Chapter 3

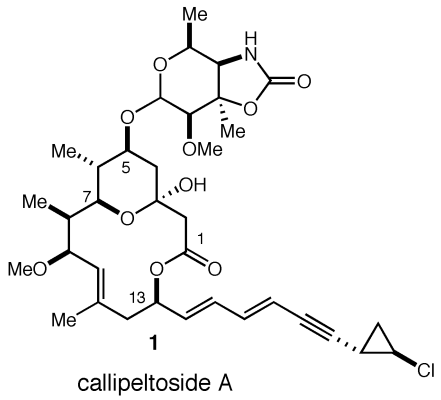
Progress towards the Total Synthesis of Callipeltoside A

I. Introduction

Isolation and biological activity

Minale and co-workers[1] first isolated callipeltoside A **1** (Figure 1) from the lithistid sponge *Callipelta* sp., which grows in the shallow waters off the east coast of New Caledonia. Preliminary *in vitro* biological investigations indicated that this structurally unique macrolide possessed potent cytotoxicity: the compound was found to inhibit the proliferation of P388 cells (IC_{50}: 11.26 μg mL^{-1}), as well as NSCLC-N6 human brochopulmonary nonsmall-cell lung carcinoma cells (IC_{50}: 15.26 μg mL^{-1}). Further results pointed to the fact that this activity was cell-cycle dependent, blocking cell proliferation in the G1 phase and thereby identified the natural product as a putative mechanism-based lead. Small amounts of two structurally related biologically active macrolides, callipeltosides B and C, which differ from callipeltoside A only in their sugar residues, were subsequently isolated from the same source.[2]

Figure 1. Callipeltoside A



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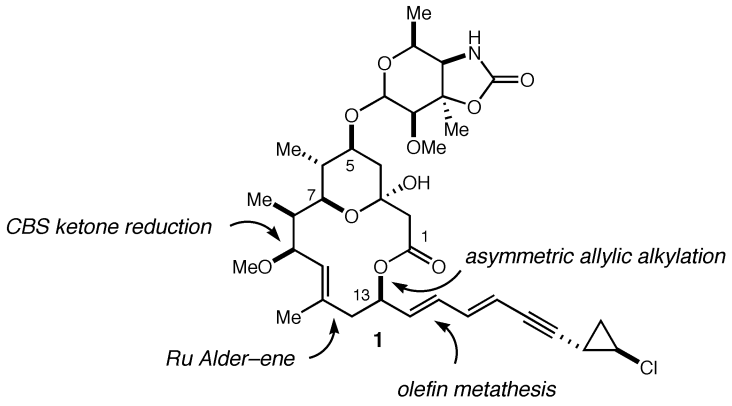
callipeltoside A

Synthetic approaches to callipeltoside A

Callipeltoside A **1** is characterized structurally by a 14-membered macrolide bearing a glycosidic linkage at C5 to a deoxyamino sugar and a dienyne *trans*-chlorocyclopropane sidechain. The macrolide bears a number of intriguing architectural features, including a six-membered hemiacetal ring, a trisubstituted olefin, and a polypropionate backbone consisting of five contiguous stereocenters. Given its unique structure and cytotoxicity, callipeltoside A has been the subject of fervent synthetic work,[3] with total syntheses of the natural product reported recently, subsequent to the commencement of the research detailed in this chapter, by Trost,[4] Evans,[5] and Paterson.[6] These syntheses have, as well, enabled the full stereochemical assignment of callipeltoside A.

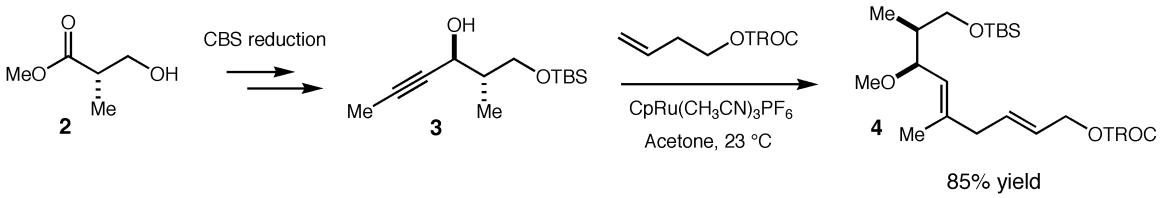
Trost's approach to callipeltoside A (Scheme 1) relies upon olefin metathesis to introduce the *trans*-chlorocyclopropane sidechain, and the deoxyamino sugar, derived from L-rhamnose, is affixed to the core *via* a glycosidic linkage. The 18 linear step construction of the macrolactone core begins with a commercially available chiral starting material, but proceeds to invoke a series of reagent-controlled asymmetric reactions to establish the required configuration of the remaining stereogenic centers. As such, the synthesis of the core utilizes a ruthenium Alder-ene coupling to establish the trisubstituted olefin geometry, a palladium catalyzed asymmetric allylic alkylation reaction, and an asymmetric CBS-oxazaborilidine ketone reduction.

Scheme 1. Trost's retrosynthesis of callipeltoside A



Elaboration of commercially available methyl (*S*)-3-hydroxy-2-methyl propionate **2** to the alkyne **3** over several steps including an asymmetric CBS-oxazaborilidine ketone reduction precedes the ruthenium catalyzed Alder-ene reaction (Figure 2), which affords alkene **4** in 85% yield.

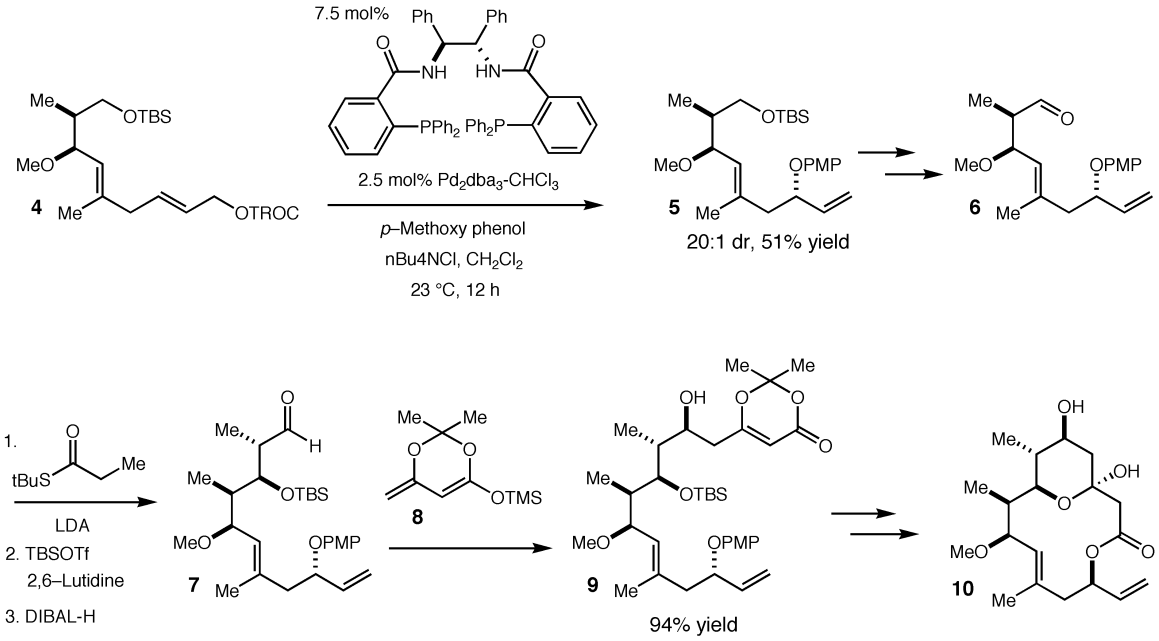
Figure 2. Ruthenium-catalyzed Alder–ene reaction



The palladium-catalyzed asymmetric allylic alkylation reaction of diene **4** proceeds in high diastereoselectivity but modest yield to afford the protected allylic alcohol **5** (Figure 3), which is elaborated to aldehyde **6** over several steps. Aldol addition of a kinetically formed *(E)* lithium enolate of *tert*–butyl thiopropionate to aldehyde **6** is followed by Felkin-Ahn addition of dienyl silyl ether **8** to the resultant aldehyde **7**. Following oxidative removal of the acetonide protecting group from **9**, several steps

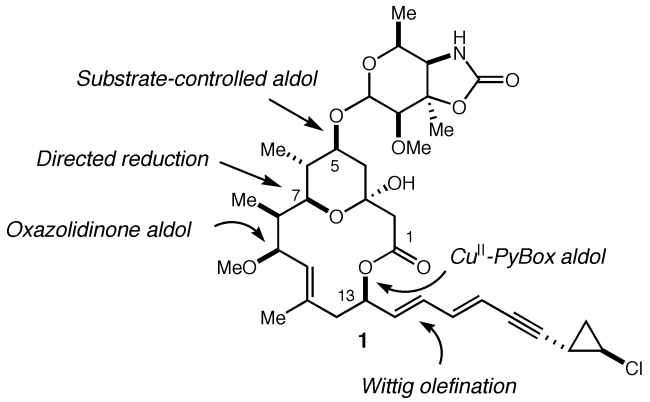
including macrolactonization and intramolecular condensation afford the callipeltoside core **10**.

Figure 3. Trost's synthesis of the callipeltoside core



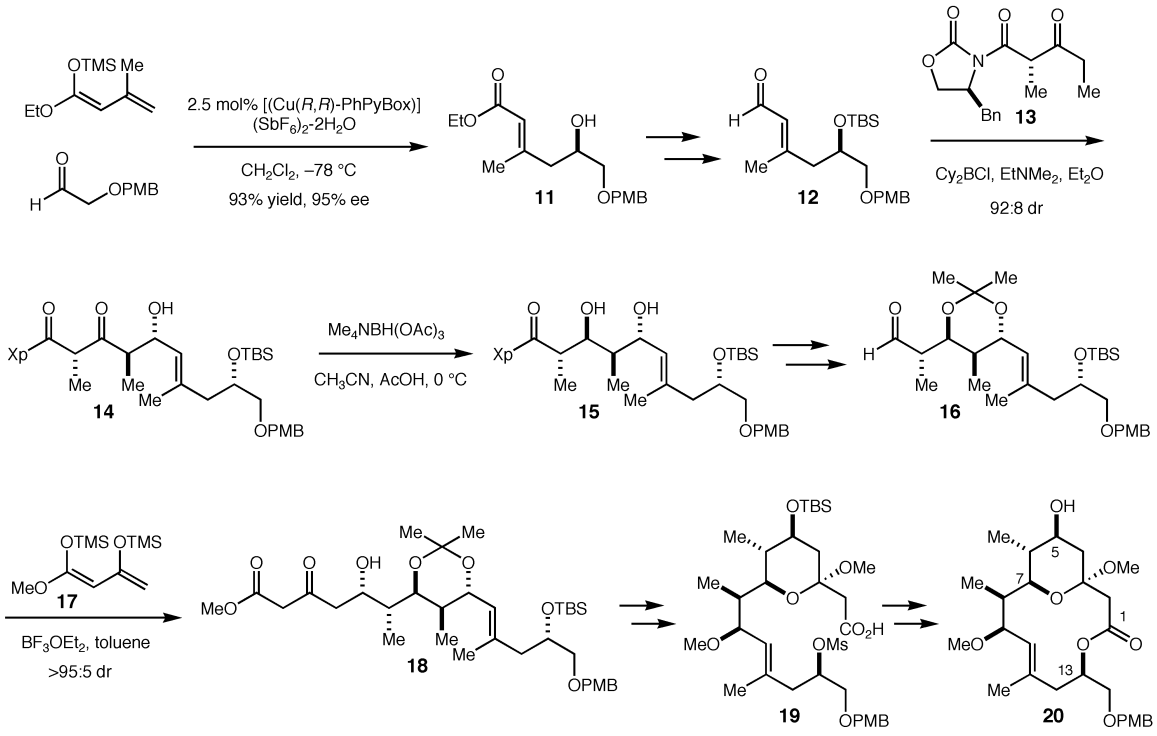
The Evans approach to callipeltoside A (Scheme 2) involves a Wittig olefination to attach the chlorocyclopropane sidechain to the macrolactone core and appends the callipeltose sugar to the core *via* NIS-mediated glycosidation. The 20-step synthesis of the macrolactone involves as key stereochemistry-determining steps an enantioselective catalytic Cu^{II}-PyBOX aldol reaction, diastereoselective chiral oxazolidinone aldol reaction, a directed ketone reduction, and a substrate-controlled aldol addition. Though marginally longer than the Trost approach to the macrolactone, this synthesis utilizes to a greater extent substrate control of stereochemical development.

Scheme 2. Evans' retrosynthesis of callipeltoside A



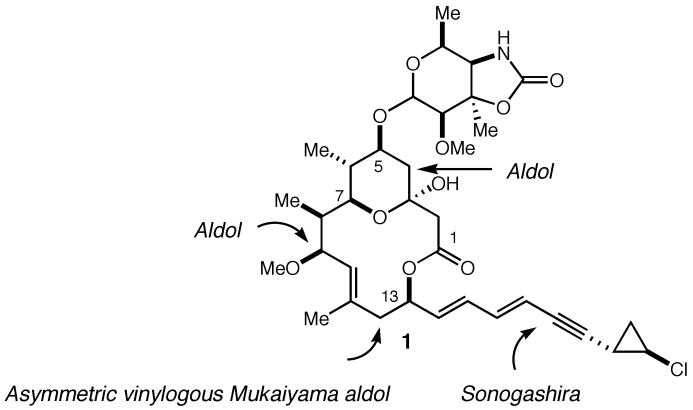
Key ester substrate **11** is prepared from available starting materials through a copper (II) catalyzed enantioselective aldol reaction in 93% yield and 95% ee (Figure 4). After derivatization to the aldehdye **12**, aldol reaction with chiral oxazolidinone **13** affords □-keto imide **14** with 92:8 diastereoselection, which then undergoes directed reduction to afford the alcohol **15**. After further elaboration, the diene **17** is employed in a substrate-controlled aldol reaction to afford □-keto ester **18**. Tetrahydropyran **19** is formed in several steps subsequent to deprotection of acetonide **18**, and the macrolatone **20** is constructed after further elaboration of **19** over multiple steps which include an intramolecular mesylate displacement.

Figure 4. Evans' synthesis of the callipeltoside macrolactone



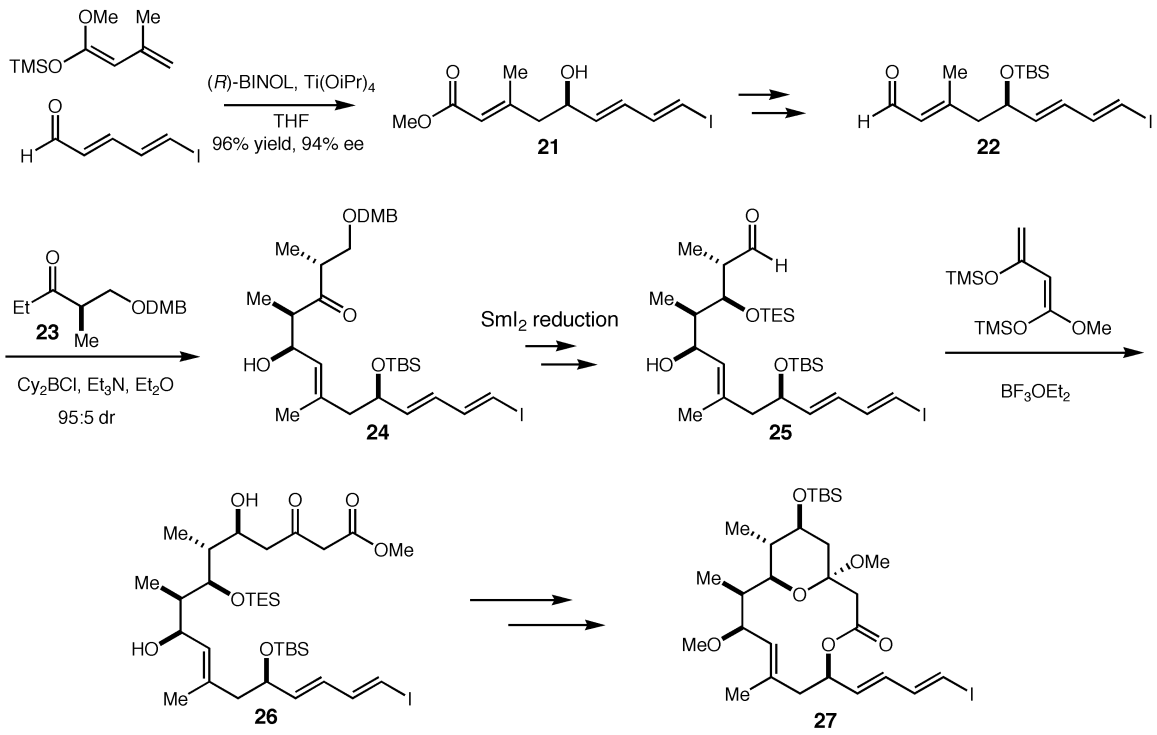
The Paterson approach to callipeltoside A (Scheme 3) employs a Sonogashira coupling to introduce the chlorocyclopropane sidechain and a Schmidt-type glycosidation to affix the L-rhamnose-derived callipeltose sugar onto the macrolactone. The macrolactone itself is constructed in 17 steps and involves coupling of three main chiral fragments. Importantly, after independent asymmetric assembly of two fragments, all further stereocenters are formed using substrate control with achiral reagents.

Scheme 3. Paterson's retrosynthesis of callipeltoside A



Asymmetric vinylogous Mukaiyama aldol reaction affords hydroxy ester **21** in 96% yield and 94% ee. Elaboration of this fragment to the aldehyde **22** precedes aldol coupling to chiral ketone **23** to produce ketone **24** in 95:5 diastereoselection. After substrate-directed SmI_2-mediated ketone reduction of ketone **24** and further elaboration to aldehyde **25**, aldol coupling produces keto-ester **26** in 95:5 diastereoselection. A sequence of steps including acid-catalyzed tetrahydropyran formation and subsequent macrolactonization affords the macrolactone **27**.

Figure 5. Paterson's synthesis of the callipeltoside macrolactone

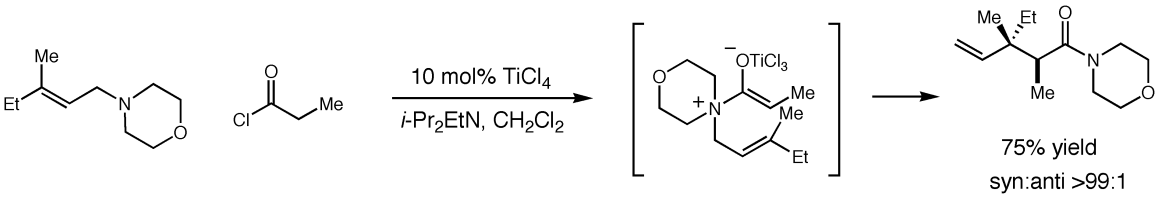


Tandem amino-sulfide acyl-Claisen rearrangement

Prior to the inception of the research detailed below, our research laboratory became interested in utilizing tandem reactions to rapidly develop a high level of molecular complexity. Our goal in the development of tandem reactions has been the application of these reactions to efficient synthesis of complex targets, and it is in the context of a total synthesis of callipeltoside A that we conceived of a new tandem Claisen rearrangement.

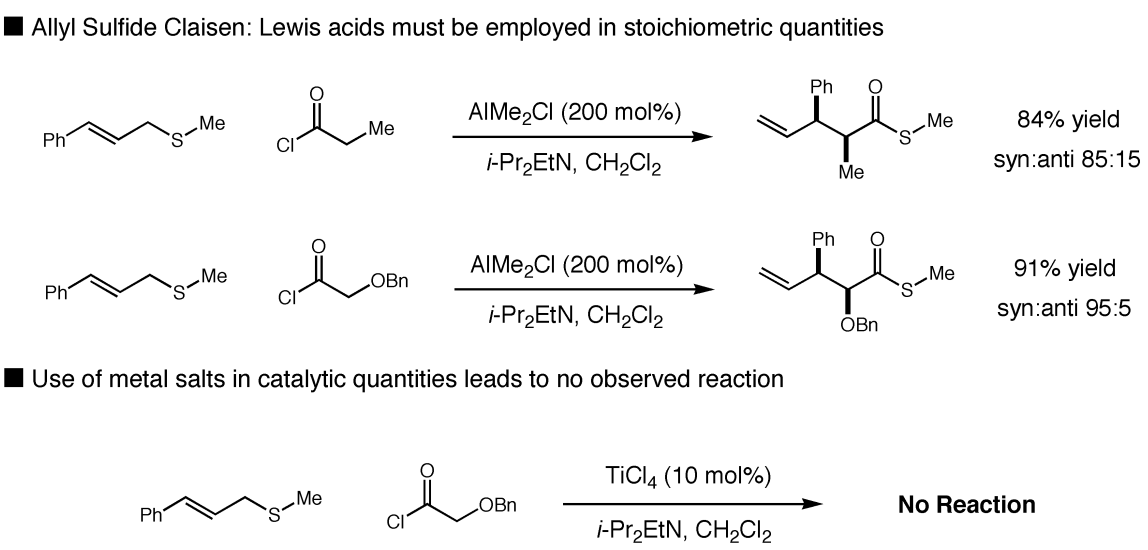
Studies from our laboratory have shown that allylic amines and acid chorides in the presence of a catalytic quantity of $TiCl_4$ will engage in a highly diastereoselective Claisen rearrangement, termed the acyl-Claisen (Figure 6).[7]

Figure 6. Acyl-Claisen rearrangement



Further investigations indicated that the allyl sulfide variant of this process was not possible in the presence of catalytic $TiCl_4$, though rearrangement was facile in the presence of stoichiometric amounts of aluminium Lewis acids (Figure 7).[8]

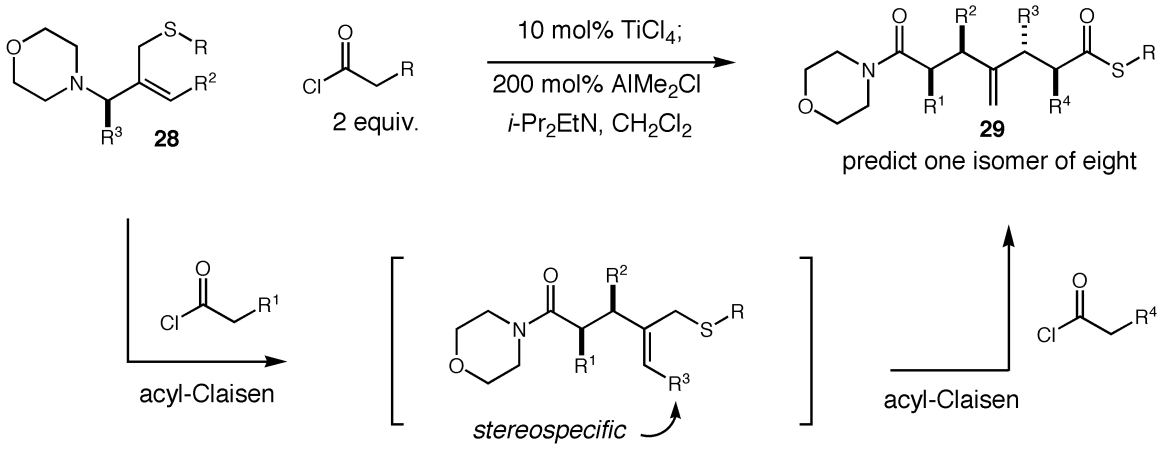
Figure 7. Sulfide acyl-Claisen rearrangement



Given these orthogonal modes of reactivity, we hoped to combine the two processes into a novel tandem reaction (Scheme 4). As such, we envisioned an allylic amino-sulfide **28** which could react first with one acid chloride in the presence of a catalytic quantity of $TiCl_4$. Once the amino sulfide **28** had been completely converted to the product of the amino acyl-Claisen rearrangement, a second acid chloride and a

stoichiometric quantity of Me_2AlCl could be introduced to allow formation of the highly functionalized amide-thioester **29**. Importantly, this product would bear differentially protected carbonyls at each terminus, allowing for facile elaboration.

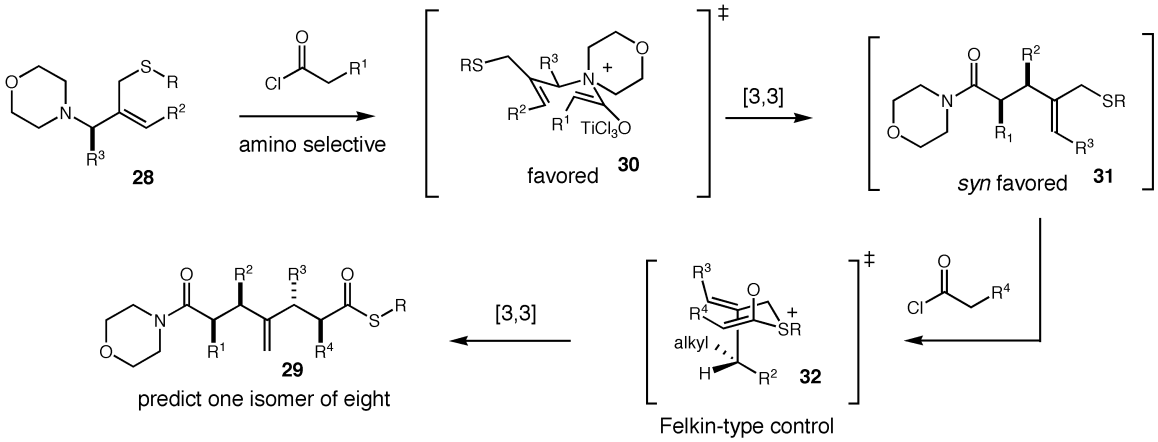
Scheme 4. Proposed tandem amino-sulfide acyl-Claisen rearrangement



Modular control of R^1, R^2, R^3, R^4; orthogonal protection of amide and thioester carbonyls

In this proposed reaction, the chirality of the amino-sulfide **28** would translate into four stereocenters on the product **29**; we believed that stereocontrol would be good based on two considerations (Scheme 5). First, the initial amino acyl-Claisen rearrangement should proceed *via* a highly ordered chair-like transition state **30** to produce products **31** of high *syn* diastereoselectivity, in accord with the high levels of diastereocontrol we had observed with the acyl-Claisen rearrangement discussed above. In the subsequent sulfide acyl-Claisen rearrangement, Felkin-type control in a transition state such as **32** was expected to dominate the selective formation of thioester **29**.[9]

Scheme 5. Stereochemical rationale for the tandem amino-sulfide acyl-Claisen rearrangement



With the appropriate choice of acid chlorides in this tandem process, the produced stereochemical array would map directly onto the backbone of the callipeltoside A macrolactone (Scheme 6). Thus we imagined that development of this novel tandem process might allow the rapid development of the stereochemical core of callipeltoside A and thereby facilitate an efficient total synthesis of this macrolide.

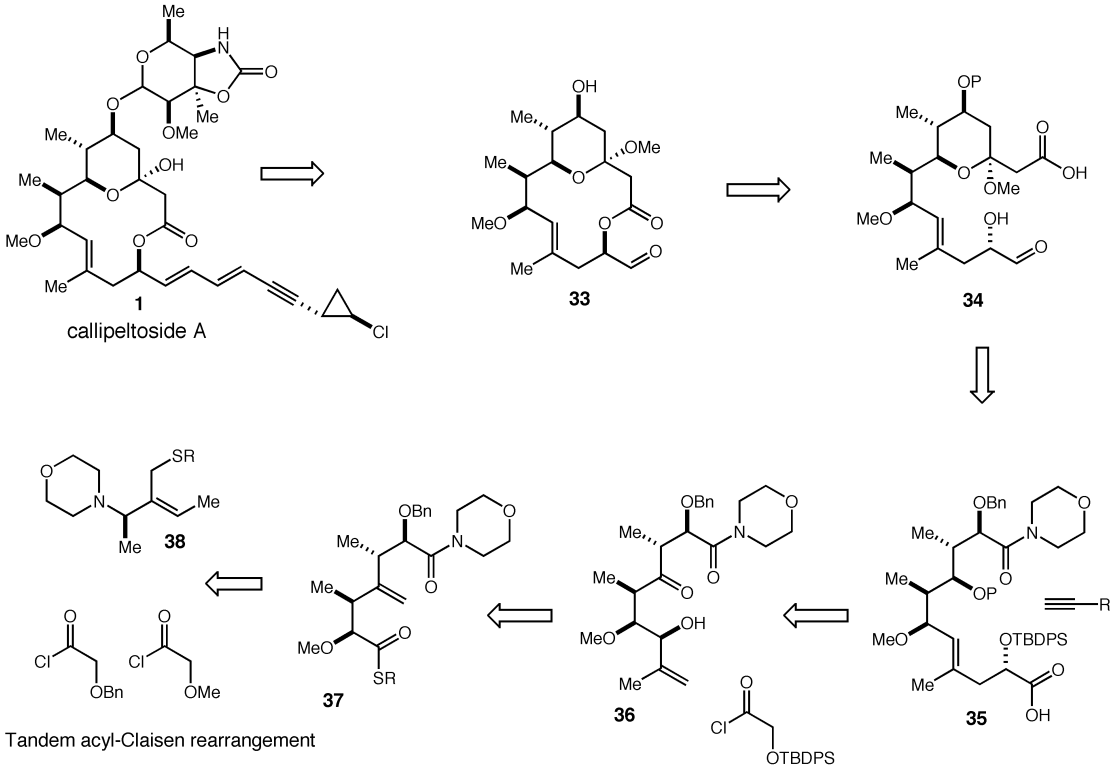
II. Results and Discussion

Retrosynthetic analysis of callipeltoside A

We envisioned that our approach to the total synthesis of callipeltoside A (Scheme 6) would involve synthesis of the macrolactone core **33** of the natural product, which would be coupled to the callipeltose sugar and the chloro cyclopropane side-chain to complete the synthesis. The macrolactone core **33**, itself containing a 6-membered tetrahydropyran ring, would derive from a macrolactonization of the acid **34**. Closure of the tetrahydropyran moiety of acid **34** would arise from intramolecular cyclization of an

alcohol with an appropriately substituted alkyne, either following the precedent of Marshall's palladium catalyzed intramolecular carbonylative cyclization[10] or through nucleophilic heteroconjugate addition. The protected homoallylic alcohol functionality of amide **35** would be installed through an Ireland Claisen rearrangement after acylation of the allylic alcohol and *anti* reduction of the central ketone functionality of compound **36**. Alcohol **36** would in turn derive from thioester **37** after reduction of the thioester and oxidation of the internal alkene to the ketone. Thioester **37** would itself be the product of our proposed tandem amino-sulfide acyl-Claisen rearrangement, utilizing two different acid chlorides and an appropriate amino-sulfide **38**. Importantly, this synthesis would involve establishment of four stereocenters of the macrolactone in a single step, followed by rapid elaboration to the macrolactone, relying on internal substrate control to establish the remaining stereocenters

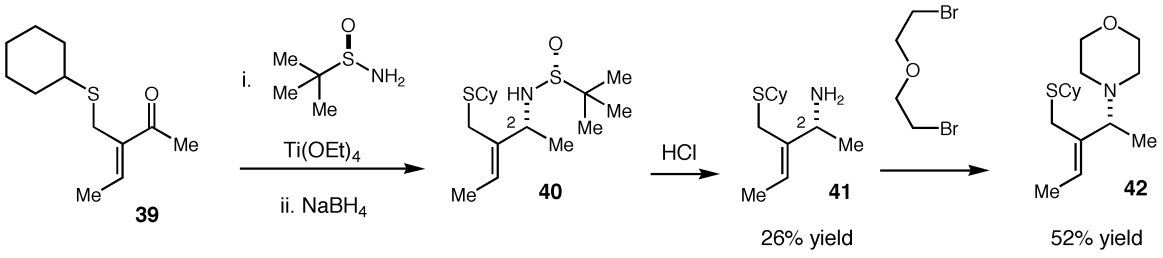
Scheme 6. First–generation retrosynthesis of callipeltoside A



Synthesis of precursor to the tandem amino-sulfide acyl-Claisen rearrangement

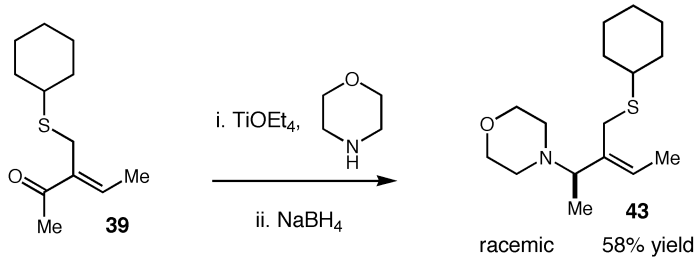
The proposed tandem Claisen rearrangement required the transfer of stereochemistry from the single stereocenter of the amino sulfide starting material **42** into the four stereocenters of the product amide thioester **45**, requiring a synthesis of enantiopure amino sulfide **42** in order to establish an enantioselective synthesis of callipeltoside A. As such, the enantioselective reductive amination technology of Ellman afforded an enantiopure route to amino sulfide **42** (Scheme 7). In the event, □,□-unsaturated ketone **39**[11] was condensed with commercially available (*R*)-*tert*-butanesulfinamide and reduced *in situ* to the sulfinamide **40** with $NaBH_4$ in the presence of $Ti(OEt)_4$, followed by acid-promoted cleavage to the amine **41**.[12] In accord with reported reductions, this reaction sequence afforded the sulfinamide **41** as a single diastereoisomer by ^1H NMR analysis, and, based on the reported stereochemical models, we believed that the (*S)* absolute configuration at C2 was produced during the course of this reaction. Morpholine formation using dibromoethyl ether afforded the desired enantiopure tandem acyl–Claisen precursor **42** in 52% yield.[13]

Scheme 7. Enantioselective synthesis of acyl–Claisen precursor



In addition to enantiopure amino-sulfide **42**, we sought to produce, if possible, large quantities of the racemate through more efficient means to conduct optimization

studies at later stages in the synthesis. As such, we found that a similar reductive amination protocol involving $NaBH_4$ and $Ti(OEt)_4$ could be employed with ketone **39** and morpholine to provide, directly, racemic amino sulfide **43** in 58% yield (Equation 1).[14]

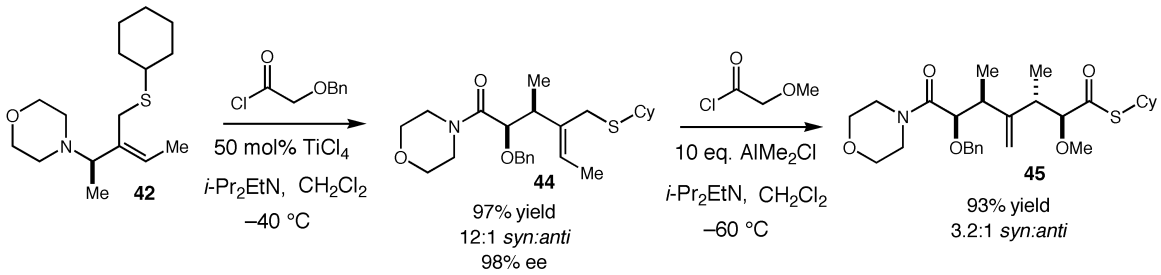


(1)

Tandem amino–sulfide acyl–Claisen rearrangement[15]

With sufficient quantities of amino-sulfide **42** in hand, we next sought to explore the tandem acyl-Claisen rearrangement. In conjunction with Dr. Jeongbeob Seo, it was determined that this transformation afforded the highest levels of reaction efficiency and selectivity when performed as a two-step process (Scheme 8).[16]

Scheme 8

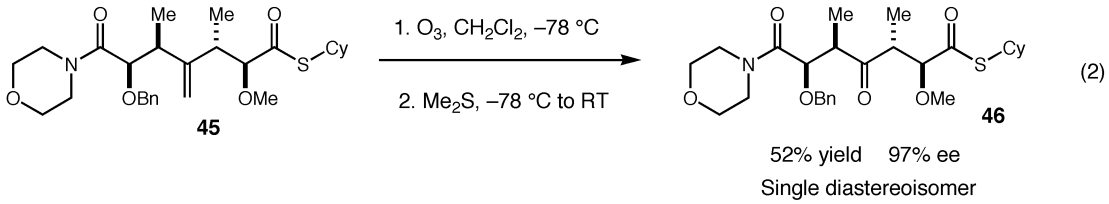


The initial amino acyl-Claisen rearrangement proceeds under conditions essentially identical to those reported previously for the acyl-Claisen rearrangement to afford the amide product **44** in 97% yield as a 12:1 *syn:anti* mixture of diastereoisomers.

Importantly, the enantiopurity of the amino-sulfide starting material **42** is preserved throughout the course of this reaction, with the amide product **44** being produced in 98% ee. As well, no evidence of any undesired sulfide acyl-Claisen rearrangement with a second equivalent of benzyloxyacetylchloride was observed, indicating, as expected, that the second rearrangement would require more reactive conditions and providing the requisite opportunity to employ a different acid chloride in the second rearrangement.

The sulfide acyl-Claisen rearrangement in the second step required a stronger Lewis acid, and, after extensive optimization of reaction conditions including solvent, Lewis acid, temperature, and reagent stoichiometry and molarity, it was determined that aluminum Lewis acids performed best and were required in large excess. It is believed this decreased reactivity can be attributed to (1) the *cis* relationship between the sulfide and the alkene alkyl substituent[17] and (2) coordination of the amido sulfide starting material **44**, containing five hetereoatoms, to the Lewis acid used. Utilizing Me_2AlCl and methoxyacetylchloride afforded the thioester product in 93% yield and a 3.2:1 ratio of the desired diastereoisomer **45** to all other isomers.[18] The observed stereochemical outcome of this tandem process is in complete accord with that predicted above.

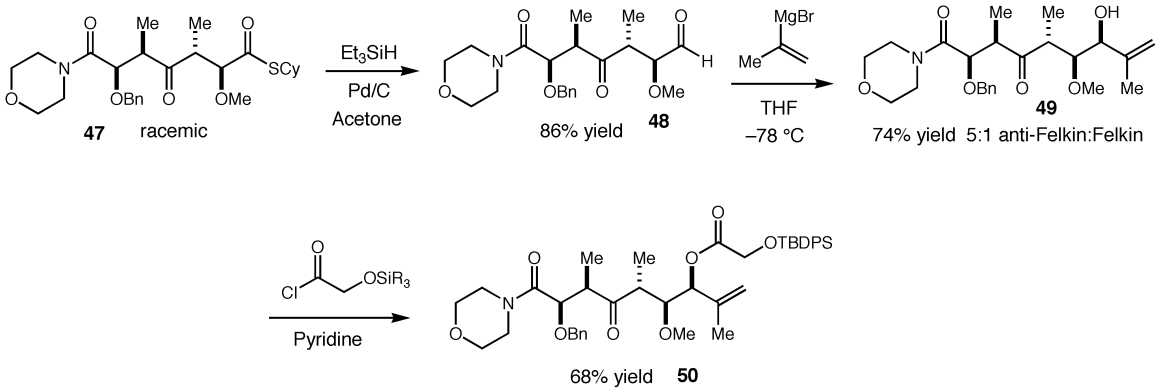
After ozonolytic cleavage of the alkene of amide-thioester **45**, the ketone **46** was separated from the other isomers deriving from the tandem Claisen transformation and isolated in 52% yield with 97% ee, indicating that the enantiopurity of the starting material was preserved through the second acyl-Claisen rearrangement (Equation 2). The relatively low yield of this reaction likely relates to oxidative decomposition of the thioester moiety.



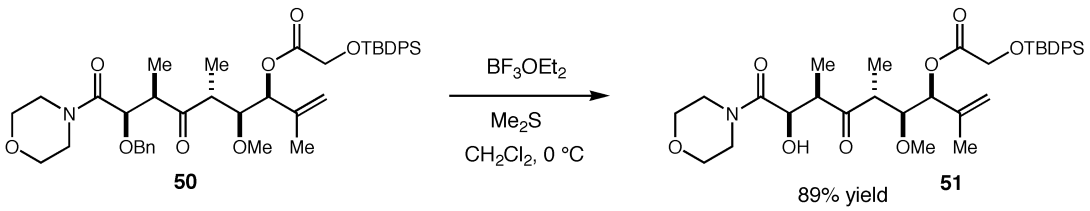
***Anti* reduction of β-hydroxy ketone and Ireland Claisen rearrangement**

Ozonolysis of the tandem amino-sulfide acyl-Claisen rearrangement product afforded the ketone moiety that would be reduced to establish the required 1,3-*anti* diol relationship in callipeltoside A. Prior to attempting this *anti* reduction, we sought to install the β-oxy ester functionality that would facilitate Ireland Claisen rearrangement subsequent to the *anti* reduction (Scheme 9). As such, the thioester **47** was reduced to the corresponding aldehyde **48** in 86% yield under Fukaiyama reduction conditions, demonstrating the ease with which this tandem rearrangement allows for differential functionalization of the termini of the complex products. This aldehyde was readily converted to the allylic alcohol **49** in 74% yield by addition of isopropenyl magnesium bromide. Chelation control governed this addition, affording a 5:1 mixture of the desired anti-Felkin to the undesired Felkin product. Allylic alcohol **49** was then immediately acylated with *tert*-butyldiphenylsilyloxyacetyl chloride in the presence of pyridine to form the ester **50** in 68% yield.

Scheme 9. Installation of β-oxy ester



At this stage, the benzyl protecting group was removed in preparation for an internally directed *anti* reduction. This deprotection was not possible using standard hydrogenation conditions, though the benzyl group was efficiently cleaved using BF_3OEt_2 and Me_2S to afford the alcohol **51** in 89% yield (Equation 3).[19] This reaction operates through coordination of the benzylic oxygen to the Lewis acid followed by nucleophilic displacement by Me_2S.

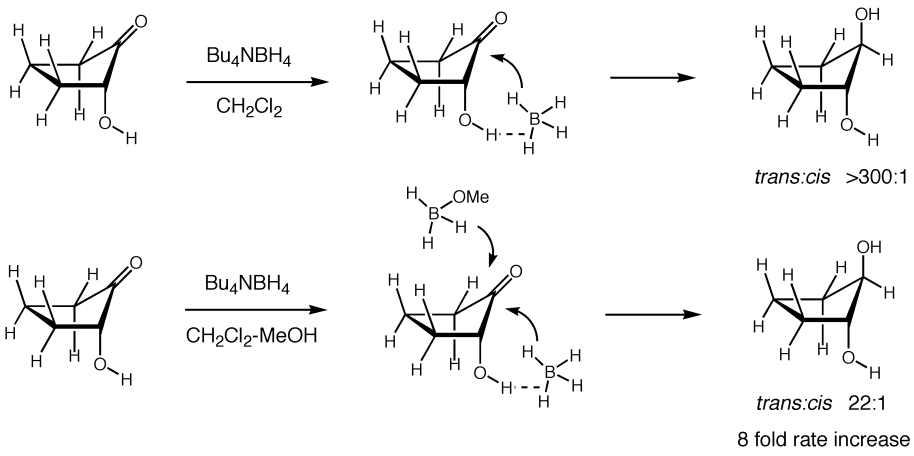


(3)

Selective *anti* reduction of the β–hydroxy ketone **51** proved difficult using standard *anti* reducing conditions such as sodium triacetoxyborohydride and SmI_2, which afforded predominantly the *syn* isomer. A report by Jackson[20] indicated that Bu_4NBH_4, when used with CH_2Cl_2, afforded preferentially the *trans* (*anti)* reduction products of cyclic hydroxy ketones. In contrast, when a solvent mixture of CH_2Cl_2 with a small

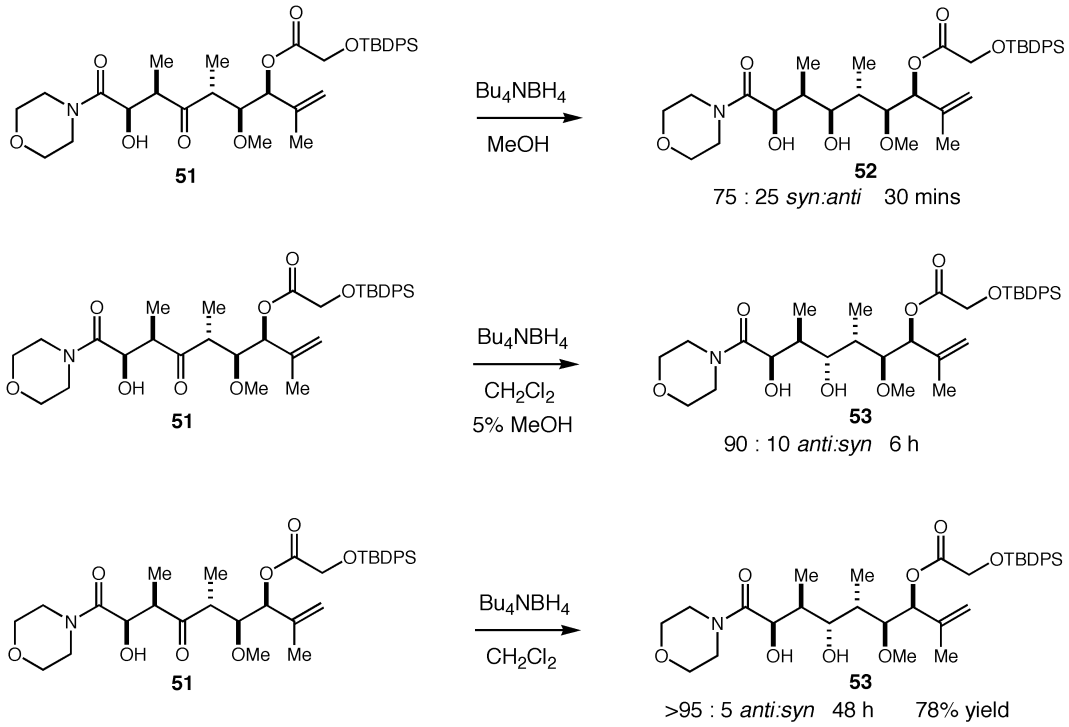
amount of MeOH was used, the reaction was much less *trans* selective and much faster. This difference is believed to result from competitive coordination of MeOH with the reducing agent; in the absence of MeOH, the reducing agent is coordinated only through an intramolecular dihydrogen bond (Scheme 10).

Scheme 10. Jackson's *anti* reduction of cyclic ketones



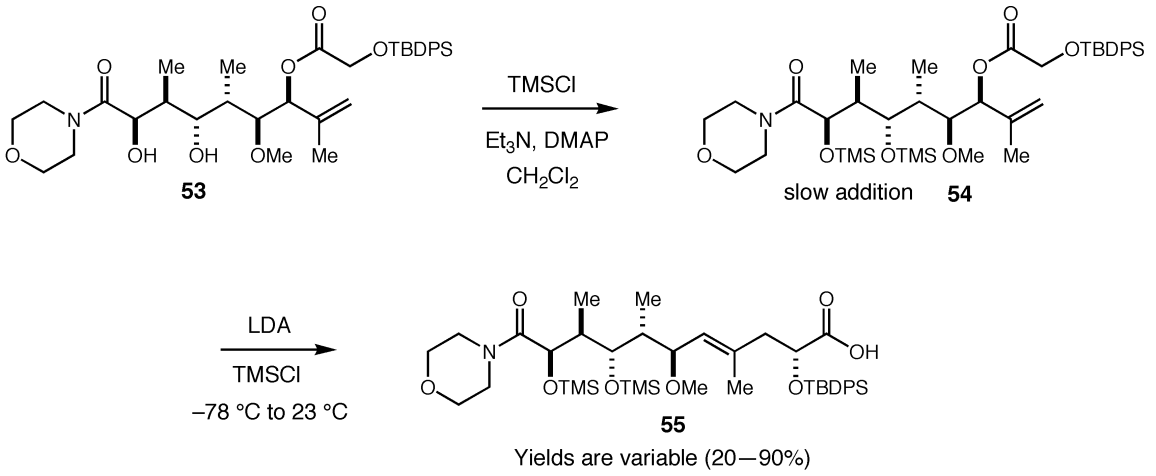
Though no reports have involved Bu_4NBH_4 used in CH_2Cl_2 to perform *anti* reductions of acyclic hydroxy ketones, we proposed that this reagent when used in CH_2Cl_2 might be able to effect the desired *anti* reduction for our system. In fact, when Bu_4NBH_4 was employed in the context of the acyclic □–hydroxy ketone **51**, a similar trend was observed (Scheme 11). Though the *anti* reduction was slow, the desired *anti* diol **53** was isolated in 78% yield after recovery of starting material (>95:5 *anti:syn*).

Scheme 11. Bu_4NBH_4 reduction stereochemistry as a function of solvent



Protection of the diol as the bis-TMS ether was effected in 75% yield, and at this stage Ireland Claisen rearrangement was attempted (Scheme 12). Though Claisen products were isolable, and the diastereoselectivity of the reaction was high, the yield of this reaction was decidedly variable; despite efforts to control the outcome of this reaction, various by-products relating to amide decomposition were frequently observed.

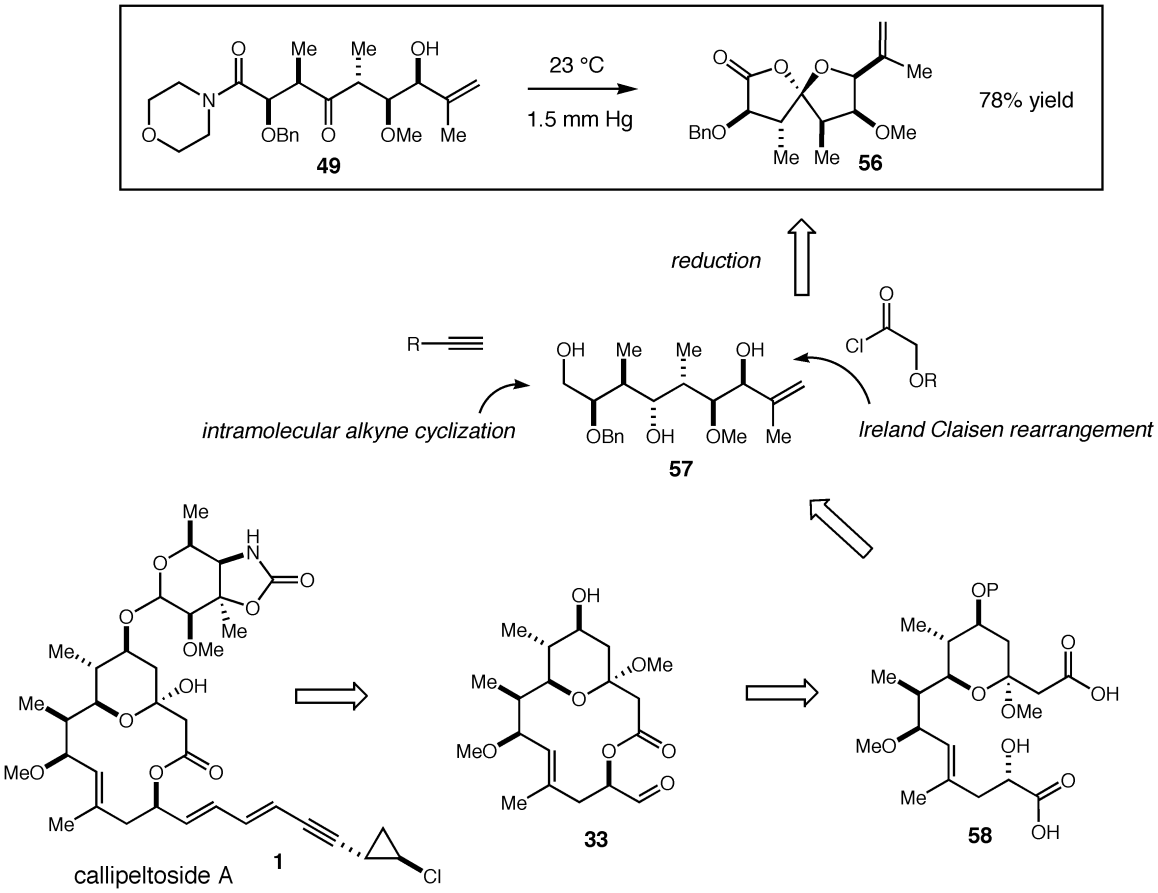
Scheme 12. Ireland Claisen rearrangement



Given the irreproducibility of this reaction and our belief that the presence of the amide was adversely affecting the rearrangement, we sought to revise our synthesis to perform the Ireland Claisen rearrangement subsequent to removal of the amide. Further, we hoped to improve upon the low reactivity observed in the *anti* reduction step.

We had noted that the allylic alcohol **49**, on standing, would spontaneously cyclize to form the spirocycle **56** (Scheme 13), and we had previously sought to avoid this perceived problem by immediately acylating to form Ireland Claisen precursor **50**. Yet, this spirocycle formation became attractive as we sought to revise our synthetic strategy. In the course of the spirocyclization, the amide functionality, so problematic during the Ireland Claisen rearrangement, was removed. Further, this spirocycle held the possibility for a reductive opening that might afford the desired and often elusive 1,3-*anti* diol relationship. Thus we revised our synthesis in an attempt to take advantage of this spontaneous spirocyclization (Scheme 13).

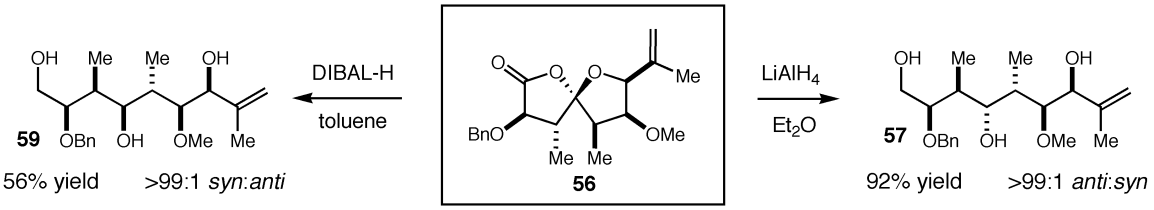
Scheme 13. Spirocyclization leads to revised retrosynthesis



Indeed, the reductive opening of spirocycle **56** was effected in high yield and excellent *anti* selectivity in the presence of $LiAlH_4$ in Et_2O (Scheme 14).[21] In contrast, an analogous reaction involving DIBAL-H as reductant and employing toluene as solvent afforded exclusively the *syn* 1,3 diol relationship. The origins of this selectivity difference will require further investigations, though it is probable that both the solvent and reducing agent are relevant variables. A coordinating solvent such as Et_2O will preclude any internal coordination between substrate and reducing agent, whereas toluene will allow significant coordination, and thus the potential exists for the two solvents to each bias the reaction toward a different transition state. Of course, the nature of the

reducing agent should have an affect as well; in accord with the proposed importance of intramolecular vs. intermolecular coordination of the reducing agent, the different Lewis acidities of $LiAlH_4$ and DIBAL-H would be expected to further differentiate between various transition states. Investigations to probe the differential selectivity should include variation of solvents and, as well, variation in the molar equivalents of reducing agent; presumably, if intramolecular coordination is important in determining the selectivity of one of these reductions, then introduction of additional equivalents of the reducing agent has the potential to introduce a non-coordinated reductant and thereby alter the selectivity of the reaction.

Scheme 14. Reductive opening of spirocycle

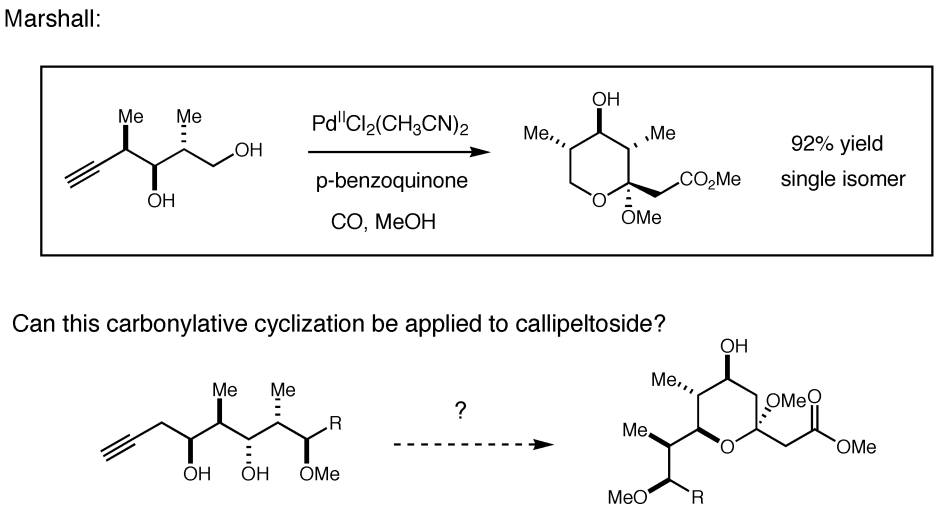


Acetylide opening of epoxide

With the desired *anti* 1,3 diol relationship in place and the amide removed, we turned to elaborating the stereochemical array **57** toward (1) performing the Ireland Claisen rearrangement and (2) introducing the tetrahydropyran moiety.

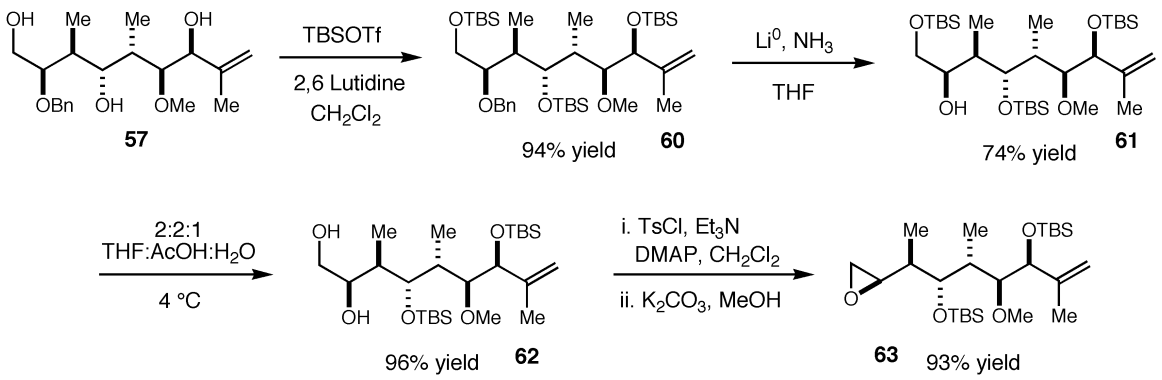
Marshall recently reported that alkynyl alcohols readily undergo a palladium catalyzed carbonylative cyclization to form tetrahydropyrans (Scheme 15).[22] We proposed that analogous conditions might be able to form the tetrahydropyran subunit of callipeltoside A.

Scheme 15. Marshall's carbonylative cyclization



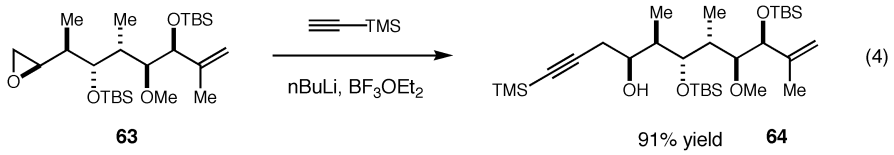
Thus we sought to introduce a protected alkyne into our stereochemical array. We imagined that the terminal 1,2 diol relationship of triol **57** might be readily transformed into an epoxide which could then be opened using an appropriately protected acetylene. As such, the triol **57** was tris-TBS protected in 94% yield and the benzyl protecting group was removed under Birch conditions in 74% yield (Scheme 16). It is noteworthy that hydrogenation conditions failed to cleave the benzyl group, and the BF_3OEt_2 conditions discussed above resulted only in substrate decomposition. Further, when the Birch reduction was performed using sodium metal rather than lithium, complete 1,3-TBS migration was observed, as has been described for other benzyl deprotections.[23] Selective removal of the primary TBS ether proceeded in 96% yield to afford the 1,2 diol **62**. Sequential one-pot treatment of the diol with toluenesulfonyl chloride/Et_3N followed by K_2CO_3 afforded epoxide **63** in 93% yield.

Scheme 16. Formation of terminal epoxide



57 **60** **61** **62** **63**

Treatment of epoxide **63** with the lithium anion of trimethylsilylacetylene in the presence of BF_3OEt_2 at –78 °C[24] effected the desired epoxide opening in 91% yield (Equation 4).



63 **64** (4)

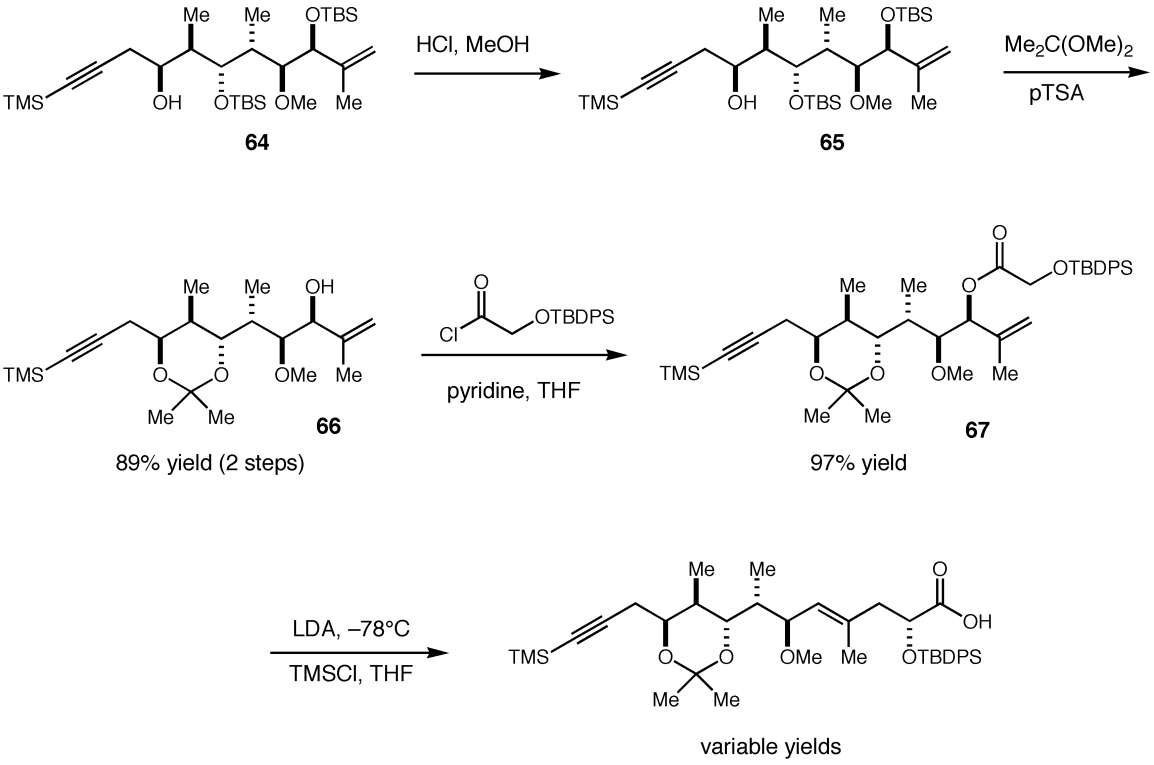
At this stage, prior to attempting the tetrahydropyran formation, we chose to perform the Ireland Claisen rearrangement. Were the THP formation conducted first, we feared that a competitive enolization of the THP-ester during the course of enolization might interfere with the Ireland Claisen rearrangement.

Ireland Claisen Rearrangement

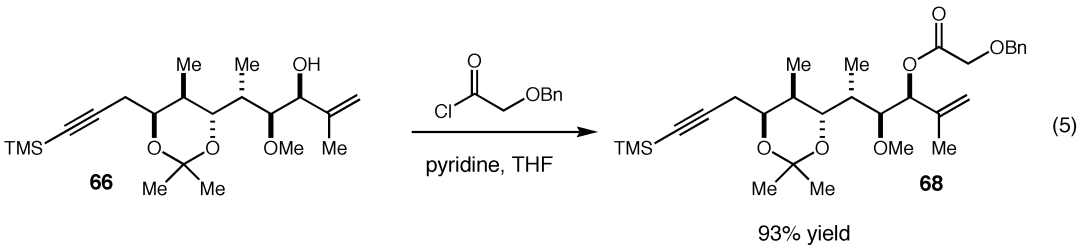
The ester precursor **67** to the Ireland Claisen rearrangement was accessed in high yield from the alkynyl alcohol **64** (Scheme 17). Removal of both TBS protecting groups

using concentrated HCl in MeOH was followed by acetonide protection of the *anti* 1,3 diol in 89% yield over two steps. The alcohol of the acetonide was then acylated with *tert*-butyldiphenylsilylacetyl chloride to afford the ester **67** in 97% yield.

Scheme 17. Synthesis of Ireland Claisen precursor

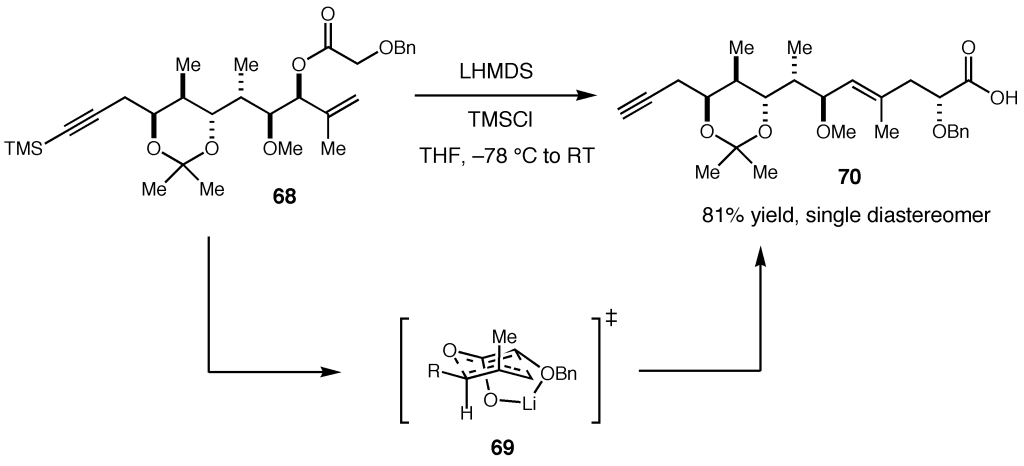


Ester **67** was poised for Ireland Claisen rearrangement, and treatment with LDA followed by TMSCl at –78 °C with subsequent warming to room temperature afforded the Claisen adduct in only variable, irreproducible yields, though again with high levels of diastereoselectivity. We proposed that the β–silyloxy moiety was responsible for the variable yields, with a silyl migration-decomposition pathway potentially in operation. Thus, the analogous β-benzyloxy substrate **68**, available in high yield from allylic alcohol **66** (Equation 5), was employed in the Ireland Claisen rearrangement.



(5)

Ester **68** performed consistently well in the Ireland Claisen rearrangement with LDA, though optimal levels of reaction efficiency were observed when LHMDS was used as the enolization base, to afford the Claisen product **70** in 81% yield as a single diastereoisomer, with concomitant deprotection of silyl-protected alkyne under the basic workup conditions (Equation 6). The high levels of diastereocontrol observed in this reaction are attributable to a chair-like transition state **69**, in accord with other Claisen rearrangements.[25]

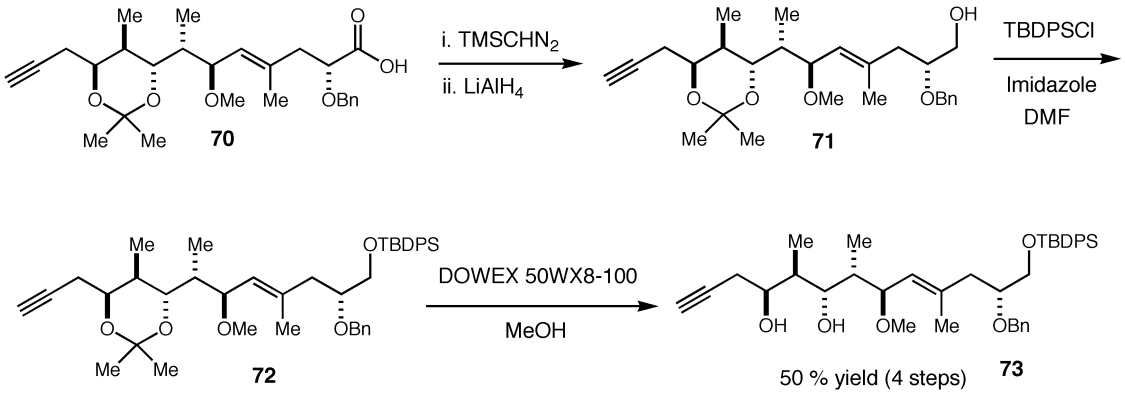


(6)

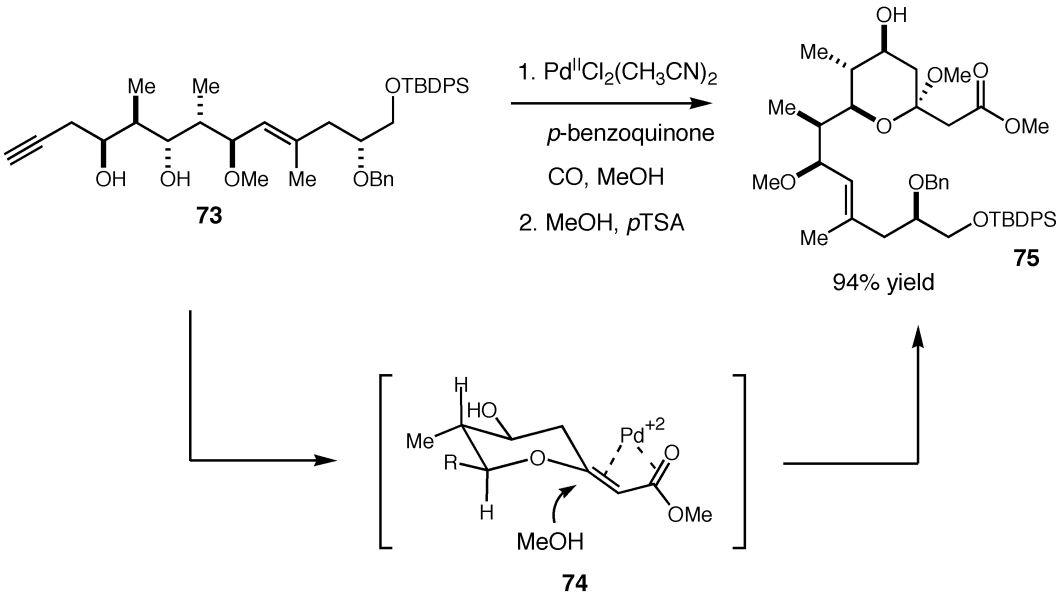
Tetrahydropyran formation

Having installed the internal alkene with the appropriate olefin geometry as well as the C13 stereocenter, we next turned our attention to closure of the tetrahydropyran ring, which would precede completion of the synthesis. Preparation of the precursor to the carbonylative cyclization entailed conversion of the acid functionality of Claisen product **70** to the corresponding methyl ester and immediate reduction to alcohol **71**. Protection of the alcohol as the TBDPS ether and cleavage of the acetonide protecting group using acidic DOWEX resin afforded the diol **73** in 50% overall yield for the rapid four-step sequence (Scheme 18).

Scheme 18. Synthesis of carbonylative cyclization precursor

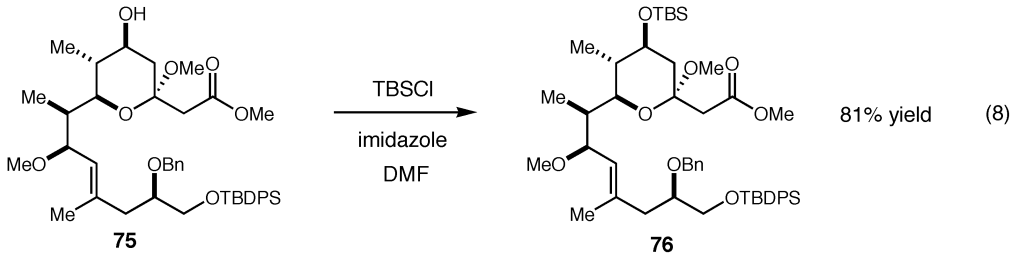


Diol **73** was next subjected to the carbonylative cyclization conditions reported by Marshall, and to our delight the THP derivative **75** was isolated in 94% yield as a single diastereoisomer (Equation 7). This high selectivity is in complete accord with the model proposed by Marshall involving a chair-like transition state.[26]



(7)

After TBS protection of tetrahydropyran **75** in 81% yield (Equation 8), attempts were made to remove the benzyl protecting group at C13 to allow for macrolactonization and completion of the synthesis.



(8)

Unfortunately, a wide variety of known conditions for removal of the benzyl protecting group resulted only in decomposition of the substrate or no reaction whatsoever. The sensitivity of the tetrahydropyran ring of **76** to acidic conditions rendered Brønsted-acid and Lewis-acid dependent deprotections deleterious, while the presence of the olefin precluded hydrogenation as a means to remove the benzyl ether.

Indeed, under various hydrogenation conditions, saturation of the olefin was typically fast, while no benzyl deprotection was observed. Oxidative conditions such as DDQ resulted in neither desired reaction nor decomposition of substrate, and it was thus concluded that a more readily removable protecting group such as a *para*-methoxybenzyl ether would be appropriate. Such a protecting group could be introduced as part of the acid chloride used to acylate allylic alcohol **66** (Equation 5) prior to the Ireland Claisen rearrangement. Following removal of that protecting group after formation of the tetrahydropyran ring, macrolactonization would likely be facile, following the precedent of Paterson, and coupling of the chlorocyclopropane sidechain and the sugar residue would allow access to callipeltoside A.

III. Conclusion

The novel tandem amino-sulfide acyl-Claisen rearrangement has been employed in research directed towards the total synthesis of callipeltoside A. The key rearrangement affords the stereochemical backbone of callipeltoside A with excellent diastereocontrol and retention of enantiopurity from starting material to the product of the Claisen rearrangement. Elaboration after the tandem Claisen has involved reductive opening of a spirocyclic intermediate with excellent stereoselectivity, a highly diastereoslective Ireland Claisen rearrangement, and an intramolecular carbonylative cyclization reaction to form a tetrahydropyran ring system. This synthetic approach relies entirely upon substrate control to establish relative stereochemical relationships subsequent to an initial enantioselective reaction. Future work will include modification of the protecting group strategy in the Ireland Claisen rearrangement which will facilitate

the macrolactonization step and give access to the macrolide core of callipeltoside A, which can then be elaborated to the natural product after coupling to the chlorocyclopropane sidechain and deoxyamino sugar in accord with literature precedent.

IV. Experimental Section

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[27] All non–aqueous reactions were performed using flame- or oven-dried glassware under an atmosphere of dry nitrogen. Non-aqueous reagents were transferred under nitrogen *via* syringe or cannula. Solvents were purified using an alumina column. Organic solutions were concentrated under reduced pressure on a Buchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method described by Still.[28] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by florescence quenching or $KMnO_4$, CAM, or anisaldehyde stain.

^{1}H NMR and ^{13}C NMR spectra were recorded on Varian Mercury-300 (300 MHz and 75 MHz, respectively), or Varian I-500 (500 MHz and 125 MHz, respectively) instruments, as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported with chemical shift (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz), and assignment. Data for ^{13}C NMR are reported with chemical shift. IR spectra were recorded on a Perkin-Elmer infrared spectrometer and are reported in terms of frequency

of absorption (cm^{-1}). Optical Rotations were recorded on a Jasco P-1010 polarimeter (WI lamp, 589 nm, 25°C). Mass spectra were obtained from the Caltech Mass Spectral Facility. HPLC analysis was performed on a Hewlett-Packard 1100 Series HPLC at 254nm using the following Chiralcel columns: OD-H (25 cm) and OD guard (5 cm), AD (25 cm) and AD guard (5 cm).

3-Cyclohexylsulfanylmethyl-pent-3-en-2-one (39). A solution of methyl magnesium iodide (1.0 M THF, 100 mL, 0.3 mol) in 300 mL dry diethyl ether in a flame dried 5 L round bottom flask under an atmosphere of argon was cooled to 0 °C. Cyclohexyl thiol (36.6 mL, 0.3 mol) in 300 mL dry diethyl ether was added via an addition funnel over 30 min to the stirring solution. A solution of methyl vinyl ketone (25 mL, 0.3 mol) and acetaldehyde (16.8 mL, 0.3 mol) in 300 mL dry diethyl ether was added to the 0 °C solution. The reaction was stirred at 0 °C for 3 h at which time it was quenched with sat. aq. NH_4Cl. The organic layer was removed and washed twice with 10% NaOH (200 mL) and once with sat. aq. NaCl (200 mL), dried over $MgSO_4$, filtered through a cotton plug, and concentrated. The oil was taken up in 245 mL dry diethyl ether in a dry 5 L round bottom flask, which was then purged with argon. Methanesulfonyl chloride (20 mL, 0.264 mol) was added *via* syringe, and the solution was cooled to 0 °C. Et_3N (34 mL, 0.264 mol) was added, and the reaction was stirred at 0 °C for 30 min at which time the mixture was filtered through a cotton plug and concentrated. The resulting oil was dissolved in 333 mL dry THF in a dry 5 L round bottom flask which was then purged with argon. DBU (50 mL, 0.333 mol) was added *via* syringe over 10 min during which time the solution became cloudy. After addition was

complete, 300 mL Et_2O was added and mixture was washed twice with H_2O (300 mL), twice with sat. aq. $CuSO_4$ (200 mL), once with sat. aq. NaCl (200 mL), dried over Na_2SO_4, filtered through a cotton plug, and concentrated. Purification of the resulting oil by silica gel chromatography (5% EtOAc/hex) provided the title compound as a yellow oil in 25% yield (16 g). IR (film) 2928, 2851, 1717, 1675, 1669, 1657, 1448, 1385, 1341. 1277, 1162, 999, 954, 829, 742, 609, 580 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 6.77 (q, J = 6.5 Hz, 1H, $H_3CC\mathbf{H}$), 3.42 (s, 3H, $COC\mathbf{H}_3$), 2.62-2.58 (m, 2H, $SC\mathbf{H}_2$), 1.92 (d, J = 6.5 Hz, 3H, $CHC\mathbf{H}_3$), 1.57-1.55 (m, 1H, SC**H**), 1.31-1.18 (m, 10H, Cy-**H**); ^{13}C NMR (125 MHz, $CDCl_3$) 198.1, 140.7, 140.4, 44.5, 33.8, 26.3, 26.1, 25.8, 24.0, 15.2; LRMS (FAB) m/z 211 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{12}H_{19}OS$) requires m/z 211.1150, found m/z 211.1157.

(1*S*)-2-Cyclohexylsulfanylmethyl-1-methyl-but-2-enylamine (41).[29] 3-Cyclohexylsulfanylmethyl-pent-3-en-2-one **39** (1.58 g, 7.5 mmol) and (*R*)-(-)-2-methyl-2-propanesulfinamide (1.00 g, 8.25 mmol, 97% ee) were dissolved in 15.0 mL dry THF in a dry 100 mL round bottom flask under argon. $Ti(OEt_4)$ (6.13 mL, 22.5 mmol) was added via syringe, and the solution was stirred at 75 °C for 16.5 h. After cooling the reaction vessel to –78 °C, the mixture was added to a –60 °C suspension of $NaBH_4$ (1.13 g, 30.0 mmol) in 15 mL dry THF, and stirred at –60 °C for 23 h. The reaction was quenched slowly by addition of MeOH (30 mL) with stirring. Sat. aq. NaCl (30 mL) was added and the mixture was extracted once with EtOAc (40 mL). The organic layer was washed once with sat. aq. NaCl (30 mL). The combined aqueous layers were extracted three times with EtOAc (50 mL). The combined organic layers were dried over Na_2SO_4,

filtered through a cotton plug, and concentrated. Purification of the resulting oil by silica gel chromatography (30% EtOAc/hex) provided a yellow oil which was immediately dissolved in 1.33 mL MeOH. A solution of HCl in dioxane (4.0 M, 1.33 mL, 5.33 mmol) was added and the solution was stirred for 15 min. 15 mL CH_2Cl_2 was added and the solution was extracted three times with 1N aq. $KHSO_4$. 10% aq. NaOH was added to the combined aqueous layers to pH >7. The aqueous phase was then extracted five times with CH_2Cl_2, dried over Na_2SO_4, filtered through a cotton plug, and concentrated to afford the title compound as an oil in 26% yield (423.3 mg). IR (film) 2926, 2851, 1575, 1557, 1447, 1368, 1262, 1199, 1100, 999, 885, 832 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 5.61 (q, *J* = 7.0 Hz, 1H, C**H**), 3.61 (q, *J* = 7.0 Hz, 1H, (vinylC)**H**NH_2), 3.35 (d, *J* = 12.0 Hz, 1H, N**H**H), 2.65-2.60 (m, 2H, C**H**$_2$S), 1.71 (d, *J* = 7.0 Hz, 3H, CHC**H**$_3$), 1.64-1.62 (m, 1H, SC**H**), 1.40-1.25 (m, 10H, Cy-**H**), 1.21 (d, *J* = 7.0 Hz, 3H, CNH_2C**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) 121.3, 51.8, 44.4, 33.9, 27.8, 26.4, 26.1, 23.4, 17.1, 13.6; LRMS (FAB) *m*/*z* 214 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{12}H_{24}NS$) requires *m*/*z* 214.1630, found *m*/*z* 214.1629.

4-[(1*S*)-2-Cyclohexylsulfanylmethyl-1-methyl-but-2-enyl)-morpholine (42). To (1*S*)-2-cyclohexylsulfanylmethyl-1-methyl-but-2-enylamine **41** (354.7 mg, 1.66 mmol) in 2.6 mL dry CH_3CN in a dry 20 mL vial under argon was added K_2CO_3 followed by dropwise addition of bis(2–bromoethyl)ether (0.209 mL, 1.66 mmol). The vial was flushed with argon, sealed, and heated to 80 °C for 12.5 h. The reaction was then cooled to ambient temperature, and Na_2SO_4 (50 mg) was added. The mixture was filtered through a cotton plug and concentrated. Purification of the resulting oil by silica gel

chromatography (10% EtOAc/hex) provided the title compound as an oil in 52% yield (246.3 mg). IR (film) 2928, 2851, 2805, 2760, 1448, 1372, 1308, 1263, 1201, 1177, 1140, 1119, 1069, 999, 947, 918, 864, 855, 837, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.52 (q, *J* = 7.0 Hz, 1H, vinylC**H**), 3.71-3.64 (m, 4H, NC$\mathbf{H}_2$C$\mathbf{H}_2$), 3.01 (q, *J* = 7.0 Hz, 1H, C**H**NR_2), 2.63-2.58 (m, 2H, SC$\mathbf{H}_2$), 2.48-2.39 (m, 4H, OC$\mathbf{H}_2$C$\mathbf{H}_2$), 1.71 (d, *J* = 7.0 Hz, 3H, CHC$\mathbf{H}_3$), 1.63-1.60 (m, 1H, SC**H**), 1.38-1.23 (m, 10H, Cy-**H**), 1.12 (d, *J* = 7.0 Hz, $CHNH_2C\mathbf{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 123.9, 67.7, 64.3, 50.4, 44.5, 33.9, 27.9, 26.4, 26.1, 14.8, 13.7; LRMS (FAB) *m/z* 282 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{16}H_{28}NOS$) requires *m/z* 282.1898, found *m/z* 282.1892.

4-(2-Cyclohexylsulfanylmethyl-1-methyl-but-2-enyl)-morpholine (43). 3-Cyclohexylsulfanylmethyl-pent-3-en-2-one **39** (7.16 g, 33.88 mmol) and morpholine (8.86 mL, 101.63 mmol) were dissolved in 67.8 mL dry THF in a 250 mL round bottom flask. $Ti(OEt_4)$ (27.71 mL, 101.63 mmol) was added via syringe, and the solution was stirred at reflux for 14 h. After cooling the reaction vessel to –78 °C, the mixture was added to a –50 °C suspension of $NaBH_4$ (5.13 g, 135.52 mmol) in 68 mL dry THF, and stirred at –50 °C for 23 h. The reaction was quenched slowly by addition of MeOH (150 mL) with stirring. Sat. aq. NaCl (150 mL) was added and the mixture was extracted once with EtOAc (200 mL). The organic layer was washed once with sat. aq. NaCl (150 mL). The combined aqueous layers were extracted three times with EtOAc (250 mL). The combined organic layers were dried over Na_2SO_4, filtered through a cotton plug, and concentrated. Purification of the resulting oil by silica gel chromatography (20% EtOAc/hex) provided the title compound as an oil in 58% yield (5.58 g). All spectral

data were in complete accord with 4-(2-Cyclohexylsulfanylmethyl-1-methyl-but-2-enyl)-morpholine **3** (*vida supra*).

(2*S*,3*S*)-2-Benzyloxy-4-cyclohexylsulfanylmethyl-3-methyl-1-morpholin-4-yl-hex-4-en-1-one (44). 4-[(1*S*)-2-Cyclohexylsulfanylmethyl-1-methyl-but-2-enyl)-morpholine **(42)** (3.00 g, 10.6 mmol) was dissolved in 15 mL CH_2Cl_2 in a dry 500 mL round bottom flask under argon. A solution of $TiCl_4(THF)_2$ (2.65 g, 7.8 mmol) in 250 mL CH_2Cl_2 was added *via* cannula, and iPr_2NEt (3.69 mL, 21.2 mmol) was then added *via* syringe. The stirring solution was cooled to –40 °C, and 21.2 mL of a 1 M solution in CH_2Cl_2 of freshly distilled benzyloxyacetylchloride (3.34 mL, 21.2 mmol) was added *via* syringe pump over 17 h. After addition, the reaction was poured into 1N aq. NaOH (200 mL) and extracted three times with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting red oil by silica gel chromatography (30% EtOAc/hex) provided the title compound as a yellow oil in 97% yield (4.41 g), 12:1 *syn* diastereomer: other diastereoisomers, *syn* 98% ee. IR (film) 3035, 2927, 2858, 1645, 1444, 1367, 1305, 1267, 1112, 1027, 966, 919, 842, 734, 703, 664 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 7.36-7.23 m, 5H, Ar-**H**), 5.51 (q, *J* = 7.2 Hz, 1H, vinylC**H**), 4.63 (d, *J* = 12.0 Hz, 1H, OC**H**H), 4.38 (d, *J* = 12.0 Hz, 1H, OCH**H**), 4.11 (d, *J* = 7.2Hz, 1H, C**H**OBn), 3.74-3.44 (m, 8H, morph-**H**), 3.29 (d, *J* = 12.3 Hz, 1H, SC**H**H), 3.01 (d, *J* = 12.3, 1H, SCH**H**), 2.72 (dq, *J* = 7.2, 7.2, 1H, CHOBnC**H**CH_3), 1.66 (d, *J* = 7.2, 3H, vinylCHC**H**$_3$), 1.62-1.59 (m, 1H, SC**H**), 1.36-1.24 (m, 10H, Cy-**H**), 1.20 (d, *J* = 7.2, 3H, CHOBnCHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 169.8, 137.0, 128.6, 128.1, 124.6, 82.5, 72.1, 67.4, 67.1, 46.1, 44.2, 42.7, 42.0, 34.0, 30.0,

26.5, 26.2, 16.9, 14.1; LRMS (FAB) *m/z* 432 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{25}H_{38}NO_3S$) requires *m/z* 432.2566, found *m/z* 432.2572. Enantiomeric ratio was determined by HPLC with Chiralcel AD column and AD guard column (4% *i*PrOH/hex, 1 mL/min flow rate); t_r = 17.1 min (major) and 19.9 min (minor).

(2*S*,3*R*)-4-[(1*S*,2*S*)-2-Benzyloxy-1-methyl-3-morpholin-4-yl-3-oxo-propyl]-2-methoxy-3-methyl-pent-4-enethioic acid *S*-cyclohexyl ester (45). (2*S*,3*S*)-2-Benzyloxy-4-cyclohexylsulfanylmethyl-3-methyl-1-morpholin-4-yl-hex-4-en-1-one **44** (12.1 g, 28.07 mmol) was dissolved in 280.7 mL CH_2Cl_2 in a dry 1 L round bottom flask under argon. Me_2AlCl (26.07 mL, 280.7 mmol) was added *via* syringe, and iPr_2NEt (34.2 mL, 196.5 mmol) was then added *via* syringe. The stirring solution was cooled to –60 °C, and 20.16 mL of a 9.7 M solution in CH_2Cl_2 of freshly distilled methoxyacetylchloride (17.96 mL, 196.49 mmol) was added *via* syringe pump over 20 h. The reaction was then stirred at –60 °C for 10 d, at which time it was quenched with 1N aq. NaOH (200 mL) and sat. aq. NaCl (100 mL). The mixture was extracted three times with Et_2O, and the combined organic extracts were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (30% EtOAc/hex) provided the title compound as a yellow oil in 93% yield (13.07 g) as a 3.2:1 mixture of diastereomers. IR (film) 2935, 2858, 2248, 1645, 1452, 1359, 1305, 1267, 1236, 1112, 973, 911, 850, 734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.36-7.25 (m, 5H, Ar-**H**), 5.05 (d, *J* = 10.8 Hz, 2H, vinylC**H**$_2$), 4.61 (d, *J* = 11.5 Hz, 1H, C**H**HAr), 4.40 (d, *J* = 11.5 Hz, 1H, CH**H**Ar), 4.09 (d, *J* = 7.2 Hz, 1H, C**H**OBn), 3.69-3.53 (m, 8H, morph-**H**), 3.49 (d, *J* = 7.2 Hz, 1H, C**H**OMe), 3.35 (s, 3H, OC**H**$_3$),

2.63 (dq, *J* = 7.2 Hz, 7.2 Hz, 1H, NC**H**CH_3), 2.46 (dq, *J* = 7.2 Hz, 7.2 Hz, SC**H**CH_3), 1.92-1.34 (m, 11H, Cy-**H**), 1.20 (d, *J* = 7.2 Hz, 3H, NCHC**H**$_3$), 0.97 (d, *J* = 7.2 Hz, 3H, SCHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 169.8, 152.0, 128.6, 128.1, 128.0, 112.5, 92.4, 81.7, 71.8, 67.4, 67.0, 59.6, 46.2, 43.3, 42.9, 41.6, 33.5, 33.3, 26.3, 25.9, 16.9, 16.5; LRMS (FAB) *m*/*z* 504 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{28}H_{42}NO_5S$) requires *m*/*z* 504.2762, found *m*/*z* 504.2784.

(2*S*,3*R*,5*S*,6*S*)-6-Benzyloxy-2-methoxy-3,5-dimethyl-7-morpholin-4-yl-4,7-dioxo-heptanethioic acid *S*-cyclohexyl ester (46). (2*S*,3*R*)-4-[(1*S*,2*S*)-2-Benzyloxy-1-methyl-3-morpholin-4-yl-3-oxo-propyl]-2-methoxy-3-methyl-pent-4-enethioic acid *S*-cyclohexyl ester 4**5** (12.9 g, 25.6 mmol) was dissolved in 128 mL dry CH_2Cl_2 in a dry 1 L 3-neck round bottom flask under argon. The stirring solution was cooled to –78 °C, and oxygen was bubbled through the solution for 10 min, after which time a stream of ozone was passed through the solution for one hour until a faint blue color appeared. The ozone stream was removed and oxygen was again bubbled through the stirring solution for 5 min, at which time dimethyl sulfide (2.8 mL, 38.4 mmol) was added and the mixture was stirred at –78 °C for 10 min and then at ambient temperature for 10 h. The reaction was then concentrated. Purification of the resulting oil by silica gel chromatography (30% EtOAc/hex) provided the title compound as a yellow oil in 52% yield (6.68 g) as a single diastereoisomer, 97% ee. IR (film) 2935, 2858, 2248, 1962, 1715, 1645, 1452, 1383, 1305, 1267, 1236, 1112, 1012, 966, 911, 857, 819, 734 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) 7.37-7.25 (m, 5H, Ar-**H**), 4.54 (d, *J* = 9.6 Hz, 1H, C**H**OBn), 4.52 (d, *J* = 11.6 Hz, 1H, C**H**HAr), 4.30 (d, *J* = 11.6 Hz, 1H, CH**H**Ar), 3.81 (d, *J* = 9.3 Hz, 1H, C**H**OMe), 3.66-

3.40 (m, 9H, morph-**H**, CHOBnC**H**Me), 3.30 (s, 3H, OC**H**$_3$), 3.04 (dq, *J* = 9.6 Hz, 7.2 Hz, 1H, CHOMeC**H**Me), 1.94-1.35 (m, 11H, Cy-**H**), 1.26 (d, *J* = 7.2 Hz, 3H, CHOBnCHC**H**$_3$), 1.00 (d, *J* = 7.2 Hz, 3H, CHOMeCHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) 212.7, 201.5, 168.8, 137.5, 128.0, 88.5, 75.9, 69.4, 67.0, 59.2, 49.0, 47.0, 46.4, 42.6, 41.7, 33.5, 33.3, 26.3, 25.9, 13.2, 13.0; LRMS (FAB) *m/z* 506 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{27}H_{40}NO_6S$) requires *m/z* 506.2567, found *m/z* 506.2576. Enantiomeric ratio was determined by HPLC with Chiralcel AD column and AD guard column (6% *i*PrOH/hex, 1 mL/min flow rate); t_r = 22.5 min (major) and 26.1 min (minor).

***(2S*,3R*,5S*,6S*)*-6-Benzyloxy-2-methoxy-3,5-dimethyl-7-morpholin-4-yl-4,7-dioxo-heptanal (48).** To a dry 100 mL round bottom flask containing 10% Pd/C (1.87 g, 1.76 mmol Pd) under a nitrogen atmosphere was added *via* cannula a solution of (2*S**,3*R**,5*S**,6*S**)-6-benzyloxy-2-methoxy-3,5-dimethyl-7-morpholin-4-yl-4,7-dioxo-heptanethioic acid *S*-cyclohexyl ester **47** (5.54 g, 10.97 mmol) in freshly distilled acetone (21.4 mmol). The stirring mixture was cooled to +4 °C, and freshly distilled Et_3SiH (8.76 mL, 54.85 mmol) which had been pre–cooled to +4 °C was added slowly *via* syringe. The reaction was monitored by TLC (50% EtOAc/hex) and upon consumption of starting material after 70 min, the reaction mixture was flushed through a pad of celite with EtOAc. The solution was concentrated. Purification of the resulting oil by silica gel chromatography (60% EtOAc/hex) provided the title compound as a colorless oil in 86% yield (3.7 g). IR (film) 3441, 2934, 2858, 1730, 1710, 1645, 1455, 1379, 1301, 1271, 1235, 1114, 1017, 967, 855, 742, 699, 578 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 9.71 (d, *J* = 2.5 Hz, CO**H**), 7.39-7.31 (m, 5H, Ar-**H**), 4.59 (d, *J* = 9.5 Hz, 1H, C**H**OBn), 4.55 (d, *J* =

12, 1H, C**H**HAr), 4.34 (d, *J* = 12 Hz, 1H, CH**H**Ar), 4.14 (dd, *J* = 7.5 Hz, 6.5 Hz, C**H**OMe), 3.70-3.46 (m, 9H, morph-**H**, CHOBnC**H**Me), 3.39 (s, 3H, OC**H**$_3$), 3.18 (dq, *J* = 6.5 Hz, 8.0 Hz, 1H, CHOMeC**H**Me), 1.29 (d, *J* = 7.5 Hz, 3H, CHOBnCHC**H**$_3$), 1.16 (d, *J* = 7.5 Hz, 3H, CHOMeCHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 212.4, 202.7, 168.8, 137.4, 128.7, 128.0, 86.6, 76.0, 69.2, 67.0, 59.4, 46.8, 46.4, 46.3, 42.7, 13.3, 12.8; LRMS (FAB) *m*/*z* 392 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{21}H_{30}NO_6$) requires *m*/*z* 392.2059, found *m*/*z* 392.2073.

(3*S,4*S**,7*S**,8*S**,9*R**)-3-Benzyloxy-7-isopropenyl-8-methoxy-4,9-dimethyl-1,6-dioxa-spiro[4.4]nonan-2-one (56).** *(*2*S**,3*R**,5*S**,6*S**)-6-Benzyloxy-2-methoxy-3,5-dimethyl-7-morpholin-4-yl-4,7-dioxo-heptanal **48** (1.56 g, 3.99 mmol) was dissolved in 64.3 mL dry THF in a 250 mL round bottom flask, and the stirring solution was cooled to –78 °C. Isopropenyl magnesium bromide (0.5M in THF, 9.6 mL, 4.79 mmol) was added *via* syringe pump over 45 min. Stirring was continued for 1.5 h after addition was complete, at which time the reaction was quenched with sat. aq. NH_4Cl and extracted four times with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (50% EtOAc/hex) provided the intermediate allylic alcohol product as a colorless oil in 74% yield (1.28 g). A portion of this oil (0.937 g) was immediately placed under high vacuum (1.5 mm Hg) for 32 d, after which time TLC analysis indicated formation of the title compound. Purification of the oil by silica gel chromatography (30% EtOAc/hex to 60% EtOAc/hex) provided recovery of 20% of the starting allylic alcohol (237.8 mg) and isolation of the title compound as a colorless oil in

58% yield (437.2 mg) from the allylic alcohol (78% yield based on recovered starting material). IR (film) 2970, 2936, 1784, 1717, 1645, 1497, 1456, 1352, 1250, 1205, 1141, 1113, 1072, 1010, 911, 742, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 7.41-7.29 (m, 5H, Ar-**H**), 5.14 (d, *J* = 11.5 Hz, 1H, C**H**HAr), 5.05 (s, 1H, vinylC**H**), 4.99 (s, 1H, vinylC**H**), 4.76 (d, *J* = 11.5 Hz, 1H, CH**H**Ar), 4.41 (d, *J* = 3.9 Hz, 1H, allylicC**H**), 4.09 (d, *J* = 10.8 Hz, 1H, C**H**OBn), 3.73 (ss, *J* = 4.8 Hz, 4.8 Hz, 1H, C**H**OMe), 3.39 (s, 3H, OC$\mathbf{H}_3$), 2.44 (dq, *J* = 6.9 Hz, 10.5 Hz, 1H, CHOBnC**H**Me), 2.28 (dq, *J* = 6.9 Hz, 5.4 Hz, 1H, CHOMeC**H**Me), 1.80 (s, 3H, vinylC$\mathbf{H}_3$), 1.14 (d, *J* = 6.9 Hz, 1H, CHOBnCHC$\mathbf{H}_3$), 1.08 (d, *J* = 6.6 Hz, 1H, CHOMeCHC$\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 174.4, 140.9, 137.2, 128.4, 128.1, 127.9, 113.5, 113.0, 87.5, 83.7, 77.8, 72.8, 60.7, 43.4, 42.3, 19.5, 10.7, 7.7; LRMS (FAB) *m/z* 347 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{20}H_{27}O_5$) requires *m/z* 347.1846, found *m/z* 347.1858.

(2*S,3*S**,4*R**,5*R**,6*S**,7*S**)-2-Benzyloxy-6-methoxy-3,5,8-trimethyl-non-8-ene-1,4,7-triol (57).** (3*S**,4*S**,7*S**,8*S**,9*R**)-3-Benzyloxy-7-isopropenyl-8-methoxy-4,9-dimethyl-1,6-dioxa-spiro[4.4]nonan-2-one **56** (76.0 mg, 0.219 mmol) was dissolved in 4.38 mL dry Et_2O in a dry 50 mL round bottom flask under argon, and the stirring solution was cooled to 0 °C. $LiAlH_4$ (33.3 mg, 0.877 mmol) was added and the flask was flushed with argon. The reaction was stirred at ambient temperature for 24 h at which time it was quenched slowly with sat. aq. Rochelle's salt solution (30 mL) and stirred for 4 d. The mixture was extracted four times with EtOAc (40 mL), dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (50% EtOAc/hex) provided the title compound as a colorless

oil in 92% yield (70.8 mg). IR (film) 3424, 3033, 2973, 2939, 1646, 1497, 1455, 1380, 1211, 1092, 1028, 979, 902, 736, 699, 540 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.35-7.28 (m, 5H, Ar-**H**), 5.00 (s, 1H, vinylC**H**), 4.92 (s, 1H, vinylC**H**), 4.71-4.66 (m, 2H, C**H**$_2$Ar), 4.10 (bs, 1H, allylic**H**), 3.96-3.29 (m, 5H, C**H**2OH, C**H**OBn, C**H**OMe, C**H**OH), 3.52 (s, 3H, OC**H**$_3$), 2.15-1.78 (m, 2H, C**H**Me, C**H**Me), 1.76, (s, 3H, vinylC**H**$_3$), 0.96 (d, *J* = 7.5 Hz, 3H, CHOBnCHC**H**$_3$), 0.77 (d, *J* = 6.5 Hz, 3H, CHOMeCHC**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) 145.3, 128.7, 128.1, 128.0, 127.9, 113.2, 86.5, 82.2, 75.9, 73.4, 71.8, 63.0, 62.3, 37.7, 35.7, 18.5, 11.8, 10.3; LRMS (FAB) *m/z* 353 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{20}H_{33}O_5$) requires *m/z* 353.2339, found *m/z* 353.2328.

[(1*S,2*S**,3*R**,4*R**,5*S**,6*S**)-3,6-Bis(*tert*-butyl-dimethyl-silanyloxy)-1-(*tert*-butyl-dimethyl-silanyloxymethyl)-5-methoxy-2,4,7-trimethyl-oct-7-enyloxymethyl]-benzene (60).** (2*S**,3*S**,4*R**,5*R**,6*S**,7*S**)-2-Benzyloxy-6-methoxy-3,5,8-trimethyl-non-8-ene-1,4,7-triol **57** (363 mg, 1.03 mmol) was dissolved in 32 mL dry CH_2Cl_2 in a 100 mL round bottom flask under argon. The solution was cooled to 0 °C and freshly distilled TBSOTf (2.37 mL, 10.3 mmol) was added, followed by freshly distilled 2,6–lutidine (1.2 mL, 10.3 mmol). The reaction was allowed to warm to ambient temperature and was then stirred for 3.5 h at which time it was quenched with sat. aq. NH_4Cl (30 mL) and extracted four times with EtOAc (30 mL), dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (5% EtOAc/hex) provided the title compound as a colorless oil in 94% yield (673.5 mg). IR (film) 2927, 2855, 1653, 1472, 1252, 1093, 836, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.37-7.24 (m, 5H, Ar-**H**), 5.09 (s, 1H, vinylC**H**), 4.91 (s,

1H, vinylC**H**), 4.78 (d, *J* = 11.7 Hz, 1H, C**H**HAr), 4.56 (d, *J* = 12.0 Hz, 1H, CH**H**Ar), 4.22 (bs, 1H, allylicC**H**), 4.14 (d, *J* = 7.2 Hz, 1H, $(CHMe)_2$C**H**OTBS), 3.78 (dd, *J* = 10.5 Hz, 5.7 Hz, 1H, C**H**HOH), 3.69 (dd, *J* = 10.5 Hz, 4.2 Hz, 1H, CH**H**OH), 3.59 (ddd, *J* = 5.1 Hz, 4.8 Hz, 5.0 Hz, 1H, C**H**OBn), 3.42 (s, 3H, OC$\mathbf{H}_3$), 3.16 (dd, *J* = 3.0 Hz, 10.2 Hz, 1H, C**H**OMe), 2.00-1.89 (m, 2H, C**H**Me, C**H**Me), 1.74 (s, 3H, vinylC$\mathbf{H}_3$), 0.95-0.86 (m, 33H, $(SitBu)_3$, $(CHMe)_2$), 0.13-0.01 (m, 18H, $(SiMe_2)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.4, 139.8, 128.3, 127.4, 127.3, 112.1, 83.7, 81.1, 75.4, 72.8, 72.1, 64.3, 57.5, 41.1, 35.7, 26.6, 26.3, 26.1, 20.5, 19.0, 18.6, 11.0, 10.9, -2.5, -3.3, -3.5, -3.9, -4.7, -4.9, -5.0; LRMS (FAB) *m*/*z* 695 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{38}H_{75}O_5Si_3$) requires *m*/*z* 695.4897, found *m*/*z* 695.4922.

(2*S,3*S**,4*R**,5*R**,6*S**,7*S**)-1,4,7-Tris-(*tert*-butyl-dimethyl-silanyloxy)-6-methoxy-3,5,8-trimethyl-non-8-en-2-ol (61).**[30] A dry 50 mL 3-neck round bottom flask under argon with a condensing aparatus attached was cooled to –78 °C and 10 mL NH_3 was condensed into the flask. Lithium metal (8 mg) was added, and the mixture was stirred until a deep blue color persisted. A solution of [(1*S**,2*S**,3*R**,4*R**,5*S**,6*S**)-3,6-bis(*tert*-butyl-dimethyl-silanyloxy)-1-(*tert*-butyl-dimethyl-silanyloxymethyl)-5-methoxy-2,4,7-trimethyl-oct-7-enyloxymethyl]-benzene **60** (17.5 mg, 0.025 mmol) in 1 mL dry THF was added, and the reaction was stirred for two minutes, at which time solid NH_4Cl (30 mg) was added, and the blue color disappeared. The mixture was allowed to warm to ambient temperature, and the mixture was stirred until the NH_3 had evaporated. Water (30 mL) was added, and the mixture was extracted three times with EtOAc (30 mL), dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the

resulting oil by silica gel chromatography (5% EtOAc/hex) provided the title compound as a colorless oil in 74% yield (11.3 mg). IR (film) 3442, 2956, 2930, 2886, 2858, 2096, 1644, 1472, 1463, 1388, 1361, 1253, 1089, 1044, 1005, 940, 836 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) □ 5.00 (s, 1H, vinylC**H**), 4.90 (s, 1H, vinylC**H**), 4.16 (d, *J* = 4.5 Hz, 1H, allylicC**H**), 4.03 (dd, *J* = 2.0 Hz, 4.0 Hz), 3.95 (m, 1H, C**H**OH), 3.55 (dd, *J* = 9.5Hz, 6.0 Hz, 1H, C**H**HOTBS), 3.51 (dd, *J* = 6.5 Hz, 9.5 Hz, 1H, CH**H**OTBS), 3.44 (s, 3H, OC$\mathbf{H}_3$), 3.23 (s, 1H, O**H**), 3.08 (dd, *J* = 4.5 Hz, 7.5 Hz, 1H, C**H**OMe), 1.95 (ddq, *J* – 7.0 Hz, 7.0 Hz, 2.0 Hz, 1H, CHOMeC**H**Me), 1.70-1.67 (m, 1H, CHOHC**H**Me), 1.56 (s, 3H, vinylC$\mathbf{H}_3$), 0.953 (d, *J* = 7.5 Hz, 1H, C**H**Me), 0.946 (d, *J* = 7.5 Hz, 1H, C**H**Me), 0.93-0.89 (m, 27H, $(SitBu)_3$), 0.11-0.02 (m, 18H, $(SiMe_2)_3$); ^{13}C NMR (125 MHz, $CDCl_3$) □ 145.4, 113.0, 86.0, 76.5, 75.4, 71.7, 65.1, 60.6, 59.1, 40.6, 37.5, 26.5, 26.1, 19.4, 18.8, 18.5, 18.4, 14.4, 12.9, 10.9, -3.6, -4.3, -4.8, -5.1, -5.2; LRMS (FAB) *m/z* 605 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{31}H_{69}O_5Si_3$) requires *m/z* 605.4447, found *m/z* 605.4453.

(2*S,3*S**,4*R**,5*R**,6*S**,7*S**)-4,7-Bis-(*tert*-butyl-dimethyl-silanyloxy)-6-methoxy-3,5,8-trimethyl-non-8-en-1,2-diol (62).** To a solution of (2*S**,3*S**,4*R**,5*R**,6*S**,7*S**)-1,4,7-tris-(*tert*-butyl-dimethyl-silanyloxy)-6-methoxy-3,5,8-trimethyl-non-8-en-2-ol **61** (56.4 mg, 0.093 mmol) in a 100 mL round bottom flask was added 32 mL of a solution of THF:AcOH:H_2O (2:2:1 v:v:v) that had been pre–cooled to +4 °C. The reaction was stirred at +4 °C for 2.5 d at which time it was quenched with $NaHCO_3$ (30 mL), extracted four times with EtOAc (30 mL), dried over Na_2SO_4, filtered through a cotton plug, and concentrated. Purification of the resulting oil by silica gel

chromatography (30% EtOAc/hex) provided the title compound as a colorless oil in 96% yield (44.0 mg). IR (film) 3418, 2953, 2927, 2855, 1652, 1472, 1387, 1250, 1092, 1005, 941, 836, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.00 (s, 1H, vinylC**H**), 4.93 (s, 1H, vinylC**H**), 4.15 (d, *J* = 4.5 Hz, 1H, allylicC**H**), 4.10 (m, 1H, $(CHMe)_2$C**H**OTBS), 4.00 (m, 1H, C**H**OHCH_2OH), 3.66-3.62 (m, 2H, C$\mathbf{H}_2$OH), 3.48 (s, 3H, OC$\mathbf{H}_3$), 3.07 (dd, *J* = 7.5 Hz, 5.5 Hz, 1H, C**H**OMe), 1.98-1.94 (m, 1H, CHOMeC**H**Me), 1.8-1.75 (m, 1H, CHOHC**H**Me), 1.57 (s, 3H, vinylC$\mathbf{H}_3$), 1.000 (d, *J* = 7.5 Hz, 3H, CHC$\mathbf{H}_3$), 0.996 (d, *J* = 7.5 Hz, 3H, CHC$\mathbf{H}_3$), 0.94 (s, 9H, tBu), 0.93 (s, 9H, tBu), 0.15 (s, 3H, SiMe), 0.14 (s, 3H, SiMe), 0.09 (s, 3H, SiMe), 0.05 (s, 3H, SiMe); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3, 113.3, 87.1, 76.6, 76.5, 72.5, 66.1, 60.1, 42.0, 38.3, 26.5, 26.2, 19.4, 18.8, 18.6, 13.9, 11.8, -3.4, -4.1, -4.2, -4.6; LRMS (FAB) *m/z* 491 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{25}H_{55}O_5Si_2$) requires *m/z* 491.3605, found *m/z* 491.3588.

(2*S)-2-[(1*S**,2*R**,3*R**,4*S**,5*S**)-2,5-Bis-(*tert*-butyl-dimethyl-silanyloxy)-4-methoxy-1,3,6-trimethyl-hept-6-enyl]-oxirane (63).** To (2*S**,3*S**,4*R**,5*R**,6*S**,7*S**)-4,7-bis-(*tert*-butyl-dimethyl-silanyloxy)-6-methoxy-3,5,8-trimethyl-non-8-en-1,2-diol **62** (61.6 mg, 0.126 mmol), toluenesolfonyl chloride (127 mg, 0.665 mmol), and DMAP (5 mg) in a 25 mL round bottom flask under argon was added 9.0 mL CH_2Cl_2. Et_3N was added (0.28 mL, 2.01 mmol), and the reaction was allowed to stir for 2.5 h, at which time the mixture was concentrated. 11.4 mL MeOH was added, followed by K_2CO_3 (257 mg), and the reaction was stirred at ambient temperature for three hours. The reaction was quenched with sat. aq. NH_4Cl (10 mL), extracted four times with EtOAc (20 mL), dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the

resulting oil by silica gel chromatography (10% EtOAc/hex) provided the title compound as a colorless oil in 93% yield (55.2 mg). IR (film) 3413, 2955, 228, 2894, 2857, 1652. 1473, 1463, 1405, 1387, 1360, 1251, 1190, 1158, 1095, 1043, 1005, 939, 899, 862, 835, 792, 774, 674 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) □ 5.06 (s, 1H, vinylC**H**), 4.95 (s, 1H, vinylC**H**), 4.22 (s, 1H, allylicC**H**), 4.01 (d, *J* = 6.0 Hz, 1H, $(CHMe)_2$C**H**OTBS), 3.44 (s, 3H, OC$\mathbf{H}_3$), 3.14 (dd, *J* = 8.5 Hz, 3.5 Hz, 1H, C**H**OMe), 2.89-2.87 (m, 1H, C**H**OCH_2), 2.81 (dd, *J* = 5.0 Hz, 5.0 Hz, 1H, C**H**HO), 2.6 (dd, *J* = 5.0 Hz, 3.0 Hz, 1H, CH**H**O), 1.95-1.91 (m, 1H, C**H**Me), 1.64-1.60 (m, 1H, C**H**Me), 1.57 (s, 3H, vinylC$\mathbf{H}_3$), 1.06 (d, *J* = 6.5 Hz, CHC$\mathbf{H}_3$), 0.93-0.91 (m, 21H, $(tBu)_2$, CHC$\mathbf{H}_3$), 0.11 (s, 3H, SiMe), 0.09 (s, 3H, SiMe), 0.08 (s, 3H, SiMe), 0.05 (s, 3H, SiMe); ^{13}C NMR (125 MHz, $CDCl_3$) □ 145.5, 112.6, 84.3, 75.9, 73.2, 58.0, 55.1, 48.8, 43.6, 37.5, 29.9, 26.4, 26.1, 19.8, 18.8, 18.5, 14.6, 11.8, -3.5, -3.9, -4.2; LRMS (FAB) *m/z* 473 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{25}H_{53}O_4Si_2$) requires *m/z* 473.3480, found *m/z* 473.3482.

(4*S,5*S**,6*R**,7*R**,8*S**,9*S**)-6,9-Bis-(*tert*-butyl-dimethyl-silanyloxy)-8-methoxy-5,7,10-trimethyl-1-(trimethyl-silanyl)-undec-10-en-1-yn-4-ol (64).**[31] To trimethylsilyl acetylene (0.132 mL, 0.934 mmol) in 2.72 mL dry THF in a dry 10 mL round bottom flask under argon at –78 °C was added nBuLi (2.36M in THF, 0.396 mL, 0.934 mmol). The reaction was stirred at –78 °C for 1 h. BF_3OEt_2 was added at –78 °C, and the reaction was stirred at –78 °C for 30 min. (2*S**)-2-[(1*S**,2*R**,3*R**,4*S**,5*S**)-2,5-bis-(*tert*-butyl-dimethyl-silanyloxy)-4-methoxy-1,3,6-trimethyl-hept-6-enyl]-oxirane **63** (55.2 mg, 0.117 mmol) was added as a solution in 1.8 mL dry THF *via* syringe, and the syringe rinsed twice with 0.9 mL dry THF. After 1 h, the reaction was quenched with

sat. aq. NH_4Cl (10 mL) and extracted four times with Et_2O (15 mL). The combined organic layers were washed once with sat. aq. NaCl (15 mL), dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (10% EtOAc/hex) provided the title compound as a colorless oil in 91% yield (60.7 mg). IR (film) 3477, 2956, 2921, 2857, 2176, 1653, 1473, 1463, 1388, 1361, 1249, 1099, 1005, 939, 903, 839, 774, 675, 651 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) □ 5.01 (s, 1H, vinylC**H**), 4.93 (s, 1H, vinylC**H**), 4.18-4.14 (m, 2H, allylicC**H**, C**H**OH), 4.05-4.03 (m, 1H, $(CHMe)_2$C**H**OTBS), 3.56 (d, *J* = 1.5 Hz, 1H, O**H**), 3.47 (s, 3H, OC$\mathbf{H}_3$), 3.09 (dd, *J* = 6 Hz, 6 Hz, 1H, C**H**OMe), 2.51 (dd, *J* = 6.0 Hz, 16.5 Hz, 1H, TMSCC**H**H), 2.36 (dd, *J* = 8.5Hz, 16.5 Hz, 1H, TMSCCH**H**), 1.99 (ddq, *J* = 3 Hz, 6.5 Hz, 6.5 Hz, 1H, CHOMeC**H**Me), 1.81-1.72 (m, 4H, vinylC$\mathbf{H}_3$, CHOHC**H**Me), 1.003 (d, *J* = 7.0 Hz, 3H, CHC$\mathbf{H}_3$), 0.995 (d, *J* = 7.0 Hz, 3H, CHC$\mathbf{H}_3$), 0.93 (s, 9H, tBu), 0.92 (s, 9H, tBu), 0.17-0.05 (m, 21H, $SiMe_3$, $(SiMe_2)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) □ 145.4, 113.3, 104.1, 86.4, 76.7, 76.6, 70.3, 59.5, 41.9, 38.0, 29.9, 26.5, 26.2, 26.1, 19.2, 18.8, 18.5, 13.3, 10.5, 0.4, -3.6, -4.2, -4.5, -4.7; LRMS (FAB) *m/z* 571 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{30}H_{63}O_4Si_3$) requires *m/z* 571.4030, found *m/z* 571.4034.

(3*S,4*S**,5*R**,6*R**,7*S**,8*S**)-4-Methoxy-2,5,7-trimethyl-11-(trimethyl-silanyl)-undec-1-en-10-yne-3,6,8-triol (65).** To (4*S**,5*S**,6*R**,7*R**,8*S**,9*S**)-6,9-bis-(*tert*-butyl-dimethyl-silanyloxy)-8-methoxy-5,7,10-trimethyl-1-(trimethyl-silanyl)-undec-10-en-1-yn-4-ol **64** (45.0 mg, 0.079 mmol) in 5 mL MeOH in a 25 mL round bottom flask was added conc. HCl (33 drops) and the reaction was allowed to stire at room temperature for 6 h, at which time sat. aq. $NaHCO_3$ (10 mL) was added, and the mixture was extracted

five times with EtOAc (10 mL). The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (50% EtOAc/hex) provided the title compound as a colorless oil in 91% yield (56.2 mg). IR (film) 3422, 2963, 2937, 2173, 1464, 1248, 1090, 1064, 841 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 5.04 (s, 1H, vinylC**H**), 4.95 (s, 1H, vinylC**H**), 4.21 (dd, *J* = 4.8 Hz, 6.3 Hz, 1H, allylicC**H**), 4.06-3.98 (m, 2H, (C**H**OH)$_2$), 3.62 (d, *J* = 1.5 Hz, O**H**), 3.59 (s, 3H, OC**H**$_3$), 3.31 (dd, *J* = 3.9 Hz, 6.6 Hz, 1H, C**H**OMe), 3.08 (d, *J* = 6.0 Hz, 1H, O**H**), 2.54 (dd, *J* = 8.1 Hz, 16.8 Hz, 1H, C**H**HCTMS), 2.43 (dd, *J* = 5.4 Hz, 16.5 Hz, 1H, CH**H**CTMS), 2.38 (d, *J* = 4.5 Hz, 1H, allylicO**H**), 1.99-1.86 (m, 1H, C**H**Me), 1.76-1.70 (m, 4H, vinylC**H**$_3$, C**H**Me), 1.04 (d, *J* = 6.9 Hz, 3H, CHC**H**$_3$), 0.75 (d, *J* = 7.2 Hz, 3H, CHC**H**$_3$), 0.14 (s, 9H, TMS); ^{13}C NMR (75 MHz, $CDCl_3$) □ 161.3, 144.6, 114.4, 104.6, 88.1, 86.9, 72.7, 62.8, 39.7, 35.7, 25.2, 18.1, 12.0, 11.4, 0.5; LRMS (FAB) *m/z* 343 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{18}H_{35}O_4Si$) requires *m/z* 343.2303, found *m/z* 343.2305.

(3*S,4*S**,5*R**)-4-Methoxy-2-methyl-5-{(4*R**,5*S**,6*S**)-2,2,5-trimethyl-6-[3-(trimethyl-silanyl)-prop-2-ynyl]-[1,3]dioxan-4-yl}-hex-1-en-3-ol (66).** To (3*S**,4*S**,5*R**,6*R**,7*S**,8*S**)-4-methoxy-2,5,7-trimethyl-11-(trimethyl-silanyl)-undec-1-en-10-yne-3,6,8-triol **65** (31.4 mg, 0.092 mmol) in a 25 mL round bottom flask was added freshly distilled 2,2-dimethoxy-propane (8 mL, 0.065 mol), followed by *para*–toluenesulfonic acid (5 mg). The reaction was stirred for 20 min and then quenched with sat. aq. $NaHCO_3$ (10 mL). The mixture was extracted five times with EtOAc (15 mL), and the combined organic layers were dried over Na_2SO_4, filtered

through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (20% EtOAc/hex) provided the title compound as a colorless oil in 98% yield (34.4 mg). IR (film) 3480, 3059, 2996, 2360, 2342, 2178, 1456, 1380, 1249, 1226, 1170, 1135, 1076, 1035, 1016, 993, 953, 887, 843, 761, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.17 (s, 1H, vinylC**H**), 4.98 (s, 1H, vinylC**H**), 4.02 (d, *J* = 8.5 Hz, 1H, allylic**CH**), 4.00-3.96 (m, 1H, $(CHMe)_2$**CH**), 3.63 (d, *J* = 8.0 Hz, 1H, $TMSCCH_2$**CH**O), 3.42 (s, 3H, O**CH**$_3$), 3.26 (d, *J* = 9.0 Hz, 1H, **CH**OMe), 2.51 (d, *J* = 9.0 Hz, 1H, O**H**), 2.40 (dd, *J* = 7.0 Hz, 16.5 Hz, 1H, TMSCC**H**H), 2.32 (dd, *J* = 7.0 Hz, 16.5 Hz, 1H, TMSCCH**H**), 1.97-1.91 (m, 1H, C**H**Me), 1.84-1.80 (m 1H, C**H**Me), 1.38 (s, 3H, CC**H**$_3$C**H**$_3$), 1.36 (s, 3H, CC**H**$_3$C**H**$_3$), 0.98 (d, *J* = 6.5 Hz, 3H, CHC**H**$_3$), 0.88 (d, *J* = 7.0 Hz, 3H, CHC**H**$_3$), 0.16 (s, 9H, TMS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.5, 119.4, 110.9, 104.0, 100.9, 82.6, 73.7, 73.3, 68.8, 61.3, 38.5, 36.0, 25.5, 24.1, 22.7, 19.9, 11.7, 10.7, 0.3; LRMS (FAB) *m/z* 383 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{21}H_{39}O_4Si$) requires *m/z* 383.2600, found *m/z* 383.2618.

Benzyloxy-acetic acid (1S*)-1-((1*S,2*R**)-1-methoxy-2-{(4*R**,5*S**,6*S**)-2,2,5-trimethyl-6-[3-(trimethyl-silanyl)-prop-2-ynyl]-[1,3]dioxan-4-yl}-propyl)-2-methyl-allyl ester (68).** To (3*S**, 4*S**,5*R**)-4-methoxy-2-methyl-5-{(4*R**,5*S**,6*S**)-2,2,5-trimethyl-6-[3-(trimethyl-silanyl)-prop-2-ynyl]-[1,3]dioxan-4-yl}-hex-1-en-3-ol **66** (17.5 mg, 0.0457 mmol) in 0.3 mL dry THF under argon in a 2-dram vial was added pyridine (18.5 uL, 0.229 mmol) and the stirring solution was cooled to 0 °C. Benzyloxyacetylchloride (28.4 uL, 0.183 mmol) was added slowly, and the reaction was allowed to warm to ambient temperature. After 5 h, the reaction was quenched with sat.

aq. $NaHCO_3$ (2 mL) and extracted three times with EtOAc (3 mL). The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (20% EtOAc/hex) provided the title compound as a colorless oil in 93% yield (22.5 mg). IR (film) 2921, 2178, 1756, 1456, 1380, 1250, 1226, 1195, 1134, 1017, 844, 760, 700, 558 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) □ 7.39-7.28 (m, 5H, Ar-**H**), 5.35 (s, 1H, vinylC**H**), 5.04 (s, 1H, vinylC**H**), 5.00 (s, 1H, vinylC**H**), 4.69 (d, *J* = 12.0 Hz, 1H, C**H**HAr), 4.65 (d, *J* = 12.0 Hz, 1H, CH**H**Ar), 4.24 (d, *J* = 16.5 Hz, 1H, C**H**HOBn), 4.19 (d, *J* = 16.5 Hz, 1H, CH**H**OBn), 3.96 (m, 1H, $(CHMe)_2C$**H**OH), 3.64 (d, *J* = 8.0 Hz, 1H, $TMSCCH_2C$**H**O), 3.44 (s, 3H, O**C**H_3), 3.35 (d, *J* = 9.0 Hz, 1H, C**H**OMe), 2.40 (dd, *J* = 7.0 Hz, 17.0 Hz, 1H, TMSCC**H**H), 2.31 (dd, *J* = 8.0 Hz, 17.0 Hz, 1H, TMSCCH**H**), 1.94-1.87 (m, 1H, C**H**Me), 1.67-1.58 (m, 4H, C**H**CH_3, vinylCH_3), 1.37 (s, 3H, CCH_3CH_3), 1.35 (s, 3H, CCH_3CH_3), 0.90 (d, *J* = 6.5 Hz, 3H, CHCH_3), 0.85 (d, *J* = 6.5 Hz, 3H, CHCH_3), 0.16 (s, 9H, TMS); ^{13}C NMR (125 MHz, $CDCl_3$) □ 169.8, 141.6, 137.3, 128.7, 128.4, 112.4, 103.9, 100.9, 86.1, 82.5, 76.3, 73.5, 73.1, 68.8, 67.1, 61.2, 38.6, 35.9, 29.9, 25.4, 24.1, 22.7, 20.5, 11.7, 10.1, 0.3; LRMS (FAB) *m/z* 531 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{30}H_{47}O_6Si$) requires *m/z* 531.3149, found *m/z* 531.3142.

(2*R,6*S**,7*R**)-2-Benzyloxy-6-methoxy-4-methyl-7-((4*R**,5*S**,6*S**)-2,2,5-trimethyl-6-prop-2-ynyl-[1,3]dioxan-4-yl)-oct-4-enoic acid (70).[32]** To a flame dried 2-dram vial under argon containing 0.38 mL dry THF was added LHMDS (1.0 M in THF) and the solution was cooled to –78 °C. A solution of benzyloxy-acetic acid (1S*)-1-((1*S**,2*R**)-1-methoxy-2-{(4*R**,5*S**,6*S**)-2,2,5-trimethyl-6-[3-(trimethyl-silanyl)-prop-2-

ynyl]-[1,3]dioxan-4-yl}-propyl)-2-methyl-allyl ester **68** which had been concentrated three times from benzene (13.4 mg, 0.025 mmol) in 0.58 mL dry THF was added over 6 min. *via* syringe, and then syringe was rinsed with 0.58 mL THF which was added over 6 min. The reaction was stirred at –78 °C for 42 min at which time freshly distilled TMSCl (8 uL, 0.063 mmol) was added *via* syringe. After 70 min the reaction was warmed to 0 °C and stirred for 25 min. The 0 °C bath was then removed and after 10 min the reaction was quenched with 2 mL of 1N aq. NaOH, and the mixture was stirred for 1 hour. The mixture was then poured into EtOAc (3 mL), and 1N aq. HCl was added to pH = 7. The aqueous layer was removed and acidified to pH = 1 with 1N aq. HCl. The aqueous layer was then extracted seven times with EtOAc (10 mL). The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (30% EtOAc/hex to 15 drops AcOH in 50 mL of 50% EtOAc/hex) provided the title compound as a colorless oil in 73% yield (8.4 mg). IR (film) 3402, 3296, 2920, 2851, 2363, 1734, 1456, 1382, 1227, 1171, 1126, 1100, 1054, 1018, 991, 939, 883, 737, 699, 635, 561 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.38-7.26 (m, 5H, Ar-**H**), 5.09 (d, *J* = 9.6 Hz, 1H, vinylC**H**), 4.68 (d, *J* = 11.0 Hz, 1H, C**H**HAr), 4.52 (d, *J* = 11.0 Hz, 1H, CH**H**Ar), 4.17 (dd, *J* = 7.2 Hz, 7.2 Hz, 1H, C**H**OBn), 4.00-3.93 (m, 1H, $(CHMe)_2$C**H**O), 3.78-3.70 (m, 2H, C**H**OMe, $HCCH_2$C**H**O), 3.18 (s, 3H, OC$\mathbf{H}_3$), 2.61-2.54 (m, 2H, C$\mathbf{H}_2$CHOBn), 2.41-2.22 (m, 2H, HCC$\mathbf{H}_2$), 1.99-1.92 (m, 1H, **H**CCH_2), 1.73 (d, *J* = 1.2 Hz, 3H, vinylC$\mathbf{H}_3$), 1.53-1.48 (m, 2H, $(C\mathbf{H}CH_3)_2$), 1.34 (s, 6H, CC$\mathbf{H}_3$C$\mathbf{H}_3$), 0.84 (d, *J* = 6.6 Hz, CHC$\mathbf{H}_3$), 0.77 (d, *J* = 7.2 Hz, CHC$\mathbf{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) □ 175.3, 136.9, 135.3, 129.7, 128.8, 128.5, 128.4, 101.0, 81.4, 78.1, 73.0, 72.1, 69.5, 68.7, 56.2, 43.0, 40.3, 35.5, 30.0, 25.2, 23.7, 21.3, 17.4, 11.4, 9.8;

LRMS (FAB) *m/z* 459 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{27}H_{39}O_6$) requires *m/z* 459.2746, found *m/z* 459.2747.

(2*R,6*S**,7*R**)-2-Benzyloxy-6-methoxy-4-methyl-7-((4*R**,5*S**,6*S**)-2,2,5-trimethyl-6-prop-2-ynyl-[1,3]dioxan-4-yl)-oct-4-en-1-ol (71).** To (2*R**,6*S**,7*R**)-2-benzyloxy-6-methoxy-4-methyl-7-((4*R**,5*S**,6*S**)-2,2,5-trimethyl-6-prop-2-ynyl-[1,3]dioxan-4-yl)-oct-4-enoic acid **70** (7.8 mg, 0.017 mmol) in 1.1 mL of a 10:1 (v:v) solution of MeOH:CH_2Cl_2 under argon in a 2-dram vial was added $TMSCHN_2$ (2.0 M solution in hexanes, 50 uL). After 5 min the reaction was quenched with sat. aq. $NaHCO_3$ (1 mL), and extracted four times with EtOAc (3 mL). The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated to afford a white film which was used immediately. As such, the white film was dissolved in 1.0 mL dry Et_2O in a 2-dram vial under argon. A solution of $LiAlH_4$ (1.0 M, Et_2O, 86.0 uL) was added via syringe, and the reaction was stirred for 15 min before being quenched slowly with sat. aq. Rochelle's salt (3 mL). EtOAc was added (3 mL) and the mixture was stirred for 10 h. Sat. aq. NaCl (2 mL) was added and the mixture was extracted four times with EtOAc (3 mL). The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (50% EtOAc/hex) provided the title compound as a colorless oil in quantitative yield (6.9 mg). IR (film) 3420, 2917, 2850, 1652, 1456, 1381, 1227, 1171, 1088, 1054, 1018, 991, 940, 883, 737, 698, 634, 512 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 7.39-7.26 (m, 5H, Ar-**H**), 5.05 (d, *J* = 9.9 Hz, 1H, vinylC**H**), 4.68 (d, *J* = 11.2 Hz, 1H, C**H**HAr), 4.55 (d, *J* = 11.2 Hz, 1H, CH**H**Ar), 4.00-3.93 (m, 1H,

(CHMe)$_2$C**H**O), 3.79-3.67 (m, 5H, HCCH$_2$C**H**O, C**H**OBn, C**H**OMe, C**H**$_2$OH), 3.19 (s, 3H, OC**H**$_3$), 2.50-2.21 (m, 4H, HCC**H**$_2$, C**H**$_2$CHOBn), 1.99-1.93 (m, 1H, **H**CCH$_2$), 1.75 (d, *J* = 1.2 Hz, 3H, vinylC**H**$_3$), 1.34 (s, 3H, CC**H**$_3$CH$_3$), 1.33 (s, 3H, CCH$_3$C**H**$_3$), 0.84 (d, *J* = 6.6 Hz, 3H, CHC**H**$_3$), 0.77 (d, *J* = 6.9 Hz, 3H, CHC**H**$_3$); ^{13}C NMR (125 MHz, CDCl$_3$) 138.5, 136.7, 128.9, 128.8, 128.0, 101.0, 81.5, 78.5, 78.1, 72.2, 71.8, 69.5, 68.7, 64.6, 56.3, 41.5, 40.5, 35.6, 29.9, 25.2, 23.7, 21.3, 17.8, 11.4, 9.8; LRMS (FAB) *m*/*z* 445 (M)$^+$; HRMS (FAB) exact mass calcd for ($C_{27}H_{41}O_5$) requires *m*/*z* 445.2963, found *m*/*z* 445.2954.

(4*S,5*S**,6*R**,7*R**,8*S**,12*R**)-12-Benzyloxy-13-(*tert*-butyl-diphenyl-silanyloxy)-8-methoxy-5,7,10-trimethyl-tridec-9-en-1-yne-4,6-diol (73).** To (2*R**,6*S**,7*R**)-2-benzyloxy-6-methoxy-4-methyl-7-((4*R**,5*S**,6*S**)-2,2,5-trimethyl-6-prop-2-ynyl-[1,3]dioxan-4-yl)-oct-4-en-1-ol **71** (6.9 mg, 0.016 mmol) in 0.7 mL dry DMF in dry 2-dram vial under argon was added imidazole (3.2 mg, 0.047 mmol) and the vial was purged with argon. TBDPSCl (11.9 uL, 0.0465 mmol) was added and the reaction was stirred at ambient temperature for 2 h. The mixture was then poured into sat. aq. NaHCO$_3$ (1 mL) and sat. aq. NaCl (1 mL) was added. The mixture was extracted four times with EtOAc (2 mL), and the combined organic layers were washed once with H$_2$O (2 mL), once with sat. aq. NaCl (2 mL), dried over Na$_2$SO$_4$, filtered through a plug of cotton, and concentrated. The oil was then dissolved in 2 mL MeOH in a 25 mL round bottom flask, and DOWEX 50WX8-100 resin (washed with MeOH and air-dried before use) was added. The mixture was stirred vigorously for 48 h and then filtered through a glass frit, washing the resin with MeOH. To the combined MeOH washings was added

0.4 mL Et_3N, and the volatiles were removed by concentration. Purification of the resulting oil by silica gel chromatography (30% EtOAc/hex) provided the title compound as a colorless oil in 50% yield (5.0 mg). IR (film) 3433, 3308, 3070, 2930, 2858, 1664, 1589, 1462, 1428, 1389, 1361, 1188, 1112, 1084, 978, 824, 740, 702, 614, 504, 457 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) □ 7.49-7.22 (m, 12H, Ar-**H**), 5.23 (d, *J* = 9.0 Hz, 1H, vinylC**H**), 4.66 (d, *J* = 11.5 Hz, 1H, C**H**HAr), 4.53 (d, *J* = 11.5 Hz, 1H, CH**H**Ar), 4.08-4.00 (m, 1H, $(CHMe)_2$C**H**OH), 3.93-3.89 (m, 2H, $HCCH_2$C**H**OH, C**H**OMe), 3.79-3.76 (m, 1H, C**H**OBn), 3.70-3.64 (m, 2H, C$\mathbf{H}_2$OTBDPS), 3.11 (s, 3H, OC$\mathbf{H}_3$), 2.50 (ddd, *J* = 8.0 Hz, 3.0 Hz, 16.5 Hz, 1H, C**H**HCHOBn), 2.41-2.30 (m, 3H, CH**H**CHOBn, HCC$\mathbf{H}_2$CHOH), 2.03 (m, 1H, **H**CCH_2), 1.95-1.92 (m, 1H, MeOCHC**H**Me), 1.69-1.63 (m, 4H, vinylC$\mathbf{H}_3$, C**H**Me$(CHOH)_2$), 1.09 (s, 9H, tBu), 0.91 (d, *J* = 6.5 Hz, 3H, CHC$\mathbf{H}_3$), 0.75 (d, *J* = 6.5 Hz, 3H, CHC$\mathbf{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) □ 139.0, 138.1, 135.9, 133.7, 129.9, 128.5, 127.9, 127.8, 127.7, 127.0, 126.9, 88.7, 82.5, 81.4, 78.4, 73.6, 72.9, 72.2, 70.0, 69.9, 66.2, 56.4, 42.4, 40.2, 39.1, 29.9, 27.1, 23.6, 19.5, 17.4, 12.2, 10.3; LRMS (FAB) *m/z* 642, $(MNa)^+$; HRMS (FAB) exact mass calcd for ($C_{40}H_{54}O_5NaSi$) requires *m/z* 665.3641, found *m/z* 665.3638.

{(2*S,4*S**,5*S**,6*R**)-6-[(1*R**,2*S**,6*R**)-6-Benzyloxy-7-(*tert*-butyl-diphenyl-silanyloxy)-2-methoxy-1,4-dimethyl-hept-3-enyl]-4-hydroxy-2-methoxy-5-methyl-tetrhydro-pyran-2-yl}-acetic acid methyl ester (75).**[33] (4*S**,5*S**,6*R**,7*R**,8*S**,12*R**)-12-Benzyloxy-13-(*tert*-butyl-diphenyl-silanyloxy)-8-methoxy-5,7,10-trimethyl-tridec-9-en-1-yne-4,6-diol **73** (4.3 mg, 0.0067 mmol) was dissolved in 0.91 mL dry MeOH in dry 5 mL round bottom flask. The flask was sealed and purged with CO and CO was

bubbled through the solution for 1 min., followed by passing a stream of CO over the solution for an additional 30 seconds. After stirring for 8 min, a solution of $PdCl_2(CH_3CN)_2$ (0.29 mg, 0.0011 mmol) and *p*–benzoquinone (1.6 mg, 0.015 mmol) in 0.34 mL dry MeOH was added *via* syringe. After 45 min the reaction was concentrated and then diluted with EtOAc (1 mL). The solution was washed twice with sat. aq. $NaHCO_3$ (2 mL), once with sat. aq. NaCl (2 mL), dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. The oil was then dissolved in 1.2 mL MeOH and 15 mg *p*TSA was added and the reaction allowed to stir for 25 min. The solution was quenched with sat. aq. $NaHCO_3$ (1 mL) and extracted four times with EtOAc (2 mL), dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (5% MeOH/CH_2Cl_2) provided the title compound as a colorless oil in 94% yield (4.6 mg). This unstable intermediate was stored in frozen benzene. IR (film) 3452, 2928, 2856, 1739, 1455, 1428, 1379, 1319, 1260, 1222, 1112, 1027, 933, 799, 740, 702, 614, 505, 458 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) 7.80-7.77 (m, 2H, Ar-**H**), 7.34-7.07 (m, 13H, Ar-**H**), 5.10 (d, *J* = 10.0 Hz, 1H, vinylC**H**), 4.61 (d, *J* = 11.7 Hz, 1H, C**H**HAr), 4.45 (d, *J* = 11.7 Hz, 1H, CH**H**Ar), 4.03-3.99 (m, 2H, C**H**OH, C**H**OCOMe), 3.90-3.76 (m, 2H, C**H**$_2$OTBPDS), 3.72-3.64 (m, 2H, C**H**$_2$OTBDPS), 3.34 (s, 3H, CO2C**H**$_3$), 3.29 (s, 3H, HCOCOC**H**$_3$), 3.04 (s, 3H, CHOC**H**$_3$), 2.64 (d, *J* = 13.5 Hz, 1H, C**H**HCO_2Me), 2.57 (d, *J* = 13.5 Hz, 1H, CH**H**CO_2Me), 2.41-2.38 (m, 2H, C**H**$_2$CHOBn), 2.22-2.04 (m, 2H, C**H**$_2$CHOH), 1.82-1.68 (m, 2H, (C**H**Me)$_2$), 1.65 (s, 3H, vinylC**H**$_3$), 1.18 (s, 9H, tBu), 0.85 (d, *J* = 6.0 Hz, CHC**H**$_3$), 0.77 (d, *J* = 7.0 Hz, CHC**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) 170.1, 139.1, 138.0, 135.9, 133.7, 129.9, 128.5, 127.9, 127.6, 122.4, 99.0, 79.2, 78.8, 72.3, 71.9, 70.5, 70.3, 66.4, 55.5, 51.9, 43.1, 42.3, 42.2,

40.0, 38.6, 29.9, 27.1, 27.0, 19.5, 17.6, 14.3, 12.2, 8.9, 5.3, 1.3; LRMS (FAB) *m/z* 732, $(MNa)^+$; HRMS (FAB) exact mass calcd for ($C_{43}H_{60}O_8NaSi$) requires *m/z* 755.3941, found *m/z* 755.3955.

{(2*S,4*S**,5*S**,6*R**)-6-[(1*R**,2*S**,6*R**)-6-Benzyloxy-7-(*tert*-butyl-diphenyl-silanyloxy)-2-methoxy-1,4-dimethyl-hept-3-enyl]-4-(*tert*-butyl-dimethyl-silanyloxy)-2-methoxy-5-methyl-tetrhydro-pyran-2-yl}-acetic acid methyl ester (76).** To {(2*S**,4*S**,5*S**,6*R**)-6-[(1*R**,2*S**,6*R**)-6-benzyloxy-7-(*tert*-butyl-diphenyl-silanyloxy)-2-methoxy-1,4-dimethyl-hept-3-enyl]-4-hydroxy-2-methoxy-5-methyl-tetrhydro-pyran-2-yl}-acetic acid methyl ester **75** (4.7 mg, 0.008 mmol) in 1.0 mL dry DMF in a dry 2-dram vial under argon was added imidazole (30.1 mg, 0.443 mmol) and TBSCl (55.8 mg, 0.370 mmol). The reaction was stirred for 2 h and then quenched with sat. aq. $NaHCO_3$ (1 mL) and extracted five times with EtOAc (2 mL). The combined organic layers were washed once with H_2O (5 mL) and once with sat. aq. NaCl (5 mL), dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (5% EtOAc/hex to 10% EtOAc/hex) provided the title compound as a colorless oil in 81% yield (4.4 mg). This unstable intermediate was stored in frozen benzene. IR (film) 2929, 2857, 2875, 1743, 1453, 1428, 1381, 1315, 1257, 1221, 1112, 1081, 1029, 1006, 932, 836, 776, 740, 702, 611, 505, 488 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) □ 7.81-7.79 (m, 3H, Ar-**H**), 7.34-7.07 (m, 12H, Ar-**H**), 5.11 (d, *J* = 10.0 Hz, 1H, vinylC**H**), 4.61 (d, *J* = 11.5 Hz, 1H, C**H**HAr), 4.45 (d, *J* = 11.5 Hz, 1H, CH**H**Ar), 4.11 (dd, *J* = 2.0 Hz, 10.5 Hz, C**H**OTBS), 4.03 (dd, *J* = 10.0 Hz, 10.0 Hz, C**H**OCOMe), 3.95 (ddd, *J* = 4.5 Hz, 11.0 Hz, 11.0 Hz, C**H**OBn), 3.84 (dd, *J* = 5.5 Hz,

10.7 Hz, CH**H**OTBDPS), 3.78 (dd, *J* = 4.5 Hz, 10.7 Hz, C**H**HOTBDPS), 3.69-3.64 (m, 1H, C**H**OMe), 3.34 (s, 3H, $CO_2C\mathbf{H}_3$), 3.31 (s, 3H, $H_2CCOC\mathbf{H}_3$), 3.06 (s, 3H, $CHOC\mathbf{H}_3$), 2.66 (d, *J* = 13.7 Hz, C**H**HCO_2Me), 2.60 (d, *J* = 13.7 Hz, CH**H**CO_2Me), 2.52 (dd, *J* = 5.0 Hz, 13.0 Hz, C**H**HCHOTBS), 2.38 (d, *J* = 6.0 Hz, 2H, $C\mathbf{H}_2$CHOBn), 1.97 (dd, *J* = 10.0 Hz, 5.0 Hz, 13.0 Hz, CH**H**CHOTBS), 1.86-1.80 (m, 1H, C**H**CH_3), 1.70-1.59 (m, 4H, vinyl$C\mathbf{H}_3$, C**H**CH_3), 1.18 (s, 9H, tBu), 0.98 (s, 9H, tBu), 0.93 (d, *J* = 6.0 Hz, 3H, $CHC\mathbf{H}_3$), 0.78 (d, *J* = 7.0 Hz, 3H, $CHC\mathbf{H}_3$), 0.12 (s, 3H, SiMe), 0.07 (s, 3H, SiMe); ^{13}C NMR (125 MHz, C_6D_6) □ 196.7, 169.2, 139.3, 137.6, 136.0, 133.8, 129.9, 129.1, 128.3, 127.5, 107.6, 99.2, 90.8, 78.8, 77.5, 72.1, 71.9, 71.3, 66.3, 55.0, 51.0, 47.8, 44.1, 42.2, 42.1, 40.4, 39.0, 30.1, 27.0, 26.0, 25.7, 19.4, 18.2, 17.5, 12.5, 8.8, 2.6, -4.0, -4.7; LRMS (FAB) *m*/*z* 845, $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{49}H_{73}O_8Si_2$) requires *m*/*z* 845.4850, found *m*/*z* 845.4844.

(1*S)-(*tert*-Butyl-diphenyl-silanyloxy)-acetic acid 1-((5*S**,1*S**,2*R**,4*S**)-5-benzyloxy-1-methoxy-2,4-dimethyl-6-morpholin-4-yl-3,6-dioxo-hexyl)-2-methyl-allyl ester (50).** *(2S*,3R*,5S*,6S*)*-6-Benzyloxy-2-methoxy-3,5-dimethyl-7-morpholin-4-yl-4,7-dioxo-heptanal **48** (1.56 g, 3.99 mmol) was dissolved in 64.3 mL dry THF in a 250 mL round bottom flask, and the stirring solution was cooled to –78 °C. Isopropenyl magnesium bromide (0.5M in THF, 9.6 mL, 4.79 mmol) was added *via* syringe pump over 45 min. Stirring was continued for 1.5 h after addition was complete, at which time the reaction was quenched with sat. aq. NH_4Cl and extracted four times with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (50%

EtOAc/hex) provided the intermediate allylic alcohol product **49** as a colorless oil in 74% yield (1.28 g), and this oil was immediately dissolved in 9.6 mL dry THF in a 100 mL round bottom flask. Freshly distilled pyridine (0.232 mL, 4.10 mmol) was added and the flask was purged with argon and cooled to 0 °C. *tert*–Butyldiphenylsilyloxyacetyl chloride (1.08 mL, 2.38 mmol) was added slowly *via* syringe, and the reaction was stirred for 30 min. at 0 °C before being warmed to ambient temperature. After 48 h at room temperature, the reaction was quenched with NH_4Cl/NH_4OH (pH = 8) solution (20 mL) and extracted three times with EtOAc (20 mL). The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (40% EtOAc/hex) provided the ester as a colorless oil in 68% yield (406 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73-7.62 (m, 6H, Ar-**H**), 7.46-7.25 (m, 9H, Ar-**H**), 5.21 (s, 1H, allylic**H**), 4.93 (bs, 2H, vinylC**H**, vinylC**H**), 4.58-4.51 (m, 2H, C**H**HAr, C**H**HOTBDPS), 4.38-4.22 (m, 4H, CH**H**Ar, CH**H**OTBDPS, C**H**OBn, C**H**OMe), 3.67-3.29 (m, 9H, morph-**H**,C**H**Me), 3.24 (s, 3H, OC**H**$_3$), 3.03-2.84 (m, 1H, C**H**CH_3), 1.82 (s, 3H, vinylC**H**$_3$), 1.22 (d, *J* = 7.2 Hz, 3H, CHC**H**$_3$), 1.11 (s, 9H, tBu), 0.98 (d, *J* = 7.2 Hz, 3H, CHC**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 163.4, 141.6, 135.8, 135.6, 135.0, 130.1, 129.9, 128.0, 127.9, 112.2, 103.9, 100.9, 86.0, 82.4, 76.1, 73.1, 68.8, 62.4, 61.1, 38.5, 35.8, 26.9, 26.8, 25.4, 24.1, 22.7, 20.4, 19.5, 11.7, 10.2, 0.3.

(1*S)-(*tert*-Butyl-diphenyl-silanyloxy)-acetic acid 1-((5*S**,1*S**,2*R**,4*S**)-5-hydroxy-1-methoxy-2,4-dimethyl-6-morpholin-4-yl-3,6-dioxo-hexyl)-2-methyl-allyl ester (51).** To (1*S**)-(*tert*-butyl-diphenyl-silanyloxy)-acetic acid 1-((5*S**,1*S**,2*R**,4*S**)-

5-benzyloxy-1-methoxy-2,4-dimethyl-6-morpholin-4-yl-3,6-dioxo-hexyl)-2-methyl-allyl ester **50** (383.0 mg, 0.525 mmol) in 10.5 mL dry CH_2Cl_2 at 0 °C in a 100 mL round bottom flask under argon was added BF_3OEt_2 (0.332 mL, 2.623 moml) followed immediately by Me_2S (0.539 mL, 7.345 mmol), and the reaction was stirred for 1 h, at which time at was quenched with NH_4Cl/NH_4OH (pH = 8) (20 mL). The mixture was extracted four times with EtOAc (20 mL), and the combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (50% EtOAc/hex) provided the ester as a colorless oil in 89% yield (299 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71-7.65 (m, 4H, Ar-**H**), 7.47-7.34 (m, 6H, Ar-**H**), 5.24 (s, 1H, allylic**CH**), 4.94 (s, 1H, vinyl**CH**), 4.92 (s 1H, vinyl**CH**), 4.66 (bs, 1H, **CH**OH), 4.36-4.26 (m, 3H, **CH**$_2$OTBDPS, **CH**OMe), 3.74-3.36 (m, 8H, morph-**H**), 3.23 (s, 3H, O**CH**$_3$), 2.96-2.86 (m, 1H, CH**CH**$_3$), 2.78-2.70 (m, 1H, **CH**CH$_3$), 1.82 (s, 3H, vinyl**CH**$_3$), 1.09 (s, 9H, tBu), 1.05 (d, *J* = 6.9 Hz, 3H, CH**CH**$_3$), 0.93 (d, *J* = 6.9 Hz, 3H, CH**CH**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.1, 171.1, 170.0, 140.2, 135.3, 132.5, 132.4, 129.9, 127.9, 127.7, 112.6, 82.9, 74.9, 67.6, 66.6, 66.4, 62.0, 60.9, 50.9, 46.1, 45.9, 42.8, 26.6, 20.1, 19.3, 13.6, 10.5.

(1*S)-(*tert*-Butyl-diphenyl-silanyloxy)-acetic acid 1-((1*S**,2*R**,3*R**,4*S**,5*S**)-3,5-dihydroxy-1-methoxy-2,4-dimethyl-6-morpholin-4-yl-6-oxo-hexyl)-2-methyl-allyl ester (53).**[34,35] To (1 *S**)-(*tert*-butyl-diphenyl-silanyloxy)-acetic acid 1-((5*S**,1*S**,2*R**,4*S**)-5-hydroxy-1-methoxy-2,4-dimethyl-6-morpholin-4-yl-3,6-dioxo-hexyl)-2-methyl-allyl ester **51** (1.04 g, 1.63 mmol) in 84 mL dry CH_2Cl_2 under argon at 0 °C in a dry 1 L round bottom flask was added Bu_4NBH_4 (376 mg, 1.46 mmol) in 26.1 mL

dry CH_2Cl_2 *via* cannula, and the cannula was rinsed into the reaction vessel with 26.1 mL dry CH_2Cl_2. The reaction was allowed to warm to ambient temperature, and after 63 h the reaction was quenched with H_2O (150 mL) and poured into sat. aq. $NaHCO_3$ (100 mL). The mixture was extracted four times with CH_2Cl_2 (200 mL) and once with EtOAc (200 mL). The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (67% EtOAc/hex) provided the starting material as an oil (603.8 mg) and the title compound as a white solid in 33% yield (406 mg) (78% yield based on recovered starting material), >95:5 *anti*:*syn* (^{1}H NMR). ^{1}H NMR (300 MHz, $CDCl_3$) □ 7.75-7.65 (m, 4H, Ar-**H**), 7.50-7.34 (m, 6H, Ar-**H**), 5.58 (d, 1H, allylicC**H**), 5.15 (s, 1H, vinylC**H**), 5.02 (s, 1H, vinylC**H**), 4.93 (d, 1H, $R_2NCOC\mathbf{H}OH$), 4.33-4.19 (m, 2H, $C\mathbf{H}_2$OTBDPS), 4.02 (d, 1H, $(CHMe)_2C\mathbf{H}OH$), 3.80-3.43 (m, 9H, morph-**H**, C**H**OMe), 3.40 (s, 3H, $OC\mathbf{H}_3$), 1.71-1.53 (m, 4H, vinyl$C\mathbf{H}_3$, $R_2NCHOHC\mathbf{H}Me$), 1.07 (s, 9H, tBu), 0.99 (d, 3H, $CHC\mathbf{H}_3$), 0.87-0.79 (m, 1H, $C\mathbf{H}CH_3$), 0.58 (d, 3H, $CHC\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) □ 173.2, 169.8, 145.9, 139.6, 135.4, 135.3, 132.6, 132.5, 129.8, 127.7, 117.4, 87.2, 79.7, 70.7, 66.9, 66.5, 62.4, 54.1, 45.5, 42.8, 39.7, 33.8, 26.7, 19.3, 18.0, 10.9, 8.5.

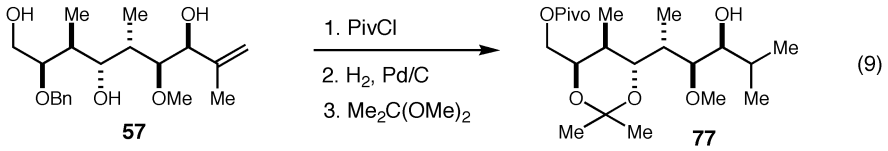
(1*S)-(*tert*-Butyl-diphenyl-silanyloxy)-acetic acid 1-[(1*S**,2*R**,3*R**,4*S**,5*S**)-1-methoxy-2,4-dimethyl-6-morpholin-4-yl-6-oxo-3,5-bis-(trimethyl-silanyloxy)-hexyl]-2-methyl-allyl ester (54).** To (1*S**)-(*tert*-butyl-diphenyl-silanyloxy)-acetic acid 1-((1*S**,2*R**,3*R**,4*S**,5*S**)-3,5-dihydroxy-1-methoxy-2,4-dimethyl-6-morpholin-4-yl-6-oxo-hexyl)-2-methyl-allyl ester **53** (341 mg, 0.531 mmol) and DMAP (154 mg) in 26.6 mL dry CH_2Cl_2 under argon in a dry 500 mL round bottom flask was added TMSCl

(0.674 mL, 5.31 mmol) and the flask was cooled to 0 °C. Et_3N (0.740 mL, 5.31 mmol) was added and the reaction was stirred for 17 h before being quenched with pH 7 phosphate buffer and extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (20% EtOAc/hex) provided the title compound as an oil in 75% yield (314.2 mg). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.65 (m, 4H, Ar-**H**), 7.45-7.34 (m, 6H, Ar-**H**), 5.33 (s, 1H, allylicC**H**), 4.92 (s, 1H, vinylC**H**), 4.85 (s, 1H, vinylC**H**), 4.78 (s, 1H, R_2NCOC**H**OTMS), 4.32 (bs, 2H, C**H**$_2$OTBDPS), 3.91 (d, *J* = 8.7 Hz, 1H, $(CHMe)_2$C**H**OTMS), 3.76-3.37 (m, 8H, morph-**H**), 3.33 (s, 3H, OC**H**$_3$), 1.90-1.61 (m, 5H, vinylC**H**$_3$, C**H**CH_3, C**H**CH_3), 1.08 (s, 9H, tBu), 0.71 (d, *J* = 6.6 Hz, 3H, CHC**H**$_3$), 0.69 (d, *J* = 6.6 Hz, 3H, CHC**H**$_3$), 0.15-0.12 (m, 18H, $(TMS)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 170.4, 141.2, 135.7, 132.9, 132.8, 130.1, 128.0, 112.0, 79.7, 76.8, 73.4, 70.8, 67.5, 67.0, 62.4, 60.0, 46.2, 42.8, 42.7, 41.3, 35.0, 27.0, 20.3, 19.6, 10.5, 9.6, 1.7, 1.5.

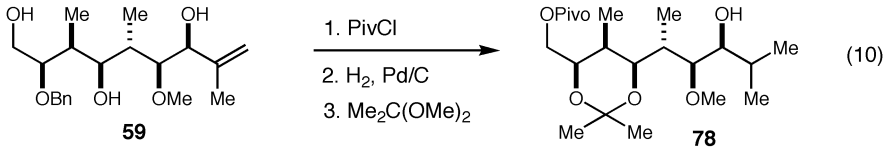
(1*S)-(*tert*-Butyl-diphenyl-silanyloxy)-acetic acid (1*S**)-1-((1*S**,2*R**)-1-methoxy-2-{(4*R**,5*S**,6*S**)-2,2,5-trimethyl-6-[3-(trimethyl-silanyl)-prop-2-ynyl]-[1,3]dioxan-4-yl}-propyl)-2-methyl-allyl ester (67).** To (3*S**,4*S**,5*R**)-4-methoxy-2-methyl-5-{(5*S**,6*S**)-2,2,5-trimethyl-6-[3-(trimethyl-silanyl)-prop-2-ynyl]-[(1*R**)-1,3]dioxan-4-yl}-hex-1-en-3-ol **66** (6.2 mg, 0.0162 mmol) in 0.3 mL dry THF under argon in a dry 2-dram vial was added pyridine (6.6 uL, 0.081 mmol) and the reaction was cooled to 0 °C. *tert*-Butyldiphenylsilyloxyacetyl chloride (20.3 uL, 0.0648 mmol) was added slowly and the reaction was allowed to warm to ambient temperature. After 22 h,

the reaction was quenched with sat. aq. $NaHCO_3$ (1 mL) and extracted four times with EtOAc (2 mL). The combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (5% EtOAc/hex to 10% EtOAc/hex) provided the title compound as an oil in 97% yield (10.7 mg). IR (film) 3447, 2929, 2856, 2359, 2178, 1762, 1653, 1472, 1428, 1380, 1249, 1225, 1136, 1113, 1016, 842, 821, 740, 702, 668, 609 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) □ 7.73-7.63 (m, 4H, Ar-**H**), 7.44-7.33 (m, 6H, Ar-**H**), 5.24 (s 1H, allylic C**H**), 4.92 (s, 1H, vinylC**H**), 4.90 (s, 1H, vinylC**H**), 4.34 (bs, 2H, C**H**$_2$OTBDPS), 3.94 (ddd, *J* = 4.5 Hz, 7.8 Hz, 7.8 Hz, 1H, TMSCCH$_2$C**H**O), 3.57 (d, *J* = 7.2 Hz, 1H, (CHMe)$_2$C**H**O), 3.38 (s, 3H, OC**H**$_3$), 3.28 (dd, *J* = 9.9 Hz, 1.5 Hz, 1H, C**H**OMe), 2.39 (dd, *J* = 7.2 Hz, 16.5 Hz, 1H, TMSCC**H**H), 2.29 (dd, *J* = 16.5 Hz, 7.8 Hz, 1H, TMSCH**H**), 1.90-1.81 (m, 4H, C**H**CH$_3$, vinylC**H**$_3$), 1.55-1.47 (m, 1H, C**H**CH$_3$), 1.34 (s, 3H, CC**H**$_3$CH$_3$), 1.33 (s, 3H, CCH$_3$C**H**$_3$), 1.09 (s, 9H, tBu), 0.80 (d, *J* = 6.6 Hz, 3H, CHC**H**$_3$), 0.79 (d, *J* = 6.6 Hz, 3H, CHC**H**$_3$), 0.15 (s, 9H, TMS); ^{13}C NMR (125 MHz, $CDCl_3$) □ 135.7, 135.0, 130.1, 129.6, 128.0, 127.5, 112.3, 100.2, 77.9, 77.5, 68.8, 62.3, 60.7, 56.9, 38.6, 35.9, 32.1, 30.1, 27.0, 26.9, 25.6, 24.2, 22.8, 21.5, 20.6, 14.6, 10.4, 7.0, 5.0, 0.5, -7.8; LRMS (FAB) *m*/*z* 679, $(MNa)^+$; HRMS (FAB) exact mass calcd for ($C_{39}H_{59}O_6Si_2$) requires *m*/*z* 679.3849, found *m*/*z* 679.3850.

Proof of *anti* relative stereochemistry of (2*S,3*S**,4*R**,5*R**,6*S**,7*S**)-2-Benzyloxy-6-methoxy-3,5,8-trimethyl-non-8-ene-1,4,7-triol 57[36]**



(9)



(10)

2,2-Dimethyl-propionic acid (4*S,5*S**,6*R**)-6-((1*R**,2*S**,3*S**)-3-hydroxy-2-methoxy-1,4-dimethyl-pentyl)-2,2,5-trimethyl-[1,3]dioxan-4-ylmethyl ester (77).** (2*S**,3*S**,4*R**,5*R**,6*S**,7*S**)-2-Benzyloxy-6-methoxy-3,5,8-trimethyl-non-8-ene-1,4,7-triol **57** (27.7 mg, 0.079 mmol) and DMAP (2.7 mg, 0.039 mmol) were dissolved in 1.58 mL freshly distilled pyridine in a dry 25 mL round bottom flask under argon, and to the stirring solution was added pivaloyl chloride (29.1 uL, 0.236 mmol). After stirring for 3.5 h, the reaction was quenched with sat. aq. NH_4Cl (5 mL), extracted four times with EtOAc (5 mL), and the combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel chromatography (20% EtOAc/hex) provided the pivaloate ester as a colorless oil in 77% yield (28.7 mg). The ester (11.4 mg, 0.024 mmol) was dissolved in 1.0 mL dry THF and10% Pd/C (10.2 mg, 0.0096 mmol) was added. The flask was purged with H_2 and pressurized to 50 PSI. After 53 h, the mixture was flushed through a pad of celite with EtOAc and concentrated. Purification of the resulting oil by silica gel chromatography (50% EtOAc/hex) provided the triol as a colorless oil in 80% yield (6.7 mg). To the triol (6.0 mg, 0.017 mmol) was added freshly distilled 2,2-dimethoxy-propane (1.5 mL) and *p*TSA (5 mg) in a 10 mL round bottom flask, and the reaction was stirred for 3 h, at

which time sat. aq. $NaHCO_3$ (5 mL) was added. Extraction four times with EtOAc (5 mL) and combination of the organic layers was followed by drying over Na_2SO_4. The solution was filtered through a plug of cotton and concentrated. Purification of the resulting oil by silica gel chromatography (20% EtOAc/hex) provided the acetonide as a colorless oil in 60% yield (3.9 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.16 (dd, *J* = 3.5 Hz, 10 Hz, 1H, C**H**HOPiv), 4.06-3.99 (m, 2H, C**H**HOPiv, PivOCH_2C**H**O), 3.60 (dd, *J* = 1.5 Hz, 7.5 Hz, 1H, (CHMe)$_2$C**H**O), 3.52 (s, 3H, OC**H**$_3$), 3.23 (d, *J* = 9.0 Hz, 1H, C**H**OH), 3.14 (dd, *J* = 9.5 Hz, 9.5 Hz, C**H**OMe), 2.07 (d, *J* = 10.0 Hz, 1H, O**H**), 1.93-1.89 (m, 1H, C**H**Me), 1.83-1.74 (m, 2H, C**H**Me, C**H**Me$_2$), 1.60 (bs, 6H, $O_2C(C\mathbf{H}_3)_2$), 1.40 (s, 3H, CHC**H**$_3$CH$_3$), 1.34 (s, 3H, CHCH$_3$C**H**$_3$), 1.22 (s, 9H, tBu), 1.06 (d, *J* = 6.5 Hz, 3H, C**H**$_3$), 0.96 (d, *J* = 7.0 Hz, 3H, C**H**$_3$), 0.92 (d, *J* = 7.0 Hz, 3H, C**H**$_3$), 0.88 (d, *J* = 7.0 Hz, 3H, C**H**$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.6, 100.8, 81.9, 77.4, 73.4, 67.8, 64.1, 61.0, 39.0, 38.3, 35.4, 32.1, 27.4, 25.4, 24.2, 19.9, 19.8, 12.1, 10.4.

2,2-Dimethyl-propionic acid (4*S,5*S**,6*S**)-6-((1*R**,2*S**,3*S**)-3-hydroxy-2-methoxy-1,4-dimethyl-pentyl)-2,2,5-trimethyl-[1,3]dioxan-4-ylmethyl ester (78).** (2*S**,3*S**,4*S**,5*R**,6*S**,7*S**)-2-Benzyloxy-6-methoxy-3,5,8-trimethyl-non-8-ene-1,4,7-triol **59** (15.8 mg, 0.045 mmol) and DMAP (4.5 mg, 0.066 mmol) were dissolved in 0.9 mL freshly distilled pyridine in a dry 10 mL round bottom flask under argon, and to the stirring solution was added pivaloyl chloride (33.0 μL, 0.268 mmol). After stirring for 12 h, the reaction was quenched with sat. aq. NH_4Cl (5 mL), extracted four times with EtOAc (5 mL), and the combined organic layers were dried over Na_2SO_4, filtered through a plug of cotton, and concentrated. Purification of the resulting oil by silica gel

chromatography (20% EtOAc/hex) provided the pivaloate ester as a colorless oil in 41% yield (8.7 mg). The ester (9.5 mg, 0.020 mmol) was dissolved in 0.8 mL dry THF and 10% Pd/C (8.5 mg, 0.008 mmol) was added. The flask was purged with H_2 and pressurized to 50 PSI. After 96 h, the mixture was flushed through a pad of celite with EtOAc and concentrated. Purification of the resulting oil by silica gel chromatography (30% EtOAc/hex) provided the triol as a colorless oil in 47% yield (3.3 mg). To the triol (3.3 mg, 0.0095 mmol) was added freshly distilled 2,2-dimethoxy-propane (0.8 mL) and *p*TSA (5 mg) in a 10 mL round bottom flask, and the reaction was stirred for 20 min, at which time sat. aq. $NaHCO_3$ (5 mL) was added. Extraction four times with EtOAc (5 mL) and combination of the organic layers was followed by drying over Na_2SO_4. The solution was filtered through a plug of cotton and concentrated. Purification of the resulting oil by silica gel chromatography (20% EtOAc/hex) provided the acetonide as a colorless oil in 82% yield (3.0 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.15-4.06 (m, 3H, C**H**$_2$OPiv, PivOCH$_2$C**H**O), 3.78 (d, *J* = 10.0 Hz, 1H, (CHMe)$_2$C**H**O), 3.49-3.42 (m, 4H, 4H, OC**H**$_3$, C**H**OH), 3.31-3.28 (m, 1H, C**H**OMe), 2.46 (d, *J* = 8.0 Hz, 1H, O**H**), 2.11-2.07 (m, 1H, C**H**Me), 1.79-1.74 (m, 2H, C**H**Me, C**H**Me$_2$), 1.41 (s, 3H, O$_2$CC**H**$_3$CH$_3$), 1.40 (s, 3H, O$_2$CCH$_3$C**H**$_3$), 1.23 (s, 9H, tBu), 0.97-0.90 (m, 12H, (CHC**H**$_3$)$_4$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.0, 99.3, 80.1, 75.4, 73.9, 71.9, 65.2, 58.3, 39.0, 35.3, 32.6, 31.1, 30.0, 29.9, 27.4, 19.7, 18.2, 10.7, 5.1.

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(15) Concurrent with but separate from the research reported here, James R. Falsey explored the optimal conditions for and scope of the tandem amino thio acyl–Claisen rearrangement.

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