# APPENDIX D

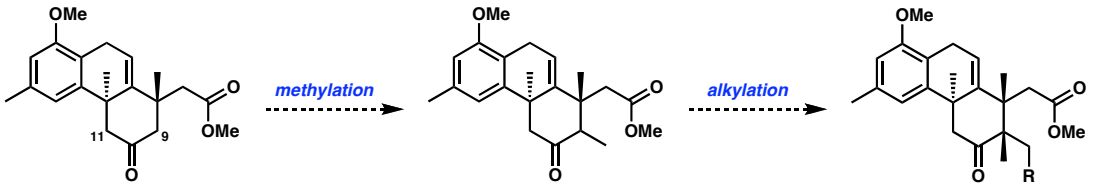
## Current and Future Investigations Toward Zoanthenol

### *D.1 Introduction*

In the preceding chapters, we described our attempts to advance C ring synthons containing vicinal quaternary stereocenters toward zoanthenol via acid-mediated cyclization approaches or conjugate radical cyclization approaches. Here, we suggest methods for utilizing intermediates developed in our early work as well as possible avenues for further exploration using our more advanced C ring synthons.

### *D.2 Proposed Methods for the Utilization of Tricycle **192***

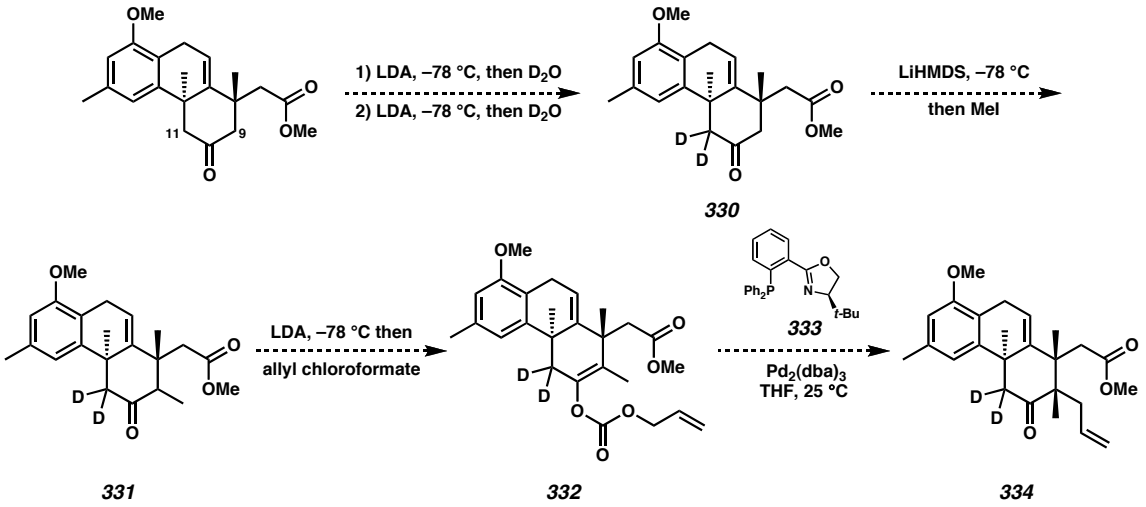
In our early work, we synthesized the key tricycle **192** but were unable to functionalize the C(9) position for further elaboration toward the natural product due to the preference for enolization to occur at C(11) instead of C(9) (Scheme D.2.1).




**Scheme D.2.1** Plan for functionalization of C(9).

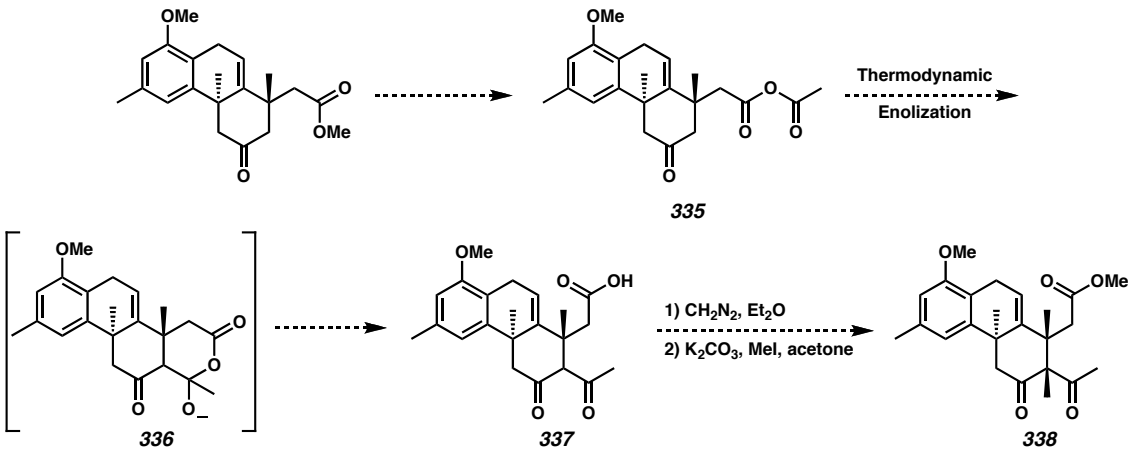
One potential method to overcome this challenge would be to take advantage of the inherent selectivity of the system to deuterate at C(11), allowing selective enolization by deprotonation instead of de-deuteration.[1] Held and Xie have measured the deuterium isotope effect for enolization of 2,2-$d_2$-3-pentanone with LDA, LITA, and LiHMDS.[2] They find $k_H/k_D$ values of 2.3, 5.2, and 6.6, respectively, for these bases. As illustrated in Scheme D.2.2, tricycle **192** will be enolized, resulting in selective deuteration at C(11) upon addition of 1.0 equivalents of $D_2O$. A second enolization and quenching with $D_2O$

should lead to di-deutero ketone **330**. Treatment with lithium hexamethyldisilazide will result in selective enolization at the desired C(9) position. Trapping this enolate with methyl iodide will furnish methyl ketone **331**. Enolization and trapping with allyl chloroformate will provide allyl enol carbonate **332**. A decarboxylative alkylation event would then provide the desired α,β,β'-quaternary ketone **334**. The deuteration at C(11) will be removed upon treatment with aqueous acid.




**Scheme D.2.2** Deuteration to functionalize C(9) by alkylation.

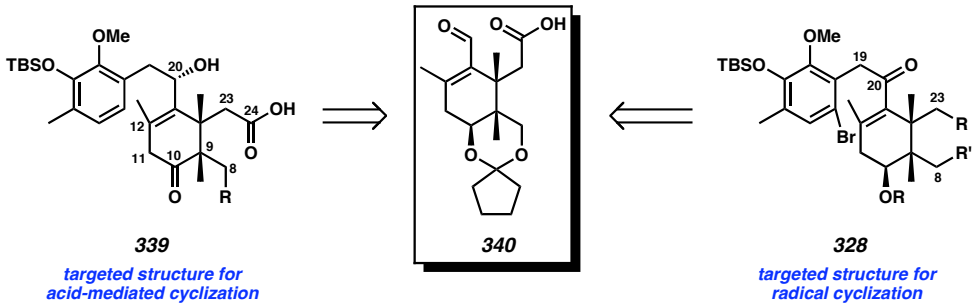
Another possible route by which to advance tricycle **192** would be via an intramolecular acylation. Conversion of ester **192** to anhydride **335** would provide a substrate for thermodynamic enolization (Scheme D.2.3). By utilizing thermodynamic enolization conditions, an equilibrium between the two enolate isomers should be established. When an enolate is generated at C(9), it can be trapped by the anhydride moiety to provide intermediate **336**, which will ultimately furnish acid **337** as the product of the alkylation. At this point, enolization at the central carbon of the β-diketone **337** will lead to the desired C(9)-quaternary ketone **338**.




**Scheme D.2.3** Thermodynamic deprotonation to functionalize C(9) by acylation.

*D.3.1 Development and Cyclization of a 6-Membered Acetal-Derived A–C Ring System with Inverted C(10) Stereochemistry*

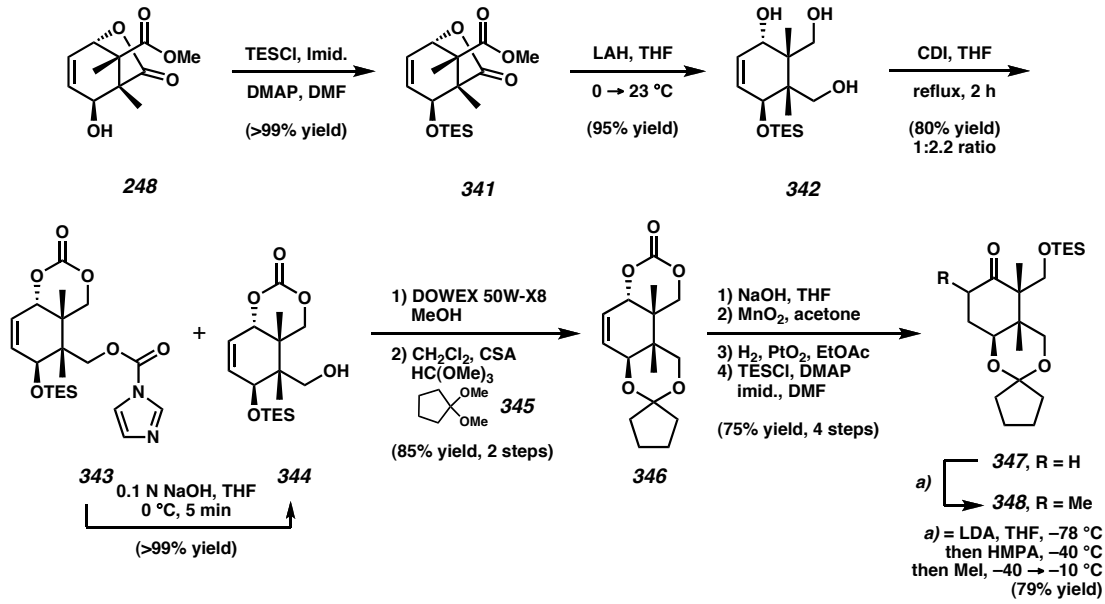
Recent efforts have been focused on the synthesis of new substrates for the acid- and radical-mediated cyclizations (**339** and **328**, respectively, Scheme D.3.1). For these substrates, we needed to develop a final C ring synthon that would allow us to access the structural features described in Chapters 3 and 4.[3] Of particular note is the stereochemistry at C(10) for the radical cyclization substrate (**328**), which is hypothesized to be critical for the stereoselectivity of the cyclization.




**Scheme D.3.1** Common intermediate for acid-mediated and radical cyclizations.

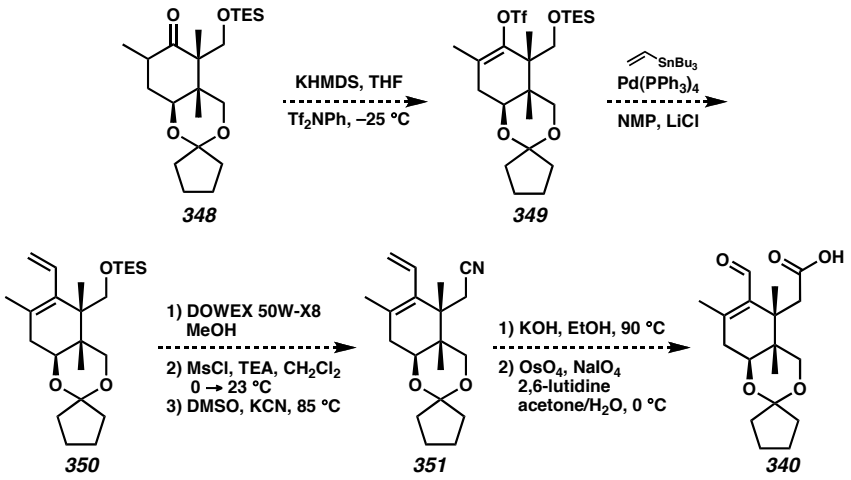
Efforts toward intermediate **340** began with silylation of allylic alcohol **248** to **341** then global reduction to form triol **342** (Scheme D.3.2). For this system, a triethylsilyl group was incorporated at C(10) in order to facilitate its later removal. Triol **342** was

treated with carbonyl diimidazole in refluxing THF to afford a mixture of carbamate **343** and carbonate **344**. Brief exposure of carbamate **343** to dilute sodium hydroxide converted it quantitatively to carbonate **344**. Desilylation with DOWEX resin and cyclopentylidene acetal formation[4] led to tetracycle **346**. The cyclopentylidene acetal was chosen with the goal of improving the efficiency of acetal removal.[3] A four-step sequence of carbonate saponification, allylic oxidation, hydrogenation, and primary alcohol silylation provided ketone **346**. Enolization of ketone **347** and trapping with MeI led to methyl ketone **348** in 79% yield.




**Scheme D.3.2** Toward an optimal C ring synthon.

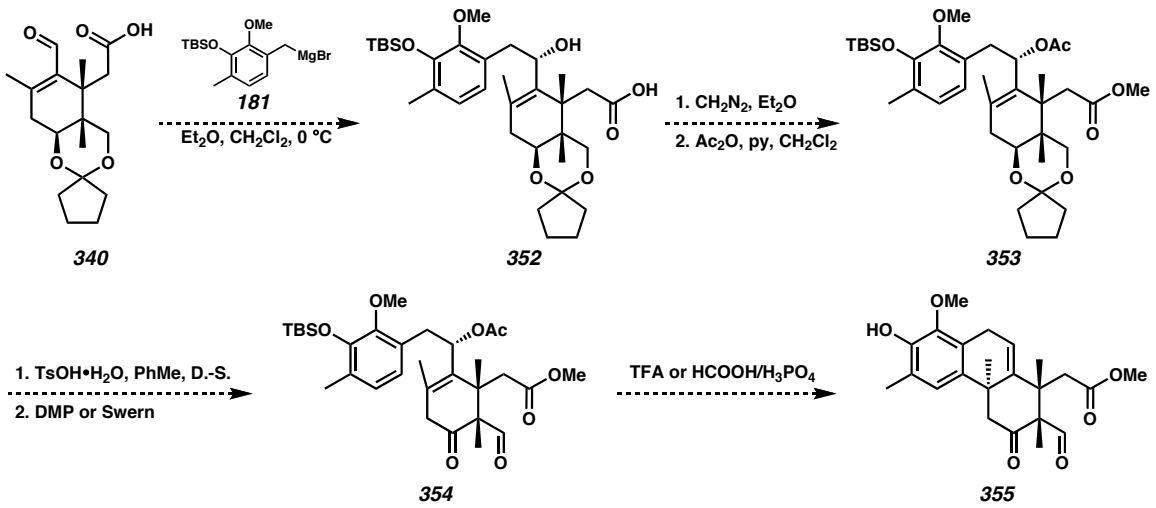
Enolization of **347** with KHMDS and trapping should provide enol triflate **349** (Scheme D.3.3). Stille coupling of enol triflate **349** with vinyl(tributyl)stannane will yield **350**. A three-step sequence of desilylation, mesylation, and nitrile displacement will provide diene **351**. Nitrile hydrolysis and oxidative cleavage should generate C ring synthon **340**.




**Scheme D.3.3** Preparation of a C ring synthon with inverted C(10) stereochemistry.

*D.3.2 Advancement of Cyclopentylidene-Derived C Ring Synthon for Acid-Mediated Cyclization*

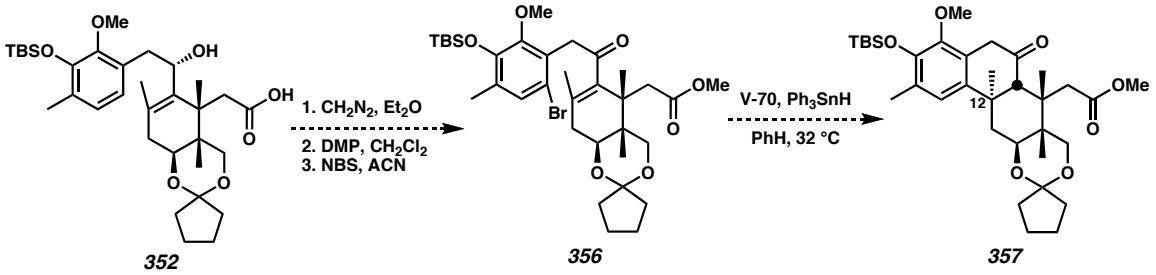
In order to advance this new C ring synthon to the acid-mediated cyclization precursor, we will need to conduct a fragment coupling with the A ring synthon (**168**, Scheme 2.1.1). Treatment of enal **340** with the Grignard reagent formed from **181** will provide alcohol **352** (Scheme D.3.4). Subsequently, treatment with diazomethane followed by acetylation of the secondary alcohol will lead to ester **353**. Acetal removal and oxidation will then produce keto-aldehyde **354**. At this point, cyclization conditions will be tested, yielding tricycle **355**.




**Scheme D.3.4** Acid-mediated cyclization of cyclopentylidene-derived C ring synthon.

*D.3.3 Advancement of Cyclopentylidene-Derived C Ring for Radical Cyclization*

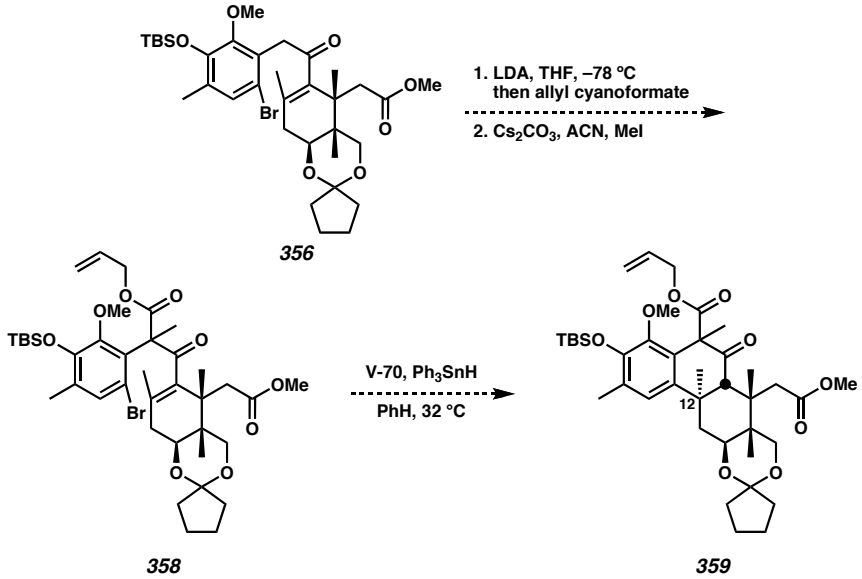
We envision accessing the substrate for radical cyclization beginning from the Grignard product described above. Esterification of **352** followed by oxidation and bromination will yield cyclization precursor **356** (Scheme D.3.5). Treatment with radical conditions should lead to formation of cyclization product **357**, with all three quaternary centers installed in a system readily advanced toward the natural product.




**Scheme D.3.5** Radical cyclization of cyclopentylidene-containing precursor.

Additionally, we propose an alternative radical cyclization substrate that would take advantage of a reactive rotamer[5] variation of the Thorpe-Ingold[6] effect to improve yields of the desired product relative to the debrominated starting material. Scheme D.3.6 outlines a method for functionalization of enone **356**. Enolization and trapping with

allyl cyanoformate followed by methylation will provide cyclization precursor **358**. This precursor will be subjected to the standard radical conditions[7] to determine the effect of substitution at C(19) on the efficacy of the cyclization, which is expected to yield **359**.



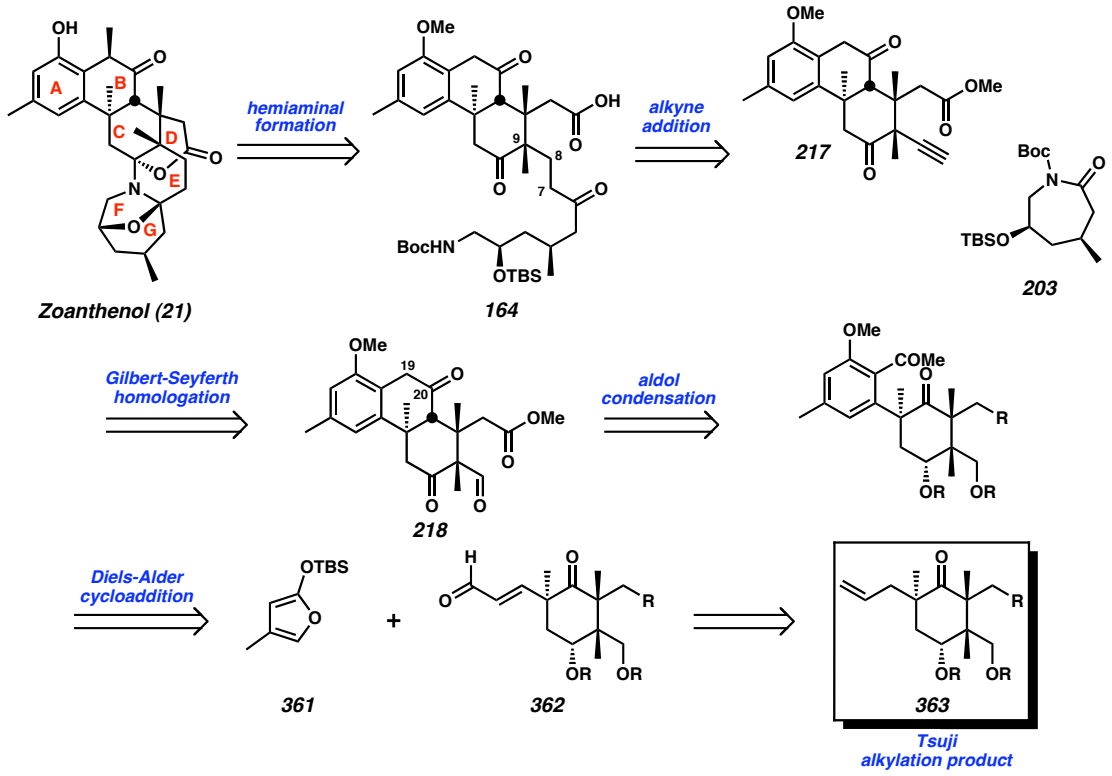

**Scheme D.3.6** Radical cyclization of C(19)-substituted cyclization precursor.

*D.4.1 Alternative Approaches to the Tricyclic Core of Zoanthenol*

In addition to our plans to access a substrate that will allow our acid-mediated and radical-based cyclization reactions to occur, we have begun efforts toward installation of the C(12) quaternary center at an earlier stage in the synthesis. Toward this end, we have identified two potential approaches that might enable this position to be functionalized prior to B ring closure: an alkylation/Diels-Alder/aldol cyclization approach and an α-arylation/alkylation/aldol cyclization approach.

*D.4.2 Allylation/Diels-Alder Approach*

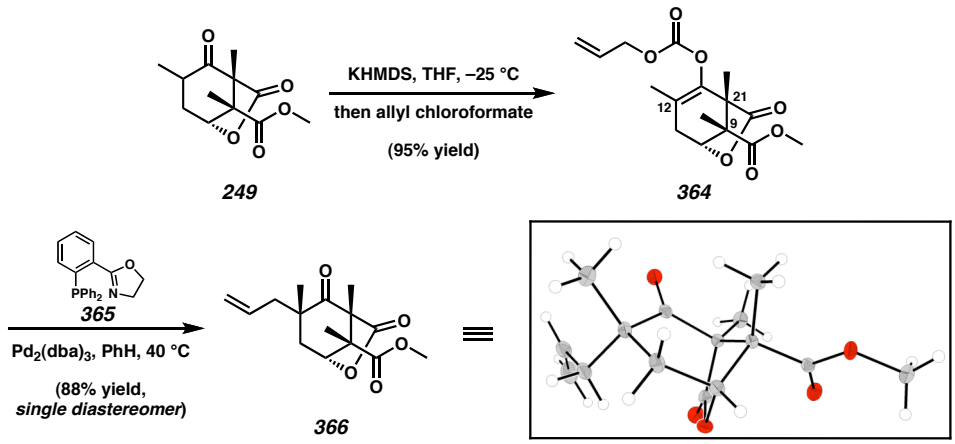
Our first alternative approach disconnects the B ring at the C(19)–C(20) bond of intermediate **218** via retro-aldol condensation to reveal retron **360**, representing a change in strategy wherein the challenging third quaternary center is constructed prior to B ring closure (Scheme D.4.1). The A ring is then disconnected by a retro-Diels-Alder cycloaddition to give synthons **361** and **362**. Enal **362** can be accessed from allyl ketone **363**, the product of a diastereoselective Tsuji alkylation.




**Scheme D.4.1** Revised retrosynthesis for allylation/Diels-Alder approach.

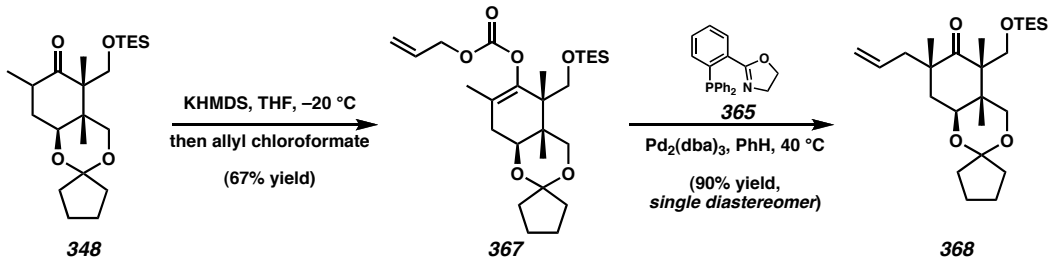
In order to access allyl ketone **363**, intermediate ketone **249** was intercepted. Its potassium enolate was trapped with allyl chloroformate to access allyl enol carbonate in 95% yield (Scheme D.4.2). Subjecting this compound to achiral glycine-derived PHOX ligand **365** led to the formation of a single diastereomer of undesired α,α',β-quaternary ketone **366** in 88% yield. Interestingly treatment with the enantioselective version of the catalyst,[8] utilizing the (*S*)-*t*-butyl PHOX ligand, provided the identical product, but at

an extremely reduced rate. Since this enantiomer of the chiral ligand is expected to provide the desired stereochemistry at C(12), it is clear that substrate control is the exclusive source of selectivity in this transformation. The C(12)–C(21) olefin is blocked on the convex face by the protruding methyl group from the C(9) quaternary center, leading to the observed allyl attack from the α-face of the substrate. This stereochemistry was confirmed by X-ray crystallographic analysis of a single crystal of **366**.[9]



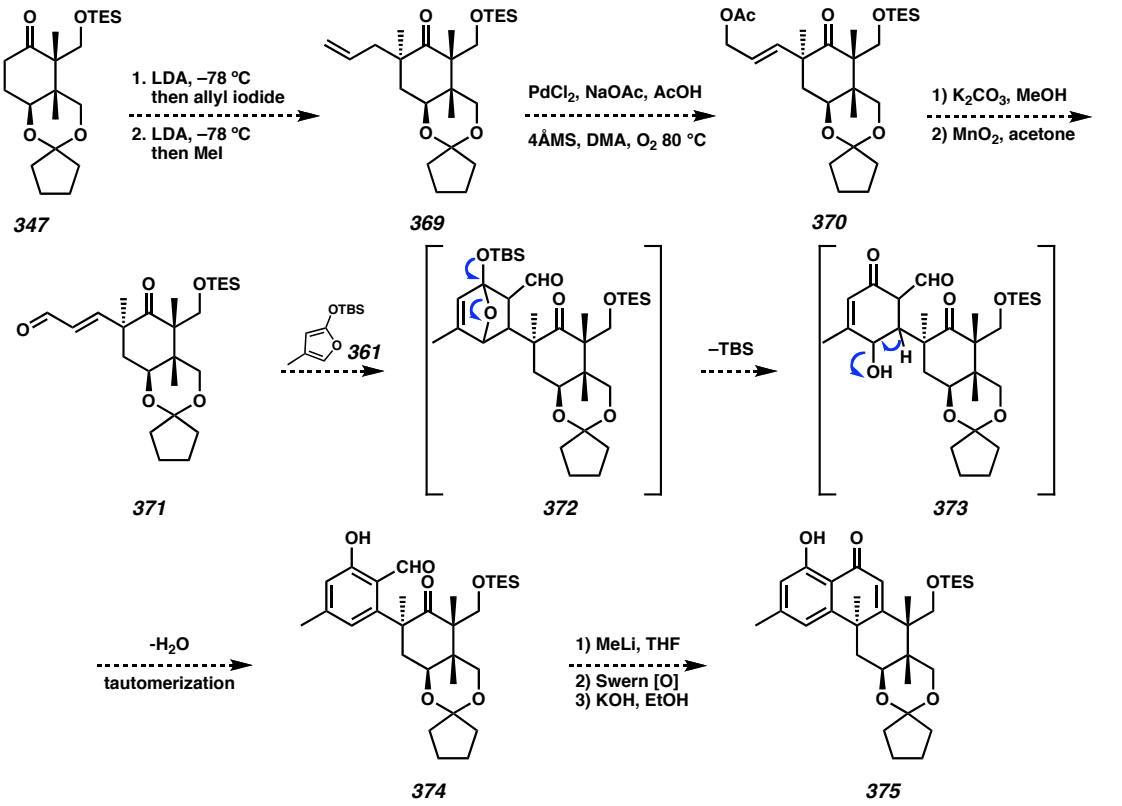

**Scheme D.4.2** Palladium-catalyzed alkylation of lactone **366**.

Given the inability of the catalyst to override the substrate control of the diastereoselectivity for the alkylation of lactone **364**, an alternative substrate possessing a substantially different ring system was targeted. Thus, enolization of methyl ketone **348** and trapping with allyl chloroformate led to allyl enol carbonate **367** (Scheme D.4.3). Treatment with achiral PHOX ligand **365** provided a single diastereomer of alkylation product **368** in 90% yield, as determined by 2D NMR analysis.




**Scheme D.4.3** Allylation of a cyclopentylidene-containing ketone.

Although the Tsuji alkylation approach resulted in exclusive formation of the undesired diastereomer in the above cases, the desired product should be accessible by reversing the order of the alkylation steps. Thus, ketone **347** may be converted to allyl methyl ketone **369** by alkylation with allyl iodide then methylation (Scheme D.4.4). In analogy to some model systems we have studied, the allyl functionality will be oxidized with allylic transposition to provide **370** using conditions developed by Kaneda.[9,10] Subsequent methanolysis and oxidation will lead to desired enal **371**. With enal **371** in hand, we will begin exploring conditions for a possible Diels-Alder cycloaddition with silyl ether substituted furan **361**. Upon [4+2] cycloaddition, intermediate **372** will be generated. Upon acidic workup, we anticipate that desilylation will occur, forming enone **373**. Further protonation of the secondary alcohol will result in dehydration, and subsequent spontaneous tautomerization will provide the desired zoanthenol A rinD. Addition of methyl lithium into the aldehyde, oxidation to the ketone, and aldol cyclized the B ring to form **375**, the carbocyclic core of zoanthenol.

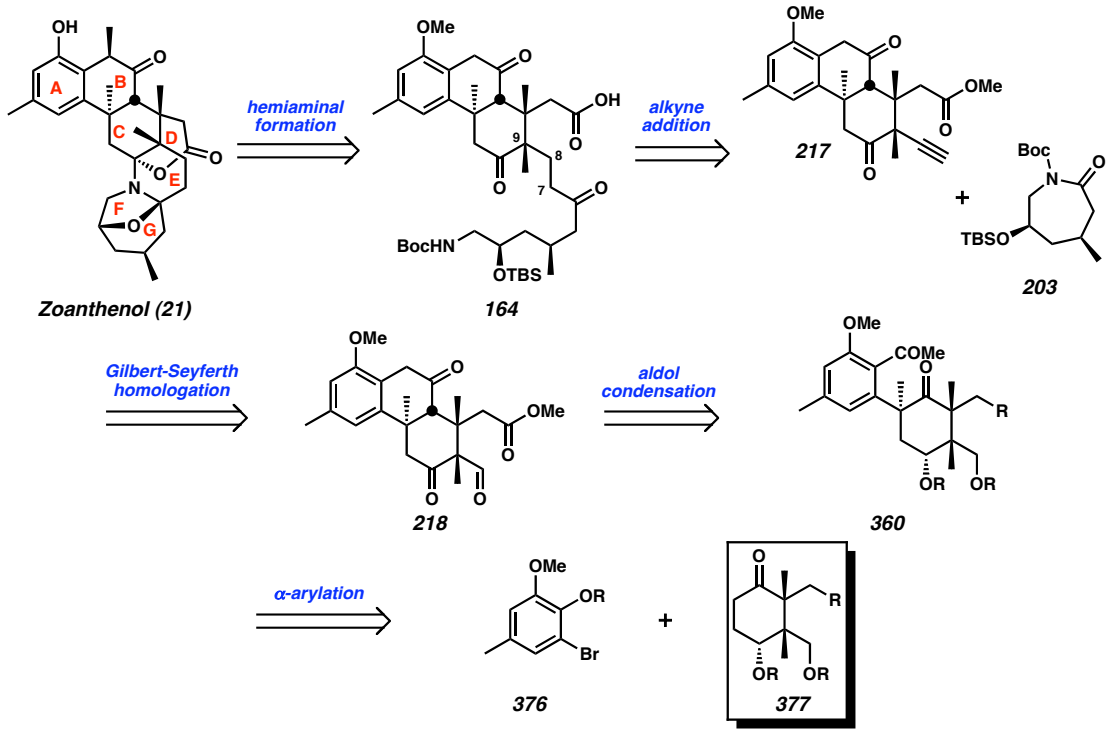



**Scheme D.4.4** Alternative alkylation and advancement of ketone **347**.

*D.4.3 α-Arylation Approach*[†]

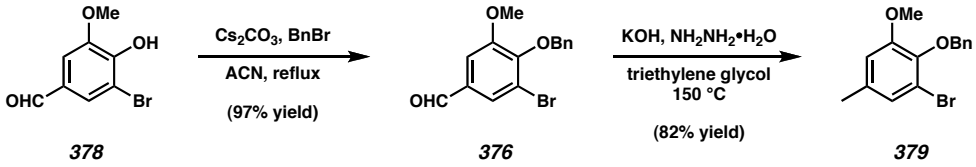
An alternative method by which the C(12) quaternary center might be disconnected involves a retro diastereoselective methylation and α-arylation[11] of retron **360** to reveal synthons **376** and **377** (Scheme D.4.5).

[†] The work in this subsection was conducted by Dr. Andrew McClory, a postdoctoral researcher in the Stoltz Group.



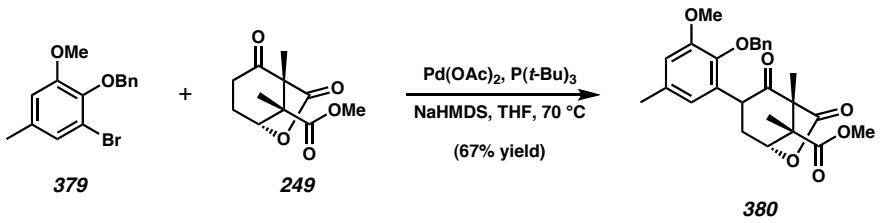

**Scheme D.4.5** Revised retrosynthesis for α-arylation approach.

In order to investigate the viability of such an approach, a suitable A ring synthon was prepared. Known bromo-phenol **378**[12] was etherified with benzyl bromide to provide aryl bromide **376** (Scheme D.4.6). Wolff-Kischner reduction of the aldehyde then provided A ring synthon **379**.



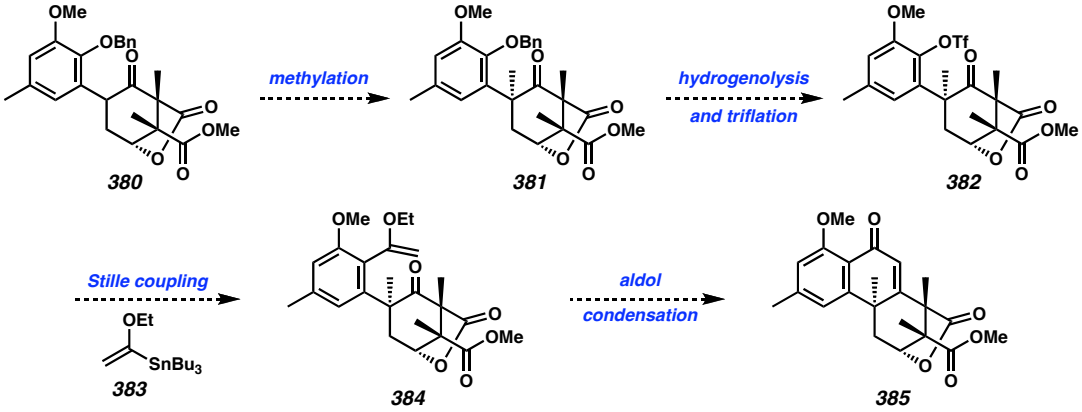

**Scheme D.4.6** Synthesis of aryl bromide **379**

Initial studies show that arylation is a viable method to append the A rinD. Treatment of ketone **249** with aryl bromide **379**, $Pd(OAc)_2$, $P(t\text{-}Bu)_3$, and NaHMDS in THF at 70 °C provided A–C ring adduct **380** in 67% yield (Scheme D.4.7).




**Scheme D.4.7** α-Arylation to form A–C ring adduct **380**.

Adduct **380** may be advanced to a tricycle through a number of potential routes. We detail one of these in Scheme D.4.8 below. Efforts to methylate **380** have proved challenging to date.[13] However, careful screening may lead to successful methylation at the C(12) position. Subsequent hydrogenolysis of the benzyl ether and triflation will provide enol triflate **382**. Stille coupling with (1-ethoxyvinyl)tributylstannane (**383**) will provide **384**, which, upon treatment with acidic conditions will undergo global deprotection and aldol condensation under acidic conditions to provide **385**.



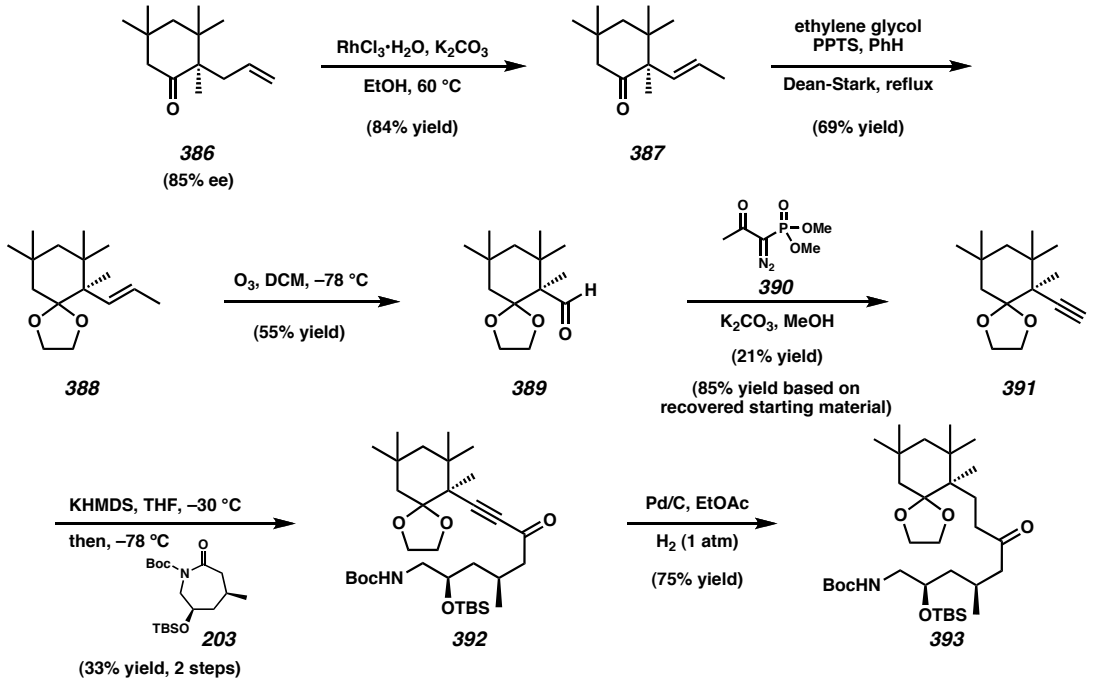

**Scheme D.4.8** B ring closure of α-arylation product **380**.

*D.5.1 Precedence for Planned Late-Stage Side Chain Couplings*

The retrosynthetic approaches outlined for our vicinal quaternary center-containing C ring synthons require a late-stage side chain attachment to an alkyne or aldehyde moiety. Some initial model studies have been conducted to test the viability of each of these routes, and they are outlined below.

*D.5.2 Alkyne Addition into Enantiopure Lactam Synthon*

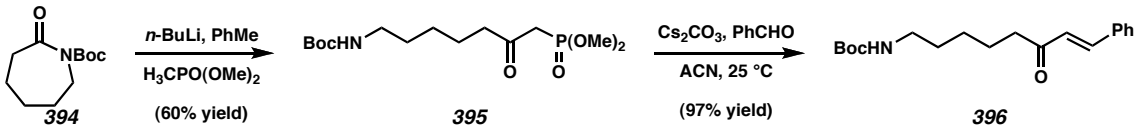
In order to determine the feasibility of an alkyne addition into lactam **203**, alkyne **391** was synthesized from a readily available asymmetric alkylation product (**386**).[8a] Allyl ketone **386** was smoothly isomerized to ketone **387**, which was then ketalized to provide olefin **388** (Scheme D.5.1). Ozonolysis with mild reductive workup allowed access to the desired model aldehyde **389**. Treatment with the Ohira-Bestman reagent (**390**)[14] proceeded sluggishly to afford alkyne **391** along with a substantial amount of recovered starting material. Deprotonation of the alkyne with KHMDS and trapping with caprolactam **203** provided alkynone **392**. Hydrogenation of the alkyne readily provided the final side-chain-appended model product **393**. This sequence of steps functions as a proof of principle that our retrosynthetic plan is viable and will ultimately allow coupling of the side chain. Yields in this section are unoptimized, and it is anticipated that they will be improved before undertaking such a coupling strategy in the fully functionalized system.




**Scheme D.5.1** Side chain functionalization of a model ketone.

*D.5.3 Synthesis of a Horner-Wadsworth-Emmons Reagent for Side Chain Synthesis*[†]

In addition to the alkyne coupling strategy, we have recently undertaken investigations toward a Horner-Wadsworth-Emmons coupling strategy that would allow us to use a C(8) aldehyde directly rather than first homologating to an alkyne. Deprotonation of dimethyl methylphosphonate and addition to Boc-protected caprolactam **394** resulted in formation of Horner-Wadsworth-Emmons reagent **395** (Scheme D.5.2). The viability of this reagent in olefinations was tested by treatment with benzaldehyde and cesium carbonate, providing an excellent yield of enone **396**. This approach remains to be tested with fully functionalized lactam **203** or with a more hindered aldehyde such as **389**.




**Scheme D.5.2** Horner-Wadsworth-Emmons coupling strategy.

*D.6.1 Summary*

In summary, we have outlined a number of remaining potential approaches to the carbocyclic core of zoanthenol. These strategies include the utilization of early acid-mediated cyclization product **192**, the synthesis of new substrates for vicinal quaternary center-containing systems for acid-mediated and radical cyclization approaches, and finally, the installation of the C(12) quaternary center prior to B-ring formation by alkylation or arylation. Additionally, we have outlined two potential methods for the late-stage coupling of the heterocyclic synthon to the carbocyclic core of zoanthenol.

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[†] The work in this subsection was primarily conducted by Dr. Andrew McClory, a postdoctoral researcher in the Stoltz Group.

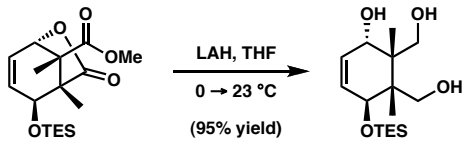
*D.7.1 Materials and Methods*

Unless otherwise stated, reactions were performed at ambient temperature (typically 19–24 °C) 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. *N*-Bromosuccinimide was recrystallized before use. TESCl and TBSCl were purchased from Gelest. Metal salts were purchased from Strem. All other commercially obtained reagents were purchased from Aldrich or Acros and used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, anisaldehyde, $KMnO_4$, or CAM staining. ICN silica gel (particle size 0.032–0.063 mm) was used for flash chromatography. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz, respectively), or a Varian Inova 500 (at 500 MHz and 125 MHz, respectively) and are reported relative to $Me_4Si$ (δ 0.0). Data for $^{1}H$ NMR spectra 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, sept. = septet, m = multiplet, comp. m = complex multiplet, app. = apparent, bs = broad singlet. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption ($cm^{-1}$). High-resolution mass spectra were obtained from the Caltech Mass Spectroscopy Facility. Crystallographic analyses were performed at the California Institute of Technology Beckman Institute X-Ray Crystallography Laboratory. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, from the CCDC by quoting the publication citation and the deposition number (see Appendix E for deposition numbers).

*D.7.2 Preparation of Compounds*


*248* *341*

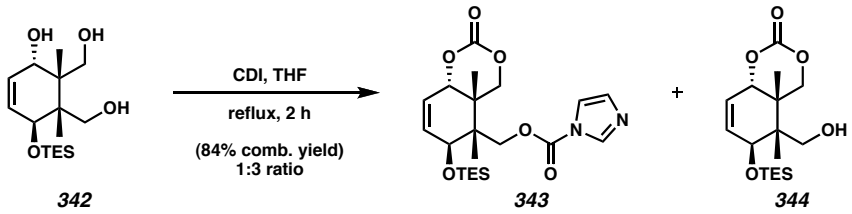
**Silyl ether 341.** To a solution of allylic alcohol **248** (2.078 g, 9.185 mmol, 1.0 equiv) in DMF (4.59 mL, 2.0 M) were added imidazole (1.88 g, 27.56 mmol, 3.0 equiv), DMAP (280.5 mg, 2.296 mmol, 0.25 equiv), and TESCl (2.0 mL, 11.94 mmol, 1.3 equiv). The reaction was stirred at ambient temperature 7h before diluting with EtOAc (500 mL). The solution was washed with sat. $NH_4Cl$ (3 x 150 mL), and the combined aqueous layers were extracted with EtOAc (4 x 150 mL). The combined organics were then dried over $MgSO_4$, concentrated to an oil, and purified by flash chromatography (5 to 10% EtOAc in hexanes) to provide pure lactone **341** (3.121 g, 9.167 mmol, > 99% yield) as an oil. $R_f$ 0.8 (35% EtOAc in hexanes); $^1$H NMR (500 MHz, $CDCl_3$) δ 6.19 (ddd, $J$ = 9.5, 5.9, 1.0 Hz, 1H), 5.91 (ddd, $J$ = 9.3, 3.2, 0.7 Hz, 1H), 4.78 (dd, $J$ = 5.9, 0.7 Hz, 1H), 4.13 (dd, $J$ = 3.4, 1.0 Hz, 1H), 3.73 (s, 3H), 1.45 (s, 3H) 1.38 (s, 3H), 0.97 (t, $J$ = 8.1 Hz, 9H), 0.63 (q, $J$ = 8.1 Hz, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 179.0, 173.8, 135.0, 126.8, 77.3, 70.6, 54.9, 52.5, 51.3, 15.7, 14.5, 6.8, 4.9; IR (Neat film NaCl) 2956, 2878, 1787, 1733, 1255, 1066, 959, 726 cm$^{-1}$; HRMS (FAB+) $[M+H]^+$ calc'd for $[C_{17}H_{28}O_5+H]^+$: $m/z$ 341.1784, found 341.1798.




*341* *342*

**Triol 342.** To a cooled (0 °C) solution of LAH (680.7 mg, 17.04 mmol, 4.0 equiv) in THF (40 mL) was added lactone **341** (1.4506 g, 4.26 mmol, 1.0 equiv) in THF (10 mL).

The ice bath was allowed to melt, bringing the solution gradually to ambient temperature and stirred 5 h. The solution was cooled again to 0 °C and slowly quenched with EtOAc until no further bubbles were observed. Celite (1.5 g) was added, and the reaction was further quenched with sat. $Na_2SO_4$ (10 mL) in a dropwise manner. The reaction was further diluted with EtOAc (30 mL), allowed to warm to ambient temperature, then filtered through a pad of celite. The pad was rinsed with EtOAc (2 x 25 mL), the combined organics were dried over $Na_2SO_4$ and concentrated to an oil (**342**, 1.200 g, 3.791 mmol, 89% yield) of sufficient purity for use in the next reaction. $R_f$ 0.13 (35% EtOAc in hexanes); $^1$H NMR (300 MHz, $CDCl_3$) δ 5.66 (app. s, 2H), 4.51 (d, *J* = 2.8 Hz, 1H), 4.21 (*bs*, 1H), 3.91 (d, *J* = 11.4 Hz, 1H), 3.75 (d, *J* = 11.4 Hz, 1H), 3.72 (d, *J* = 11.4 Hz, 1H), 3.53 (d, *J* = 11.4 Hz, 1H), 2.97 (bs, 1H), 2.68 (bs, 1H), 1.16 (s, 3H), 0.97 (t, *J* = 7.9 Hz, 9H), 0.87 (s, 3H), 0.64 (q, *J* = 7.9 Hz, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 131.3, 129.3, 73.8, 69.9, 65.8, 63.7, 46.1, 45.2, 15.9, 13.2, 6.9, 5.2; IR (Neat film NaCl) 3282, 2955, 2915, 2879, 1458, 1078, 1026, 845, 727 cm$^{-1}$; HRMS (ESI) $[M+H]^+$ calc'd for $[C_{16}H_{32}O_4Si+H]^+$: *m/z* 317.2148, found 317.2147.

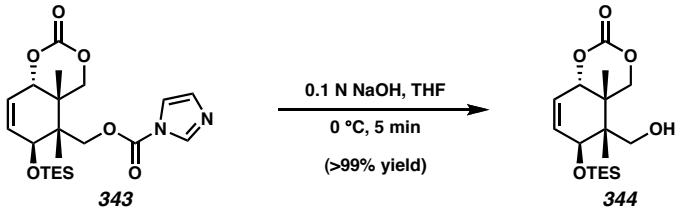



**Carbamate 343 and Alcohol 344.** To a solution of triol **342** (2.449 g, 7.74 mmol, 1.0 equiv) in THF (50 mL, 0.15 M) was added carbonyl diimidazole (2.01 g, 12.38 mmol, 1.6 equiv). The solution was heated to reflux 22 h before cooling to ambient temperature. Silica gel was added to the solution to generate a slurry, and the solvent was removed by careful rotary evaporation. The resulting powder was loaded onto a flash column for

purification (10 to 50% EtOAc in hexanes), providing carbamate **343** (707.2 mg, 21% yield) as a white powder and alcohol **344** (1.664 g, 63% yield) as a white powder.

**Carbamate 343.** $R_f$ 0.18 (35% EtOAc in hexanes); $^1$H NMR (500 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.36 (s, 1H), 7.14 (d, *J* = 0.7 Hz, 1H), 5.89 (dt *J* = 10.5, 2.2 Hz, 1H), 5.79 (dt, *J* = 10.5, 1.7 Hz, 1H), 4.75 (ddd, *J* = 4.9, 4.1, 2.0 Hz, 1H), 4.57 (d, *J* = 10.7 Hz, 1H), 4.48 (comp. m, 2H), 4.37 (d, *J* = 11.7 Hz, 1H), 4.22 (dd, *J* = 10.7, 2.0 Hz, 1H), 1.39 (s, 3H), 1.01 (s, 3H), 0.92 (t, *J* = 8.1 Hz, 9H), 0.58 (comp. m, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 147.9, 147.4, 136.8, 132.0, 131.5, 125.6, 116.7, 81.4, 70.8, 68.1, 66.5, 45.8, 37.6, 16.2, 11.8, 6.7, 4.9; IR (Neat film NaCl) 2956, 2907, 2877, 1755 (br), 1391, 1290, 1241, 1078, 1003, 832, 744 cm$^{-1}$; HRMS (FAB+) $[M+H]^+$ calc'd for $[C_{21}H_{22}O_6SiN_2+H]^+$: *m/z* 437.2108, found 437.2104.

**Alcohol 344.** $R_f$ 0.6 (35% EtOAc in hexanes); $^1$H NMR (500 MHz, $CDCl_3$) δ 5.80 (dt, *J* = 10.5, 2.2 Hz, 1H), 5.74 (dt, *J* = 10.5, 1.7 Hz, 1H), 4.68 (ddd, *J* = 4.9, 4.2, 2.0 Hz, 1H), 4.59 (dd, *J* = 11.2, 2.0 Hz, 1H), 4.59 (m, 1H), 4.45 (d, *J* = 11.5 Hz, 1H), 3.66 (d, *J* = 2.2 Hz, 1H), 1.32 (s, 3H), 0.97, (t, *J* = 7.8 Hz, 9H), 0.79 (s, 3H), 0.64 (comp. m, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 148.5, 133.0, 125.3, 82.0, 71.8, 66.2, 63.6, 47.0, 37.8, 15.6, 11.6, 6.8, 5.0; IR (Neat film NaCl) 3472, 2954, 2915, 2879, 1737, 1713, 1478, 1424, 1370, 1287, 1243, 1199, 1045, 842, 727 cm$^{-1}$; HRMS (FAB+) $[M+H]^+$ calc'd for $[C_{17}H_{30}O_5Si+H]^+$: *m/z* 343.1941, found 343.1953.




*343* *344*

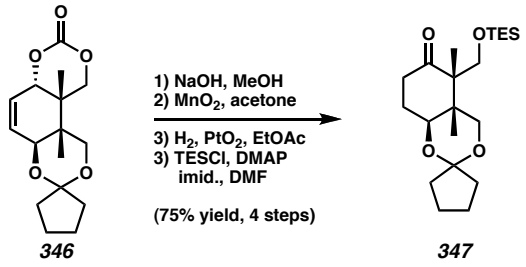
**Alcohol 344 from carbamate 343**. To a cooled (0 °C) solution of carbamate **344** (942.3 mg, 2.158 mmol, 1.0 equiv) in THF (43 mL, 0.05 M) was added a cooled (0 °C) 0.1

N solution of NaOH (21.58 mL, 2.158 mmol, 1.0 equiv). The reaction was stirred 5 min then quenched by addition of HCl (2.16 mL, 1.0 M) and allowed to warm to ambient temperature. The reaction mixture was diluted with $H_2O$ (75 mL) and EtOAc (50 mL). The aqueous layer was extracted with EtOAc (4 x 25 mL), then the combined organic layers were washed with brine (75 mL), dried over $MgSO_4$, and concentrated to an oil, which was purified by flash chromatography (10 to 50% EtOAc in hexanes) to provide carbonate **343** (741.9 mg, 2.166 mmol, > 99% yield) as a white solid.


**Acetal 346.** To a solution of alcohol **344** (250.6 mg, 0.730 mmol, 1.0 equiv) in MeOH (7.3 mL, 0.1 M) was added DOWEX 50W-X8 resin (270 mg). The suspension was stirred at ambient temperature for 3 h, filtered, concentrated, and redissolved in $CH_2Cl_2$ (7.3 mL, 0.1M). Acetal **345**[*,15] (475 mg, 3.65 mmol, 5 equiv), camphor sulfonic acid (5.1 mg, 0.022 mmol, 0.03 equiv) were added, and the solution was stirred at ambient temperature for 12 h. Additional acetal **345**[*] (200 mg, 1.54 mmol, 2.1 equiv) was added, and the reaction was stirred an additional 1 h before quenching by dropwise addition of sat $NaHCO_3$ until no further bubbling was observed. The reaction was diluted with $H_2O$ (25 mL) and $CH_2Cl_2$ (18 mL), the aqueous layer was extracted with $CH_2Cl_2$ (3 x 25 mL), dried over $MgSO_4$, and concentrated to an oil before purification by flash chromatography (10 to 50% EtOAc in hexanes) to provide acetal **346** (170.6 mg, 0.580 mmol, 79% yield) as an oil. $R_f$ 0.7 (50% acetone in hexanes); $^1$H NMR (500 MHz, $CDCl_3$)

[*] Acetal **345** contained 10 mol% $HC(OMe)_3$, as determined by $^1$H NMR.

δ 5.84 (dt, *J* = 10.5, 2.4 Hz, 1H), 5.79 (dt, *J* = 11.7, 1.2 Hz, 1H), 4.78 (ddd, *J* = 5.4, 4.2, 2.2 Hz, 1H), 4.48 (d, *J* = 10.5 Hz, 1H), 4.35 (dd, *J* = 4.4, 2.9 Hz, 1H), 4.04 (dd, *J* = 10.7, 2.2 Hz, 1H), 3.72 (d, *J* = 10.7 Hz, 1H), 3.62 (d, *J* = 10.7 Hz, 1H), 2.01 (m, 1H), 1.89 (m, 1H), 1.8–1.61 (comp. m, 4H), 1.23 (s, 3H), 1.21 (app. d, *J* = 0.5 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 148.2, 130.5, 125.7, 111.9, 83.0, 71.5, 69.3, 66.3, 40.4, 39.9, 36.4, 30.9, 24.3, 22.5, 15.1, 12.4; IR (Neat film NaCl) 2961, 2873, 1756, 1185, 1122, 1084 cm$^{-1}$; HRMS (FAB+) $[M+H]^+$ calc'd for $[C_{16}H_{22}O_5+H]^+$: *m/z* 295.1545, found 295.1533.




*346* *347*

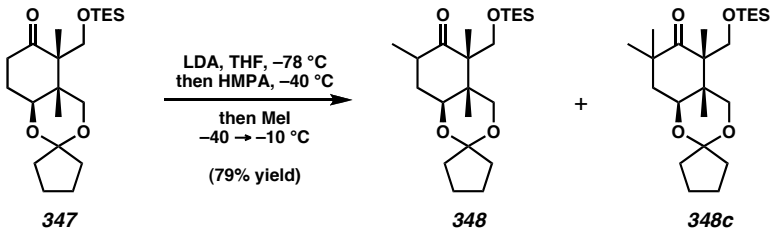
**Ketone 347.** To a solution of carbonate **346** (1.214 g, 4.123 mmol, 1.0 equiv) in MeOH (65 mL, 0.06 M) was added 0.2 M NaOH (41 mL, 8.25 mmol, 2.0 equiv), and the solution was stirred at ambient temperature 70 min. The MeOH was removed by rotary evaporation, and the resulting solution was brought to pH 7 by addition of solid $NH_4Cl$, diluted with EtOAc (50 mL), and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organics were dried over $MgSO_4$ and concentrated.

The crude diol was redissolved in acetone (137 mL, 0.03 M), $MnO_2$ (12.65 g, 123.7 mmol, 30 equiv) was added, and the resulting suspension was stirred 2.5 h, filtered through #2 Whatman paper, and concentrated to an oil.

The crude enone was dissolved in EtOAc (260 mL, 0.016 M), $PtO_2$ (93.6 mg, 0.412 mmol, 0.1 equiv) was added, and the suspension was sparged with $H_2$ until it turned from brown to black. The reaction mixture was then stirred under $H_2$ (1 atm) 10.5 h,

filtered through #2 Whatman paper, and concentrated to an oil, which was carried on without further purification.

The primary alcohol was then dissolved in DMF (3 mL, 1 M) and DMAP (365.3 mg, 2.99 mmol, 1.0 equiv), imidazole (610.7 mg, 8.97 mmol, 3.0 equiv), and TESCl (653.1 μL, 3.89 mmol, 1.3 equiv) were added. The mixture was stirred at ambient temperature for 17 h, then additional TESCl (300 μL, 1.79 mmol, 0.6 equiv) was added. The reaction was stirred an additional 3 h then diluted with sat. $NH_4Cl$ (100 mL) and extracted with EtOAc (5 x 25 mL). The combined organics were washed with brine (25 mL), dried over $MgSO_4$, and concentrated to an oil. The crude product was purified by flash chromatography (10 to 40% EtOAc in hexanes) to provide silyl ether **347** (863 mg, 3.081 mmol, 75% yield over 4 steps) as an oil. $R_f$ 0.56 (25% acetone in hexanes); $^1$H NMR (300 MHz, $CDCl_3$) δ 4.67 (dd, *J* = 11.7, 5.0 Hz, 1H), 4.02 (d, *J* = 10.8 Hz, 1H), 3.91 (d, *J* = 10.0 Hz, 1H), 3.52 (d, *J* = 10.8 Hz, 1H), 3.51 (d, *J* = 10.0 Hz, 1H), 2.59 (m, 1H), 2.44 (ddd, *J* = 14.9, 5.0, 1.8 Hz, 1H), 2.08–1.61 (m, 10H), 1.03 (s, 3H), 0.94 (t, *H* 8.2 Hz, 9H), 0.93 (s, 3H), 0.59 (app. dd, *J* = 15.8, 7.6 Hz, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 211.7, 110.8, 70.5, 68.0, 66.3, 55.5, 40.2, 39.9, 38.2, 31.0, 27.3, 24.3 22.5, 14.8, 14.0, 6.7, 4.2; IR (Neat film NaCl) 2956, 2879, 1721, 1336, 1118, 1084, 1008, 977, 813, 747 cm$^{-1}$; HRMS (FAB+) $[M]^+$ calc'd for $[C_{21}H_{38}O_4Si]^+$: *m/z* 382.2539, found 382.2543.




*347* *348* *348c*

**Methyl ketone 348.** To a solution of DIPA (97.6 μL, 0.696 mmol, 1.3 equiv) in THF (5.0 mL, 0.1 M to *n*-BuLi) at 0 °C was added *n*-butyllithium (245 μL, 2.16 M, 0.530 mmol, 0.99 equiv) dropwise. The solution was stirred at 0 °C 30 min, then cooled to –78

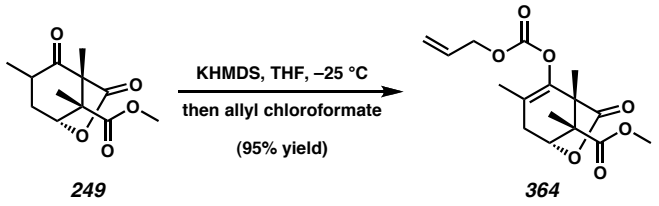
°C. Ketone **347** (204.9 mg, 0.5355 mmol, 1.0 equiv) was added as a solution in THF (5.5 mL, 0.1 M) dropwise, then stirred at –78 °C 2 h. HMPA (279.5 μL, 1.607 mmol, 3.0 equiv) was added and stirred 20 min. The solution was then warmed to –40 °C and MeI (667 μL, 10.71 mmol, 20 equiv) was added all at once. The reaction was stirred an additional 90 min, while slowly warming to –10 °C, then was quenched with $H_2O$ (1 mL) and allowed to come to ambient temperature. Brine (25 mL) was added, and the mixture was extracted with EtOAc (5 x 20 mL), dried over $MgSO_4$, concentrated to an oil, and purified by flash chromatography (0 to 10% $Et_2O$ in hexanes, slow gradient) to provide a mixture of partially separable methyl ketones **348** (168.6 mg, 0.425 mmol, 79% yield) as well as a small amount of bis-methylated ketone **348c**. (Use of > 0.99 equiv *n*-BuLi resulted in significant formation of this undesired product.)

**Methyl ketone 348a.** (high $R_f$ diastereomer) $R_f$ 0.39 (20% $Et_2O$ in hexanes); $^1$H NMR (500 MHz, $CDCl_3$) δ 4.65 (dd, *J* = 12.0, 4.6 Hz, 1H), 3.97 (d, *J* = 11.0 Hz, 1H), 3.96 (d, *J* = 10.0 Hz, 1H), 3.52 (d, *J* = 10.0 Hz, 1H), 3.51 (d, *J* = 10.7 Hz, 1H), 2.68 (m, 1H), 2.06–1.97 (comp. m, 2H), 1.94–1.81 (comp. m, 3H), 1.77–1.61 (comp. m, 5H), 1.05 (d, *J* = 6.3 Hz, 3H), 0.97 (s, 3H), 0.93 (t, *J* = 7.8 Hz, 9H), 0.57 (comp. m, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 212.2, 110.8, 70.4, 68.1, 66.0, 55.4, 40.89, 40.87, 39.9, 36.3, 31.0, 24.3, 22.5, 14.8, 14.6, 14.2, 6.7, 4.2; IR (Neat film NaCl) 2956, 2876, 1718, 1458, 1335, 1109, 1084, 1003, 816, 745 cm$^{-1}$; HRMS (FAB+) $[M]^+$ calc'd for $[C_{22}H_{40}O_4Si]$: *m/z* 396.2696, found 396.2690.

**Methyl ketone 348b.** (low $R_f$ diastereomer) $R_f$ 0.30 (20% $Et_2O$ in hexanes); $^1$H NMR (500 MHz, $CDCl_3$) δ 4.61 (dd, *J* = 11.5, 5.9 Hz, 1H), 4.07 (d, *J* = 11.0 Hz, 1H), 3.67 (d, *J* = 10.0 Hz, 1H), 3.57 (d, *J* = 10.0 Hz, 1H), 3.43 (d, *J* = 10.7 Hz, 1H), 2.64 (m, 1H), 2.00–1.85 (comp. m, 3H), 1.80 (t, *J* = 7.1 Hz, 1H), 1.68–1.54 (comp m., 5H), 1.13 (d, *J* = 7.6 Hz, 1H), 1.09 (s, 3H), 0.88 (t, *J* = 7.8 Hz, 9 H), 0.85 (s, 3H), 0.53 (q, *J* = 7.8 Hz, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 216.1, 110.6, 68.4, 68.0, 67.0, 54.7, 41.1, 40.0, 39.0, 33.2, 31.2, 24.2,

22.6, 18.7, 16.6, 15.8, 6.8, 4.1; IR (Neat film NaCl) 2955, 2979, 1706, 1456, 1336, 1114, 1083, 1006, 812, 745 $cm^{-1}$; HRMS (FAB+) $[M]^+$ calc'd for $[C_{22}H_{40}O_4Si]$: *m/z* 396.2696, found 396.2681.

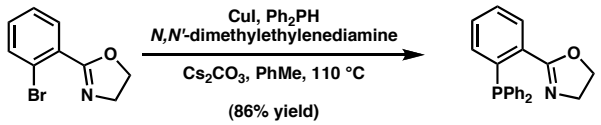
**Bis-methyl ketone 348c.** $R_f$ 0.47 (20% $Et_2O$ in hexanes); $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.70 (dd, *J* = 5.0, 4.7 Hz, 1H), 4.74 (d, *J* = 11.1 Hz, 1H), 3.66 (app. dd, *J* = 12.3, 10.0 Hz, 2H), 3.49 (d, *J* = 11.1 Hz, 1H), 2.00 (comp. m, 2H), 1.86 (comp. m, 2H), 1.77–1.62 (comp. m, 6H), 1.55 (s, 3H), 1.20 (s, 3H), 1.05 (s, 3H), 0.943 (t, *J* = 8.2 Hz, 9H), 0.59 (q, *J* = 7.9 Hz, 6H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 217.5, 110.6, 68.2, 67.9, 67.4, 55.8, 44.3, 40.7, 40.1, 39.4, 31.1, 28.5, 27.9, 24.3, 22.6, 16.5, 16.1, 6.8, 4.1; IR (Neat film NaCl) 2956, 2876, 1696, 1461, 1335, 1117, 1084, 1016, 815, 745 $cm^{-1}$; HRMS (FAB+) $[M]^+$ calc'd for $[C_{23}H_{42}O_4Si]$: *m/z* 410.2852, found 410.2870.




***249*** ***364***

**Allyl methyl ketone 364.** To a solution of KHMDS (546.1 mg, 2.737 mmol, 1.3 equiv) in THF (27 mL, 0.1 M) at –25 °C was added a solution of ketone **249** (505.9 mg, 2.106 mmol, 1.0 equiv) in THF (20 mL + 2 x 0.5 mL rinse). The solution was stirred at –25 °C for 2 h then allyl chloroformate (314.6 μL, 2.948 mmol, 1.4 equiv) was added and stirred at –20 °C an additional 1 h. The reaction was quenched with sat. $NaHCO_3$ (25 mL) and allowed to warm to ambient temperature. Further dilution with $H_2O$ (25 mL) was followed by extraction with EtOAc (50, 3 x 20 mL). The combined organics were washed with brine (25 mL), dried over $MgSO_4$, and concentrated to an oil, which was purified by flash chromatography (25 to 55% EtOAc in hexanes) to provide allyl enol carbonate **364** (646.8 mg, 1.994 mmol, 95% yield) as a clear oil. $R_f$ 0.50 (50% EtOAc in hexanes); $^1H$

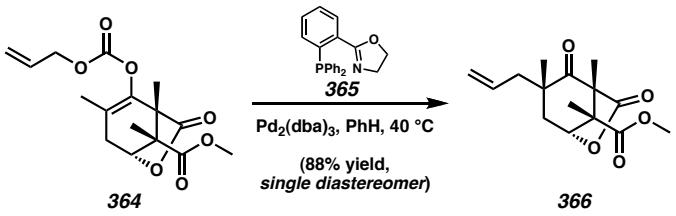
NMR (500 MHz, $CDCl_3$) δ 5.93 (dddd, *J* = 17.1, 10.5, 5.9, 5.6 Hz, 1H), 5.39 (ddd, *J* = 17.1, 2.7, 1.5 Hz, 1H), 5.30 (ddd, *J* = 10.5, 2.4, 1.2 Hz, 1H), 4.67 (ddd, *J* = 4.6, 2.2, 1.0 Hz, 1H), 4.58 (app. t, *J* = 2.7 Hz, 1H), 3.73 (s, 3H), 2.44 (app. t, *J* = 1.22 Hz, 1H), 1.61 (s, 3H), 1.37 (s, 3H), 1.29 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 175.1, 172.8, 152.8, 138.7, 130.9, 122.1, 119.4, 77.7, 69.3, 54.4, 52.7, 50.1, 33.7, 15.3, 12.7, 8.9; IR (Neat film NaCl) 2989, 2953, 1790, 1761, 1732, 1454, 1252, 1225, 1200, 1159, 1075, 1033, 976, 782 $cm^{-1}$; HRMS (FAB+) $[M+H]^+$ calc'd for $[C_{16}H_{20}O_7+H]^+$: *m/z* 325.1287, found 325.1272.




*365a* *365*

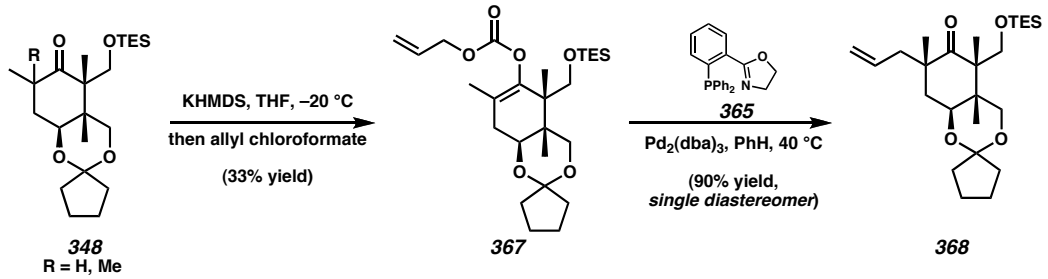
**Phosphine 365:** A 250-mL Schlenk flask was charged with CuI (66.7 mg, 0.35 mmol), $Ph_2PH$ (4.12g, 3.85 mL, 22.1 mmol) and then *N,N'*-dimethylethylenediamine (156 mg, 191 μL, 1.77 mmol) followed by toluene (18 ml). The solution was stirred at 23 °C for 20 min. Oxazole **365a** (4.0 g, 17.7 mmol) was azeotroped with toluene (2 x 5 ml) under reduced pressure, then dissolved in toluene (18 mL) and transferred quantitatively to the Schlenk flask by use of positive pressure cannulation. $Cs_2CO_3$ (8.65 g, 26.5 mmol) was added in one portion, and the flask was evacuated and backfilled with Ar (x 3). The Teflon valve was sealed and the yellow heterogenous reaction mixture was placed in an oil bath, heated to 110 °C, and stirred vigorously. After 20 h stirring at 110 °C, the mixture was allowed to cool to ambient temperature and filtered through a pad of celite using $CH_2Cl_2$ (2 x 50 mL). The filtrate was concentrated under reduced pressure to afford a clear orange oil. The crude oil was flushed through a plug of silica gel (5.0 x 10 cm $SiO_2$, hexanes → 10% $Et_2O$ in $CH_2Cl_2$) to afford **365** (5.03 g, 86% yield) as a colorless viscous oil that crystallized upon standing; $R_f$ = 0.50 (30% EtOAc in hexanes); $^{31}P$ NMR (121 MHz, $CDCl_3$) δ –3.99 (s); $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 7.6, 3.4 Hz, 1H),

7.37–7.26 (comp. m, 12H), 6.89 (dd, $J$ = 7.6, 4.1 Hz, 1H), 4.08 (t, $J$ = 9.5 Hz, 2H), 3.78 (t, $J$ = 9.5 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 164.5 (d, $J_{CP}$ = 2.8 Hz), 139.1 (d, $J_{CP}$ = 24.9 Hz), 138.0 (d, $J_{CP}$ = 11.5 Hz), 134.1 (d, $J_{CP}$ = 20.7 Hz), 133.7 (d, $J_{CP}$ = 1.8 Hz), 131.9 (d, $J_{CP}$ = 18.9 Hz), 130.5, 129.9 (d, $J_{CP}$ = 2.8 Hz), 128.7, 128.5 (d, $J_{CP}$ = 7.4 Hz), 128.1, 67.2, 55.0; IR (Neat Film NaCl) 3053, 3000, 2971, 2901, 2876, 1650, 1585, 1562, 1478, 1434, 1354, 1326, 1248, 1133, 1089, 1070, 1041, 974, 942, 898, 743 cm$^{-1}$; HRMS (FAB+) $[M]^+$ *m/z* calc'd for $[C_{21}H_{19}NOP]^+$: 332.1204, found 332.1218; mp = 99–101 °C.




**Allyl methyl ketone 366.** To a 50-mL round-bottomed flask in the glovebox was added $Pd_2(dba)_3$ (35.3 mg, 0.0385 mmol, 0.05 equiv) and PHOX ligand[16] **365** (56.2 mg, 0.1696 mmol, 0.22 equiv). The flask was removed from the glovebox, purged for 5 min under vacuum and refilled with $N_2$ (3x). Benzene (25.7 mL, 0.03 M, sparged with argon 30 min) was added via cannula, and the pre-catalyst mixture was heated to 40 °C for 30 min (a color change from red to orange was observed). A solution of allyl enol carbonate **364** (250 mg, 0.7708 mmol, 1.0 equiv) in benzene (1 mL, sparged with argon 5 min) was transferred via cannula to the catalyst solution (a color change from orange to green was observed after 5 min). The reaction was stirred at 40 °C for 4 h then cooled to ambient temperature. The reaction mixture was concentrated then loaded directly onto a flash column and purified (10 to 40% EtOAc in hexanes), yielding allyl methyl ketone **366** (191 mg, 0.681 mmol, 88% yield) as a white solid. m.p. 77–78 °C; $R_f$ 0.62 (50% EtOAc in hexanes); $^1$H NMR (500 MHz, $CDCl_3$) δ 5.60 (dddd, $J$ = 16.8, 10.2, 7.8, 7.0 Hz, 1H), 5.12 (dd, $J$ = 11.0, 0.7 Hz, 1H), 5.06 (dd, $J$ = 16.8, 1.22 Hz, 1H), 4.90 (dd, $J$ = 3.7, 2.0 Hz, 1H),

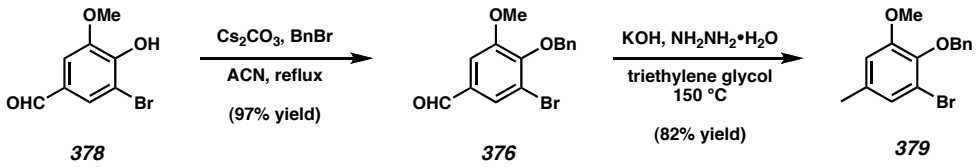
3.76 (s, 3H), 2.46 (dd, *J* = 15.4, 3.7 Hz, 1H), 2.33 (dd, *J* = 14.2, 7.1 Hz, 1H), 2.22 (dd, *J* = 13.9, 7.8 Hz, 1H), 1.77 (dd, *J* = 15.4, 2.0 Hz, 1H), 1.28 (s, 3H), 1.19 (app. s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 204.0, 173.2, 171.6, 131.8, 120.1, 80.4, 61.7, 57.4, 53.0, 47.4, 46.7, 36.5, 24.5, 15.0, 10.3; IR (Neat film NaCl) 3079, 2985, 2954, 1789, 1732, 1715, 1640, 1440, 1342, 1261, 1228, 1157, 1094, 976 cm$^{-1}$; HRMS (FAB+) $[M+H]^+$ calc'd for $[C_{15}H_{20}O_5+H]^+$: *m/z* 281.1389, found 281.1376. Stereochemistry assigned via X-ray crystallographic analysis.




**Allyl methyl ketone 368.** To a solution of KHMDS (33.2 mg, 0.1665 mmol, 1.3 equiv) in THF (2.0 mL, 0.08 M) at –20 °C was added a solution of ketone **348**[*] (50.8 mg, 0.1281 mmol, 1.0 equiv) in THF (1 mL + 2 x 0.5 mL rinse). The solution was stirred at –20 °C 2 h then allyl chloroformate (19.1 μL, 0.1793 mmol, 1.4 equiv) was added and stirred an additional 1.5 h. The reaction was quenched with $H_2O$ (1 mL), diluted with EtOAc (1 mL) and allowed to warm to ambient temperature. Further dilution with $H_2O$ (20 mL) was followed by extraction with EtOAc (4 x 15 mL). The combined organics were washed with brine (25 mL), dried over $MgSO_4$, and concentrated to an oil, which was purified by flash chromatography (0 to 10% EtOAc in hexanes, slow gradient) to provide allyl enol carbonate **367** (20.5 mg, 0.0427 mmol, 33% yield) as well as recovered bis-methyl ketone **348c** (17.8 mg, 0.0434 mmol, 34% yield).

[*] The sample was a mixture of methyl ketone **348** and bis-methyl ketone **348c**.

To a 20-mL vial containing allyl enol carbonate **367** (20.5 mg, 0.0427 mmol, 1.0 equiv) was added a flame-dried stirbar and it was cycled into the glovebox and benzene (0.4 mL) was added. In a separate 1-dram vial in the glovebox, $Pd_2(dba)_3$, PHOX ligand **365**, and benzene (1 mL) were combined, sealed, and heated to 40 °C for 30 min (a color change from red to orange was observed). At this point, it was transferred via syringe to the vial containing allyl enol carbonate **367**, sealed, and removed from the glovebox (a color change from orange to green was observed). The reaction was stirred at 40 °C 6.5 h (a color change from green to brown was observed), then cooled to ambient temperature. The reaction mixture was loaded directly onto a flash column and purified (0 to 10% EtOAc in hexanes, slow gradient), yielding allyl methyl ketone **368** (16.7 mg, 0.0391 mmol, 90% yield) as a clear oil. $^1$H NMR (500 MHz, $CDCl_3$) δ 5.68 (m, 1H), 5.10 (m, 1H), 5.03 (ddd, *J* = 17.2, 3.4, 2.2 Hz, 1H), 4.68 (dd, *J* = 12.2, 4.9 Hz, 1H), 4.11 (d, *J* = 11.0 Hz, 1H), 3.68 (d, *J* = 10.0 Hz, 1H), 3.62 (d, *J* = 10.0 Hz, 1H), 3.49 (d, *J* = 11.0 Hz, 1H), 2.34 (dd, *J* = 13.7, 8.1 Hz, 1H), 2.28 (dd, *J* = 13.9, 6.6 Hz, 1H), 1.98 (comp. m, 2H), 1.87–1.60 (comp. m, 10 H), 1.07 (s, 3H), 1.05 (s, 3H), 0.97 (s, 3H), 0.94 (comp. m, 9H), 0.60 (q, *J* = 8.1 Hz, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 217.1, 133.6, 118.5, 110.6, 67.89, 67.88, 67.6, 55.8, 47.5, 42.5, 40.0, 39.3, 37.5, 31.2, 25.2, 24.3, 22.5, 16.8, 16.3, 6.8, 4.1; IR (Neat film NaCl) 2957, 2877, 1694, 1460, 1336, 1117, 1084, 1006, 813, 745 cm$^{-1}$; HRMS (FAB+) $[M]^+$ calc'd for $[C_{25}H_{44}O_4Si]$: *m/z* 436.3009, found 436.2993. Stereochemistry assigned using a combination of HSQC, HMBC, COSY, and NOESY 2D experiments.

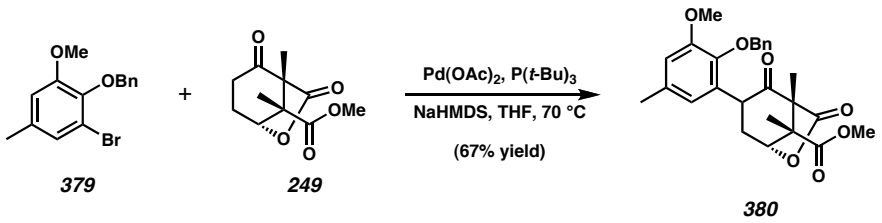



*378* *376* *379*

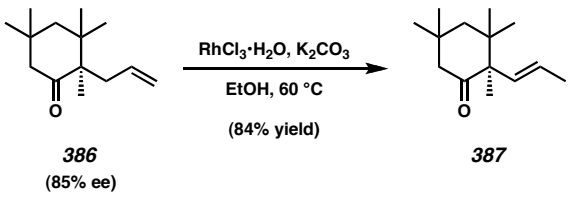
**Aryl Bromide 379.** To a flask equipped with a reflux condenser and containing a mixture of phenol **378** (2.00 g, 8.66 mmol, 1.0 equiv) and $Cs_2CO_3$ (3.53 g, 10.8 mmol,

1.25 equiv) was added ACN (34.6 mL) followed by benzyl bromide (1.13 mL, 9.53 mmol, 1.1 equiv). The reaction was stirred at 85 °C (reflux) for 1 h then cooled to ambient temperature. The mixture was diluted with $H_2O$ (100 mL) and extracted with EtOAc (3 x 25 mL). The combined organics were washed with brine (25 mL), dried over $MgSO_4$, and concentrated. The crude product was purified by flash chromatography (10 to 50% $Et_2O$ in petroleum ether) to give benzyl ether **376** (2.70 g, 8.4 mmol, 97% yield) as a slightly yellow powder. m.p. 48–48.5 °C; $R_f$ 0.4 (25% EtOAc in pet. ether).

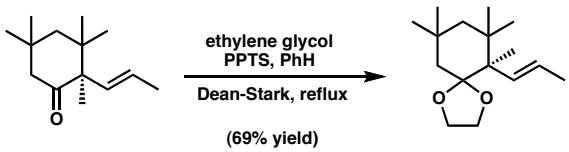
To a flask equipped with a reflux condenser and containing a solution of aldehyde **376** (1.99 g, 6.2 mmol, 1.0 equiv) in triethylene glycol (12.4 mL) was added hydrazine monohydrate (752 μL, 15.5 mmol, 2.5 equiv). The resulting mixture was heated to 110 °C and to the resulting clear solution was added KOH pellets (1.74 g, 31.0 mmol, 5.0 equiv) one-by-one through the condenser over 20 min. The mixture was then heated to 150 °C and stirred for 30 min. The solution was cooled to ambient temperature then to 0 °C, then diluted with 1 M HCl (aq., 40 mL) followed by $H_2O$ (40 mL), and extracted with EtOAc (4 x 20 mL). The combined organics were washed with brine (25 mL), dried over $MgSO_4$, and concentrated to an oil, which was purified by flash chromatography (5 to 10% EtOAc in pet. ether) to provide aryl bromide **379** (1.56 g, 5.8 mmol, 82% yield) as a clear, nonviscous oil. $R_f$ 0.33 (10% EtOAc in pet. ether); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.56 (comp. m, 2H), 7.38 (comp m, 2H), 7.33 (m, 1H), 6.97 (dd, $J$ = 2.0, 0.7 Hz, 1H), 6.68 (d, $J$ = 1.7 Hz, 1H), 4.99 (s, 2H), 3.84 (s, 3H), 2.30 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 153.5, 143.0, 137.3, 135.2, 128.5, 128.3, 128.0, 117.6, 112.7, 74.7, 56.0, 21.0; IR (Neat film NaCl) 3032, 2938, 2868, 1597, 1568, 1485, 1456, 1406, 979, 830, 728, 696 cm$^{-1}$; HRMS (FAB+) $[M+H]^+$ calc'd for $[C_{15}H_{15}O_2Br+H]^+$: *m/z* 307.0334, found 307.0325.




**Aryl ketone 380.** To a vial containing aryl bromide **379** (62 mg, 0.201 mmol, 1.0 equiv) and ketone **249** (50 mg, 0.221 mmol, 1.1 equiv) was added $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 0.1 equiv). The mixture was brought into the glovebox under vacuum. NaHMDS (5.5 mg, 0.302 mmol, 1.5 equiv), THF (0.8 mL, 0.25 M), and P(*t*-Bu)$_3$ (5.1 mg, 0.025 mmol, 1.25 equiv) were added. The vial was sealed, removed from the glovebox, and heated to 70 ºC for 5 h. The reaction was cooled to ambient temperature and extracted from 1M $NaHSO_4$ (aq, 10 mL) with $Et_2O$ (3 x 5 mL). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated to an oil. Purification by flash chromatography (15 to 33% EtOAc in hexanes) provided aryl ketone **380** (61 mg, mmol, 67% yield). $R_f$ ~ 0.3 (33% EtOAc in hexanes); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.33 (comp. m, 5H), 6.73 (s, 1H), 6.40 (s, 1H), 4.95 (s, 2H), 4.85 (d, *J* = 3.7 Hz, 1H), 4.16 (app. t, *J* = 9.6 Hz, 1H), 3.88 (s, 3H), 3.75 (s, 3H), 2.35 (m, 1H), 2.30 (s, 3H), 2.19 (dd, *J* = 13.9, 11.0 Hz, 1H), 1.29 (s, 3H), 1.21 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 199.5, 173.9, 171.6, 152.3, 143.7, 137.1, 129.1, 128.8, 128.5, 128.1, 121.2, 113.1, 79.3, 74.7, 62.3, 57.7, 55.7, 53.0, 45.8, 33.1, 21.4, 14.3, 9.9; IR (Neat film NaCl) 2951, 1790, 1732, 1488, 1465, 1254, 1153, 1077, 1016, 734 cm$^{-1}$; HRMS (FAB+) $[M+H]^+$ calc'd for $[C_{26}H_{27}O_7+H]^+$: *m/z* 452.1825, found 452.1852.



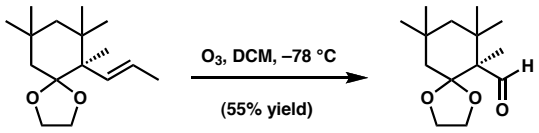
**Vinyl ketone 387.** To a solution of allyl ketone **386** (905 mg, 4.35 mmol, 1.00 equiv) in EtOH (45 mL) in a sealable Schlenk flask (100 mL) was added $K_2CO_3$ (601 mg, 4.35 mmol, 1.00 equiv) and $RhCl_3 \bullet H_2O$ (49.4 mg, 0.218 mmol, 0.05 equiv). The reaction mixture was sparged with Ar for 10 min, sealed and heated to 60 °C for 12 h. After cooling to ambient temperature, the reaction mixture was filtered, washed with EtOH, concentrated, and purified by flash chromatography on silica gel (7.5 to 10% $Et_2O$ in pentane) to give vinyl ketone **387** (759 mg, 84% yield of a 10:1 mixture containing allyl ketone **386** as the minor component) as an amorphous solid. $R_f$ 0.67, 0.46 (25% $Et_2O$ in hexanes, 5% $Et_2O$ in hexanes developed twice); $^1$H NMR (300 MHz, $CDCl_3$) δ 5.88 (dq, $J$ = 1.8, 15.5 Hz, 1H), 5.42 (dq, $J$ = 15.3, 6.3 Hz, 1H), 2.53 (d, $J$ = 13.2 Hz, 1H), 2.11 (dd, $J$ = 13.5, 1.8 Hz, 1H), 1.85 (d, $J$ = 14.4 Hz, 1H), 1.71 (dd, $J$ = 6.5, 1.7 Hz, 3H), 1.42 (dd, $J$ = 14.4, 1.8 Hz, 1H), 1.09 (s, 3H), 1.04 (s, 3H), 1.01 (s, 3H), 0.90 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 214.1, 132.5, 126.2, 56.4, 50.7, 49.6, 40.6, 35.4, 33.7, 30.2, 26.9, 26.8, 18.6, 15.6; IR (Neat film NaCl) 2957, 1707, 1458, 1391, 1370, 1283, 977 cm$^{-1}$; HRMS (EI) $[M]^+$ calc'd for $[C_{14}H_{24}O]^+$: $m/z$ 208.1827, found 208.1820; $[\alpha]_D^{25}$ –59.07 (*c* 1.04, $CHCl_3$, 85% ee).




*387* *388*

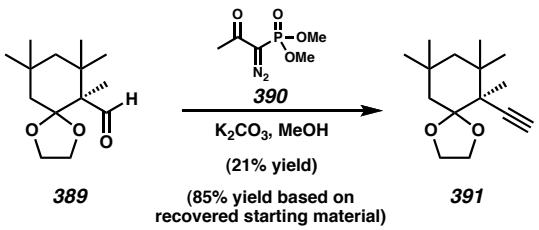
**Ketal 388.** A solution of the vinyl ketone **387** (700 mg, 3.36 mmol, 1.00 equiv), ethylene glycol (1.30 mL, 23.5 mmol, 7.00 equiv), and pyridinium *p*-toluenesulfonate (211 mg, 0.84 mmol, 0.25 equiv) in benzene (70 mL) was fitted with a Dean-Stark apparatus and refluxed at 100 °C for 30 h. The reaction mixture was cooled to ambient temperature, diluted with saturated aqueous $NaHCO_3$ (40 mL), and extracted with Ph-H (3 x 30 mL). The combined organics were washed with brine (20 mL), dried ($Na_2SO_4$), concentrated, and purified by flash chromatography on silica gel (1 to 2% $Et_2O$ in

hexane) to give acetal **388** (585 mg, 70% yield) as an oil: $R_f$ 0.61, 0.67 (5% $Et_2O$ in hexanes developed twice, 25% $Et_2O$ in hexanes); $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.74 (dq, *J* = 15.8, 1.5 Hz, 1H), 5.44 (dq, *J* = 15.8, 6.3 Hz, 1H), 3.92–3.78 (m, 4H), 1.72 (dd, *J* = 6.5, 1.7 Hz, 3H), 1.52 (s, 2H), 1.37 (d, *J* = 14.1 Hz, 1H), 1.30 (d, *J* = 14.1 Hz, 1H), 1.03 (s, 6H), 1.02 (s, 3H), 0.96 (s, 3H), 0.95 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 133.7, 124.3, 113.8, 64.6, 64.4, 49.8, 48.6, 42.2, 38.0, 32.3, 32.0, 31.5, 28.3, 27.7, 18.7, 14.2; IR (Neat film NaCl) 2952, 1455, 1388, 1225, 1146, 1124, 1078, 981 $cm^{-1}$; HRMS (EI) $[M]^+$ calc'd for $[C_{16}H_{28}O]^+$: *m/z* 252.2089, found 252.2090; $[\alpha]_D^{24}$ +1.51 (*c* 1.11, $CHCl_3$, 85% ee).

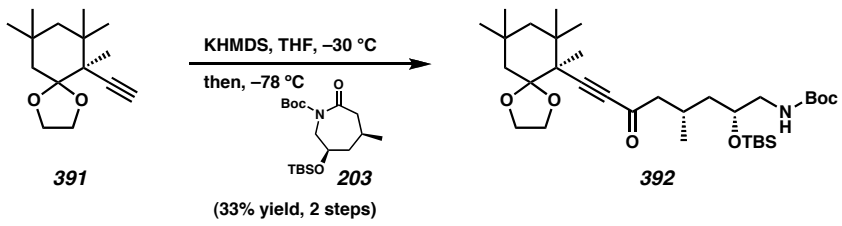



***388*** ***389***

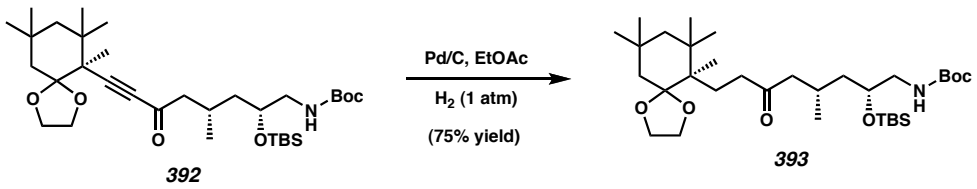
**Aldehyde 389.** Through a cooled (–78 °C) solution of acetal **388** (252 mg, 1.00 mmol, 1.00 equiv) in $CH_2Cl_2$ (25 mL) was bubbled a stream of ozone until the reaction mixture turned blue. The reaction mixture was quenched with dimethyl sulfide (0.20 mL), allowed to warm to ambient temperature, concentrated to an oil, and purified by flash chromatography on silica gel (2.5 to 10% $Et_2O$ in hexane) to give aldehyde **389** (132 mg, 55% yield) as an oil: $R_f$ 0.41, 0.29 (25% $Et_2O$ in hexanes, 5% $Et_2O$ in hexanes developed twice); $^1H$ NMR (300 MHz, $CDCl_3$) δ 9.93 (s, 1H), 3.98–3.85 (m, 4H), 1.69 (d, *J* = 14.4 Hz, 3H), 1.57 (dd, *J* = 14.4, 1.2 Hz, 1H), 1.50 (d, *J* = 14.4 Hz, 1H), 1.37 (dd, *J* = 14.4, 1.2 Hz, 1H), 1.08 (s, 3H), 1.07 (s, 3H), 1.06 (s, 3H), 1.04 (s, 3H), 1.03 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 206.2, 112.1, 64.5, 64.3, 58.0, 50.3, 43.0, 38.1, 32.9, 31.6, 30.6, 27.8, 27.7, 11.1; IR (Neat film NaCl) 2954, 2899, 1722, 1241, 1110, 1075, 964 $cm^{-1}$; HRMS (EI) $[M]^+$ calc'd for $[C_{14}H_{24}O_3]^+$: *m/z* 240.1726, found 240.1720; $[\alpha]_D^{24}$ –39.53 (*c* 0.385, $CHCl_3$, 85% ee).



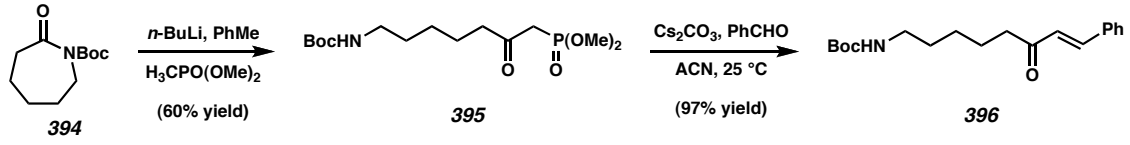

**Alkyne 391.** To a solution of aldehyde **389** (75.0 mg, 0.312 mmol, 1.00 equiv), and $K_2CO_3$ (108 mg, 0.780 mmol, 2.50 equiv) in MeOH (3.10 mL) was added diazoketone **390** (89.9 mg, 0.468 mmol, 1.5 equiv). After 1 h, an additional portion of $K_2CO_3$ (214 mg, 1.56 mmol, 5.00 equiv) and of diazoketone **390** (150 mg, 0.780 mmol, 2.5 equiv) were added. After a further 4 h, a final portion of $K_2CO_3$ (200 mg, 1.45 mmol, 4.65 equiv) and of diazoketone **390** (200 mg, 1.05 mmol, 3.37 equiv) were added. After stirring for 20 h, the reaction mixture was diluted with $H_2O$ (10 mL), extracted with $CH_2Cl_2$ (8 x 5 mL), dried ($MgSO_4$), concentrated, and purified by flash chromatography on silica gel (1 to 7% $Et_2O$ in hexanes) to give recovered aldehyde **389** (55.6 mg, 74% yeld) and alkyne **391** (15.5 mg, 21% yield, 85% yield based on recovered aldehyde **389**) as an oil: $R_f$ 0.40 (5% $Et_2O$ in hexanes developed twice); $^1$H NMR (300 MHz, $C_6D_6$) δ 3.62–3.40 (m, 4H), 2.01 (d, $J$ = 14.1 Hz, 1H), 1.93 (s, 1H), 1.72 (d, $J$ = 14.1 Hz, 1H), 1.47 (dd, $J$ = 13.8, 1.8 Hz, 1H), 1.36 (s, 3H), 1.34 (s, 3H), 1.22 (s, 3H), 1.17 (dd, $J$ = 14.3, 1.7 Hz, 1H), 1.10 (s, 3H), 1.04 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 112.5, 89.1, 76.6, 70.7, 65.5, 64.2, 49.8, 47.3, 42.5, 38.0, 34.6, 31.4, 29.8, 28.8, 24.9, 16.2; IR (Neat film NaCl) 3309, 2954, 2911, 2111, 1454, 1390, 1367, 1235, 1148, 1088, 1073, 984 cm$^{-1}$; HRMS (EI) $[M]^+$ calc'd for $[C_{15}H_{24}O_2]^+$: $m/z$ 236.1776, found 236.1786; $[\alpha]_D^{26}$ –20.35 ($c$ 1.25, $CH_2Cl_2$, 85% ee).



**Ynone 392.** To a cooled (–30 °C) solution of KHMDS (24.1 mg, 0.121 mmol, 2.20 equiv) in THF (1.00 mL) was added alkyne **391** (13.0 mg, 0.055 mmol, 1.00 equiv) in THF (1.00 mL). The solution was maintained for 30 min each at –30 °C, 0 °C, and 22 °C. The alkyne anion was cooled to –78 °C, and caprolactam **203** (23.6 mg, 0.066 mmol, 1.2 equiv) in THF (1.00 mL) was added. After 1 h, additional KHMDS (12.0 mg, 0.061 mmol, 1.10 equiv) in THF (0.50 mL) was added. After a further 5 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (0.50 mL), diluted with $H_2O$ (2 mL), brine (4 mL), and $Et_2O$ (4 mL), and extracted with $Et_2O$ (6 x 4 mL) and $CH_2Cl_2$ (2 x 2 mL). The combined organics were dried ($Na_2SO_4$), and concentrated to an oil, which was purified by flash chromatography on silica gel (2.5 to 15% EtOAc in hexanes) to give ynone **392** (10.9 mg, 33% yield) as an oil: $R_f$ 0.24, 0.50 (10% EtOAc in hexanes developed twice, 20% EtOAc in hexanes); $^1$H NMR (500 MHz, $CDCl_3$) δ 4.78 (s, 1H), 4.07–4.02 (m, 1H), 4.00–3.94 (m, 3H), 3.84 (bs, 1H), 3.38–3.30 (m, 1H), 2.97 (dt, *J* = 14.5, 6.0 Hz, 1H), 2.58 (dd, *J* = 15.5, 5.5 Hz, 1H), 2.38 (dd, *J* = 15.5, 8.0 Hz, 1H), 2.26–2.16 (m, 1H), 1.76 (d, *J* = 14.0 Hz, 1H), 1.62–1.44 (comp. m, 4H), 1.46 (s, 9H), 1.40–1.30 (m, 1H), 1.26 (s, 3H), 1.17 (s, 3H), 1.14 (s, 3H), 1.07 (s, 3H), 1.01 (s, 3H), 1.00 (s, 3H), 0.91 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 187.2, 155.9, 112.1, 98.7, 83.7, 79.1, 69.4, 65.5, 64.6, 53.2, 49.8, 48.1, 45.9, 43.0, 42.2, 38.7, 33.8, 31.4, 29.7, 29.6, 28.4, 28.0, 26.3, 25.9, 25.6, 20.2, 18.0, –4.5, –4.6; IR (Neat film NaCl) 3383, 2955, 2930, 2208, 1716, 1673, 1504, 1391, 1366, 1252, 1171, 1090, 836 cm$^{-1}$; HRMS (FAB+) $[M+H]^+$ calc'd for $[C_{33}H_{59}NO_6Si+H]^+$: *m/z* 594.4190, found 594.4208; $[\alpha]_D^{26}$ –36.12 (*c* 0.545, EtOAc).



**Ketone 393.** To a solution of ynone **392** (10.9 mg, 18.3 μmol, 1.00 equiv) in EtOAc (6 mL) was added 10% Pd/C (4.0 mg), and the reaction mixture was sparged with $H_2$ (5 min). After 18 h of vigorous stirring under an atmosphere of $H_2$ (balloon), the reaction mixture was concentrated, and purified by flash chromatography on silica gel (5 to 10% EtOAc in hexanes). NMR analysis of the chromatographed product indicated the presence of some partially hydrogenated material. A solution of this material in EtOAc (5 mL) was treated again with 10% Pd/C (5.0 mg) under an atmosphere of $H_2$ (balloon) for 4 h. The reaction mixture was concentrated to an oil and purified by flash chromatography on silica gel (5 to 10% EtOAc in hexanes) to give ketone **393** (8.2 mg, 75% yield) as a oil: $R_f$ 0.53 (20% EtOAc in hexanes); $^1$H NMR (500 MHz, $CDCl_3$) δ 4.79 (s, 1H), 3.96 (app. t, $J$ = 6.8 Hz, 1H), 3.83 (app. q, $J$ = 7.0 Hz, 1H), 3.79 (bs, 1H), 3.74 (app. q, $J$ = 7.0 Hz, 1H), 3.34–3.26 (m, 1H), 2.98 (dt, $J$ = 13.5, 6.5 Hz, 1H), 2.60–2.50 (m, 1H), 2.48–2.36 (m 2H), 2.20 (dd, $J$ = 16.3, 7.8 Hz, 1H), 2.12–2.02 (m, 1H), 2.00–1.92 (m, 1H), 1.56–1.24 (comp. m, 9H), 1.44 (s, 9H), 1.15 (d, $J$ = 14.0 Hz, 1H), 1.11 (s, 3H), 1.05 (s, 3H), 0.96 (s, 3H), 0.92-0.89 (m, 6H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 211.9, 156.2, 115.2, 79.3, 69.8, 64.9, 62.6, 50.6, 50.5, 46.2, 44.2, 42.7, 41.4, 40.9, 39.1, 34.7, 31.5, 30.0, 29.4, 28.7, 28.3, 26.8, 26.1, 26.0, 24.4, 20.6, 18.3, 16.8, −4.3; IR (Neat film NaCl) 3391, 2953, 2930, 1714, 1503, 1366, 1253, 1173, 1076, 836, 776 cm$^{-1}$; HRMS (FAB+) $[M+H]^+$ calc'd for $[C_{33}H_{63}NO_6Si+H]^+$: *m/z* 598.4503, found 598.4489; $[\alpha]_D^{26}$ 9.33 (*c* 0.105, $CH_2Cl_2$).



394 395 396

**Enone 396.** To a solution of dimethyl methylphosphonate (285 μL, 2.63 mmol, 1.05 equiv) in toluene (12.5 mL) at −78 °C was added *n*-butyllithium (1.47 mL, 2.63 mmol, 1.05 equiv). The solution was stirred at −78 °C for 20 min then transferred dropwise via

cannula (20 gauge) over 30 min to a cooled (–78 °C) solution of Boc-caprolactam **394**[17] in toluene (12.5 mL). The reaction was stirred an additional 1 h at –78 °C then warmed to ambient temperature over 30 min and quenched with $KH_2PO_4$ (1 M, aq., 20 mL) and extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine (20 mL), dried over $MgSO_4$, and concentrated to an oil. The crude product was purified by flash chromatography to provide phosphonate **395** (0.507 g, 1.5 mmol, 60% yield) as a clear viscous oil.

To a solution of phosphonate **395** (103 mg, 0.305 mmol, 1.0 equiv) in ACN (3.1 mL, 0.1 M) was added benzaldehyde (31 μL, 0.305 mmol, 1.0 equiv) followed by $Cs_2CO_3$ (124 mg, 0.381 mmol, 1.25 equiv). The heterogeneous mixture was stirred vigorously for 4 h at 25 °C then extracted from $KH_2PO_4$ (1 M, aq., 5 mL) with EtOAc (3 x 5 mL). The combined organics were washed with brine (5 mL), dried over $MgSO_4$, and concentrated. The crude product was dissolved in a minimal amount of $Et_2O$, loaded onto a flash column, and purified (10 to 25% EtOAc in pet. ether) to give enone **396** (94 mg, 0.296 mmol, 97% yield) as a white solid. m.p. 62–64.5 °C; $R_f$ 0.29 (25% EtOAc in pet. ether); $^1$H NMR (300 MHz, $CDCl_3$) δ 7.55 (comp. m, 3H), 7.39 (comp. m, 3H), 6.73 (d, $J$ = 16.2 Hz, 1H), 4.55 (*bs*, 1H), 3.15 (d, $J$ = 6.6 Hz, 1H), 3.10 (d, $J$ = 6.6 Hz, 1H), 2.67 (app. t, $J$ = 7.4 Hz, 2H), 1.70 (comp. m, 2H), 1.51 (comp. m, 2H), 1.44 (s, 9H), 1.37 (comp. m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 200.3, 155.9, 142.4, 134.5, 130.4, 128.9, 128.2, 126.1, 40.6, 40.4, 28.4, 26.4, 23.8; IR (Neat film NaCl) 3381, 2979, 2946, 2867, 1688, 1527, 1364, 1251, 1178, 988, 742, 689 cm$^{-1}$; HRMS (FAB+) $[M+H]^+$ calc'd for $[C_{19}H_{27}O_3N+H]^+$: *m/z* 318.2069, found 318.2066.

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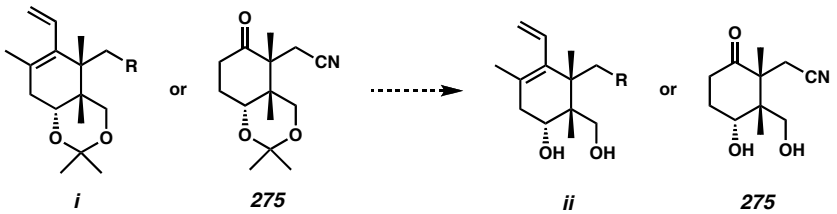
3. We were unable to deprotect the 6–membered acetonide in order to access a homologated substrate with C(10) in the ketone oxidation state.




*i* *275* *ii* *275*

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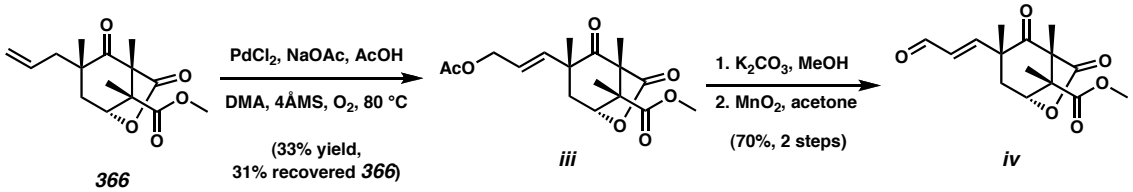
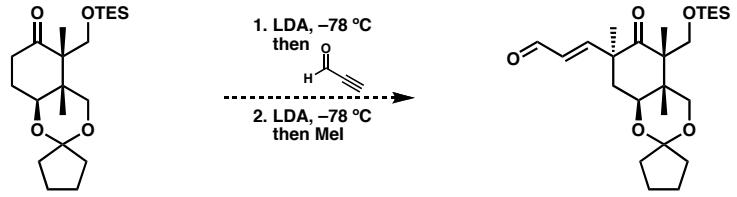
9. We took advantage of this product in order to test our ideas for functionalization of the allyl group, and we found that the allyl group can be converted to the corresponding enone over a three-step sequence in good yield. Treatment of **366** with $Pd(OAc)_2$, NaOAc, AcOH, and DMA in the presence of 4Å molecular sieves led to oxidation with transposition of the olefin to provide **iii**. Methanolysis of the acetate and oxidation provided enal **iv**.




*366* *iii* *iv*

First step from: Mitsudome, T.; Umetani, T.; Nosaka, N.; Mori, K.; Mizugaki, T. Ebitani, K.; Kaneda, K. *Angew. Chem. Int. Ed.* **2006**, *45*, 481–485.

10. An alternative method to access enal **371** would be to add the enolate of ketone **347** directly to formyl acetylene then methylate the intermediate enal.

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