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Evolution of a Strategy for the Enantioselective Total Synthesis of (+)-Psiguadial B

Lauren M. Chapman, **Jordan C. Beck**[‡], **Caitlin R. Lacker**[‡], **Linglin Wu**, and **Sarah E. Reisman**[*]

The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

Abstract

(+)-Psiguadial B is a diformyl phloroglucinol meroterpenoid that exhibits anti-proliferative activity against the HepG2 human hepatoma cancer cell line. This full account details the evolution of a strategy that culminated in the first enantioselective total synthesis of (+)-psiguadial B. A key feature of the synthesis is the construction of the *trans*-cyclobutane motif by a Wolff rearrangement with *in situ* catalytic, asymmetric trapping of the ketene. An investigation of the substrate scope of this method to prepare enantioenriched 8-aminoquinolinamides is disclosed. Three routes toward (+)-psiguadial B were evaluated that featured the following key steps: 1) an *ortho*-quinone methide hetero–Diels–Alder cycloaddition to prepare the chroman framework; 2) a Prins cyclization to form the bridging bicyclo[4.3.1]decane system, and 3) a modified Norrish–Yang cyclization to generate the chroman. Ultimately, the successful strategy employed a ring-closing metathesis to form the seven-membered ring and an intramolecular *O*-arylation reaction to complete the polycyclic framework of the natural product.

INTRODUCTION

Plant extracts used in traditional folk medicine have long served as rich sources of structurally complex, bioactive compounds. For example, the bark, leaves, and fruit of the *Psidium guajava* plant are known for their medicinal properties, and have been used to treat ailments such as diabetes and hypertension.[1] Efforts to isolate and characterize the bioactive constituents have identified a variety of diformyl phloroglucinol meroterpenoids with interesting structures,[2] including **1** and **2** (Figure 1), which inhibit phosphodiesterase-4 (PDE4D2), a drug target for inflammatory and respiratory diseases.[3] In 2010, Shao and coworkers reported the discovery of four new meroterpenoids, psiguadials A–D (**3**–**6**),[4,5] which exhibit potent cytotoxicity against the HepG2 human hepatoma cancer cell line (IC_{50} = 46–128 nM). The most potent antiproliferative agent in this family, (+)-psiguadial B (**3**), is

[*]**Corresponding Author**: reisman@caltech.edu.

[‡]**Author Contributions**: These authors contributed equally.

Supporting Information

Synthetic schemes, additional reaction optimization tables, spectral data for all compounds, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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unique from a structural standpoint in that it possesses a strained bicyclo[4.3.1]decane terpene core, fused to a *trans*-cyclobutane ring.

Biosynthetically, this motif is proposed to arise via a mixed terpene-polyketide pathway.[5] Intramolecular cyclization of farnesyl pyrophosphate (**7**) generates humulyl cation **8**,[6] which undergoes stereoselective ring closure guided by caryophyllene synthase to produce β-caryophyllene (**9**, Scheme 1). Michael reaction of **9** with *ortho*-quinone methide (*o*-QM) **10**—likely derived from the known *P. guajava* metabolite 3,5-dimethyl-2,4,6-trihydroxybenzophenone[7]—is proposed to afford tertiary carbocation **11**,[8] which can cyclize to give (−)-guajadial (**1**)[1g] and (+)-psidial A (**12**),[9] isomeric natural products that have also been isolated from *P. guajava*. Alternatively, carbocation **11** can isomerize through proton transfer processes to form tertiary carbocation **13**,[5] which can undergo transannular ring closure to generate bridgehead cation **14**. Finally, this species can be trapped by the pendant phenol to furnish (+)-psiguadial B (3). Cramer[8,10] and Lee[11] have validated this biosynthetic hypothesis by semi-syntheses of **3**, **1**, and **11**, from β-caryophyllene (**9**).

While semi-synthetic approaches to phloroglucinol meroterpenoids provide direct access to β-caryophyllene-derived natural products, we viewed an abiotic approach to **3** as an opportunity to develop new chemistry and strategy concepts that could be applicable in broader synthetic contexts. Here, we describe a full account of our efforts to develop an enantioselective total synthesis of (+)-psiguadial B (**3**),[12,13] which was enabled by an asymmetric Wolff-rearrangement to construct the *trans*-fused cyclobutane.

DESIGN PLAN: FIRST GENERATION STRATEGY

As disclosed in our prior communication,[12] the construction of the central bicyclo[4.3.1]decane, which is *trans*-fused to a cyclobutane, was recognized as the primary synthetic challenge posed by **3**. Closer analysis identified the C1−C2 bond (Figure 2), which links the A and C rings through vicinal stereogenic centers, as a strategic disconnection. On the basis of this analysis, we were interested in forming this bond by a Pd-catalyzed C(sp^3)−H alkenylation reaction between cyclobutane **18** and vinyl iodide **19**.

Having identified a tactic to join the A and C rings, a retrosynthesis of **3** was conceived in which the 7-membered B ring would be generated via a late-stage intramolecular Prins cyclization, thus allowing simplification of **3** to **15**. Although the ring closure to form this strained system was expected to be challenging, the Prins reaction has been previously used for the preparation of bridging polycycles.[14] Tricycle **15** could be assembled through a bioinspired *ortho*-quinone methide hetero-Diels–Alder (*o*-QMHDA) reaction between enol ether **17** and an *o*-QM generated from **16**.[15] Although *o*-QMHDA reactions are widely used to construct chroman frameworks, simple acyclic enol ethers or styrenes are typically employed as dienophiles, and are used in excess to avoid *o*-QM dimerization.[16] In contrast, the proposed strategy necessitates use of a functionalized cyclic enol ether, ideally as the limiting reagent. At the outset of these studies, we were unaware of any reported examples in which cyclohexanone-derived enol ethers were employed as dienophiles in *o*-QMHDA cycloadditions; thus, the proposed studies could potentially contribute a new substrate class for *o*-QMHDA reactions.[17] Based on stereochemical analysis of reported *o*-QMHDA

cycloadditions, we anticipated that the reaction would favor the desired *anti*-relationship between C1′ and C9, however, whether the stereochemistry of **17** would impart the desired facial selectivity in the approach of the heterodiene was less clear.[15,18]

Enol ether **17** was envisioned to be accessible in short order from the product of the directed C(sp^3)−H alkenylation reaction, joining fragments **18** and **19**. Although the direct product of this reaction would be a *cis*-cyclobutane, the thermodynamically more stable *trans*-cyclobutane was anticipated to be accessible through an epimerization process. While C(sp^3)−H functionalization using 8-aminoquinoline as a directing group was well established as a powerful strategy in the context of total synthesis,[19,20] it was uncertain whether the proximal methyl C−H bonds might intervene unproductively. Finally, the required cyclobutane, **18**, could be easily prepared from known diazoketone **20** via photochemical Wolff rearrangement.[21]

A key question presented by the proposed retrosynthesis was how best to synthesize cyclobutane **18** in enantioenriched form. Elegant studies by Fu and coworkers had demonstrated that *N*-acylpyrroles can be prepared with excellent enantioselectivity from the reaction between aryl ketenes (e.g. **21**) and 2-cyanopyrrole (**22**) using chiral DMAP catalyst **23** (Scheme 2a).[22] We hypothesized that a similar transformation could be used to prepare **18** directly from **20** by using 8-aminoquinoline (**29**) as a nucleophile in the presence of an appropriate catalyst. While there were no examples from Fu's work in which the ketene was generated *in situ* photochemically, a single example from Lectka showed that a ketene could be generated *in situ* by a Wolff rearrangement, and engage in an enantioselective reaction (Scheme 2b).[23]

Following a survey of chiral nucleophilic catalysts known to engage with ketenes, [22–24] it was discovered that irradiation of a mixture of **20** and 3 equiv **29**[25] in the presence of 50 mol % (+)-cinchonine (**30**) produced **18** in 61% yield, and 79% ee (Table 1, entry 1). Investigation of various solvents revealed that THF provided the highest levels of enantioselectivity.[26] More concentrated reaction mixtures led to lower yields, presumably due to poor light penetration as a result of the sparing solubility of **30** in THF. When scaling the reaction to quantities relevant for total synthesis (30 mmol), the catalyst loading of **30** could be reduced to 10 mol %, which provided **18** in 62% yield and 79% ee (see Scheme 3). Moreover, enantiomerically pure **18** was obtained after a single recrystallization by layer diffusion.

Although our total synthesis efforts focused on the preparation of **18**, we wondered if this tandem Wolff rearrangement/enantioselective addition reaction could be applied to other α-diazoketone substrates. Unfortunately, substantially lower levels of enantioinduction (9–64% ee) were observed using **30** as a catalyst with these substrates (Table 1, entries 9, 17, 25, and 33). Evaluation of alternative cinchona derivatives **31**–**37** revealed that synthetically useful levels of enantioselectivity could be achieved for each substrate, depending on the catalyst. For instance, while **31**–**37** produced **18** with lower enantioinduction (16–64% ee, entries 2–8), catalysts **34** and **33** proved optimal for the 6- and 7-membered analogs of **20**, providing amides **42** and **43** each in 71% ee (entries 13 and 20). When these reactions were conducted on preparative scale, the catalyst loading could be dropped to 20 mol %, providing

cyclopentyl amide **42** (n = 2) in 80% yield and 67% ee and cyclohexyl amide **43** (n = 3) in 67% yield and 67% ee.[26] On the other hand, benzo-fused diazoketones, **40** and **41**, performed best in the presence of dimeric cinchona catalysts **37** and **36** (entries 32 and 39). At present, a general catalyst for the tandem Wolff rearrangement/enantioselective addition of 8-aminoquinoline has not been identified, though further mechanistic investigations may inform future efforts to improve the generality of this reaction.

Having identified conditions to prepare multigram quantities of **18** in enantiopure form, we were pleased to find that treatment of **18** with $Pd(OAc)_2$ (15 mol %), Ag_2CO_3, and **19** in TBME at 90 °C smoothly effected the C(sp^3)–H alkenylation reaction to give **46** in 75% yield on gram scale (Scheme 3). Exposure of **46** to DBU furnished the requisite *trans*-cyclobutane via selective epimerization at C2, as determined by deuterium-labeling studies.[26] It was at this stage that single crystals of *trans*-cyclobutane **47** suitable for X-ray diffraction were obtained. Unfortunately, **47** was found to be in the incorrect enantiomeric series for elaboration to natural **3**. To our dismay, this problem could not be circumvented by simply employing (−)-cinchonidine (**32**) in the tandem Wolff rearrangement/asymmetric ketene addition, as this *pseudoenantiomeric* catalyst afforded (+)-**18** in only 57% ee (Table 1, entry 3). Nevertheless, we elected to advance (–)-**47** in the interest of validating the key reactions in our retrosynthetic analysis as soon as possible.

To this end, attention turned to formation of the C1 quaternary center (Scheme 3). Subjection of *cis*-cyclobutane **46** to a number of standard conjugate addition conditions provided only trace yields of the corresponding product (not shown), presumably due to steric encumbrance by the proximal large aminoquinoline group. On the other hand, treatment of *trans*-cyclobutane **47** with excess Gilman's reagent smoothly furnished **49** and **50** in near quantitative yield as a 2.5:1 mixture of diastereomers, respectively. Separation of the diastereomers by HPLC allowed single crystals of **50** to be obtained, and X-ray analysis unambiguously confirmed that the major diastereomer (**49**) possessed the desired (*R*) configuration of the methyl group at the C1 quaternary center.

In an effort to improve the diastereoselectivity of this transformation, we turned to asymmetric catalysis. Fortunately, application of the conditions developed by Alexakis and coworkers for copper-catalyzed conjugate addition[27] provided **49** in 62% yield and 30:1 dr, albeit using 50 mol % [Cu(OTf)2]•PhMe and a stoichiometric equivalent of phosphoramidite ligand **48**. Presumably, the high catalyst loading is required due to the presence of the highly-coordinating 8-aminoquinolinamide, which can deactivate the catalyst or inhibit turnover.

With the quaternary center secured, ketone **49** was converted to the corresponding dimethyl ketal **51** (Scheme 4a), a precursor to the dienophile for the *o*-QMHDA reaction (*vide infra*). While phenolic aldol conditions[28] failed to produce **16**, this acid-labile *o*-QM precursor was prepared from phloroglucinol **54**[29] via the morpholine adduct (**55**, Scheme 4b).[30] A control experiment determined that heating of **51** to 170 °C in toluene results in thermal extrusion of methanol to afford a 1:1 mixture of enol ethers **17** (Scheme 5).[31] When a mixture of **51** and **16** was heated to 170 °C for 21 h, the cycloadduct was obtained in 68% yield, albeit as a complex mixture of diastereomers.

Analytically pure samples of the four highest abundance diastereomers (**57**–**60**) were obtained by HPLC purification. Spectroscopic analysis by 2D NMR led to the assignment of **57** and **58** as the two major diastereomers, which bear the expected relative *anti* relationship between C9 and C1′. The formation of these products in a ~1:1 ratio indicates that **17** does not exert significant facial selectivity in the *o*-QMHDA reaction. The *trans*-fused isomer, **60**, presumably results from thermal equilibration of the ketal under the reaction conditions.

In considering how to improve the selectivity for desired diastereomer **57**, we drew inspiration from Evans' highly enantioselective inverse-demand hetero-Diels–Alder chemistry, which proceeds via bidentate coordination of heterodienes such as **61** to a chiral Cu(II)-BOX Lewis acid catalyst (Scheme 6a).[32] We envisioned that chelation of the aminoquinoline in **17** to a Cu complex could engage **56** as depicted in Scheme 6b, thereby directing the *o*-QM to the top face of enol ether **17** (Scheme 6b). Formation of **56** could be induced by the equivalent of triflic acid generated via complexation of $Cu(OTf)_2$ with aminoquinoline.[17,3333]

To test this hypothesis, enol ether **17** was prepared by heating in PhMe,[34] and after exchanging the solvent for CH_2Cl_2, $Cu(OTf)_2$ and **16** were added. Analysis of the crude reaction mixture by ^1H NMR revealed that although the ratio of **57**:**58** had improved relative to the thermal reaction, significant quantities of the undesired isomers, **59** and **60**, were still formed. Moreover, this reaction suffered from lower overall yields due to rapid hydrolysis of **17** and reversion of **16** to phloroglucinol **54**. At this stage, it was clear that implementation of this strategy would require a significant investment in reaction optimization and we felt that such an effort would only be warranted if the proposed late-stage Prins reaction were proved feasible. Thus, attention turned to assessing this key reaction in a model system.

To this end, the aminoquinoline auxiliary in **51** was reductively cleaved by treatment with Schwartz's reagent to furnish aldehyde **62**, which was homologated to alkyne **63** using the Ohira–Bestmann reagent (Scheme 7). Nickel-catalyzed hydrothiolation[35] proceeded with good regioselectivity to give vinyl sulfide **65** in low yield, mainly due to the facile conversion of this intermediate to a mixture of enol ethers **64** under the reaction conditions.

Unfortunately, exposure of ketal **65** to a variety of Lewis acids led to hydrolysis, yielding ketone **67** in nearly all cases. The use of $InCl_3$,[36] however, delivered the desired Prins product **66** in 11% yield. Formation of the 7-membered ring was confirmed by a key HMBC correlation between the C12 axial proton and the distinct sp^2 C7 signal at δ 140 ppm. Although the formation of the seven-membered ring through a Prins cyclization was promising, our excitement was tempered by the fact that **66** was obtained in poor yield and challenges were encountered with reproducibility. Taken together with the significant diastereoselectivity issues plaguing the *o*-QMHDA reaction, we revised our retrosynthetic analysis.

SECOND GENERATION STRATEGY

In our revised retrosynthesis, we envisioned that the chroman substructure could be constructed via a modified Norrish–Yang cyclization,[37] revealing **68** as a key intermediate

(Figure 3a). Benzophenones such as **68** are known to undergo photoexcitation upon irradiation with UV light[38] to give triplet species (i.e. **68***) that can engage in Norrish type-II 1,5-hydrogen atom abstraction and subsequent radical recombination.[37,39] In the absence of any available γ or δ-hydrogens, it was hypothesized that **68*** could abstract a hydrogen atom from C9 to generate diradical **72**.[40] Recombination of the carbon-centered radicals would furnish the core of 3. We recognized that achieving the desired *regioselectivity* could prove challenging since the C7 and C12 methylenes in **68*** were also within range for 1,7-H–atom abstraction (Figure 3b). Although the outcome of this transformation was uncertain, conformational analysis suggested that the product resulting from hydrogen atom abstraction at C9 would produce the least sterically encumbered chroman product. Moreover, this strategy was particularly appealing since it was expected that **68** could be assembled in an expedient and convergent fashion. Benzophenone **68** was envisioned to be accessible from tertiary alcohol **70** via an intermolecular *O*-arylation reaction with aryl bromide **69**.[41] We reasoned that the strained 7-membered ring in **70** could be formed by ring-closing metathesis,[42] leading back to vinyl ketone **71**, which could in turn be synthesized from known intermediates prepared during our studies of the C(sp^3)–H alkenylation/asymmetric Wolff rearrangement.

With this revised retrosynthetic plan, we set out to prepare vinyl ketone **71**, and to also address two key challenges identified in the first generation approach: 1) to lower the catalyst loading in the conjugate addition reaction used to set the C1 quaternary center, and 2) to develop an epimerization sequence to prepare vinyl ketone **71** in the correct enantiomeric series from quinolinamide (–)-**18**. In terms of the latter challenge, we anticipated that the desired enantiomeric series could be accessed by epimerization of compounds derived from **18** (e.g. **46**) at C5 instead of C2 (Scheme 8). A straightforward approach would involve disfavoring γ-deprotonation at C2 by masking the ketone of **46** in order to advance to a C5 epimerization substrate. Unfortunately, these efforts proved unfruitful, as ketalization of **46** under a variety of conditions always resulted in rapid epimerization at C2 to furnish *trans*-cyclobutane **77** in low yields.[43]

Instead, it was recognized that **74** could be accessed directly by coupling **18** with vinyl iodide **73**.[44] To our delight, the Pd-catalyzed coupling with vinyl iodide **73** performed even better than its enone counterpart (**19**), requiring only 2 equiv of **73** to furnish **74** in 72% yield on a gram scale. Exposure of **74** to Schwartz's reagent effected reduction to the corresponding *cis*-aldehyde, which was epimerized at C5 by treatment with KOH in methanol to give *trans*-aldehyde **75** in 70% yield over the two steps. Gratifyingly, Wittig methylenation and hydrolysis provided (+)-**76**, the required enantiomer for synthesis of natural psiguadial B (**3**). In addition, cross-coupling of **73** eliminated a linear protection step and substantially improved the material throughput.[45]

To demonstrate that either enantiomer of **76** can be prepared using a single enantiomer of organocatalyst, an alternative sequence was also developed. Epimerization of **46** to the *trans*-cyclobutane under the previously developed conditions, followed by ketalization provided **77**. Reductive cleavage of the aminoquinoline auxiliary gave the corresponding aldehyde

(*ent*-**75**), which was telescoped through a Wittig olefination and hydrolysis as before to afford vinyl enone (−)-**76** in 58% yield over the two steps.

With the desired enantiomer of enone **76** in hand, attention turned to the installation of the C1 quaternary center using a catalytic asymmetric conjugate addition. In the absence of the amino-quinoline auxiliary, we were pleased to find that use of CuTC (15 mol %) in conjunction with ligand *ent*-**48** (30 mol %) provided **71** in 94% yield and 19:1 dr (Scheme 9). Addition of vinyl Grignard to ketone **71** proceeded uneventfully, providing alcohol **78** in excellent yield and diastereoselectivity. Gratifyingly, exposure of **78** to second-generation Hoveyda–Grubbs catalyst at elevated temperature delivered bridged bicycle **70** in 93% yield. Subsequent hydrogenation under standard conditions led to tertiary alcohol **79**. After some experimentation, we found that the combination of $Pd(OAc)_2$ and dppf catalyzed the intermolecular *O*-arylation between **79** and aryl bromide **69**, affording aryl ether **68** in 45% yield. Unfortunately, the reproducibility of this transformation proved capricious, and attempts to improve the yield through further optimization were unsuccessful. Nevertheless, a sufficient amount of **68** was obtained to evaluate the key Norrish–Yang cyclization.

In the event, irradiation of **68** with 254 nm light in rigorously deoxygenated dioxane led to complete consumption of starting material within 1 hour and produced a complex mixture of several new products.[46] The formation of the undesired Norrish–Yang product **80** was confirmed by 2D NMR spectroscopy; a prominent HMBC correlation was apparent between C5 and the newly formed methine proton at C7, and several key NOE signals were consistent with the stereochemical assignment (Scheme 10). Thus, while the anticipated *reactivity* was observed, **80** results from the wrong *regioselectivity*, and was isolated in a mere 6.5% yield—a result that would likely be difficult to substantially improve through reaction optimization.

Notably, the major compound isolated from this reaction is phenol **83**,[47] which was obtained in 28% yield. This side product presumably arises by fragmentation of diradical species **72** (or the diradical resulting from H-atom abstraction at C7), wherein C–O bond cleavage expels enol tautomer **82**; the resulting terpene-based fragment likely undergoes further decomposition, as alkene **84** or related compounds were not isolated.[48] In an effort to investigate whether this competing pathway could be suppressed, we examined a number of different solvents and irradiation wavelengths in a model system, but observed rapid formation of phenol **83** in all cases. Having determined that the late-stage Norrish–Yang cyclization was an untenable strategy to complete the chroman core of **3**, an alternative synthetic route was devised.

THIRD GENERATION STRATEGY

In our final revision of the retrosynthesis, we simplified **3** to **85** and elected to construct the C9–C1′ bond at an earlier stage (Figure 4). Invoking a similar disconnection through the C–O aryl bond as in our second-generation route, it was anticipated that an *intra*molecular ring closure would prove more reliable than the challenging intermolecular arylation employed previously (see Scheme 9). This bond scission revealed aryl bromide **86**, which could be

accessed using the established ring-closing metathesis, while the arene functionality at C9 could be installed via aldol condensation with vinyl ketone **71**.

In the forward sense, a methanolic solution of vinyl ketone **71** and aldehyde **87** was treated with potassium hydroxide at elevated temperature to afford *exo*-enone **88** in 92% yield (Scheme 11). Attempts to incorporate the C1′ phenyl group at this stage via conjugate addition were met with limited success, yielding only trace amounts of **90** as an inseparable mixture of diastereomers at C9 and C1′. An alternative aldol condensation between **71** and benzophenone **69** (see Figure 3 for structure) failed to produce **89** under otherwise identical conditions or Mukaiyama aldol conditions. Given the inability to introduce the C1′ phenyl substituent at this point, we elected to advanced **88** and attempt to install this group at a later stage in the synthesis.

In contrast to the previous system lacking substitution at C9 (i.e. **71**), 1,2-addition into this more sterically hindered ketone proved challenging. Treatment of **88** with vinyl magnesium bromide under the conditions used previously led to incomplete conversion—presumably due to competitive α-deprotonation— affording **91** (Scheme 12) in low yields and moderate diastereoselectivity.[26] Attempts to improve conversion using Lewis acid activators gave higher yields of **91**, but resulted in lower levels of diastereoselectivity (<2:1). Ultimately, the desired allylic alcohol was obtained in good yield with serviceable dr by employing vinyllithium in THF at −78 °C, allowing isolation of **91** as a single diastereomer in 54% yield. The ring-closing metathesis proceeded with equal efficiency on this new substrate to furnish **86** in 93% yield. With the strained sesquiterpene framework secured, both the di- and trisubstituted olefins in **86** were hydrogenated in the presence of Crabtree's catalyst, which engaged in a hydroxyl-directed reduction[49] to establish the C9 stereogenic center with 16:1 dr, providing **93** in excellent yield. The final ring of the psiguadial framework was formed by a Cu-catalyzed intramolecular *O*-arylation reaction, which furnished pentacycle **94** in 75% yield.[50]

With the successful development of a scalable and high-yielding route to **94**, the task of appending the C1′ phenyl group was now at hand. Ideally, the electron rich arene in **94** would be engaged directly in a benzylic arylation reaction; a possible mechanism would involve benzylic oxidation at C1′ followed by trapping with a phenyl nucleophile. Whereas a number of laboratories have shown that electron rich arenes can trap benzylic cations in simple systems,[51] it was unclear whether an electronically neutral, unsubstituted phenyl group would be sufficiently reactive to engage as the nucleophile in this type of transformation. Nonetheless, we investigated this possibility with reagents commonly used in flavonoid chemistry (e.g. DDQ,[51a,d,52] Chloranil, Pb_3O_4,[53] Oxone/$CuSO_4$,[54] and $NOBF_4$[55]), followed by trapping with benzene, PhMgBr, or $PhB(OH)_2$, all without success. Efforts to apply Shi's $FeCl_2$-catalyzed benzylic dehydrogenative arylation,[56] or Muramatsu's C(sp^3)–H arylation using DDQ and PIFA[57] were also unfruitful.

Having failed to achieve a direct arylation, a stepwise protocol was employed. Oxidation with DDQ in the presence of ethoxyethanol[52] afforded **95**—a relatively stable product—which could be isolated in modest yields. The remaining mass balance of the reaction consisted of side products suspected to result from over oxidation and elimination of the

benzylic ether. A survey of reaction parameters revealed that adding acetonitrile as a co-solvent led to cleaner reaction profiles, albeit at the expense of conversion. Presumably, the acetonitrile solvent helps to stabilize the intermediate benzylic cation (i.e. **96**), favoring more efficient trapping with ethoxyethanol over unproductive side reactions. Synthetically useful yields of **95** were obtained under these conditions by re-subjecting recovered **94** to the reaction conditions a second time.

With respect to the stereochemistry at C1′, **95** was isolated as a 4.8:1 mixture of diastereomers, favoring the α-disposed ether. Conformational analysis of **94** indicates that the 7-membered ring protrudes from the bottom face of the molecule, suggesting that C–O bond formation appears to proceed with contrasteric selectivity. The observed stereochemical outcome might result from an overall double inversion process that proceeds by initial association of DDQ from the less hindered top face of **94** to form a tightly bound charge-transfer complex (i.e. **96**).[58] If this complex remains closely associated, ethoxyethanol would then attack from the bottom face, thus leading to α-ether **95** as the major diastereomer.

With a functional handle installed at C1′, TMSOTf was initially investigated as a Lewis acid to activate the ethoxyethyl benzyl ether, however, no phenylated product was obtained using $PhB(OH)_2$, or PhMgBr as nucleophiles (Table 2, entries 1 and 2).[52b] Simple heating[59] or nickel-catalyzed Kumada coupling with PhMgBr in PhMe[60] yielded only eliminated products and complex reaction profiles (entries 3–5). Likewise, Bode's conditions for the addition of aryl trifluoroborates to oxonium ions, which use BF_3•OEt_2 as the Lewis acid, failed to produce **85** (entries 6 and 7).[61] We were therefore delighted to obtain a near quantitative yield of **85** (in 1.7:1 dr) by treating a mixture of **95** and lithium diphenylcyanocuprate with BF_3•OEt_2 (entry 8).[62] After some experimentation, it was found that the diastereoselectivity could be slightly improved to 2:1 by holding the reaction at –45 °C (entry 9). Although colder temperatures led to a further improvement in dr, this was accompanied by a lower yield (entry 10).

As the C1′ diastereomers of **85** were inseparable by silica gel chromatography, the mixture was subjected to pyridine hydrochloride at 200 °C, which afforded the corresponding demethylated products in 92% combined yield (Scheme 13). At this stage, the diastereomeric resorcinols were readily separable by column chromatography, providing **97** as a single diastereomer in 62% yield. Finally, the remaining two aryl aldehydes were simultaneously installed using Rieche formylation conditions,[63] delivering (+)-psiguadial B (**3**) in 50% yield. Synthetic **3** was found to be spectroscopically identical in all respects to the natural sample reported by Shao et al.[4]

CONCLUSION

In summary, the first enantioselective total synthesis of the cytotoxic natural product, (+)-psiguadial B (**3**), was achieved in **15** steps from diazoketone **20**. The successful synthetic strategy was enabled by the implementation of a tandem photochemical Wolff rearrangement/asymmetric ketene addition reaction. Having developed a novel protocol for the enantioselective preparation of quinolinamide **18**, a variety of substrates were evaluated

and conditions were identified to prepare the corresponding 5- and 6-membered ring products. *De novo* construction of the *trans*-fused cyclobutane ring in **3** was accomplished using a strategic Pd-catalyzed C(sp^3)−H alkenylation reaction, followed by one of two distinct epimerization strategies, which permit access to both enantiomers of the natural product from a single enantiomer of organocatalyst.

In the course of this work, three different synthetic routes toward (+)-psiguadial B were investigated. These studies have led to the evaluation of several challenging transformations, including 1) an *o*-QMHDA cycloaddition between a highly functionalized enol ether and a phloroglucinol-derived *o*-QM; 2) a seven-membered ring-forming Prins cyclization; and 3) a modified Norrish–Yang cyclization. Ultimately, the strained sesquiterpene core was built using a remarkably efficient ring-closing metathesis, and elaborated through a short sequence to afford the natural product in 1.3% overall yield. We believe that the development of this route to 3 may enable the synthesis of unnatural analogs of **3**, that would be difficult to access through semi-synthetic methods. Application of the key strategy concepts described herein to the synthesis of other *trans*-cyclobutane-containing natural products are currently ongoing in our laboratory.

EXPERIMENTAL

General Procedures

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), acetonitrile (MeCN), benzene (PhH), 1,4-dioxane, and toluene (PhMe) were dried by passing through activated alumina columns. Triethylamine (Et_3N) and methanol (MeOH) were distilled over calcium hydride prior to use. Unless otherwise stated, chemicals and reagents were used as received. All reactions were monitored by thin-layer chromatography (TLC) using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, *p*-anisaldehyde, or 2,4-dinitrophenylhydrazine staining. Flash column chromatography was performed either as described by Still et al.[64] using silica gel (particle size 0.032-0.063) purchased from Silicycle or using prepackaged RediSep®Rf columns on a CombiFlash Rf system (Teledyne ISCO Inc.). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III HD with Prodigy cryoprobe (at 400 MHz and 101 MHz respectively), a Varian 400 MR (at 400 MHz and 101 MHz, respectively), a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), or a Varian Inova 600 (at 600 MHz and 150 MHz, respectively), and are reported relative to internal $CHCl_3$ (^1H, δ = 7.26) and $CDCl_3$ (^{13}C, δ = 77.1), C_6H_5 (^1H, δ = 7.16) and C_6D_6 (^{13}C, δ = 128), or d_8-THF (^1H, δ = 3.58) and (^{13}C, δ = 67.6). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM) ionization mode.

Analytical SFC was performed with a Mettler SFC supercritical CO2 analytical chromatography system with a Chiralcel AD-H column (4.6 mm × 25 cm).

Procedures and characterization data for compounds **3**, **18**, **20**, **46**, **47**, **71**, **73**, **74**, **75**, **76**, **77**, **85**, **86**, **88**, **91**, **93**, **94**, **95**, **97** were reported previously.[12]

Preparation of diazoketone 20:[21,65]

To each of two flame-dried 1 L round-bottom flasks was added NaH (60% dispersion in mineral oil, 3.17 g, 79.2 mmol, 1.20 equiv) and the atmosphere was exchanged for N_2 one time. Dry Et_2O (30.0 mL) was then added via syringe and the suspension cooled to 0 °C. Ethyl formate (12.4 mL, 152 mmol, 2.30 equiv) was then added, followed by 2,2-dimethylcyclopentanone (7.40 g, 66.0 mmol) either neat, or as a 3.0 M solution in Et_2O. A catalytic amount of wet methanol (~100 μL) was then added and the reaction left to stir at 0 °C.[66] Upon completion, the reaction solidifies to a chunky, white solid that dissolved readily upon the addition of DI H_2O. At this point, both reaction mixtures were combined for workup: after dilution with Et_2O, the layers were separated and the aqueous layer was washed with Et_2O 3x to remove organic impurities and a small amount of unreacted starting material. The aqueous layer was then cooled to 0 °C and acidified to pH = 3 using 5 M HCl. Et_2O was then added and the acidified aqueous layer was extracted 6x. The combined organics were then dried over Mg_2SO_4, filtered, and concentrated *in vacuo* into a 500 mL round-bottom flask.

The crude α-formyl ketone was taken up in CH_2Cl_2 (132 mL) and the solution cooled to –10 °C. Triethylamine (55.2 mL, 396 mmol, 5.00 equiv) was added, followed by solid *p*-ABSA[67] (31.8 g, 132 mmol, 1.00 equiv) in three portions. The reaction was stirred for 3 hours and allowed to gradually reach 10 °C, at which point an aqueous solution of KOH (55.0 mL, 4 M) was added. Additional CH_2Cl_2 and H_2O were added, the layers were separated and the aqueous layer extracted with CH_2Cl_2 until no product remains by TLC. The combined organics were dried over Mg_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (20–30% Et_2O/pentane) to afford **20** (17.4 g, 95% yield) as a bright yellow oil. ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 2.88 (t, *J* = 7.0 Hz, 2H), 1.77 (t, *J* = 7.2 Hz, 2H), 1.04 (d, *J* = 1.0 Hz, 6H). ^{1}**H NMR** (400 MHz, d_8-THF) δ 2.94 (t, *J* = 7.0 Hz, 2H), 1.79 (t, *J* = 7.2 Hz, 2H), 1.04 (s, 6H). ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 204.8, 56.6, 46.3, 35.7, 24.1, 21.2. ^{13}**C NMR** (101 MHz, d_8-THF) δ 203.6, 56.1, 46.9, 36.6, 24.5, 21.9. **FTIR** (NaCl, thin film) 3754, 3414, 3332, 2962, 2934, 2892, 2869, 2672, 2642, 2578, 2510, 2080, 1981, 1673, 1581, 1471, 1460, 1382, 1362, 1339, 1309, 1267, 1245, 1204, 1133, 1110, 1058, 1030, 994, 977, 948, 919, 893, 780, 726, 697 $cm.^{-1}$

Diazoketones **38**–**41** were prepared according to the procedure developed for **20**. Spectroscopic data for **40** and **41** are consistent with that reported in the literature.[68]

(38)

Yellow Oil, (1.76 g, 36% yield over 2 steps). ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 2.71 (t, *J* = 6.5 Hz, 2H), 1.82 – 1.73 (m, 2H), 1.68 –1.61 (m, 2H), 1.15 (s, 6H). ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 200.1, 62.6, 42.0, 37.5, 26.7, 22.9, 18.5. **FTIR** (NaCl, thin film) 2943, 2864,

2082, 1626, 1472, 1449, 1381, 1342, 1317, 1275, 1261, 1220, 1201, 1162, 1122, 1044, 1011, 910, 853, 738, 658 $cm.^{-1}$ **HRMS** (EI) calc'd for $C_8H_{12}N_2O$ $[M]^+$ 152.0950, found 152.0956.

(39)

Yellow Oil, (400.0 mg, 26% yield over 2 steps) ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 2.55 (ddt, *J* = 7.0, 4.8, 2.3 Hz, 2H), 1.75 (dt, J = 4.4, 2.8 Hz, 4H), 1.57 (ddt, *J* = 6.3, 3.4, 1.7 Hz, 2H), 1.17 (s, 6H). ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 202.2, 68.3, 47.0, 37.9, 29.5, 25.8, 25.7, 25.6. **FTIR** (NaCl, thin film) 2981, 2966, 2927, 2858, 2083, 1704, 1617, 1474. 1448, 1387. 1364, 1350, 1324, 1272, 1251, 1231, 1203, 1147, 1113, 1057, 1020, 980, 953, 871, 845, 736, 656 $cm.^{-1}$ **HRMS** (EI) calc'd for $C_9H_{14}N_2O$ $[M]^+$ 166.1106, found 166.1095.

Small-scale screening protocol for enantioenriched amides 18, 42–45

Oven-dried quartz tubes were each charged with aminoquinoline (21.6 mg, 0.150 mmol, 3.00 equiv) and catalyst (50 mol %). Inside a N_2-filled glovebox, diazoketones 20, 38–40 (0.05 mmol) were then added to each as a solution in 0.500 mL THF (excluding diazoketone **41**, which was added as a solid outside of the glovebox). The reactions were then sealed with a 19/38 rubber septum around the outside of each tube and sealed with electrical tape. The reactions were then brought out of the glovebox and placed in a bottomless test tube rack in front of a Honeywell 254 nm lamp. The reactions were irradiated with stirring at room temperature for 18 hours. The reactions were then concentrated *in vacuo*, and the crude reaction mixtures were analyzed by ^{1}H NMR with an added internal standard to determine % yield. The crude residues were purified by silica gel preparative TLC (2% Et_2O/CH_2Cl_2) to provide 18, 42–45 in varying yields and enantiopurities.

Large-scale protocol for enantioenriched amide 18:[65]

To a flame-dried, 1 L quartz flask was added 8-aminoquinoline (**29**) (12.9 g, 89.5 mmol, 3.00 equiv) and (+)-cinchonine (**30**) (879 mg, 2.99 mmol, 0.100 equiv). The flask was evacuated and backfilled with N_2 three times and dry THF (600 mL) was then added via cannula. Diazoketone **20** (4.12 g, 29.8 mmol, 1.00 equiv) was added last via syringe and the reaction was irradiated with stirring using a Honeywell 254 nm lamp at room temperature. Reaction progress was monitored by TLC (72-168 hours are typically required for complete conversion on this scale, and rotation of the flask every day provided faster conversion).[69] Upon completion, the reaction mixture was concentrated *in vacuo*, the solids were taken up in CH_2Cl_2, and the suspension filtered. The filter cake was washed with CH_2Cl_2 three times and the filtrate was concentrated *in vacuo* to give a crude residue that was purified by silica gel flash chromatography (isocratic: 6% EtOAc/hexane) to provide **18** (4.69 g, 62%) as a pale-yellow solid. The enantiomeric excess was determined to be 79% by chiral SFC analysis (AD-H, 2.5 mL/min, 20% IPA in CO_2, λ = 254 nm): t_R (major) = 4.23 min, t_R (minor) = 5.64 min. $[\alpha]_D^{25.0} = -66.0°$ (c = 0.560, $CHCl_3$). Enantioenriched cyclobutane 18 was dissolved in a minimal amount of CH_2Cl_2 in a 100 mL round-bottom flask. An equal amount of hexanes was carefully layered on top of the CH_2Cl_2 to form a biphasic mixture. The layers were allowed to diffuse overnight to provide **18** as white, crystalline needles (mp: 66–68 °C). The supernatant was concentrated under reduced pressure and this process was

repeated again to provide additional **18** (3.50 g total, 83% recovery of theoretical total of the desired enantiomer, 46% overall from **20**): $[\alpha]_D^{25.0} = -109°$ (c = 0.720, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 8.80 (t, *J* = 1.8 Hz, 1H), 8.79 (dd, *J* = 13.6, 1.6 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.52 (q, *J* = 8.2, 7.5 Hz, 1H), 7.48 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 3.07 (ddd, *J* = 9.1, 8.2, 0.9 Hz, 1H), 2.48 (dq, *J* = 11.4, 9.4 Hz, 1H), 2.06 (dtd, *J* = 11.6, 8.6, 3.3 Hz, 1H), 1.85 (dt, *J* = 10.8, 9.1 Hz, 1H), 1.74 (dddd, *J* = 10.7, 9.5, 3.3, 0.9 Hz, 1H), 1.39 (s, 3H), 1.14 (s, 3H). **^{13}C NMR** δ 171.8, 148.3, 138.6, 136.4, 134.7, 128.1, 127.6, 121.7, 121.3, 116.4, 51.0, 40.4, 32.3, 30.9, 23.4, 17.4. **FTIR** (NaCl, thin film) 3353, 3047, 2952, 2861, 1685, 1595, 1577, 1526, 1485, 1460, 1424, 1385, 1324, 1261, 1239, 1187, 1169, 1153, 825, 791,756 cm.$^{-1}$ **HRMS** (MM) calc'd for $C_{16}H_{19}N_2O$ $[M+H]^+$ 255.1492, found 255.1501.

(42)

0.2 mmol scale: An oven-dried quartz tube was charged with aminoquinoline (**29**) (86.5 mg, 0.600 mmol, 3.00 equiv) and (**34**) (32.5 mg, 0.100 mmol, 0.500 equiv) and brought into a N_2 filled glovebox. Diazoketone (**38**) (33.2 mg, 0.200 mmol, 1.00 equiv) was added as a solution in 2.00 mL THF and the tube was sealed with a 19/38 rubber septum and secured with electrical tape. The reaction was removed from the glovebox and placed in a bottomless test tube rack in front of a Honeywell 254 nm lamp for 48 hours. The reaction mixture was then concentrated *in vacuo*. The crude residue was purified via silica gel flash chromatography (6% EtOAc/hexanes) to afford **42** (37.5 mg, 77% yield) as a brown oil. The enantiomeric excess was determined to be 71% by chiral SFC analysis (AD-H, 2.5 mL/min, 20% IPA in CO2, λ = 254 nm): t_R (major) = 4.28 min, t_R (minor) = 5.41 min.

(42)

1 mmol scale: An oven-dried quartz tube was charged with aminoquinoline (**29**) (433 mg, 3.00 mmol, 3.00 equiv) and (**34**) (64.9 mg, 0.200 mmol, 0.200 equiv) and brought into a N_2 filled glovebox. Diazoketone (**38**) (166 mg, 1.00 mmol, 1.00 equiv) was added as a solution in 10.0 mL THF and the tube was sealed with a 19/38 rubber septum and secured with electrical tape. The reaction was removed from the glovebox and placed in a bottomless test tube rack in front of a Honeywell 254 nm lamp for 48 hours. The reaction mixture was then concentrated *in vacuo*. The crude residue was purified via silica gel flash chromatography (6% EtOAc/hexanes) to afford **42** (215 mg, 80% yield) as a brown oil. The enantiomeric excess was determined to be 67% by chiral SFC analysis (AD-H, 2.5 mL/min, 20% IPA in CO2, λ = 254 nm): t_R (major) = 4.28 min, t_R (minor) = 5.41 min. $[\alpha]_D^{25.0} = -32.5°$ (c = 2.075, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 8.81 (d, *J* = 1.7 Hz, 1H), 8.80 (dd, *J* = 3.0, 1.7 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.57 – 7.47 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.61 (t, *J* = 8.4 Hz, 1H), 2.38 – 2.22 (m, 1H), 2.02 (dtd, *J* = 13.2, 8.5, 4.4 Hz, 1H), 1.95 – 1.82 (m, 1H), 1.79 – 1.65 (m, 2H), 1.63 – 1.57 (m, 1H), 1.31 (s, 3H), 1.01 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.1, 148.3, 138.6, 136.5, 134.8, 128.1, 127.6, 121.7, 121.3, 116.4, 58.1, 43.2, 42.1, 29.7, 27.9, 24.0, 22.5. **FTIR** (NaCl, thin film) 3362, 2957, 2924, 2854, 1729, 1690, 1525, 1486, 1464, 1424, 1381, 1325, 1262, 1164, 1145, 1132, 1072, 825, 791, 720 cm.$^{-1}$ **HRMS** (MM) calc'd for $C_{17}H_{21}N_2O$ $[M+H]^+$ 269.1648, found 269.1645.

(43)

0.2 mmol scale: An oven-dried quartz tube was charged with 8-aminoquinoline (**29**) (86.5 mg, 0.600 mmol, 3.00 equiv) and (**33**) (32.5 mg, 0.100 mmol, 0.500 equiv) and brought into a N_2 filled glovebox. Diazoketone (**39**) (31.0 mg, 0.200 mmol, 1.00 equiv) was added as a solution in 2.00 mL THF and the tube was sealed with a 19/38 rubber septum and secured with electrical tape. The reaction was removed from the glovebox and placed in a bottomless test tube rack in front of a Honeywell 254 nm lamp for 48 hours. The reaction mixture was then concentrated *in vacuo*. The crude residue was purified via silica gel flash chromatography (6% EtOAc/hexanes) to afford **43** (33.3 mg, 59% yield) as a brown oil. The enantiomeric excess was determined to be 71% by chiral SFC analysis (AD-H, 2.5 mL/min, 12% IPA in CO2, λ = 254 nm): t_R (major) = 9.67 min, t_R (minor) = 10.34 min.

(43)

1 mmol scale: An oven-dried quartz tube was charged with 8-aminoquinoline (**29**) (433 mg, 3.00 mmol, 3.00 equiv) and (**33**) (64.9 mg, 0.200 mmol, 0.200 equiv) and brought into a N_2 filled glovebox. Diazoketone (**39**) (152 mg, 1.00 mmol, 1.00 equiv) was added as a solution in 10.0 mL THF and the tube was sealed with a 19/38 rubber septum and secured with electrical tape. The reaction was removed from the glovebox and placed in a bottomless test tube rack in front of a Honeywell 254 nm lamp for 48 hours. The reaction mixture was then concentrated *in vacuo*. The crude residue was purified via silica gel flash chromatography (6% EtOAc/hexanes) to afford **43** (189 mg, 67% yield) as a brown oil. The enantiomeric excess was determined to be 67% by chiral SFC analysis (AD-H, 2.5 mL/min, 12% IPA in CO2, λ = 254 nm): t_R (major) = 9.67 min, t_R (minor) = 10.34 min. $[\alpha]_D^{25.0} = -17.3°$ (c = 1.68, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 8.82 (d, *J* = 1.7 Hz, 1H), 8.80 (dd, *J* = 2.7, 1.7 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.57 – 7.47 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.30 (dd, *J* = 11.8, 3.5 Hz, 1H), 1.99 – 1.78 (m, 3H), 1.55 – 1.47 (m, 2H), 1.39 – 1.27 (m, 3H), 1.13 (s, 3H), 1.10 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.6, 148.3, 138.6, 136.5, 134.7, 128.1, 127.6, 121.7, 121.3, 116.5, 56.5, 41.6, 33.4, 31.5, 25.7, 25.7, 22.1, 21.2. **FTIR** (NaCl, thin film) 3364, 2956, 2923, 2852, 1729, 1691, 1523, 1486, 1462, 1424, 1378, 1326, 1273, 1129, 1072, 825, 790 $cm.^{-1}$ **HRMS** (MM) calc'd for $C_{18}H_{23}N_2O$ $[M+H]^+$ 283.1805, found 283.1796.

(44)

An oven-dried quartz tube was charged with aminoquinoline (**29**) (86.5 mg, 0.600 mmol, 3.00 equiv) and (**37**) (85.7 mg, 0.100 mmol, 0.500 equiv) and brought into a N_2 filled glovebox. Diazoketone (**40**) (31.6 mg, 0.200 mmol, 1.00 equiv) was added as a solution in 2.00 mL THF and the tube was sealed with a 19/38 rubber septum and secured with electrical tape. The reaction was removed from the glovebox and placed in a bottomless test tube rack in front of a Honeywell 254 nm lamp for 48 hours. The reaction mixture was then concentrated *in vacuo*. The crude residue was purified via silica gel flash chromatography (5–50 % EtOAc/hexanes followed by 0–1% Et_2O/CH_2Cl_2) to afford **44** (16.8 mg, 31% yield). The enantiomeric excess was determined to be 34% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO2, λ = 254 nm): t_R (major) = 5.06 min, t_R (minor) = 6.89 min.

$[\alpha]_D^{25.0} = -4.1°$ (c = 0.565, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.21 (s, 1H), 8.79 (dd, *J* = 11.5, 1.7 Hz, 1H), δ 8.78 (d, *J* = 1.7 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.54 (dd, *J* = 8.3, 7.2 Hz, 1H), 7.50 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.38 – 7.29 (m, 2H), 7.22 – 7.16 (m, 1H), 4.56 (ddt, *J* = 5.8, 2.9, 0.8 Hz, 1H), 3.69 (ddd, *J* = 14.2, 5.7, 0.7 Hz, 1H), 3.60 (ddd, *J* = 14.2, 2.9, 0.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.6, 148.4, 144.7, 142.9, 138.7, 136.4, 134.5, 128.6, 128.0, 127.8, 127.5, 123.5, 122.7, 121.7, 121.7, 116.5, 49.3, 35.2. **FTIR** (NaCl, thin film) 3347, 3066, 2928, 2851, 1680, 1596, 1578, 1526, 1485, 1458, 1424, 1386, 1328, 1262, 1240, 1202, 1162, 1132, 869, 826, 791, 759, 734, 707, 679 cm.$^{-1}$ **HRMS** (MM) calc'd for $C_{18}H_{15}N_2O$ $[M+H]^+$ 275.1179, found 275.1178.

(45)

An oven-dried quartz tube was charged with diazoketone (**41**) (34.4 mg, 0.200 mmol, 1.00 equiv), aminoquinoline (**29**) (86.5 mg, 0.600 mmol, 3.00 equiv), and diazoketone (**36**) (88.1 mg, 0.100 mmol, 0.500 equiv) and brought into a N_2 filled glovebox. The mixture was suspended in 2.00 mL THF and the tube was sealed with a 19/38 rubber septum and secured with electrical tape. The reaction was removed from the glovebox and placed in a bottomless test tube rack in front of a Honeywell 254 nm lamp for 48 hours. The reaction mixture was then concentrated *in vacuo*. The crude residue was purified via silica gel flash chromatography (5–10% EtOAc/hexanes) to afford **45** (24.1 mg, 42% yield) as a brown oil. The enantiomeric excess was determined to be 75% by chiral SFC analysis (AD-H, 2.5 mL/min, 30% IPA in CO2, λ = 254 nm): t_R (major) = 5.73 min, t_R (minor) = 4.86 min. $[\alpha]_D^{25.0} = 65.0°$ (c = 0.91, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 8.79 (dd, *J* = 7.1, 1.9 Hz, 1H), 8.75 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.56 – 7.46 (m, 3H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.33 (d, *J* = 7.2 Hz, 1H), 7.31 – 7.18 (m, 2H), 4.27 (dd, *J* = 8.4, 6.1 Hz, 1H), 3.23 (dt, *J* = 15.2, 7.4 Hz, 1H), 3.09 – 2.95 (m, 1H), 2.69 – 2.48 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.7, 148.4, 144.8, 141.5, 138.7, 136.4, 134.7, 128.0, 127.9, 127.53, 126.9, 125.1, 125.0, 121.7, 121.7, 116.6, 54.0, 32.1, 30.4. **FTIR** (NaCl, thin film) 3347, 2957, 2923, 2852, 1728, 1689, 1524, 1484, 1461, 1424, 1380, 1325, 1272, 1163, 1132, 1072, 826, 791, 743 cm.$^{-1}$ **HRMS** (MM) calc'd for $C_{19}H_{17}N_2O$ $[M+H]^+$ 289.1335, found 289.1334.

(50)

To a flame-dried 100 mL flask was added copper (I) iodide (1.48 g, 7.75 mmol, 5.00 equiv) and Et_2O (15.5 mL). The resulting suspension was cooled to –40 °C and methyllithium (1.6 M in Et_2O; 9.68 mL, 15.5 mmol, 10 equiv) was added dropwise. The reaction mixture was stirred at −40 °C for 2 hours before **47** (540 mg, 1.55 mmol) was added dropwise as a solution in 5:2 CH_2Cl_2/Et_2O. The reaction mixture was gradually warmed to 0 °C over 4 hours, then quenched with saturated aqueous NH_4Cl (10 mL) and diluted with EtOAc. NH_4OH was added until all of the solid copper salts were sequestered and two homogenous layers remained. The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organics dried over MgSO4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (isocratic: 20% EtOAc/Hexane) to afford a 2.5:1 mixture of **49** and **50** (543 mg, 96% yield), respectively as a white amorphous solid. Subsequent purification by reverse-phase HPLC using two Agilent Eclipse XDB-C8

5um 9.4 × 250 mm columns connected in series (gradient: 77–85%MeCN/H_2O) afforded analytically pure samples of each diastereomer, from which **50** was crystallized for X-Ray analysis[26] (mp: 80–83 °C). Data for minor diastereomer **50**: $[\alpha]_D^{25.0} = -25.5°$ (c = 1.50, $CHCl_3$). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.64 (s, 1H), 8.82 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.75 (dd, *J* = 7.4, 1.6 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.46 (dd, *J* = 8.2, 4.2 Hz, 1H), 2.89 – 2.77 (m, 2H), 2.35 – 2.26 (m, 2H), 2.24 (d, *J* = 13.3 Hz, 1H), 2.09 (d, *J* = 13.4 Hz, 1H), 2.07 – 1.99 (m, 1H), 1.88 – 1.77 (m, 1H), 1.72 – 1.61 (m, 3H), 1.55 – 1.48 (m, 1H), 1.35 (s, 3H), 1.13 (s, 3H), 0.92 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 212.4, 170.6, 148.4, 138.5, 136.5, 134.6, 128.1, 127.6, 121.7, 121.4, 116.4, 51.5, 50.8, 41.2, 39.8, 39.6, 35.2, 34.1, 33.0, 30.8, 23.7, 22.2, 21.3. **FTIR** (NaCl, thin film) 3349, 3044, 2952, 2863, 1706, 1687, 1595, 1577, 1523, 1484, 1460, 1424, 1383, 1325, 1238, 1228, 1163, 827, 792 $cm.^{-1}$ **HRMS** (MM) calc'd for $C_{23}H_{29}N_2O_2$ $[M+H]^+$ 365.2224, found 365.2261. **XRCD**: A suitable crystal of $C_{23}H_{28}N_2O_2$ (**50**) was selected for analysis. Low-temperature diffraction data (φ- and ω-scans) were collected on a Bruker AXS D8 VENTURE KAPPA diffractometer coupled to a PHOTON 100 CMOS detector with Cu-Kα radiation (λ = 1.54178 Å) from a IμS HB micro-focus sealed X-ray tube. All diffractometer manipulations, including data collection, integration, and scaling were carried out using the Bruker APEXII software.[70]

(49)

Inside a N_2-filled glovebox, $[Cu(OTf)]_2$•PhMe (72.4 mg, 0.140 mmol, 0.25 equiv) and (*S,R,R*) ligand **48**[71] (302 mg, 0.560 mmol, 1.00 equiv) were added to a 25 mL flask. The reagents were suspended in Et_2O (5.60 mL) and stirred at room temperature for 30 mins before *trans*-cyclobutane **47** (195 mg, 0.560 mmol) was added as a solid, in one portion. The reaction was sealed under N_2, removed from the glovebox and cooled to –30 °C under argon using a cryocool unit to control the temperature. Me_3Al (2.0 M in heptane; 560 μL, 1.12 mmol, 2.00 equiv) was then added dropwise, taking care to avoid an exotherm and the reaction mixture stirred vigorously at –30 °C for 16 hours. MeOH (1.00 mL) was then added to quench excess Me_3Al and then the reaction was warmed to room temperature. The mixture was diluted with EtOAc and H_2O, then the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organics dried over MgSO4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (2% Et_2O/CH_2Cl_2 until ligand/impurities elute, then 4% Et_2O/ CH_2Cl_2) to afford a 30:1 mixture of **49** and **50** (126 mg, 62% yield), respectively as a white solid: $[\alpha]_D^{25.0} = -84.7°$ (c = 0.600, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.64 (s, 1H), 8.81 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.75 (dd, *J* = 7.2, 1.8 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.56 – 7.47 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.89 – 2.76 (m, 2H), 2.36 – 2.28 (m, 2H), 2.25 (ddd, *J* = 12.5, 6.6, 1.1 Hz, 1H), 2.04 (dt, *J* = 13.4, 2.0 Hz, 1H), 1.96 (ddq, *J* = 13.7, 7.0, 3.6 Hz, 1H), 1.81 (dtt, *J* = 13.7, 12.0, 5.0 Hz, 1H), 1.68 – 1.62 (m, 2H), 1.62 – 1.51 (m, 2H), 1.35 (s, 3H), 1.13 (s, 3H), 0.89 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 212.4, 170.6, 148.3, 138.5, 136.5, 134.6, 128.1, 127.5, 121.7, 121.4, 116.4, 51.5, 50.4, 41.3, 40.9, 39.5, 35.2, 33.8, 32.6, 30.8, 23.7, 22.1, 20.8. **FTIR** (NaCl, thin film) 3351, 3047, 2954, 2870, 1708, 1688, 1524, 1485, 1460, 1424, 1384, 1325, 1281, 1259, 1240, 1228, 1163, 919,

827, 792, 757, 732 cm.$^{-1}$ **HRMS** (MM) calc'd for $C_{23}H_{29}N_2O_2$ $[M+H]^+$ 365.2224, found 365.2228.

(51)

To a flame-dried 15 mL flask was added ketone **49** (100 mg, 0.274 mmol) and dissolved in freshly distilled MeOH (2.7 mL). Trimethylorthoformate (150 μL, 1.37 mmol, 5.00 equiv) was then added, followed by *p*-toluenesulfonic acid monohydrate (2.60 mg, 0.014 mmol, 0.05 equiv). The reaction was topped with a reflux condenser and heated to 65 °C for 1 hour, then quenched with saturated aqueous NaHCO3. The aqueous layer was extracted with EtOAc (3 × 5 mL), and the combined organics were dried over MgSO4, filtered, and concentrated *in vacuo*. The crude residue was purified by Florisil® flash chromatography (isocratic: 10% EtOAc/Hexane) to afford **51** (106 mg, 94% yield) as a white, foamy solid: $[\alpha]_D^{25.0} = -83.3°$ (c = 1.60, $CHCl_3$). ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.81 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.78 (dd, *J* = 7.4, 1.6 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.56 – 7.46 (m, 2H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 3.16 (s, 3H), 3.13 (s, 3H), 2.80 (d, *J* = 10.0 Hz, 1H), 2.69 (q, *J* = 9.7 Hz, 1H), 2.01 (ddd, *J* = 13.2, 3.5, 1.6 Hz, 1H), 1.74 (dt, *J* = 14.0, 2.4 Hz, 1H), 1.70 – 1.50 (m, 4H), 1.31 (s, 3H), 1.28 – 1.13 (m, 4H), 1.11 (s, 3H), 1.01 (s, 3H). ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 171.0, 148.3, 138.5, 136.4, 134.7, 128.0, 127.6, 121.6, 121.2, 116.4, 100.8, 51.3, 47.9, 47.3, 42.3, 38.6, 34.8, 34.7, 34.0, 33.3, 32.5, 30.7, 23.9, 21.4, 18.8. **FTIR** (NaCl, thin film) 3356, 3048, 2950, 2867, 2828, 1690, 1525, 1485, 1460, 1424, 1384, 1368, 1325, 1288, 1276, 1261, 1242, 1155, 1108, 1096, 1048, 946, 927, 826, 792, 756, 690, 666 cm.$^{-1}$ **HRMS** (MM) calc'd for $C_{24}H_{31}N_2O_2$ $[M–OCH_3]^+$ 379.2380, found 379.2376.

(17)

To a 15 mL thick-walled, screw top pressure vessel were added dimethyl ketal **51** (59.8 mg, 0.146 mmol) and PhMe (5.0 mL). The tube sealed under a stream of N_2. The reaction was heated to 170 °C in a preheated oil bath for 3.5 hours. The reaction was then cooled to room temperature and concentrated *in vacuo* to afford **17** (55.1 mg, quantitative yield), an inseparable ~1:1 mixture of enol ether isomers, as a foamy colorless gum: $[\alpha]_D^{25.0} = -78.8°$ (c = 1.25, $CHCl_3$). ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 9.70 (s, 1H), 8.90 – 8.72 (m, 2H), 8.15 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.57 – 7.40 (m, 3H), 4.48 (s, 1H), 3.48 (s, 3H), 2.87 – 2.74 (m, 2H), 2.12 – 1.93 (m, 2H), 1.74 – 1.57 (m, 4H), 1.48 – 1.36 (m, 1H), 1.33 (s, 3H), 1.31 – 1.27 (m, 1H), 1.12 (s, 3H), 0.97 (s, 3H). ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 171.6, 171.0, 156.3, 154.3, 148.3, 148.3, 138.6, 138.5, 136.4, 136.4, 134.8, 134.7, 128.5, 128.1, 128.1, 127.6, 126.9, 126.8, 121.7, 121.6, 121.2, 121.2, 116.4, 116.3, 99.4, 92.1, 54.1, 53.9, 52.6, 51.5, 40.9, 40.1, 36.4, 35.4, 35.2, 34.0, 33.5, 33.0, 32.6, 30.9, 30.8, 30.7, 29.9, 28.2, 26.1, 25.1, 24.1, 23.9, 21.2, 20.7, 19.5. **FTIR** (NaCl, thin film) 3354, 3051, 2949, 2930, 2862, 1690, 1668, 1524, 1484, 1461, 1424, 1384, 1368, 1326, 1238, 1215, 1162, 1147, 1026, 826, 791, 756, 694 cm.$^{-1}$ **HRMS** (MM) calc'd for $C_{24}H_{31}N_2O_2$ $[M+H]^+$ 379.2380, found 379.2395.

(55)

To a flame-dried 100 mL round-bottom flask were added phloroglucinol **54**[72] (1.00g, 4.13 mmol), followed by freshly distilled MeOH (41.0 mL). Benzaldehyde (421 μL, 4.13 mmol,

1.00 equiv), morpholine (361 μL, 4.13 mmol, 1.00 equiv), and triethylamine (576 μL, 4.13 mmol, 1.00 equiv) were then added successively via syringe and the reaction stirred at room temperature for 24 hours. The precipitate thus formed was collected by vacuum filtration and washed with MeOH (20 mL) and dried under high vacuum to afford analytically pure **55** (1.19 g, 69% yield) as a white powder. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 15.34 (s, 1H), 13.16 (s, 1H), 12.53 (s, 1H), 7.45 (d, *J* = 7.2 Hz, 2H), 7.34 – 7.20 (m, 3H), 4.88 (s, 1H), 3.99 (s, 3H), 3.91 (s, 3H), 3.90 – 3.40 (br m, 4H), 3.08 (br s, 1H), 2.46 (ddd, *J* = 11.9, 6.2, 3.1 Hz, 2H), 2.18 (br s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.7, 166.2, 165.6, 165.1, 138.2, 128.9, 128.4, 103.8, 96.5, 94.2, 69.0, 66.6, 52.7, 52.6. **FTIR** (NaCl, thin film) 3404 (br), 3062, 3030, 2955, 2894, 2854, 2716, 2562 (br), 2252, 1953 (br), 1731, 1654, 1603, 1494, 1454, 1431, 1403, 1326, 1290, 1250, 1205, 1169, 1121, 1080, 1029, 1006, 986, 942, 915, 878, 843, 825, 808, 761, 732, 700, 648 $cm.^{-1}$**HRMS** (MM) calc'd for $C_{21}H_{24}NO_8$ $[M+H]^{+}$418.1496, found 418.1515.

(16)

To a 50 mL round-bottom flask was added benzhydryl morpholine **55** (200 mg, 0.479 mmol), followed by a 1:1 mixture of THF/H2O (9.6 mL). *p*-Toluenesulfonic acid monohydrate (91.1 mg, 0.479 mmol, 1.00 equiv) was then added in one portion and the reaction was heated to 60 °C for 4 hours. Note: it is best to monitor this reaction closely by TLC to mitigate degradation of the product to **54**, presumably via acid-mediated retro aldol. Upon completion, the reaction was cooled to room temperature and quenched with saturated aqueous NaHCO3. The reaction was diluted with EtOAc and the organic layer separated. The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic layers were dried over MgSO4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (isocratic: 5% EtOAc/CH_2Cl_2 + 0.5% AcOH, necessary to avoid streaking on the column). Fractions containing pure product were combined, washed with saturated aqueous NaHCO3, dried over MgSO4, filtered, and concentrated *in vacuo* to afford **16** (82.0 mg, 49% yield) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.89 (s, 2H), 11.70 (s, 1H), 7.46 – 7.39 (m, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.26 – 7.19 (m, 1H), 6.38 – 6.23 (m, 1H), 4.09 (d, *J* = 11.6 Hz, 1H), 4.02 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.9, 165.0, 164.7, 143.9, 128.2, 127.0, 125.6, 110.2, 94.5, 68.1, 53.2. **FTIR** (NaCl, thin film) 3563 (br), 3357 (br), 3085, 3058, 3028, 3006, 2956, 2851, 2749 (br), 1727, 1655, 1623, 1599, 1492, 1434, 1333, 1318, 1245, 1201, 1170, 1129, 1039, 1026, 972, 909, 836, 816, 733, 698, 622 $cm.^{-1}$ **HRMS** (MM) calc'd for $C_{17}H_{15}O_7$ $[M–OH]^{+}$331.0812, found 331.0825.

(57–60, thermal reaction)

To a 15 mL thick-walled, screw top pressure vessel were added dimethyl ketal **51** (105 mg, 0.256 mmol) and *o*-QM precursor **16** (98.0 mg, 0.281 mmol, 1.10 equiv). PhMe (4.3 mL) was then added and the tube sealed under a stream of argon. The reaction was heated to 170 °C in a preheated oil bath for 21 hours. The reaction was then cooled to room temperature and concentrated *in vacuo*. The crude residue was first purified by silica gel flash chromatography to remove separable impurities (4% EtOAc/CH_2Cl_2 + 0.5% AcOH) to afford a complex mixture of diastereomers, including **57**–**60** (109 mg, 68% yield).

Analytically pure samples of the four diastereomers produced in greatest abundance (i.e. **57**–**60**) were obtained by subsequent reverse-phase HPLC purification using an Agilent XDB-C18 5 μm 30 × 250 mm column (gradient: 83–100% MeCN/H_2O).

Data for 57 (peak 2)

$[\alpha]_D^{25.0} = -32.2°$ (c = 0.360, $CHCl_3$) White Solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.81 (s, 1H), 12.08 (s, 1H), 9.65 (s, 1H), 8.78 – 8.74 (m, 2H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.22 (d, *J* = 7.5 Hz, 2H), 7.14 – 7.07 (m, 3H), 3.93 (s, 3H), 3.93 (s, 3H), 3.91 (d, *J* = 7.8 Hz, 1H), 3.39 (s, 3H), 2.82 – 2.76 (m, 2H), 2.12 (s, 1H), 1.86 – 1.73 (m, 2H), 1.69 – 1.49 (m, 5H), 1.33 (s, 3H), 1.25 (d, *J* = 9.6 Hz, 1H), 1.10 (s, 3H), 1.05 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.4, 170.8, 169.9, 166.0, 164.7, 158.9, 148.3, 145.9, 138.5, 136.5, 134.7, 128.1, 128.1, 127.8, 127.6, 126.0, 121.7, 121.3, 116.3, 104.2, 104.1, 97.1, 95.7, 52.7, 52.7, 52.2, 49.0, 44.2, 41.7, 39.9, 37.7, 35.1, 35.1, 33.9, 30.8, 28.9, 24.0, 23.5, 22.8. **FTIR** (NaCl, thin film) 3412 (br), 3354 (br), 3059, 3022, 3006, 2951, 2928, 2864, 1731, 1686, 1654, 1648, 1643, 1594, 1524, 1484, 1459, 1426, 1384, 1338, 1325, 1249, 1222, 1201, 1157, 1122, 1081, 1092, 1028, 976, 945, 936, 847, 826, 792, 755, 700, 667 $cm.^{-1}$ **HRMS** (MM) calc'd for $C_{41}H_{45}N_2O_9$ $[M+H]^+$ 709.3120, found 709.3141.

Data for 58 (peak 1)

$[\alpha]_D^{25.0} = -13.8°$ (c = 0.420, $CHCl_3$) White Solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.22 (s, 1H), 11.68 (s, 1H), 9.65 (s, 1H), 8.81 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.77 (dd, *J* = 7.3, 1.7 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.46 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.24 – 7.16 (m, 2H), 7.16 – 7.09 (m, 1H), 7.09 – 7.02 (m, 2H), 3.96 (s, 3H), 3.93 (s, 3H), 3.91 (s, 1H), 3.05 (s, 3H), 2.82 – 2.67 (m, 2H), 2.16 (dd, *J* = 12.4, 3.5 Hz, 1H), 1.98 (d, *J* = 13.8 Hz, 1H), 1.76 (dd, *J* = 13.3, 4.1 Hz, 1H), 1.70 – 1.39 (m, 6H), 1.32 (s, 3H), 1.12 (s, 3H), 0.96 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.0, 170.8, 169.9, 165.0, 163.1, 157.2, 148.3, 145.6, 138.5, 136.5, 134.7, 128.1, 127.8, 127.6, 127.3, 125.6, 121.7, 121.3, 116.4, 102.4, 102.1, 99.0, 95.3, 52.8, 52.5, 51.3, 47.8, 45.3, 41.9, 41.4, 40.1, 34.7, 34.6, 32.7, 32.6, 30.8, 27.4, 23.8, 22.3. **FTIR** (NaCl, thin film) 3410 (br), 3355 (br), 3055, 3021, 3000, 2950, 2864, 1734, 1686, 1654, 1643, 1599, 1524, 1484, 1460, 1426, 1384, 1336, 1326, 1279, 1247, 1225, 1163, 1142, 1093, 1063, 988, 973, 949, 841, 826, 791, 754, 698, 667 $cm.^{-1}$ **HRMS** (MM) calc'd for $C_{41}H_{45}N_2O_9$ $[M+H]^+$ 709.3120, found 709.3119.

Data for 59 (peak 3)

$[\alpha]_D^{25.0} = -98.4°$ (c = 0.206, $CHCl_3$) White Solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.11 (s, 1H), 11.61 (s, 1H), 9.64 (s, 1H), 8.82 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.76 (dd, *J* = 7.3, 1.7 Hz, 1H), 8.16 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.57 – 7.43 (m, 3H), 7.30 (dd, *J* = 8.6, 5.1 Hz, 2H), 7.17 (s, 2H), 6.81 (s, 1H), 4.54 (d, *J* = 7.3 Hz, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 3.21 (s, 3H), 2.74 (q, *J* = 9.8 Hz, 2H), 2.10 (d, *J* = 13.7 Hz, 1H), 1.97 – 1.83 (m, 1H), 1.62 (d, *J* = 8.9 Hz, 2H), 1.45 (d, *J* = 13.8 Hz, 1H), 1.32 (s, 3H), 1.29 – 1.24 (m, 1H), 1.18 (d, *J* = 13.2 Hz, 1H), 1.11 (s, 3H), 1.10 – 1.06 (m, 1H), 1.04 (s, 3H), 0.76 (dd, *J* = 13.1, 3.9 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.0, 170.9, 169.7, 164.9, 162.7, 158.0, 148.3, 142.2, 138.5, 136.5, 134.7,

128.5, 128.1, 127.7, 127.6, 125.9, 121.7, 121.3, 116.4, 104.2, 102.2, 99.3, 95.5, 52.8, 52.5, 51.3, 49.0, 43.7, 42.2, 40.3, 38.5, 34.8, 34.4, 33.0, 32.6, 30.8, 23.8, 22.1, 21.7. **FTIR** (NaCl, thin film) 3408 (br), 3354 (br), 3059, 3022, 3009, 2952, 2868, 1738, 1732, 1682, 1658, 1652, 1645, 1599, 1525, 1485, 1462, 1455, 1426, 1385, 1327, 1281, 1251, 1225, 1165, 1133, 1090, 1077, 1031, 991, 946, 872, 826, 792, 755, 703 cm.$^{-1}$ **HRMS** (MM) calc'd for $C_{41}H_{45}N_2O_9$ $[M+H]^+$ 709.3120, found 709.3133.

Data for 60 (peak 4)

$[\alpha]_D^{25.0} = -13.4°$ (c = 0.226, $CHCl_3$) White Solid. ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 11.95 (s, 1H), 11.23 (s, 1H), 9.66 (s, 1H), 8.81 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.76 (dd, *J* = 7.3, 1.7 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.55 – 7.42 (m, 3H), 7.22 (dd, *J* = 7.9, 6.5 Hz, 2H), 7.18 – 7.13 (m, 1H), 7.10 (d, *J* = 7.4 Hz, 2H), 3.90 (s, 3H), 3.87 (s, 3H), 3.67 (d, *J* = 11.0 Hz, 1H), 3.16 (s, 3H), 2.81 – 2.66 (m, 2H), 2.10 (dd, *J* = 14.2, 1.6 Hz, 1H), 1.71 (td, *J* = 10.8, 5.3 Hz, 1H), 1.64 (dd, *J* = 9.2, 2.6 Hz, 2H), 1.56 – 1.48 (m, 2H), 1.45 (d, *J* = 14.3 Hz, 1H), 1.38 – 1.32 (m, 1H), 1.31 (s, 3H), 1.21 – 1.14 (m, 1H), 1.12 (s, 3H), 1.08 (s, 3H). ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 170.8, 170.8, 169.5, 164.0, 162.4, 157.4, 148.3, 145.4, 138.5, 136.5, 134.7, 128.1, 128.1, 127.6, 125.9, 121.7, 121.3, 116.4, 108.0, 101.7, 99.6, 95.5, 52.7, 52.5, 51.2, 49.4, 49.0, 42.0, 41.1, 36.2, 35.3, 34.8, 33.3, 32.6, 30.8, 23.8, 22.5, 21.1. **FTIR** (NaCl, thin film) 3412 (br), 3354 (br), 3055, 3023, 3003, 2950, 2866, 1732, 1688, 1656, 1598, 1524, 1484, 1453, 1426, 1384, 1327, 1277, 1248, 1225, 1165, 1062, 993, 954, 925, 826, 792, 755, 702 cm.$^{-1}$ **HRMS** (MM) calc'd for $C_{41}H_{45}N_2O_9$ $[M+H]^+$ 709.3120, found 709.3139.

(57–60, Cu-mediated reaction)

Inside a N_2-filled glovebox, methyl enol ether **17** (17.0 mg, 0.045 mmol) and *o*-QM precursor **16** (16.4 mg, 0.047 mmol, 1.05 equiv) were added to a 1 dram vial and dissolved in CH_2Cl_2 (400 μL). Cu(OTf)2 was then added as a solid in one portion and the reaction immediately turns a light green color, then yellow-brown within the first 5 minutes. The reaction was stirred at room temperature for 1 hour, then quenched with saturated aqueous NaHCO3 and diluted with $CHCl_3$. The reaction mixture was extracted with $CHCl_3$ (3 × 1 mL) and the organics filtered through a plug of Na_2SO_4 and concentrated in vacuo. The crude residue was analyzed by ^{1}H NMR and determined to contain **57**, **58**, **59**, and **60** in an approximate ratio of 2:1:3:3, respectively.

(62)

Inside a N_2-filled glovebox, Schwartz's reagent (119 mg, 0.462 mmol, 2.00 equiv) was added to a 10 mL flask and sealed under N_2. The flask was removed from the glovebox and THF (1.2 mL) was added via syringe. To the milky-white suspension was added ketal **51** (94.8 mg, 0.231mmol) as a solution in THF (1.2 mL) in a quick drip. The reaction immediately beings to turn yellow, eventually becoming a darker orange color over 1 hour, at which time the reaction was quenched by the addition of saturated aqueous NaHCO3. The reaction was diluted with EtOAc and the organic layer separated. The aqueous layer was extracted with EtOAc (2 × 5 mL) and the combined organic layers were dried over MgSO4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (isocratic: 5% EtOAc/hexane + 1% Et_3N) to afford **62** (36.9 mg, 63% yield)

as a pale yellow oil: $[\alpha]_D^{25.0} = -33.1°$ (c = 0.500, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.70 (d, *J* = 3.0 Hz, 1H), 3.14 (s, 3H), 3.09 (s, 3H), 2.64 (td, *J* = 9.7, 8.5 Hz, 1H), 2.58 (dd, *J* = 9.9, 3.0 Hz, 1H), 1.86 (ddt, *J* = 13.6, 4.2, 2.6 Hz, 1H), 1.61 (t, *J* = 10.3 Hz, 1H), 1.57 – 1.44 (m, 4H), 1.34 – 1.18 (m, 2H), 1.16 (s, 3H), 1.14 (s, 3H), 1.13 – 1.05 (m, 2H), 0.89 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 204.7, 100.5, 55.2, 47.6, 47.1, 39.8, 39.3, 35.7, 34.4, 33.9, 33.0, 32.7, 31.1, 24.3, 21.7, 18.6. **FTIR** (NaCl, thin film) 2952, 2868, 2828, 2705, 1713, 1461, 1383, 1368, 1341, 1288, 1262, 1246, 1180, 1166, 1110, 1098, 1048, 1009, 945, 924, 823, 828 $cm.^{-1}$ **HRMS** (FAB) calc'd for $C_{15}H_{25}O_2$ $[M–OCH_3]^+$ 237.1849, found 237.1855.

(63)

To a 10 mL round bottom flask were added aldehyde **62** (36.0 mg, 0.134 mmol) and K_2CO_3 (37.0 mg, 0.268 mmol, 2.00 equiv). The flask was fitted with a septum and the atmosphere exchanged 2x for N_2. Freshly distilled MeOH (1.5 mL) was then added via syringe and the solution cooled to 0 °C. Dimethyl-1-diazo-2-oxopropylphosphonate[73] (38.6 mg, 0.201 mmol, 1.50 equiv) was weighed into a tared syringe and added dropwise to the reaction, neat. The reaction was allowed to gradually warm to room temperature and stirred for 12 hours. The reaction was then diluted with Et_2O, saturated aqueous NaHCO3 was added, and the organic layer separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried over MgSO4, filtered, and concentrated *in vacuo*. The crude residue was purified by Florisil® flash chromatography (isocratic: 5% Et_2O/pentane) to afford 63 (32.9 mg, 93% yield) as a pale yellow oil: $[\alpha]_D^{25.0} = -43.6°$ (c = 0.355, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.17 (s, 3H), 3.13 (s, 3H), 2.43 (dd, *J* = 10.1, 2.4 Hz, 1H), 2.16 – 2.05 (m, 2H), 2.04 – 1.93 (m, 1H), 1.69 (ddd, *J* = 13.9, 2.8, 1.8 Hz, 1H), 1.59 – 1.50 (m, 2H), 1.48 (d, *J* = 9.6 Hz, 2H), 1.29 – 1.17 (m, 5H), 1.16 (d, *J* = 2.7 Hz, 4H), 1.03 (s, 3H), 0.97 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 100.7, 85.8, 70.5, 49.1, 47.9, 47.3, 39.1, 35.2, 35.1, 34.0, 33.5, 33.2, 33.2, 29.9, 24.8, 21.1, 18.8. **FTIR** (NaCl, thin film) 3310, 3263, 2953, 2866, 2828, 1459, 1383, 1364, 1342, 1323, 1288, 1266, 1243, 1180, 1157, 1106, 1094, 1048, 945, 926, 858, 830, 655, 621 $cm.^{-1}$ **HRMS** (MM) calc'd for $C_{16}H_{25}O_2$ $[M–OCH_3]^+$233.1900, found 233.1887.

(64–65)

Inside a N_2-filled glovebox, THF (400 μL) was added to a 1 dram vial containing alkyne **63** (12.4 mg, 0.047 mmol), followed by Ni(acac)2 as a stock solution in THF (0.10 M, 70 μL, 0.007 mmol, 0.15 equiv). The reaction was stirred for 10 minutes at room temperature before thiophenol (10 μL, 0.094 mmol, 2.00 equiv) was added neat. The reaction was sealed with a Teflon cap and heated to 60 ° C in a preheated aluminum block inside the glovebox. After 3 hours, the reaction was cooled to room temperature and diluted with CH_2Cl_2. The reaction mixture was filtered over a small pad of celite, washed with CH_2Cl_2 until the filtrate runs colorless, and concentrated in vacuo. The crude residue was taken up in EtOAc and shaken with 5M NaOH (to remove excess thiophenol). The organic layer was then filtered through a plug of Na_2SO_4, concentrated, and purified by silica gel preparative TLC (5% EtOAc/hexane + 1% Et_3N) to afford **64** (8.50 mg, 53% yield) and **65** (2.7 mg, 15% yield) each as colorless oils.

Data for 65

$[\alpha]_D^{25.0} = +12.3°$ (c = 0.115, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 8.1, 1.6 Hz, 2H), 7.36 – 7.28 (m, 3H), 5.17 (d, *J* = 1.3 Hz, 1H), 4.96 (s, 1H), 3.17 (s, 3H), 3.13 (s, 3H), 2.51 (d, *J* = 10.2 Hz, 1H), 2.26 (q, *J* = 9.7 Hz, 1H), 2.04 – 1.92 (m, 1H), 1.65 (ddd, *J* = 13.8, 2.8, 1.6 Hz, 1H), 1.50 (ddd, *J* = 9.6, 7.0, 3.7 Hz, 2H), 1.45 – 1.39 (m, 2H), 1.21 – 1.12 (m, 4H), 1.11 (s, 3H), 0.98 (s, 3H), 0.91 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.9, 133.8, 133.4, 129.2, 127.9, 111.6, 100.8, 49.4, 47.9, 47.3, 45.1, 39.7, 35.6, 34.8, 34.6, 33.2, 32.4, 30.6, 23.2, 21.7, 18.9. **FTIR** (NaCl, thin film) 2950, 2863, 2827, 1610, 1583, 1476, 1459, 1439, 1379, 1364, 1322, 1274, 1260, 1247, 1178, 1145, 1130, 1100, 1083, 1049, 1024, 946, 926, 856, 831, 822, 747, 691 $cm.^{-1}$ **HRMS** (MM) calc'd for $C_{22}H_{31}OS$ $[M–OCH3]^+$343.2090, found 343.2073.

Data for 64

$[\alpha]_D^{25.0} = -11.0°$ (c = 0.982, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.36 (m, 2H), 7.36 – 7.27 (m, 3H), 5.23 – 4.84 (m, 2H), 4.63 – 4.29 (m, 1H), 3.40 (s, 3H), 2.58 – 2.50 (m, 1H), 2.40 (dq, *J* = 34.9, 9.5 Hz, 1H), 2.11 – 1.91 (m, 3H), 1.64 (ddd, *J* = 15.0, 5.9, 2.4 Hz, 2H), 1.48 – 1.40 (m, 2H), 1.39 – 1.30 (m, 1H), 1.11 (d, *J* = 9.9 Hz, 3H), 1.00 (d, *J* = 2.4 Hz, 3H), 0.83 (d, *J* = 21.0 Hz, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.3, 154.4, 146.0, 145.9, 133.8, 133.5, 133.4, 133.3, 129.2, 129.1, 127.9, 127.7, 112.3, 111.1, 100.6, 92.0, 54.1, 53.9, 50.2, 49.5, 43.5, 40.9, 37.7, 36.1, 35.1, 35.1, 34.5, 34.1, 32.9, 32.6, 31.6, 30.6, 30.5, 28.2, 25.8, 23.3, 23.2, 22.0, 20.8, 19.4. **FTIR** (NaCl, thin film) 3061, 2991, 2950, 2930, 2862, 2843, 1667, 1609, 1583, 1476, 1460, 1453, 1440, 1380, 1366, 1251, 1215, 1148, 1066, 1024, 940, 817, 747, 691 $cm.^{-1}$ **HRMS** (MM) calc'd for $C_{22}H_{31}OS$ $[M+H]^+$ 343.2090, found 343.2087.

(66–67)

Inside a N_2-filled glovebox, CH_2Cl_2 was added to a 1 dram vial containing **65** (9.30 mg, 0.025 mmol), followed by $InCl_3$ (5.49 mg, 0.025 mmol, 1.00 equiv). The reaction was stirred at room temperature for 2 hours, then quenched with saturated aqueous NaHCO3 and diluted with CH_2Cl_2. The reaction was extracted with CH_2Cl_2 (3 × 500 μL), the combined organics filtered a plug of Na_2SO_4, and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (40–60% CH_2Cl_2/hexane) to afford **66** (0.900 mg, 11% yield) as a colorless oil, with the remaining mass balance accounted for by ketone **67**, as determined by crude ^{1}H NMR.

Data for 66

$[\alpha]_D^{25.0} = +58.2°$ (c = 0.053, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.36 (m, 2H), 7.30 (ddd, *J* = 8.3, 7.1, 0.8 Hz, 2H), 7.24 – 7.18 (m, 1H), 5.52 (dd, *J* = 2.8, 1.7 Hz, 1H), 3.18 (s, 3H), 2.91 – 2.81 (m, 1H), 2.00 – 1.72 (m, 5H), 1.66 (ddd, *J* = 11.6, 6.8, 3.5 Hz, 1H), 1.44 – 1.37 (m, 2H), 1.35 (dd, *J* = 12.3, 1.7 Hz, 1H), 1.29 (m, 1H), 1.28 (s, 3H), 1.19 (dd, *J* = 14.1, 7.0 Hz, 1H), 1.00 (s, 3H), 0.80 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.7, 139.6, 135.0, 131.7, 129.2, 127.2, 80.6, 52.4, 50.2, 49.2, 48.6, 40.1, 38.3, 36.2, 33.7, 31.3, 31.2, 28.9, 22.4, 21.2. **FTIR** (NaCl, thin film) 3062, 2945, 2927, 2860, 2820, 1734, 1718, 1701,

1654, 1583, 1560, 1476, 1458, 1438, 1370, 1294, 1254, 1232, 1151, 1086, 1066, 1024, 950, 870, 840, 800, 743, 690 cm.$^{-1}$ **HRMS** (MM) calc'd for $C_{22}H_{31}OS$ $[M+H]^+$343.2090, found 343.2077.

Data for 67

$[\alpha]_D^{25.0} = +31.6°$ (c = 0.100, $CHCl_3$). ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 8.1, 1.6 Hz, 2H), 7.40 – 7.32 (m, 3H), 5.13 (d, *J* = 1.3 Hz, 1H), 4.98 (s, 1H), 2.53 (d, *J* = 10.1 Hz, 1H), 2.38 (td, *J* = 10.0, 8.9 Hz, 1H), 2.32 – 2.23 (m, 2H), 2.17 (d, *J* = 13.6 Hz, 1H), 2.02 (dt, *J* = 13.4, 1.9 Hz, 1H), 1.93 – 1.90 (m, 1H), 1.82 (dddd, *J* = 9.7, 8.1, 3.9, 2.3 Hz, 1H), 1.57 (q, *J* = 4.4 Hz, 1H), 1.49 – 1.44 (m, 1H), 1.44 – 1.33 (m, 2H), 1.16 (s, 3H), 1.03 (s, 3H), 0.82 (s, 3H). ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 212.6, 145.5, 134.1, 133.0, 129.3, 128.2, 111.4, 51.1, 49.8, 43.1, 41.3, 40.3, 35.1, 34.2, 32.5, 30.6, 23.1, 22.1, 21.8. **FTIR** (NaCl, thin film) 3059, 2953, 2927, 2860, 1711, 1680, 1611, 1583, 1476, 1461, 1440, 1381, 1364, 1347, 1311, 1283, 1253, 1228, 1151, 1087, 1067, 1024, 890, 855, 749, 692 cm.$^{-1}$ **HRMS** (MM) calc'd for $C_{21}H_{29}OS$ $[M+H]^+$ 329.1934, found 329.1943.

(78)

To a 15 mL round-bottom flask was added vinyl ketone **71** (91.0 mg, 0.413 mmol) and the atmosphere was exchanged 3x for N_2. Dry THF (4.10 mL) was then added via syringe and the reaction cooled to –30 °C using a closely monitored acetone/CO2 bath. Vinylmagnesium bromide (2.06 mL, 1.0 M in THF, 2.06 mmol, 5.00 equiv) was then added dropwise. The reaction was maintained at –30 °C for 30 minutes, then quenched at that temperature with saturated aqueous NaH_2PO_4. The reaction mixture was diluted with Et_2O and the layers separated. The aqueous layer was extracted with Et_2O (2 × 5 mL) and the combined organics were dried over Mg_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (10% EtOAc/hexane) to afford **78** (92.7 mg, 91% yield) as a colorless oil: $[\alpha]_D^{25.0} = +54.4°$ (c = 1.75, $CHCl_3$). ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 5.88 (dd, *J* = 17.3, 10.6 Hz, 1H), 5.75 (ddd, *J* = 17.1, 10.2, 8.7 Hz, 1H), 5.18 (dd, *J* = 17.3, 1.3 Hz, 1H), 5.01 – 4.85 (m, 3H), 2.32 (t, *J* = 9.3 Hz, 1H), 1.92 (q, *J* = 9.6 Hz, 1H), 1.82 (qt, *J* = 13.5, 3.4 Hz, 1H), 1.55 (dddd, *J* = 14.0, 5.3, 3.5, 1.9 Hz, 1H), 1.48 (dq, *J* = 13.8, 3.5 Hz, 1H), 1.45 – 1.39 (m, 2H), 1.35 (dd, *J* = 13.5, 4.0 Hz, 1H), 1.31 – 1.22 (m, 3H), 1.16 – 1.11 (m, 1H), 1.11 (s, 1H), 1.06 (s, 3H), 0.97 (s, 3H), 0.97 (s, 3H). ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 148.1, 140.6, 114.6, 110.5, 73.1, 49.0, 48.0, 45.0, 37.6, 34.6, 34.3, 33.9, 32.8, 30.1, 23.8, 22.7, 17.8. **FTIR** (NaCl, thin film) 3601, 3452 (br), 3077, 2996, 2950, 2932, 2865, 1635, 1459, 1441, 1413, 1380, 1367, 1343, 1291, 1275, 1250, 1200, 1170, 1081, 1058, 994, 974, 909, 858, 846, 666 cm.$^{-1}$ **HRMS** (ESI) calc'd for $C_{17}H_{27}$ $[M–OH]^+$ 231.2107, found 231.2101.

(70)

A 50 mL round-bottom flask containing divinyl alcohol **78** (88.0 mg, 0.355 mmol) was pumped into a N_2-filled glovebox where Hoveyda–Grubbs second-generation catalyst (22.2 mg, 0.035 mmol, 0.100 equiv) was added. The flask was sealed under nitrogen, removed from the glovebox and dry PhH (17.7 mL) was added via syringe. The green reaction mixture was heated to 80 °C for 3.5 hours, then cooled to room temperature. Ethyl vinyl

ether was added to inactivate the catalyst and stirred for 15 minutes before the reaction mixture was concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (isocratic: 30% Et_2O/hexane) to afford allylic alcohol **70** (72.5 mg, 93% yield) as a pale yellow oil and a single diastereomer at C1: $[\alpha]_D^{25.0} = -62.9°$ (c = 2.67, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.84 (dd, *J* = 10.9, 2.5 Hz, 1H), 5.15 (ddd, *J* = 11.0, 2.9, 2.2 Hz, 1H), 2.41 (dt, *J* = 11.6, 2.7 Hz, 1H), 2.09 (td, *J* = 11.5, 10.7, 7.9 Hz, 2H), 1.69 (ddd, *J* = 13.0, 3.2, 1.1 Hz, 1H), 1.64 (s, 1H), 1.63 – 1.56 (m, 2H), 1.54 – 1.41 (m, 2H), 1.34 – 1.25 (m, 2H), 1.15 (dd, *J* = 12.8, 2.2 Hz, 1H), 1.12 – 1.06 (m, 1H), 1.05 (s, 3H), 1.03 (s, 3H), 0.87 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 134.1, 132.5, 75.1, 49.9, 45.3, 43.9, 39.0, 38.1, 37.8, 35.0, 32.6, 30.9, 26.9, 21.3, 20.2. **FTIR** (NaCl, thin film) 3350 (br), 3004, 2948, 2930, 2866, 1460, 1443, 1369, 1380, 1366, 1329, 1270, 1256, 1238, 1175, 1106, 1044, 1030, 999, 973, 958, 925, 875, 864, 766, 723 cm.$^{-1}$ **HRMS** (MM) calc'd for $C_{15}H_{23}$ $[M–OH]^+$ 203.1794, found 203.1790.

(79)

To a 100 mL round-bottom flask were added allylic alcohol 70 (107 mg, 0.486 mmol) and Pd/C (103 mg, 10% by weight, 0.097 mmol, 0.200 equiv). The flask was fitted with a septum and the atmosphere exchanged 1x for N_2. MeOH (9.7 mL) was then added via syringe and the reaction placed under a balloon atmosphere of H2 (purged through a needle for 30 seconds). The reaction was stirred vigorously at room temperature for 2.5 hours, at which time the atmosphere was purged with argon. The reaction mixture was filtered over celite, washed thoroughly with Et_2O, and the filtrate concentrated in vacuo. The crude residue was purified by silica gel flash chromatography (isocratic: 40% Et_2O/pentane) to afford **79** (101 mg, 94% yield) as a colorless oil: $[\alpha]_D^{25.0} = +6.37°$ (c = 0.800, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.97 (ddd, *J* = 11.8, 10.7, 7.9 Hz, 1H), 1.86 – 1.78 (m, 1H), 1.78 – 1.68 (m, 3H), 1.67 (d, *J* = 0.8 Hz, 3H), 1.51 – 1.39 (m, 2H), 1.34 (dt, *J* = 3.5, 2.0 Hz, 1H), 1.33 – 1.22 (m, 4H), 1.15 – 1.04 (m, 1H), 1.02 (d, *J* = 12.8 Hz, 1H), 0.97 (s, 3H), 0.96 (s, 3H), 0.80 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 74.0, 50.2, 46.3, 40.3, 40.1, 39.7, 38.2, 36.4, 34.6, 32.8, 30.7, 27.1, 22.7, 20.9, 20.7. **FTIR** (NaCl, thin film) 3368 (br), 2948, 2927, 2863, 1460, 1443, 1384, 1364, 1332, 1288, 1249, 1217, 1183, 1124, 1102, 1050, 1022, 993, 976, 936, 918, 873, 862 cm.$^{-1}$ **HRMS** (ESI) calc'd for $C_{15}H_{25}$ $[M–OH]^+$ 205.1951, found 205.1951.

(68)

Inside a N_2-filled glovebox, to a 1 dram vial containing tertiary alcohol **79** (14.4 mg, 0.065 mmol) were added $Pd(OAc)_2$ (4.36 mg, 0.019 mmol, 0.300 equiv), dppf (21.6 mg, 0.039 mmol, 0.600 equiv), and NaH (95%, 3.11 mg, 0.130 mmol, 2.00 equiv). PhMe (650 μL) was then added and the orange reaction mixture stirred at room temperature for 5 minutes before aryl bromide **69**[74] (22.8 mg, 0.071 mmol, 1.10 equiv) was added as a solid in one portion. The reaction was sealed with a Teflon cap and heated to 110 °C in a preheated aluminum block inside the glovebox. After 13.5 hours, the reaction was cooled to room temperature, diluted with EtOAc and saturated aqueous Na_2HPO_4 was added. The layers were separated and the aqueous layer was extracted with EtOAc until the organic layer was colorless. The combined organics were filtered over a plug of celite and Na_2SO_4. The filtrate was

concentrated *in vacuo* and the crude residue purified by silica gel flash chromatography (isocratic: 30% hexane/CH_2Cl_2 + 1% EtOAc) to afford **68** (13.4 mg, 45% yield) as a milky white gum: $[\alpha]_D^{25.0} = +1.27°$ (c = 0.345, $CHCl_3$). ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.86 – 7.76 (m, 2H), 7.51 (tt, *J* = 7.5, 2.7 Hz, 1H), 7.44 – 7.35 (m, 2H), 6.29 (d, *J* = 2.1 Hz, 1H), 6.23 (d, *J* = 2.1 Hz, 1H), 3.83 (s, 3H), 3.70 (s, 3H), 1.90 (ddd, *J* = 12.0, 10.7, 7.9 Hz, 1H), 1.78 (d, *J* = 2.3 Hz, 1H), 1.73 (t, *J* = 6.5 Hz, 2H), 1.68 (dt, *J* = 13.0, 2.3 Hz, 1H), 1.65 – 1.57 (m, 1H), 1.55 – 1.45 (m, 2H), 1.45 – 1.35 (m, 3H), 1.27 – 1.23 (m, 2H), 1.22 – 1.11 (m, 2H), 1.04 (d, *J* = 12.9 Hz, 1H), 0.92 (s, 3H), 0.91 (s, 3H), 0.69 (s, 3H). ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 196.0, 161.3, 158.7, 155.2, 138.8, 132.8, 129.6, 128.3, 116.8, 100.3, 92.5, 86.9, 55.9, 55.6, 47.6, 45.6, 39.7, 37.5, 36.8, 36.2, 36.1, 34.6, 32.7, 30.7, 27.1, 22.5, 20.9, 20.5. **FTIR** (NaCl, thin film) 3059, 2948, 2930, 2861, 1671, 1601, 1582, 1458, 1451, 1438, 1420, 1364, 1335, 1312, 1266, 1216, 1199, 1157, 1138, 1107, 1052, 1015, 998, 948, 917, 843, 819, 802, 721, 702, 689 $cm.^{-1}$ **HRMS** (MM) calc'd for $C_{30}H_{38}NaO_4$ $[M+Na]^+$ 485.2662, found 485.2672.

(80)

To a 13 × 100 quartz test tube was added benzophenone **68** (15.5 mg, 0.034 mmol). The tube was fitted with a 19/38 rubber septum and the atmosphere was exchanged 3 × for N_2. Rigorously degassed dioxane (4.70 mL, freeze-pump-thawed 3x) was then added via syringe and the tube was sealed with electrical tape. The reaction was then placed in a bottomless test tube rack in front of a Honeywell 254 nm lamp and irradiated for 1 hour at room temperature. The reaction mixture was transferred to a cone-bottom flask and concentrated in vacuo. The crude residue was purified by silica gel preparative TLC (30% hexane/CH_2Cl_2 + 1% EtOAc) to afford **83**[75] (2.4 mg, 28% yield) as a white solid and **80** (1.00 mg, 6.5% yield) as a colorless oil: $[\alpha]_D^{25.0} = +13.8°$ (c = 0.050, $CHCl_3$). Note: an additional ~18% yield of a complex mixture of products is also isolated as a single band. Although this mixture generally appears similar to 80 by ^{1}**H NMR**, definitive characterization was not achieved. ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 1H), 7.24 – 7.09 (m, 4H), 6.11 (dd, *J* = 2.5, 1.1 Hz, 1H), 6.01 (dd, *J* = 2.4, 1.2 Hz, 1H), 3.95 (d, *J* = 1.1 Hz, 1H), 3.78 (d, *J* = 1.2 Hz, 3H), 3.35 (d, *J* = 1.1 Hz, 3H), 2.65 (dd, *J* = 12.7, 3.5 Hz, 1H), 2.62 – 2.52 (m, 1H), 2.40 (t, *J* = 14.4 Hz, 1H), 2.26 (q, *J* = 10.4 Hz, 1H), 2.11 – 1.90 (m, 1H), 1.86 (d, *J* = 13.0 Hz, 1H), 1.83 – 1.72 (m, 1H), 1.69 – 1.57 (m, 1H), 1.43 – 1.34 (m, 2H), 1.30 – 1.09 (m, 4H), 0.80 (s, 3H), 0.78 (s, 3H), 0.75 (s, 3H), 0.50 (dt, *J* = 14.5, 4.2 Hz, 1H). ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 160.5, 158.8, 154.3, 149.3, 127.4, 126.1, 125.8, 111.4, 94.2, 93.5, 80.6, 74.6, 55.6, 55.4, 48.5, 48.1, 44.0, 37.3, 36.8, 35.7, 35.5, 34.6, 33.2, 30.5, 26.4, 25.0, 20.6, 20.4. **FTIR** (NaCl, thin film) 3542 (br), 3312, 3187 (br), 2960, 2924, 2854, 1738, 1726, 1710, 1666, 1614, 1592, 1492, 1462, 1453, 1445, 1423, 1376, 1366, 1351, 1332, 1261, 1215, 1203, 1150, 1112, 1045, 1020, 865, 800, 736, 702, 664 $cm.^{-1}$ **HRMS** (MM) calc'd for $C_{30}H_{37}O_3$ $[M–OH]^+$ 445.2737, found 445.2729.

(+)-psiguadial B (3):[76]

To a 2-dram vial was added resorcinol **97** (15.4 mg, 0.037 mmol) and the atmosphere exchanged three times for N_2. CH_2Cl_2 (1.30 mL) was then added via syringe, followed by dichloromethyl methyl ether (0.083 mL, 0.920 mmol, 25.0 equiv). The solution was cooled to –78 °C and a freshly prepared stock solution of $TiCl_4$ (0.190 mL, 0.912 M in CH_2Cl_2,

0.173 mmol, 4.68 equiv) was added dropwise. The reaction immediately turns dark red. The reaction was stirred at –78 °C for 5 minutes, then warmed to room temperature and stirred for an additional 3 hours and 40 minutes. DI H_2O (2.00 mL) was then added via syringe and the reaction stirred vigorously for 15 minutes before the layers were separated. The aqueous layer was extracted five times with CH_2Cl_2 and the combined organic layers were filtered over a plug of Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (isocratic: 2% EtOAc/hexane + 1% AcOH) to afford (+)-psiguadial B (3) (8.7 mg, 50%) as an ivory solid. Note: 3 is streaky on SiO2 and after an initial concentrated band elutes, approximately 12% of the product is contained in the following very dilute fractions. The natural product is weakly UV active, but can also be visualized by TLC using 2,4-dinitrophenylhydrazine stain. $[\alpha]_D^{25.0} = +94.0°$ (c = 0.265, $CHCl_3$). ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 13.51 (s, 1H), 13.04 (s, 1H), 10.07 (s, 2H), 7.26 (dd, *J* = 14.6, 1.5 Hz, 2H), 7.23 – 7.17 (m, 1H), 7.10 (br s, 2H), 3.49 (d, *J* = 11.5 Hz, 1H), 2.20 – 2.12 (m, 1H), 2.09 (dd, *J* = 12.7, 2.4 Hz, 1H), 1.92 (ddd, *J* = 14.9, 12.8, 4.2 Hz, 1H), 1.82 (ddd, *J* = 12.3, 8.8, 5.6 Hz, 1H), 1.73 – 1.59 (m, 3H), 1.53 – 1.44 (m, 1H), 1.49 (ddd, *J* = 11.6, 8.1, 2.9 Hz, 2H), 1.44 – 1.29 (m, 4H), 1.05 (dd, *J* = 7.6, 5.8 Hz, 1H), 1.02 (s, 3H), 1.00 (s, 3H), 0.85 (s, 3H). ^{13}**C NMR** (101 MHz, $CDCl_3$) δ 192.3, 191.5, 169.6, 168.5, 163.5, 143.4, 128.2, 126.2, 105.7, 104.6, 104.1, 84.1, 50.0, 47.4, 44.0, 40.4, 37.6, 36.9, 35.4, 35.1, 33.4, 30.6, 29.3, 26.1, 23.9, 20.7, 20.1. **FTIR** (NaCl, thin film) 3026, 2945, 2926, 2864, 2720, 1633, 1603, 1493, 1437, 1382, 1363, 1300, 1270, 1251, 1231, 1184, 1154, 1143, 1031, 1006, 976, 926, 917, 875, 851, 840, 824, 768, 701, 636, 618, 606, 564 $cm.^{-1}$ **HRMS** (MM) calc'd for $C_{30}H_{35}O_5$ $[M+H]^+$ 475.2479, found 475.2487.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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42. We were aware of unsuccessful efforts to prepare β-caryophyllene by ring-closing metathesis. See:Dowling MS, Vanderwal CD. Ring-Closing Metathesis of Allylsilanes As a Flexible Strategy toward Cyclic Terpenes. Short Syntheses of Teucladiol, Isoteucladiol, Poitediol, and Dactylol and an Attempted Synthesis of Caryophyllene. J Org Chem. 2010; 75:6908–6922. [PubMed: 20836562]
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44. Iodide 73 was prepared as an inconsequential 8:1 mixture of olefin isomers.

45. The major side product in the epimerization of 46 to 47 is spirocyclic lactam S1 (see Supporting Information). Formation of S1 is precluded using this alternative sequence, since aza-Michael addition cannot occur when the enone is protected as the corresponding dioxolane.
46. We were unable to separate all the components in this complex reaction mixture with sufficient purity for definitive characterization.
47. Spectroscopic data for 83 matches that reported in the literature:Lee H, Yi CS. Synthesis of 2-Acylphenol and Flavene Derivatives from the Ruthenium-Catalyzed Oxidative C–H Acylation of Phenols with Aldehydes. Eur J Org Chem. 2015; 2015:1899–1904.
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65. Characterization for this compound was reported previously (reference 12). It is re-presented here for the convenience of the readers.
66. We have found that concentrated reaction mixtures (e.g. ≥2.2 M) react to full conversion at 0 °C, whereas more dilute reactions (i.e. 1.5 M, as reported in ref 21a) often require warming to room temperature in order to initiate. This can be dangerous on large scale, as the reaction proceeds quickly and produces H2.
67. For safety reasons, *p*-4-acetamidobenzenesulfonyl azide (*p*-ABSA) was used as an alternative diazo transfer reagent in place of tosyl azide.
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69. Reaction time varies with the age of the lamp. A UV-opaque film slowly develops on the inside surface of the flask facing the lamp upon prolonged irradiation. This film can be removed by soaking the flask in an alkali base bath (KOH, 4:1 i-PrOH/H_2O).
70. APEX2, Version 2 User Manual, M86-E0 1078 Bruker Analytical X-ray Systems, Madison, WI, June 2006.

71. Prepared according to the ligand protocol described in:Bao H, Qi X, Tambar UK. Catalytic Enantioselective [2,3]-Rearrangements of Amine N-Oxides. J Am Chem Soc. 2011; 133:1206–1208. We found that the use of CH_2Cl_2 as a reaction solvent provided higher and more reproducible yields, compared with THF. [PubMed: 21218772]

72. Prepared directly in <10% yield according to:Leuchs H, Theodorescu G. Chem Ber. 1910; 43:1243.The corresponding ethyl ester can also be prepared in higher yield (~20%) according to: (b) Zhang Q, Botting NP, Kay C. A Gram Scale Synthesis of a Multi-^{13}C-Labelledanthocyanin, [6,8,10,3′,5′-^{13}C5]Cyanidin-3-Glucoside, for Use in Oral Tracer Studies in Humans. Chem Commun. 2011; 47:10596–10598.

73. Ohira–Bestmann reagent prepared according to:Pietruszka J, Witt A. Synthesis of the Bestmann-Ohira Reagent. Synthesis. 2006; 2006:4266–4268.

74. Prepared according to:Gambacorti-Passerini C, Mologni L, Scapozza L, Bisson W, Ahmed S, Goekjian P, Tardy S, Orsato A, Gueyrard D, Benoit J. Alpha-carbolines for the treatment of cancer WO 201316. 2013; 7730

75. Spectroscopic data for 83 matches that reported in the literature:Lee H, Yi CS. Synthesis of 2-Acylphenol and Flavene Derivatives from the Ruthenium-Catalyzed Oxidative C-H Acylation of Phenols with Aldehydes. Eur J Org Chem. 2015; 2015:1899–1904.

76. The characterization data were fully consistent with the isolation data reported in ref 4a. See Supporting Information for NMR comparison tables.

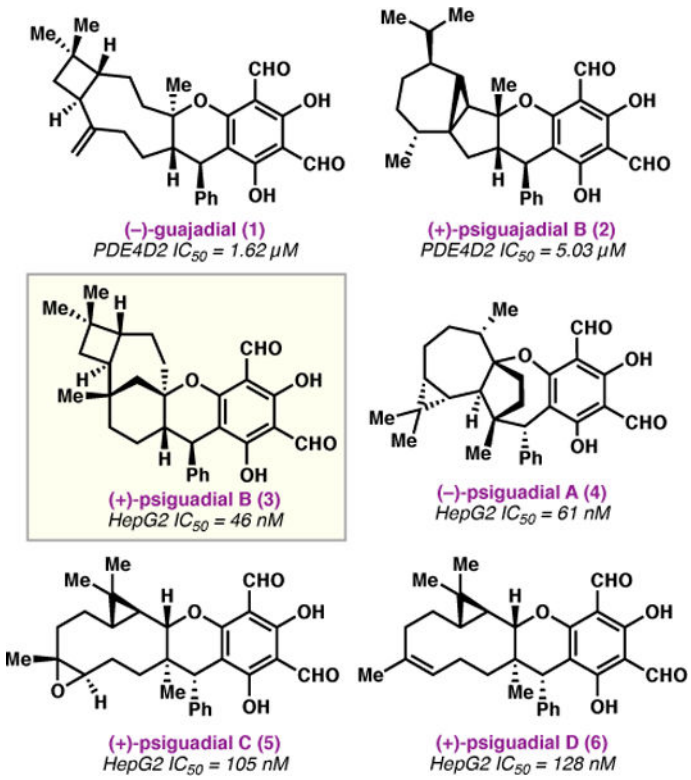


Figure 1.
Bioactive diformyl phloroglucinol meroterpenoids isolated from *Psidium guajava*.

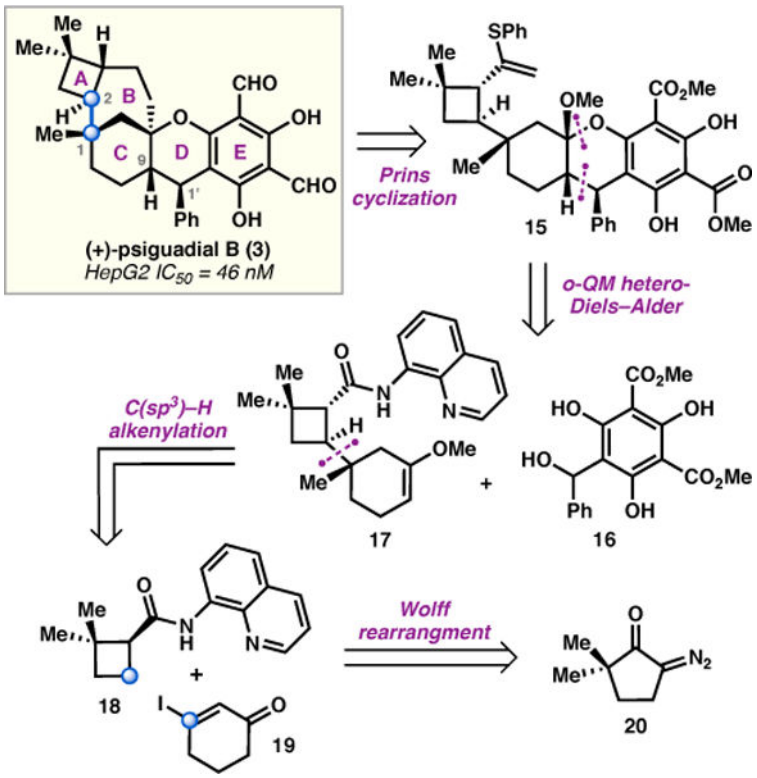


Figure 2.
First generation retrosynthetic analysis.

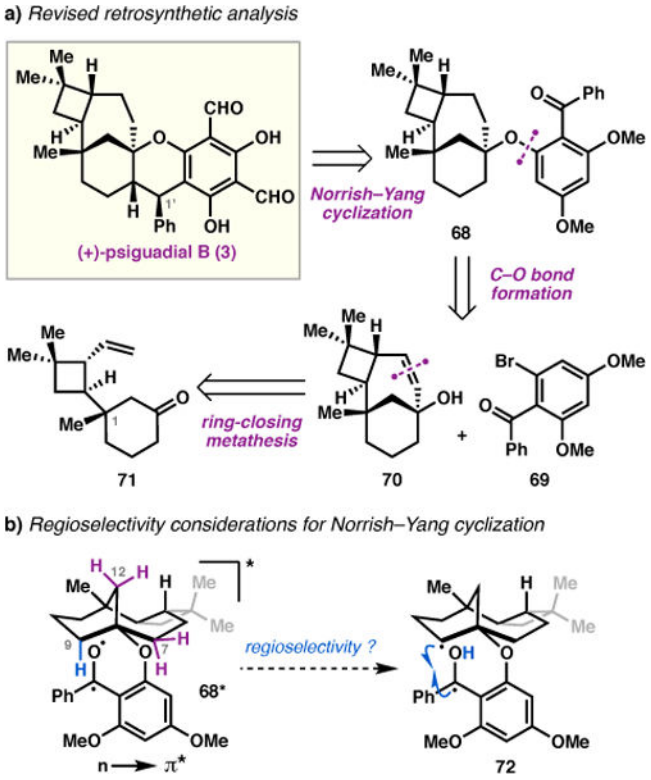


Figure 3.
Second-generation retrosynthetic analysis.

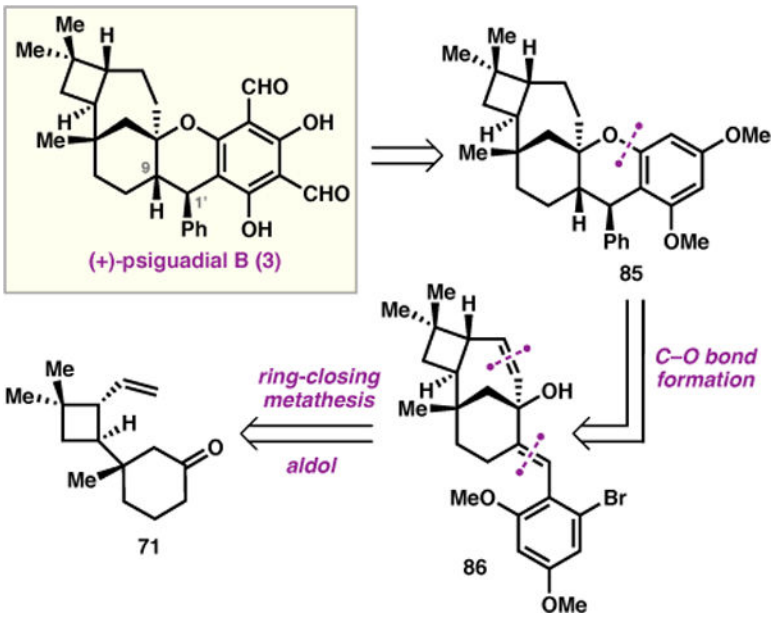


Figure 4.
Third generation retrosynthetic analysis.

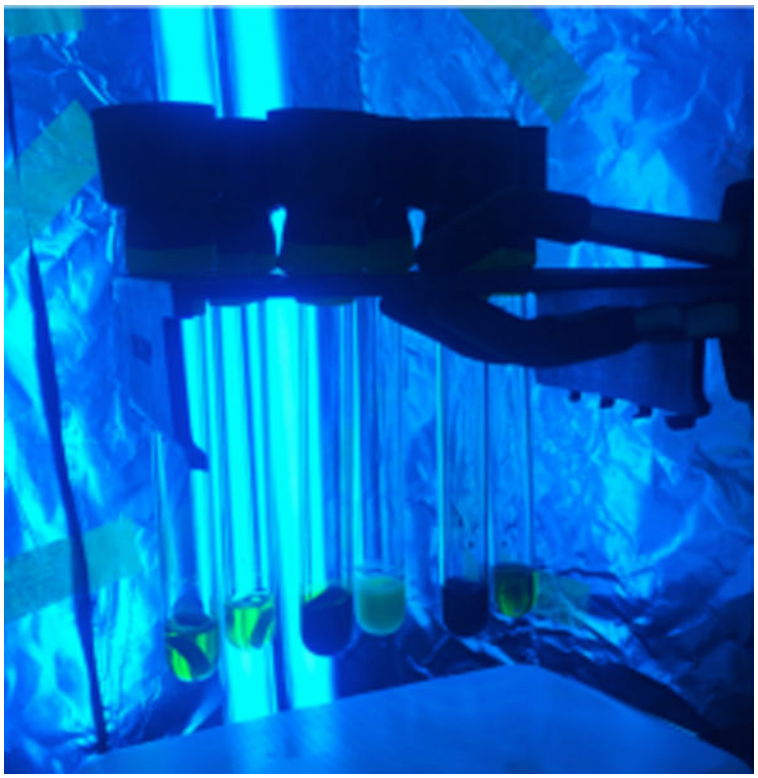
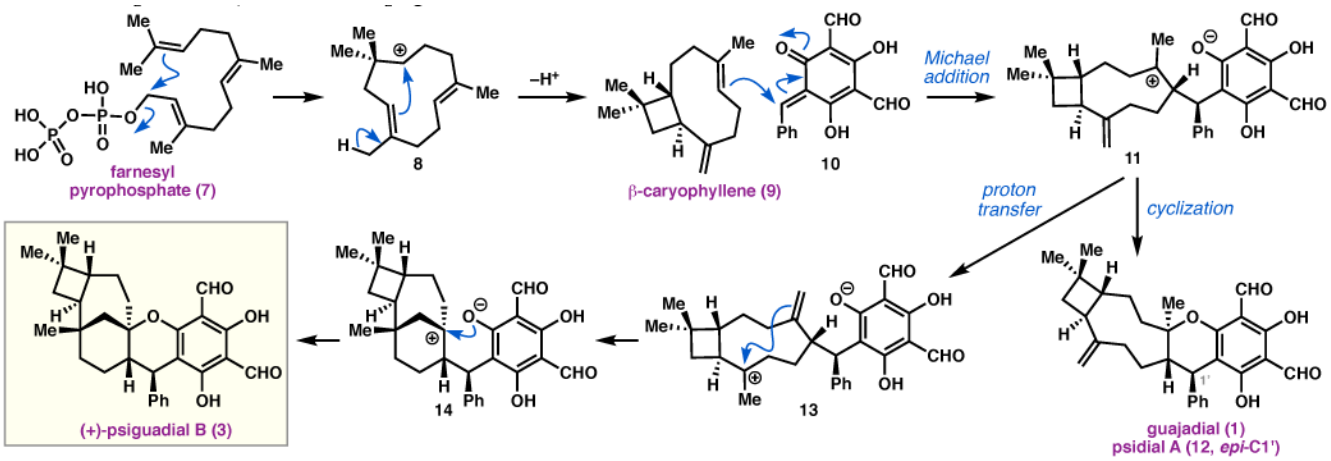
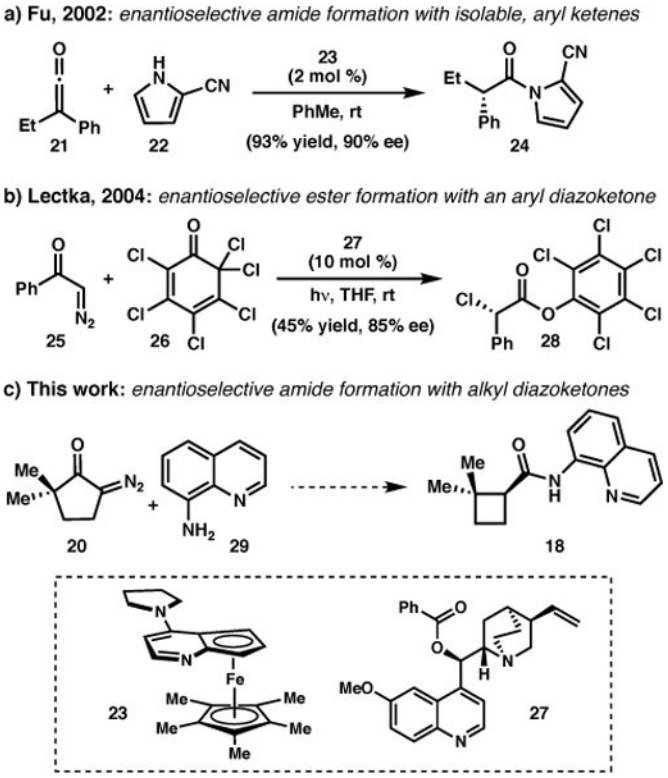


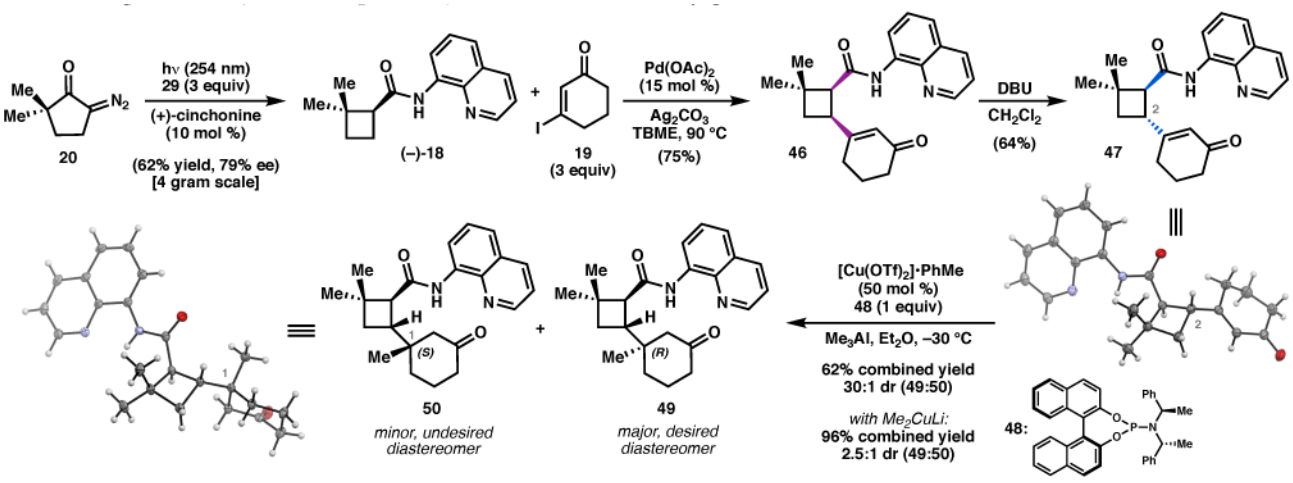
Figure 5.
Setup for small scale photochemical reaction screening.



Scheme 1.
Proposed biosynthesis of (+)-psiguadial B.

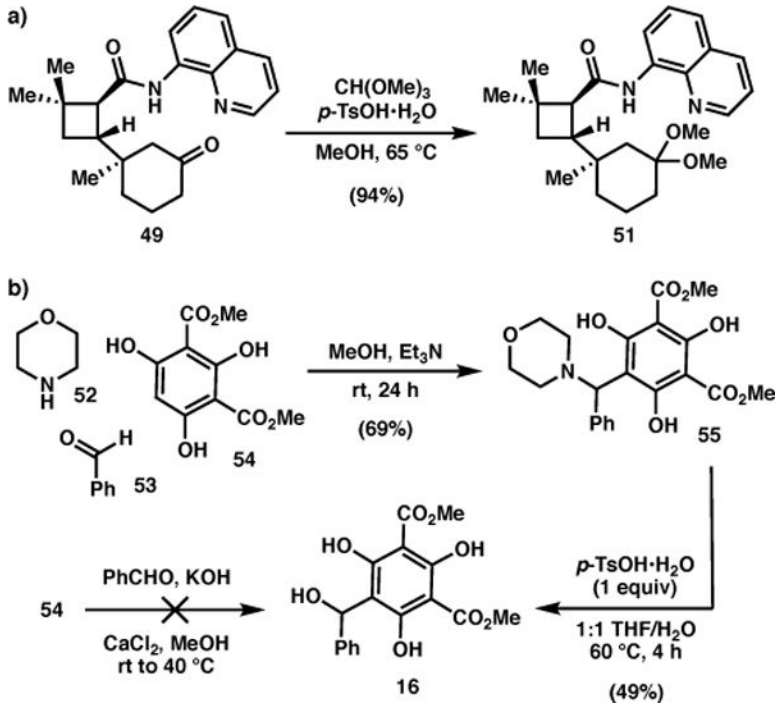


Scheme 2.
Enantioselective reactions with ketenes.

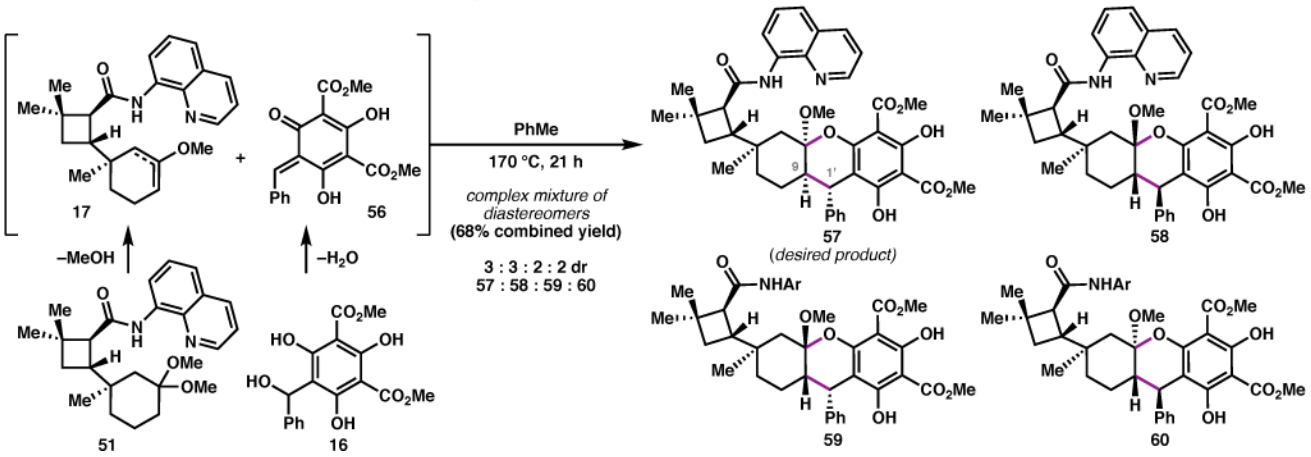


Scheme 3.

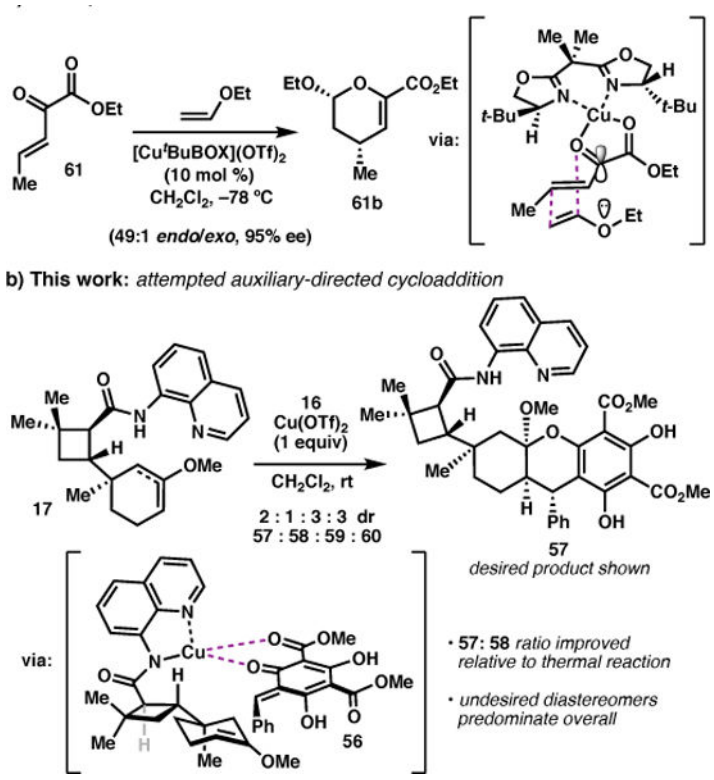
C(sp^3)–H alkenylation and quaternary center formation via conjugate addition.



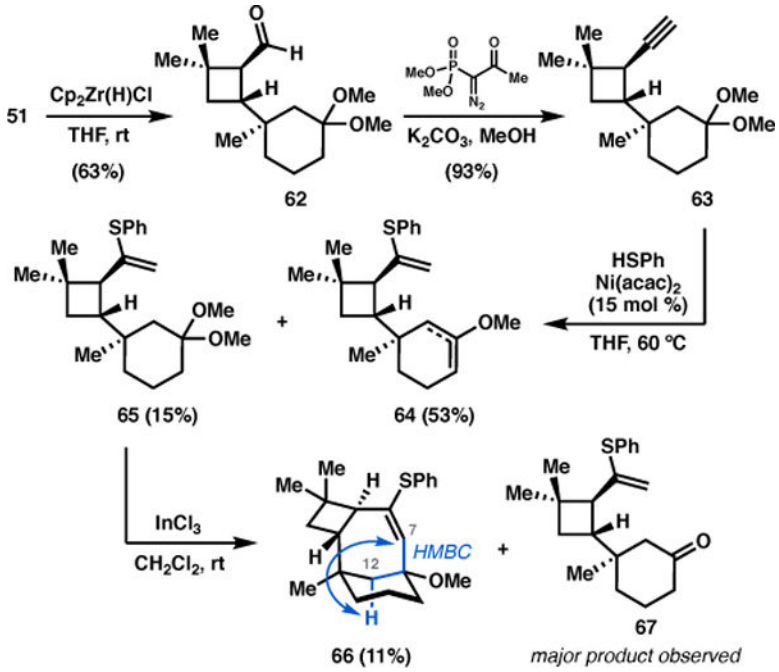
Scheme 4.
Synthesis of *o*-QMHDA cycloaddition reactants.



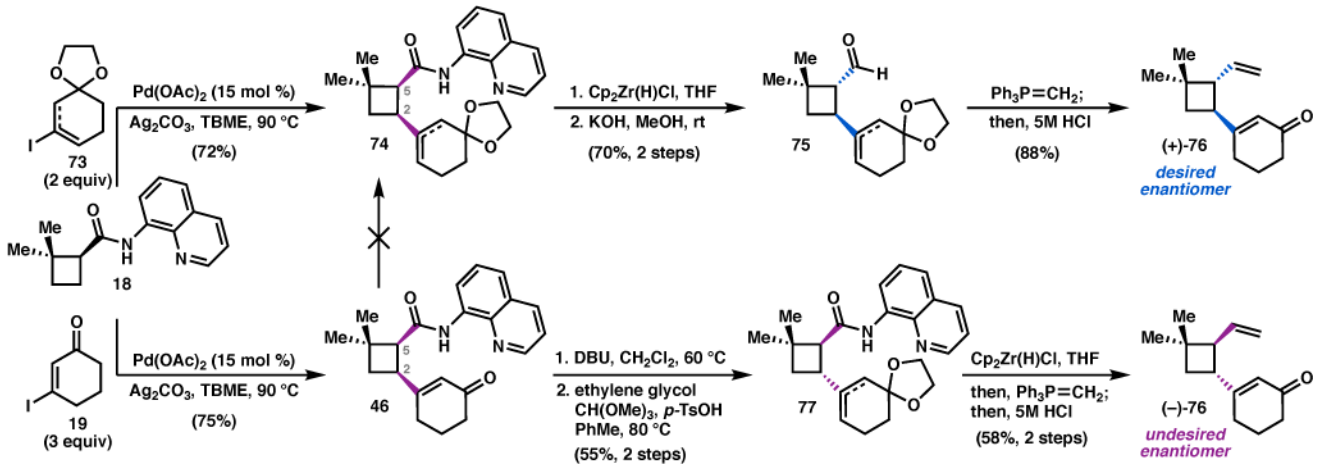
Scheme 5.
Evaluation of the thermal *o*-QMHDA cycloaddition.



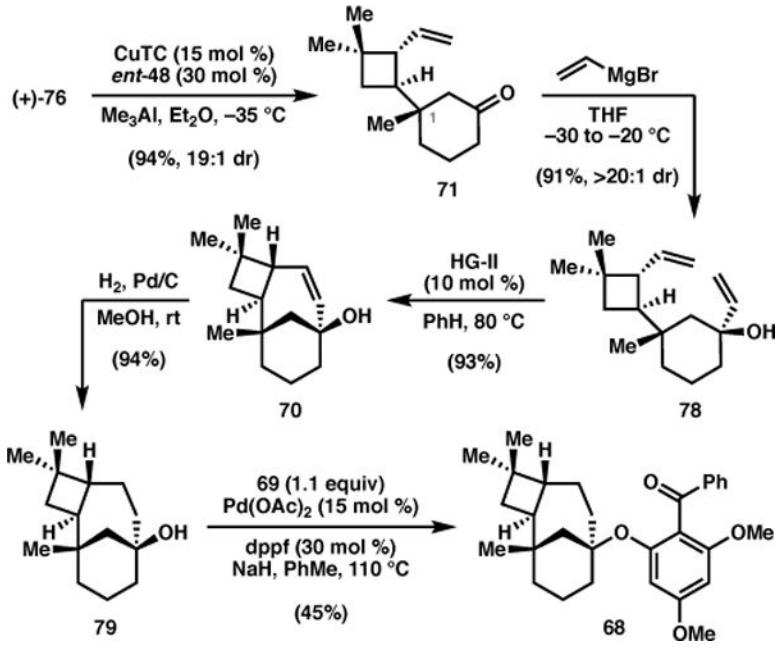
Scheme 6.
Attempted auxiliary-directed cycloaddition.



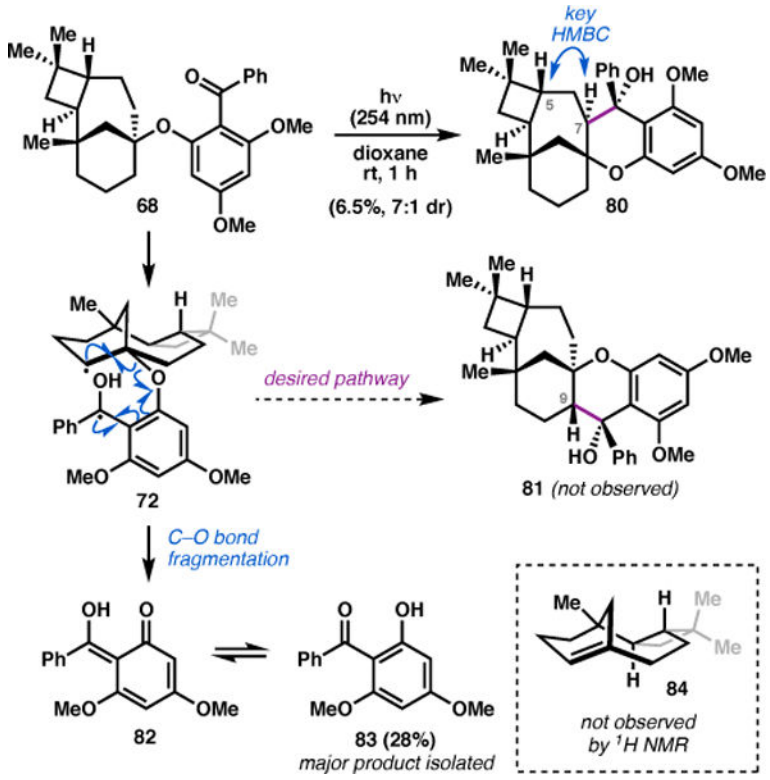
Scheme 7.
Model studies toward Prins cyclization.



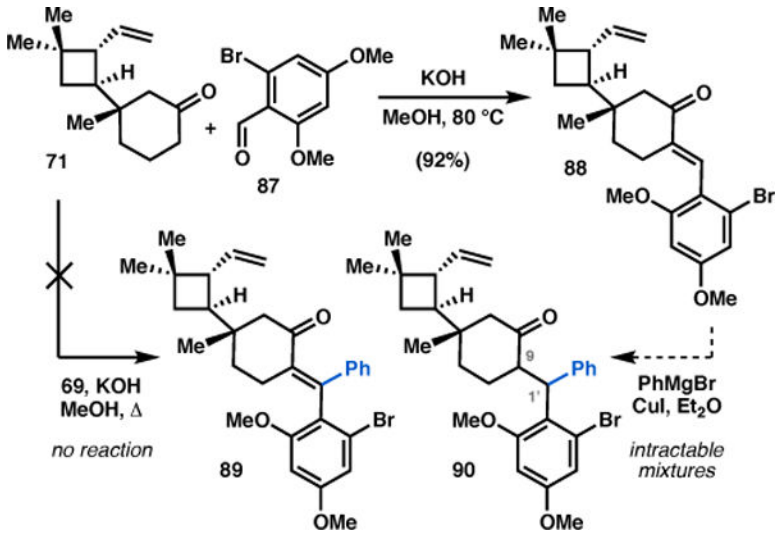
Scheme 8.
Development of enantiodivergent epimerization strategies.



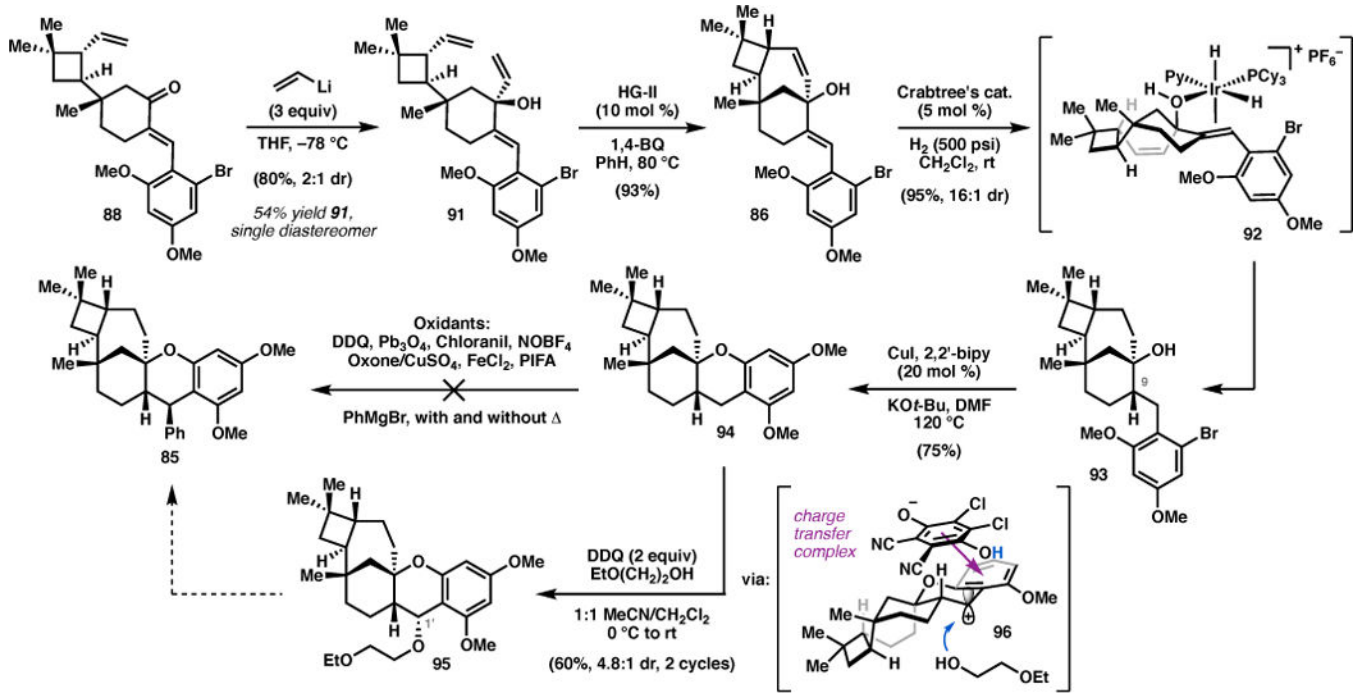
Scheme 9.
Elaboration to Norrish–Yang benzophenone.



Scheme 10.
Evaluation of the Norrish–Yang cyclization.

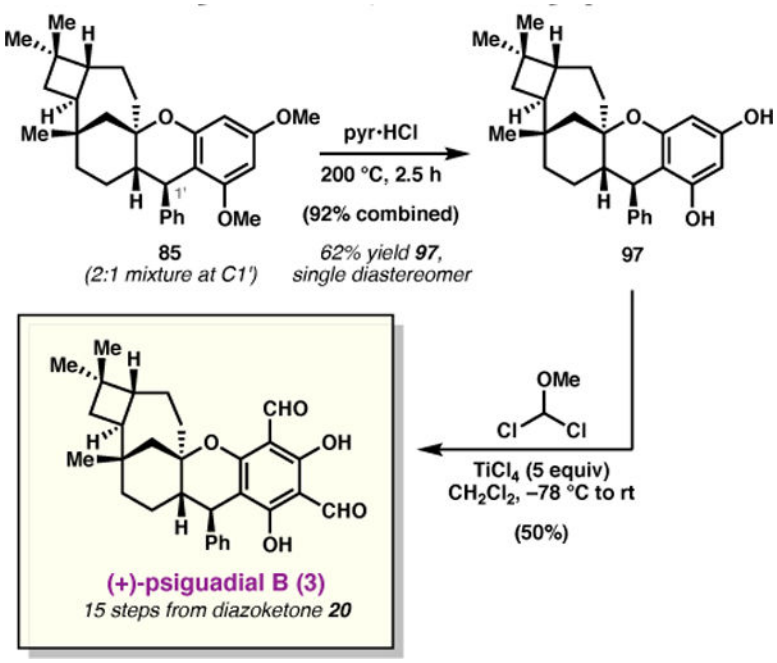


Scheme 11.
Installation of C9–C1′ bond via aldol reaction.



Scheme 12.

Synthesis of the core of (+)-psiguadial B.

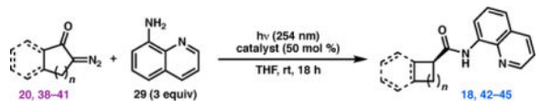


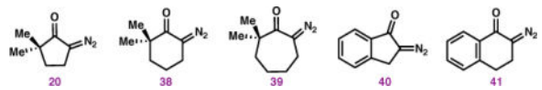
Scheme 13.

Completion of the synthesis of (+)-psiguadial B.

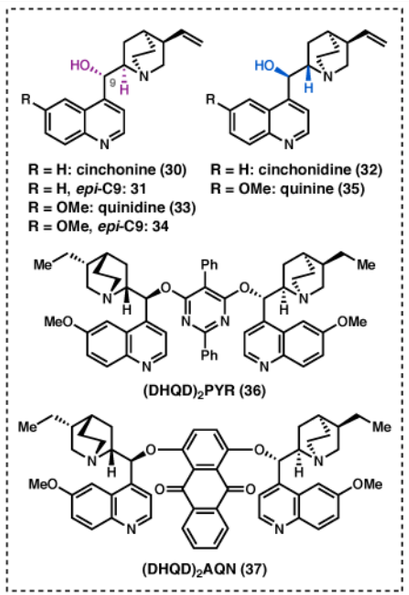
Table 1

Optimization and exploration of substrate scope for tandem Wolff rearrangement/ketene addition.





catalyst	18 entry	yield[a] (%)	ee[b] (%)	42 entry	yield[a] (%)	ee[b] (%)	43 entry	yield[a] (%)	ee[b] (%)	44 entry	yield[a] (%)	ee[b] (%)	45 entry	yield[a] (%)	ee[b] (%)
	1	**61**[c]	**79**	**9**	*64*	*58*	**17**	*49*	*64*	**25**	*48*	*9*	**33**	*54*	*35*
	2	*50*	*24*	**10**	*52*	*64*	**18**	*60*	*7*	**26**	*43*	*7*	**34**	*65*	*42*
	3	*64*	*−57*	**11**	*62*	*−22*	**19**	*56*	*−51*	**27**	*48*	*−3*	**35**	*38*	*−20*
	4	*67*	*64*	**12**	*69*	*50*	**20**	**59**[c]	**71**	**28**	*48*	*25*	**36**	*42*	*23*
	5	*58*	*48*	**13**	**77**[c]	**71**	**21**	*55*	*−39*	**29**	*40*	*7*	**37**	*61*	*41*
	6	*65*	*−54*	**14**	*66*	*0*	**22**	*54*	*−34*	**30**	48	−26	**38**	*42*	*−23*
	7	*90*	*−16*	**15**	*60*	*−59*	**23**	*65*	*−7*	**31**	*47*	*−5*	**39**	**42**[c]	**−75**
	8	*50*	*53*	**16**	*49*	*−23*	**24**	*50*	*37*	**32**	**31**[c]	**34**	**40**	*35*	*−1*



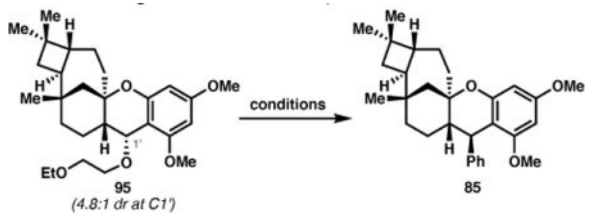
[a] Reactions performed on 0.050 mmol scale and irradiated for 18 hours. Yield determined by ^{1}H NMR analysis versus an added internal standard.

[b] Determined by SFC using a chiral stationary phase.

[c] Reactions performed on 0.200 mmol scale and irradiated for 48 hours, isolated yield reported.

Table 2

Investigation of the C1′ Phenylation.



entry	Lewis acid or catalyst	nucleophile	solvent	T (°C)	yield (%)85 (dr)[a]
1	TMSOTf	$PhB(OH)_2$	THF	–78 to 0	0
2	TMSOTf	PhMgBr	THF	⁻78 to 0	0
3	none	PhMgBr	PhMe	110	0
4	$Ni(dppe)Cl_2$	PhMgBr	PhMe	25	0
5	$Ni(dppe)Cl_2/MgI_2$	PhMgBr	PhMe	25	0
6	$BF_3•OEt_2$	$PhBF_3K$	CH_2Cl_2	0 to 25	0
7	$BF_3•OEt_2$	$PhBF_3K$	MeCN	0 to 25	0
8	$BF_3•OEt_2$	$Ph_2Cu(CN)Li$	Et_2O	⁻78 to 0	99 (1.7:1)
9	$BF_3•OEt_2$	$Ph_2Cu(CN)Li$	Et_2O	⁻78 to –45	90 (2.0:1)
10	$BF_3•OEt_2$	$Ph_2Cu(CN)Li$	Et_2O	⁻78 to –60	57 (3.3:1)

[a]Diastereomeric ratio obtained by ^1H NMR analysis of crude reaction mixture, provided in parenthesis.