Tetrahedron 67 (2011) 5083–5097

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Studies for the enantiocontrolled preparation of substituted tetrahydropyrans: applications for the synthesis of leucascandrolide A macrolactone

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ARTICLE INFO

Article history:
Received 11 March 2011
Received in revised form 20 April 2011
Accepted 6 May 2011
Available online 14 May 2011

Keywords:
Nonracemic 1,5-diols
Tetrahydropyran synthesis
Asymmetric induction
S_E' reactions
Boron-auxiliary

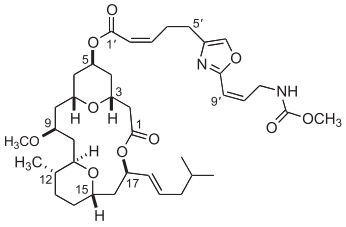
ABSTRACT

Strategies for the stereocontrolled preparations of 2,6-*cis*- and 2,6-*trans*-substituted tetrahydropyrans have been devised. These studies have explored methodology for asymmetric induction in S_E' reactions using chiral 1,3,2-diazaborolidine controllers. Reactions with aldehydes at −78 °C yield nonracemic 1,5-diols for chemoselective internal backside displacements. This concept is developed as a flexible and reliable strategy in studies toward leucascandrolide A macrolactone **2** via the sequential applications of S_E' reactions leading to the C_1–C_9 aldehyde **14**, and the bis-tetrahydropyran **59**, respectively.

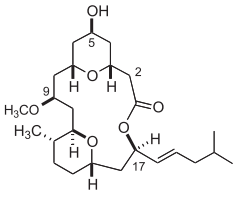
1. Introduction

Calcareous sponges possess skeletons composed exclusively of calcium carbonate spicules, and are relatively rare species compared to marine sponges of other classes. The calcareous genera, *Leucetta* and *Clathrina* have been systematically examined and have been shown to yield metabolites that characteristically embody the 2-aminoimidazole motif.[1] In 1996, Pietra and co-workers reported the isolation of the first bioactive macrocyclic metabolites from *Leucascandra caveolata*, a calcareous sponge found along the northeastern coast of New Caledonia.[2,3] Two novel macrolides, leucascandrolide A (**1**) and B were identified. The structure of **1** was elucidated by extensive spectroscopic studies and Mosher ester analysis, which revealed a pattern of 1,3-oxygenations in an 18-membered macrolactone. Two trisubstituted tetrahydropyran rings were incorporated within the features of the macrocycle via bridging ethers at C_3/C_7 and C_{11}/C_{15}. An unusual ester side chain containing two *Z*-alkenes, a central 2,4-disubstituted-1,3-oxazole and a terminal methyl carbamate was attached at the C_5 hydroxyl of the macrolide **2**.

The biological profile of leucascandrolide A displayed potent cytotoxicity based on in vitro assays with KB tumor and P338 murine leukemia cell lines (IC_{50} 0.05 and 0.25 μg/mL, respectively).



Leucascandrolide A (**1**)



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In addition, strong inhibition of *Candida albicans*, a pathogenic yeast infecting immune-compromised individuals, was also observed. Subsequently, it was found that the macrolactone **2** was essential for cytotoxicity, whereas the oxazole-containing ester side chain of **1** contributed significantly to the antifungal properties of the natural product. Recent cell-based studies to investigate the mechanism of action have unambiguously established cytochrome bc_1 complex as the principal cellular target of leucascandrolide A.[4] Samples of sponge harvested from other locations failed to yield traces of either leucascandrolide A or B, which has led to suggestions that these metabolites may originate from sources of opportunistic microbial colonization of extensively dead portions of the sampled sponge. As a result, numerous efforts have recorded successful pathways toward the synthesis of the racemic and optically active natural product and its macrolactone **2**.[5] In this report, we provide a full account of our previous study for an

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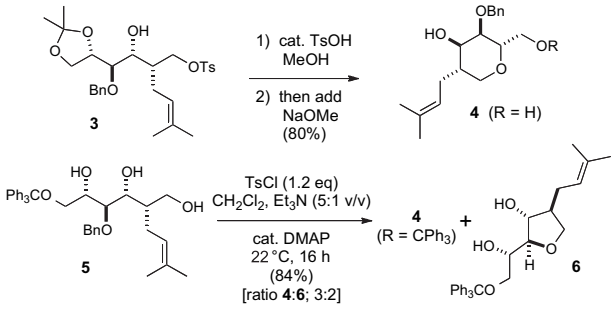
0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.05.020

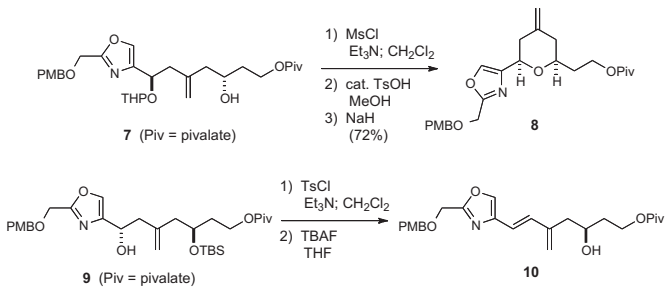
enantiocontrolled synthesis of leucascandrolide A macrolactone **2** as a thematic investigation of synthetic methodology for the construction of tetrahydropyran-containing natural metabolites.[6a,b]

Tetrahydropyrans (THP) are common structural features among marine natural products of polyketide origin. The presence of two distinct tetrahydropyranyl rings in **2** attracted our interest in developing a general strategy, which could offer sufficient flexibility to meet the requirements for stereoselective formation of the 2,6-*cis*-substituted THP (spanning the C_3–C_7 region of **2**) as well as the 2,6-*trans*-substitution of the second THP system (C_{11}–C_{15} region). This objective would appear to be aligned with the obvious advantages for a convergent synthesis. However, our implementation of a thematic approach must also meet the crucial demands of enantioselectivity in the formation of two independent, but tethered, THP ring systems.

These considerations led us to evaluate our previous efforts for the intramolecular dehydration of 1,5-diols affording the ring closure of THP systems via C–O nucleophilic backside displacement. Clearly, some level of chemoselectivity can be anticipated for such reactions as the ring closure of the triol resulting from mild hydrolysis of **3** occurs by the addition of sodium methoxide at 22 °C to give the expected THP **4** (80%).[7]



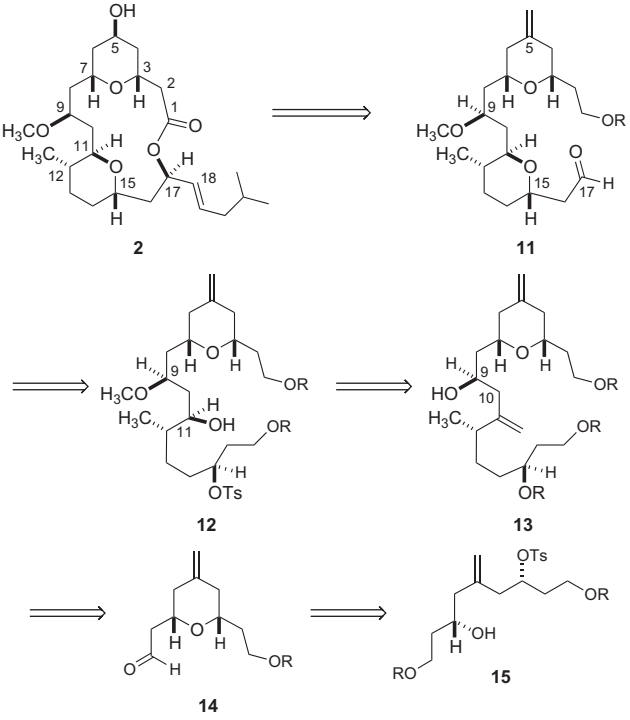
The robust reaction also proceeds uniformly for diastereomers of **3** yielding, in each case, the anticipated THP isomer. Competing formation of four-membered and seven-membered cyclic ethers is not observed. However, the treatment of the analogous triol (**5**) with tosyl chloride (1.1 equiv) and triethylamine in CH_2Cl_2 containing small amounts of 4-dimethylaminopyridine (DMAP) over 16 h provided substantial amounts of the tetrahydrofuranyl byproduct **6** in addition to the THP **4** (R=CPh_3). This evidence indicates that strongly nucleophilic conditions favor the execution of the desired internal backside displacement. On the other hand, we have also examined the generality of alkoxide-mediated displacements for the formation of 2,6-*cis*- and *trans*-substituted THP ethers in the course of our studies of phorboxazole A.[8]



In this study, 1,5-diol derivative **7** is treated with methanesulfonyl chloride followed by deprotection with mild acid (cat. TsOH, MeOH), and subsequent addition of NaH provides the facile alkoxide-induced displacement to afford only the *cis*-THP **8**. Unfortunately, the alternative cyclization from **9** yields substantial amounts of diene **10** upon mesylation or tosylation of this activated homoallylic alcohol. Further attempts for desilylation (TBAF) of the sulfonates of **9** resulted only in elimination. Overall, these results outlined some key parameters and potential pitfalls for stereocontrolled dehydrations of 1,5-diol derivatives.

2. The retrosynthetic plan

Based on these experiences, we devised a retrosynthetic approach to leucascandrolide A macrolactone **2** as illustrated in Scheme 1. The 18-membered lactone **2** evolves from the bis-tetrahydropyranyl precursor **11** by nucleophilic addition of the *E*-alkenyl side chain to the C_{17} aldehyde **11**. Subsequent oxidations at C_1 and C_5 include a stereocontrolled hydride reduction to establish the C_5 β-hydroxy substituent. Each THP ring system is sequentially formed by intramolecular displacements from chiral 1,5-diol intermediates **12** and **15**. This idea focused our attention on the formation of the C_9–C_{10} bond of **12** and the stereoselective introduction of C_9 chirality as the key convergent step of the plan. To address this issue, we envisioned the use of the aldehyde **14** in an S_E' reaction which would unite two nonracemic components in the formation of the homoallylic alcohol **13**. In similar fashion, asymmetric induction in the S_E' process would offer a convenient preparation of the starting, nonracemic 1,5-diol derivative **15**.

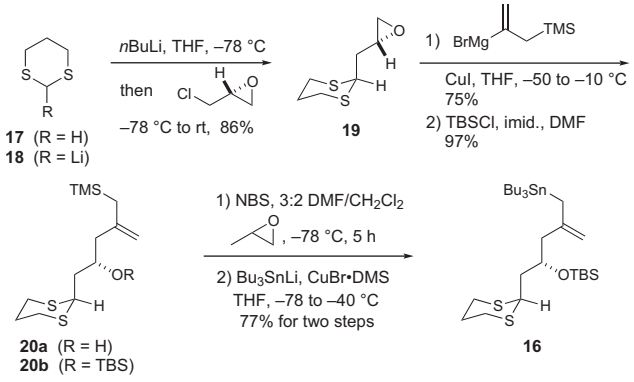


Scheme 1. Retrosynthetic analysis for macrolide **2** (R=protecting unit).

3. Results and discussion

Our proposed study relies upon an effective S_E' methodology for asymmetric induction in key C–C bond constructions, and we chose to examine the Corey 'Stein' protocol[9] for boron-mediated allylations based upon our prior studies to extend the scope of this reaction.[10] These efforts have notably led to total syntheses of hennoxazole A,[11] amphidinolide K,[12] and phorboxazole A.[13] To apply this approach toward the synthesis of C_1–C_9 aldehyde **14**, we first prepared the allylic stannane **16** (Scheme 2), commencing with

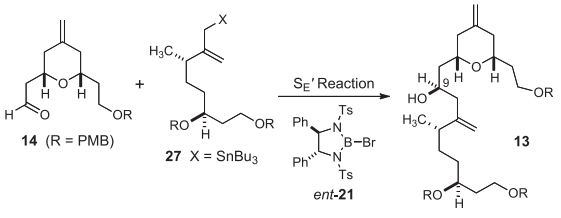
the alkylation of 2-lithio-1,3-dithiane with (*R*)-epichlorohydrin.[14] Effectively, this reaction proceeds with net inversion via initial opening of the oxirane and subsequent internal displacement of chloride to give **19** (86%). Copper-catalyzed addition of the Grignard reagent prepared from 2-bromo-3-trimethylsilylpropene[15] to epoxide **19** was followed by protection of the resulting alcohol as the *tert*-butyldimethylsilyl (TBS) ether **20b**. Chemoselective conversion of the allylic silane **20** to its corresponding bromide in the presence of the dithiane moiety was accomplished using freshly recrystallized *N*-bromosuccinimide (NBS) at −78 °C by incorporating anhydrous DMF as a solvent, and this material was directly utilized for reaction with tributylstannylcuprate to yield **16** in 77% overall yield.[16] Our asymmetric S_E' reaction is effected following the mild and quantitative transmetallation of **16** with (4*S*,5*S*)-2-bromo-1,3-bis[(4-methylphenyl)sulfonyl]-4,5-diphenyl-1,3,2-diazaborolidine (**21**)[17] in CH_2Cl_2 at 22 °C. Whereas the analogous transposition from allylic silane **20** does not proceed, the in situ generation of allylborane **22** is followed by condensation with aldehyde **23** at −78 °C. The activated complexation in **24** leads to a favored Zimmerman–Traxler transition state, which affords high diastereofacial selectivity in the production of the (*S*)-homoallylic alcohol **25** [dr 11:1]. Furthermore, our studies using the enantiomer of **16** showed that the observed asymmetric induction was solely attributed to the C_2-symmetric auxiliary and was not affected by the chirality of the homoallylic TBS silyl ether.

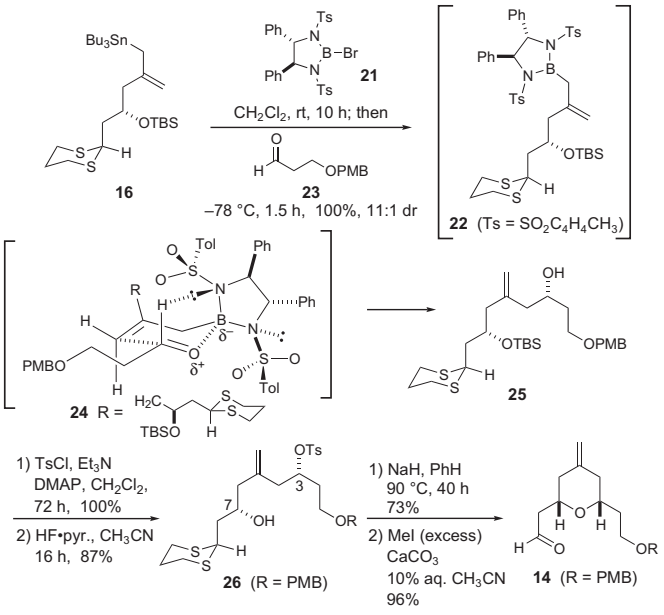


Scheme 2. Formation of allylic stannane **16**.

The quantitative formation of **25**, contaminated with small amounts of its diastereomer (dr 11:1), directly led to tosylation and mild cleavage of the TBS silyl ether under buffered conditions to minimize elimination side reactions. Subsequent treatment of **26** with sodium hydride in benzene produced an effective cyclization to the tetrahydropyran via internal displacement with inversion. Chromatographic purification was followed by mild hydrolysis of the dithiane acetal to yield the desired 2,6-*cis*-THP **14** (Scheme 3).

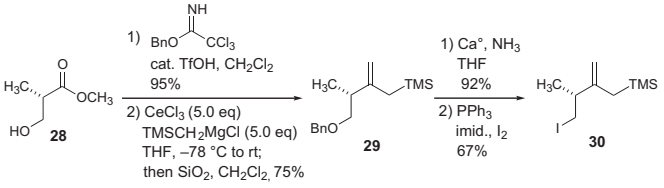
The convergent operation of our retrosynthetic plan was designed to link aldehyde **14** with the C_{10}–C_{17} component **27**, providing a stereoselective formation of the C_9 homoallylic alcohol **13** (of Scheme 1).





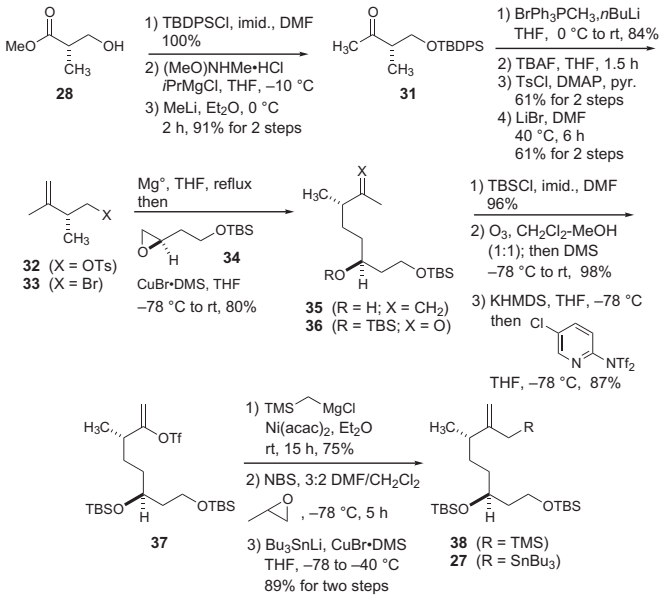
Scheme 3. Synthesis of 2,6-*cis*-THP **14**.

For this transformation, we chose to examine asymmetric induction in the S_E' reaction of the stannane **27** with the incorporation of the nonracemic (*R*,*R*)-1,3,2-diazaborolidine auxiliary *ent*-**21**. Several attempts explored pathways for the preparation of this stannane precursor. For example, protection of commercially available methyl-(*S*)-(+)-3-hydroxy-2-methylpropionate (**28**) as its benzyl ether was followed by the cerium chloride-mediated addition of (trimethylsilylmethyl)-magnesium chloride to directly yield allylic silane **29** (Scheme 4).[18] Dissolving metal reduction with calcium in liquid ammonia–THF led to the preparation of iodide **30** as well as its corresponding bromide, which were to be utilized in a copper-catalyzed Grignard reaction with the nonracemic epoxide **34** (shown in Scheme 5). Unfortunately, iodide **30**, as well as the analogous bromide, proved unstable and rapidly decomposed on standing at room temperature. An alternative route (Scheme 5) was devised from propionate **28** by adapting the reports of White and co-workers to provide 2(*S*)-2,3-dimethyl-3-buten-1-ol.[19] In this manner, formation of the tosylate **32** and exchange with LiBr in DMF afforded gram quantities of 2(*S*)-1-bromo-2,3-dimethyl-3-butene (**33**), which led to a well-behaved Grignard reagent for copper(I)-catalyzed addition to optically pure **34**.[20] Protection of the secondary hydroxyl of **35**, oxidative cleavage of the terminal alkene, and kinetic deprotonation of methyl ketone **36** led to excellent yields of the enol triflate **37** by quenching the intermediate potassium enolate with Comins reagent.[21] In 1999 Busacca and co-workers reported the nickel(O)-catalyzed cross-coupling of cyclic and acyclic enol triflates with simple Grignard reagents,[22] and the application of this approach led to reactions with commercially available (trimethylsilylmethyl)magnesium chloride in the presence of $Ni(acac)_2$ yielding the allylic silane **38**. Final conversion of **38** to the corresponding stannane **27** proceeded smoothly as described previously in the case of silane **20** via the formation of the bromide, which was used without purification to afford the



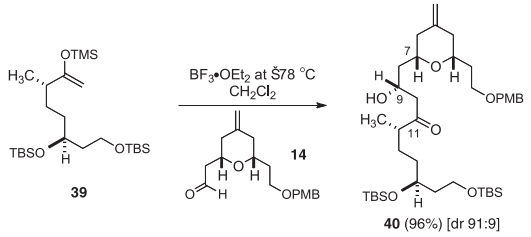
Scheme 4. Preparation of optically active silane **30**.

C_{10}–C_{17} component **27** (R=$SnBu_3$). Although we had also devised a related route to **27** with notably fewer steps, Scheme 5 was preferred for multigram-scale reactions with minimal requirements for chromatographic separations.



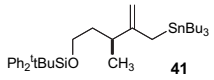
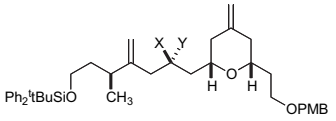
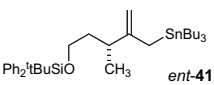
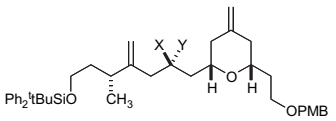
Scheme 5. Preparation of nonracemic allylic stannane **27**.

Since stereocontrolled introduction of asymmetry at C_9 was a critical aspect of our retrosynthetic hypothesis, we conducted a number of preliminary experiments to evaluate the role of allylic chirality in the starting stannane **27** as well as the features of β-asymmetry of the aldehyde component **14**. Indeed, S_E' reactions of **27** with aldehyde **14** are catalyzed with BF_3 etherate in CH_2Cl_2 at −78 °C, and result in the desired adduct, albeit as a mixture of C_9 diastereomers. Subsequent studies showed that the major isomer was of the undesired (9*S*)-configuration.[23] An examination of the aldol union between methyl ketone **36** and **14** provided additional clarity. While our reaction attempts using the lithium enolate (LiHMDS, THF, −78 °C, then **14**) or the boron enolate (*c*-hex$_2$BCl; Et_3N; 0 °C; then −78 °C, then **14**) were marred by poor stereoselection, the Mukaiyama aldol reaction of the corresponding trimethylsilyl enol ether **39** with aldehyde **14** proved to be highly diastereoselective (dr 91:9) in favor of the unwanted C_9 stereochemistry of **40**. This reaction is anticipated to occur via an open transition state, and the results can be rationalized on the basis of the Evans polar model, which has been advanced to predict the preferential formation of 1,3-*anti*-products in condensations of silyl enol ethers with β-alkoxyaldehydes.[24]



A model study was designed to advance our understanding of the S_E' reactions derived by incorporation of the chiral auxiliary of nonracemic 1,3,2-diazaborolidines as summarized in Table 1.[25] In each case, transmetallations of the starting stannane (CH_2Cl_2; 22 °C) with (*S*,*S*)-bromoborane **21** or its corresponding (*R*,*R*)-isomer *ent*-**21** were followed by reactions with nonracemic stannanes **41** and *ent*-**41** at −78 °C. Diastereomeric alcohols were analyzed by NMR spectroscopy and chiral HPLC, and major products were purified and characterized by NMR analysis of their corresponding Mosher esters.[26] While a clear trend shows that the inclusion of the boron controller dictates the stereochemistry of the major adduct, it is also evident that mismatched stereogenicity at the allylic carbon of the starting stannane can be detrimental. Since the initial transmetallations of **41** with **21** and with *ent*-**21** lead to the formation of diastereomeric allylborane reagents, we concluded that substitutions at the allylic site lead to non-reinforcing, destabilizing interactions in the preferred, closed

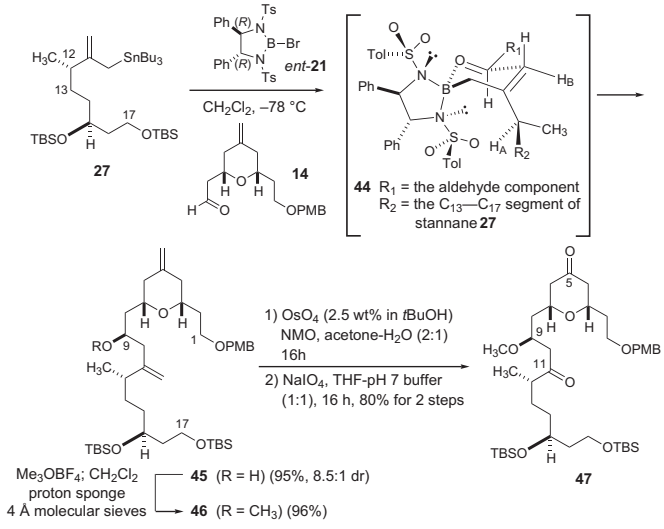
Table 1
S_E' reactions of aldehyde **14** using nonracemic 1,3,2-diazaborolidines

Entry	Stannane[a]	Boron-auxiliary	Major product[b]	Yield [dr][c,d]
1	 **41**	*ent*-**21** (*R*,*R*)	 **42a** X = OH; Y = H	100% **42a**/**42b** [dr 91:9]
2	**41**	**21** (*S*,*S*)	**42b** X=H; Y=OH	98% **42a**/**42b** [dr 33:67]
3	 *ent*-**41**	*ent*-**21** (*R*,*R*)	 **43a** X = OH; Y = H	97% **43a**/**43b** [dr 69:31]
4	*ent*-**41**	**21** (*S*,*S*)	**43b** X=H; Y=OH	93% **43a**/**43b** [dr 12:88]

[a] The tin–boron exchange was conducted at 22 °C in CH_2Cl_2 and condensations with **14** were carried out at −78 °C in CH_2Cl_2.
[b] Major products were isolated by careful chromatography or HPLC and fully characterized using the Mosher ester analysis.[26]
[c] Yields are based on isolation of the diastereomeric mixture following a short path flash silica gel chromatography.
[d] Ratios were calculated from ^1H NMR (400 MHz) data in C_6D_6 via integration of alkenyl hydrogen signals.

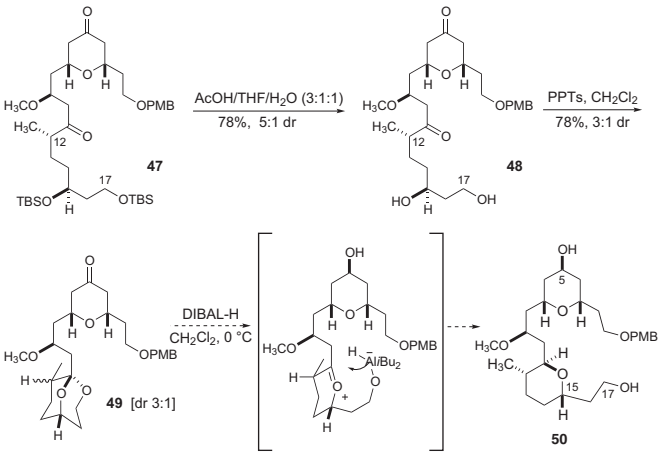
transition state arrangement, whereas the alternative allylic diastereomer could be incorporated as a harmless, or perhaps reinforcing, influence. In addition, the S_E' reactions of stannane **41** using **21** (*S*,*S*) and *ent*-**21** (*R*,*R*) with achiral aldehydes gave similar trends to those in Table 1, suggesting that stereogenicity at the β-carbon of aldehyde **14** was not vital in determining the stereoselectivity of these reactions.

The application of these results to our leucascandrolide studies utilized (*R*,*R*)-bromoborane *ent*-**21** for exchange with stannane **27** (from Scheme 5) in CH_2Cl_2 (10 h, 22 °C) as shown in Scheme 6. Addition of **14** at −78 °C provided a facile condensation yielding the desired (*R*)-alcohol **45** as the major adduct (dr 8.5:1). The arrangement depicted in **44** displays the favorable features of the boron-mediated S_E' closed transition state and indicates the reinforcing properties of the allylic stereochemistry, which projects the small hydrogen substituent H_A into the region of the sulfonyl oxygen. The sterically demanding chain (R_1) is disposed away from the developing transition state while minimizing the outcome for A(1,3) interactions by placing methyl into the plane of the vinyl hydrogen (H_B). Flash chromatographic separation of the diastereomers afforded the pure C_9 homoallylic alcohol in 88% yield, and O-methylation using Meerwein's salt was followed by oxidative cleavage of the terminal alkenes to provide the diketone **47**. The presence of pH 7 phosphate buffer in the $NaIO_4$ cleavage was essential to avoid epimerization of the C_{12} stereochemistry.



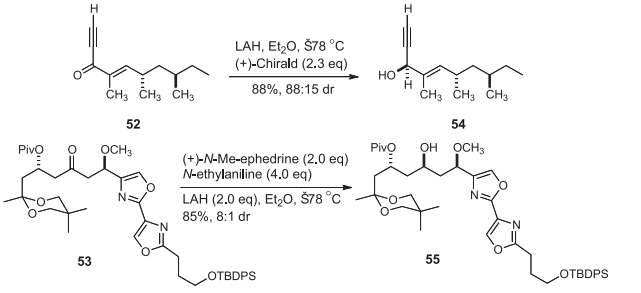
Scheme 6. The convergent S_E' reaction of nonracemic stannane **27** and **14**.

For transformation of **47** into the 2,6-*trans* THP **50** of leucascandrolide A, we sought to employ an internally directed reduction of the bicyclic acetal **49** (Scheme 7) to establish the desired C_{11} stereochemistry via diisobutylaluminum hydride according to the original reports of Kotsuki and Yamamoto.[27] Exposure of **47** to tetrabutylammonium fluoride (TBAF) in aqueous THF led to rapid elimination of methanol and formation of the C_9–C_{10} conjugated enone. The addition of various buffers with aqueous TBAF prevented the elimination, but failed to cleave the C_{15} silyl ether. In these attempts, we observed evidence of epimerization of the C_{12} stereochemistry. Finally, we were able to achieve desilylation of **47** using aqueous acetic acid in THF at 22 °C, which resulted in diol **48** (78%) along with small quantities of its C_{12} diastereomer. These keto alcohols were separated by careful column chromatography, and diol **48** was dehydrated to afford bicyclic acetal **49** using catalytic pyridinium tosylate (PPTs) in CH_2Cl_2 (0.01 M). Unfortunately, proton NMR data showed that **49** was a 3:1 mixture of C_{12} epimers.



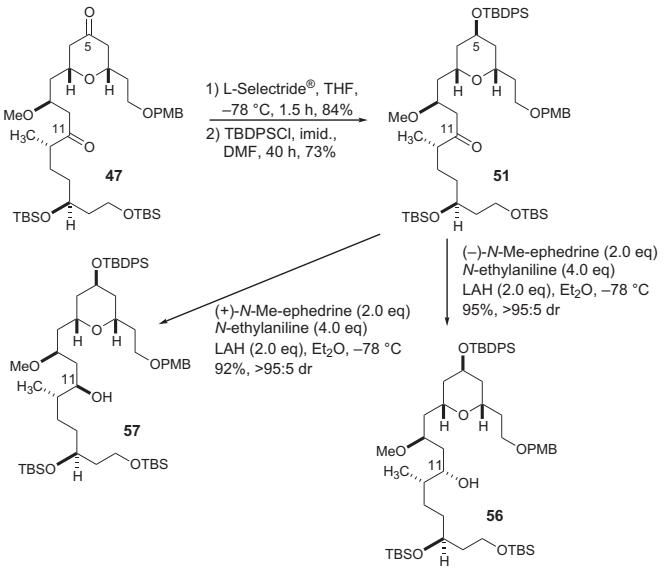
Scheme 7. Formation of cyclic ketal **49**.

The loss of stereochemical integrity led us to abandon the acetal approach and seek opportunities for direct reductions of diketone **47**. Surprisingly, the exposure of **47** to L-Selectride at −78 °C resulted in chemoselective reduction of only the C_5 carbonyl (Scheme 8). Equatorial hydride delivery provided the axial alcohol, which was then protected as its *tert*-butyldiphenylsilyl ether **51**. However, the stereocontrolled reduction of the acyclic ketone **51** presented a challenge since preliminary reactions with common hydride reagents gave nearly 1:1 mixtures of diastereomeric alcohols. For this reason, we chose to explore reagent-based control using chiral hydrides. In fact, timely results in our laboratories had registered the noteworthy reductions of **52** and **53** to their respective alcohols **54** and **55** using nonracemic amino alcohols in combination with $LiAlH_4$.[11,28]

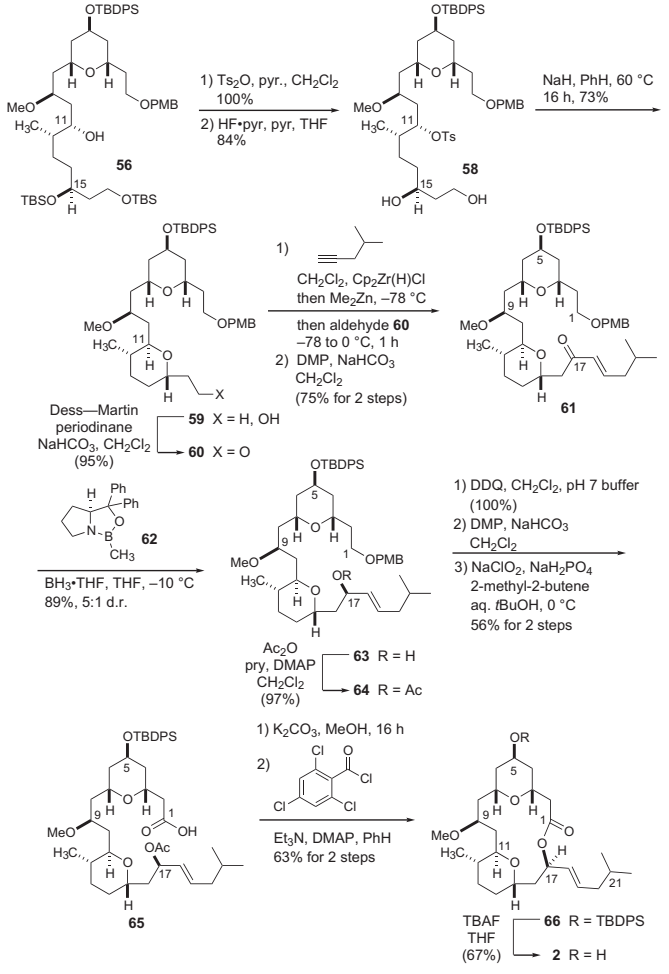


Formation of **55**, in the course of our studies of hennoxazole A, was a particularly interesting and unprecedented example because the Terashima reagent[29] was devised for the selective reduction of alkynyl and alkenyl ketones. In the event, the reduction of acyclic ketone **51** (Scheme 8) via the chiral aluminum hydride prepared from (−)-*N*-methylephedrine (1.0 equiv) and *N*-ethylaniline (2.0 equiv) resulted in the formation of the desired *anti*-Felkin product **56** with >95% diastereoselectivity. Furthermore, the use of the (+)-*N*-methylephedrine ligand under identical conditions gave the Felkin product **57** with equally impressive selectivity and yield.

Our strategy for construction of the 2,6-*trans*-THP was designed to effect stereocontrol via an internal backside displacement. Thus, the tosylation of **56** with *p*-toluenesulfonic anhydride proceeded quantitatively, whereas *p*-toluenesulfonyl chloride led to ineffective, slow conversions indicative of a sterically hindered alcohol (Scheme 9). Removal of the TBS ethers was readily accomplished using commercial HF–pyridine, which was buffered by additional quantities of pyridine.[30] The resulting diol was



Scheme 8. The stereocontrolled formation of nonracemic 1,5-diol derivatives.



Scheme 9. Completion of the synthesis of **2**.

directly utilized for ring closure with NaH in benzene at 60 °C to give **59** (73%), and subsequent oxidation yielded aldehyde **60** (95%).

Within reach of our final objective, we planned the nucleophilic attachment of the C_{18}–C_{22} alkenyl chain and macrolactonization. To this end, hydrozirconation of 4-methyl-1-pentyne was followed by transmetallation with dimethylzinc as adapted from the reports by Wipf and co-workers.[31] We had anticipated characteristics of β-chelation control in the addition of the alkenylzinc species to a Lewis acid-coordinated aldehyde **60**. However, this did not materialize, and a mixture of C_{17} diastereomers [dr 1:1] was immediately oxidized to give the enone **61** (75%). Since the Terashima reagent offered significant precedence for the asymmetric reduction of enone systems, we were surprised to observe conjugate hydride reduction as the major reaction pathway in the application to enone **61**. On the other hand, the Corey–Bakshi–Shibata (CBS) borohydride reduction[32] gave an 89% yield of a 5:1 mixture of separable C_{17} diastereomers, in favor of the desired *R*-alcohol **63**. The minor product was recycled via the oxidation–CBS reduction sequence and acetylation to **64** was followed by oxidative deprotection of the primary OPMB ether. A two-step oxidation afforded carboxylic acid **65** (56% overall yield), and methanolysis produced a crude seco-acid, which was directly subjected to the Yonemitsu-modified Yamaguchi protocol[30] to give the macrolactone **66** (63% for two steps). Fluoride deprotection at C_5 then yielded the leucascandrolide A macrolactone **2**, which was identical in all respects with physical and spectroscopic data provided by Leighton and co-workers[5a] as utilized in their esterification to afford synthetic leucascandrolide A (**1**).

4. Conclusions

In summary, a convergent, enantiocontrolled synthesis of leucascandrolide A macrolactone **2** has been achieved and establishes a route for the formal total synthesis of leucascandrolide A. A general strategy has been developed for asymmetric induction in S_E' reactions with aldehydes using chiral 1,3,2-diazaborolidine auxiliaries, which were incorporated by quantitative exchange with allylstannanes. The role of pre-existing chirality at the allylic site of the starting stannane led to reinforcing and non-reinforcing steric interactions in closed transition states of the S_E' reaction. Stereodefined 1,5-diol derivatives were prepared as precursors for internal backside displacements to yield 2,6-*cis*- and 2,6-*trans*-substituted THP ring systems. These efforts have uncovered unprecedented stereoselectivity in the reductions of acyclic β-alkoxy ketones using the chirally modified Terashima hydride reagent. Finally, our studies have demonstrated an effective and reliable strategy, which is generally applicable for the stereocontrolled synthesis of substituted tetrahydropyranyl ring systems encountered in marine macrolide natural products.

5. Experimental

5.1. General procedures

Infrared (FT-IR) spectra were recorded on a Mattson Galaxy 4020-IR instrument or Nicolet Avatar 360 FT-IR spectrometer and are reported in wavenumbers (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on Varian XL-300, Varian VXR-400, or Varian Inova 500 instruments. ^1H NMR chemical shifts are reported in parts per million on the δ scale, using the reference of the appropriate signal for residual solvent hydrogens. Carbon magnetic resonance (^{13}C NMR) spectra were recorded on Varian VXR-400 or Varian Inova 500 instruments. ^{13}C NMR shifts are reported in parts per million using $CDCl_3$ as an internal standard (77.0 ppm). Optical rotations were measured on a Perkin–Elmer 241 polarimeter at 589 nm (sodium D line) using a 10 cm path length and a 1 mL volume. Concentration (*c*) is reported as g/100 mL and temperature is reported in °C. Mass spectra were obtained on a Kratos MS80 RFAQQ instrument.

Diethyl ether (Et_2O) and tetrahydrofuran (THF) were freshly distilled from sodium benzophenone ketyl. Methylene chloride

(CH_2Cl_2), dimethylformamide (DMF), pyridine (pyr), propylene oxide, acetonitrile (CH_3CN), triethylamine (Et_3N), benzene, dimethyl sulfide (DMS), acetic anhydride, iodomethane, and *N*-ethylaniline were distilled from calcium hydride prior to use.

Bulk solvents, ethyl acetate (EtOAc), and hexanes (hex) for flash chromatography were distilled prior to use. Column chromatography was conducted using silica gel 60 (230–400 mesh) from E.M. Science. Analytical thin-layer chromatography (TLC) was performed on glass-backed silica gel plates precoated (0.25 mm thick) with 60 (F_{254}) from E.M. Scientific. Spots were visualized under UV light and/or staining with ethanolic *p*-anisaldehyde or ceric ammonium molybdate.

Chemicals were purchased from Aldrich Chemical Company and Acros, and were used without further purification unless noted. All alkyllithium reagents were periodically titrated, using menthol as a standard and 2,2-bipyridine as an indicator. Anhydrous reactions were performed in flame-dried glassware under an inert atmosphere.

*5.1.1. (R)-2-[1,3]Dithian-2-ylmethyloxirane (**19**).* To a cold (−78 °C) solution of 1,3-dithiane (13.9 g, 116 mmol) in THF (150 mL) was added *n*-BuLi (51.0 mL of a 2.5 M solution in THF, 127 mmol). The yellow solution was stirred for 20 min at −78 °C, and then warmed to −20 °C over 2.5 h. The reaction mixture was again cooled to −78 °C, and (*R*)-epichlorohydrin (12.7 mL, 162 mmol) was added dropwise. The yellow solution was stirred for 1 h at −78 °C, and then warmed to ambient temperature overnight. After quenching the reaction mixture with saturated aq $NaHCO_3$, the solution was diluted with Et_2O (250 mL). The solution was washed with saturated aq $NaHCO_3$ (250 mL) and saturated aq NaCl (250 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (500 g SiO_2, 5–10% EtOAc/hexanes) to yield 17.5 g (86%) of epoxide **19**: $[\alpha]_D^{24}$+4.6 (*c* 1.5, $CHCl_3$); R_f=0.20 in 5% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 (t, *J*=7.0 Hz, 1H), 3.18–3.14 (m, 1H), 2.97–2.81 (m, 5H), 2.55 (dd, *J*=5.0, 2.7 Hz, 1H), 2.17–2.09 (m, 1H), 1.96 (t, *J*=6.6 Hz, 2H), 1.94–1.83 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 49.6, 47.4, 44.7, 38.6, 30.4, 30.2, 25.6; IR (neat) 3038, 2991, 2899, 2820, 1482, 1416, 1277, 1258, 1178, 974, 921, 836 cm^{-1}; MS (DCI, CH_4) 176 (67), 146 (18), 120 (18), 117 (6), 85 (27), 74 (38), 73 (12), 71 (34); HRMS *m*/*e* calcd for $C_7H_{12}OS_2$ (M^+) 176.0330, found 176.0331.

*5.1.2. (S)-1-[1,3]Dithian-2-yl-4-(trimethylsilanylmethyl)pent-4-en-2-ol (**20a**).* A solution of 2-bromoallylsilane (17.3 g, 89.3 mmol) in THF (60 mL) was added dropwise to a stirred suspension of magnesium turnings (6.49 g, 268 mmol) in THF (40 mL) at such a rate as to maintain a gentle reflux during the course of the addition (30 min). The light gray solution of the Grignard reagent was added dropwise to a −50 °C solution of epoxide **19** (10.5 g, 59.6 mmol) and copper (I) iodide (1.70 g, 8.93 mmol) in THF (120 mL). The orange solution was warmed to −10 °C, and stirred for 2 h. The reaction mixture was quenched with saturated aq NH_4Cl and warmed to room temperature. The solution was diluted with Et_2O (250 mL), and washed with saturated aq NH_4Cl (250 mL) and saturated aq NaCl (250 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (500 g SiO_2, 10% EtOAc/hexanes) to yield 13.0 g (75%) of alcohol **20a** as a pale yellow oil: $[\alpha]_D^{24}$+21 (*c* 1.9, $CHCl_3$); R_f=0.24 in 20% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (d, *J*=4.0 Hz, 2H), 4.31 (dd, *J*=8.6, 5.8 Hz, 1H), 4.08–4.01 (m, 1H), 2.97–2.81 (m, 4H), 2.16–1.83 (m, 6H), 1.56 (A of AB, J_{AB}=13.7 Hz, 1H), 1.53 (B of AB, J_{AB}=13.7 Hz, 1H), 0.03 (s, 9H); ^{13}C NMR (101 MHz, $CHCl_3$) δ 144.3, 111.0, 65.6, 46.8, 44.5, 42.7, 30.7, 30.3, 26.9, 26.2, −1.1; IR (neat) 3440, 3077, 2945, 2892, 1633, 1422, 1251, 1152, 1060, 855 cm^{-1}; MS (DCI/CH_4) 290 (1), 162 (13), 161 (12), 141 (20), 134 (12), 105 (16), 101 (10), 93 (16), 75 (32), 73 (100); HRMS *m*/*e* calcd for $C_{13}H_{26}OS_2Si$ (M^+) 290.1194, found 290.1207.

*5.1.3. 2-[(S)-(tert-Butyldimethylsilanyloxy)-4-(trimethylsilanylmethyl)pent-4-enyl]-[1,3]dithiane (**20b**).* To a solution of alcohol **20a** (3.13 g, 10.8 mmol) in DMF (54.0 mL) was added imidazole (1.47 g, 21.6 mmol) and *tert*-butyldimethylsilyl chloride (1.95 g, 12.9 mmol). The colorless solution was stirred for 18 h, and then diluted with 30% Et_2O/hexanes (100 mL). The solution was washed with saturated aq NH_4Cl (100 mL) and saturated aq NaCl (100 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (150 g SiO_2, 1% EtOAc/hexanes) to yield 4.22 g (97%) of allylsilane **20b** as a thick colorless oil: $[\alpha]_D^{24}$+17 (*c* 2.9, $CHCl_3$); R_f=0.70 in 20% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.62 (s, 1H), 4.57 (s, 1H), 4.13–4.07 (m, 2H), 2.92–2.74 (m, 4H), 2.22 (A of ABX, J_{AB}=13.6 Hz, J_{AX}=4.9 Hz, 1H), 2.15–1.83 (m, 3H), 2.05 (B of ABX, J_{AB}=13.7 Hz, J_{BX}=8.0 Hz, 1H), 1.73 (ddd, *J*=13.6, 8.7, 4.4 Hz, 1H), 1.55 (A of AB, J_{AB}=13.4 Hz, 1H), 1.47 (B of AB, J_{AB}=13.4 Hz, 1H), 0.90 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H), 0.02 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5, 110.4, 67.5, 46.8, 44.1, 42.4, 30.5, 29.9, 26.9, 26.1, 25.9, 18.0, −1.4, −4.3, −4.6; IR (neat) 3084, 2945, 2899, 2846, 1640, 1475, 1416, 1244, 1073, 842 cm^{-1}; MS (DCI/CH_4) 404 (3), 347 (30), 275 (26), 219 (28), 191 (60), 165 (12), 147 (32), 121 (15), 93 (16), 75 (20), 73 (100); HRMS *m*/*e* calcd for $C_{19}H_{40}OS_2Si_2$ (M^+) 404.2059, found 404.2073.

*5.1.4. Tributyl-((S)-5-[1,3]dithian-2-yl-4-(tert-butyldimethylsilanyloxy)-2-methylenepentyl)stannane (**16**).* To a cold (−78 °C) solution of allylsilane **20b** (5.00 g, 12.4 mmol) in 60% DMF/CH_2Cl_2 (62 mL) was added propylene oxide (8.64 mL, 124 mmol) and *N*-bromosuccinimide (6.62 g, 37.2 mmol). The cloudy reaction mixture was stirred for 5 h at −78 °C, and then cannulated into a vigorously stirring 0 °C mixture of Et_2O (100 mL) and saturated aq $NaHSO_3$ (100 mL). The layers were separated, and the organic layer was washed with water (100 mL) and saturated aq NaCl (100 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude allyl bromide was used without further purification for the next step: R_f=0.50 in 5% EtOAc/hexanes.

To a cold (0 °C) solution of tributyltin hydride (6.98 mL, 25.9 mmol) in THF (36 mL) was added LDA (25.9 mL of a freshly prepared 1.0 M solution in THF, 25.9 mmol). The yellow solution was stirred at 0 °C for 30 min, and then transferred via cannula to a cold (−78 °C) suspension of copper(I) bromide dimethyl sulfide (4.90 g, 23.5 mmol) in THF (72 mL). The brown reaction mixture was stirred for 2 h at −78 °C, and then the allyl bromide was added as a solution in THF (18 mL). The purple solution was warmed to −40 °C over 45 min, and then quenched with saturated aq NH_4Cl. The biphasic mixture was diluted with Et_2O (150 mL), filtered through a plug of Celite, and then washed with saturated aq NH_4Cl (100 mL) and saturated aq NaCl (100 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (250 g of Et_3N-deactivated SiO_2, 100% hexanes) to provide 5.94 g (77% yield for the two steps) of allylstannane **16** as a colorless oil: $[\alpha]_D^{24}$+10 (*c* 1.2, $CHCl_3$); R_f=0.60 in 5% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.56 (s, 1H), 4.47, s(1H), 4.15–4.08 (m, 2H), 2.92–2.74 (m, 4H), 2.19 (dd, *J*=13.3, 5.1 Hz, 1H), 2.15–2.07 (m, 1H), 2.03–1.84 (m, 3H)1.79 (A of AB, J_{AB}=11.4 Hz, 1H), 1.70 (B of AB, J_{AB}=11.4 Hz, 1H), 1.73 (ddd, *J*=13.8, 8.9, 4.7 Hz, 1H), 1.51–1.44 (m, 6H), 1.34–1.25 (m, 6H), 0.91–0.84 (m, 24), 0.12 (s, 3H), 0.09 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.0, 107.9, 67.7, 46.8, 44.1, 42.4, 30.5, 29.8, 29.1, 27.4, 26.1, 25.9, 19.2, 18.0, 13.7, 9.4, −4.3, −4.6; IR (neat) 3066, 2918, 2854, 1625, 1473, 1424, 1360, 1247, 1084, 942, 839 cm^{-1}; HRMS *m*/*e* calcd for $C_{28}H_{58}OS_2SiSn$ 620.2720, found 620.2716.

*5.1.5. (S)-5-[(S)-2-(tert-Butyldimethylsilanyloxy)-3-[1,3]dithian-2-ylpropyl]-1-(4-methoxybenzyloxy)hex-5-en-3-ol (**25**).* A flame-dried Schlenk flask was charged with (*S,S*)-1,2-bis-*para*-toluenesulfonyl-1,2-diphenylethane (2.00 g, 3.85 mmol), diluted with CH_2Cl_2 (25 mL), and cooled to 0 °C. Fresh BBr_3 (3.85 mL of 1.0 M solution in CH_2Cl_2, 3.85 mmol) was added dropwise and the reaction was warmed to ambient temperature. The orange reaction mixture was stirred for 1 h, and then the CH_2Cl_2 and HBr were removed under reduced pressure (0.1 mmHg). The reaction was diluted again with CH_2Cl_2 (25 mL) and, after 10 min, concentrated under high vacuum. The resulting white solid was diluted with CH_2Cl_2 (23 mL) and cooled to 0 °C. A solution of stannane **16** (2.66 g, 4.28 mmol) in CH_2Cl_2 (5 mL) was added and the yellow solution was stirred for 16 h at ambient temperature.

The reaction mixture was cooled to −78 °C, and a solution of aldehyde **23** (0.55 g, 2.85 mmol) in CH_2Cl_2 (4 mL) was added over 5 min. After 1.5 h the reaction was quenched with saturated aq $NaHCO_3$ and warmed to ambient temperature. The solution was diluted with CH_2Cl_2 (100 mL) and washed with saturated aq $NaHCO_3$ (100 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting residue was suspended in Et_2O and filtered through a fritted glass funnel. The remaining white solid (recovered bis-sulfonamide) can be recrystallized from $CHCl_3$ and reused. The clear ethereal solution was concentrated in vacuo. The crude residue was purified by flash chromatography (75 g SiO_2, 20% EtOAc/hexanes) to yield 1.54 g (quant., 11:1 dr) of homoallylic alcohol **25** as a colorless oil: $[\alpha]_D^{22}$+16 (*c* 1.2, $CHCl_3$); R_f=0.40 in 40% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.24 (m, 2H), 6.90–6.86 (m, 2H), 4.89 (s, 2H), 4.45 (s, 2H), 4.15–4.08 (m, 2H), 3.98–3.91 (m, 1H), 3.80 (s, 3H), 3.72–3.59 (m, 2H), 2.91–2.74 (m, 5H), 2.29 (dd, *J*=13.8, 5.4 Hz, 1H), 2.21–2.15 (m, 2H), 2.14–2.07 (m, 2H), 1.93–1.71 (m, 5H), 0.89 (s, 9H), 0.11 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 142.8, 130.1, 129.3, 115.4, 113.8, 72.9, 68.9, 68.5, 67.3, 55.2, 44.4, 44.4, 44.0, 42.3, 36.2, 30.5, 29.9, 26.0, 25.9, 18.0, −4.3, −4.6; IR (neat) 3459, 3066, 2948, 2849, 1615, 1502, 1473, 1419, 1247, 1094, 1040, 942, 843 cm^{-1}; MS (DCI/CH_4) 526 (0.4), 395 (20), 275 (38), 274 (31), 273 (100), 254 (8), 241 (9); HRMS *m/e* calcd for $C_{27}H_{46}O_4S_2Si$ (M^+) 526.1607, found 526.2607.

5.1.6. Toluene-4-sulfonic acid (1S,5S)-5-(tert-butyldimethylsilanyloxy)-6-[1,3]dithian-2-yl-1-[2-(4-methoxybenzyloxy)-ethyl]-3-methylenehexyl ester. To a solution of alcohol **25** (0.99 g, 1.89 mmol) in CH_2Cl_2 (19 mL) at ambient temperature was added Et_3N (1.32 mL, 9.45 mmol), 4-(dimethylamino)pyridine (0.25 g, 2.08 mmol), and *para*-toluenesulfonyl chloride (0.90 g, 4.72 mmol). The brown reaction mixture was stirred for 72 h, and then diluted with Et_2O (50 mL). The solution was washed with saturated aq NH_4Cl (50 mL) and saturated aq $NaHCO_3$ (50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (50 g SiO_2, 5–10% EtOAc/hexanes) to yield 1.32 g (quant.) of the tosylate of **25** as a light yellow oil: $[\alpha]_D^{22}$ +15 (*c* 1.8, $CHCl_3$); R_f=0.39 in 20% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J*=8.1 Hz, 2H), 7.27 (d, *J*=8.1 Hz, 2H), 7.19 (d, *J*=8.6 Hz, 2H), 6.85 (d, *J*=8.6 Hz, 2H), 4.90–4.83 (m, 1H), 4.80 (s, 1H), 4.78 (s, 1H), 4.28 (A of AB, J_{AB}=11.4 Hz, 1H), 4.24 (B of AB, J_{AB}=11.4 Hz, 1H), 4.09–3.99 (m, 2H), 3.79 (s, 3H), 3.44–3.28 (m, 2H), 2.90–2.80 (m, 2H), 2.78 (dd, *J*=7.6, 3.7 Hz, 2H), 2.40 (s, 3H), 2.39 (A of ABX, J_{AB}=14.3, J_{AX}=5.7 Hz, 1H), 2.29 (B of ABX, J_{AB}=14.3 Hz, J_{BX}=7.4 Hz, 1H), 2.14–1.74 (m, 7H), 1.71–1.64 (m, 1H), 0.86 (s, 9H), 0.09 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 144.4, 140.6, 134.6, 130.5, 129.7, 129.1, 127.9, 127.8, 117.0, 113.8, 79.6, 72.5, 67.2, 65.5, 55.3, 44.2, 43.9, 42.4, 41.8, 34.3, 30.5, 30.0, 26.1, 25.9, 21.6, 18.0, −4.3, −4.6; IR (neat) 3071, 2938, 2859, 1615, 1517, 1438, 1360, 1261, 1193, 1183, 1094, 1020, 907, 824 cm^{-1}; MS (DCI/CH_4) 623 (1), 273 (4), 241 (2), 227 (14), 223 (2), 121 (100); HRMS *m/e* calcd for $C_{30}H_{43}O_6S_3Si$ ($M^+-C_4H_9$) 623.1991, found 623.1974.

*5.1.7. Toluene-4-sulfonic acid (1S,5S)-6-[1,3]dithian-2-yl-5-hydroxy-1-[2-(4-methoxybenzyloxy)ethyl]-3-methylene-hexyl ester (**26**).* To a solution of the tosylate from **25** (1.37 g, 2.01 mmol) in CH_3CN was added hydrogen fluoride–pyridine (60–70%, 6.3 mL). After stirring at room temperature for 16 h, the acidic reaction mixture was neutralized with saturated aq $NaHCO_3$. The solution was diluted with Et_2O (150 mL), and washed carefully with saturated aq $NaHCO_3$ (150 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (60 g SiO_2, 30–40% EtOAc/hexanes) to yield 0.99 g (87%) of alcohol **26** as a colorless oil: $[\alpha]_D^{22}$+12 (*c* 1.1, $CHCl_3$); R_f=0.30 in 40% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J*=8.2 Hz, 2H), 7.30 (d, *J*=8.2 Hz, 2H), 7.21 (d, *J*=8.6 Hz, 2H), 6.88 (d, *J*=8.6 Hz, 2H), 4.91 (s, 1H), 4.89 (s, 1H), 4.91–4.86 (m, 1H), 4.00–3.96 (m, 1H), 4.32–4.22 (m, 3H)3.81 (s, 3H), 3.45–3.29 (m, 2H), 2.95–2.80 (m, 4H), 2.43 (s, 3H), 2.38 (d, *J*=6.3 Hz, 2H), 2.17–2.09 (m, 3H), 2.03 (dd, *J*=14.2, 8.7 Hz, 1H), 1.95–1.80 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 144.6, 140.6, 134.2, 130.2, 129.7, 129.2, 127.9, 117.2, 113.8, 79.4, 72.6, 65.8, 65.4, 55.3, 44.1, 42.4, 41.4, 34.4, 30.3, 30.0, 21.6, 10.4; IR (neat) 3453, 3064, 2932, 1647, 1614, 1515, 1343, 1258, 1178, 1093, 921, 809 cm^{-1}; HRMS (FAB, NBA, Na^+) *m/e* calcd for $C_{28}H_{39}O_6S_3$ (M^++H) 567.1909, found 567.1920.

5.1.8. (2S,6R)-2-[1,3]Dithian-2-ylmethyl-6-[2-(4-methoxybenzyloxy) ethyl]-4-methylenetetrahydropyran. To a solution of tosylate **26** (0.99 g, 1.75 mmol) in benzene (58 mL) was added NaH (280 mg of a 60% dispersion in mineral oil, 7.00 mmol). The reaction mixture was heated to 90 °C, and stirred for 40 h. The suspension was then cooled to ambient temperature, and diluted with Et_2O (100 mL) and saturated aq NaCl (100 mL). The layers were separated, and the resulting aqueous layer was extracted with Et_2O (100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (50 g SiO_2, 10–30% Et_2O/hexanes) to yield 504 mg (73%) of 2,6-*cis*-pyran as a light yellow oil: $[\alpha]_D^{22}$−15 (*c* 0.79, $CHCl_3$); R_f=0.52 in 40% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J*=8.6 Hz, 2H), 6.88 (d, *J*=8.6 Hz, 2H), 4.72–4.71 (m, 2H), 4.46 (A of AB, J_{AB}=11.4 Hz, 1H), 4.43 (B of AB, J_{AB}=11.4 Hz, 1H), 4.23 (dd, *J*=9.9, 4.7 Hz, 1H), 3.80 (s, 3H), 3.61–3.54 (m, 3H), 3.47–3.41 (m, 1H), 2.92–2.72 (m, 4H), 2.19 (d, *J*=13.6 Hz, 2H), 2.12–2.04 (m, 1H), 2.01–1.74 (m, 7H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 144.2, 130.7, 129.3, 113.8, 108.9, 75.3, 74.2, 72.8, 66.6, 55.3, 43.6, 41.8, 40.7, 40.7, 36.4, 30.3, 29.9, 26.0; IR (neat) 3064, 2939, 2892, 2853, 1647, 1614, 1515, 1416, 1251, 1086, 1027, 816 cm^{-1}; MS (DCI/CH_4) 394 (2), 274 (15), 273 (67), 141 (70), 122 (22), 121 (100), 97 (28), 93 (24), 77 (10); HRMS *m/e* calcd for $C_{21}H_{30}O_3S_2$ (M^+) 394.1636, found 394.1625.

*5.1.9. {(2S,6R)-6-[2-(4-Methoxybenzyloxy)ethyl]-4-methylenetetrahydropyran-2-yl}-acetaldehyde (**14**).* To a solution of the dithianyl THP derived from **26** (500 mg, 1.27 mmol) in 10% aqueous CH_3CN (127 mL) was added iodomethane (30.7 mL, 493 mmol) and calcium carbonate (2.29 g, 22.9 mmol). The suspension was stirred overnight at ambient temperature, and then diluted with Et_2O (200 mL) and saturated aq NaCl (200 mL). The layers were separated, and the resulting organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (25 g SiO_2, 15% EtOAc/hexanes) to yield 372 mg (96%) of aldehyde **14** as a clear, colorless oil: $[\alpha]_D^{22}$−15 (*c* 1.0, $CHCl_3$); R_f=0.41 in 40% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (t, *J*=2.0 Hz, 1H); 7.26–7.24 (m, 2H), 6.89–6.87 (m, 2H), 4.75 (s, 2H), 4.43 (A of AB, J_{AB}=11.6 Hz, 1H), 4.40 (B of AB, J_{AB}=11.6 Hz, 1H), 3.82–3.75 (m, 1H), 3.80 (s, 3H), 3.57–3.46 (m, 3H), 2.59 (d of A of ABX, J_{AB}=16.2 Hz, J_{AX}=8.4 Hz, *J*=2.8 Hz, 1H), 2.48 (d

of B of ABX, J_{AB}=16.2 Hz, J_{BX}=4.5 Hz, J=2.0 Hz, 1H), 2.27–2.19 (m, 2H), 2.02–1.96 (m, 2H), 1.80–1.74 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.2, 159.1, 143.5, 130.6, 129.3, 113.7, 109.4, 77.2, 75.6, 73.5, 72.6, 66.0, 55.3, 49.6, 40.4, 36.3; IR (neat) 3070, 2932, 2860, 2721, 1719, 1660, 1607, 1515, 1363, 1244, 1093, 1033 cm^{-1}; MS (DCI/CH_4) 304 (3), 193 (2), 176 (16), 138 (16), 137 (83), 122 (27), 121 (100) 118 (48); HRMS *m*/*e* calcd for $C_{18}H_{24}O_4$ (M^+) 304.1675, found 304.1678.

*5.1.10. (R)-4-Bromo-2,3-dimethylbut-1-ene (**33**).* To a cold (0 °C) solution containing 2(*S*)-2,3-dimethyl-3-buten-1-ol (3.12 g, 28.3 mmol) in pyridine (140 mL) were added 4-(dimethylamino) pyridine (0.35 g, 2.83 mmol) and *para*-toluenesulfonyl chloride (10.8 g, 56.6 mmol). The mixture was then warmed to ambient temperature and stirred for 16 h. The reaction mixture was diluted with Et_2O (250 mL) and 5% aq HCl (250 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (250 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified via filtration through a plug of silica gel to provide the corresponding tosylate. This material was taken on to the next step without further purification.

To a solution of the tosylate in DMF (140 mL) was added lithium bromide (7.27 g, 83.7 mmol). The suspension was heated to 40 °C, and stirred for 16 h. The reaction mixture was cooled to ambient temperature, and diluted with pentane (250 mL). The organic solution was washed with saturated aq NaCl (3×250 mL), dried ($MgSO_4$), filtrated, and concentrated in vacuo at 0 °C. The crude residue was purified by flash chromatography (150 g SiO_2, 100% pentane) to yield 2.79 g (61% for two steps) of homoallyl bromide **33** as a clear, colorless oil: $[\alpha]_D^{22}$+7.4 (*c* 1.9, $CHCl_3$); R_f=0.61 in 100% pentane; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (s, 1H), 4.79 (s, 1H), 3.44 (A of ABX, J_{AB}=9.9 Hz, J_{AX}=6.3 Hz, 1H), 3.34 (B of ABX, J_{AB}=9.9 Hz, J_{BX}=7.3 Hz, 1H), 2.54 (sextet, J=6.9 Hz, 1H), 1.73 (s, 3H), 1.17 (d, J=6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.6, 111.7, 43.1, 38.1, 19.7, 18.2; IR (neat) 3066, 2972, 2918, 1645, 1606, 1463, 1438, 1370, 1222, 1104 cm^{-1}; MS (DEI) 163 (38), 142 (28), 120 (21), 118 (22), 113 (44), 83 (43), 81 (100), 80 (22), 69 (41); HRMS *m*/*e* calcd for $C_6H_{12}Br$ (MH^+)163.1022, found 162.9949.

*5.1.11. (3S,6S)-1-(tert-Butyldimethylsilanyloxy)-6,7-dimethyloct-7-en-3-ol (**35**).* Preparation of the Grignard reagent: to a 25 mL two-neck round bottom flask fitted with a reflux condenser was added Mg turnings (0.50 g, 20.4 mmol). The flask was flame-dried, and then cooled to ambient temperature. The turnings were combined with THF (4 mL), and then a solution of homoallyl bromide **33** (0.50 g, 3.07 mmol) in THF (3+1 mL) was added dropwise. The light green solution was refluxed for 10 min, and then was allowed to cool to ambient temperature.

The solution of Grignard reagent was added dropwise to a cold (−78 °C) solution of epoxide **34**[20] (0.42 g, 2.04 mmol) and copper(I) iodide (78 mg, 0.41 mmol) in a mixture of THF/DMS (9 mL; 20:1 by volume). The mixture was stirred for 1 h at −78 °C, and then quenched carefully with the addition of saturated aq NH_4Cl. The biphasic mixture was warmed to ambient temperature and diluted with Et_2O (50 mL). The organic solution was washed with saturated aq NH_4Cl (50 mL) and saturated aq NaCl (50 mL). The combined aqueous layers were extracted with Et_2O (50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (25 g SiO_2, 5% EtOAc/hexanes) to yield 0.41 g (70%) of alcohol **35** as a clear, colorless oil: $[\alpha]_D^{22}$ −13.3 (*c* 0.24, $CHCl_3$); R_f=0.23 in 10% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.67 (br s, 2H), 3.87 (m, 1H), 3.83–3.74 (m, 2H), 3.49 (br s, 1H), 2.12 (m, 1H), 1.64 (s, 3H), 1.64–1.61 (m, 2H), 1.49–1.30 (m, 4H), 1.00 (d, J=6.8 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.0, 109.5, 72.6, 63.0, 41.3, 38.2, 35.5, 30.8, 25.8, 19.7, 18.8, 18.1, −5.6; IR (neat) 3452, 3072, 2954, 2930, 2857, 1643, 1467, 1258, 1082, 829 cm^{-1}; HRMS *m*/*e* calcd for $C_{16}H_{34}O_2Si$ (M^+) 286.2328, found 286.2338.

5.1.12. (3S,6S)-6,8-Bis-(tert-butyldimethylsilanyloxy)-2,3-dimethyl-oct-1-ene. To a solution of alcohol **35** (1.59 g, 5.55 mmol) in DMF (28 mL) were added imidazole (0.76 g, 11.1 mmol) and *tert*-butyldimethylsilyl chloride (1.00 g, 6.66 mmol). The reaction mixture was stirred for 16 h at ambient temperature. The solution was diluted with 30% Et_2O/hexanes (50 mL) and saturated aq NH_4Cl (50 mL). The layers were separated, and the organic layer was washed with saturated aq NaCl (50 mL). The organic solution was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (75 g SiO_2, 2% EtOAc/hexanes) to yield 2.13 g (96%) of the silyl ether of **35** (R=TBS) as a clear, colorless oil: $[\alpha]_D^{22}$+10.3 (*c* 1.15, $CHCl_3$); R_f=0.75 in 20% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.68–4.67 (m, 2H), 3.80–3.76 (m, 1H), 3.70–3.60 (m, 2H), 2.12–2.05 (m, 1H), 1.66–1.61 (m, 2H), 1.64 (s, 3H), 1.40–1.32 (m, 4H), 0.99 (d, J=6.7 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.04 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.0, 109.4, 69.4, 60.1, 41.2, 40.0, 35.1, 30.2, 25.9, 25.9, 19.8, 18.9, 18.3, 18.1, −4.4, −4.6, −5.3; IR (neat) 3061, 2948, 2849, 1645, 1468, 1389, 1261, 1094, 839 cm^{-1}; MS (DCI/CH_4) 401 (1), 343 (41), 219 (13), 189 (33), 149 (24), 133 (13), 109 (100), 95 (63), 81 (72), 75 (33), 73 (67); HRMS *m*/*e* calcd for $C_{22}H_{49}O_2Si_2$ (MH^+) 401.3271, found 401.3254.

*5.1.13. (3S,6S)-6,8-Bis-(tert-butyldimethylsilanyloxy)-3-methyl-octan-2-one (**36**).* The silyl ether of **35** was dissolved in 1:1 MeOH/CH_2Cl_2 (54 mL), and the colorless solution was cooled to −78 °C. A stream of ozone was introduced until the color of the solution was light blue. The reaction mixture was purged with Ar for 10 min at −78 °C, and then quenched by the addition of Me_2S (4 mL). The solution was warmed to ambient temperature and stirred for an additional 16 h. At this time the mixture was concentrated in vacuo and the crude residue purified by flash chromatography (75 g SiO_2, 2–4% EtOAc/hexanes) to give 2.09 g (98%) of methyl ketone **36** as a clear, colorless oil: $[\alpha]_D^{22}$+15.7 (*c* 1.50, $CHCl_3$); R_f=0.57 in 20% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82–3.77 (m, 1H), 3.64 (t, J=6.6 Hz, 2H), 2.51–2.42 (m, 1H), 2.12 (s, 3H), 1.70–1.56 (m, 3H), 1.47–1.33 (m, 3H), 1.07 (d, J=7.0 Hz, 3H), 0.88 (s, 9H), 0.88 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H), 0.03 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.6, 69.1, 59.8, 47.2, 40.0, 34.7, 28.3, 27.9, 25.9, 25.9, 18.2, 18.1, 16.1, −4.5, −4.6, −5.3; IR (neat) 2965, 2860, 1719, 1469, 1356, 1244, 1093, 842 cm^{-1}; MS (DCI/CH_4) 403 (1), 345 (71), 271 (20), 245 (41), 214 (24), 213 (82), 197 (27), 185 (19), 171 (24), 159 (55), 147 (78), 140 (13), 139 (83), 129 (38), 121 (62), 113 (22), 95 (40), 89 (80), 73 (100); HRMS *m*/*e* calcd for $C_{21}H_{47}O_3Si_2$ (MH^+) 403.3064, found 403.3084.

*5.1.14. Trifluoromethanesulfonic acid (2S,5S)-5,7-bis-(tert-butyl-dimethylsilanyloxy)-2-methyl-1-methyleneheptyl ester (**37**).* To a cold (−78 °C) solution of potassium bis(trimethylsilyl)amide (1.56 mL of a 0.5 M solution in toluene, 0.78 mmol) in THF (7.8 mL) was added a solution of methyl ketone **36** (300 mg, 0.75 mmol) in THF (1.8 mL) over 45 min. After the addition was complete, the solution was allowed to stir for an additional 30 min. At this time a solution of Comins reagent[21] (0.35 g, 0.89 mmol) in THF (500 μL) was added dropwise, and the reaction mixture stirred for 4 h at −78 °C. The solution was quenched with saturated aq NH_4Cl, warmed to ambient temperature, and diluted with Et_2O (25 mL). The extracts were washed with saturated aq NH_4Cl (25 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (25 g SiO_2, 2% Et_2O/hexanes) to give 0.35 g (87%) of enol triflate **37** as a clear, colorless, oil: $[\alpha]_D^{22}$+10.5 (*c* 1.71, $CHCl_3$); R_f=0.60 in 10% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.10 (d, J=3.9 Hz, 1H), 4.91 (d, J=3.9 Hz, 1H), 3.83–3.81 (m, 1H), 3.65 (t, J=6.5 Hz, 2H), 2.41–2.36 (m, 1H), 1.71–1.41 (m, 6H), 1.14 (d,

J=6.8 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.04 (m, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.8, 102.4, 69.0, 59.8, 40.0, 38.5, 34.0, 29.0, 25.9, 25.8, 18.2, 18.0, 17.7, −4.5, −4.6, −5.4; IR (neat) 2953, 2928, 2854, 1665, 1478, 1424, 1256, 1207, 1143, 1089, 932, 829 cm^{-1}.

*5.1.15. (3S,6S)-6,8-Bis-(tert-butyldimethylsilanyloxy)-3-methyl-2-(trimethylsilanylmethyl)-oct-1-ene (**38**).* To a cold (0 °C) solution of enol triflate **37** (0.29 g, 0.53 mmol) in THF (5.3 mL) were added $Ni(acac)_2$ (27 mg, 0.11 mmol) and (trimethylsilylmethyl)magnesium chloride (1.60 mL of a 1.0 M solution in Et_2O, 1.60 mmol). The reaction mixture was warmed to ambient temperature and stirred for 16 h. The solution was quenched with pH 7 phosphate buffer (15 mL), and diluted with Et_2O (15 mL). The layers were separated, and the organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (10 g SiO_2, 1–2% EtOAc/hexanes) to yield 0.19 g (75%) of allylsilane **38** as a clear, colorless oil; R_f=0.76 in 10% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.59 (s, 1H), 4.54 (s, 1H), 3.81–3.76 (m, 1H), 3.65 (app dt, J=6.6, 1.4 Hz, 2H), 1.93–1.84 (m, 1H), 1.69–1.60 (m, 2H), 1.50 (s, 2H), 1.47–1.38 (m, 3H), 1.38–1.26 (m, 1H), 0.99 (d, J=6.9 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.04 (s, 12H), 0.01 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.4, 105.5, 69.5, 60.1, 40.9, 40.0, 35.2, 30.9, 26.0, 25.9, 25.6, 19.7, 18.3, 18.1, −1.2, −4.4, −4.6, −5.3; IR (neat) 3077, 2945, 2853, 1633, 1475, 1251, 1073, 855 cm^{-1}; MS (DCI/CH_4) 473 (2), 415 (32), 340 (14), 329 (19), 209 (24), 197 (18), 191 (14), 155 (35), 148 (27), 115 (33), 95 (51), 89 (45), 74 (61), 73 (100); HRMS m/e calcd for $C_{25}H_{57}O_2Si_3$ (MH^+) 473.3666, found 473.3684.

*5.1.16. (3S,6S)-6,8-Bis-(tert-butyldimethylsilanyloxy)-3-methyl-2-(tributylstannylmethyl)oct-1-ene (**27**).* To a cold (−78 °C) solution of allylsilane **38** (833 mg, 1.76 mmol) in 60% DMF/CH_2Cl_2 (8.8 mL) were added propylene oxide (1.23 mL, 17.6 mmol) and *N*-bromosuccinimide (1.25 g, 7.04 mmol). The cloudy reaction mixture was stirred for 1 h at −78 °C, and then warmed to −10 °C over 2.5 h. The reaction mixture was cooled back down to −78 °C and quenched with saturated aq $NaHSO_3$. After warming to ambient temperature, the light yellow solution was diluted with Et_2O (25 mL). The organic solution was washed with water (25 mL) and saturated aq NaCl (25 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. This allyl bromide was identified and used without further purification for the next step: R_f=0.74 in 10% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 (s, 1H), 4.98 (s, 1H), 3.98 (m, 2H), 3.82–3.78 (m, 1H), 3.65 (t, J=6.4 Hz, 2H), 2.38–2.30 (m, 1H), 1.69–1.38 (m, 5H), 1.31–1.19 (m, 1H), 1.08 (d, J=6.4 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.07 (s, 3H), 0.04 (m, 9H).

To a cold (0 °C) solution of tributyltin hydride (1.00 mL, 3.70 mmol) in THF (5 mL) was added LDA (3.70 mL of a freshly prepared 1.0 M solution in THF, 3.70 mmol). The yellow solution was stirred at 0 °C for 30 min, and then transferred via cannula to a cold (−78 °C) suspension of copper(I) bromide dimethyl sulfide (0.70 g, 3.34 mmol) in THF (10 mL). The brown reaction mixture was stirred for 2 h at −78 °C, and then the allyl bromide, prepared as above, was added as a solution in THF (2.5 mL). The purple solution was warmed to −40 °C over 45 min, and then quenched with saturated aq NH_4Cl. The biphasic mixture was diluted with Et_2O (50 mL), filtered through a plug of Celite, and then washed with saturated aq NH_4Cl (50 mL) and saturated aq NaCl (50 mL). The crude residue was purified by flash chromatography (60 g of Et_3N-deactivated SiO_2, 100% pentane) to give 1.08 g (89% for two steps) of allylstannane **27** as a clear, colorless oil: $[\alpha]_D^{22}$+10.6 (c 1.11, $CHCl_3$); R_f=0.75 in 10% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (s, 1H), 4.47(s, 1H), 3.81–3.75 (m, 1H), 3.65 (dt, J=6.7, 1.2 Hz, 2H), 1.90–1.82 (s, 1H), 1.77 (A of AB, J_{AB}=11.9 Hz, 1H), 1.74 (B of AB, J_{AB}=11.9 Hz, 1H), 1.70–1.58 (m, 2H), 1.52–1.25 (m, 16H), 1.00 (d, J=6.9 Hz, 3H), 0.90–0.82 (m, 15H), 0.89 (s, 9H), 0.88 (s, 9H), 0.04 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6, 103.5, 69.5, 60.1, 40.9, 40.1, 35.2, 31.1, 30.6, 29.1, 27.5, 27.4, 25.9, 19.7, 18.3, 18.1, 17.7, 13.7, 9.9, 9.5, −4.4, −4.6, −5.3; IR (neat) 3081, 2958, 2849, 1620, 1458, 1360, 1266, 1099, 843 cm^{-1}; HRMS (FAB, NBA, Na^+) m/e calcd for $C_{30}H_{65}O_2Si_2Sn$ ($M^+-C_4H_9$) 633.3545, found 633.3668.

*5.1.17. (R)-4-[(1S,4S)-4,6-Bis-(tert-butyldimethylsilanyloxy)-1-methylhexyl]-1-{2S,6R}-6-[2-(4-methoxybenzyloxy)ethyl]-4-methylenetetrahydropyran-2-yl}-pent-4-en-2-ol (**45**).* A flame-dried Schlenk flask was charged with (*R*,*R*)-1,2-bis-*para*-toluenesulfonyl-1,2-diphenylethane (590 mg, 1.13 mmol), diluted with CH_2Cl_2 (7.8 mL), and cooled to 0 °C. Fresh BBr_3 (1.13 mL of 1.0 M solution in CH_2Cl_2, 1.13 mmol) was added dropwise and the solution was warmed to ambient temperature. The orange reaction mixture was stirred for 1 h, and then the CH_2Cl_2 and HBr were removed under reduced pressure (0.1 mmHg). The reaction was diluted again with CH_2Cl_2 (7.8 mL) and, after 10 min, concentrated under high vacuum. The resulting white solid was diluted with CH_2Cl_2 (7.3 mL) and cooled to 0 °C. A solution of stannane **27** (873 mg, 1.27 mmol) in CH_2Cl_2 (1.0 mL) was added and the resulting yellow solution was stirred for 16 h at ambient temperature.

The solution was cooled to −78 °C, and a solution of aldehyde **14** (257 mg, 0.84 mmol) in CH_2Cl_2 (1 mL) was added over 5 min. After 1.5 h the reaction was quenched with saturated aq $NaHCO_3$ and warmed to ambient temperature. The mixture was diluted with CH_2Cl_2 (25 mL) and washed with saturated aq $NaHCO_3$ (25 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo, and the resulting residue was suspended in Et_2O and filtered through a fritted glass funnel. The remaining white solid (recovered bis-sulfonamide) can be recrystallized from $CHCl_3$ and reused. The clear ethereal solution was concentrated in vacuo. The crude residue was purified by flash chromatography (50 g SiO_2, 7.5% EtOAc/hexanes) to yield 522 mg (88%) of alcohol **45**, as well as 51 mg (9%) of the minor diastereomer. Characterization data for the major product **45** was as follows: $[\alpha]_D^{22}$+7.9 (c 2.1, $CHCl_3$); R_f=0.36 in 20% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J=8.6 Hz, 2H), 6.87 (d, J=8.6 Hz, 2H), 4.84 (s, 1H), 4.81 (s, 1H), 4.71 (s, 2H), 4.44 (A of AB, J_{AB}=11.6 Hz, 1H), 4.42 (B of AB, J_{AB}=11.6 Hz, 1H), 4.02–4.00 (m, 1), 3.80 (s, 3H), 3.80–3.75 (m, 1H), 3.71 (s, 1H), 3.65 (t, J=6.7 Hz, 2H), 3.55–3.52 (m, 4H), 2.28–1.29 (m, 17H), 1.01 (d, J=7.0 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.04 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 151.3, 143.8, 130.4, 129.3, 113.7, 110.1, 109.0, 79.4, 76.0, 72.7, 70.1, 69.4, 66.4, 60.0, 55.2, 42.5, 42.2, 41.0, 40.5, 40.1, 40.0, 36.2, 35.0, 31.0, 25.9, 25.9, 19.9, 18.3, 18.1, −4.3, −4.6, −5.3; IR (neat) 3498, 3071, 2943, 2869, 1655, 1620, 1512, 1468, 1360, 1261, 1114, 1045, 839 cm^{-1}; HRMS (FAB, NBA, Na^+) m/e calcd for $C_{40}H_{72}O_6Si_2Na$ (M^++Na) 727.4766, found 727.4749.

*5.1.18. (2S,6R)-2-[(2R,5S,8S)-8,10-Bis-(tert-butyldimethylsilanyloxy)-2-methoxy-5-methyl-4-methylenedecyl]-6-[2-(4-methoxybenzyloxy)ethyl]-4-methylenetetrahydropyran (**46**).* To a solution of alcohol **45** (156 mg, 221 μmol) in CH_2Cl_2 (7 mL) at ambient temperature were added proton sponge (403 mg, 1.88 mmol), crushed 4 Å molecular sieves (402 mg), and trimethyloxonium tetrafluoroborate (229 mg, 1.55 mmol). The reaction mixture was stirred for 16 h, and then filtered through a pad of Celite to remove the solids. The filtrate was diluted with Et_2O (50 mL), and washed with 1 M aq HCl (2×25 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (10 g SiO_2, 7.5% EtOAc/hexanes) to yield 152 mg (96%) of methyl ether **46** as a clear, colorless oil: $[\alpha]_D^{22}$+6.1 (c 1.1, $CHCl_3$); R_f=0.36 in 20% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.24 (m, 2H), 6.88–6.86 (m, 2H), 4.81 (s, 2H), 4.71–4.70 (m, 2H), 4.43 (A of AB, J_{AB}=11.5, 1H), 4.41 (B of AB, J_{AB}=11.5 Hz, 1H), 3.80 (s, 3H), 3.80–3.75 (m, 1H), 3.65 (t, J=6.8 Hz, 2H), 3.56 (t, J=6.7 Hz, 2H), 3.51–3.36 (m, 3H), 3.31 (s, 3H), 2.30–1.35 (m, 17H), 1.00 (d, J=6.7 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.04 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1,

151.2, 144.7, 130.6, 129.2, 113.7, 110.0, 108.5, 76.8, 75.5 (2), 72.6, 69.4, 66.6, 60.0, 56.4, 55.2, 40.9, 40.8, 40.3, 40.1, 39.7, 39.0, 36.5, 35.0, 30.9, 25.9 (2), 19.9, 18.3, 18.1, −4.4, −4.6, −5.3; IR (neat) 3070, 2952, 2833, 1647, 1607, 1502, 1462, 1244, 1106, 1027 cm^{-1}; HRMS (MALDI) *m/e* calcd for $C_{41}H_{74}O_6Si_2Na$ (M^++Na) 741.4922, found 741.3160.

*5.1.19. (2R,6S)-2-[(2S,5S,8S)-8,10-Bis-(tert-butyldimethylsilanyloxy)-2-methoxy-5-methyl-4-oxodecyl]-6-[2-(4-methoxybenzyloxy)ethyl]-tetrahydropyran-4-one (**47**).* To a solution of olefin **46** (339 mg, 471 μmol) in 33% aq acetone (3.2 mL) were added 4-methylmorpholine *N*-oxide (138 mg, 1.18 mmol) and osmium tetroxide (500 μL of a 2.5 wt % solution in *tert*-BuOH, 38 μmol). The reaction mixture was stirred for 16 h at ambient temperature, and then quenched with sodium bisulfite (1 g). The solution was diluted with EtOAc (15 mL) and saturated aq NaCl (15 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (2×15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude tetrol was taken into the next reaction without purification.

To a solution of crude tetrol in 1:1 THF/pH 7 phosphate buffer (2.4 mL) was added sodium periodate (302 mg, 1.41 mmol). The cloudy reaction mixture was stirred for 16 h at ambient temperature, and then diluted with Et_2O (15 mL) and saturated aq NaCl (15 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (20 g SiO_2, 25% EtOAc) to yield 274 mg (80% overall) of diketone **47** as a clear, colorless oil: $[\alpha]_D^{22}$+3.1 (*c* 2.0, $CHCl_3$); R_f=0.41 in 40% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J*=8.6 Hz, 2H), 6.87 (d, *J*=8.6 Hz, 2H), 4.42 (s, 2H), 3.88–3.82 (m, 1H), 3.80 (s, 3H), 3.80–3.70 (m, 3H), 3.63 (t, *J*=6.6 Hz, 2H), 3.65–3.52 (m, 2H), 3.27 (s, 3H), 2.77 (A of ABX, J_{AB}=16.6 Hz, J_{AX}=7.0 Hz, 1H), 2.50 (B of ABX, J_{AB}=16.6 Hz, J_{BX}=5.4 Hz, 1H), 2.47–2.35 (m, 3H), 2.29–2.20 (m, 2H), 1.96–1.87 (m, 2H), 1.84–1.76 (m, 1H), 1.69–1.55 (m, 4H), 1.43–1.32 (m, 3H), 1.06 (d, *J*=6.9 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.03 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.6, 206.9, 159.1, 130.3, 129.2, 113.8, 74.0, 73.9, 73.6, 72.7, 69.1, 65.9, 59.8, 57.0, 55.2, 47.7 (2), 47.2, 45.3, 40.2, 40.0, 36.5, 34.7, 27.9, 25.9, 25.8, 18.2, 18.0, 15.9, −4.4, −4.6, −5.3; IR (neat) 2958, 2929, 2879, 1712, 1620, 1508, 1462, 1370, 1244, 1086, 1020, 829 cm^{-1}; HRMS (MALDI) *m/e* calcd for $C_{39}H_{70}O_8Si_2Na$ (M^++Na) 745.4507, found 745.3170.

5.1.20. (2S,5S,8S)-8,10-Bis-(tert-butyldimethylsilanyloxy)-1-{(2S,4R,6S)-4-hydroxy-6-[2-(4-methoxybenzyloxy)ethyl]-tetrahydropyran-2-yl}-2-methoxy-5-methyldecan-4-one. To a cold (−78 °C) solution of diketone **47** (355 mg, 491 μmol) in THF (24 mL) was added L-Selectride® (589 μL of a 1.0 M solution in THF, 589 μmol). The reaction mixture was stirred at −78 °C for 1.5 h. The solution was quenched with MeOH (1 mL), stirred for 15 min, and then warmed to ambient temperature. The solution was diluted with Et_2O (50 mL) and saturated aq $NaHCO_3$ (50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (25 g SiO_2, 50% EtOAc/hexanes) to yield 300 mg (84%) of the C_5 hydroxy–C_{11} ketone as a clear, colorless oil: $[\alpha]_D^{22}$ +6.5 (*c* 2.1, $CHCl_3$); R_f=0.29 in 50% in EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J*=7.6 Hz, 2H), 6.86 (d, *J*=7.6 Hz, 2H), 4.44 (A of AB, J_{AB}=11.6 Hz, 1H), 4.41 (B of AB, J_{AB}=11.6 Hz, 1H), 4.22 (m, 1H), 3.92–3.82 (m, 4H), 3.79 (s, 3H), 3.63 (t, *J*=6.4 Hz, 2H), 3.56 (t, *J*=6.7 Hz, 2H), 3.28 (s, 3H), 2.73 (A of ABX, J_{AB}=16.2 Hz, J_{AX}=8.0 Hz, 1H), 2.52 (B of ABX, J_{AB}=16.2 Hz, J_{BX}=4.5 Hz, 1H), 2.49–2.44 (m, 1H), 1.82–1.61 (m, 8H), 1.50–1.34 (m, 6H), 1.05 (d, *J*=7.0 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.03 (s, 6H), 0.03 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.0, 159.0, 130.6, 129.2, 113.7, 74.4, 72.6, 69.1, 68.8, 68.3, 66.6, 64.6, 59.8, 57.0, 55.2, 47.2, 45.7, 40.0, 38.8, 36.6, 34.8, 30.3, 28.0, 25.9, 25.9, 18.2, 18.1, 15.9, −4.4, −4.6, −5.3; IR (neat) 3435, 2943, 2849, 1710, 1507, 1458, 1365, 1261, 1099 cm^{-1}; HRMS (FAB, NBA, Na^+) *m/e* calcd for $C_{39}H_{72}O_8Si_2$ (M^++Na) 747.4663, found 747.4672.

*5.1.21. (2S,5S,8S)-8,10-Bis-(tert-butyldimethylsilanyloxy)-1-{(2R,4R,6S)-4-tert-butyldiphenylsilanyloxy}-6-[2-(4-methoxybenzyloxy)ethyl]-tetrahydropyran-2-yl}-2-methoxy-5-methyldecan-4-one (**51**).* To a solution of the alcohol prepared above from **47** (300 mg, 0.41 mmol) in DMF (2 mL) were added imidazole (141 mg, 2.07 mmol) and *tert*-butyldiphenylsilyl chloride (0.29 mL, 1.24 mmol). The reaction mixture was stirred for 48 h, and then diluted with 30% Et_2O/hexanes (15 mL) and saturated aq NH_4Cl (15 mL). The layers were separated, and the aqueous layer was extracted with 30% Et_2O/hexanes (15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (25 g SiO_2, 7.5% EtOAc/hexanes) to yield 290 mg (73%) of silyl ether **51** as a clear, colorless oil: $[\alpha]_D^{22}$+5.2 (*c* 0.8, $CHCl_3$); R_f=0.64 in 50% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.62 (m, 4H), 7.44–7.33 (m, 6H), 7.26 (d, *J*=8.6 Hz, 2H), 6.87 (d, *J*=8.6 Hz, 2H), 4.44 (s, 2H), 4.21 (m, 1H), 4.09–4.05 (m, 2H), 3.85–3.75 (m, 2H), 3.80 (s, 3H), 3.64 (t, *J*=6.7 Hz, 2H), 3.56 (t, *J*=6.7 Hz, 2H), 3.27 (s, 3H), 2.75 (A of ABX, J_{AB}=16.2 Hz, J_{AX}=7.7 Hz, 1H), 2.51 (B of ABX, J_{AB}=16.2 Hz, J_{BX}=5.0 Hz, 1H), 2.49 (m, 1H), 1.79–1.54 (m, 8H), 1.49–1.33 (m, 3H), 1.29–1.23 (m, 3H), 1.08 (s, 9H), 1.07 (d, *J*=7.0 Hz, 3H), 0.88 (s, 9H), 0.88 (m, 9H), 0.04 (s, 6H), 0.03 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.0, 159.0, 135.7, 134.2, 130.8, 129.6, 129.1, 127.6, 113.7, 74.4, 72.6, 69.3, 69.1, 68.6, 67.0, 66.2, 59.8, 57.0, 55.2, 47.1, 45.8, 40.3, 40.1, 39.0, 38.9, 36.4, 34.9, 28.0, 27.0, 25.9, 25.9, 19.3, 18.2, 18.1, 16.0, −4.4, −4.6, −5.3; IR (neat) 3066, 3046, 2943, 2854, 1704, 1606, 1512, 1458, 1419, 1360, 1237, 1104, 1035, 843 cm^{-1}; HRMS (FAB, NBA, Na^+) *m/e* calcd for $C_{55}H_{90}O_8Si_3Na$ (M^++Na) 985.5841, found 985.5839.

*5.1.22. (2R,4S,5S,8S)-8,10-Bis-(tert-butyldimethylsilanyloxy)-1-{(2R,4R,6S)-4-(tert-butyldiphenylsilanyloxy)-6-[2-(4-methoxybenzyloxy)ethyl]-tetrahydropyran-2-yl}-2-methoxy-5-methyldecan-4-ol (**56**).* Preparation of the Terashima reagent: a flame-dried, two-neck round bottom flask equipped with a reflux condenser was charged with lithium aluminum hydride (104 mg, 2.74 mmol). After diluting with Et_2O (3 mL), a solution of (−)-*N*-methylephedrine (491 mg, 2.74 mmol) in Et_2O (8 mL) was added slowly over 15 min. The suspension was heated to reflux and stirred for 1 h. *N*-Ethylaniline (690 mL, 5.48 mmol) was then added dropwise, and the suspension refluxed an additional hour. The finely dispersed, light gray reagent was cooled to ambient temperature, and was directly used as a suspension in ether.

To a cold (−78 °C) solution of ketone **51** (256 mg, 0.27 mmol) in Et_2O (2.66 mL) was added freshly prepared Terashima reagent (2.12 mL of a finely dispersed suspension in Et_2O, est. 0.53 mmol). The reaction mixture was stirred for 2 h at −78 °C, quenched with saturated aq $NaHCO_3$, and warmed to room temperature. The mixture was diluted with Et_2O (15 mL) and saturated aq $NaHCO_3$ (15 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (25 g SiO_2, 15% EtOAc/hexanes) to yield 244 mg (95%) of alcohol **56** as a clear, colorless oil: $[\alpha]_D^{22}$+4.1 (*c* 0.78, $CHCl_3$); R_f=0.43 in 30% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.62 (m, 4H), 7.45–7.33 (m, 6H), 7.26 (d, *J*=8.6 Hz, 2H), 6.86 (d, *J*=8.6 Hz, 2H), 4.43 (s, 2H), 4.20 (m, 1H), 4.08–3.97 (m, 2H), 3.79 (s, 3H), 3.79–3.74 (m, 1H), 3.71–3.62 (m, 3H), 3.57–3.53 (m, 3H), 3.31 (s, 3H), 1.81–1.13 (m, 14H), 1.08 (s, 9H), 0.89 (m, 21H), 0.05 (s, 3H), 0.04 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 135.7, 134.1, 130.6, 129.7, 129.1, 127.6, 113.7,

79.8, 74.9, 72.7, 69.7, 69.3, 68.5, 66.9, 66.1, 60.0, 56.0, 55.3, 40.2, 39.7, 39.4, 39.1, 39.0, 38.0, 36.3, 35.5, 28.3, 27.0, 25.9 (2), 19.3, 18.3, 18.1, 14.1, −4.3, −4.6, −5.3; IR (neat) 3484, 3071, 2933, 2849, 1625, 1586, 1517, 1468, 1419, 1350, 1261, 1084, 1045, 843 cm^{-1}; HRMS (FAB, NBA, Na^+) *m/e* calcd for $C_{55}H_{92}O_8Si_3Na$ (M^++Na) 987.5998, found 987.6254.

A small sample of **56** was characterized by conversion to its (*S*)-Mosher ester derivative upon reaction with (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (Aldrich) in $CDCl_3$ containing Et_3N and a crystal of 4-dimethylaminopyridine: ^1H NMR (400 MHz, $CDCl_3$) δ 7.66–7.30 (m, 15H), 7.24 (d, *J*=8.7 Hz, 2H), 6.86 (d, *J*=8.7 Hz, 2H), 5.19–5.14 (m, 1H), 4.42 (s, 2H), 4.20 (m, 1H), 4.12–4.01 (m, 2H), 3.79 (s, 3H), 3.76–3.69 (m, 1H), 3.64 (t, *J*=6.7, 6.7 Hz, 2H), 3.56–3.50 (m, 2H), 3.48 (s, 3H), 3.19–3.11 (m, 1H), 3.15 (s, 3H), 1.91 (ddd, *J*=14.2, 8.4, 5.8 Hz, 1H), 1.83–1.10 (m, 16H), 1.07 (s, 9H), 0.91–0.83 (m, 3H), 0.88 (s, 9H), 0.87 (S, 9H), 0.04 (s, 9H), 0.02 (s, 3H).

In similar fashion, a sample of **56** was converted into its (*R*)-Mosher ester via reaction with (*R*)-(−)-α-methoxy-α-trifluoromethylphenylacetyl chloride (Aldrich) and was characterized as follows: ^1H NMR (400 MHz, $CDCl_3$) δ 7.68–7.30 (m, 15H), 7.24 (d, *J*=8.6 Hz, 2H), 6.85 (d, *J*=8.7 Hz, 2H), 5.23–5.17 (m, 1H), 4.41 (s, 2H), 4.20 (s, 1H), 4.12–4.01 (m, 2H), 3.79 (s, 3H), 3.71–3.60 (m, 3H), 3.56–3.49 (m, 2H), 3.55 (s, 3H), 3.32–3.23 (m, 1H), 3.20 (s, 3H), 2.03–1.91 (m, 1H), 1.83–1.14 (m, 16H), 1.07 (s, 9H), 0.91–0.84 (m, 3H), 0.89 (s, 9H), 0.86 (s, 9H), 0.04 (s, 6H), 0.02 (s, 3H), 0.00 (s, 3H).

*5.1.23. (2R,4R,5S,8S)-8,10-Bis-(tert-butyldimethylsilanyloxy)-1-{(2R, 4R,6S)-4-(tert-butyldiphenylsilanyloxy)-6-[2-(4-methoxybenzyloxy) ethyl]-tetrahydropyran-2-yl}-2-methoxy-5-methyldecan-4-ol (**57**).* The Terashima reagent was prepared as described in the preparation of **56** except for the use of (+)-*N*-methylephedrine. Reaction with the ketone **51** (18 mg; 18.7 μmol) was carried out using the same conditions as indicated for **56**. Formation of a new diastereomer was observed (>95:5 ratio), and upon work up, the crude residue was purified by flash chromatography (10 g SiO_2, 15% EtOAc/hexanes) to yield 16.6 mg (92%) of alcohol **57** as a clear, colorless oil: R_f=0.35 in 30% EtOAc/hexanes; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67–7.60 (m, 4H), 7.46–7.32 (m, 6H), 7.26 (d, *J*=8.6 Hz, 2H), 6.86 (d, *J*=8.6 Hz, 2H), 4.44 (s, 2H), 4.20 (m, 1H), 4.10–3.97 (m, 2H), 3.80 (s, 3H), 3.81–3.76 (m, 1H), 3.70–3.60 (m, 4H), 3.59–3.51 (m, 2H), 3.32 (s, 3H), 3.23 (d, *J*=3.4 Hz, 1H), 1.90 (ddd, *J*=14.1, 8.7, 5.3 Hz, 1H), 1.81–1.10 (m, 16H), 1.08 (s, 9H), 0.89 (s, 18H), 0.86 (d, 6.8 Hz, 3H), 0.05 (s, 6H), 0.04 (s, 6H); IR (neat) 3481, 3070, 2933, 2848, 1625, 1585, 1516, 1464 cm^{-1}; HRMS (FAB, NBA, Na^+) *m/e* calcd for $C_{55}H_{92}O_8Si_3Na$ (M^++Na) 987.5998, found 987.6098.

5.1.24. Toluene-4-sulfonic acid (1S,2S,5S)-5,7-bis-(tert-butyldimethylsilanyloxy)-1-((S)-3-{(2R,4R,6S)-4-(tert-butyldiphenylsilanyloxy)-6-[2-(4-methoxybenzyloxy)ethyl]-tetrahydropyran-2-yl}-2-methoxypropyl)-2-methylheptyl ester. To a cold (0 °C) solution of alcohol **56** (120 mg, 0.24 mmol) in CH_2Cl_2 (1.24 mL) were added pyridine (80.0 μL, 0.99 mmol) and *p*-toluenesulfonic anhydride (81.0 mg, 0.25 mmol). The light brown reaction mixture was allowed to warm to ambient temperature and stirred for 30 min. The solution was diluted with Et_2O (15 mL) and saturated aq NH_4Cl (15 mL). The layers were separated, and the aqueous layer extracted with Et_2O (15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (7.5 g SiO_2, 15% EtOAc) to yield 140 mg (100%) of the tosylate of **56** as a thick, colorless oil: $[\alpha]_D^{22}$−1.2 (*c* 0.97, $CHCl_3$); R_f=0.30 in 20% EtOAc/hexanes; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J*=8.2 Hz, 2H), 7.66–7.63 (m, 4H), 7.43–7.33 (m, 6H), 7.30–7.24 (m, 4H), 6.86 (d, *J*=8.9 Hz, 2H), 4.70–4.67 (m, 1H), 4.42 (s, 2H), 4.22–4.19 (m, 1H), 4.07–4.02 (m, 2H), 3.80 (s, 3H), 3.69–3.61 (m, 3H), 3.55–3.51 (m, 2H), 3.33–3.30 (m, 1H), 3.22 (s, 3H), 2.41 (s, 3H), 1.99–1.92 (m, 1H), 1.81–1.71 (m, 3H), 1.67–1.51 (m, 6H), 1.41–1.32 (m, 2H), 1.30–1.18 (m, 5H), 1.09 (s, 9H), 0.90 (s, 9H), 0.87 (s, 9H), 0.84 (d, *J*=7.0 Hz, 3H), 0.05 (s, 6H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 144.2, 135.7, 134.8, 134.2, 134.1, 130.7, 129.7, 129.6, 129.1, 127.7, 127.6, 127.6, 113.7, 84.9, 74.5, 72.6, 69.4, 69.3, 68.6, 67.0, 66.1, 59.9, 56.0, 55.2, 40.0, 39.7, 38.9, 36.4, 36.3, 35.5, 35.4, 27.8, 27.0, 25.9, 25.9, 21.6, 19.3, 18.3, 18.0, 13.9, −4.4, −4.6, −5.3; IR (neat) 3071, 2933, 2854, 1615, 11,517, 1468, 1419, 1360, 1247, 1178, 1119, 1045, 902, 834 cm^{-1}; HRMS (FAB, NBA, Na^+) *m/e* calcd for $C_{62}H_{98}O_{10}SSi_3Na$ (M^++Na) 1141.6087, found 1141.6092.

*5.1.25. Toluene-4-sulfonic acid (1S,2S,5S)-1-((S)-3-{(2R,4R,6S)-4-(tert-butyldiphenylsilanyloxy)-6-[2-(4-methoxybenzyloxy)ethyl]-tetrahydropyran-2-yl}-2-methoxypropyl)-5,7-dihydroxy-2-methylheptyl ester (**58**).* Preparation of pyridinium hydrofluoride stock solution: to a nalgene container was added 2.0 g of pyridinium hydrofluoride (Aldrich), 4 mL of pyridine, and 16 mL of THF.

A solution of the tosylate (prepared from **56**) in THF (1.2 mL) was placed in a small plastic reaction vessel, and HF·pyr stock solution (6 mL) was added dropwise followed by stirring the reaction mixture for 16 h at ambient temperature. The acidic solution was neutralized to pH 7 with saturated aq $NaHCO_3$ (10 mL), and then diluted with Et_2O (15 mL). The layers were separated, and the aqueous layer extracted with Et_2O (15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (10 g SiO_2, 80–90% EtOAc/hexanes) to yield 89 mg (84%) of diol **58** as a thick colorless oil: $[\alpha]_D^{22}$−6.9 (*c* 0.45, $CHCl_3$); R_f=0.22 in 80% EtOAc/hexanes; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J*=8.2 Hz, 2H), 7.65–7.62 (m, 4H), 7.43–7.24 (m, 10H), 6.86 (d, *J*=8.9 Hz, 2H), 4.73 (ddd, *J*=6.1, 6.1, 3.1 Hz, 1H), 4.42 (s, 2H), 4.22–4.18 (m, 1H), 4.07–3.97 (m, 2H), 3.84–3.68 (m, 3H), 3.80 (s, 3H), 3.53–3.50 (m, 2H), 3.35–3.32 (m, 1H), 3.20 (s, 3H), 2.58 (s, 1H, −OH), 2.41 (s, 3H), 1.95–1.12 (m, 17H), 1.08 (s, 9H), 0.85 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 144.4, 135.7, 134.8, 134.2, 130.7, 129.7, 129.1, 127.7, 127.6, 113.8, 84.7, 74.6, 72.5, 71.8, 69.4, 68.4, 67.0, 66.1, 61.9, 55.9, 55.3, 39.4, 39.0, 38.9, 38.2, 36.3, 35.7, 35.5, 35.0, 27.8, 27.0, 21.6, 19.3, 14.2; IR (neat) 3400, 3061, 2948, 2864, 1615, 1522, 1473, 1429, 1350, 1242, 1163, 1104, 1035, 902, 804 cm^{-1}; HRMS (FAB, NBA, Na^+) *m/e* calcd for $C_{50}H_{70}O_{10}SSiNa$ (M^++Na) 913.4357, found 913.4388.

*5.1.26. 2-[(2S,5S,6R)-6-((R)-3-{(2R,4R,6S)-4-(tert-Butyldiphenylsilanyloxy)-6-[2-(4-methoxybenzyloxy)ethyl]-tetrahydropyran-2-yl}-2-methoxypropyl)-5-methyltetrahydropyran-2-yl]-ethanol (**59**).* To a solution of diol **58** (89 mg, 0.10 mmol) in benzene (10 mL) at ambient temperature was added NaH (20 mg of a 60% dispersion in mineral oil, 0.50 mmol). The suspension was heated to 60 °C, with stirring for 16 h. The cream-colored reaction mixture was cooled to room temperature and quenched with saturated aq NH_4Cl. The quenched reaction mixture was diluted with Et_2O (15 mL) and saturated aq NH_4Cl (15 mL). The layers were separated and the aqueous phase was extracted with Et_2O (15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (7.5 g SiO_2, 50% EtOAc) to yield 51 mg (71%) of alcohol **59** as a clear, colorless oil: $[\alpha]_D^{22}$+9.8 (*c* 0.95, $CHCl_3$); R_f=0.51 in 80% EtOAc/hexanes; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65–7.62 (m, 4H), 7.45–7.40 (m, 2H), 7.38–7.34 (m, 4H), 7.26 (d, *J*=8.2 Hz, 2H), 6.86 (d, *J*=8.2 Hz, 2H), 4.43 (s, 2H), 4.22–4.18 (m, 1H), 4.10–4.00 (m, 2H), 3.93–3.85 (m, 1H), 3.80 (s, 3H), 3.78–3.70 (m, 2H), 3.68–3.64 (m, 1H), 3.61–3.52 (m, 3H), 3.31 (s, 3H), 2.97–2.94 (m, 1H, −OH), 2.01–1.90 (m, 2H), 1.82–1.18 (m, 15H), 1.08 (s, 9H), 1.01 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 135.7, 134.2, 134.1, 130.7, 129.6, 129.1, 127.6, 113.7, 74.5, 73.0, 72.5, 70.1, 69.2, 68.6, 66.9, 66.2, 61.1, 56.3, 55.2, 39.4, 39.4, 38.9, 37.0, 36.3, 35.7, 33.2, 27.8, 27.0, 26.0, 19.3, 18.5;

IR (neat) 3439, 3056, 3046, 2933, 2864, 1610, 1507, 1463, 1424, 1360, 1247, 1109, 1050, 824 cm^{-1}; HRMS (FAB, NBA, NA^+) *m/e* calcd for $C_{43}H_{62}O_7SiNa$ (M^++Na) 741.4163, found 741.4147.

*5.1.27. [(2S,5S,6R)-((R)-3-{(2R,4R,6S)-4-(tert-Butyldiphenylsilanyloxy)-6-[2-(4-methoxybenzyloxy)ethyl]-tetrahydropyran-2-yl}-2-methoxypropyl)-5-methyltetrahydropyran-2-yl]acetaldehyde (**60**).* To a solution of alcohol **59** (51 mg, 71 μmol) in CH_2Cl_2 (1.0 mL) was added sodium bicarbonate (30 mg, 0.36 mmol) followed by the Dess–Martin periodinane (45 mg, 0.11 mmol). After allowing the solution to stir for 1 h at ambient temperature, the reaction mixture was quenched with saturated aq $Na_2S_2O_3$ (0.5 mL). The mixture was then diluted with Et_2O (15 mL) and saturated aq NH_4Cl (15 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (7.5 g SiO_2, 30% EtOAc/hexanes) to yield 49 mg (95%) of aldehyde **60** as a thick clear oil: $[\alpha]_D^{22}$+15 (*c* 0.85, $CHCl_3$); R_f=0.44 in 50% EtOAc/hexanes; ^1H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.66–7.63 (m, 4H), 7.43–7.33 (m, 6H), 7.26 (d, *J*=8.5 Hz, 2H), 6.86 (d, *J*=8.5 Hz, 2H), 4.44 (s, 2H), 4.40–4.34 (m, 1H), 4.20 (br s, 1H), 4.10–4.05 (m, 2H), 3.80 (s, 3H), 3.59–3.46 (m, 4H), 3.28 (s, 3H), 2.85 (d of A of ABX, J_{AB}=16.0 Hz, J_{AX}=9.0 Hz, *J*=3.0 Hz, 1H), 2.40 (d of AB of ABX, J_{AB}=16.0 Hz, J_{BX}=4.9 Hz, *J*=1.5 Hz, 1H), 1.77–1.23 (m, 15H), 1.08 (s, 9H), 0.96 (d, *J*=6.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.6, 159.0, 135.7, 134.2, 130.8, 129.6, 129.1, 127.6, 113.7, 74.1, 72.8, 72.6, 69.2, 68.5, 67.0, 66.7, 66.3, 56.7, 55.2, 46.4, 39.9, 39.4, 39.0, 38.2, 36.4, 33.8, 27.8, 27.0, 26.4, 19.3, 18.3; IR (neat) 3066, 2933, 2854, 2731, 1719, 1615, 1512, 1438, 1237, 1104, 1045, 824 cm^{-1}; HRMS (FAB, NBA, Na^+) *m/e* calcd for $C_{43}H_{60}O_7SiNa$ (M^++Na) 739.4006, found 739.4003.

*5.1.28. (E)-1-[(2S,5S,6R)-6-((S)-3-{(2R,4R,6S)-4-(tert-Butyldiphenylsilanyloxy)-6-[2-(4-methoxybenzyloxy)ethyl]-tetrahydropyran-2-yl}-2-methoxypropyl)-5-methyltetrahydropyran-2-yl]-6-methylhept-3-en-2-one (**61**).* To a solution of 4-methyl-1-pentyne (55.3 μL, 0.47 μmol) in CH_2Cl_2 (700 μL) at ambient temperature was added Schwartz's reagent (Cp_2ZrHCl; Aldrich) (121 mg, 470 μmol). The yellow reaction mixture was stirred for 10 min, and then cooled to −78 °C. Dimethylzinc (235 μL of a 2.0 M solution in CH_2Cl_2, 470 μmol) was added dropwise, and the solution stirred for 15 min at −78 °C. A solution of aldehyde **60** (38.6 mg, 47.0 μmol) in CH_2Cl_2 (300+200 μL) was added dropwise, and the reaction mixture warmed to 0 °C. After stirring for 1 h at 0 °C, the reaction mixture was quenched carefully with saturated aq NH_4Cl and warmed to room temperature. The suspension was diluted with Et_2O (25 mL), and filtered through a pad of Celite. The filtrate was washed with saturated aq NH_4Cl (25 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude allylic alcohol was filtered through a pad of silica gel (30% EtOAc), and taken on to the next step without purification.

To a solution of the crude allyl alcohol in CH_2Cl_2 (500 μL) at 22 °C were added sodium bicarbonate (18.0 mg, 0.22 mmol) and Dess–Martin periodinane (27.3 mg, 64.4 μmol). The mixture was stirred at ambient temperature for 1 h, and then saturated aq $Na_2S_2O_3$ was added dropwise. After stirring for 10 min, the solution was diluted with Et_2O (15 mL) and saturated aq NH_4Cl (15 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (4 g SiO_2, 20% EtOAc) to provide enone **61** (75%) as a clear, colorless oil: $[\alpha]_D^{22}$+9.1 (*c* 1.0, $CHCl_3$); R_f=0.57 in 50% EtOAc/hexanes; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66–7.63 (m, 4H), 7.43–7.33 (m, 6H), 7.26 (d, *J*=8.6 Hz, 2H), 6.86 (d, *J*=8.6 Hz, 2H), 6.82 (dt, *J*=15.9, 7.3 Hz, 1H), 6.11 (d, *J*=15.9 Hz, 1H), 4.43 (s, 2H), 4.37–4.30 (m, 1H), 4.20 (br s, 1H), 4.10–4.02 (m, 2H), 3.80 (s, 3H), 3.57 (t, *J*=6.7 Hz, 2H), 3.59–3.48 (m, 2H), 3.29 (s, 3H), 2.89 (A of ABX, J_{AB}=15.6 Hz, J_{AX}=6.4 Hz, 1H), 2.76 (B of ABX, J_{AB}=15.6 Hz, J_{BX}=7.0 Hz, 1H), 2.08 (dd, *J*=7.3, 7.3 Hz, 2H), 1.79–1.23 (m, 16H), 1.08 (s, 9H), 0.96 (d, *J*=6.1 Hz, 3H), 0.92 (d, *J*=6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.3, 159.0, 146.6, 135.7, 134.2, 131.7, 130.8, 129.6, 129.1, 127.6, 113.6, 74.2, 73.1, 72.6, 69.2, 68.5, 67.7, 67.1, 66.3, 57.0, 55.2, 43.3, 41.7, 40.2, 39.4, 39.0, 38.3, 36.4, 33.9, 27.9, 27.6, 26.6, 22.4, 19.3, 18.3; IR (neat) 3071, 3041, 2963, 2849, 1704, 1669, 1620, 1512, 1458, 1355, 1242, 1104, 1030, 814 cm^{-1}; HRMS (FAB, NBA, Na^+) *m/e* calcd for $C_{49}H_{70}O_7SiNa$ (M^++Na) 821.4789, found 821.4793.

*5.1.29. (E)-(R)-1-[(2S,5S,6R)-6-((R)-3-{(2R,4R,6S)-4-(tert-Butyldiphenylsilanyloxy)-6-[2-(4-methoxybenzyloxy)ethyl]-tetrahydropyran-2-yl}-2-methoxypropyl)-5-methyltetrahydropyran-2-yl]-6-methylhept-3-en-2-ol (**63**).* To a −10 °C solution of (*S*) CBS-oxazaborolidine **62** (62 μL of a 1.0 M solution in toluene, 62 μmol) in THF (200 μL) was added BH_3·THF (31 μL of a 1.0 M solution in THF, 31 μmol). The mixture was stirred for 10 min at −10 °C, and then a solution of enone **61** (24.8 mg, 31.0 μmol) in THF (400 μL) was added dropwise. The colorless reaction mixture was stirred for 10 min at −10 °C, and then quenched with water (200 μL). The biphasic mixture was stirred for 10 min while warming to room temperature, and then was diluted with Et_2O (10 mL) and saturated aq NaCl (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (4 g SiO_2, 30% EtOAc/hexanes) to yield 22.1 mg (89%) of allyl alcohol **63** as the major component of a 5:1 mixture of diastereomers. Purification by flash chromatography (4 g SiO_2, 20% EtOAc/hexanes, using two columns in sequence) allowed for the separation into two fractions; 16 mg (65%) of pure major diastereomer **63** and 6.1 mg (24%) of a mixture of C_{17} diastereomers, which were recycled via oxidation. Characterization data for the major diastereomer **63** is as follows: $[\alpha]_D^{24}$+11 (*c* 0.97, $CHCl_3$); R_f=0.50 in 50% EtOAc/hexanes; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65–7.62 (m, 4H), 7.44–7.33 (m, 6H), 7.26–7.24 (m, 2H), 6.87–6.84 (m, 2H), 5.65 (ddd, *J*=15.6, 7.0, 7.0 Hz, 1H), 5.49 (dd, *J*=15.6, 6.4 Hz, 1H), 4.43 (s, 2H), 4.38–4.30 (m, 1H), 4.20 (m, 1H), 4.10–3.98 (m, 3H), 3.80 (s, 3H), 3.64–3.54 (m, 4H), 3.32 (s, 3H), 2.94 (d, *J*=4.3 Hz, 1H), 1.95–1.84 (m, 4H), 1.80–1.20 (m, 16H), 1.08 (s, 9H), 1.00 (d, *J*=6.4 Hz, 3H), 0.87 (d, *J*=6.7 Hz, 3H), 0.86 (d, *J*=6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.0, 135.7, 134.2, 134.2, 130.7, 129.6, 129.5, 129.1, 127.6, 113.7, 74.8, 73.2, 72.5, 69.2, 69.0, 68.6, 67.4, 66.9, 66.3, 56.6, 55.3, 41.6, 40.4, 39.5, 39.4, 39.0, 37.3, 36.3, 33.5, 28.2, 27.6, 27.0, 26.2, 22.4, 22.2, 19.3, 18.5; IR (neat) 3435, 3061, 2938, 2854, 1748, 1606, 1517, 1458, 1424, 1252, 1109, 1035, 824 cm^{-1}; HRMS (FAB, NBA, Na^+) *m/e* calcd for $C_{49}H_{72}O_7Si$ (M^++Na) 823.4945, found 823.4977.

*5.1.30. Acetic acid (R)-(E)-1-[(2S,5S,6R)-6-((R)-3-{(2R,4R,6S)-4-(tert-butyldiphenylsilanyloxy)-6-[2-(4-methoxybenzyloxy)ethyl]-tetrahydopyran-2-yl}-2-methoxypropyl]-5-methyltetrahydropyran-2-ylmethyl)-5-methylhex-2-enyl ester (**64**).* To a solution of alcohol **63** (16.0 mg, 20.0 μmol) in CH_2Cl_2 (200 μL) were added pyridine (6.5 μL, 80 μmol), acetic anhydride (4.0 μL, 40 μmol), and a catalytic amount of 4-(dimethylamino)pyridine (two crystals). The reaction mixture was stirred for 16 h at ambient temperature, and then diluted with Et_2O (10 mL) and saturated aq NH_4Cl (10 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (2.5 g SiO_2, 20% EtOAc) to yield 16.3 mg (97%) of acetate **64** as a clear, colorless oil: $[\alpha]_D^{22}$+32 (*c* 0.93, $CHCl_3$); R_f=0.50 in 40% EtOAc/hexanes; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66–7.62 (m, 4H), 7.43–7.33 (m, 6H), 7.26 (d, *J*=8.6 Hz, 2H), 6.86 (d, *J*=8.6 Hz, 2H), 5.70 (ddd, *J*=14.6, 7.3, 7.3 Hz, 1H), 5.43–5.31 (m, 2H), 4.42

(s, 2H), 4.19 (m, 1H), 4.11–4.04 (m, 2H), 3.89–3.83 (m, 1H), 3.80 (s, 3H), 3.64–3.56 (m, 3H), 3.51–3.47 (m, 1H), 3.38 (s, 3H), 2.02 (s, 3H), 2.08–1.97 (m, 1H), 1.93–1.86 (m, 2H), 1.82–1.22 (m, 17H), 1.08 (s, 9H), 0.94 (d, J=5.8 Hz, 3H), 0.86 (d, J=6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 159.0, 135.7, 135.7, 134.3, 134.2, 132.7, 130.9, 129.7, 129.6, 129.1, 127.6, 113.7, 73.8, 72.6, 71.9, 71.6, 69.2, 68.1, 67.3, 67.3, 66.4, 56.5, 55.3, 41.5, 39.6, 39.4, 39.0, 38.6, 36.8, 36.5, 34.6, 28.1, 28.1, 27.0, 26.9, 22.2, 22.2, 21.4, 19.3, 18.4; IR (neat) 3076, 2943, 2854, 1724, 1620, 1507, 1473, 1424, 1360, 1232, 1114, 1035, 819 cm^{-1}; HRMS (FAB, NBA, Na$^+$) m/e calcd for $C_{51}H_{74}O_8SiNa$ (M^++Na) 865.5051, found 865.5089.

5.1.31. Acetic acid (R)-(E)-1-((2S,5S,6R)-6-{(R)-3-[(2R,4R,6S)-4-(tert-butyldiphenylsilanyloxy)-6-(2-hydroxyethyl)tetrahydropyran-2-yl]-2-methoxypropyl}-5-methyltetrahydropyran-2-ylmethyl)-5-methylhex-2-enyl ester. To a solution of the PMB ether **64** (18.5 mg, 21.9 μmol) in CH_2Cl_2 (1.8 mL), pH 7 phosphate buffer (450 μL), and *tert*-butanol (45 μL) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (14.9 mg, 65.8 μmol). The reaction mixture was stirred for 1.5 h at ambient temperature, and then diluted with Et_2O (15 mL). The organic solution was washed with water (2×10 mL) and saturated aq $NaHCO_3$ (15 mL). The combined aqueous layers were extracted with Et_2O (15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (2.5 g SiO_2, 30% EtOAc) to yield 16.1 mg (100%) of primary C_1-alcohol from **64** as a clear, colorless oil: $[\alpha]_D^{22}$+32 (*c* 0.79, $CHCl_3$); R_f=0.41 in 50% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.63 (m, 4H), 7.44–7.34 (m, 6H), 5.70 (ddd, J=15.3, 7.3, 7.3 Hz, 1H), 5.41 (dd, J=15.3, 7.0 Hz, 1H), 5.34–5.29 (m, 1H), 4.20 (m, 1H), 4.16–4.11 (m, 1H), 4.08–4.04 (m, 1H), 3.98–3.92 (m, 1H), 3.86–3.76 (m, 1H), 3.74–3.62 (m, 2H), 3.50–3.43 (m, 1H), 3.39 (s, 3H), 3.27–3.22 (m, 1H), 2.11–1.99 (m, 1H), 2.03 (s, 3H), 1.90 (t, J=7.0 Hz, 2H), 1.84–1.74 (m, 2H), 1.72–1.22 (m, 15H), 1.08 (s, 9H), 0.92 (d, J=6.1 Hz, 3H), 0.86 (d, J=6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 135.7, 134.2, 132.8, 129.6, 127.6, 73.8, 71.7, 71.5, 70.5, 68.9, 67.9, 66.3, 59.5, 56.4, 41.5, 39.3, 39.0, 39.0, 38.4, 37.9, 35.9, 35.2, 28.4, 28.1, 27.1, 27.0, 22.2, 22.2, 21.3, 19.3, 18.2; IR (neat) 3430, 3066, 2933, 2864, 1748, 1620, 1463, 1424, 1384, 1252, 1119, 1040, 819 cm^{-1}; HRMS (FAB, NBA, Na$^+$) m/e calcd for $C_{43}H_{66}O_7SiNa$ (M^++Na) 745.4476, found 745.4499.

5.1.32. Acetic acid (R)-(E)-1-((2S,5S,6R)-6-{(R)-3-[(2R,4S,6R)-4-(tert-butyldiphenylsilanyloxy)-6-(2-oxoethyl)tetrahydropyran-2-yl]-2-methoxypropyl}-5-methyltetrahydropyran-2-ylmethyl)-5-methylhex-2-enyl ester. To a solution of alcohol, prepared from **64** as described above, (15.8 mg, 21.9 μmol) in CH_2Cl_2 (300 μL) were added sodium bicarbonate (9.2 mg, 0.11 mmol) and Dess–Martin periodinane (13.9 mg, 32.8 μmol). The mixture was stirred for 1.5 h at ambient temperature, and then quenched with saturated aq $Na_2S_2O_3$. After stirring for an additional 10 min, the mixture was then diluted with Et_2O (15 mL) and saturated aq NH_4Cl (15 mL). The layers were separated and the aqueous layer extracted with Et_2O (15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (3.5 g SiO_2, 20% EtOAc) to yield 15.6 mg (99%) of the corresponding aldehyde as a clear, colorless oil: $[\alpha]_D^{22}$+34 (*c* 0.71, $CHCl_3$); R_f=0.67 in 50% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (t, J=2.4 Hz, 1H), 7.66–7.63 (m, 4H), 7.45–7.35 (m, 6H), 5.69 (ddd, J=14.7, 7.0, 7.0 Hz, 1H), 5.40 (dd, J=14.7, 7.0 Hz, 1H), 5.37–5.31 (m, 1H), 4.49–4.43 (m, 1H), 4.21–4.13 (m, 2H), 3.90–3.85 (m, 1H), 3.64–3.61 (m, 1H), 3.48–3.44 (m, 1H), 3.37 (s, 3H), 2.46 (d of A of ABX, J_{AB}=16.0 Hz, J_{AX}=8.8 Hz, J=3.0 Hz, 1H), 2.34 (d of B of ABX, J_{AB}=16 Hz, J_{BX}=4.3 Hz, J=2.1 Hz, 1H), 2.05–1.98 (m, 1H), 2.02 (s, 3H), 1.78–1.25 (m, 15H), 1.09 (s, 9H), 0.93 (d, J=6.1 Hz, 3H), 0.86 (d, J=6.4 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.2, 170.1, 135.7, 134.0, 132.6, 129.7, 127.6, 73.7, 71.9, 71.5, 68.4, 67.6, 67.4, 66.0, 56.5, 49.6, 41.5, 39.1, 39.1, 38.7, 38.6, 36.7, 34.7, 28.2, 28.1, 27.0, 26.9, 22.2, 22.2, 21.3, 19.2, 18.3; IR (neat) 3071, 2943, 2859, 2717, 1724, 1620, 1463, 1438, 1355, 1227, 1099, 1025, 819 cm^{-1}; HRMS (FAB, NBA, Na$^+$) m/e calcd for $C_{43}H_{64}O_7SiNa$ (M^++Na) 743.4319, found 743.4336.

*5.1.33. [(2R,4S,6R)-6-{(S)-3-[(2R,3R,6S)-6-((R)-(E)-2-Acetoxy-6-methyhept-3-enyl)-3-methoxytetrahydropyran-2-yl]-2-methylpropyl}-4-(tert-butyldiphenylsilanyloxy)-tetrahydropyran-2-yl] acetic acid (**65**).* To a cold (0 °C) solution of aldehyde (prepared above) (15.6 mg, 21.6 μmol) in a mixture of CH_3CN *tert*-butanol (400 μL; 1:1 by volume) was added 2-methyl-2-butene (79 μL) and 135 μL of a pre-mixed oxidant solution (prepared by dissolving 35.2 mg sodium chlorite and 41.4 mg sodium dihydrogen phosphate in 270 μL of water). The reaction mixture was stirred for 30 min at 0 °C, and then diluted with Et_2O (10 mL). The organic solution was washed with water (15 mL), saturated aq $Na_2S_2O_3$ (10 mL), and saturated aq NaCl (10 mL). The combined aqueous layers were extracted with Et_2O (2×15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (2.5 g SiO_2, 40% EtOAc) to yield 8.9 mg (56%) of carboxylic acid **65** as a clear, colorless oil: $[\alpha]_D^{22}$+39 (*c* 0.45, $CHCl_3$); R_f=0.43 in 50% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.62 (m, 4H), 7.45–7.35 (m, 6H), 5.73 (ddd, J=14.3, 7.3, 7.3 Hz, 1H), 5.45–5.35 (m, 2H), 4.34–4.30 (m, 1H), 4.19 (m, 1H), 4.02–3.97 (m, 2H), 3.66–3.61 (m, 1H), 3.46–3.42 (m, 1H), 3.37 (s, 3H), 2.44–2.33 (m, 2H), 2.21–2.15 (m, 1H), 2.10 (s, 3H), 1.90 (t, J=7.0 Hz, 2H), 1.87–1.25 (m, 15H), 1.08 (s, 9H), 0.89 (d, J=5.8 Hz, 3H), 0.86 (d, J=6.4 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 171.8, 135.7, 134.0, 133.9, 132.8, 129.8, 129.7, 129.5, 127.7, 127.6, 73.7, 71.9, 71.2, 69.4, 69.1, 67.9, 65.9, 56.3, 41.5, 41.3, 40.3, 39.4, 39.1, 38.3, 35.6, 35.4, 28.7, 28.0, 27.4, 22.3, 22.2, 21.5, 19.2, 18.3; IR (neat) 3366 (br), 3081, 2953, 1738, 1635, 1453, 1433, 1374, 1227, 1124, 1040 cm^{-1}; HRMS (FAB, NBA, Na$^+$) m/e calcd for $C_{43}H_{64}O_8SiNa$ (M^++Na) 759.4269, found 759.4268.

*5.1.34. (1R,3R,5R,7S,9R,13R,15S,18S)-7-(tert-Butyldiphenylsilanyloxy)-3-methoxy-18-methyl-13-((E)-4-methylpent-1-enyl)-12,19,20-trioxatricyclo[13.3.1.1^{0,0}]eicosan-11-one (**66**).* To a solution of carboxylic acid **65** (8.9 mg, 12.1 μmol) in MeOH (1.2 mL) was added potassium carbonate (109 mg, 0.79 mmol). The suspension was stirred for 16 h at ambient temperature, and then diluted with pH 4 buffer (10 mL). The aqueous solution was extracted with EtOAc (3×10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The seco-acid (C_{17} hydroxy of **65**) was carried onto the next step without additional purification.

To a solution of the seco-acid in benzene (120 mL) were added triethylamine (0.10 mL, 0.75 mmol), 2,4,6-trichlorobenzoyl chloride (79 μL, 0.51 mmol), and 4-(dimethylamino)pyridine (15 mg, 0.12 mmol). The reaction mixture was stirred for 1 h at ambient temperature, and then more DMAP (15 mg, 0.12 mmol) was added. The solution was then stirred for 20 h, and subsequently quenched with aqueous 0.1 M $NaHSO_4$ (100 mL). The aqueous solution was extracted with CH_2Cl_2 (2×100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (2.5 g SiO_2, 15% EtOAc) to yield 5.2 mg (63% for two steps) of macrolactone **66** as a colorless film: $[\alpha]_D^{22}$+44 (*c* 0.26, $CHCl_3$); R_f=0.59 in 50% EtOAc/hexanes; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65–7.63 (m, 4H), 7.46–7.35 (m, 6H), 5.72 (ddd, J=15.0, 7.07.0 Hz, 1H), 5.41 (dd, J=15.0, 6.7 Hz, 1H), 5.38–5.32 (m, 1H), 4.36–4.26 (m, 2H), 3.95–3.90 (m, 3H), 3.67 (t, J=10.4 Hz, 1H), 3.54 (t, J=10.4 Hz, 1H), 3.34 (s, 3H), 2.52–2.44 (m, 2H), 2.28–2.22 (m, 1H), 2.00–1.24 (m, 15H), 1.19 (d, J=7.0 Hz, 3H), 1.11 (s, 9H), 1.10–1.00 (m, 2H), 0.86 (d, J=6.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 135.6, 135.6, 134.0, 132.1, 130.2, 129.9, 129.8, 127.7, 73.6, 73.5, 70.7, 69.5, 69.4, 66.3, 63.2, 57.3, 43.2, 43.1, 41.6, 39.0, 38.6, 38.6, 35.6, 30.9, 28.1, 27.2, 27.0, 24.1, 22.3, 19.4, 18.2; IR (neat) 3066, 2948, 2849, 1738, 1655, 1556, 1468, 1419, 1261, 1109,

1060, 1045, 834 cm^{-1}; HRMS (FAB, NBA, Na^+) *m/e* calcd for $C_{41}H_{60}O_6SiNa$ (M^++Na) 699.4057, found 699.4085.

*5.1.35. Leucascandrolide A macrolactone (**2**).* To a solution of the silyl ether **66** (10.4 mg, 15.2 μmol) in THF (250 μL) was added TBAF (200 μL of a 1.0 M solution in THF). The light brown solution was stirred for 16 h at ambient temperature, and then diluted with EtOAc (15 mL) and saturated aq NaCl (15 mL). The layers were separated, and the aqueous layer extracted with EtOAc (15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (1 g SiO_2, 60% EtOAc/hexanes) to give 4.4 mg (67%) of the Leucascandrolide A macrolactone **2**, which was characterized as follows: $[\alpha]_{D^{20}}$ +23 (*c* 0.22, EtOH), lit.[2] $[\alpha]_D^{20}$+24 (*c* 0.05, EtOH); R_f=0.17 in 60% EtOAc/hexanes; ^1H NMR (500 MHz, C_5D_5N) δ 6.38 (s, 1H, −OH), 5.82–5.74 (m, 2H), 5.56 (dd, *J*=15.9, 6.9 Hz, 1H), 4.65 (app t, *J*=11.4 Hz, 1H), 4.43 (m, 1H), 4.19 (t, *J*=11.4 Hz, 1H), 4.07 (d, *J*=11.6 Hz, 1H), 3.94 (t, *J*=10.7 Hz, 1H), 3.76 (t, *J*=10.9 Hz, 1H), 3.39 (s, 3H), 2.69 (ABq, *J*=13.0, 3.7 Hz, 1H), 2.54–2.47 (m, 2H), 2.15–2.10 (m, 1H), 1.96–1.83 (m, 5H), 1.76–1.61 (m, 3H), 1.55–1.48 (m, 2H), 1.44–1.18 (5H), 1.09 (d, *J*=7.0 Hz, 3H), 1.10–1.02 (m, 1H), 0.80 (d, *J*=6.6 Hz, 3H), 0.79 (d, *J*=6.6 Hz, 3H); ^{13}C NMR (101 MHz, C_5D_5N) δ 170.3, 131.9, 131.6, 73.9 (2C), 70.9, 69.9, 69.7, 63.8, 63.2, 56.7, 44.0, 43.4, 41.8, 40.0, 39.7, 39.5, 35.9, 31.4, 28.3, 27.4, 24.3, 22.3 (2C), 18.5; IR (neat) 3420, 2963, 2869, 1738, 1460, 1389, 1281, 1188, 1153, 1084, 1060 cm^{-1}; MS (DEI) 438 (6), 329 (21), 208 (11), 165 (15), 159 (40), 142 (24), 121 (10), 111 (30), 95 (64), 93 (45), 87 (29), 81 (60), 79 (56), 71 (33); HRMS *m/e* calcd for $C_{25}H_{42}O_6$ (M^+) 438.2961, found 438.2961. The comparisons of our data with those reported by Leighton and co-workers[5a] for **2** confirms these materials as identical.

Acknowledgements

The authors gratefully acknowledge the National Institutes of Health (GM042897) for the generous support of our work.

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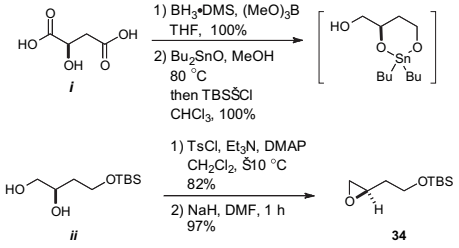

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