35.

(2S,4aS,8aS)-2-(2-((tert-Butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromene-5-carbaldehyde (60): A flame-dried, 25 mL round-bottomed flask was charged with hydrazone **59** (0.48 g, 0.92 mmol, 1.00 equiv) and THF (9.5 mL) under an atmosphere of N₂. The solution was cooled to -50 °C, and ⁿBuLi (1.70 M in hexanes, 3.25 mL, 5.52 mmol, 6.00 equiv) was added over a period of ~2 min, producing a dark orange color. The reaction was allowed to stir 30 min, whereupon a venting needle was added, and the mixture was warmed to 0 °C and stirred 5 min. The reaction was then warmed to rt and stirred until complete consumption of the starting material was observed by TLC analysis, typically 20 min. The venting needle was removed, DMF (0.71 mL, 9.2 mmol, 10.0 equiv) was added, and the reaction was stirred 20 min. The mixture was diluted with H₂O (15 mL) and Et₂O (10 mL) and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et₂O (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried with magnesium sulfate and concentrated in vacuo. The product was purified via flash chromatography (95:5 to 90:10 hexanes/EtOAc) to afford aldehyde **60** (0.21 g, 62% yield) as a yellow, viscous oil. Analytical data: $[\alpha]_{\text{D}}^{28}$ -151.8 (*c* = 0.80, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 10.05 (br s, 1H), 3.16 (m, 1H), 3.11 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.65 (m, 1H), 2.38 (m, 1H), 2.28 (m, 1H), 2.06 (s, 3H), 1.69 (m, 2H), 1.62–1.53 (m, 3H), 1.22 (s, 3H), 1.17 (s, 3H), 1.14 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 191.9, 153.9, 140.3, 85.8, 80.6, 74.9, 35.7, 34.3, 33.5, 27.1, 25.8, 25.1, 23.7, 21.6, 18.8, 18.2, 18.1, -2.1, -2.2; HRMS (ESI⁺) calcd for C₂₁H₃₈O₃Si+Na, 389.2488; found 389.2481; IR (thin film, cm⁻¹) 2954, 2928, 2855, 1733, 1674, 1472, 1376, 1251, 1095, 1005, 835; TLC (90:10 hexanes/EtOAc) *R_f* = 0.50.

tert-Butyl((2-((2S,4aS,8aS)-4a,6-dimethyl-5-vinyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-2-yl)propan-2-yl)oxy)dimethylsilane (61): A flame-dried, 25 mL round-bottomed flask was charged with methyltriphenylphosphonium bromide (1.90 g, 5.28 mmol, 8.00 equiv) and THF (7 mL) under an atmosphere of N₂. The mixture was cooled to 0 °C and ⁿBuLi (1.69 M in hexanes, 2.94 mL, 4.95 mmol, 7.50 equiv) was added dropwise. The deep yellow mixture was allowed to stir 1 h at 0 °C upon which the aldehyde **60** (0.24 g,

0.66 mmol, 1.00 equiv) was added as a solution in THF (2 mL). The reaction was allowed to stir until complete consumption of the starting material was observed by TLC analysis, typically 15 min. The reaction was diluted with H₂O (15 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with Et₂O (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (100:0 to 99:1 to 97.5:2.5 hexanes/EtOAc) to afford diene **61** (0.20 g, 82% yield) as a clear oil. Analytical data: $[\alpha]_D^{28}$ -94.4 (*c* = 1.50, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 6.13 (dd, *J* = 12.0, 6.0 Hz, 1H), 5.23 (dd, *J* = 8.4, 3.0 Hz, 1H), 4.96 (dd, *J* = 15.6, 2.4 Hz, 1H), 3.19 (dd, *J* = 7.2, 4.8 Hz, 1H), 3.08 (dd, *J* = 6.6, 4.2 Hz, 1H), 2.18 (m, 1H), 2.08 (dd, *J* = 11.4, 6.6 Hz, 1H), 1.84 (dt, *J* = 6.0, 4.2 Hz, 1H), 1.66 (br s, 4H), 1.55 (br s, 3H), 1.28 (m, 1H), 1.23 (s, 3H), 1.17 (s, 3H), 1.02 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 138.1, 134.3, 127.5, 118.0, 85.2, 81.4, 75.0, 36.2, 35.2, 31.6, 27.3, 25.9, 25.1, 24.3, 21.8, 20.5, 18.7, 18.2; HRMS (ESI⁺) calcd for C₂₂H₄₀O₂Si+Na, 387.2695; found 387.2688; IR (thin film, cm⁻¹) 2954, 2855, 1717, 1471, 1376, 1253, 1167, 1039, 880, 741; TLC (90:10 hexanes/EtOAc) *R*_f = 0.93.

((2-((2S,4aS,8aS)-5-((Z)-Buta-1,3-dien-1-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-2-yl)propan-2-yl)oxy)(tert-butyl) dimethylsilane (63): A flame-dried, 20 mL scintillation vial was charged with allyltriphenylphosphonium bromide (1.31 g, 3.43 mmol, 8.00 equiv) and THF (5 mL) under an atmosphere of N₂. The mixture was cooled to 0 °C and ⁿBuLi (2.64 M in hexanes, 1.22 mL, 3.21 mmol, 7.50 equiv) was added dropwise. The deep yellow mixture was allowed to stir 1 h at 0 °C, whereupon the aldehyde **60** (0.16 g, 0.43 mmol, 1.00 equiv) was added as a solution in THF (2 mL). The reaction was allowed to stir until complete consumption of the starting material was observed by TLC analysis, typically 12 h. The reaction was diluted with H₂O (15 mL) and transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with Et₂O (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (100:0 to 99:1 to 97.5:2.5 hexanes/EtOAc) to afford triene **63** (0.06 g, 36% yield) as a clear oil. Analytical data: $[\alpha]_D^{28}$ -49.8 (*c* = 1.25, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 6.37 (m, 1H), 6.05 (m, 2H), 5.15 (d, *J* = 16.8 Hz, 1H), 5.03 (d, *J* = 10.2 Hz, 1H), 3.19 (dd, *J* = 7.2, 4.8 Hz, 1H), 2.20 (m, 1H), 2.11 (dd, *J* = 12.6, 5.4 Hz, 1H), 1.88 (dt, *J* = 6.0, 3.0 Hz, 1H), 1.68 (br s, 5H), 1.56 (m, 2H), 1.27 (m, 1H), 1.23 (s, 3H), 1.17 (s, 3H), 1.04 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 137.7, 137.1, 133.9, 130.7, 128.7, 115.4, 85.2, 81.4, 74.9, 36.6, 35.3, 31.8, 27.3, 25.8, 25.0, 24.2, 21.8, 20.8, 18.9, 18.2, -2.1, -2.2; HRMS (ESI⁺) calcd for C₂₄H₄₂O₂Si +Na, 413.2852; found 413.2843; IR (thin film, cm⁻¹) 3420, 2929, 2855, 1670, 1497, 1457, 1387, 1265, 1165, 1040, 835; TLC (90:10 hexanes/EtOAc) *R*_f = 0.94.

((2-((2S,4aS,8aS,E)-5-(But-3-en-1-ylidene)-4a-methyl-6-methyle-neoctahydro-2H-chromen-2-yl)propan-2-yl)oxy)(tert-butyl)-dimethylsilane (65): The triene **63** (0.017 g, 0.043 mmol, 1.00 equiv) was taken up into hexanes and transferred to a toroidal photochemical reactor equipped with a water-cooled Pyrex immersion well. A 450 W Hanovia medium pressure mercury vapor lamp was lowered inside the immersion well, and

the triene solution was irradiated for 1 h. The solution was subsequently concentrated in vacuo. The product was purified via flash chromatography to give rearrangement product **65** (0.009 g, 53% yield) as a clear, viscous oil. Analytical data: $[\alpha]_{\text{D}}^{28} -11.8$ ($c = 0.10$, CHCl_3); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 5.83 (m, 1H), 5.20 (t, $J = 7.8$ Hz, 1H), 5.01 (m, 1H), 4.97 (m, 1H), 4.66 (t, $J = 1.8$ Hz, 1H), 3.10 (dd, $J = 7.8, 4.2$ Hz, 1H), 3.05 (m, 1H), 2.90 (m, 2H), 2.33 (m, 1H), 2.06 (m, 1H), 1.70 (m, 2H), 1.66–1.55 (m, 6H), 1.22 (s, 3H), 1.17 (s, 3H), 0.94 (s, 3H), 0.85 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 148.0, 144.1, 138.3, 119.1, 114.3, 112.8, 85.2, 82.5, 74.9, 39.8, 34.5, 33.8, 33.2, 28.5, 27.2, 25.8, 25.1, 21.9, 18.2, 17.9, -2.1, -2.2; HRMS (ESI⁺) calcd for $\text{C}_{24}\text{H}_{42}\text{O}_2\text{Si} + \text{Na}$, 413.2852; found 413.2843; IR (thin film, cm^{-1}) 3053, 2956, 2855, 1749, 1670, 1540, 1456, 1265, 1046, 835; TLC (90:10 hexanes/EtOAc) $R_f = 0.97$.

Synthesis of Enol Silane **66**

1-((2S,4aS,8aS)-2-(2-((tert-Butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-5-yl)ethan-1-one (S4): A flame-dried, 25 mL round-bottomed flask was charged with hydrazone **59** (0.30 g, 0.57 mmol, 1.00 equiv) and THF (6 mL) under an atmosphere of N_2 . The solution was cooled to -50 °C, and $n\text{BuLi}$ (2.64 M in hexanes, 1.30 mL, 3.44 mmol, 6.00 equiv) was added over a period of ~2 min, producing a dark orange color. The reaction was allowed to stir 30 min, whereupon a venting needle was added, and the mixture was warmed to 0 °C and stirred 5 min. The reaction was then warmed to rt and stirred until complete consumption of the starting material was observed by TLC analysis, typically 20 min. The venting needle was removed, the mixture was cooled to -78 °C, and acetaldehyde (0.32 mL, 5.74 mmol, 10.0 equiv) was added dropwise. The reaction was allowed to stir 25 min, whereupon H_2O (5 mL) and Et_2O (5 mL) were added, and the mixture was warmed to rt and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic extracts were washed with brine (10 mL), dried with magnesium sulfate, and concentrated in vacuo to give the crude alcohol, which was taken on to the next step without further purification.

The crude residue was taken up into CH_2Cl_2 (5 mL) and transferred to a 20 mL scintillation vial. Dess-Martin periodinane (0.29 g, 0.68 mmol, 2.00 equiv) was added to the vial, and the mixture was allowed to stir until TLC analysis indicated complete consumption of the starting material, typically 15 min. The mixture was then quenched via a 1:1 solution of saturated $\text{NaHCO}_3(\text{aq})$ and saturated $\text{Na}_2\text{S}_2\text{O}_3(\text{aq})$ (5 mL), and the mixture was stirred 5 min. The reaction mixture was then diluted with Et_2O (10 mL) and partitioned in a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo. The product was purified via flash chromatography (100:0 to 97.5:2.5 to 95:5 hexanes/EtOAc) to afford ketone **S4** (0.09 g, 43% yield) as a yellow, viscous oil. Analytical data: $[\alpha]_{\text{D}}^{28} -31.6$ ($c = 0.50$, CHCl_3); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 3.21 (dd, $J = 6.0, 3.6$ Hz, 1H), 3.09 (dd, $J = 5.4, 3.6$ Hz, 1H), 2.25 (s, 3H), 2.16 (m, 1H), 2.08 (m, 1H), 1.67 (m, 2H), 1.56–1.54 (m, 6H), 1.44 (m, 1H), 1.21 (s, 3H), 1.17–1.15 (m, 6H), 0.83 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); $^{13}\text{C NMR}$ (150 MHz, CDCl_3) δ 208.2, 143.5, 128.5, 85.4, 80.4, 74.8, 35.4, 34.4, 33.3, 30.6, 27.3, 25.8, 25.0, 23.8, 21.3, 20.1, 19.6, 18.1, -2.1, -2.2; HRMS

(ESI⁺) calcd for C₂₂H₄₀O₃Si+Na, 403.2644; found 403.2636; IR (thin film, cm⁻¹) 2955, 2854, 1829, 1686, 1488, 1361, 1249, 1095, 835, 739; TLC (90:10 hexanes/EtOAc) *R_f* = 0.38.

tert-Butyl(1-((2S,4aS,8aS)-2-(2-((tert-butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-5-yl)vinyl)oxydimethylsilane (66): A flame-dried, 20 mL scintillation vial was charged with ketone **S4** (0.06 g, 0.16 mmol, 1.00 equiv) and THF (2 mL) under an atmosphere of N₂. The reaction was cooled to 0 °C, and NEt₃ (0.07 mL, 0.47 mmol, 3.00 equiv) and TBSOTf (0.075 mL, 0.32 mmol, 2.00 equiv) were added sequentially. The reaction mixture was warmed to rt and stirred until TLC analysis showed complete consumption of the starting material, typically 3 h. The reaction was quenched via addition of saturated NaHCO_{3(aq)} (2 mL) and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with pentane (3 × 5 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo. The product was purified via flash chromatography (100:0 to 98:2 to 97.5:2.5 hexanes/EtOAc) to afford silyloxydiene **66** (0.077 g, 99% yield) as a clear, viscous oil. Analytical data: [*α*]_D²⁸ -20.8 (*c* = 0.33, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 4.27 (s, 1H), 3.90 (s, 1H), 3.15 (dd, *J* = 7.2, 4.8 Hz, 1H), 3.08 (dd, *J* = 7.8, 3.0 Hz, 1H), 2.15 (m, 1H), 2.06 (dd, *J* = 11.4, 6.6 Hz, 1H), 1.81 (d, *J* = 13.2 Hz, 1H), 1.66 (br s, 5H), 1.54 (m, 2H), 1.39 (m, 1H), 1.23 (s, 3H), 1.16 (s, 3H), 1.07 (s, 3H), 0.92 (s, 9H), 0.84 (s, 9H), 0.20 (s, 3H), 0.17 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 155.6, 138.9, 128.6, 85.3, 81.1, 75.0, 34.7, 30.5, 27.2, 25.9, 25.8, 25.7, 25.2, 24.1, 21.9, 20.8, 18.2, 18.1, -2.1, -2.2, -4.5, -4.6; HRMS (ESI⁺) calcd for C₂₈H₅₄O₃Si₂+Na, 517.3509; found 517.3499; IR (thin film, cm⁻¹) 2930, 2896, 1611, 1497, 1376, 1265, 1165, 1038, 835, 775; TLC (90:10 hexanes/EtOAc) *R_f* = 0.94.

(E)-1-((2S,4aS,8aS)-2-(2-((tert-Butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-5-yl)but-2-en-1-one (67): A flame-dried, 25 mL round-bottomed flask was charged with hydrazone **59** (0.30 g, 0.57 mmol, 1.00 equiv) and THF (6 mL) under an atmosphere of N₂. The solution was cooled to -50 °C, and ⁿBuLi (2.64 M in hexanes, 1.30 mL, 3.44 mmol, 6.00 equiv) was added over a period of ~2 min, producing a dark orange color. The reaction was allowed to stir 30 min, whereupon a venting needle was added, and the mixture was warmed to 0 °C and stirred 5 min. The reaction was then warmed to rt and stirred until complete consumption of the starting material was observed by TLC analysis, typically 20 min. The venting needle was removed, the mixture was cooled to -78 °C, and (*E*)-crotonaldehyde (0.48 mL, 5.74 mmol, 10.0 equiv) was added dropwise. The reaction was allowed to stir 25 min, whereupon H₂O (5 mL) and Et₂O (5 mL) were added, and the mixture was warmed to rt and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried with magnesium sulfate, and concentrated in vacuo to give the crude alcohol, which was taken on to the next step without further purification

The crude residue was taken up into CH₂Cl₂ (5 mL) and transferred to a 20 mL scintillation vial. Dess-Martin periodinane (0.29 g, 0.68 mmol, 2.00 equiv) was added to the vial, and the

mixture was allowed to stir until TLC analysis indicated complete consumption of the starting material, typically 15 min. The mixture was then quenched via a 1:1 solution of saturated $\text{NaHCO}_3(\text{aq})$ and saturated $\text{Na}_2\text{S}_2\text{O}_3(\text{aq})$ (5 mL), and the mixture was stirred 5 min. The reaction mixture was then diluted with Et_2O (10 mL) and partitioned in a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo. The product was purified via flash chromatography (100:0 to 97.5:2.5 to 95:5 hexanes/ EtOAc) to afford ketone **67** (0.10 g, 46% yield) as a yellow, viscous oil. Analytical data: $[\alpha]_{\text{D}}^{28} -72.2$ ($c = 0.48$, CHCl_3); ^1H NMR (600 MHz, CDCl_3) δ 6.73 (m, 1H), 6.14 (dd, $J = 13.8, 1.8$ Hz, 1H), 3.26 (dd, $J = 6.6, 5.4$ Hz, 1H), 3.09 (dd, $J = 7.8, 1.8$ Hz, 1H), 2.21 (m, 1H), 2.11 (dd, $J = 11.4, 6.6$ Hz, 1H), 1.93 (dd, $J = 5.4, 1.8$ Hz, 3H), 1.74–1.70 (m, 2H), 1.51–1.47 (m, 6H), 1.38 (m, 1H), 1.22 (s, 3H), 1.15 (s, 3H), 1.14 (s, 3H), 0.83 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 200.7, 146.4, 140.2, 134.6, 130.2, 85.4, 80.4, 74.9, 35.7, 34.5, 30.5, 27.2, 25.8, 25.0, 23.9, 21.4, 20.7, 19.7, 18.4, 18.1, -2.1, -2.2; HRMS (ESI⁺) calcd for $\text{C}_{24}\text{H}_{42}\text{O}_3\text{Si}+\text{Na}$, 429.2801; found 429.2792; IR (thin film, cm^{-1}) 2955, 2855, 1671, 1472, 1361, 1265, 1165, 1041, 835, 739; TLC (90:10 hexanes/ EtOAc) $R_f = 0.56$.

tert-Butyl((2-((2S,4aR,8aS)-5-iodo-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-2-yl)propan-2-yl)oxy)dimethylsilane (68): A flame-dried, 20 mL scintillation vial was charged with hydrazone **59** (0.30 g, 0.57 mmol, 1.00 equiv) and THF (6 mL) under an atmosphere of N_2 . The solution was cooled to -50 °C, and $^n\text{BuLi}$ (1.70 M in hexanes, 2.00 mL, 3.42 mmol, 6.00 equiv) was added over a period of ~2 min, producing a dark orange color. The reaction was allowed to stir 30 min, whereupon a venting needle was added, and the mixture was warmed to 0 °C and stirred 5 min. The reaction was then warmed to rt and stirred until complete consumption of the starting material was observed by TLC analysis, typically 20 min. The venting needle was removed, the mixture was cooled to 0 °C, and I_2 (0.43 g, 1.71 mmol, 3.00 equiv) was added portionwise. The reaction was allowed to stir 20 min, whereupon H_2O (5 mL) and Et_2O (5 mL) were added, and the mixture was warmed to rt and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organic extracts were washed with brine (10 mL) and saturated $\text{Na}_2\text{S}_2\text{O}_3(\text{aq})$, dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (100:0 to 99:1 to 98:2) to afford iodide **68** (0.18 g, 67% yield) containing 17% of the inseparable vinyl C–H compound (arising from protic quenching of the transient vinylolithium) by ^1H NMR analysis. Analytical data: $[\alpha]_{\text{D}}^{28} -248.0$ ($c = 1.00$, CHCl_3); ^1H NMR (600 MHz, CDCl_3) δ 3.32 (dd, $J = 7.8, 4.2$ Hz, 1H), 3.07 (dd, $J = 9.0, 3.0$ Hz, 1H), 2.30 (m, 1H), 2.22 (dd, $J = 11.4, 6.0$ Hz, 1H), 1.90 (m, 1H), 1.85 (s, 3H), 1.70 (m, 1H), 1.60 (br s, 1H), 1.55 (m, 2H), 1.28 (m, 1H), 1.24 (s, 3H), 1.18 (s, 3H), 0.99 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 136.2, 131.2, 114.8, 85.5, 81.1, 74.6, 41.5, 41.3, 32.3, 29.8, 27.4, 25.8, 25.0, 24.2, 22.7, 18.5, 18.1, -2.1, -2.2; HRMS (ESI⁺) calcd for $\text{C}_{20}\text{H}_{37}\text{IO}_2\text{Si}+\text{Na}$, 487.1505; found 487.1497; IR (thin film, cm^{-1}) 2954, 2854, 1771, 1670, 1488, 1376, 1264, 1162, 1040, 834; TLC (90:10 hexanes/ EtOAc) $R_f = 0.91$.

((2S,4aS,8aS)-2-(2-((tert-Butyldimethylsilyloxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-5-yl)methanol (69): A flame-dried, 50 mL round-bottomed flask was charged with hydrazone **59** (0.58 g, 1.10 mmol, 1.00 equiv) and THF (11 mL) under an atmosphere of N₂. The solution was cooled to -50 °C, and ^tBuLi (1.55 M in hexanes, 4.27 mL, 6.62 mmol, 6.00 equiv) was added over a period of ~2 min, producing a dark orange color. The reaction was allowed to stir 30 min, whereupon a venting needle was added, and the mixture was warmed to 0 °C and stirred 5 min. The reaction was then warmed to rt and stirred until complete consumption of the starting material was observed by TLC analysis, typically 20 min. The venting needle was removed, (HCHO)_n (0.35 g, 11.0 mmol, 10.0 equiv) was added to the mixture in one portion, and the reaction was allowed to stir 40 min at rt. H₂O (10 mL) and Et₂O (5 mL) were added, and the mixture was transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried with magnesium sulfate and concentrated in vacuo. The product was purified via flash chromatography (100:0 to 95:5 to 90:10 to 80:20 hexanes/EtOAc) to afford alcohol **69** (0.26 g, 65% yield) as a yellow, viscous oil. Analytical data: [α]_D²⁸ -53.7 (*c* = 0.70, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 4.20 (d, *J* = 11.4 Hz, 1H), 4.07 (d, *J* = 11.4 Hz, 1H), 3.18 (dd, *J* = 6.0, 4.2 Hz, 1H), 3.09 (dd, *J* = 6.6, 3.6 Hz, 1H), 2.17 (m, 1H), 2.06 (m, 1H), 1.98 (dt, *J* = 6.0, 3.6 Hz, 1H), 1.71 (s, 3H), 1.66 (m, 2H), 1.60 (m, 2H), 1.44 (m, 1H), 1.23 (s, 3H), 1.17 (s, 3H), 1.00 (s, 3H), 0.84 (s, 9H), 0.80 (s, 3H), 0.05 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 137.4, 132.2, 85.2, 81.3, 74.9, 58.2, 31.5, 25.8, 25.0, 24.2, 21.7, 19.4, 19.0, 18.1, -2.16, -2.21; HRMS (ESI⁺) calcd for C₂₁H₄₀O₃Si+Na, 391.2645; found 391.2652; IR (thin film, cm⁻¹) 3409, 2953, 2855, 1641, 1461, 1377, 1252, 1168, 1092, 834; TLC (85:15 hexanes/EtOAc) *R*_f = 0.29.

Procedure for One-Pot Synthesis of **69** from Alcohol **49**

((2S,4aS,8aS)-2-(2-((tert-Butyldimethylsilyloxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-5-yl)methanol (69): A flame-dried, 250 mL round-bottomed flask was charged with hydrazone **49** (1.50 g, 2.95 mmol, 1.00 equiv) and THF (30 mL) under an atmosphere of N₂. The solution was cooled to -50 °C, and ^tBuLi (3.97 mL, 2.6 M in hexanes, 10.32 mmol, 3.50 equiv) was added dropwise, producing a dark orange color. The reaction mixture was allowed to stir 40 min at this temperature, then MeI (0.46 mL, 7.37 mmol, 2.50 equiv) was added. The reaction was allowed to stir at -50 °C until TLC analysis confirmed complete conversion of **49**, typically 20 min. An additional charge of ^tBuLi (9.07 mL, 2.6 M in hexanes, 23.6 mmol, 8.00 equiv) was added to the reaction, and the resulting mixture was stirred 30 min. The flask was fitted with a venting needle, and the reaction mixture was then warmed to 0 °C, stirred 5 min, then warmed to rt and stirred until complete consumption of the intermediate hydrazone was observed by TLC analysis, typically 15–25 min (scale dependent). The septum was partially removed, and (HCHO)_n (0.89 g, 29.5 mmol, 10.0 equiv) was added in one portion with vigorous stirring. The reaction was allowed to stir 30 min at rt, at which time the mixture was diluted with H₂O (25 mL) and Et₂O (20 mL) and transferred to a separatory funnel. The organic layer was separated and the aqueous layer was extracted with Et₂O (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried with magnesium sulfate, and

concentrated in vacuo. The product was purified via flash chromatography (100:0 to 95:5 to 90:10 to 80:20 hexanes/EtOAc) to afford alcohol **69** (0.76 g, 66% yield).

((2S,4aS,8aS)-2-(2-((tert-Butyldimethylsilyloxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,

7,8,8a-hexahydro-2H-chromen-5-yl)methyl acetate (70a): A flame-dried, 20 mL scintillation vial was charged with alcohol **69** (0.05 g, 0.14 mmol, 1.00 equiv) and CH₂Cl₂ under an atmosphere of N₂. The mixture was cooled to 0 °C, and NEt₃ (0.04 mL, 0.27 mmol, 2.00 equiv), DMAP (0.002 g, 0.014 mmol, 0.1 equiv), and last Ac₂O (0.03 mL, 0.27 mmol, 2.00 equiv) were added sequentially. The mixture was allowed to stir at this temperature until TLC analysis showed complete consumption of the starting material, typically 3 h. The mixture was diluted with H₂O (7 mL) and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with CH₂Cl₂ (3 × 7 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (100:0 to 98:2 to 95:5 to 90:10 hexanes/EtOAc) to afford acetate **70a** (0.046 g, 83% yield) as a clear, viscous oil. Analytical data: [α]_D²⁸ -59.0 (*c* = 1.35, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 4.59 (dd, *J* = 12.0, 5.4 Hz, 2H), 3.19 (dd, *J* = 6.0, 4.8 Hz, 1H), 3.08 (dd, *J* = 6.0, 4.2 Hz, 1H), 2.20 (m, 1H), 2.11 (m, 1H), 2.05 (s, 3H), 1.82 (m, 1H), 1.67 (br s, 5H), 1.57 (m, 1H), 1.36 (m, 1H), 1.23 (s, 3H), 1.17 (s, 3H), 0.99 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 171.3, 134.8, 132.2, 85.1, 81.0, 74.9, 60.4, 36.3, 33.9, 31.6, 27.3, 25.8, 25.0, 24.1, 21.6, 21.2, 19.3, 19.2, 18.1, -2.1, -2.2; HRMS (ESI⁺) calcd for C₂₃H₄₂O₄Si+Na, 433.2750; found 433.2741; IR (thin film, cm⁻¹) 2955, 2856, 1771, 1730, 1472, 1377, 1249, 1092, 1039, 835, 759; TLC (90:10 hexanes/EtOAc) *R*_f = 0.54.

((2S,4aS,8aS)-2-(2-((tert-Butyldimethylsilyloxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,

7,8,8a-hexahydro-2H-chromen-5-yl)methyl propionate (70b): A flame-dried, 20 mL scintillation vial was charged with CH₂Cl₂ (3 mL) and propionic acid (0.02 g, 0.27 mmol, 2.00 equiv) at rt under an atmosphere of N₂. DCC (0.06 g, 0.27 mmol, 2.00 equiv) and DMAP (0.002 g, 0.014 mmol, 0.10 equiv) were added followed last by a solution of alcohol **69** (0.05 g, 0.14 mmol, 1.00 equiv) in CH₂Cl₂ (1 mL), and the reaction was allowed to stir at rt until TLC analysis confirmed complete conversion of the starting material, typically 3.5 h. The reaction mixture was filtered through cotton into a separatory funnel, and H₂O (10 mL) and EtOAc (10 mL) were added. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with saturated NaHCO_{3(aq)} (10 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (100:0 to 98:2 to 95:5 hexanes/EtOAc) to afford ester **70b** (0.05 g, 86% yield) as a clear, viscous oil. Analytical data: [α]_D²⁸ -51.4 (*c* = 1.25, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 4.60 (dd, *J* = 12.0, 7.8 Hz, 2H), 3.19 (dd, *J* = 5.4, 5.4 Hz, 1H), 3.08 (dd, *J* = 6.0, 4.2 Hz, 1H), 2.32 (q, *J* = 7.2 Hz, 2H), 2.19 (m, 1H), 2.09 (dd, *J* = 12.6, 4.8 Hz, 1H), 1.82 (dt, *J* = 6.0, 3.6 Hz, 1H), 1.67 (br s, 5H), 1.56 (m, 1H), 1.37 (m, 1H), 1.23 (s, 3H), 1.17 (s, 3H), 1.40 (t, *J* = 7.2 Hz, 3H), 0.99 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 174.6, 134.6, 132.3, 85.1, 81.0, 74.9, 60.3, 36.3, 34.0, 27.7, 27.3, 25.8, 25.0, 24.2, 21.7, 19.3, 19.2, 18.2, 9.2, -2.1, -2.2; HRMS (ESI⁺) calcd for C₂₄H₄₄O₄Si +Na, 447.2907; found 447.2897; IR (thin film, cm⁻¹) 3053, 2955, 2855, 1731, 1540, 1472, 1322, 1265, 1179, 1071, 835; TLC (90:10 hexanes/EtOAc) *R*_f = 0.68.

((2S,4aS,8aS)-2-(2-((tert-Butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-5-yl)methyl 2-(1H-indol-2-yl)propanoate (70d): A 20 mL scintillation vial was charged with ethyl 2-(1H-indol-2-yl)propanoate⁵⁰ (0.2 g, 0.92 mmol, 1.00 equiv) and a 3:1 mixture of MeOH/THF (5 mL). LiOH (4 M in H₂O, 0.7 mL, 2.76 mmol, 3.00 equiv) was added, and the mixture was allowed to stir at rt until complete consumption of the starting material was observed by TLC analysis, typically 6 h. The reaction mixture was concentrated on a rotary evaporator, and the residue was diluted with H₂O (10 mL) and transferred to a separatory funnel. The aqueous layer was extracted with EtOAc (2 × 10 mL), and the aqueous layer was then acidified to pH = 0 with 1 M HCl_(aq) and extracted with CH₂Cl₂ (3 × 10 mL). The combined CH₂Cl₂ extracts were dried with magnesium sulfate and concentrated in vacuo to give the crude carboxylic acid. This material could not be isolated due to spontaneous decarboxylation, but could be carried forward directly to the next step without further purification.

The crude acid (~4.00 equiv) was dissolved in CH₂Cl₂ (3 mL) and transferred to a flame-dried, 20 mL scintillation vial under an atmosphere of N₂. DCC (0.095 g, 0.46 mmol, 2.00 equiv) was added followed by DMAP (0.003 g, 0.023 mmol, 0.10 equiv) and last a solution of alcohol **69** (0.085 g, 0.23 mmol, 1.00 equiv) in CH₂Cl₂ (1 mL). The reaction was allowed to stir until TLC analysis confirmed complete consumption of the starting material, typically 20 min. The reaction mixture was filtered through cotton into a separatory funnel, and H₂O (10 mL) and EtOAc (10 mL) were added. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with saturated NaHCO_{3(aq)} (10 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (100:0 to 95:5 to 90:10 hexanes/ EtOAc) to afford an inseparable mixture of diastereomeric esters **70d** (0.14 g, 99% yield) as a brown, viscous oil. Analytical data: $[\alpha]_D^{28} -68.4$ ($c = 0.43$, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 8.59 (m, 1H), 7.56 (m, 1H), 7.32 (m, 1H), 7.15 (m, 1H), 7.09 (m, 1H), 6.37 (br s, 1H), 4.66 (m, 2H), 3.95 (m, 1H), 3.17 (m, 1H), 3.06–2.98 (m, 1H), 2.21 (m, 1H), 2.10 (m, 1H), 1.68–1.66 (m, 4H), 1.64–1.62 (m, 4H), 1.46 (m, 2H), 1.32 (m, 2H), 1.23–1.21 (m, 3H), 1.16–1.14 (m, 3H), 0.97–0.96 (m, 3H), 0.86 (s, 9H), 0.10–0.09 (m, 3H), 0.07 (m, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 173.6, 136.7, 136.6, 136.0, 135.4, 131.9, 128.0, 121.7, 120.2, 119.7, 110.6, 100.1, 85.1, 85.0, 80.9, 74.8, 61.3, 61.2, 41.5, 39.3, 39.2, 36.2, 33.9, 31.6, 27.2, 27.1, 26.1, 25.8, 25.2, 25.1, 24.1, 23.3, 21.5, 19.2, 18.1, 17.4, 17.2, 14.1, –2.2, –2.3; HRMS (ESI⁺) calcd for C₃₂H₄₉NO₄Si+Na, 562.3329; found 562.3320; IR (thin film, cm⁻¹) 3392, 2954, 2855, 1716, 1471, 1377, 1250, 1172, 1069, 835; TLC (90:10 hexanes/EtOAc) $R_f = 0.41$.

((2S,4aS,8aS)-2-(2-((tert-Butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-5-yl)methyl 3-((tert-butyldimethylsilyl)oxy)-2-methylpropanoate (70e): A flame-dried, 20 mL scintillation vial was charged with CH₂Cl₂ (3 mL) and 3-((tert-butyldimethylsilyl)oxy)-2-methylpropanoic acid⁵¹ (0.05 g, 0.22 mmol, 2.00 equiv) at rt under an atmosphere of N₂. DCC (0.04 g, 0.22 mmol, 2.00 equiv) and DMAP (0.002 g, 0.014 mmol, 0.10 equiv) were added followed last by a solution of alcohol **69** (0.04 g, 0.11 mmol, 1.00 equiv) in CH₂Cl₂ (1 mL), and the reaction was allowed to stir at rt until TLC analysis confirmed complete conversion of the starting material, typically 3.5 h. The reaction mixture was filtered through cotton into a separatory funnel, and H₂O (10 mL)

and EtOAc (10 mL) were added. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with saturated NaHCO_{3(aq)} (10 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (100:0 to 98:2 to 95:5 hexanes/EtOAc) to afford an inseparable mixture of diastereomeric esters **70e** (0.047 g, 76% yield) as a clear, viscous oil. Analytical data: [α]_D²⁸ -42.1 (*c* = 1.20, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 4.58 (m, 2H), 3.79 (m, 1H), 3.64 (m, 1H), 3.18 (m, 1H), 3.08 (dd, *J* = 7.2, 3.6 Hz, 1H), 2.62 (m, 1H), 2.19 (m, 1H), 2.09 (m, 1H), 1.82 (m, 1H), 1.67–1.66 (m, 5H), 1.57 (m, 2H), 1.37 (m, 1H), 1.23 (s, 3H), 1.17 (s, 3H), 1.14–1.12 (m, 3H), 0.99 (m, 3H), 0.87 (s, 9H), 0.84 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H), 0.03 (br s, 6H); ¹³C NMR (150 MHz, CDCl₃) δ 175.1, 134.6, 134.5, 132.3, 85.1, 81.0, 74.9, 65.3, 65.2, 60.4, 60.3, 42.7, 36.3, 34.1, 34.0, 31.7, 27.4, 27.3, 25.9, 25.8, 25.0, 24.2, 21.7, 21.6, 19.3, 19.2, 18.2, 13.6, -2.1, -2.2, -5.5; HRMS (ESI⁺) calcd for C₃₁H₆₀O₅Si₂+Na, 591.3877; found 591.3867; IR (thin film, cm⁻¹) 3053, 2955, 2884, 2857, 1727, 1471, 1377, 1265, 1179, 1049, 836; TLC (90:10 hexanes/EtOAc) *R*_f = 0.73.

((2S,4aS,8aS)-2-(2-((tert-Butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-5-yl)methyl (S)-2-Bromopropanoate (70f): A flame-dried, 20 mL scintillation vial was charged with CH₂Cl₂ (3 mL) and (*S*)-2-bromopropanoic acid₅₂ (0.04 g, 0.27 mmol, 2.00 equiv) at rt under an atmosphere of N₂. DCC (0.06 g, 0.27 mmol, 2.00 equiv) and DMAP (0.002 g, 0.014 mmol, 0.10 equiv) were added followed last by a solution of alcohol **69** (0.05 g, 0.14 mmol, 1.00 equiv) in CH₂Cl₂ (1 mL), and the reaction was allowed to stir at rt until TLC analysis confirmed complete conversion of the starting material, typically 3.5 h. The reaction mixture was filtered through cotton into a separatory funnel, and H₂O (10 mL) and EtOAc (10 mL) were added. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with saturated NaHCO_{3(aq)} (10 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (100:0 to 98:2 to 95:5 hexanes/EtOAc) to afford ester **70f** (0.062 g, 90% yield) as a clear, viscous oil. Analytical data: [α]_D²⁸ -49.2 (*c* = 1.50, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 4.68 (br s, 1H), 4.36 (q, *J* = 6.6 Hz, 1H), 3.19 (dd, *J* = 6.0, 4.2 Hz, 1H), 3.08 (dd, *J* = 6.6, 3.6 Hz, 1H), 2.20 (m, 1H), 2.10 (m, 1H), 1.83–1.81 (m, 5H), 1.69–1.66 (m, 5H), 1.58 (m, 1H), 1.38 (m, 1H), 1.23 (s, 3H), 1.17 (s, 3H), 1.01 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 170.4, 135.7, 131.6, 85.1, 80.9, 74.9, 62.0, 40.3, 36.2, 34.1, 31.7, 27.3, 25.8, 25.0, 24.1, 21.7, 21.6, 19.4, 19.3, 18.1, -2.1, -2.2; HRMS (ESI⁺) calcd for C₂₄H₄₃BrO₄Si+Na, 525.2012; found 525.2004; IR (thin film, cm⁻¹) 2929, 2856, 1732, 1472, 1378, 1329, 1217, 1159, 1070, 835; TLC (90:10 hexanes/ EtOAc) *R*_f = 0.62.

((2S,4aS,8aS)-2-(2-((tert-Butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-5-yl)methyl (Z)-2-Methylbut-2-enoate (70g): A flame-dried, 20 mL scintillation vial was charged with CH₂Cl₂ (3 mL) and angelic acid (0.03 g, 0.27 mmol, 2.00 equiv) at rt under an atmosphere of N₂. DCC (0.06 g, 0.27 mmol, 2.00 equiv) and DMAP (0.002 g, 0.014 mmol, 0.10 equiv) were added followed last by a solution of alcohol **69** (0.05 g, 0.14 mmol, 1.00 equiv) in CH₂Cl₂ (1 mL), and the reaction was allowed to stir at rt until TLC analysis confirmed complete conversion of the starting material, 30 h. In some cases, an additional 2.00 equiv of angelic acid and DCC were added

after 12 h to aide starting material conversion. The reaction mixture was filtered through cotton into a separatory funnel, and H₂O (10 mL) and EtOAc (10 mL) were added. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with saturated NaHCO_{3(aq)} (10 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (100:0 to 98:2 to 95:5 hexanes/EtOAc) to afford ester **70g** (0.040 g, 59% yield) as a pale yellow, viscous oil. Analytical data: $[\alpha]_{\text{D}}^{28} -53.1$ ($c = 1.00$, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 6.83 (q, $J = 6.6$ Hz, 1H), 4.65 (br s, 2H), 3.19 (dd, $J = 5.4, 5.4$ Hz, 1H), 3.09 (dd, $J = 6.0, 3.6$ Hz, 1H), 2.19 (m, 1H), 2.10 (m, 1H), 1.97 (m, 1H), 1.88–1.83 (m, 4H), 1.79 (d, $J = 6.6$ Hz, 3H), 1.67 (br s, 4H), 1.56 (m, 2H), 1.37 (m, 1H), 1.23 (s, 3H), 1.16 (s, 3H), 1.01 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 168.3, 137.4, 136.9, 134.3, 132.4, 128.8, 85.1, 81.0, 74.9, 60.4, 36.2, 34.1, 31.7, 31.6, 27.2, 25.8, 25.0, 24.2, 21.7, 19.4, 19.2, 14.4, 12.1, -2.1, -2.2; HRMS (ESI⁺) calcd for C₂₆H₄₆O₄Si+Na, 473.3063; found 473.3055; IR (thin film, cm⁻¹) 2955, 2855, 1731, 1703, 1636, 1487, 1361, 1263, 1070, 835, 758; TLC (90:10 hexanes/EtOAc) $R_f = 0.65$.

2-((2S,4aS,8aS)-2-(2-((tert-Butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-5-yl)methyl 3-(dimethyl(phenyl)silyl)-2-

methylpropanoate (70h): A flame-dried, 20 mL scintillation vial was charged with CH₂Cl₂ (5 mL) and 3-(dimethyl(phenyl)silyl)-2-methylpropanoic acid⁵³ (0.18 g, 0.81 mmol, 2.00 equiv) at rt under an atmosphere of N₂. DCC (0.17 g, 0.81 mmol, 2.00 equiv) and DMAP (0.005 g, 0.04 mmol, 0.10 equiv) were added followed last by a solution of alcohol **69** (0.15 g, 0.41 mmol, 1.00 equiv) in CH₂Cl₂ (2 mL), and the reaction was allowed to stir at rt until TLC analysis confirmed complete conversion of the starting material, 5 h. The reaction mixture was filtered through cotton into a separatory funnel, and H₂O (10 mL) and EtOAc (10 mL) were added. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic extracts were washed with saturated NaHCO_{3(aq)} (10 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (100:0 to 98:2 to 98:2 to 95:5 hexanes/EtOAc) to afford ester **70h** (0.21 g, 91% yield) as a clear, viscous oil. Analytical data: $[\alpha]_{\text{D}}^{28} -42.5$ ($c = 1.30$, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 7.51 (br s, 2H), 7.36 (br s, 3H), 4.56 (dd, $J = 7.8, 4.2$ Hz, 1H), 4.50 (d, $J = 12.0$ Hz, 1H), 3.20 (dd, $J = 6.0, 4.2$ Hz, 1H), 3.10 (dd, $J = 6.0, 3.6$ Hz, 1H), 2.54 (m, 1H), 2.20 (m, 1H), 2.10 (m, 1H), 1.79 (d, $J = 12.6$ Hz, 1H), 1.68–1.66 (m, 5H), 1.58 (m, 2H), 1.32 (m, 2H), 1.25 (s, 3H), 1.19 (s, 3H), 1.15 (d, $J = 6.6$ Hz, 3H), 1.00 (s, 3H), 0.94–0.89 (m, 2H), 0.87 (s, 9H), 0.31 (br s, 6H), 0.10 (s, 3H), 0.08 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 177.6, 138.8, 134.5, 133.5, 132.3, 129.1, 128.9, 127.9, 127.785.1, 81.0, 74.9, 60.3, 36.6, 36.3, 36.2, 34.1, 31.6, 27.3, 27.2, 25.8, 25.1, 24.1, 21.7, 20.7, 20.6, 20.5, 19.8, 19.3, 19.2, 19.2, 18.1, -2.1, -2.2, -2.3, -2.4, -2.6; HRMS (ESI⁺) calcd for C₃₃H₅₆O₄Si₂+Na, 595.3615; found 595.3604; IR (thin film, cm⁻¹) 3052, 2956, 2856, 1809, 1718, 1487, 1457, 1361, 1265, 1198, 1047, 835; TLC (90:10 hexanes/EtOAc) $R_f = 0.78$.

2-((2S,4aS,6S,8aS)-2-(2-((tert-Butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-5-

methyleneoctahydro-2H-chromen-6-yl)-3-(dimethyl(phenyl)silyl)-2-methylpropanoic acid (71b): A flamedried, 20 mL scintillation vial was charged with THF (2 mL) under an atmosphere of N₂. The mixture was cooled to -78 °C, and a premade solution of LDA (0.5

M in THF/hexanes, 0.52 mL, 0.26 mmol, 3.00 equiv) was added followed by a solution of ester **70h** (0.05 g, 0.087 mmol, 1.00 equiv) in THF (1 mL). The reaction was allowed to stir 45 min at this temperature at which point TMSCl (0.04 mL, 0.26 mmol, 3.00 equiv) was added, and the mixture was warmed to rt and stirred 5 min. The septum was replaced with a screw cap, the vial was sealed, and the mixture was warmed to 75 °C and stirred until TLC analysis indicated complete consumption of the starting material, typically 12 h. The mixture was cooled to rt and quenched via addition of 1 M HCl_(aq) (4 mL). The mixture was transferred to a separatory funnel and diluted with Et₂O (10 mL). The organic layer was separated, and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organic extracts were washed with brine (10 mL) and concentrated in vacuo to give the crude rearrangement product in a 6.6:1.1:1 diastereomeric ratio. The diastereomeric ratio was determined by ¹H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 5.25 (minor diastereomer), δ 5.10 (major diastereomer), and δ 5.04 (minor diastereomer, overlapping signals). The product was purified via flash chromatography (100:0 to 95:5 to 90:10 hexanes/EtOAc) to afford carboxylic acid **71b** (0.032 g, 62% yield) as a clear viscous oil. Analytical data: [α]_D²⁸ -18.3 (*c* = 1.25, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 7.51 (m, 2H), 7.34 (m, 3H), 5.10 (s, 1H), 5.01 (s, 1H), 3.11 (dd, *J* = 6.0, 4.8 Hz, 1H), 3.01 (m, 1H), 1.97–1.90 (m, 2H), 1.74 (m, 1H), 1.66–1.54 (m, 6H), 1.38 (s, 3H), 1.27 (m, 2H), 1.22 (s, 3H), 1.17 (s, 3H), 1.16 (s, 3H), 1.15 (m, 1H), 1.07 (s, 3H), 1.05 (m, 1H), 0.84 (s, 9H), 0.37 (s, 3H), 0.29 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 184.0, 160.8, 140.3, 133.5, 128.8, 127.7, 111.7, 84.7, 80.4, 74.8, 52.5, 46.5, 39.3, 36.8, 36.6, 32.7, 30.2, 27.3, 25.9, 25.0, 24.7, 24.5, 23.3, 23.1, 22.1, 22.1, 18.2, -1.2, -1.4, -2.1, -2.2; HRMS (ESI⁺) calcd for C₃₃H₅₆O₄Si₂+Na, 595.3615; found 595.3605; IR (thin film, cm⁻¹) 3420, 3053, 2956, 2956, 2855, 1716, 1689, 1487, 1377, 1265, 1093, 896, 835; TLC (90:10 hexanes/EtOAc) *R*_f = 0.46.

((2S,4aS,8aS)-2-(2-((tert-Butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-3,4,4a,7,8,8a-hexahydro-2H-chromen-5-yl)methyl Isobutyrate (70c): A flame-dried, 500 mL round-bottomed flask was charged with CH₂Cl₂ (110 mL) and isobutyric acid (2.22 mL, 24.47 mmol, 2.00 equiv) at rt under an atmosphere of N₂. DCC (5.05 g, 24.47 mmol, 2.00 equiv) and DMAP (0.15 g, 1.22 mmol, 0.10 equiv) were added followed last by a solution of alcohol **69** (4.51 g, 12.23 mmol, 1.00 equiv) in CH₂Cl₂ (10 mL), and the reaction was allowed to stir at rt until TLC analysis confirmed complete conversion of the starting material, typically 2.5 h. The reaction mixture was filtered through cotton into a separatory funnel, and H₂O (40 mL) and EtOAc (100 mL) were added. The mixture was extracted with EtOAc (3 × 30 mL), and the combined organic extracts were washed with saturated NaHCO_{3(aq)} (2 × 30 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (100:0 to 97.5:2.5 to 95:5 hexanes/EtOAc) to afford ester **70c** (4.01 g, 75%) as a clear, viscous oil. Analytical data: [α]_D²⁸ -73.0 (*c* = 0.75, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 4.58 (br s, 2H), 3.19 (dd, *J* = 5.4, 4.8 Hz, 1H), 3.08 (dd, *J* = 5.4, 4.2 Hz, 1H), 2.54 (m, 1H), 2.19 (m, 1H), 2.09 (m, 1H), 1.82 (dt, *J* = 6.0, 3.0 Hz, 1H), 1.67–1.65 (m, 5H), 1.57 (m, 2H), 1.37 (m, 1H), 1.23 (s, 3H), 1.17 (br s, 6H), 1.15 (d, *J* = 2.4 Hz, 3H), 0.99 (s, 3H), 0.84 (s, 3H), 0.08 (s, 3H), 0.05 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 177.3, 134.5, 132.3, 85.1, 81.0, 74.9, 60.3, 25.8, 24.2, 21.7, 19.3, 19.2,

19.1, 19.0, 18.2, -2.1, -2.2; HRMS (ESI⁺) calcd for C₂₅H₄₆O₄Si+Na, 461.3063; found 461.3062; IR (thin film, cm⁻¹) 2955, 2856, 1721, 1470, 1378, 1215, 1092, 835, 756; TLC (85:15 hexanes/EtOAc) *R_f* = 0.66.

2-((2S,4aS,6S,8aS)-2-(2-((tert-Butyldimethylsilyloxy)propan-2-yl)-4a,6-dimethyl-5-methyleneoctahydro-2H-chromen-6-yl)-2-methylpropanoic acid (71a): A flame-dried, 250 mL round-bottomed flask was charged with THF (80 mL) and diisopropylamine (3.84 mL, 27.42 mmol, 3.00 equiv) under an atmosphere of N₂. The mixture was cooled to 0 °C and ⁿBuLi (1.85 M solution in hexanes, 14.82 mL, 27.42 mmol, 3.00 equiv) was added slowly. After being stirred for 30 min at 0 °C, the mixture was cooled to -78 °C, and isobutyrate **70c** (4.01 g, 9.14 mmol, 1.00 equiv) was added as a solution in THF (15 mL). The mixture was allowed to stir for 45 min at which time TMSCl (3.52 mL, 27.42 mmol, 3.00 equiv) was added. The reaction mixture was then allowed to warm to rt, stirred for 5 min, and subsequently warmed to 75 °C and stirred until TLC analysis indicated complete conversion of the starting material, typically 12h. The reaction mixture was cooled to rt and quenched via 1 M HCl_(aq) (25 mL). The mixture was then partitioned in a separatory funnel and extracted with Et₂O (3 × 20 mL). The combined organic extracts were washed with 6 M HCl (2 × 30 mL), dried with magnesium sulfate, and concentrated in vacuo to provide the crude acid as a 6:1 mixture of diastereomers. The diastereomeric ratio was determined by ¹H NMR spectroscopic analysis of the crude reaction mixture by comparison of the integration of the resonances at δ 5.13 (minor diastereomer) and δ 5.12 (major diastereomer). The product was purified via flash chromatography (100:0 to 90:10 to 80:20 hexanes/EtOAc) to afford acid **71a** (3.14 g, 78% yield) as a clear, viscous oil in an inseparable 6:1 diastereomeric ratio. Analytical data: [*α*]_D²⁸ -43.5 (*c* = 0.70, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 5.12 (s, 1H), 5.04 (s, 1H), 3.12 (dd, *J* = 6.6, 2.4 Hz, 1H), 3.04 (m, 1H), 2.09 (m, 1H), 1.95 (m, 1H), 1.66 (m, 2H), 1.59 (m, 2H), 1.54 (m, 1H), 1.41 (m, 1H), 1.33 (s, 3H), 1.31 (s, 3H), 1.25 (s, 3H), 1.23 (s, 3H), 1.17 (s, 3H), 1.09 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 184.5, 161.1, 110.4, 84.7, 81.0, 74.8, 50.2, 44.4, 39.5, 36.9, 33.2, 28.3, 27.4, 25.6, 25.0, 24.6, 23.7, 23.6, 22.4, 22.1, 18.2, -2.2; HRMS (ESI⁺) calcd for C₂₅H₄₆O₄Si+Na, 461.3063; found 461.3063; IR (thin film, cm⁻¹) 3406, 2955, 2856, 1693, 1641, 1471, 1378, 1252, 1170, 1094, 1042, 835, 760; TLC (85:15 hexanes/EtOAc) *R_f* = 0.40.

Synthesis of Ketone 72

Methyl 2-((2S,4aS,6S,8aS)-2-(2-((tert-Butyldimethylsilyloxy)propan-2-yl)-4a,6-dimethyl-5-methyleneoctahydro-2H-chromen-6-yl)-2-methylpropanoate (S5): The acid **71a** (3.14 g, 7.16 mmol, 1.00 equiv) was dissolved in MeOH/C₇H₈ (2:1, 75 mL) in a 250 mL round-bottomed flask with magnetic stirring at rt. TMSCHN₂ (2 M in Et₂O, 10.00 mL, 20 mmol, 2.79 equiv) was added dropwise until the yellow color of excess TMSCHN₂ in solution persisted. AcOH (1.50 g, 24.98 mmol, 3.50 mmol) was added dropwise, giving a clear solution. The resulting mixture was concentrated in vacuo and purified via flash chromatography (100:0 to 97.5:2.5 to 95:5 hexanes/EtOAc) to afford ester **S5** (3.06 g, 94% yield) as a clear, viscous oil in an inseparable 6.3:1 diastereomeric ratio (as determined by integration of the resonances at δ 3.64 (minor diastereomer) and δ 3.62 (major diastereomer)). Analytical data: [*α*]_D²⁸ -89.7 (*c* = 0.60, CHCl₃); ¹H NMR (600 MHz,

CDCl₃) δ 5.01 (s, 1H), 5.00 (s, 1H), 3.62 (s, 3H), 3.08 (m, 1H), 3.03 (dd, $J = 6.0, 2.4$ Hz, 1H), 2.08 (m, 1H), 1.95 (dt, $J = 5.4, 3.6$ Hz, 1H), 1.65 (m, 2H), 1.59 (m, 2H), 1.57 (br s, 1H), 1.50 (m, 1H), 1.39 (m, 1H), 1.29 (s, 3H), 1.28 (s, 3H), 1.22 (s, 3H), 1.21 (s, 3H), 1.16 (s, 3H), 1.08 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 178.7, 161.4, 110.0, 84.8, 81.0, 74.9, 51.4, 50.3, 44.3, 39.5, 36.9, 33.1, 28.5, 27.3, 25.6, 25.0, 24.6, 23.9, 23.7, 22.4, 22.1, 18.2, -2.1, -2.2; HRMS (ESI⁺) calcd for C₂₆H₄₈O₄Si+Na, 475.3220; found 475.3221; IR (thin film, cm⁻¹) 2954, 2855, 1722, 1601, 1451, 1378, 1169, 1051, 835, 741; TLC (85:15 hexanes/EtOAc) $R_f = 0.66$.

3-((2S,4aS,6S,8aS)-2-(2-((tert-Butyldimethylsilyl)oxy)propan-2-yl)-4a,6-dimethyl-5-methyleneoctahydro-2H-chromen-6-yl)-3-methylbutan-2-one (72): A flame-dried, 500 mL round-bottomed flask was charged with ester **S5** (3.82 g, 8.44 mmol, 1.00 equiv) and Et₂O (84 mL) under an atmosphere of N₂. The mixture was cooled to 0 °C, and MeLi (1.6 M in Et₂O, 21.09 mL, 33.75 mmol, 4.00 equiv) was added. The mixture was warmed to rt, whereupon TLC analysis showed incomplete conversion of the starting material. A second addition of MeLi (4.00 equiv) was carried out, upon which TLC analysis showed remaining starting material. A third addition of MeLi (4.00 equiv) was carried out, upon which TLC analysis showed complete conversion of the starting material. The reaction mixture was cooled to 0 °C and quenched carefully with saturated NH₄Cl_(aq) (25 mL). The mixture was partitioned in a separatory funnel, and the aqueous layer was extracted with Et₂O (3 × 20 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo. The product was purified via flash chromatography (100:0 to 97.5:2.5 to 95:5 hexanes/EtOAc) to afford ketone **72** (3.52 g, 86% yield) as a clear, viscous oil in an inseparable 7:1 ratio of diastereomers (as determined by integration of the resonances at δ 5.05 (major diastereomer) and δ 5.03 (minor diastereomer)). Analytical data: $[\alpha]_D^{28} -92.2$ ($c = 0.60$, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 5.05 (s, 1H), 4.90 (s, 1H), 3.15 (dd, $J = 5.4, 4.8$ Hz, 1H), 3.04 (m, 1H), 2.18 (s, 3H), 1.96 (m, 1H), 1.66 (m, 1H), 1.61–1.59 (m, 3H), 1.53 (m, 1H), 1.44 (m, 1H), 1.30 (s, 3H), 1.23 (s, 3H), 1.22 (s, 3H), 1.16 (br s, 6H), 1.08 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 215.1, 161.4, 111.1, 84.7, 80.5, 74.8, 54.7, 44.9, 39.4, 36.8, 33.0, 29.7, 29.4, 27.4, 25.8, 25.0, 24.6, 23.6, 23.5, 22.7, 22.0, 18.1, -2.1, -2.2; HRMS (ESI⁺) calcd for C₂₆H₄₈O₃Si+Na, 459.3271; found 459.3267; IR (thin film, cm⁻¹) 2955, 2856, 1694, 1620, 1470, 1377, 1251, 1094, 835; TLC (85:15 hexanes/EtOAc) $R_f = 0.54$.

3-((2S,4aS,5R,6S,8aS)-2-(2-((tert-Butyldimethylsilyl)oxy)propan-2-yl)-5-(hydroxymethyl)-4a,6-dimethyloctahydro-2H-chromen-6-yl)-3-methylbutan-2-ol (73):

A flame-dried, 250 mL round-bottomed flask was charged with ketone **72** (1.63 g, 3.74 mmol, 1.00 equiv) and THF (70 mL) under an atmosphere of N₂. BH₃·THF (1 M in THF, 16.82 mL, 4.50 equiv) was added, and the mixture was warmed to 50 °C and stirred until complete conversion of the starting material was observed by TLC analysis, typically 12 h. The reaction mixture was then cooled to 0 °C, and 3 M NaOH_(aq) (7.5 mL) was added slowly followed by H₂O₂ (30% w/w in H₂O, 7.5 mL). The resulting mixture was warmed to rt and stirred for 2.5 h, upon which the mixture was partitioned in a separatory funnel, diluted with H₂O (30 mL), and extracted with Et₂O (3 × 20 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo to afford the crude

diol as an inseparable mixture of diastereomers at C12c and C6a. The diastereoselection of this reaction at C4b was determined via ^1H NMR analysis of the subsequent intermediate **74**. The product was purified via flash chromatography (80:20 to 70:30 hexanes/EtOAc) to afford diol **73** (1.27 g, 74% yield) as a white, viscous foam. This diastereomeric mixture was carried on to the next step without further separation. Analytical data: $[\alpha]_{\text{D}}^{28} -83.9$ ($c = 0.60$, CHCl_3); ^1H NMR (600 MHz, CDCl_3) δ 4.18 (m, 2H), 3.88 (t, $J = 12.6$ Hz, 2H), 3.68 (dd, $J = 9.0, 3.0$ Hz, 1H), 3.56 (d, $J = 12.0$ Hz, 1H), 3.06 (m, 2H), 2.93 (dd, $J = 6.0, 4.8$ Hz, 1H), 2.86 (dd, $J = 7.2, 4.2$ Hz, 1H), 1.98 (m, 3H), 1.76 (s, 1H), 1.59–1.49 (m, 11H), 1.42–1.36 (m, 3H), 1.25 (d, $J = 6.0$ Hz, 5H), 1.21 (s, 6H), 1.15 (s, 7H), 1.01 (s, 2H), 0.95 (br s, 9H), 0.90 (br s, 4H), 0.89 (s, 3H), 0.86 (s, 2H), 0.83 (br s, 22H), 0.07 (s, 7H), 0.05 (s, 7H); ^{13}C NMR (150 MHz, CDCl_3) δ 85.1, 84.9, 84.2, 83.7, 74.9, 68.7, 61.5, 61.0, 54.2, 52.9, 45.8, 45.1, 42.5, 42.4, 39.0, 38.5, 37.9, 37.8, 34.0, 33.5, 27.4, 27.3, 25.8, 25.2, 25.0, 24.9, 24.6, 21.5, 21.4, 21.2, 19.8, 18.1, 17.8, 17.5, 14.7, 14.2, -2.1, -2.2; HRMS (ESI⁺) calcd for $\text{C}_{26}\text{H}_{52}\text{O}_4\text{Si}+\text{Na}$, 479.3533; found 479.3549; IR (thin film, cm^{-1}) 3320, 2955, 2855, 1471, 1379, 1251, 1172, 1100, 834, 759; TLC (85:15 hexanes/EtOAc) $R_f = 0.14$.

(3S,4aS,6aS,10aR,10bS)-3-(2-((tert-Butyldimethylsilyloxy)-propan-2-yl)-6a,7,7,10b-tetramethyl-2,3,5,6,6a,7,10a,10b-octahydro-1H-benzof[chromen-8(4aH)-one (75): A flame-dried, 250 mL round-bottomed flask was charged with CH_2Cl_2 (70 mL) and $(\text{COCl})_2$ (1.71 mL, 19.92 mmol, 5.00 equiv) under an atmosphere of N_2 . The mixture was cooled to -78 °C, and DMSO (2.83 mL, 39.84 mmol, 10.00 equiv) was added slowly. The mixture was allowed to stir 30 min at -78 °C then the diol **73** (1.82 g, 3.98 mmol, 1.00 equiv) was added as a solution in CH_2Cl_2 (10 mL). The reaction mixture was stirred at this temperature for 2 h then DIPEA (13.88 mL, 79.69 mmol, 20.0 equiv) was added. The reaction was stirred 30 min at -78 °C then warmed to 0 °C and stirred 15 min. At this time TLC analysis confirmed complete conversion of the starting material. The reaction was quenched with saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (25 mL), and the mixture was partitioned in a separatory funnel. The mixture was extracted with CH_2Cl_2 (3×20 mL), and the combined organic extracts were washed with brine (20 mL), dried with magnesium sulfate and concentrated in vacuo to afford the crude ketoaldehyde **74**, which was carried to the next step without further purification. (Note: at this stage, a single diastereomer was observed in the ^1H NMR spectrum of the crude aldehyde, thereby establishing complete control of the C4b methine stereocenter in the hydroboration/oxidation step. This crude spectrum is provided in the Supporting Information.)

The crude ketoaldehyde **74** was dissolved in MeOH/THF (1:1, 80 mL) in a 250 mL round-bottomed flask and cooled to 0 °C with magnetic stirring. $\text{KOH}_{(\text{aq})}$ (2 M, 8 mL) was added, and the reaction was warmed to rt and stirred for 12 h. The resulting mixture was concentrated on a rotary evaporator and partitioned with EtOAc (30 mL) and H_2O (30 mL) in a separatory funnel. The mixture was extracted with EtOAc (3×20 mL), and the combined organic extracts were dried with magnesium sulfate and concentrated in vacuo. The product was purified via flash chromatography (100:0 to 97.5:2.5 to 95:5 to 90:10 hexanes/EtOAc) to afford the enone **75** (1.29 g, 75% yield) as a yellow, viscous oil. Analytical data: $[\alpha]_{\text{D}}^{28} -109.0$ ($c = 0.85$, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 6.73 (d, $J = 12.6$ Hz, 1H), 5.99 (dd, $J = 7.0, 3.5$ Hz, 1H), 3.14 (dd, $J = 9.0, 3.0$ Hz, 1H), 2.97 (dd, $J =$

5.0, 5.0 Hz, 1H), 2.29 (br s, 1H), 1.96 (d, $J = 9.0$ Hz, 1H), 1.70–1.58 (m, 6H), 1.43 (m, 1H), 1.23 (s, 3H), 1.17 (s, 3H), 1.07 (s, 3H), 1.00 (s, 3H), 0.95 (s, 3H), 0.93 (s, 3H), 0.84 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 204.9, 146.2, 129.0, 85.6, 85.0, 74.8, 51.5, 49.7, 43.8, 37.3, 35.5, 30.5, 27.4, 25.8, 24.9, 23.8, 21.2, 20.3, 18.1, 16.9, 16.6, 14.7, -2.1, -2.2; HRMS (ESI⁺) calcd for $\text{C}_{26}\text{H}_{46}\text{O}_3\text{Si}+\text{Na}$, 457.3114; found 457.3129; IR (thin film, cm^{-1}) 2954, 2855, 1677, 1461, 1389, 1251, 1174, 1103, 1041, 834, 756; TLC (85:15 hexanes/EtOAc) $R_f = 0.43$.

((3S,4aS,6aS,10aR,10bS,E)-3-(2-((tert-Butyldimethylsilyloxy)propan-2-yl)-6a,7,7,10b-tetramethyldecahydro-1H-benzo[f]-chromen-8(4aH)-one O-Benzyl Oxime (76): The enone **75** (1.61 g, 3.70 mmol, 1.00 equiv) was dissolved in EtOAc (60 mL) in a 250 mL round-bottomed flask and charged with Pd/C (2.40 g, 1.50 mass equiv). The reaction mixture was placed under 1 atm (balloon) of H_2 and stirred until full conversion of the starting material was observed by TLC analysis, typically 30 min. The mixture was then filtered through a pad of Celite, and the filter cake was washed with two 20 mL portions of EtOAc. The solution was then concentrated in vacuo to afford the crude ketone, which was carried to the next step without further purification.

The residue was dissolved in MeOH/ H_2O (5:1, 80 mL) in a 250 mL round-bottomed flask. BnONH_3Cl (11.84 g, 74.19 mmol, 20.00 equiv) and NaOAc (4.56 g, 55.64 mmol, 15.00 equiv) were added, and the resulting suspension was fitted with a reflux condenser and heated to 85 °C with stirring until TLC analysis confirmed complete consumption of the starting material, typically 16 h. The reaction mixture was cooled to rt and concentrated on a rotary evaporator. The residue was taken up into H_2O (30 mL) and CH_2Cl_2 (30 mL), and the mixture was partitioned in a separatory funnel and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with H_2O (30 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (100:0 to 98:2 to 97.5:2.5 to 95:5 hexanes/EtOAc) to afford oxime **76** (1.66 g, 83% yield) as a clear, viscous oil. Analytical data: $[\alpha]_{\text{D}}^{28} -112.8$ ($c = 0.45$, CHCl_3); ^1H NMR (600 MHz, CDCl_3) δ 7.37–7.28 (m, 5H), 5.08 (br s, 2H), 3.35 (dd, $J = 9.6, 4.2$ Hz, 1H), 3.10 (dd, $J = 8.4, 3.0$ Hz, 1H), 2.88 (dd, $J = 6.0, 4.2$ Hz, 1H), 1.82 (m, 2H), 1.66–1.45 (m, 7H), 1.36 (m, 1H), 1.23 (s, 3H), 1.16 (s, 3H), 1.13 (s, 3H), 1.01 (s, 3H), 0.85 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 165.2, 138.7, 128.1, 128.0, 127.4, 85.4, 85.3, 75.1, 74.9, 45.9, 45.5, 41.1, 38.2, 36.2, 31.3, 27.3, 25.8, 25.0, 24.5, 23.3, 21.4, 20.9, 20.0, 19.0, 18.1, 16.8, 13.3, -2.2; HRMS (ESI⁺) calcd for $\text{C}_{33}\text{H}_{55}\text{NO}_3\text{Si}+\text{Na}$, 564.3849; found 564.3862; IR (thin film, cm^{-1}) 2951, 2855, 1626, 1470, 1378, 1250, 1173, 1040, 898, 835, 757; TLC (85:15 hexanes/EtOAc) $R_f = 0.77$.

((3S,4aS,6aS,7R,10aR,10bS,E)-8-((Benzoyloxy)imino)-3-(2-((tert-butyltrimethylsilyloxy)propan-2-yl)-6a,7,10b-trimethyldecahydro-1H-benzo[f]chromen-7-yl)methyl acetate (78): A 100 mL round-bottomed flask was charged with oxime **76** (1.66 g, 3.06 mmol, 1.00 equiv) and AcOH:Ac₂O (1:1, 31 mL) with magnetic stirring at rt. $\text{Pd}(\text{OAc})_2$ (0.10 g, 0.46 mmol, 0.15 equiv) and $\text{PhI}(\text{OAc})_2$ (1.48 g, 4.60 mmol, 1.50 equiv) were added sequentially, and the reaction mixture was warmed to 100 °C. This temperature was maintained until TLC analysis showed complete conversion of the starting material,

typically 1 h. The mixture was cooled to rt, diluted with pentane (30 mL) and H₂O (20 mL), and transferred to a separatory funnel. Saturated NaHCO_{3(aq)} (30 mL) was added dropwise into the separatory funnel, and the mixture was allowed to stand 10 min upon completion of the addition. The layers were separated, and the aqueous layer was extracted with pentane (3 × 20 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo to afford the crude acetate **78** as a single diastereomer (as determined by ¹H NMR spectroscopic analysis of the crude reaction mixture, which revealed a single compound). The product was purified via flash chromatography (100:0 to 95:5 to 90:10 hexanes/EtOAc) to afford the acetate **78** (1.49 g, 81% yield) as a reddish-brown, viscous oil. Analytical data: [α]_D²⁸ -66.2 (*c* = 0.70, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 7.34–7.27 (m, 5H), 5.04 (br s, 2H), 4.55 (d, *J* = 10.8 Hz, 1H), 4.03 (d, *J* = 11.4 Hz, 1H), 3.36 (dd, *J* = 10.8, 13.6 Hz, 1H), 3.09 (dd, *J* = 8.4, 3.0 Hz, 1H), 2.88 (dd, *J* = 5.4, 4.8 Hz, 1H), 1.94 (s, 3H), 1.82–1.74 (m, 2H), 1.63–1.52 (m, 8H), 1.35 (m, 1H), 1.22 (s, 3H), 1.21 (s, 3H), 1.15 (s, 3H), 0.91 (s, 3H), 0.84 (s, 12H), 0.08 (s, 3H), 0.06 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 171.1, 161.6, 128.2, 128.0, 127.4, 85.3, 85.1, 75.4, 74.8, 65.6, 48.4, 46.0, 42.1, 38.2, 36.3, 32.0, 27.3, 25.8, 25.0, 24.4, 21.4, 21.1, 20.8, 20.1, 18.1, 17.3, 17.0, 13.5, -2.2; HRMS (ESI⁺) calcd for C₃₅H₅₇NO₅Si+Na, 622.3904; found 622.3908; IR (thin film, cm⁻¹) 2953, 2884, 1732, 1470, 1380, 1249, 1038, 835, 756; TLC (60:40 hexanes/EtOAc) *R*_f = 0.80.

Synthesis of Ketoaldehyde **83**

(3S,4aS,6aS,7S,10aR,10bS)-7-(Hydroxymethyl)-3-(2-hydroxypropan-2-yl)-6a,7,10b-trimethyldecahydro-1H-benzof[chromen-8(4aH)-one (S6):

A 50 mL roundbottomed flask was charged with acetate **78** (0.71 g, 1.18 mmol, 1.00 equiv) and 2 M HCl_(aq)/MeOH/THF/acetone (10:10:10:1, 12 mL). The mixture was warmed to 85 °C and stirred until full convergence to a single product was observed by TLC analysis, typically 5 h. The mixture was cooled to rt and concentrated on a rotary evaporator, and the residue was taken up into H₂O (15 mL) and CH₂Cl₂ (15 mL) and partitioned in a separatory funnel. The mixture was extracted with CH₂Cl₂ (3 × 10 mL), and the combined organic extracts were dried with magnesium sulfate and concentrated in vacuo. The product was purified via flash chromatography (60:40 EtOAc:hexanes) to afford hydroxy ketone **S6** (0.28 g, 71% yield) as a reddish-brown, viscous oil. Analytical data: [α]_D²⁸ -159.6 (*c* = 0.30, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 4.12 (dd, *J* = 8.4, 3.0 Hz, 1H), 3.22 (m, 2H), 3.02 (dd, *J* = 6.0, 3.0 Hz, 1H), 2.64 (dd, *J* = 7.2, 3.0 Hz, 1H), 2.59 (br s, 1H), 2.55 (m, 1H), 2.29 (m, 1H), 1.89–1.86 (m, 2H), 1.80 (m, 1H), 1.70–1.60 (m, 6H), 1.46 (m, 1H), 1.40 (dt, *J* = 6.0, 3.6 Hz, 1H), 1.31 (s, 3H), 1.23 (m, 1H), 1.18 (s, 3H), 1.15 (s, 3H), 0.99 (s, 3H), 0.91 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 219.3, 85.0, 84.6, 71.8, 63.6, 57.4, 45.3, 42.1, 37.9, 37.6, 36.4, 30.7, 26.1, 23.9, 23.7, 21.7, 21.2, 18.2, 16.9, 13.5; HRMS (ESI⁺) calcd for C₂₀H₃₄O₄+Na, 361.2355; found 361.2360; IR (thin film, cm⁻¹) 3450, 2950, 1692, 1425, 1166, 1102, 735, 685; TLC (60:40 hexanes/EtOAc) *R*_f = 0.12.

(3S,4aS,6aS,7S,10aR,10bS)-3-(2-Hydroxypropan-2-yl)-6a,7,10b-trimethyl-8-

oxododecahydro-1H-benzof[chromene-7-carbaldehyde (83): A 20 mL scintillation vial was charged with alcohol **S6** (0.29 g, 0.84 mmol, 1.00 equiv) and CH₂Cl₂ (8 mL). Dess-Martin periodinane (0.71 g, 1.68 mmol, 2.00 equiv) was added at rt with stirring. The reaction mixture was allowed to stir at room temperature until TLC analysis confirmed

complete conversion of the starting material, typically 20 min. The mixture was then quenched via a 1:1 solution of saturated $\text{NaHCO}_3(\text{aq})$ and saturated $\text{Na}_2\text{S}_2\text{O}_3(\text{aq})$ (10 mL), and the mixture was stirred 5 min. The reaction mixture was then diluted with Et_2O (15 mL) and partitioned in a separatory funnel. The aqueous layer was extracted with Et_2O (3×10 mL), and the combined organic extracts were dried with magnesium sulfate and concentrated in vacuo. The product was purified via flash chromatography (60:40 to 50:50 hexanes/ EtOAc) to afford the ketoaldehyde **83** (0.28 g, 99% yield) as a pale white powder. Analytical data: mp 121–125 °C; $[\alpha]_{\text{D}}^{28} -223.7$ ($c = 0.50$, CHCl_3); ^1H NMR (600 MHz, CDCl_3) δ 10.06 (s, 1H), 3.22 (dd, $J = 9.0, 3.0$ Hz, 1H), 3.02 (dd, $J = 6.0, 2.4$ Hz, 1H), 2.52–2.46 (m, 2H), 1.94–1.82 (m, 3H), 1.57–1.70 (m, 5H), 1.47 (m, 1H), 1.26 (s, 3H), 1.24 (s, 3H), 1.22 (m, 1H), 1.18 (s, 3H), 1.15 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 214.0, 204.2, 84.9, 84.6, 71.9, 64.7, 45.1, 43.4, 37.8, 37.6, 36.5, 31.6, 26.1, 23.7, 23.5, 21.6, 20.9, 19.5, 14.8, 13.6; HRMS (ESI⁺) calcd for $\text{C}_{20}\text{H}_{32}\text{O}_4 + \text{Na}$, 359.2199; found 359.2198; IR (thin film, cm^{-1}) 3019, 2955, 2857, 2400, 1721, 1388, 1265, 1215, 1098; TLC (60:40 hexanes/ EtOAc) $R_f = 0.24$.

(3S,4aS,6aS,7S,10aR,10bS)-7-(1-Hydroxyallyl)-3-(2-hydroxypropan-2-yl)-6a,7,10b-trimethyl-8-vinyldodecahydro-1H-benzof[*f*]-chromen-8-ol (84): A flame-dried, 20 mL scintillation vial was charged with LiCl (0.30 g, 7.13 mmol, 20.00 equiv equiv), anhydrous CeCl_3 (0.88 g, 3.57 mmol, 10.00 equiv), and a stir bar in a nitrogen-filled glovebox. The vial was removed from the glovebox and placed under an N_2 atmosphere. THF (5 mL) was added, and this mixture was stirred at rt for 2.5 h. A separate flame-dried, 20 mL scintillation vial was charged with aldehyde **83** (0.12 g, 0.36 mmol, 1.00 equiv) and THF (2 mL) under an atmosphere of N_2 . The $\text{CeCl}_3 \cdot 2\text{LiCl}$ suspension was added to the solution of **83** at rt, and the resulting mixture was stirred 2.5 h. The reaction was subsequently cooled to -78 °C, and vinylmagnesium bromide (1 M in THF, 3.57 mL, 3.57 mmol, 10 equiv) was added. The reaction mixture was allowed to stir at this temperature until TLC analysis confirmed complete consumption of the starting material, typically 20 min. The reaction was quenched with MeOH (3 mL), and the mixture was immediately warmed to rt upon which 5% $\text{AcOH}(\text{aq})$ (2 mL) and Et_2O (2 mL) were added with stirring. Once the vial had reached rt, the solution was transferred to a separatory funnel, diluted with H_2O (15 mL) and extracted with Et_2O (3×15 mL). The combined organic extracts were washed with saturated $\text{NaHCO}_3(\text{aq})$ (10 mL), dried with magnesium sulfate and concentrated in vacuo. The product was purified via flash chromatography (80:20 to 70:30 to 60:40 hexanes/ EtOAc) to afford an inseparable 2.6:1 mixture of diol diastereomers **84** (0.14 g, 99% yield) as a pale white, viscous foam. Analytical data: $[\alpha]_{\text{D}}^{28} -182.8$ ($c = 0.25$, CHCl_3); ^1H NMR (600 MHz, CDCl_3) δ 6.30 (dd, $J = 10.8, 6.0$ Hz, 1H), 6.14 (m, 1H), 5.24 (d, $J = 17.4$ Hz, 1H), 5.08 (d, $J = 10.8$ Hz, 1H), 5.03–4.99 (m, 2H), 4.40 (d, $J = 8.4$ Hz, 1H), 3.16 (m, 1H), 2.88 (m, 1H), 1.83 (m, 3H), 1.72 (m, 2H), 1.59 (m, 3H), 1.53 (s, 3H), 1.45–1.36 (m, 5H), 1.15 (s, 3H), 1.14 (s, 3H), 1.03 (m, 1H), 0.90 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 145.8, 140.7, 116.4, 112.6, 85.7, 84.5, 80.0, 79.6, 72.0, 49.4, 47.3, 43.1, 38.0, 36.3, 35.9, 32.4, 26.0, 24.3, 23.6, 21.9, 19.5, 18.6, 17.0, 13.3; HRMS (ESI⁺) calcd for $\text{C}_{24}\text{H}_{40}\text{O}_4 + \text{Na}$, 415.2825; found 415.2829; IR (thin film, cm^{-1}) 3303, 2949, 2877, 1621, 1461, 1301, 1089, 920, 737; TLC (60:40 hexanes/ EtOAc) $R_f = 0.32$.

(2S,4aS,4bR,9aS,9bS,11aS)-2-(2-Hydroxypropan-2-yl)-4a,9a,9b-trimethyl-3,4,4a,4b,5,6,9,9a,9b,10,11,11a-dodecahydroindeno[5,4-f]chromene-6a,9(2H)-diol (85): A flame-dried, 20 mL scintillation vial was charged with Grubbs' second generation catalyst (0.99 g, 0.12 mmol, 0.20 equiv) and a stir bar in a nitrogen-filled glovebox. The vial was removed from the glovebox and charged with CH₂Cl₂ (12 mL) under an atmosphere of N₂. Diol **84** (0.23 g, 0.59 mmol, 1.00 equiv) was added as a solution in CH₂Cl₂ (3 mL), and the mixture was allowed to stir at rt until complete conversion of the starting material was observed by TLC analysis, typically 3 h. The reaction mixture was concentrated in vacuo, and the product was purified via flash chromatography (80:20 to 70:30 to 60:40 hexanes/EtOAc) to afford allylic alcohol **85** (0.16 g, 73% yield) as a pale-brown viscous foam. Analytical data: [α]_D²⁸ -62.8 (*c* = 0.75, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 6.22 (d, *J* = 5.4 Hz, 1H), 6.14 (dd, *J* = 3.0, 2.4 Hz, 1H), 4.42 (br s, 1H), 3.18 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.95 (dd, *J* = 7.8, 3.6 Hz, 1H), 2.69 (br s, 1H), 2.26 (d, *J* = 5.4 Hz, 1H), 2.22 (br s, 1H), 1.83–1.75 (m, 8H), 1.63 (s, 3H), 1.56–1.54 (m, 3H), 1.42 (m, 2H), 1.17 (s, 3H), 1.16 (s, 3H), 0.94 (s, 3H), 0.92 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 143.2, 137.2, 87.3, 86.0, 84.6, 83.3, 71.9, 52.5, 47.9, 41.8, 38.3, 36.3, 32.9, 30.4, 26.8, 26.1, 23.9, 23.6, 21.9, 20.2, 17.7, 13.2; HRMS (ESI⁺) calcd for C₂₂H₃₆O₄+Na, 387.2512; found 387.2519; IR (thin film, cm⁻¹) 3400, 2951, 2675, 1729, 1449, 1384, 1256, 1097, 1023, 910, 754; TLC (60:40 hexanes/EtOAc) *R*_f = 0.25.

(2S,4aS,4bR,9aS,9bS,11aS)-2-(2-Hydroxypropan-2-yl)-4a,9a,9b-trimethyl-3,4,4a,4b,5,6,8,9a,9b,10,11,11a-dodecahydroindeno[5,4-f]chromen-9(2H)-one (86): A flame-dried, 20 mL scintillation vial was charged with diol **85** (0.15 g, 0.40 mmol, 1.00 equiv) and CH₂Cl₂ (9 mL) under an atmosphere of N₂. The mixture was cooled to 0 °C, and TFA (0.15 mL, 2.02 mmol, 5.00 equiv) was added. The reaction mixture was warmed to rt and allowed to stir until complete conversion of the starting material was observed by TLC analysis, typically 30 min. The reaction was quenched with saturated NaHCO_{3(aq)} (5 mL), and the mixture was partitioned in a separatory funnel. The aqueous layer was extracted with CH₂Cl₂ (3 × 5 mL), and the combined organic extracts were dried with Na₂SO₄ and concentrated in vacuo. The product was purified via flash chromatography (90:10 to 80:20 to 70:30 hexanes/EtOAc) to afford the nonconjugated enone **86** (0.10 g, 71% yield) as a pale brown, viscous oil. Analytical Data: [α]_D²⁸ -77.7 (*c* = 0.50, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 5.64 (m, 1H), 3.17 (dd, *J* = 9.0, 2.4 Hz, 1H), 2.95 (dd, *J* = 5.4, 4.8 Hz, 1H), 2.83 (m, 1H), 2.69 (m, 1H), 2.61 (br s, 1H), 2.40 (m, 1H), 2.10 (br s, 1H), 1.84 (m, 2H), 1.64 (m, 3H), 1.55 (m, 2H), 1.43–1.33 (m, 3H), 1.16 (s, 3H), 1.13 (br s, 4H), 1.12 (s, 3H), 0.91 (s, 3H), 0.83 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 223.0, 148.2, 116.3, 85.5, 84.4, 71.8, 59.3, 46.6, 43.0, 41.1, 37.9, 36.5, 30.9, 27.6, 26.1, 24.0, 23.7, 21.8, 21.7, 17.6, 17.4, 13.4; HRMS (ESI⁺) calcd for C₂₂H₃₄O₃+Na, 369.2406; found 369.2398; IR (thin film, cm⁻¹) 3053, 2979, 2977, 1734, 1558, 1472, 1373, 1265, 1139, 1086, 971, 921, 704; TLC (80:20 hexanes/EtOAc) *R*_f = 0.23.

(2S,4aS,4bR,6aR,9aS,9bS,11aS)-2-(2-Hydroxypropan-2-yl)-4a,9a,9b-trimethyltetradecahydroindeno[5,4-f]chromen-9(2H)-one (87): A 20 mL scintillation vial was charged with ketone **86** (0.008 g, 0.02 mmol, 1.00 equiv) and EtOH (2 mL), and Pd/C (0.013 g, 1.50 mass equiv) was added. The reaction mixture was placed under 1 atm

H₂ (balloon), and the mixture was allowed to stir overnight. The reaction was filtered through a Celite plug, and the filtrate was concentrated on a rotary evaporator to give the crude ketone as a single diastereomer (as determined by ¹H NMR spectroscopic analysis of the crude reaction mixture, which revealed a single compound). The product was purified via flash chromatography (90:10 to 80:20 to 70:30 hexanes/EtOAc) to afford ketone **87** as a clear, viscous oil. Analytical data: [α]_D²⁸ -45.2 (*c* = 0.35, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 3.18 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.92 (d, *J* = 6.6, 4.2 Hz, 1H), 2.60 (br s, 1H), 2.33 (m, 1H), 2.21 (m, 1H), 2.03 (m, 1H), 1.92–1.82 (m, 3H), 1.74 (m, 2H), 1.64–1.41 (m, 11H), 1.17 (s, 3H), 1.14 (s, 3H), 1.10 (s, 3H), 1.04 (s, 3H), 0.85 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 224.9, 85.4, 84.4, 71.8, 54.5, 47.5, 46.2, 39.3, 38.8, 37.8, 36.3, 32.5, 26.8, 26.2, 26.1, 23.7, 23.5, 21.8, 20.9, 19.5, 17.3, 13.5; HRMS (ESI⁺) calcd for C₂₂H₃₆O₃+Na, 371.2562; found 371.2554; IR (thin film, cm⁻¹) 3446, 2955, 2852, 1731, 1636, 1520, 1473, 1396, 1085, 754; TLC (80:20 hexanes/EtOAc) *R*_f = 0.20.

(2S,4aS,4bR,9S,9aS,9bS,11aS)-2-(2-Hydroxypropan-2-yl)-4a,9a,9b-trimethyl-2,3,4,4a,4b,5,6,8,9,9a,9b,10,11,11a-tetradecahydroindeno[5,4-f]chromen-9-ol (88): A flame-dried, 20 mL scintillation vial was charged with diol **86** (0.16 g, 0.43 mmol, 1.00 equiv) and CH₂Cl₂ (9 mL) under an atmosphere of N₂. The mixture was cooled to 0 °C, and TFA (0.17 mL, 2.14 mmol, 5.00 equiv) was added. The reaction mixture was warmed to rt and allowed to stir until complete conversion of the starting material was observed by TLC analysis, typically 30 min. The reaction was quenched with saturated NaHCO_{3(aq)} (5 mL), and the mixture was partitioned in a separatory funnel. The aqueous layer was extracted with CH₂Cl₂ (3 × 5 mL), and the combined organic extracts were dried with Na₂SO₄ and concentrated in vacuo to afford the crude nonconjugated enone **86**, which was carried to the next step without further purification.

A flame-dried, 20 mL scintillation vial was charged with the crude ketone **86** and THF (5 mL) under an atmosphere of N₂. The reaction mixture was cooled to 0 °C, and LiAlH₄ (1 M in THF, 2.00 mL, 2.00 mmol, 4.70 equiv) was added dropwise. The reaction mixture was allowed to stir at this temperature until TLC analysis indicated complete consumption of the starting material, typically 30 min. The reaction was then carefully quenched with saturated NH₄Cl_(aq) (4 mL) and stirred 5 min at rt. The resulting mixture was partitioned in a separatory funnel and extracted with Et₂O (3 × 5 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo to afford the crude alcohol **88** as a single diastereomer (as determined by ¹H NMR spectroscopic analysis of the crude reaction mixture, which revealed a single compound). The crude product was purified via flash chromatography (80:20 to 70:30 to 60:40 hexanes/ EtOAc) to afford alcohol **88** (0.90 g, 60% yield) as a pale yellow foam. Analytical data: [α]_D²⁸ -116.4 (*c* = 0.50, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 5.22 (s, 1H), 4.37 (t, *J* = 8.4 Hz, 1H), 3.18 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.95 (m, 1H), 2.68 (br s, 1H), 2.54 (m, 1H), 2.25 (d, *J* = 10.8 Hz, 1H), 2.20 (m, 1H), 1.94 (br s, 1H), 1.80 (d, *J* = 2.4 Hz, 1H), 1.69–1.59 (m, 6H), 1.50 (m, 1H), 1.42–1.36 (m, 3H), 1.19 (s, 3H), 1.17 (s, 3H), 1.14 (s, 3H), 0.86 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 148.1, 117.5, 85.8, 85.2, 84.4, 71.9, 55.1, 48.1, 43.9, 40.9, 38.0, 36.7, 31.8, 27.0, 26.1, 24.6, 23.8, 23.6, 22.8, 21.9, 16.7, 13.5; HRMS (ESI⁺) calcd for C₂₂H₃₆O₃+Na, 371.2562; found

371.2570; IR (thin film, cm^{-1}) 3433, 2979, 2678, 2399, 1452, 1373, 1215, 1093, 955, 755, 668; TLC (60:40 hexanes/EtOAc) $R_f = 0.36$

(2S,4aS,4bR,6aS,9aS,9bS,11aS)-2-(2-Hydroxypropan-2-yl)-4a,9a,9b-trimethyltetradecahydroindeno[5,4-f]chromen-9(2H)-one (91)

A flame-dried, 20 mL scintillation vial was charged with Crabtree's catalyst (0.01 g, 0.01 mmol, 0.15 equiv) in a nitrogen-filled glovebox. The vial was sealed with a rubber-septum, removed from the glovebox, and placed under an atmosphere of N_2 . CH_2Cl_2 (4 mL, freshly degassed via N_2 bubbling for 30 min) was added followed by a solution of alcohol **88** (0.025 g, 0.07 mmol, 1.00 equiv) in degassed CH_2Cl_2 (2 mL), and the resulting mixture was placed under an atmosphere of H_2 (balloon) and allowed to stir 36 h at rt. The resulting mixture was concentrated in vacuo to afford the crude alcohol **90**, which was carried forward to the next step without purification. Although this material was not isolated, the diastereomeric ratio was determined by ^1H NMR spectroscopic analysis of the crude reaction mixture, which revealed a single compound. This crude ^1H NMR spectrum is included in the Supporting Information.

A 20 mL scintillation vial was charged with the crude alcohol **90** and CH_2Cl_2 (3 mL) with magnetic stirring. Dess-Martin periodinane (0.045 g, 0.11 mmol, 1.50 equiv) was added, and the reaction mixture was allowed to stir at rt until complete conversion of the starting material was observed by TLC analysis, typically 20 min. The reaction was then quenched via a 1:1 solution of saturated $\text{NaHCO}_3(\text{aq})$ and saturated $\text{Na}_2\text{S}_2\text{O}_3(\text{aq})$ (3 mL), and the mixture was stirred 5 min. The reaction mixture was then diluted with Et_2O (5 mL) and partitioned in a separatory funnel. The aqueous layer was extracted with Et_2O (3×5 mL), and the combined organic extracts were dried with magnesium sulfate and concentrated in vacuo. The product was purified via flash chromatography (90:10 to 80:20 to 70:30 hexanes/EtOAc) to afford ketone **91** (0.022 g, 89% yield) as a clear semisolid. Slow evaporation from HPLC-grade hexanes provided crystals suitable for X-ray crystallographic analysis. Analytical data: mp 125–130 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{27} -89.3$ ($c = 0.85$, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 3.16 (dd, $J = 9.0, 3.0$ Hz, 1H), 2.93 (m, 1H), 2.65 (br s, 1H), 2.32 (dd, $J = 11.0, 8.5$ Hz, 1H), 2.19–2.14 (m, 2H), 2.00 (m, 1H), 1.78–1.23 (m, 15H), 1.16 (s, 3H), 1.14 (s, 3H), 1.02 (s, 3H), 0.92 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 221.2, 85.7, 84.4, 71.8, 56.1, 46.9, 40.2, 39.9, 37.8, 37.5, 36.5, 31.1, 26.1, 25.8, 24.2, 23.8, 23.7, 21.9, 21.2, 18.9, 12.9, 10.3; HRMS (ESI $^+$) calcd for $\text{C}_{22}\text{H}_{36}\text{O}_3 + \text{Na}$, 371.2562; found 371.2560; IR (thin film, cm^{-1}) 3566, 3446, 2946, 2876, 1772, 1731, 1472, 1385, 1259, 1158, 1098, 974, 735; TLC (70:30 hexanes/EtOAc) $R_f = 0.60$.

Note: The following sequence for conversion of **91** to paspaline was adapted from the previously published protocol by Smith and coworkers.^{12a,d}

(2S,4aS,4bR,6aS,9aS,9bS,11aS)-2-(2-Hydroxypropan-2-yl)-4a,9a,9b-trimethyl-8-

(methylthio)tetradecahydroindeno[5,4-f]-chromen-9(2H)-one (S7): A flame-dried, 20 mL scintillation vial was cooled to 0 $^\circ\text{C}$ and charged with THF (1 mL) and a freshly prepared solution of lithium diisopropylamide (0.5 M in THF, 0.57 mL, 0.29 mmol, 5.00 equiv) under an atmosphere of N_2 . The resulting solution was then charged with a solution of ketone **91** (0.02 g, 0.06 mmol, 1.00 equiv) in THF (0.5 mL), and the reaction mixture was

allowed to stir 15 min at 0 °C. HMPA (0.6 mL) was added followed by Me₂S₂ (0.031 mL, 0.34 mmol, 6.00 equiv), and the reaction was allowed to stir until TLC analysis showed complete conversion of the starting material, typically 10 min. The reaction was quenched via addition of H₂O (5 mL). The resulting mixture was transferred to a separatory funnel, and the organic layer was separated. The aqueous layer was extracted with Et₂O (3 × 5 mL), and the combined organic extracts were washed with brine (2 × 10 mL), dried with magnesium sulfate, and concentrated in vacuo. The product was purified via flash chromatography (90:10 to 80:20 to 70:30 hexanes/EtOAc) to afford an inseparable, diastereomeric mixture of thioethers **S7** (0.019 g, 84% yield) as a yellow, viscous oil. Analytical data: [α]_D²⁷ -57.9 (*c* = 0.70, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 3.16 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.94 (m, 2H), 2.61 (br s, 1H), 2.25 (br s, 3H), 2.22–2.13 (m, 3H), 1.63–1.57 (m, 11H), 1.47 (m, 10H), 1.17 (s, 3H), 1.14 (s, 3H), 1.02 (s, 3H), 1.01 (s, 3H), 0.83 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 218.4, 85.6, 84.4, 71.8, 56.6, 49.8, 46.6, 40.1, 38.1, 37.8, 36.4, 31.8, 31.1, 26.1, 25.2, 24.2, 23.7, 21.8, 21.1, 19.0, 15.4, 12.9, 11.0; HRMS (ESI⁺) calcd for C₂₃H₃₈O₃S+Na, 417.2439; found 417.2438; IR (thin film, cm⁻¹) 3446, 2946, 2874, 1732, 1652, 1519, 1456, 1386, 1232, 1152, 1086, 946; TLC (70:30 hexanes/EtOAc) *R*_f = 0.63.

(2S,4aS,4bR,6aS,9aS,9bS,11aS)-8-(2-Aminophenyl)-2-(2-hydroxypropan-2-yl)-4a,9a,9b-trimethyltetradecahydroindeno[5,4-f]-chromen-9(2H)-one (S8): A flame-dried, 20 mL scintillation vial was charged with a solution of aniline (0.25 M in CH₂Cl₂, 0.26 mL, 0.07 mmol, 2.00 equiv) under an atmosphere of N₂, and the resulting solution was cooled to -78 °C. The lights in the fume hood were turned off, and a solution of ^tBuOCl (0.25 M in CH₂Cl₂, 0.26 mL, 0.07 mmol, 2.00 equiv) was added dropwise. The reaction mixture was allowed to stir 15 min, upon which a solution of thioether **S8** (0.013 g, 0.03 mmol, 1.00 equiv) in CH₂Cl₂ (1.5 mL) was added. The mixture was allowed to stir 50 min, upon which NEt₃ (0.02 mL, 0.13 mmol, 4.00 equiv) was added. The reaction was then warmed to rt and allowed to stir until a bright orange color was observed, typically 5 min. The resulting solution was diluted with H₂O (5 mL) and Et₂O (10 mL) and partitioned in a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et₂O (3 × 5 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo to afford a crude mixture of diastereomeric keto-anilines, which was carried directly on to the next step without further purification.

The residue was taken up into EtOH (1 mL) in a 20 mL scintillation vial, and a slurry of Raney Ni in H₂O (150 mg) was added. The reaction mixture was stirred vigorously at rt until complete conversion of the intermediate thioether was observed by TLC analysis, typically 1 h. The reaction mixture was filtered through a Celite plug, and the resulting solution was concentrated in vacuo. The crude product was purified via flash chromatography (90:10 to 80:20 to 70:30 to 60:40 hexanes/EtOAc) to afford ketoaniline **S8** (0.009 g, 62% yield) as yellow, viscous oil. Analytical data: [α]_D²⁷ +26.6 (*c* = 0.45, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 7.06 (m, 2H), 6.77 (m, 2H), 4.21 (br s, 2H), 3.54 (t, *J* = 9.0 Hz, 1H), 3.16 (dd, *J* = 9.6, 2.4 Hz, 1H), 2.94 (m, 1H), 2.62 (br s, 1H), 2.35 (m, 1H), 2.14–2.04 (m, 3H), 1.84–1.37 (m, 16H), 1.17 (s, 3H), 1.15 (s, 1H), 1.11 (s, 3H), 0.98 (s, 3H), 0.86 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 221.0, 146.0, 127.6, 125.8, 125.4, 119.1,

117.5, 85.6, 84.5, 71.8, 57.0, 51.5, 46.8, 40.1, 38.0, 37.8, 36.5, 31.3, 28.9, 26.1, 25.4, 24.2, 23.7, 21.9, 21.2, 19.2, 12.9, 10.0; HRMS (ESI⁺) calcd for C₂₈H₄₁NO₃+Na, 462.2984; found 462.2983; IR (thin film, cm⁻¹) 3421, 3053, 2984, 2877, 2305, 1732, 1652, 1456, 1362, 1265, 738; TLC (70:30 hexanes/EtOAc) *R*_f = 0.30.

Paspaline (1)—A 1 mL dram vial was charged with ketone **S8** (0.007 g, 0.02 mmol, 1.00 equiv), CH₂Cl₂ (1.2 mL), and PTSA (0.002 g, 0.01 mmol, 0.66 equiv). The vial was sealed, and the mixture was warmed to 50 °C and stirred for 16 h. The reaction mixture was cooled to rt, diluted with H₂O (10 mL) and Et₂O (10 mL), and transferred to a separatory funnel. The organic layer was separated, and the aqueous layer was extracted with Et₂O (3 × 5 mL). The combined organic extracts were dried with magnesium sulfate and concentrated in vacuo. The product was purified via flash chromatography (90:10 to 80:20 hexanes/EtOAc) to afford paspaline (0.006 g, 89% yield) as a yellow foam. Slow evaporation from HPLC-grade hexanes provided crystals suitable for X-ray crystallographic analysis. Analytical data: [*a*]_D²⁵ -16.4 (*c* = 0.30, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ 7.72 (br s, 1H), 7.42 (m, 1H), 7.30 (m, 1H), 7.07 (m, 2H), 3.21 (dd, *J* = 9.6, 2.4 Hz, 1H), 3.03 (dd, *J* = 8.4, 3.6 Hz, 1H), 2.77–2.65 (m, 3H), 2.32 (dd, *J* = 10.8, 2.4 Hz, 1H), 1.96 (m, 1H), 1.84–1.77 (m, 3H), 1.70–1.56 (m, 6H), 1.49–1.37 (m, 3H), 1.19 (s, 3H), 1.17 (s, 3H), 1.13 (s, 3H), 1.03 (s, 3H), 0.88 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 150.8, 139.3, 125.1, 120.4, 119.5, 118.4, 118.2, 111.4, 85.7, 84.7, 71.9, 53.0, 48.7, 46.4, 40.0, 37.6, 36.5, 33.9, 27.5, 26.1, 25.2, 24.6, 23.7, 22.0, 21.9, 20.0, 14.6, 12.6; HRMS (ESI⁺) calcd for C₂₈H₃₉NO₂+H, 422.3059; found 422.3056; IR (thin film, cm⁻¹) 3565, 3467, 3053, 2982, 2930, 2855, 1455, 1386, 1375, 1331, 1265, 1158, 1087, 1037; TLC (70:30 hexanes/EtOAc) *R*_f = 0.42.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The project described was supported by Award No. R01 GM084927 from the National Institute of General Medical Sciences. R.J.S. acknowledges an NSF Graduate Research Fellowship and ACS Division of Organic Chemistry graduate fellowship. X-ray crystallography was performed by Dr. Peter White (UNC). The authors thank Dr. Shubin Liu (UNC) for assistance with DFT structure optimization calculations.

References

1. Sings H, Singh S. Alkaloids: Chemistry and Biology 2003. 60:51.
2. Miedaner T, Geiger HH. Toxins. 2015; 7:659. and references therein. [PubMed: 25723323]
3. (a) Steyn, PS.; Vleggar, R. Progress in the Chemistry of Organic Natural Products. Springer-Verlag; New York: 1985. (b) Mantle PG, Mortimer PB, White EP. Res Vet Sci. 1977; 24:49. [PubMed: 625600] (c) DiMenna ME, Mantle PB. Res Vet Sci. 1977; 24:347. (d) Mantle PG, Day JB, Haigh CR, Penny HC. Vet Rec. 1978; 103:403. [PubMed: 726205] (e) Cole RJ, Dorner JW, Lansden JA, Cox RH, Pape C, Cunfer B, Nicholson SS, Bedell DM. J Agric Food Chem. 1977; 25:1197. [PubMed: 893851]
4. (a) Fehr T, Acklin W. Helv Chim Acta. 1966; 49:1907. (b) Gysi, RP. PhD Dissertation. Eidgenossische Technische Hochschule; Zürich, Switzerland: 1973. (c) Leutwiler, A. Dissertation No 5163. Eidgenossische Technische Hochschule; Zürich, Switzerland: 1973.
5. Munday-Finch SC, Wilkins AL, Miles CO. Phytochemistry. 1996; 41:327.

6. (a) Cole RJ, Dorner JW, Springer JP, Cox RH. *J Agric Food Chem.* 1981; 29:293.(b) Gallagher RT, Finer J, Clardy J, Leutwiler A, Weibel F, Acklin W, Arigoni D. *Tetrahedron Lett.* 1980; 21:231. and references therein.
7. Ogata M, Ueda J-y, Hoshi M, Hashimoto J, Nakashima T, Anzai K, Takagi M, Shin-ya K. *J Antibiot.* 2007; 60:645. [PubMed: 17965481]
8. (a) Cole RJ, Kirksey JW, Wells JM. *Can J Microbiol.* 1974; 20:1159. [PubMed: 4425383] (b) Springer JP, Clardy J, Wells JM, Cole RJ, Kirksey JW. *Tetrahedron Lett.* 1975; 16:2531.
9. (a) Brnardic, E.; Doherty, JB.; Dorsey, J.; Ellwood, C.; Fillmore, M.; Malaska, M.; Nelson, K.; Soukri, M. Preparation of Indole Diterpene Alkaloids as Maxi-K Channel Blockers for the Treatment of Glaucoma. Patent WIPO. 2009/048559. 2009. (b) Garcia, ML.; Goetz, MA.; Kaczorowski, GJ.; McManus, OB.; Monaghan, RL.; Strohl, WR.; Tkacz, JS. Novel Maxi-K Channel Blockers, Methods of Use and Process for Making the Same. US Patent. 0239863. 2005. (c) Brnardic, E.; Doherty, JB.; Ellwood, C.; Fillmore, M.; Malaska, M. Maxi-K Channel Blockers and Methods of Use. US Patent. 048558. 2009.
10. Sheehan JJ, Benedetti BL, Barth AL. *Epilepsia.* 2009; 50:711. [PubMed: 19054419]
11. (a) Springer JP, Clardy J. *Tetrahedron Lett.* 1980; 21:231.(b) Dorner JP, Cole RJ, Cox RH, Cunfer BM. *J Agric Food Chem.* 1984; 32:1069.
12. (a) Smith AB III, Mewshaw R. *J Am Chem Soc.* 1985; 107:1769.(b) Smith AB III, Leenay TL. *Tetrahedron Lett.* 1988; 29:2787.(c) Smith AB III, Leenay TL. *Tetrahedron Lett.* 1988; 29:2791. (d) Mewshaw RE, Taylor MD, Smith AB III. *J Org Chem.* 1989; 54:3449.(e) Smith AB III, Leenay TL. *J Am Chem Soc.* 1989; 111:5761.(f) Smith AB III, Sunazuka T, Leenay TL, Kingery-Wood J. *J Am Chem Soc.* 1990; 112:8197.(g) Smith AB III, Kingery-Wood J, Leenay TL, Nolen EG, Sunazuka T. *J Am Chem Soc.* 1992; 114:1438.(h) Zou Y, Melvin JE, Gonzales SS, Spafford MJ, Smith AB III. *J Am Chem Soc.* 2015; 137:7095. [PubMed: 26029849]
13. (a) Guile SD, Saxton JE, Thornton-Pett MJ. *Chem Soc, Perkin Trans.* 1992; 1:1763.(b) Clark JS, Myatt J, Roberts L, Walshe N. *Synlett.* 2005:697–699.(c) Enomoto M, Kuwahara S. *J Org Chem.* 2010; 75:6286. [PubMed: 20718438] (d) Oikawa M, Hashimoto R, Sasaki M. *Eur J Org Chem.* 2011; 2011:538.(e) Isaka T, Hasegawa M, Toshima H. *Biosci, Biotechnol, Biochem.* 2011; 75:2213. [PubMed: 22056442] (f) Adachi M, Higuchi K, Thasana N, Yamada H, Nishikawa T. *Org Lett.* 2012; 14:114. [PubMed: 22126279] (g) Okano K, Yoshii Y, Tokuyama H. *Heterocycles.* 2012; 84:1325.
14. (a) Churruca F, Fousteris M, Ishikawa Y, Rekowski MW, Hounsou C, Surrey T, Giannis A. *Org Lett.* 2010; 12:2096. [PubMed: 20387880] (b) Bradshaw B, Etxebarria-Jardi G, Bonjoch J. *J Am Chem Soc.* 2010; 132:5966. [PubMed: 20384301] (c) Enomoto S, Morita A, Kuwahara S. *Angew Chem, Int Ed.* 2012; 51:12833.(d) Bian M, Wang Z, Xiong X, Sun Y, Matera C, Nicolaou KC, Li A. *J Am Chem Soc.* 2012; 134:8078. [PubMed: 22537293] (e) Goetz AE, Silberstein AL, Corsello MA, Garg NK. *J Am Chem Soc.* 2014; 136:3036. [PubMed: 24524351]
15. (a) Nicewicz DA, Satterfield DA, Schmitt DS, Johnson JS. *J Am Chem Soc.* 2008; 130:17281. [PubMed: 19053214] (b) Campbell MJ, Johnson JS. *J Am Chem Soc.* 2009; 131:10370. [PubMed: 19601576] (c) Sanders S, Ruiz-Olalla A, Johnson JS. *Chem Commun.* 2009:5135.(d) Campbell MJ, Johnson JS. *Synthesis.* 2010:2841.(e) Greszler SN, Malinowski JT, Johnson JS. *Org Lett.* 2011; 13:3206. [PubMed: 21591684] (f) Malinowski JT, McCarver SJ, Johnson JS. *Org Lett.* 2012; 14:2878. [PubMed: 22617016] (g) Malinowski JT, Sharpe RJ, Johnson JS. *Science.* 2013; 340:180. [PubMed: 23580525] (h) Sharpe RJ, Malinowski JT, Johnson JS. *J Am Chem Soc.* 2013; 135:17990. [PubMed: 24245656] (i) Sharpe RJ, Malinowski JT, Sorana F, Luft JC, Bowerman CJ, DeSimone JM, Johnson JS. *Bioorg Med Chem.* 2015; 23:1849. [PubMed: 25792144]
16. Sharpe RJ, Johnson JS. *J Am Chem Soc.* 2015; 137:4968. [PubMed: 25856767]
17. (a) Chu Y, White JB, Duclos BA. *Tetrahedron Lett.* 2001; 42:3815.(b) Iguchi M, Niwa M, Yamamura S. *J Chem Soc D.* 1971:974.
18. (a) Stewart IC, Ung T, Pletnev AA, Berlin JM, Grubbs RH, Schrodi Y. *Org Lett.* 2007; 9:1589. [PubMed: 17378575] (b) Vorfalt T, Leuhausser S, Plenio H. *Angew Chem, Int Ed.* 2009; 48:5191.
19. McMurry JE, Fleming MP, Kees KL, Krepski LR. *J Org Chem.* 1978; 43:3255.
20. Gharpure SJ, Reddy SRB. *Org Lett.* 2009; 11:2519. [PubMed: 19445488]
21. Breit B, Zahn SK. *J Org Chem.* 2001; 66:4870. [PubMed: 11442419]

22. The selectivity was determined via the collective NOESY analyses of **19**, **20**, and the ethyl ketone precursor of **21**. The same selectivity was observed by Deslongchamps and Germain in their synthesis of momilactone A. See: Germain J, Deslongchamps P. *J Org Chem.* 2002; 67:5269. [PubMed: 12126415]
23. (a) Gianturco MA, Friedel P. *Tetrahedron.* 1963; 19:2039. [PubMed: 5879211] (b) House, HO. *Modern Synthetic Reactions.* Benjamin; Menlo Park: 1972. p. 520-532.c Stowell, JC. *Carbanions in Organic Synthesis.* Wiley; New York: 1979. p. 205-210.
24. Demir AS, Enders DJ. *J Prakt Chem/Chem-Ztg.* 1997; 339:553.
25. The current method for preparing these compounds involves bisalkylation of 1,5-dimethoxy-1,4-cyclohexadiene. See: Piers E, Grierson JR. *J Org Chem.* 1977; 42:3755.
26. Watanabe H, Iwamoto M, Nakada M. *J Org Chem.* 2005; 70:4652. [PubMed: 15932301]
27. (a) Katoh T, Mizumoto S, Fudesaka M, Nakashima Y, Kajimoto T, Node M. *Synlett.* 2006; 37:2076.(b) Katoh T, Mizumoto S, Fudesaka M, Takeo M, Kajimoto T, Node M. *Tetrahedron: Asymmetry.* 2006; 17:1655.
28. Becke AD. *J Chem Phys.* 1993; 98:5648.Lee CT, Yang WT, Parr RG. *Phys Rev B: Condens Matter Mater Phys.* 1988; 37:785.Hariharan PC, Pople JA. *Theor Chim Acta.* 1973; 28:213.Francl MM, Pietro WJ, Henre WJ, Binley JS, Gordon MS, Frees DJ, Pople JA. *J Chem Phys.* 1982; 77:3654.See Supporting Information for additional computational details..
29. Other examples of remote direction in alkene functionalization: Zhang W, Yamamoto H. *J Am Chem Soc.* 2007; 129:286. [PubMed: 17212403] Wan KK, Iwasaki K, Umotoy JC, Wolan DW, Shenvi RA. *Angew Chem, Int Ed.* 2015; 54:2410.
30. (a) Shapiro RH, Heath MJ. *J Am Chem Soc.* 1967; 89:5734.(b) Shapiro RH. *Org React (NY).* 1975; 23:405.
31. (a) Stork G, Darling SD. *J Am Chem Soc.* 1960; 82:1512.(b) Stork G, Rosen P, Goldman N, Coombs RV, Tsuji J. *J Am Chem Soc.* 1965; 87:275.
32. Vilkas M. *Bull Soc Chem Fr.* 1959:1401.
33. (a) Stork G, Kahn M. *J Am Chem Soc.* 1985; 107:500.(b) Stork G, Sher PM. *J Am Chem Soc.* 1986; 108:303.
34. (a) Ireland RE, Mueller RH. *J Am Chem Soc.* 1972; 94:5897.(b) Ireland RE, Mueller RH, Willard AK. *J Am Chem Soc.* 1976; 98:2868.
35. (a) Desai LV, Hull KL, Sanford MS. *J Am Chem Soc.* 2004; 126:9542. [PubMed: 15291549] (b) Neufeldt SR, Sanford MS. *Org Lett.* 2010; 12:532. [PubMed: 20041702]
36. Zhu C, Tang P, Yu B. *J Am Chem Soc.* 2008; 130:5872. [PubMed: 18407637]
37. Siler DA, Mighion JD, Sorensen EJ. *Angew Chem, Int Ed.* 2014; 53:5332.
38. Krasovskiy A, Kopp F, Knochel P. *Angew Chem, Int Ed.* 2006; 45:497.
39. Abad A, Agullo C, Arno M, Domingo LR, Zaragoza RJ. *J Org Chem.* 1990; 55:2369. and references therein.
40. (a) Evans DA, Morrissey M. *J Am Chem Soc.* 1984; 106:3866.(b) Evans DA, Morrissey M. *Tetrahedron Lett.* 1984; 25:4637.
41. (a) St André AF, MacPhillamy HB, Nelson JA, Shabica AC, Scholz CR. *J Am Chem Soc.* 1952; 74:5506.(b) Gabbard RB, Segaloff A. *Steroids.* 1983; 41:791. [PubMed: 6665822] (c) Haddad M, Blazejewski JC, Wakselman C, Dorai V, Duc I. *Eur J Med Chem.* 1994; 29:627.(d) Khripach VA, Zhabinskii VN, Fando GP, Kuchto AI, Lyakhov AS, Govorova AA, Groen MB, Van Der Louw J, De Groot A. *Steroids.* 2004; 69:495. [PubMed: 15246779]
42. Gassman PG, van Bergen TJ, Gilbert DP, Cue BW Jr. *J Am Chem Soc.* 1974; 96:5495.
43. Breit B, Zahn SK. *J Org Chem.* 2001; 66:4870. [PubMed: 11442419]
44. Abecassis K, Gibson SE. *Eur J Org Chem.* 2010; 2010:2938.
45. Frisch, MJ.; Trucks, GW.; Schlegel, HB.; Scuseria, GE.; Robb, MA.; Cheeseman, JR.; Montgomery, JA., Jr; Vreven, T.; Kudin, KN.; Burant, JC.; Millam, JM.; Iyengar, SS.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, GA.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, JE.; Hratchian, HP.; Cross, JB.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, RE.; Yazyev, O.; Austin, AJ.; Cammi, R.;

Pomelli, C.; Ochterski, JW.; Ayala, PY.; Morokuma, K.; Voth, GA.; Salvador, P.; Dannenberg, JJ.; Zakrzewski, VG.; Dapprich, S.; Daniels, AD.; Strain, MC.; Farkas, O.; Malick, DK.; Rabuck, AD.; Raghavachari, K.; Foresman, JB.; Ortiz, JV.; Cui, Q.; Baboul, AG.; Clifford, S.; Cioslowski, J.; Stefanov, BB.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, RL.; Fox, DJ.; Keith, T.; Al-Laham, MA.; Peng, CY.; Nanayakkara, A.; Challacombe, M.; Gill, PMW.; Johnson, B.; Chen, W.; Wong, MW.; Gonzalez, C.; Pople, JA. Gaussian 03, revision D.01. Gaussian, Inc; Wallingford, CT: 2004.

46. Xiang S-K, Zhang Bo, Zhang L-H, Cui Y, Jiao N. Chem Commun. 2011; 47:8097.
47. Zhang H-B, Liu L, Liu Y-L, Chen Y-J, Wang J, Wang D. Synth Commun. 2007; 37:173.
48. Westermaier M, Mayr H. Org Lett. 2006; 8:4791. [PubMed: 17020304]
49. Zimmerman HE, Wang P. J Org Chem. 2002; 67:9216. [PubMed: 12492323]
50. Van Goor, FF.; Burton, WL. Compositions for Treatment of Cystic Fibrosis and Other Chronic Diseases. US Patent. 61254180. 2011.
51. Hettche F, Hoffmann RW. New J Chem. 2003; 27:172.
52. Archer CH, Thomas NR, Gani D. Tetrahedron: Asymmetry. 1993; 4:1141.
53. Nyfeler E, Renaud P. Org Lett. 2008; 10:985. [PubMed: 18271594]

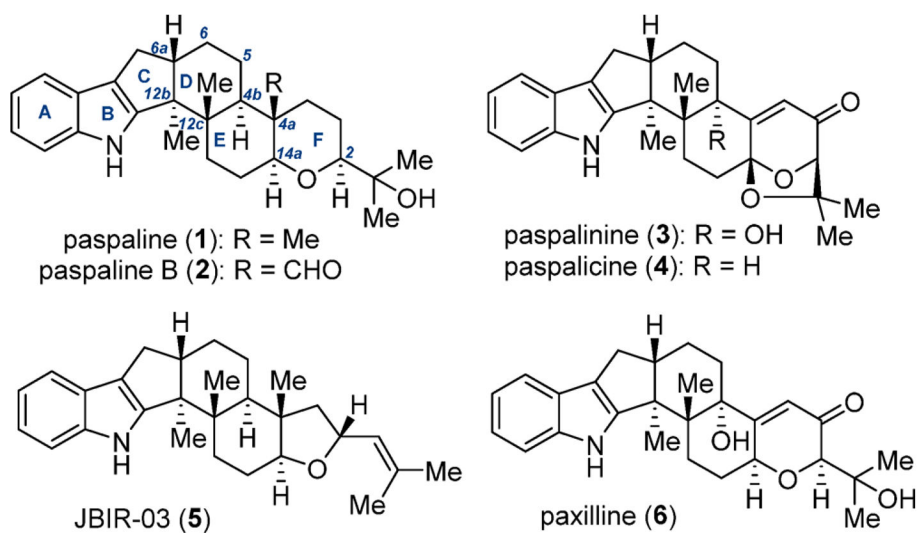
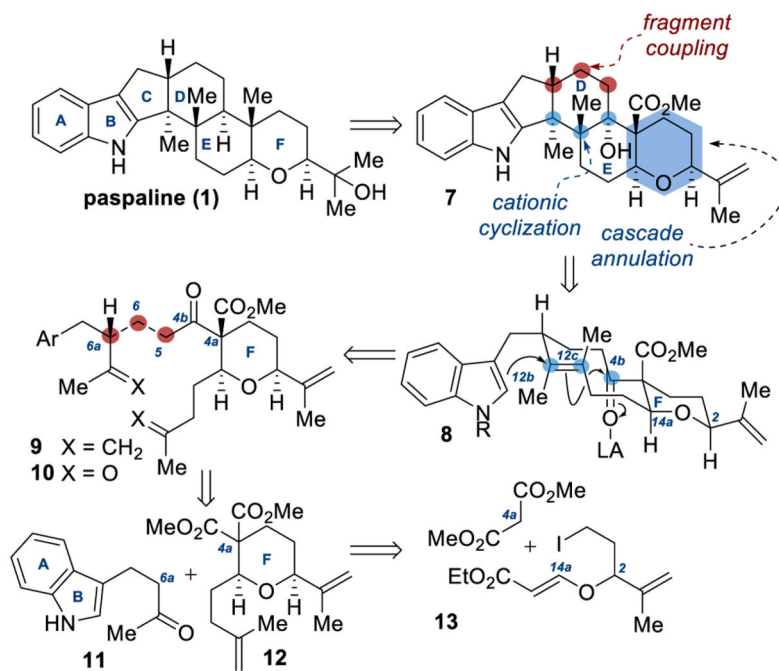
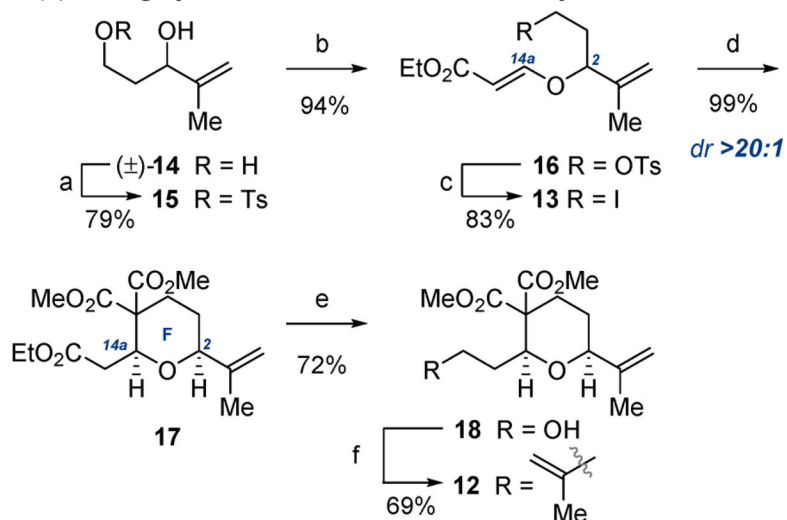
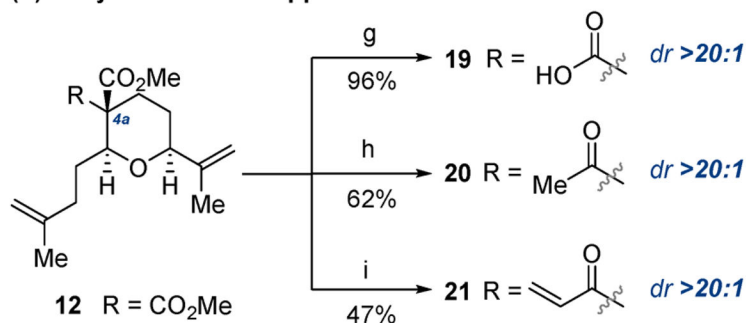


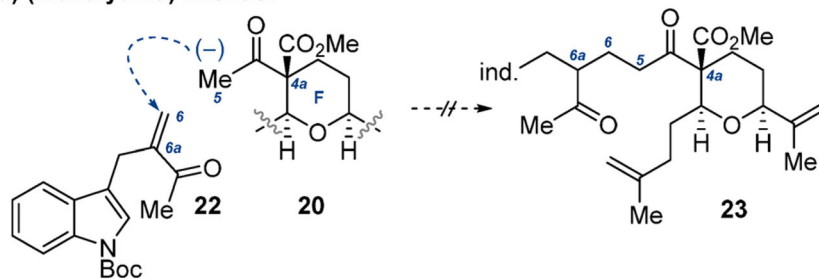
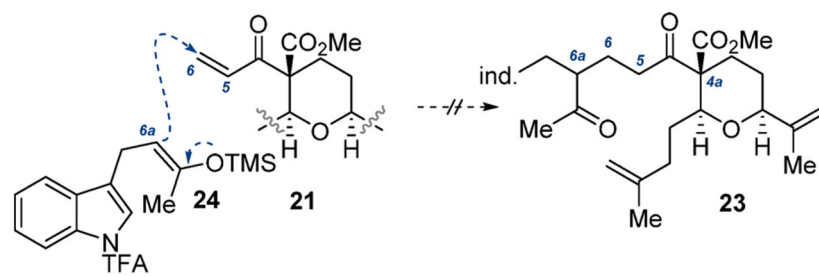
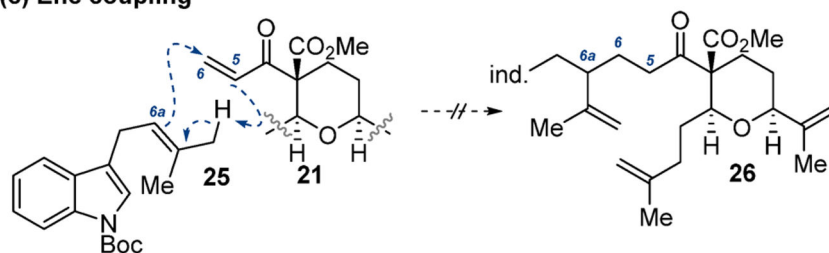
Figure 1.
Paspaline and related indole diterpenoid natural products.



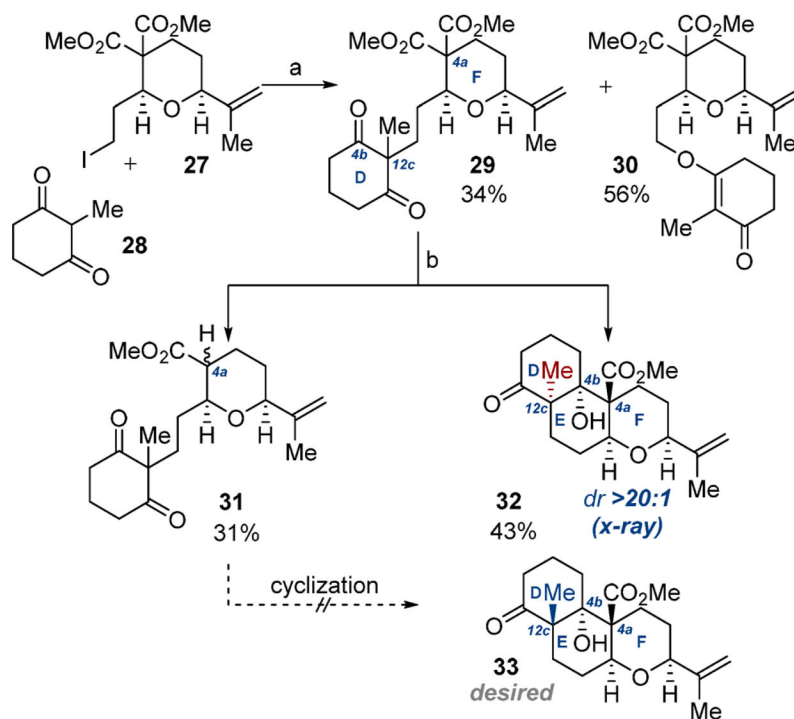
Scheme 1.
Preliminary Synthesis Plan for Paspaline

(a) F-Ring synthesis via tandem Michael/alkylation cascade**(b) Desymmetrization approaches to C4a stereocenter****Scheme 2. Synthesis of Tetrahydropyranyl F Ring and C4a Stereocenter^a**

^aReagents and conditions: (a) TsCl, NEt₃, DMAP (10 mol %), CH₂Cl₂, 0 °C; (b) *N*-methylmorpholine, ethyl propiolate, CH₂Cl₂, rt; (c) NaI, acetone, rt; (d) CH₂(CO₂Me)₂, Cs₂CO₃, DMF, rt; (e) DIBAL-H, THF, 0 °C; (f) (i) I₂, PPh₃, imidazole, CH₂Cl₂, 0 °C to rt; (ii) (isopropenyl)₂CuLi, Et₂O, -78 to 0 °C; (g) KOH, THF/MeOH (1.75:1), rt; (h) MeLi, THF, -78 °C; (i) (i) EtLi, THF, -78 °C; (ii) LDA, THF, -78 °C, then PhSeBr; (iii) H₂O₂(aq), CH₂Cl₂, 0 °C.

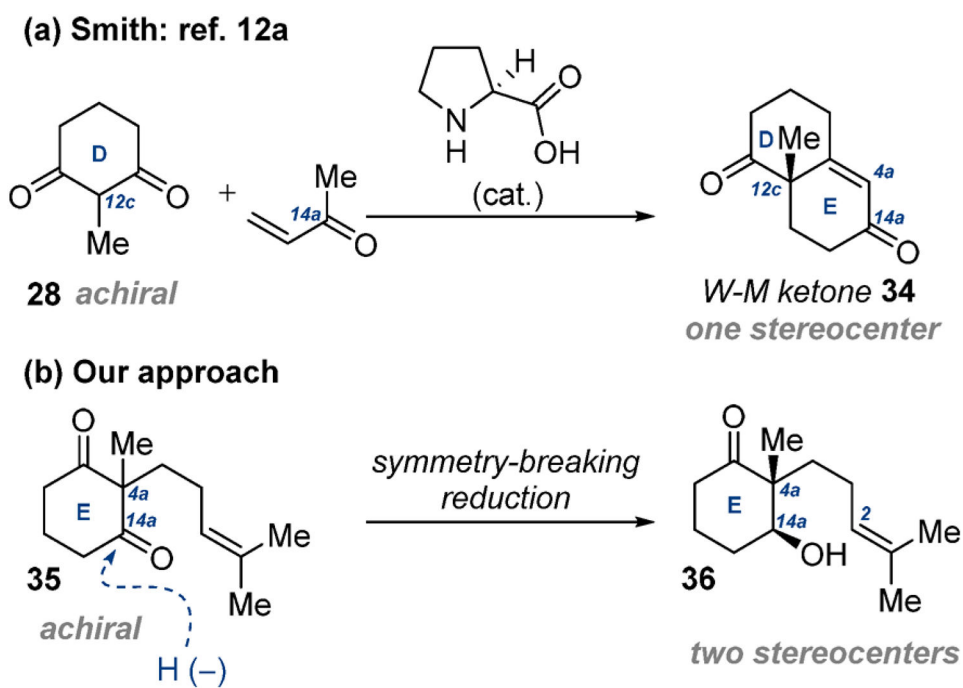
(a) (Mukaiyama) Michael**(b) Mukaiyama Michael - reversed polarity****(c) Ene coupling****Scheme 3.**

Unsuccessful Approaches to C5–C6a Bond Construction

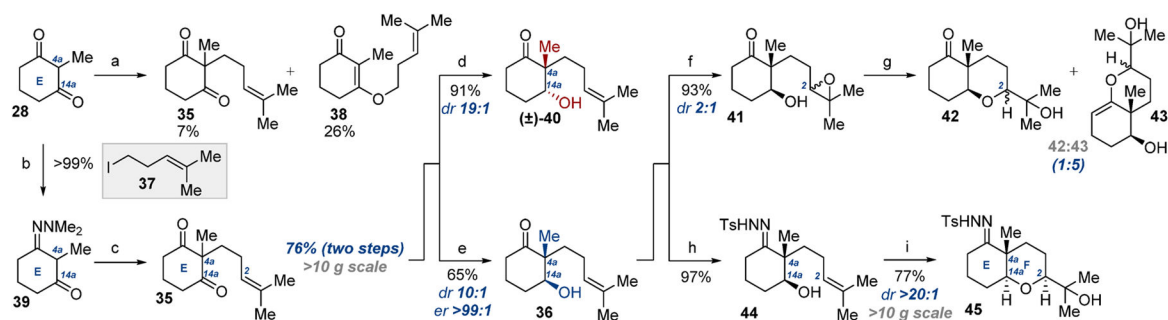


Scheme 4. Decarboxylative Annulation Approach to Paspaline D,E Rings^a

^aReagents and conditions: (a) Cs₂CO₃, DMF, 65 °C; (b) NaCl, DMSO, 150 °C.

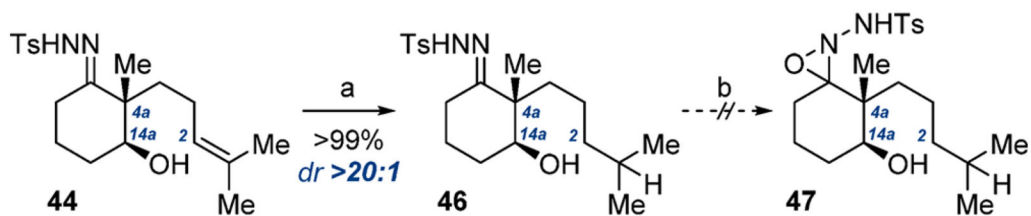
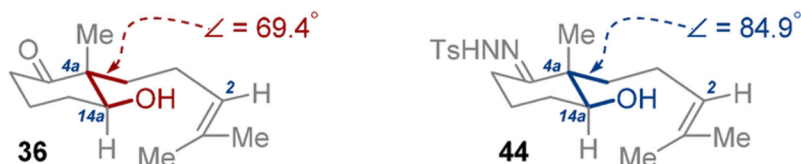
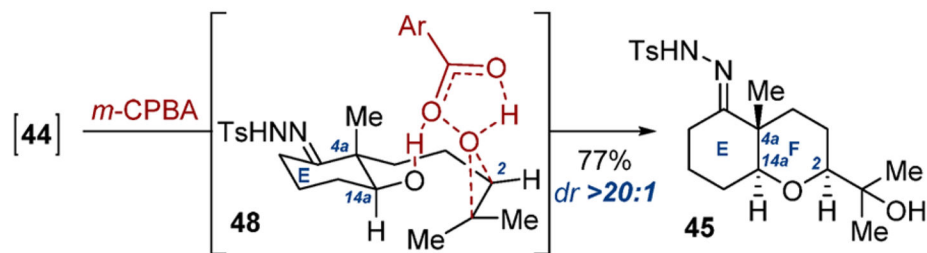


Scheme 5.
Revised Approach to 1 via Enantioselective Desymmetrization

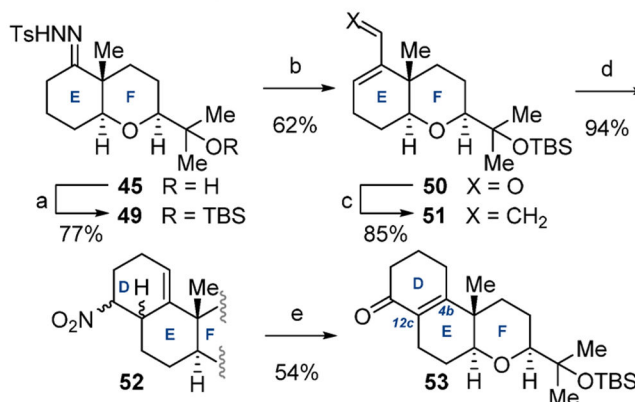


Scheme 6. Desymmetrization Approach to 1: E,F Ring Synthesis^a

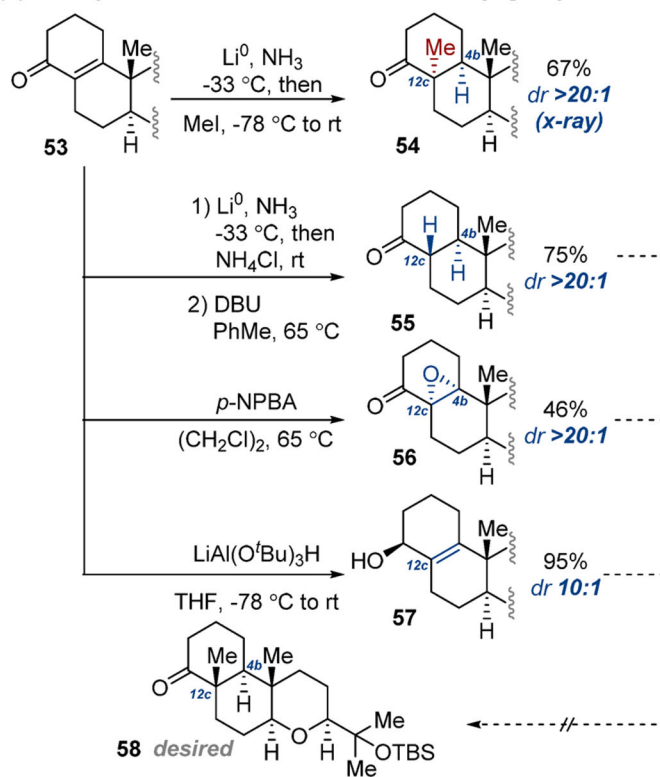
^aReagents and conditions: (a) NaH, DMF, 0 °C, then **37**, rt; (b) H₂NNMe₂, TsOH (3.0 mol %), C₆H₆, 100 °C; (c) (i) KH, THF, 0 °C, then **37**, -78 °C to rt; (ii) Cu(OAc)₂, THF/H₂O (1:1), rt; (d) NaBH₄, MeOH, 0 °C; (e) YSC-2, H₂O/DMSO (10:1), 30 °C; (f) *m*-CPBA, CH₂Cl₂, 0 °C; (g) PPTS (20 mol %), CH₂Cl₂, rt; (h) TsHNNH₂, C₇H₈, 70 °C; (i) *m*-CPBA, CH₂Cl₂, 0 °C, then PPTS.

(a) Examining feasibility of intramolecular epoxidation via 47**(b) Calculated structures of 36 and 44****(c) Mechanistic hypothesis for the conversion of 44 to 45****Scheme 7. Mechanistic Investigations in the Conversion of 44 to 45^a**

^aReagents and conditions: (a) H₂ (1 atm), Pd/C (1.50 mass equiv), MeOH, rt; (b) *m*-CPBA, CH₂Cl₂, 0 °C.

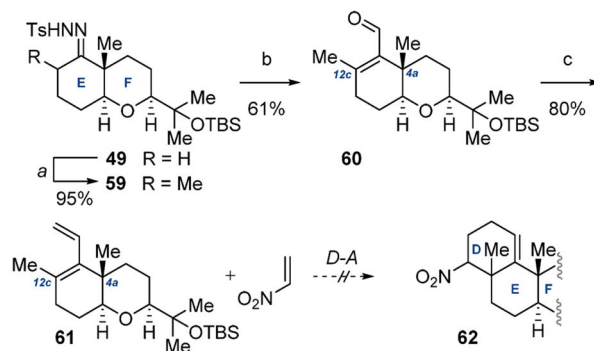
(a) Synthesis of D-ring enone substrate **53**

(b) Attempts to access C4a-C12c diaxial methyl groups

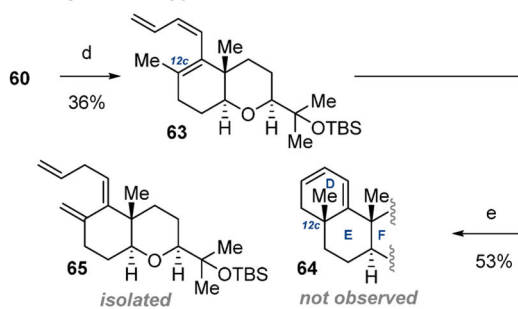
Scheme 8. Synthesis of Enone **53** and Attempts at D Ring Synthesis^a

^aReagents and conditions: (a) TBSOTf, 2,6-lutidine, CH₂Cl₂, -50 °C; (b) *n*-BuLi, THF, -50 °C to rt, then DMF; (c) Ph₃P=CH₂, THF, 0 °C; (d) nitroethylene, CH₂Cl₂, 65 °C; (e) (i) KOH, MeOH, rt, then MsOH, 0 °C to rt; (ii) DBU, CH₂Cl₂, rt.

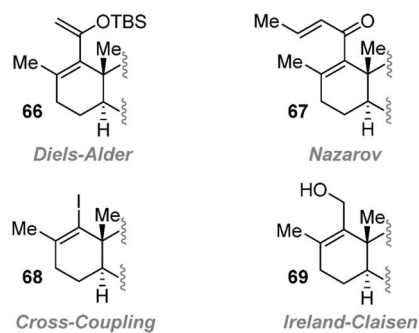
(a) Direct Diels-Alder approach to D-ring and C12c stereocenter



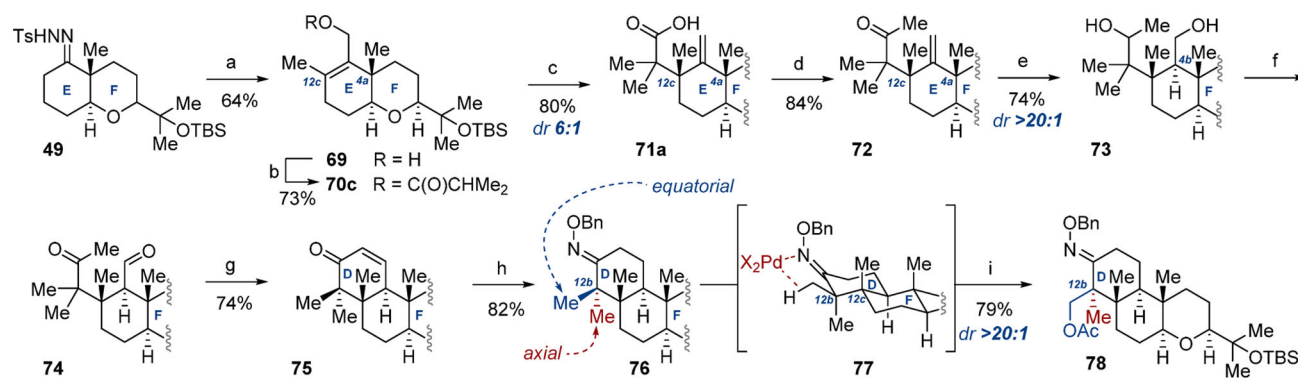
(b) Electrocyclization approach



(c) Alternative Shapiro adducts explored

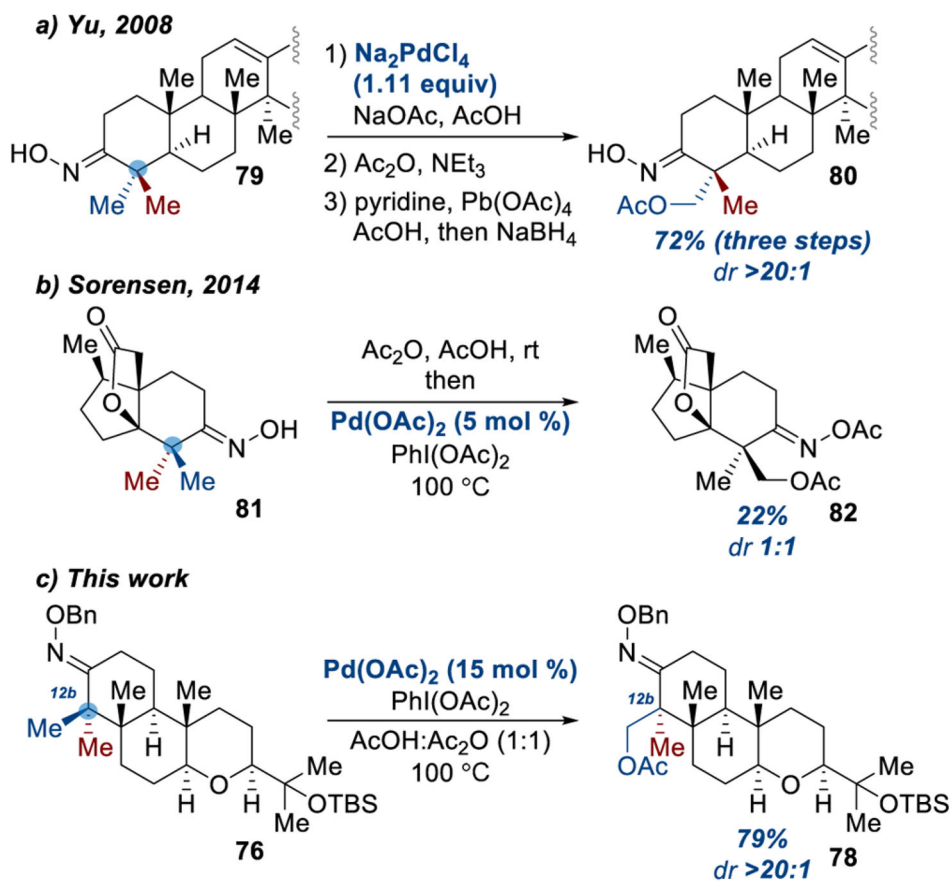
Scheme 9. Strategies Examined toward D Ring Synthesis via Methyl-Group-First Approach^a

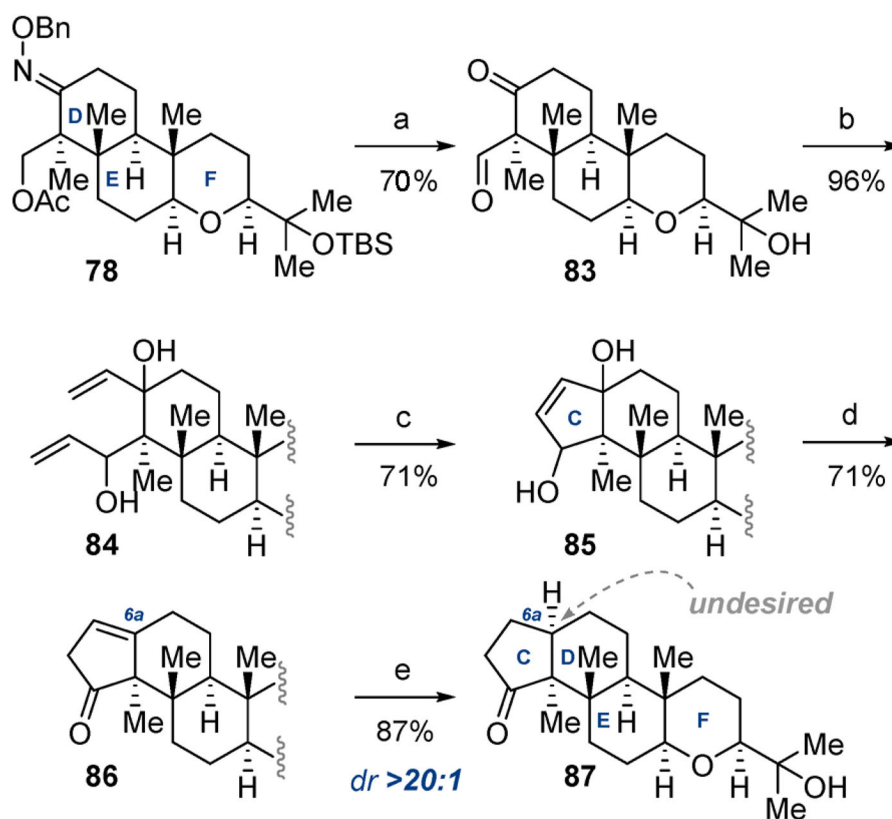
^aReagents and conditions: (a) *n*-BuLi, THF, -50 °C, then MeI; (b) *n*-BuLi, THF, -50 °C to rt, then DMF; (c) Ph₃P=CH₂, THF, 0 °C; (d) Ph₃P=CHCHCH₂, THF, 0 °C to rt; (e) *hν*, hexanes, rt.



Scheme 10. D Ring Synthesis Completion and Symmetry-Breaking C–H Activation of C12b Stereocenter^a

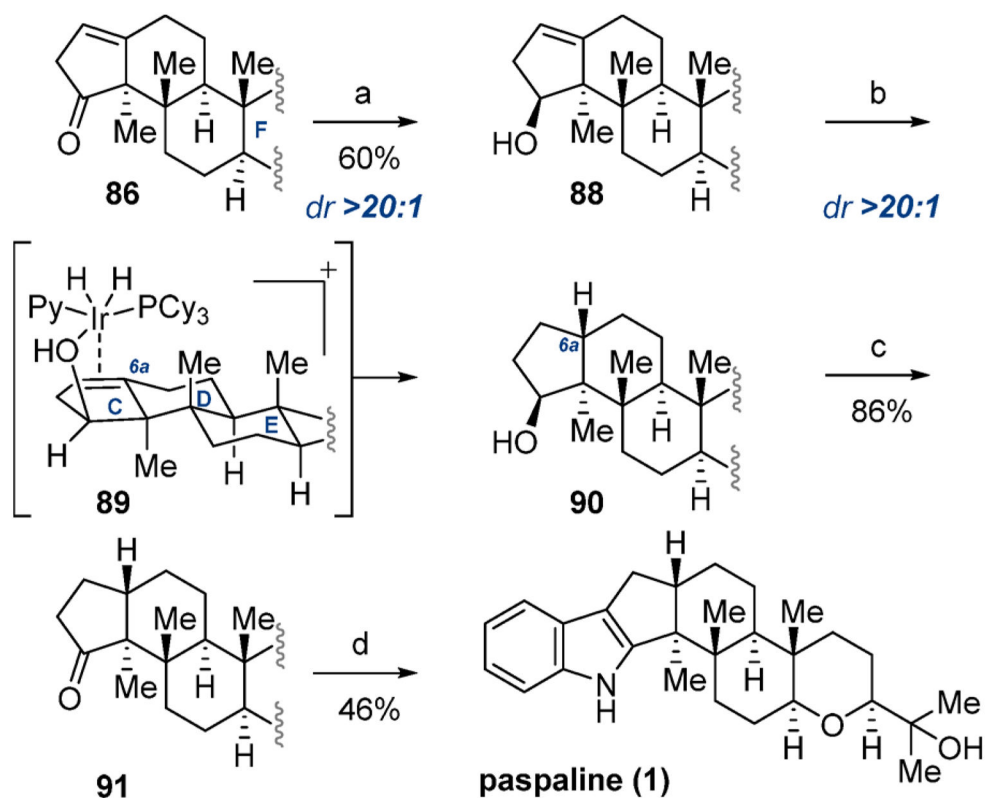
^aReagents and conditions: (a) *n*-BuLi, THF, $-50\text{ }^{\circ}\text{C}$, then MeI; *n*-BuLi, $-50\text{ }^{\circ}\text{C}$ to rt, then (HCHO)_{*n*}; (b) isobutyric acid, DCC, DMAP (10 mol %), CH₂Cl₂, rt; (c) LDA, THF, $-78\text{ }^{\circ}\text{C}$, then TMSCl, -78 to $75\text{ }^{\circ}\text{C}$; (d) (i) TMSCHN₂, MeOH/C₇H₈ (2:1), rt; (ii) MeLi, Et₂O, $0\text{ }^{\circ}\text{C}$ to rt; (e) BH₃T·HF, THF, $50\text{ }^{\circ}\text{C}$, then H₂O₂, NaOH, $0\text{ }^{\circ}\text{C}$ to rt; (f) (COCl)₂, DMSO, CH₂Cl₂, $-78\text{ }^{\circ}\text{C}$, then DIPEA, -78 to $0\text{ }^{\circ}\text{C}$; (g) KOH_(aq), THF/ MeOH (1:1), $0\text{ }^{\circ}\text{C}$ to rt; (h) (i) H₂ (1 atm), Pd/C (1.50 mass equiv), EtOAc, rt; (ii) NH₂OBn·HCl, NaOAc, MeOH/H₂O (5:1), $85\text{ }^{\circ}\text{C}$; (i) Pd(OAc)₂ (15 mol %), PhI(OAc)₂, AcOH/Ac₂O (1:1), $100\text{ }^{\circ}\text{C}$.

**Scheme 11.**Recent Examples of Substrate-Directed sp^3 C–H Oxidation/Desymmetrization



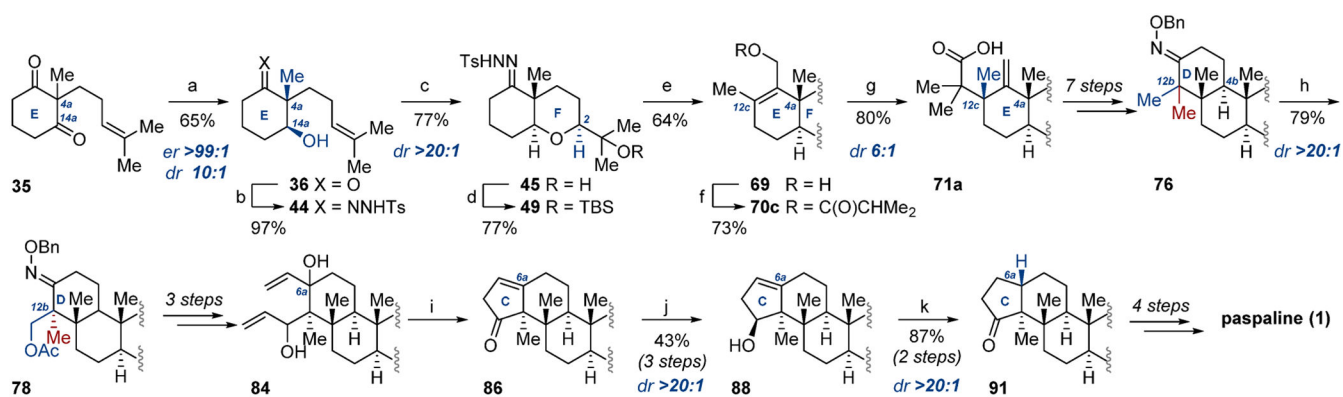
Scheme 12. Paspaline C Ring Construction and Synthesis of C6a Epimeric Ketone^a

^aReagents and conditions: (a) (i) HCl, H₂O/MeOH/THF/acetone (10:10:10:1), 85 °C; (ii) DMP, CH₂Cl₂, rt; (b) vinylmagnesium bromide, CeCl₃·2LiCl, THF, -78 °C; (c) Grubbs second generation catalyst (20 mol %), CH₂Cl₂, rt; (d) TFA, CH₂Cl₂, 0 °C to rt; (e) H₂ (1 atm), Pd/C (1.50 mass equiv), EtOH, rt.



Scheme 13. Substrate-Directed Control of the C6a Stereocenter and Completion of the Total Synthesis of Paspaline^a

^aReagents and conditions: (a) LiAlH₄, THF, 0 °C; (b) H₂ (1 atm), C₈H₁₂IrP(C₆H₁₁)₃C₅H₅N]PF₆ (15 mol %), CH₂Cl₂, rt; (c) DMP, CH₂Cl₂, rt; (d) (i) LDA, THF, 0 °C, then HMPA, Me₂S₂; (ii) *N*-chloroaniline, CH₂Cl₂, -78 °C, then NEt₃; (iii) Raney Ni, EtOH, rt; (iv) TsOH (66 mol %), CH₂Cl₂, 50 °C.

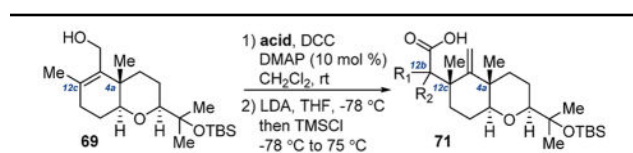


Scheme 14. Summary of Paspaline Total Synthesis^a

^aReagents and conditions: (a) YSC-2, H₂O/DMSO (10:1), 30 °C; (b) TsHNNH₂, C₇H₈, 70 °C; (c) *m*-CPBA, CH₂Cl₂, 0 °C, then PPTS; (d) TBSOTf, 2,6-lutidine, CH₂Cl₂, -50 °C; (e) *n*-BuLi, THF, -50 °C, then MeI; *n*-BuLi, -50 °C to rt, then (HCHO)_{*n*}; (f) isobutyric acid, DCC, DMAP (10 mol %), CH₂Cl₂, rt; (g) LDA, THF, -78 °C, then TMSCl, -78 to 75 °C; (h) Pd(OAc)₂ (15 mol %), PhI(OAc)₂, AcOH/Ac₂O (1:1), 100 °C; (i) (i) Grubbs second generation catalyst (20 mol %), CH₂Cl₂, rt; (ii) TFA, CH₂Cl₂, 0 °C to rt; (j) LiAlH₄, THF, 0 °C; (k) (i) H₂ (1 atm), C₈H₁₂IrP(C₆H₁₁)₃C₅H₅N]PF₆ (15 mol %), CH₂Cl₂, rt; (ii) DMP, CH₂Cl₂, rt.

Table 1

Ireland–Claisen Screenings for D Ring Assembly



entry	acid	ester (yield) ^a	acid (yield, dr) ^a
1	Ac ₂ O	70a (82%) ^b	--
2		70b (83%)	--
3		70c (73%)	71a (80%, 6:1) ^c
4		70d (93%)	--
5		70e (63%)	--
6		70f (74%)	--
7		70g (54%)	--
8		70h (87%)	71b (57%, 6.6:1.1:1) ^c

^a Isolated yields.

^b Conditions: Ac₂O, NEt₃, DMAP (10 mol %), CH₂Cl₂, rt.

^c Determined by ¹H NMR analysis of crude mixtures.