APPENDIX 9

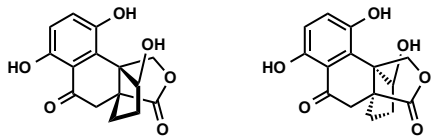
Studies Toward the Enantioselective Total Synthesis of (+)-Lingzhiol

A9.1 INTRODUCTION

A9.1.1 Isolation studies of the lingzhiols

The Ganoderma genus of mushrooms is native to southern China and contains around 80 species of mushrooms, many of which have long been used in traditional eastern medicine for ailments of the kidneys.[120] Recently, investigation into this genus led to the isolation of (+)-lingzhiol (**158**) and (–)-lingzhiol (**159**) from the *Ganoderma lucidum* mushroom (commonly called the Lingzhi mushroom) (Figure A9.1.1.1).[121] (+)-Lingzhiol (**158**) and (–)-lingzhiol (**159**) are a pair of enantiomeric meroterpenoids, or natural products bearing both polyketide and terpenoid sub-units. Vicinal all-carbon quaternary stereocenters (C-3'–C-7') define a common axis about which three of the four rings in the novel 5/5/6/6 rotor-like structure of the lingzhiols hinge. Extensive NMR studies and single crystal X-ray diffraction studies of **158** and **159** enabled the unambiguous assignment of the stereochemistry of the compounds.[121] To date, only one total synthesis of lingzhiol has been reported.[122]

Figure A9.1.1.1. *The structures of (+)-lingzhiol and (–)-lingzhiol*



(+)-Lingzhiol 158 ***(–)-Lingzhiol 159***

A9.1.2 Biological studies on and bioactivity profile of lingzhiol

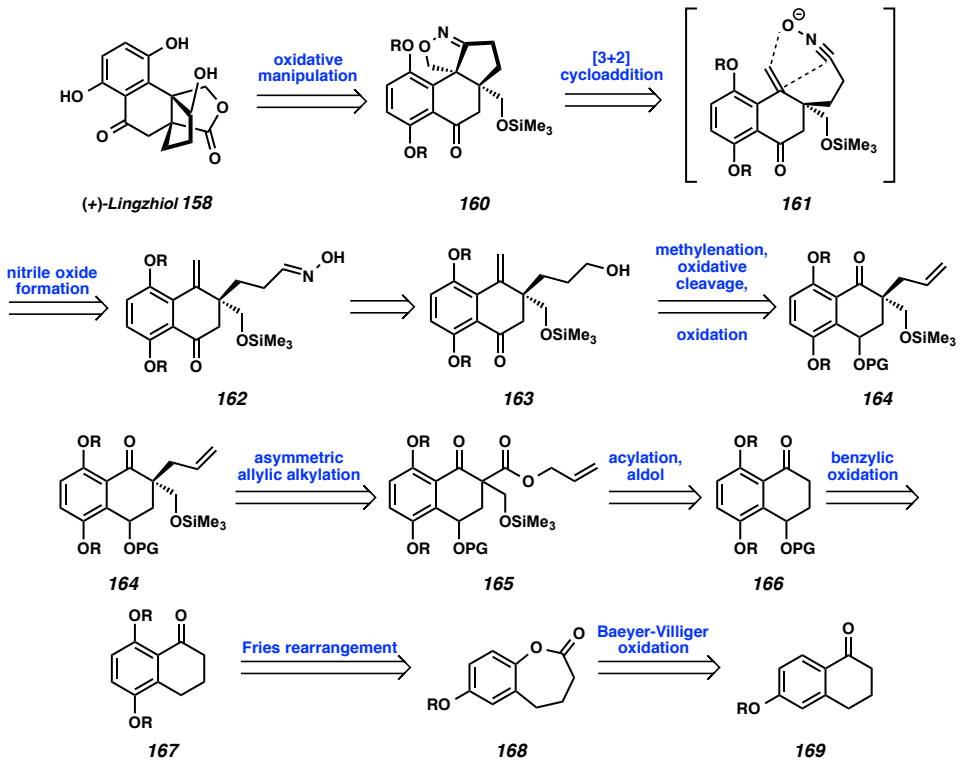
Studies conducted subsequent to the isolation lingzhiol have shown it to possess a swath of biological activity against pathogenesis in diabetic nephropathy and renal fibrosis. Diabetic nephropathy and renal fibrosis are prevalent complications that arise in longstanding cases of diabetes and may lead to liver failure, which is usually life-threatening.[123] Pathogenic factors contributing to diabetic nephropathy and renal fibrosis include oxidative stress,[124] extra cellular matrix (ECM) buildup, chronic inflammation and associated disorder of the TGF-β/Smads signaling pathways.[125] Lingzhiol has been shown to both inhibit ROS directly and to induce nuclear factor erythroid 2-related factor 2 (Nrf2), which up-regulates the production of protective antioxidant species in instances of high oxidative stress.[126] Chronic inflammation and buildup of ECM in chronic kidney disease have been linked to the deregulation of TGF-β/Smad signaling pathway; in particular, the hyper-phosphorylation of Smad2/3 and loss of Smad 7 have been implicated in the renal scar formation, diabetic nephropathy and renal fibrosis.[127] Lingzhiol has been shown to selectively inhibit Smad3 phosphorylation, while allowing Smad 2 phosphorylation, which, when taken alone, may have a renal protective role.[121]

This striking biological profile has prompted our investigation into the total synthesis of lingzhiol.

A9.2 RETROSYNTHETIC ANALYSIS OF (+)-LINGZHIOL

Retrosynthetically, we envisioned that (+)-lingzhiol (**158**) could originate from tetracycle **160** via oxidative manipulation. Tetracycle **160** could arise from the intramolecular (3+2) dipolar cycloaddition of a pendant nitrile oxide across the exocyclic olefin bourn by tetralone derivative **161**. The oxime precursor to tetralone derivative **161**, **162**, would then be obtained by simple condensation subsequent to oxidation of alcohol **163**. Alcohol **163**, in turn, would arise from elaboration of α-quaternary ketone **164**. α-Quaternary ketone **164** would be derived in enantioselective fashion from the decarboxylative allylic alkylation of β-ketoester **165**, which may be prepared by the acylation and aldol reaction of tetralone derivative **166**. Bicycle **166** would be generated via benzylic oxidation of known tetralone derivative **167**, which may be prepared from Fries rearrangement of benzannulated lactone **168**. Finally, lactone **168** may be prepared via the Baeyer-Villiger oxidation of commercially available 7-methoxy tetralone **169**.

Scheme A9.2.1. *First-generation retrosynthetic analysis for (+)-lingzhiol*



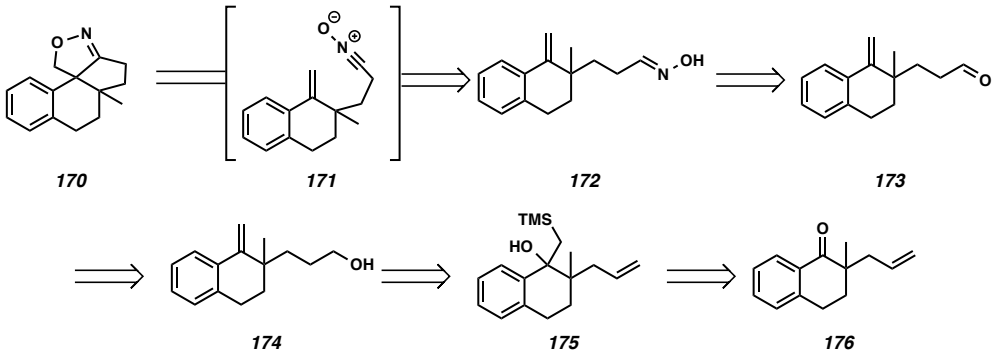
A9.3 MODEL STUDIES TO INVESTIGATE KEY (3+2) CYCLOADDITION IN THE SYNTHESIS (+)-LINGZHIOL

A9.3.1 Retrosynthetic plan for lingzhiol model system

In order to rapidly evaluate the viability of our proposed key (3 + 2) cycloadditions, we began our investigation into the total synthesis of (+)-lingzhiol in the context of a somewhat simplified model system. We reasoned that by eliminating much of the oxidation about the core of lingzhiol we could streamline access to the carbocyclic core (**170**) and, thereby, rapidly arrive at a capable (3+2) cycloaddition substrate such as nitrile oxide **171** (Figure A9.3.1.1). Oxime **172** could arise from the condensation of hydroxylamine onto aldehyde **173**, which could be accessed via the oxidation of primary

alcohol **174**. Carefully orchestrated hydroboration/oxidation and Grignard addition/elimination sequences of known tetralone derivative **176** were planned to access styrenyl alcohol **175**. Tetralone derivative **176** could then be delivered via a palladium catalyzed allylic alkylation.

Scheme A9.3.1.1. *First-generation retrosynthetic analysis for (+)-lingzhiol model system*

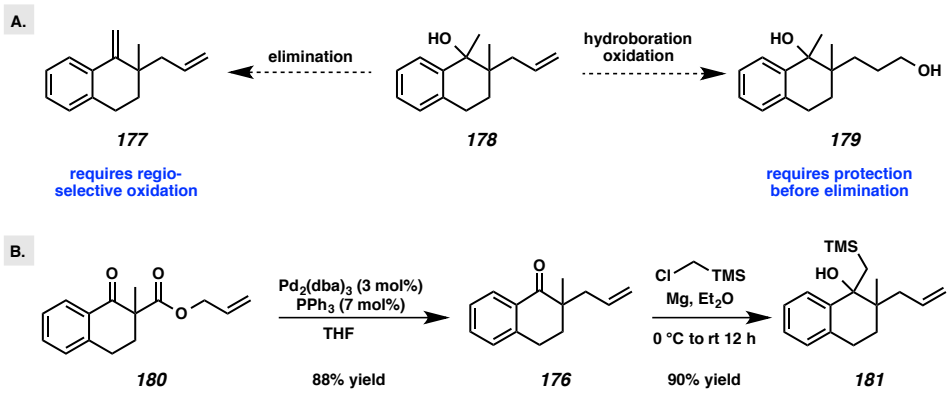


A9.3.2 Synthesis of lingzhiol model system and testing of key (3+2) cycloaddition

Known α-quaternary ketone was accessed in a racemic fashion via the palladium-catalyzed allylic alkylation of allyl β-ketoester **176** (see Chapter 1, vide infra). Although ketone to olefin transposition is known to proceed via methyl Grignard addition/elimination, we decided to first explore a Peterson olefination as opposed to something less exotic: our reasoning was twofold (Figure A9.3.2.1A). On one hand, we believed that simple methyl Grignard addition to α-quaternary ketone **176** followed by elimination would give diene **177** and require a subsequent regioselective hydroboration/oxidation. On the other hand, if hydroboration oxidation was carried out prior to methyl Grignard addition, elimination of the tertiary alcohol would be

complicated by the presence of the primary alcohol, **179**, and require an additional protection/deprotection sequence. Peterson olefination, however, would obviate these issues, and allow for simultaneous olefin formation and oxidation. After some optimization we found that the desired tertiary alcohol **181** could be prepared in 90% yield from addition of the Grignard of (chloromethyl)trimethylsilane to ketone **176** (Figure A9.3.2.1B).

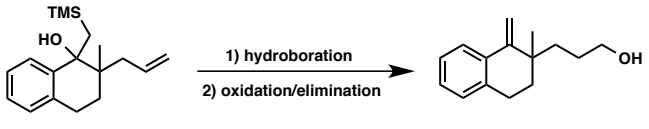
Scheme A9.3.2.1 *A. Foreseeable difficulties in advancing methyl Grignard addition to ketone* ***176****; B. Synthesis of olefin* ***181***



With tertiary alcohol **181** in hand, we began studies to identify effective hydroboration/oxidation conditions to access primary alcohol **174**. We were encouraged to find that treatment of olefin **181** with BH_3•THF complex, followed by aqueous hydrogen peroxide and sodium hydroxide, delivered the primary alcohol with concurrent elimination of trimethylsilyl alcohol to afford the desired styrenyl alcohol in 86% yield, when performed on 0.05 g scale (Scheme A9.3.2.2, entry 1). Unfortunately, this result proved difficult to replicate when carried out on larger scale, or when newly purchased reagents were employed (entry 2). Similarly, BH_3•DMS complex proved to be less

efficient than the THF complex. To our delight, we discovered that conditions for the iridium-catalyzed regioselective hydroboration/oxidation developed by Crudden and coworkers,[128] delivered the desired product in excellent and consistent yields irrespective of reaction scale (entries 4–6).

Scheme A9.3.2.2. *Optimization studies for the tandem hydroboration/oxidation elimination of* ***181***



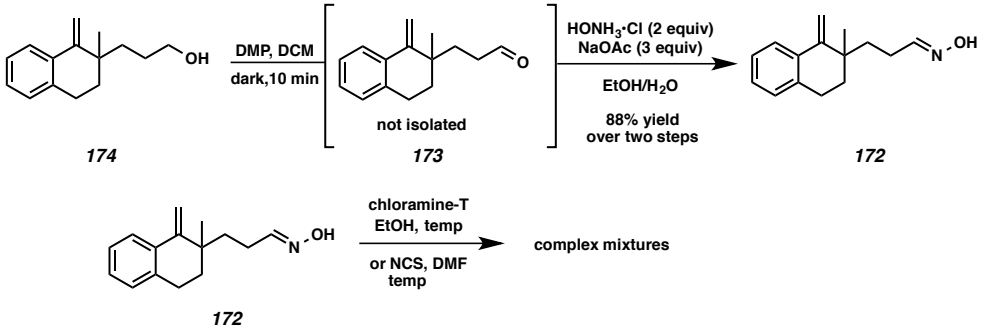
181 ***174***

entry	scale	conditions	% yield of XX
1	0.05 g	1) BH_3·THF 2) H_2O_2, NaOH	86
2	0.5 g	1) BH_3·THF 2) H_2O_2, NaOH	11–66
3	0.05	1) BH_3·DMS 2) H_2O_2, NaOH	5
4	0.1 g	1) $[Ir(cod)Cl]_2$, HBPin, THF 2) $NaBO_3$, THF/H_2O	88
5	1.1 g	1) $[Ir(cod)Cl]_2$, HBPin, THF 2) H_2O_2, NaOH	90
6	1.4 g	1) $[Ir(cod)Cl]_2$, HBPin, THF 2) $NaBO_3$, THF/H_2O	92

Dess-Martin periodinane (DMP) oxidation of primary alcohol **174** proceeded smoothly, to give aldehyde **173**, which was observed by ^{1}H NMR, and without rigorous isolation subjected conditions for oxime formation (Scheme A9.3.2.3). When crude aldehyde **173** was treated with hydroxylamine hydrochloride (5 equiv), pyridine (15 equiv), in EtOH a 25% yield (over 2 steps) of oxime **172** was observed. However, by changing the base employed to sodium acetate and reducing the equivalents of hydroxylamine hydrochloride (below, Scheme A9.3.2.3), an 88% yield was observed for the formation of oxime **172**. Pleased with these results, we next attempted to affect our

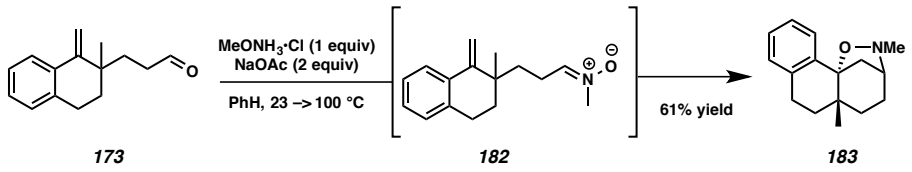
key (3+2) cycloaddition addition reaction, via the *in situ* formation of the corresponding nitrile oxide.[129] Attempts using chloramine-T[130] in ethanol at a variety of temperature failed to deliver anything other than complex mixtures. Likewise, attempts at nitrile oxide formation/(3+2) cycloaddition using N-chlorosuccinamide (NCS) and other oxidants[131] also delivered complex mixtures of products, none of which appeared to be the desired tetracycle.

Scheme A9.3.2.3. *Synthesis of oxime **172** and attempts at (3+2) cycloaddition*



While we were discouraged by these results, we reasoned that the styrene functionality of oxime **172** may be unstable, and that attempting a (3+2) cycloaddition via the corresponding nitrone might be less harsh and limit the degree of undesired reactivity observed. We therefore subjected aldehyde **173** to N-methylhydroxylamine hydrochloride and sodium acetate in benzene at increasing temperature and, finally, observed a (3+2) cycloaddition in 61% yield. Unfortunately, the regioselectivity by which the cycloaddition proceeded afforded the undesired, albeit interesting bridged product (**183**, Scheme A9.3.2.4).

Scheme A9.3.2.4. *The intramolecular (3+2) cycloaddition of nitrone* ***182*** *to form tetracycle* ***183***



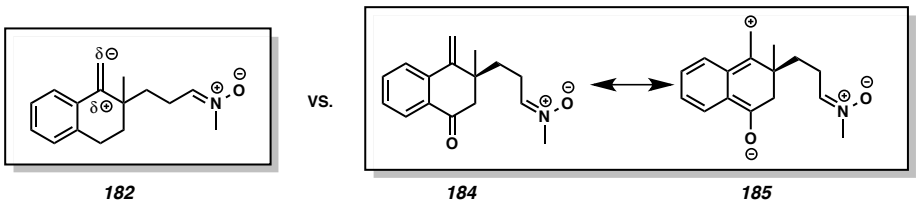
[a] Unless otherwise noted, full characterization data for compounds depicted in this scheme have not been collected.

A9.4 REVISED MODEL STUDIES TO INVESTIGATE KEY (3+2) CYCLOADDITION IN THE SYNTHESIS (+)-LINGZHIOL

A9.4.1 Rationale and revised plan for (+)-lingzhiol model system

With the disappointing results described in Section A9.3 in mind, we returned to our model system with the goal of biasing the electronics of the styrene olefin, such that we could invert the regioselectivity observed in the (3+2) cycloaddition. We believe that, due to inductive donation from the aryl group, a partial positive charge is present at the terminal position of the exocyclic olefin and that this was, in part, the source of regioselectivity we observed in the intramolecular cycloaddition of nitrone **182** (Figure A9.4.1.1). We reasoned that by introducing the ketone present in the natural product at an earlier stage, the benzylogous enolate resonance contributor might serve to invert the electronics of the exocyclic olefin in **184** (Figure A9.4.1.1). By this rationale, we hypothesized that we might affect an inversion in the regioselectivity of the (3+2) cycloaddition in favor of the desired pathway. Therefore, we set about constructing a new model compound with which we would test our key cycloaddition.

Figure A9.4.1.1. *A hypothesis regarding the electronics of exocyclic olefin* ***182***



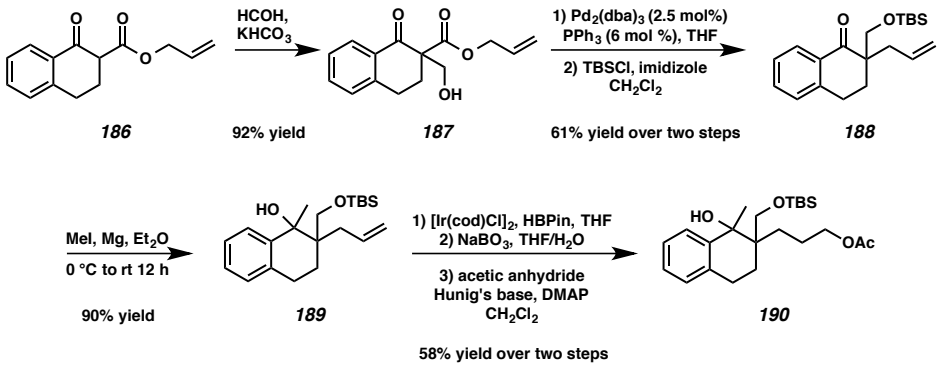
182 ***184*** ***185***

A9.4.2 Synthesis of the revised model system for (+)-lingzhiol

As we wished to install the requisite ketone via late stage benzylic oxidation, our early experiments towards a revised model system involved attempts to directly oxidize substrates generated in our previous model system. However, as most benzylic oxidation processes involve the formation of a benzylic radical, the presence of an exocyclic styrenyl olefin or allyl group in the benzylic oxidation substrate proved troublesome. As a consequence of this, a new route in which formation of the styrenyl olefin and hydroboration were reordered was required.

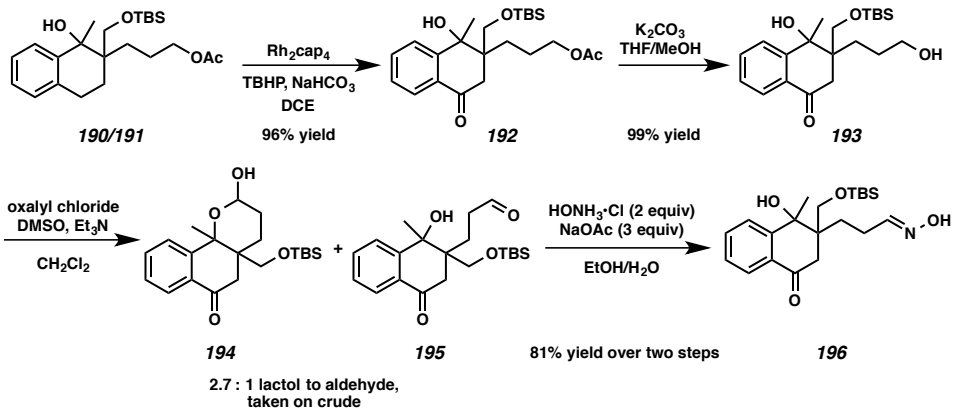
Ultimately we chose to pursue the route shown below in Scheme A9.4.2.1. Beginning with acylated tetralone derivative **186**, aldol reaction with formaldehyde, palladium catalyzed allylic alkylation, and silyl protection of the primary alcohol proceeded smoothly to give silyl ether **188** in 56% yield over the three steps. The reaction of ketone **188** with methyl Grignard reagent furnished tertiary alcohol **189** in 90% yield. This alcohol was then elaborated to bicycle **190** by iridium-catalyzed hydroboration, oxidation with sodium perborate and, finally, acetate protection, all of which proceeded in 58% yield overall.

Scheme A9.4.2.1. *Synthesis of revised model for (3+2) cycloaddition studies*



With acetate **190** in hand, we were poised to explore benzylic oxidation strategies. After numerous failed attempts to first brominate and then affect a Kornblum-type oxidation, we turned to a report from Doyle and co-workers,[132] in which benzylic oxidation is catalyzed by dirhodium tetracaprolactamate. This strategy proved successful in the event, and we were pleased to isolate benzylic ketone **192** in 96% yield in just a single step from bicycle **191** (Scheme A9.4.2.2). An uneventful deprotection of the primary acetate under standard conditions liberated primary alcohol **193**, which was oxidized to a 2.7:1 mixture of lactol **194** and aldehyde **195** and via Swern oxidation. This mixture was then subjected directly to the conditions for oxime formation with which we had previous success. In the present case, these conditions furnished oxime **196** in 81% yield overall from primary alcohol **193**.

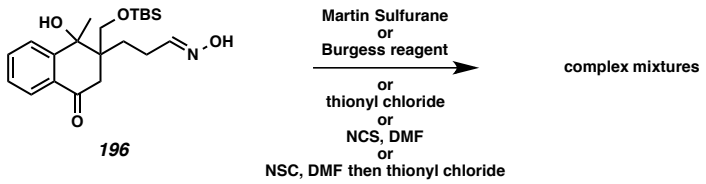
Scheme A9.4.2.2. *Synthesis of revised model for (3+2) cycloaddition studies*



With a reliable route to access oxime **196** in place, we set about attempting to affect the formation of our desired (3+2) cycloaddition precursor. Concerned over the stability of the pendant oxime, we began our investigation by employing relatively mild dehydrating agents such as Martin sulfurane[133] and Burgess reagent.[134] Unfortunately, neither of these experiments nor experiments employing harsher reagents such as thionyl chloride proved fruitful, and in all cases resulted in complex mixtures of products, none of which were believed to be the desired styrene (Scheme A9.4.2.3). We believe these disappointing results may be, in part, accounted for by the incompatibility of an electrophilic styrene moiety and nucleophilic oxime oxygen both present in the desired product. Efforts to first form the α-chloro oxime using NCS[129] and subsequently affect simultaneous olefin and nitrile oxide formation were also met with failure. Noting the relative instability of the oxime moiety to the conditions required for dehydration, we attempted to preclude these difficulties by dehydrating at an earlier point in the synthesis. However, efforts to advance styrenyl compounds in which the protected alcohol had yet

to be oxidized were met with what we believe to be hetero-Michael addition processes by the alcohol oxygen into the styrene olefin.

Scheme A9.4.2.3. *Studies toward the dehydration of tertiary alcohol* ***196***

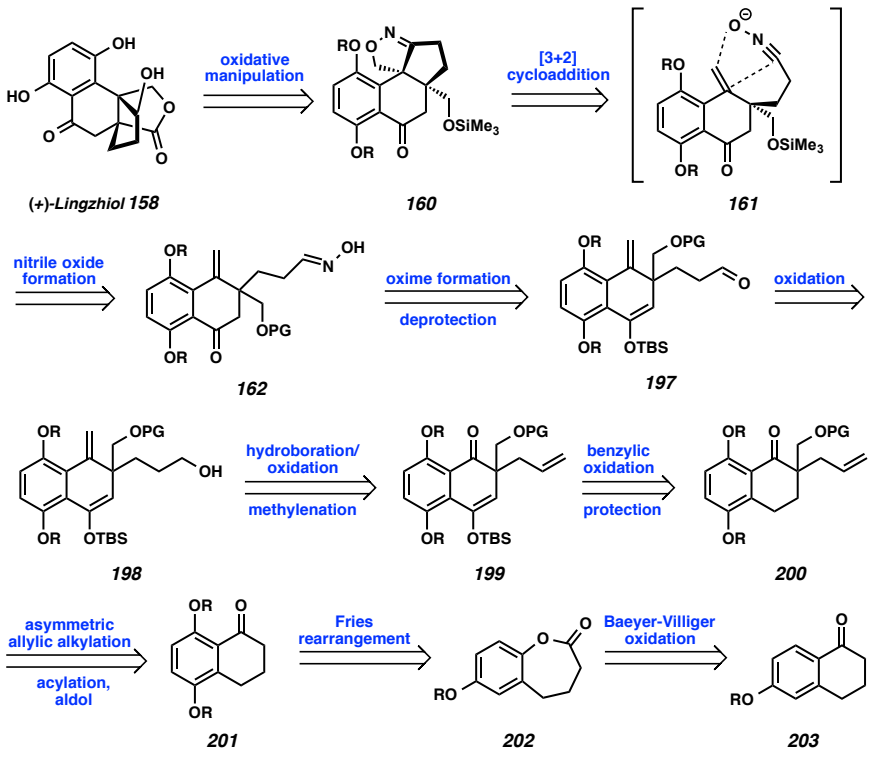


A9.5 REVISED STRATEGY FOR THE SYNTHESIS OF (+)-LINGZHIOL

Disappointed with the failure of our model system, we sought to take advantage of the lessons learned in our attempts to model (+)-lingzhiol in a revised overall strategy. One thing that became apparent over the course of our revised model system studies was the high electrophilicity of the styrene moiety once the benzylic ketone was in place. Indeed, this system could also aptly be described as a benzylogous enone. We believe that this reactivity can be exploited and efforts toward a new route to do so are underway. A revised retrosynthetic analysis detailing how such reactivity may be harnessed is depicted below in Scheme A9.5.1.

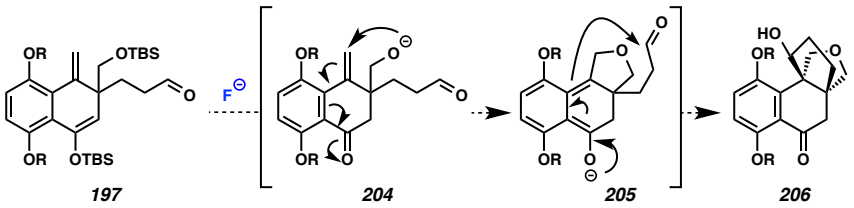
While much of our initial retrosynthesis (Scheme A9.1.1.2, vide infra) is survived in the revised version shown below, the benzylogous enone moiety (i.e., **162**) is unveiled later in the synthesis, such that oxidative manipulation of the primary alcohol formed from hydroboration/oxidation (**198**) of the allyl fragment is already complete (Scheme A9.5.1). We believe this reordering to be crucial to the success of the route.

Scheme A9.5.1. *Second-generation retrosynthetic analysis toward the synthesis of (+)-lingzhiol*



An additional benefit inherent to the revised synthetic plan is that it will enable our exploration of alternative endgame strategies that exploit the high electrophilicity of the benzylogous enone moiety. In particular, we believe that by simultaneously deprotecting both the silyl enol ether and primary silyl (PG = SiR_3) in bicycle **197**, we may be able to affect a conjugate addition/aldol cascade, wherein alkoxide **204** acts as a nucleophile and undergoes intramolecular conjugate addition to afford benzylogous enolate **205** (Scheme A9.5.2). Intramolecular aldol addition of the benzylogous enolate **205** to the pendent aldehyde may then take place to furnish tetracycle **206**. Tetracycle **206** may then undergo oxidative manipulation to furnish the natural product.

Scheme A9.5.2. *Second-generation retrosynthetic analysis toward the synthesis of (+)-lingzhiol*



A9.6 CONCLUDING REMARKS

Described herein is our progress toward the asymmetric total synthesis of marine natural product (+)-lingzhiol. Two iterations of model systems were explored in order to evaluate the feasibility of a proposed key intramolecular (3+2) cycloaddition, which would furnish vicinal quaternary carbons and two rings in a single step. Key discoveries uncovered in our model systems include the use of interrupted Peterson olefination to install a sterically-hindered exocyclic olefin and the successful employment of dirhodium tetracaprolactamate catalysis to affect the benzylic oxidation of highly functionalized intermediate **191**. Finally, a new retrosynthetic analysis, which makes use of information gained in our model studies, is presented.

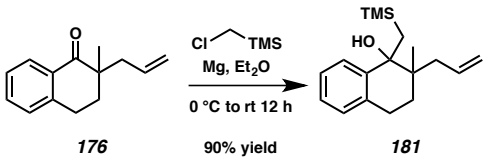
A9.7 EXPERIMENTAL SECTION

A9.7.1 Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon.[61] Reaction progress was monitored by thin-layer chromatography (TLC). TLC was performed using E. Merck

silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or $KMnO_4$ staining. Silicycle Silia*Flash*® P60 Academic Silica gel (particle size 40–63 nm) was used for flash chromatography. ^1H NMR spectra were recorded on Varian Inova 300 MHz and 500 MHz spectrometers and are reported relative to residual $CHCl_3$ (δ 7.26 ppm) or C_6HD_5 (δ 7.16 ppm). ^{13}C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer (125 MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm) or C_6HD_5 (δ 128.06 ppm). Data for ^1H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet, app = apparent. Data for ^{13}C NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained by use of a Perkin Elmer Spectrum BXII spectrometer or Nicolet 6700 FTIR spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). Reagents were purchased from Sigma-Aldrich, Gelest, Strem, or Alfa Aesar and used as received unless otherwise stated.

A9.7.2 Procedures for the preparation of and spectroscopic data for compounds in scheme A9.3.2.1

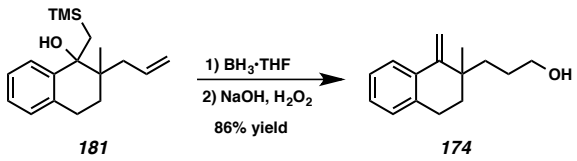


To a 25 mL 3-neck round bottom flask was added 0.122 g (5.0 mmol) of magnesium turnings. The central neck of the flask was fitted with a reflux condenser, which was fitted with a rubber septum, and the remaining two necks of the flask were

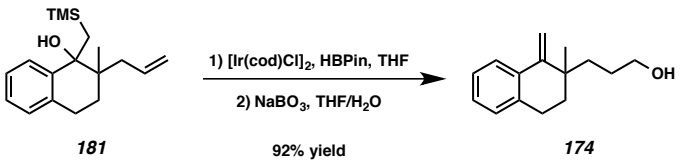
also capped rubber septa. The flask was put under vacuum and vigorously flame dried for ca. 5 min. The flask was allowed to cool under vacuum for 15 min, at which point it was back filled with Ar_2 (x3). 0.05 mL of 1,2-dibromoethane was added, along with a minimal amount of Et_2O, ca. 0.5 mL. A syringe containing 2.5 mL of Et_2O was fitted through one septum where it remained until the addition of reagents was complete. A second syringe containing 0.7 mL (chloromethyl)trimethylsilane (5.0 mmol) was fitted through another septum and added in a drop-wise fashion until an exotherm was perceptible by touching the bottom of the flask. Shortly after the generation of heat had become perceptible, the reaction mixture began to boil. Additional (chloromethyl)trimethylsilane was added to the flask at a rate that maintained a gentle reflux. If ever the exotherm went beyond that of a gentle boil, additional Et_2O was added to slow the exotherm. This process was continued until the addition of (chloromethyl)trimethylsilane was complete, at which point the reaction was heated to 40 °C via oil bath and allowed to stir for 2 hours. At this point only trace magnesium turnings remained in the reaction mixture. The reaction vessel was removed from the oil bath, and placed in a water ice bath and an additional 2 mL of Et_2O were added. Finally, 0.10 g of α-quaternary ketone **176** (0.5 mmol) in 0.5 mL of Et_2O was added drop-wise and the reaction was allowed to warm to 25 °C and stirred for an hour. The reaction was then judged to be complete by TLC analysis and then carefully quenched with saturated aqueous NH_4Cl, acidified to pH 5 by the addition of 1 N aqueous HCl, and extracted with EtOAc (10 mL x3). The combined organic washings were dried over $MgSO_4$, filtered and concentrated *in vacuo*. 0.13 g of tertiary alcohol **181** (0.4 mmol) in a 6:1 ratio of diastereomers was then isolated by flash column chromatography (SiO_2, 5% EtOAc in

hexanes to 15% EtOAc in hexanes) as a colorless oil. 90% yield. R_f = 0.4 (10% EtOAc in hexanes); ^{1}H NMR for minor diastereomer (300 MHz, $CDCl_3$) δ 8.05 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.46 (td, *J* = 7.4, 1.4 Hz, 1H), 7.34–7.28 (m, 1H), 7.23 (d, *J* = 7.7 Hz, 1H), 5.79 (ddt, *J* = 15.2, 10.8, 7.4 Hz, 1H), 5.13 (d, *J* = 9.9 Hz, 1H), 5.09–5.06 (m, 1H), 2.99 (q, *J* = 5.7 Hz, 2H), 2.28 (dd, *J* = 13.9, 7.6 Hz, 1H), 2.13–2.08 (m, 1H), 1.96–1.90 (m, 1H), 1.73–1.69 (m, 1H), 1.20 (s, 3H), -0.12 (s, 17H); ^{1}H NMR for major diastereomer (300 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.20–7.10 (m, 2H), 7.07–7.00 (m, 1H), 6.06–5.87 (m, 1H), 5.10 (td, *J* = 4.9, 3.7, 1.8 Hz, 1H), 5.04–4.86 (m, 1H), 2.79 (td, *J* = 8.8, 4.6 Hz, 2H), 2.27 (ddd, *J* = 207.5, 13.6, 7.8 Hz, 1H), 1.86 (ddd, *J* = 14.4, 9.0, 5.9 Hz, 2H), 1.74–1.62 (m, 2H), 1.37 (dd, *J* = 14.9, 1.3 Hz, 1H), 1.10 (s, 2H), 1.05 (dd, *J* = 14.9, 1.3 Hz, 1H), 0.81 (s, 1H), -0.11 (d, *J* = 2.2 Hz, 9H); ^{13}C NMR for minor diastereomer (75 MHz, $CDCl_3$) δ 144.6, 136.3, 134.7, 128.3, 126.3, 125.7, 125.6, 117.2, 41.4, 41.1, 33.3, 30.6, 28.5, 25.2, 21.9, 18.9, 0.3; ^{13}C NMR for major diastereomer (75 MHz, $CDCl_3$) δ 144.7, 136.6, 135.0, 128.4, 126.3, 125.6, 125.4, 117.4, 41.4, 41.2, 39.0, 30.2, 29.4, 24.9, 20.2, 0.3.

A9.7.3 Procedures for the preparation of and spectroscopic data for compounds in scheme A9.3.2.2



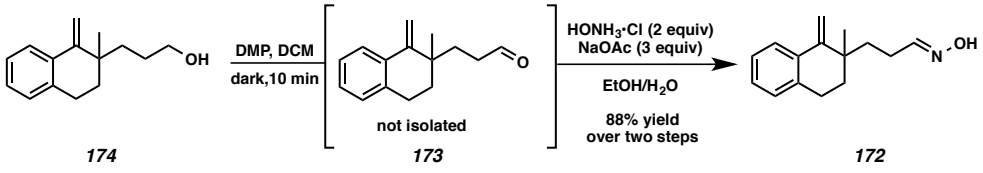
General procedure for the hydroboration/oxidation of tertiary alcohol **181** by borane•THF complex: To a solution of 0.05 g of tertiary alcohol **181** (0.173 mmol) in 1.7 mL of Et_2O was added 0.21 mL of 1 M BH_3•THF complex solution (0.21 mmol, 1.2 equiv) in a drop-wise fashion over 5 min at 25 °C. The reaction mixture was then allowed to stir for an additional 2 hours, at which point 0.020 mL of H_2O_2 (34% aqueous solution, 0.21 mmol, 1.2 equiv) and 0.692 mL of 1 N aqueous NaOH (0.692 mmol, 0.4 equiv) were added sequentially. This mixture was allowed to stir for 12 hours, at which point it was poured into 5 mL of H_2O, acidified to pH 7 with 1 N aqueous HCl, and extracted with Et_2O (5 mL x 4). The combined organic fractions were dried over $MgSO_4$, and concentrated *in vacuo*. 0.032 g of primary alcohol **174** (0.4 mmol) was then isolated by flash column chromatography (SiO_2, 1% EtOAc in hexanes to 25% EtOAc in hexanes) as a colorless oil. 86% yield. R_f = 0.3 (25% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (dd, J = 7.3, 2.0 Hz, 1H), 7.22–7.12 (m, 2H), 7.12–7.01 (m, 1H), 5.49 (s, 1H), 5.03 (s, 1H), 3.60–3.50 (m, 2H), 2.99–2.71 (m, 2H), 1.80–1.66 (m, 2H), 1.65–1.37 (m, 5H), 1.30–1.20 (m, 2H), 1.19 (s, 3H).



The general procedure for the hydroboration/oxidation of tertiary alcohol **181** by iridium catalysis was adapted from a procedure reported by Crudden and coworkers: In a nitrogen-filled glove box, a previously flame dried 50 mL round bottom flask charged with magnetic stirring bar was charged with 0.062 g of $[Ir(cod)Cl]_2$ (0.093 mmol, 0.025 equiv), and 0.08 g of 1,4-bis(diphenylphosphino)butane (0.186 mmol, 0.05 equiv) and

dissolved in 4 mL of THF. To this solution, 1.07 g of tertiary alcohol **181** (3.71 mmol, 1 equiv) in 6 mL of THF was added and the mixture was allowed to stir at 25 °C for 15 min. 0.63 g of pinacolborane (4.34 mmol, 1.2 equiv) was then added, the reaction vessel capped with a rubber septum and the mixture allowed to stir for an additional 24 hours. At this point the reaction mixture was removed from the glove-box and concentrated *in vacuo*. The crude reaction mixture was subject then taken up in 17 mL of THF, and combined with 17 mL of H_2O, 1.58 g of $NaBO_3 \cdot 4H_2O$ (10.3 mmol, 3 equiv) and stirred for an additional 12 hours. This mixture was then extracted with EtOAc (10 mL x 3), the combined organic fractions were dried over $MgSO_4$, and concentrated *in vacuo*. 0.74 g of primary alcohol **174** (0.4 mmol) was then isolated by flash column chromatography (SiO_2, 10% EtOAc in hexanes to 25% EtOAc in hexanes) as a colorless oil. 92% yield.

A9.7.4 Procedures for the preparation of and spectroscopic data for compounds in scheme A9.3.2.3

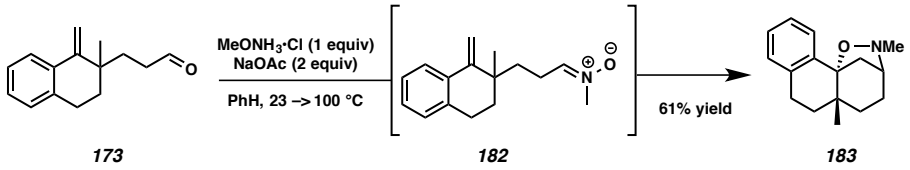


Dess-Martin periodinane (DMP) was prepared following literature procedure.[135] 0.185 g of primary alcohol **174** (0.856 mmol, 1 equiv) was transferred to a 25 mL round bottom flask with 0.93 mL of CH_2Cl_2 containing 0.417 g of DMP (0.984 mmol, 1.15 equiv) in 2.5 mL of CH_2Cl_2. The reaction was judged to be complete in 10 min, at which point the reaction mixture was poured into 7 mL of saturated aqueous $NaHCO_3$

containing 10 weight % $Na_2S_2O_3$ (1.85 g), and this mixture stirred for 5 min. The mixture was then extracted with 7 mL of Et_2O, and the organic fraction was washed with 3 mL of saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude reaction mixture was >95% pure by ^{1}H NMR, and taken on without further purification. ^{1}H NMR for aldehyde **173** (300 MHz, $CDCl_3$) δ 9.78–9.51 (m, 1H), 7.55 (dd, J = 7.0, 2.2 Hz, 1H), 7.24–7.02 (m, 3H), 5.53 (s, 1H), 5.03 (s, 1H), 3.06–2.71 (m, 3H), 2.55–2.25 (m, 2H), 2.01–1.60 (m, 5H), 1.18 (s, 3H).

To 0.055 g of freshly prepared aldehyde **173** (0.259 mmol, 1 equiv), in 1.7 mL of H_2O and 3.3 mL of EtOH was added 0.036 g of H_3NO•HCl (0.518 mmol, 2 equiv), and the reaction mixture was cooled to 0 °C using an ice water bath. To the cooled reaction mixture, 0.064 g of NaOAc (0.777 mmol, 3 equiv) was added portion-wise over 15 min and the mixture was allowed to warm to room temperature and stir for 12 hours, at which point the reaction was judged to be complete by TLC analysis. The EtOH was removed *in vacuo* and the remaining aqueous mixture was extracted with EtOAc (5 mL x 3). The combined organic fractions were dried over $MgSO_4$, concentrated *in vacuo*, and the resulting crude oil was purified by flash column chromatography (SiO_2, 3% EtOAc in hexanes to 4% EtOAc in hexanes) to give 0.052 g of oxime **172** as a colorless oil. 88% yield over two steps. R_f = 0.5 (25% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.56 (dd, J = 7.3, 2.0 Hz, 1H), 7.34 (t, J = 5.9 Hz, 1H), 7.21–7.13 (m, 2H), 7.09 (ddd, J = 6.3, 2.7, 0.9 Hz, 1H), 6.78 (s, 1H), 5.51 (s, 1H), 5.03 (s, 1H), 2.99–2.74 (m, 2H), 2.31–1.98 (m, 2H), 1.84–1.70 (m, 2H), 1.68–1.58 (m, 1H), 1.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.7, 150.4, 135.9, 135.0, 128.7, 127.5, 126.1, 125.5, 108.2, 37.4, 35.4, 34.2, 25.9, 25.6, 24.8.

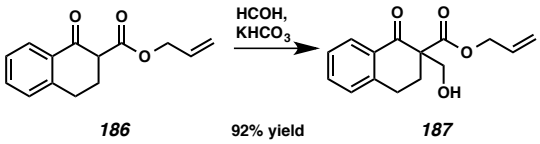
A9.7.5 Procedures for the preparation of and spectroscopic data for compounds in scheme A9.3.2.4



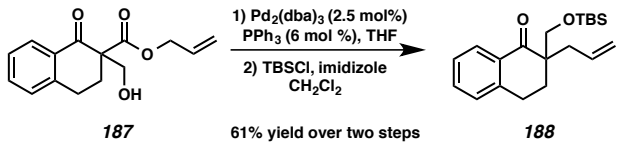
173 *182* *183*

To a flame dried 5 mL microwave vial was charged 0.015 g of crude aldehyde **172** (0.07 mmol, 1 equiv), 0.006 g of $MeH_2NOH•HCl$ (0.07 mmol, 1 equiv), 0.0193 g of K_2CO_3 (0.14 mmol, 2 equiv), and 1 mL of benzene. The microwave vial was capped with a rubber septum and stirred for 6 hours at room temperature, at which point all starting materials had by consumed by TLC analysis. The reaction mixture was then heated to 100 °C for 24 hours. The mixture was then concentrated *in vacuo*, and the crude oil was purified directly by flash column chromatography (SiO_2, 12% EtOAc in hexanes to 60% EtOAc in hexanes) to give 0.0103 g of tetracycle **183** as a colorless oil. 61% yield. R_f = 0.3 (25% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, J = 7.3, 1.9 Hz, 1H), 7.24–7.17 (m, 2H), 7.13–7.09 (m, 1H), 3.44 (t, J = 4.7 Hz, 1H), 2.93–2.82 (m, 1H), 2.81 (s, 3H), 2.79–2.66 (m, 2H), 2.17 (d, J = 12.2 Hz, 1H), 2.07 (td, J = 13.2, 5.8 Hz, 1H), 1.92–1.79 (m, 2H), 1.78–1.68 (m, 1H), 1.37–1.29 (m, 2H), 0.95 (t, J = 0.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 138.9, 133.7, 129.7, 127.7, 127.1, 126.3, 66.0, 64.8, 53.6, 47.7, 36.9, 34.5, 33.7, 32.9, 28.3, 25.9.

A9.7.6 Procedures for the preparation of and spectroscopic data for compounds in scheme A9.4.2.1



To a 100 mL round bottom flask containing a magnetic stirring bar was added 3.8 g of β-ketoester **186** (16.5 mmol, 1 equiv), 4.95 g of $KHCO_3$ (49.5 mmol, 3 equiv) and 47 mL of THF. The mixture was cooled to 0 °C via an ice water bath, and 9.24 mL of 37 wt. % formaldehyde in H_2O (113.9 mmol, 6.9 equiv) was added slowly over 5 min. The mixture was then allowed to warm to room temperature and stirred for 12 hours, at which point the reaction was judged to be complete by TLC analysis. The crude reaction mixture was diluted with H_2O (50 mL), and CH_2Cl_2 (100 mL) and extracted with CH_2Cl_2 (30 mL x 4). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude oil was then purified by flash column chromatography (SiO_2, 20% EtOAc in hexanes to 25% EtOAc in hexanes) to give 3.96 g of alcohol **187** as a colorless oil. 92% yield. R_f = 0.2 (33% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (ddd, *J* = 7.9, 1.6, 0.5, 1H), 7.51 (td, *J* = 7.5, 1.5, 1H), 7.34 (dddd, *J* = 8.0, 7.3, 1.4, 0.7, 1H), 7.24 (dd, *J* = 7.2, 1.2, 1H), 5.80 (ddt, *J* = 17.5, 10.2, 5.5, 1H), 5.21–5.15 (m, 1H), 5.14–5.10 (m, 1H), 4.68–4.57 (m, 2H), 4.06–3.85 (m, 2H), 3.42–3.25 (m, 1H), 3.00 (dt, *J* = 9.6, 4.8, 2H), 2.46 (dt, *J* = 13.6, 4.5, 1H), 2.18 (ddd, *J* = 13.6, 10.6, 5.6, 1H).

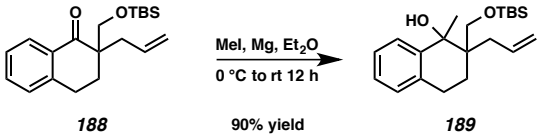


187 **61% yield over two steps** ***188***

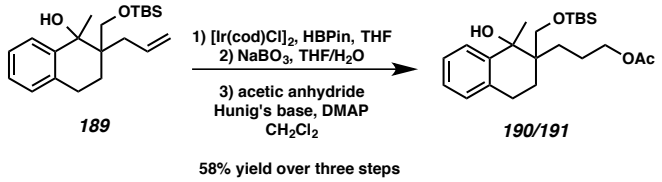
In a nitrogen-filled glove-box at 27 °C, a 250 mL round bottom flask containing a magnetic stirring bar was charged with 0.156 g of $Pd_2(dba)_3$ (0.171 mmol, 0.025 equiv), 0.107 g of PPh_3 (0.41 mmol, 0.06 equiv) and 100 mL of THF, and allowed to stir for 30 min. To this mixture was added 1.78 g of β-ketoester **187** as a solution in 35 mL THF, the flask was capped with a rubber septum, the lip of the septum sealed with electrical tape, and the flask removed from the glove-box. After stirring for 12 hours, the reaction was judged to be complete by TLC analysis. The crude reaction mixture was concentrated *in vacuo* and the resulting oil was passed through a silica plug (SiO_2, 20% EtOAc in hexanes to 30% EtOAc in hexanes), to give 1.47 g of crude product. This oil was then taken on without further purification. R_f = 0.2 (25% EtOAc in hexanes).

To a 200 mL round bottom flask containing a magnetic stirring bar was added 1.47 of the crude ketone, 1.54 g of TBSCl (10.25 mmol, 1.5 equiv based on previous reaction), 2.32 g of imidizole (34.15 mmol, 5 equiv based on previous reaction), and 70 mL of CH_2Cl_2, at 25 °C and the reaction mixture wa allowed to stir for 12 hours, at which point the reaction was judged to be complete by TLC analysis. The crude reaction mixture was poured into 100 mL of H_2O and extracted with CH_2Cl_2 (50 mL x 4), washed with saturated aqueous NH_4Cl (50 mL), washed with brine (50 mL), and then concentrated *in vacuo*. The crude oil was then purified by flash column chromatography (SiO_2, 3% EtOAc in hexanes to 10% EtOAc in hexanes) to give 1.38 g of silyl ether **188** (4.18 mmol) as a colorless oil. 61% yield over two steps. R_f = 0.4 (10% EtOAc in hexanes); ^{1}H NMR data for the precursor alcohol **188'** (300 MHz, $CDCl_3$) δ δ 8.01 (dd, *J*

= 7.9, 1.4 Hz, 1H), 7.48 (td, *J* = 7.5, 1.4 Hz, 1H), 7.35–7.27 (m, 1H), 7.26–7.22 (m, 1H), 5.95–5.66 (m, 1H), 5.25–5.14 (m, 1H), 5.13 (q, *J* = 1.1 Hz, 1H), 3.70 (qd, *J* = 11.5, 1.0 Hz, 2H), 3.24–3.03 (m, 1H), 2.94 (t, *J* = 4.6 Hz, 1H), 2.88 (t, *J* = 4.6 Hz, 1H), 2.58–2.26 (m, 2H), 2.14–1.98 (m, 1H), 1.98–1.84 (m, 1H).



Tertiary alcohol **188** was prepared following the same procedure as that which was employed to prepare tertiary alcohol **181** (vide supra). Compound **189** was isolated by flash column chromatography (SiO_2, 5% EtOAc in hexanes to 10% EtOAc in hexanes) as a colorless oil. 90% yield. R_f = 0.4 (10% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.65 (dd, *J* = 7.8, 1.5 Hz, 2H), 6.01–5.71 (m, 2H), 5.23–5.03 (m, 5H), 4.15 (s, 2H), 3.69–3.65 (m, 3H), 3.61 (d, *J* = 10.3 Hz, 1H), 3.54–3.50 (m, 2H), 3.47 (t, *J* = 7.0 Hz, 4H), 3.06–2.50 (m, 9H), 2.16 (dd, *J* = 13.7, 7.3 Hz, 1H), 1.96 (dd, *J* = 14.7, 6.9 Hz, 2H), 1.82–1.65 (m, 2H), 1.53 (s, 5H), 1.48–1.40 (m, 2H), 1.37 (s, 3H), 1.21 (t, *J* = 7.0 Hz, 8H), 0.96 (s, 15H), 0.81 (s, 9H), 0.13 (d, *J* = 5.6 Hz, 10H), -0.11 (d, *J* = 31.4 Hz, 6H).



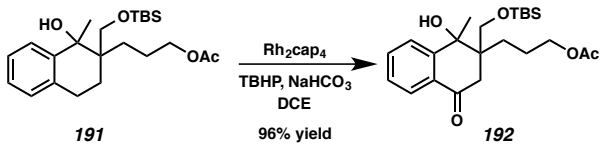
Hydroboration and oxidation of olefin **189** was accomplished following the general procedure detailed above for the synthesis of alcohol **174** (vide supra), beginning

with 1.3 g of olefin **189**. The crude reaction mixture was extracted with EtOAc, the combined organic fractions were dried over $MgSO_4$, and concentrated *in vacuo* to give 1.35 g of the intermediate diol as a colorless oil. R_f = 0.4 (10% EtOAc in hexanes); ^{1}H NMR for diastereomer 1 of boronate intermediate (300 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.18 (ddd, *J* = 8.8, 7.5, 1.4 Hz, 1H), 7.10 (td, *J* = 7.3, 1.5 Hz, 1H), 7.03–6.98 (m, 1H), 4.13 (s, 1H), 3.69 (s, 2H), 2.91 (dt, *J* = 18.6, 9.7 Hz, 1H), 2.69 (dt, *J* = 17.5, 3.9 Hz, 1H), 1.92 (ddd, *J* = 14.0, 11.3, 5.6 Hz, 1H), 1.58 (d, *J* = 5.3 Hz, 1H), 1.52 (s, 3H), 1.50–1.42 (m, 2H), 1.41–1.31 (m, 1H), 1.29–1.17 (m, 3H), 1.13 (d, *J* = 6.8 Hz, 12H), 0.94 (s, 9H), 0.85 (d, *J* = 19.9 Hz, 1H), 0.77–0.65 (m, 1H), 0.13 (d, *J* = 4.1 Hz, 5H). ^{1}H NMR for diastereomer 2 of boronate intermediate (300 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.15 (dtd, *J* = 18.9, 7.3, 1.7 Hz, 2H), 7.03–6.96 (m, 1H), 4.79 (s, 1H), 3.62 (s, 2H), 2.90–2.61 (m, 2H), 2.06–1.91 (m, 1H), 1.89–1.78 (m, 1H), 1.77–1.65 (m, 1H), 1.58 (dd, *J* = 7.6, 3.6 Hz, 1H), 1.54–1.38 (m, 2H), 1.35 (s, 3H), 1.23 (s, 12H), 1.14 (d, *J* = 4.7 Hz, 2H), 0.92 (s, 1H), 0.81 (s, 10H), 0.13 (s, 1H), -0.09 (d, *J* = 32.0 Hz, 6H).

A 25 mL round bottom flask was charged with 1.35 g of the crude diol, 0.77 g of Hunig's base (4.44 mmol, 1.2 equiv based on previous reactions), 0.045 g of DMAP (0.37 mmol, 0.1 equiv based on previous reactions), and 5.3 mL of CH_2Cl_2, and cooled to 0 °C. 0.378 mL of acetic anhydride was then added drop-wise to the cooled solution and the mixture was stirred for 3 hours, at which point the reaction was judged to be complete by TLC analysis. The crude reaction mixture was quenched with 5 wt. % HCl in H_2O, neutralized with 1 N NaOH (ca. 5 mL) and washed with brine. The organic fraction was dried over $MgSO_4$ and then concentrated *in vacuo*. The crude oil was then purified by flash column chromatography (SiO_2, 5% EtOAc in hexanes to 10% EtOAc in

hexanes) and the diastereomers separated. 0.5 g of diastereomer A (**190**) and 0.380 g of diastereomer B (**191**) were isolated as colorless oils. 58% yield over three steps. R_f = 0.3 (10% EtOAc in hexanes); ^{1}H NMR for diastereomer 1 (**190**) (300 MHz, $CDCl_3$) δ 7.73–7.59 (m, 1H), 7.23–7.09 (m, 2H), 7.08–7.00 (m, 1H), 2.91–2.64 (m, 3H), 1.74 (ddd, *J* = 8.1, 6.7, 2.8 Hz, 2H), 1.58 (d, *J* = 3.6 Hz, 3H), 1.44 (d, *J* = 1.2 Hz, 3H), 1.41–1.18 (m, 3H), 1.01 (d, *J* = 0.5 Hz, 2H), 0.98–0.92 (m, 2H), 0.91–0.86 (m, 2H).; ^{1}H NMR for diastereomer 2 (**191**) (300 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.25–7.07 (m, 2H), 7.07–6.95 (m, 1H), 4.61 (s, 1H), 4.19–4.03 (m, 2H), 3.69–3.49 (m, 2H), 2.90–2.60 (m, 2H), 2.23–2.09 (m, 1H), 2.05 (d, *J* = 0.6 Hz, 3H), 1.70 (dddd, *J* = 15.4, 12.0, 8.1, 5.0 Hz, 4H), 1.48–1.36 (m, 1H), 1.34 (s, 3H), 1.28–1.24 (m, 3H), 0.98–0.84 (m, 3H), 0.81 (d, *J* = 0.6 Hz, 9H), -0.10 (d, *J* = 34.0 Hz, 5H); ^{13}C NMR for diastereomer 2 (**191**) (75 MHz, $CDCl_3$) δ 171.2, 145.3, 133.6, 127.8, 126.3, 126.3, 126.1, 126.1, 125.5, 66.2, 65.4, 65.2, 41.4, 27.4, 27.0, 26.7, 26.0, 25.9, 25.8, 25.8, 25.7, 25.6, 24.6, 23.2, 21.0, 17.9, -6.0, -6.1

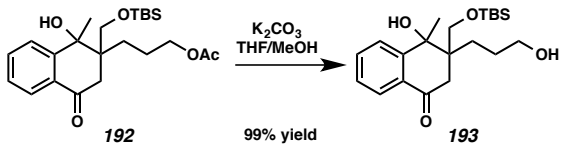
A9.7.7 Procedures for the preparation of and spectroscopic data for compounds in scheme A9.4.2.2



191 *192*

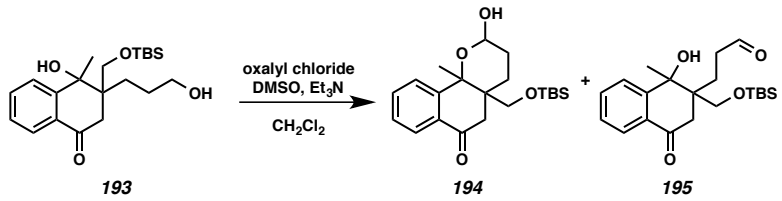
To a 1 mL microwave vial containing a magnetic stirring bar 25 °C, was charged with 0.05 g of diastereomer A of tertiary alcohol **191** (0.123 mmol, 1 equiv), 0.0004 g or $Rh_2(cap)_4$ (0.0006 mmol, 0.005 equiv), 0.005 g of $NaHCO_3$ (0.0615 mmol, 0.5 equiv) and 0.5 mL of DCE. This mixture was then allowed to stir for 30 min until all of tertiary

alcohol **191** was solubilized. To this mixture was added 0.06 mL of TBHP (0.615 mmol, 5 equiv), and the flask was fitted with a balloon filled with Ar_2 and heated to 40 °C. After stirring for 3 hours, an additional 0.0004 g or $Rh_2(cap)_4$ (0.0006 mmol, 0.005 equiv) and 0.06 mL of TBHP (0.615 mmol, 5 equiv) were added. The reaction was stirred for 36 hours, at which point it was judged to be complete by TLC analysis. The crude reaction mixture was adsorbed into 0.1 g SiO_2 by concentration *in vacuo* and the resulting fine particulate was then purified by flash column chromatography (SiO_2, 2% EtOAc in hexanes to 25% EtOAc in hexanes), to give 0.05 g of ketone **192** as a colorless oil. 96% yield. R_f = 0.3 (25% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (dddd, J = 9.1, 7.9, 1.4, 0.6 Hz, 2H), 7.65 (ddd, J = 7.9, 7.3, 1.4 Hz, 1H), 7.38 (td, J = 7.5, 1.2 Hz, 1H), 5.06 (d, J = 1.7 Hz, 1H), 4.14 (dt, J = 7.9, 6.3 Hz, 2H), 3.74–3.50 (m, 2H), 2.62 (d, J = 18.5 Hz, 1H), 2.46 (d, J = 18.5 Hz, 1H), 2.29 (td, J = 12.8, 4.4 Hz, 1H), 2.08 (s, 3H), 1.75–1.59 (m, 3H), 1.51 (d, J = 61.1 Hz, 12H), 0.82 (s, 9H), -0.10 (d, J = 67.5 Hz, 5H).



To 0.350 g of ketone **192** (0.832 mmol, 1 equiv) was added 0.138 g of K_2CO_3 (1.0 mmol, 1.2 equiv), 3 mL of THF and 1 mL of MeOH. The mixture was stirred at 25 °C for 12 hours and then judged to be complete by TLC analysis. The crude mixture was diluted with 20 mL EtOAc, washed with 10 mL H_2O, 10 mL brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting crude oil was then purified by flash column chromatography (SiO_2, 20% EtOAc in hexanes to 60% EtOAc in hexanes), to give 3.14 g of primary alcohol **193** as a colorless oil. 99% yield. R_f = 0.3 (50% EtOAc in hexanes);

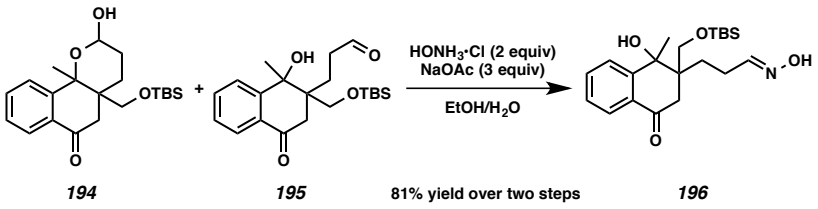
^{1}H NMR for diastereomer 1 (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 3.87 (d, *J* = 10.4 Hz, 1H), 3.61 (d, *J* = 10.4 Hz, 1H), 3.43 (t, *J* = 6.7 Hz, 2H), 2.43 (d, *J* = 17.3 Hz, 1H), 2.32 (d, *J* = 17.4 Hz, 1H), 1.99 (ddd, *J* = 14.3, 12.2, 4.8 Hz, 1H), 1.61 (s, 3H), 1.48–1.32 (m, 2H), 1.28–1.18 (m, 1H), 0.93 (d, *J* = 1.6 Hz, 9H), 0.14 (d, *J* = 13.7 Hz, 5H); ^{13}C NMR for diastereomer 1 (75 MHz, $CDCl_3$) δ 195.5, 149.9, 134.6, 129.7, 127.0, 125.9, 125.8, 76.1, 65.9, 63.0, 45.3, 41.5, 28.5, 27.1, 25.7, 18.0, -5.7, -5.8; ^{1}H NMR for diastereomer 2 (**193**) (500 MHz, $CDCl_3$) δ 7.91 (dddd, *J* = 13.3, 8.0, 1.4, 0.6 Hz, 2H), 7.64 (ddd, *J* = 7.8, 7.3, 1.4 Hz, 1H), 7.38 (td, *J* = 7.5, 1.2 Hz, 1H), 5.09 (s, 1H), 3.80–3.70 (m, 2H), 3.70–3.59 (m, 2H), 2.61 (d, *J* = 18.6 Hz, 1H), 2.50 (d, *J* = 18.6 Hz, 1H), 2.29–2.19 (m, 1H), 1.60 (dddd, *J* = 15.7, 12.2, 8.6, 6.2 Hz, 3H), 1.46 (s, 3H), 0.81 (s, 9H), -0.10 (d, *J* = 64.7 Hz, 5H); ^{13}C NMR for diastereomer 2 (**193**) (75 MHz, $CDCl_3$) δ 196.1, 151.1, 134.5, 130.1, 127.2, 126.3, 125.4, 66.7, 63.4, 44.5, 44.0, 27.2, 26.8, 26.6, 25.5, 17.8, -6.0, -6.2.



193 ***194*** ***195***

To a septum capped 1 mL microwave vial containing a magnetic stirring bar was added 5.43 μL of oxalyl chloride (0.06 mmol, 1.48 equiv) in 0.25 mL of CH_2Cl_2. The mixture was cooled to –78 °C and 7.5 μL of DMSO (0.1056 mmol, 2 equiv) in 0.25 mL CH_2Cl_2 was added drop-wise over 20 min and the mixture was stirred for an additional 30 min. 0.02 g of diastereomer 1 of primary alcohol **193** (0.053 mmol, 1 equiv) in 0.5 mL CH_2Cl_2 was then added drop-wise over 45 min and the mixture was stirred for an

additional 30 min. 30.0 μL of Et_3N was then added neat over 1 minute, and the mixture was stirred vigorously for 30 min as it was allowed to warm to 0 °C. 1 mL of H_2O was then added , the mixture was washed with 0.5 M HCl (1 mL), H_2O (1 mL), saturated aqueous $NaHCO_3$ (1 mL) and brine (1 mL). The organic fraction was dried over $MgSO_4$, and concentrated *in vacuo* to give 0.0197 g of lactol **194** and aldehyde **195** as a 2.7:1 mixture. Lactol **194** and aldehyde **195** were taken on without further purification. ^{1}H NMR for lactol **194** (300 MHz, $CDCl_3$) δ 8.08–7.93 (m, 1H), 7.67–7.52 (m, 2H), 7.38 (ddd, *J* = 7.8, 6.5, 2.0 Hz, 1H), 6.37 (ddd, *J* = 6.2, 2.4, 1.5 Hz, 1H), 4.56 (td, *J* = 5.6, 5.0, 2.2 Hz, 1H), 3.87–3.61 (m, 2H), 2.81 (d, *J* = 2.1 Hz, 2H), 2.10 (ddd, *J* = 17.9, 5.1, 1.5 Hz, 1H), 1.69–1.58 (m, 2H), 1.54 (s, 3H), 0.89 (s, 11H), 0.05 (d, *J* = 3.8 Hz, 6H); ^{1}H NMR for aldehyde **195** (300 MHz, $CDCl_3$) δ 8.01 (ddd, *J* = 7.9, 1.4, 0.6 Hz, 1H), 7.74–7.61 (m, 2H), 7.50–7.40 (m, 1H), 3.91–3.71 (m, 2H), 2.79 (d, *J* = 3.2 Hz, 2H), 2.53 (dt, *J* = 18.1, 8.9 Hz, 1H), 2.21 (ddd, *J* = 18.5, 8.5, 3.6 Hz, 1H), 2.07–1.94 (m, 1H), 1.75 (dt, *J* = 14.3, 8.9 Hz, 1H), 1.67 (d, *J* = 0.6 Hz, 3H), 0.91 (d, *J* = 0.6 Hz, 10H), 0.10 (d, *J* = 2.3 Hz, 6H); ^{13}C NMR for aldehyde **195** (75 MHz, $CDCl_3$) δ 194.9, 170.5, 147.0, 135.3, 129.7, 128.5, 126.8, 125.6, 84.4, 64.6, 44.7, 27.1, 26.4, 25.8, 24.8, 18.2, -5.6, -5.7.



0.01 g of the mixture of crude diastereomer 2 of lactol **194** and diastereomer 2 of aldehyde **195** were combined with 0.0037 g of $HONH_2$•HCl (0.053 mmol, 2 equiv from previous reaction), 0.0065 g NaOAc (0.0797 mmol, 3 equiv), 0.18 mL H_2O and 0.35 mL

EtOH in a 1 mL microwave containing a magnetic stirring bar and stirred at 25 °C for 12 hours. The crude reaction mixture was adsorbed into 0.1 g SiO_2 by concentration *in vacuo* and the resulting fine particulate was then purified by flash column chromatography (SiO_2, 10% EtOAc in hexanes to 40% EtOAc in hexanes), to give 0.085 g of a mixture of *E* and *Z* oximes **196** as a colorless oil. 81% yield over two steps. R_f = 0.2 (33% EtOAc in hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99–7.82 (m, 2H), 7.64 (td, *J* = 7.6, 1.5 Hz, 1H), 7.49 (t, *J* = 5.7 Hz, 0H), 7.45–7.31 (m, 1H), 6.82 (s, 1H), 5.06 (s, 1H), 3.75–3.54 (m, 2H), 3.53–3.43 (m, 0H), 2.66 (d, *J* = 3.2 Hz, 0H), 2.60 (d, *J* = 3.1 Hz, 1H), 2.51 (d, *J* = 7.4 Hz, 1H), 2.48–2.41 (m, 1H), 2.33–2.23 (m, 1H), 2.10 (s, 1H), 2.04 (s, 1H), 1.84–1.63 (m, 1H), 1.44 (s, 3H), 1.33–1.13 (m, 2H), 0.96–0.85 (m, 0H), 0.80 (d, *J* = 0.8 Hz, 9H), -0.05 (d, *J* = 1.1 Hz, 3H), -0.19 (s, 3H).

A9.8 REFERENCES AND NOTES

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