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A Failed Late-Stage Epimerization Thwarts an Approach to Ineleganolide

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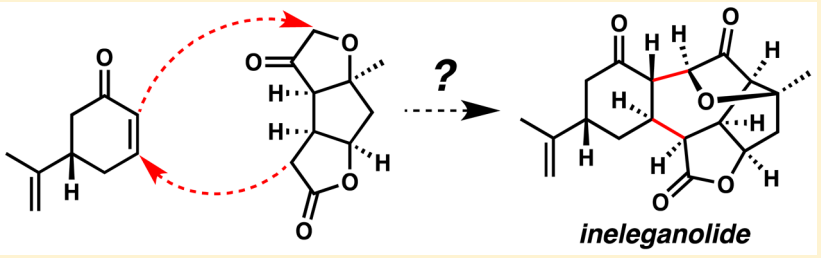
Supporting Information



ABSTRACT: Significant efforts were made to complete a synthesis of the complex norcembranoid ineleganolide via a seemingly attractive strategy involving late-stage creation of the central seven-membered ring. While the two key enantioenriched building blocks were made via high-yielding sequences and their convergent union was efficient, the critical C4−C5 bond of this sterically congested natural product could never be forged. Several interesting examples of unexpected acid−base behavior and unanticipated proximity-induced reactivity accounted for most of the problems in the execution of the synthesis plan.

I. INTRODUCTION

The complex norcembranoid ineleganolide (**1**, Figure 1) was isolated in 1999 by Duh and co-workers from the soft coral

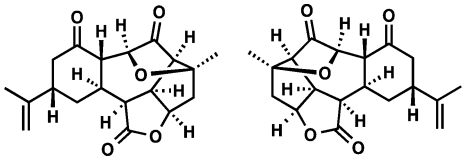


Figure 1. Structure of ineleganolide. Originally depicted enantiomer shown on left; likely natural enantiomer shown on right.

species *Sinularia inelegans*.[1] The fascinating structure of ineleganolide was determined by spectroscopic methods and confirmed by X-ray crystallography.[2] Preliminary biological screening of ineleganolide revealed moderate activity against P-388 murine leukemia cells; however, further testing was precluded by its scarce availability from natural sources. This promising biological activity, along with ineleganolide's intriguing molecular architecture, prompted our work toward a synthesis of **1**. A concise synthesis would provide sufficient quantities of ineleganolide for further biological evaluation, and its complex polycyclic framework should provide inspiration for the development of interesting strategies for synthesis.

The norcembranoid natural products are biogenetically related to the cembranoids by the excision of a single carbon from the cembrene C_{20} skeleton.[3] This family of norditerpenes is composed of a wide range of oxidized butenolide macrocycles, typified by sinuleptolide (**2**)[4] and 5-episinuleptolide (**3**),[5] as well as a number of complex polycyclic norcembranoids[6] including scabrolides A and B (**4** and **5**),[7] horiolide (**6**),[8] sinulochmodin C (**7**),[9] and dissectolide (**8**)[10] (Figure 2). These polycyclic norcembranoids are thought to arise from rearrangements and transannular reactions of macrocyclic precursors.[6] For example, the biogenesis of ineleganolide was proposed by Pattenden to arise from the macrocyclic norcembranoid 5-episinuleptolide (**3**) (Scheme 1). A 6-*exo*-*trig* cyclization of **3** to join the C4 and C13 carbons provides the hypothetical norcembranoid **9**. Dehydration of **9** to butenolide **10** followed by a transannular Michael reaction to form the C7−C11 bond delivers ineleganolide.

The Pattenden group further probed the biogenetic relationships of the norcembranoids from *Sinularia* via a semisynthesis of ineleganolide and sinulochmodin C.[11] Treating a small sample (ca. 10 mg) of 5-*epi*-sinuleptolide (**3**) obtained from a specimen of *Sinularia scabra* first with pyridine and acetic anhydride to acetylate the C11 hydroxyl and then with KHMDS provided ineleganolide, albeit in low yield. The ease of this transformation under nonenzymatic conditions supports the proposed biosynthesis of ineleganolide shown in Scheme 1.

II. SYNTHESIS DESIGN

Drawn to the challenging molecular architecture of **1**, as well as the potential to supply significant quantities for further biological evaluation, we developed a strategy for the total synthesis of ineleganolide. The importance of a concise route to ineleganolide was further emphasized by the intriguing

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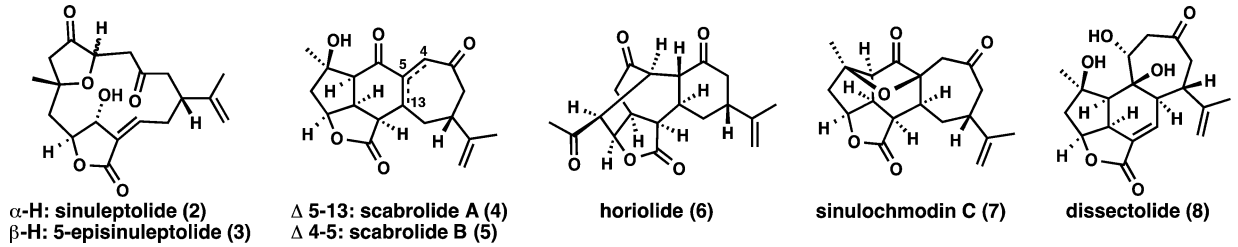
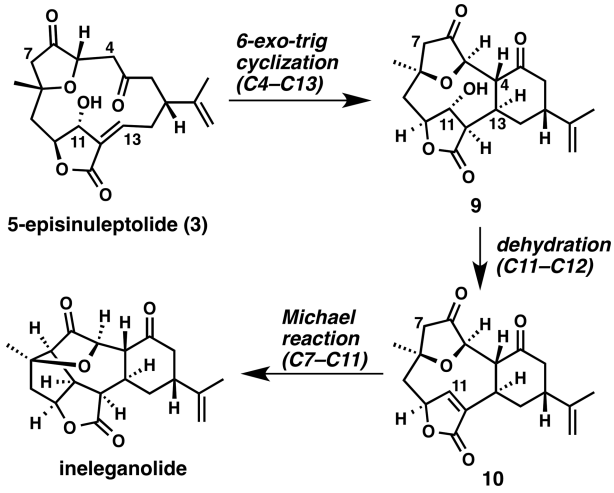


Figure 2. Examples of norcembranoids isolated from soft corals of the genus *Sinularia*.

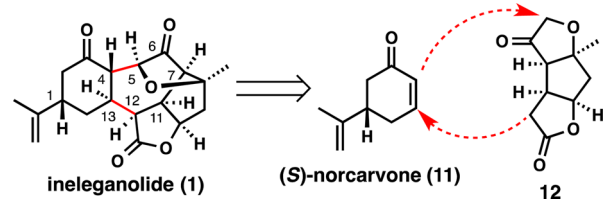
Scheme 1. Proposed Biosynthesis of Ineleganolide and Sinulariadiolide from 5-Episinuleptolide



possibility of using **1** to access other norcembranoids via biogenetic interrelationships similar to those shown in Scheme 1. While, in the midst of our synthetic studies, the Pattenden group demonstrated that ineleganolide can be accessed via semisynthesis, the scarcity of 5-episinuleptolide (**3**) limits the utility of this strategy to supply substantial quantities of **1**, unless an efficient synthesis of **3** can be developed. To date, no total synthesis of ineleganolide has been reported, although work toward this target has been undertaken by a number of groups.[12]

Our general strategy for the synthesis of ineleganolide is shown in Scheme 2. By retrosynthetic analysis, disconnection of

Scheme 2. General Strategy for the Synthesis of Ineleganolide



the C4−C5 and C12−C13 bonds of **1** breaks the central seven-membered ring of ineleganolide and reveals simpler fragments (*S*)-norcarvone (**11**) and tricycle **12**. (*S*)-Norcarvone is a known compound that has previously been prepared in seven steps from inexpensive carvone.[13] The tricyclic framework of **12** would be formed through a radical bicyclization reaction.[14]

Three key steps for the synthesis of ineleganolide are shown in Scheme 3. First, a Mukaiyama−Michael addition of silyl ketene acetal **13**, which bears a latent C5 oxocarbenium ion, onto norcarvone (**11**) will generate the key C12−C13 bond while also rendering C4 nucleophilic as enoxysilane **14**. This conjugate addition should proceed with high stereoselectivity at C13 owing to preferred axial attack of the nucleophilic silyl ketene acetal on the lowest energy conformer of the enone. However, the undesired C12 configuration is anticipated as a consequence of convex-face addition of the bowl-shaped tricycle to norcarvone. In order to correct the C12 stereochemistry, epimerization by enolization of lactone **14** followed by a kinetic, convex-face protonation would lead to lactone **15**. The epimer **15** is restricted to a conformation where C4 and C5 are held in close proximity. At this point, revealing the latent oxocarbenium **16** would render C5 electrophilic and elicit coupling with the nucleophilic enoxysilane at C4. Owing to the restricted conformation of **16**, C4−C5 bond formation should proceed with complete diastereoselectivity and directly provide ineleganolide.

This general strategy requires the selective formation of an oxocarbenium ion at C5 in **16**. There were two primary considerations in evaluating methods to generate this reactive intermediate. First, the method must be tolerant of the other reactive functional groups in the molecule. Second, the oxocarbenium ion precursor must be compatible with the conditions required for the Mukaiyama−Michael reaction and the subsequent stereochemical correction. In light of these considerations, it was proposed that the requisite oxocarbenium ion might be generated via the fragmentation of an appropriate enol ether derivative. We reasoned that an enol triflate or phosphate should be relatively stable, but under appropriate conditions, expulsion of a triflinate or phosphinate anion would result in the formation of the oxocarbenium ion **16**.

A number of examples of this type of *β*-heteroatom-substituted vinyl triflate fragmentation have been reported.[15] Initially, this reactivity had been observed as an unexpected side reaction when attempting palladium-catalyzed cross-coupling reactions with vinyl triflates derived from ketones bearing *α*-nitrogen or oxygen heteroatoms (eqs 1 and 2, respectively). Under the required thermal conditions for cross-coupling, the desired product was not observed, and instead, products resulting from oxocarbenium ion trapping (**18**)[15a,b] or elimination (**20**)[15c] were isolated. The reactivity of these substituted vinyl triflates was further expanded on by the Overman group; subjecting *β*-sulfur substituted vinyl triflates such as **21** to heating in DMSO with 2,6-lutidine furnished *α*-sulfenyl enones **22** (eq 3).[15d]

Given the precedent for fragmentation of *β*-heteroatom substituted vinyl triflates, such a functional group arrangement appeared to be suitable oxocarbenium ion precursor to incorporate in the synthesis of ineleganolide (Scheme 4). The alkoxy vinyl triflate should be stable to both the Mukaiyama−Michael reaction as well as the basic conditions

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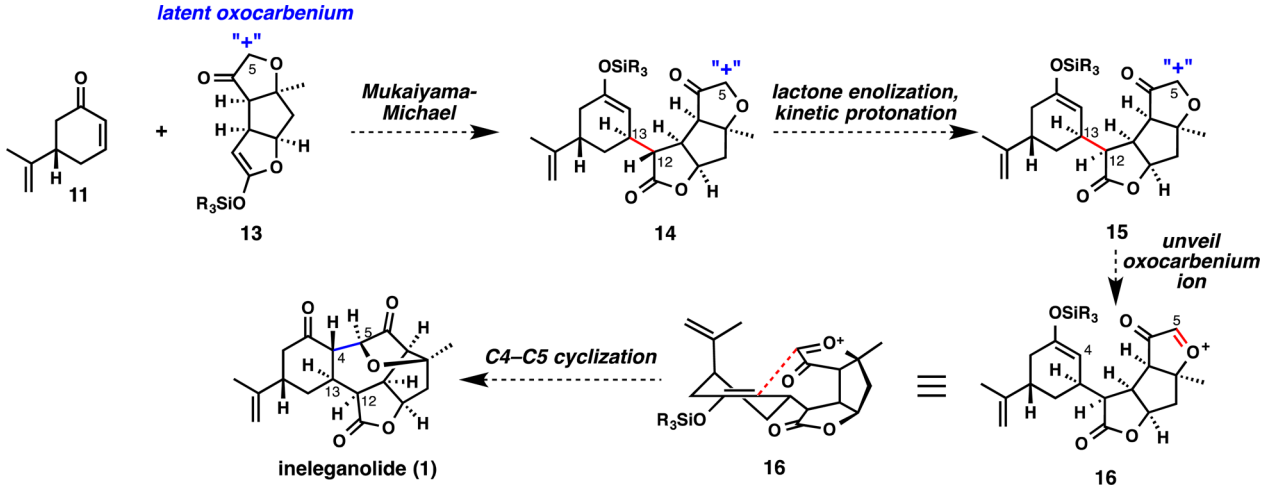
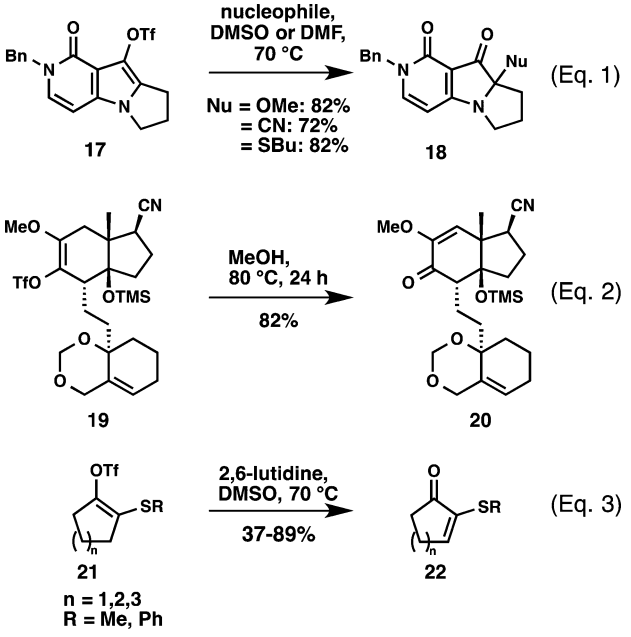
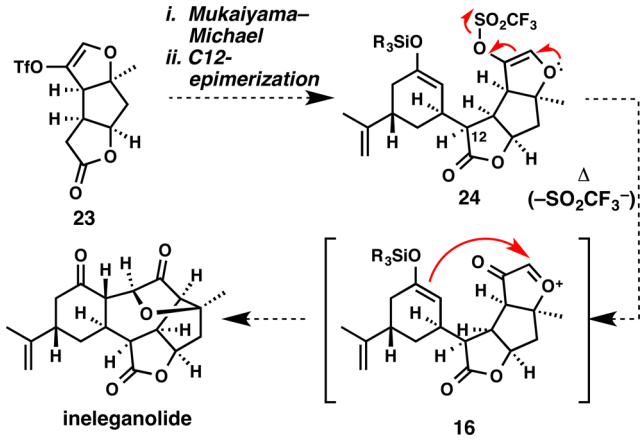
Scheme 3. Three Strategic Steps to Ineleganolide: Mukaiyama−Michael Reaction, C12 Epimerization, and C4−C5 Cyclization





Scheme 4. Proposed Implementation of Triflate Fragmentation in Our Synthesis of Ineleganolide



needed to effect lactone enolization/C12 epimerization. Using this strategy, tricycle **23** would be coupled with norcarvone (**11**) in a Mukaiyama−Michael reaction followed by C12 epimerization to afford cyclization precursor **24**. Heating **24** would fragment the vinyl triflate to reveal oxocarbenium ion intermediate **16**, which should undergo spontaneous cyclization with the C4 enoxysilane moiety to give ineleganolide. A key feature of this strategy is the selective masking of the two ketones in the Mukaiyama−Michael product, such that the lactone could be selectively enolized in the enolization/kinetic protonation sequence needed for C12 epimerization.

III. RESULTS AND DISCUSSION

A. Synthesis of Tricycle 23. Our synthesis of **23** began with hydroxycyclopentenone **25** (Scheme 5).[16] Although optically active **25** can be accessed via a number of methods, for exploratory purposes, we began our studies using racemic **25**, which is readily available via the Piancatelli reaction of furfuryl alcohol.[17] Protection of **25** as the *tert*-butyldimethylsilyl (TBS) ether **26** followed by a highly diastereoselective 1,2-addition of methyllithium yielded tertiary alcohol **27**[18] in 91% yield. Treatment of alcohol **27** with sodium hydride followed by propargyl bromide provided alkyne **28** in 97% yield. Silyl ether cleavage of **28** with tetra-*N*-butylammonium fluoride (TBAF), followed by treatment of the resultant alcohol **29** with ethyl vinyl ether and *N*-bromosuccinimide (NBS), furnished bromide **30** as a 1:1 mix of acetal epimers. With **30** in hand, we were set to attempt the key radical bicyclization to tricycle **31**. To our delight, we found that treatment of bromide **30** with tributyltin hydride and a catalytic amount of 2,2′-azobis(isobutyronitrile) (AIBN) gave tricycle **31** as the major product. Ozonolysis of **31** provided ketones **32** and **33**, and although these acetal epimers were easily separated by chromatography, treatment of the mixture of **32** and **33** with a catalytic amount of toluenesulfonic acid (TsOH) in ethanol resulted in epimerization of **32** to acetal **33** in high yield. Acetal epimer **32** was crystalline, and we were able to obtain an X-ray crystal structure, which confirmed both its identity and the relative stereochemistry of the acetal carbon (see the Supporting Information).

With access to ketone **33**, all that was needed to complete the synthesis of tricycle **23** was vinyl triflate formation and oxidation of the acetal to the lactone. Subjection of ketone **33** to thermodynamic enolization conditions (<1 equiv of KHMDS in THF) followed by trapping of the resulting enolate with $PhNTf_2$ delivered the desired regioisomer of vinyl triflate **34** almost exclusively. It is notable that triflate **34** arises from

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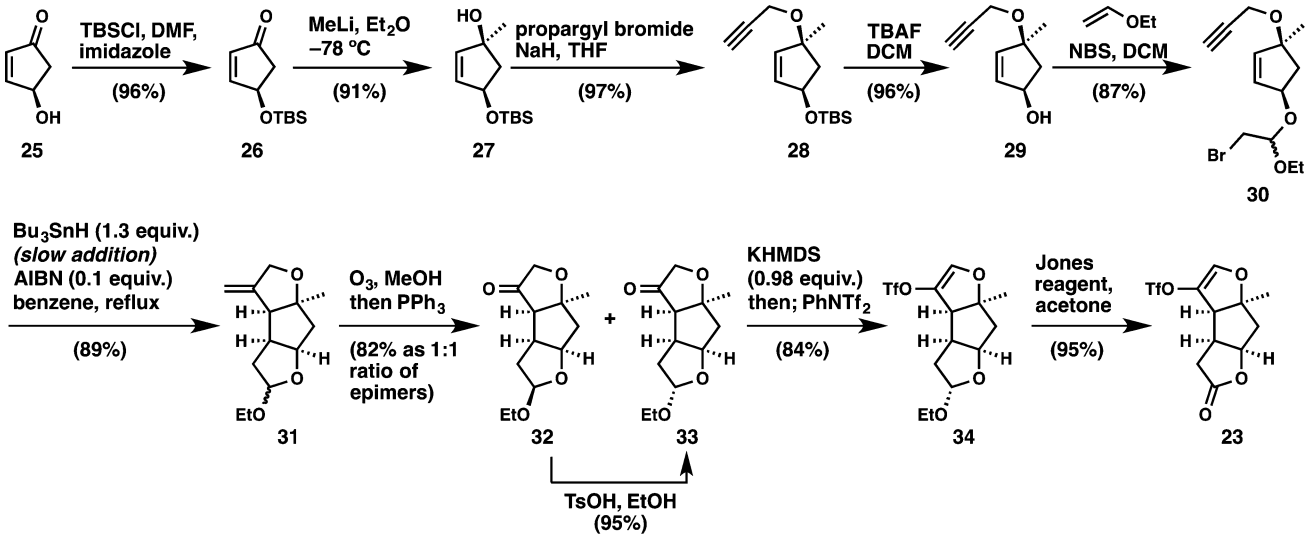
Scheme 5. Synthesis of Tricyclic Vinyl Triflate 35

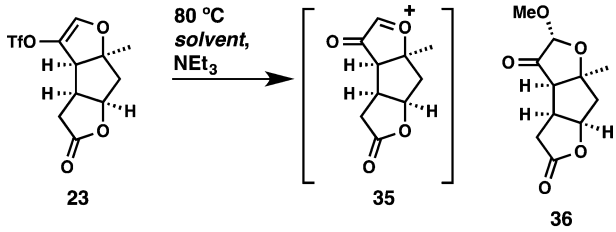


trapping of the less substituted enolate of ketone **33**, while typically thermodynamic enolization conditions provide the more substituted enolate. We propose that the strain present in the more substituted enolate of **33** (not shown) accounts for the high selectivity of **34** under thermodynamically controlled enolization conditions. Interestingly, the use of conditions for kinetic enolate generation led predominantly to the undesired, more substituted vinyl triflate isomer, likely owing to the particularly good orbital overlap of the C−H bond with the carbonyl. A similar apparent "reversal" of selectivity of this type was observed by the Shea group in studies toward the synthesis of taxanes.[19] Treatment of **34** with the Jones reagent provided lactone **23**, the desired coupling partner for the Mukaiyama−Michael reaction.

After considerable optimization, the synthesis of tricycle **23** could be accomplished in up to 42% yield over nine steps from known enone **26**, and using this sequence, multiple grams of **23** could be prepared. Moreover, starting from enantioenriched **26**,[20] we could use the same route to access enantioenriched tricycle **23**. The high efficiency of this sequence was welcome because access to sufficient quantities of **23** was critical to evaluate the endgame steps of our synthesis, including the Mukaiyama−Michael reaction, C12 epimerization, and C4−C5 cyclization (Scheme 4).

Before continuing, we sought to evaluate the feasibility of the proposed thermal triflate fragmentation shown in Scheme 4 using lactone **23** to ensure that the well-precedented fragmentation reactivity could be realized in systems relevant to our efforts (Scheme 6). Heating **23** with NEt_3 in various solvents led to rapid reaction; in most cases, the substrate was no longer observed by TLC after only 15 min. Most of these reactions resulted in complex mixtures of decomposition products with poor mass recovery; however, when the reaction was conducted in MeOH or DMSO, products arising from the trapping of oxocarbenium ion intermediate **35** were observed. Heating lactone **23** in MeOH delivered acetal **36** in 60% yield, while heating **23** in DMSO provided 1,2-dicarbonyl **37**. Formation of the latter product can be attributed to interception of the oxocarbenium ion with DMSO followed by a Kornblum-like oxidation.[21] These initial experiments demonstrated the ease of triflate fragmentation under mild thermal conditions and were

Scheme 6. Investigations into the Triflate Thermal Fragmentation of Tricyclic Enol Triflate



Solvent	temp.	time	result[i]
benzene	80 °C	15 min	decomp.
toluene	80 °C	15 min	decomp.
MeCN	60 °C	10 min	decomp
THF	60 °C	60 min	decomp + **30**
DMF	80 °C	10 min	decomp
MeOH	60 °C	15 min	**36** (60%)
DMSO	80 °C	30 min	**37**[ii]

i. all reaction run on 2 – 5 mg scale; *ii.* pdt observed in crude ^{1}H NMR spectra and by ESIMS but we were unable to isolate due to aqueous solubility

encouraging for implementation of our strategy shown in Scheme 4.

B. Convergent Coupling. With both lactone **23** and norcarvone (**11**)[22] accessible in optically active form, we next attempted the convergent coupling of the two fragments. Soft enolization of lactone **23** using 2,2,6,6-tetramethylpiperidine (TMP) and triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) afforded the silyl ketene acetal intermediate (not shown), which was treated with a catalytic amount of $La(OTf)_3$ and 2 equiv of (*S*)-norcarvone (**11**) to provide lactone **38** (Scheme 7).[23] These optimized conditions afforded the coupled product in up to 91% yield as a single diastereomer. As expected, the Mukaiyama−Michael reaction delivered lactone **38** with high diastereoselectivity at the C12 and C13 stereocenters (see above). While the stereochemistry at C13 matches that of the natural product, the configuration at C12 is epimeric to ineleganolide and requires inversion by the enolization/kinetic protonation sequence discussed earlier.

While synthetic strategies to access optically active forms of both coupling partners had been developed, the cost, time, and

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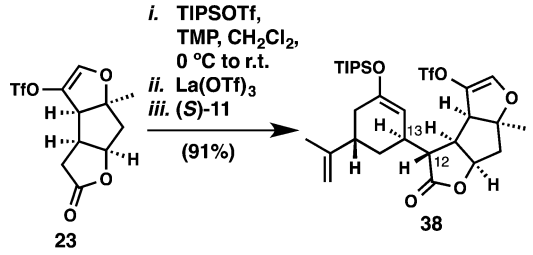
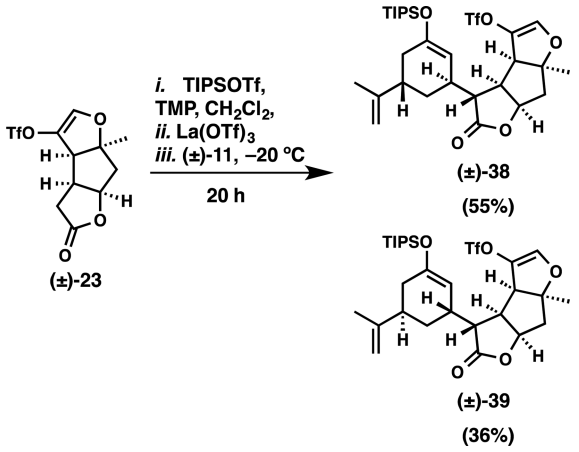
Scheme 7. Mukaiyama–Michael Addition of Lactone 23 to (*S*)-Norcarvone (11)



efficiency associated with accessing enantioenriched material (in particular, accessing enone (+)-**26**) prompted an investigation of the efficiency of a Mukaiyama–Michael reaction using racemic coupling partners. It was anticipated that the high level of *relative* diastereocontrol in the asymmetric coupling would be observed in the racemic coupling (i.e., a *trans* relationship on the cyclohexyl moiety and the attachment of the six-membered ring to the convex face of the tricycle). However, when these two fragments were coupled as racemates a 1:1 mixture of diastereomers was expected, arising from the reaction of (+)-**23** (or (−)-**23**) with both (+)-**11** and (−)-**11** to provide the desired lactone (±)-**38** along with the undesired diastereomeric lactone (±)-**39** (Scheme 8). Nonetheless, we reacted (±)-**23**

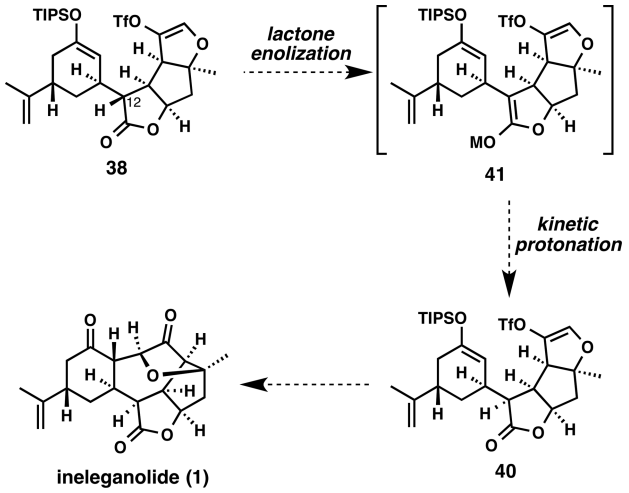
Scheme 8. Coupling of Lactone (±)-23 with (±)-Norcarvone (11)



with (±)-norcarvone under the previously optimized Mukaiyama–Michael conditions to provide a 55:45 diastereomeric ratio of lactones (±)-**38** and (±)-**39**. Lowering the reaction temperature to −20 °C, in an attempt to increase the selectivity, resulted in a 60:40 diastereomeric ratio and led to a 55% isolated yield of (±)-**38**. The modest diastereoselectivity in this coupling is a subtle example of double diastereodifferentiation,[24] but the overall efficiency of the convergent reaction permitted access to significant quantities of (±)-**38** for further studies. In the short term, this approach proved preferable to lengthier sequences involving the generation of enantiopure coupling partners.

C. C12 Epimerization Studies. With an efficient synthesis of lactone **38** developed, efforts toward the epimerization of the C12 stereocenter could be investigated. As discussed previously, we envisioned that enolization of lactone **38** followed by kinetic protonation would afford the tetracycle **40** with the desired configuration at the C12 stereocenter (Scheme 9).

Scheme 9. Proposed C12 Epimerization of 38 by Lactone Enolization/Kinetic Protonation



It was expected that protonation of enolate **41** would proceed via the convex face of the *cis,syn,cis* tricycle to provide lactone **40** because the top face of **41** is sterically shielded. This strategy presents a number of challenges. Enolization of lactone **38** requires deprotonation from the sterically encumbered concave face of the tricyclic system. Furthermore, inversion of the C12 stereocenter to lactone **40** situates the norcarvone and tricyclic groups in close proximity to each other, potentially engendering steric strain on the system. While steric interactions may make it difficult to form lactone **40**, the close proximity of these substituents would be advantageous during the final C4–C5 bond-forming step of the synthesis.

Lactone **38** was subjected to a number of strong bases in various solvents, followed by low temperature quenching with methanol (Scheme 10); however, C12 epimerization to **40** was not observed. Instead, hydrolysis of the vinyl triflate moiety led to ketone **42**. We suspected that nucleophilic methoxide formed upon quenching with methanol caused cleavage of the vinyl triflate. We reasoned that the conjugate base of a more acidic quenching agent should be less nucleophilic, thereby reducing triflate hydrolysis. By comparison, the reaction of lactone **38** and LDA with quenching by MeOH resulted in 60% conversion to ketone **42**, while quenching protocols employing either ammonium chloride or phenol resulted in survival of the triflate moiety, although no C12 epimerization was observed and only starting material recovered.

Having attenuated the decomposition of triflate **38** under basic conditions and identified an effective quenching protocol, an extensive evaluation of conditions to promote C12 epimerization by the proposed enolization/kinetic protonation sequence was undertaken. Despite an exhaustive screen of bases, solvents, additives, reaction times, and temperatures, reaction conditions to epimerize C12 to the desired tetracycle **40** were not identified. In almost all cases, the major product was either ketone **42** or unreacted starting material.

Treatment of lactone **38** with an excess of LDA in THF followed by the addition of deuterated phenol did not lead to deuterium incorporation at C12 (Scheme 11). This result suggests that enolization of the lactone did not occur under the reaction conditions. Surprisingly, these deuteration experiments indicated that deprotonation of the vinyl triflate at C5 lactone is more facile than C12 deprotonation. To further probe the competing acidity of the vinyl triflate moiety, enolization/deuterium

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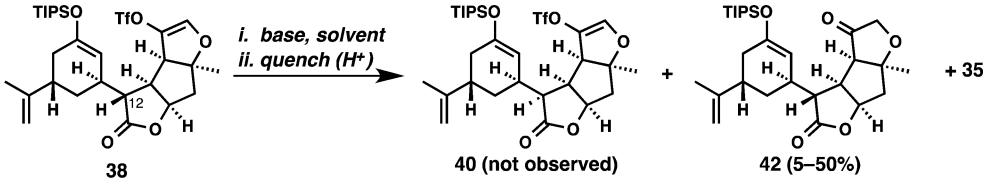
Scheme 10. Failed Attempts To Epimerize Lactone 38 via Enolization Using Strong Base



quench[i]	ratio of 38:42[ii]
MeOH	40:60
PhOH	99:1
NH_4Cl	99:1

[i] quenching after treatment with 2 equiv. LDA in THF at −70 °C
[ii] ratio determined by ^{1}H NMR

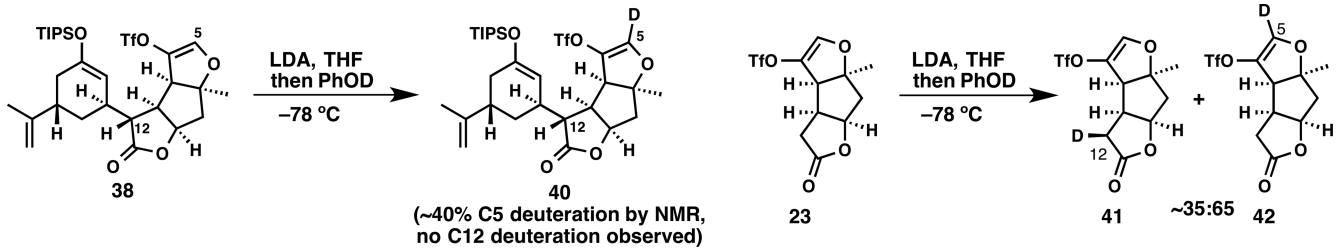
Representative enolization conditions:

Bases: LDA, KDA, Li·TMP, Li·pyrrolidide, NaH, KH, LiH, *n*-BuLi, *t*-BuLi, KO*t*-Bu

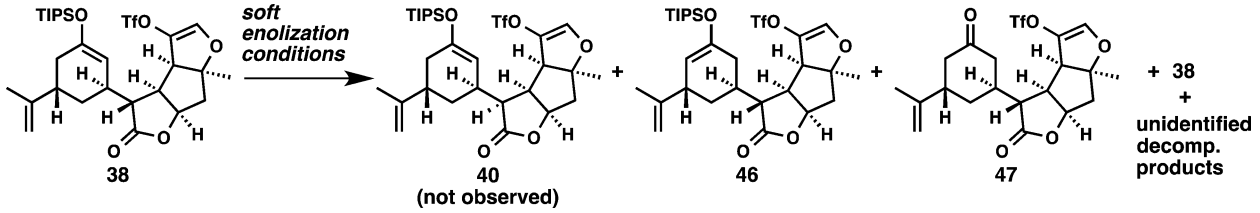
Solvents: THF, Et_2O, *t*-BuOMe, DME, diglyme, benzene, CH_2Cl_2, hexane

Additives: LiCl, LiI, DMPU, HMPA, TMEDA, crown ethers, DMSO

Scheme 11. Deuterium Quenching Experiment Reveals the Unexpected Acidity of the Vinyl Triflate



Scheme 12. Attempts To Epimerize Lactone 38 Using Soft Enolization/Kinetic Protonation



Representative soft enolization conditions:

Lewis acids: $TiCl_4$, $Ti(Oi\text{-}pr)_3$, $SnCl_4$, $Sn(OTf)_2$, $SiCl_4$, $BF_3{\cdot}OEt_2$, Bu_2BOTf, R_3SiX, $Sc(OTf)_3$, $La(OTf)_3$, $AlMe_2Cl$
Bases: NEt_3, $NHEt_2$, $EtNi\text{-}Pr_2$, $HNi\text{-}Pr_2$, pyrrolidine, DABCO, DBU, 1,1,3,3-tetramethylguanidine
Solvents: CH_2Cl_2, $CHCl_3$, Et_2O, toluene, benzene, hexane

quench studies using the simpler tricyclic lactone **23** were undertaken. Treating **23** with excess LDA in THF followed by quenching with PhOD provided approximately a 65:35 ratio of C5 to C12 deuterium incorporation (ineleganolide numbering). This result was surprising; we assumed that the α-position of lactone **23** would be deprotonated in preference to the vinyl triflate, especially considering the facile enolization of lactone **23** under the soft enolization conditions used previously in the Mukaiyama−Michael reaction.

The unexpected acidity of the C5 proton and the failure to effectively enolize lactone **38** under strongly basic conditions prompted us to evaluate soft enolization for the formation of enolate **41**, since it would be unlikely that competing C5 deprotonation would occur under these conditions (Scheme 12). We evaluated a wide range of soft enolization conditions to effect this epimerization; however, the desired lactone **40** was never formed. Unfortunately, under many of these conditions, we observed the isomerization of the TIPS enol ether in **38** to the undesired enoxysilane **46** as well as silyl ether cleavage to give ketone **47**. We were unable to separate enoxysilanes **38** and **46** by chromatography, although treatment of the mixture of these isomers with HCl in THF cleanly protodesilylated both to afford ketone **47**. Unfortunately, all attempts to selectively enolize **47** led only to mixtures of **38** and **46**. The isomerization of **38** to **46** occurs very readily, and we found that storing **38** at room temperature resulted in significant isomerization and decomposition, even after only 8 h.

The instability of the enoxysilane moiety in **38** would prove problematic throughout our studies. While our optimized synthesis of **38** allowed us to access significant quantities of this complex intermediate, the isomerization to **46** and desilylation to ketone **47**, even when stored at −78 °C, plagued our efforts. Storing enoxysilane **38** in base-treated glassware in a solution of 1% NEt_3 in benzene retarded the decomposition; however, this isomerization is still observed upon concentration and during prolonged storage.

Careful analysis of the reaction conditions and products has led to the identification of the major unproductive/decomposition pathways preventing the successful C12 epimerization of lactone **38**. These pathways are (1) metalation of the vinyl triflate under strongly basic conditions; (2) nucleophilic detriflation with alkoxide and hydroxide nucleophiles to yield ketone **42**; (3) facile enol ether isomerization of **38** to enoxysilane **46**; and (4) desilylation of TIPS enol ether to yield ketone **47**. Despite significant effort, no evidence of C12 epimerization or enolization of lactone **38** was observed.

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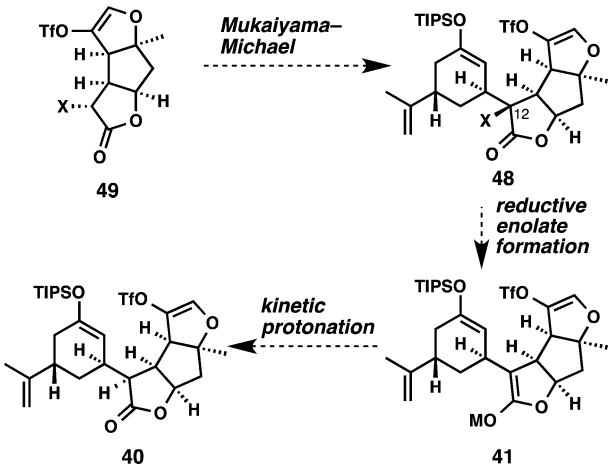
D. C12 Epimerization via Reductive Enolate formation. In light of the unsuccessful attempts to form enolate **41** via deprotonation of lactone **38**, a new strategy for enolization was required. Incorporation of an appropriate functional handle at C12 could facilitate the formation of enolate **41** by reductive methods (Scheme 13). We reasoned that reductive enolate

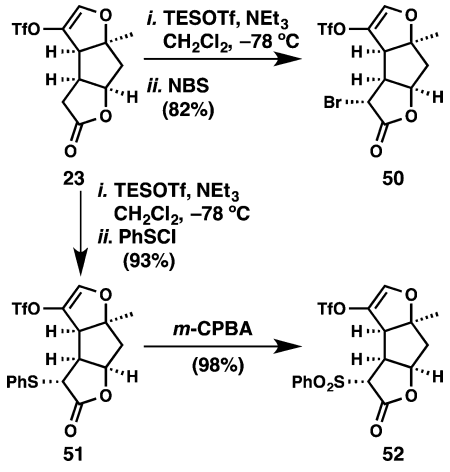
Scheme 13. Proposed Incorporation of a C12 Functional Handle for Reductive Epimerization



formation from a substrate such as **48** would avoid the issue of competitive vinyl triflate deprotonation encountered when attempting to enolize the lactone under basic conditions. One potential issue with this strategy is that the Mukaiyama–Michael reaction to access **48** would require enolization of C12 functionalized lactone **49**. Based on our previous experience failing to enolize lactone **38**, steric shielding of the α-proton and competitive C5 deprotonation may complicate the enolization of lactone **49** as well. We reasoned that selection of a functional handle (X) that would not only serve as a group to permit reductive epimerization but also further acidify the C12 proton could enable enolization and subsequent Michael addition of this more substituted lactone.

Soft enolization of lactone **23** using TESOTf and NEt_3, followed by in situ treatment of the silyl ketene acetal with NBS or PhSCl, yielded α-bromo ketone **50** and α-sulfenyl ketone **51** in 82% and 93% yield, respectively (Scheme 14). In addition,

Scheme 14. Preparation of α-Substituted Lactones 50–52



sulfide **51** could be oxidized to sulfone **52**, which we hoped would further acidify the α-proton of the lactone and allow for the enolization required for the Michael reaction. With **50**, **51**, and **52** in hand, multiple enolization conditions were investigated, and the Mukaiyama–Michael addition attempted. Unfortunately, neither formation of the Michael adduct **48** nor epimerization of the starting material was observed. Because these reactions were quenched under conditions that should have resulted in kinetic enolate protonation (had any enolate formed), epimerization (or lack thereof) served as a proxy for the observation of enolate formation; we therefore believe that enolization was unsuccessful.

During the course of these experiments, an X-ray crystal structure of bromide **50** was obtained (Figure 3). This structure

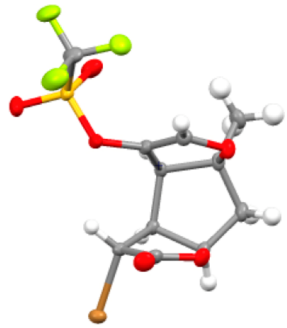


Figure 3. X-ray crystal structure of α-bromo lactone **50** shows poor orbital overlap for enolization.

confirmed our suspicions that lactone enolization of C12-substituted tricycles, including bromide **50** and tetracycle **38**, have been unsuccessful because the C12 C–H σ-orbital and lactone C–O π^* orbital have poor overlap. As a result, the C12 proton is not significantly acidified by the lactone carbonyl. In addition, as we already knew, the concave tricyclic lactone **50** places the C12 proton in a sterically encumbered environment, hindering the approach of base during enolization conditions.

At this stage, we had exhausted obvious options for the correction of the C12 configuration in advanced compounds of type **38**. We attribute the difficulty of epimerization via enolization to three issues: (1) competing acidity of the C5 proton of the vinyl triflate; (2) decreased kinetic acidity of the C12 proton due to poor orbital overlap between the C–H σ orbital with the C–O π^* orbital of the lactone carbonyl; and (3) C12 proton steric encumbrance from the concavity of the tricycle. These problems, along with the decomposition of the lactone **38**, led us to abandon the strategy of epimerization via enolization/kinetic protonation shown in Scheme 3. Additionally, we concluded that even if the Mukaiyama–Michael product **48** could be accessed, the reductive enolization would suffer from the same steric and stereoelectronic issues.

E. Use of Lactone Ring-Opened Intermediates. Despite the fact that the Mukaiyama–Michael reaction provides lactone **38** with the C12 configuration epimeric to the natural product and that we have been unable to induce C12 epimerization, the efficiency with which lactone **38** could be prepared warranted further efforts to convert it to ineleganolide via an alternative strategy.

Assessing the molecular architecture of ineleganolide along with lactone **53** (derived from triflate fragmentation of Mukaiyama–Michael product **38**) and C12 epimeric lactone **16**, it is clear that it is geometrically impossible to form the key

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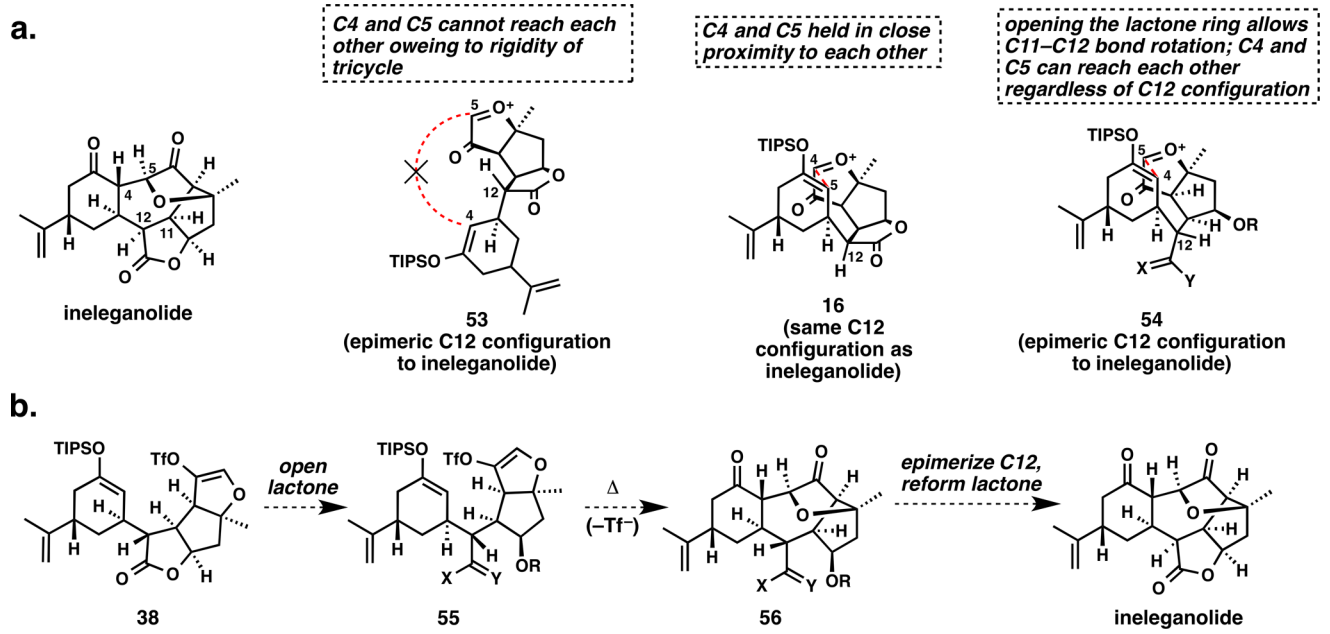
Scheme 15. (a) Analysis of Potential C4−C5 Bond Formation Using Various Substrates. (b) Strategy for C4−C5 Bond Formation Using a Lactone-Opened Substrate

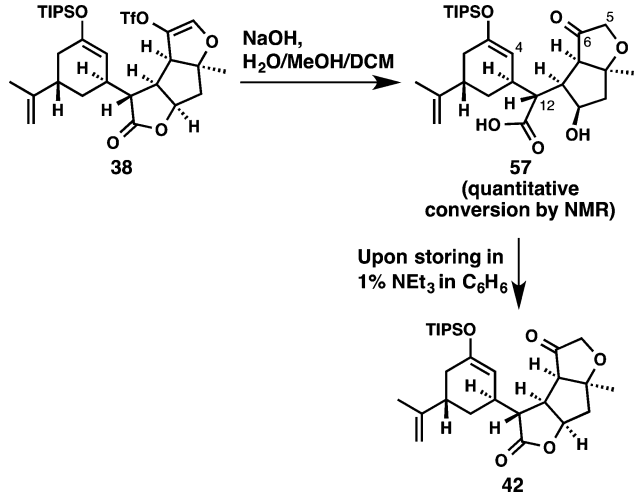


C4−C5 bond from lactone **53** because the rigid tricycle holds the C4 and C5 carbons at a distance (Scheme 15a). On the other hand, lactone **16** can only exist in a restricted conformation that places the C4 and C5 carbons in close proximity to each other and poised for bond formation. A lactone ring-opened intermediate such as **54** would have added degrees of conformational flexibility and would permit the formation of the C4−C5 bond even with the "incorrect" configuration at C12. As with the original approach, C4−C5 bond formation can only deliver the desired diastereomer about the C4 and C5 positions. After C4−C5 cyclization of an appropriate lactone-opened substrate such as carboxylic acid derivative **55** to form diketone **56**, it should be possible to epimerize the C12 stereocenter and reform the lactone ring to yield the natural product (Scheme 15b). The C12 epimerization of intermediate **53** could be carried out via an enolization/kinetic protonation sequence similar to that proposed earlier. While previously prepared tricyclic substrates such as lactone **38** resisted enolization under all conditions, a lactone-opened substrate such as **55** or **56** should be more amenable to productive reactivity. These substrates are able to freely rotate about the C11−C12 bond, allowing sufficient orbital overlap for deprotonation; furthermore, the proton at C12 in **55** and **56** appears to be less sterically hindered than in lactone **38**.

We investigated a number of strategies to open the lactone ring while leaving the vinyl triflate functional handle intact. While we were able to access a few substrates via sequences such as reduction of the lactone to a 1,4-diol, these substrates were especially prone to decomposition and other undesired proximity-induced reactions. For these reasons, and after substantial effort, we decided to abandon the vinyl triflate fragmentation strategy to construct the C4−C5 bond and began to consider other methods that could be carried out under milder, nonthermal conditions.

While evaluating conditions to open the lactone **38**, we discovered that treatment with NaOH in a solution of MeOH and CH_2Cl_2 resulted in hydrolysis of both the lactone and vinyl triflate to cleanly provide the hydroxy acid **57** (Scheme 16).

Scheme 16. Hydrolysis of Lactone 38 to Hydroxy Acid 57 and Subsequent Lactonization to 42



Unfortunately, but not surprisingly, 1,4-hydroxy acid **57** was found to lactonize to **42** upon storage under any conditions. We surmised that by implementing an appropriate protecting group strategy we might avoid this lactonization. We therefore proposed a new strategy for C4−C5 bond formation using an oxidative cyclization.

Suitably protecting ketone **57** as derivative **58**, followed by regioselective formation of enolate **59** (or an enolate equivalent such as an enol acetate, enoxysilane, or enamine), would allow us to form the C4−C5 bond via an intramolecular oxidative coupling to provide **60** (Scheme 17). This type of process is similar to a number of oxidative enolate couplings that have recently been employed in the synthesis of complex natural products.[25] An advantage of this strategy over the thermal triflate fragmentation is that oxidative-coupling reactions of enolate derivatives are often conducted at room temperature or lower, and therefore, isomerization and decomposition of the

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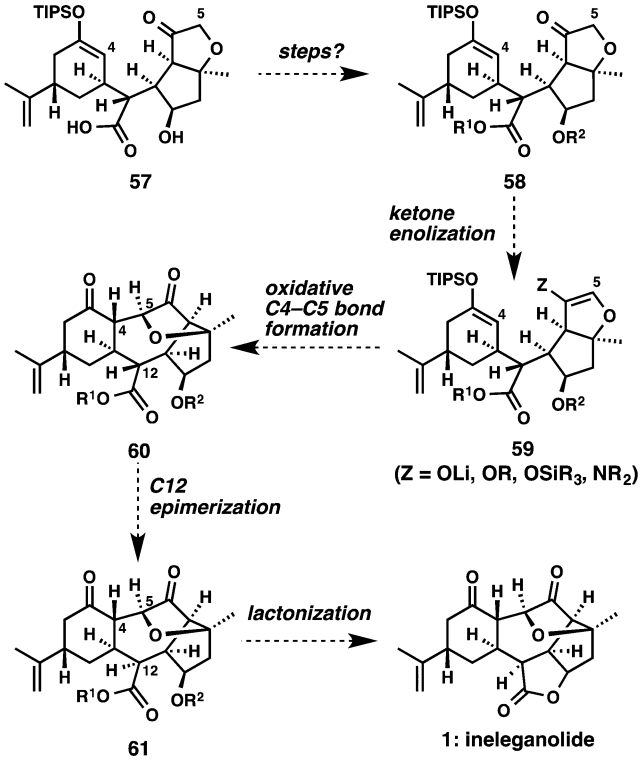
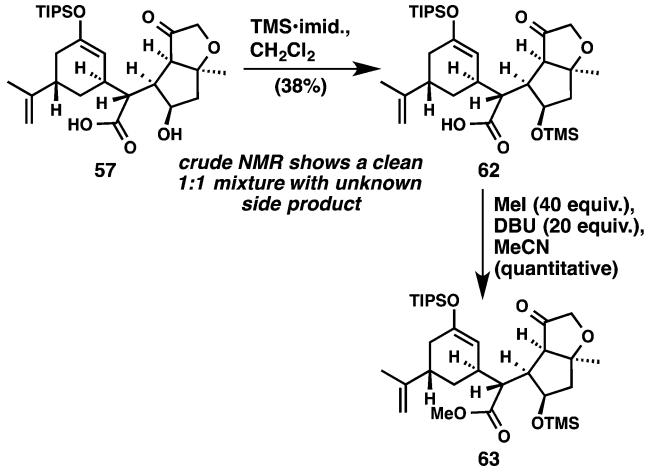
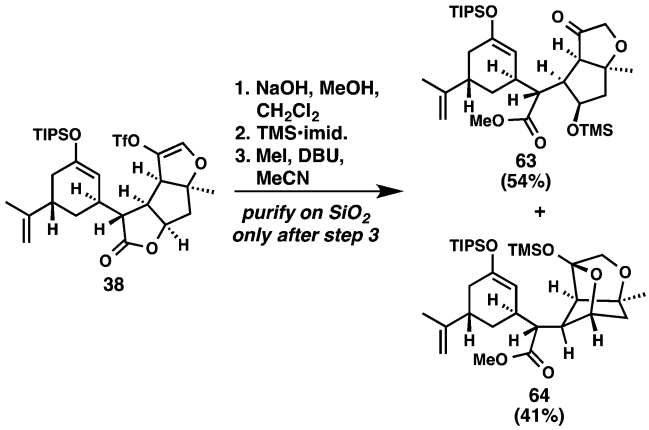
Scheme 17. Alternative Strategy for C4−C5 Bond Formation Using an Oxidative Cyclization



Scheme 18. Conversion of Hydroxy Acid 57 to Methyl Ester 63



Scheme 19. Three-Step Sequence for Formation of 63 and Ketal Side Product 64



TIPS enol ether might be mitigated. Furthermore, the multitude of methods and reagents available for this type of transformation should enable more control over the reactivity compared to thermal fragmentation. After cyclization of enolate **59** to diketone **60**, C12 epimerization by an enolization/protonation sequence followed by deprotection and lactonization would provide ineleganolide.

We first sought to protect the secondary alcohol and carboxylic acid functional groups in **57** to prevent decomposition and lactonization as well as to enable selective deprotonation of the C5 proton to form the requisite enolate. On the basis of some previous success using silylimidazole reagents, **57** was subjected to a large excess of TMS-imidazole (Scheme 18). After aqueous workup, NMR analysis showed clean conversion of **57** to a 1:1 mixture of the desired silyl ether **62** and an unknown isomer; however, **62** was extremely difficult to purify by silica chromatography, and only low isolated yields were obtained. Furthermore, we were unable to isolate or identify the unknown side product of the reaction. Protection of the carboxylic acid was next evaluated, and we found that treating **62** with MeI and DBU in MeCN afforded methyl ester **63** in excellent yield and with minimal decomposition. Ester **63** can be easily purified by NEt_3-treated silica gel chromatography and should be a suitably stable precursor for the formation of the enolate equivalents needed to evaluate our proposed oxidative cyclization reaction.

Looking to streamline the preparation of ester **63**, lactone **38** was subjected to the hydrolysis, alcohol protection, and esterification reaction sequence with each step being performed using crude, unchromatographed material (Scheme 19). The final reaction mixture was then chromatographed, providing **63** along with the unexpected isomeric ketal **64**, in 54% and 41% yield, respectively. Analysis of the ^1H NMR spectra of aliquots of the reaction mixtures after each transformation revealed that the ketal functionality in **64** is formed during TMS protection of **57**, and this type of ketal (as the free carboxylic acid) was the unknown side product in our first silylation experiments on **57**.

We hoped that treatment of ketal **64** with either Lewis acidic or strongly basic conditions might induce ketal opening to provide enoxysilane **65** (Scheme 20). We attempted this transformation, but the desired product was never observed. Instead, we discovered that treatment of **64** with NaOH in MeOH/DCM induced hydrolysis of the acetal as well as the methyl ester to provide **57** in high yield. We were able to utilize this hydrolysis to recycle the undesired ketal **64** to a 1:1 mixture of **63** and **64** by resubjecting **57** to the conditions in Scheme 19, which enabled us to obtain high overall yields of ester **63** from **38**.

With reliable access to ketone **63**, we next evaluated conditions for formation of the C6 ketone enolate and enolate equivalents that would render the C5 position nucleophilic for the oxidative cyclization. A potential concern with this step was the regioselectivity of enolate formation, since earlier in our synthesis the enolization of a related tricyclic ketone provided a mixture of enolate isomers and a significant amount of optimization was required to achieve sufficient regioselectivity. However, treatment of ketone **63** under enolization conditions (an excess of LDA in THF at 0 °C) followed by quenching with CD_3OD revealed selective deuteration at C5 with minimal

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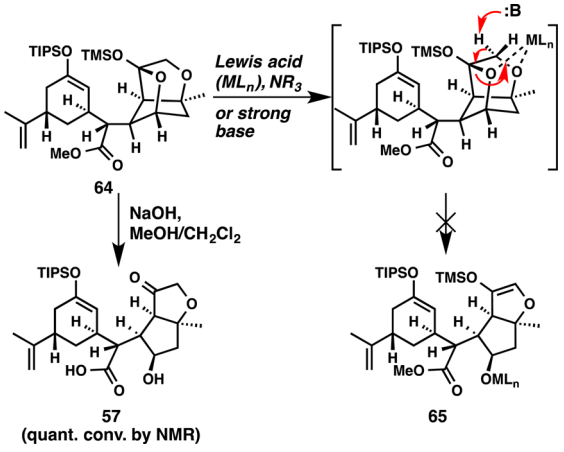
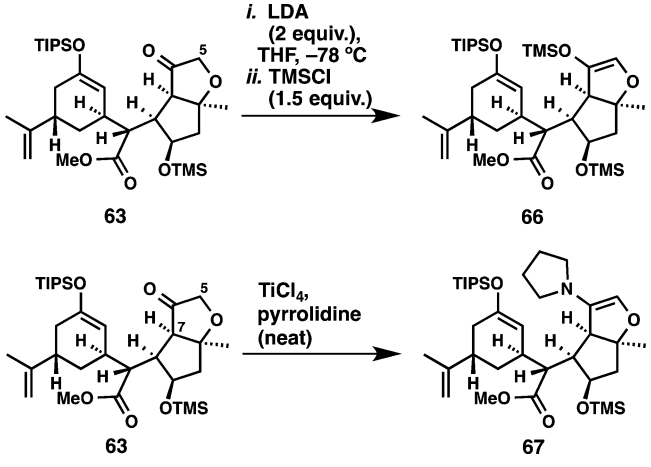
Scheme 20. Attempts To Access Enoxysilane 65 via Elimination of Ketal 64 and Hydrolysis of 64 to Hydroxy Acid 57



deuterium incorporation at C7, indicating that under these conditions the desired enolate is formed with high selectivity.

In addition to the lithium enolate, we aimed to access other enolate equivalents that could be used for the proposed oxidative cyclization shown in Scheme 17. An enol ether or enamine would be less sensitive to protonation compared to the lithium enolate and, therefore, should be compatible with a larger variety of oxidative conditions (protic solvents, more acidic reagents, etc.). Also important, these more stable enolate surrogates might prove isolable, which would simplify evaluation of conditions for the oxidative cyclization. Treatment of ketone **63** with LDA followed by quenching of the resulting enolate intermediate provided enoxysilane **66** (Scheme 21). Careful control over the quantity of LDA was important in order to obtain high yields of **66**; an excess of base resulted in C5 lithiation and silylation of the product **66** to provide an unstable vinylsilane (not shown), while too little base resulted in incomplete conversion. While enoxysilane **66** was found to be unstable to purification by column chromatography, by carefully controlling the reagent stoichiometry, **66** could be obtained in high conversion and in ~85% purity in the crude reaction mixture. In addition to enoxysilane **66**, we were also able to access enamine **67** by exposing ketone **63** to $TiCl_4$ in neat pyrrolidine.

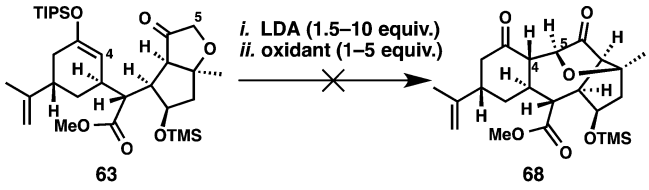
Scheme 21. Formation of Enoxysilane 66 and Enamine 67 from Ketone 63



Similar to enoxysilane **66**, we found that enamine **67** was extremely susceptible to hydrolysis and therefore not stable to purification by silica gel chromatography; however, the reaction provided **67** in near-quantitative conversion.

With access to the enolate of ketone **63**, enoxysilane **66**, and enamine **67**, we next evaluated the oxidative cyclization to form the key C4–C5 bond. Our initial efforts were to induce oxidative cyclization via the lithium enolate of **63** (Scheme 22).

Scheme 22. Attempted Oxidative Cyclization via the Lithium Enolate of 63

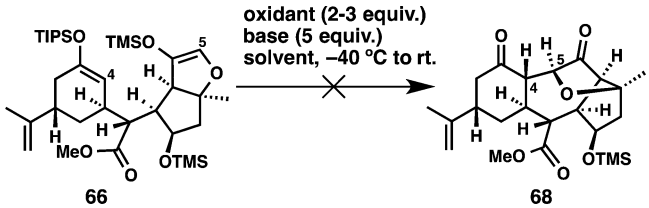


oxidants include: O_2, $[Fe(dmf)_3Cl_2][FeCl_4]$, $Fe(phen)_3PF_6$, $Fe(acac)_3$, Ag_2O, CAN, $CuCl_2$, $CuOTf_2$, $Mn(OAc)_3$, CrO_3, I_2, NBS

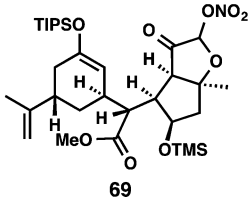
Ketone **63** was treated with LDA in THF, followed by the addition of various oxidants. These oxidizing reagents included $Fe^{(III)}$,[26] $Ag^{(I)}$,[27] $Ce^{(IV)}$,[28] $Cu^{(II)}$,[29] and $Mn^{(III)}$[30] metal oxidants, each of which have been shown to effect related oxidative couplings. Molecular oxygen, iodine,[31] and *N*-bromosuccinimide were also investigated; however, under no conditions was the desired product ever observed. In most cases only starting material was recovered, and the use of stronger oxidants or elevated temperatures resulted only in complex mixtures of unidentified decomposition products.

We next evaluated conditions for the oxidative cyclization of bis-enoxysilane **66**. Initially, we evaluated a number of conditions employing Ce^{IV} oxidants (Scheme 23). Treating **66** with

Scheme 23. Attempts at Oxidative Cyclization of Bis-enoxysilane 66



oxidants include: CAN, TBACN, Ag_2O,$Mn(acac)_3$, $Mn(hfacac)_3$, CrO_3, $Pb(OAc)_4$, NBS, I_2



ceric ammonium nitrate (CAN) in a variety of solvents resulted in decomposition to a mixture of unknown products, and no evidence of the desired product was observed by NMR or ESIMS. The instability of the TMS enol ether is likely at fault; even upon standing in MeCN, it undergoes desilylation. When the acidic oxidant was buffered with either $NaHCO_3$ or 2,6-di-*tert*-butylpyridine (DTBP), we observed what appeared to be formation of the highly unstable nitrate ester **69**. This result

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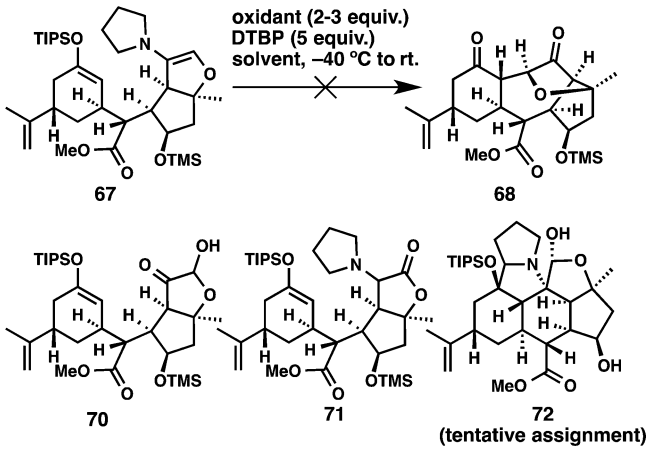
indicated that selective oxidation of the TMS enol ether was indeed occurring under these conditions; however, before C4−C5 cyclization could take place, the radical cation was further oxidized and trapped by the nitrate anion. Not dissuaded by this result, a number of different reaction conditions were evaluated in an effort to induce the desired cyclization. Additional oxidants were screened, including $(n\text{-}Bu_4N)_2Ce(NO_3)_6$ (TBACN),[32] manganese(III) acetylacetonate [$Mn(acac)_3$], and manganese(III) hexafluoroacetylacetonate [$(Mn(hfacac)_3)$],[33] which was suggested to us by the Herzon group after their successful oxidative dimerization in the synthesis of lomaiviticin aglycon.[25h] Despite these numerous attempts, none of the desired product **68** was ever observed, and in most cases, the reactions only resulted in mixtures of ketone **63** and decomposition products.

For our final efforts to induce C4−C5 bond formation via the strategy shown in Scheme 17, enamine **67** was treated with a number of oxidants to effect the desired cyclization (Scheme 24);[34] not surprisingly, enamine **67** was found to be more reactive than enoxysilane **66** toward oxidation conditions. Treating **67** with CAN buffered with 2,6-di-*tert*-butylpyridine (DTBP) only resulted in decomposition and trace amounts of ketone **63**. While we were unable to isolate and identify any products from these reactions, we often observed the evidence of oxidized products in the mass spectrum of the crude reaction. We believe that the electron-rich enamine was oxidized under these conditions; however, the radical cation or oxocarbenium ion intermediates generated likely undergo multiple decomposition pathways in preference to C4−C5 bond formation. Based on the high reactivity of enamine **67** to the oxidizing conditions initially evaluated, we began evaluating milder, nontraditional oxidants for this cyclization. Treatment of **67** with $Pd(OAc)_2$ in DMF resulted in a mixture of ketone **63** and a highly unstable compound that we believe might be lactol **70**. Subjection of **67** to $Pd(OAc)_2$ or $NiCl_2$ in toluene provided a mixture of lactol **70** and amine **71**. Even though C4−C5 bond formation was not observed, we were encouraged that these conditions seemed to cleanly oxidize the enamine functional group. We continued to evaluate conditions to effect oxidative cyclization using other palladium complexes and conditions, but most conditions only converted enamine **67** to complex mixtures of decomposition products. An exception was found with $PdCl_2$ in DMF, which delivered a new compound with molecular formula $C_{33}H_{55}NO_6Si$ that we have *tentatively* assigned as the hexacyclic structure **72**. Further evaluation of other group 10 metal oxidants led to the discovery that $PtCl_2$ in DMF converted **67** to **72** in 80% yield. This reaction was reproducible and scaled to 5 mg to isolate sufficient material for full characterization and structure determination. All data appear consistent with this structure but without X−ray crystallographic analysis or a sound mechanism to account for its formation we acknowledge that this assignment could be incorrect.

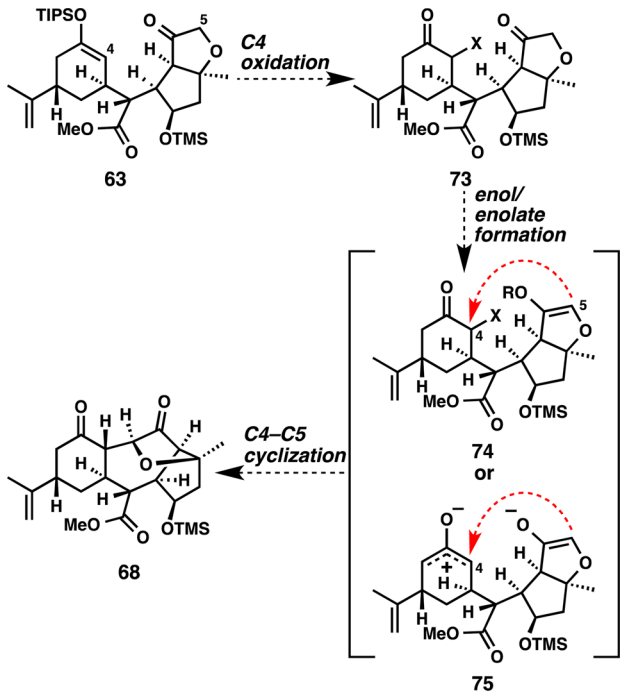
Scheme 24. Attempts at Oxidative Cyclization of Enamine 67



While conditions for oxidative cyclization have not been completely exhausted, we believe that the steric and torsional strain required to bring C4 and C5 into close proximity might be too high and that the oxidized reactive intermediates (i.e., radical cations) formed under these conditions undergo multiple decomposition pathways in preference to C4−C5 bond formation.

In a final effort to induce the pivotal C4−C5 cyclization, we attempted a two-step sequence for bond formation whereby we would first oxidize the C4 position of **63** to an electrophilic α-halo ketone **73** and then attempt to form the critical bond by enolization of the C6 ketone and displacement of the C4 halide (Scheme 25). Enoxysilane **63** was treated with NBS in CH_2Cl_2 at −78 °C to provide bromide **73** as a mixture of diastereomers (Scheme 26), along with small amounts of the allylic bromide **76** as a single diastereomer (stereochemistry of C4 not determined). Interestingly, α-bromo ketone **73** was observed in >9:1 dr in the ^1H NMR spectrum of the crude reaction mixture; however, after purification via SiO_2 column chromatography, **73** was isolated with 3:1 dr, indicating epimerization of the C4 stereocenter via presumed facile keto−enol tautomerization.

Scheme 25. Proposed Two-Step Process for C4−C5 Bond Formation from Ketone 63



Unfortunately, subjection of **73** to conditions to effect bromide displacement and C4−C5 bond formation proved unsuccessful (Scheme 27). Treatment of **73** with strong bases such as LDA or KHMDS only resulted in recovered starting material and

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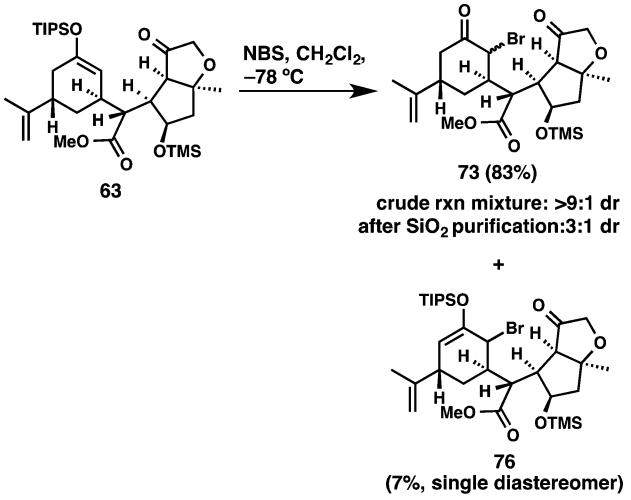
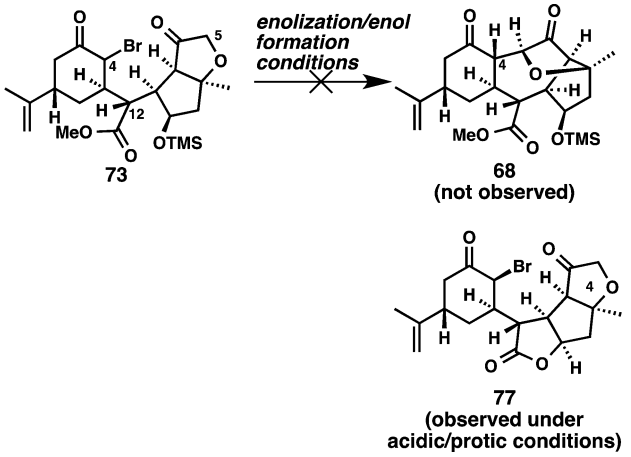
Scheme 26. Bromination of 63



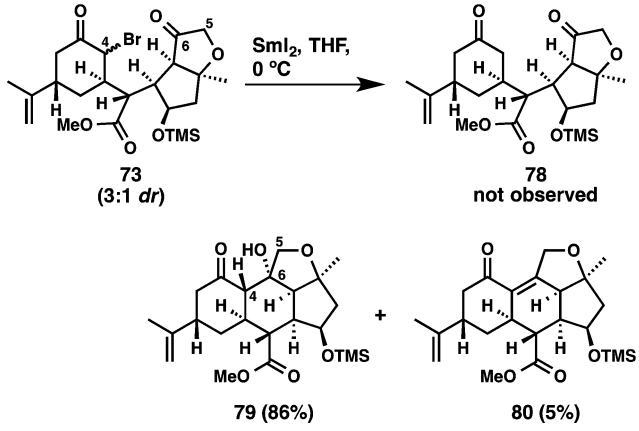
Scheme 27. Attempts at C4−C5 Cyclization of Bromide 73



decomposition products that we suspect were due to elimination of the α-bromide. We acknowledge that under these conditions it would likely be difficult to selectively form the C5 enolate over the C4 enolate; therefore, we also treated **73** with conditions known to promote keto−enol tautomerization, hoping that the C5 enol would be nucleophilic enough to displace the C4 bromide given their proximity. Often under these conditions, varying amounts of lactone **77** were isolated, which we attribute to cleavage of the TMS ether and cyclization. Bromide **73** was also treated with silver(I) salts in an attempt to induce cyclization via an α-acyl carbenium ion;[35] unfortunately, these conditions only resulted in decomposition.

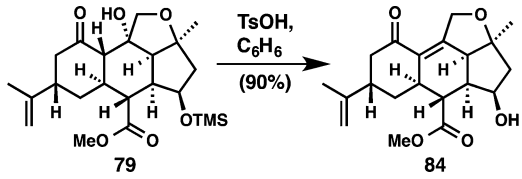
F. Reformatsky Cyclization Strategy. In the previously discussed reactions, bromide **73** was used as a 3:1 ratio of isomers that we assumed to be epimeric at the C4 bromide-bearing stereocenter. In an effort to confirm that **73** was a mixture of epimers at C4 (rather than epimeric at C12, or other isomers), we treated a solution of **73** in THF with excess SmI_2 at 0 °C, expecting the reduction of the epimeric bromides to converge on ketone **78** (Scheme 28).[36] We observed immediate consumption of the starting material by TLC, and mass spectrometry indicated that the bromide had been reduced. However, upon further analysis, we discovered that the reaction generated alcohol **79** and enone **80** in a Reformatsky-type cyclization of the samarium enolate[37] and none of the expected ketone **78**.

Scheme 28. Attempts To Reduce Bromide 73 to Ketone 78 Results in Conversion to Reformatsky Products 79 and 80



While the C4−C6 bond formed in the Reformatsky cyclization of bromide **73** to tetracycle **79** (and **80**) is not present in ineleganolide (or any other related natural products), we were encouraged by this reaction, and considered the possibilities of accessing the carbon framework of ineleganolide from this unexpected product. According to our analysis by hand-held molecular models, we postulated that generation of oxocarbenium ion **81** could result in a 1,2-pinacol-type shift to deliver **68**, which contains the C4−C5 connectivity found in ineleganolide (Scheme 29a).[38] The rigid conformation of **81** situates the C4−C6 σ-bond with good orbital overlap between the π^*_{c-o} orbital of the oxocarbenium ion, boding well for the desired alkyl shift to occur.

Evaluation of the pinacol shift strategy shown in Scheme 29 required access to oxocarbenium ion intermediate **81**. Alkene isomerization of enone **80** might provide the cyclic enol ether **82** (Scheme 29b). Oxidation of **82** could form the strained epoxide **83**, which under Lewis acidic conditions would open to deliver oxocarbenium ion **81**. With this strategy in mind, tertiary alcohol **79** was exposed to a variety of acidic conditions in an attempt to cleanly effect dehydration. While many of these conditions provided mixtures of **79** along with desilylated enone **84**, treating **79** with TsOH in benzene provided alcohol **84** in satisfactory yield (eq 4).



(Eq. 4)

Unfortunately, we were unable to convert **80** or **84** to alkene isomer **82** under a variety of conditions; only starting material was recovered (Scheme 30). The failure to isomerize might be due to the competitive formation of the cross-conjugated enolate **85**. During these isomerization attempts, ester enolization or epimerization of the C12 stereocenter was never observed. We had hoped that under strongly basic conditions enolization/protonation of C12 could occur to provide products with the analogous C12 configuration to ineleganolide, such as **86** and **87**. Unfortunately, even treatment of **80** with a large excess of LDA resulted only in recovered starting material. At this point in the project, we were forced to acknowledge that C12 epimerization

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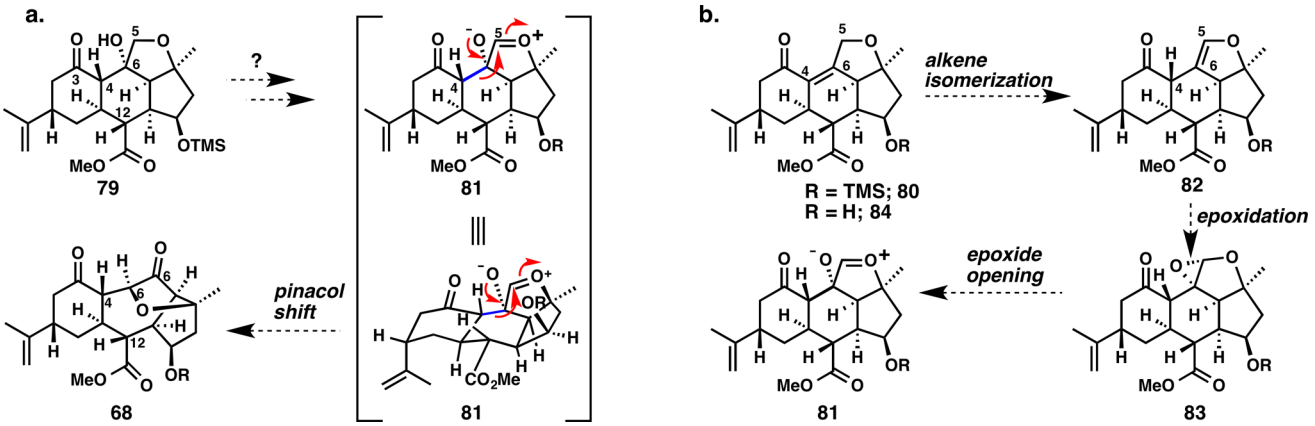
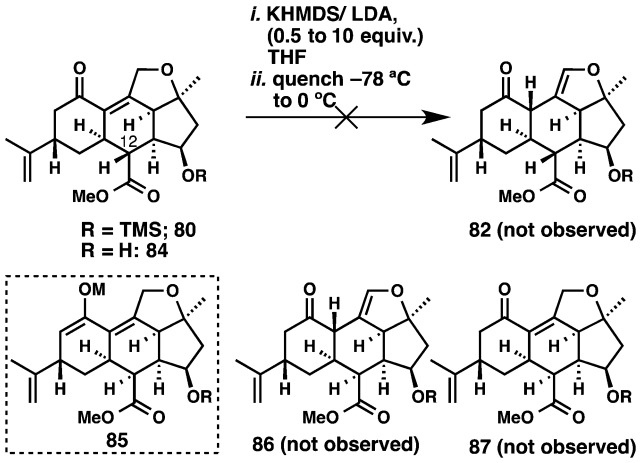
Scheme 29. (a) Proposed Synthesis of the Carbon Skeleton of Ineleganolide via 1,2 Shift of 81. (b) Proposed Formation of 81



Scheme 30. Attempts To Isomerize Enones 80 and 84

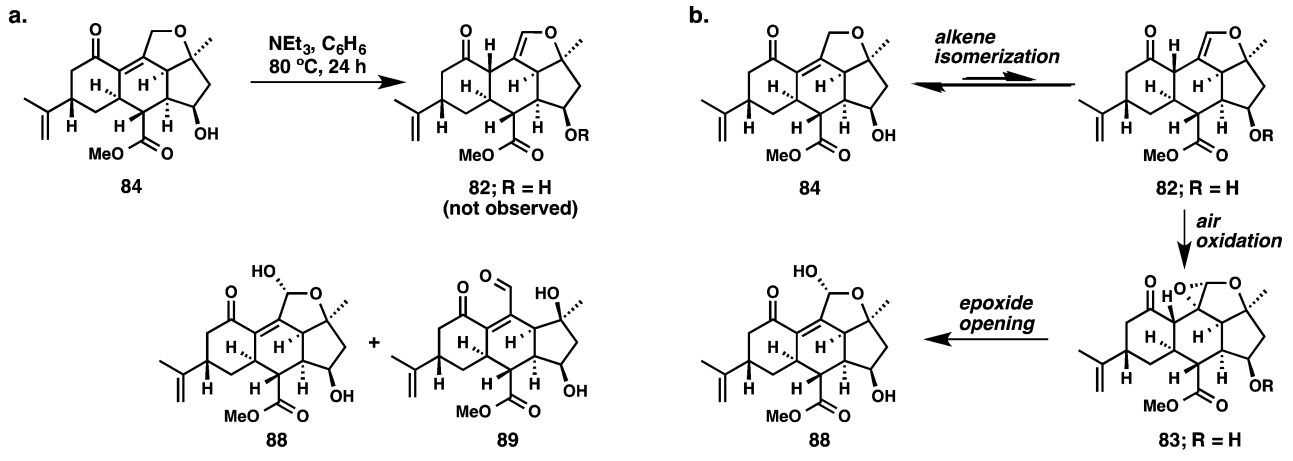


may never be realized in any of these substrates and that even if we were to form the correct C4−C5 bond via a pinacol shift of **81** (Scheme 29) C12 epimerization may still be difficult.

In a final attempt to isomerize enone **84**, we discovered that heating **84** in benzene with NEt_3 for 24 h resulted in the formation of a product that we have tentatively assigned as lactol **88** (Scheme 31). This chemistry was performed on a small scale (≤1 mg), and complete characterization was not possible; however, we found this reaction to be reproducible, and running the reaction under an atmosphere of oxygen provided higher conversion of **88**. To further support our proposed structure, upon purification by column chromatography, **88** was isolated along with trace amounts of an unidentified product sharing many similarities with the proton spectrum of **88** but containing a singlet at δ 11.05 in the ^{1}H NMR spectrum. We postulate this could be the product of lactol ring-opening to give an aldehyde such as **89**. While there are a number of possible mechanisms through which such a C−H oxidation to provide **88** might occur, including a simple and direct air oxidation involving a highly stabilized, delocalized captodative radical, one other possibility involves the autoxidation[39] of the strained alkene **82** (Scheme 31b). This mechanistic scenario closely parallels the design shown in Scheme 29b.

The formation of lactol **88** was an unexpected result, and we were intrigued by this transformation. Unfortunately, one proposed mechanism for the formation of **88** proceeds via the intermediacy of epoxide **83**, and we had hoped that this intermediate might result in rearrangement to oxocarbenium ion **81** (Scheme 29). While it may be possible to exploit an equilibrium between lactol **88**, epoxide **83**, and oxocarbenium ion **81**, the desired 1,2-shift might well be extremely challenging. This chemistry was run on small scale, and we have by no means exhausted all of the options available to achieve this desired transformation.

Scheme 31. (a) Attempts To Isomerize Alkene 84 and Unexpected Oxidation under Thermal Conditions; (b) Proposed Mechanism for the Aerobic Oxidation of Enone 84 to Lactol 88



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IV. CONCLUSION

We have described our efforts toward the synthesis of ineleganolide for which we chose a particularly attractive convergent design and never wavered from that general plan. This approach entailed Mukaiyama−Michael addition of a complex tricyclic lactone to norcarvone, a difficult stereochemical correction at C12, and a final, challenging C4−C5 bond construction that was projected to proceed via an uncommon β-alkoxyvinyl triflate fragmentation to unveil a reactive oxocarbenium ion. Owing to the facility with which the starting materials for the convergent Michael addition could be made, as well as the efficiency of this conjugate addition, a number of different specific endgames could be evaluated in detail. Unfortunately, the requisite stereochemical correction was never accomplished, and several workarounds involving opening of the lactone ring were investigated, with no success. In the end, the synthesis was thwarted, at least in part, by our inability to effect that change in configuration and also in part by the instability of many key intermediates, which in several cases underwent undesired proximity-induced reactions.

We are strong believers in finding the most direct and attractive routes to complex natural products and pursuing their execution in a steadfast way. After about eight years of difficult work with such a strategy toward ineleganolide, we were forced to accept that the planned stereochemical correction of C12 was probably the Achilles heel in a strategy that was likely otherwise sound.

V. EXPERIMENTAL SECTION

General Methods. All reactions were carried out under an inert atmosphere of nitrogen or argon in oven-dried or flame-dried glassware with magnetic stirring, unless otherwise noted. Solvents were dried by passage through columns of activated alumina. All amine bases, including pyridine, diisopropylethylamine, triethylamine, 2,2,6,6-tetramethylpiperidine (TMP), and 2,6-di*tert*-butylpyridine (DTBP), were distilled from calcium hydride prior to use. Triisopropylsilyl trifluoromethanesulfonate (TIPSOTf), triethylsilyl trifluoromethanesulfonate (TESOTf), and titanium(IV) chloride were distilled under reduced pressure over calcium hydride. Tributyltin hydride was distilled under reduced pressure and used immediately. *N*-Bromosuccinimide (NBS) was recrystallized from H_2O. SmI_2 solutions in THF (opaque dark blue over excess Sm powder) were prepared from Sm powder (metallic powder) and 1,2-diiodoethane (white crystalline solid) according to the procedures of Reisman[40] and Wood[41] and stored in a Schlenk flask sealed under an Ar atmosphere in the dark. All other reagents were prepared by known literature procedures or used as obtained from commercial sources, unless otherwise indicated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm coated commercial silica gel plates (F254 precoated glass plates) using UV light as visualizing agent and $KMnO_4$ and heat as a developing agent. Flash chromatography was performed on silica gel (230−400 mesh). Melting points were uncorrected. ^{1}H and ^{13}C NMR spectra were obtained at 500 or 400 MHz at 298 K. Abbreviations for multiplicity are as follows: app, apparent; br, broad; d, doublet; t, triplet; q, quartet; m, multiplet. Chemical shifts are reported in ppm referenced to the internal solvent residual of C_6D_6 or $CDCl_3$ at 7.16 and 7.26 ppm for ^{1}H NMR and 128.06 and 77.16 ppm for ^{13}C NMR, respectively. IR spectra were obtained on an FT-IR spectrophotometer using NaCl plates. High-resolution mass spectrometry data were obtained by LC-ESI (quadrupole mass analyzer). Compounds containing the enoxysilane functional group were found to be extremely unstable and were handled and stored using base-treated glassware.[42]

4-((*tert*-Butyldimethylsilyl)oxy)cyclopent-2-en-1-one (26). A stirred solution of TBSCl (2.5 g, 16.8 mmol) and imidazole (76 mg, 1.12 mmol) in DCM (11 mL) under argon was cooled to 0 °C. (±)-4-Hydroxycyclopent-2-en-1-one (**25**)[17] (1.1 g, 11.2 mmol) was added dropwise, and the reaction mixture was allowed to stir at room temperature for 8 h. The reaction solution was diluted with hexane (150 mL), washed successively with satd aq $NaHCO_3$ (2 × 100 mL) and satd aq NaCl (100 mL) solutions, and concentrated in vacuo. The resulting brown oil was purified by column chromatography (SiO_2, 20% EtOAc in hexanes) to afford **26** as a brown oil (2.28 g, 96%). ^{1}H and ^{13}C NMR spectral data were in complete agreement with those reported previously.[18]

(1*S*,4*R*)-4-((*tert*-Butyldimethylsilyl)oxy)-1-methylcyclopent-2-en-1-ol (27). To a −78 °C solution of **26** (4.4 g, 20.7 mmol) in Et_2O (70 mL) was added MeLi (1.4 M, 17.7 mL, 24.8 mmol) dropwise over 30 min. The solution was allowed to stir at −78 °C for 15 min and then allowed to warm to room temperature over 4 h. Saturated aqueous NH_4Cl was added (50 mL), and the organic layer was separated. The aqueous layers were extracted with 3 × 50 mL Et_2O, and the combined organics were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting brown oil was purified by column chromatography (SiO_2, 15% EtOAc in hexanes) to provide **27** (4.48 g, 19.6 mmol, 95%) as a yellow oil. The reaction was also performed using (+)-**26**[20] (1.1 g, 5.17 mmol) to provide (−)-**27** (1.07 g, 91%). Spectral data were in complete agreement with those reported previously.[18]

Alkyne 28. A suspension of sodium hydride (60% dispersion in mineral oil, 680 mg, 17 mmol) in THF (80 mL) under argon was cooled to −78 °C. To the suspension was added a solution of alcohol **27** (2.6 g, 11.4 mmol) in THF (40 mL) slowly over 10 min, after which time the reaction solution was allowed to warm to room temperature over 30 min. The suspension was cooled to −78 °C, and a solution of propargyl bromide (80% wt in toluene, 3.3 mL, 17 mmol) was added dropwise over 20 min. The reaction solution was allowed to warm to room temperature and stirred for 8 h. Water (200 mL) was added, the organic layer was separated, and the aqueous layer was extracted with Et_2O (100 mL × 3). The combined organic extracts were washed with satd aq NaCl solution (100 mL), dried over Na_2SO_4, and filtered, and the solvent was removed in vacuo. The resulting oil was purified by column chromatography (SiO_2, 2.5−4% EtOAc in hexanes) to yield **28** (1.52 g, 57.0 mmol, 97%). The reaction was also performed using (−)-**27** (0.95 g, 38.9 mmol) to provide (+)-**28** (1.05 g, 94%): $[\alpha]^{25}_D$ +41.3 (*c* 0.1, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (dd, *J* = 5.6, 2.2 Hz, 1H), 5.74 (dd, *J* = 5.5, 1.1 Hz, 1H), 4.68 (dddd, *J* = 7.1, 3.5, 2.1, 1.1 Hz, 1H), 4.10 (dd, *J* = 15.6, 2.5 Hz, 1H), 4.02 (dd, *J* = 15.6, 2.5 Hz, 1H), 2.37 (t, *J* = 2.4 Hz, 1H), 2.20 (dd, *J* = 14.4, 7.2 Hz, 1H), 1.90 (dd, *J* = 14.4, 3.6 Hz, 1H), 1.35 (s, 3H), 0.89 (s, 9H), 0.07 (s, 6H).^{13}C NMR (126 MHz, $CDCl_3$) δ 137.3, 137.0, 87.3, 81.9, 75.0, 73.2, 51.8, 45.3, 27.7, 26.0, 18.2, −4.5, −4.5.; IR (thin film) ν 3012, 2930, 2360, 1472 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{26}O_2SiNa$ $(M + Na)^+$ 289.1600, found 289.1605.

Alcohol 29. To a solution of alkyne **28** (1.9 g, 7.13 mmol) in THF (50 mL) was added a solution of tetrabutylammonium fluoride (1 M in THF, 12.1 mL, 12.1 mmol). Upon addition, the solution quickly changed from a light yellow to a dark brown color. The reaction solution was stirred at room temperature for 2 h and concentrated in vacuo to afford a dark-brown viscous oil. The crude oil was purified by column chromatography (SiO_2, 40% EtOAc in hexanes) to yield **29** (1.07 g, 7.0 mmol, 98%) as a yellow oil. The reaction was also performed using (+)-**28** (1.0 g, 4.4 mmol) to provide (+)-**29** (650 mg, 96%): $[\alpha]^{25}_D$ + 23.1 (*c* 0.2, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (dd, *J* = 5.6, 2.1 Hz, 1H), 5.79 (dd, *J* = 5.6, 1.1 Hz, 1H), 4.04 (dd, *J* = 15.5, 2.4 Hz, 1H), 3.99 (dd, *J* = 15.5, 2.4 Hz, 1H), 3.10 (d, *J* = 5.4 Hz, 1H), 2.37 (t, *J* = 2.4 Hz, 1H), 2.20 (dd, *J* = 14.4, 7.3 Hz, 1H), 1.88 (dd, *J* = 14.4, 3.9 Hz, 1H), 1.28 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.7, 136.5, 87.3, 81.6, 75.1, 73.7, 51.8, 45.4, 26.6; IR (thin film) ν 3428, 3302, 2968, 2256 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_9H_{12}O_2Na$ $(M + Na)^+$ 175.0735, found 175.0727.

Bromoacetal 30. To a −20 °C cooled solution of alcohol **29** (1.03 g, 6.77 mmol) in CH_2Cl_2 (30 mL) were added *N*-bromosuccinimide (1.29 g, 7.25 mmol) and ethylvinyl ether (0.87 mL, 8.8 mmol). The solution was allowed to slowly warm to room temperature and stirred for 40 h. Water (30 mL) was added to the reaction solution, the organic layer was separated, and the aqueous

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layer was extracted with CH_2Cl_2 (30 mL × 3). The combined organics were dried over Na_2SO_4, and the solvent was removed in vacuo. The residue was purified by column chromatography (SiO_2, 25% EtOAc in hexanes) to yield **30** (1.8 g, 5.9 mmol, 87%) as a 1:1 mixture of epimers that were not separated: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70 (m, 2H), 5.58 (t, J = 6.15 Hz, 2H), 4.50 (dd, J = 12.5, 5.6 Hz, 2H), 4.25 (m, 2H), 4.06 (m, 2H), 3.99 (m, 4H), 3.37−3.15 (m, 4H), 3.07 (m, 4H), 2.03 (m, 4H), 1.87 (m, 2H), 1.23 (s, 3H), 1.22 (s, 3H), 1.02 (t, J = 7.0 Hz, 3H), 1.01 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.3, 139.2, 134.3, 133.8, 101.3, 101.0, 86.9, 86.9, 81.6, 81.5, 79.1, 79.0, 62.3, 61.7, 51.8, 51.8, 42.8, 42.0, 32.0, 31.9, 27.6, 27.4, 15.3, 15.2; IR (thin film) ν 3012, 2938, 1497, 2286; HRMS (ESI) m/z calcd $C_{13}H_{19}Br\ O_3Na$ $(M + Na)^+$ 325.0415, found 325.0419.

Tricycle 31. A solution of bromoacetal **30** (1.5 g, 4.91 mmol) in benzene (100 mL) was heated to reflux. Catalytic AIBN (48 mg, 0.29 mmol) was added, followed by tributyltin hydride (0.66 mL, 2.46 mmol). After heating at reflux for 2 h, additional tributyltin hydride (1.05 mL, 3.9 mmol) in benzene (10 mL) was added dropwise over 1 h. The reaction solution was allowed to reflux for an additional 1 h and cooled to room temperature, and the solvent was evaporated in vacuo to afford a brown oil that was purified by column chromatography (SiO_2, 10% EtOAc in hexane) to yield **31** (980 mg, 4.4 mmol, 89%) as a mixture of diastereomers: ^{1}H NMR (500 MHz, C_6D_6) δ 5.11 (m, 2H), 5.08 (brs, 2H), 4.92 (s, 1H), 4.64 (t, J = 6.4 Hz, 1H), 4.56 (m, 2H), 4.33 (m, 4H), 3.77 (dq, J = 14.2, 7.1 Hz, 1H), 3.69 (tt, J = 14.2, 7.2 Hz, 1H), 3.48 (m, 1H), 2.89 (ddd, J = 13.6, 10.2, 6.9 Hz, 1H), 2.81 (dd, J = 10.7, 3.8 Hz, 1H), 2.31 (dd, J = 14.6, 5.0 Hz, 1H), 2.25 (d, J = 15.5 Hz, 1H), 2.10 (m, 2H), 1.90 (m, 4H), 1.28 (s, 3H), 1.27 (s, 3H), 1.17 (m, 6H); ^{13}C NMR (126 MHz, C_6D_6) δ 151.1, 150.9, 107.1, 106.7, 106.5, 105.3, 94.9, 93.8, 85.3, 84.8, 71.7, 71.5, 63.9, 62.8, 57.3, 56.4, 46.5, 45.8, 44.5, 44.2, 36.1, 35.3, 25.9, 25.0, 15.0; IR (thin film) ν 2971, 2928, 1663, 1445, 1374; HRMS (ESI) m/z calcd for $C_{13}H_{20}O_3Na$ $(M + Na)^+$ 247.1310, found 247.1315.

Ketones 32 and 33. Ozone was bubbled through a solution of alkene **31** (690 mg, 3.07 mmol) in MeOH (30 mL) at −78 °C. After 30 min PPh_3 (887 mg, 3.38 mmol) was added, and the reaction solution was allowed to warm to room temperature. The solution was concentrated in vacuo and purified by column chromatography (SiO_2, 20% EtOAc in hexanes) to yield **32** (278 mg, 1.2 mmol, 40%) and **33** (291 mg, 1.3 mmol, 42%) as a white crystalline solid and a clear viscous oil, respectively. X-ray quality crystals of (±)-**32** were grown by vapor diffusion crystallization (EtOAc/hexane) to give colorless opaque needles. **32**: mp = 126−132; $[\alpha]^{25}_D$ −159.1 (c 1.7, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 4.92 (d, J = 5.7 Hz, 1H), 4.31 (td, J = 7.1, 4.3 Hz, 1H), 4.21 (d, J = 16.4 Hz, 1H), 3.85 (d, J = 16.4 Hz, 1H), 3.65 (dq, J = 9.9, 7.1 Hz, 1H), 3.20 (dq, J = 9.8, 7.2 Hz, 1H), 2.58 (d, J = 13.9 Hz, 1H), 2.43−2.31 (m, 2H), 1.92 (d, J = 11.8 Hz, 1H), 1.70−1.62 (m, 2H), 1.03 (s, 3H), 0.99 (t, J = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 216.9, 105.8, 93.3, 86.6, 71.7, 63.1, 57.8, 45.4, 44.6, 33.5, 26.2, 15.1; IR (thin film) ν 2969, 1752, 1376, 1094; HRMS (ESI) m/z calcd for $C_{12}H_{18}O_4Na$ $(M + Na)^+$ 249.1103, found 249.1109.

33: $[\alpha]^{25}_D$ +23.4 (c 2.1, CH_2Cl_2); ^{1}H NMR (500 MHz, C_6D_6) δ 4.98 (dd J = 5.5, 2.6 Hz, 1H), 4.20 (t, J = 4.9 Hz, 1H), 4.10 (d, J = 16.6 Hz, 1H), 3.82 (d, J = 16.6 Hz, 1H), 3.69 (m, 1H), 3.22 (dq, J = 14.2, 7.1 Hz, 1H), 2.87 (dd, J = 13.7, 5.6 Hz, 1H), 2.36 (m, 1H), 2.22 (d, J = 15.64 Hz, 1H), 1.86 (ddd, J = 13.6, 7.9, 2.5 Hz, 1H), 1.62 (d, J = 9.8 Hz, 1H), 1.56 (dd, J = 15.6, 5.6 Hz, 1H), 1.08 (s, 3H), 1.07 (t, J = 7.2 Hz); ^{13}C NMR (126 MHz, C_6D_6) δ 216.6, 105.9, 93.6, 83.6, 71.3, 63.8, 56.6, 48.8, 44.4, 34.7, 27.6, 15.8; IR (thin film) ν 2971, 1751, 1442, 1081; HRMS (ESI) m/z calcd for $C_{12}H_{18}O_4Na$ $(M + Na)^+$ 249.1103, found 249.1110.

Epimerization of Acetal 32 to 33. A solution of acetal **32** (200 mg, 0.95 mmol) and p-toluenesulfonic acid (9.5 mg, 0.05 mmol) in EtOH (10 mL) was stirred at room temperature for 29 h. Saturated aqueous $NaHCO_3$ (10 mL) was added, and the solution was extracted with CH_2Cl_2 (20 mL × 3). The organic layers were combined and dried over $MgSO_4$, and the solvent was concentrated in vacuo. The crude reaction oil was purified by column chromatography (SiO_2, 20% EtOAc in hexanes) to yield **33** (196 mg, 98%).

Vinyl Triflate 34. To a solution of ketone **33** (30 mg, 0.13 mmol) in THF (1.2 mL) at 0 °C was added 0.5 M KHMDS in toluene (190 μL, 0.028 mmol). The reaction solution was stirred at 0 °C for 10 min, and a solution of KHMDS (0.5 M in toluene, 70 μL, 0.035 mmol) in THF (0.2 mL) was added slowly over 2 h by syringe pump. A solution of $PhNTf_2$ (85 mg, 0.24 mmol) in THF (0.3 mL) was added at once to the reaction solution and allowed to stir at 0 °C for 1 h. The reaction solution was warmed to room temperature, and saturated aqueous NH_4Cl (2 mL) was added. The organic layer was separated, and the aqueous layer was washed with 3 × 5 mL of Et_2O. The combined organic layers were concentrated in vacuo to an amber oil, which was purified by column chromatography (SiO_2, 5−10% EtOAc in hexanes) to yield **34** (39 mg, 0.11 mmol, 84%) as an amber oil which was found to decompose rapidly both in solution and upon concentration: ^{1}H NMR (500 MHz, C_6D_6) δ 6.06 (s, 1H), 5.08 (dd, J = 5.6, 2.5 Hz, 1H), 4.32 (td, J = 5.3, 1.6 Hz, 1H), 3.75 (tt, J = 14.2, 7.1 Hz, 1H), 3.29 (ddt, 10.9, 7.0, 5.4 Hz, 1H), 2.80 (d, J = 9.5 Hz, 1H), 2.32 (m, 1H), 2.26 (d, J = 15.3 Hz, 1H), 2.21 (ddd, J = 14.0, 5.5, 3.7 Hz, 1H), 1.98 (ddd, J = 14.0, 8.6, 2.6 Hz, 1H), 1.35 (dd, J = 15.3, 5.1 Hz, 1H), 1.12 (t, J = 7.1 Hz, 3H), 1.02 (s, 3H); ^{13}C NMR (126 MHz, C_6D_6) δ 139.0, 132.9, 105.9, 100.5, 84.9, 63.3, 54.6, 47.4, 44.4, 35.9, 26.1, 15.5; IR (thin film) ν 2927, 2359, 1424, 1212; HRMS (ESI) m/z calcd for $C_{13}H_{17}F_3O_6SNa$ $(M + Na)^+$ 381.0596, found 381.0601.

Lactone 23. The procedure for vinyl triflate **34** was repeated as above using ketone **33** (100 mg, 0.44 mmol) in THF (4 mL), KHMDS (0.5 M in toluene, 900 μL, 0.45 mmol), and $PhNTf_2$ (330 mg, 0.92 mmol). After the addition of $PhNTf_2$, the reaction solution was allowed to stir at room temperature for 1 h. The solvent was removed in vacuo, and the crude reaction mixture was redissolved in acetone (4 mL) and cooled to 0 °C. Jones reagent (1.25 M, 1.9 mL, 1.5 mmol) was added, the reaction solution was stirred for 90 min and then neutralized with saturated aqueous $NaHCO_3$ (3 mL), and the aqueous suspension was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with satd aq $NaHCO_3$, concentrated in vacuo, and purified by column chromatography (SiO_2, 5−8% EtOAc in hexanes) to yield **23** (126 mg, 0.4 mmol, 88%) as a yellow oil. Compound **23** was found to decompose when stored at room temperature for prolonged periods and was therefore stored as a solution in benzene frozen at −78 °C. The reaction was also performed using (+)-**33** (100 mg, 0.44 mmol) to provide (+)-**23** (118 mg, 82%): $[\alpha]^{25}_D$ + 49.2 (c 1.5, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (s, 1H), 3.90 (t, J = 5.3 Hz, 1H), 2.67 (d, J = 9.5 Hz, 1H), 2.34 (d, J = 17.7 Hz, 1H), 2.17 (d, J = 15.9 Hz, 1H), 1.91 (dd, J = 17.8, 8.7 Hz, 1H), 1.80 (td, J = 8.8, 5.1 Hz, 1H), 0.99 (dd, J = 15.8, 5.1 Hz, 1H), 0.91 (s, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.8, 140.6, 131.2, 100.18, 86.6, 54.6, 44.2, 43.4, 32.2, 25.4; IR (thin film) ν 2923, 2360, 1769, 1423; HRMS (ESI) m/z calcd for $C_{11}H_{11}F_3O_6SNa$ $(M + Na)^+$ 351.0126, found 351.0129.

Acetal 36. To a solution of triflate **23** (5 mg, 0.015 mmol) in MeOH (600 μL) was added NEt_3 (6 μL, 3 equiv). The reaction vial was sealed and heated in an 80 °C oil bath. After 15 min, no starting material remained in the reaction solution by TLC. The reaction was allowed to cool to room temperature, and the solvent was removed in vacuo. The crude reaction was purified by column chromatography (SiO_2, 20−40% EtOAc in hexanes) to provide **36** (2 mg, 60%) as a colorless oil: R_f = 0.5 (50% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 4.41 (s, 1H), 4.02 (td, J = 6.9, 3.7 Hz, 1H), 3.09 (s, 3H), 2.67 (dd, J = 18.2, 4.1 Hz, 1H), 2.30 (dd, J = 15.1, 3.8 Hz, 1H), 2.15 (dtd, J = 11.1, 6.9, 3.5 Hz, 1H), 2.05 (d, J = 10.4 Hz, 1H), 2.02 (d, J = 10.5 Hz, 1H), 1.81 (d, J = 11.2 Hz, 1H), 0.80 (s, 3H); ^{13}C NMR (126 MHz, C_6D_6) δ 209.1, 100.6, 90.5, 84.2, 56.7, 55.6, 45.6, 41.5, 31.4, 30.2, 26.7; HRMS (ESI) m/z calcd for $C_{11}H_{14}O_5Na$ $(M + Na)^+$ 249.0739, found 249.0741.

Mukaiyama−Michael Adduct (+)-38. To a solution of (+)-**23** (50 mg, 0.15 mmol) in CH_2Cl_2 (1.5 mL) was added 2,2,6,6-tetramethylpiperidine (130 μL, 0.76 mmol). The reaction solution was cooled to 0 °C, and TIPSOTf (123 μL, 0.46 mmol) was added dropwise. After being stirred at 0 °C for 5 min the solution became opaque and was allowed to warm to room temperature over 30 min. The rubber septum was temporarily removed, and $La(OTf)_3$ (18 mg, 0.03 mmol) was added under a stream of argon. After the solution was

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stirred for an additional 5 min, a solution of (+)-**11** (42 mg, 0.31 mmol) in CH_2Cl_2 (400 μL) was added, and the reaction was allowed to stir for 11 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL), filtered through Celite, and concentrated in vacuo to provide a colorless, opaque oil. The crude reaction mixture was purified by column chromatography (SiO_2, 5−8% EtOAc in hexanes) to afford (+)-**38** (89 mg, 91%) as a clear oil. Compound **38** was found to decompose at room temperature and was stored and transferred as a solution of 1% NEt_3 in benzene in base-treated glassware to slow down this decomposition: $[\alpha]^{25}_D$ + 26.9 (*c* 0.25, CH_2Cl_2); R_f = 0.65 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 5.82 (s, 1H), 4.93 (d, *J* = 4.0 Hz, 1H), 4.91 (s, 1H), 4.86 (s, 1H), 4.36 (t, *J* = 5.5 Hz, 1H), 2.92 (d, *J* = 9.9 Hz, 1H), 2.81 (d, *J* = 7.2 Hz, 1H), 2.64 (m, 1H), 2.53 (m, 1H), 2.50 (dd, *J* = 10.0, 5.9 Hz, 1H), 2.34 (dd, *J* = 17.0, 7.5 Hz, 1H), 2.30 (d, *J* = 16.1 Hz, 1H), 2.23 (ddt, *J* = 17.0, 7.5, 1.7 Hz, 1H), 1.96 (ddd, *J* = 13.5, 5.2, 3.3 Hz, 1H), 1.70 (s, 3H), 1.66 (ddd, *J* = 13.4, 9.5, 5.6 Hz, 1H), 1.20 (dd, *J* = 7.0, 3.3 Hz, 1H), 1.15 (brs, 24H); ^{13}C NMR (126 MHz, C_6D_6) δ 175.4, 152.8, 146.6, 139.4, 130.2, 119.3, 116.7, 109.1, 101.6, 98.9, 84.3, 54.1, 48.6, 46.6, 43.0, 36.8, 34.0, 23.7, 20.5, 17.3, 12.1; IR (thin film) ν 1748, 1019, 897 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{29}H_{43}F_3NaO_7SSi$ (M + Na)$^+$ 643.2349, found 643.2351.

(±)-38 and (±)-39. To a solution of (±)-**23** (100 mg, 0.31 mmol) in CH_2Cl_2 (3 mL) was added 2,2,6,6-tetramethylpiperidine (260 μL, 1.52 mmol). The reaction solution was cooled to 0 °C, and TIPSOTf (250 μL, 0.92 mmol) was added dropwise. After being stirred at 0 °C for 5 min, the solution became opaque and was allowed to warm to room temperature for 30 min. The rubber septum was temporarily removed, and La(OTf)$_3$ was added under a stream of argon. After the solution was stirred for an additional 5 min, a solution of (±)-**11**[29] (83 mg, 0.61 mmol) in CH_2Cl_2 (1 mL) was added, and the reaction was allowed to stir for 14 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL), filtered through Celite, and concentrated in vacuo to provide a clear, opaque oil. The crude reaction mixture was purified by column chromatography (SiO_2, 3−8% EtOAc in hexanes) to afford (±)-**38** (105 mg, 55%) and (±)-**39** (69 mg, 36%) as clear oils. **39**: R_f = 0.6 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, C_6H_6) δ 5.74 (s, 1H), 5.08 (d, *J* = 3.8 Hz, 1H), 4.93 (s, 2H), 4.88 (s, 2H), 4.19 (t, *J* = 5.3 Hz, 1H), 2.82 (d, *J* = 10.0 Hz, 1H), 2.78 (d, *J* = 8.2 Hz, 1H), 2.51 (dd, *J* = 8.5, 4.6 Hz, 2H), 2.36−2.15 (m, 3H), 1.69 (s, 3H), 1.60 (ddd, *J* = 13.0, 9.8, 5.7 Hz, 1H), 1.42 (dt, *J* = 13.6, 4.1 Hz, 1H), 1.36−1.27 (m, 2H), 1.21 (t, *J* = 7.1 Hz, 21H), 1.06 (dd, *J* = 16.0, 5.1 Hz, 1H), 1.01 (s, 3H); ^{13}C NMR (126 MHz, C_6D_6) δ 175.79, 152.62, 147.59, 140.29, 131.24, 128.35, 128.25, 128.06, 127.87, 110.25, 103.30, 99.85, 85.28, 55.12, 49.50, 47.97, 43.85, 37.84, 35.10, 34.71, 30.31, 24.88, 21.11, 18.36, 18.29, 18.25, 13.11, 13.01; IR (thin film) ν 2861, 1739, 897 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{29}H_{43}F_3NaO_7SSi$ (M + Na)$^+$ 643.2349, found 643.2356.

Ketone 42. To a solution of **38** (2 mg, 0.003 mmol) in CH_2Cl_2 (100 μL) were added NaOMe (1 mg, 0.019 mmol) and MeOH (100 μL). The reaction solution was allowed to stir for 15 min at which point no starting material was visible by TLC. The reaction solution was diluted with Et_2O (4 mL) and washed with satd aq $NaHCO_3$ (3 × 4 mL) and NaCl (4 mL). The resulting organic layer was dried over $MgSO_4$ and concentrated in vacuo to a yellow oil which was purified by column chromatography (SiO_2, 20−50% EtOAc in hexanes with 0.2% NEt_3) to afford **42** (1 mg, 60%) as a yellow oil: IR (thin film) ν 2841, 1749, 1720, 845 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 4.91 (s, 1H), 4.87 (s, 1H), 4.84 (d, *J* = 3.7 Hz, 1H), 4.47 (t, *J* = 6.8 Hz, 1H), 3.58 (d, *J* = 17.9 Hz, 1H), 3.49 (d, *J* = 17.8 Hz, 1H), 2.88−2.82 (m, 1H), 2.80 (ddd, *J* = 10.9, 7.1, 2.9 Hz, 1H), 2.73 (dd, *J* = 5.7, 3.0 Hz, 1H), 2.47−2.41 (m, 1H), 2.33 (dd, *J* = 17.2, 5.8 Hz, 1H), 2.23 (d, *J* = 15.9 Hz, 1H), 1.95 (d, *J* = 11.4 Hz, 1H), 1.79 (dt, *J* = 13.8, 4.5 Hz, 1H), 1.71 (s, 3H), 1.64 (ddd, *J* = 14.1, 9.2, 5.8 Hz, 1H), 1.28 (dd, *J* = 15.5, 6.6 Hz, 1H), 1.21 (dd, *J* = 7.3, 4.1 Hz, 1H), 1.16−1.12 (m, 21H), 0.79 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 215.5, 176.7, 154.1, 147.6, 110.12, 101.8, 92.46, 84.4, 71.5, 59.4, 48.6, 45.8, 44.6, 37.8, 35.7, 34.8, 31.4, 22.4, 21.6, 18.3, 18.3, 13.1; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{44}NaO_5Si$ (M + Na)$^+$ 511.2856, found 511.2855.

Ketone 47. To a solution of **38** (10 mg, 0.016 mmol) in THF (300 μL) was added a solution of HCl (4 M in dioxane, 8 μL, 0.032 mmol). The reaction solution was allowed to stir for 2 h at room temperature, at which point no starting material was visible by TLC. The reaction solution was diluted with Et_2O (10 mL) and washed with satd aq $NaHCO_3$ (7 mL × 3) and NaCl (7 mL). The resulting organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to a yellow oil to afford **47** (6 mg, 80%) as a clear oil: R_f = 0.55 (50% EtoAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 5.82 (s, 1H), 4.85 (s, 1H), 4.83 (s, 1H), 3.93 (t, *J* = 5.3 Hz, 1H), 2.75 (d, *J* = 9.7 Hz, 1H), 2.47 (d, *J* = 7.2 Hz, 1H), 2.44−2.35 (m, 3H), 2.30 (dt, *J* = 10.1, 1.9 Hz, 1H), 2.20 (d, *J* = 15.9 Hz, 1H), 2.03 (dd, *J* = 14.3, 5.7 Hz, 1H), 2.01−1.96 (m, 1H), 1.88−1.78 (m, 4H), 1.52 (s, 4H), 1.44 (ddd, *J* = 14.1, 10.2, 4.3 Hz, 1H), 1.08 (dd, *J* = 16.0, 5.1 Hz, 1H), 1.00 (s, 4H); ^{13}C NMR (126 MHz, C_6 D_6) δ 207.1, 175.1, 146.7, 140.5, 130.8, 112.5, 99.6, 85.0, 54.5, 48.5, 47.5, 45.9, 44.6, 43.8, 40.2, 34.5, 31.1, 25.0, 21.9; IR (thin film) ν 1739, 1720, 892 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{23}F_3NaO_7S$ (M + Na)$^+$ 487.1014, found 487.1021.

Bromolactone 50. To a solution of lactone **23** (39 mg, 0.12 mmol) in CH_2Cl_2 (1.2 mL) was added NEt_3 (100 μL, 0.71 mmol, 6 equiv) followed by TIPSOTf (95 μL, 0.36 mmol, 3 equiv). The reaction solution was stirred at 0 °C for 30 min and cooled to −20 °C, and NBS (33 mg, 0.18 mmol, 1.5 equiv) was added in CH_2Cl_2 (300 μL). The reaction solution was stirred for 4 h. During this time the solution color changed from light yellow to dark brown. The reaction solution was diluted with Et_2O (4 mL) and washed with satd aq $NaHCO_3$ (3 × 4 mL) and brine (4 mL). The organic layer was dried over $MgSO_4$, filtered through cotton, and concentrated in vacuo. Purification via flash chromatography (SiO_2, 7−10% EtOAc in hexanes) afforded **50** as a white solid (41 mg, 82%). X-ray quality crystals of **50** were grown by vapor diffusion crystallization (acetone/pentane) to give colorless translucent needles. **50**: mp =115 dec; ^{1}H NMR (500 MHz, C_6D_6) δ 5.74 (s, 1H), 4.39 (s, 1H), 4.34 (t, *J* = 4.6 Hz, 1H), 2.64 (d, *J* = 9.8 Hz, 1H), 2.12 (dd, *J* = 10.0, 4.7 Hz, 1H), 2.10 (d, *J* = 16.2 Hz, 1H), 0.85 (dd, *J* = 16.3, 4.6 Hz, 1H), 0.84 (s, 3H); ^{13}C (125 MHz, C_6D_6) ∂ 170.8, 140.9, 129.1, 100.0, 85.7, 53.8, 53.6, 42.8, 40.3, 25.0; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{10}BrF_3NaO_6S$ (M + Na)$^+$ 428.9231, found 428.9236.

Sulfide 51. To a solution of lactone **23** (39 mg, 0.12 mmol) in CH_2Cl_2 (1.2 mL) was added 2,2,6,6-tetramethylpiperidine (124 μL, 0.73 mmol, 6 equiv) followed by TIPSOTf (130 μL, 0.49 mmol, 4 equiv). The reaction solution was stirred at 0 °C while PhSCl was prepared. Following the procedure of Fuchs,[43] a solution of NCS (1.33 mg, 0.98 mmol) in CH_2Cl_2 (1 mL) was stirred at −20 °C while thiophenol (100 μL, 0.98 mmol) was added dropwise slowly to avoid exotherm. The solution was allowed to stir for 15 min, resulting in an orange solution of approximately 1 M PhSCl in CH_2Cl_2. To the reaction solution of **23** was added the freshly prepared solution of PhSCl (1 M in CH_2Cl_2, 490 μL, 0.487 mmol, 4 equiv), and the resulting solution was allowed to stir at −20 °C for 5 h. The red solution was diluted with Et_2O (40 mL) and washed with satd aq $Na_2S_2O_3$ (40 mL), satd aq $NaHCO_3$ (3 × 40 mL), and satd aq NaCl (40 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification via flash chromatography (SiO_2, 10−20% EtOAc in hexanes) afforded **51** as a white solid (49 mg, 93%): R_f = 0.3 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 7.52 (d, *J* = 7.7 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 2H), 6.95 (t, *J* = 7.4 Hz, 1H), 5.77 (s, 1H), 4.30 (t, *J* = 5.1 Hz, 1H), 4.10 (s, 1H), 2.76 (d, *J* = 9.8 Hz, 1H), 2.34 (dd, *J* = 9.8, 5.4 Hz, 1H), 2.14 (d, *J* = 16.0 Hz, 1H), 0.97 (dd, *J* = 16.0, 5.0 Hz, 1H), 0.89 (s, 3H); ^{13}C NMR (126 MHz, C_6D_6) δ 172.5, 140.7, 133.2, 129.7, 128.9, 128.6, 119.0 (q, *J* = 327 Hz, CF_3), 99.7, 85.3, 54.2, 51.2, 48.2, 43.5, 24.8; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{15}F_3NaO_6S_2$ (M + Na)$^+$ 459.0160, found 459.0159.

Sulfone 52. To stirred solution of sulfide **51** (50 mg, 0.11 mmol) in CH_2Cl_2 (1.2 mL) at 0 °C was added a solution of *m*-CPBA (70 mg, 0.29 mmol, 2.5 equiv) in CH_2Cl_2 (500 μL) dropwise over 5 min. After the solution was stirred at 0 °C for 2 h, the reaction vial was removed from the cooling bath and the solution allowed to stir at room temperature. After 2 h, no sulfide **51** or the intermediate sulfoxide was present in the reaction as observed by TLC. The reaction solution was

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diluted with Et_2O (20 mL) and washed with 0.5 M aq $Na_2S_2O_3$ (15 mL), satd aq $NaHCO_3$ (2 × 20 mL), and satd aq NaCl (20 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude material was purified by column chromatography (SiO_2, 10−30% EtOAc in hexanes) to afford **52** (51 mg, 98%) as a white solid: R_f = 0.6 (33% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 7.93 (d, J = 7.1 Hz, 2H), 6.93−6.82 (m, 3H), 5.58 (s, 1H), 4.88 (t, J = 5.4 Hz, 1H), 4.17 (s, 1H), 3.44 (dd, J = 10.1, 5.7 Hz, 1H), 2.86 (d, J = 10.0 Hz, 1H), 2.15 (d, J = 16.2 Hz, 1H), 1.00 (dd, J = 16.3, 5.2 Hz, 1H), 0.87 (s, 3H); ^{13}C NMR (126 MHz, C_6D_6) δ 166.98, 141.08, 137.38, 134.57, 130.07, 129.45, 99.65, 87.29, 69.02, 54.11, 45.00, 43.35, 24.45; HRMS (ESI) m/z calcd for $C_{17}H_{15}F_3NaO_8S_2$ $(M + Na)^+$ 491.0058, found 491.0054.

Hydroxy Acid 57. Lactone **38** (46 mg, 0.0741 mmol) was concentrated in vacuo into a base-treated 20 mL vial from a solution of 1% NEt_3 in benzene (ca. 5 mL). Upon concentration, CH_2Cl_2 (1.5 mL) was immediately added followed by the addition of NaOH (1 M in 1:9 H_2O/MeOH, 740 mL, 0.740 mmol) and MeOH (1 mL), and the resulting cloudy solution was stirred for 4 h at room temperature. The reaction solution was diluted with Et_2O (70 mL) and washed with satd aq $NaHCO_3$ (3 × 40 mL) and satd aq NaCl (40 mL). NEt_3 (0.5 mL) was added, and the organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to yield **57** as a triethylammonium complex that was used without further purification: R_f = 0.15 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 5.25 (d, J = 4.9 Hz, 1H), 5.04 (s, 1H), 4.90 (s, 0H), 4.66 (d, J = 16.0 Hz, 1H), 4.43 (dd, J = 4.5, 2.4 Hz, 1H), 3.96 (d, J = 15.9 Hz, 1H), 3.68 (t, J = 8.8 Hz, 1H), 3.34 (brm, 1H), 3.09 (brm, 1H), 2.54−2.40 (m, 3H), 2.14 (d, J = 13.3 Hz, 1H), 1.83 (s, 3H), 1.81−1.70 (m, 2H), 1.41 (s, 3H), 1.40−1.33 (m, 2H), 1.25−1.15 (m, 21H); ^{13}C NMR (126 MHz, C_6D_6) δ 180.4, 151.4, 149.6, 109.3, 105.8, 90.1, 74.9, 71.8, 55.3, 52.4, 48.2, 47.9, 44.7, 37.8, 35.9, 35.8, 31.5, 30.2, 28.7, 21.5, 18.5, 18.4, 13.2, 8.4; IR (thin film) ν 3108, 1748, 1716, 892 cm^{-1}; HRMS (ESI) m/z calcd for $C_{34}H_{62}NO_6Si$ $(M + HNEt_3)^+$ 608.4346, found 608.4351.

TMS Ether 62. Hydroxy acid **57** (40 mg, 0.0805 mmol) was concentrated in vacuo into a base-treated 20 mL vial from a solution of 1% NEt_3 in benzene (ca. 5 mL). Immediately upon concentration, a rubber septum was placed over the vial and CH_2Cl_2 (1 mL) and TMS-imidazole (1 mL) were added. The resulting solution was stirred for 15 min at room temperature. The reaction vial was placed into an ice bath and allowed to cool to 0 °C. The reaction was diluted with Et_2O (5 mL), and MeOH (1 mL) was added to quench the excess TMS-imidazole. The slurry was warmed to room temperature, diluted with Et_2O (50 mL), and washed with satd aq $NaHCO_3$ (100 mL × 4) and satd aq NaCl (100 mL). NEt_3 (0.2 mL) was added to the organic layer to prevent decomposition. The organic layer was dried over $MgSO_4$ and concentrated in vacuo into a base-treated vial. The resulting oil was purified by column chromatography (SiO_2, 2−5% EtOAc with 1% NEt_3 in hexanes) to afford **62** as a clear oil in approximately 90% purity by ^{1}H NMR (14 mg, 31%). Acid **62** was found to decompose and therefore was stored at −78 °C in a frozen solution of 1% NEt_3 in benzene: R_f = 0.55 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 5.34 (d, J = 3.5 Hz, 1H), 5.03 (s, 1H), 4.95 (s, 1H), 4.24−4.18 (m, 2H), 3.87 (d, J = 16.3 Hz, 1H), 3.47 (dd, J = 11.5, 3.6 Hz, 1H), 3.27 (brs, 1H), 2.62−2.56 (m, 2H), 2.48 (ddd, J = 11.3, 8.4, 2.6 Hz, 1H), 2.44−2.38 (m, 2H), 2.31 (dd, J = 17.0, 8.3 Hz, 1H), 2.16 (d, J = 8.2 Hz, 1H), 2.03−2.02 (m, 1H), 1.91 (d, J = 14.7 Hz, 1H), 1.81 (s, 3H), 1.46 (dd, J = 14.8, 4.0 Hz, 2H), 1.32−1.16 (m, 24H); ^{13}C NMR (126 MHz, C_6D_6) δ 215.3, 179.1, 150.8, 148.7, 110.0, 106.0, 89.7, 75.1, 71.7, 54.3, 51.1, 49.6, 45.3, 38.5, 35.0, 34.8, 28.5, 28.4, 21.6, 18.5, 13.1, 0.0; HRMS (ESI) m/z calcd for $C_{37}H_{70}NO_6Si_2$ $(M + HNEt_3)^+$ 680.4747, found 680.4740.

Methyl Ester 63. Carboxylic acid **62** (4 mg, 0.007 mmol) was concentrated in vacuo into a base-treated 1 dram vial from a solution of 1% NEt_3 in benzene (1 mL). A solution of DBU (20 μL, 0.14 mmol in MeCN (400 μL) was added under argon, and the reaction vial was placed in an ice bath and allowed to cool to 0 °C. MeI (17 μL, 0.28 mmol) was added, and the reaction solution was stirred at 0 °C for 8 h. To the reaction vial was added benzene (1 mL), and the reaction was concentrated in vacuo to approximately 200 μL total volume. The solution was diluted with Et_2O (4 mL) and hexane (4 mL), and NEt_3 (250 μL) was added to prevent decomposition of the desired product and to remove residual MeI. The solution was allowed to stand at room temperature for 15 min. The opaque organic solution was washed with satd aq $NaHCO_3$ (4 mL × 5) and satd aq NaCl (4 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo into a base-treated vial. The residue was purified by column chromatography (SiO_2, 2−4% EtOAc in hexanes with 0.1% NEt_3) to afford **63** (4 mg, quantitative) as a colorless oil: R_f = 0.70 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 5.34 (d, J = 3.3 Hz, 1H), 4.99 (s, 1H), 4.91 (t, J = 1.6 Hz, 1H), 4.20 (d, J = 16.3 Hz, 1H), 4.12 (dd, J = 3.9, 2.7 Hz, 1H), 3.87 (dd, J = 16.3, 1.2 Hz, 1H), 3.46 (s, 3H), 3.44 (d, J = 3.4 Hz, 1H), 3.24−3.21 (m, 1H), 2.53 (ddd, J = 11.4, 8.3, 2.8 Hz, 1H), 2.43−2.24 (m, 2H), 2.15 (d, J = 8.3 Hz, 1H), 1.96 (dt, J = 13.2, 3.3 Hz, 2H), 1.88 (d, J = 14.8 Hz, 1H), 1.77 (s, 2H), 1.62 (ddd, J = 13.4, 9.6, 6.7 Hz, 1H), 1.45 (dd, J = 14.8, 4.0 Hz, 1H), 1.28−1.15 (m, 24H); ^{13}C NMR (126 MHz, C_6D_6) δ 215.3, 174.8, 150.8, 148.4, 110.02, 105.9, 89.6, 74.9, 71.6, 54.3, 51.0, 50.9, 49.5, 45.1, 38.4, 34.9, 34.6, 28.4, 28.0, 21.5, 18.4, 13.1, −0.2; IR (thin film) ν 1748, 1732, 1712, 906 cm^{-1}; HRMS (ESI) m/z calcd for $C_{32}H_{56}O_6Si_2Na$ $(M + Na)^+$ 615.3513, found 615.3510.

Methyl Ester 63 and Ketal 64. Hydroxy acid **57** (38 mg, 0.074 mmol) was concentrated in vacuo into a base-treated 20 mL vial from a solution of 1% NEt_3 in benzene (5 mL). Immediately upon concentration a rubber septa was placed over the vial, and CH_2Cl_2 (1 mL) followed by TMS-imidazole (1 mL) were added. The resulting solution was stirred for 15 min at room temperature. The reaction vial was placed into an ice bath and allowed to cool to 0 °C. The reaction was diluted with Et_2O (5 mL), and MeOH (1 mL) was added with vigorous stirring. The slurry was warmed to room temperature, diluted with Et_2O (50 mL), and washed with satd aq $NaHCO_3$ (4 × 100 mL) and satd aq NaCl (100 mL). NEt_3 (0.2 mL) was added to the organic layer to prevent decomposition. The organic layer was dried over $MgSO_4$ and concentrated in vacuo into a base-treated 20 mL vial. Under argon, a solution of DBU (210 μL, 1.4 mmol) in MeCN (1.5 mL) was added, and the reaction vial was placed in an ice bath and allowed to cool to 0 °C. MeI (175 μL, 2.8 mmol) was added, and the reaction solution was stirred at 0 °C for 8 h. To the reaction vial was added benzene (5 mL), and the reaction was concentrated in vacuo to approximately 400 μL total volume. The solution was diluted with Et_2O (30 mL) and hexane (30 mL), and NEt_3 (1 mL) was added to prevent decomposition and to remove residual MeI. The opaque organic solution was washed with satd aq $NaHCO_3$ (5 × 60 mL) and satd aq NaCl (60 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo into a base-treated vial. The residue was purified by column chromatography (SiO_2, 2.5−6% EtOAc in hexanes with 1% NEt_3) to afford **63** (24 mg, 54%) and **64** (18 mg, 41%) as colorless oils. **64**: R_f = 0.75 (20% EtOAc in hexanes); 1H NMR (500 MHz, C_6D_6) δ 5.06 (d, J = 3.8 Hz, 1H), 4.95 (s, 1H), 4.87 (s, 1H), 4.16 (s, 1H), 3.98 (d, J = 8.2 Hz, 1H), 3.88 (d, J = 8.2 Hz, 1H), 3.53 (dd, J = 11.1, 5.8 Hz, 1H), 3.41 (s, 3H), 2.82−2.76 (m, 1H), 2.51−2.45 (m, 1H), 2.43 (s, 1H), 2.33 (dd, J = 17.2, 5.6 Hz, 1H), 2.26 (d, J = 10.6 Hz, 1H), 2.26−2.19 (m, 1H), 1.86 (dt, J = 13.6, 4.1 Hz, 1H), 1.76−1.71 (m, 1H), 1.72 (s, 3H), 1.59 (ddd, J = 13.3, 9.5, 6.0 Hz, 1H), 1.30−1.26 (m, 2H), 1.27 (s, 3H), 1.22−1.18 (m, 19H), 0.25 (s, 9H); ^{13}C NMR (126 MHz, C_6D_6) δ 175.4, 151.4, 148.1, 128.3, 128.1, 127.9, 110.9, 110.0, 105.1, 85.3, 79.8, 74.5, 57.1, 51.0, 47.3, 45.4, 38.2, 35.4, 35.0, 30.2, 28.8, 25.0, 21.4, 18.4, 13.13, 1.6; IR (thin film) ν 1748, 1732, 883 cm-1; HRMS (ESI) m/z calcd for $C_{32}H_{56}O_6Si_2Na$ $(M + Na)^+$ 615.3513, found 615.3508.

Conversion of Ketal 64 to Hydroxy Acid 57. Ketal **64** (34 mg, 0.057 mmol) was concentrated in vacuo into a base-treated 20 mL vial from a solution of 1% NEt_3 in benzene (ca. 5 mL). Upon concentration, CH_2Cl_2 (1 mL) was immediately added followed by the addition of NaOH (1 M in 1:9 H_2O/MeOH, 530 μL, 0.53 mmol) and MeOH (700 μL), and the resulting cloudy solution was stirred for 4 h at room temperature. The reaction solution was diluted with Et_2O (40 mL) and washed with satd aq $NaHCO_3$ (3 × 40 mL) and satd aq NaCl (40 mL). The organic layer was dried over $MgSO_4$ and concentrated in vacuo to yield **57** as a triethylammonium salt that was

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used without further purification. All spectral data were in complete agreement with previously prepared samples of **54**.

Enoxysilane 66. Ketone **63** (7.0 mg, 0.012 mmol) was concentrated in vacuo into a base-treated 1 dram vial from a solution of 1% NEt_3 in benzene (1 mL). Under argon, THF (400 μL) was added, and the reaction solution was cooled to −78 °C. As solution of freshly prepared lithium diisopropylamide (0.4 M in THF, 60 mL, 0.024 mmol) was added followed by a solution of TMSCl (2.3 μL, 0.018 mmol) in THF (50 μL). The reaction vial was placed in a 0 °C ice bath and allowed to stir for 30 min, at which time only trace starting material remained by TLC. NEt_3 (100 μL) was then added, and the reaction was diluted with Et_2O (5 mL). The crude reaction solution was washed with satd aq $NaHCO_3$ (3 × 4 mL) and satd aq NaCl (4 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo into a base treated 1 dram vial to provide **66** as a colorless oil (7 mg, 90%). The crude oil was used without further purification in subsequent reactions. Purification by column chromatography (SiO_2, 1−3% EtOAc in hexanes with 1% NEt_3) provided **66** (2.3 mg, 31%) as well as recovered ketone **63** (3.5 mg). Enoxysilane **66** was found to easily undergo desilylation, and was therefore stored at −78 °C in a frozen solution of 1% NEt_3 in benzene: R_f = 0.72 (10% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 5.93 (s, 1H), 5.08 (s, 1H), 4.99 (s, 1H), 4.93 (s, 1H), 4.38 (t, J = 3.9 Hz, 1H), 3.54−3.43 (s, 3H), 3.11 (dd, J = 11.4, 3.8 Hz, 1H), 3.12−2.90 (m, 2H), 2.46−2.41 (m, 2H), 2.40−2.23 (m, 2H), 2.15 (d, J = 14.6 Hz, 1H), 1.99−1.93 (m, 1H), 1.77 (s, 3H), 1.76−1.71 (m, 3H), 1.46 (dd, J = 14.6, 4.3 Hz, 1H), 1.29 (s, 3H), 1.23−1.13 (m, 24H), 0.16 (s, 9H), 0.14 (s, 9H); ^{13}C NMR (126 MHz, C_6D_6) δ 175.8, 150.1, 147.7, 136.2, 126.7, 110.2, 106.7, 92.5, 76.3, 55.4, 50.8, 48.8, 46.7, 38.5, 34.7, 33.2, 27.6, 27.4, 22.0, 18.4, 18.4, 13.1, 0.4, −0.1; HRMS (ESI) m/z calcd for $C_{35}H_{64}O_6Si_3Na$ $(M + Na)^+$ 687.3908, found 687.3911.

Enamine 67. Ketone **63** (10 mg, 0.017 mmol) was concentrated in vacuo into a base-treated 1 dram vial from a solution of 1% NEt_3 in benzene (1 mL). Pyrrolidine (500 μL was added under argon, and the reaction solution was cooled to 0 °C. A freshly prepared solution of $TiCl_4$ (10% v/v in benzene, 150 μL, 0.14 mmol) was added to the reaction, resulting in color change from pale yellow to dark brown. The reaction vial was removed from the ice bath and allowed to stir at room temperature for 18 h. The reaction solution was diluted with Et_2O (5 mL), and satd aq $NaHCO_3$ was added (1 mL) to quench excess $TiCl_4$. After the evolution of CO_2 had stopped, the organic layer was removed and washed with satd aq $NaHCO_3$ (3 × 4 mL) and satd aq NaCl (4 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo along with 1% NEt_3 in benzene (5 mL) into a base-treated vial to provide **67** (10 mg, 90%) as a yellow oil. Enamine **67** was found to be unstable to silica chromatography, including TLC, and therefore, crude oil was used in further reactions without purification: ^{1}H NMR (500 MHz, C_6D_6) δ 5.85 (s, 1H), 5.04 (d, J = 2.9 Hz, 1H), 4.98 (s, 1H), 4.90 (s, 1H), 4.56 (t, J = 3.9 Hz, 1H), 3.51 (s, 3H), 3.44 (dd, J = 11.0, 3.4 Hz, 1H), 2.83 (d, J = 8.7 Hz, 1H), 2.79−2.72 (m, 3H), 2.46−2.23 (m, 5H), 2.19 (d, J = 14.5 Hz, 1H), 1.93 (dt, J = 6.6, 3.3 Hz, 1H), 1.78 (s, 3H), 1.74 (dd, J = 13.9, 7.0 Hz, 1H), 1.68 (t, J = 3.6 Hz, 4H), 1.41 (dd, J = 14.5, 4.1 Hz, 1H), 1.31 (s, 3H), 1.27−1.14 (m, 26H), 0.18 (s, 9H); ^{13}C NMR (126 MHz, C_6D_6) δ 175.2, 150.1, 148.2, 130.1, 129.1, 110.0, 107.1, 94.1, 77.0, 54.0, 52.6, 51.0, 50.7, 47.2, 46.6, 38.5, 34.8, 34.2, 28.0, 26.4, 24.0, 21.9, 18.4, 13.1, 0.5; HRMS (ESI) m/z calcd for $C_{36}H_{64}NO_5Si_2$ $(M + H)^+$ 646.4323, found 646.4328.

Unknown Oxidation Product 72. Enamine **67** (5 mg, 0.008 mmol) was concentrated in vacuo into a base-treated 1 dram vial from 1% NEt_3 in benzene. Under argon, 2,2,6,6-di-*tert*-butylpyridine (25 μL, 0.115 mmol) and DMF (1 mL) were added, and the solution was allowed to stir at room temperature for 1 min. $PtCl_2$ (2.6 mg, 0.016 mmol) was added, and the solution was stirred at room temperature. After 12 h, a significant amount of Pt(0) had precipitated onto the flask. The reaction solution was diluted with Et_2O (10 mL) and filtered through Celite. The resulting solution was washed with satd aq $NaHCO_3$ (8 mL × 3) and satd aq NaCl (8 mL), dried over $MgSO_4$ filtered, and concentrated in vacuo to a yellow oil. Purification of the crude material by column chromatography (SiO_2, 0.5−3% EtOAc in hexanes) provided **72** (3.6 mg, 80%) as a yellow oil: R_f = 0.55 (20% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 6.05 (s, 1H), 5.12 (s, 1H), 5.06 (dd, J = 5.5, 3.0 Hz, 1H), 4.91 (s, 1H), 4.58 (s, 0H), 3.84 (d, J = 5.6 Hz, 1H), 3.43 (s, 3H), 2.93−2.84 (m, 2H), 2.77−2.68 (m, 2H), 2.48 (dt, J = 11.4, 5.8 Hz, 1H), 2.36 (d, J = 10.9 Hz, 1H), 2.06−1.98 (m, 2H), 1.96−1.88 (m, 4H), 1.89 (s, 3H), 1.73−1.64 (m, 1H), 1.57 (dq, J = 12.9, 6.6 Hz, 1H), 1.50 (dd, J = 12.3, 6.6 Hz, 1H), 1.46 (s, 1H), 1.44 (s, 3H), 1.38−1.29 (m, 2H), 1.17−1.05 (m, 21H); ^{13}C NMR (126 MHz, C_6D_6) δ 177.3, 150.2, 114.5, 109.4, 96.9, 96.1, 78.6, 75.4, 70.2, 51.2, 51.0, 50.8, 49.2, 47.7, 46.7, 45.6, 36.6, 34.5, 32.4, 31.8, 31.1, 29.2, 25.8, 21.3, 18.5, 13.2; IR (thin film) ν 3406, 3229, 1742, 1088 cm^{-1}; HRMS (ESI) m/z calcd for $C_{33}H_{55}NNaO_6Si$ $(M + Na)^+$ 612.3696, found 612.3692.

Bromides 73 and 76. Enoxysilane **63** (20 mg, 0.034 mmol) was concentrated in vacuo into a base-treated 1 dram vial from 1% NEt_3 in benzene. CH_2Cl_2 (1.5 mL) was added under argon, and the reaction solution was placed in a−78 °C cooling bath and allowed to stir for 5 min. A solution of NBS (9 mg, 0.051 mmol) in CH_2Cl_2 (300 μL) was added dropwise over 5 min, and the resulting pale yellow solution was stirred at −78 °C for 15 min. Saturated aq $Na_2S_2O_3$ (300 μL) was added dropwise with vigorous stirring, and the reaction flask was removed from the cooling bath and allowed to slowly warm to room temperature. The biphasic solution was diluted with Et_2O (20 mL), and the organic layer was washed with satd aq $NaHCO_3$ (3 × 20 mL) and satd aq NaCl (20 mL). The solution was dried over $MgSO_4$, filtered, and concentrated to provide a yellow oil. The crude material was found to contain **73** as a single isomer in approximately 90% purity by ^{1}H NMR, along with trace amounts of the C4 bromide epimer and enoxysilane **76**. The crude oil was purified by column chromatography (SiO_2, 3−15% EtOAc in hexanes) to provide bromide **73** (14.5 mg, 83%, 3:1 mixture of C4 epimers) and enoxysilane **76** (2 mg, 7%). **73**: R_f = 0.4 (20% EtOAc/hexanes); ^{1}H NMR (500 MHz, C_6D_6 δ 4.81 (s, 1H), 4.77−4.71 (m, 2H), 4.15 (d, J = 16.3 Hz, 1H), 4.10 (t, J = 3.4 Hz, 1H), 3.84 (d, J = 16.3 Hz, 1H), 3.67 (dd, J = 11.5, 4.2 Hz, 1H), 3.34 (s, 3H), 3.31 (t, J = 4.8 Hz, 1H), 2.97 (dd, J = 14.7, 10.4 Hz, 1H), 2.55−2.47 (m, 1H), 2.35 (ddd, J = 11.1, 7.9, 2.5 Hz, 1H), 2.21−2.11 (m, 2H), 1.90 (d, J = 8.1 Hz, 1H), 1.86−1.80 (m, 2H), 1.55 (d, J = 7.4 Hz, 1H), 1.53 (s, 3H), 1.17 (s, 3H), − 0.05 (s, 9H); ^{13}C NMR (126 MHz, C_6D_6) δ 214.6, 200.6, 174.2, 146.6, 111.7, 89.4, 74.5, 71.5, 56.2, 53.8, 50.9, 50.6, 49.2, 43.9, 43.7, 41.4, 40.2, 28.4, 26.9, 20.5, −0.3; IR (thin film) ν 1781, 1732, 1708, 1108 cm-1; HRMS (ESI) m/z calcd for $C_{23}H_{35}BrNaO_6Si$ $(M + Na)^+$ 537.1284, found 537.1288.

76: R_f = 0.4 (20% EtOAc/hexanes); ^{1}H NMR (499 MHz, C_6D_6) δ 5.11 (s, 1H), 5.03 (d, J = 3.9 Hz, 1H), 4.98 (d, J = 4.6 Hz, 1H), 4.92 (t, J = 1.7 Hz, 1H), 4.18 (d, J = 16.3 Hz, 1H), 4.10 (dd, J = 4.0, 2.8 Hz, 1H), 3.87 (dd, J = 16.2, 1.2 Hz, 1H), 3.81 (dd, J = 11.4, 5.1 Hz, 1H), 3.46−3.42 (m, 1H), 3.41 (s, 3H), 3.35−3.30 (m, 1H), 2.48 (ddd, J = 11.0, 7.9, 2.8 Hz, 1H), 2.21 (ddd, J = 14.1, 8.1, 4.0 Hz, 1H), 2.01 (d, J = 7.9 Hz, 1H), 1.84 (d, J = 14.9 Hz, 1H), 1.83−1.77 (m, 1H), 1.76 (s, 3H), 1.44 (dd, J = 14.9, 4.2 Hz, 1H), 1.26−1.14 (m, 24H), − 0.02 (s, 9H); ^{13}C NMR (126 MHz, C_6D_6) δ 214.2, 174.6, 150.2, 147.7, 112.8, 108.9, 89.4, 74.6, 71.5, 53.8, 53.6, 51.1, 50.9, 49.2, 42.6, 42.6, 40.7, 30.2, 28.4, 26.0, 20.7, 18.4, 18.0, 13.1, 12.7, −0.2; HRMS (ESI) m/z calcd for $C_{32}H_{55}BrNaO_6Si_2$ $(M + Na)^+$ 693.2618, found 693.2617.

Lactone 77. To a stirring solution of bromide **73** (7 mg, 0.014 mmol) in CH_2Cl_2 (600 μL) was added AgOTf (7 mg, 0.028 mmol, 3 equiv). The solution was stirred for 15 min at room temperature and then diluted with Et_2O (1 mL) and filtered through Celite. The filtrate was diluted with Et_2O (4 mL) and washed with satd aq $NaHCO_3$ (4 mL × 3) and satd aq NaCL (4 mL), dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was purified by column chromatography (SiO_2, 20−50% EtOAc in hexanes) to provide lactone **77** (2 mg, 40%) as a colorless oil: R_f = 0.5 (60% EtOAc in hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 4.74 (s, 2H), 4.59 (d, J = 6.6 Hz, 1H), 4.03 (td, J = 6.5, 1.7 Hz, 1H), 3.72 (d, J = 17.8 Hz, 1H), 3.49 (d, J = 17.8 Hz, 1H), 3.22 (dd, J = 7.7, 2.9 Hz, 1H), 2.80 (dd, J = 14.5, 8.4 Hz, 1H), 2.47 (dt, J = 8.5, 4.1 Hz, 1H), 2.14 (dd, J = 15.8, 1.6 Hz, 1H), 2.10−2.02 (m, 3H), 1.82 (ddd, J = 12.4, 8.1, 3.9 Hz, 1H), 1.78−1.71 (m, 1H), 1.52 (s, 3H), 1.21 (dd, J = 15.7, 6.5 Hz, 1H), 0.79 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 214.4, 200.3, 174.4, 145.6,

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112.3, 92.1, 84.0, 71.3, 57.7, 56.2, 47.8, 44.8, 44.5, 44.3, 41.8, 39.6, 28.3, 23.5, 21.2; HRMS (ESI) m/z calcd for $C_{19}H_{23}BrNaO_5$ $(M + Na)^+$ 433.0627, found 433.0631.

Alcohol 79 and Enone 80. Bromide **73** (8 mg, 0.016 mmol) was concentrated in vacuo from benzene (1 mL) into a 1 dram vial. THF (150 mL) was added, and the solution was degassed using the freeze/pump/thaw method. The solution was cooled to 0 °C, and SmI_2 (approximately 0.05 M in THF) was added dropwise until the blue color of the reagent persisted in the solution (approximately 900 μL). At 0 °C, the reaction vial was opened to air, satd aq $NaHCO_3$ (1 mL) was added with vigorous stirring, and the biphasic solution was allowed to slowly warm to room temperature. The organic layer was separated, diluted with 4 mL Et_2O, and filtered through Celite. The filtrate was washed with satd aq $NaHCO_3$ (4 mL × 3) and satd aq NaCl (4 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a bright yellow oil. The crude material was purified by column chromatography (SiO_2, 5−30% EtOAc in hexanes with 0.2% NEt_3) to afford alcohol **79** (5 mg, 86%) and enone **80** (0.3 mg, 5%). **79**: R_f = 0.4 (40% EtOAc/hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 4.79 (s, 1H), 4.77 (s, 1H), 4.17 (d, J = 9.1 Hz, 1H), 4.14 (d, J = 9.1 Hz, 1H), 3.93−3.87 (m, 2H), 3.44 (s, 3H), 2.69 (ddd, J = 9.7, 7.8, 6.0 Hz, 1H), 2.59−2.47 (m, 2H), 2.42 (d, J = 10.3 Hz, 1H), 2.45−2.36 (m, 1H), 2.28 (d, J = 11.9 Hz, 1H), 2.23 (brs, 1H), 2.03−1.94 (m, 2H), 1.93 (ddd, J = 15.0, 6.1, 1.2 Hz, 1H), 1.63 (dd, J = 13.3, 5.6 Hz, 1H), 1.54 (s, 3H), 1.34−1.30 (m, 1H), 1.28 (s, 3H), 0.05 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.2, 175.8, 145.5, 113.5, 88.6, 79.7, 79.3, 75.5, 58.2, 57.4, 51.1, 48.2, 47.7, 45.5, 43.5, 40.6, 33.2, 32.9, 27.4, 21.9, −0.1; IR (thin film) ν 3342, 1710, 1742, 741 cm^{-1}; HRMS (ESI) m/z calcd for $C_{23}H_{36}NaO_6Si$ $(M + Na)^+$ 459.2179, found 459.2172.

Enone 80: R_f = 0.2 (15% EtOAc/hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 5.26 (d, J = 17.6 Hz, 1H), 5.17 (d, J = 17.9 Hz, 1H), 4.77 (s, 1H), 4.73 (s, 1H), 3.91 (q, J = 4.8 Hz, 1H), 3.42 (s, 3H), 2.74−2.59 (m, 2H), 2.38−2.30 (m, 2H), 2.26 (d, J = 9.9 Hz, 1H), 1.85 (dd, J = 13.8, 4.2 Hz, 1H), 1.80 (dd, J = 10.6, 4.5 Hz, 1H), 1.69−1.62 (m, 1H), 1.60 (s, 3H), 1.42−1.27 (m, 3H), 1.22 (s, 3H), 0.00 (s, 9H); HRMS (ESI) m/z calcd for $C_{23}H_{34}O_5SiNa$ $(M + Na)^+$ 441.2068, found 441.2073.

Enone 84. Alcohol **79** (4 mg, 0.009 mmol) was concentrated in vacuo into a 1 dram vial. Under air atmosphere, benzene (300 μL) was added followed by $TsOH·H_2O$ (1.7 mg, 0.009 mmol). The reaction solution was stirred at room temperature for 2 h. The solution was diluted with Et_2O (4 mL) and washed with satd aq $NaHCO_3$ (4 mL × 3) and satd aq NaCl (4 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to provide a yellow oil. The crude material was purified by column chromatography (SiO_2, 15−30% EtOAc in hexanes) to provide enone **84** (3 mg, 90%) as a clear oil: R_f = 0.2 (40% EtOAc/hexanes); ^{1}H NMR (500 MHz, C_6D_6) δ 5.20 (dt, J = 15.7, 1.8 Hz, 1H), 4.75 (s, 1H), 4.68 (s, 1H), 4.57 (ddd, J = 15.7, 3.2, 1.8 Hz, 1H), 3.90 (dt, J = 8.5, 4.2 Hz, 1H), 3.41 (s, 3H), 3.01 (dd, J = 11.0, 7.4 Hz, 1H), 2.67 (m, 1H), 2.41 (ddd, J = 11.4, 7.4, 4.3 Hz, 1H), 2.36−2.19 (m, 3H), 2.07−2.00 (m, 2H), 1.93 (dd, J = 14.6, 1.2 Hz, 1H), 1.93−1.84 (m, 1H), 1.63−1.59 (m, 1H), 1.57 (s, 3H), 1.18 (dd, J = 14.5, 4.4 Hz, 1H), 0.98 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.0, 176.6, 158.1, 147.0, 110.9, 89.6, 74.7, 70.3, 53.3, 51.4, 49.7, 46.9, 44.9, 44.3, 37.5, 36.7, 31.6, 23.8, 21.3; IR (thin film) ν 3420, 1729, 1674 cm-1; HRMS (ESI) m/z calcd for $C_{20}H_{26}NaO_5$ $(M + Na)^+$ 369.1678, found 369.1675.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02550.

NMR spectra for new compounds (PDF)

Crystallographic data for **32** (CIF)

Crystallographic data for **50** (CIF)

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Notes

The authors declare no competing financial interest.

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