Chapter 1

The Total Synthesis of (+)-Psiguadial B[†]

1.1 INTRODUCTION

The leaves and fruit from the flowering plant *Psidium guajava* have long been used in traditional Chinese medicine to treat a variety of ailments and maladies.[1–5] Intrigued by this plant's medicinal properties, isolation chemists have studied the bioactive constituents, and as a result have isolated a number of bioactive natural products from this shrub.[1–3] Many of these natural products are diformyl phloroglucinol containing natural products, bearing a highly oxygenated aryl ring attached to a terpene fragment.[6–9]

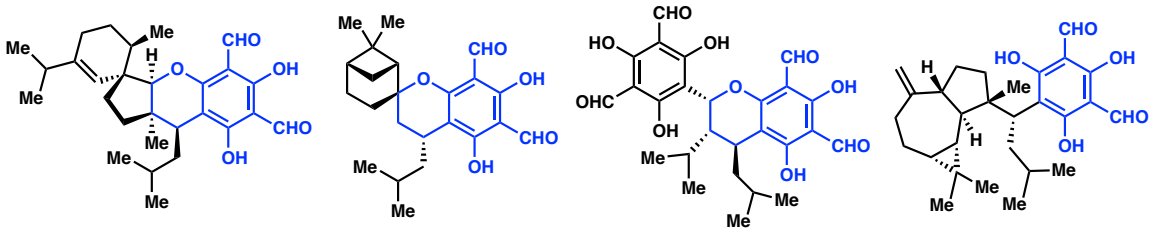
Diformyl phloroglucinol meroterpenoids are a subset of this family which possess excellent medicinal properties.[3–10] These diformyl phloroglucinol containing natural

---

[†] Portions of this chapter were adapted from the following communication: Chapman, L. M.; Beck, J. C.; Lacker, C. R.; Wu, L.; Reisman, S. E. *The Journal of Organic Chemistry* **2018**, *83*, 6066, DOI: 10.1021/acs.joc.8b00728, copyright 2018 American Chemical Society. The research discussed in this chapter was completed in collaboration with Dr. Lauren M. Chapman, a former graduate student in the Reisman Lab and Caitlin R. Lacker, a graduate student in the Reisman Lab.

products are of particular interest to biologists and chemists alike. Biologically, these molecules are known to possess potent anti-cancer, anti-viral, and anti-microbial activities (**1-4**, Figure **1.1**).[6–11] More broadly, the phloroglucinol-containing natural products are a large class of bioactive molecules, comprising over 700 known compounds to date.[6–9] The compounds euglobal-In-3 (**1**),[8] robustadial A (**2**)[12] sideroxylonal B (**3**),[13] and macrocarpal C (**4**, Figure **1.1**),[14] are just a handful of natural products from this family that possess intriguing bioactivity against a variety of pathogens.

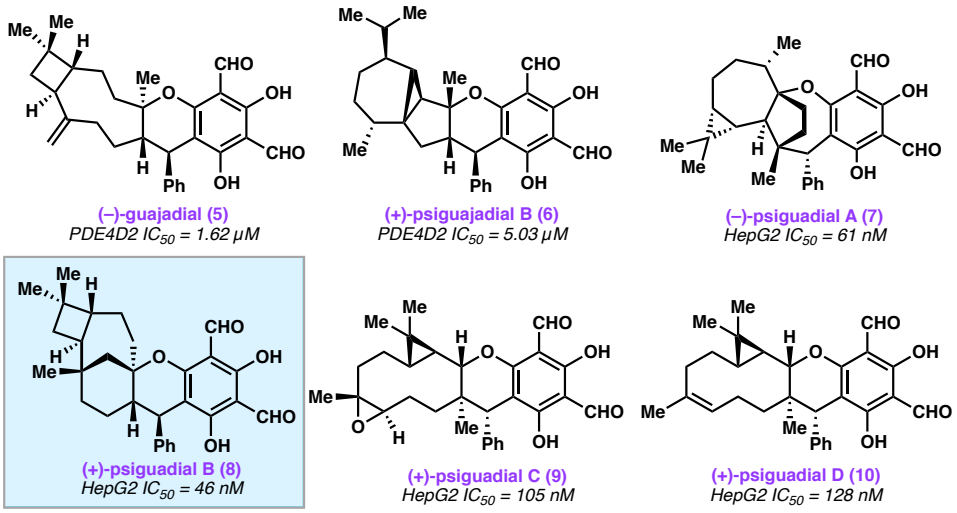
Figure 1.1. *Bioactive diformyl phloroglucinol terpenes*



More recently, four new diformyl phloroglucinol meroterpenoids, psiguadials A–D, were isolated from the leaves of the evergreen shrub, *psidium guajava* (**7–10**, Figure **1.2**).[15,16] The psiguadials are structurally unified in that they all contain a diformyl phloroglucinol subunit attached to a peripheral terpene fragment, joined through an oxygenated heterocycle and a diaryl methane moiety. The terpene fragment of each molecule contains a small, strained ring with geminal-dimethyl substitution. While each of these molecules possesses potent antiproliferative activity, we were particularly drawn to psiguadial B (**8**), as it exhibits the most potent anti-proliferative activity of the group (IC_{50} hep2G = 46 nM), and is the only member of the family containing a *trans*-fused cyclobutane ring.[15] This feature contributes to a synthetically challenging, highly strained

4,7,6 fused framework with six stereogenic centers, including one all-carbon quaternary center.

Figure 1.2. *Diformyl phloroglucinol natural products with remarkable biological activity.*

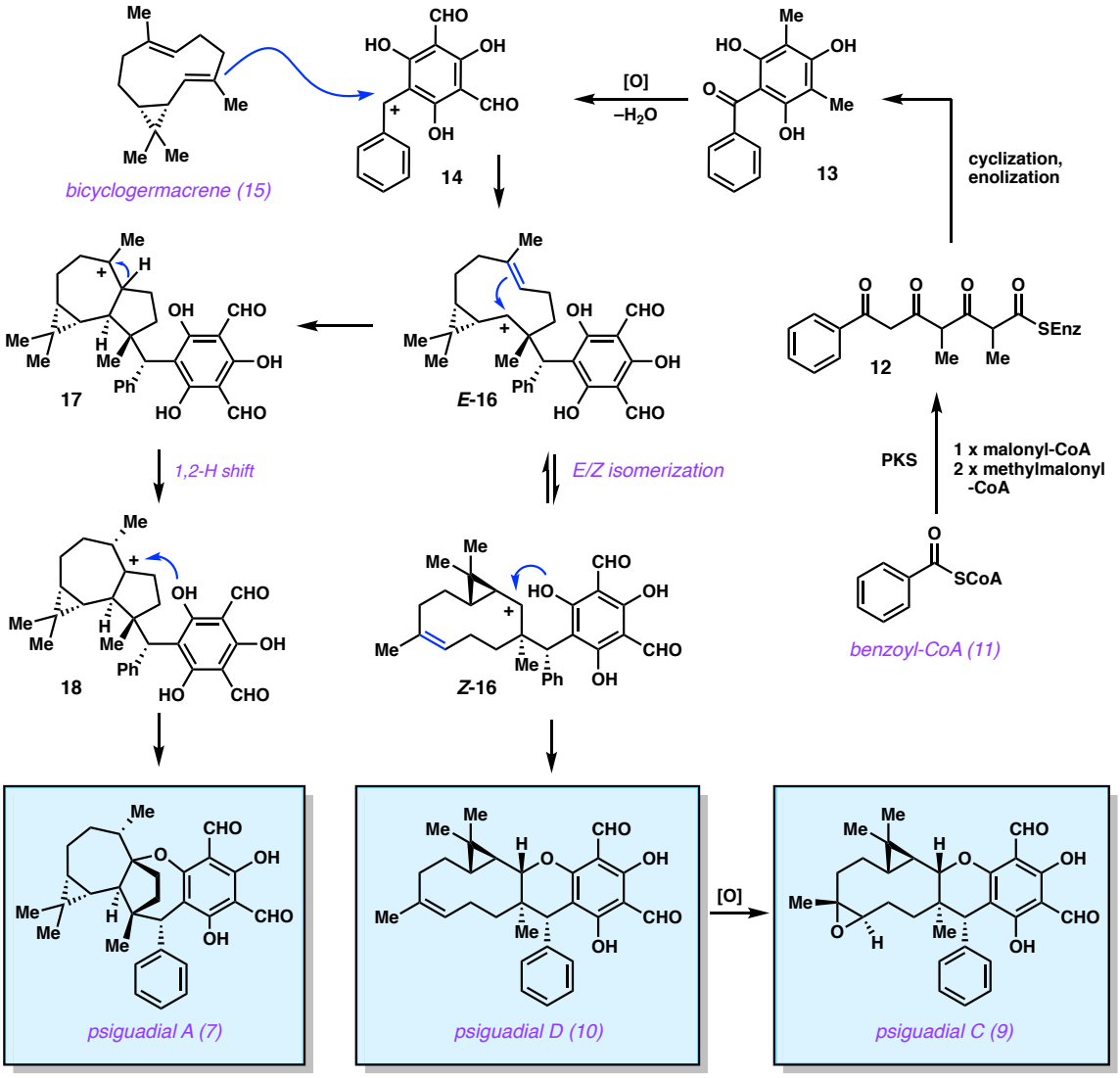


1.2 PROPOSED BIOSYNTHESIS OF THE PSIGUADIAL FAMILY

In their isolation report of psiguadials C and D (**9**–**10**), Shao et al. provided a detailed hypothesis for the biosynthesis of the psiguadial natural products.[16] They propose that synthesis of the psiguadials begins with condensation of benzoyl-CoA units to build the polyketide framework present in **7**–**10** (Scheme **1.1**). Cyclization and enolization of **12** provides diaryl ketone **13**, which is a known isolate from *Psidium guajava*. Benzylic oxidation of **13** followed by formation of the benzylic cation delivers **14**, which is thought to undergo nucleophilic capture by bicyclogermacrene (**15**). Reaction between **14** and **15** produces cyclopropylcarbinyl cation ***E*–16**, which triggers either of two cationic cyclization pathways: C-C bond formation forges the 7-5 ring system that leads to **7**, while **10** arises through isomerization of the olefin, followed by trapping of carbocation in ***Z*-16**

with the pendant phenol. Finally, **9** may be produced by oxidation of the trisubstituted olefin in **10**.

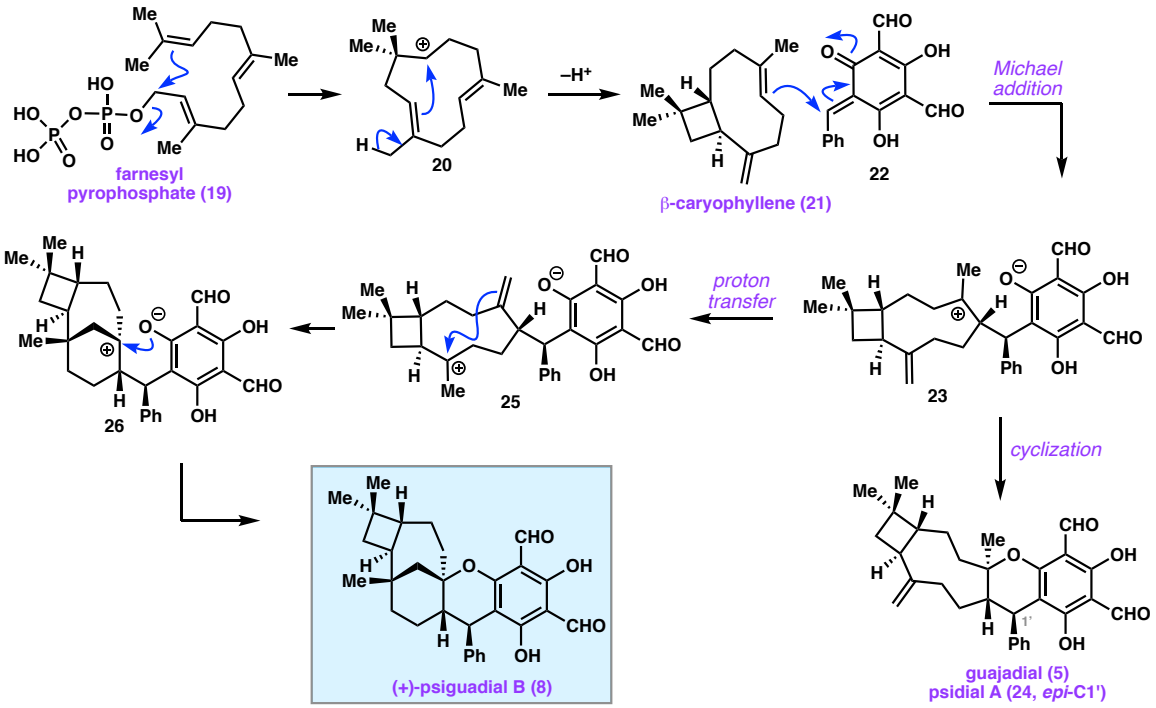
Scheme 1.1. *Proposed biosynthesis of psiguadials A, C, and D (**7**, **9**, **10**)*



An analogous cation cyclization pathway is thought to deliver **8**, from farnesyl pyrophosphate (**19**).[17,18] Intramolecular cyclization of **19** is thought to forge the 11-membered ring present in **20**. Subsequent cyclization provides β-caryophyllene (**21**), which is then thought to undergo a Michael addition with *ortho*-quinone methide (*o*-QM) **22**—likely derived from the known *P. guajava* metabolite 3,5-dimethyl-2,4,6-

trihydroxybenzophenone.[19–21] The resulting compound **23** can directly cyclize to generate **5** and **24**, or can undergo a trans-annular Prins-type cyclization to forge the central bridging ring structure. Bridgehead cation **26** is then poised to undergo cyclization to deliver **8**. Cramer[20,21] and Lee[22] have validated this biosynthetic hypothesis by semi-syntheses of **5**, **8**, and **24** from β-caryophyllene (**21**).

Scheme 1.2. *Proposed biosynthesis of (+)-psiguadial B (**8**).*



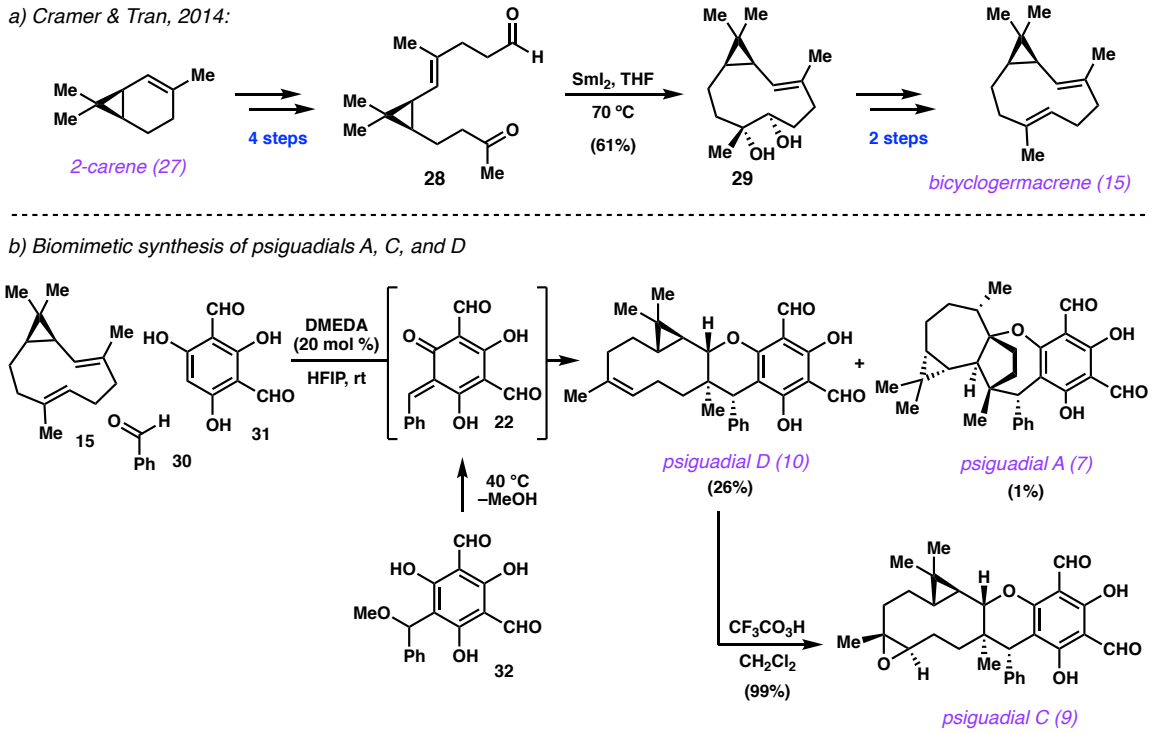
1.3 SYNTHESIS OF RELATED NATURAL PRODUCTS

1.3.1 Biomimetic Strategies for Semi-Synthesis

In 2014, Cramer and Tran were able to access bicyclogermacrene (**15**) starting from naturally occurring 2-carene (**27**) (Scheme **1.3**).[20] Four steps were required to access keto aldehyde **28**, which was poised to undergo reductive cyclization mediated by SmI_2. Further reduction provided **15**. With **15** in hand, Cramer could demonstrate that they could access psiguadials A, C, and D (**7**, **9**, and **10** respectively) through a biomimetic cyclization,

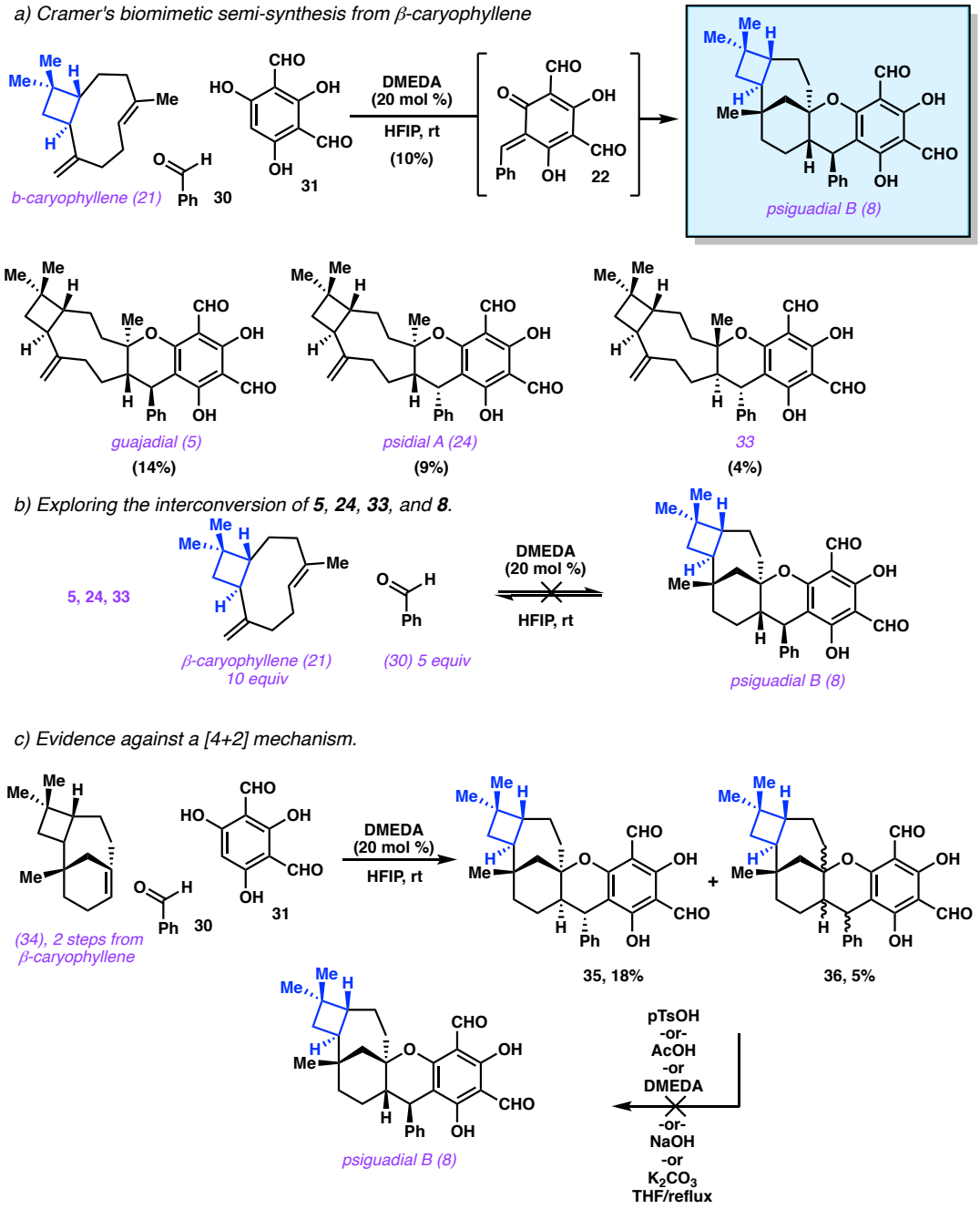
presumably through the intermediacy of **22**. Stepwise Michael addition followed by cationic rearrangement and nucleophilic capture produced **7** and **10**. Psiguadial D (**10**) could be oxidized to deliver psiguadial C (**9**).

Scheme 1.3. *Cramer's biomimetic synthesis of psiguadials A, C, and D*



More recently, Cramer and coworkers published a thorough report in which they investigated the feasibility of accessing psiguadial B (**8**) through a biomimetic cyclization cascade (Scheme **1.4**).[21] Through careful optimization, they found that treatment of **21** with three equivalents of **30** and three equivalents of **31** with catalytic DMEDA in HFIP delivered 10.4% yield of **8** in a single step. This procedure also delivers 26% yield of a mixture of **5**, **24**, and **33**. The authors demonstrate the utility of their method by performing the reaction on a 55 mmol scale. Treatment of the resulting crude mixture with ozone selectively degrades the side products, enabling clean isolation of **8**.[21]

Scheme 1.4. *Cramer's biomimetic semi-synthesis of psiguadial B*



Cramer and Tran also performed a number of calculations and mechanistic experiments to elucidate the biosynthetic formation of **8**. Their calculations indicate that the cyclization cascade is not mediated by an enzyme and that the proposed Michael

addition is exergonic and likely occurs over previously proposed Alder-ene or [4+2] reaction mechanisms. They experimentally observe that **5**, **24**, **33**, and **8** do not interconvert under the reaction conditions and that bridgehead olefin **34** does not produce **8**, solely delivering diastereomeric **35** and **36**. Any attempts to convert **35** and **36** to psiguadial B (**8**) under acid or base promoted cycloreversion were unsuccessful.

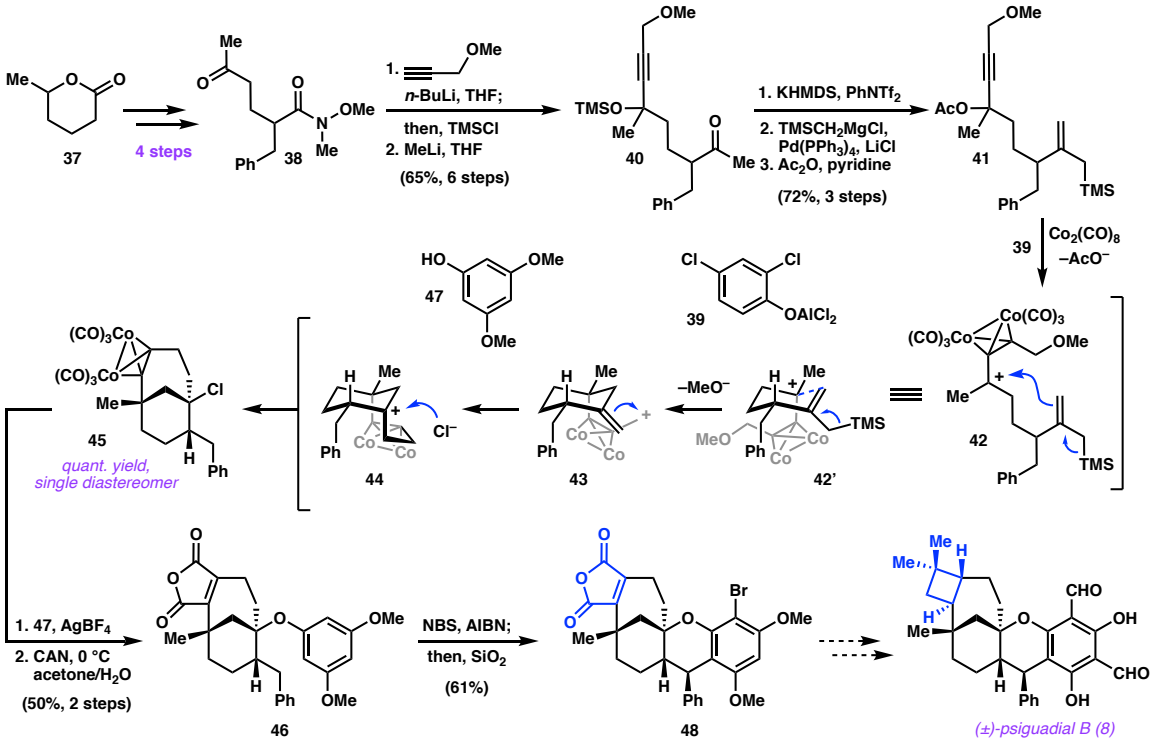
1.3.2 Total Synthesis Efforts Toward Psiguadial B

In February of 2017, Tanino and coworkers disclosed their progress toward a total synthesis of (±)-**8** (Scheme **1.5**).[23] Their synthesis commenced with commercially available lactone **37**. They were able to elaborate **37** to Weinreb amide **38** in 4 steps, which was then subjected to an alkylation protocol in which two 1,2-additions were performed to access TMS ether **40**. Generation of the corresponding enol triflate and subsequent Kumada coupling and acylation delivered **41**, their substrate for a key cyclization reaction. Treatment with $Co_2(CO)_8$ generates cation **42**, which can be intercepted by the pendant allyl silane. A subsequent ionization initiated by loss of methanol enables an isomerization and trapping with chloride to deliver **45**.

With **45** in hand, S_N1 substitution with **47** as the nucleophile followed by oxidative decomplexation of the dicobalt complex provides maleic anhydride **46** with the pendant aryl ether. At this point, benzylic functionalization mediated by NBS and AIBN followed by treatment with silica gel forges the requisite benzylic-aryl bond in **48**. While this step completes the synthesis of the core of **8**, the authors conclude their report stating that efforts to convert **48** to **8** are under way. It is important to note that the installation of the key trans-fused cyclobutane remains a challenge for the Tanino group in their current strategy. To

the best of our knowledge, the work reviewed herein constitutes the only synthetic studies toward psiguadial B (**8**).

Scheme 1.5. *Tanino's progress toward a total synthesis of (±)-psiguadial B*



1.4 A DE NOVO SYNTHETIC STRATEGY FOR THE TOTAL SYNTHESIS OF (+)-PSIGUADIAL B

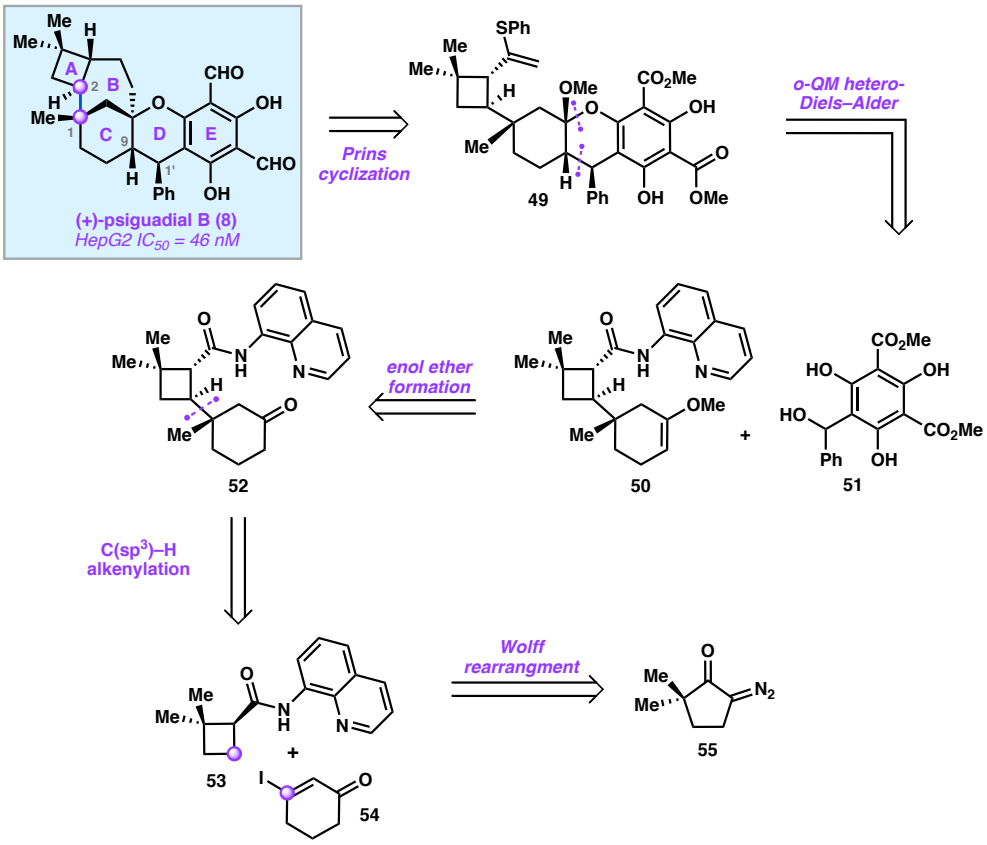
1.4.1 A [4+2] Cycloaddition Strategy

While the previously discussed semi-synthetic campaigns provide direct access to β-caryophyllene-derived natural products, we felt that an abiotic approach to the synthesis of **8** could enable the investigation of novel chemistry that could potentially be applied in broader synthetic contexts.

With this goal in mind, we turned our attention to the structure of **8** and identified a strategic disconnection through the B ring (Scheme **1.6**). We felt that scission of this

carbon-carbon bond would greatly simplify the synthesis of **8**. In the forward sense, we envisioned forming the key 7-membered ring through an intramolecular Prins cyclization between a methyl ketal and a vinyl sulfide (**49**). 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.[24–26]

Scheme 1.6. *First generation retrosynthesis of (+)-psiguadial B*



We hypothesized that pyran **49** could be assembled through a bioinspired *ortho*-quinone methide hetero-Diels–Alder (*o*-QMHDA) reaction between enol ether **50** and an *o*-QM generated from **51**.[27] 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.[28–31] 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. 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 **50** would impart the desired facial selectivity in the approach of the heterodiene was less clear.[28,29,32–34]

We envisioned preparing **50** through enolization of the corresponding ketone **52**, which we planned to access through a selective C(sp^3)–H alkenylation reaction between **53** and **54**. While **54** was known,[35] we imagined preparing **53** through a novel Wolff rearrangement with asymmetric trapping of the resulting ketene in order to set the first stereocenter present in **8**.

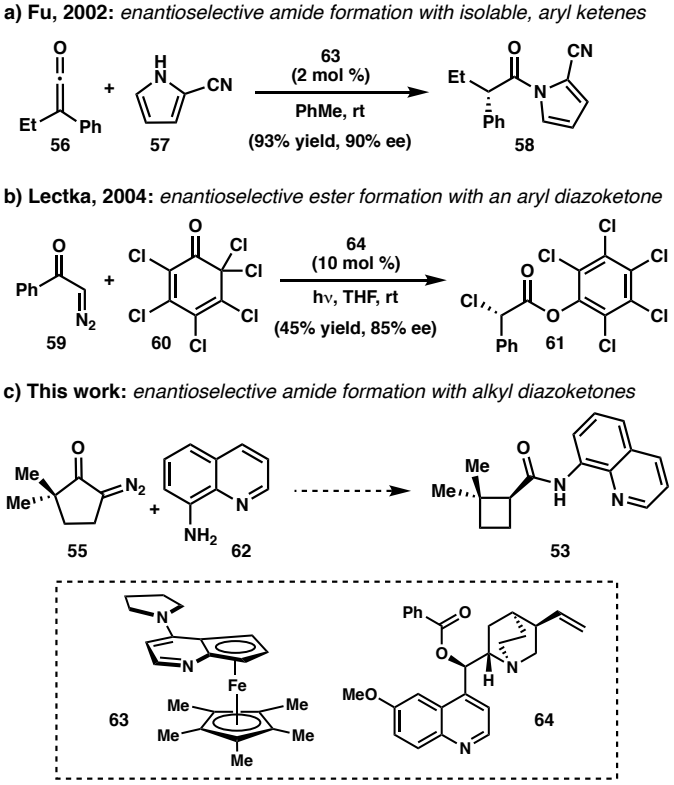
1.4.2 Development of an Asymmetric Wolff Rearrangement

A key question presented by the proposed retrosynthesis was how best to synthesize cyclobutane **53** 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. **56**) and 2-cyanopyrrole (**57**) using chiral DMAP catalyst **63** (Scheme **1.7a**).[36,37] We hypothesized that a similar transformation could be used to prepare **53** directly from **55** by using 8-aminoquinoline (**62**) 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 **1.7b**).[38]

Following a survey of chiral nucleophilic catalysts known to engage with ketenes,[39–41] it was discovered that irradiation of a mixture of **55** and 3 equivalents of **62** in the presence of 50 mol % (+)-cinchonine (**73**) produced **53** in 61% yield, and 79% ee (Table **1.1**, entry 1). Investigation of various solvents revealed that THF provided the

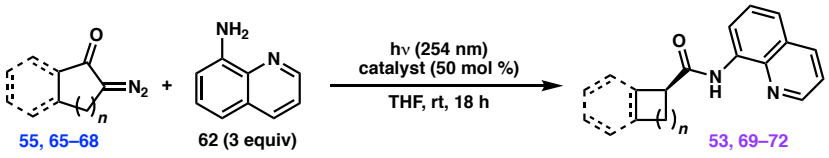
Scheme 1.7. *Enantioselective reactions with ketenes and proposed transformation*

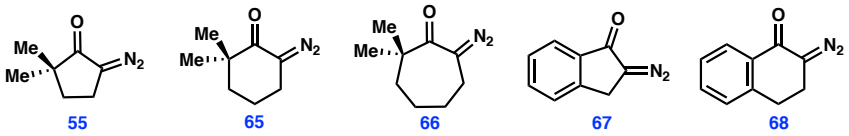


highest levels of enantioselectivity. More concentrated reaction mixtures led to lower yields, presumably due to poor light penetration as a result of the sparing solubility of **73** in THF. When scaling the reaction to quantities relevant for total synthesis (30 mmol), the catalyst loading of **73** could be reduced to 10 mol %, which provided **53** in 62% yield and

79% ee (see Scheme **1.8**). Moreover, enantiomerically pure **53** was obtained after a single recrystallization by layer diffusion.

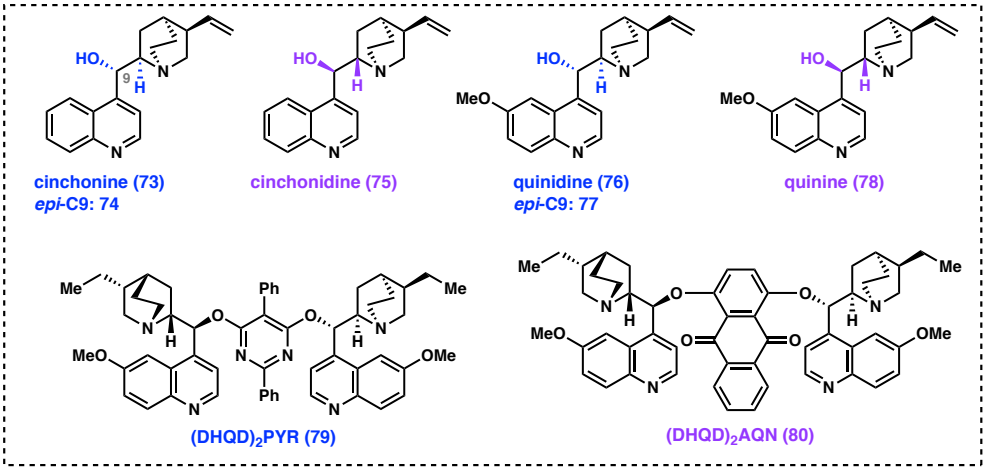
Table 1.1. *Optimization and exploration of substrate scope for tandem Wolff rearrangement/ketene addition*





catalyst	53 entry	yield[a] (%)	ee[b] (%)	69 entry	yield[a] (%)	ee[b] (%)	70 entry	yield[a] (%)	ee[b] (%)	71 entry	yield[a] (%)	ee[b] (%)	72 entry	yield[a] (%)	ee[b] (%)
73	1	61[c]	79	9	*64*	*58*	17	*49*	*64*	25	*48*	*9*	33	*54*	*35*
74	2	*50*	*24*	10	*52*	*64*	18	*60*	*7*	26	*43*	*7*	34	*65*	*42*
75	3	*64*	*–57*	11	*62*	*–22*	19	*56*	*–51*	27	*48*	*–3*	35	*38*	*–20*
76	4	*67*	*64*	12	*69*	*50*	20	59[c]	71	28	*48*	*25*	36	*42*	*23*
77	5	*58*	*48*	13	77[c]	71	21	*55*	*–39*	29	*40*	*7*	37	*61*	*41*
78	6	*65*	*–54*	14	*66*	*0*	22	*54*	*–34*	30	48	*–26*	38	*42*	*–23*
79	7	*90*	*–16*	15	*60*	*–59*	23	*65*	*–7*	31	*47*	*–5*	39	42[c]	*–75*
80	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.



Although our total synthesis efforts focused on the preparation of **53**, we wondered if this tandem Wolff rearrangement/enantioselective addition reaction could be applied to other α-diazoketone substrates (**65**–**68**). Unfortunately, substantially lower levels of

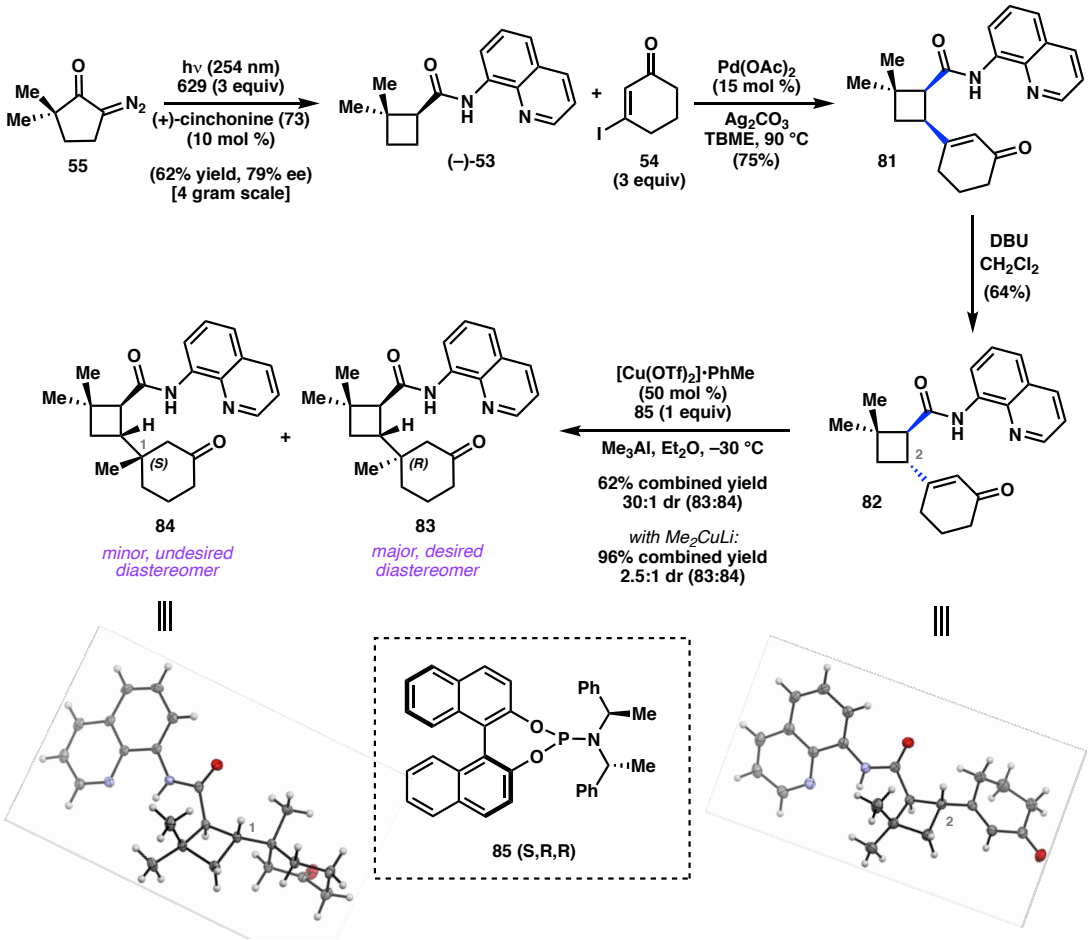
enantioinduction (9–64% ee) were observed using **73** as a catalyst with these substrates (Table **1.1**, entries 9, 17, 25, and 33). Evaluation of alternative cinchona derivatives **74**–**80** revealed that synthetically useful levels of enantioselectivity could be achieved for each substrate, depending on the catalyst. For instance, while **74**–**80** produced **53** with lower enantioinduction (16–64% ee, entries 2–8), catalysts **77** and **76** proved *optimal* for the 6- and 7-membered analogs of **55**, providing amides **69** and **70** 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 **69** (n = 2) in 81% yield and 68% ee and cyclohexyl amide **70** (n = 3) in 67% yield and 65% ee. On the other hand, benzo-fused diazoketones, **67** and **68**, performed best in the presence of dimeric cinchona catalysts **80** and **79** (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.

1.4.3 A Convergent Catalytic Alkenylation

Having identified conditions to prepare multigram quantities of **53** in enantiopure form, we were pleased to find that treatment of **53** with $Pd(OAc)_2$ (15 mol %), Ag_2CO_3, and 3 equivalents of **54** in TBME at 90 °C smoothly effected the $C(sp^3)$–H alkenylation reaction to give **81** in 75% yield on gram scale (Scheme **1.8**). Exposure of **81** to DBU furnished the requisite *trans*-cyclobutane (**82**) via selective epimerization at C2, as determined by deuterium-labeling studies. It was at this stage that single crystals of *trans*-cyclobutane **82** suitable for X-ray diffraction were obtained. Unfortunately, **82** was found to be in the incorrect enantiomeric series for elaboration to natural **8**. To our dismay, this

problem could not be circumvented by simply employing (−)-cinchonidine (**75**) in the tandem Wolff rearrangement/asymmetric ketene addition, as this *pseudoenantiomeric* catalyst afforded (+)-**53** in only 57% ee (Table 1, entry 3). Nevertheless, we elected to advance (–)-**53** in the interest of validating the key reactions in our retrosynthetic analysis as soon as possible.

Scheme 1.8. *C(sp^3)–H alkenylation and quaternary center formation via conjugate addition*

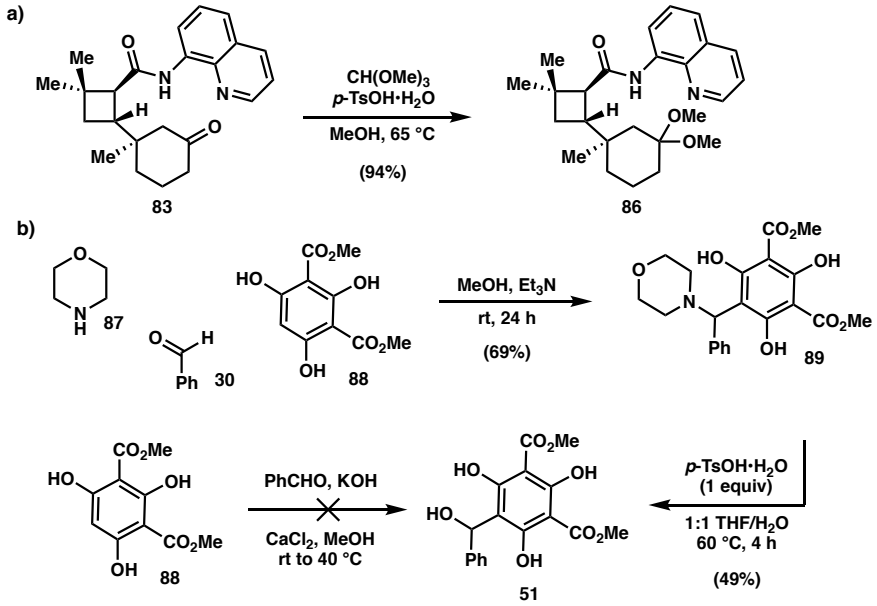


To this end, attention turned to formation of the C1 quaternary center (Scheme **1.8**). Subjection of *cis*-cyclobutane **81** to a number of standard conjugate addition conditions provided only trace yields of the corresponding product (not shown), presumably due to steric encumbrance by the proximal large aminoquinoline group. On the other hand,

treatment of *trans*-cyclobutane **82** with excess Gilman's reagent smoothly furnished **83** and **84** in near quantitative yield as a 2.5:1 mixture of diastereomers, respectively. Separation of the diastereomers by HPLC allowed single crystals of **84** to be obtained, and X-ray analysis unambiguously confirmed that the minor diastereomer (**84**) possessed the undesired (*S*) configuration of the methyl group at the C1 quaternary center, and by analogy, the major diastereomer (**83**) possessed the correct (*R*) configuration at C1.

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[42,43] provided **83** in 62% yield and 30:1 dr, albeit using 50 mol % $[Cu(OTf)_2]$•PhMe and a stoichiometric equivalent of phosphoramidite ligand **85**. 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.

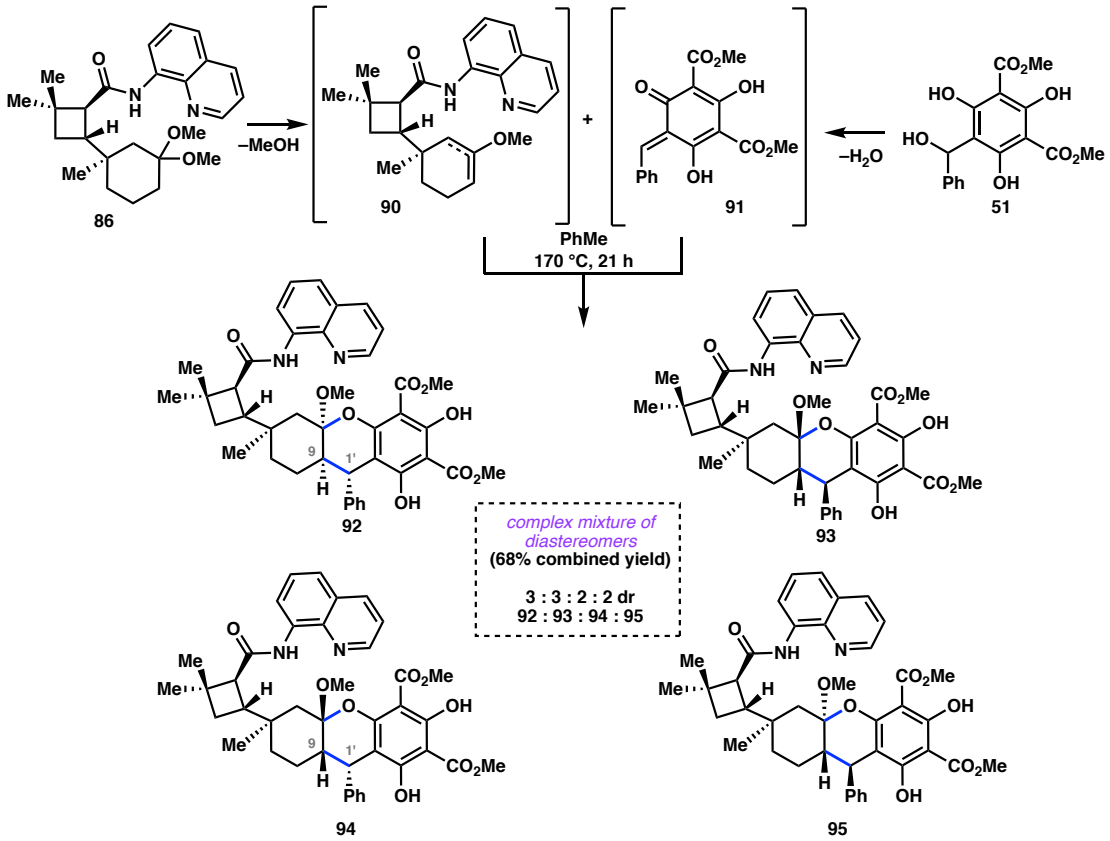
Scheme 1.9. *Synthesis of o-QMHDA cycloaddition reactants*



1.4.4 Investigation of the Key [4+2]

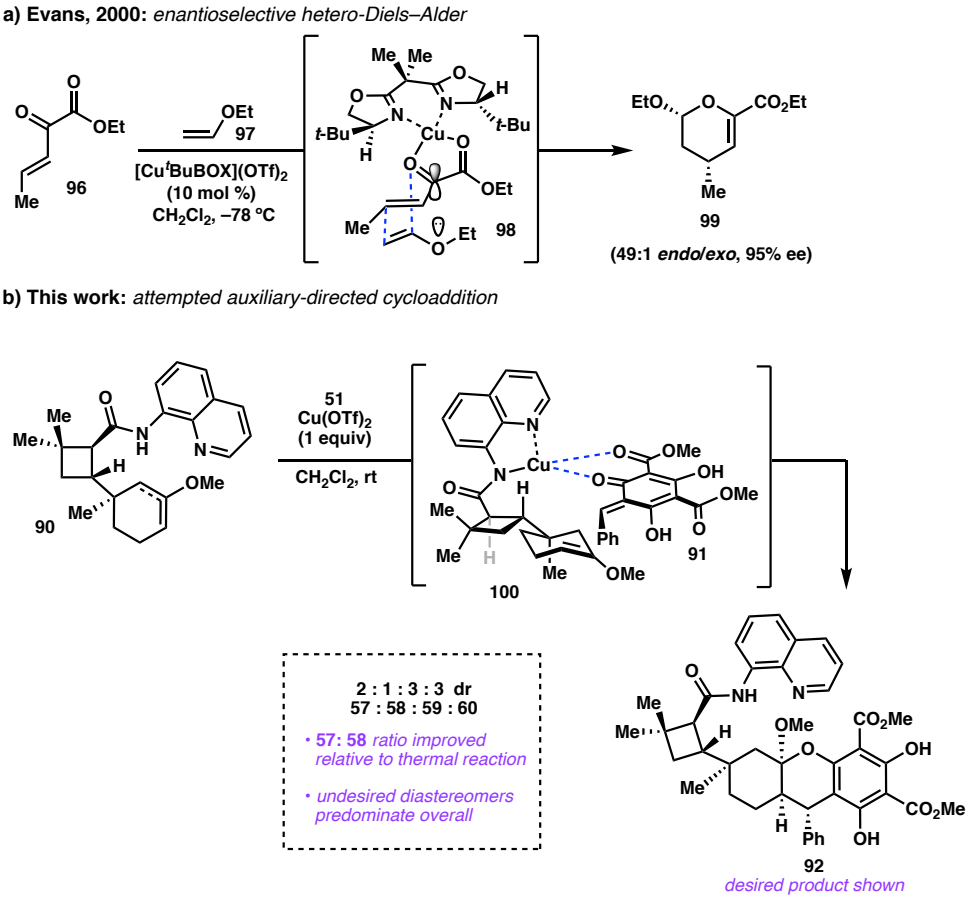
With the quaternary center secured, ketone **83** was converted to the corresponding dimethyl ketal **86** (Scheme 1.9), a precursor to the dienophile for the *o*-QMHDA reaction (*vide infra*). While phenolic aldol conditions failed to produce **51**, this acid-labile *o*-QM precursor was prepared from phloroglucinol **88**[44,45] via the morpholine adduct (**89**, Scheme 1.9b). A control experiment determined that heating of **86** to 170 °C in toluene results in thermal extrusion of methanol to afford a 1:1 mixture of enol ethers **90** (Scheme **1.10**). When a mixture of **86** and **51** was heated to 170 °C for 21 h, the cycloadduct was obtained in 68% yield, albeit as a complex mixture of diastereomers.

Scheme 1.10. *Evaluation of the thermal o-QMHDA cycloaddition*



Analytically pure samples of the four highest abundance diastereomers (**92**–**95**) were obtained by HPLC purification. Spectroscopic analysis by 2D NMR led to the assignment of **92** and **93** 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 **90** does not exert significant facial selectivity in the *o*-QMHDA reaction. The *trans*-fused isomer, **95**, presumably results from thermal equilibration of the ketal under the reaction conditions.

Scheme 1.11. *Attempted auxiliary-directed cycloaddition*



In considering how to improve the selectivity for desired diastereomer **92**, we drew inspiration from Evans' highly enantioselective inverse-demand hetero-Diels–Alder

chemistry, which proceeds via bidentate coordination of heterodienes such as **96** to a chiral Cu(II)-BOX Lewis acid catalyst (Scheme **1.11a**).[46] We envisioned that chelation of the aminoquinoline in **90** to a Cu complex could engage **91** as depicted in Scheme **1.11b**, thereby directing the *o*-QM to the top face of enol ether **90** (Scheme **1.11b**). Formation of **91** could be induced by the equivalent of triflic acid generated via complexation of $Cu(OTf)_2$ with aminoquinoline.[47,48]

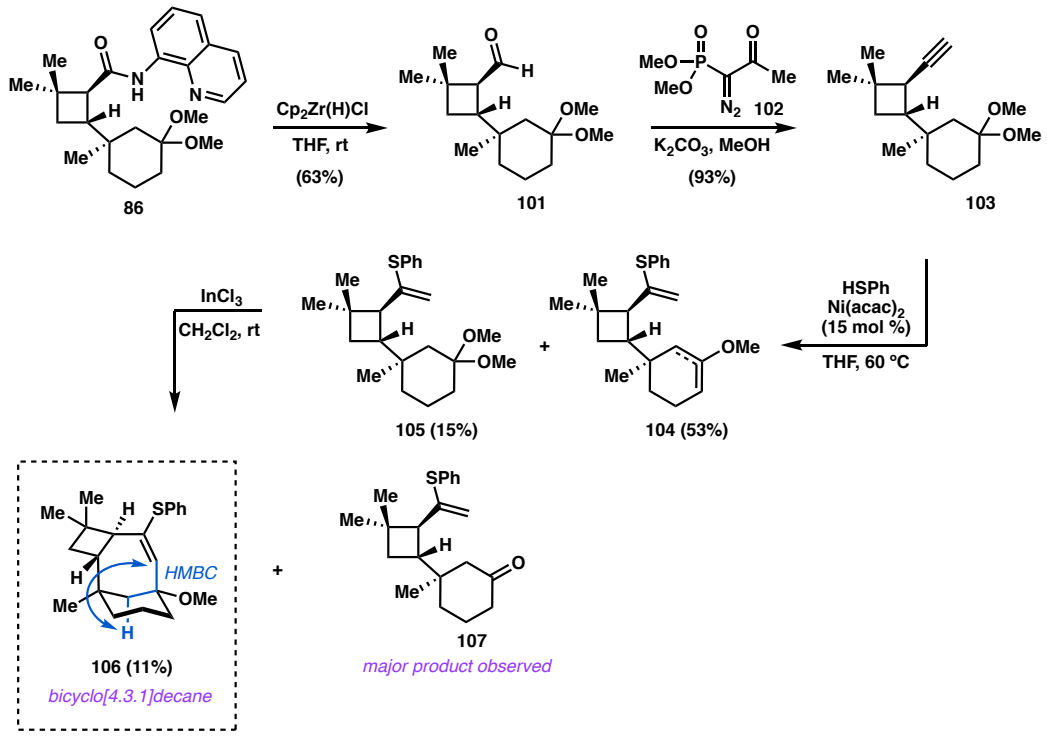
To test this hypothesis, enol ether **90** was prepared by heating in PhMe, and after exchanging the solvent for CH_2Cl_2, $Cu(OTf)_2$ and **51** were added. Analysis of the crude reaction mixture by ^1H NMR revealed that although the ratio of **92**:**93** had improved relative to the thermal reaction, significant quantities of the undesired isomers, **94** and **95**, were still formed. Moreover, this reaction suffered from lower overall yields due to rapid hydrolysis of **90** and reversion of **51** to phloroglucinol **88**. 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.

1.4.5 Exploring a Model Prins Cyclization

To this end, the aminoquinoline auxiliary in **86** was reductively cleaved by treatment with Schwartz's reagent to furnish aldehyde **101**, which was homologated to alkyne **103** using the Ohira–Bestmann reagent (**102**) (Scheme **1.12**). Nickel-catalyzed hydrothiolation[49] proceeded with good regioselectivity to give vinyl sulfide **105** in low yield, mainly due to the facile conversion of this intermediate to a mixture of enol ethers **104** under the reaction conditions.

Unfortunately, exposure of ketal **105** to a variety of Lewis acids led to hydrolysis, yielding ketone **107** in nearly all cases. The use of $InCl_3$,[50] however, delivered the desired Prins product **106** 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 **106** 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 retrosynthesis.

Scheme 1.12. *Model studies toward Prins cyclization*

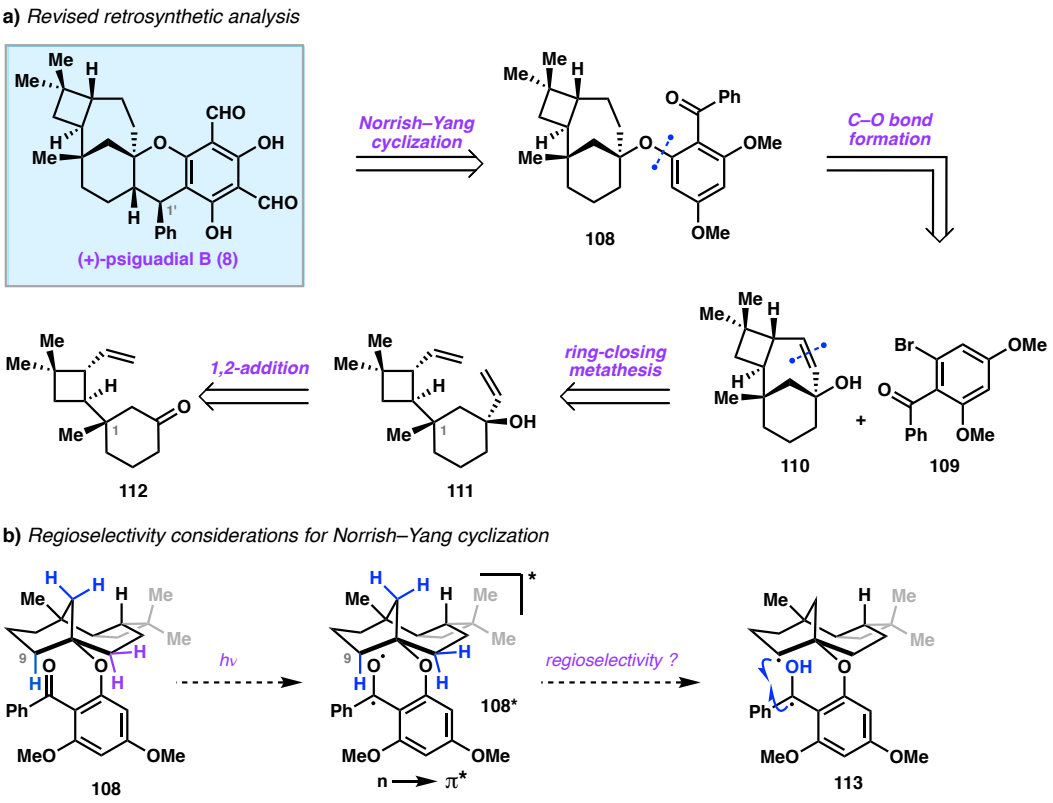


1.4.6 Second Generation Norrish-Yang Cyclization Strategy

In our revised retrosynthesis, we envisioned that the chroman substructure could be constructed via a modified Norrish–Yang cyclization,[51–53] revealing **108** as a key

intermediate (Scheme **1.13**). Benzophenones such as **108** are known to undergo photoexcitation upon irradiation with UV light to give triplet species (i.e. **108***) that can engage in Norrish type-II 1,5-hydrogen atom abstraction and subsequent radical recombination.[54–56] In the absence of any available γ or δ-hydrogens, it was hypothesized that **108*** could abstract a hydrogen atom from C9 to generate diradical **113**.[57–59] Recombination of the carbon-centered radicals would furnish the core of **8**.

Scheme 1.13. *Second generation retrosynthetic analysis*



We recognized that achieving the desired *regioselectivity* could prove challenging since the C7 and C12 methylenes in **108*** were also within range for 1,7-H–atom abstraction (Scheme 1.13b). 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.

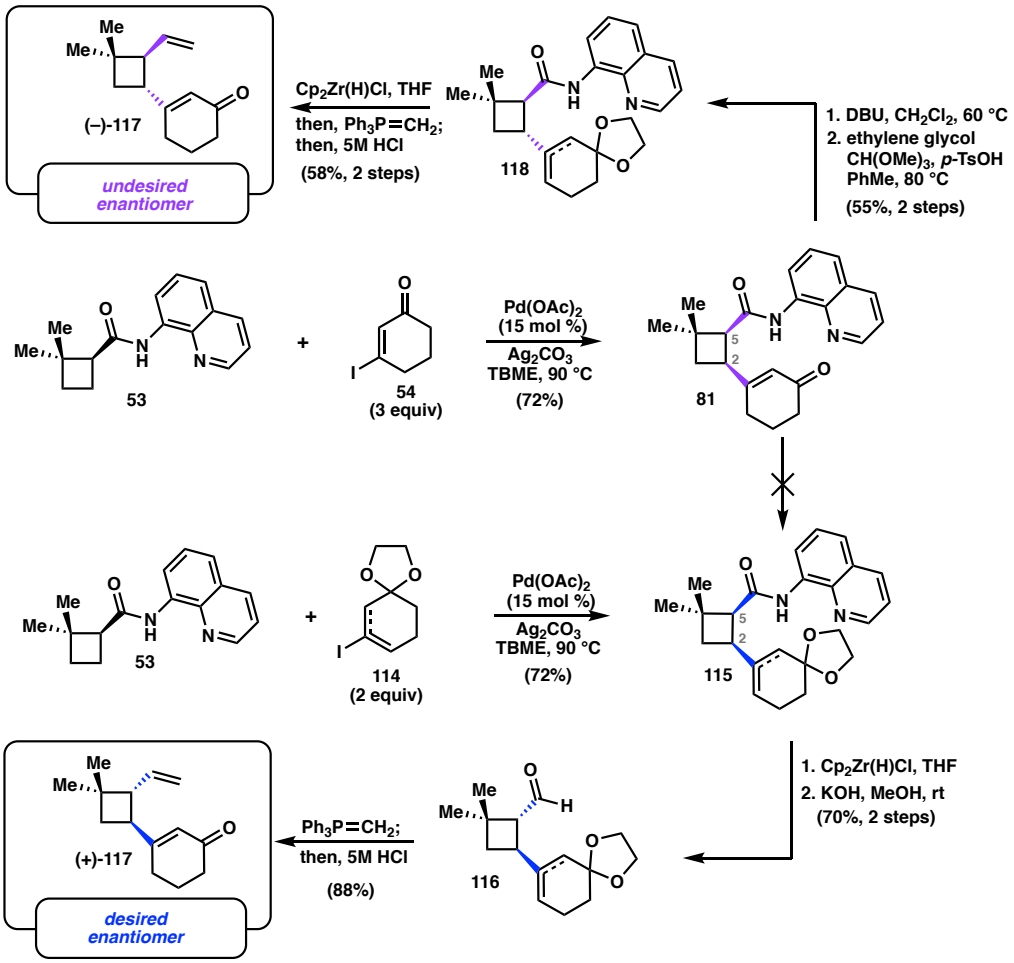
Moreover, this strategy was particularly appealing since it was expected that **108** could be assembled in an expedient and convergent fashion. Benzophenone **108** was envisioned to be accessible from tertiary alcohol **110** via an intermolecular *O*-arylation reaction with aryl bromide **109**.[60–63] We reasoned that the strained 7-membered ring in **110** could be formed by ring-closing metathesis, leading back to vinyl ketone **112**, 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 **112**, 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 **112** in the correct enantiomeric series from quinolinamide (–)-**53**. In terms of the latter challenge, we anticipated that the desired enantiomeric series could be accessed by epimerization of compounds derived from **53** (e.g. **81**) at C5 instead of C2 (Scheme **1.14**). A straightforward approach would involve disfavoring γ-deprotonation at C2 by masking the ketone of **81** in order to advance to a C5 epimerization substrate. Unfortunately, these efforts proved unfruitful, as ketalization of **81** under a variety of conditions always resulted in rapid epimerization at C2 to furnish *trans*-cyclobutane **118** in low yields.

Instead, it was recognized that **115** could be accessed directly by coupling **53** with vinyl iodide **114**. To our delight, the Pd-catalyzed coupling with vinyl iodide **114** performed even better than its enone counterpart (**54**), requiring only 2 equiv of **114** to furnish **115** in 72% yield on a gram scale. Exposure of **115** 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 **116** in 70% yield over the two steps. Gratifyingly, Wittig methylenation and hydrolysis provided (+)-**117**, the required enantiomer for synthesis of natural psiguadial B (**8**). In addition, cross-coupling of **114** eliminated a linear protection step and substantially improved the material throughput.

Scheme 1.14. *Development of enantiodivergent cross-coupling strategies*



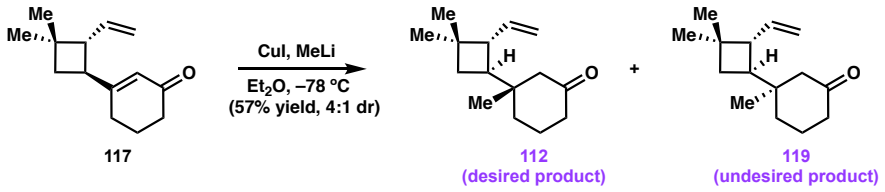
To demonstrate that either enantiomer of **117** can be prepared using a single enantiomer of organocatalyst, an alternative sequence was also developed. Epimerization of **81** to the *trans*-cyclobutane (**82**) under the previously developed conditions, followed by ketalization provided **118**. Reductive cleavage of the aminoquinoline auxiliary gave the

corresponding aldehyde (*ent*-**116**), which was telescoped through a Wittig olefination and hydrolysis as before to afford vinyl enone (−)-**117** in 58% yield over the two steps.

1.4.7 Development of a Catalytic Conjugate Addition

With the desired enantiomer of enone **117** in hand, attention turned to the installation of the C1 quaternary center using a catalytic asymmetric conjugate addition. While we were pleased we could observe high levels of the desired diastereomer using a chiral controller with substrate **82** (Scheme **1.8**), we hypothesized that high catalyst loadings were necessary because the aminoquinoline was sequestering the copper and therefore precluding catalyst turnover. After determining that we were no longer going to rely on using this moiety to direct the [4+2] reaction, we reasoned that installation of the quaternary methyl group after cleavage of the directing group could enable the development of a much more efficient conjugate addition, this time on a substrate lacking the strongly coordinating aminoquinoline.

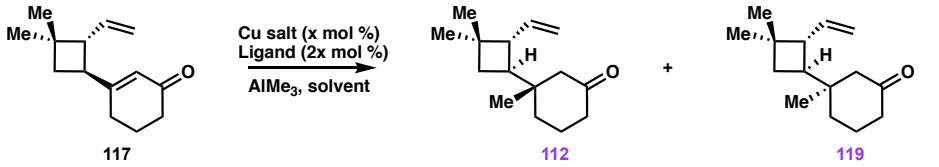
Scheme 1.15. *Assessing substrate-controlled diastereoselectivity*



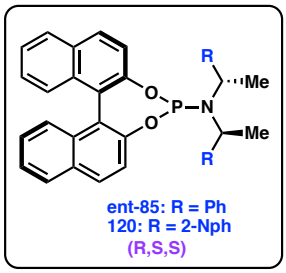
In order to assess the inherent selectivity for conjugate addition of **117**, we performed a conjugate addition of **117** using the achiral Gilman's reagent.[64] As with the original *trans*-cyclobutane **82**, we observed slight selectivity for the desired diastereomer. We hoped to enhance this intrinsic selectivity by exploring chiral copper catalysts reported by the Alexakis lab.[42,43]

Initial experiments performed to investigate our ability to *enhance* the intrinsic diastereoselectivity for the conjugate addition indicated improved diastereoselectivity, with significantly enhanced dr with the enantiomeric ligand (***ent*-85**) we had previously employed on the quinolinamidyl enone **82** (Table **1.2**, entries 1–5). We hoped that lowering the reaction temperature would restrict the conformational freedom of the sigma bond linking the cyclobutane and the cyclohexene rings and improve the dr; however, we found that the best balance of yield and diastereoselectivity was achieved at –30 ºC (Table **1.2**, entry 3). We hypothesize that the poorer reactivity observed at lower temperatures was due to decreased catalyst solubility.

Table 1.2. *Optimization and exploration a copper-catalyzed conjugate addition*



	entry	Cu source	Cu mol %	temp °C	solvent	dr (112 :119)	isolated yield
ent-85	1	CuTC	10	–30	Et_2O	9.9:1	51
	2	CuTC	15	–30	Et_2O	8.9:1	97
	3	CuTC	10	–78 to rt	Et_2O	9.9:1	62
	4	$(CuOTf)_2$·PhMe	10	–78 to –60	TBME/DME	8.7:1	75
	5	$(CuOTf)_2$·PhMe	15	–30	TBME	8.4:1	72
120	6	CuTC	10	–30	Et_2O	8.5:1	70
	7	CuTC	15	–30	Et_2O	6.9:1	95
	8	$(CuOTf)_2$·PhMe	15	–30	TBME	6.8:1	77
	9	$(CuOTf)_2$·PhMe	10	–30	Et_2O	6.9:1	86
	10	CuTC	10	–30	TBME/DME	7.2:1	84
	11	$(CuOTf)_2$·PhMe	10	–30	TBME/DME	7.1:1	82
	12	$(CuOTf)_2$·PhMe	10	–78 to –60	TBME/DME	6.5:1	85

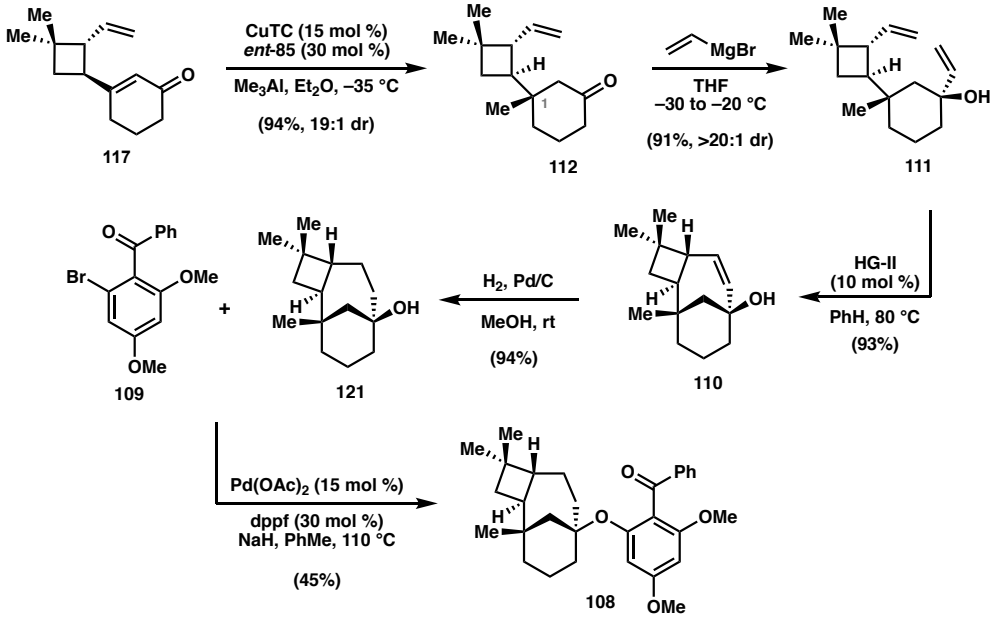


We also attempted to investigate the use of a bulkier ligand in order to further enhance the observed diastereoselectivity. We initially thought that extending the chiral information through the incorporation of a napthyl substituent would impart more diastereocontrol. Much to our surprise, the utilization of the bulkier (*R*,*S*,*S*)-configured **120**

failed to enhance the diastereoselectivity of the catalytic conjugate addition. We were unable to identify any conditions superior to the combination of CuTc and ***ent*-85** at –30 ºC, and we ultimately used these conditions to set the all carbon quaternary center for elaboration to psiguadial B (**8**).

1.4.8 Elaboration to a Norrish-Yang Substrate

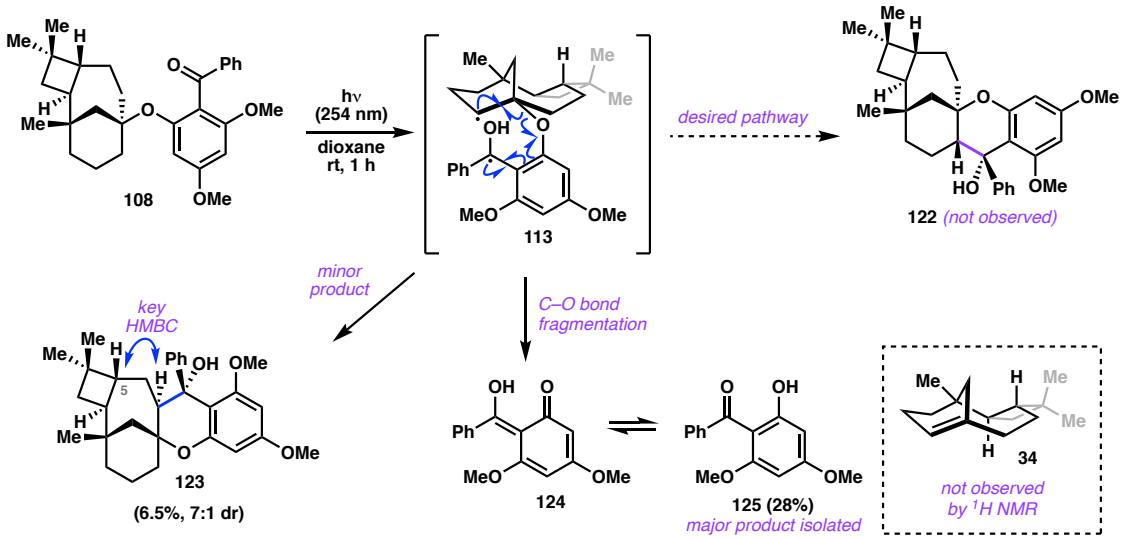
Scheme 1.16. *Elaboration to Norrish-Yang benzophenone*



Gratifyingly we were pleased to find that use of CuTC (15 mol %) in conjunction with ligand ***ent*-85** (30 mol %) provided **112** in 94% yield and 19:1 dr (Scheme **1.16**), providing superior results to what we had observed during reaction optimization. We hypothesize that this is due to improved stirring and more efficient cooling of the reaction in a flask rather than in a vial. Addition of vinyl Grignard to ketone **112** proceeded uneventfully, providing alcohol **111** in excellent yield and diastereoselectivity. Gratifyingly, exposure of **111** to second-generation Hoveyda–Grubbs catalyst at elevated temperature delivered bridged bicycle **110** in 93% yield. Subsequent hydrogenation under

standard conditions led to tertiary alcohol **121**. After some experimentation, we found that the combination of $Pd(OAc)_2$ and dppf catalyzed the intermolecular *O*-arylation between **121** and aryl bromide **109**, affording aryl ether **108** in 45% yield. Unfortunately, this transformation proved capricious, and attempts to improve the yield through further optimization were unsuccessful. Nevertheless, a sufficient amount of **108** was obtained to evaluate the key Norrish–Yang cyclization.

Scheme 1.17. *Evaluation of the Norrish-Yang cyclization*



With **108** in hand, we were poised to investigate the key Norrish-Yang cyclization event. Irradiation of **108** with 254 nm light in deoxygenated dioxane led to complete consumption of starting material within 1 hour and produced a complex mixture of new products. The formation of the undesired Norrish–Yang product **123** 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 **1.17**). Thus, while the anticipated *reactivity* was

observed, **123** results from the wrong *regioselectivity*, and was isolated in 6.5% yield—a result that would likely be difficult to substantially improve through reaction optimization.

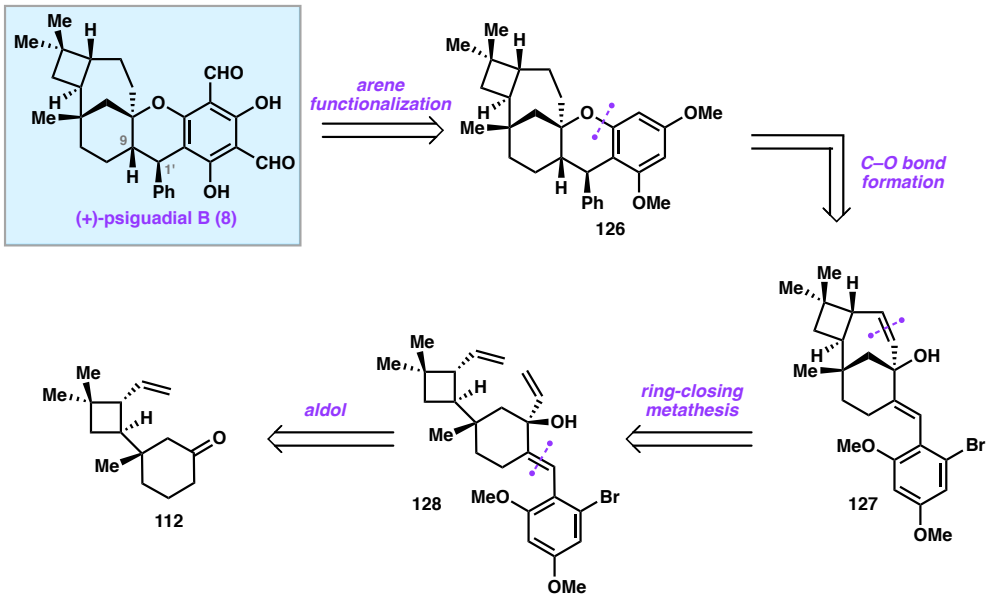
Notably, the major compound isolated from this reaction is phenol **125**, which was obtained in 28% yield. This side product presumably arises by fragmentation of diradical species **113** (or the diradical resulting from H-atom abstraction at C7), wherein C–O bond cleavage expels enol tautomer **124**; the resulting terpene-based fragment likely undergoes further decomposition, as alkene **34** or related compounds were not isolated. 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 **125** in all cases. Having determined that the late-stage Norrish–Yang cyclization was an untenable strategy to complete the chroman core of **8**, an alternative synthetic route was devised.

1.4.9 A Third Generation Strategy

While our previous strategies were unsuccessful in delivering **8**, we were pleased to see that we had established that we could form the challenging bicyclo[4.3.1]decane through a ring-closing metathesis reaction and that we could forge a difficult O-aryl bond under transition metal catalysis. With these key findings in mind, we sought to revise our synthetic plan (Scheme **1.18**). We simplified **8** to **126** and elected to construct the C9–C1' bond at an earlier stage (Scheme **1.16**). 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 **1.16**). This bond scission revealed aryl bromide **127**, 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 **112** and a suitable aldehyde.

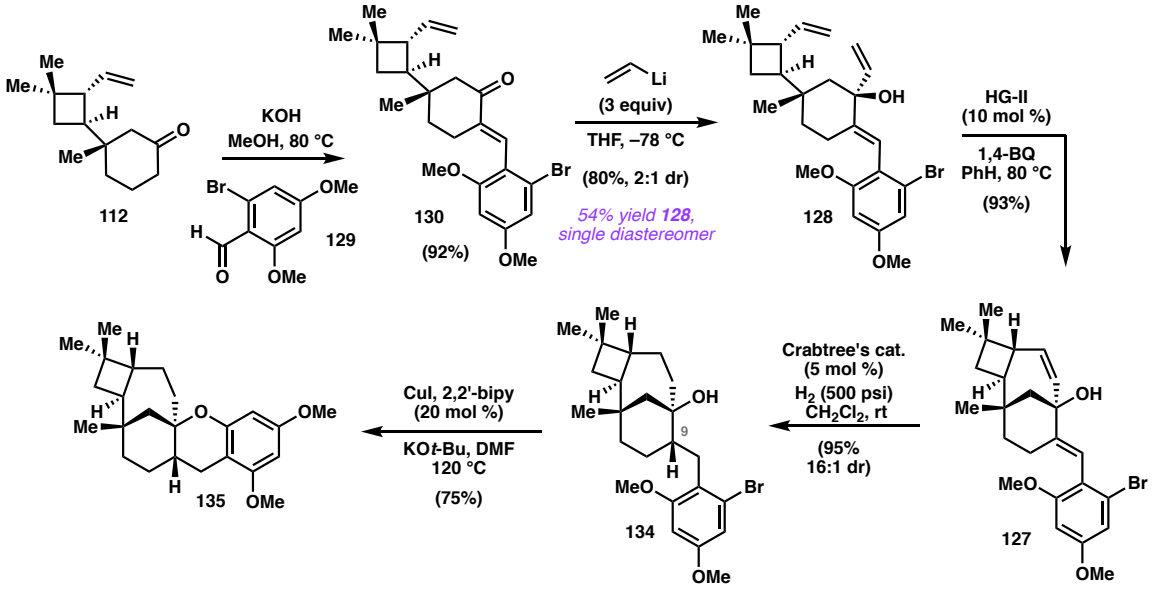
Scheme 1.18. *Our third generation retrosynthesis*



In the forward sense, a methanolic solution of vinyl ketone **112** and aldehyde **129** were treated with potassium hydroxide at elevated temperature to afford *exo*-enone **130** in 92% yield (Scheme **1.19**). In contrast to the previous system lacking substitution at C9 (i.e. **112**), 1,2-addition into this more sterically hindered ketone proved challenging. Treatment of **130** with vinyl magnesium bromide under the conditions used previously led to incomplete conversion—presumably due to competitive α-deprotonation—affording **128** (Scheme 1.20) in low yields and moderate diastereoselectivity. Attempts to improve conversion using Lewis acid activators gave higher yields of **128**, 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 **128** as a single diastereomer in 54% yield. The ring-closing metathesis

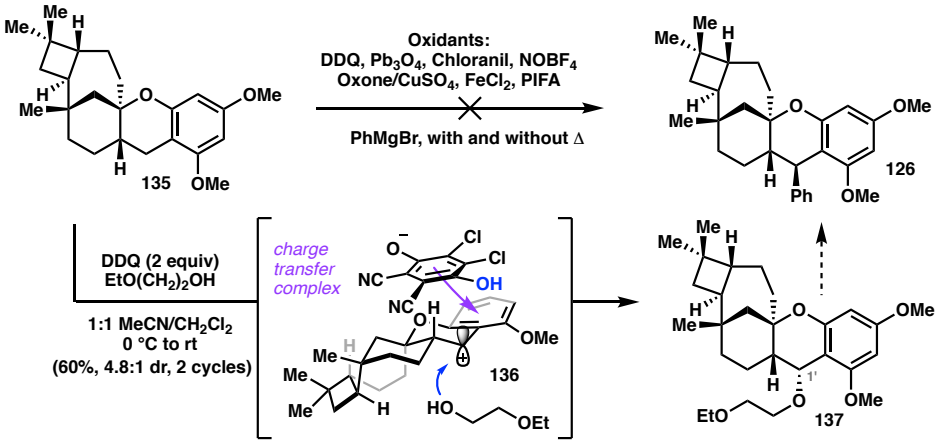
proceeded with equal efficiency on this new substrate to furnish **127** in 93% yield.

Scheme 1.19. *Synthesis of the core of (+)-psiguadial B*



With the strained sesquiterpene framework secured, both the di- and trisubstituted olefins in **127** were hydrogenated in the presence of Crabtree's catalyst, which engaged in a hydroxyl-directed reduction[65,66] to establish the C9 stereocenter with 16:1 dr, providing **134** in excellent yield. The final ring of the psiguadial framework was formed by a Cu-catalyzed intramolecular *O*-arylation reaction, furnishing pentacycle **135** in 75% yield.[67]

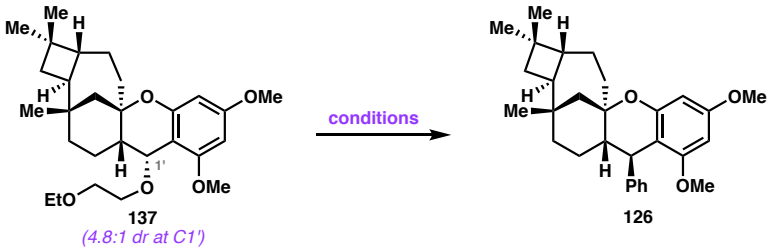
Scheme 1.20. *Attempts to install functionality at C1′*



With the successful development of a scalable and high-yielding route to **135**, the task of appending the C1' phenyl group was now at hand. Ideally, the electron rich arene in **135** 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,[33,68–70] 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,[33,70–72] Chloranil, Pb_3O_4, [30] Oxone/$CuSO_4$,[69] and $NOBF_4$[73,74]), followed by trapping with benzene, PhMgBr, or $PhB(OH)_2$, all without success (Scheme **1.20**). Efforts to apply Shi's $FeCl_2$-catalyzed benzylic dehydrogenative arylation,[75] or Muramatsu's C(sp^3)–H arylation using DDQ and PIFA[76] were also unfruitful.

Having failed to achieve a direct arylation, a stepwise protocol was employed. Oxidation with DDQ in the presence of ethoxyethanol[71,72] afforded **137**—a relatively stable product—which could be isolated in modest yields (Scheme **1.20**). 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 helps stabilize the intermediate benzylic cation (i.e. **136**), favoring more efficient trapping with ethoxyethanol over unproductive side reactions. Synthetically useful yields of **137** were obtained under these conditions by re-subjecting recovered **135** to the reaction conditions a second time.

Table 1.3. *Investigation of the C1′ phenylation*



137 *(4.8:1 dr at C1′)* **126**

entry	Lewis acid or catalyst	nucleophile	solvent	T (°C)	yield (dr)
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	$BF_3{\cdot}OEt_2$	$PhBF_3K$	CH_2Cl_2	0 to 25	0
7	$BF_3{\cdot}OEt_2$	$PhBF_3K$	MeCN	0 to 25	0
8	$BF_3{\cdot}OEt_2$	$Ph_2Cu(CN)Li$	Et_2O	–78 to 0	99 (1.7:1)
9	$BF_3{\cdot}OEt_2$	$Ph_2Cu(CN)Li$	Et_2O	–78 to –45	90 (2.0:1)
10	$BF_3{\cdot}OEt_2$	$Ph_2Cu(CN)Li$	Et_2O	–78 to –60	57 (3.3:1)

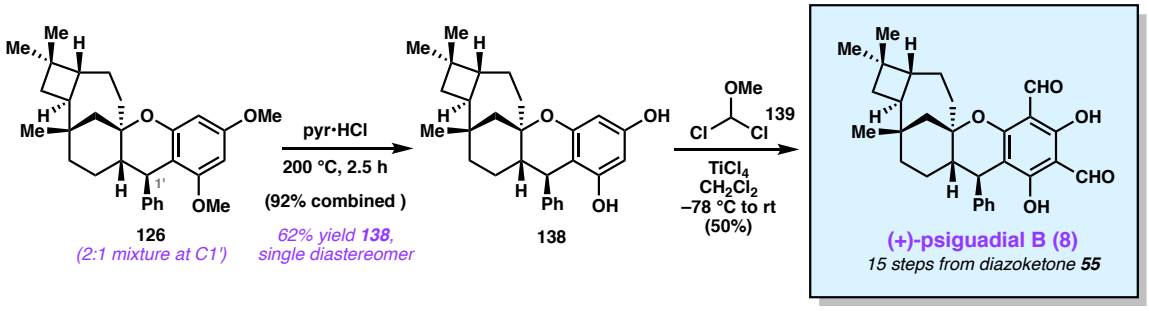
With respect to the stereochemistry at C1', **137** was isolated as a 4.8:1 mixture of diastereomers, favoring the α-disposed ether. Conformational analysis of **135** indicates that the 7-membered ring protrudes from the bottom face of the molecule, suggesting that C–O bond formation appears to proceed 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 **135** to form a tightly bound charge-transfer complex (i.e. **136**).[31] If this complex remains closely associated, ethoxyethanol would then attack from the bottom face, thus leading to α-ether **137** 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 **1.3**, entries 1 and 2).[72] Simple heating[77] or nickel-catalyzed Kumada coupling with PhMgBr in PhMe[78–80] 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 **126** (entries 6 and 7).[81,82] We were therefore delighted to obtain a near quantitative yield of **126** (in 1.7:1 dr) by treating a mixture of **137** and lithium diphenylcyanocuprate with BF_3•OEt_2 (entry 8).[83,84] 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 **126** 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 **1.21**). At this stage, the diastereomeric resorcinols were readily separable by column chromatography, providing **138** as a single diastereomer in 62% yield. Finally, the remaining two aryl aldehydes were simultaneously installed using Rieche formylation conditions,[85–87] delivering (+)-psiguadial B (**8**) in 50% yield. Synthetic **8** was found to be spectroscopically identical in all respects to the natural sample reported by Shao et al.[15]

Scheme 1.21. *Completion of the synthesis of (+)-psiguadial B*



1.5 CONCLUDING REMARKS

In summary, the first enantioselective total synthesis of the cytotoxic natural product, (+)-psiguadial B (**8**), was achieved in 15 steps from diazoketone **55**. 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 **53**, 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 **8** 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 **8** may enable the synthesis of unnatural analogs of **3**, which 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.

1.6 EXPERIMENTAL SECTION

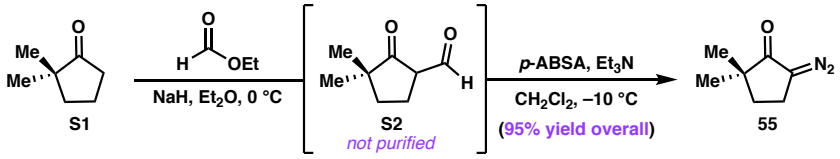
1.6.1 Materials and Methods

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), *tert*-butyl methyl ether (TBME), benzene (PhH), and toluene (PhMe) were dried by passing through activated alumina columns. Triethylamine (Et_3N), N,N-diisopropylethylamine (DIPEA), and methanol (MeOH) was 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.[88] using silica gel (particle size 0.032-0.063) purchased from Silicycle or using pre-packaged 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, $\delta = 7.26$) and $CDCl_3$ (^{13}C, $\delta = 77.1$), C_6H_5 (^1H, $\delta = 7.16$) and C_6D_6 (^{13}C, $\delta = 128$), or d_8-THF (^1H, $\delta = 3.58$) and (^{13}C, $\delta = 67.6$). 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, or obtained from the Caltech Mass Spectral Facility in fast-atom bombardment mode (FAB). Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system with a Chiralcel AD-H column (4.6 mm x 25 cm).

1.6.2 Preparative Procedures and Spectroscopic Data

1.6.2.1 Preparation of Diazoketone Substrates



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 (**S1**)[89] (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.[90] 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 $MgSO_4$, filtered, and concentrated *in vacuo* into a 500 mL round-bottom flask.[91,92]

The crude formyl ketone **S2** 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[1] (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 H2O 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 **55** (17.4 g, 95% yield) as a bright yellow oil.

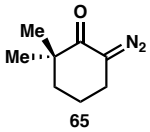
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.88 (t, *J* = 7.0 Hz, 2H), 1.77 (t, *J* = 7.2 Hz, 2H), 1.04 (d, *J* = 1.0 Hz, 6H).; **^{1}H NMR** (400 MHz, d_8-THF) δ 2.94 (t, *J* = 7.0 Hz, 2H), 1.79 (t, *J* = 7.2 Hz, 2H), 1.04 (s, 6H).

^{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.$^{-1}$

HRMS (MM) calc'd for $C_7H_{11}N_2O$ $[M+H]^+$ 139.0866, found 139.0860.

Diazoketones **65–68** were prepared according to the above procedure. Spectroscopic data for **67** and **68** are consistent with that reported in the literature.[93–95]



65

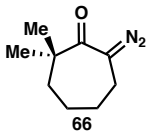
65: Yellow Oil, (1.76 g, 36% yield over 2 steps)

^{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.



66

66: 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).

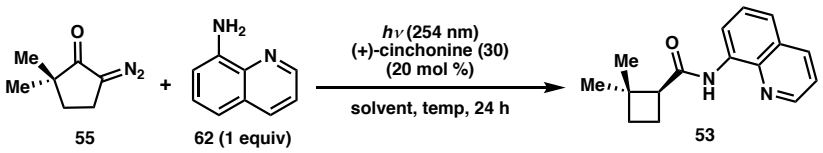
^{13}C NMR (101 MHz, $CDCl_3$) δ 202.2, 68.3, 47.0, 37.9, 29.5, 25.8, 25.7, 25.6.

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.

1.6.2.2 Small-scale screening protocol for enantioenriched amides 53, 69–72.

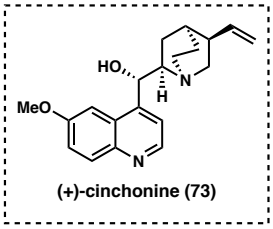
Oven-dried quartz tubes were each charged with aminoquinoline (**62**) (21.6 mg, 0.150 mmol, 3.00 equiv) and catalyst (50 mol %). Inside a N_2-filled glovebox, diazoketones **55**, **65**–**67** (0.05 mmol) were then added to each as a solution in 0.500 mL THF (excluding diazoketone **68**, which was 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 **53, 69–72** in varying yields and enantiopurities.



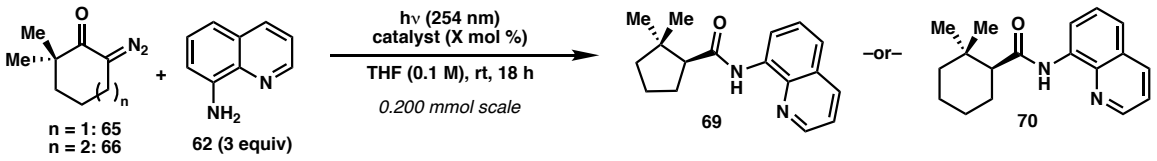
55 62 (1 equiv) 53

entry	solvent	temp °C	vessel	atm	% yield[a]	% ee[b]
1	THF	25	quartz	N_2	63	79
2	DMF	25	quartz	N_2	76	50
3	CH_2Cl_2	25	quartz	N_2	62	47
4	toluene	25	quartz	N_2	65	59
5	dioxane	25	quartz	N_2	69	79
6	MeCN	25	quartz	N_2	43	74
7	THF	0	quartz	N_2	28	79
8	THF	25	quartz	air	18	75
9	THF	25	quartz	CO	33	69
10	THF	25	vycor	N_2	29	79
11	THF	25	pyrex	N_2	20	75

[a] Determined by ^{1}H NMR via integration relative to an added internal standard, isolated yield provided in parentheses. [b] Determined by SFC using a chiral stationary phase.

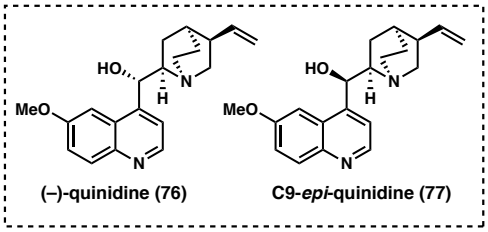


(+)-cinchonine (73)

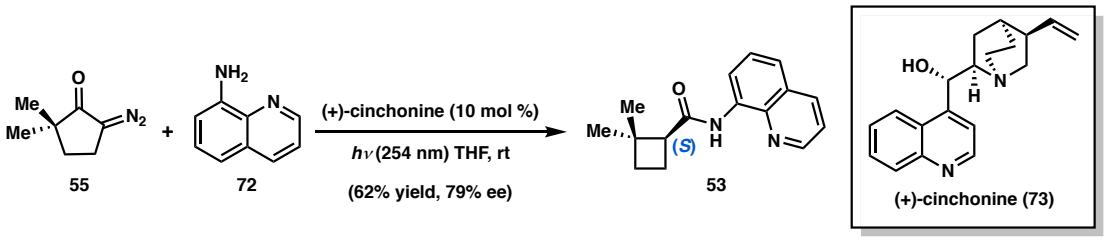


entry	diazo.	catalyst (mol %)	product	% yield[a] (isolated)	%ee[b]
1	65	77 (50)	69	78 (73)	71
2	65	77 (30)	69	73 (81)	69
3	65	77 (20)	69	84 (76)	67
4	65	77 (10)	69	82 (81)	63
5	66	76 (50)	70	57 (66)	73
6	66	76 (30)	70	66 (71)	66
7	66	76 (20)	70	66 (61)	62
8	66	76 (10)	70	62 (61)	55

[a] Determined by ^{1}H NMR via integration relative to an added internal standard, isolated yield provided in parentheses. [b] Determined by SFC using a chiral stationary phase.

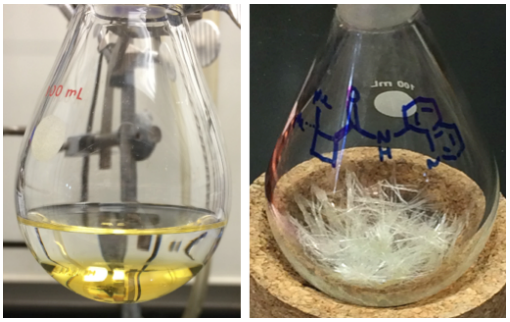


1.6.2.3 Large-scale preparation of enantioenriched amides.



To a flame-dried, 1 L quartz flask was added 8-aminoquinoline (**72**) (12.9 g, 89.5 mmol, 3.00 equiv) and (+)-cinchonine (**73**) (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 **55** (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).[96] 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 **53** (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 **53** 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 **53** as white needles. The supernatant was concentrated under reduced pressure and this process was repeated again to provide additional **53** (3.50 g total, 83% recovery of theoretical total of the desired enantiomer, 46% overall from **55**). Melting point: 66–68 ºC.

$[\alpha]_D^{25.0}$ = –109° (c = 0.720, $CHCl_3$).

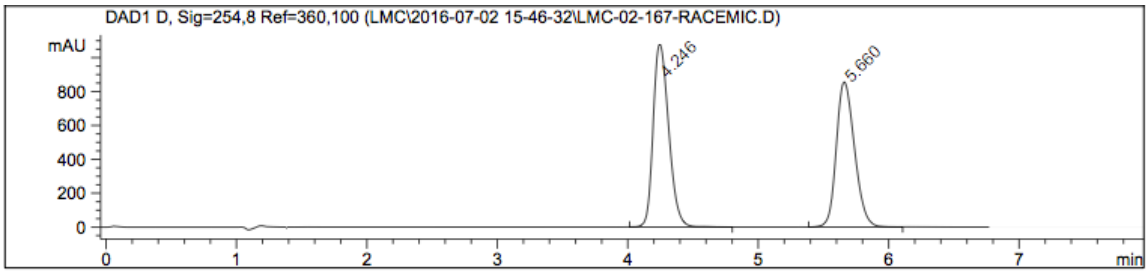
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 8.80 (t, *J* = 1.8 Hz, 1H), 8.79 (dd, *J* = 13.6, 1.6 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.52 (q, *J* = 8.2, 7.5 Hz, 1H), 7.48 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 3.07 (ddd, *J* = 9.1, 8.2, 0.9 Hz, 1H), 2.48 (dq, *J* = 11.4, 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.$^{-1}$

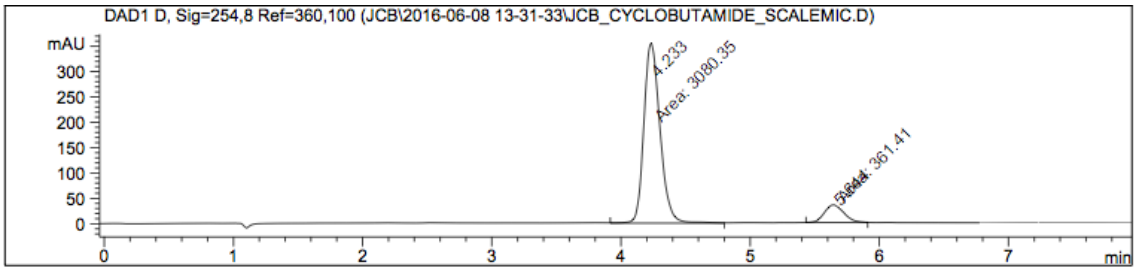
HRMS (MM) calc'd for $C_{16}H_{19}N_2O$ $[M+H]^+$ 255.1492, found 255.1501.

SFC data for racemic 53:



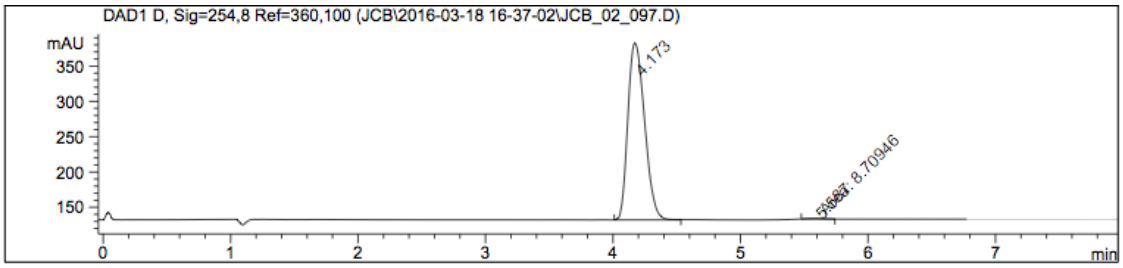
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.246	BB	0.1286	8934.03320	1078.74268	51.8271
2	5.660	BB	0.1532	8304.11426	855.84570	48.1729

Enantioenriched 53 isolated directly from reaction:

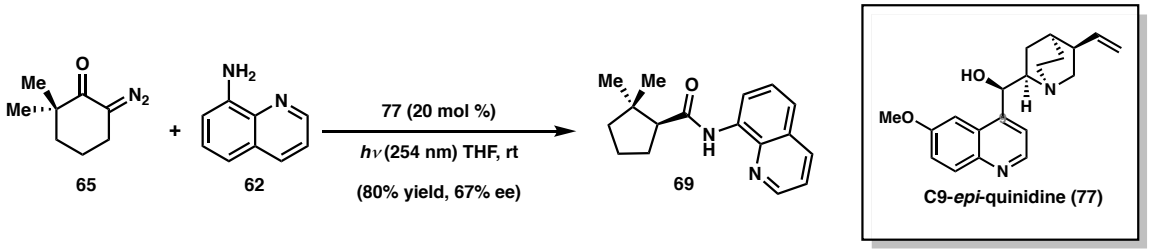


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.233	MM	0.1444	3080.35034	355.58780	89.4993
2	5.644	MM	0.1739	361.41000	34.64573	10.5007

Enantiopure 53 after a single recrystallization:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	4.173	BB	0.1464	2285.16455	250.58836	99.6203
2	5.587	MM	0.1518	8.70946	9.55969e-1	0.3797



0.2 mmol scale: Inside a N_2 filled glovebox, an oven-dried quartz tube was charged with aminoquinoline (**62**) (86.5 mg, 0.600 mmol, 3.00 equiv) and (**77**) (32.5 mg, 0.100 mmol, 0.500 equiv). Diazoketone (**65**) (33.2 mg, 0.200 mmol, 1.00 equiv) was added as a solution in 2.000 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 **69** (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 CO_2, λ = 254 nm): t_R (major) = 4.28 min, t_R (minor) = 5.41 min.

1.0 mmol scale: Inside a N_2 filled glovebox, an oven-dried quartz tube was charged with aminoquinoline (**62**) (432.5 mg, 3.000 mmol, 3.00 equiv) and (**77**) (64.9 mg, 0.200 mmol, 0.200 equiv). Diazoketone (**65**) (166.2 mg, 1.000 mmol, 1.00 equiv) was added as a solution in 2.50 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 **69** (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 CO_2, λ = 254 nm): t_R (major) = 4.28 min, t_R (minor) = 5.41 min.

$[\alpha]_D^{25.0}$ = –32.5° (c = 2.075, $CHCl_3$).

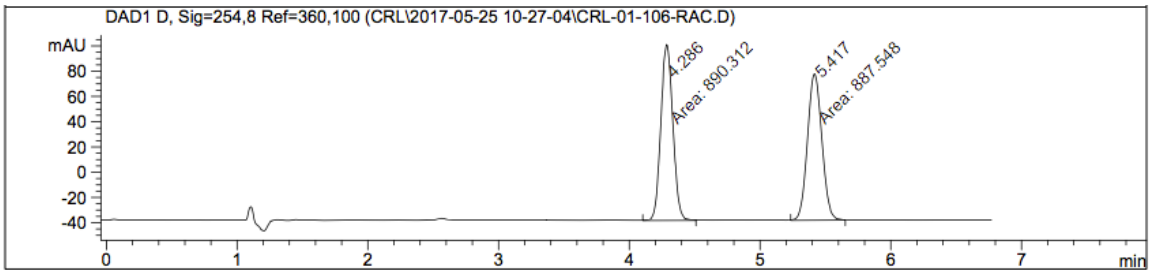
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 8.81 (d, *J* = 1.7 Hz, 1H), 8.80 (dd, *J* = 3.0, 1.7 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.57 – 7.47 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.61 (t, *J* = 8.4 Hz, 1H), 2.38 – 2.22 (m, 1H), 2.02 (dtd, *J* = 13.2, 8.5, 4.4 Hz, 1H), 1.95 – 1.82 (m, 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.$^{-1}$

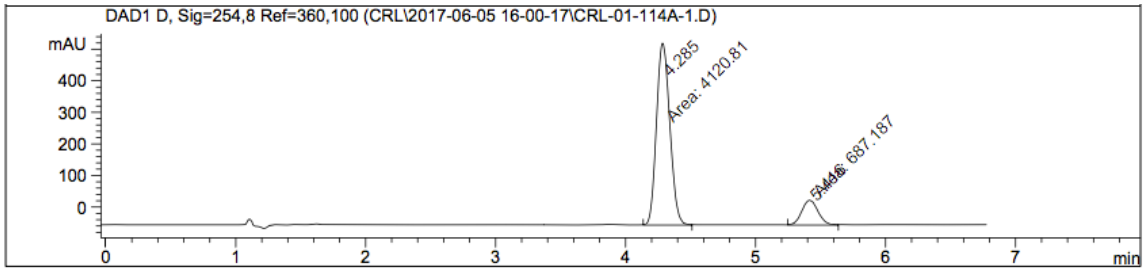
HRMS (MM) calc'd for $C_{17}H_{21}N_2O$ $[M+H]^+$ 269.1648, found 269.1645.

SFC data for racemic 69:



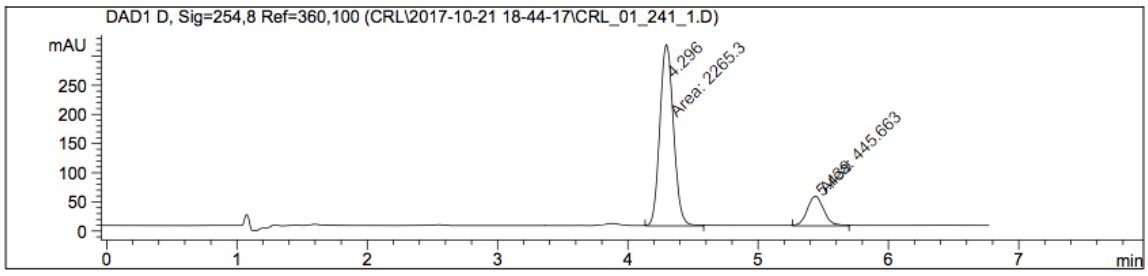
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	4.286	MM	0.1063	890.31165	50.0777
2	5.417	MM	0.1274	887.54810	49.9223

Enantioenriched 69:

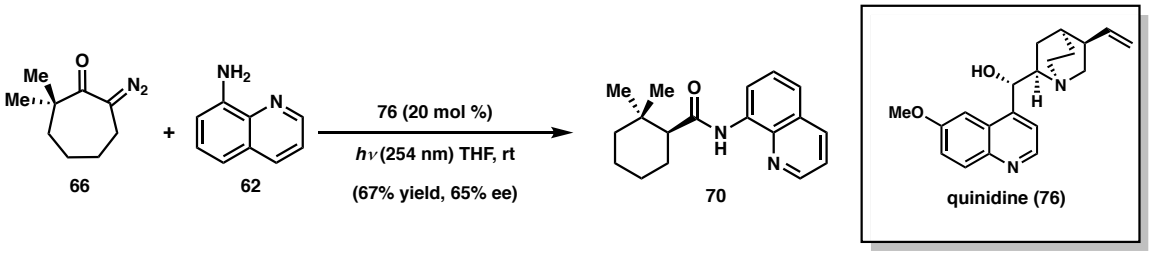


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	4.285	MM	0.1189	4120.80518	85.7074
2	5.416	MM	0.1449	687.18732	14.2926

Enantioenriched 69 using 20 mol % catalyst loading:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	4.296	MM	0.1212	2265.30225	83.5607
2	5.439	MM	0.1461	445.66309	16.4393



0.2 mmol scale: Inside a N_2 filled glovebox, an oven-dried quartz tube was charged with 8-aminoquinoline (**62**) (86.5 mg, 0.600 mmol, 3.00 equiv) and (**76**) (32.5 mg, 0.100 mmol, 0.500 equiv). Diazoketone (**66**) (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 **70** (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 CO_2, λ = 254 nm): t_R (major) = 9.67 min, t_R (minor) = 10.34 min.

1.0 mmol scale: Inside a N_2 filled glovebox, an oven-dried quartz tube was charged with 8-aminoquinoline (**62**) (432.5 mg, 3.000 mmol, 3.00 equiv) and (**76**) (64.9 mg, 0.200 mmol, 0.200 equiv). Diazoketone (**66**) (152.2 mg, 1.000 mmol, 1.00 equiv) was added as a solution in 2.50 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 **70** (189 mg, 67% yield) as a brown oil.

The enantiomeric excess was determined to be 65% by chiral SFC analysis (AD-H, 2.5 mL/min, 20% IPA in CO_2, λ = 254 nm): t_R (major) = 9.67 min, t_R (minor) = 10.34 min. $[\alpha]_D^{25.0}$ = –17.3° (c = 1.68, $CHCl_3$).

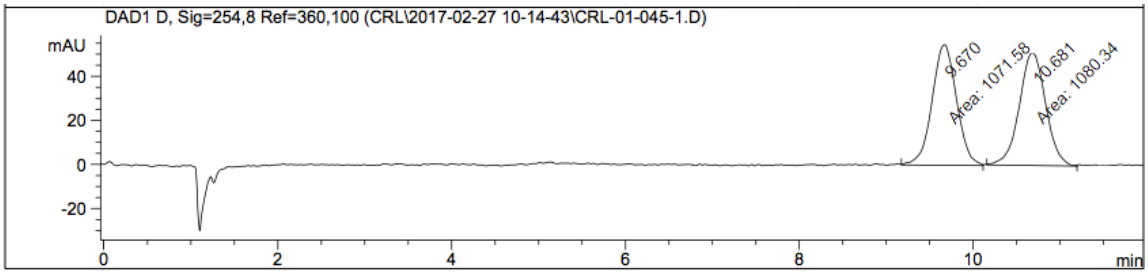
^{1}H NMR (400 MHz, CDCl3) δ 9.79 (s, 1H), 8.82 (d, *J* = 1.7 Hz, 1H), 8.80 (dd, *J* = 2.7, 1.7 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.57 – 7.47 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.30 (dd, *J* = 11.8, 3.5 Hz, 1H), 1.99 – 1.78 (m, 3H), 1.55 – 1.47 (m, 2H), 1.39 – 1.27 (m, 3H), 1.13 (s, 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.$^{-1}$

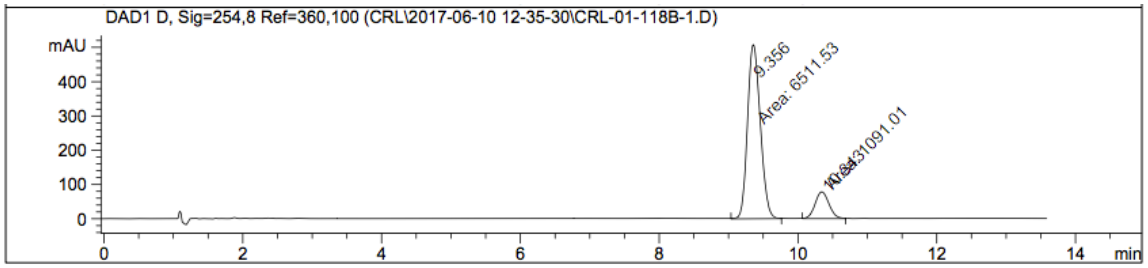
HRMS (MM) calc'd for $C_{18}H_{23}N_2O$ $[M+H]^+$ 283.1805, found 283.1796.

SFC data for racemic 70:



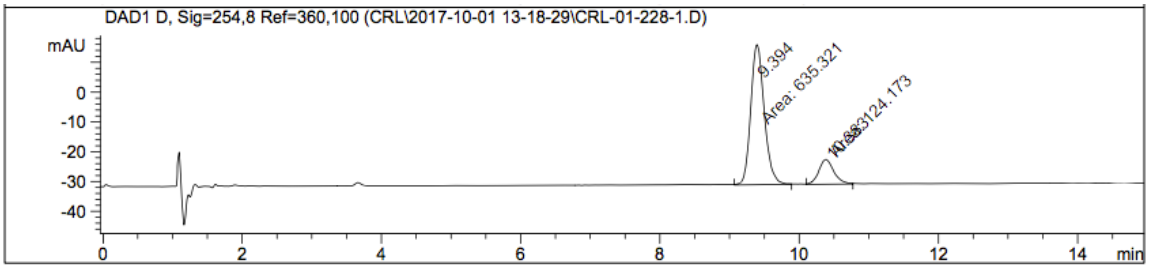
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	9.670	MM	0.3268	1071.58496	49.7965
2	10.681	MM	0.3511	1080.34424	50.2035

Enantioenriched 70:

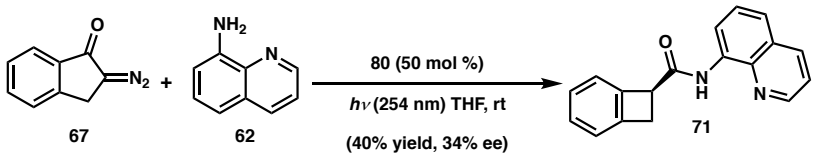


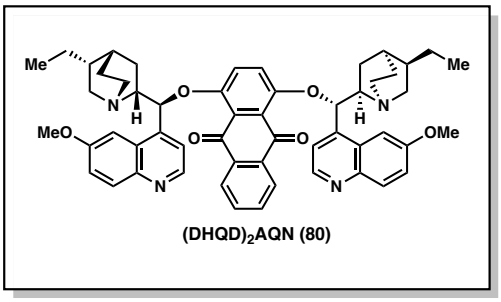
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	9.356	MM	0.2135	6511.52734	85.6494
2	10.343	MM	0.2316	1091.00696	14.3506

Enatioenriched 70 using 20 mol % catalyst loading:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	9.394	MM	0.2252	635.32117	83.6505
2	10.383	MM	0.2495	124.17338	16.3495





Inside a N_2 filled glovebox, an oven-dried quartz tube was charged with aminoquinoline (**62**) (86.5 mg, 0.600 mmol, 3.00 equiv) and (**80**) (85.7 mg, 0.100 mmol, 0.500 equiv). Diazoketone (**67**) (31.6 mg, 0.200 mmol, 1.00 equiv) was added as a solution in 0.500 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 18 hours. The reaction mixture was then concentrated *in vacuo*. The crude residue was purified via silica gel flash chromatography (0–1% Et_2O/CH_2Cl_2) to afford **71** (21.9 mg, 40% yield) as a white solid. The enantiomeric excess was determined to be 34% by chiral SFC analysis (AD-H, 2.5 mL/min, 20% IPA in CO_2, λ = 254 nm): t_R (major) = 5.06 min, t_R (minor) = 6.89 min.

$[\alpha]_D^{25.0}$ = –4.1° (c = 0.565, $CHCl_3$).

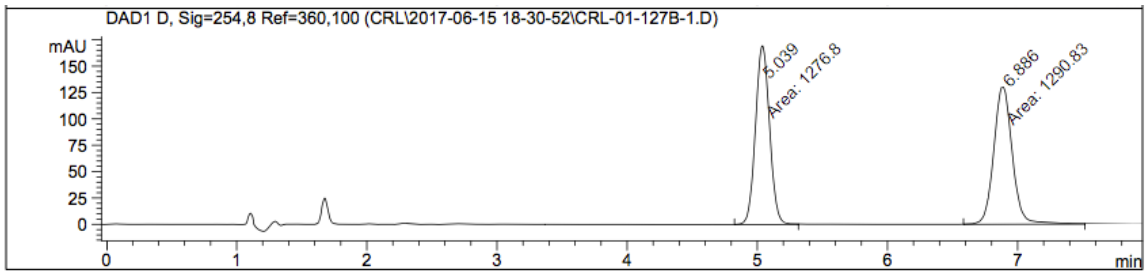
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.21 (s, 1H), 8.79 (dd, *J* = 11.5, 1.7 Hz, 1H), δ 8.78 (d, *J* = 1.7 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.54 (dd, *J* = 8.3, 7.2 Hz, 1H), 7.50 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.46 – 7.41 (m, 2H), 7.38 – 7.29 (m, 2H), 7.22 – 7.16 (m, 1H), 4.56 (ddt, *J* = 5.8, 2.9, 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, CDCl3) 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.$^{-1}$

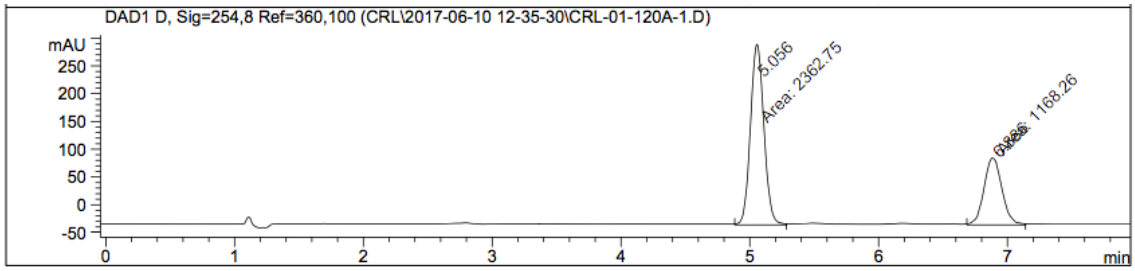
HRMS (MM) calc'd for $C_{18}H_{15}N_2O$ $[M+H]^+$ 275.1179, found 275.1178.

SFC data for racemic 71:

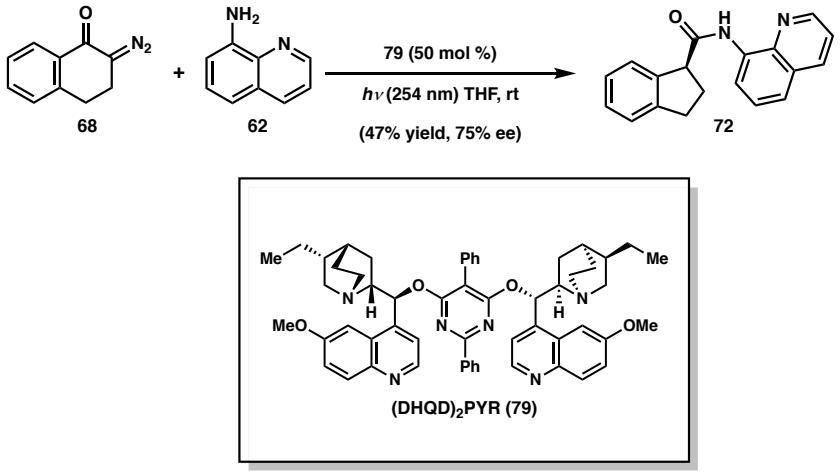


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.039	MM	0.1254	1276.80469	49.7268
2	6.886	MM	0.1641	1290.83447	50.2732

Enantioenriched 71:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	5.056	MM	0.1210	2362.74805	66.9143
2	6.886	MM	0.1605	1168.25940	33.0857



An oven-dried quartz tube was charged with diazoketone (**68**) (34.4 mg, 0.200 mmol, 1.00 equiv). The tube was brought into a N_2 filled glovebox, and subsequently charged with aminoquinoline (**62**) (86.5 mg, 0.600 mmol, 3.00 equiv) and (**79**) (88.1 mg, 0.100 mmol, 0.500 equiv). The mixture was suspended in 0.500 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 **72** (27.1 mg, 47% yield) as a brown oil. The enantiomeric excess was determined to be 75% by chiral SFC analysis (AD-H, 2.5 mL/min, 20% IPA in CO_2, λ = 254 nm): t_R (major) = 5.73 min, t_R (minor) = 4.86 min.

$[\alpha]_D^{25.0}$ = 65.0° (c = 0.91, $CHCl_3$).

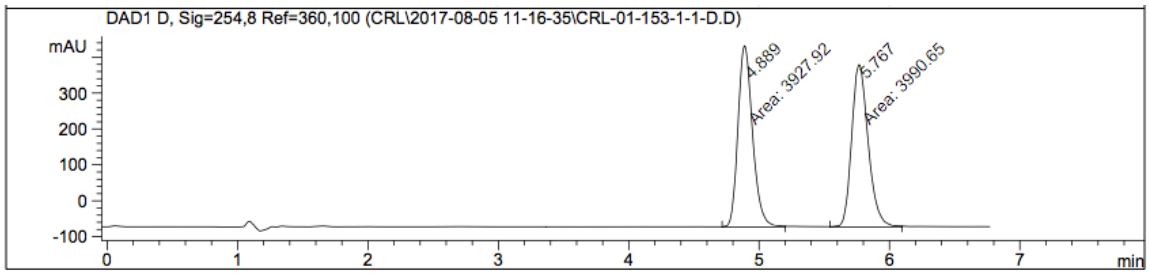
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 8.79 (dd, *J* = 7.1, 1.9 Hz, 1H), 8.75 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.56 – 7.46 (m, 3H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.33 (d, *J* = 7.2 Hz, 1H), 7.31 – 7.18 (m, 2H), 4.27 (dd, *J* = 8.4, 6.1 Hz, 1H), 3.23 (dt, *J* = 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.$^{-1}$

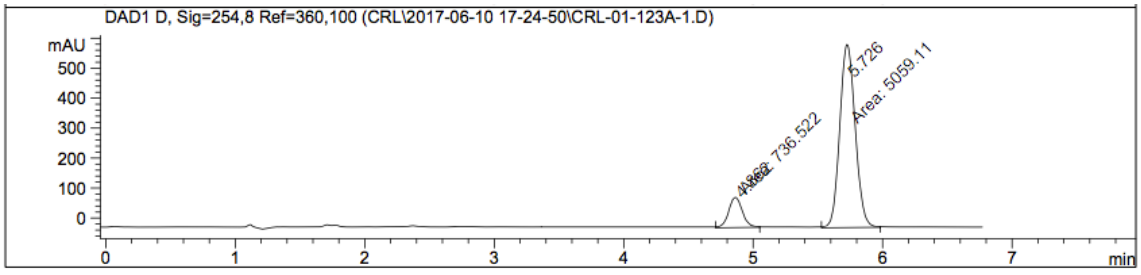
HRMS (MM) calc'd for $C_{19}H_{17}N_2O$ $[M+H]^+$ 289.1335, found 289.1334.

SFC data for racemic 72:

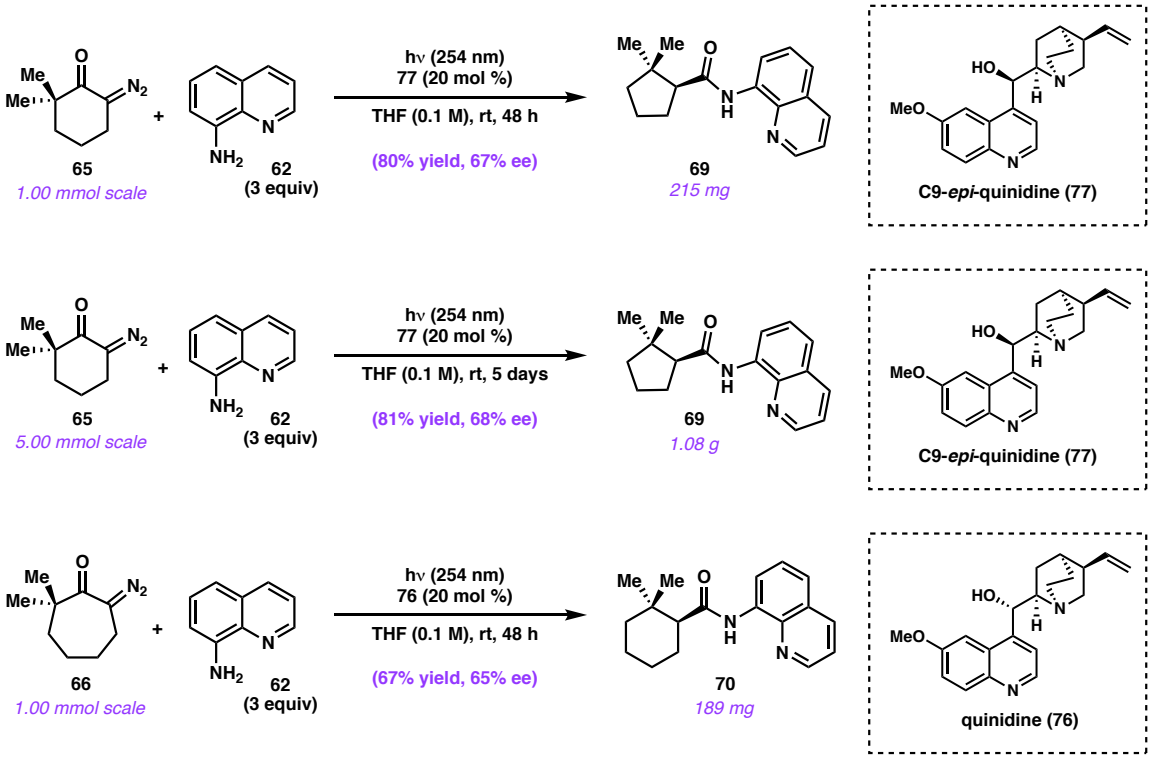


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	4.889	MM	0.1294	3927.92065	49.6039
2	5.767	MM	0.1468	3990.65186	50.3961

Enantioenriched 72:

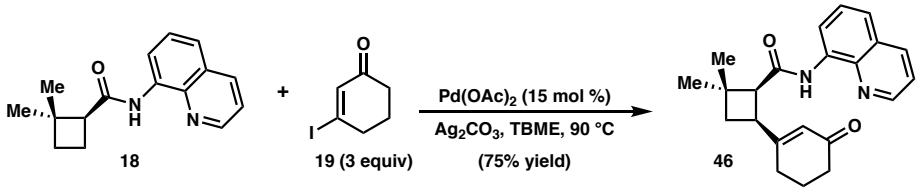


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Area %
1	4.862	MM	0.1218	736.52246	12.7082
2	5.726	MM	0.1379	5059.11182	87.2918


Me
Me
O
N2
65
1.00 mmol scale
+
NH2
N
62
(3 equiv)
hν (254 nm)
77 (20 mol %)
THF (0.1 M), rt, 48 h
(80% yield, 67% ee)
Me
Me
O
N
H
N
69
215 mg
HO
MeO
N
H
C9-epi-quinidine (77)
65
5.00 mmol scale
62
(3 equiv)
hν (254 nm)
77 (20 mol %)
THF (0.1 M), rt, 5 days
(81% yield, 68% ee)
69
1.08 g
C9-epi-quinidine (77)
66
1.00 mmol scale
62
(3 equiv)
hν (254 nm)
76 (20 mol %)
THF (0.1 M), rt, 48 h
(67% yield, 65% ee)
70
189 mg
quinidine (76)

1.6.2.4 Synthetic Procedures Toward (+)-Psiguadial B.

Preparation of *cis*-cyclobutane 81.



To a flame-dried 150 mL pressure vessel were added cyclobutane **53** (2.87 g, 11.3 mmol), vinyl iodide (**54**)[97] (7.50 g, 33.8 mmol, 3.00 equiv), $Pd(OAc)_2$ (379 mg, 1.69 mmol, 0.150 equiv), and Ag_2CO_3 (3.11 g, 11.3 mmol, 1.00 equiv). The reagents were suspended in TBME (56.0 mL) and the vessel sealed under ambient conditions. The reaction was heated to 90 °C for 16 hours, then cooled to room temperature and filtered over a pad of celite. The filtrate was concentrated directly onto celite and purified by silica gel flash chromatography (20–40% EtOAc/hexane) to afford *cis*-cyclobutane **81** (2.95 g, 75% yield) as a pale yellow foam.

$[\alpha]_D^{25.0}$ = +84.4° (c = 0.350, $CHCl_3$).

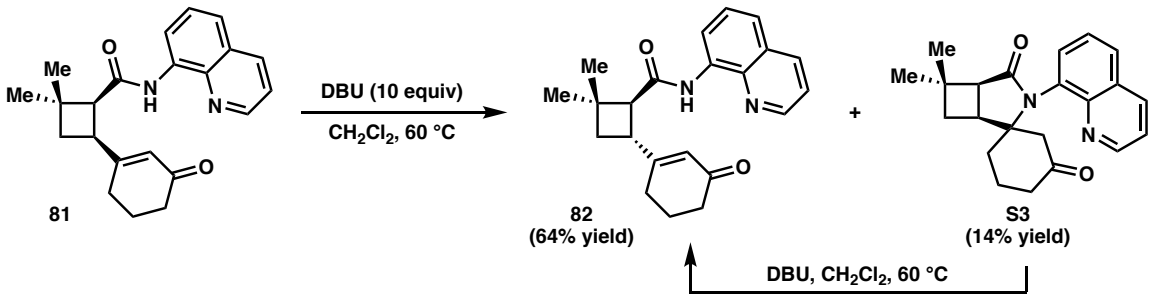
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73 (s, 1H), 8.78 (dd, *J* = 12.4, 2.1 Hz, 1H), 8.78 (t, *J* = 1.8 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.51 (dd, *J* = 8.3, 5.0 Hz, 1H), 7.50 (d, *J* = 0.9 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.00 (q, *J* = 1.6 Hz, 1H), 3.45 (ddddd, *J* = 10.8, 8.5, 7.6, 2.1, 1.0 Hz, 1H), 3.27 (ddd, *J* = 8.8, 2.8, 0.8 Hz, 1H), 2.48 (t, *J* = 10.8 Hz, 1H), 2.31 (ddd, *J* = 7.5, 5.7, 3.5 Hz, 2H), 2.20 (qd, *J* = 6.0, 5.5, 1.1 Hz, 2H), 2.01 (ddd, *J* = 11.0, 8.3, 2.8 Hz, 1H), 1.95 – 1.84 (m, 2H), 1.46 (s, 3H), 1.13 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.5, 170.2, 166.5, 148.3, 138.4, 136.3, 134.4, 127.9, 127.4, 124.9, 121.6, 121.5, 116.5, 56.9, 37.5, 37.5, 36.8, 35.7, 29.9, 27.8, 24.9, 22.6.

FTIR (NaCl, thin film) 3348, 2929, 2865, 1662, 1623, 1595, 1576, 1522, 1485, 1424, 1386, 1347, 1322, 1258, 1191, 1165, 1132, 827, 793 cm.$^{-1}$

HRMS (MM) calc'd for $C_{22}H_{25}N_2O_2$ $[M+H]^+$ 349.1911, found 349.1910.

Preparation of *trans*-cyclobutane 82 and spirolactam S3.



To a 150 mL pressure vessel were added *cis*-cyclobutane **81** (2.74 g, 7.86 mmol) and wet CH_2Cl_2 (27.5 mL). The colorless solution was treated with DBU (11.7 mL, 78.6 mmol, 10.0 equiv) and a bright yellow color was observed immediately. The vessel was sealed under ambient conditions and heated to 60 °C for 20 hours. The reaction mixture was diluted with 100 mL of water and 100 mL of CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (isocratic: 40% EtOAc/hexane until **81** eluted completely, then 10% MeOH/ CH_2Cl_2) to afford **82** (1.74 g, 64% yield) and **S3** (367 mg, 14% yield), each as a pale yellow solid.

Data for *trans*-cyclobutane **82**:

$[\alpha]_D^{25.0} = -129.0°$ (c = 1.43, $CHCl_3$).

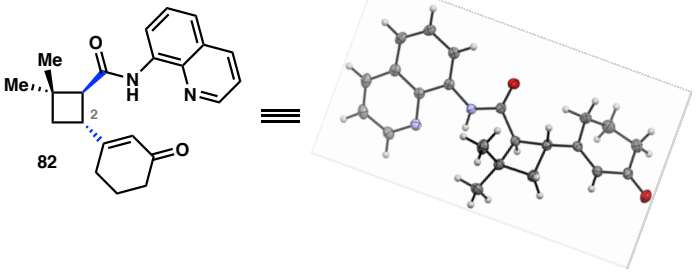
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.68 (s, 1H), 8.79 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.73 (dd, *J* = 7.2, 1.8 Hz, 1H), 8.15 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.52 (dd, *J* = 8.3, 7.2 Hz, 1H), 7.49 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.92 (q, *J* = 1.5 Hz, 1H), 3.58 (ddq, *J* = 18.5, 8.7, 1.6, 0.8, 0.8 Hz, 1H), 2.97 (dd, *J* = 9.8, 0.7 Hz, 1H), 2.41 – 2.29 (m, 4H), 2.05 – 1.92 (m, 3H), 1.85 (t, *J* = 10.4 Hz, 1H), 1.40 (s, 3H), 1.19 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.8, 169.6, 167.5, 148.3, 138.3, 136.3, 134.2, 127.9, 127.3, 123.9, 121.7, 121.5, 116.3, 55.5, 37.5, 36.8, 36.4, 36.3, 30.7, 27.6, 23.1, 22.6.

FTIR (NaCl, thin film) 3344, 3046, 2952, 2865, 2246, 1669, 1623, 1595, 1577, 1526, 1485, 1461, 1424, 1323, 1346, 1326, 1292, 1253, 1191, 1161, 1133, 915, 884, 827, 792, 757,731 cm.$^{-1}$

HRMS (MM) calc'd for $C_{22}H_{25}N_2O_2$ $[M+H]^+$ 349.1911, found 349.1919.

XRCD: A suitable crystal of $C_{22}H_{24}N_2O_2$ (**82**) was selected for analysis. All measurements were made on a Bruker APEX-II CCD with filtered Cu-Kα radiation at a temperature of 120 K. Using Olex2, the structure was solved with the ShelXS structure solution program using Direct Methods and refined with the ShelXL refinement package using Least Squares minimization. The absolute stereochemistry was determined on the basis of the absolute structure parameter, -0.04(4).



Data for spirolactam **S3**, 2.5:1 mixture of diastereomers:

$[\alpha]_D^{25.0} = -56.5°$ (c = 1.085, $CHCl_3$).

^{1}H NMR (asterisk denotes minor diast., 400 MHz, $CDCl_3$) δ 8.92 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.85* (dd, *J* = 4.1, 1.8 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.8 Hz, 1H), 8.13* (dd, *J* = 8.3, 1.8 Hz, 1H), 7.87 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.63 – 7.53 (m, 2H), 7.49 (dd, *J* = 7.2, 1.5 Hz, 1H), 7.42 (dd, *J* = 8.3, 4.1 Hz, 1H), 7.37* (dd, *J* = 8.3, 4.1 Hz, 1H), 3.07* (ddd, *J* = 7.3, 3.2, 0.9 Hz, 1H), 2.93 (dd, *J* = 6.0, 3.3 Hz, 1H), 2.86 (d, *J* = 13.2 Hz, 1H), 2.83 – 2.73 (m, 1H), 2.53 (dt, *J* = 13.1, 2.4 Hz, 1H), 2.41 – 2.33 (m, 1H), 2.27 (ddq, *J* = 15.1, 11.3, 2.1 Hz, 1H), 2.15 – 1.94 (m, 2H), 1.94 – 1.83 (m, 1H), 1.71 (dtd, *J* = 13.2, 8.6, 7.6, 3.0 Hz, 1H), 1.52 – 1.38* (m, 1H), 1.35 (s, 3H), 1.34* (s, 3H), 1.31 (s, 3H), 1.14* (s, 3H), 1.03 (td, *J* = 13.7, 4.0 Hz, 1H).

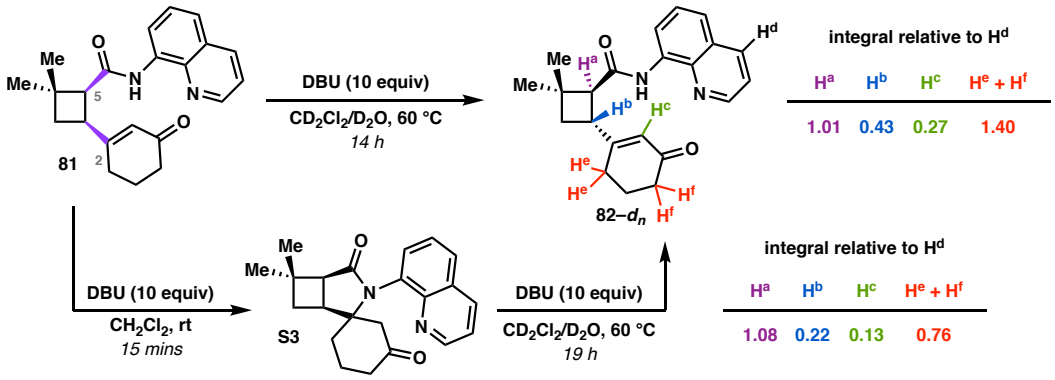
^{13}C NMR (major diastereomer, 101 MHz, $CDCl_3$) δ 209.2, 175.5, 150.7, 146.3, 136.1, 134.2, 130.7, 129.6, 129.1, 126.2, 121.9, 69.2, 53.2, 49.9, 40.7, 35.8, 34.8, 34.1, 30.2, 29.0, 25.6, 20.1.

^{13}C NMR (minor diastereomer, 101 MHz, $CDCl_3$) δ 210.0, 175.5, 150.7, 145.6, 136.0, 134.2, 131.5, 129.6, 129.2, 126.0, 121.7, 68.9, 52.9, 49.8, 40.4, 35.0, 34.8, 34.6, 31.3, 30.0, 26.1, 20.1.

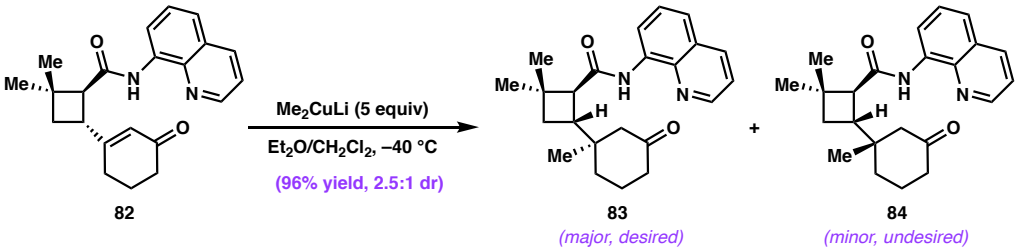
FTIR (NaCl, thin film) 3356, 3039, 2953, 2933, 2866, 1705, 1687, 1616, 1596, 1574, 1525, 1496, 1472, 1426, 1391, 1341, 1312, 1279, 1250, 1223, 1134, 1124, 1038, 1027, 905, 831, 795, 753, 664, 643 cm.$^{-1}$

HRMS (MM) calc'd for $C_{22}H_{25}N_2O_2$ $[M+H]^+$ 349.1911, found 349.1916.

Deuterium-labeling studies to determine site of epimerization:



Preparation of ketones 83 and 84 using Gilman's reagent.



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 **82** (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 x 20 mL) and the combined organics dried over $MgSO_4$, 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 **83** and **84** (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 x 250 mm columns connected in series (gradient: 77–85%MeCN/H_2O) afforded analytically pure samples of each diastereomer, from which **84** was crystallized. Melting point: 80–83 ºC.

Data for minor diastereomer **84**: $[\alpha]_D^{25.0}$ = –25.5° (c = 1.50, $CHCl_3$).

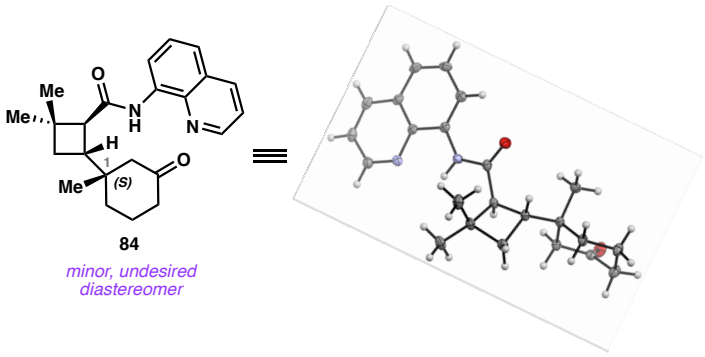
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (s, 1H), 8.82 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.75 (dd, *J* = 7.4, 1.6 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.46 (dd, *J* = 8.2, 4.2 Hz, 1H), 2.89 – 2.77 (m, 2H), 2.35 – 2.26 (m, 2H), 2.24 (d, *J* = 13.3 Hz, 1H), 2.09 (d, *J* = 13.4 Hz, 1H), 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.

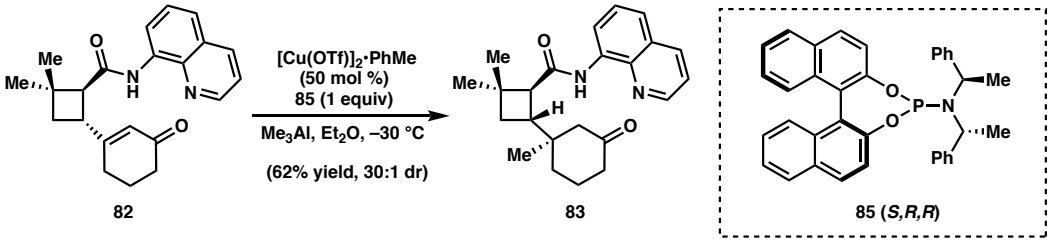
FTIR (NaCl, thin film) 3349, 3044, 2952, 2863, 1706, 1687, 1595, 1577, 1523, 1484, 1460, 1424, 1383, 1325, 1238, 1228, 1163, 827, 792 cm.$^{-1}$

HRMS (MM) calc'd for $C_{23}H_{29}N_2O_2$ $[M+H]^+$ 365.2224, found 365.2261.

XRCD: A suitable crystal of $C_{23}H_{28}N_2O_2$ (**84**) 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.



Selective preparation of ketone 83 using copper-catalyzed conjugate addition.



Inside a N_2-filled glovebox, $[Cu(OTf)]_2$•PhMe (72.4 mg, 0.140 mmol, 0.25 equiv) and (*S,R,R*) ligand **85** (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 minutes before *trans*-cyclobutane **82** (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 x 5 mL) and the combined organics dried over $MgSO_4$, 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 **83** and **84** (126 mg, 62% yield), as a white solid: $[\alpha]_D^{25.0} = -84.7°$ (c = 0.600, $CHCl_3$).

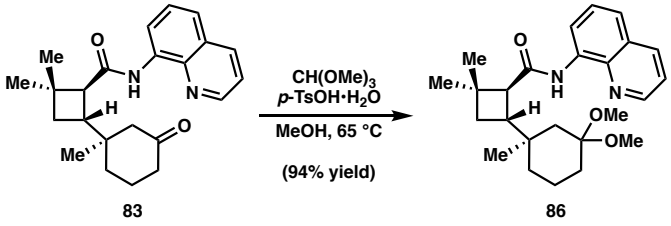
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1H), 8.81 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.75 (dd, *J* = 7.2, 1.8 Hz, 1H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.56 – 7.47 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 2.89 – 2.76 (m, 2H), 2.36 – 2.28 (m, 2H), 2.25 (ddd, *J* = 12.5, 6.6, 1.1 Hz, 1H), 2.04 (dt, *J* = 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.

Preparation of dimethyl ketal 86.



83 86

To a flame-dried 15 mL flask was added ketone **83** (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 $NaHCO_3$. The aqueous layer was extracted with EtOAc (3 x 5 mL), and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by Florisil® flash chromatography (isocratic: 10% EtOAc/Hexane) to afford **86** (106 mg, 94% yield) as a white, foamy solid: $[\alpha]_D^{25.0}$ = –83.3° (c = 1.60, $CHCl_3$).

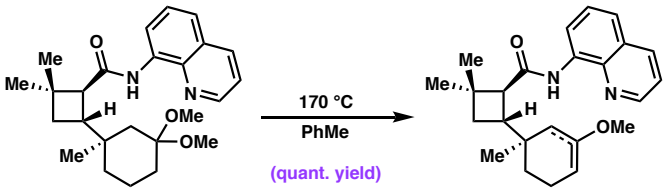
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.81 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.78 (dd, *J* = 7.4, 1.6 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.56 – 7.46 (m, 2H), 7.44 (dd, *J* = 8.3, 4.2 Hz, 1H), 3.16 (s, 3H), 3.13 (s, 3H), 2.80 (d, *J* = 10.0 Hz, 1H), 2.69 (q, *J* = 9.7 Hz, 1H), 2.01 (ddd, *J* = 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.

Preparation of methyl enol ether 90.



86 90

(1:1 mixture of enol ethers)

To a 15 mL thick-walled, screw top pressure vessel were added dimethyl ketal **86** (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 **90** (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, $CHCl_3$).

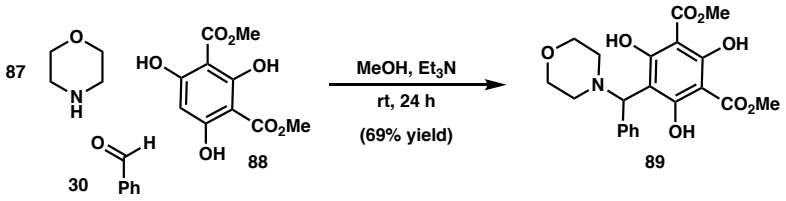
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 1H), 8.90 – 8.72 (m, 2H), 8.15 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.57 – 7.40 (m, 3H), 4.48 (s, 1H), 3.48 (s, 3H), 2.87 – 2.74 (m, 2H), 2.12 – 1.93 (m, 2H), 1.74 – 1.57 (m, 4H), 1.48 – 1.36 (m, 1H), 1.33 (s, 3H), 1.31 – 1.27 (m, 1H), 1.12 (s, 3H), 0.97 (s, 3H).

^{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.

Preparation of benzhydryl morpholine 89.



To a flame-dried 100 mL round-bottom flask were added phloroglucinol **88** (1.00g, 4.13 mmol), followed by freshly distilled MeOH (41.0 mL). Benzaldehyde (**30**) (421 μL, 4.13 mmol, 1.00 equiv), morpholine (**87**) (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 **89** (1.19 g, 69% yield) as a white powder.

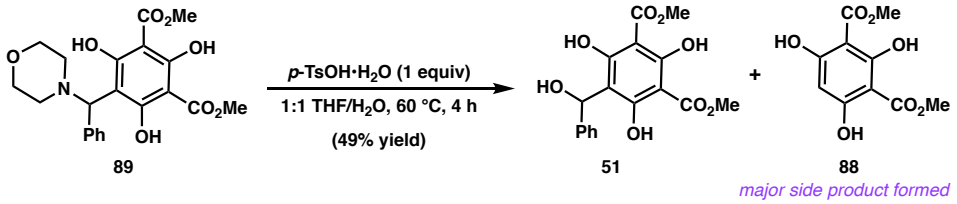
^{1}H NMR (400 MHz, $CDCl_3$) δ 15.34 (s, 1H), 13.16 (s, 1H), 12.53 (s, 1H), 7.45 (d, J = 7.2 Hz, 2H), 7.34 – 7.20 (m, 3H), 4.88 (s, 1H), 3.99 (s, 3H), 3.91 (s, 3H), 3.90 – 3.40 (br m, 4H), 3.08 (br s, 1H), 2.46 (ddd, J = 11.9, 6.2, 3.1 Hz, 2H), 2.18 (br s, 1H).

^{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.

Preparation of fully oxidized *o*-QM precursor 51.



To a 50 mL round-bottom flask was added benzhydryl morpholine **89** (200 mg, 0.479 mmol), followed by a 1:1 mixture of THF/H_2O (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 **88**, presumably via acid-mediated retro aldol. Upon completion, the reaction was cooled to room temperature and quenched with saturated aqueous $NaHCO_3$. The reaction was diluted with EtOAc and the organic layer separated. The aqueous layer was extracted with EtOAc (2 x 5 mL) and the combined organic layers were dried over $MgSO_4$, 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 $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford **51** (82.0 mg, 49% yield) as a white solid.

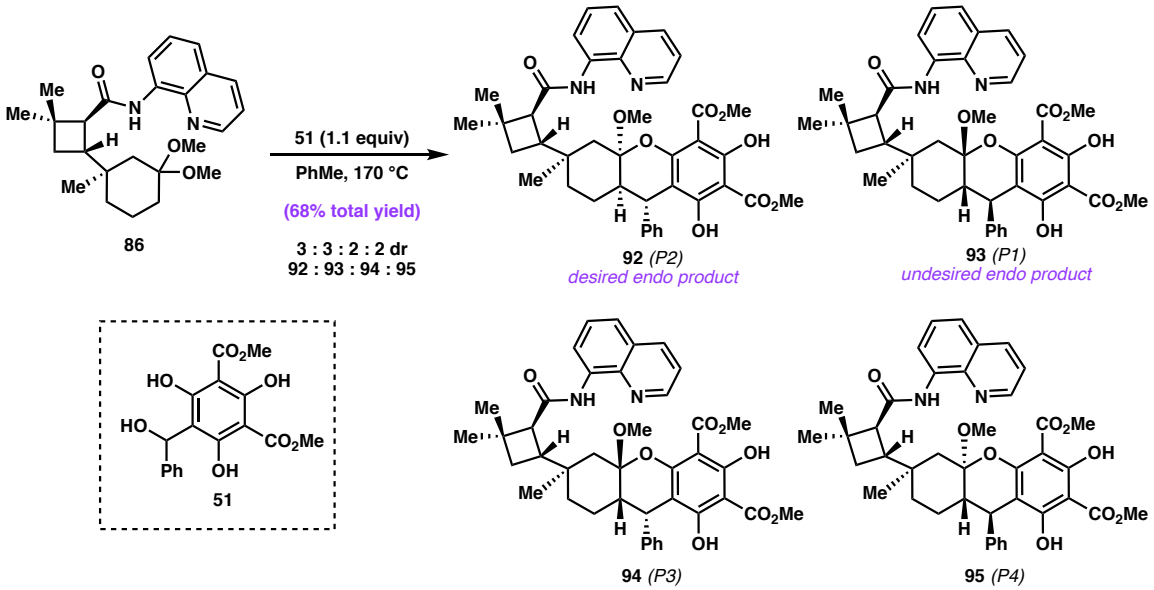
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.89 (s, 2H), 11.70 (s, 1H), 7.46 – 7.39 (m, 2H), 7.31 (t, J = 7.4 Hz, 2H), 7.26 – 7.19 (m, 1H), 6.38 – 6.23 (m, 1H), 4.09 (d, J = 11.6 Hz, 1H), 4.02 (s, 6H).

^{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.

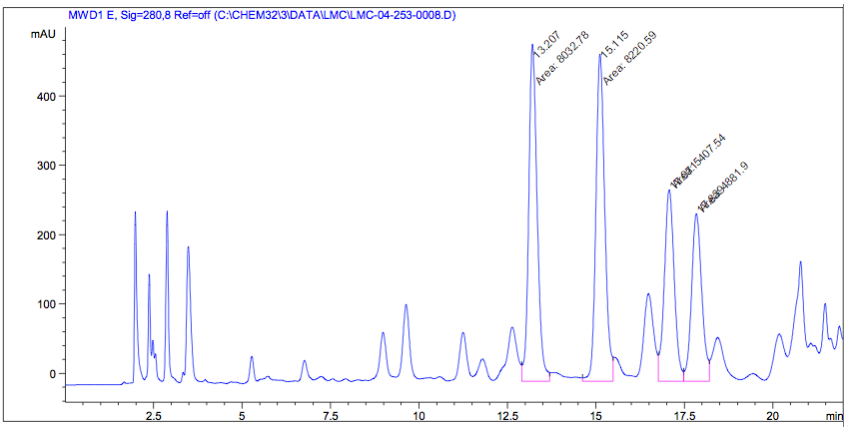
Preparation of tricyclic ketals 92–95 by thermal cycloaddition.



To a 15 mL thick-walled, screw top pressure vessel were added dimethyl ketal **86** (105 mg, 0.256 mmol) and *o*-QM precursor **51** (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 **92–95** (109 mg, 68% yield). Analytically pure samples of the four diastereomers produced in greatest abundance (i.e.

92–95) were obtained by subsequent reverse-phase HPLC purification using an Agilent XDB-C18 5 µm 30 x 250 mm column (gradient: 83–100% MeCN/H_2O).

Chromatogram from HPLC separation:



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.207	MF	0.2752	8032.78027	486.56299	30.2635
2	15.115	MF	0.2903	8220.58984	472.01566	30.9711
3	17.071	MF	0.3263	5407.54297	276.19736	20.3729
4	17.839	MF	0.3366	4881.89746	241.74495	18.3925

Data for **92** (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 **93** (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 **94** (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 **95** (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 –

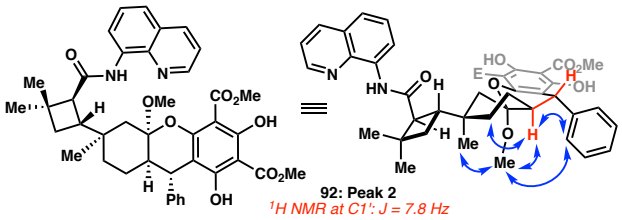
1.48 (m, 2H), 1.45 (d, J = 14.3 Hz, 1H), 1.38 – 1.32 (m, 1H), 1.31 (s, 3H), 1.21 – 1.14 (m, 1H), 1.12 (s, 3H), 1.08 (s, 3H).

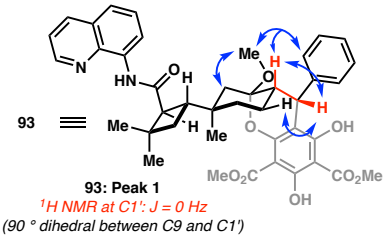
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 170.8, 169.5, 164.0, 162.4, 157.4, 148.3, 145.4, 138.5, 136.5, 134.7, 128.1, 128.1, 127.6, 125.9, 121.7, 121.3, 116.4, 108.0, 101.7, 99.6, 95.5, 52.7, 52.5, 51.2, 49.4, 49.0, 42.0, 41.1, 36.2, 35.3, 34.8, 33.3, 32.6, 30.8, 23.8, 22.5, 21.1.

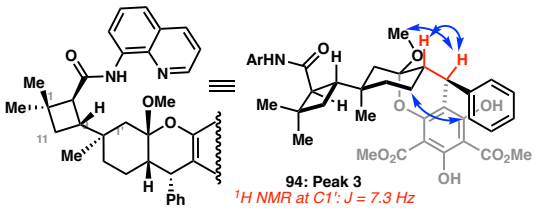
FTIR (NaCl, thin film) 3412 (br), 3354 (br), 3055, 3023, 3003, 2950, 2866, 1732, 1688, 1656, 1598, 1524, 1484, 1453, 1426, 1384, 1327, 1277, 1248, 1225, 1165, 1062, 993, 954, 925, 826, 792, 755, 702 cm.$^{-1}$

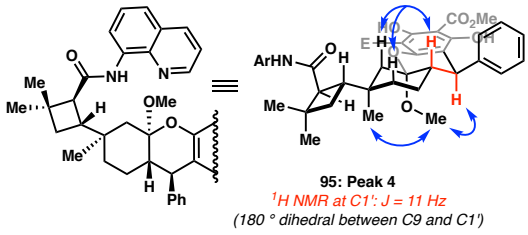
HRMS (MM) calc'd for $C_{41}H_{45}N_2O_9$ $[M+H]^+$ 709.3120, found 709.3139.

Summary of Key NOE correlations for stereochemical assignment of 92–95:

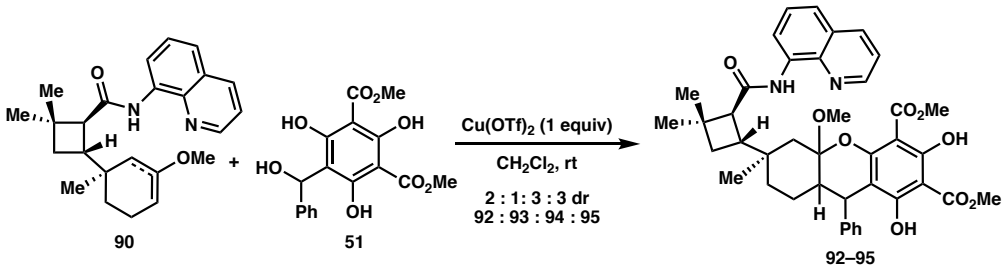






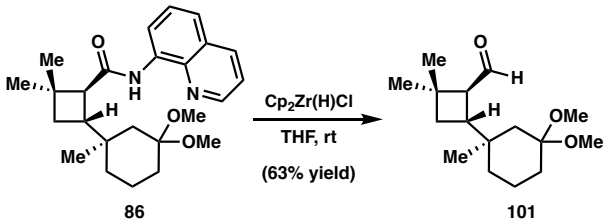


Preparation of tricyclic ketals 92–95 by $Cu(OTf)_2$-mediated cycloaddition.



Inside a N_2-filled glovebox, methyl enol ether **90** (17.0 mg, 0.045 mmol) and *o*-QM precursor **51** (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 $NaHCO_3$ and diluted with $CHCl_3$. The reaction mixture was extracted with $CHCl_3$ (3 x 1 mL) and the organics filtered through a plug of Na_2SO_4 and concentrated *in vacuo*. The crude residue was analyzed by ^1H NMR and determined to contain **92**, **93**, **94**, and **95** in an approximate ratio of 2 : 1 : 3 : 3, respectively. For spectroscopic characterization data, see above.

Preparation of aldehyde 101.



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 **86** (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 $NaHCO_3$. The reaction was diluted with EtOAc and the organic layer separated. The aqueous layer was extracted with EtOAc (2 x 5 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (isocratic: 5% EtOAc/hexane + 1% Et_3N) to afford **101** (36.9 mg, 62% yield) as a pale yellow oil: $[\alpha]_D^{25.0} = -33.1°$ (c = 0.500, $CHCl_3$).

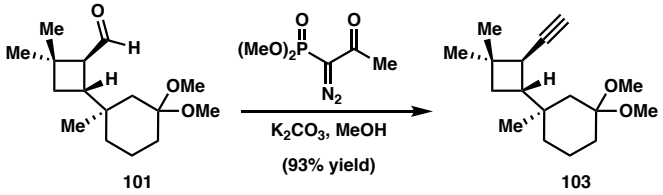
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, *J* = 3.0 Hz, 1H), 3.14 (s, 3H), 3.09 (s, 3H), 2.64 (td, *J* = 9.7, 8.5 Hz, 1H), 2.58 (dd, *J* = 9.9, 3.0 Hz, 1H), 1.86 (ddt, *J* = 13.6, 4.2, 2.6 Hz, 1H), 1.61 (t, *J* = 10.3 Hz, 1H), 1.57 – 1.44 (m, 4H), 1.34 – 1.18 (m, 2H), 1.16 (s, 3H), 1.14 (s, 3H), 1.13 – 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 (MM) calc'd for $C_{15}H_{25}O_2$ $[M–OCH_3]^+$ 237.1849, found 237.1855.

Preparation of alkyne 103.



To a 10 mL round bottom flask were added aldehyde **101** (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 (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 $NaHCO_3$ was added, and the organic layer separated. The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by Florisil® flash chromatography (isocratic: 5% Et_2O/pentane) to afford **103** (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 –

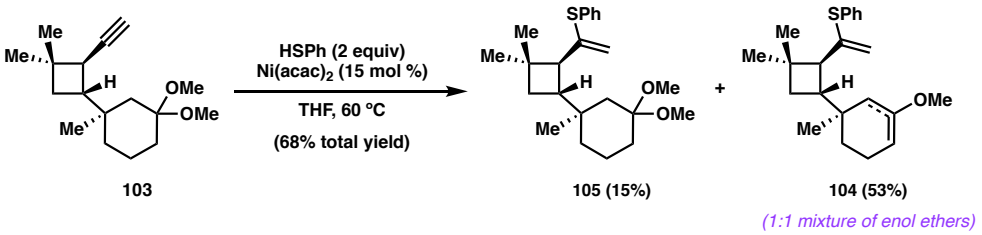
1.50 (m, 2H), 1.48 (d, J = 9.6 Hz, 2H), 1.29 – 1.17 (m, 5H), 1.16 (d, J = 2.7 Hz, 4H), 1.03 (s, 3H), 0.97 (s, 3H).

^{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.

Preparation of vinyl sulfides 104 and 105.



103 105 (15%) 104 (53%)

(1:1 mixture of enol ethers)

Inside a N_2-filled glovebox, THF (400 μL) was added to a 1 dram vial containing alkyne **103** (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 **104** (8.50 mg, 53% yield) and **105** (2.7 mg, 15% yield) each as colorless oils.

Data for ketal **105**: $[\alpha]_D^{25.0}$ = +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 $C_{22}H_{31}OS$ $[M–OCH_3]^+$ 343.2090, found 343.2073.

Data for enol ether **104**: $[\alpha]_D^{25.0}$ = –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).

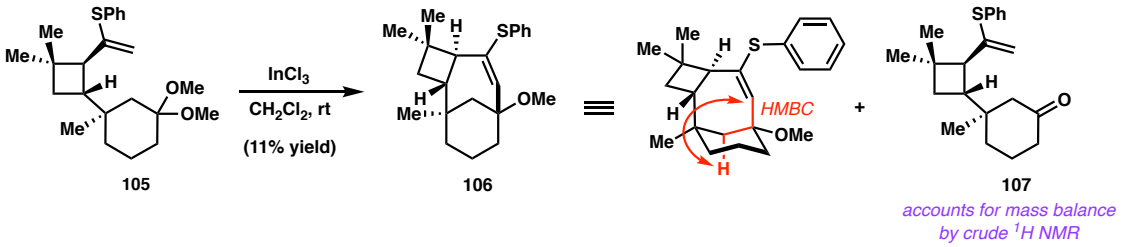
^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3, 154.4, 146.0, 145.9, 133.8, 133.5, 133.4, 133.3, 129.2, 129.1, 127.9, 127.7, 112.3, 111.1, 100.6, 92.0, 54.1, 53.9, 50.2, 49.5, 43.5, 40.9,

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.

Preparation of bridged bicycle 106.



Inside a N_2-filled glovebox, CH_2Cl_2 was added to a 1 dram vial containing **105** (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 $NaHCO_3$ and diluted with CH_2Cl_2. The reaction was extracted with CH_2Cl_2 (3 x 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 **106** (0.900 mg, 11% yield) as a colorless oil, with the remaining mass balance accounted for by ketone **107**, as determined by crude ^{1}H NMR.

Data for bridged bicycle **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 ketone **107**: $[\alpha]_D^{25.0}$ = +31.6° (c = 0.100, $CHCl_3$).

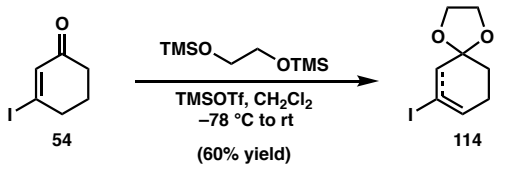
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 8.1, 1.6 Hz, 2H), 7.40 – 7.32 (m, 3H), 5.13 (d, *J* = 1.3 Hz, 1H), 4.98 (s, 1H), 2.53 (d, *J* = 10.1 Hz, 1H), 2.38 (td, *J* = 10.0, 8.9 Hz, 1H), 2.32 – 2.23 (m, 2H), 2.17 (d, *J* = 13.6 Hz, 1H), 2.02 (dt, *J* = 13.4, 1.9 Hz, 1H), 1.93 – 1.90 (m, 1H), 1.82 (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.

Preparation of protected iodide 114.



Inside a N_2-filled glove box, a 250 mL round bottom flask was charged with TMSOTf (0.410 mL, 0.230 mmol, 0.010 equiv) and CH_2Cl_2 (20.0 mL). The flask was sealed, removed from the glove box, and placed under a N_2 atmosphere. The reaction mixture was cooled to –78 ºC, and 1,2-bistrimethylsilyloxyethane (11.0 mL, 45.0 mmol, 2.00 equiv) was added via syringe. (Note: best results were obtained when 1,2-bistrimethylsilyloxyethane was sparged with argon for 30 min prior to addition). Vinyl iodide **54** (5.00 g, 22.5 mmol, 1.00 equiv) was added to the flask dropwise as a solution in CH_2Cl_2 (20.0 mL), via cannula transfer. An additional portion of CH_2Cl_2 (5.00 mL) was used to complete the transfer. The colorless reaction mixture was allowed to stir at –78 ºC for 1 hour, at which point the reaction mixture was warmed to 0 ºC. The reaction mixture became yellow immediately upon warming and was allowed to warm to room temperature over 16 hours. The reaction mixture became dark orange and was quenched with the addition of DIPEA (11.0 mL), at which point the reaction became yellow. The mixture was poured into a separatory funnel and diluted with saturated $NaHCO_3$ solution. The aqueous layer was extracted three times with CH_2Cl_2. The organic layers were combined, dried over a 1:1 mixture of anhydrous K_2CO_3 and Na_2SO_4, filtered, and concentrated to provide a yellow residue that was purified by flash silica gel chromatography (5% EtOAc, 1%

Et_3N/hexane – 20% EtOAc, 1% Et_3N/hexane) to provide **114** (3.61 g, 60% yield) as a 8:1 mixture of olefin isomers, as a pale yellow oil.

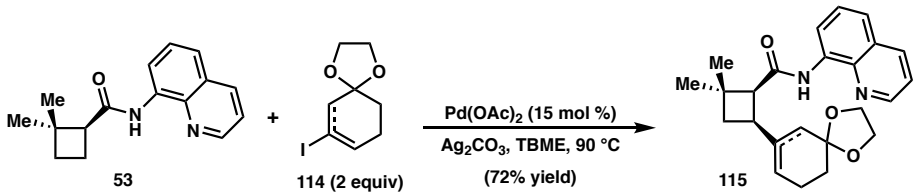
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (tt, *J* = 4.0, 1.9 Hz, 1H), 3.98 (p, *J* = 1.7 Hz, 4H), 2.72 (q, *J* = 2.3 Hz, 2H), 2.36 – 2.22 (m, 2H), 1.77 (t, *J* = 6.5 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.6, 108.1, 91.1, 64.7, 49.3, 30.2, 27.5.

FTIR (NaCl, thin film) 3040, 2955, 2934, 2881, 2836, 2684, 1637, 1474, 1443, 1429, 1418, 1360, 1330, 1300, 1243, 1207, 1142, 1114, 1076, 1058, 1021, 970, 948, 889, 848, 827, 776, 738, 662 cm.$^{-1}$

HRMS (FAB) calc'd for $C_8H_{11}IO_2$ $[M]^+$ 266.9876, found 266.9888.

Preparation of *cis*-dioxolane 115.



A 100 mL, thick-walled pressure vessel was charged with $Pd(OAc)_2$ (132 mg, 0.590 mmol, 0.150 equiv), Ag_2CO_3 (1.08 g, 3.93 mmol, 1.00 equiv), and **53** (1.00 g, 3.93 mmol, 1.00 equiv). Vinyl iodide **114** (2.09 g, 7.86 mmol, 2.00 equiv) was then added to the flask as a solution in TBME (19.7 mL). The reaction vessel was sealed with a screw top under ambient conditions and heated to 90 ºC in an oil bath. The heterogeneous reaction mixture is olive green upon addition of vinyl iodide. After heating for five minutes, the reaction mixture became black. After 16 hours, the flask was removed from the oil bath and allowed to cool to room temperature. The reaction mixture was filtered over a pad of celite and the

filter cake was washed with CH_2Cl_2. The filtrate was concentrated, and the crude orange residue was purified by flash silica gel chromatography (30% EtOAc, 1% Et_3N/hexane–35% EtOAc, + 1% Et_3N/hexane) to provide **115** (1.11 g, 72% yield) as a white foam: $[\alpha]_D^{25.0} = -29.3°$ (c = 1.95, $CHCl_3$).

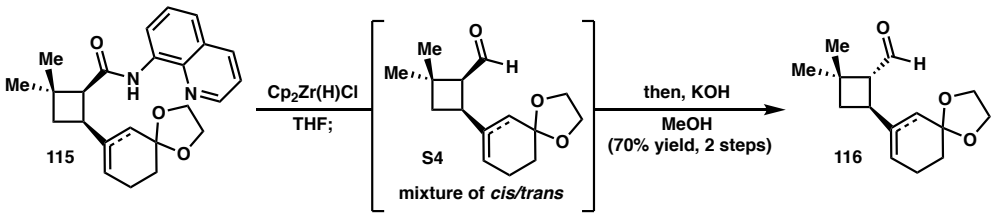
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (s, 1H), 8.81 (ddd, *J* = 24.2, 7.3, 1.5 Hz, 2H), 8.13 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.49 (td, *J* = 8.2, 7.5, 6.6 Hz, 1H), 7.45 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.42 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.65 (dd, *J* = 17.8, 9.1 Hz, 1H), 4.03 – 3.81 (m, 2H), 3.76 – 3.64 (m, 2H), 3.25 (q, *J* = 9.1, 8.2 Hz, 1H), 3.05 (dd, *J* = 8.7, 2.8 Hz, 1H), 2.46 (t, *J* = 10.9 Hz, 1H), 2.40 – 2.23 (m, 2H), 2.19 (dt, *J* = 16.5, 2.1 Hz, 1H), 2.06 – 1.97 (m, 1H), 1.93 (ddd, *J* = 11.1, 8.3, 2.9 Hz, 1H), 1.71 – 1.59 (m, 1H), 1.57 – 1.48 (m, 1H), 1.40 (s, 3H), 1.11 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.0, 147.9, 138.7, 136.3, 134.9, 134.8, 127.9, 127.5, 121.4, 121.2, 120.8, 116.6, 108.3, 64.3, 64.1, 55.9, 37.2, 37.1, 36.7, 35.4, 30.8, 30.2, 25.1, 24.4.

FTIR (NaCl, thin film) 3357, 3300, 3043, 3006, 2952, 2928, 2881, 1685, 1664, 1596, 1577, 1523, 1485, 1460, 1424, 1385, 1324, 1255, 1208, 1160, 1132, 1106, 1060, 1039, 1020, 947, 846, 826, 792, 755, 666 cm.$^{-1}$

HRMS (MM) calc'd for $C_{24}H_{29}N_2O_3$ $[M+H]^+$ 393.2173, found 393.2183.

Preparation of *trans*-aldehyde 116.



Inside a N_2-filled glove box, a 250 mL round bottom flask was charged with Schwartz's reagent (2.30 g, 8.92 mmol, 2.06 equiv) and THF (22.3 mL). *Cis*-dioxolane **115** (1.70 g, 4.32 mmol, 1.00 equiv) was added to the flask as a solution in THF (22.3 mL). The flask was sealed, removed from the glove box and put under a N_2 atmosphere. The flask was covered with aluminum foil and allowed to stir for one hour, at which point the reaction was quenched with the addition of saturated $NaHCO_3$ solution. (Note, it is important that the quench be conducted very quickly to avoid decomposition of excess Schwartz's reagent and formation of HCl). The reaction mixture was diluted with EtOAc and the organic layer separated. The aqueous layer was filtered through a pad of celite and sand and then extracted 5x with EtOAc. The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated to provide a yellow residue that was purified by flash silica gel chromatography (15% EtOAc, 1% Et_3N/hexanes) to provide **S4** (755 mg, 3.01 mmol) as a yellow oil as a 1.8:1 (*cis*/*trans*) mixture of diastereomers at C5. The oil was concentrated directly into a 200 mL round bottom flask and dissolved in wet MeOH (60.0 mL). The flask was then charged with KOH (3.36 g, 59.9 mmol, 20.0 equiv) and the mixture allowed to stir for 1 hour at room temperature. The mixture was then concentrated to a volume of ~3 mL and diluted with pH 7 buffer. A pale yellow precipitate formed upon addition of buffer. The solution was slowly acidified using dilute citric acid until pH 7 was achieved. The mixture was then poured into a separatory funnel and extracted 3x with EtOAc. The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated to provide *trans*-aldehyde **116** (755 mg, 70% over 2 steps) as a mixture of olefin isomers. The yellow oil was analytically pure and used directly in the next step:

$[\alpha]_D^{25.0}$ = +35.2° (c = 0.295, $CHCl_3$). Note: it is recommended that the aldehyde be used immediately in the next step to avoid decomposition.

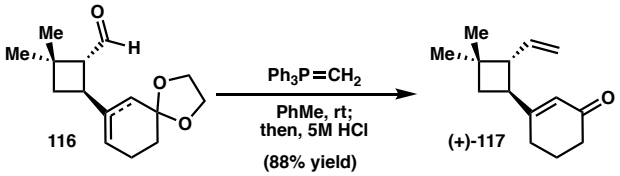
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, *J* = 2.2 Hz, 1H), 5.37 (dt, *J* = 3.8, 1.9 Hz, 1H), 3.97 (dd, *J* = 2.5, 1.3 Hz, 4H), 3.14 (q, *J* = 9.2 Hz, 1H), 2.73 (dt, *J* = 10.0, 2.1 Hz, 1H), 2.22 (dp, *J* = 6.5, 2.1 Hz, 2H), 2.16 – 1.97 (m, 2H), 1.77 (ddd, *J* = 15.5, 9.4, 2.0 Hz, 2H), 1.69 (td, *J* = 6.5, 2.1 Hz, 2H), 1.24 (s, 3H), 1.14 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 203.2, 137.1, 118.8, 108.3, 64.4, 59.5, 37.3, 37.1, 36.7, 34.3, 31.2, 30.7, 24.0, 24.0.

FTIR (NaCl, thin film) 2954, 2929, 2896, 2873, 2707, 1712, 1670, 1577, 1522, 1461,1449, 1434, 1420, 1383, 1367, 1340, 1312, 1297, 1249, 1209, 1179, 1103, 1059, 1039, 1018, 948, 846, 793 cm.$^{-1}$

HRMS (MM) calc'd for $C_{15}H_{23}O_3$ $[M+H]^+$ 251.1642, found 251.1645.

Preparation of vinyl enone (+)-117



A 250 mL round bottom flask was charged with *trans*-aldehyde, **116** (720 mg, 2.88 mmol, 1.00 equiv). The flask was evacuated and backfilled three times with N_2 and charged with toluene (2.30 mL). The flask was then charged with freshly prepared ylide solution (36.0 mL, 0.4 M, 5.00 equiv) and the reaction mixture was allowed to stir for 30 minutes at room temperature. The reaction was quenched with the addition of saturated $NaHCO_3$ solution (10.0 mL). The organic layer was separated and the aqueous layer extracted 3x

with Et_2O. The combined organics were concentrated and dissolved in a 1:1 mixture of THF and 5M HCl (28 mL.0). The reaction mixture was allowed to stir over 16 hours, at which point the mixture was diluted with Et_2O and water. The layers were separated and the aqueous layer extracted 3x with Et_2O. The combined organics were dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude yellow residue was purified by flash silica gel chromatography (20–30% Et_2O/pentane) to provide (+)-**117** (520 mg, 88%) as a pale yellow oil: $[\alpha]_D^{25.0}$ = +102° (c = 0.705, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (q, *J* = 1.6 Hz, 1H), 5.81 (dddt, *J* = 16.8, 10.6, 7.9, 0.5, 0.5 Hz, 1H), 5.04 (qd, *J* = 1.9, 1.0 Hz, 1H), 5.01 (ddd, *J* = 10.8, 1.9, 1.1 Hz, 1H), 2.88 (q, *J* = 9.7, 9.1, 9.0 Hz, 1H), 2.48 (ddq, *J* = 9.8, 7.9, 1.0 Hz, 1H), 2.34 (t, *J* = 7.0, 6.5 Hz, 2H), 2.20 (qdd, *J* = 6.0, 1.5, 0.8 Hz, 2H), 1.95 (dt, *J* = 7.7, 6.1 Hz, 2H), 1.85 (ddd, *J* = 10.8, 8.3, 0.8 Hz, 1H), 1.67 (t, *J* = 10.3 Hz, 1H), 1.05 (s, 3H), 1.04 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 168.8, 137.4, 123.4, 116.1, 53.8, 41.1, 37.5, 37.3, 36.0, 30.0, 27.9, 23.1, 22.6.

FTIR (NaCl, thin film) 3320, 3076, 3039, 2953, 2934, 2891, 2866, 2827, 1671, 1622, 1456, 1428, 1417, 1382, 1368, 1346, 1324, 1290, 1251, 1191, 1124, 995, 968, 942, 912, 886, 755 cm.$^{-1}$

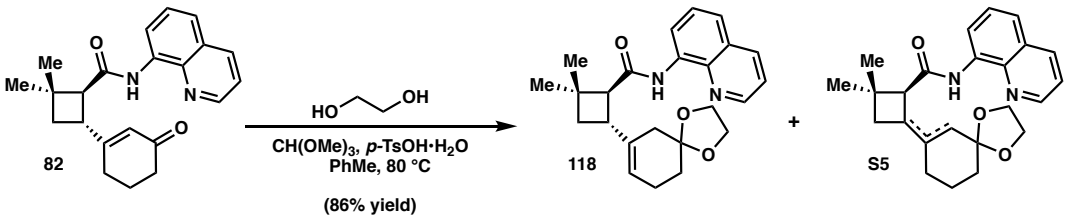
HRMS (MM) calc'd for $C_{14}H_{21}O$ $[M+H]^+$ 205.1587, found 205.1587.

Preparation of Wittig ylide.

Inside a N_2-filled glovebox, methyltriphenylphosphonium bromide (22.2 g, 62.1 mmol) and KO*t*-Bu (7.36 g, 65.6 mmol, 1.06 equiv) were added to a flame-dried 500 mL round-bottom flask and sealed under nitrogen. The flask was brought out of the box and

dry PhMe (155 mL) was added via syringe. The flask was fitted with a reflux condenser under a stream of N_2 and heated to 110 °C for 4 hours, at which time the reaction was cooled to room temperature and the salts were allowed to settle for 3 hours before the bright yellow supernatant (~0.40 M salt-free ylide) was used for the methylenation of aldehydes **S4** and **S6** (*vide infra*).

Preparation of *trans*-dioxolanes 118 & S5.



To a flame-dried 200 mL round-bottom flask was added *trans*-cyclobutane **82** (2.59 g, 7.43 mmol) and the atmosphere was exchanged for N_2 three times. Dry PhMe (74 mL) was then added, followed by ethylene glycol (16.6 mL, 297 mmol, 40.0 equiv) and trimethyl orthoformate (2.44 mL, 22.3 mmol, 3.00 equiv) via syringe. Finally, *p*-toluenesulfonic acid monohydrate (141 mg, 0.743 mmol, 0.10 equiv) was added as a solid in one portion under a stream of N_2. The reaction mixture was heated to 80 ºC for 15 hours, at which point the reaction mixture was cooled to room temperature and quenched with a saturated solution of aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (isocratic: 20% EtOAc/hexane + 1% Et_3N) to afford *trans*-dioxolanes **118** and **S5** (2.50 g, 86% yield) as a partially separable mixture of

inconsequential olefin isomers. An analytically pure sample of the major dioxolane (**118**) was obtained and a representative spectrum of the mixture as used in the next step is also provided.

Data for **118** (major product, peak 1): $[\alpha]_D^{25.0}$ = –80.5° (c = 1.40, $CHCl_3$)

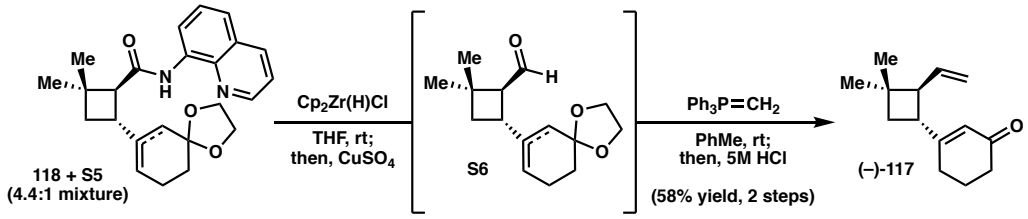
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 8.78 (dd, *J* = 11.0, 1.6 Hz, 1H), 8.78 (d, *J* = 1.6 Hz, 1H), 8.14 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.50 (dt, *J* = 15.8, 8.2, 7.5 Hz, 2H), 7.47 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.43 (dd, *J* = 8.3, 4.2 Hz, 1H), 5.54 (dt, *J* = 3.6, 1.8 Hz, 1H), 3.96 (q, *J* = 4.4, 3.9 Hz, 4H), 3.30 (q, *J* = 9.4 Hz, 1H), 2.88 (d, *J* = 9.8 Hz, 1H), 2.25 (d, *J* = 2.8 Hz, 4H), 1.87 (dd, *J* = 10.5, 8.6 Hz, 1H), 1.81 – 1.61 (m, 3H), 1.36 (s, 3H), 1.17 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 148.2, 138.4, 137.3, 136.3, 134.6, 127.9, 127.4, 121.6, 121.2, 119.1, 116.3, 108.4, 64.4, 55.2, 36.7, 36.7, 36.4, 36.1, 30.9, 30.8, 24.1, 23.4.

FTIR (NaCl, thin film) 3350, 3046, 2952, 2929, 2893, 2839, 1686, 1596, 1578, 1525, 1485, 1460, 1424, 1383, 1368, 1326, 1248, 1209, 1161, 1102, 1059, 1021, 948, 826, 792, 756 cm.$^{-1}$

HRMS (MM) calc'd for $C_{24}H_{29}N_2O_3$ $[M+H]^+$ 393.2173, found 393.2188.

Preparation of vinyl enone (–)-117.



Inside a N_2-filled glovebox, two flame-dried 200 mL round-bottom flasks were each charged with Schwartz's reagent (1.60 g, 6.21 mmol, 2.04 equiv) and sealed under

N_2. The flasks were removed from the glovebox and THF (15.5 mL) was added to each via syringe. To each of the milky-white suspensions was added a mixture of *trans*-dioxolanes **118** and **S5** (1.19 g, 3.04 mmol) as a solution in THF (16.0 mL) in a quick drip at room temperature. The mixtures immediately began to turn yellow, darkening to orange over the course of 1 hour, at which point the reactions were quenched with saturated aqueous $NaHCO_3$ and combined together. The layers were separated and the aqueous layer was extracted twice with EtOAc. The combined organic layers were washed twice with 100 mL of a 0.6 M aqueous solution of $CuSO_4$ to remove the liberated 8-aminoquinoline. The organic layer was then dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude aldehyde (**S6**, 1.70 g) was dissolved in dry PhMe (20 mL) and treated with freshly prepared ylide (80 mL, 32.0 mmol, 5.26 equiv) at room temperature. The reaction was stirred for 2 hours and monitored by TLC. Upon complete conversion, the reaction was cooled to 0 °C and quenched with 5 M HCl. The layers were separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were concentrated *in vacuo* and the solvent replaced with THF (30 mL). The dioxolane was hydrolyzed by stirring vigorously with 5 M HCl for 8 hours, at which time Et_2O was added and the layers separated. The aqueous layer was extracted twice with Et_2O and the combined organics washed with aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (isocratic: 30% Et_2O/hexanes) to afford vinyl enone (–)-**117** (715 mg, 58% yield over 2 steps) as a clear oil: $[\alpha]_D^{25.0} = -100°$ (c = 1.02, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (q, *J* = 1.5 Hz, 1H), 5.81 (dddt, *J* = 16.8, 10.6, 7.9, 0.5, 0.5 Hz, 1H), 5.04 (qd, *J* = 1.9, 1.0 Hz, 1H), 5.01 (ddd, *J* = 10.4, 2.0, 1.1 Hz, 1H), 2.88 (q, *J* = 9.7, 9.1, 9.0 Hz, 1H), 2.48 (ddq, *J* = 9.8, 7.9, 1.0 Hz, 1H), 2.34 (t, *J* = 7.0, 6.5 Hz, 2H),

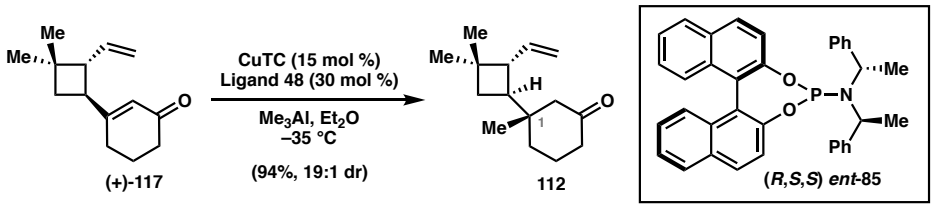
2.21 (qdd, J = 5.9, 1.5, 0.8 Hz, 2H), 1.95 (dt, J = 7.7, 6.1 Hz, 2H), 1.85 (ddd, J = 10.7, 8.3, 0.8 Hz, 1H), 1.67 (t, J = 10.4 Hz, 1H), 1.05 (s, 3H), 1.04 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.1, 168.7, 137.4, 123.4, 116.1, 53.8, 41.1, 37.5, 37.3, 36.0, 30.0, 27.9, 23.1, 22.6.

FTIR (NaCl, thin film) 3320, 3076, 3039, 2953, 2934, 2891, 2866, 2827, 1671, 1622, 1456, 1428, 1417, 1382, 1368, 1346, 1324, 1290, 1251, 1191, 1124, 995, 968, 942, 912, 886, 755 cm.$^{-1}$

HRMS (MM) calc'd for $C_{14}H_{21}O$ $[M+H]^+$ 205.1587, found 205.1587.

Preparation of vinyl ketone 112.



Inside a N_2-filled glovebox, CuTC (105 mg, 0.551 mmol, 0.150 equiv) and ligand (*R*,*S*,*S*) *ent*-**85** (594 mg, 1.10 mmol, 0.30 equiv) were added to a flame dried 100 mL round-bottom flask. The reagents were suspended in Et_2O (18.0 mL) and stirred at room temperature for 30 minutes before vinyl enone (+)-**117** (750 mg, 3.67 mmol) was added as a solution in Et_2O (18.0 mL). The reaction was sealed under N_2, removed from the glovebox and placed under a balloon atmosphere of argon. The reaction mixture was allowed to equilibrate to –35 °C for 5 minutes using a cryocool unit to maintain the temperature. Me_3Al (2.0 M in heptane; 3.67 mL, 7.34 mmol, 2.00 equiv) was then added dropwise and the reaction stirred at –35 °C for 17 hours, at which point wet MeOH (5 mL) was slowly added to quench excess Me_3Al. The mixture was warmed to room temperature,

filtered over a plug of silica gel, and washed thoroughly with Et_2O and CH_2Cl_2 (until no product remained in eluent). The filtrate was concentrated *in vacuo* and the crude residue purified by silica gel flash chromatography (isocratic: 20% hexane/CH_2Cl_2) to afford vinyl ketone **112** (760 mg, 94% yield) as a 19:1 mixture of inseparable diastereomers at C1, colorless oil. Note: this 19:1 mixture is carried through the next three reactions, and a single diastereomer at C1 is isolable after the ring-closing metathesis: $[\alpha]_D^{25.0}$ = +37.6° (c = 1.05, $CHCl_3$).

^{1}H NMR (400 MHz, C_6D_6) δ 5.68 (ddd, *J* = 16.9, 10.5, 8.6 Hz, 1H), 4.96 (qd, *J* = 2.2, 0.8 Hz, 1H), 4.93 (ddd, *J* = 11.3, 2.2, 0.8 Hz, 1H), 2.20 (ddt, *J* = 9.6, 8.6, 0.9 Hz, 1H), 2.11 (dtt, *J* = 13.9, 4.8, 1.4 Hz, 1H), 1.92 (dd, *J* = 3.3, 1.7 Hz, 2H), 1.90 – 1.79 (m, 2H), 1.50 – 1.40 (m, 2H), 1.31 – 1.21 (m, 2H), 1.21 – 1.13 (m, 1H), 0.99 (dtt, *J* = 13.4, 4.7, 4.5, 1.5, 1.1 Hz, 1H), 0.94 (s, 3H), 0.93 (s, 3H), 0.66 (s, 3H).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (ddd, *J* = 17.1, 10.3, 8.7 Hz, 1H), 5.08 – 4.81 (m, 2H), 2.33 (ddd, *J* = 9.6, 8.7, 0.9 Hz, 1H), 2.30 – 2.19 (m, 2H), 2.16 (d, *J* = 13.5 Hz, 1H), 2.07 (td, *J* = 10.1, 8.5 Hz, 1H), 1.99 (dt, *J* = 13.4, 1.8 Hz, 1H), 1.90 (ddq, *J* = 14.0, 6.2, 4.7 Hz, 1H), 1.85 – 1.72 (m, 1H), 1.56 (ddd, *J* = 13.6, 11.1, 4.4 Hz, 1H), 1.51 – 1.34 (m, 3H), 0.98 (s, 3H), 0.97 (s, 3H), 0.83 (s, 3H).

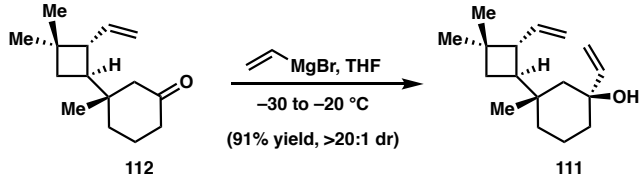
^{13}C NMR (101 MHz, C_6D_6) δ 209.3, 139.9, 115.3, 51.0, 49.5, 45.2, 41.2, 39.7, 34.7, 33.9, 32.9, 30.1, 23.7, 22.1, 21.8.

^{13}C NMR (101 MHz, $CDCl_3$) δ 212.8, 139.6, 115.3, 51.2, 49.5, 45.2, 41.3, 40.1, 34.8, 34.0, 33.0, 30.1, 23.7, 22.1, 21.8.

FTIR (NaCl, thin film) 3075, 2953, 2873, 1713, 1633, 1460, 1422, 1382, 1368, 1312, 1285, 1253, 1228, 1172, 1049, 995, 910 cm.$^{-1}$

HRMS (FAB) calc'd for $C_{15}H_{24}O$ $[M]^+$ 221.1900, found 221.1897.

Preparation of divinyl alcohol 111.



112 111

To a 15 mL round-bottom flask was added vinyl ketone **112** (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/CO_2 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 x 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 **111** (92.7 mg, 91% yield) as a colorless oil: $[\alpha]_D^{25.0}$ = +54.4° (c = 1.75, $CHCl_3$).

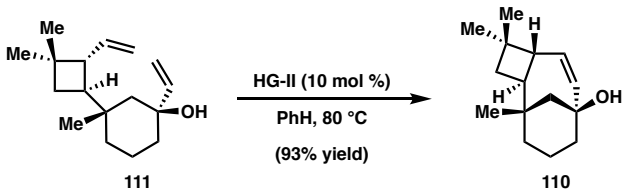
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (dd, *J* = 17.3, 10.6 Hz, 1H), 5.75 (ddd, *J* = 17.1, 10.2, 8.7 Hz, 1H), 5.18 (dd, *J* = 17.3, 1.3 Hz, 1H), 5.01 – 4.85 (m, 3H), 2.32 (t, *J* = 9.3 Hz, 1H), 1.92 (q, *J* = 9.6 Hz, 1H), 1.82 (qt, *J* = 13.5, 3.4 Hz, 1H), 1.55 (dddd, *J* = 14.0, 5.3, 3.5, 1.9 Hz, 1H), 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.

Preparation of allylic alcohol 110.



A 50 mL round-bottom flask containing divinyl alcohol **111** (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 benzene (17.7 mL) was added via syringe. The green reaction mixture was heated to 80 °C for 3.5 hours, and 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 **110** (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*

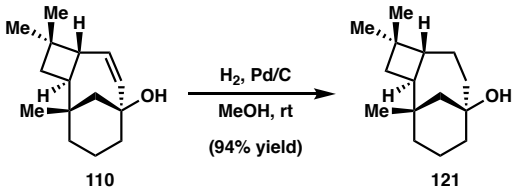
= 13.0, 3.2, 1.1 Hz, 1H), 1.64 (s, 1H), 1.63 – 1.56 (m, 2H), 1.54 – 1.41 (m, 2H), 1.34 – 1.25 (m, 2H), 1.15 (dd, *J* = 12.8, 2.2 Hz, 1H), 1.12 – 1.06 (m, 1H), 1.05 (s, 3H), 1.03 (s, 3H), 0.87 (s, 3H).

^{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.

Preparation of tertiary alcohol 121.



110 121

To a 100 mL round-bottom flask were added allylic alcohol **110** (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 H_2 (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 **121** (101 mg, 94% yield) as a colorless oil: $[\alpha]_D^{25.0}$ = +6.37° (c = 0.800, $CHCl_3$).

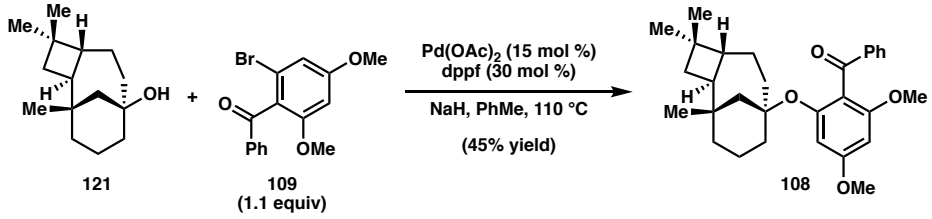
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.97 (ddd, *J* = 11.8, 10.7, 7.9 Hz, 1H), 1.86 – 1.78 (m, 1H), 1.78 – 1.68 (m, 3H), 1.67 (d, *J* = 0.8 Hz, 3H), 1.51 – 1.39 (m, 2H), 1.34 (dt, *J* = 3.5, 2.0 Hz, 1H), 1.33 – 1.22 (m, 4H), 1.15 – 1.04 (m, 1H), 1.02 (d, *J* = 12.8 Hz, 1H), 0.97 (s, 3H), 0.96 (s, 3H), 0.80 (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.

Preparation of benzophenone 108.



Inside a N_2-filled glovebox, to a 1 dram vial containing tertiary alcohol **121** (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 **109** (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 **108** (13.4 mg, 45% yield) as a milky white gum: $[\alpha]_D^{25.0}$ = +1.27° (c = 0.345, $CHCl_3$).

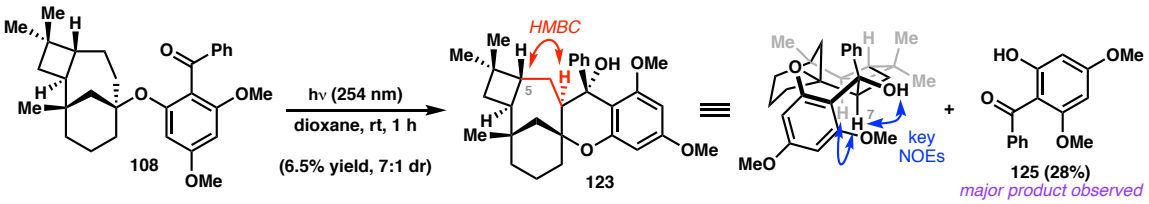
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.76 (m, 2H), 7.51 (tt, *J* = 7.5, 2.7 Hz, 1H), 7.44 – 7.35 (m, 2H), 6.29 (d, *J* = 2.1 Hz, 1H), 6.23 (d, *J* = 2.1 Hz, 1H), 3.83 (s, 3H), 3.70 (s, 3H), 1.90 (ddd, *J* = 12.0, 10.7, 7.9 Hz, 1H), 1.78 (d, *J* = 2.3 Hz, 1H), 1.73 (t, *J* = 6.5 Hz, 2H), 1.68 (dt, *J* = 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.

Preparation of Norrish–Yang product 123



To a 13 x 100 quartz test tube was added benzophenone **108** (15.5 mg, 0.034 mmol). The tube was fitted with a 19/38 rubber septum and the atmosphere was exchanged 3 x 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 **125** (2.4 mg, 28% yield) as a white solid and **123** (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 **123** by ^{1}H NMR, definitive characterization was not achieved.

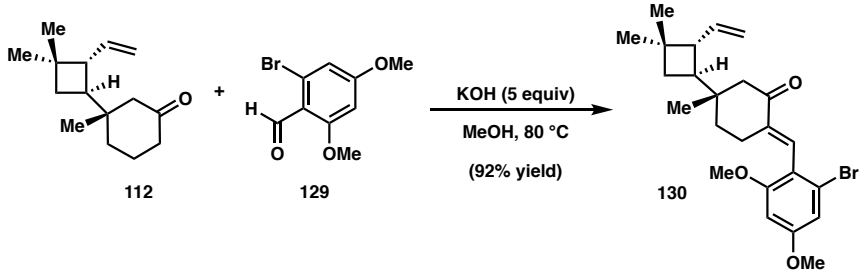
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 1H), 7.24 – 7.09 (m, 4H), 6.11 (dd, *J* = 2.5, 1.1 Hz, 1H), 6.01 (dd, *J* = 2.4, 1.2 Hz, 1H), 3.95 (d, *J* = 1.1 Hz, 1H), 3.78 (d, *J* = 1.2 Hz, 3H), 3.35 (d, *J* = 1.1 Hz, 3H), 2.65 (dd, *J* = 12.7, 3.5 Hz, 1H), 2.62 – 2.52 (m, 1H), 2.40 (t, *J* = 14.4 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.

Preparation of *exo*-enone 130.



To a 200 mL round-bottom flask were added vinyl ketone **112** (884 mg, 4.01 mmol), aryl aldehyde **129** (1.08 g, 4.41 mmol, 1.10 equiv), and KOH (1.13 g, 20.1 mmol, 5.00 equiv). Freshly distilled MeOH (40.1 mL) was then added, the flask fitted with a reflux condenser under ambient conditions and heated to 80 °C for 12 hours. At completion, the volume of MeOH was reduced *in vacuo* and the reaction quenched with a saturated solution of aqueous NH_4Cl. Et_2O was added and the layers were separated. The aqueous layer was extracted twice with Et_2O and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash

chromatography (isocratic: 20% Et_2O/hexane) to afford *exo*-enone **130** (1.66 g, 92% yield) as an off-white solid: $[\alpha]_D^{25.0}$ = +11.4° (c = 1.08, $CHCl_3$).

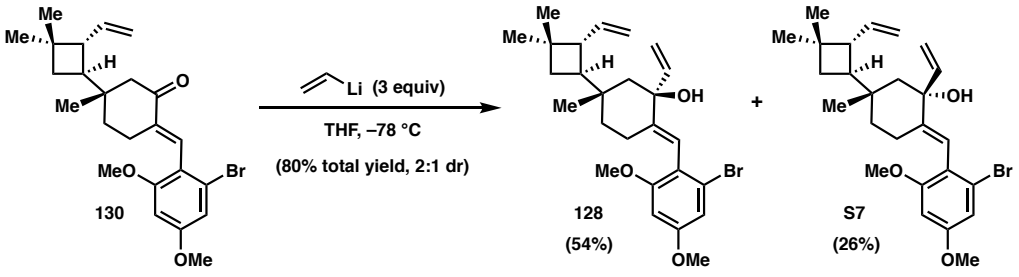
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (t, *J* = 2.0 Hz, 1H), 6.75 (d, *J* = 2.3 Hz, 1H), 6.40 (d, *J* = 2.3 Hz, 1H), 5.74 (ddd, *J* = 17.1, 10.3, 8.6 Hz, 1H), 4.95 (ddd, *J* = 24.7, 2.1, 0.8 Hz, 1H), 4.94 (td, *J* = 2.3, 0.8 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 2.44 – 2.20 (m, 5H), 2.12 (td, *J* = 10.0, 8.5 Hz, 1H), 1.55 (ddd, *J* = 13.3, 10.3, 6.0 Hz, 1H), 1.50 (ddd, *J* = 10.7, 8.4, 0.6 Hz, 1H), 1.45 (d, *J* = 10.4 Hz, 1H), 1.38 (dtd, *J* = 11.0, 5.0, 2.1 Hz, 1H), 0.99 (s, 3H), 0.98 (s, 3H), 0.93 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 202.2, 160.8, 158.6, 139.6, 139.2, 130.5, 125.1, 118.7, 115.3, 109.0, 98.1, 55.8, 55.7, 50.3, 49.4, 45.0, 36.5, 34.9, 33.2, 32.5, 30.1, 24.7, 23.7, 22.6.

FTIR (NaCl, thin film) 3073, 2952, 2863, 1686, 1599, 1558, 1482, 1461, 1435, 1407, 1381, 1367, 1303, 1259, 1214, 1153, 1051, 1035, 996, 938, 911, 960, 831, 795 cm.$^{-1}$

HRMS (MM) calc'd for $C_{24}H_{32}BrO_3$ $[M+H]^+$ 447.1529, found 447.1520.

Preparation of divinyl alcohols 128 and S7.



A 100 mL round-bottom flask was flame dried under vacuum and backfilled with N_2. Dry THF (21.2 mL) was then added, followed by freshly prepared vinyllithium as a solution in THF (8.42 mL, 0.756 M, 3.00 equiv). The solution was cooled to –78 °C and

exo-enone **130** (928 mg, 2.07 mmol) was taken up in 5.0 mL THF and added dropwise over 5 minutes. After 40 minutes, the reaction was quenched with a saturated solution of NH_4Cl and warmed to room temperature. The mixture was diluted with Et_2O and the layers were separated. The aqueous layer was extracted twice with Et_2O and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (30% hexane/CH_2Cl_2 + 1% EtOAc until unreacted **130** and **S7** elute, then 5% EtOAc/CH_2Cl_2) to afford **128** (536 mg, 54%) as a thick, colorless oil, **S7** (260 mg, 26%) as a thick, colorless oil, and recovered **130** (164 mg, 18%).

Preparation of vinyllithium:

THF (38.0 mL) was added to a flame-dried 200 mL round-bottom flask under N_2, followed by tetravinyl tin (2.10 mL, 11.5 mmol). The solution was cooled to –78 °C and *n*-BuLi (17.3 mL, 2.5 M in hexanes, 43.3 mmol, 3.76 equiv) was added dropwise. The reaction was stirred for 20 minutes at –78 °C, then lifted out of the ice bath and allowed to warm to room temperature. The reaction was allowed to stir at room temperature for at least 2 hours before use, provides a ~0.756 M solution of vinyllithium (note: highest yields for 1,2-addition are obtained after stirring for 6 hours, at which time the mixture should be slightly milky grey in appearance).

Data for **128** (major diastereomer, peak 2): $[\alpha]_D^{25.0}$ = –23.8° (c = 1.07, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (d, *J* = 2.3 Hz, 1H), 6.40 (d, *J* = 2.3 Hz, 1H), 6.19 (dd, *J* = 17.2, 10.6 Hz, 1H), 6.04 (d, *J* = 1.5 Hz, 1H), 5.77 (ddd, *J* = 17.1, 10.2, 8.9 Hz, 1H), 5.46 (dd, *J* = 17.3, 1.6 Hz, 1H), 5.21 (dd, *J* = 10.6, 1.5 Hz, 1H), 4.92 (dddd, *J* = 17.0, 14.0, 2.2, 0.8 Hz, 2H), 3.79 (s, 3H), 3.74 (s, 3H), 2.40 – 2.22 (m, 2H), 2.07 (q, *J* = 9.6 Hz, 1H),

1.92 (dt, *J* = 14.3, 4.5 Hz, 1H), 1.51 (q, *J* = 14.0, 13.3 Hz, 2H), 1.44 (d, *J* = 12.7 Hz, 1H), 1.41 (d, *J* = 9.4 Hz, 2H), 1.35 – 1.17 (m, 2H), 1.12 (s, 3H), 0.97 (d, *J* = 1.2 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.7, 158.3, 146.6, 145.3, 140.5, 125.3, 120.4, 119.7, 114.8, 112.9, 108.5, 98.1, 76.1, 55.8, 55.7, 49.3, 47.0, 46.1, 34.7, 34.6, 34.4, 33.1, 30.0, 23.8, 23.4, 22.9.

FTIR (NaCl, thin film) 3424 (br) 3001, 2950, 2930, 2858, 2832, 1599, 1560, 1483, 1459, 1434, 1406, 1379, 1366, 1301, 1268, 1210, 1145, 1053, 1037, 994, 910, 879, 811 cm.$^{-1}$

HRMS (MM) calc'd for $C_{26}H_{34}BrO_2$ $[M–OH]^+$ 457.1742, found 457.1744.

Data for **S7** (minor diastereomer, peak 1): $[\alpha]_D^{25.0}$ = –34.2° (c = 1.03, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (d, *J* = 2.4 Hz, 1H), 6.42 (d, *J* = 2.3 Hz, 1H), 6.23 (d, *J* = 1.4 Hz, 1H), 6.09 (dd, *J* = 17.4, 10.3 Hz, 1H), 5.77 (ddd, *J* = 17.2, 10.2, 8.7 Hz, 1H), 5.48 (dd, *J* = 17.4, 1.5 Hz, 1H), 5.16 (dd, *J* = 10.3, 1.5 Hz, 1H), 4.93 (dddd, *J* = 18.0, 15.2, 2.2, 0.8 Hz, 2H), 3.79 (s, 3H), 3.74 (s, 3H), 2.35 (t, *J* = 9.3 Hz, 1H), 2.15 – 2.02 (m, 2H), 1.90 (dddd, *J* = 14.3, 12.8, 4.4, 1.6 Hz, 1H), 1.77 – 1.65 (m, 2H), 1.59 (d, *J* = 13.2 Hz, 1H), 1.49 – 1.41 (m, 2H), 1.34 (td, *J* = 12.8, 4.3 Hz, 1H), 1.11 (dtd, *J* = 12.6, 4.0, 1.9 Hz, 1H), 0.97 (d, *J* = 1.1 Hz, 6H), 0.89 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 158.4, 146.2, 144.9, 140.6, 125.4, 120.9, 117.9, 115.6, 114.8, 108.4, 98.1, 75.8, 55.8, 55.7, 49.6, 49.1, 46.5, 35.6, 34.9, 34.5, 33.1, 30.1, 25.0, 23.8, 22.3.

FTIR (NaCl, thin film) 3451 (br) 3073, 2998, 2951, 2934, 2858, 1630, 1560, 1560, 1482, 1461, 1434, 1406, 1380, 1366, 1301, 1266, 1211, 1150, 1038, 996, 936, 909, 884, 830, 813 cm.$^{-1}$

HRMS (MM) calc'd for $C_{26}H_{34}BrO_2$ $[M–OH]^+$ 457.1742, found 457.1744.

Preparation of allylic alcohol 127.

A 250 mL round-bottom flask containing divinyl alcohol **128** (807 mg, 1.70 mmol) was pumped into a N_2-filled glovebox where Hoveyda–Grubbs second-generation catalyst (106 mg, 0.170 mmol, 0.100 equiv) and 1,4-benzoquinone (18.4 mg, 0.170 mmol, 0.100 equiv) were added. The flask was sealed under nitrogen, removed from the glovebox, and dry benzene (85.0 mL) was added via syringe. The green reaction mixture was heated to 80 °C for 12 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 (20–30% Et_2O/hexane) to afford allylic alcohol **127** (704 mg, 93%) as a white foam and a single diastereomer at C1: $[\alpha]_D^{25.0}$ = +95.5° (c = 0.815, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (d, *J* = 2.4 Hz, 1H), 6.41 (d, *J* = 2.4 Hz, 1H), 6.32 (d, *J* = 1.7 Hz, 1H), 5.84 (dd, *J* = 10.8, 2.4 Hz, 1H), 5.34 (ddd, *J* = 10.8, 2.8, 2.1 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 2.53 (dt, *J* = 11.6, 2.6 Hz, 1H), 2.37 (td, *J* = 11.2, 7.9 Hz, 1H), 2.28 (dd, *J* = 12.8, 2.3 Hz, 1H), 2.18 (dddd, *J* = 15.1, 11.0, 6.0, 1.9 Hz, 1H), 2.08 (ddd, *J* = 15.1,

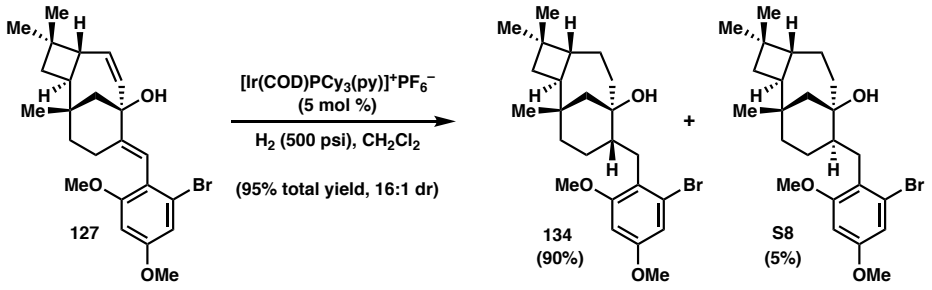
5.2, 3.6 Hz, 1H), 1.75 (s, 1H), 1.60 – 1.46 (m, 2H), 1.41 (dd, J = 12.9, 2.2 Hz, 1H), 1.37 – 1.22 (m, 2H), 1.08 (s, 3H), 1.06 (s, 3H), 0.90 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 158.5, 147.7, 134.6, 131.6, 125.5, 120.8, 116.3, 108.5, 98.2, 76.7, 55.9, 55.7, 50.9, 45.4, 43.4, 38.3, 37.5, 35.1, 32.3, 30.9, 26.2, 24.5, 21.5.

FTIR (NaCl, thin film) 3422 (br) 3002, 2949, 2930, 2862, 1599, 1562, 1481, 1462, 1455, 1434, 1405, 1366, 1302, 1267, 1211, 1149, 1037, 1015, 979, 938, 870, 858, 830, 813, 772, 755 cm.$^{-1}$

HRMS (MM) calc'd for $C_{24}H_{30}BrO_2$ $[M–OH]^+$ 429.1429, found 429.1429.

Preparation of aryl bromides 134 and S8.



Inside a N_2-filled glovebox, Crabtree's catalyst (59.6 mg, 0.074 mmol, 0.05 equiv) was added to a 100 mL round-bottom flask containing allylic alcohol **127** (663 mg, 1.48 mmol). CH_2Cl_2 (14.8 mL) was added and the flask was placed inside a steel bomb, which was closed under nitrogen and brought out of the glovebox. The pressure gauge was quickly attached and all bolts on the bomb tightened with a wrench. The bomb was connected to a H_2 inlet and the vessel purged with 250 psi H_2 three times before being charged to 500 psi. The reaction was stirred at room temperature for 3 hours, at which time H_2 was vented from the reaction. CH_2Cl_2 was removed *in vacuo* and the crude residue

purified by silica gel flash chromatography (isocratic: 40% Et_2O/hexane) to afford aryl bromides **134** (599 mg, 90%) and **S8** (37.4 mg, 5%) as white, crystalline solids.

Data for **134** (major diastereomer, peak 2): $[\alpha]_D^{25.0}$ = –20.5° (c = 0.900, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (d, *J* = 2.4 Hz, 1H), 6.40 (d, *J* = 2.4 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.03 (dd, *J* = 13.2, 2.7 Hz, 1H), 2.61 (dd, *J* = 13.2, 10.0 Hz, 1H), 2.08 (ddd, *J* = 11.9, 10.6, 7.9 Hz, 1H), 1.95 (ddd, *J* = 13.8, 10.4, 3.6 Hz, 1H), 1.83 (dd, *J* = 12.8, 2.6 Hz, 1H), 1.78 – 1.57 (m, 4H), 1.57 – 1.34 (m, 5H), 1.34 – 1.23 (m, 2H), 1.01 (s, 3H), 0.99 (s, 3H), 0.96 (dd, *J* = 12.9, 5.6 Hz, 2H), 0.77 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 158.9, 125.9, 122.8, 108.9, 98.4, 76.2, 55.9, 55.6, 51.7, 50.1, 45.4, 38.7, 38.0, 36.0, 35.0, 33.9, 33.3, 30.8, 28.5, 26.6, 26.3, 21.3, 21.0.

FTIR (NaCl, thin film) 3474 (br), 3000, 2946, 2930, 2862, 1603, 1568, 1482, 1461, 1435, 1410, 1294, 1272, 1212, 1198, 1151, 1130, 1054, 1038, 999, 937, 876, 831, 756 cm.$^{-1}$

HRMS (MM) calc'd for $C_{24}H_{34}BrO_2$ $[M–OH]^+$ 433.1737, found 433.1685.

Data for **S8** (minor diastereomer, peak 1): $[\alpha]_D^{25.0}$ = –27.7° (c = 0.950, $CHCl_3$).

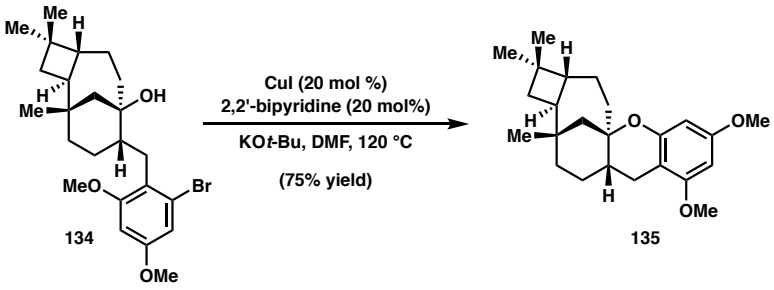
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (d, *J* = 2.5 Hz, 1H), 6.40 (d, *J* = 2.4 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 2.85 (dd, *J* = 13.6, 5.8 Hz, 1H), 2.59 (dd, *J* = 13.6, 8.1 Hz, 1H), 2.29 (dddd, *J* = 11.4, 8.0, 5.8, 3.5 Hz, 1H), 1.98 (ddd, *J* = 11.0, 9.4, 6.7 Hz, 2H), 1.80 – 1.52 (m, 4H), 1.52 – 1.37 (m, 4H), 1.37 – 1.26 (m, 4H), 1.25 (s, 1H), 0.94 (s, 6H), 0.78 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.9, 158.5, 126.1, 123.0, 109.2, 98.3, 75.2, 55.8, 55.7, 49.3, 46.4, 45.4, 41.0, 38.5, 36.9, 36.6, 33.8, 30.5, 30.4, 29.2, 27.6, 24.2, 24.1, 21.5.

FTIR (NaCl, thin film) 3482 (br), 2998, 2945, 2928, 2859, 1690, 1648, 1602, 1567, 1482, 1459, 1435, 1409, 1381, 1364, 1294, 1273, 1211, 1198, 1154, 1134, 1051, 1039, 973, 937, 830, 809, 756.

HRMS (MM) calc'd for $C_{24}H_{35}BrO_3Na$ $[M+Na]^+$ 475.1818, found 475.1858.

Preparation of pentacycle 135.



Aryl bromide **134** (274 mg, 0.607 mmol) was added to each of two 20 mL scintillation vials and pumped inside a N_2-filled glovebox, where CuI (23.1 mg, 0.121 mmol, 0.200 equiv), 2,2'-bipyridine (18.9, 0.121 mmol, 0.200 equiv), and KO*t*-Bu (204, 1.82 mmol, 3.00 equiv) were added as solids to each. Dry DMF (6.10 mL) was then added, the reaction sealed under N_2 with a Teflon screw-cap and heated to 120 °C in a pre-heated aluminum block inside the glovebox for 3.5 hours. After cooling to room temperature, the reaction mixtures were combined and loaded directly onto a short silica gel column, pre-equilibrated with 5% Et_2O/hexane. The column was eluted with 5% Et_2O/hexane (isocratic) to afford pentacycle **135** (339 mg, 75%) as a white solid: $[\alpha]_D^{25.0}$ = +42.4° (c = 1.08, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (d, *J* = 2.4 Hz, 1H), 6.00 (d, *J* = 2.4 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 2.55 (dd, *J* = 16.6, 4.0 Hz, 1H), 2.20 – 2.03 (m, 2H), 1.97 (dd, *J* = 12.6,

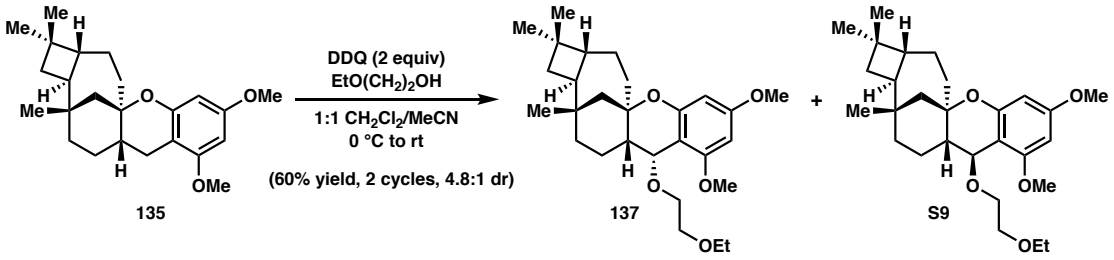
2.3 Hz, 1H), 1.77 (dddd, *J* = 18.7, 9.0, 7.4, 4.8 Hz, 2H), 1.69 – 1.55 (m, 4H), 1.52 – 1.41 (m, 3H), 1.32 (t, *J* = 10.7, 9.6 Hz, 2H), 1.32 – 1.20 (m, 1H), 1.17 (dd, *J* = 12.6, 1.1 Hz, 1H), 0.99 (s, 3H), 0.97 (s, 3H), 0.86 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 158.3, 154.4, 104.5, 94.2, 90.8, 79.9, 55.5, 55.4, 48.0, 44.3, 40.9, 38.0, 36.9, 35.6, 35.1, 33.5, 30.8, 28.4, 27.1, 26.5, 22.8, 20.9, 19.9.

FTIR (NaCl, thin film) 2995, 2945, 2928, 2862, 2843, 1617, 1589, 1494, 1460, 1420, 1363, 1288, 1215, 1201, 1186, 1164, 1145, 1108, 1074, 1054, 1033, 1008, 942, 928, 810 cm.$^{-1}$

HRMS (MM) calc'd for $C_{24}H_{35}O_3$ $[M+H]^+$ 371.2581, found 371.2578.

Preparation of benzylic ethers 137 and S9.



To a flame-dried 25 mL round-bottom flask was added pentacycle **135** (80.0 mg, 0.216 mmol) and the atmosphere exchanged three times for argon. A 1:1 mixture of dry MeCN/CH_2Cl_2 (6.40 mL) was then added, followed by ethoxyethanol (1.54 mL) via syringe and the solution cooled to 0 °C. A previously prepared stock solution of DDQ in dry MeCN (0.860 mL, 0.508 M, 2.00 equiv) was then added dropwise. The reaction turned grey/blue immediately upon addition of DDQ and slowly turned green-blue by the end of addition. Once the addition was complete, the reaction was lifted from the ice bath and gradually warmed to room temperature. The color became an olive green-brown after 1

hour, indicating the reaction had stalled at ~50% conversion (as judged by TLC). At this point, the reaction was quenched with a saturated solution of aqueous $NaHCO_3$ and stirred vigorously for 10 minutes before the layers were separated. The aqueous layer was extracted twice more with CH_2Cl_2 and the combined organic layers were washed with one portion of DI H_2O, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography: SiO_2 was first deactivated by applying a few drops of aqueous NH_4OH (28%) to the top of a dry column and equilibrating with 100 mL of 5% Et_2O/hexane. The crude residue was then applied and eluted with fresh 5% Et_2O/hexane until unreacted **135** elutes completely, then 20% Et_2O/hexane until complete elution of second diastereomer to afford a mixture of **137** and **S9** (41.0 mg, 41% yield) as a colorless, foamy residue, and recovered starting material **135** (40.8 mg, 51%). The recovered starting material was re-subjected to the reaction conditions described above to afford additional **137** and **S9** (18.8 mg, 60% total over 2 cycles) and **135** (15.2 mg, 74% overall brsm). Analytically pure samples of **137** and **S9** were obtained by silica gel preparative TLC (30% Et_2O, 1% Et_3N/hexane) and a representative spectrum of the mixture as used in the next step is also provided.

Data for **95** (major diastereomer, peak 1): $[\alpha]_D^{25.0}$ = +43.5° (c = 0.815, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 (d, *J* = 2.4 Hz, 1H), 5.94 (d, *J* = 2.3 Hz, 1H), 4.27 (d, *J* = 3.3 Hz, 1H), 3.98 (dt, *J* = 9.8, 4.9 Hz, 1H), 3.81 (dd, *J* = 10.9, 5.1 Hz, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.58 (dd, *J* = 5.9, 4.9 Hz, 2H), 3.53 (q, *J* = 7.0 Hz, 2H), 2.48 – 2.36 (m, 1H), 2.21 (qd, *J* = 14.4, 4.1 Hz, 1H), 2.10 (ddd, *J* = 12.2, 10.7, 7.9 Hz, 1H), 2.00 (dd, *J* = 12.7, 2.3 Hz, 1H), 1.79 – 1.61 (m, 3H), 1.59 – 1.41 (m, 4H), 1.42 – 1.20 (m, 4H), 1.20 (t, *J* = 7.0 Hz, 3H), 0.99 (s, 3H), 0.98 (s, 3H), 0.86 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.1, 159.7, 154.7, 106.6, 93.8, 91.2, 80.5, 72.1, 71.4, 70.5, 66.7, 55.4, 55.4, 49.3, 47.6, 46.1, 39.4, 39.3, 36.3, 34.8, 33.5, 32.4, 30.8, 26.8, 23.1, 22.3, 20.8, 15.4.

FTIR (NaCl, thin film) 2948, 2930, 2864, 1614, 1589, 1491,1462, 1438, 1424, 1365, 1353, 1332, 1320, 1287, 1215, 1202, 1189, 1166, 1148, 1109, 1053, 1033, 1005, 951, 921, 866, 811, 731, 638 cm.$^{-1}$

HRMS (MM) calc'd for $C_{24}H_{33}O_3$ $[M–O(CH_2)_2OEt]^+$ 369.2424, found 369.2430.

Data for **S9** (minor diastereomer, peak 2): $[\alpha]_D^{25.0}$ = +29.6° (c = 0.230, $CHCl_3$).

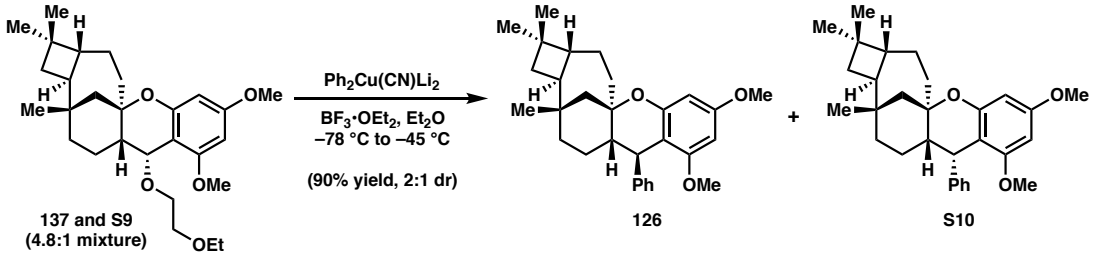
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.02 (d, *J* = 2.4 Hz, 1H), 5.92 (d, *J* = 2.4 Hz, 1H), 4.30 (d, *J* = 10.4 Hz, 1H), 3.78 (s, 3H), 3.75 (ddd, *J* = 9.1, 3.0, 1.3 Hz, 1H), 3.73 (s, 3H), 3.58 – 3.45 (m, 5H), 2.24 – 2.04 (m, 2H), 1.92 (ddt, *J* = 14.7, 9.9, 3.2 Hz, 2H), 1.80 – 1.64 (m, 2H), 1.65 – 1.40 (m, 5H), 1.36 – 1.19 (m, 4H), 1.19 (t, *J* = 7.0 Hz, 3H), 0.97 (s, 3H), 0.96 (s, 3H), 0.86 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.0, 160.0, 155.9, 105.8, 94.2, 91.7, 81.7, 73.4, 70.5, 67.8, 66.7, 55.5, 55.4, 48.2, 47.2, 44.4, 37.8, 37.2, 35.6, 35.1, 33.2, 30.8, 28.4, 26.4, 23.7, 20.9, 20.4, 15.4.

FTIR (NaCl, thin film) 2947, 2934, 2864, 1613, 1587, 1490, 1459, 1438, 1421, 1364, 1349, 1312, 1288, 1267, 1245, 1216, 1202, 1147, 1107, 1054, 1034, 1002, 973, 943, 868. 812, 736, 636 cm.$^{-1}$

HRMS (MM) calc'd for $C_{24}H_{33}O_3$ $[M–O(CH_2)_2OEt]^+$ 369.2424, found 369.2427.

Preparation of diarylmethanes 126 and S10.



A 10 mL round-bottom flask containing CuCN (11.9 mg, 0.133 mmol, 2.05 equiv) was flame-dried under vacuum. After cooling to room temperature, the flask was backfilled with argon and dry Et_2O (2.70 mL) was added via syringe. The suspension was cooled to –78 °C under argon and PhLi (0.140 mL, 1.9 M in dibutyl ether, 0.266 mmol, 4.09 equiv) was added dropwise. After stirring at –78 °C for 5 minutes, the reaction was warmed to 0 °C and stirred for an additional 30 minutes. The higher-order cuprate was then cooled back to –78 °C and the 4.8:1 mixture of benzylic ethers **137** and **S9** (30.0 mg, 0.065 mmol) was as a solution in Et_2O (1.00 mL). The reaction was stirred for 1-2 minutes before BF_3•OEt_2 (0.160 mL, 1.30 mmol, 20.0 equiv) was added dropwise via syringe. The reaction was stirred at –78 °C for 10 minutes, then quickly transferred to a pre-equilibrated bath at –55 °C, which was allowed to –50 °C over 5 minutes, then maintained at or just below –45 °C for another 30 minutes. The reaction was checked for completion by TLC, then quenched with aqueous $NaHCO_3$ and warmed to room temperature. The layers were separated and the aqueous layer extracted twice with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (isocratic: 5% Et_2O/hexane) to afford diarylmethanes **126** and **S10**

(26.3 mg, 90%) as a 2:1 inseparable mixture, white solid: $[\alpha]_D^{25.0}$ = +2.08° (c = 1.23, $CHCl_3$).

^{1}H NMR (2:1 dr, asterisk denotes minor diastereomer, 400 MHz, $CDCl_3$) δ 7.24 – 6.96 (m, 5H), 6.10* (d, *J* = 2.4 Hz, 1H), 6.07 (d, *J* = 2.5 Hz, 1H), 6.03* (d, *J* = 2.4 Hz, 1H), 5.93 (d, *J* = 2.4 Hz, 1H), 4.10* (d, *J* = 6.4 Hz, 1H), 3.79* (s, 3H), 3.76 (s, 3H), 3.46* (s, 3H), 3.47 (d, *J* = 11.3 Hz, 1H), 3.20 (s, 3H), 2.23 – 2.06 (m, 1H), 2.00 (dd, *J* = 12.7, 2.4 Hz, 1H), 1.93* (dd, *J* = 12.6, 2.5 Hz, 1H), 1.88 – 1.73 (m, 2H), 1.73 – 1.60 (m, 3H), 1.55 – 1.41 (m, 4H), 1.39 – 1.26 (m, 5H), 1.20 (q, *J* = 13.1, 12.1 Hz, 1H), 1.00 (s, 3H), 0.99 (s, 3H), 0.92* (s, 3H), 0.83 (s, 3H), 0.82* (s, 3H), 0.74* (s, 3H).

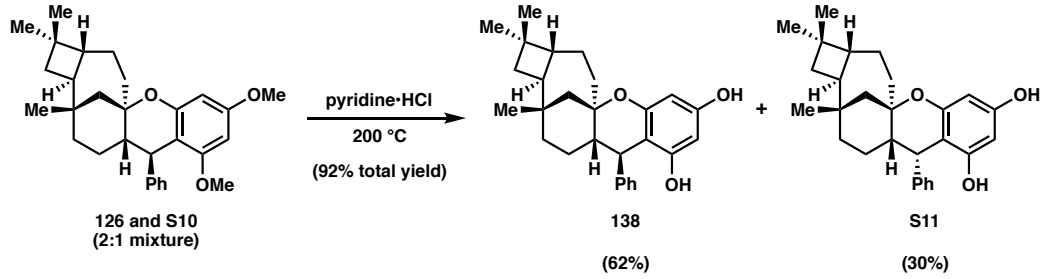
^{13}C NMR (**126**, major diastereomer, 101 MHz, $CDCl_3$) δ 160.0, 159.2, 155.2, 146.7, 129.8, 127.7, 125.4, 109.2, 94.5, 92.7, 80.4, 55.3, 55.2, 50.7, 48.1, 44.3, 41.9, 37.9, 36.9, 35.6, 35.1, 33.3, 30.8, 28.2, 26.3, 24.3, 20.9, 20.2.

^{13}C NMR (**S9**, minor diastereomer 101 MHz, $CDCl_3$) δ 160.1, 159.2, 155.1, 141.5, 128.9, 127.0, 125.5, 106.4, 94.1, 91.5, 80.7, 55.6, 55.4, 50.0, 45.8, 44.3, 39.3, 38.5, 36.7, 35.5, 35.0, 33.2, 32.7, 30.8, 26.2, 25.8, 20.9, 20.4.

FTIR (NaCl, thin film) 3081, 3059, 3025, 2998, 2948, 2934, 2864, 2843, 1614, 1588, 1490,1460, 1454, 1440, 1420, 1364, 1307, 1288, 1274, 1249, 1216, 1202, 1166, 1148, 1123, 1105, 1076, 1054, 1033, 1005, 943, 870, 811, 759, 740, 701 cm.$^{-1}$

HRMS (MM) calc'd for $C_{30}H_{39}O_3$ $[M+H]^+$ 447.2894, found 447.2905.

Preparation of resorcinols 138 and S11.



Solid pyridine•HCl (1.44 g, 12.5 mmol, 307 equiv) was weighed into each of two 2-dram vials, containing a 2:1 mixture of diarylmethanes **126** and **S10** (18.2 mg, 0.041 mmol). The vials were sealed with a Teflon screw-cap under a stream of argon and heated to 200 °C in a pre-heated aluminum block for 2.5 hours. (Note: it is important to choose a vial/heating block combination that will cover the entire volume of the solid to ensure that it stays completely melted during the course of the reaction). The reactions were cooled to room temperature, during which time the mixture solidified. The crude solids were dissolved in DI H_2O, and combined by pipetting dropwise into an Erlenmeyer flask containing a saturated solution of aqueous $NaHCO_3$. EtOAc was then added and the layers were separated. The aqueous layer was extracted three times with EtOAc and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (isocratic: 10% EtOAc, 1% AcOH/hexane) to separate resorcinols **138** and **S11**. The concentrated fractions for each diastereomer (initially a pale orange oil) were each passed through another short plug of silica gel (eluting with 20% EtOAc/heaxnes) to remove residual AcOH and remaining trace impurities to afford **138** (21.3 mg, 62%) and **S11** (10.3 mg, 30%) as white solids.

Data for **138** (major diastereomer, peak 1): $[\alpha]_D^{25.0} = -28.2°$ (c = 0.475, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.26 (m, 5H), 6.00 (d, *J* = 2.6 Hz, 1H), 5.88 (d, *J* = 2.6 Hz, 1H), 4.73 (s, 1H), 4.46 (s, 1H), 3.49 (d, *J* = 11.4 Hz, 1H), 2.16 (ddd, *J* = 12.3, 10.4, 7.9 Hz, 1H), 2.01 (dd, *J* = 12.8, 2.3 Hz, 1H), 1.85 – 1.58 (m, 4H), 1.54 – 1.44 (m, 2H), 1.44 – 1.30 (m, 4H), 1.28 (m, 1H), 1.18 (d, *J* = 12.9 Hz, 1H), 1.10 – 1.03 (m, 1H), 1.00 (s, 3H), 0.99 (s, 3H), 0.85 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 155.8, 155.4, 142.3, 128.0, 106.3, 97.7, 96.8, 80.1, 50.5, 48.1, 44.2, 41.8, 37.8, 36.9, 35.6, 35.2, 33.3, 30.8, 28.6, 26.3, 24.0, 20.9, 20.0.

FTIR (NaCl, thin film) 3511 (br), 3386 (br), 3060, 3024, 2948, 2928, 2863, 1702, 1627, 1598, 1509, 1492, 1459, 1364, 1349, 1320, 1272, 1248, 1228, 1166, 1138, 1087, 1072, 1057, 1034, 1014, 925, 869, 831, 761, 738, 703, 667, 638, 571, 516 $cm.^{-1}$

HRMS (MM) calc'd for $C_{28}H_{35}O_3$ $[M+H]^+$ 419.2581, found 419.2591.

Data for **S11** (minor diastereomer, peak 2): $[\alpha]_D^{25.0}$ = +26.7° (c = 0.180, $CHCl_3$).

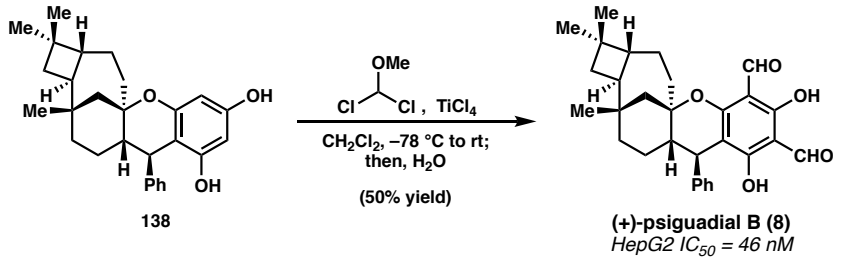
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.21 (m, 5H), 6.02 (d, *J* = 2.5 Hz, 1H), 5.96 (d, *J* = 2.5 Hz, 1H), 4.73 (s, 1H), 4.30 (s, 1H), 4.00 (d, *J* = 7.0 Hz, 1H), 2.16 (ddd, *J* = 12.5, 7.0, 3.9 Hz, 1H), 1.93 (dd, *J* = 12.7, 2.3 Hz, 2H), 1.79 (ddd, *J* = 12.3, 10.3, 7.8 Hz, 1H), 1.66 (ddd, *J* = 12.4, 8.7, 5.4 Hz, 1H), 1.57 – 1.43 (m, 5H), 1.39 – 1.28 (m, 4H), 1.23 – 1.12 (m, 3H), 1.09 – 0.95 (m, 2H), 0.91 (s, 3H), 0.82 (s, 3H), 0.75 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.2, 155.7, 155.4, 138.6, 127.4, 104.8, 97.6, 95.9, 80.4, 49.7, 45.6, 44.2, 39.6, 38.3, 36.6, 35.4, 35.1, 33.2, 32.0, 30.8, 29.9, 26.1, 25.4, 20.8, 20.3.

FTIR (NaCl, thin film) 3385 (br), 3027, 2949, 2925, 2857, 1624, 1600, 1508, 1493, 1459, 1452, 1377, 1364, 1247, 1190, 1163, 1143, 1086, 1055, 1034, 1015, 925, 826, 761, 721, 701 $cm.^{-1}$

HRMS (MM) calc'd for $C_{28}H_{35}O_3$ $[M+H]^+$ 419.2581, 419.2595.

Preparation of (+)-psiguadial B (8).



To a 2-dram vial was added resorcinol **138** (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 turned 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 (**8**) (8.7 mg, 50%) as an ivory solid. Note: **3** is streaky on SiO_2 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, $CHCl_3$).

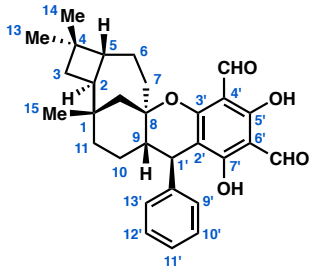
^{1}H NMR (400 MHz, $CDCl_3$) δ 13.51 (s, 1H), 13.04 (s, 1H), 10.07 (s, 2H), 7.26 (dd, *J* = 14.6, 1.5 Hz, 2H), 7.23 – 7.17 (m, 1H), 7.10 (br s, 2H), 3.49 (d, *J* = 11.5 Hz, 1H), 2.20 – 2.12 (m, 1H), 2.09 (dd, *J* = 12.7, 2.4 Hz, 1H), 1.92 (ddd, *J* = 14.9, 12.8, 4.2 Hz, 1H), 1.82 (ddd, *J* = 12.3, 8.8, 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.

(+)-psiguadial B (**8**) carbon numbering as reported by Shao et al.[15]



Comparison of ^{1}H NMR spectral data for natural and synthetic (+)-psiguadial B (3).

carbon number	**Natural (+)-psiguadial B** ^{1}H NMR, 500 MHz, $CDCl_3$	**Synthetic (+)-psiguadial B** ^{1}H NMR, 400 MHz, $CDCl_3$
5'-OH	δ 13.51 (s, 1H)	δ 13.51 (s, 1H)
7'-OH	13.04 (s, 1H)	13.04 (s, 1H)
14', 15'	10.08 (s, 2H)	10.07 (s, 2H)
9', 13'	7.23 (2H)	7.26 (dd, *J* = 14.6, 1.5 Hz, 2H)
11'	7.18 (3H)	7.23 – 7.17 (m, 1H)
10', 12'	–	7.10 (br m, 2H)
1'	3.49 (d, *J* = 11.5 Hz, 1H)	3.49 (d, *J* = 11.5 Hz, 1H)
2	2.16 (1H)	2.20 – 2.12 (m, 1H)
12	2.08 (1H)	2.09 (dd, *J* = 12.7, 2.4 Hz, 1H)
7	1.93 (1H)	1.92 (ddd, *J* = 14.9, 12.8, 4.2 Hz, 1H)
5	1.82 (m, 1H)	1.82 (ddd, *J* = 12.3, 8.8, 5.6 Hz, 1H)
9	1.68 (1H)	1.73 – 1.59 (m, 3H)
6	1.65 (1H)	–
7	1.58 (m, 1H)	–
3	1.52 (1H)	1.53 – 1.44 (m, 1H)
10	1.49 (m, 2H)	1.49 (ddd, *J* = 11.6, 8.1, 2.9 Hz, 2H)
6, 11	1.41 (2H)	–
3	1.37 (1H)	1.44 – 1.29 (m, 4H)
12	1.29 (1H)	–
11	1.10 (1H)	1.05 (dd, *J* = 7.6, 5.8 Hz, 1H)
13	1.02 (s, 3H)	1.02 (s, 3H)
14	1.01 (s, 3H)	1.00 (s, 3H)
15	0.86 (s, 3H)	0.85 (s, 3H)

Comparison of ^{13}C NMR spectroscopic data for natural and synthetic (+)-psiguadial B (8).

carbon number	**Natural (+)-psiguadial B** ^{13}C NMR, 125 MHz, $CDCl_3$	**Synthetic (+)-psiguadial B** ^{13}C NMR, 101 MHz, $CDCl_3$	Δ
15'	192.3	192.3	0.0
14'	191.4	191.5	0.1
7'	169.6	169.6	0.0
5'	168.5	168.5	0.0
3'	163.5	163.5	0.0
8'	143.4	143.4	0.0
9', 11', 13'	128.2	128.2	0.0
10', 12'	126.2	126.2	0.0
2'	105.7	105.7	0.0
4'	104.6	104.6	0.0
6'	104.2	104.1	–0.1
8	84.1	84.1	0.0
9	50.0	50.0	0.0
12	47.5	47.4	–0.1
5	44.1	44.0	–0.1
1'	40.4	40.4	0.0
11	37.6	37.6	0.0
2	37.0	36.9	–0.1
3	35.5	35.4	–0.1
4	35.1	35.1	0.0
1	33.4	33.4	0.0
13	30.6	30.6	0.0
7	29.4	29.3	–0.1
15	26.1	26.1	0.0
10	23.9	23.9	0.0
14	20.7	20.7	0.0
6	20.1	20.1	0.0

1.7 NOTES AND REFERENCES

(1) Arima, H.; Danno, G. *Biosci. Biotechnol. Biochem.* **2002**, *66*, 1727.
(2) Begum, S.; Hassan, S. I.; Siddiqui, B. S.; Shaheen, F.; Nabeel Ghayur, M.; Gilani, A. H. *Phytochemistry* **2002**, *61*, 399.
(3) Mukhtar, H. M.; Ansari, S. H.; Bhat, Z. A.; Naved, T.; Singh, P. *Pharmazie* **2006**, *61*, 725.
(4) Oh, W. K.; Lee, C. H.; Lee, M. S.; Bae, E. Y.; Sohn, C. B.; Oh, H.; Kim, B. Y.; Ahn, J. S. *J. Ethnopharmacol.* **2005**, *96*, 411.
(5) Yang, X.-L.; Hsieh, K.-L.; Liu, J.-K. *Org. Lett.* **2007**, *9*, 5135.
(6) Singh, I. P.; Sidana, J.; Bharate, S. B.; Foley, W. J. *Nat. Prod. Rep.* **2010**, *27*, 393.
(7) Wang, J.; Zhai, W. Z.; Zou, Y. K.; Zhu, J. J.; Xiong, J.; Zhao, Y.; Yang, G. X.; Fan, H.; Hamann, M. T.; Xia, G.; et al. *Tetrahedron Lett.* **2012**, *53*, 2654.
(8) Ghisalberti, E. L. *Phytochemistry* **1996**, *41*, 7.
(9) Shang, Z.-C.; Yang, M.-H.; Liu, R.-H.; Wang, X.-B.; Kong, L.-Y. *Sci. Rep.* **2016**, *6*.
(10) Chao, E. C.; Henry, R. R. *Nat. Rev. Drug Discov.* **2010**, *9*, 551.
(11) Yang, X.; Guo, Q.; Wang, Y.; Xu, W.; Tian, L.; Tian, X. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1107.
(12) Xu, R.; Snyder, J. K.; Nakanishi, K. *J. Am. Chem. Soc.* **1984**, *106*, 734.
(13) Soliman, F. M.; Fathy, M. M.; Salama, M. M.; Al-Abd, A. M.; Saber, F. R.; El-Halawany, A. M. *Sci. Rep.* **2014**, *4*, 5410.
(14) Kato, E.; Kawakami, K.; Kawabata, J. *J. Enzyme Inhib. Med. Chem.* **2018**, *33*, 106.
(15) Shao, M.; Wang, Y.; Liu, Z.; Zhang, D.-M.; Cao, H.-H.; Jiang, R.-W.; Fan, C.-L.; Zhang, X.-Q.; Chen, H.-R.; Yao, X.-S.; et al. *Org. Lett.* **2010**, *12*, 5040.
(16) Shao, M.; Wang, Y.; Jian, Y.-Q.; Huang, X.-J.; Zhang, D.-M.; Tang, Q.-F.; Jiang, R.-W.; Sun, X.-G.; Lv, Z.-P.; Zhang, X.-Q.; et al. *Org. Lett.* **2012**, *14*, 5262.
(17) Dehal, S. S.; Croteau, R. *Arch. Biochem. Biophys.* **1988**, *261*, 346.
(18) Cai, Y.; Jia, J.-W.; Crock, J.; Lin, Z.-X.; Chen, X.-Y.; Croteau, R. *Phytochemistry* **2002**, *61*, 523.
(19) Moussa, G. E. *Acta Chem. Scand.* **1968**, *22*, 3329.
(20) Tran, D. N.; Cramer, N. *Chem. – Eur. J.* **2014**, *20*, 10654.
(21) Newton, C. G.; Tran, D. N.; Wodrich, M. D.; Cramer, N. *Angew. Chem. Int. Ed.* **2017**, *56*, 13776.
(22) Lawrence, A. L.; Adlington, R. M.; Baldwin, J. E.; Lee, V.; Kershaw, J. A.; Thompson, A. L. *Org. Lett.* **2010**, *12*, 1676.
(23) Kinebuchi, M.; Uematsu, R.; Tanino, K. *Tetrahedron Lett.* **2017**, *58*, 1382.
(24) Sasmal, P. K.; Maier, M. E. *Org. Lett.* **2002**, *4*, 1271.
(25) López, F.; Castedo, L.; Mascareñas, J. L. *Org. Lett.* **2005**, *7*, 287.
(26) Blumenkopf, T. A.; Bratz, M.; Castaneda, A.; Look, G. C.; Overman, L. E.; Rodriguez, D.; Thompson, A. S. *J. Am. Chem. Soc.* **1990**, *112*, 4386.
(27) Willis, N. J.; Bray, C. D. *Chem. – Eur. J.* **2012**, *18*, 9160.
(28) Selenski, C.; Pettus, T. R. R. *J. Org. Chem.* **2004**, *69*, 9196.
(29) Marsini, M. A.; Huang, Y.; Lindsey, C. C.; Wu, K.-L.; Pettus, T. R. R. *Org. Lett.* **2008**, *10*, 1477.

(30) Feng, Z.-G.; Bai, W.-J.; Pettus, T. R. R. *Angew. Chem. Int. Ed.* **2015**, *54*, 1864.
(31) Ferreira, S. B.; Silva, F. de C. da; Pinto, A. C.; Gonzaga, D. T. G.; Ferreira, V. F. *J. Heterocycl. Chem.* **2009**, *46*, 1080.
(32) Selenski, C.; Mejorado, L. H.; Pettus, T. R. R. *Synlett* **2004**, *2004*, 1101.
(33) Selenski, C.; Pettus, T. R. R. *Tetrahedron* **2006**, *62*, 5298.
(34) Wenderski, T. A.; Marsini, M. A.; Pettus, T. R. R. *Org. Lett.* **2011**, *13*, 118.
(35) Arai, S.; Koike, Y.; Hada, H.; Nishida, A. *J. Am. Chem. Soc.* **2010**, *132*, 4522.
(36) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10006.
(37) Wiskur, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 6176.
(38) France, S.; Wack, H.; Taggi, A. E.; Hafez, A. M.; Wagerle, T. R.; Shah, M. H.; Dusich, C. L.; Lectka, T. *J. Am. Chem. Soc.* **2004**, *126*, 4245.
(39) Pracejus, H. *Justus Liebigs Ann. Chem.* **1960**, *634*, 9.
(40) Zhang, Y.-R.; He, L.; Wu, X.; Shao, P.-L.; Ye, S. *Org. Lett.* **2008**, *10*, 277.
(41) Paull, D. H.; Weatherwax, A.; Lectka, T. *Tetrahedron* **2009**, *65*, 6771.
(42) d'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 1376.
(43) Vuagnoux-d'Augustin, M.; Alexakis, A. *Chem. – Eur. J.* **2007**, *13*, 9647.
(44) Scholl, R.; Seer, C.; Weitzenböck, R. *Berichte Dtsch. Chem. Ges.* **1910**, *43*, 2202.
(45) Zhang, Q.; Botting, N. P.; Kay, C. *Chem. Commun.* **2011**, *47*, 10596.
(46) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635.
(47) Hsiao, C.-C.; Raja, S.; Liao, H.-H.; Atodiresei, I.; Rueping, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 5762.
(48) Gharpure, S. J.; Sathiyanarayanan, A. M.; Vuram, P. K. *RSC Adv.* **2013**, *3*, 18279.
(49) Ananikov, V. P.; Orlov, N. V.; Beletskaya, I. P. *Organometallics* **2006**, *25*, 1970.
(50) Cho, Y. S.; Kim, H. Y.; Cha, J. H.; Pae, A. N.; Koh, H. Y.; Choi, J. H.; Chang, M. H. *Org. Lett.* **2002**, *4*, 2025.
(51) Yang, N. C.; Yang, D.-D. H. *J. Am. Chem. Soc.* **1958**, *80*, 2913.
(52) Chen, C. *Org. Biomol. Chem.* **2016**, *14*, 8641.
(53) Paquette, L. A.; Sugimura, T. *J. Am. Chem. Soc.* **1986**, *108*, 3841.
(54) Bach, T.; Aechtner, T.; Neumüller, B. *Chem. – Eur. J.* **2002**, *8*, 2464.
(55) Singhal, N.; Koner, A. L.; Mal, P.; Venugopalan, P.; Nau, W. M.; Moorthy, J. N. *J. Am. Chem. Soc.* **2005**, *127*, 14375.
(56) Fleming, I.; Kemp-Jones, A. V.; Long, W. E.; Thomas, E. J. *J. Chem. Soc. Perkin Trans. 2* **1976**, *0*, 7.
(57) Breslow, R.; Winnik, M. A. *J. Am. Chem. Soc.* **1969**, *91*, 3083.
(58) Breslow, R.; Rothbard, J.; Herman, F.; Rodriguez, M. L. *J. Am. Chem. Soc.* **1978**, *100*, 1213.
(59) Andreu, I.; Palumbo, F.; Tilocca, F.; Morera, I. M.; Boscá, F.; Miranda, M. A. *Org. Lett.* **2011**, *13*, 4096.
(60) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333.
(61) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395.
(62) Parrish, C. A.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 2498.
(63) Vorogushin, A. V.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 8146.
(64) Gilman, H.; Jones, R. G.; Woods, L. A. *J. Org. Chem.* **1952**, *17*, 1630.
(65) Hong, A. Y.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2014**, *53*, 5248.
(66) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(67) Suchand, B.; Krishna, J.; Mritunjoy, K.; Satyanarayana, G. *RSC Adv.* **2014**, *4*, 13941.
(68) Achilonu, M. C.; Bonnet, S. L.; van der Westhuizen, J. H. *Org. Lett.* **2008**, *10*, 3865.
(69) Bezuidenhoudt, B. C. B.; Brandt, E. V.; Roux, D. G. *J. Chem. Soc. Perkin 1* **1984**, *0*, 2767.
(70) Hayes, C. J.; Whittaker, B. P.; Watson, S. A.; Grabowska, A. M. *J. Org. Chem.* **2006**, *71*, 9701.
(71) Saito, A.; Nakajima, N.; Tanaka, A.; Ubukata, M. *Tetrahedron* **2002**, *58*, 7829.
(72) Dennis, E. G.; Jeffery, D. W.; Johnston, M. R.; Perkins, M. V.; Smith, P. A. *Tetrahedron* **2012**, *68*, 340.
(73) Day, J. J.; McFadden, R. M.; Virgil, S. C.; Kolding, H.; Alleva, J. L.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2011**, *50*, 6814.
(74) Olah, G. A.; Salem, G.; Staral, J. S.; Ho, T.-L. *J. Org. Chem.* **1978**, *43*, 173.
(75) Li, Y.-Z.; Li, B.-J.; Lu, X.-Y.; Lin, S.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2009**, *48*, 3817.
(76) Muramatsu, W.; Nakano, K. *Org. Lett.* **2014**, *16*, 2042.
(77) Willson, T. M.; Amburgey, J.; Denmark, S. E. *J. Chem. Soc. Perkin 1* **1991**, *0*, 2899.
(78) Greene, M. A.; Yonova, I. M.; Williams, F. J.; Jarvo, E. R. *Org. Lett.* **2012**, *14*, 4293.
(79) Yonova, I. M.; Johnson, A. G.; Osborne, C. A.; Moore, C. E.; Morrissette, N. S.; Jarvo, E. R. *Angew. Chem. Int. Ed.* **2014**, *53*, 2422.
(80) Dawson, D. D.; Jarvo, E. R. *Org. Process Res. Dev.* **2015**, *19*, 1356.
(81) Mitchell, T. A.; Bode, J. W. *J. Am. Chem. Soc.* **2009**, *131*, 18057.
(82) Vo, C.-V. T.; Mitchell, T. A.; Bode, J. W. *J. Am. Chem. Soc.* **2011**, *133*, 14082.
(83) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *J. Org. Chem.* **1984**, *49*, 3938.
(84) Lipshutz, B. H.; Parker, D. A.; Kozlowski, J. A.; Nguyen, S. L. *Tetrahedron Lett.* **1984**, *25*, 5959.
(85) Rieche, A.; Gross, H.; Höft, E. *Chem. Ber.* **1960**, *93*, 88.
(86) Aukrust, I. R.; Skattebøl, L.; Dahl, O.; Hvistendahl, G.; Leskelä, M.; Polamo, M.; Homsi, M. N.; Kuske, F. K. H.; Haugg, M.; Trabesinger-Rüf, N.; et al. *Acta Chem. Scand.* **1996**, *50*, 132.
(87) Kraus, G. A.; Mengwasser, J.; Maury, W.; Oh, C. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1399.
(88) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(89) With the exception of substituting hexyllithium with t-BuLi, S1 was prepared according to: Caille, S.; Crockett, R.; Ranganathan, K.; Wang, X.; Woo, J. C. S.; Walker, S. D. J. Org. Chem. 2011, 76, 5198.
(90) 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 reference 2) often require warming to room temperature in order to initiate. This can be dangerous on large scale, as the reaction proceeds quickly and the production of H2, combined with heat from the accompanying exotherm, can ignite a fire.
(91) Banerjes, U. K.; Venkateswaran, R. V. *Tetrahedron Lett.* **1983**, *24*, 423.

(92) Ghosh, A.; Banerjee, U. K.; Venkateswaran, R. V. *Tetrahedron* **1990**, *46*, 3077.
(93) Vuluga, D.; Legros, J.; Crousse, B.; Bonnet-Delpon, D. *Green Chem.* **2009**, *11*, 156.
(94) Sato, Y.; Fujisawa, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1275.
(95) Rosenfeld, M. J.; Shankar, B. K. R.; Shechter, H. *J. Org. Chem.* **1988**, *53*, 2699.
(96) 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/H2O).
(97) Piers, E.; Grierson, J. R.; Lau, C. K.; Nagakura, I. *Can. J. Chem.* **1982**, *60*, 210.