Chapter 5

A Semi-Pinacol Approach for the Synthesis of the Enmein-Type Ent-Kauranoids

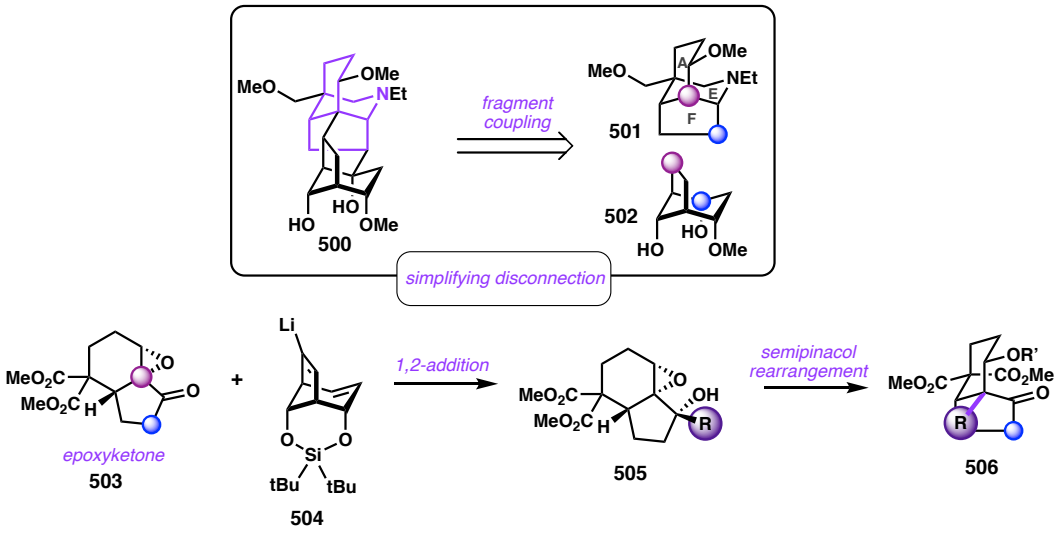
5.1 INTRODUCTION

While our first generation strategy approach focusing on construction of the enmein-type *ent*-kauranoid core through a cross-electrophile coupling was unsuccessful, we remained committed to the development of a convergent route to access **301** and related natural products. From a conceptual point of view, we felt that disconnection through the central B-ring lactone would still be the most expedient route to **301**, and we thought that we could potentially use some of the chemistry we had previously developed in our first generation route toward **301**. With this in mind, we became interested in employing a 1,2-addition/semi-Pinacol rearrangement sequence to bring together two complex fragments

and forge the key all-carbon quaternary center we had attempted to form through a convergent cross-coupling.

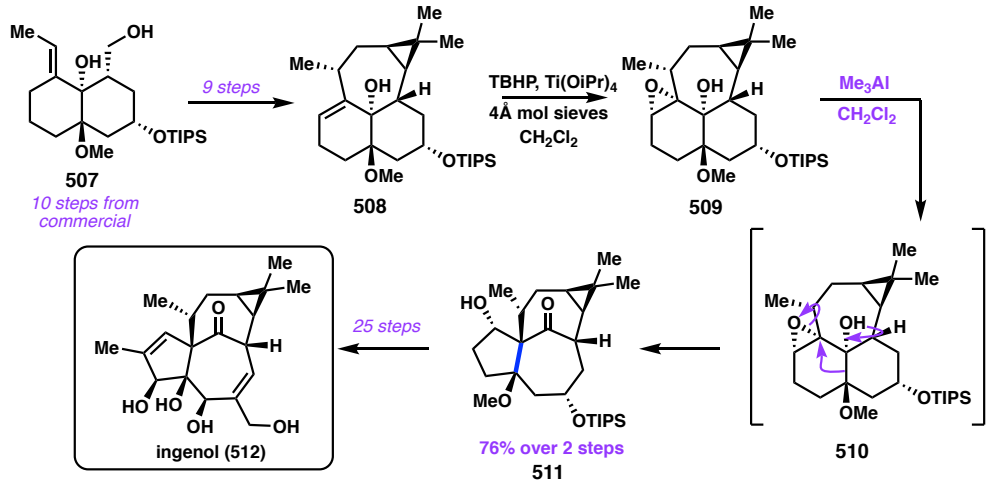
We drew inspiration from elegant work happening on the other side of the lab focused on the synthesis of the C_{19} diterpenoid alkaloids (**500**) (Scheme **5.1**). Our lab's strategy for the synthesis of these structurally analogous natural products involved a convergent fragment coupling between two complex fragments, namely epoxy ketone **503** and an alkenyl organometallic **504**. A highly selective 1,2-addition followed by subsequent semi-pinacol rearrangement delivered **505**, which maps on beautifully to the diterpenoid alkaloid core. Intrigued by this approach to forging an all-carbon quaternary center between two highly complex fragments, we wondered if we could apply a similar strategy to the synthesis of the enmein-type *ent*-kauranoids.

Scheme 5.1 *The Reisman approach to the C_{19} diterpenoid alkaloids (**500**)*



We were also aware of other salient examples of type III semi-Pinacol rearrangements in the context of complex molecule total synthesis. We were intrigued by the Tanino's group use of a type III semi-Pinacol rearrangement to forge an all-carbon quaternary center present in Ingenol (**512**) (Scheme **5.2**).[1] Epoxy alcohol **509** succumbs to a 1,2-migration upon treatment with Me_3Al. In doing so, they are able to forge an all-carbon quaternary center and build the central 5,7,7-core of the natural product. While it takes them an additional 25 steps to access ingenol (**512**), their rapid synthesis of the core is notable.

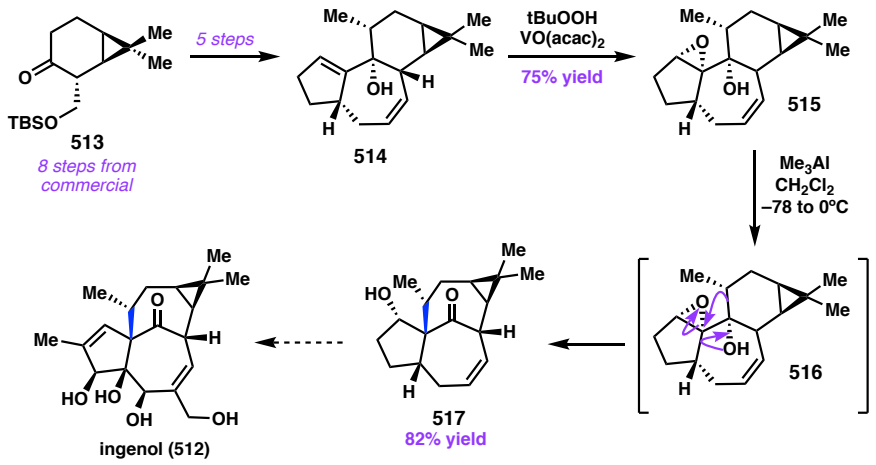
Scheme 5.2 *Tanino's synthesis of ingenol (**512**).*



The Cha lab reported a distinct strategy in the progress toward their synthesis of Ingenol (**512**), using a different type III semi-Pinacol rearrangement (Scheme **5.3**).[2,3] They first generate a 7-membered ring containing a tertiary alcohol **514**. From here, a directed epoxidation delivers **515**, which is poised to undergo a key semi-Pinacol rearrangement to forge the carbocyclic skeleton of ingenol (**512**). Treatment of **515** with Me_3Al delivers **517**,

through a highly diastereoselective semi-Pinacol rearrangement. Of note is how the stereochemistry at the epoxide controls which bond migrates. While their strategy was not successfully applied to the total synthesis of **512**, this result highlights the versatility of the semi-Pinacol rearrangement in total synthesis and is a good example of how the conformational requirements of the type III semi-Pinacol rearrangements render this transformation highly stereo- and regioselective.

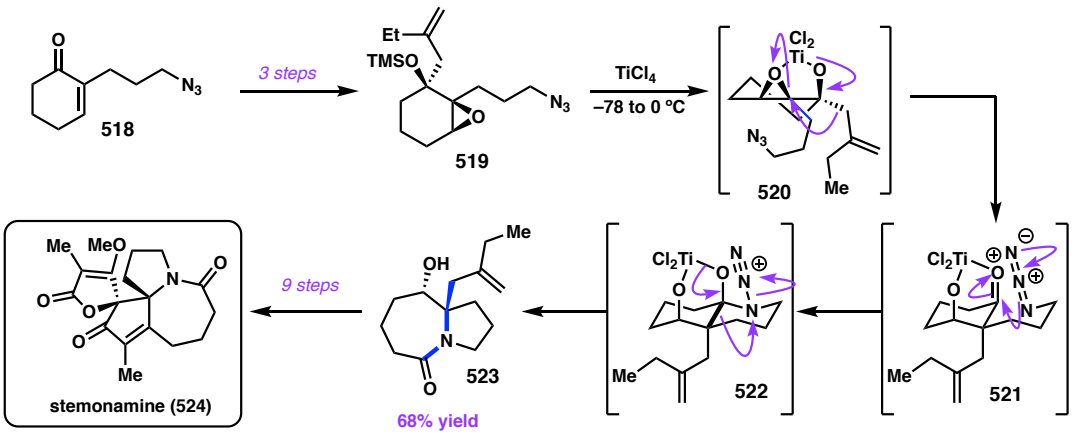
Scheme 5.3 *Cha's progress toward ingenol (**512**).*



Another elegant example of a type III semi-Pinacol rearrangement comes from the Tu lab in their impressive synthesis of stemonamine (**524**) (Scheme **5.4**).[4] Their synthesis commences from azido enone **518**, which can be elaborated in three steps to silyl protected epoxy alcohol **519**. Treatment of **519** with $TiCl_4$ initiates an impressive cascade. First, a type III semi-Pinacol rearrangement delivers **521**, forming an all-carbon quaternary center. This intermediate **521** is then poised to undergo a subsequent reaction—the pendant azide can then add into the ketone, generating a diazonium ion **522**, and a second semi-Pinacol

rearrangement forges a new carbon-nitrogen bond. This strategy uses a single Lewis acid to migrate two bonds, which is crucial in construction of the bicyclic lactam core **523**.

Scheme 5.4 *Tu's synthesis of stemonamine (**524**)*

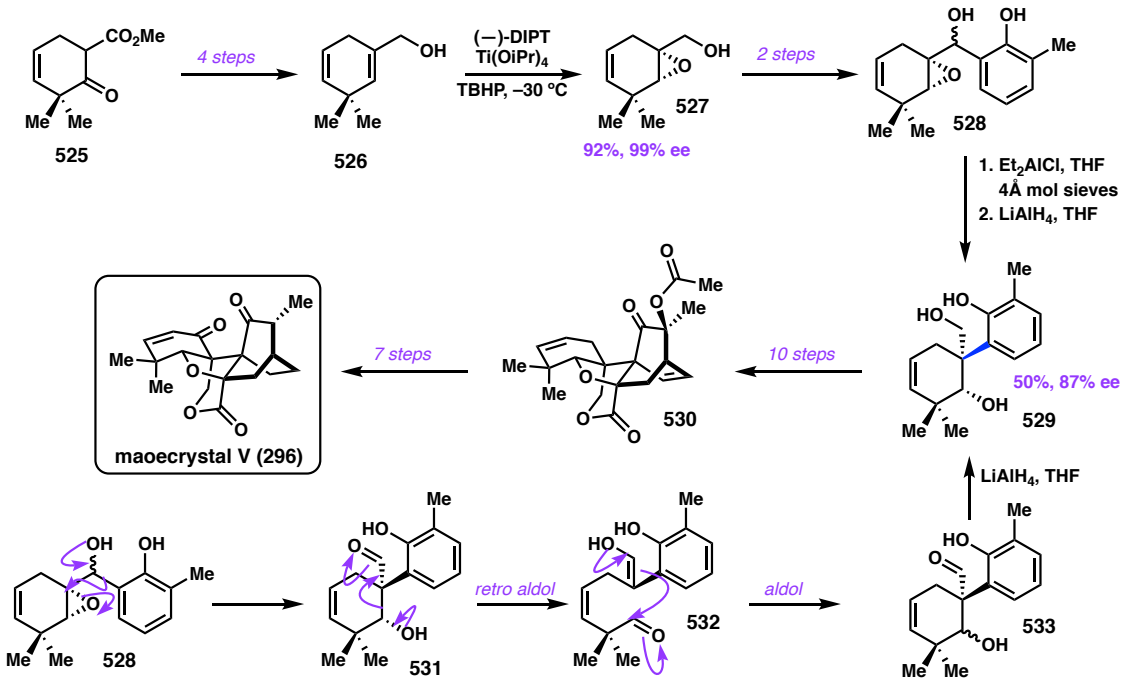


Of particular interest was a report from Yang and coworkers in their total synthesis of maoecrystal V (**296**) (Scheme **5.5**). Diene **526** can be accessed in four steps from **525**. From here, the first stereocenter can be established through a Sharpless epoxidation, giving epoxy alcohol **527** in excellent yield and enantioselectivity. Two additional steps delivers epoxy alcohol **528**, which is their substrate for a semi-Pinacol rearrangement. Treatment with diethylaluminum chloride followed by a reduction provides access to **529**; however, they observed significant erosion in enantiopurity. This is thought to occur through a retro-aldol/aldol process, wherein semi-Pinacol rearrangement delivers **531**. Hydroxy aldehyde **531** can then undergo a retro-aldol to give formyl enol **532**, which is achiral. Aldol reaction of **532** can regenerate **533**, with loss of enantiopurity.

While we were excited by this report of forging an all-carbon quaternary center in these structurally related natural products, we took note of this observed erosion of

enantiopurity. Because of this, we hypothesized that migrations of silyl protected epoxy alcohols would be better in this particular transformation, to avoid the retro-aldol/aldol reactivity.

Scheme 5.5 *Yang's synthesis of* ***296***.



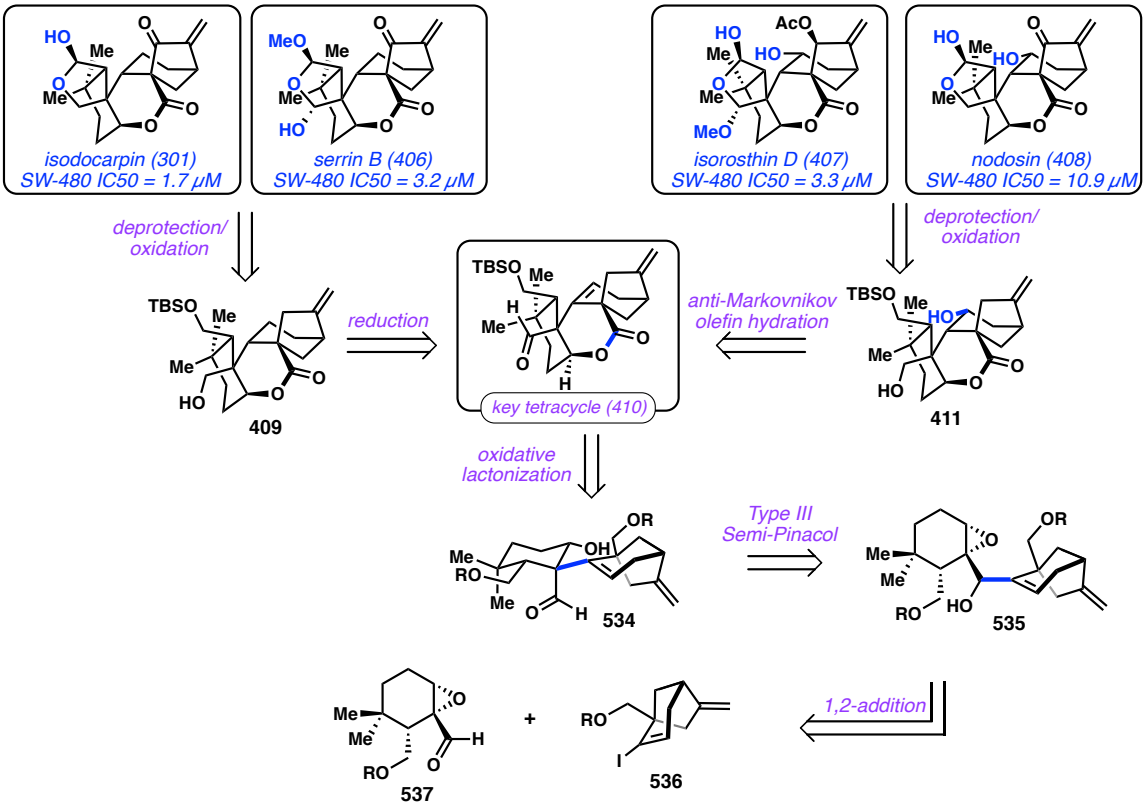
5.2 FIRST GENERATION SEMI-PINACOL STRATEGY

5.2.1 Retrosynthetic Analysis

Strategically, we felt we could access the same four natural products through a divergent strategy. Again, **301** and **406** would be accessed through a deprotection/oxidation sequence from alcohol **409** (Scheme **5.6**). This intermediate could form through a reduction of aldehyde **410**. This intermediate could also be elaborated to **407** and **408** through the intermediacy of diol **411**, making **410** a versatile intermediate. The key tetracyclic

framework could be disconnected through the lactone to reveal hydroxy aldehyde **534**, which could be elaborated to **410** in the forward sense through an oxidative lactonization.

Scheme 5.6 *Retrosynthetic analysis featuring a key semi-Pinacol rearrangement*



The synthesis of **534** could be achieved through a type III semi-Pinacol rearrangement of the corresponding epoxy alcohol **535**. We were excited at the prospect of using a semi-Pinacol rearrangement that had been analogously employed in the synthesis of the diterpenoid alkaloid core, and we were confident as this strategy had been used in our lab to construct an all-carbon quaternary center. We hoped to construct epoxy alcohol **535** through a 1,2-addition between epoxy aldehyde **537** and an organometallic reagent

derived from vinyl iodide **536**—both of which we thought we could access in short order from intermediates we had previously prepared in our first generation strategy.

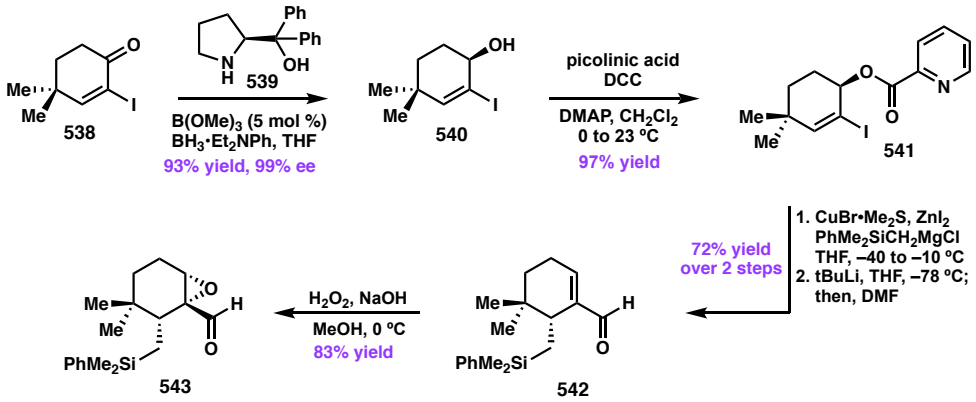
5.2.2 Epoxy Aldehyde Synthesis

In the forward sense, our synthesis of **537** commenced with the iodination of 4,4-dimethyl cyclohexenone. Treatment under reported conditions with 4-DMAP as the catalyst delivered **538** in good yield.[5] The iodoenone **538** could then be advanced through a CBS reduction, delivering excellent yield and enantiomeric excess of alcohol **540** (Scheme **5.7**).[6] With a robust means of preparing **538** and its enantiomer, we turned our attention toward installing the neopentyl stereocenter. While we had initially anticipated using a [2,3]-Wittig-Still rearrangement from the corresponding α-alkoxysilane[7] or the α-alkoxystannane[8] to carry out an anionic transposition, we were unable to achieve the desired reactivity on our system.

We turned our attention toward elegant work presented by the Knochel lab in which they were able to perform a stereoinvertive cross-coupling mediated by copper between allylic phosphonates and organozinc reagents.[9] While we were able to prepare the necessary allylic phosphonate, we didn't observe the desired reactivity under Knochel's conditions. However, we found that we could carry out an analogous reaction between an allylic picolinamide (**541**) and a silyl Grignard reagent, delivering the desired product in excellent yield.[10–12] We could then perform a standard formylation, delivering enal **542**. We were pleased to see that nucleophilic epoxidation delivered epoxy aldehyde **543** with the correct stereochemistry. While **543** was not in the correct oxidation state, we felt

confident that we could perform a late-stage Tamao-Fleming oxidation to convert silane **543** to the requisite alcohol present in **537**.[13–16]

Scheme 5.7 *A simplifying convergent strategy to access* ***543***.



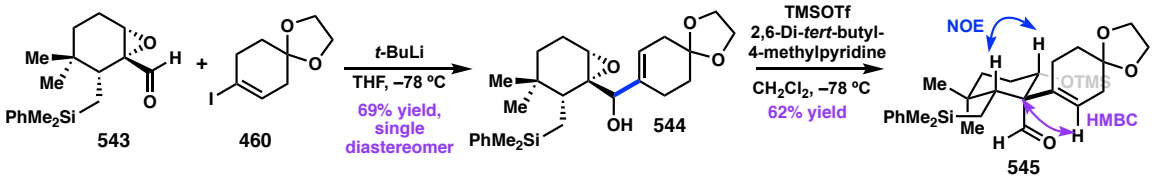
5.2.3 Model Semi-Pinacol Exploration

With a robust means of preparing **543**, we turned our attention toward ascertaining the feasibility of a semi-Pinacol reaction to install the all-carbon quaternary center. Due to the difficulties associated with the preparation of a single enantiomer of bicyclic vinyl iodides of structure **536**, we elected to first investigate a model semi-Pinacol rearrangement with other alkenyl iodides.

We were excited to see that we could generate the corresponding vinyl lithium from **460** through treatment with two equivalents of *t*-BuLi. After formation of the vinyl lithium, we found that addition into the aldehyde smoothly delivered a single diastereomer of **544** (Scheme **5.8**). While we were unsure of which diastereomer we were forming in this reaction, we were eager to begin exploring the feasibility of a 1,2-migration event. We hypothesized that either diastereomer should be able to undergo rearrangement due to the

free rotation of the acyclic alcohol. We were delighted to see that treatment of **544** with TMSOTf as the Lewis acid and 2,6-di*tert*butyl-4-methylpyridine afforded clean conversion to aldehyde **545**.

Scheme 5.8 *A monocyclic semi-Pinacol model experiment*

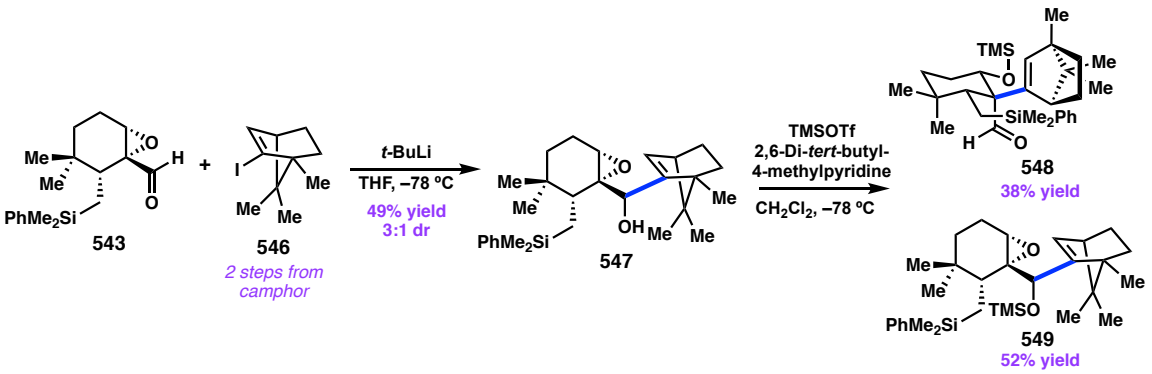


Excited by this result, we became interested in investigating the feasibility of migrating a bicyclic alkene group, which we felt would be a better model for the actual system we were looking to apply this strategy to. We hypothesized that a camphor-derived system would be a good surrogate for the steric-bulk present in **536**. We were delighted to see that preparation of **546** through the intermediacy of the corresponding hydrazone proceeded well, as reported in the literature (Scheme **5.9**).[17] As with **460**, lithium-iodine exchange proceeded smoothly. Subsequent 1,2-addition into epoxy aldehyde **543** delivered epoxy alcohol **547** as a mixture of diastereomers. While the mixture of diastereomers at this step made characterization of **547** difficult, we hypothesized that both diastereomers would be competent substrates for a 1,2-migration event and should converge to give a single diastereomer, with the stereochemistry of the product ultimately controlled by the configuration of the epoxide.

With **547** in hand, we were pleased to see that treatment with TMSOTf with 2,6-Di-*tert*-butyl-4-methylpyridine at low temperature delivered an appreciable amount of **548**.

Interestingly, the other product we identified was **549**, which could be isolated as a single diastereomer. It appeared that only a single isomer of **547** could be converted to **548** under the reaction conditions. While it is still unclear which isomer of **547** is a competent substrate for the migration, further investigation of the required stereochemistry for the migration is currently underway.

Scheme 5.9 *Migration of a camphor-derived alkene*

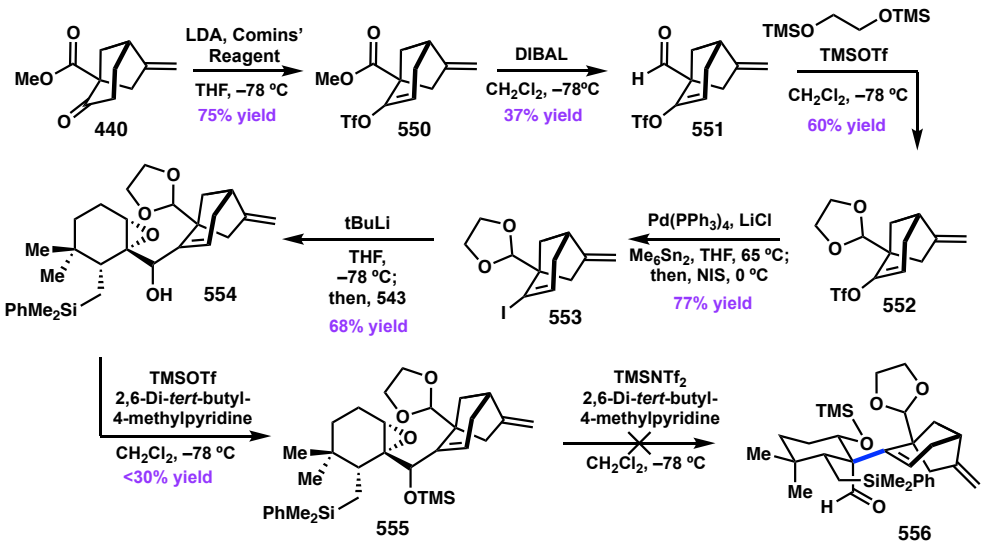


5.2.4 Semi-Pinacol Rearrangement of a [3.2.1]-bicycle.

Pleased that we could migrate a more complex alkene, we turned our attention toward applying these addition/migration conditions on a substrate that could be elaborated to **301**. Starting from **440**, which could be accessed as a single enantiomer through chiral preparative HPLC, we could form the corresponding enol triflate **550** under canonical conditions (Scheme **5.10**). From here, treatment with one equivalent of DIBAL at –78 ºC allowed us to access serviceable quantities of aldehyde **551**. While this reaction was not particularly high yielding, we felt that we could explore additional reduction conditions or a two-step protocol to access substantial quantities of the aldehyde **551**. From here,

protection of the aldehyde as its cyclic acetal followed by Stille cross-coupling with hexamethylditin and a subsequent iodination delivered **553**, which was poised to undergo 1,2-addition into our aldehyde.

Scheme 5.10 *First attempts to install and migrate a [3.2.1]-bicycle.*

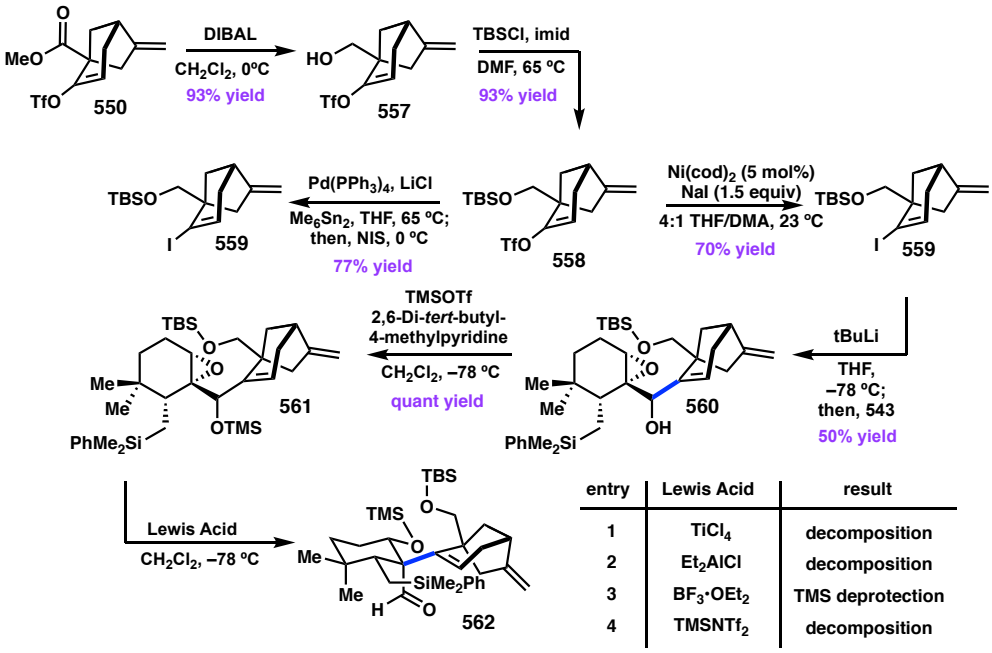


With **553** in hand, we found that 1,2-addition provided a single diastereomer of epoxy alcohol **554**, but unfortunately, treatment with the conditions that had worked on the model system only delivered low yields of TMS protected alcohol **555**. Disappointingly, treatment of **555** with $TMSNTf_2$, a stronger Lewis acid, solely resulted in decomposition. We hypothesized that the lability of the acetal protecting group was playing a role in the unwanted reactivity we observed, and so we devised a synthesis of a compound we felt would be a more robust substrate.

From **550**, we were pleased to see that treatment with three equivalents of DIBAL, this time at 0ºC delivered excellent yields of alcohol **557**, which could be silylated to give

558 (Scheme **5.11**). We hypothesized that a silyl protected alcohol **558** would be more stable under the strongly Lewis acidic conditions we knew were required to migrate large groups. From **558**, an analogous Stille reaction delivered **559**.

Scheme 5.11 *Preparation and migration of a more robust bicycle*



At this point, we had been using significant amounts of toxic hexamethylditin to convert the enol triflate (**558**) to the corresponding alkenyl iodide (**559**), and we were interested in finding a workaround that would obviate the need to use stoichiometric tin, especially on scale. With the help of Kelsey Poremba, a graduate student in the Reisman lab, we were pleased to see that under nickel catalysis, we could achieve a tin-free iodination of **558**, under very mild conditions. With iodide **559** in hand, we were then poised to investigate the key 1,2-addition/migration sequence that we had been hoping to explore. While the 1,2-addition worked well to deliver a single diastereomer of **560**,

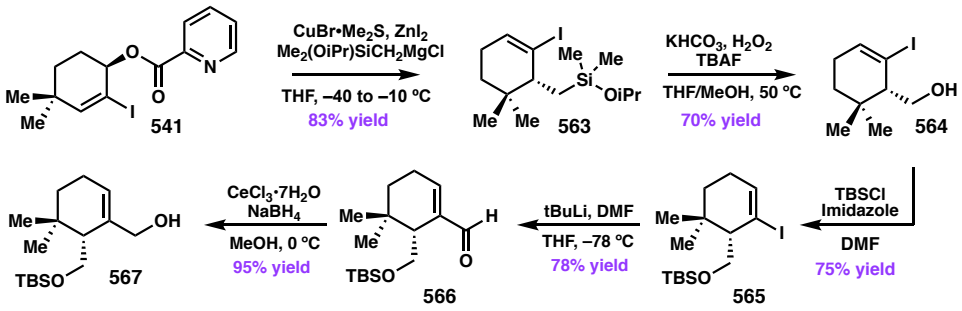
treatment with TMSOTf and 2,6-Di-*tert*-butyl-4-methylpyridine solely delivered TMS protected alcohol **561**. Further treatment of **561** with other Lewis acids provided us with either decomposition or TMS deprotection.

We hypothesized that our inability to migrate a [3.2.1]-bicyclooctane was due to the steric bulk of the adjacent silyl group. We wondered if the bulk of this group, combined with the increased bulk from the larger bicycle, limited the conformational flexibility of the cyclohexene oxide, making the necessary reactive conformation inaccessible. With this in mind, we turned our attention toward the modification of this group.

5.2.5 A Second Generation Epoxy Aldehyde

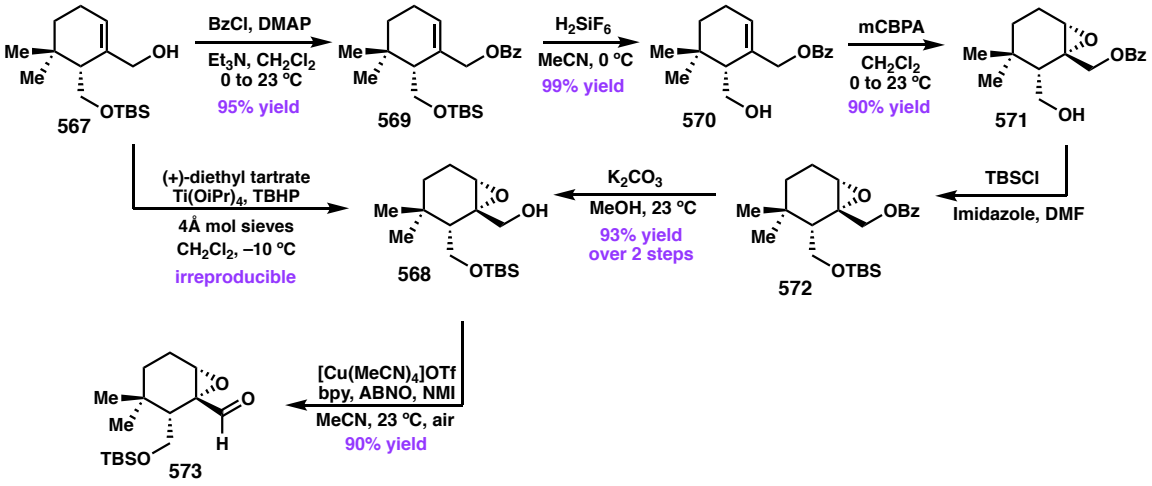
While we had initially hoped to use a Tamao-Fleming oxidation of **543** to install the necessary oxidation and modify the steric profile of the adjacent group, our attempts to functionalize the silane were unsuccessful (not shown), so we had to return to our picolinamide substrate **541** and identify a new cross-coupling partner that could enable more facile incorporation of an alcohol at this position.

Scheme 5.12 *Route to allylic alcohol* ***567****.*



Looking into the literature, it became clear that a silyl group with a hydrogen or an alkoxy group bound would be much more easily oxidized than the dimethylphenylsilyl group we had installed through the S_N2' chemistry.[13,14] From **541**, we found that we could install the more easily oxidizable silyl group and then subsequently perform a Tamao oxidation to deliver vinyl iodide **564** (Scheme **5.12**).[15,18–20] At this point, silylation of the primary alcohol, followed by formylation with DMF delivered **566**. Unfortunately, attempts to epoxidize **566** directly were met with poor levels of diastereoselectivity (not shown), so we advanced enal **566** through a Luche reduction to provide allylic alcohol **567**, which we planned to use as a substrate in a Sharpless epoxidation to access a single epoxide diastereomer.

Scheme 5.13 *Synthesis of epoxy aldehyde* ***573***.

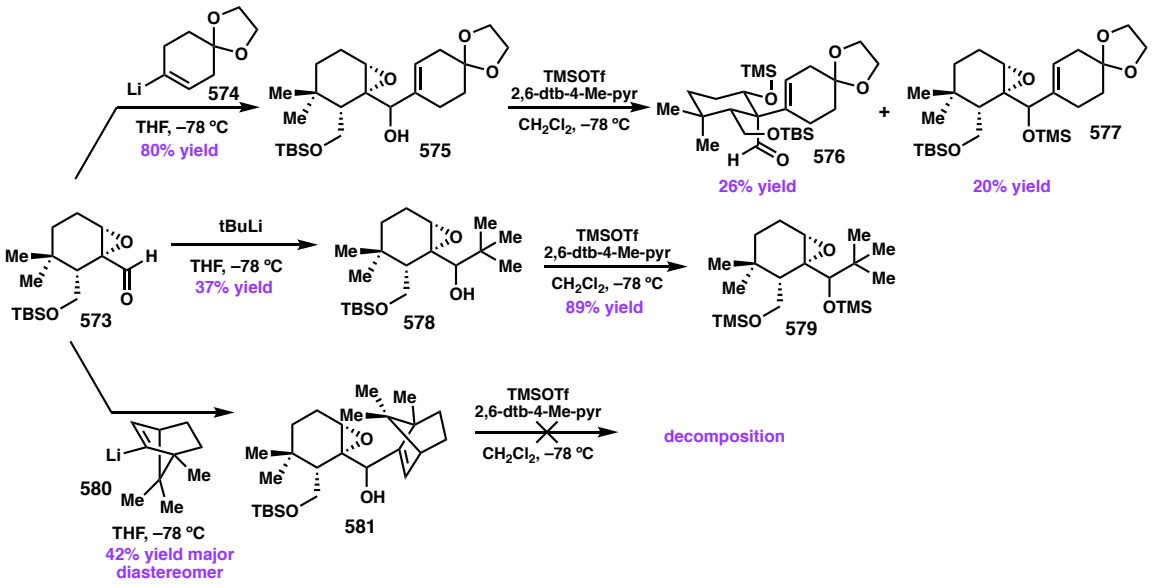


Unfortunately, subjection of **567** to standard Sharpless conditions provided inconsistent results. We found this reaction to be particularly capricious, and we found it very difficult to strike a balance between reaction temperatures that would give good

conversion and reaction temperatures that would give high levels of selectivity. In the interest in developing a scalable route to **568**, we elected to pursue a more lengthy sequence that would circumvent this persnickety reaction.

Allylic alcohol **567** could be treated with benzoyl chloride to access benzoate **569**, at which point the silyl group could be removed through treatment with H_2SiF_6. The free alcohol (**570**) could then direct an epoxidation to give **571**. This epoxy alcohol **571** could then be resilylated under standard conditions and the benzoyl group cleaved to give **568**. While this is a particularly lengthy sequence, each of the reactions proceeded in excellent yields and enabled a scalable synthesis of **568**, which could be subsequently oxidized to the corresponding epoxy aldehyde **573** under Stahl conditions.

Scheme 5.14 *Model 1,2-addition/migration sequences with epoxy aldehyde* ***573***.



With aldehyde **573** in hand, we turned our attention toward investigating the feasibility of an addition/migration sequence to set the all-carbon quaternary center. While

the 1,2-additions smoothly provided epoxy alcohols **575**, **578**, and **581**, we observed different outcomes in the semi-Pinacol step. Treatment of **575** under the TMSOTf conditions delivered a mixture of the migration product **576** and TMS protection product **577**. Interestingly, treatment of the *t*-Bu addition product under the same conditions delivered solely the TMS protection product. With a bicyclic adduct, we observed complete decomposition of **581**.

With these results, we remain interested in exploring the synthesis of [3.2.1]-bicyclooctane adducts that could undergo a semi-Pinacol rearrangement to assemble the core of **301**. In doing so, we hope to improve our synthesis of **559** to obviate the need for a preparative HPLC separation, and we feel that this investigation will enable development of catalytic reactions to assemble complex [3.2.1]-bicyclooctane structures. We are eager to explore additional Lewis acids as well as alternative additives that could promote the desired 1,2-migration with a more sterically encumbered system.

5.3 SECOND GENERATION SEMI-PINACOL STRATEGY

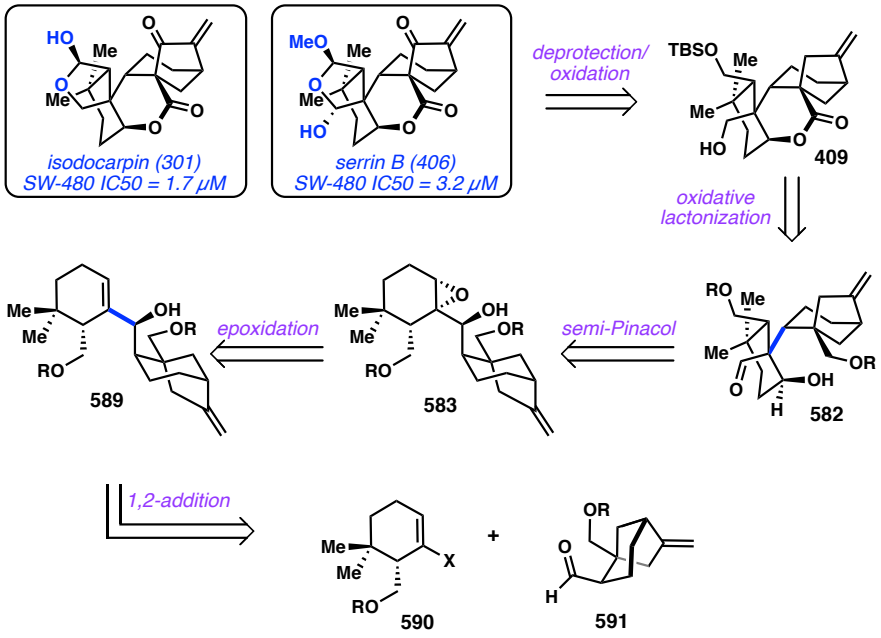
5.3.1 Retrosynthetic Analysis

While we had learned quite a bit about the migration of alkenyl groups to generate all-carbon quaternary centers through a type III semi-Pinacol rearrangement, our inability to migrate the fragment necessary for elaboration to **301** and our difficulties associated with the synthesis of a bicyclic fragment warranted a retooling of our synthetic strategy.

We wondered if we might have more success migrating a secondary alkyl group rather than an alkenyl group, and in doing so, identify a more direct route to synthesize a

bicyclic fragment. We felt we could use a similar end-game strategy to access **301** and **406** from lactone **409** (Scheme **5.15**). We felt that we could prepare lactone **409** through an oxidation/lactonization sequence from **582**, a key intermediate that contains two all-carbon quaternary centers. In **582**, the key bond shown in blue could be forged through a type III semi-Pinacol rearrangement from epoxy alcohol **583**, where the secondary alkyl group migrates to set the all-carbon quaternary center. This could be simplified to allylic alcohol **589**, which we hoped to forge through a 1,2-addition reaction between **590** and aldehyde **591**.

Scheme 5.15 *A second generation retrosynthesis of* ***301*** *and* ***406****.*



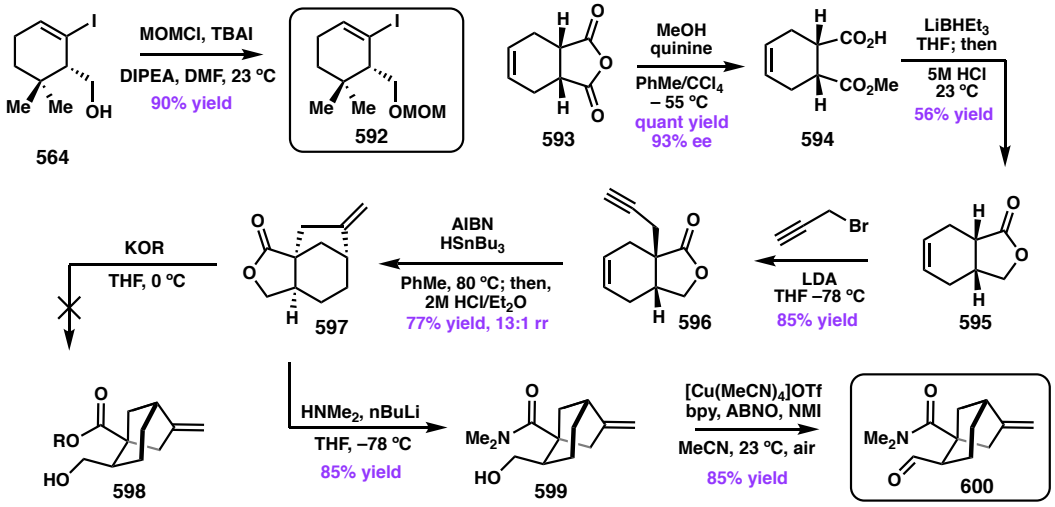
5.3.2 Fragment Synthesis

We were pleased to see that we could readily access **592** from **564**, which we had developed for our first generation route to **301** (Scheme **5.16**). For the bicyclic aldehyde

fragment, our synthesis commenced from meso anhydride **593**. A desymmetrization mediated by a cinchona alkaloid delivered half-ester **594**, which could be reduced and lactonized to give **595**, with high levels of enantioselectivity achieved in the desymmetrization step.[21] Bicyclic lactone could be propargylated to give a single diastereomer of **596**.[22] Through modification of a known procedure, we found that we could achieve high levels of selectivity for the [3.2.1]-bicyclooctane (**597**).[23] Key to the success of this strategy is the use of a bicyclic substrate—hydrolysis of the lactone prior to radical cyclization was reported to deliver significant amounts of the undesired [2.2.2]-bicyclooctane.

With the tricyclic lactone **597** in hand, we turned our attention toward the opening of the lactone. Unfortunately using a variety of alcohol nucleophiles delivered low levels of the ring opening product (**598**)—any conversion we observed seemed to be reversible and we were unable to isolate any of the hydroxy ester products. We were aware that the opening of the gamma lactone would be difficult, but we were pleased to see that lactone aminolysis delivered **599** in excellent yield.[24] While we had hoped to open the lactone to access an ester product, we were satisfied that we could get to **599**, which was in the correct oxidation state for elaboration to **301**. With **599** in hand, we found that we could use Stahl oxidation conditions to provide our key aldehyde **600**. We were concerned that we might observe epimerization to the equatorially disposed aldehyde, but it appeared that **600** was stable, so we turned our attention toward investigation of the 1,2-addition between **592** and **600**.

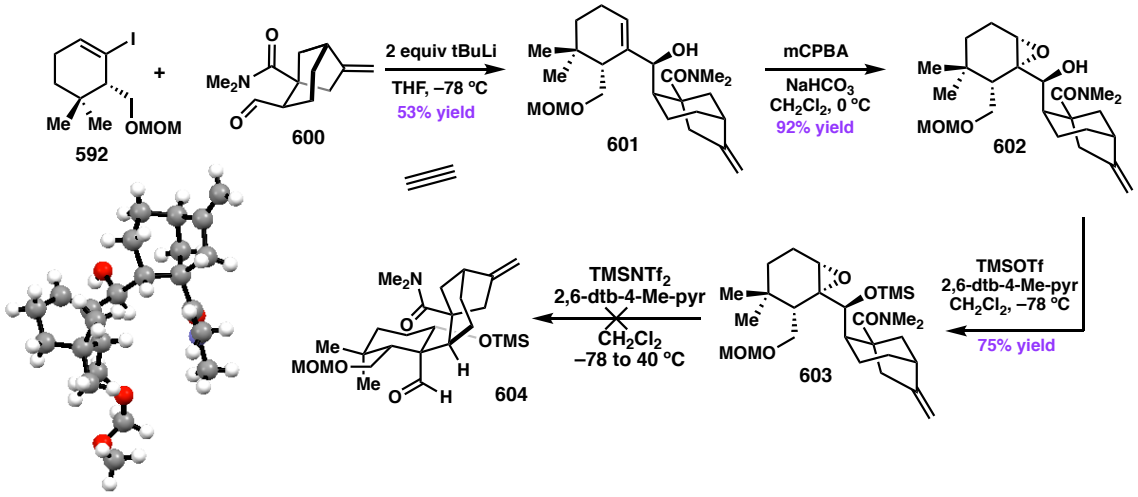
Scheme 5.16 *Synthesis of vinyl iodide* ***592*** *and aldehyde* ***600***



5.3.3 Convergent Union of a Vinyl Iodide and Bicyclic Aldehyde

Using the conditions we had previously employed for the lithiation of vinyl iodides enabled clean addition to the bicyclic aldehyde, delivering **601** as a single diastereomer (Scheme **5.17**). We were delighted to see that we could and confirm both the connectivity and stereochemistry of **601** through single crystal X-ray diffraction. This was particularly exciting, as the diastereomer formed through the 1,2-addition was the correct one needed for elaboration to the correct epoxide diastereomer. Treatment of **601** with mCPBA provided a single diastereomer of **602**, reacting through the lower-energy $A_{1,3}$-minimized conformer. With a single diastereomer of **602**, we were eager to begin exploring the feasibility of setting the all-carbon quaternary center through the envisioned semi-Pinacol rearrangement.

Scheme 5.17 *Initial 1,2-addition and semi-Pinacol results*

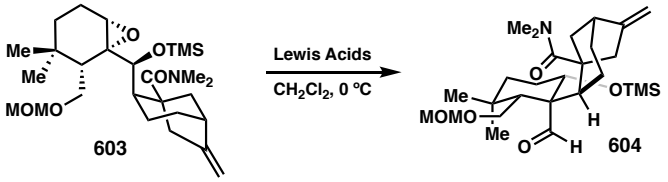


Unfortunately, treatment of **602** with TMSOTf only delivered the TMS protection product **603**. Treatment with the stronger Lewis acid solely delivered decomposition products. With a significant amount of **603** in hand, we wanted to conduct a thorough investigation of additional Lewis acids that could be used to carry out this transformation.

We began exploring a variety of Lewis acids that had previously been employed in the successful implementation of semi-Pinacol rearrangements in the literature (Table **5.1**).[1–4,25,26] Unfortunately, we had difficulty tuning the desired reactivity of the Lewis acids. Several of the Lewis acids we explored were too reactive, providing substantial decomposition (entries 1–2, 5, 11–12), while the other ones we explored only delivered recovered starting material. We hypothesized that the amide present in **603** may be intervening, enabling significant decomposition through known reactivity of amides with strong Lewis acids.[27–32] In the cases where we were only able to recover starting material, we hypothesized that the amide was sopping up the Lewis acid, preventing epoxide

activation, so we turned our attention toward the preparation of a substrate lacking a Lewis basic amide.

Table 5.1. *Screening of Lewis acids for the key semi-Pinacol rearrangement.*

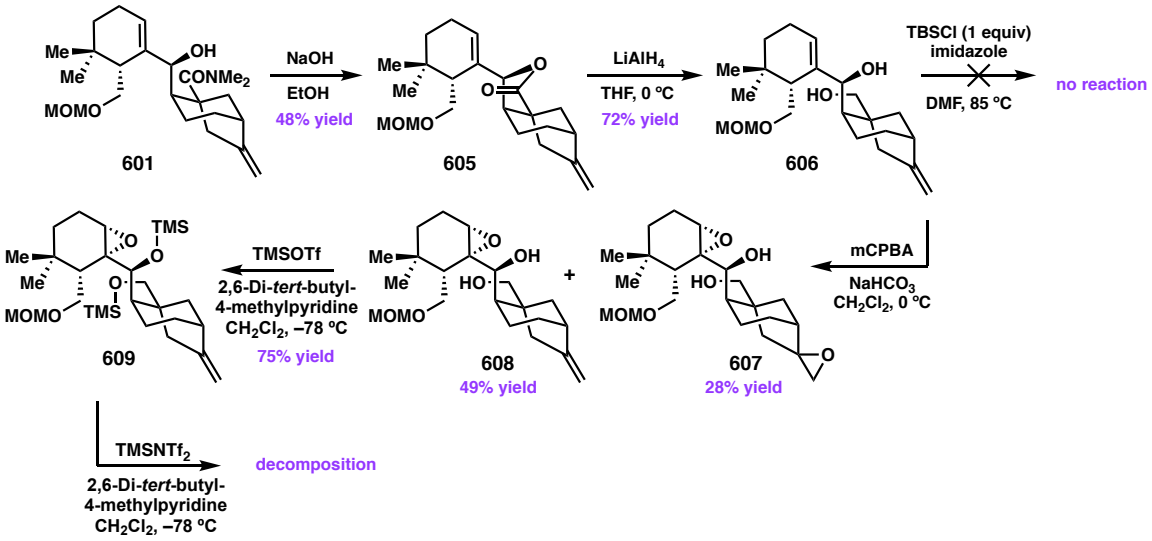


Entry	Scale	Lewis Acid	LA equiv	result
1	5 mg	$TiCl_4$	3	Decomp at 0 °C
2	5 mg	$SnCl_4$	3	Decomp at 0 °C
3	5 mg	$AlMe_3$	3	SM
4	5 mg	$Yb(OTf)_3$	3	SM
5	5 mg	HBF_4OEt_2	3	Decomp at 0 °C
6	5 mg	Et_3OBF_4	3	SM
7	5 mg	$MgBr_2$	3	SM
8	5 mg	$TiCl(OiPr)_3$	3	SM
9	5 mg	Et_2AlCl	3	SM
10	5 mg	$Zn(OTf)_2$	3	SM
11	5 mg	$BF_3{\cdot}OEt_2$	3	Decomp at 0 °C
12	5 mg	$Sc(OTf)_3$	3	Decomp at 0 °C

5.3.4 Synthesis of a Less Lewis Basic Substrate

In order to eliminate some of the issues we hypothesized were keeping us from successfully employing a semi-Pinacol rearrangement of **603**, we turned our attention toward the preparation of a substrate where some of these issues would be mitigated. We hoped to move away from a strongly Lewis basic amide and instead were interested in using a substrate with a silyl protecting group instead. In doing so, we hoped that we could still use our synthetic route to **601** and some of the knowledge we had gained in our previous chemistry.

Scheme 5.18 *Synthesis of a Diol Substrate*

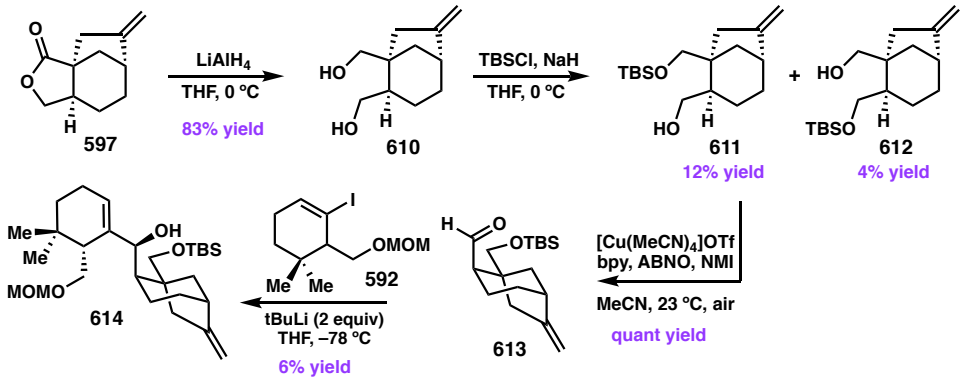


We found that treatment of **601** with NaOH in EtOH smoothly delivered lactone **605** (Scheme **5.18**). Treatment of **605** with $LiAlH_4$ delivered diol **606**. While this compound was no longer in the correct oxidation state needed for elaboration to **301**, we felt that this compound would be less problematic in the semi-Pinacol rearrangement. From **606**, silylation proved difficult, so we elected to perform an epoxidation at this stage. While we observed some over epoxidation, we could access some of the desired product upon treatment of **606** with mCPBA. Unfortunately treatment of **608** with TMSOTf resulted in low yields of **609**, and any attempts to migrate **609** under more forcing conditions solely resulted in decomposition.

We looked at trying to perform an earlier reduction. From bicyclic lactone **597**, treatment with $LiAlH_4$ delivered diol **610** (Scheme **5.19**). We were interested in discriminating between the two primary alcohols as had been previously reported;[22]

however, in our hands we observed poor selectivity for the desired product (**611**) and found it was nearly impossible to separate the two isomers. While we could obtain small quantities of the neopentyl alcohol protection product and could cleanly oxidize the remaining alcohol to the corresponding aldehyde **613**, 1,2-addition into this aldehyde proved capricious and we were unable to advance this material any further.

Scheme 5.19 *Diol Desymmetrization Strategy*



5.4 CONCLUDING REMARKS

While we have had trouble identifying conditions to enable smooth semi-Pinacol rearrangement in either the unsaturated or the saturated systems, we have learned quite a bit about the preparation of these complex fragments and how to bring them together in a robust manner. We have developed some elegant chemistry and have identified scalable approaches to both of the fragments in each iteration of our strategy. Future efforts should focus on deeper exploration of the alkenyl migration, as it seems that the preliminary results on the alkenyl model systems are more promising. Should a semi-Pinacol approach not be

realized successfully, it would be prudent to investigate other means of assembling all-carbon quaternary centers through transition-metal cross coupling.

5.5 EXPERIMENTAL DATA

5.5.1 Materials and Methods

General Procedures. Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), acetonitrile (MeCN), *tert*-butyl methyl ether (TBME), benzene (PhH), and toluene (PhMe) were dried by passing through activated alumina columns. Triethylamine (Et_3N), N,N-diisopropylethylamine (DIPEA), and methanol (MeOH) were distilled over calcium hydride prior to use. Unless otherwise stated, chemicals and reagents were used as received. All reactions were monitored by thin-layer chromatography (TLC) using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, *p*-anisaldehyde, $KMnO_4$, or CAM staining. Flash column chromatography was performed either as described by Still et al.[33] using silica gel (particle size 0.032-0.063) purchased from Silicycle or using pre-packaged RediSep®Rf columns on a CombiFlash Rf system (Teledyne ISCO Inc.). Optical rotations were measured on a Jasco P-2000 polarimeter using a 100 mm path-length cell at 589 nm. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III HD with Prodigy cryoprobe (at 400 MHz and 101 MHz respectively), a Varian 400 MR (at 400 MHz and 101 MHz, respectively), a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), or a Varian Inova 600 (at 600 MHz and 150

MHz, respectively), and are reported relative to internal $CHCl_3$ (^1H, δ = 7.26) and $CDCl_3$ (^{13}C, δ = 77.1), C_6H_5 (^1H, δ = 7.16) and C_6D_6 (^{13}C, δ = 128), or d_8-THF (^1H, δ = 3.58) and (^{13}C, δ = 67.6). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM) ionization mode, or obtained from the Caltech Mass Spectral Facility in fast-atom bombardment mode (FAB). Analytical SFC was performed with a Mettler SFC supercritical CO_2 analytical chromatography system with a Chiralcel AD-H column (4.6 mm x 25 cm).

5.5.2 General Procedures

General Procedure 1: 1,2-addition

A flame-dried flask was charged with alkenyl iodide (1 equiv) and evacuated and back-filled with N_2 three times. The flask was charged with THF (0.1 M) and the flask was cooled to –78 ºC, at which point, *t*-BuLi (2 equiv) was added dropwise and stirred for fivec minutes. A separate flask was charged with aldehyde (1 equiv) and evacuated and back-filled with N_2 three times. The aldehyde was dissolved in THF (0.1 M) and cooled to –78 ºC. The alkenyl lithium reagent was transferred to the aldehyde solution and the reaction

was allowed to stir for 10 minutes at –78 ºC, at which point the reaction was quenched with the addition of saturated $NH_4Cl_{(aq)}$. The aqueous layer was extracted with Et_2O three times, dried over $MgSO_4$, filtered, and concentrated in vacuo to give a crude residue that was purified by silica gel chromatography.

General Procedure 2: Semi-Pinacol Rearrangement

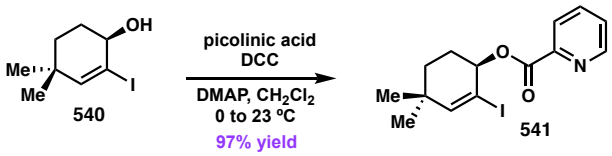
A flame-dried flask was charged with epoxy alcohol (1 equiv) and azeotroped with PhMe three times. The flask was then charged with 2,6-di-*tert*-butyl-4-methylpyridine (3 equiv) and evacuated and backfilled with N_2 three times. The solids were dissolved in CH_2Cl_2 (0.1 M) and the reaction mixture was cooled to –78 ºC. TMSOTf (2 equiv) was added as a solution in CH_2Cl_2 dropwise, and the reaction was stirred for 30 minutes at –78 ºC. The reaction was then quenched upon addition of saturated $NaHCO_{3\ (aq)}$. The mixture was diluted with water and the aqueous layer was extracted with CH_2Cl_2 three times. The combined organics were dried over Na_2SO_4 and concentrated in vacuo. The resulting crude residue was purified by silica gel chromatography.

General Procedure 3: Stille Iodination

A pressure flask was charged with enol triflate (1 equiv) then pumped into a N_2-filled glovebox. The flask was charged with LiCl (6 equiv), $Pd(PPh_3)_4$ (0.05 equiv), and THF (0.1 M). Then hexamethylditin (1 equiv) was added as a liquid directly. The flask was sealed and removed from the box. The flask was heated in an oil bath at 65 ºC for 16 hours,

at which point the flask was cooled to 0 ºC over 30 min. The flask was opened, and NIS (1.3 equiv) was added in one portion. The reaction was allowed to stir at 0 ºC for 2 hours, at which point the solvent was removed *in vacuo*. The residue was suspended in MeOH (0.2 M) and Et_2O (0.2 M). KF (5 equiv) was then added. The mixture was allowed to stir at room temperature for 4 hours, at which point the reaction mixture was filtered over a pad of Celite, eluting with Et_2O. The solvent was removed *in vacuo*, and the crude residue was purified by column chromatography.

5.5.3 Preparative Procedures and Spectroscopic Data



A flame-dried 200 mL round bottom flask was charged with 2-picolinic acid (3.22 g, 26.2 mmol, 1.1 equiv). The acid was dissolved in CH_2Cl_2 (60 mL) and the flask was cooled to 0 ºC with an ice bath. DCC (6.38 g, 30.9 mmol, 1.3 equiv) was added as a solid in one portion, followed by DMAP (1.45 g, 11.9 mmol, 0.5 equiv). The cloudy mixture stirred at 0 ºC for 30 min, at which point **540** (6.0 g, 23.8 mmol, 1 equiv) was added as a solution in CH_2Cl_2 (40 mL) dropwise via cannula over 1 hour. Once the addition was complete, the reaction was allowed to stir at 0 ºC for an additional 20 minutes. The reaction was then warmed to room temperature and stirred at 23 ºC for 4 hours, at which point TLC indicated that the reaction was complete. The suspension was filtered over a pad of celite, eluting with 300 mL of CH_2Cl_2. The solvent was removed *in vacuo* and the crude residue

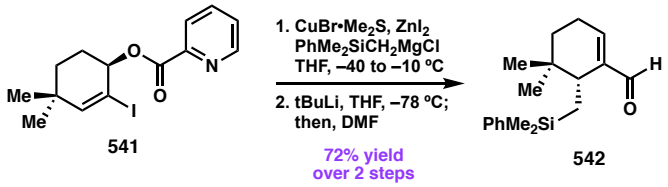
purified by column chromatography using silica gel (20% EtOAc/hexanes → 30% EtOAc/hexanes→ 40% EtOAc/hexanes) to give **541** (8.24 g, 97% yield) as an amorphous, colorless solid.

$\mathbf{R_f}$ = 0.30 (silica gel, 30% EtOAc/Hex, UV and p-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (ddd, *J* = 4.7, 1.8, 0.9 Hz, 1H), 8.17 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.85 (td, *J* = 7.7, 1.8 Hz, 1H), 7.48 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 6.44 (d, *J* = 1.0 Hz, 1H), 5.63 (td, *J* = 5.3, 1.1 Hz, 1H), 2.20 (dddd, *J* = 14.1, 9.9, 5.1, 3.5 Hz, 1H), 2.03 (dddd, *J* = 14.1, 8.1, 5.3, 3.3 Hz, 1H), 1.68 (ddd, *J* = 13.3, 9.9, 3.3 Hz, 1H), 1.62 – 1.51 (m, 1H), 1.09 (s, 3H), 1.04 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 164.4, 153.4, 150.3, 148.2, 137.1, 127.0, 125.5, 93.8, 74.9, 37.4, 32.4, 28.9, 28.0, 27.1.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{14}H_{16}INO_2$ $[M+H]^+$: 358.0298; found: 358.0298.



Procedure for Grignard formation:

A 250 mL round-bottom flask was charged with magnesium turnings (851 mg, 35 mmol, 6.2 equiv). The charged flask was briefly flame-dried under vacuum (1 minute or less), and allowed to cool to room temperature under vacuum. The dried magnesium was allowed to stir at 800 rpm under vacuum for one hour. The flask was then backfilled with

THF (8 mL). Chloromethylphenyldimethylsilane (4.5 mL, 25 mmol, 4.4 equiv) was added in one portion via syringe. The suspension was heated with a heat gun until the reaction began to initiate (indicated by vigorous bubbling), at which point a second portion of THF (8.7 mL) was added and the flask was submerged in an oil bath at 90 ºC. The reaction was heated at reflux for 90 minutes, at which point the flask was removed from the oil bath and cooled to room temperature. The Grignard reagent was titrated against 2-hydroxybenzaldehyde phenylhydrazone in triplicate to yield a final concentration of 1.176 M (78% yield).

A separate 100 mL round-bottom flask was pumped into a N_2-filled glovebox, where it was charged with CuBr•Me_2S (1.75 g, 8.53 mmol, 1.5 equiv) and ZnI_2 (2.73 g, 8.53 mmol, 1.5 equiv). The flask was sealed with a septum and removed from the glovebox. The flask was then charged with THF (28.5 mL) and cooled to 0 ºC. The flask was charged with freshly prepared dimethylphenylsilylmethylmagnesium chloride (see above) (14.5 mL, 17 mmol, 1.176 M, 3 equiv) via cannula. This mixture stirred for 30 minutes at 0 ºC and was then cooled to –40 ºC in a dry ice/acetone bath. Iodopicolonate **541** (2.03 g, 5.68 mmol, 1 equiv) was then added as a solution in THF (28.5 mL) via cannula. The reaction was allowed to gradually warm to –10 ºC over 90 minutes, at which point the reaction was quenched with the addition of saturated $NH_4Cl_{(aq)}$ solution (30 mL). The mixture was warmed to room temperature and diluted with water (30 mL) and pentane (100 mL). The aqueous layer was extracted with pentane (3 x 100 mL), and the combined organics were then washed with saturated $NH_4Cl_{(aq)}$ solution (3 x 100 mL), water (2 x 100 mL), and brine

(100 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a crude residue which was taken forward without any purification.

A 100 mL round-bottom flask was charged with the crude mixture and the flask was evacuated and back-filled with N_2 three times. The residue was dissolved in THF (28.5 mL) and the flask was cooled to –78 ºC. Then *t*-BuLi (6.7 mL, 1.7M, 11.4 mmol) was added via syringe fast dropwise. The mixture immediately became bright yellow. After stirring for 5 minutes, dry DMF (3.5 mL, 45.5 mmol, 8 equiv) was added. The reaction stirred at this temperature for 10 minutes, at which point the reaction mixture was poured into a 250 mL conical flask containing a mixture of KH_2PO_4 (4.64 g, 34.1 mmol, 6 equiv) in Et_2O (45.5 mL) and water (45.5 mL) at 0 ºC. This biphasic mixture was stirred for five minutes, at which point the mixture was poured into a separatory funnel. The aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (hexanes → 2.5% EtOAc/hexanes→ 5% EtOAc/hexanes→7.5% EtOAc/hexanes) to give **542** (1.17 g, 72% yield) as a colorless oil.

$\mathbf{R_f}$ = 0.66 (silica gel, 10% EtOAc/Hex, UV and p-anisaldehyde).

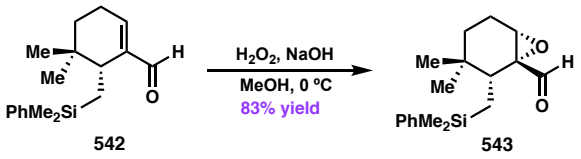
$\mathbf{[\alpha]_D^{25}}$ = +95.5° (c = 0.44, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.18 (s, 1H), 7.51 – 7.47 (m, 2H), 7.34 – 7.30 (m, 3H), 6.51 (t, *J* = 3.8 Hz, 1H), 2.42 (dtd, *J* = 8.0, 3.4, 1.6 Hz, 1H), 2.37 – 2.25 (m, 2H), 1.76 – 1.65 (m, 1H), 1.23 – 1.16 (m, 1H), 1.09 – 0.99 (m, 1H), 0.90 (s, 3H), 0.74 (s, 3H), 0.57 (dd, *J* = 15.0, 7.8 Hz, 1H), 0.35 – 0.31 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 194.2, 149.0, 148.0, 133.9, 128.7, 127.7, 127.6, 36.6, 32.3, 29.6, 28.5, 26.2, 24.7, 19.8, -1.6, -2.2.

FTIR (NaCl, thin film, cm^{-1}): 3720, 2953, 2913, 2352, 1682, 1424, 1248, 1112, 834, 818, 700.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{18}H_{30}NOSi$ $[M+NH_4]^+$: 304.2091; found: 304.2090.



A 25 mL round-bottom flask was charged with enal **542** (286 mg, 1.0 mmol, 1 equiv) and dissolved in MeOH (10 mL). The flask was cooled to 0ºC and NaOH (50 µL, 0.3 mmol, 6M, 0.3 equiv) was added. Hydrogen peroxide (134 µL, 1.3 mmol, 30 wt%, 1.3 equiv) was added and the reaction was allowed to stir for 2.5 hours at this temperature. The reaction was quenched with the addition of saturated $Na_2S_2O_{3\ (aq)}$ solution (5 mL). The mixture was diluted with water (5 mL) and then extracted with Et_2O (5 x 15 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (hexanes → 5% EtOAc/hexanes) to give **543** (259.6 mg, 86% yield) as a pale yellow solid.

R_f = 0.66 (silica gel, 10% EtOAc/Hex, p-anisaldehyde).

$[\alpha]_D^{25}$ = +2.7° (c = 1.8, $CHCl_3$).

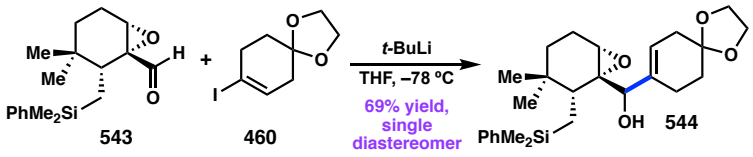
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37 (s, 1H), 7.52 – 7.47 (m, 2H), 7.36 – 7.32 (m, 3H), 3.28 (dd, *J* = 2.7, 1.1 Hz, 1H), 2.41 (ddd, *J* = 12.2, 2.5, 1.7 Hz, 1H), 2.04 (ddt, *J* = 15.7,

5.7, 1.5 Hz, 1H), 1.89 – 1.75 (m, 1H), 1.39 (dt, *J* = 13.0, 6.7 Hz, 1H), 0.97 – 0.84 (m, 3H), 0.84 (s, 3H), 0.78 (s, 3H), 0.28 (s, 3H), 0.25 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 200.7, 138.9, 134.1, 129.0, 127.7, 65.3, 57.7, 33.8, 31.0, 27.8, 26.7, 26.6, 21.4, 12.9, -2.0, -2.9.

FTIR (NaCl, thin film, cm^{-1}): 2956, 1725, 1427, 1249, 1172, 1113, 881, 839, 814, 794, 729, 700.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{18}H_{30}O_2SiN$ $[M+NH_4]^+$: 320.2040; found: 320.2033.



544 was prepared according to general procedure 1 using **543** (15.0 mg, 0.05 mmol) and **470** (13.2 mg, 0.05 mmol) and purified using silica gel (20% EtOAc/hexanes isocratic) to give **542** (15.1 mg, 69% yield) as a colorless oil.

R_f = 0.38 (silica gel, 40% EtOAc/Hex, p-anisaldehyde).

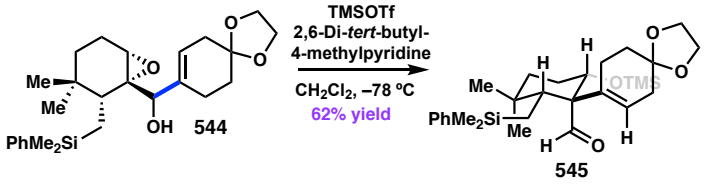
$[\alpha]_D^{25}$ = +22.1° (c = 0.27, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 – 7.49 (m, 2H), 7.42 – 7.29 (m, 3H), 5.51 (tq, *J* = 3.2, 1.4 Hz, 1H), 4.05 – 3.89 (m, 4H), 3.64 (d, *J* = 2.9 Hz, 1H), 3.16 (t, *J* = 1.9 Hz, 1H), 2.26 (dq, *J* = 4.1, 1.8 Hz, 2H), 2.06 – 1.85 (m, 3H), 1.84 – 1.63 (m, 3H), 1.61 – 1.54 (m, 1H), 1.52 (d, *J* = 3.6 Hz, 1H), 1.36 (td, *J* = 12.9, 5.7 Hz, 1H), 1.11 (dd, *J* = 16.0, 3.8 Hz, 1H), 0.82 (dd, *J* = 16.0, 7.0 Hz, 1H), 0.75 (s, 3H), 0.71 (s, 3H), 0.35 (s, 3H), 0.34 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 140.5, 136.5, 134.0, 128.8, 127.8, 120.3, 108.0, 79.1, 65.4, 64.5, 58.5, 37.1, 35.5, 31.3, 31.0, 28.5, 27.1, 27.1, 26.4, 21.8, 14.0, -1.2, -1.2.

FTIR (NaCl, thin film, cm^{-1}): 3442, 2928, 2363, 1428, 1366, 1247, 1112, 1060, 938, 907, 833, 824, 732, 699.

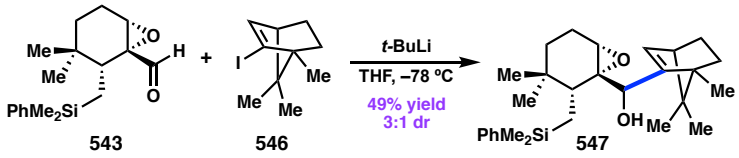
HRMS (ESI-TOF, *m/z*): calc'd for $C_{26}H_{42}NO_4Si$ $[M+NH_4]^+$: 460.2878; found: 460.2865.



545 was prepared according to general procedure 2 using **544** (13 mg, 0.03 mmol) and purified using silica gel neutralized with NH_4OH (2% EtOAc/hexanes → 3% EtOAc/hexanes→ 4% EtOAc/hexanes) to give **545** (9.3 mg, 62% yield) as a colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.96 (s, 1H), 7.58 – 7.47 (m, 2H), 7.32 (dp, *J* = 5.7, 1.5 Hz, 3H), 5.26 (d, *J* = 3.7 Hz, 1H), 3.94 (q, *J* = 1.2 Hz, 4H), 3.70 (d, *J* = 6.7 Hz, 1H), 2.30 – 2.19 (m, 3H), 2.06 (q, *J* = 7.5, 6.9 Hz, 1H), 1.91 – 1.55 (m, 5H), 1.43 (m, 2H), 1.31 (dd, *J* = 16.2, 1.8 Hz, 1H), 0.99 – 0.87 (m, 1H), 0.72 (s, 3H), 0.68 (s, 3H), 0.32 (s, 3H), 0.25 (s, 3H), 0.07 (s, 9H).

HRMS (ESI-TOF, *m/z*): calc'd for $C_{29}H_{47}O_4Si_2$ $[M+H]^+$: 515.3007; found: 515.2999.



547 was prepared according to general procedure 1 using **543** (30.2 mg, 0.1 mmol) and **546** (26.2 mg, 0.1 mmol) and purified using silica gel (hexanes → 5% EtOAc/hexanes→ 10% EtOAc/hexanes) to give **547** (21.6 mg, 49% yield as a 3:1 mixture of diastereomers) as a colorless solid.

$\mathbf{R_f}$ = 0.52 (silica gel, 10% EtOAc/Hex, p-anisaldehyde).

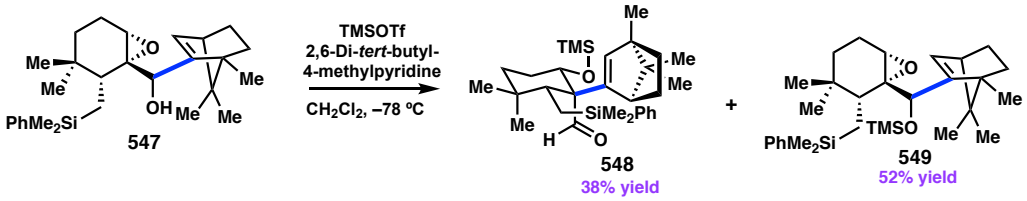
$\mathbf{[\alpha]_D^{23}}$ = +63.7° (c = 1.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 – 7.52 (m, 2H), 7.35 (td, *J* = 5.0, 1.9 Hz, 3H), 5.73 (dd, *J* = 3.2, 1.2 Hz, 1H), 3.80 (d, *J* = 1.2 Hz, 1H), 3.24 (d, *J* = 2.0 Hz, 1H), 2.25 (t, *J* = 3.4 Hz, 1H), 2.02 (ddd, *J* = 6.9, 3.0, 1.5 Hz, 1H), 1.88 (ddq, *J* = 17.1, 6.2, 1.9 Hz, 1H), 1.83 – 1.71 (m, 2H), 1.45 – 1.30 (m, 3H), 1.29 – 1.24 (m, 1H), 1.03 (dd, *J* = 16.4, 3.1 Hz, 1H), 0.91 (s, 3H), 0.88 (s, 3H), 0.85 – 0.76 (m, 1H), 0.74 (s, 3H), 0.70 (s, 3H), 0.70 (m, 1H) 0.68 (d, *J* = 2.2 Hz, 3H), 0.38 (d, *J* = 2.2 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 149.5, 140.0, 134.0, 129.3, 129.1, 127.9, 86.6, 71.4, 66.2, 55.5, 55.4, 55.0, 51.8, 39.4, 32.2, 31.5, 28.1, 28.0, 27.0, 25.5, 21.8, 19.7, 19.7, 13.6, 12.2, -1.6, -1.9.

FTIR (NaCl, thin film, cm^{-1}): 3472, 3068, 2952, 2872, 2360, 2341, 1699, 1386, 1248, 1112, 836, 730, 701

HRMS (ESI-TOF, *m/z*): calc'd for $C_{28}H_{46}NO_2Si$ $[M+NH_4]^+$: 456.3292; found: 456.3297.



Compounds **548** and **549** were prepared according to general procedure 2, using epoxy alcohol **547** (18 mg, 0.04 mmol). The mixture was purified using silica gel (hexanes → 2% EtOAc/hexanes→ 4% EtOAc/hexanes) to provide a mixture of **548** (5.8 mg, 38% yield) and **549** (6.4 mg, 52% yield).

Characterization data for **548**:

R_f = 0.43 (silica gel, 5% EtOAc/Hex, p-anisaldehyde).

$[\alpha]_D^{23}$ = +6.6° (c = 0.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.12 (s, 1H), 7.47 (ddd, *J* = 5.5, 4.1, 2.3 Hz, 2H), 7.31 (pd, *J* = 4.0, 3.6, 2.8 Hz, 3H), 5.70 (d, *J* = 3.6 Hz, 1H), 3.81 (t, *J* = 8.3 Hz, 1H), 2.16 (t, *J* = 3.6 Hz, 1H), 1.98 – 1.91 (m, 1H), 1.91 – 1.83 (m, 2H), 1.74 – 1.64 (m, 1H), 1.48 – 1.39 (m, 4H), 0.94 (s, 3H), 0.89 (m, 1H), 0.79 (s, 3H), 0.72 (s, 3H), 0.70 (s, 3H), 0.64 (s, 3H), 0.34 (s, 3H), 0.21 (s, 3H), 0.11 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 206.6, 141.4, 133.9, 133.6, 128.6, 128.6, 127.8, 62.5, 58.0, 56.4, 51.1, 40.2, 36.0, 34.2, 32.9, 31.5, 30.5, 30.2, 27.6, 25.4, 22.8, 22.0, 20.9, 20.3, 14.5, 13.9, 1.4.

FTIR (NaCl, thin film, cm^{-1}): 2952, 2876, 1713, 1454, 1364, 1291, 1250, 1111, 1250, 1087, 1068, 838, 824, 674

HRMS (ESI-TOF, *m/z*): calc'd for $C_{31}H_{51}O_2Si_2$ $[M+H]^+$: 511.3422; found: 511.3430.

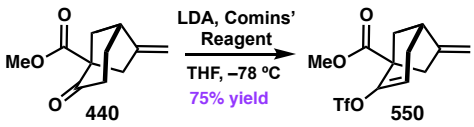
Characterization data for **549**:

$\mathbf{R_f}$ = 0.45 (silica gel, 5% EtOAc/Hex, p-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 – 7.49 (m, 2H), 7.34 (tt, *J* = 3.6, 2.3 Hz, 3H), 5.72 (dd, *J* = 3.2, 1.4 Hz, 1H), 4.19 – 4.12 (m, 1H), 3.24 (d, *J* = 1.9 Hz, 1H), 2.23 (t, *J* = 3.3 Hz, 1H), 1.90 – 1.71 (m, 4H), 1.50 – 1.42 (m, 1H), 1.40 – 1.29 (m, 2H), 1.12 (dd, *J* = 16.4, 2.1 Hz, 1H), 1.00 (s, 3H), 0.87 (m, 5H), 0.71 (d, *J* = 2.3 Hz, 6H), 0.66 (s, 3H), 0.38 (d, *J* = 3.0 Hz, 6H), 0.03 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 147.8, 140.2, 133.8, 130.1, 128.9, 127.9, 73.4, 66.8, 56.2, 55.1, 54.9, 51.6, 40.7, 32.5, 31.5, 29.9, 28.6, 27.6, 27.4, 25.4, 21.7, 19.8, 19.7, 13.6, 12.7, 0.9, -0.9, -1.3.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{31}H_{51}O_2Si_2$ $[M+H]^+$: 511.3422; found: 511.3414.



A 2-dram vial was charged with **440** (19.4 mg, 0.1 mmol, 1 equiv). The vial was evacuated and back-filled with nitrogen three times. The ester was dissolved in THF (500 µL) and cooled to –78 ºC. Then a solution of freshly prepared LDA (160 µL, 1.2 equiv, 0.75M) was added dropwise. The reaction was stirred at this temperature for 30 minutes, at which point Comins' reagent (45.2 mg, 0.115 mmol, 1.15 equiv) was added as a solid in

one portion. After 4 hours, the reaction was warmed to room temperature and quenched by addition of water (2 mL). The mixture was diluted with saturated $NH_4Cl_{(aq)}$ (2 mL) and extracted with Et_2O (3 x 5 mL). The combined organics were washed with 3M NaOH (10 mL), filtered through a plug of Na_2SO_4 and then concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (hexanes → 5% EtOAc/hexanes) to give **550** (23.7 mg, 73% yield) as an amorphous, colorless solid.

R_f = 0.67 (silica gel, 30% EtOAc/Hex, $KMnO_4$).

$[\alpha]_D^{22}$ = –1.3° (c = 1.0, $CHCl_3$).

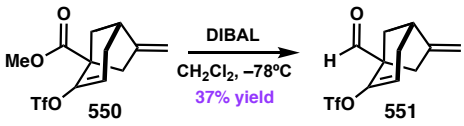
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.61 (dd, *J* = 4.9, 2.7 Hz, 1H), 5.06 (p, *J* = 1.3 Hz, 1H), 5.04 – 5.01 (m, 1H), 3.77 (s, 3H), 3.09 – 2.93 (m, 2H), 2.88 (dt, *J* = 16.4, 2.9 Hz, 1H), 2.59 (ddd, *J* = 17.5, 4.3, 2.7 Hz, 1H), 2.25 – 2.04 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.2, 151.9, 149.5, 118.5 (q, J_{C-F} = 320 Hz), 115.6, 109.5, 54.0, 52.6, 44.1, 41.1, 39.7, 34.9.

^{19}F NMR (282 MHz, $CDCl_3$): δ –74.5

FTIR (NaCl, thin film, cm^{-1}): 2958, 1745, 1670, 1420, 1292, 1244, 1215, 1165, 1143, 1077, 1043, 888, 862, 605.

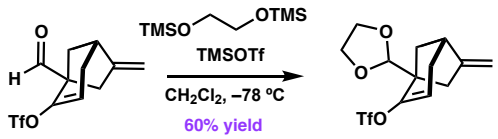
HRMS (ESI-TOF, *m/z*): calc'd for $C_{13}H_{16}F_3O_5S$ $[M+H]^+$: 327.0509; found: 327.0513.



A 25 mL round-bottom flask was charged with **550** (160 mg, 0.47 mmol, 1 equiv). The flask was evacuated and back-filled with N_2 three times, then charged with CH_2Cl_2 (4.7 mL, 0.1 M). The flask was cooled to –78 ºC, and DIBAL (84 µL, 0.47 mmol, 1 equiv) was added dropwise via syringe. The reaction stirred at –78 ºC for 20 minutes, at which point, the reaction was quenched with Rochelle's salt $_{(aq)}$ (5 mL) and warmed to room temperature. The mixture stirred vigorously for an hour, and then the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (3% EtOAc/hexanes → 20% EtOAc/hexanes) to give **551** (102 mg, 37% yield) as a colorless oil.

R_f = 0.68 (silica gel, 30% EtOAc/Hex, $KMnO_4$).

^{1}H NMR (600 MHz, $CDCl_3$): δ 9.83 (d, *J* = 1.0 Hz, 1H), 5.73 (dd, *J* = 4.7, 2.8 Hz, 1H), 5.11 (s, 1H), 5.07 (s, 1H), 3.04 (s, 1H), 2.92 (d, *J* = 16.2 Hz, 1H), 2.85 (dd, *J* = 16.2, 3.0 Hz, 1H), 2.60 (dt, *J* = 17.7, 3.7 Hz, 1H), 2.26 – 2.15 (m, 1H), 2.08 – 2.04 (m, 1H), 2.01 (dd, *J* = 10.9, 5.3 Hz, 1H).

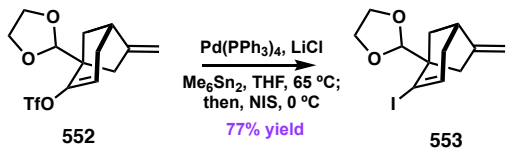


551 **552**

A 2-dram vial was charged with **551** (80 mg, 0.26 mmol, 1 equiv) and azeotroped with PhMe (3 x 1 mL). The vial was evacuated and back-filled three times with N_2. The vial was then charged with CH_2Cl_2 (2.25 mL), followed by 1,2-bistrimethysilyloxyethane (95 µL, 0.39 mmol, 1.5 equiv). The vial was cooled to –78 ºC, then TMSOTf (24 µL, 0.13 mmol) was added as a solution in CH_2Cl_2 (250 µL). The vial was allowed to warm to –20 ºC over the course of 2 hours, at which point the TLC showed complete conversion. The reaction was quenched with the addition of dry Hünig's base (500 µL). The crude mixture was concentrated *in vacuo*, and the crude residue was purified by column chromatography using silica gel (3% EtOAc/hexanes → 5% EtOAc/hexanes) to give **552** (28.1 mg, 44% yield) as a colorless oil.

R_f = 0.16 (silica gel, 5% EtOAc/Hex, $KMnO_4$).

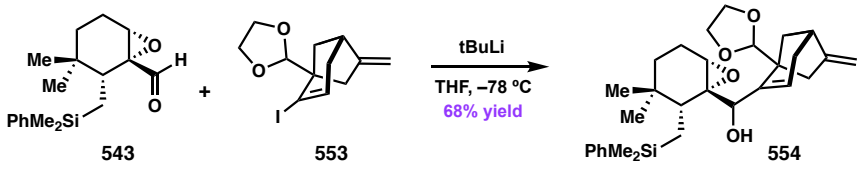
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.64 – 5.48 (m, 1H), 5.04 (dt, *J* = 2.8, 1.3 Hz, 1H), 5.01 (s, 1H), 5.00 – 4.97 (m, 1H), 4.11 – 4.06 (m, 1H), 3.98 (q, *J* = 6.8 Hz, 1H), 3.93 (td, *J* = 7.2, 5.1 Hz, 1H), 3.88 (q, *J* = 7.1 Hz, 1H), 2.96 – 2.87 (m, 2H), 2.56 – 2.49 (m, 2H), 2.17 – 2.07 (m, 1H), 1.98 (ddd, *J* = 10.9, 5.6, 1.1 Hz, 1H), 1.86 (dd, *J* = 10.9, 2.7 Hz, 1H).



Vinyl iodide **553** was prepared according to general procedure 3, using **552** (25 mg, 0.07 mmol, 1 equiv) as the substrate. The crude residue was purified by column chromatography using silica gel (2% EtOAc/hexanes → 3% EtOAc/hexanes) to give **553** (18.1 mg, 77% yield) as a colorless oil.

R_f = 0.23 (silica gel, 5% EtOAc/Hex, UV and p-anisaldehyde).

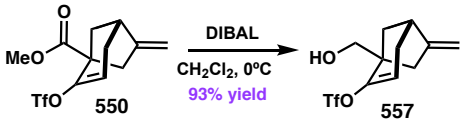
^{1}H NMR (600 MHz, $CDCl_3$): δ 6.26 (ddd, *J* = 4.8, 2.5, 1.0 Hz, 1H), 5.11 (d, *J* = 0.7 Hz, 1H), 5.01 (ddt, *J* = 3.0, 2.0, 1.0 Hz, 1H), 4.94 (tp, *J* = 1.7, 0.8 Hz, 1H), 4.04 – 3.99 (m, 1H), 3.99 – 3.92 (m, 3H), 2.97 – 2.90 (m, 1H), 2.54 (ddd, *J* = 17.2, 4.3, 2.5 Hz, 1H), 2.50 (ddtd, *J* = 15.8, 2.7, 1.7, 1.0 Hz, 1H), 2.45 – 2.40 (m, 1H), 2.06 (ddd, *J* = 11.0, 5.7, 1.6 Hz, 1H), 2.04 – 1.99 (m, 1H), 1.88 (dd, *J* = 10.9, 2.5 Hz, 1H).



Epoxy alcohol **554** was prepared according to general procedure 1, using **543** (10 mg, 0.03 mmol) and **553** (11 mg, 0.03 mmol). The mixture was purified using silica gel (hexanes → 5% EtOAc/hexanes→ 10% EtOAc/hexanes) to provide **554** (11.6 mg, 69% yield).

R_f = 0.42 (silica gel, 15% EtOAc/Hex, p-anisaldehyde).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.58 – 7.51 (m, 2H), 7.36 – 7.29 (m, 3H), 5.71 (ddt, *J* = 4.5, 2.3, 1.0 Hz, 1H), 5.17 (s, 1H), 4.93 (ddt, *J* = 3.0, 2.0, 1.1 Hz, 1H), 4.83 (dq, *J* = 2.2, 1.3 Hz, 1H), 4.59 (d, *J* = 4.7 Hz, 1H), 3.88 – 3.81 (m, 2H), 3.76 – 3.71 (m, 1H), 3.71 – 3.65 (m, 1H), 3.30 (dd, *J* = 2.8, 1.4 Hz, 1H), 2.81 (d, *J* = 5.3 Hz, 1H), 2.53 (dt, *J* = 16.1, 2.7 Hz, 1H), 2.45 (dd, *J* = 16.1, 2.1 Hz, 1H), 2.38 – 2.30 (m, 1H), 2.09 (ddd, *J* = 8.4, 2.3, 1.3 Hz, 1H), 2.02 – 1.94 (m, 2H), 1.89 (ddt, *J* = 15.5, 5.6, 2.2 Hz, 1H), 1.77 (dddd, *J* = 15.5, 11.6, 6.3, 2.8 Hz, 1H), 1.45 – 1.40 (m, 1H), 1.18 – 1.11 (m, 1H), 0.92 – 0.84 (m, 1H), 0.83 (s, 3H), 0.80 – 0.71 (m, 1H), 0.67 (s, 3H), 0.37 (s, 2H), 0.36 (s, 2H).



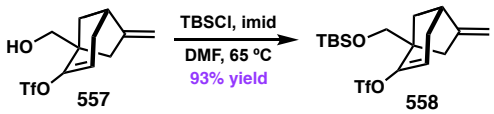
A 50 mL round-bottom flask was charged with **550** (400 mg, 1.18 mmol, 1 equiv). The flask was evacuated and back-filled with N_2 three times, then charged with CH_2Cl_2 (11.8 mL, 0.1 M). The flask was cooled to 0 ºC, and DIBAL (630 µL, 3.53 mmol, 3 equiv) was added dropwise via syringe. The reaction stirred at 0 ºC for 1 hour, at which point, the reaction was quenched with 1M HCl (4 mL) and warmed to room temperature. The mixture was diluted with water (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

The crude residue was purified by column chromatography using silica gel (20% Et_2O/hexanes → 30% Et_2O/hexanes) to give **557** (343 mg, 93% yield) as a colorless oil.

$\mathbf{R_f}$ = 0.22 (silica gel, 20% Et_2O/hexanes, p-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.59 (dd, *J* = 4.6, 2.8 Hz, 1H), 5.05 (q, *J* = 1.5 Hz, 1H), 4.98 (s, 1H), 4.00 (d, *J* = 11.3 Hz, 1H), 3.61 (d, *J* = 11.3 Hz, 1H), 2.93 (d, *J* = 5.1 Hz, 1H), 2.74 (ddq, *J* = 15.9, 2.7, 1.4 Hz, 1H), 2.56 (ddd, *J* = 17.4, 4.3, 2.8 Hz, 1H), 2.27 (dt, *J* = 15.9, 2.8 Hz, 1H), 2.21 – 2.07 (m, 1H), 2.03 (dd, *J* = 11.0, 2.8 Hz, 1H), 1.85 (ddd, *J* = 11.0, 5.5, 1.1 Hz, 1H), 1.74 (s, 1H).

^{19}F NMR (282 MHz, $CDCl_3$): δ –74.3.

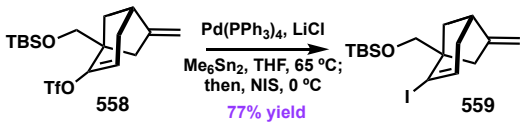


A 25 mL round-bottom flask was charged with **557** (150 mg, 0.48 mmol, 1.0 equiv) and imidazole (65 mg, 0.96 mmol, 2.0 equiv). The solids were dissolved in DMF (5 mL) and then TBSCl (87 mg, 0.576 mmol, 1.2 equiv) was added as a solid. The flask was then heated to 65 ºC and allowed to stir for 16 hours at this temperature, at which point the flask was removed from the oil bath and allowed to cool to room temperature. The reaction was quenched with the addition of water (5 mL) and then diluted with hexanes (25 mL) and additional water (20 mL). The aqueous layer was extracted with hexanes (3 x 25 mL), and the combined organics were washed with saturated $NH_4Cl_{(aq)}$ (3 x 50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was

purified by column chromatography using silica gel (hexanes → 3% Et_2O/hexanes) to give **558** (189 mg, 93% yield) as a colorless oil.

R_f = 0.90 (silica gel, 20% EtOAc/Hex, p-anisaldehyde).

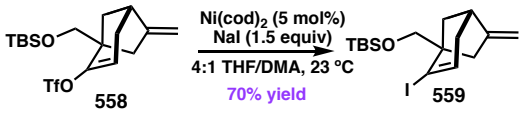
^{1}H NMR (500 MHz, $CDCl_3$): δ 5.53 (ddd, *J* = 4.6, 2.7, 0.8 Hz, 1H), 5.03 (ddt, *J* = 2.8, 1.9, 0.9 Hz, 1H), 4.96 (tp, *J* = 1.6, 0.7 Hz, 1H), 3.90 (d, *J* = 10.1 Hz, 1H), 3.54 (d, *J* = 10.1 Hz, 1H), 2.97 – 2.83 (m, 1H), 2.74 – 2.60 (m, 1H), 2.54 (ddd, *J* = 17.2, 4.4, 2.7 Hz, 1H), 2.31 (dt, *J* = 15.8, 2.7 Hz, 1H), 2.11 (dddt, *J* = 17.4, 4.7, 2.1, 1.0 Hz, 1H), 1.97 – 1.84 (m, 3H), 0.89 (s, 9H), 0.05 (s, 6H).



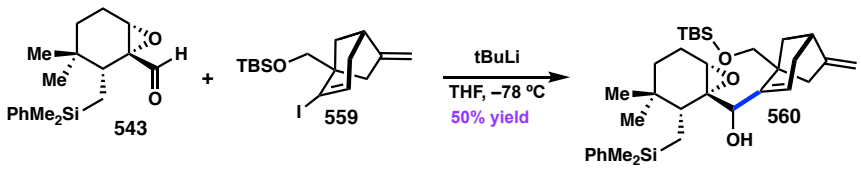
Iodide **559** could be prepared according to general procedure 3, using **558** (115 mg, 0.269 mmol, 1 equiv) as the subtrate. The mixture was purified using silica gel (hexanes) to provide **559** (83.4 mg, 77% yield).

R_f = 0.54 (silica gel, hexanes, p-anisaldehyde).

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.22 (ddd, *J* = 4.5, 2.5, 0.9 Hz, 1H), 4.99 (ddt, *J* = 2.8, 1.8, 1.0 Hz, 1H), 4.92 (dd, *J* = 2.3, 1.2 Hz, 1H), 3.68 (d, *J* = 9.9 Hz, 1H), 3.51 (d, *J* = 9.9 Hz, 1H), 2.91 (d, *J* = 5.7 Hz, 1H), 2.52 (ddd, *J* = 17.1, 4.4, 2.5 Hz, 1H), 2.33 (dtd, *J* = 15.8, 2.6, 1.3 Hz, 1H), 2.21 (dt, *J* = 15.8, 2.8 Hz, 1H), 2.05 – 1.94 (m, 2H), 1.89 (dd, *J* = 11.0, 2.6 Hz, 1H), 0.91 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H).



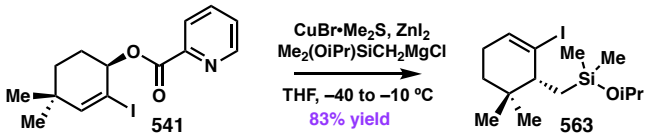
Inside a N_2-filled glovebox, a 2-dram vial was charged with $Ni(cod)_2$ (4.3 mg, 0.016 mmol, 5 mol %) and NaI (70.1 mg, 0.468 mmol, 1.5 equiv). The vial was then charged with THF (1.2 mL), DMA (0.6 mL), and enol triflate **558** (133 mg, 0.311 mmol, 1 equiv) as a solution in THF (1.2 mL). The vial was sealed and removed from the glovebox. The reaction stirred on the bench for 16 hours, at which point the reaction was quenched with the addition of water (3 mL). The mixture was diluted with additional water (5 mL) and Et_2O (5 mL). The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organics were washed with water (25 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (hexanes → 1% Et_2O/hexanes) to give **559** (88 mg, 70% yield) as a colorless oil. See above for characterization data for **559**.



Alcohol **560** was prepared according to general procedure 1, using **543** (30.2 mg, 0.1 mmol) and **559** (40.4 mg, 0.1 mmol). The mixture was purified using silica gel (hexanes → 2.5% EtOAc/hexanes) to provide **560** (27.7 mg, 48% yield).

$\mathbf{R}_f$ = 0.87 (silica gel, 20% EtOAc/Hex, p-anisaldehyde).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.61 – 7.49 (m, 2H), 7.39 – 7.31 (m, 3H), 5.59 (t, *J* = 3.3 Hz, 1H), 4.92 (s, 1H), 4.82 (s, 1H), 3.90 (d, *J* = 3.9 Hz, 1H), 3.80 (d, *J* = 10.0 Hz, 1H), 3.52 (d, *J* = 10.0 Hz, 1H), 3.31 (d, *J* = 2.5 Hz, 1H), 2.78 (d, *J* = 5.1 Hz, 1H), 2.45 (dt, *J* = 16.1, 2.7 Hz, 1H), 2.36 (dt, *J* = 17.3, 3.3 Hz, 1H), 2.29 (d, *J* = 15.4 Hz, 1H), 2.05 – 1.85 (m, 4H), 1.86 – 1.73 (m, 2H), 1.48 (dd, *J* = 10.7, 2.5 Hz, 1H), 1.38 (td, *J* = 12.6, 5.8 Hz, 1H), 1.05 (dd, *J* = 16.3, 2.8 Hz, 1H), 0.91 (s, 9H), 0.84 (s, 3H), 0.80 – 0.72 (m, 1H), 0.69 (s, 3H), 0.35 (d, *J* = 4.5 Hz, 6H), 0.07 (d, *J* = 10.8 Hz, 6H).



A 500 mL round-bottom flask was pumped into a N_2-filled glovebox, where it was charged with CuBr•Me_2S (3.27 g, 15.9 mmol, 1.5 equiv) and ZnI_2 (5.08 g, 15.9 mmol, 1.5 equiv). The flask was sealed with a septum and removed from the glovebox. The flask was then charged with THF (53 mL) and cooled to 0 ºC. The flask was charged with freshly prepared isopropoxydimethylsilylmethylmagnesium chloride[20] (55 mL, 31.8 mmol, 0.578 M, 3 equiv) via cannula. This mixture stirred for 30 minutes at 0 ºC and was then cooled to –40 ºC in a dry ice/acetone bath. Iodopicolonate **541** (3.78 g, 10.6 mmol, 1 equiv) was then added as a solution in THF (53 mL) via cannula. The reaction was allowed to gradually warm to –10 ºC over 3 hours, at which point the reaction was quenched with the addition of saturated $NH_4Cl_{(aq)}$ solution (30 mL). The mixture was warmed to room temperature and diluted with water (100 mL) and Et_2O (100 mL). The aqueous layer was extracted with

Et_2O (3 x 150 mL), and the combined organics were then washed with saturated $NH_4Cl_{(aq)}$ solution (200 mL), saturated $NaHCO_{3\,(aq)}$ (200 mL), water (200 mL) and brine (200 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a crude residue which was purified using silica gel (hexanes → 6% Et_2O/hexanes) to provide **563** (3.18 g, 83% yield).

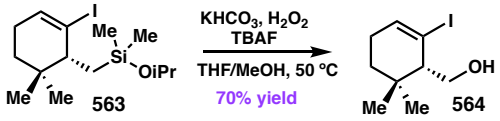
R_f = 0.90 (silica gel, 30% EtOAc/Hex, UV and p-anisaldehyde).

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.15 (dd, *J* = 4.5, 3.3 Hz, 1H), 4.04 (hept, *J* = 6.0 Hz, 1H), 2.28 (dddd, *J* = 6.6, 3.7, 1.8, 0.9 Hz, 1H), 2.20 – 1.97 (m, 2H), 1.62 – 1.56 (m, 1H), 1.16 (dd, *J* = 6.1, 1.4 Hz, 6H), 1.00 (s, 3H), 0.93 (s, 3H), 0.89 – 0.79 (m, 2H), 0.21 (d, *J* = 8.8 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 134.9, 109.0, 65.0, 52.6, 35.3, 29.2, 28.7, 27.3, 27.2, 26.0, 20.4, 0.3, 0.0.

FTIR (NaCl, thin film, cm^{-1}): 2970, 2920, 2874, 1631, 1464, 1450, 1366, 1251, 1172, 1130, 1028, 931, 886, 838, 822.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{14}H_{28}IOSi$ $[M+H]^+$: 367.0949; found: 367.0959.



A 25 mL round-bottom flask was charged with **563** (750 mg, 2.05 mmol, 1 equiv) followed by $KHCO_3$ (205 mg, 2.05 mmol, 1 equiv) and MeOH (2 mL). Then a solution of TBAF (4.1 mL, 4.09 mmol, 1 M in THF, 2 equiv) was added to the flask. At this point,

aqueous hydrogen peroxide (390 μL, 6.82 mmol, 50 wt%, 3.3 equiv) was added to the flask. The flask was added to a pre-heated oil bath at 50 ºC and left open to the atmosphere. After 90 minutes, TLC indicated complete consumption of starting material and formation of a much more polar product. The flask was removed from the oil bath and quenched with the addition of saturated $Na_2S_2O_{3\ (aq)}$ (10 mL). The mixture was diluted with Et_2O (5 mL) and the biphasic mixture was allowed to stir for an additional 30 min. The aqueous phase was extracted with Et_2O (3 x 10 mL), and the combined organics were washed with saturated $Na_2S_2O_{3\ (aq)}$ (30 mL), saturated $NaHCO_{3\ (aq)}$ (30 mL), and brine (30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a crude residue which was purified using silica gel (10% Et_2O/hexanes → 20% Et_2O/hexanes) to provide **564** (387 mg, 70% yield).

$\mathbf{R_f}$ = 0.57 (silica gel, 30% EtOAc/Hex, UV and p-anisaldehyde).

^{1}H NMR (600 MHz, $CDCl_3$): δ 6.59 – 6.54 (m, 1H), 3.94 (dt, *J* = 12.0, 4.1 Hz, 1H), 3.81 (ddd, *J* = 12.0, 8.7, 2.4 Hz, 1H), 2.15 – 2.08 (m, 2H), 2.02 (dh, *J* = 3.6, 1.2 Hz, 1H), 1.75 (ddd, *J* = 13.3, 10.0, 6.7 Hz, 1H), 1.30 (td, *J* = 8.5, 5.2 Hz, 2H), 1.07 (s, 4H), 1.01 (s, 4H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 140.7, 100.0, 62.1, 58.6, 34.5, 31.7, 28.1, 27.9, 27.2.

HRMS (ESI-TOF, *m/z*): calc'd for $C_9H_{19}INO$ $[M+NH_4]^+$: 284.0506; found: 284.0495.

A 2-dram vial was charged with **564** (266 mg, 1.0 mmol, 1.0 equiv) and imidazole (136 mg, 2.0 mmol, 2.0 equiv). The solids were dissolved in DMF (5 mL) and then TBSCl (181 mg, 1.2 mmol, 1.2 equiv) was added as a solid. The vial was sealed and the reaction was allowed to stir at room temperature for 16 hours, at which point the reaction was quenched with the addition of water (2 mL) and then diluted with hexanes (10 mL) and additional water (5 mL). The aqueous layer was extracted with hexanes (3 x 10 mL), and the combined organics were washed with saturated $NH_4Cl_{(aq)}$ (3 x 50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (hexanes) to give **565** (286 mg, 75% yield) as a colorless oil.

R_f = 0.90 (silica gel, 10% Et_2O/Hex, UV and p-anisaldehyde).

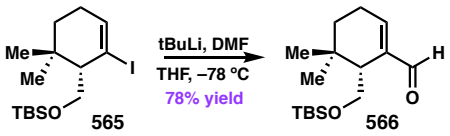
$[\alpha]_D^{24}$ = +76.8° (c = 0.20, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.49 – 6.34 (m, 1H), 3.88 – 3.71 (m, 2H), 2.17 – 1.96 (m, 2H), 1.92 (dtt, *J* = 3.7, 2.3, 1.1 Hz, 1H), 1.85 (ddd, *J* = 13.0, 10.9, 6.5 Hz, 1H), 1.22 – 1.14 (m, 1H), 1.04 (s, 3H), 0.98 (s, 3H), 0.88 (s, 9H), 0.07 (d, *J* = 2.1 Hz, 5H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 139.1, 101.5, 62.1, 58.7, 34.6, 31.1, 28.5, 27.8, 27.2, 26.0, 18.3, -5.2, -5.2.

FTIR (NaCl, thin film, cm^{-1}): 2954, 2927, 1634, 1470, 1389, 1362, 1256, 1111, 1138, 1034, 998, 883, 837, 776.

HRMS (FAB, *m/z*): calc'd for $C_{15}H_{28}IOSi$ $[M–H]^+$: 379.0955; found: 379.0962.



A 50 mL round-bottom flask was charged with **565** (1.16 g, 3.05 mmol, 1 equiv) and the flask was evacuated and back-filled with N_2 three times. The iodide was dissolved in THF (15.2 mL) and the flask was cooled to –78 ºC. Then *t*-BuLi (4 mL, 1.5M, 6.0 mmol, 2 equiv) was added via syringe fast dropwise. The mixture immediately became bright yellow. After stirring for 5 minutes, dry DMF (1.89 mL, 24.4 mmol, 8 equiv) was added. The reaction stirred at this temperature for 10 minutes, at which point the reaction mixture was poured into a 250 mL conical flask containing a mixture of KH_2PO_4 (2.49 g, 18.3 mmol, 6 equiv) in Et_2O (24 mL) and water (24 mL) at 0 ºC. This biphasic mixture was stirred for five minutes, at which point the mixture was poured into a separatory funnel. The aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (hexanes → 5% EtOAc/hexanes→10% EtOAc/hexanes) to give **566** (676 mg, 78% yield) as a colorless oil.

$\mathbf{R_f}$ = 0.59 (silica gel, 10% EtOAc/Hex, UV and p-anisaldehyde).

$\mathbf{[\alpha]_D^{23}}$ = +78.8° (c = 1.5, $CHCl_3$).

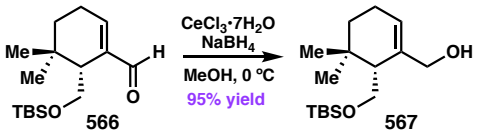
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.43 (s, 1H), 6.88 (dd, *J* = 4.2, 3.0 Hz, 1H), 3.76 (dd, *J* = 10.5, 2.8 Hz, 1H), 3.68 (dd, *J* = 10.6, 3.8 Hz, 1H), 2.44 – 2.26 (m, 2H), 2.28 – 2.19 (m,

2H), 2.01 (ddd, J = 13.2, 10.2, 7.1 Hz, 1H), 1.27 – 1.19 (m, 1H), 1.06 (s, 3H), 0.81 (s, 8H), 0.78 (s, 3H), -0.03 (s, 3H), -0.09 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 194.6, 153.3, 141.5, 61.9, 43.4, 32.1, 31.3, 27.8, 27.6, 25.9, 24.7, 18.2, -5.5, -5.5.

FTIR (NaCl, thin film, cm^{-1}): 2956, 2929, 2358, 1687, 1644, 1471, 1254, 1136, 1103, 1031, 996, 838, 776, 688.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{16}H_{31}O_2Si$ $[M+H]^+$: 283.2088; found: 283.2094.



A 2-dram vial was charged with enal **566** (30 mg, 0.106 mmol, 1 equiv). The enal was dissolved in MeOH (350 µL) and the vial was cooled to 0 ºC. Freshly ground $CeCl_3$•$7H_2O$ (39.5 mg, 0.106 mmol, 1 equiv) was added to the vial in one portion, and the yellow mixture was allowed to stir for 10 minutes. Then $NaBH_4$ (5 mg, 0.127 mmol, 1.2 equiv) was added as a solid. The reaction stirred at 0 ºC for 30 minutes, at which point the reaction was quenched with brine (1 mL). The mixture was diluted with water (2 mL) and Et_2O (4 mL). The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (10% Et_2O/hexanes → 30% Et_2O/hexanes) to give **567** (28.6 mg, 95% yield) as a colorless oil.

R_f = 0.42 (silica gel, 15% EtOAc/Hex, p-anisaldehyde).

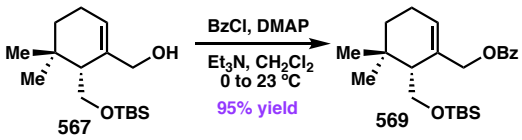
$[\alpha]_D^{24}$ = +73.4° (c = 1.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.70 (td, *J* = 3.6, 1.1 Hz, 1H), 4.25 – 4.08 (m, 1H), 4.02 – 3.82 (m, 2H), 3.56 (dd, *J* = 10.0, 8.1 Hz, 1H), 3.39 (t, *J* = 6.5 Hz, 1H), 2.12 – 1.91 (m, 3H), 1.50 – 1.36 (m, 1H), 1.35 – 1.19 (m, 1H), 0.95 (s, 3H), 0.90 (s, 9H), 0.87 (s, 3H), 0.09 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 138.8, 125.2, 67.8, 64.4, 48.8, 34.0, 31.6, 28.4, 26.0, 25.2, 22.9, 18.4, -5.3, -5.4.

FTIR (NaCl, thin film, cm^{-1}): 3347, 2956, 2928, 2859, 2360, 1471, 1389, 1362, 1256, 1105, 1055, 1006, 938, 892, 882, 838, 776, 668.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{16}H_{33}O_2Si$ $[M+H]^+$: 285.2250; found: 285.2238.



A 50 mL round-bottom flask was charged with alcohol **567** (300 mg, 10.5 mmol, 1 equiv) and dissolved in CH_2Cl_2 (21 mL). The flask was cooled to 0 ºC, and Et3N (1.5 mL, 10.5 mmol, 10 equiv) was added via syringe. Benzoyl chloride (366 µL, 3.15 mmol, 3 equiv) was added via syringe fast dropwise, then DMAP (65 mg, 0.528 mmol, 0.5 equiv) was added in one portion. The reaction stirred at 0 ºC for 1 hour, at which point the reaction mixture was pipetted onto a preequilibrated silica plug, eluting with 20% EtOAc/hexanes (200 mL). The volatiles were removed *in vacuo*, and the crude residue was purified by

column chromatography using silica gel (hexanes → 4% EtOAc/hexanes) to give **569** (388 mg, 95% yield) as a colorless oil.

R_f = 0.52 (silica gel, 10% EtOAc/Hex, UV and p-anisaldehyde).

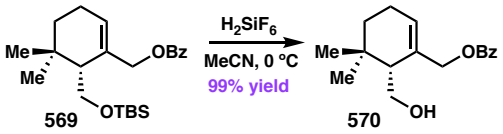
$[\alpha]_D^{22}$ = +36.1° (c = 0.73, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.04 (d, *J* = 7.8 Hz, 2H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 5.88 (d, *J* = 3.6 Hz, 1H), 4.89 (d, *J* = 12.3 Hz, 1H), 4.75 (d, *J* = 12.3 Hz, 1H), 3.79 (dd, *J* = 10.5, 4.6 Hz, 1H), 3.70 (dd, *J* = 10.5, 4.6 Hz, 1H), 2.17 – 1.97 (m, 2H), 1.92 (d, *J* = 4.7 Hz, 1H), 1.68 (dt, *J* = 13.1, 8.3 Hz, 1H), 1.21 (dt, *J* = 13.2, 4.9 Hz, 1H), 1.00 (s, 3H), 0.93 (s, 3H), 0.87 (s, 9H), 0.03 (d, *J* = 4.8 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.6, 133.3, 132.9, 130.7, 129.7, 128.5, 127.7, 68.6, 63.1, 47.9, 32.2, 31.7, 27.7, 27.6, 26.0, 23.1, 18.3, -5.3, -5.4.

FTIR (neat, cm^{-1}): 2953, 2927, 2855, 1719, 1471, 1268, 1106, 1069, 835, 774, 709.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{23}H_{37}O_3Si$ $[M+H]^+$: 389.2506; found: 389.2504.



A 25 mL round-bottom flask was charged with **269** (385 mg, 0.966 mmol, 1 equiv). Acetonitrile (9.7 mL) was added to the flask, and the mixture was cooled to 0 ºC with an ice bath. H_2SiF_6 (2.3 mL, 4.82 mmol, 5 equiv, 25 wt %) was added to the flask, and the mixture was allowed to stir at 0 ºC for 4 hours, at which point TLC showed complete consumption of starting material. The reaction was quenched with the addition of saturated

$NaHCO_{3\ (aq)}$ (20 mL). The mixture was diluted with water (20 mL) and the aqueous layer was extracted with EtOAc (3 x 40 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide **570** (263 mg, 99% yield) as a colorless oil.

$\mathbf{R_f}$ = 0.52 (silica gel, 30% EtOAc/Hex, UV and p-anisaldehyde).

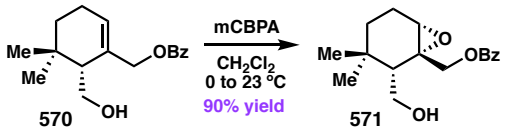
$\mathbf{[\alpha]_D^{25}}$ = +50.5° (c = 0.44, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 – 8.00 (m, 2H), 7.62 – 7.52 (m, 1H), 7.45 (dd, *J* = 8.4, 7.0 Hz, 2H), 6.01 (t, *J* = 3.7 Hz, 1H), 4.91 (dq, *J* = 12.4, 1.8 Hz, 1H), 4.75 (dd, *J* = 12.4, 1.1 Hz, 1H), 3.98 – 3.72 (m, 2H), 2.11 (ddtd, *J* = 8.4, 5.0, 3.2, 1.6 Hz, 2H), 1.88 (d, *J* = 4.1 Hz, 1H), 1.69 (dt, *J* = 13.4, 8.5 Hz, 1H), 1.57 (s, 2H), 1.25 (dtd, *J* = 13.4, 4.8, 4.3, 1.4 Hz, 1H), 1.05 (s, 3H), 0.92 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.7, 133.2, 132.0, 130.4, 129.7, 129.5, 128.6, 68.4, 62.5, 48.5, 32.2, 31.8, 27.8, 27.6, 23.1.

FTIR (neat, cm^{-1}): 3019, 2359, 1712, 1245, 1193, 1111, 1026, 720.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{17}H_{23}O_3$ $[M+H]^+$: 275.1638; found: 275.1642.



A 50 mL round-bottom flask was charged with alcohol **570** (265 mg, 0.97 mmol, 1 equiv) and CH_2Cl_2 (9.7 mL) then cooled to 0 ºC. To the reaction mixture was added mCPBA (200 mg, 1.16 mmol, 1.2 equiv, 99% mCPBA) in one portion. The reaction was allowed to stir at 0 ºC for 2.5 hours, at which point TLC indicated that the starting material

had been consumed. The reaction was quenched with saturated $Na_2S_2O_{3\ (aq)}$ (8 mL) and saturated $NaHCO_{3\ (aq)}$ (4 mL). The biphasic mixture was diluted with water (5 mL) and CH_2Cl_2 (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organics were washed with saturated $Na_2S_2O_{3\ (aq)}$ (30 mL), saturated $NaHCO_{3\ (aq)}$ (30 mL), and brine (30 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (10% EtOAc/hexanes → 25% EtOAc/hexanes) to give **571** (252 mg, 90% yield) as a colorless solid.

R_f = 0.38 (silica gel, 30% EtOAc/Hex, p-anisaldehyde).

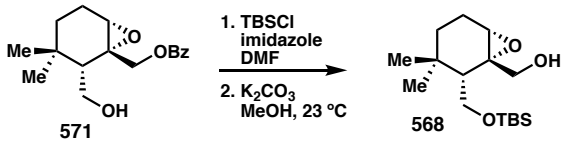
$[\alpha]_D^{22}$ = +50.5° (c = 0.44, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 – 7.97 (m, 2H), 7.58 (ddt, *J* = 7.9, 6.9, 1.4 Hz, 1H), 7.53 – 7.37 (m, 2H), 4.49 (d, *J* = 11.7 Hz, 1H), 4.36 (d, *J* = 11.7 Hz, 1H), 3.99 (dt, *J* = 11.4, 3.9 Hz, 1H), 3.92 – 3.76 (m, 1H), 3.30 (t, *J* = 1.9 Hz, 1H), 2.39 (t, *J* = 6.2 Hz, 1H), 2.02 (ddt, *J* = 15.7, 6.0, 1.6 Hz, 1H), 1.90 (dddd, *J* = 15.7, 12.4, 6.4, 2.4 Hz, 1H), 1.80 (ddd, *J* = 7.4, 4.2, 1.5 Hz, 1H), 1.66 – 1.58 (m, 1H), 1.00 (dd, *J* = 9.1, 7.1 Hz, 1H), 0.96 (s, 3H), 0.93 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 166.4, 133.4, 129.8, 129.8, 128.6, 68.1, 62.1, 59.8, 57.7, 44.2, 30.3, 28.6, 28.0, 27.2, 21.4.

FTIR (neat, cm^{-1}): 3019, 2359, 1718, 1451, 1272, 1215, 1115, 727, 712, 668.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{17}H_{23}O_4$ $[M+H]^+$: 291.1591; found: 291.1577.



A 50 mL round-bottom flask was charged with **571** (240 mg, 0.826 mmol, 1 equiv) and imidazole (113 mg, 1.65 mmol, 2 equiv). The solids were dissolved in DMF (8.3 mL) and then TBSCl (150 mg, 0.99 mmol, 1.2 equiv) was added as a solid. The flask was sealed and the reaction was allowed to stir at room temperature for 16 hours, at which point the reaction was quenched with the addition of water (10 mL) and then diluted with hexanes (10 mL) and additional water (5 mL). The aqueous layer was extracted with hexanes (3 x 10 mL), and the combined organics were washed with saturated $NH_4Cl_{(aq)}$ (3 x 50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

The crude epoxy benzoate was added to a 50 mL round-bottom flask and dissolved in MeOH (14 mL). To the reaction mixture was added K_2CO_3 (1.15 g, 8.3 mmol, 12 equiv). The reaction stirred vigorously (800 rpm) for 40 minutes, at which point the reaction was quenched with the addition of saturated $NH_4Cl_{(aq)}$ (50 mL). The aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to provide **568** (263 mg, 93% yield over two steps) as a colorless oil.

R_f = 0.58 (silica gel, 30% EtOAc/Hex, p-anisaldehyde).

$[\alpha]_D^{22}$ = +59.8° (c = 0.21, $CHCl_3$).

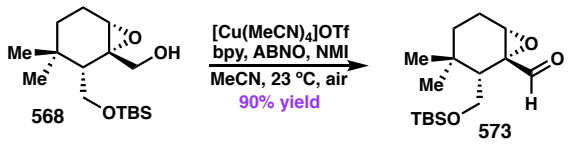
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.86 (dd, *J* = 11.8, 4.3 Hz, 1H), 3.72 (ddd, *J* = 8.9, 4.9, 0.5 Hz, 1H), 3.62 (dd, *J* = 10.2, 8.9 Hz, 1H), 3.53 (dd, *J* = 6.2, 4.3 Hz, 1H), 3.39 (dd, *J* = 11.8,

6.1 Hz, 1H), 3.14 (t, *J* = 1.9 Hz, 1H), 2.02 – 1.88 (m, 2H), 1.83 (dddd, *J* = 15.6, 12.1, 6.5, 2.6 Hz, 1H), 1.37 – 1.24 (m, 1H), 0.92 (s, 9H), 0.91 (s, 3H), 0.85 (s, 3H), 0.12 (d, *J* = 5.1 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$): δ 67.6, 61.6, 61.2, 55.8, 45.2, 30.1, 28.3, 27.7, 27.7, 26.0, 21.5, 18.5, -5.4, -5.4.

FTIR (neat, cm^{-1}): 3752, 2927, 2359, 2340, 2161, 1684, 1675, 1576, 1506, 1040, 837, 775.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{16}H_{33}O_3Si$ $[M+H]^+$: 301.2193; found: 301.2195.



A 25 mL round-bottom flask was charged with epoxy alcohol **568** (160 mg, 0.533 mmol, 1 equiv) and dissolved in wet acetonitrile (11 mL). To this solution was added Stahl solution (135 μL, containing 0.2M bpy, 0.04M ABNO, and 0.4M NMI in MeCN) followed by $[Cu(MeCN)_4]OTf$ (10 mg, 0.027 mmol, 0.05 mol %). The solution was sparged with a balloon of O_2 for 10 minutes and then allowed to stir open to air for 3.5 hours. The reaction mixture was then filtered through a SiO_2 plug, eluting with 20% EtOAc/hexanes (100 mL). The volatiles were removed *in vacuo* to provide **573** (143 mg, 90% yield) as a light yellow oil.

R_f = 0.64 (silica gel, 30% EtOAc/Hex, p-anisaldehyde).

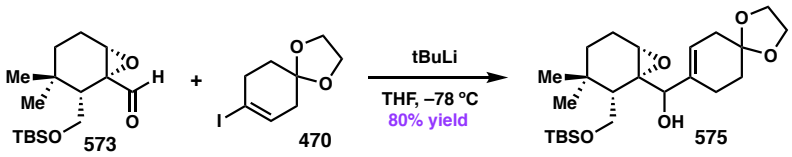
$[\alpha]_D^{22}$ = +64.1° (c = 2.8, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.02 (s, 1H), 3.68 (ddd, *J* = 8.8, 5.6, 0.6 Hz, 1H), 3.49 (dd, *J* = 11.0, 8.8 Hz, 1H), 3.41 (d, *J* = 1.9 Hz, 1H), 2.64 (ddd, *J* = 11.0, 5.5, 1.5 Hz, 1H), 2.08 (dddd, *J* = 15.5, 5.3, 2.3, 1.7 Hz, 1H), 1.87 (dddd, *J* = 15.6, 12.3, 5.8, 2.2 Hz, 1H), 1.49 – 1.36 (m, 1H), 1.01 – 0.90 (m, 1H), 0.89 (s, 3H), 0.86 (s, 3H), 0.85 (s, 9H), 0.03 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 200.5, 63.3, 60.5, 56.8, 42.1, 28.8, 28.6, 28.1, 27.0, 26.0, 21.3, 18.3, -5.4.

FTIR (neat, cm^{-1}): 2955, 2928, 2856, 2359, 1730, 1506, 1472, 1109, 1082, 1256, 1109, 1082, 837, 776.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{16}H_{31}O_3Si$ $[M+H]^+$: 299.2037; found: 299.2030.



Epoxy alcohol **575** was prepared according to general procedure 1, using **573** (15 mg, 0.10 mmol) and **470** (26.6 mg, 0.10 mmol, 2 equiv). The mixture was purified using silica gel (10% EtOAc/hexanes → 30% EtOAc/hexanes) to provide **575** (17.5 mg, 80% yield).

R_f = 0.24 (silica gel, 30% EtOAc/Hex, p-anisaldehyde).

$[\alpha]_D^{22}$ = +35.4° (c = 0.35, $CHCl_3$).

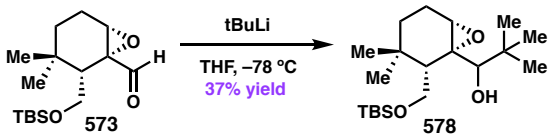
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85 (tq, *J* = 3.3, 1.4 Hz, 1H), 5.60 (d, *J* = 2.5 Hz, 1H), 3.94 (dd, *J* = 3.7, 1.5 Hz, 4H), 3.69 (dd, *J* = 8.7, 4.9 Hz, 1H), 3.59 (dd, *J* = 11.0, 8.7 Hz,

1H), 3.56 – 3.50 (m, 1H), 3.16 (t, *J* = 1.9 Hz, 1H), 2.40 – 2.19 (m, 3H), 2.11 (dddd, *J* = 15.9, 10.9, 5.0, 1.9 Hz, 2H), 1.98 (ddt, *J* = 15.5, 5.9, 1.6 Hz, 1H), 1.88 – 1.79 (m, 1H), 1.74 (ddt, *J* = 8.6, 6.4, 1.1 Hz, 2H), 0.95 (s, 9H), 0.88 (qd, *J* = 7.3, 6.5, 2.5 Hz, 2H), 0.82 (s, 3H), 0.79 (s, 3H), 0.16 (s, 3H), 0.15 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 136.8, 121.4, 108.2, 80.1, 64.4, 64.3, 62.2, 61.7, 57.0, 41.5, 35.6, 31.3, 29.6, 28.2, 28.1, 27.5, 26.6, 26.0, 21.5, 18.5, -5.5, -5.5.

FTIR (neat, cm^{-1}): 3372, 2953, 2927, 2856, 2360, 1700, 1113, 1084, 1060, 836, 777, 733.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{24}H_{43}O_5Si$ $[M+H]^+$: 439.2874; found: 439.2854.



Alcohol **578** was prepared according to general procedure 1 with **573** (15 mg, 0.05 mmol) and *t*-BuLi (67 µL, 0.10 mmol, 1.7M, 2 equiv) as the organolithium reagent. The crude residue was purified using silica gel chromatography (hexanes → 10% EtOAc/hexanes) to provide **576** (6.8 mg, 37% yield).

R_f = 0.53 (silica gel, 10% EtOAc/Hex, p-anisaldehyde).

$[\alpha]_D^{22}$ = +60.6° (c = 0.30, $CHCl_3$).

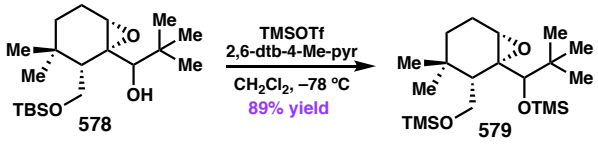
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.34 (d, *J* = 2.3 Hz, 1H), 3.73 (dd, *J* = 9.1, 4.9 Hz, 1H), 3.66 (td, *J* = 9.5, 9.0, 1.0 Hz, 1H), 3.16 (d, *J* = 1.9 Hz, 1H), 2.75 (d, *J* = 2.1 Hz, 1H), 2.21 (ddd, *J* = 10.2, 5.0, 1.3 Hz, 1H), 1.98 (ddt, *J* = 15.5, 5.5, 2.0 Hz, 1H), 1.87 (dddd, *J* = 15.4, 12.4, 6.1, 2.2 Hz, 1H), 1.43 (d, *J* = 1.0 Hz, 1H), 1.37 (td, *J* = 12.9, 5.5 Hz, 1H), 1.02 (s,

4H), 1.00 (d, *J* = 1.0 Hz, 9H), 0.96 (d, *J* = 1.0 Hz, 9H), 0.84 (s, 3H), 0.16 (d, *J* = 2.8 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 85.9, 62.5, 61.8, 57.9, 43.4, 36.1, 30.6, 29.3, 28.7, 28.3, 27.4, 26.1, 21.4, 18.7.

FTIR (neat, cm^{-1}): 3360, 2929, 2858, 2359, 1388, 1069, 906, 836, 730.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{20}H_{41}O_3Si$ $[M+H]^+$: 357.2819; found: 357.2813.



Epoxide **579** was prepared according to general procedure 2, using **578** (6 mg, 0.017 mmol) as the substrate. The mixture was purified using preparative TLC (10% Et_2O/hexanes) to provide **579** (3 mg, 89% NMR yield).

R_f = 0.79 (silica gel, 20% EtOAc/Hex, UV).

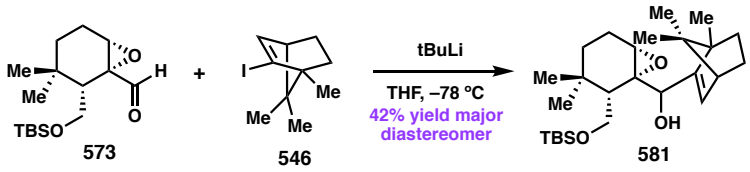
$[\alpha]_D^{23}$ = –5.1° (c = 0.25, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.14 (dd, *J* = 10.6, 2.3 Hz, 1H), 3.53 – 3.42 (m, 1H), 2.96 (t, *J* = 2.2 Hz, 1H), 2.83 (s, 1H), 2.10 (dt, *J* = 8.0, 1.8 Hz, 1H), 1.92 – 1.79 (m, 2H), 1.47 – 1.40 (m, 3H), 0.99 (s, 3H), 0.97 (s, 9H), 0.92 (s, 3H), 0.90 – 0.81 (m, 2H), 0.16 (s, 9H), 0.11 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 88.7, 62.9, 62.3, 58.5, 45.2, 36.0, 31.4, 29.7, 29.4, 28.0, 27.6, 21.6, 1.0, 0.0.

FTIR (NaCl, thin film, cm^{-1}): 2922, 2362, 1382, 1035, 826, 810, 708, 683.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{20}H_{43}O_3Si_2$ $[M+H]^+$: 387.2745; found: 387.2746.

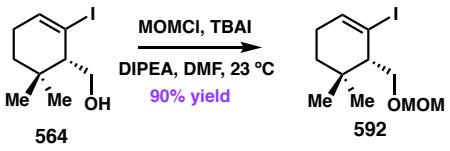


Epoxide **581** was prepared according to general procedure 1, using **573** (15 mg, 0.05 mmol) and **546** (26.2 mg, 0.10 mmol, 2 equiv). The mixture was purified using silica gel (hexanes → 5% EtOAc/hexanes) to provide **581** (17 mg, 42% NMR yield of major diastereomer).

$\mathbf{R_f}$ = 0.52 (silica gel, 20% Et_2O/Hex, p-anisaldehyde).

$\mathbf{[\alpha]_D^{23}}$ = +21.0° (c = 0.85, $CHCl_3$).

HRMS (ESI-TOF, *m/z*): calc'd for for $C_{26}H_{47}O_3Si$ $[M+H]^+$: 435.3289; found: 435.3285.



A 50 mL round-bottom flask was charged with **564** (380 mg, 1.43 mmol, 1 equiv). The flask was evacuated and backfilled with N_2 three times and then DMF (7 mL) was added via syringe. To the reaction mixture was added TBAI (264 mg, 0.71 mmol, 0.5 equiv) followed by Hünig's base (1.5 mL, 8.57 mmol, 6 equiv). The reaction was cooled to 0 ºC, at which point MOMCl (325 µL, 4.29 mmol, 3 equiv) was added dropwise via syringe. The reaction stirred at 0 ºC for 15 minutes and was then warmed to room

temperature, where it stirred for an additional 16 hours, when TLC indicated that starting material had been consumed. The reaction was quenched with the addition of 1M NaOH (10 mL). The mixture was diluted with water (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organics were washed with 1M NaOH (50 mL), water (50 mL), and saturated $NH_4Cl_{(aq)}$ (2 x 50 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (4% Et_2O/hexanes → 5% Et_2O/hexanes) to give **592** (408 mg, 90% yield) as a colorless oil.

R_f = 0.74 (silica gel, 25% Et_2O/Hex, UV and p-anisaldehyde).

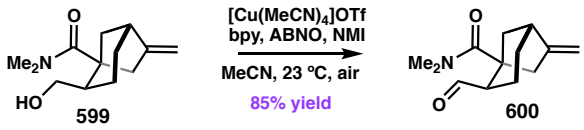
$[\alpha]_D^{22}$ = +70.2° (c = 0.42, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.46 – 6.41 (m, 1H), 4.68 – 4.56 (m, 2H), 3.76 – 3.66 (m, 2H), 3.39 (s, 3H), 2.14 – 2.04 (m, 3H), 1.70 (ddd, *J* = 13.2, 9.9, 7.2 Hz, 1H), 1.30 – 1.20 (m, 1H), 1.04 (s, 3H), 1.01 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 139.2, 100.9, 96.8, 67.5, 56.9, 55.7, 34.5, 31.2, 28.2, 27.6, 27.1.

FTIR (NaCl, thin film, cm^{-1}): 2923, 2878, 1629, 1460, 1387, 1317, 1250, 1210, 1150, 1111, 1071, 1039, 962, 917.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{11}H_{19}IO_2$ $[M–H]^+$: 309.0352; found: 309.0362.



A 2-dram vial was charged with amido alcohol **599** (8 mg, 0.358 mmol, 1 equiv) and dissolved in wet acetonitrile (700 µL). To this solution was added Stahl solution (9 µL, containing 0.2M bpy, 0.04M ABNO, and 0.4M NMI in MeCN) followed by $[Cu(MeCN)_4]OTf$ (0.7 mg, 0.0018 mmol, 0.05 mol %). The solution was allowed to stir open to air for 30 minutes. The reaction mixture was diluted with water (1 mL) and EtOAc (1 mL). The aqueous layer was extracted with EtOAc (3 x 1 mL), and the combined organics were washed with brine (3 mL), with saturated $NH_4Cl_{(aq)}$ (3 mL), and brine (3 mL). The organic layer was filtered over a plug of Na_2SO_4, and the volatiles were removed in vacuo to provide **600** (4.5 mg, 72% yield).

R_f = 0.68 (silica gel, 20% MeOH/CH_2Cl_2, I_2 and p-anisaldehyde).

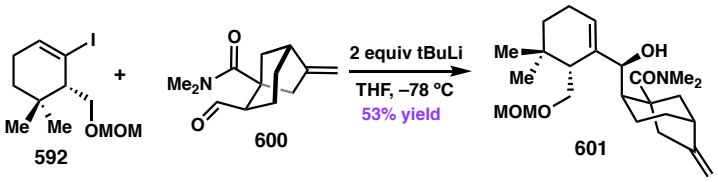
$[\alpha]_D^{22}$ = –14.7° (c = 0.42, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.69 (d, *J* = 1.0 Hz, 1H), 4.94 – 4.89 (m, 1H), 4.89 – 4.85 (m, 1H), 3.06 (d, *J* = 6.0 Hz, 7H), 2.84 – 2.70 (m, 2H), 2.70 – 2.59 (m, 2H), 2.13 (dtd, *J* = 12.0, 5.9, 3.1 Hz, 2H), 1.79 – 1.64 (m, 2H), 1.64 – 1.42 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 203.4, 174.4, 152.8, 105.8, 53.1, 51.6, 41.7, 41.2, 39.8, 37.8, 30.3, 19.0.

FTIR (NaCl, thin film, cm^{-1}): 3480, 3421, 3239, 2938, 2210, 1714, 1618, 1412, 1045, 970, 878, 786, 660.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{13}H_{19}NO_2$ $[M+H]^+$: 222.1475; found: 222.1473.

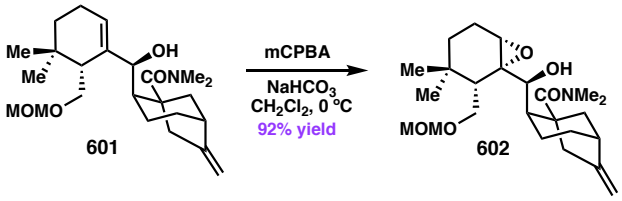


Allylic alcohol **601** was prepared according to general procedure 1, using **592** (22 mg, 0.10 mmol, 1 equiv) and **600** (31 mg, 0.10 mmol, 1 equiv). The crude residue was purified using silica gel (30% EtOAc/hexanes → 50% EtOAc/hexanes) to provide **601** (21.3 mg, 53% yield). Slow evaporation from hexanes enabled the preparation of crystals of quality that could be used for single crystal X-ray diffraction to establish connectivity (but not for publication).

$\mathbf{R}_f$ = 0.29 (silica gel, 50% EtOAc/Hex, p-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90 – 5.73 (m, 1H), 4.85 (tt, *J* = 2.5, 1.0 Hz, 1H), 4.79 (d, *J* = 1.8 Hz, 1H), 4.53 (d, *J* = 1.1 Hz, 2H), 4.24 (dt, *J* = 3.3, 1.6 Hz, 1H), 3.50 (dd, *J* = 10.2, 5.7 Hz, 1H), 3.38 – 3.28 (m, 4H), 3.08 (s, 3H), 2.93 (s, 3H), 2.63 (m, 3H), 2.59 – 2.50 (m, 1H), 2.10 – 1.99 (m, 2H), 1.89 – 1.77 (m, 4H), 1.76 (d, *J* = 5.8 Hz, 1H), 1.58 – 1.45 (m, 2H), 1.28 – 1.12 (m, 2H), 0.97 (s, 3H), 0.80 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 176.4, 155.0, 141.0, 121.0, 104.3, 96.9, 73.4, 69.5, 55.7, 55.3, 46.6, 42.5, 37.9, 31.9, 31.7, 31.2, 28.5, 26.8, 22.6, 17.1.



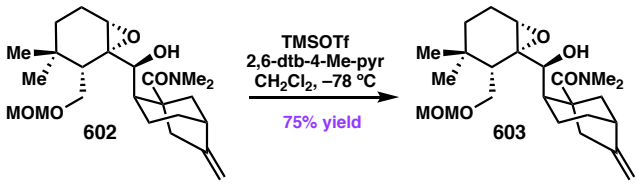
A 25 mL round-bottom flask was charged with allylic alcohol **601** (140 mg, 0.345 mmol, 1 equiv), $NaHCO_3$ (64 mg, 0.759 mmol, 2.2 equiv), and CH_2Cl_2 (6.8 mL) then cooled to 0 ºC. To the reaction mixture was added mCPBA (200 mg, 1.16 mmol, 1.2 equiv, 99% mCPBA) in one portion. The reaction was allowed to stir at 0 ºC for 15 minutes, at which point TLC indicated that the starting material had been consumed. The reaction was quenched with saturated $Na_2S_2O_{3\ (aq)}$ (15 mL). The biphasic mixture was diluted with water (5 mL) and CH_2Cl_2 (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), and the combined organics were washed with saturated $Na_2S_2O_{3\ (aq)}$ (30 mL), saturated $NaHCO_{3\ (aq)}$ (30 mL), and brine (30 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (20% EtOAc/hexanes → 60% EtOAc/hexanes) to give **602** (252 mg, 90% yield) as a colorless solid.

R_f = 0.57 (silica gel, 80% EtOAc/Hex, p-anisaldehyde).

^{1}H NMR (400 MHz, DMSO-d_6): δ 4.81 (s, 1H), 4.79 – 4.73 (m, 1H), 4.54 – 4.43 (m, 2H), 4.23 – 4.12 (m, 1H), 3.65 (d, J = 3.3 Hz, 1H), 3.35 (s, 2H), 3.24 (s, 3H), 3.21 (s, 1H), 3.04 (s, 3H), 2.79 (s, 3H), 2.71 (d, J = 17.3 Hz, 1H), 2.45 (d, J = 2.5 Hz, 1H), 2.41 (d, J = 2.6 Hz, 1H), 2.18 (s, 1H), 2.14 (d, J = 6.5 Hz, 1H), 1.91 (tq, J = 6.2, 3.8, 3.1 Hz, 1H), 1.81 (dd,

J = 15.4, 5.6 Hz, 1H), 1.78 – 1.66 (m, 1H), 1.58 (tt, *J* = 12.9, 6.0 Hz, 3H), 1.50 (d, *J* = 5.3 Hz, 2H), 1.33 – 1.25 (m, 2H), 0.83 (s, 6H).

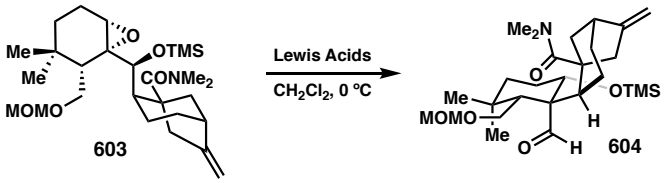
HRMS (ESI-TOF, *m/z*): calc'd for $C_{24}H_{43}N_2O_5$ $[M+NH_4]^+$: 439.3166; found: 439.3185.



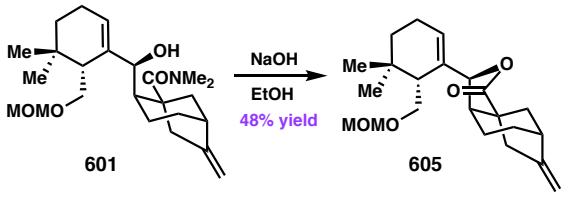
Epoxide **603** was prepared according to general procedure 2, using **602** (90 mg, 0.213 mmol) as the substrate. The mixture was purified using silica gel (10% EtOAc/Hexanes → 30% EtOAc/hexanes) to provide **603** (79.1 mg, 75% yield).

General Procedure 4: Lewis acid Screen

An oven-dried 1-dram vial was pumped into the glove box and charged with a Lewis acid (3 equiv). The vial was sealed and removed from the glovebox, then CH_2Cl_2 (100 µL) was added. The vial was cooled to 0 ºC and **603** (0.01 mmol) was added as a solution in CH_2Cl_2 (100 µL). After two hours, the mixture was filtered over a pad of silica gel eluting with 20% EtOAc/Hexanes (10 mL). The volatiles were removed *in vacuo* and analyzed by TLC and NMR.



Entry	Scale	Lewis Acid	LA equiv	result
1	5 mg	$TiCl_4$	3	Decomp at 0 °C
2	5 mg	$SnCl_4$	3	Decomp at 0 °C
3	5 mg	$AlMe_3$	3	SM
4	5 mg	$Yb(OTf)_3$	3	SM
5	5 mg	HBF_4OEt_2	3	Decomp at 0 °C
6	5 mg	Et_3OBF_4	3	SM
7	5 mg	$MgBr_2$	3	SM
8	5 mg	$TiCl(OiPr)_3$	3	SM
9	5 mg	Et_2AlCl	3	SM
10	5 mg	$Zn(OTf)_2$	3	SM
11	5 mg	$BF_3{\cdot}OEt_2$	3	Decomp at 0 °C
12	5 mg	$Sc(OTf)_3$	3	Decomp at 0 °C

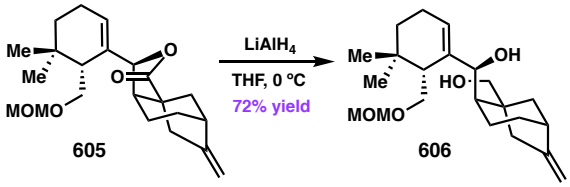


A 2-dram vial was charged with alcohol **601** (25 mg, 0.0616 mmol, 1 equiv) and then NaOH (37 mg, 0.925 mmol, 15 equiv). EtOH (600 μL) was then added and the vial was sealed with a Teflon cap. The mixture was heated to 130 ºC and stirred for 10 minutes. The vial was removed from the heating block and cooled to room temperature. 1M HCl was added (1.2 mL) and the reaction stirred for 1 hour. The mixture was then diluted with water (1 mL) and extracted with EtOAc (5 x 2 mL). The combined organics were filtered over a SiO_2 plug and the volatiles removed *in vacuo*. The crude residue was

purified by column chromatography using silica gel (5% EtOAc/hexanes → 25% EtOAc/hexanes) to give **605** (10.7 mg, 48% yield) as a colorless solid.

$\mathbf{R_f}$ = 0.69 (silica gel, 80% EtOAc/Hex, p-anisaldehyde).

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.79 – 5.71 (m, 1H), 5.26 (d, *J* = 9.6 Hz, 1H), 5.00 (q, *J* = 3.6, 2.4 Hz, 1H), 4.83 (s, 1H), 4.63 – 4.52 (m, 2H), 3.67 (dd, *J* = 10.4, 4.4 Hz, 1H), 3.52 – 3.43 (m, 1H), 3.36 (s, 3H), 2.80 (dt, *J* = 16.1, 2.9 Hz, 1H), 2.73 (dd, *J* = 9.1, 4.5 Hz, 1H), 2.51 (td, *J* = 10.6, 7.4 Hz, 1H), 2.28 (d, *J* = 14.0 Hz, 1H), 2.18 – 2.01 (m, 2H), 1.79 (d, *J* = 5.0 Hz, 1H), 1.73 (dd, *J* = 11.2, 2.6 Hz, 1H), 1.68 (dd, *J* = 11.2, 4.6 Hz, 1H), 1.49 (dddt, *J* = 13.5, 9.5, 6.3, 3.3 Hz, 3H), 1.39 – 1.30 (m, 1H), 1.21 (t, *J* = 7.0 Hz, 1H), 0.99 (s, 3H), 0.95 (s, 3H), 0.91 – 0.85 (m, 1H).



A 2-dram vial was charged directly with lactone **605** (10 mg, 0.027 mmol, 1 equiv). The vial was evacuated and backfilled with N_2 3 times. THF (270 µL) was added to the vial, then the reaction mixture was cooled to 0 ºC. A solution of $LiAlH_4$ (110 µL, 0.11 mmol, 1M in THF, 4 equiv) was then added to the vial, and the reaction was allowed to stir for 20 minutes at this temperature. The reaction was quenched with 1M HCl (500 µL). The aqueous layer was extracted with EtOAc (3 x 1 mL) and the combined organics were filtered over a plug of Na_2SO_4. The volatiles were removed *in vacuo*, and the crude residue

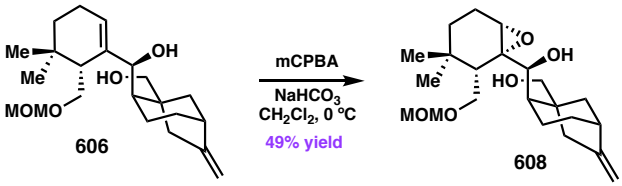
was purified by column chromatography using silica gel (20% EtOAc/hexanes → 30% EtOAc/hexanes) to give **606** (7.3 mg, 72% yield) as a colorless oil.

R_f = 0.29 (silica gel, 30% EtOAc/Hex, p-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.78 (td, *J* = 3.7, 1.4 Hz, 1H), 4.83 (ddt, *J* = 3.1, 2.3, 1.1 Hz, 1H), 4.78 (qd, *J* = 1.9, 1.0 Hz, 1H), 4.74 (s, 1H), 4.64 (d, *J* = 6.6 Hz, 1H), 4.59 (d, *J* = 6.6 Hz, 1H), 4.11 – 4.01 (m, 1H), 3.76 (dd, *J* = 9.9, 4.2 Hz, 1H), 3.41 (dd, *J* = 9.9, 5.8 Hz, 1H), 3.36 (s, 4H), 2.75 (t, *J* = 6.4 Hz, 1H), 2.67 (d, *J* = 4.9 Hz, 1H), 2.43 (dq, *J* = 17.0, 2.3 Hz, 1H), 2.28 (dt, *J* = 17.0, 2.7 Hz, 1H), 2.08 (ddd, *J* = 17.2, 8.7, 5.7 Hz, 3H), 1.88 – 1.75 (m, 3H), 1.60 (q, *J* = 5.9 Hz, 3H), 1.52 – 1.35 (m, 3H), 0.99 (s, 3H), 0.84 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.3, 142.8, 119.8, 103.5, 96.5, 72.7, 70.9, 69.4, 55.7, 48.1, 45.7, 45.0, 43.3, 39.4, 36.2, 33.5, 31.9, 31.5, 28.4, 26.7, 22.8, 16.9.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{22}H_{36}NaO_4$ $[M+Na]^+$: 387.2506; found: 387.2524



A 2-dram vial was charged with allylic alcohol **606** (10 mg, 0.0275 mmol, 1 equiv), $NaHCO_3$ (5 mg, 0.0604 mmol, 2.2 equiv), and CH_2Cl_2 (275 µL) then cooled to 0 ºC. To the reaction mixture was added mCPBA (5.2 mg, 0.0302 mmol, 1.1 equiv, 99% mCPBA) in one portion. The reaction was allowed to stir at 0 ºC for 30 minutes, at which point TLC indicated that the starting material had been consumed. The reaction was quenched with

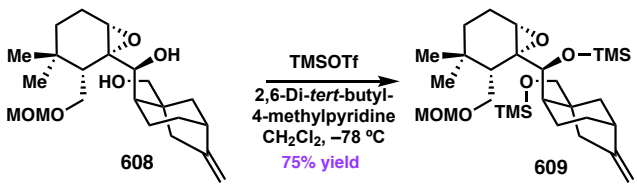
saturated $Na_2S_2O_{3\ (aq)}$ (1 mL). The biphasic mixture was diluted with water (1 mL) and CH_2Cl_2 (1 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 1 mL), and the combined organics were washed with saturated $Na_2S_2O_{3\ (aq)}$ (3 mL), saturated $NaHCO_{3\ (aq)}$ (3 mL), and brine (3 mL). The organic layer was filtered over a Na_2SO_4 plug and concentrated *in vacuo*. The crude residue was purified by column chromatography using silica gel (20% EtOAc/hexanes → 50% EtOAc/hexanes) to give **608** (5.1 mg, 49% yield) as a colorless solid.

R_f = 0.62 (silica gel, 50% EtOAc/Hex, p-anisaldehyde).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.83 (tt, *J* = 3.0, 2.3, 1.0 Hz, 1H), 4.78 (d, *J* = 2.1 Hz, 1H), 4.66 (d, *J* = 6.5 Hz, 1H), 4.61 (d, *J* = 6.5 Hz, 1H), 4.36 (s, 1H), 4.02 (d, *J* = 11.6 Hz, 1H), 3.68 – 3.61 (m, 2H), 3.56 (d, *J* = 2.1 Hz, 1H), 3.38 (s, 3H), 3.35 (d, *J* = 11.6 Hz, 1H), 2.64 (q, *J* = 4.1 Hz, 1H), 2.44 (dq, *J* = 17.1, 2.4 Hz, 1H), 2.34 – 2.23 (m, 1H), 2.13 (s, 1H), 2.09 – 1.94 (m, 4H), 1.92 – 1.79 (m, 1H), 1.65 – 1.54 (m, 2H), 0.88 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.3, 103.5, 96.7, 70.0, 69.3, 67.1, 64.1, 55.8, 55.6, 48.1, 44.6, 43.3, 42.1, 37.6, 35.8, 33.1, 30.4, 29.9, 28.9, 27.7, 27.7, 21.3, 19.2.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{22}H_{40}NO_5$ $[M+H]^+$: 398.2901; found: 398.2896.



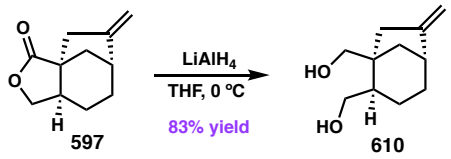
Epoxide **609** was prepared according to general procedure 2, using **608** (10 mg, 0.026 mmol) as the substrate. The mixture was purified using silica gel (2% Et_2O/hexanes → 10% Et_2O/hexanes) to provide **609** (10.3 mg, 75% yield).

R_f = 0.71 (silica gel, 20% EtOAc/Hex, p-anisaldehyde).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.80 (s, 1H), 4.75 (s, 1H), 4.66 – 4.56 (m, 2H), 4.38 (s, 1H), 3.83 (d, *J* = 10.1 Hz, 1H), 3.59 – 3.50 (m, 2H), 3.37 (s, 3H), 3.30 (d, *J* = 2.7 Hz, 2H), 2.62 (s, 1H), 2.27 – 2.19 (m, 2H), 2.06 – 1.97 (m, 2H), 1.95 – 1.87 (m, 2H), 1.84 (dd, *J* = 10.5, 2.0 Hz, 1H), 1.76 (tdd, *J* = 15.0, 6.1, 2.1 Hz, 1H), 1.62 – 1.55 (m, 2H), 1.50 (tt, *J* = 13.4, 6.5 Hz, 1H), 1.43 – 1.31 (m, 2H), 1.12 (dd, *J* = 10.9, 5.3 Hz, 1H), 0.84 (d, *J* = 5.2 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.7, 102.9, 97.0, 71.5, 68.4, 67.3, 63.1, 55.4, 52.9, 47.9, 44.5, 43.9, 41.4, 38.6, 34.6, 33.0, 30.5, 30.3, 29.9, 28.5, 28.2, 27.2, 21.4, 19.4, 1.2, –0.4.

HRMS (ESI-TOF, *m/z*): calc'd for $C_{28}H_{52}O_5Si_2$ $[M+H]^+$: 525.3426; found: 525.3402.



A 25 mL round-bottom flask was charged directly with lactone **597** (100 mg, 0.561 mmol, 1 equiv). The flask was evacuated and backfilled with N_2 3 times. THF (5.6 mL) was added to the flask, then the reaction mixture was cooled to 0 ºC. A solution of $LiAlH_4$ (2.25 mL, 2.24 mmol, 1M in THF, 4 equiv) was then added to the flask, and the reaction

was allowed to stir for 20 minutes at this temperature. The reaction was quenched with 1M HCl (2 mL). The aqueous layer was extracted with EtOAc (3 x 5 mL) and the combined organics were filtered over a plug of Na_2SO_4. The volatiles were removed *in vacuo* to give **610** (85.1 mg, 83% yield) as a colorless oil.

$\mathbf{R_f}$ = 0.12 (silica gel, 50% EtOAc/Hex, p-anisaldehyde).

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.85 (ddt, *J* = 3.2, 2.2, 1.0 Hz, 1H), 4.80 (d, *J* = 2.2 Hz, 1H), 4.00 (dd, *J* = 10.9, 8.5 Hz, 1H), 3.68 (d, *J* = 11.3 Hz, 1H), 3.58 (dd, *J* = 10.9, 4.2 Hz, 1H), 3.52 (d, *J* = 11.3 Hz, 1H), 2.75 (s, 1H), 2.66 (d, *J* = 5.3 Hz, 1H), 2.44 (s, 1H), 2.37 (dt, *J* = 17.1, 2.4 Hz, 1H), 2.16 (dt, *J* = 16.9, 2.7 Hz, 1H), 1.92 – 1.75 (m, 3H), 1.65 – 1.51 (m, 2H), 1.35 – 1.27 (m, 2H).

5.6 NOTES AND REFERENCES

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