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\(_2\)O. A second enolization and quenching with D\(_2\)O
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 \( \alpha,\beta,\beta' \)-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 \( \beta \)-diketone **337** will lead to the desired C(9)-quaternary ketone **338**.
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. 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](image)

**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\textsuperscript{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 \( \alpha \)-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 retrom 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.](image)

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, 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.

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.\textsuperscript{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 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 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 ring D. Treatment of ketone 249 with aryl bromide 379, Pd(OAc)$_2$, P(t-Bu)$_3$, and NaHMDS in THF at 70 °C provided A–C ring adduct 380 in 67% yield (Scheme D.4.7).
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. 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). 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) 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](image_url) 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, KMnO₄, 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. ¹H and ¹³C 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 Me₄Si (δ 0.0). Data for ¹H 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

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 7 h before diluting with EtOAc (500 mL). The solution was washed with sat. NH₄Cl (3 x 150 mL), and the combined aqueous layers were extracted with EtOAc (4 x 150 mL). The combined organics were then dried over MgSO₄, 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. Rf 0.35% EtOAc in hexanes; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 [C₁₇H₂₈O₅+H]⁺: m/z 341.1784, found 341.1798.

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. Na₂SO₄ (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 Na₂SO₄ 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, CDCl₃) \( \delta \) 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, CDCl₃) \( \delta \) 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) \([\text{M+H}]^+\) calc’d for [C\(_{16}\)H\(_{32}\)O\(_4\)Si+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$_3$) $\delta$ 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$_3$) $\delta$ 147.9, 147.4, 136.8, 132.0, 118.7, 81.4, 70.8, 68.1, 66.5, 45.8, 36.6, 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$_6$SiN$_2$+H]$^+$: m/z 437.2108, found 437.2104.

**Alcohol 344.** $R_f$ 0.6 (35% EtOAc in hexanes); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_5$Si+H]$^+$: m/z 343.1941, found 343.1953.

**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 H2O (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 MgSO4, 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 CH2Cl2 (7.3 mL, 0.1M). Acetal 345∗,† (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 NaHCO3 until no further bubbling was observed. The reaction was diluted with H2O (25 mL) and CH2Cl2 (18 mL), the aqueous layer was extracted with CH2Cl2 (3 x 25 mL), dried over MgSO4, 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. Rf 0.7 (50% acetone in hexanes); 1H NMR (500 MHz, CDCl3)

* Acetal 345 contained 10 mol% HC(OMe)3, as determined by 1H 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); 13C NMR (125 MHz, CDCl₃) 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 [C₁₆H₂₂O₅+H]⁺: m/z 295.1545, found 295.1533.

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 NH₄Cl, diluted with EtOAc (50 mL), and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organics were dried over MgSO₄ and concentrated.

The crude diol was redissolved in acetone (137 mL, 0.03 M), MnO₂ (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), PtO₂ (93.6 mg, 0.412 mmol, 0.1 equiv) was added, and the suspension was sparged with H₂ until it turned from brown to black. The reaction mixture was then stirred under H₂ (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. NH₄Cl (100 mL) and extracted with EtOAc (5 x 25 mL). The combined organics were washed with brine (25 mL), dried over MgSO₄, 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. Rf 0.56 (25% acetone in hexanes); ¹H NMR (300 MHz, CDCl₃) 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, J = 8.2 Hz, 9H), 0.93 (s, 3H), 0.59 (app. dd, J = 15.8, 7.6 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃) 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 [C₂₁H₃₈O₄Si]+: m/z 382.2539, found 382.2543.

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 H₂O (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 MgSO₄, concentrated to an oil, and purified by flash chromatography (0 to 10% Et₂O 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 Rᵢ diastereomer) Rᵢ 0.39 (20% Et₂O in hexanes); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 [C₂₂H₄₀O₄Si]: m/z 396.2696, found 396.2690.

**Methyl ketone 348b.** (low Rᵢ diastereomer) Rᵢ 0.30 (20% Et₂O in hexanes); ¹H NMR (500 MHz, CDCl₃) δ 3.61 (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); ¹³C NMR (125 MHz, CDCl₃) 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 [C₂₂H₄₀O₄Si]: m/z 396.2696, found 396.2681.

**Bis-methyl ketone 348c.** Rf 0.47 (20% Et₂O in hexanes); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 [C₂₃H₄₂O₄Si]: m/z 410.2852, found 410.2870.

**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. NaHCO₃ (25 mL) and allowed to warm to ambient temperature. Further dilution with H₂O (25 mL) was followed by extraction with EtOAc (50, 3 x 20 mL). The combined organics were washed with brine (25 mL), dried over MgSO₄, 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. Rf 0.50 (50% EtOAc in hexanes); ¹H
NMR (500 MHz, CDCl$_3$) $\delta$ 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, $J$ = 1.2 Hz, 1H), 1.61 (s, 3H), 1.37 (s, 3H), 1.29 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 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.

**Phosphine 365**: A 250-mL Schlenk flask was charged with CuI (66.7 mg, 0.35 mmol), Ph$_2$PH (4.12 g, 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$_2$CO$_3$ (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$_2$Cl$_2$ (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 $\rightarrow$ 10% Et$_2$O in CH$_2$Cl$_2$) 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$_3$) $\delta$ -3.99 (s); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.85 (dd, $J$ = 7.6, 3.4 Hz, 1H),
Allyl methyl ketone 366. To a 50-mL round-bottomed flask in the glovebox was added \(\text{Pd}_2(\text{dba})_3\) (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 \(\text{N}_2\) (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\(_3\)) \(\delta\) 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); ¹³C NMR (125 MHz, CDCl₃)  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 [C₁₅H₂₀O₅+H]^+: m/z 281.1389, found 281.1376. Stereochemistry assigned via X-ray crystallographic analysis.

![Chemical Structure](image)

**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 H₂O (1 mL), diluted with EtOAc (1 mL) and allowed to warm to ambient temperature. Further dilution with H₂O (20 mL) was followed by extraction with EtOAc (4 x 15 mL). The combined organics were washed with brine (25 mL), dried over MgSO₄, 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$_4$Si]: m/z 436.3009, found 436.2993. Stereochemistry assigned using a combination of HSQC, HMBC, COSY, and NOESY 2D experiments.

**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$_2$CO$_3$ (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 H₂O (100 mL) and extracted with EtOAc (3 x 25 mL). The combined organics were washed with brine (25 mL), dried over MgSO₄, and concentrated. The crude product was purified by flash chromatography (10 to 50% Et₂O 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; Rₚ 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 H₂O (40 mL), and extracted with EtOAc (4 x 20 mL). The combined organics were washed with brine (25 mL), dried over MgSO₄, 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. Rₚ 0.33 (10% EtOAc in pet. ether); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 [C₁₅H₁₅O₂Br+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$_2$O (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$_3$) $\delta$ 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$_3$) $\delta$ 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.

![Diagram](image-url)
**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$_2$CO$_3$ (601 mg, 4.35 mmol, 1.00 equiv) and RhCl$_3$•H$_2$O (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$_2$O 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$_2$O in hexanes, 5% Et$_2$O 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).

**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$_2$SO$_4$), concentrated, and purified by flash chromatography on silica gel (1 to 2% Et$_2$O in
hexane) to give acetal 388 (585 mg, 70% yield) as an oil: $R_f$ 0.61, 0.67 (5% Et$_2$O in hexanes developed twice, 25% Et$_2$O in hexanes); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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).

Aldehyde 389. Through a cooled (–78 °C) solution of acetal 388 (252 mg, 1.00 mmol, 1.00 equiv) in CH$_2$Cl$_2$ (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$_2$O in hexane) to give aldehyde 389 (132 mg, 55% yield) as an oil: $R_f$ 0.41, 0.29 (25% Et$_2$O in hexanes, 5% Et$_2$O in hexanes developed twice); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_2$CO$_3$ (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$_2$CO$_3$ (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$_2$CO$_3$ (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$_2$O (10 mL), extracted with CH$_2$Cl$_2$ (8 x 5 mL), dried (MgSO$_4$), concentrated, and purified by flash chromatography on silica gel (1 to 7% Et$_2$O in hexanes) to give recovered aldehyde 389 (55.6 mg, 74% yield) and alkyn 391 (15.5 mg, 21% yield, 85% yield based on recovered aldehyde 389) as an oil: $R_f$ 0.40 (5% Et$_2$O in hexanes developed twice); $^1$H NMR (300 MHz, C$_6$D$_6$) $\delta$ 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, $J = 13.8$, 8.1 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$_3$) $\delta$ 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; $[\alpha]_D^{26}$ $-$20.35 (c 1.25, CH$_2$Cl$_2$, 85% ee).

Alkyne 391. To a solution of aldehyde 389 (75.0 mg, 0.312 mmol, 1.00 equiv), and K$_2$CO$_3$ (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$_2$CO$_3$ (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$_2$CO$_3$ (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$_2$O (10 mL), extracted with CH$_2$Cl$_2$ (8 x 5 mL), dried (MgSO$_4$), concentrated, and purified by flash chromatography on silica gel (1 to 7% Et$_2$O in hexanes) to give recovered aldehyde 389 (55.6 mg, 74% yield) and alkyn 391 (15.5 mg, 21% yield, 85% yield based on recovered aldehyde 389) as an oil: $R_f$ 0.40 (5% Et$_2$O in hexanes developed twice); $^1$H NMR (300 MHz, C$_6$D$_6$) $\delta$ 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, $J = 13.8$, 8.1 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$_3$) $\delta$ 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; $[\alpha]_D^{26}$ $-$20.35 (c 1.25, CH$_2$Cl$_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 NaHCO₃ (0.50 mL), diluted with H₂O (2 mL), brine (4 mL), and Et₂O (4 mL), and extracted with Et₂O (6 x 4 mL) and CH₂Cl₂ (2 x 2 mL). The combined organics were dried (Na₂SO₄), 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: Rf 0.24, 0.50 (10% EtOAc in hexanes developed twice, 20% EtOAc in hexanes); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 [C₃₃H₅₉NO₆Si+H]⁺: m/z 594.4190, found 594.4208; [α]D²⁶ −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 H₂ (5 min). After 18 h of vigorous stirring under an atmosphere of H₂ (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 H₂ (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, CDCl₃) 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, CDCl₃) 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 \([C_{33}H_{63}NO_6Si]+\): m/z 598.4503, found 598.4489; \([\alpha]_D^{26}\) 9.33 (c 0.105, CH₂Cl₂).

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 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$_2$PO$_4$ (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 (0.507 g, 1.5 mmol, 60% yield) as a clear viscous oil.

To a solution of phosphonate (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$_2$CO$_3$ (124 mg, 0.381 mmol, 1.25 equiv). The heterogeneous mixture was stirred vigorously for 4 h at 25 °C then extracted from KH$_2$PO$_4$ (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$_2$O, loaded onto a flash column, and purified (10 to 25% EtOAc in pet. ether) to give enone (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$_9$H$_{27}$O$_3$N+H]$^+$: m/z 318.2069, found 318.2066.
References

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.

![Reaction scheme]

7. See Chapter 4.
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 ozidation with transposition of the olefin to provide iii. Methanolysis of the acetate and oxidation provided enal iv.

![Reaction scheme]

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.


13. Thus far, only O-alkylated products have been observed.


