Asymmetric Synthesis of Calyculin C. 1. Synthesis of the C_1−C_{25} Fragment

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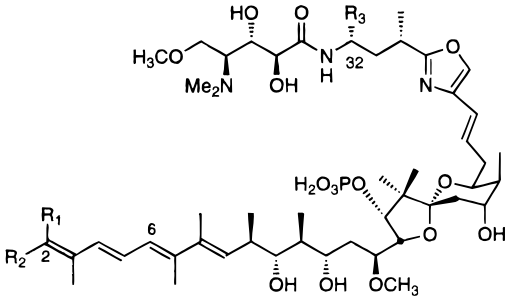
We report our synthesis of the C_1−C_{25} fragment of serine/threonine phosphatase PP1 and PP2A inhibitor, calyculin C. Synthetic efforts were directed initially toward the synthesis of a spiroketal core fragment (**7**), which culminated in completion of the bottom half of the natural product. The synthesis of fragment **7** and subsequent elaboration relied on an allylboration strategy for introduction of chirality. The C_1−C_8 fragment representing the potentially unstable tetraene moiety was introduced as a separate entity.

Introduction

The calyculins represent a novel class of secondary metabolites isolated from the marine sponge *Discodermia calyx* which was collected in the Sea of Sagami off the coast of Japan.[3] This unique class of compounds is represented by eight different related structures which vary by substitution at C_{32} and by the olefin geometry of the tetraene moiety[3c] (see Figure 1). Ishihara and others have shown that one of these metabolites, calyculin A, is a selective inhibitor of serine/threonine phosphatases PP1 and PP2A (2.0 and 1.0 nM, respectively), two of the four main classes of phosphatases in the cytosol of human cells.[4] The relative stereochemistry of calyculin A was established by X-ray crystallography. The absolute stereochemistry was subsequently elucidated by Hamada and Shiori through the synthesis of a C_{33}−C_{37} acid fragment that was identical by ^{1}H NMR but opposite in its specific rotation to a degradation product isolated from a mixture of calyculins A, B, E, and F.[5] Work done by Fusetani[3b] has suggested identical solution conformations for both calyculins A and C. By the use of an NOE correlation involving the C_{30}−N_3 portion of each natural product, Fusetani[3b] has assigned the relative stereochemistry of the C_{32}-methyl in calyculin C. Both calyculins A and C have similar potency in starfish *Asterina pectinifera*, sea urchin *Hemicetrotus pulcherrimus*, and L1210 leukemia assays. Within this family of PP1 and PP2A inhibitors are the microcystins,[6] nodularin,[7] motuporin,[8] tautomycin,[9] and okadaic acid.[10]



		R_1	R_2	R_3	C_6-geometry
calyculins	**A:**	CN	H	H	E
	B:	H	CN	H	E
	C:	CN	H	CH_3	E
	D:	H	CN	CH_3	E
	E:	CN	H	H	Z
	F:	H	CN	H	Z
	G:	CN	H	CH_3	Z
	H:	H	CN	CH_3	Z

Figure 1.

Our interest in the synthesis of calyculin C stems from ongoing work toward the synthesis, structure−activity relationships (SAR), and conformational studies involving tautomycin and nodularin. Using a combination of molecular modeling and 2D-NMR analysis, we have derived an overlay of the proposed ground state structures of calyculin, tautomycin, microcystin, nodularin, and okadaic acid in an effort to understand the common structural motifs associated with these diverse natural products. The recent elucidation of the X-ray structure of a cocrystal of PP1 and microcystin should provide assistance in developing a comprehensive analysis of these inhibitors.[11]

Related to our specific interest in calyculin C, the C_{17}-phosphate provides a unique structural motif that organizes the hydrogen-bonding network of the compound that greatly influences its tertiary structure. This structural motif is exhibited through X-ray structural[3a] and 2D-NMR analysis. The synthesis of the natural product, in addition to salient analogs, would be of great interest in our efforts toward understanding the enzymes.

Retrosynthesis

Retrosynthetic analysis of the calyculin backbone revealed several possibilities for disconnection involving

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(1) Taken in part from the Ph.D. Thesis of Gerard R. Scarlato, University of California, Los Angeles, 1990.

(2) Taken in part from the Ph.D. Thesis of John A. DeMattei, University of California, Los Angeles, 1994.

(3) (a) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Fujita, S.; Furuya, T. *J. Am. Chem. Soc.* **1986**, *108*, 2780. (b) Kato, Y.; Fusetani, N.; Matsunaga, S.; Hashimoto, K.; Koseki, K. *J. Org. Chem.* **1988**, *53*, 3930. (c) Matsunaga, S.; Fujiki, H.; Sakata, D. *Tetrahedron* **1991**, *47*, 2999.

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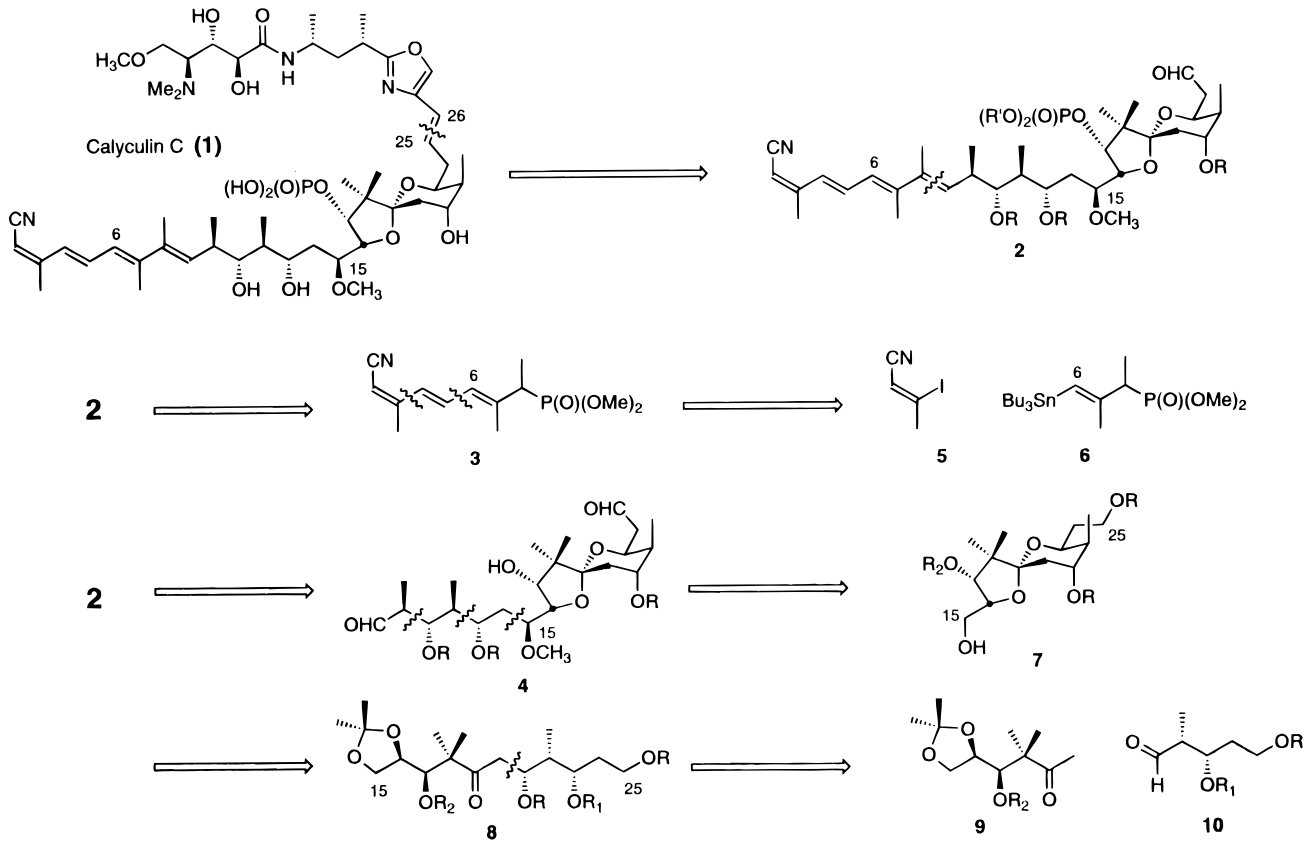
Scheme 1



carbon−carbon bonds. Our strategy centered on an initial disconnection at the $C_{25}-C_{26}$ double bond which divided the natural product into two halves of similar functional density. Coupling at this junction was perceived to provide the most convergent synthetic approach, a strategy which was employed in our initial model studies.[12] This approach paralleled other synthetic efforts, most notably the two completed syntheses of calyculin A.[13,14] In maintaining our desired degree of convergence, a synthetic design addressing the C_1-C_{25} fragment **2** as a whole was adopted.

Several functionalities within the C_1-C_{25} bottom half strongly influenced our synthetic plan (Scheme 1). The C_{17}-phosphate, which is resistant toward chemical and enzymatic hydrolysis, required the judicious choice of blocking groups. Our plan, therefore, called for incorporation of the phosphate downstream in the overall synthesis. Equal consideration was given to the potential instability toward isomerization of the C_1-C_9 cyanotetraene moiety.[15] This potential photolability and reactivity toward oxygen prompted the disconnection at the C_8-C_9 olefin, thereby allowing for its late introduction into the synthesis of the bottom half of the molecule. The above primary concerns gave a C_9-C_{25} polyhydroxylated spiroketal fragment as the initial target compound in the synthesis of the C_1-C_{25} portion of calyculin. Dissection of the C_9-C_{25} system yielded two primary components: the $C_{15}-C_{25}$ spiroketal fragment **7** whose synthesis was pivotal for success and the C_9-C_{14} polypropionate side chain which was foreseen as resulting from homologation of spiroketal **7** *via* stereoselective allylborations. Consideration of the spiroketal core focused on a concerted spirocyclization reaction derived from fully protected open chain precursor **8**. Such a strategy led to the identification of the $C_{20}-C_{21}$ bond as an aldol retron which afforded a high degree of stereochemical control with respect to C_{21}.[16]

Examination of the spiroketal core suggested a requirement for orthogonality with respect to four sets of hydroxyl protecting groups. The C_{21}-hydroxyl protecting group assumed a critical role in an overall strategy based on a final deprotection step in the total synthesis. The desire to reserve the C_{16}- and C_{23}-hydroxyls as latent members of the spiroketal suggested the choice of mild acid-labile protecting groups to accommodate a sequential

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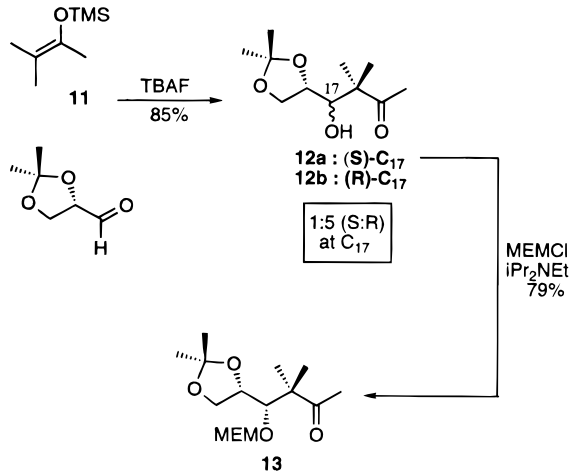
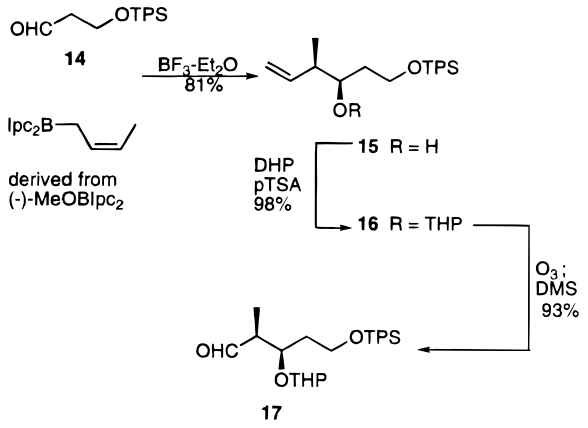
Scheme 2



Scheme 3

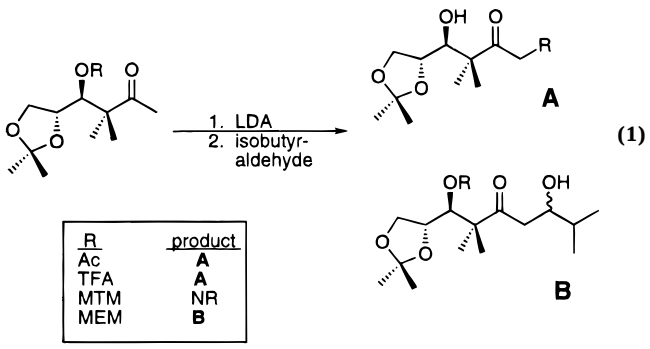


deprotection−cyclization reaction. C_{17}-Hydroxyl protection was designed to allow for its downstream removal and introduction of the phosphate moiety. Finally, the nature of the C_{25}-oxidation state and subsequent protection was considered. Early results supported the use of a protected C_{25}-alcohol[1] in the synthesis of the C_1-C_{25} fragment.

Synthesis of the *ent*-Spiroketal Core Fragment ($C_{15}-C_{25}$)

At the outset of our efforts toward the total synthesis of calyculin, the absolute configuration had not yet been established for the natural product.[5] Although initial studies resulted in the stereospecific synthesis of the enantiomer of the desired $C_{15}-C_{25}$ spiroketal fragment,[1] it nonetheless laid a foundation for future work.

The synthesis of **13** was initiated by condensation of silyl enol ether **11**[17] with 2,3-*O*-isopropylidene-L-glyceraldehyde.[18] The reaction proceeded under Felkin−Ahn stereochemical control,[19] affording the desired ketone **12a** as the minor product (Scheme 2). The reaction of model ketones bearing varying protecting groups at the C_{17}-hydroxyl with isobutyraldehyde led to the choice of (2-methoxyethoxy)methyl (MEM) (eq 1). The MEM group



(1)

was found to be stable to the Lewis acid ($ZnBr_2$) conditions used for spirocyclization. Extended reaction times and greater stoichiometries of Lewis acid resulted in the loss of MEM in spiroketal containing substrates.

The synthesis of aldehyde **17** was founded on a stereoselective allylboration strategy (Scheme 3). Addition of an allylborane derived from (−)-*B*-methoxydiisopinocampheylborane (MeOB(Ipc)$_2$) to propionaldehyde **14** at −78 °C in the presence of $BF_3{\cdot}Et_2O$ afforded homoallylic alcohol **15** as a single diastereomer in high yield after DMS workup.[20] The issue of C_{23}-hydroxyl protection proved significant as the eventual open chain $C_{15}-C_{25}$ fragment was likely to possess great diversity in terms of protection functionality.

Model experiments on various blocking groups suggested that tetrahydropyran (THP) would provide an ideal choice for C_{23}-protection. Although the choice of THP complicated NMR analysis of subsequent products, its mild acid lability accommodated a strategy employing deprotection conditions as a means of effecting spirocyclization in a two-reaction−one-step process. The choice of *tert*-butyldiphenylsilyl (TPS) as the C_{25}-hydroxyl protecting group was again made on the basis of experimental work on model compounds and its compatibility with our overall protecting group scheme. Preliminary work revealed that 4-methoxybenzyl (PMB) failed to survive the proposed Lewis acid spirocyclization conditions, while the TPS system remained intact. We also felt that the selective removal of a TPS protecting group on a 1° alcohol in the presence of 2° benzoyl or silyl groups was in accord with literature precedent.[21]

The aldol coupling of ketone **13** with aldehyde **17** proceeded in acceptable yield and with excellent stereoselectivity (10:1). Similar high selectivity was also observed in a condensation used by Kishi in the synthesis of monensin.[16] Stereochemical assignments were conclusively made post-spirocyclization due to complications arising from the THP group in the acyclic precursors. Other substrates bearing different C_{17}- and/or C_{23}-hydroxyl protecting groups did not condense or showed a low degree of diastereoselectivity. Spirocyclization was achieved in excellent yield by treatment of ketone **17** with $ZnBr_2$ at room temperature (Scheme 4). In this one-pot transformation, the THP and isopropylidene moieties were concomitantly removed, and the ketone was converted to a ketal. The resulting product contained only a single free hydroxyl to be used in elaboration of the side chain. It should be noted that attempted cyclization with a free C_{21}-hydroxyl led to isolation of β-eliminated starting material, limiting the variability with regard to choice of substrate. The stereochemical integrity of the spiroketal product **19** was verified by extensive NOE difference analysis.[22] Discussion of the relevant NOE

(17) Noyori, R.; Yokoyama, K.; Sakata, J. *J. Am. Chem. Soc.* **1977**, *99*, 1265.
(18) Hubschwerlen, C.; Specklin, J-L. *Org. Synth.* **1993**, *72*, 1.
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(20) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919 and references cited therein.
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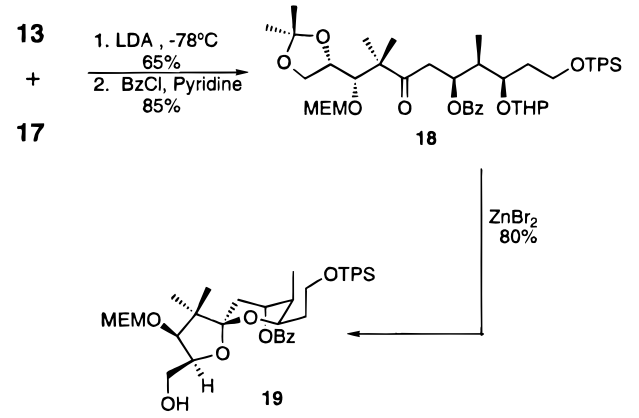
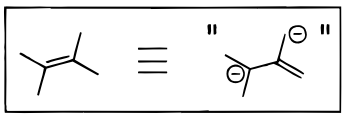
Scheme 4



assignments relating to proof of structure will be presented below.

Construction of the C_{15}–C_{25} Spiroketal Core

Elucidation of the absolute stereochemistry of the calyculins[5] necessitated the synthesis of spiroketal **26** which was enantiomeric with respect to **19**. The route to **19** suffered two potential drawbacks: (1) the aldol reaction to afford **12a** yielded the undesired diastereomer as the major product and (2) the yield of the second aldol to generate **18** was mediocre. We believed that both issues would be redressed by the use of allylboration technology. To this end, we sought to develop methodology that utilized the potentially novel dianion equivalent of tetramethylethylene in our spiroketal synthesis. Although formation of allylboranes from several substituted allyl systems had been reported, no examples had employed a tetrasubstituted olefin. This offered a significant opportunity to expand on current methodology.[23] Tetramethylethylene provided a unique synthon in that the product from the first allylboration could be used to generate a second boronane derived from a symmetric allylic anion (eq 2). Success to this end would result in the head and tail homologation of a previously unfunctionalized allylic system, a method that could prove general in its application to other targets containing a *gem*-dimethyl moiety.



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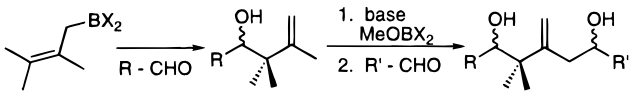
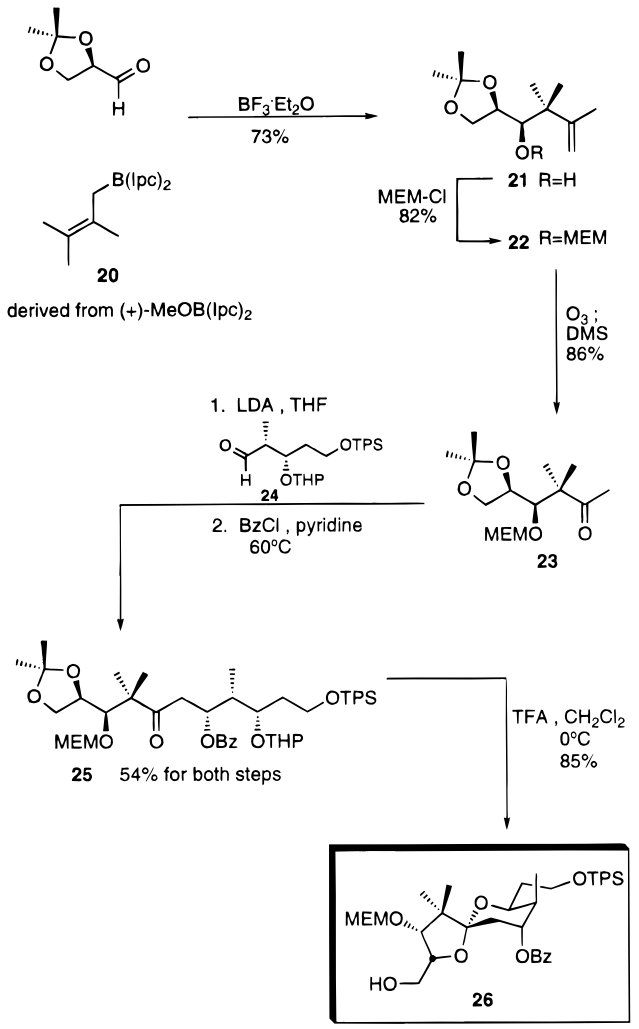


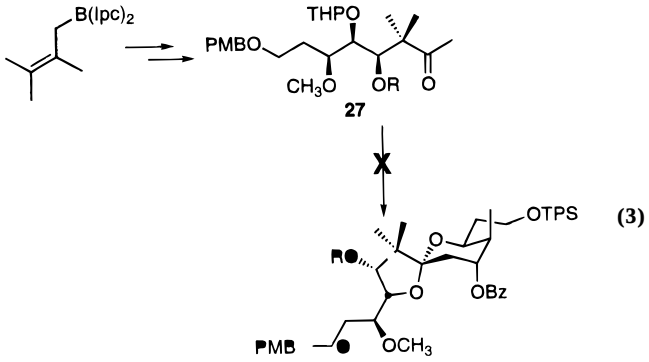
Addition of allylborane **20** to 2,3-*O*-isopropylidene-D-glyceraldehyde[24] afforded alcohol **21** in high yield and with excellent stereoselectivity (Scheme 5). When the enantiomeric ligand was reacted with the above aldehyde, excellent diastereoselectivity and yields were also observed in spite of the substrate–borane mismatch.[20] This is in stark contrast to the unsubstituted allylborane reagent where the mismatched case gave only about 80%

Scheme 5



de (results not included). Bromination of **22** readily afforded the allylic bromide. However, we were unable to generate an allylic anion for subsequent condensations. Even attempted conversion to other organometallic reagents (Mg, e.g.) failed to provide condensation products with simple aldehydes.

A significant effort was also made to enhance the convergence of the overall synthesis by targeting ketone **27** as a means of limiting the number of linear steps in elaboration of the polypropionate chain attached to the ketal (eq 3). The aldol condensation of **27** proved



(3)

problematic, and difficulties in generating the appropriate allylborane species from derivatives of **21** necessitated convergence on the previously established route to the spiroketal core.[25] Protection of the C_{17}-hydroxyl afforded MEM ether **22** which was ozonized to ketone **23** in high

(22) Neuhaus, D.; Williamson, M. *The Nuclear Overhauser Effect in Structural and Conformational Analysis*; VCH: New York, 1989.
(23) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535.
(24) Schmid, C. R.; Bryant, J. D. *Org. Synth.* **1993**, *72*, 6.

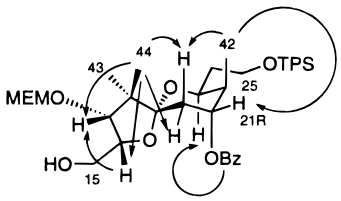


Figure 2.

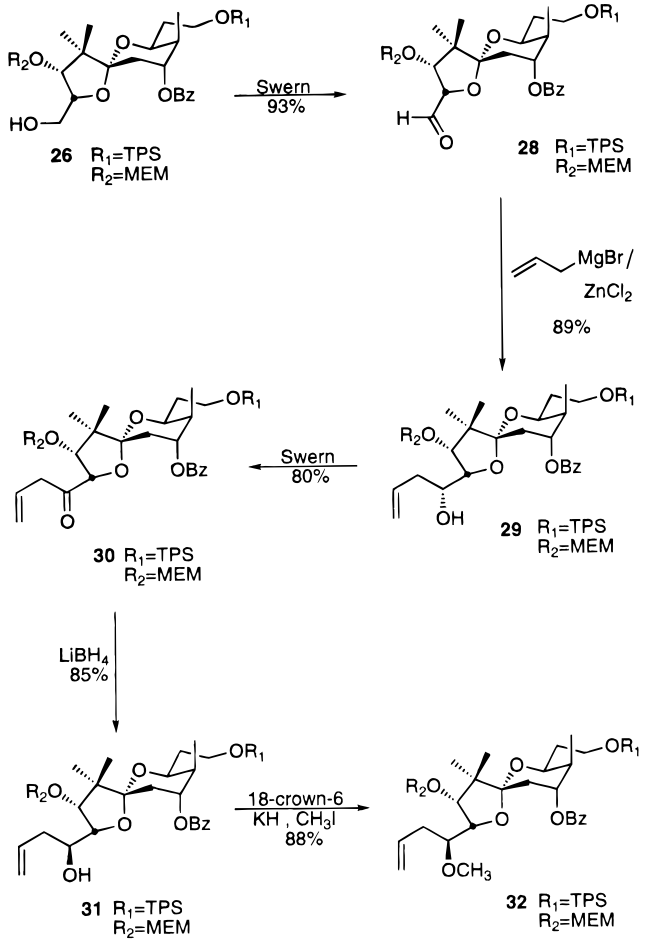
yield. Subsequent condensation with aldehyde **24**[26] afforded an aldol adduct which was benzoylated to yield open chain spiroketal precursor **25**. Treatment with trifluoroacetic acid (TFA) at 0 °C effected the desired tandem deprotection−cyclization to generate spiroketal **26** whose analytical data were identical to those of enantiomeric spiroketal **19** with the exception of optical rotation which was opposite in sign.

The relative and absolute stereochemistry of **26** was obtained from analysis of NOE difference experiments[22] (Figure 2). Under the assumption that the pyran exists in a chair conformation, the two new stereocenters generated in the aldol−spirocyclization sequence allow for eight possible diastereomers of the spiroketal to exist. Six of these structures were subsequently eliminated due to strong NOE correlations observed between the aromatic benzoate hydrogens and the C_{23}-methine, suggesting an *R*-configuration at C_{21}. An NOE correlation between the C_{42}-methyl and C_{21}-methine provided corroboration for the previous conclusion, thereby establishing a trans-diaxial relationship between the C_{42}-methyl and C_{21}-benzoate. Final evidence for the proposed structure of **26** was found in the NOE data surrounding the C_{44}-methyl. Given a syn-relationship between the C_{16}- and C_{17}-methine hydrogens,[27] enhancements linking the C_{44}-methyl with the C_{16}-methine, the C_{17}-methine, and both C_{20}-hydrogens strongly supported the claim that all four sets of hydrogens were syn-facial with respect to the furan ring. The sum of all NOE data served as verification of the proposed spiroketal structure **26**.

Introduction of the C_9−C_{14} Polypropionate Chain

Extension of the polypropionate chain from spiroketal **26** was initiated by Swern oxidation[28] to aldehyde **28** in excellent yield (Scheme 6). Allylation of the resulting aldehyde was found to proceed optimally *via* addition of an allylmagnesium bromide−$ZnCl_2$ mixture at −78 °C. Simple addition of allyl Grignard resulted in competitive debenzoylation, and use of allylsilanes proved less efficient in alkylation. The stereochemical identity of **29** was again verified by NOE study of isopropylidene **33** derived from removal of MEM and subsequent formation of the 1,3-acetonide. Utilizing the work of Rychnovsky[29] and Evans,[30] the stereochemical relationship between the C_{15}- and C_{17}-hydroxyls was shown to be anti. Empirical evidence has shown that the ^{13}C NMR chemical shifts of

Scheme 6



the acetonide methyls and ketal carbon serve to indicate the relationship of the 1,3-diol system bound in the isopropylidene framework. The observed ^{13}C NMR chemical shifts for **33** were 24.0 and 25.5, which was indicative of an anti relationship[29,30] and, unfortunately, the undesired stereochemistry at C_{15}. Evidently the nature of the spiroketal dictated that nucleophilic addition to the C_{15}-aldehyde **28** exclusively followed the Felkin−Ahn model,[19] and all attempts at chelation control were overridden by this bias.

Inversion at C_{15} was effected by reoxidation under Swern conditions[28] to ketone **30**, and subsequent reduction with $LiBH_4$ to afford alcohol **31** in good overall yield. Reduction attempts involving $NaBH_4$ resulted in isolation of the saturated alcohol which presumably arose from olefin migration followed by sequential 1,4−1,2 reduction. Diisobutylaluminum hydride in toluene at −78 °C led to concomitant removal of the benzoyl group as well as ketone reduction. NOE analysis[22] and ^{13}C NMR chemical shift correlation[29,30] of acetonide **34**, derived from a similar deprotection−isopropylidination sequence as previously mentioned, corroborated the assignment of stereochemistry (Scheme 7). Clean conversion of **31** to the C_{15}-methyl ether **(32)** was accomplished in superb yield by reaction with an excess of KH/CH_3I and 18-crown-6 at 0 °C in THF. This success prompted the introduction of a ^{13}C label at C_{15}-methyl ether in accordance with our previously outlined plan related to the study of serine/threonine phosphatases.

Incorporation of the C_{11}−C_{12} carbons proceeded with ozonolysis of **32**, followed by reaction with the crotylborane derived from *trans*-2-butene and (+)-MeOB(Ipc)$_2$, affording homoallylic alcohol **35** (Scheme 8).[20] The ster-

(25) Numerous attempts to effect coupling proved unfruitful due to difficulties in generating the required boronate reagent despite a variety of strategies and methods.

(26) Aldehyde **24** is stable toward chromatography, but undergoes *β*- elimination in the precense of mildly basic conditions (NEt_3, e.g.)

(27) C_{16}-stereochemistry was derived from glyceraldehyde, and the syn-relationship with the C_{17}-methine was established through NOE data (Figure 1).

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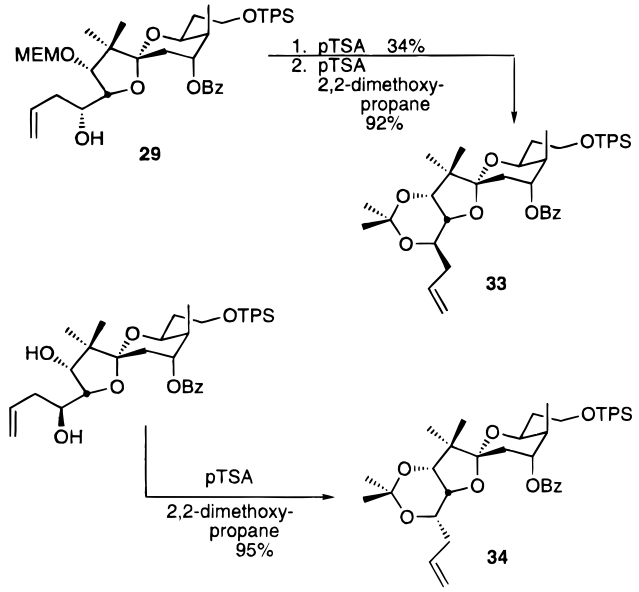
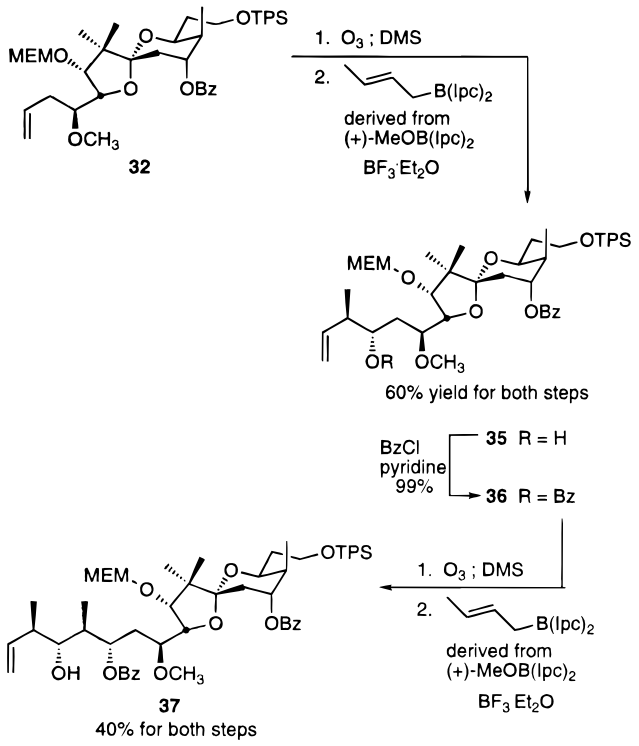
Scheme 7

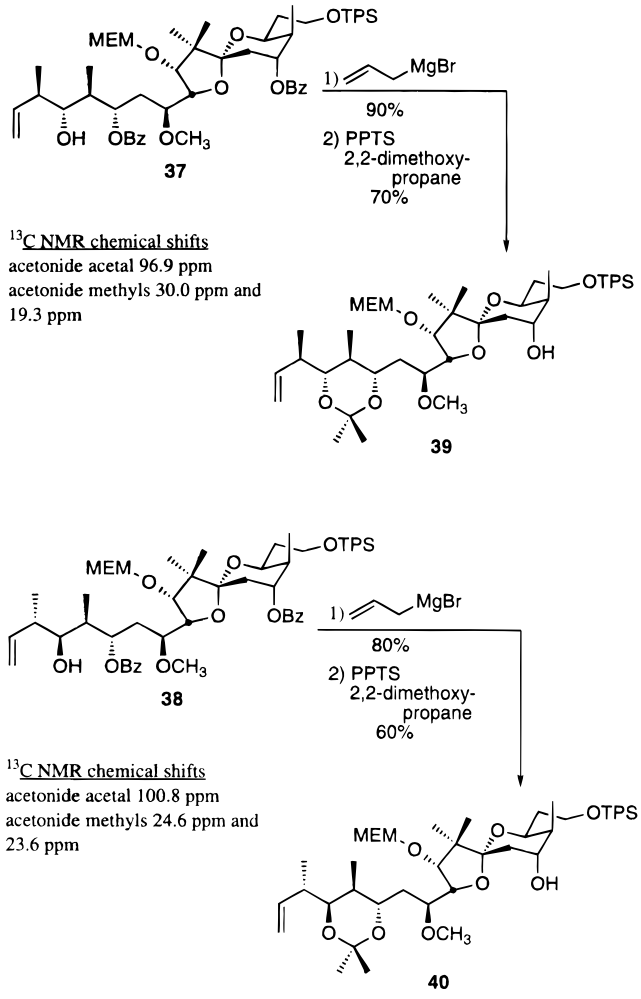


Scheme 8



eochemical identity of the newly introduced chiral centers was verified by an X-ray crystal structure of **35**.[39] Ozonolysis of benzoylated spiroketal **36** afforded an aldehyde substrate for the final allylboration[20] to alcohol **37**. The stereochemical outcome of this reaction was disappointing in that it yielded only a ~1.3:1 ratio of separable diastereomers (**37** and **38**, respectively). The structures of the desired product and its C_{10},C_{11}-diastereomer were inferred from ^{13}C NMR analysis of acetonides **39** and **40** involving the C_{11}- and C_{13}-hydroxyls.[29,30] The ^{13}C chemical shifts assigned to the acetonide methyls were 30.0 and 19.3 for the major product (**39**), provided strong evidence for a syn 1,3-diol relationship (Scheme 9). Corroboration for this hypothesis lies in ^{13}C data obtained likewise from the C_{11},C_{13}-acetonide of the minor diastereomer (**40**) in which chemical shifts of 24.6 and 23.6 suggested an anti relationship.

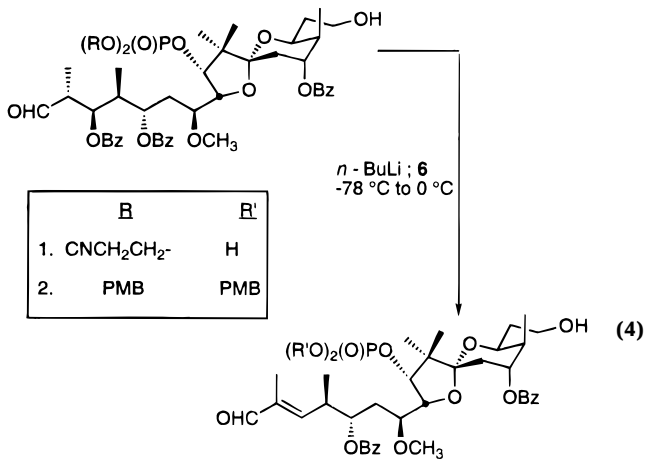
Scheme 9



^{13}C NMR chemical shifts
acetonide acetal 96.9 ppm
acetonide methyls 30.0 ppm and 19.3 ppm

^{13}C NMR chemical shifts
acetonide acetal 100.8 ppm
acetonide methyls 24.6 ppm and 23.6 ppm

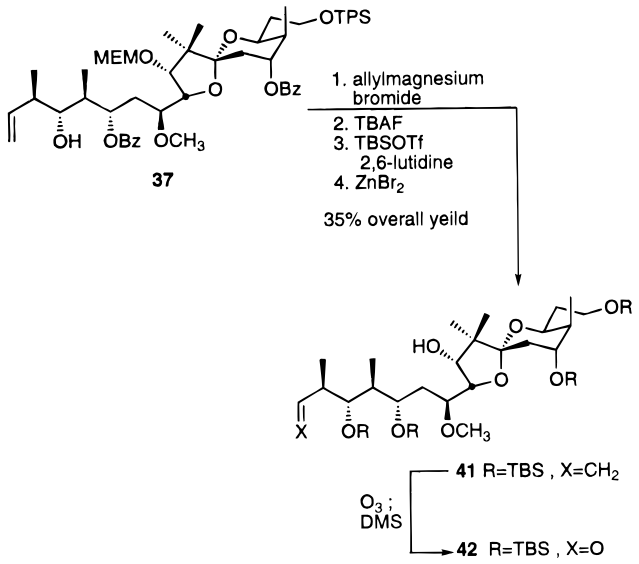
The completion of C_9–C_{25} spiroketal fragment **41** signaled the need to consider a strategy for incorporation of the phosphate in compliance with the overall protecting group strategy. Our initial approach relied on base cleavage of a global benzoate protection scheme in conjunction with delayed introduction of the tetraene moiety. β-Cyanoethoxy protection of phosphorus[31] at the phosphate oxidation state appeared compatible and was proposed to facilitate a single final deprotection step. Model studies incorporating such a strategy led to complications given problematic deprotection of the phosphate under Horner–Emmons olefination conditions (eq 4). 4-Methoxybenzyl protection of the phosphate was



(4)

examined with little success in studies designed to model

Scheme 10



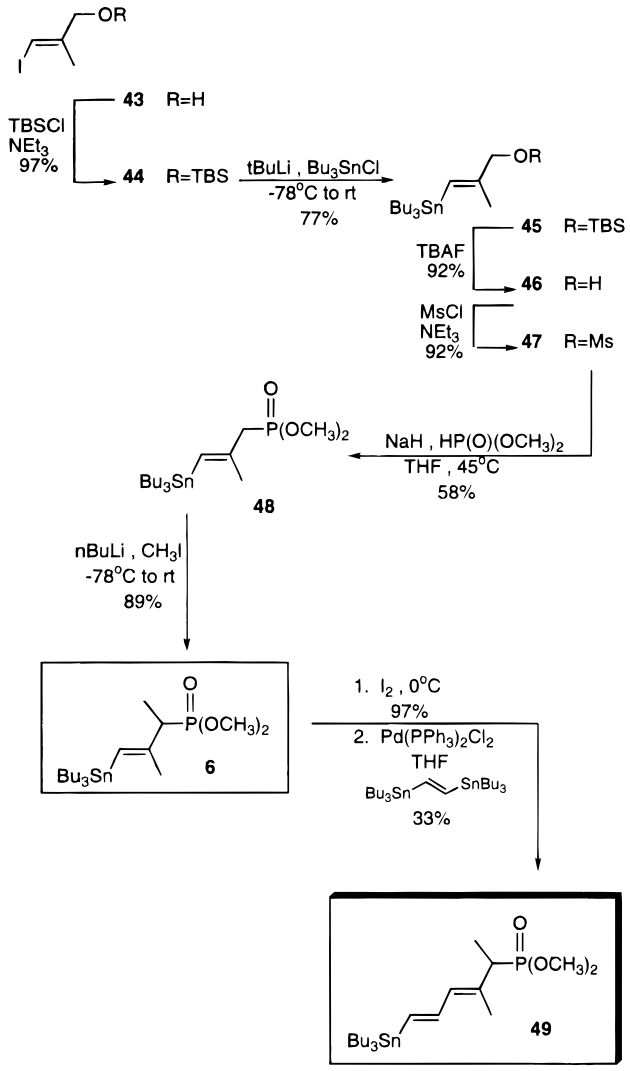
olefination at C_9. This evidence suggested that perhaps the phosphate was detrimental to the success of condensation reactions, which prompted convergence on the silyl protection strategy utilized by Evans.[13a] A series of deprotection and reprotection reactions initiating at benzoate **36** afforded olefin **41** (Scheme 10). Ozonolysis of **41** led to aldehyde **42** whose spectral data were identical to those of an advanced target in the synthesis of *ent*-calyculin A reported by Evans.[13a]

Incorporation of the C_1-C_9 Tetraene

Our plan for the introduction of the C_1-C_9 portion of calyculin was based on two key issues relative to the perceived instability of the cyanotetraene moiety. Concern for the geometric integrity of the C_2-C_3 double bond suggested the use of Stille cross-coupling as sp^2-sp^2 bond formation[32] precluded difficulties related to selectivity. The other issue to be addressed was the need for *E*-selective formation of the C_8-C_9 olefin. Horner–Emmons olefination provided an excellent method of generating a homologated product with the desired geometry. Phosphonate **6** provided a target bearing functionality that met both of the above synthetic concerns. It was also our belief that the extent of conjugation would have little effect on the Horner–Emmons olefination and no foreseeable impact on the subsequent Stille cross-coupling. However, the design of phosphonate **6** provided sufficient flexibility in its potential for facile extension to a stannyl diene species if the need arose.

The synthesis of **6** proceeded from known allylic alcohol **43**[33] *via* initial silylation (**44**) followed by trapping of the lithiated intermediate species with tributyltin chloride affording **45** in excellent yield (Scheme 11). In the course of synthetic work involving vinyl tin compounds, it was observed, not unexpectedly, that the tin–carbon bond was readily hydrolyzed in the presence of even weakly acidic media. Desilylation under basic conditions (TBAF) was necessary to avoid the unwanted hydrolysis previously mentioned, and subsequent mesylation afforded **47**

Scheme 11



in reasonable yield. Initial work directed toward the synthesis of phosphonate **6** indicated a need to introduce the phosphonate functionality prior to methylation as direct displacement of 2°-electrophiles proved unsuccessful. Direct displacement of the allylic mesylate, therefore, with sodium dimethyl phosphite[34] was followed by α-methylation to provide the target phosphonate **6** in good overall yield.

With the desired phosphonate in hand, coupling studies designed to model the proposed C_8-C_9 double-bond formation were undertaken (eq 5). In order to mimic the branching observed at the aldehyde α-carbon, two systems were selected for study. Isobutyraldehyde served as a simple preliminary model, while an aldehyde derived from Brown allylboration of phenylacetaldehyde[20] afforded a system that more adequately mimicked the local functionality with respect to the C_9-aldehyde in **42**. Multiple attempts at coupling onto the latter model aldehyde using phosphonate **6** under a myriad of reaction conditions failed to yield the desired olefin. Our original hypothesis was that the tributyltin moiety affected the nucleophilic behavior of **6**. Conclusive evidence for the ineffectiveness of monoene phosphonate in our hands was provided in the successful coupling of the hydrolyzed substrate. However, it should be noted that Masamune used phosphonate **6** successfully in the total synthesis

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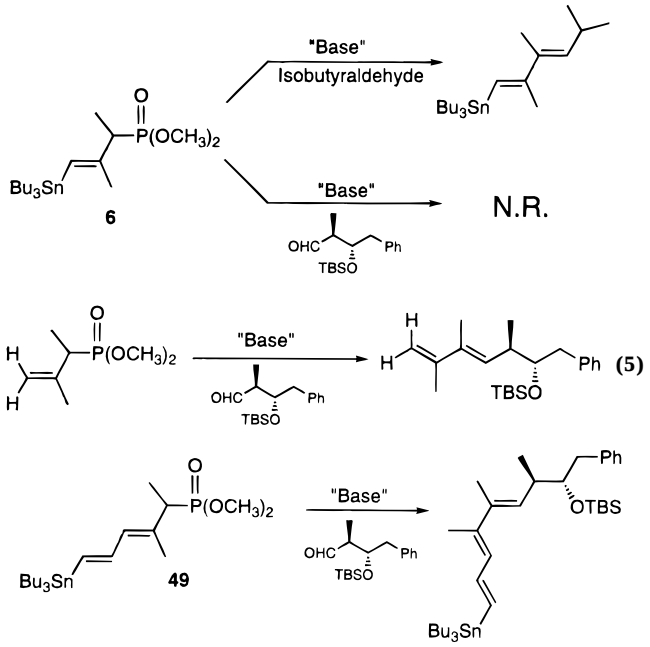


of calyculin A.[13b] In light of the above results, we decided to harness the flexibility implanted into the design of **6** *via* conversion to diene **49** which was used by Evans in his synthesis of calyculin A.[13a]

The synthesis of diene phosphonate **49** required a tin−halogen exchange on monoene precursor **6**, which was followed by Stille coupling[32] with *trans*-bis(tributylstannyl)ethylene[35] to afford **49**. Model studies involving this particular nucleophile proved efficacious, which provided a clear avenue to the C_1-C_{25} fragment of calyculin.

Final elaboration to the completed bottom half of the natural product proceeded with formation of the ylide at −78 °C, followed by warming and subsequent addition of aldehyde **42** to afford the desired olefin product. Completion of a protected C_1-C_{25} fragment involved submission of the crude product from the preceding reaction to Stille coupling[32] with vinyl iodide **5**[36] to yield tetraene **50** as a single diastereomer (Scheme 12). Proof of structure was developed from comparison of spectral evidence from **50** with the identical intermediate reported by Evans.[13a]

Completion of the C_1-C_{25} Fragment to Dephosphocalyculin C

In keeping with our interest in SAR work involving phosphatases PP1 and PP2A, we chose to explore elaboration of fragment **50** to aldehyde **52** which was compatible with our synthetic plans for the synthesis of dephosphocalyculin C. Given a strategy that assumed Wittig coupling to generate the $C_{25}-C_{26}$ double bond *via* a fully deprotected $C_{26}-C_{37}$ phosphonium salt,[37] we felt justified in maintaining a C_{17}-free hydroxyl species. In the event, however, that protection of the aforementioned hydroxy group became necessary, we felt that this strategy possessed the required flexibility to effect such a change.

Ether **50** was, therefore, desilylated under HF/pyridine conditions to afford diol **51**. The mildly acidic reaction conditions were thought to preclude nucleophilic attack onto the tetraene, as might be expected under basic TBAF deprotection conditions. Dess−Martin oxidation[38] yielded the target aldehyde **52** in excellent yield for both steps. This result established a completed C_1-C_{25} bottom-half fragment that could be utilized in the synthesis of dephosphocalyculin C.

Conclusion

We have successfully completed a synthesis of the C_1-C_{25} fragment in our effort directed toward the total synthesis of calyculin C. Our approach to this fragment was based on initial synthesis of a spiroketal core followed by subsequent homologation to introduce the necessary stereochemistry. Principally, these homologations were accomplished *via* a chiral allylboration strategy.[20] In the following paper, we report the synthesis of the complementary $C_{26}-C_{37}$ fragment of calyculin C and model studies for the construction of the $C_{25}-C_{26}$ double bond, thereby joining both halves of the natural product.

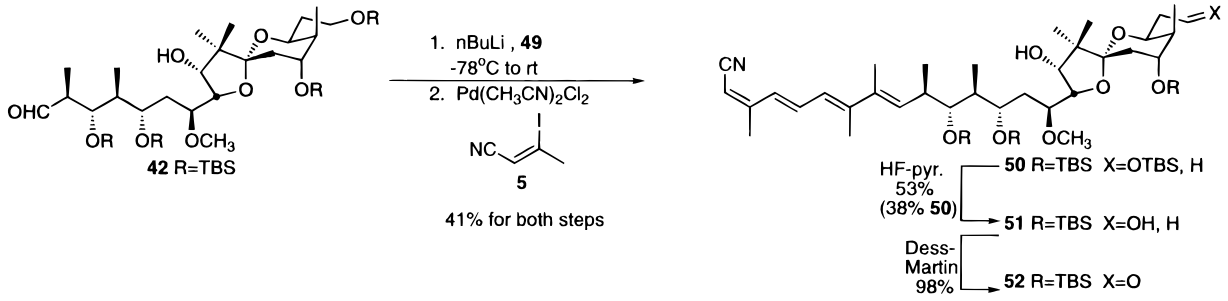
Experimental Section

General. High-resolution FAB mass spectra were obtained by the Mass Spectroscopy Facilities at the University of California Riverside. Elemental analysis was obtained from Desert Analysis of Tuscon, AZ. For CI and FAB mass spectra, $2\sigma = 4$ ppm.

Solvents and reagents were used as supplied from commercial sources with the following exceptions. Tetrahydrofuran, diethyl ether, and toluene were distilled from sodium benzophenone ketyl immediately prior to use. Dichloromethane was distilled from phosphorus pentoxide. Methanol was distilled from magnesium turnings. Dimethylformamide, dimethyl sulfoxide, and in some cases diisopropylamine were distilled from barium oxide and stored over 4Å molecular sieves. All reactions involving moisture-sensitive reagents were performed under either a nitrogen or an argon atmosphere.

(4*S*)-4-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-4-hydroxybutan-3-one (12a). To a solution of 2,3-*O*-isopropylidene-L-glyceraldehyde (9.35 g, 0.072 mol) and enol ether **11** (11.1 g, 0.070 mol) in THF (100 mL) at 0 °C was added a 1 M TBAF (70 mL, 0.070 mol) THF solution. The reaction was stirred for 2 h, at which time the solvent was removed under reduced pressure to give a thick oil. Column chromatography afforded a mixture of ketones **12a:12b (1:5)** (12.8 g, 85% overall yield). For **12a**: $[\alpha]_D = +4.4$ (*c* 0.01, $CHCl_3$); IR (thin film) 3506, 2985, 2937, 1708, 1470, 1371, 1217, 1064 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 4.05 (2H, m), 3.91 (1H, m), 3.84 (1H, m), 2.59 (1H, d, $J = 5.3$ Hz), 2.19 (3H, s), 1.37 (3H, s), 1.32

Scheme 12



(3H, s), 1.20 (3H, s), 1.18 (3H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 214.5, 109.1, 76.8, 76.1, 67.1, 51.0, 26.5, 26.4, 25.4, 21.3, 21.0. Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 59.16; H, 9.17. For **12b**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.14 (1H, ddd, J = 7.5, 6.6, 2.6 Hz), 4.03 (1H, dd, J = 6.5, 6.4 Hz), 3.61 (1H, dd, J = 8.3, 2.6 Hz), 3.07 (1H, d, J = J = 8.3 Hz), 2.20 (3H, s), 1.39 (3H, s), 1.35 (3H, s), 1.22 (3H, s), 1.17 (3H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 214.3, 109.3, 75.2, 74.7, 66.9, 50.6, 26.7, 25.9, 25.5, 22.0, 20.9. Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 59.11; H, 9.03.

(4*S*)-4-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2,2-dimethyl-1-(((2-methoxyethoxy)methyl)oxy)butan-3-one (13). (Methoxyethoxy)methyl chloride (MEMCl) (0.81 mL, 7.1 mmol) was added to a solution of alcohol **12a** (1.4 g, 6.5 mmol) in *N*,*N*-diisopropylethylamine (5 mL) and heated for 12 h at 50 °C. The amine was removed under reduced pressure, and the resulting crude product was purified by column chromatography to afford ether **13** (1.55 g, 79%) as a clear oil: $[\alpha]_D$ = −34.5 (*c* 0.014, $CHCl_3$); IR (thin film) 2938, 2933, 1701, 1468, 1369, 1212, 1158, 1107 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.83 (2H, d, J = 7.0 Hz), 4.14 (1H, m), 3.90 (1H, m), 3.77 (1H, d, J = 5.8 Hz), 3.70 (3H, m), 3.52 (2H, m), 3.36 (1H, s), 2.18 (3H, s), 1.35 (3H, s), 1.28 (3H, s), 1.15 (3H, s), 1.13 (3H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 212.2, 108.7, 97.6, 82.7, 76.1,71.6, 68.0, 66.1, 59.0, 51.5, 26.6, 26.1, 25.2, 22.0, 21.0. Anal. Calcd for $C_{15}H_{28}O_6$: C, 59.19; H, 9.27. Found: C, 58.73; H, 9.20.

(3*R*,4*R*)-5-(*tert*-Butyldiphenylsiloxy)-4-hydroxy-3-methylhexene (15). A 1.9 M solution of *n*-butyllithium in THF (13.5 mL, 0.026 mol) was added via syringe to dry potassium *tert*-butoxide (2.64 g, 0.023 mol) and *cis*-2-butene (7.0 mL, 0.08 mol) in THF (5 mL) at −78 °C, and the resulting mixture was stirred for 1 h at −40 °C. A solution of (−)-*B*-methoxydiisopinocampheylborane (10.5 g, 0.033 mol) in toluene (20 mL) was added to this yellow anionic solution at −78 °C, and the resulting mixture was stirred for 1 h. Boron trifluoride etherate (4.4 mL, 0.037 mol) was added to the reaction at −78 °C and stirred for 30 min, after which aldehyde **14** (4 mL, 0.01 mol) was added at −78 °C and stirred for 3 h. then 3 N sodium hydroxide (7 mL) and 30% H_2O_2 (7 mL) were added to the stirring solution, which was allowed to warm to rt. The reaction mixture was extracted with diethyl ether, and the organic layer was dried over $MgSO_4$ and chromatographed to afford olefin **15** (3.8 g, 81%) as a clear oil: $[\alpha]_D$ = +5.5 (*c* 0.014, $CHCl_3$); IR (thin film) 3509, 2957, 2929, 1638, 1588, 1472, 1427, 1388, 1111, 1076 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.68 (4H, m), 7.47 (6H, m), 5.79 (1H, ddd, J = 17.3, 10.5, 7.62 Hz), 5.05 (2H, ddd, J = 17.3, 10.5, 1.50 Hz), 3.88 (2H, m), 3.76 (1H, dt, J = 6.1, 2.4 Hz), 3.23 (1H, d, J = 2.4 Hz), 2.29 (1H, hex, J = 6.8 Hz), 1.69 (2H, m), 1.07 (3H, d, J = 7.0 Hz), 1.05 (9H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 141.1, 135.5, 133.1, 132.9, 129.8, 127.8, 114.8, 74.9, 63.7, 43.9, 35.4, 26.8, 19.0, 15.1. Anal. Calcd for $C_{23}H_{32}O_2Si$: C, 74.95; H, 8.75. Found: C, 75.24; H, 8.68.

(3*R*,4*R*)-6-(*tert*-Butyldiphenylsiloxy)-4-(2′-tetrahydropyranyl)-3-methylhexene (16). Dihydropyran (0.635 mL, 6.97 mmol) was added to a solution of alcohol **15** (2.33 g, 6.34 mmol) and pTSA (15 mg) in CH_2Cl_2 (10 mL) at rt. The reaction was stirred for 10 min and subsequently neutralized with triethylamine. The solvent was removed under reduced pressure and the resultant material chromatographed to give 2.8 g of **16** (98%) as a mixture of diastereomers. Anal. Calcd for $C_{28}H_{40}O_3Si$: C, 74.29; H, 8.91. Found: C, 74.48; H, 8.85.

(2*R*,3*R*)-5-(*tert*-Butyldiphenylsiloxy)-3-((2′-tetrahydropyranyl)oxy)-2-methylpentanal (17). Ozone was bubbled into a solution of ether **16** (0.569 g, 1.26 mmol) in CH_2Cl_2 at −78 °C until the solution turned light blue. Dimethyl sulfide (DMS) was added at −78 °C, and the mixture was allowed to warm to rt and stirred for 48 h. The CH_2Cl_2 and DMS were removed under reduced pressure, and the resultant liquid was azeotroped with toluene to give aldehyde **17** (0.53 g, 93%) as a clear oil.

(1*S*,5*S*,6*R*,7*R*)-1-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1-(((2-methoxyethoxy)methyl)oxy)-5-(benzoyloxy)-7-((2′-tetrahydropyranyl)oxy)-9-(*tert*-butyldiphenylsiloxy)-2,2,6-trimethylnonan-3-one (18). Lithium diisopropylamide (1.70 mL, 1.31 mmol, 0.77 M in THF) was added to a stirring solution of ketone **13** (0.36 g, 1.2 mmol) in THF (5 mL) at −78 °C. The solution was stirred for 45 min at −40 °C, and the temperature was then reduced to −78 °C. Aldehyde **17** (0.535 g, 1.2 mmol) in THF (5 mL) was added, and the resulting mixture was stirred for 5 min. Saturated NH_4Cl was added to the mixture, and the frozen mixture was allowed to warm to rt. The THF was removed under reduce pressure, and the aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and chromatographed to give a mixture of aldolate and starting material which was carried on as a crude product to the next reaction.

Benzoyl chloride (0.156 mL, 1.3 mmol) was added to a solution of the above mixture in pyridine (5 mL). The reaction was heated to 50 °C for 2 h, and the pyridine was removed under reduced pressure. The resultant material was chromatographed to give ketone **18** (0.621g, 60% for two steps): IR (thin film) 2931, 2359, 2340, 1717, 1472, 1427, 1273, 1157, 1111, 1071 cm^{-1}.

(2*R*,3*S*,4*S*,6*S*,8*S*,9*S*)-8-(Hydroxymethyl)-9-(((2-methoxyethoxy)methyl)oxy)-2-[2-(*tert*-butyldiphenylsiloxy)-1-ethyl]-3,10,10-trimethyl-1,7-dioxospiro[4.5]decane (19). Zinc bromide (10 mg) was added to a stirred solution of ketone **18** (50 mg, 0.058 mmol) in CH_2Cl_2 (5 mL), and the resulting mixture was stirred at rt for 5 h. The reaction mixture was concentrated under reduced pressure, and the resultant crude product was chromatographed to afford spiroketal **19** (33 mg, 80%): $[\alpha]_D$ = +86.4 (*c* 0.012, $CHCl_3$); IR (thin film) 3488, 3069, 2887, 1713, 1601, 1451, 1427, 1363, 1314, 1278, 1219, 1174, 1111, 1084 cm^{-1}; ^{1}H NMR (360 MHz, C_6D_6) δ 7.0−8.5 (15H, m), 5.15 (1H, dt, J = 3.6, 2.0 Hz), 4.67 (1H, m), 4.24 (2H, m), 4.22 (1H, m), 3.9−4.1 (4H, m), 3.47 (1H, d, J = 5.7 Hz), 3.26−3.36 (2H, m), 3.19 (2H, m), 3.06 (3H, s), 1.81 (1H, m), 1.69 (1H, m), 1.46 (1H, m), 1.41 (1H, dd, J = 14.9, 3.6 Hz), 1.19 (9H, s), 0.89 (3H, s), 0.69 (3H, d, J = 7.1 Hz), 0.51 (3H, s); ^{13}C NMR (90 MHz, C_6D_6) δ 165.8, 136.0, 136.0, 134.7, 134.5, 132.8, 131.8, 130.2, 129.9, 129.8, 128.6, 128.1, 106.7, 97.5, 87.5, 81.2, 73.0, 72.0, 67.7, 63.9, 62.1, 61.7, 58.7, 50.5, 36.1, 34.9, 27.4, 27.1, 23.0, 19.3, 17.0, 10.1. Anal. Calcd for $C_{41}H_{56}O_9Si$: C, 68.3; H, 7.83. Found: C, 68.41; H, 7.75.

(1*R*)-1-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1-hydroxy-2,2,3-trimethylbut-3-ene (21). To a suspension of potassium *tert*-butoxide (13.6 g, 121 mmol, 1.30 equiv) in THF (135 mL) at −78 °C was added 2,3-dimethyl-2-butene (1.0 M in THF, 167 mL, 167 mmol, 1.80 equiv). 2,2,6,6-Tetramethylpiperidine (20.3 mL, 120 mmol, 1.30 equiv) followed by *n*-butyllithium (2.0 M in hexanes, 60.4 mL, 121 mmol, 1.30 equiv) was added, and the resulting yellow mixture was allowed to stir at −45 °C for 20 min. The reaction mixture was recooled to −78 °C, and a solution of (+)-*B*-methoxydiisopinocampheylborane (38.3 g, 120.8 mmol, 1.30 equiv) in THF (130 mL) was added. The resulting light yellow mixture was stirred at −78 °C for 5 min and then allowed to warm to 25 °C over 45 min. The reaction mixture was recooled to −78 °C, and $BF_3{\cdot}Et_2O$ (17.2 mL, 139 mmol, 1.50 equiv) was added, followed by 2,3-*O*-isopropylidene-D-glyceraldehyde (12.2 g, 92.9 mmol, 1.00 equiv) in THF (100 mL). The thick white mixture was stirred at −78 °C for 1 h. The reaction was quenched by the addition of 3 N aqueous NaOH (130 mL) followed by 30% aqueous H_2O_2 (40.0 mL). The reaction mixture was warmed to 45 °C and stirred for 4 h. The mixture was cooled and diluted with ethyl acetate (100 mL) and saturated aqueous NaCl (300 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 150 mL). The combined organic extracts were washed with saturated aqueous NaCl (300 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to give a clear colorless oil. The oil was chromatographed on silica

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(39) The author has deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

gel (5−20% ethyl acetate−hexane) to give **21** as a colorless oil (14.6 g, 73.0%): R_f 0.75 (30% ethyl acetate in hexane); $[\alpha]_D$ = +7.0 (*c* 1.36, $CHCl_3$); IR (thin film) 3559, 2985, 2936, 1636, 1454, 1380, 1217, 1064 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.86 (1H, m), 4.83 (1H, m), 4.10 (1H, m), 3.98 (1H, dd, *J* = 7.9, 6.7 Hz), 3.69 (1H, dd, *J* = 7.9, 7.9 Hz), 3.46 (1H, dd, *J* = 7.3, 3.7 Hz), 2.46 (1H, d, *J* = 7.3 Hz), 1.74 (3H, s), 1.41 (3H, s), 1.36 (3H, s), 1.12 (3H, s), 1.05 (3H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 150.3, 111.7, 109.1, 74.9, 74.4, 67.8, 43.1, 26.4, 25.8, 24.3, 21.4, 20.1; HRMS NH_3CI calcd for MH^+ ($C_{12}H_{22}O_3$) 215.1647, found 215.1655 (error 3.6 ppm).

(1*R*)-1-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-1-(((2-methoxyethoxy)methyl)oxy)-2,2,3-trimethylbut-3-ene (22). To a solution of alcohol **21** (6.49 g, 30.3 mmol, 1.00 equiv) in $CHCl_3$ (10 mL) was added diisopropylethylamine (12.0 mL, 68.9 mmol, 2.27 equiv) followed by MEMCl (7.00 mL, 61.3 mmol, 2.02 equiv). The reaction was heated at 55 °C for 2 h. The dark brown solution was cooled and diluted with saturated aqueous NaCl (50.0 mL) and CH_2Cl_2 (50.0 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated to a brown oil. The residue was chromatographed on silica gel (10−30% ethyl acetate−hexane) to give ether **22** (7.51 g, 82.0%) as a yellow oil: R_f 0.60 (30% ethyl acetate in hexane); $[\alpha]_D$ = +66.3 (*c* 1.05, $CHCl_3$); IR (thin film) 2984, 2934, 1636, 1455, 1378, 1249, 1216, 1107 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.96 (1H, d, *J* = 7.3 Hz), 4.78 (2H, s), 4.76 (1H, d, *J* = 7.3 Hz), 4.04 (1H, m), 3.86 (1H, dd, *J* = 8.5, 6.1 Hz), 3.77 (1H, m), 3.73 (1H, m), 3.52 (3H, m), 3.46 (1H, dd, *J* = 8.5, 8.5 Hz), 3.35 (3H, s), 1.73 (3H, s), 1.33 (3H, s), 1.28 (3H, s), 1.08 (3H, s), 1.06 (3H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 149.6, 112.0, 107.7, 97.4, 82.9, 77.1, 71.7, 67.8, 67.3, 58.9, 42.9, 26.4, 25.6, 25.5, 21.5, 20.1; HRFABMS calcd for MH^+ $C_{16}H_{31}O_5$ 303.2171, found 303.2170 (error 0.5 ppm).

(1*R*)-1-[2,2-Dimethyl-1,3-dioxolan-4(*R*)-yl]-2,2-dimethyl-1-(((2-methoxyethoxy)methyl)oxy)butan-3-one (23). Ozone was bubbled through a solution of olefin **22** (8.83 g, 29.2 mmol, 1.00 equiv) in CH_2Cl_2 (160 mL) and methanol (1.2 mL, 29.2 mmol, 1.00 equiv) at −78 °C. The reaction was monitored by TLC for the consumption of the olefin at which time dimethyl sulfide (21.4 mL, 292 mmol, 10.0 equiv) was added. The solution was allowed to warm to 25 °C and stirred for 12 h. The solution was concentrated to give a yellow oil. The oil was chromatographed on silica gel (10% ethyl acetate−hexane) to give ketone **23** as a colorless oil (7.63 g, 86.2%): R_f 0.30 (30% ethyl acetate in hexane); $[\alpha]_D$ = +37.9 (*c* 0.965, $CHCl_3$); IR (thin film) 2984, 2935, 1704, 1370, 1213, 1159, 1110 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.91 (1H, d, *J* = 7.0 Hz), 4.78 (1H, d, *J* = 7.0 Hz), 4.16 (1H, ddd, *J* = 6.5, 6.5, 5.9 Hz), 3.92 (1H, dd, *J* = 8.1, 6.5 Hz), 3.79 (1H, d, *J* = 5.9 Hz), 3.71 (3H, m), 3.53 (2H, m), 3.38 (3H, s), 2.20 (3H, s), 1.37 (3H, s), 1.30 (3H, s), 1.16 (3H, s), 1.15 (3H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 212.3, 108.8, 97.6, 82.7, 76.2, 71.7, 68.0, 66.7, 59.0, 51.5, 26.6, 26.1, 25.2, 22.1, 21.0; HRFABMS calcd for MNa^+ ($C_{15}H_{28}O_6$-Na) 327.1770, found 327.1784 (error 4.2 ppm).

(1*R*,5*R*,6*R*,7*S*)-9-[(*tert*-Butyldiphenylsiloxy]-1-(2,2-dimethyl-1,3-dioxolan-4(*R*)-yl)-5-(benzoyloxy)-1-(((2-methoxyethoxy)methyl)oxy)-7-(2-tetrahydropyranyl)-2,2,6-trimethylnonan-3-one (25). To a solution of diisopropylamine (6.00 mL, 43.1 mmol, 1.91 equiv) in THF (17.0 mL) at −20 °C was added *n*-butyllithium (2.01 M in hexane, 20.9 mL, 43.1 mmol, 1.91 equiv). The solution was cooled to −78 °C, and after 5 min at −78 °C the ketone **23** (8.74 g, 28.7 mmol, 1.27 equiv) in THF (20.0 mL) was added. The resulting brown solution was allowed to stir at −78 °C for 30 min at which time the aldehyde **24** (10.3 g, 22.6 mmol, 1.00 equiv) in THF (10.0 mL) was added. After the solution was stirred for 30 min at −78 °C, the reaction was quenched by the addition of saturated aqueous NaCl (75.0 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 40.0 mL). The combined organic extracts were washed with saturated aqueous NaCl (40.0 mL), dried over Na_2SO_4, and concentrated to give the aldolate as a yellow oil: R_f 0.25 (30% ethyl acetate in hexane).

To a solution of the crude aldolate (17.2 g, 22.6 mmol, 1.00 equiv) in pyridine (50.0 mL) was added benzoyl chloride (5.50 mL). The solution was heated to 55 °C and allowed to stir for 2 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (50 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 50.0 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (100 mL), dried over Na_2SO_4, and concentrated to a dark brown oil. The oil was chromatographed on silica gel (20% ethyl acetate−hexane) to give compound **25** (15.8 g, 54.4% for the two steps): R_f 0.65 (40% ethyl acetate in hexane); IR (thin film) 2934, 1717, 1602, 1585, 1472, 1451, 1273, 1111, 1071 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97−8.12, 7.29−7.68, 5.69, 4.84, 4.77, 4.72, 4.57, 3.63−4.18, 3.32−3.57, 3.05, 2.11−2.25, 0.91−1.95; ^{13}C NMR (90 MHz, $CDCl_3$) δ 211.4, 210.8, 165.6, 165.4, 135.5, 135.47, 135.44, 133.9, 133.87, 133.7, 133.5, 133.4, 132.8, 132.6, 130.6, 130.5, 130.0, 129.6, 129.5, 129.4, 128.4, 128.3, 128.2, 127.6, 127.5, 127.4, 108.8, 108.7, 99.4, 97.7, 97.6, 82.0, 81.8, 77.4, 77.0, 76.6, 76.2, 76.0, 75.7, 74.2, 72.2, 71.7, 71.1, 68.0, 67.9, 66.7, 66.6, 64.0, 62.5, 61.0, 60.2, 59.0, 51.8, 51.7, 41.0, 40.4, 40.2, 38.1, 34.7, 34.5, 31.4, 31.0, 26.8, 26.7, 26.2, 26.1, 25.4, 25.2, 25.1, 22.6, 22.4, 20.8, 20.5, 20.3, 19.7, 19.0, 10.9, 10.6; HRFABMS calcd for MNa^+ ($C_{49}H_{70}O_{11}SiNa$) 885.4578, found 885.4585 (error 0.8 ppm).

(2*R*,3*R*,5*R*,7*S*,8*R*,9*R*)-9-(Benzoyloxy)-7-[2-(*tert*-butyldiphenylsiloxy)ethyl]-2-(hydroxymethyl)-3-(((2-methoxyethoxy)methyl)oxy)-4,4,8-trimethyl-1,6-dioxaspiro[4.5]decane (26). To a solution of benzoate **25** (15.8 g, 18.3 mmol, 1.00 equiv) in CH_2Cl_2 (183 mL) at 0 °C was added trifluoroacetic acid (21.1 mL, 274 mmol, 15.0 equiv). The resulting yellow solution was allowed to stir for 20 min; then the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (100 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to give a yellow oil. The oil was chromatographed on silica gel (15% ethyl acetate−hexane) to give the spiro compound **26** as a colorless oil (11.2 g, 85.0%): R_f 0.45 (40% ethyl acetate in hexane); $[\alpha]_D$ = −64 (*c* 0.98, $CHCl_3$); IR (thin film) 3489, 2930, 1713, 1472, 1427, 1389, 1276, 1111 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 8.44 (2H, m), 7.82 (4H, m), 7.21 (9H, m), 5.15 (1H, ddd, *J* = 3.6, 3.6, 2.0 Hz), 4.67 (1H, m), 4.28 (1H, d, *J* = 5.8 Hz), 4.22 (2H, m), 3.90−4.10 (4H, m), 3.47 (1H, d, *J* = 5.7 Hz), 3.36 (1H, m), 3.25 (1H, m), 3.19 (2H, m), 3.06 (3H, s), 1.81 (1H, m), 1.69 (2H, m), 1.46 (1H, m), 1.41 (1H, dd, *J* = 14.9, 3.7 Hz), 1.19 (9H, s), 0.89 (3H, s), 0.69 (3H, d, *J* = 7.1 Hz), 0.51 (3H, s); ^{13}C NMR (90 MHz, C_6D_6) δ 165.8, 136.0, 135.9, 134.7, 134.5, 132.8, 131.8, 130.2, 129.9, 129.8, 128.6, 128.3, 106.7, 97.5, 87.4, 81.2, 73.0, 72.0, 67.7, 63.9, 62.1, 61.7, 58.7, 50.5, 36.1, 34.9, 27.4, 27.1, 23.0, 19.3, 17.0, 10.1; HRFABMS CH_2Cl_2/NBA calcd for MH^+ ($C_{41}H_{57}O_9Si$) 721.3772, found 721.3790 (error 2.5 ppm).

(2*R*,3*R*,5*R*,7*S*,8*R*,9*R*)-9-(Benzoyloxy)-7-[2-(*tert*-butyldiphenylsiloxy)ethyl]-2-formyl-3-(2-methoxyethoxymethyl)oxy-4,4,8-trimethyl-1,6-dioxaspiro[4.5]decane (28). To a solution of oxalyl chloride (5.57 mL, 63.9 mmol, 5.00 equiv) in CH_2Cl_2 (125 mL) at −78 °C was added dropwise DMSO (9.07 mL, 128 mmol, 10.0 equiv). The solution was stirred at −78 °C for 5 min; then the alcohol **26** (9.22 g, 12.8 mmol, 1.00 equiv) in CH_2Cl_2 (25.0 mL) was added dropwise. The resulting yellow solution was allowed to stir at −40 °C for 10 min; then the solution was recooled to −78 °C. Triethylamine (26.7 mL, 192 mmol, 15.0 equiv) was added, and the resulting white slurry was allowed to warm to rt. The reaction was diluted with saturated aqueous NaCl (150 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 75 mL). The combined organic extracts were washed with saturated aqueous NaCl (100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to give a yellow oil. The oil was chromatographed on silica gel (25% ethyl acetate−hexane) to give aldehyde **28** as a colorless oil (8.59 g, 93.4%): R_f 0.60 (40% ethyl acetate in hexane); $[\alpha]_D$ = −10.5 (*c* 1.15, $CHCl_3$); IR (thin film) 2931, 1721, 1451, 1428, 1273, 1111 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 9.55 (1H, d, *J* = 2.9 Hz), 8.05 (2H, m), 7.68 (4H, m), 7.45 (9H, m), 5.38 (1H, ddd, *J* = 10.9, 10.9, 4.7 Hz), 4.64 (2H, s), 4.42

(1H, d, J = 8.6 Hz), 4.30 (1H, ddd, J = 12.6, 5.7, 2.4 Hz), 4.10 (1H, dd, J = 8.6, 2.9 Hz), 3.77 (2H, m), 3.68 (1H, m), 3.62 (1H, m), 3.54 (2H, m), 3.38 (3H, s), 2.39 (1H, dd, J = 12.6, 4.7 Hz), 2.18 (2H, m), 1.70 (2H, m), 1.07 (3H, s), 1.06 (9H, s), 0.98 (3H, d, J = 6.9 Hz), 0.88 (3H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 201.3, 166.0, 135.5, 133.8, 133.7, 133.0, 130.3, 130.2, 129.7, 129.6, 129.5, 128.4, 127.7, 111.0, 96.0, 85.8, 81.2, 74.7, 71.6, 70.8, 67.5, 60.9, 59.0, 48.4, 39.0, 35.3, 32.3, 26.9, 20.3, 19.2, 18.0, 13.5; HRFABMS CH_2Cl_2/NBA calcd for M^+ ($C_{41}H_{54}O_9Si$) 718.3537, found 718.3560 (error 3.2ppm).

(2*R*,3*R*,5*R*,7*S*,8*R*,9*R*)-9-[(Benzoyl)oxy]-7-[2-(*tert*-butyldiphenylsiloxy)ethyl]-2-[1(*R*)-hydroxybut-3-enyl]-3-(((2-methoxyethoxy)methyl)oxy)-4,4,8-trimethyl-1,6-dioxaspiro[4.5]decane (29). To a solution of aldehyde **28** (8.59 g, 11.9 mmol, 1.00 equiv) in CH_2Cl_2 (85 mL) at −78 °C was added a slurry of allylmagnesium bromide (1.0 M in THF, 17.9 mL, 17.9 mmol, 1.50 equiv) and $ZnCl_2$ (1.0 M in THF, 20.9 mL, 20.9 mmol, 1.75 equiv) via cannula. The reaction was stirred at −78 °C for 15 min; then the reaction was quenched by the addition of saturated aqueous NaCl (100 mL). The mixture was filtered, and the filtrate was transferred to a separatory funnel. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 35 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give a light yellow oil. The oil was chromatographed on silica gel (20% ethyl acetate−hexane) to give alcohol **29** (8.07 g, 88.8%): R_f 0.55 (40% ethyl acetate in hexane): $[\alpha]_D$ = −64.9 (*c* 1.26, $CHCl_3$); IR (thin film) 3478, 3071, 2931, 1716, 1472, 1428, 1363, 1277, 1112 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (2H, m), 7.66 (4H, m), 7.53 (1H, m), 7.35 (8H, m), 5.80 (1H, m), 5.14 (1H, m), 4.96 (2H, m), 4.36 (1H, d, J = 5.8 Hz), 4.27 (2H, m), 4.04 (1H, m), 3.89 (1H, dd, J = 9.6, 5.5 Hz), 3.71 (2H, m), 3.64 (1H, d, J = 5.5 Hz), 3.56 (1H, br s), 3.39 (4H, m), 3.32 (3H, s), 2.59 (1H, m), 2.23 (1H, m), 1.88 (1H, m), 1.77 (3H, m), 1.58 (1H, m), 1.02 (9H, s), 1.01 (3H, s), 0.96 (3H, d, J = 7.2 Hz), 0.87 (3H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 165.9, 135.5, 135.4, 135.3, 134.2, 132.8, 130.6, 129.7, 129.5, 129.4, 128.2, 127.6, 127.5, 116.5, 106.6, 97.7, 87.9, 82.6, 72.8, 71.6, 68.3, 67.4, 64.2, 62.5, 58.9, 50.4, 38.0, 35.7, 34.9, 27.3, 26.8, 22.9, 19.0, 16.9, 10.2; HRFABMS CH_2Cl_2/NBA calcd for MH^+ ($C_{44}H_{61}O_9Si$) 761.4085, found 761.4041 (error 5.8 ppm).

(2*R*,3*R*,5*R*,7*S*,8*R*,9*R*)-9-[(Benzoyl)oxy]-7-[2-(*tert*-butyldiphenylsiloxy)ethyl]-2-(1-oxobut-3-enyl)-3-(2-methoxyethoxymethyl)oxy-4,4,8-trimethyl-1,6-dioxaspiro[4.5]decane (30). To a solution of oxalyl chloride (2.10 mL, 24.1 mmol, 5.06 equiv) in CH_2Cl_2 (20.0 mL) at −78 °C was added dropwise DMSO (3.40 mL, 47.9 mmol, 10.1 equiv). The solution was stirred at −78 °C for 5 min; then the alcohol **29** (3.62 g, 4.76 mmol, 1.00 equiv) in CH_2Cl_2 (10.0 mL) was added dropwise. The resulting yellow solution was allowed to stir at −40 °C for 10 min; then the solution was recooled to −78 °C. Triethylamine (10.0 mL, 71.7 mmol, 15.1 equiv) was added, and the resulting white slurry was allowed to warm to rt. The reaction was diluted with CH_2Cl_2 (20.0 mL) and saturated aqueous NaCl (50.0 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed with saturated aqueous NaCl (50.0 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to give a yellow oil. The oil was chromatographed on silica gel (15% ethyl acetate−hexane) to give ketone **30** as a colorless oil (2.89 g, 80.0%): R_f 0.60 (40% ethyl in hexane); $[\alpha]_D$ = −85.5 (*c* 1.14, $CHCl_3$); IR (thin film) 3071, 2930, 2857, 1716, 1472, 1428, 1362, 1277, 1112 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (2H, m), 7.63 (2H, m), 7.53 (1H, m), 7.39 (10H, m,), 5.80 (1H, m), 5.20 (1H, m), 5.06 (1H, m), 4.96 (1H, m), 4.68 (1H, m), 4.55 (1H, d, J = 4.9 Hz), 4.35 (1H, d, J = 7.0 Hz), 4.21 (1H, d, J = 7.0 Hz), 4.00 (1H, d, J = 5.5 Hz), 3.88 (1H, m), 3.77 (1H, m), 3.27−3.54 (9H, m), 1.62−2.02 (5H, m), 1.06 (3H, s), 0.98 (3H, d, J = 6.7 Hz), 0.97 (9H, s), 0.88 (3H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 210.1, 165.8, 135.4, 133.8, 132.9, 130.7, 130.3, 129.7, 129.5, 128.3, 127.6, 118.5, 108.9, 96.1, 86.6, 86.5, 72.6, 71.6, 67.4, 65.1, 61.6, 59.0, 50.4, 45.1, 35.5, 34.0, 27.8, 26.7, 22.7, 19.0, 17.3, 10.2; HRFABMS CH_2Cl_2/NBA calcd for MH^+ ($C_{44}H_{59}O_9Si$) 759.3928, found 759.3926 (error 0.3 ppm).

(2*R*,3*R*,5*R*,7*S*,8*R*,9*R*)-9-[(Benzoyl)oxy]-7-[2-(*tert*-butyldiphenylsiloxy)ethyl]-2-[1(*S*)-hydroxybut-3-enyl]-3-(((2-methoxyethoxy)methyl)oxy)4,4,8-trimethyl-1,6-dioxaspiro[4.5]decane (31). To a solution of ketone **30** (2.89 g, 3.81 mmol, 1.00 equiv) in THF (10.0 mL) at −10 °C was added $LiBH_4$ (2.0 M in THF, 2.90 mL, 5.80 mmol, 1.52 equiv). After 1 h, the reaction was quenched by the addition of saturated aqueous NaCl (25.0 mL). The mixture was diluted with ethyl acetate (25.0 mL), and the resulting layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 20.0 mL), and the combined organic extracts were washed with saturated aqueous NaCl (50.0 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrtated under reduced pressure. The resulting oil was chromatographed on silica gel (15% ethyl acetate−hexane) to give the alcohol **31** (2.46 g, 85.0%): R_f 0.50 (30% ethyl acetate in hexane); $[\alpha]_D$ = −62.8 (*c* 1.07, $CHCl_3$); IR (thin film) 3531, 2931, 1713, 1471, 1428, 1364, 1277, 1111 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.17 (2H, m), 7.64 (4H, m), 7.51 (1H, m), 7.36 (8H, m), 5.81 (1H, m), 5.16 (1H, m), 4.95 (2H, m), 4.62 (1H, m), 4.58 (1H, d, J = 7.2 Hz), 4.48 (1H, d, J = 7.2 Hz), 4.09 (1H, dd, J = 5.8, 2.8 Hz), 3.76 (4H, m), 3.64 (1H, m), 3.48 (3H, m), 3.37 (3H, s), 2.37 (2H, m), 1.58−1.92 (5H, m), 1.03 (3H, s), 0.98 (9H, s), 0.93 (3H, d, J = 7.2 Hz), 0.87 (3H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 165.9, 135.6, 135.5, 135.4, 134.0, 133.9, 132.8, 130.7, 129.8, 129.4, 128.3, 127.5, 116.7, 106.4, 96.7, 87.7, 81.0, 72.8, 71.6, 70.3, 67.8, 64.8, 61.3, 59.8, 59.0, 50.6, 38.3, 35.1, 33.9, 27.2, 26.7, 23.3, 21.3, 19.0, 17.1, 10.2; HRFABMS CH_2Cl_2/NBA calcd for MH^+ ($C_{44}H_{61}O_9Si$) 761.4085, found 761.4122 (error 4.9 ppm).

(2*R*,3*R*,5*R*,7*S*,8*R*,9*R*)-9-[(Benzoyl)oxy]-7-[2-(*tert*-butyldiphenylsiloxy)ethyl]-2-[1(*S*)-methoxybut-3-enyl]-3-(((2-methoxyethoxy)methyl)oxy)4,4,8-trimethyl-1,6-dioxaspiro[4.5]decane (32). To a solution of 18-crown-6 (2.10 g, 2.69 mmol, 1.00 equiv) in THF (20.0 mL) at 0 °C was added potassium hydride (350 mg, 8.73 mmol, 3.25 equiv). The resulting yellow suspension was stirred for 5 min; then iodomethane (440 μL, 7.02 mmol, 2.61 equiv) was added. The reaction mixture foamed and was stirred for 5 min. Next the alcohol **31** (2.05 g, 2.69 mmol, 1.00 equiv) in THF (8 mL) was added dropwise and stirred for 12 h at 25 °C. The reaction was quenched by the addition of saturated aqueous NaCl (20.0 mL) and diluted with ethyl acetate (15.0 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10.0 mL). The combined organic extracts were washed with saturated aqueous NaCl (30.0 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting oil was chromatographed on silica gel (20% ethyl acetate−hexane) to give the methyl ether **32** (1.84 g, 88.2%): R_f 0.62 (30% ethyl acetate in hexane). $[\alpha]_D$ = −66.8 (*c* 1.66, $CHCl_3$); IR (thin film) 3070, 2929, 1716, 1472, 1451, 1428, 1361, 1277, 1111 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (2H, m), 7.67 (4H, m), 7.52 (1H, m), 7.38 (8H, m), 5.73 (1H, m), 5.15 (1H, m), 5.02 (2H, m), 4.47 (1H, d, J = 7.0 Hz), 4.41 (1H, m), 4.25 (1H, d, J = 7.0 Hz), 4.02 (2H, m), 3.78 (1H, m), 3.55 (1H, d, J = 5.1 Hz), 3.23−3.41 (5H, m), 3.35 (3H, s), 3.34 (3H, s), 2.29 (1H, m), 1.54−2.04 (6H, m), 1.02 (3H, s), 1.01 (9H, s), 0.98 (3H, d, J = 7.1 Hz), 0.85 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 135.4, 135.3, 135.1, 134.1, 134.0, 132.7, 130.8, 129.9, 129.5, 129.4, 128.2, 127.60, 127.58, 106.4, 97.2, 86.9, 83.1, 80.4, 73.0, 71.5, 67.7, 64.1, 62.7, 59.3, 59.0, 50.5, 35.9, 35.0, 34.9, 27.6, 26.7, 22.8, 19.1, 17.6, 10.2; HRFABMS CH_2Cl_2/NBA/NaCl calcd for MNa^+ ($C_{45}H_{62}O_9SiNa$) 797.4061, found 797.4105 (error 5.5 ppm).

(2*R*,3*R*,5*R*,7*S*,8*R*,9*R*)-9-[(Benzoyl)oxy]-7-[2-(*tert*-butyldiphenylsiloxy)ethyl]-2-[(1*S*,3*S*,4*R*)-3-hydroxy-1-methoxy-4-methylhex-5-enyl]-3-(2-methoxyethoxymethyl)oxy-4,4,8-trimethyl-1,6-dioxaspiro[4.5]decane (35). Ozone was bubbled through a solution of olefin **32** (1.37 g, 1.76 mmol, 1.00 equiv) in methanol (71.0 μL, 1.76 mmol, 1.00 equiv) and CH_2Cl_2 (10.0 mL) at −78 °C. The reaction was monitored by TLC for the consumption of the olefin at which time dimethyl sulfide (0.65 mL, 8.9 mmol, 5.0 equiv) was added. The solution was allowed to warm to 25 °C and stirred for 12 h. The solution was concentrated to afford the crude aldehyde as a yellow oil which was used directly in the next reaction.

To a suspension of potassium *tert*-butoxide (310 mg, 2.76 mmol, 1.57 equiv) in THF (8.0 mL) at −78 °C was added *trans*-2-butene (550 mg, 9.80 mmol, 5.57 equiv). *n*-Butyllithium (2.0 M in hexanes, 1.35 mL, 2.70 mmol, 1.54 equiv) was added, and the resulting yellow mixture was allowed to stir at −45 °C for 20 min. The reaction mixture was recooled to −78 °C, and a solution of (+)-*B*-methoxydiisopinocampheylborane (850 mg, 2.69 mmol, 1.53 equiv) in THF (2.0 mL) was added. The resulting light yellow mixture was stirred at −78 °C for 35 min. $BF_3{\cdot}Et_2O$ (440 μL, 3.58 mmol, 2.03 equiv) was added followed by the above-mentioned aldehyde (1.368 g, 1.76 mmol, 1.00 equiv) in THF (5.0 mL). The thick white mixture was stirred at −78 °C for 1 h. The reaction was quenched by addition of 3 N aqueous NaOH (10 mL) followed by 30% aqueous H_2O_2 (10 mL). The reaction mixture was warmed to 25 °C and stirred for 1 h. The mixture was cooled and diluted with ethyl acetate (20 mL) and saturated aqueous NaCl (20 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with saturated aqueous NaCl (25 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to give a clear colorless oil. The oil was chromatographed on silica gel (15% ethyl acetate−hexane) to give **35** as a colorless oil (880 mg, 60.0% for the two steps): R_f 0.50 (30% ethyl acetate in hexane) $[\alpha]_D = -103$ (*c* 1.50, $CHCl_3$); IR (thin film) 3498, 3070, 2931, 1714, 1472, 1452, 1428, 1278, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16 (2H, m), 7.64 (4H, m), 7.51 (1H, m), 7.35 (8H, m), 5.82 (1H, m), 5.15 (1H, m), 5.07 (2H, m), 4.44 (2H, m), 4.36 (1H, d, *J* = 6.6 Hz), 4.18 (1H, dd, *J* = 9.6, 4.9 Hz), 3.97 (1H, m), 3.75 (1H, m), 3.67 (1H, m), 3.51 (3H, m), 3.41 (3H, s), 3.35 (3H, s), 3.28−3.42 (3H, m), 3.01 (1H, d, *J* = 4.4 Hz), 2.16 (1H, m), 1.38−1.93 (7H, m), 1.03 (6H, m), 0.99 (9H, s), 0.97 (3H, d, *J* = 7.1 Hz), 0.88 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 140.8, 135.5, 135.4, 134.1, 134.0, 132.7, 129.9, 129.5, 128.1, 127.6, 115.1, 106.5, 97.8, 87.7, 83.2, 79.8, 73.1, 71.7, 71.5, 67.8, 64.2, 62.5, 59.9, 58.9, 50.6, 44.4, 35.8, 34.8, 34.2, 27.7, 26.8, 22.8, 19.0, 17.6, 16.0, 10.2; HRFABMS CH_2Cl_2/NBA/NaCl calcd for MNa^+ ($C_{48}H_{68}O_{10}SiNa$) 855.4479, found 855.4500 (error 2.4 ppm).

(2*R*,3*R*,5*R*,7*S*,8*R*,9*R*)-9-(benzoyloxy)-7-[2-(*tert*-butyldiphenylsiloxy)ethyl]-2-[(1*S*,3*S*,4*R*)-3-(benzoyloxy)-1-methoxy-4-methylhex-5-enyl]-3-(2-methoxyethoxymethyl)oxy-4,4,8-trimethyl-1,6-dioxaspiro[4.5]decane (36). To a solution of the alcohol **35** (880 mg, 1.06 mmol, 1.00 equiv) in pyridine (20 mL) was added benzoyl chloride (1.00 mL, 8.61 mmol, 8.16 equiv). The solution was heated to 60 °C and allowed to stir for 2 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (50 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (100 mL), dried over $NaSO_4$, and concentrated to a dark brown oil. The oil was chromatographed on silica gel (20% ethyl acetate−hexane) to give **36** (1.00 g, 99%): R_f 0.40 (30% ethyl acetate in hexane). $[\alpha]_D = -76.9$ (*c* 0.854, $CHCl_3$); IR (thin film) 3070, 2930, 1716, 1602, 1584, 1451, 1363, 1274, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97−8.21 (4H, m), 7.26−7.66 (16H, m), 5.85 (1H, m), 5.45 (1H, m), 5.05−5.14 (3H, m), 4.64 (1H, d, *J* = 6.8 Hz), 4.54 (1H, d, *J* = 6.8 Hz), 4.48 (1H, m), 4.11 (1H, dd, *J* = 9.1, 5.0 Hz), 3.33−3.68 (8H, m), 3.48 (3H, s), 3.36 (3H, s), 2.55 (1H, m), 1.41-1.86 (7H, m), 1.06 (6H, m), 0.89 (15H, m); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 166.1, 139.3, 135.4, 133.8, 133.7, 132.7, 130.7, 130.0, 129.9, 129.5, 128.3, 128.1, 127.5, 115.8, 106.5, 98.0, 87.9, 84.1, 78.2, 74.1, 73.0, 71.7, 67.8, 64.6, 61.5, 60.3, 59.0, 50.4, 42.4, 35.1, 34.1, 33.4, 27.8, 26.6, 23.1, 18.9, 17.7, 15.9, 10.0.

[3*R*,4*R*,5*S*,6*S*,8*S*,8(2*R*,3*R*,5*R*,7*S*,8*R*,9*R*)]-8-{9-[(Benzoyl)oxy]-7-[2-(*tert*-butyldiphenylsiloxy)ethyl]-3-(((2-methoxyethoxy)methyl)oxy)4,4,8-trimethyl-1,6-dioxaspiro-[4.5]dec-2-yl}-6-(benzoyloxy)-4-hydroxy-8-methoxy-3,5-dimethyloct-1-ene (37). Ozone was bubbled through a solution of olefin **36** (387 mg, 0.413 mmol, 1.00 equiv) in CH_2Cl_2 (10.0 mL) at −78 °C. The reaction was monitored by TLC for the consumption of the olefin at which time dimethyl sulfide (100 μL, 1.4 mmol, 3.3 equiv) was added. The solution was allowed to warm to 25 °C and stirred for 12 h. The solution was concentrated to afford a crude aldehyde as a yellow oil which was used directly in the next reaction.

To a suspension of potassium *tert*-butoxide (69 mg, 0.62 mmol, 1.5 equiv) in THF (5.0 mL) at −78 °C was added *trans*-2-butene (120 mg, 2.1 mmol, 5.2 equiv). *n*-Butyllithium (2.0 M in hexanes, 310 μL, 0.62 mmol, 1.5 equiv) was added, and the resulting yellow mixture was allowed to stir at −45 °C for 20 min. The reaction mixture was recooled to −78 °C, and a solution of (+)-*B*-methoxydiisopinocampheylborane (210 mg, 0.66 mmol, 1.6 equiv) in THF (2.0 mL) was added. The resulting light yellow mixture was stirred at −78 °C for 35 min. $BF_3{\cdot}Et_2O$ (81 μL, 0.66 mmol, 1.5 equiv) was added followed by the crude aldehyde (390 mg, 0.41 mmol, 1.0 equiv) in THF (5.0 mL). The thick white mixture was stirred at −78 °C for 1 h. The reaction was quenched by addition of 3 N aqueous NaOH (10 mL) followed by 30% aqueous H_2O_2 (10 mL). The reaction mixture was warmed to 25 °C and stirred for 1 h. The mixture was cooled and diluted with ethyl acetate (20 mL) and saturated aqueous NaCl (20 mL). The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic extracts were washed with saturated aqueous NaCl (25 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to give a clear colorless oil. The oil was chromatographed on silica gel (15% ethyl acetate−hexane) to give the diastereomers **37** (170 mg, 40%) and **38** (130 mg, 30%). For **37**: R_f 0.30 (30% ethyl acetate in hexane). $[\alpha]_D = -58$ (*c* 0.75, $CHCl_3$); IR (thin film) 3425, 2928, 1713, 1451, 1429, 1277, 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03−8.10 (4H, m), 7.26−7.58 (16H, m), 5.82 (1H, m), 5.64 (1H, m), 5.08 (3H, m), 4.62 (1H, d, *J* = 6.7 Hz), 4.54 (1H, d, *J* = 6.7 Hz), 4.42 (1H, m), 4.10 (1H, m), 3.30−3.77 (9H, m), 3.51 (3H, s), 3.33 (3H, s), 2.69 (1H, br s), 2.40 (1H, m), 2.11 (1H, m), 1.40−1.89 (7H, m), 1.15 (3H, d, *J* = 6.8 Hz), 1.06 (3H, s), 0.96 (3H, d, *J* = 6.8 Hz), 0.89 (15H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.9, 139.1, 135.5, 133.9, 133.8, 132.8, 132.7, 130.8, 130.6, 129.9, 129.6, 129.5, 129.4, 128.3, 128.2, 127.6, 116.2, 106.6, 97.9, 87.7, 84.2, 79.1, 76.6, 73.1, 72.7, 71.7, 67.9, 64.5, 61.7, 60.5, 59.0, 50.5, 40.5, 39.6, 35.3, 34.2, 31.4, 27.8, 26.7, 23.1, 19.0, 17.8, 17.7, 11.3, 10.0; HRFABMS CH_2Cl_2/NBA/NaCl calcd for MNa^+ ($C_{58}H_{78}O_{12}SiNa$) 1017.5160, found 1017.5104 (error 5.5 ppm).

[3*S*,4*S*,5*S*,6*S*,8*S*,8(2*R*,3*R*,5*R*,7*S*,8*R*,9*R*)]-8-{9-[(Benzoyl)oxy]-7-[2-(*tert*-butyldiphenylsiloxy)ethyl]-3-((2-methoxyethoxy)methoxy)-4,4,8-trimethyl-1,6-dioxaspiro[4.5]dec-2-yl}-6-(benzoyloxy)-4-hydroxy-8-methoxy-3,5-dimethyloct-1-ene (38). For **38**: R_f 0.20 (30% ethyl acetate in hexane). $[\alpha]_D = -58$ (*c* 0.96, $CHCl_3$); IR (thin film) 3507, 3060, 2931, 1714, 1601, 1451, 1362, 1276, 1112 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01−8.12 (4H, m), 7.26−7.54 (16H, m), 5.84 (1H, m), 5.42 (1H, m), 5.09 (3H, m), 4.69 (1H, d, *J* = 6.7 Hz), 4.60 (1H, d, *J* = 6.7 Hz), 4.44 (1H, m), 4.12 (1H, dd, *J* = 9.0, 5.1 Hz), 3.34−3.65 (9H, m), 3.41 (3H, s), 3.36 (3H, s), 2.62 (1H, br s), 2.32 (1H, m), 1.41−2.02 (8H, m), 1.06 (3H, s), 0.97 (3H, d, *J* = 6.9 Hz), 0.93 (3H, d, *J* = 6.8 Hz), 0.88 (15H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 166.3, 141.8, 135.5, 135.4, 133.8, 133.6, 133.0, 132.7, 130.6, 130.2, 129.9, 129.7, 129.5, 128.4, 128.1, 127.5, 115.3, 106.6, 97.9, 87.5, 84.3, 78.3, 74.3, 73.7, 73.1, 71.8, 68.0, 64.7, 61.4, 60.4, 59.1, 50.5, 41.0, 39.3, 35.0, 34.0, 33.5, 27.7, 26.6, 23.1, 18.9, 17.7, 16.5, 10.0, 8.7; HRFABMS CH_2Cl_2/NBA/NaCl calcd for MNa^+ ($C_{58}H_{78}O_{12}SiNa$) 1017.5160, found 1017.5117 (error 4.3 ppm).

[3*R*,4*R*,5*S*,6*S*,8*S*,8(2*R*,3*R*,5*R*,7*S*,8*R*,9*R*)]-8-{9-[(*tert*-Butyldimethylsiloxy]-7-[2-(*tert*-butyldimethylsiloxy)ethyl]-3-hydroxy-4,4,8-trimethyl-1,6-dioxaspiro[4.5]dec-2-yl}-4,6-bis(*tert*-butyldimethylsiloxy)-8-methoxy-3,5-dimethyloct-1-ene (41). To a solution of the dibenzoate **37** (482 mg, 0.484 mmol, 1.00 equiv) in CH_2Cl_2 (10 mL) at −78 °C was added allylmagnesium bromide (1.0 M in Et_2O, 3.9 mL, 3.9 mmol, 8.1 equiv). The solution was allowed to warm to 25 °C over 30 min; then the reaction was quenched by the addition of H_2O (4.0 mL). The resulting slurry was filtered, and the funnel was rinsed with CH_2Cl_2 (2 × 10 mL). The filtrate was poured in to a separatory funnel and diluted with CH_2Cl_2 (20 mL) and saturated aqueous NaCl (30 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with saturated aqueous NaCl (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure to afford the crude triol as an oil which was used directly in the next step.

The crude triol was dissloved in THF (15 mL), and TBAF (1.0 M, 0.50 mL, 0.50 mmol, 1.0 equiv) was added. The solution turned brown and was allowed to stir for 12 h. The solution was concentrated to dryness and chromatographed on silica gel (5% methanol in CH_2Cl_2) to give the 260 mg of a tetrol. To a solution of the tetrol (250 mg, 0.456 mmol, 1.00 equiv) in CH_2Cl_2 (20 mL) at −78 °C was added 2,6-lutidine (350 μL, 3.00 mmol, 6.58 equiv) followed by TBSOTf (570 mL, 2.48 mmol, 5.44 equiv). The solution was warmed to 0 °C over 1 h; then the reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (20 mL). The combined organic extracts were washed wilth saturated aqueous NaCl (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting oil was chromatographed on silica gel (ethyl acetate−hexane) to give 234 mg of a MEM ether product. To a solution of the MEM ether (230 mg, 0.229 mmol, 1.00 equiv) in CH_2Cl_2 (10 mL) was added $ZnBr_2$ (40 mg, 0.18 mmol, 0.78 equiv). The suspension was allowed to stir at 25 °C for 24 h at which time the solvent was removed under reduced presure. The resulting oil was chromatographed on silica gel (5% ethyl acetate−hexane) to give **41** (147 mg, 35% for four steps): R_f 0.90 (10% ethyl acetate in hexane). $[\alpha]_D = -54.0$ (*c* 0.92, $CHCl_3$); IR (thin film) 3510, 2953, 2929, 1472, 1361, 1255, 1097 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.90 (1H, m), 4.97 (2H, m), 4.58 (1H, m), 4.28 (1H, m), 3.98 (1H, dd, J = 8.8, 4.0 Hz), 3.63 (3H, d, J = 141.1 Hz), 3.61 (2H, m), 3.36−3.54 (5H, m), 2.43 (1H, m), 1.87 (1H, m), 1.75 (1H, dd, J = 14.2, 4.0 Hz), 1.56−1.70 (4H, m), 1.49 (1H, dd, J = 14.2, 1.8 Hz), 1.28 (1H, m), 1.10 (3H, s), 1.05 (3H, d, J = 7.1 Hz), 0.92 (9H, s), 0.89 (9H, s), 0.88 (12H, s), 0.87 (9H, s), 0.83 (3H, d, J = 7.1 Hz), 0.78 (3H, d, J = 6.6 Hz), 0.14 (3H, s), 0.09 (3H, s), 0.06 (6H, s), 0.05 (3H, s), 0.03 (6H, s), 0.02 (3H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 141.5, 113.6, 108.5, 87.9, 80.2, 78.9, 77.6, 70.6, 68.2, 65.3, 60.5, 60.5, 60.4, 60.1, 60.0, 59.9 (-O^{13}CH$_3$), 59.6, 56.0, 49.3, 43.9, 42.4, 37.3, 35.5, 33.8, 30.4, 26.3, 26.0, 25.98, 25.93, 25.88, 22.1, 18.5, 18.3, 18.2, 18.1, 16.6, 16.0, 10.5, 10.1, −3.7, −3.8, −3.9, −4.3, −4.7, −5.0, −5.4; HRFABMS NaCl calcd for MNa^+ ($C_{48}H_{100}O_8NaSi_4$) 940.64266, found 940.6408 (error 2.0 ppm).

(*E*)-1-(*tert*-Butyldimethylsiloxy)-3-iodo-2-methyl-2-propene (44). To a solution of alcohol **43** (4.96 g, 25.0 mmol) at 0 °C in CH_2Cl_2 (50 mL) were added triethylamine (7.0 mL, 50.1 mmol), TBS-Cl (4.15 g, 27.5 mmol), and DMAP (62 mg, 2 mol %). The resulting mixture was warmed to rt and stirred for 18 h. The solvent was removed under reduced pressure, and the resulting crude product was suspended in ether (50 mL). The suspension was washed with saturated aq NH_4Cl (100 mL) and 5% aqueous $NaHCO_3$ (50 mL), dried over $MgSO_4$, and concentrated to afford **44** as a crude oil (7.5 g, 97%). The product was deemed pure by ^1H NMR and carried on without purification: IR (thin film) 2954, 2928, 1464, 1362, 1279, 1251, 1143, 1106 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.20 (1H, s), 4.10 (2H, s), 1.78 (3H, s), 0.90 (9H, s), 0.05 (6H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 146.8, 75.9, 67.1, 31.6, 25.8, 25.7, 22.6, 21.2, 18.8, 14.1; HRFABMS calcd for M^+ ($C_{10}H_{21}IOSi$) 312.0408, found 312.0406 (error 0.6 ppm).

(*E*)-1-(*tert*-Butyldimethylsiloxy)-2-methyl-3-(tributylstannyl)-2-propene (45). To a solution of vinyl iodide **44** (8.60 g, 26.6 mmol) at −78 °C in THF (200 mL) was added dropwise *tert*-butyllithium (32.4 mL, 55.1 mmol, 1.7 M in pentane) over a period of 30 min. The mixture was stirred at −78 °C for 30 min, at which time tributyltin chloride (8.2 mL, 28.9 mmol) was added slowly. This mixture was stirred at −78 °C for 30 min and then warmed to rt. After stirring at rt for 15 min, the mixture was concentrated under reduced pressure. The resulting crude product was suspended in hexanes (150 mL) and washed with H_2O (2 × 50 mL). The organic layer was then dried over Na_2SO_4, concentrated, and purified by column chromatography on silica gel (20% triethylamine in hexanes) to afford vinylstannane **45** (15.7 g, 77%): IR (thin film) 2955, 2926, 1250, 1136, 1103 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.89 (1H, s), 4.07 (2H, s), 1.71 (3H, s), 1.51−1.45 (6H, m), 1.34−1.27 (6H, m), 0.9−0.8 (24H, m), 0.06 (6H, s); ^{13}C NMR (90 MHz, $CDCl_3$) δ 157.7, 120.1, 68.9, 29.2, 27.3, 26.0, 21.0, 18.4, 13.7, 10.0, −5.3; HRFABMS calcd for M^+ ($C_{22}H_{48}OSiSn$) 475.2496, found 475.2491 (error 1.0 ppm).

(*E*)-3-(Tributylstannyl)-2-methylpropen-1-ol (46). To a solution of silyl ether **45** (3.0 g, 6.3 mmol) at 0 °C in THF (40 mL) was added dropwise TBAF (6.3 mL, 6.3 mmol, 1 M in THF). After 10 min at 0 °C, the reaction mixture was warmed to rt, stirred for an additional 40 min, and quenched via addition of a saturated aq NH_4Cl solution (∼1 mL). The resulting mixture was concentrated at reduced pressure and dissolved in ether (25 mL). The organic phase was washed with H_2O (20 mL), dried over $MgSO_4$, and concentrated. Purification via column chromatography on silica gel (20% ethyl acetate−hexanes) afforded **46** (2.2 g, 92%): IR (thin film) 3312, 2955, 2922, 1521, 1464, 1456, 1374 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.80 (1H, s), 4.07 (2H, d, J = 4.2 Hz), 1.77 (3H, s), 1.46−1.50 (6H, m), 1.27−1.33 (6H, m), 0.85−0.95 (15H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 152.3, 120.7, 68.8, 29.2, 27.3, 21.3, 13.7, 10.0.

(*E*)-3-(Tributylstannyl)-1-(methanesulfonyloxy-2-methyl-2-propene (47). To a solution of alcohol **46** (257 mg, 0.713 mmol) at 0 °C in ethyl ether (10 mL) were added triethylamine (198 μL, 1.42 mmol), DMAP (2 mg), and methanesulfonyl chloride (61 μL, 0.78 mmol). The mixture was warmed to rt and stirred for 30 min, at which time the suspension was filtered. The resulting organic layer was washed with H_2O (2 × 5 mL), dried over Na_2SO_4, and concentrated to afford mesylate **47** (287 mg, 92%). Purity of the product was established by ^1H NMR, and therefore, the crude product was carried on without purificaton: IR (thin film) 2956, 2926, 1603, 1251 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.00 (1H, s), 4.66 (2H, s), 3.01 (3H, s), 1.84 (3H, s), 1.46−1.51 (6H, m), 1.27-1.33 (6H, m), 0.85−0.90 (15H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 145.7, 131.1, 76.0, 37.8, 29.3, 21.1, 13.6, 10.0.

(*E*)-3-(Tributylstannyl)-2-methyl-1-(dimethylphosphono)-2-propene (48). Dimethyl phosphite (2.5 mL, 27 mmol) was added slowly to a suspension of sodium hydride (1.085 g, 27.1 mmol, 60% oil dispersion) in THF (45 mL). This mixture was stirred for 2 h and cannulated into a solution of mesylate **47** (1.986 g, 4.52 mmol) in THF (5 mL). The resulting mixture was heated to 45 °C and stirred for 1 h. The mixture was then concentrated, and the resulting crude product was suspended in ether (100 mL). The suspension was washed with saturated aq NH_4Cl (2 × 75 mL), H_2O (1 × 75 mL) and dried over Na_2SO_4, and concentrated. Purification via column chromatography on silica gel (0−25% ethyl acetate−35% triethylamine−hexane) afforded phosphonate **48** (1.18 g, 58%): IR (thin film) 2955, 2925, 1603, 1465, 1457, 1375, 1256, 1183 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.69 (1H, dt, J = 27.0, 5.0 Hz), 3.73 (6H, d, J = 10.9 Hz), 2.74 (2H, d, J = 22.3 Hz), 1.91 (3H, d, J = 3.2 Hz), 1.45−1.51 (6H, m), 1.27−1.33 (6H, m), 0.86−0.92 (15H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 143.6 (d, J = 43 Hz), 129.9 (d, J = 48 Hz), 52.7 (d, J = 27 Hz), 38.6 (d, J = 532 Hz), 25.6, 29.1, 27.3, 13.7, 10.1; HRFABMS calcd for MH^+ ($C_{18}H_{40}O_3PSn$) 455.1737, found 455.1737 (error 0.0 ppm).

(*E*)-1-(Tributylstannyl)-2-methyl-3-(dimethylphosphono)-1-butene (6). To a solution of phosphonate **48** (1.18 g, 2.6 mmol) at −78 °C in THF (25 mL) was added *n*-butyllithium (1.36 mL, 2.73 mmol, 2 M in pentane). The orange solution was stirred at −78 °C for 15 min, at which time iodomethane (187 μL, 3.0 mmol) in THF (1 mL) was added. The mixture was allowed to warm to rt over 40 min and then poured into H_2O (50 mL). The aqueous layer was extracted with ether (2 × 75 mL), and the combined organics were washed with brine (50 mL), dried over Na_2SO_4, and concentrated. Purification via column chromatography on silica gel (20% ethyl acetate−35% triethylamine−hexane) afforded phosphonate **6** (1.08 g, 89%): IR (thin film) 2955, 2925, 1457, 1250, 1183 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.75 (1H, dt, J = 27.0, 5.0 Hz), 3.71 (3H, d, J = 10.7 Hz), 3.70 (3H, d, J = 10.3 Hz), 2.78 (1H, dq, J = 23.1, 7.3 Hz), 1.90 (3H, d, J = 2.8 Hz), 1.45−1.51 (6H, m), 1.35 (3H, d, J = 7.3 Hz), 1.27−1.33 (6H, m), 0.87−0.92 (15H, m); ^{13}C NMR (90 MHz, $CDCl_3$) δ 149.7 (d, J = 36 Hz), 127.4 (d, J = 46 Hz), 53.1 (d, J = 28 Hz), 52.8 (d, J = 28 Hz), 42.7 (d, J = 529 Hz), 29.1, 27.3,24.0, 14.4, 13.7, 10.1; HRFABMS calcd for M^+ ($C_{19}H_{42}O_3PSn$) 469.1893, found 469.1893 (error 0.0 ppm).

(1*E*,3*E*)-1-(Tributylstannyl)-4-methyl-5-(dimethylphosphono)-1,3-hexadiene (49). To a solution of stannane **6** (107 mg, 0.23 mmol) in THF (3 mL) at 0 °C was added

dropwise a solution of I_2 (58 mg, 0.23 mmol) in THF (1 mL). The resulting mixture was allowed to warm to rt over 30 min, at which time the mixture was partitioned between ether (20 mL) and 10% aqueous $Na_2S_2O_3$ (10 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated. Purification via column chromatography on silica gel (0−5% CH_3OH−CH_2Cl_2) afforded 63 mg of a yellow oil that was dissolved in THF (2 mL). To this mixture was added bis(triphenylphosphine)palladium(II) chloride (5 mg, 3 mol %), followed by *trans*-bis(tributylstannyl)ethylene (200 mg, 0.33 mmol). The reaction mixture was stirred at rt for 20 h, at which time it was concentrated. The resulting crude product was partitioned between CH_2Cl_2 (20 mL) and saturated aqueous $NaHCO_3$ (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (1 × 20 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification via column chromatography on silica gel (0−40% ethyl acetate−1% triethylamine−hexane) afforded diene **49** (36 mg, 33%). The ^{1}H NMR data matched the identical compound reported by Evans.[13a]

[2*Z*,4*E*,6*E*,8*E*,10*R*,11*R*,12*S*,13*S*,15*S*,15(2*R*,3*R*,5*R*,7*S*,8*S*,9*R*)]-15-[9-(*tert*-Butyldimethylsiloxy)-7-[2-(*tert*-butyldimethylsiloxy)ethyl]-3-hydroxy-4,4,8-trimethyl-1,6-dioxospiro[4.5]dec-2-yl]-11,13-bis(*tert*-butyldimethylsiloxy)-15-methoxy-3,7,8,10,12-pentamethyl-2,4,6,8-pentadecatetraenenitrile (50). To a solution of phosphonate **49** (36 mg, 0.073 mmol) in THF (0.7 mL) at −78 °C was added dropwise *n*-butyllithium (37 μL, 0.073 mmol, 1.95 M in pentane). The yellow solution was stirred for 2 min at -78 °C and then warmed to rt over 10 min. A solution of aldehyde **42** (19 mg, 0.021 mmol) in THF (0.5 mL + 2 × 0.5 mL rinses) was added, and the resulting red solution was stirred at rt. After 20 min, the reaction was quenched via addition of saturated aq NH_4Cl (2 mL) and H_2O (1 mL). This mixture was extracted with CH_2Cl_2 (4 × 5 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated to afford a yellow oil which was dissolved in 1-methyl-2-pyrrolidinone (1.2 mL). To this mixture was added vinyl iodide **5** (15 μL, 0.146 mmol), followed by bis(acetonitrile)palladium(II) chloride (0.5 mg). The resulting black solution was stirred at rt. After 36 h, 0.5 mg of the Pd catalyst was added, and after 42 h, an additional 0.5 mg of Pd catalyst and 5 μL of **5** were added. After 80 h, the reaction was quenched via addition of saturated aqueous $NaHCO_3$ (20 mL). The aqueous phase was extracted with ether (4 × 10 mL). The combined organics were washed with H_2O (10 mL), dried over Na_2SO_4, filtered, and concentrated. Purification via preparative thin layer chromatography on silica gel (0−10% ethyl acetate−5% triethylamine−hexane) afforded tetraene **50** (9 mg, 41%). ^{1}H and ^{13}C data mtached the enantiomer of **50** which was reported by Evans,[13a] with the exception of the methoxy group at C_{15} which bore a ^{13}C-label. **50**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (1H, dd, J = 14.9, 11.2 Hz), 6.81 (1H, d, J = 15 Hz), 6.33 (1H, d, J = 11.1 Hz), 6.05 (1H, d, J = 9.0 Hz), 5.04 (1H, s), 4.56 (1H, m), 4.22 (1H, m), 4.00 (1H, dd, J = 8.8, 4.1 Hz), 3.87 (1H, m), 3.67 (3H, d, J = 140.7 Hz), 3.66 (2H, m), 3.57−3.49 (3H, m), 3.42 (1H, d, J = 12 Hz), 2.73 (1H, m), 2.05 (3H, s), 2.00 (3H, s), 1.85 (3H, s), 1.72 (1H, dd, J = 14.2, 3.9 Hz), 1.57−1.66 (4H, m), 1.47 (1H, m), 1.23 (1H, m), 1.07 (3H, s), 1.00 (3H, d, J = 7.0 Hz), 0.92 (9H, s), 0.86 (18H, s), 0.85 (12H, s), 0.80 (3H, d, J = 7.0 Hz), 0.74 (3H, d, J = 7.0 Hz), 0.15 (3H, s), 0.07 (3H, s), 0.06 (3H, s), 0.03 (3H, s), 0.02 (3H, s), 0.01 (3H, s), −0.01 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 144.3, 134.4, 133.9, 133.4, 128.5, 124.0, 117.5, 108.5, 94.6, 87.9, 80.2, 77.6, 70.6, 68.4, 65.3, 60.1, 60.0, 59.8, 49.3, 46.2, 37.3, 35.5, 26.4, 26.0, 26.0, 25.9, 22.1, 19.4, 18.6, 18.3, 18.2, 18.1, 16.6, 14.5, 10.1, −3.5, −3.7, −4.2, −5.0, −5.3; HRFABMS DCM/NBA/NaCl calcd for MNa^+ ($C_{57}{}^{13}CH_{111}NO_8Si_4Na$) 1085.7318, found 1085.7365 (error 4.7 ppm).

[2*Z*,4*E*,6*E*,8*E*,10*R*,11*R*,12*S*,13*S*,15*S*,15(2*R*,3*R*,5*R*,7*S*,8*S*,9*R*)]-15-[9-(*tert*-Butyldimethylsiloxy)-7-(2-hydroxyethyl)-3-hydroxy-4,4,8-trimethyl-1,6-dioxaspiro-[4.5]dec-2-yl]-11,13-bis(*tert*-butyldimethylsiloxy)-15-methoxy-3,7,8,10,12-pentamethyl-2,4,6,8-pentadecatetraenenitrile (51). A stock solution of HF−pyridine was prepared by addition of HF−pyridine (0.5 mL, Aldrich) to pyridine (1 mL) and THF (4 mL). To a solution of tetraene **50** (24 mg, 0.023 mmol) in THF (2 mL) was added the above stock HF solution (0.8 mL). After the solution was stirred for 2.5 h at rt, the reaction was quenched via addition of saturated aqueous $NaHCO_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (5 × 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification via preparative thin layer chromatography on silica gel (17% ethyl acetate−hexane) afforded diol **51** (11.3 mg, 53%, 84% based on recovered starting material) and starting material **50** (9 mg). **51**: R_f 0.44 (20% ethyl acetate−hexane). $[\alpha]_D = -99.5$ (c 0.22, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (1H, dd, J = 14.9, 11.2 Hz), 6.88 (1H, d, J = 15.0 Hz), 6.39 (1H, d, J = 11.1 Hz), 6.11 (1H, d, J = 9.1 Hz), 5.17 (1H, s), 4.61 (1H, m), 4.31 (1H, m), 4.02 (1H, m), 3.86 (1H, m), 3.76 (2H, m), 3.66 (3H, d, J = 140 Hz), 3.57 (4H, m), 2.78 (1H, m), 2.11 (3H, d, J = 1.3 Hz), 2.05 (3H, s), 1.89 (3H, s), 1.70−1.84 (4H, m), 1.50−1.60 (3H, m), 1.38 (1H, m), 1.14 (3H, s), 1.07 (3H, d, J = 7.0 Hz), 0.98 (9H, s), 0.90−0.95 (21H, m), 0.89 (3H, d, J = 7.2 Hz), 0.80 (3H, d, J = 3.8 Hz), 0.22 (3H, s), 0.15 (3H, s), 0.13 (3H, s), 0.12 (3H, s), 0.10 (3H, s), 0.06 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 144.2, 134.5, 133.9, 133.1, 128.5, 124.1, 108.3, 94.7, 87.7, 80.2, 77.7, 70.7, 68.6, 66.0, 61.2, 59.8, 59.8, 59.5, 49.4, 44.9, 38.8, 37.3, 35.3, 30.4, 26.4, 26.0, 25.9, 22.4, 19.4, 18.6, 18.2, 18.1, 16.7, 14.5, 14.0, 14.1, 10.4, −3.5, −3.8, −3.9, −4.1, −4.7, −5.0; HRFABMS DCM/NBA/NaCl calcd for MNa^+ ($C_{51}{}^{13}CH_{97}NO_8Si_3Na$) 971.6453, found 971.6509 (error 5.7 ppm).

[2*E*,4*E*,6*E*,8*E*,10*R*,11*R*,12*S*,13*S*,15*S*,15(2*R*,3*R*,5*R*,7*S*,8*S*,9*R*)]-15-[9-(*tert*-Butyldimethylsiloxy)-7-(2-oxoethyl)-3-hydroxy-4,4,8-trimethyl-1,6-dioxaspiro[4.5]dec-2-yl]-11,13-bis(*tert*-butyldimethylsiloxy)-15-methoxy-3,7,8,10,12-pentamethyl-2,4,6,8-pentadecatetraenenitrile (52). To a solution of diol **51** (12.5 mg, 0.013 mmol) in CH_2Cl_2 (1 mL) was added pyridine (10 mL), followed by portions of Dess−Martin periodinane[37] (122 mg) over 2.5 h at rt. The reaction was quenched via addition of saturated aqueous $NaHCO_3$ (1 mL) and 1.5 M $Na_2S_2O_3$ (1 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 5 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. Purification via preparative thin layer chromatography on silica gel (20% ethyl acetate−hexane) afforded aldehyde **52** (12 mg, 98%): ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.75 (1H, d, J = 2.0 Hz), 6.99 (1H, dd, J = 11.1, 4.9 Hz), 6.80 (1H, d, J = 15.0 Hz), 6.33 (1H, d, J = 11.1 Hz), 6.05 (1H, d, J = 9.2 Hz), 5.01 (2H, m), 4.21 (1H, m), 3.97 (1H, dd, J = 8.2, 4.1 Hz), 3.83 (1H, m), 3.59 (3H, d, J = 140.7 Hz), 3.43−3.52 (3H, m), 2.97 (1H, d, J = 12.0 Hz), 2.70 (1H, m), 2.48 (2H, m), 2.05 (3H, s), 1.98 (3H, s), 1.85 (3H, s), 1.73 (1H, dd, J = 14.3, 3.7 Hz), 1.62 (2H, m), 1.51 (1H, m), 1.20−1.35 (2H, m), 1.06 (3H, s), 1.00 (3H, d, J = 6.8 Hz), 0.91 (9H, s), 0.81−0.89 (24H, m), 0.74 (3H, d, J = 7.0 Hz), 0.15 (3H, s), 0.07 (3H, s), 0.06 (3H, s), 0.05 (3H, s), 0.03 (3H, s), 0.01 (3H, s).

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Supporting Information Available: Procedures and characterization data for **14**, **24**, **33**, **34**, **39**, **40**, and **42**, an ORTEP diagram of compound **35**, and NMR spectra to indicate purity of new compounds (74 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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