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Enantioselective Total Synthesis of Altohyrtin C (Spongistatin 2)

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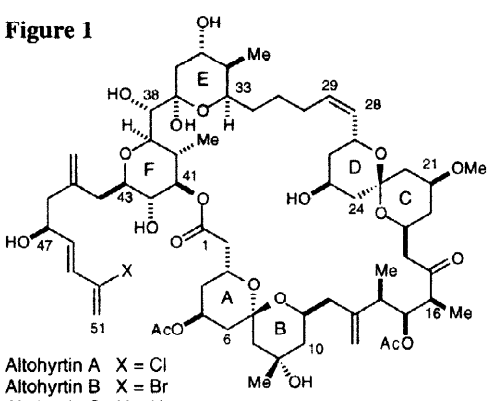
Abstract: The first total synthesis of a spongipyran macrolide, altohyrtin C, is described. The convergent synthesis strategy relies on a regioselective macrolactonization, a stereoselective Wittig coupling of the two major synthetic fragments, a complex *anti* aldol reaction to join the C_1-C_{15} and C_{16}-C_{28} spiroketal regions, and an anomeric sulfone acylation to join the C_{29}-C_{37} and C_{38}-C_{43} pyran regions. The incorporation of the C_{44}-C_{51} sidechain in the final stages of the synthesis establishes a viable route for the construction of variants in this pharmacologically important region. Methodological developments *en route* to the total synthesis include a 1,5 *anti*-selective methyl ketone aldol reaction and a diastereoselective approach to Lewis acid mediated β-*C*-glycosidation. Completion of the synthesis has confirmed the stereochemical assignments proposed in the altohyrtin series and has established the identity of the altohyrtin and spongistatin marine macrolides.

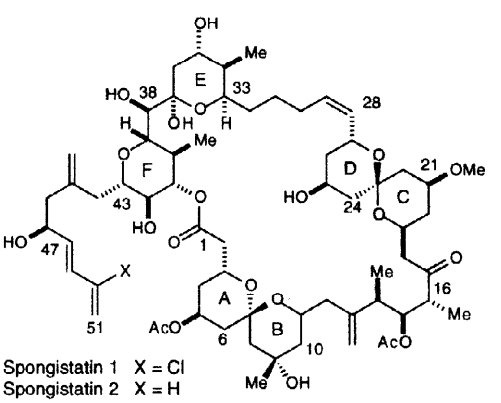
Keywords: asymmetric synthesis; antitumour compounds; marine metabolites; aldol reactions

Introduction

Since the initial reports of their isolation from marine sponges in 1993, the spongipyran macrolides have generated considerable interest in the fields of synthetic organic chemistry[1] and chemical biology.[2] Spongistatin 1 (isolated from *Spongia*),[3a] altohyrtin A (from *Hyrtios altum*),[4a] and cinachyrolide A (from *Cinachyra*)[5] were independently characterized by the Pettit, Kitagawa, and Fusetani groups and shown to comprise some of the most potent antitumor substances known. Against a National Cancer Institute panel of 60 highly chemoresistant tumor cell lines, spongistatin 1 exhibited IC_{50} values in the range of 0.03 nM; similar antitumor activities were noted for altohyrtin A and cinachyrolide A. Continued efforts by the Pettit and Kitagawa groups have isolated additional spongistatins (2-9)[3b-e] and altohyrtins (B, C, and 5-desacetylaltohyrtin A),[4b] all of which demonstrate potent *in vitro* antitumor activity. Preliminary biological investigations have demonstrated that the spongistatins inhibit tubulin polymerization by binding at a site distinct from those occupied by other known inhibitors.[2a]

Figure 1





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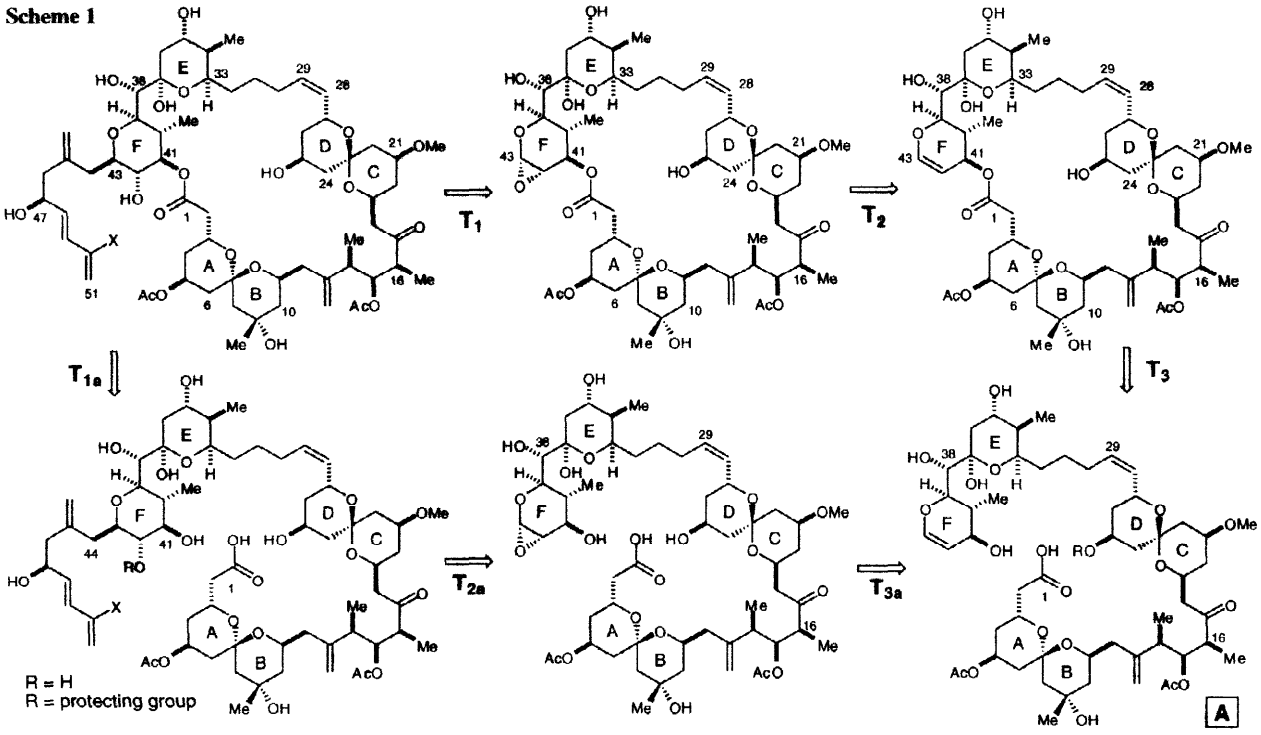
Structure Elucidation. The spongipyrans have been obtained from nature in minute quantities (the largest isolation yet reported yielded 14 mg of spongistatin 1 from 200 kg of *Spongia*),[6] and the scarcity of these natural products has prevented the unambiguous elucidation of their structures. Inspection of Figure 1 reveals that the structures proposed for the altohyrtins and spongistatins possess identical carbon connectivities and oxygenation patterns but differ with regard to internal stereochemical relationships.[7] Because the initial structural assignments of the natural products were based on NMR investigations, rigorous correlations of relative stereochemical assignments between subunits could not be obtained. The resulting uncertainty, in conjunction with the similar biological activities of the three families of molecules, raised the possibility that the spongistatins, altohyrtins, and cinachyrolides might all share an identical stereostructure.

Subsequent to the initial isolation reports, Kobayashi and Kitagawa have presented a convincing case for the altohyrtin structural assignment shown in Figure 1. A detailed Mosher ester analysis led to a complete absolute stereochemical proposal for the altohyrtins. This analysis was consistent with a circular dichroism exciton chirality assignment of the C_{47} sidechain stereocenter.[8a,b] Most recently, a restrained molecular dynamics study incorporating NMR data has corroborated the stereochemical assignment of the C_{14}-C_{16} propionate region.[8c]

Synthesis Plan. The extensive structural assignment work of Kobayashi and Kitagawa dictated the choice of the altohyrtins as primary targets for total synthesis. The synthesis strategy was guided by three imperatives: (1) the need for a convergent approach which could be readily altered to provide antipodes of stereochemically controversial subunits; (2) the desirability of an efficient route which might easily access natural product analogs with potential relevance to biological studies; and (3) an emphasis on development of new reaction methodology to achieve these objectives.

The retrosynthesis initially focused on the C_{44}-C_{51} sidechain as a potentially important contributor to pharmacological activity. In both the spongistatin and altohyrtin families, the identity of the substituent at C_{50} (Cl, H, or Br) appeared to significantly influence the observed IC_{50} values.[9] We therefore planned to add a sidechain allyl nucleophile to an advanced F-ring epoxide intermediate (Scheme 1, transform $\mathbf{T_1}$ or $\mathbf{T_{2a}}$) which could be derived from the corresponding dihydropyran (transform $\mathbf{T_2}$ or $\mathbf{T_{3a}}$). Successful implementation of this late stage sidechain addition would allow incorporation of a variety of C_{44}-C_{51} sidechains, natural or designed, into a common, fully elaborated intermediate.

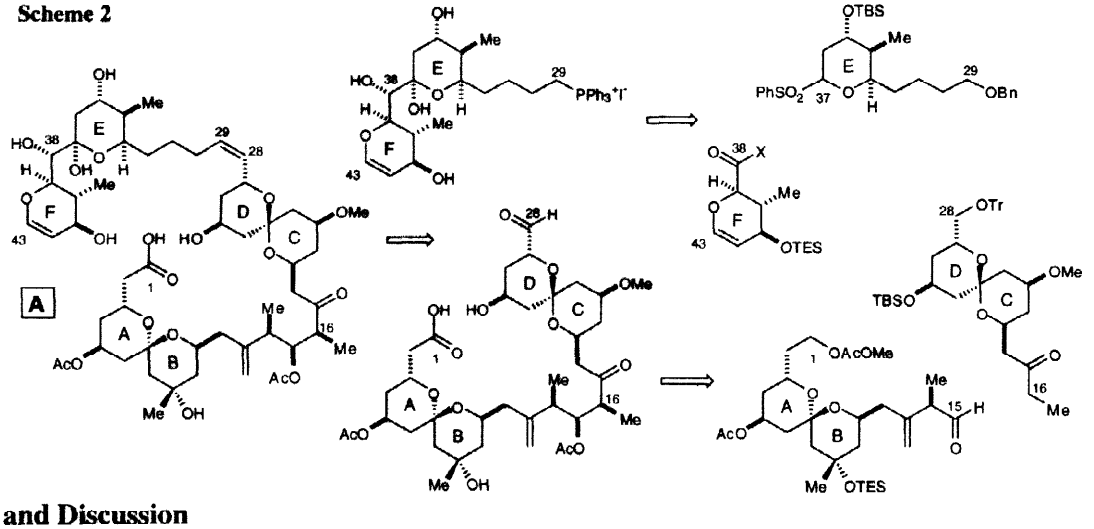
Scheme 1



The incorporation of the sidechain was intimately tied to our strategy for macrocyclization to form the 32-membered spongipyran lactone (Scheme 1, transform $\mathbf{T_3}$ or $\mathbf{T_{1a}}$). Macrolactonization involving the C_{41} hydroxyl and the C_1 carboxylate was clearly indicated, but the congested environment at C_{41} caused some concern. We believed that a C_{42}-protected seco acid precursor would be severely hindered and therefore difficult to cyclize (transform $\mathbf{T_{1a}}$, R = protecting group).[10] Any lactonization attempted with the C_{42} hydroxyl in place was therefore predicated on a regioselective C_{41}, C_{42} diol macrolactonization (transform $\mathbf{T_{1a}}$, R = H). An alternative approach involved macrolactonization before incorporation of the C_{42} hydroxyl. This strategy focused on the cyclization of a dihydropyran hydroxy acid (transform $\mathbf{T_3}$) followed by epoxidation (transform $\mathbf{T_2}$) and sidechain addition (transform $\mathbf{T_1}$).

Common to the two strategies was hydroxy acid **A**, which contains a complex array of six pyran rings (A, B, C, D, E and F) containing 21 stereogenic centers. Four of the pyran subunits participate in [5.5] dioxaspiroundecane spiroketal systems. To manage the synthesis of this complex target, a convergent synthesis plan was developed (Scheme 2). Our analysis provides for three strategic disconnections to yield four principal fragments. These fragments will be joined in three successive operations: (1) a stereoselective aldol reaction to join the AB and CD spiroketal systems; (2) formation of the EF bicycle by the addition of an E-ring anomeric sulfone anion to an F-ring carbonyl electrophile; and (3) union of these two complex fragments (ABCD + EF) by a Wittig coupling of a C_{29} unstabilized phosphonium ylide with a C_{28} aldehyde.

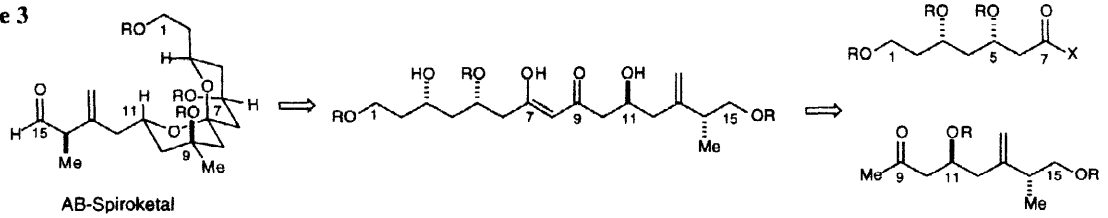
Scheme 2



Results and Discussion

Synthesis of the AB Spiroketal. The C_1-C_{15} fragment contains six stereogenic centers arrayed on a [5.5] spiroketal framework. Because the configuration of the anomeric carbon (C_7) of this system corresponds to the thermodynamically favored diaxial arrangement,[11] acid-catalyzed spirocyclization of a dihydroxy ketone precursor under equilibrating conditions should generate the desired spiroketal (Scheme 3). The acyclic precursor can be retrosynthetically bisected at the C_7-C_8 bond by a methyl ketone aldol or enolate acylation reaction to provide two segments of comparable complexity.

Scheme 3

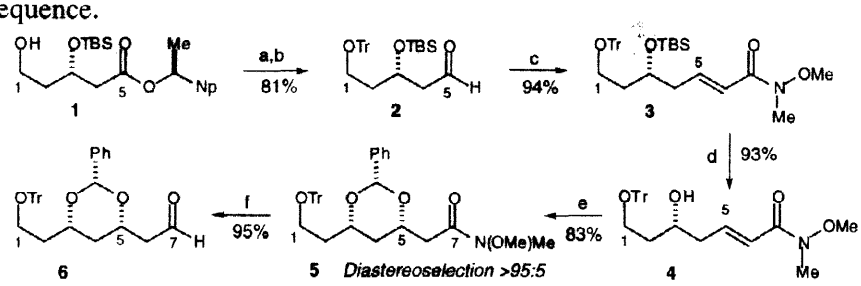


AB-Spiroketal

Synthesis of C_1-C_7 fragment **6** (Scheme 4) began from (*S*) alcohol **1**,[12] prepared from TBS-protected glutaric anhydride.[13] Successive trityl protection and DIBAlH reduction afforded aldehyde **2** (81%) along with recovered (*S*)-2-naphthylethanol. Wittig homologation[14] and silyl deprotection afforded **4**, which was subjected to base-induced internal heteroconjugate addition through the derived benzaldehyde hemiacetal to

afford the 1,3-*syn* acetal **5** (83%, dr >95:5).[15] DIBAlH reduction provided aldehyde **6** in 56% overall yield for the six-step sequence.

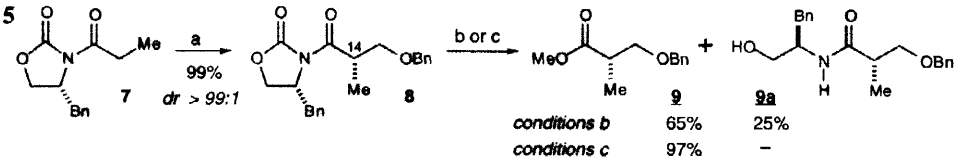
Scheme 4



(a) TrCl, Et_3N, CH_2Cl_2; (b) DIBAlH, toluene, -78 °C; (c) $Ph_3P{=}CHCO_2N(OMe)Me$, CH_2Cl_2; (d) TBAF, THF; (e) KO*t*-Bu, PhCHO, 0 °C; (f) DIBAlH, CH_2Cl_2, -78 °C.

The synthesis of the C_8-C_{15} fragment was initiated by alkylation of the *(Z)*-titanium enolate of the *N*-propionyloxazolidinone **7** with benzyloxymethylchloride to provide the known crystalline adduct **8** in 99% yield and >99:1 diastereoselection (Scheme 5).[16] Attempted methanolysis of the oxazolidinone chiral auxiliary in **8** using either stoichiometric or catalytic amounts of K_2CO_3 (MeOH, 0 °C) led to mixtures (2:1) of the desired ester **9** and amide byproduct **9a** resulting from endocyclic cleavage of the oxazolidinone ring. We subsequently found that the use of catalytic $Sm(OTf)_3$ in dry MeOH provided the desired methyl ester **9** in high yield. Recovery of the oxazolidinone auxiliary in this reaction is nearly quantitative (Scheme 5).

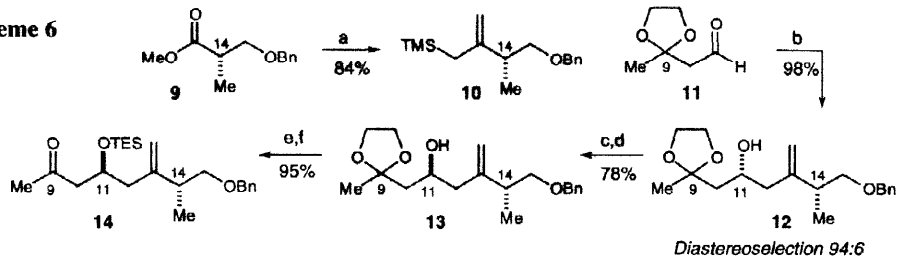
Scheme 5



	9	**9a**
conditions *b*	65%	25%
conditions *c*	97%	–

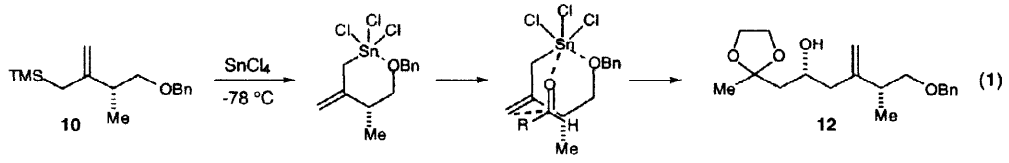
(a) i. $TiCl_4$, CH_2Cl_2, 0 °C; ii. Et_3N; iii. $PhCH_2OCH_2Cl$; (b) MeOH, K_2CO_3, 0 °C; (c) $Sm(OTf)_3$ (10 mol%), MeOH.

Scheme 6



(a) i. $TMSCH_2MgCl$, $CeCl_3$, THF, -78→ 25 °C; ii. silica gel, CH_2Cl_2, 25 °C; (b) i. **10**, $SnCl_4$ (1.1 equiv), CH_2Cl_2, -78 °C; ii. **11**, CH_2Cl_2; (c) *p*-$NO_2C_6H_4CO_2H$, PPh_3, di-*t*-butyl azodicarboxylate, toluene/THF, 0 °C; (d) K_2CO_3, MeOH; (e) PPTS, acetone, reflux; (f) TESOTf, 2,6-lutidine, CH_2Cl_2, -78 °C.

Transformation of methyl ester **9** to the derived allylsilane **10** was achieved with trimethylsilyl methylmagnesium chloride and cerium(III) chloride followed by acidic silica gel induced elimination (Scheme 6).[17] The optimal conditions for the allylsilane addition to aldehyde **11**[18] involved pre-treatment of **10** with $SnCl_4$ followed by addition of **11**. This protocol provided **12** in 98% yield (dr = 94:6); the observed stereoselectivity suggests a closed transition state involving an internally chelated allylstannane (eq. 1).[19] Mitsunobu inversion of the C_{11} alcohol[20] (79%) and subsequent methanolysis (99%) provided **13** possessing the desired absolute stereochemical relationships at both C_{11} and C_{14}. Successive ketal hydrolysis and silyl protection afforded the C_8-C_{15} methyl ketone fragment **14** in 53% overall yield for the seven-step sequence.

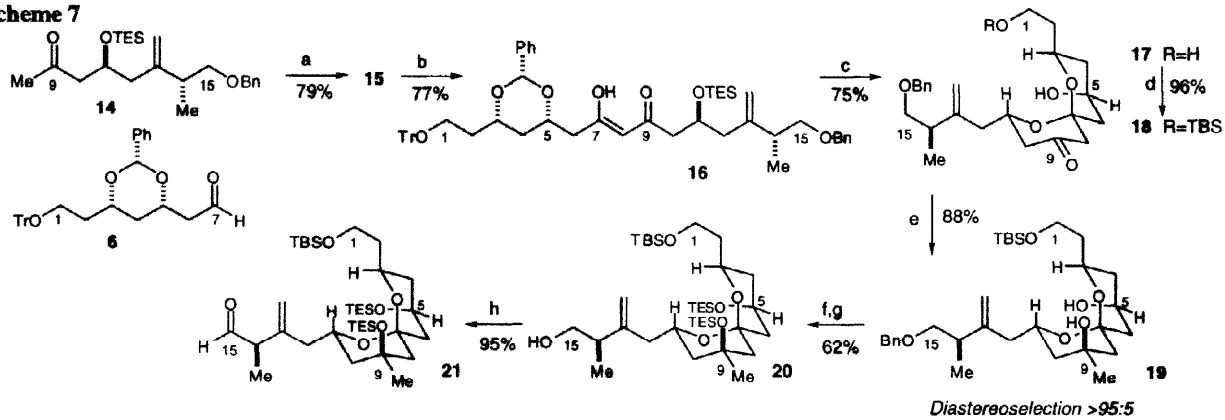


Union of the C_1-C_7 and C_8-C_{15} fragments was initiated by enolization of methyl ketone **14** with dibutylboron triflate and *i*-Pr_2NEt[21] followed by addition of aldehyde **6** to provide aldol adduct **15** (79%) as an incon-

sequential 1:1 mixture of C_7 diastereomers (Scheme 7). Oxidation of this mixture with chromium trioxide/pyridine/Celite[22] gave β-diketone **16** in 77% yield along with 12% recovered **15**. Multiple deprotection and spiroketalization of this substrate was achieved by treatment with $HF/H_2O/CH_3CN$. As anticipated, the only spiroketal diastereomer obtained (75%) from this transformation was the thermodynamically favored anomer **17**.[23]

After silylation of the C_1 terminus, construction of the requisite C_9 tertiary carbinol stereocenter was achieved by treatment of **18** with methyllithium and cerium trichloride in THF to provide axial alcohol **19** (88%; dr >95:5).[24] Silyl protection was followed by debenzylation (LDBB)[25] to afford the primary alcohol **20** in 62% yield (2 steps). Oxidation (Dess-Martin periodinane, pyridine, 95%) to aldehyde **21** proceeded without epimerization of the C_{14} stereocenter. It is noteworthy that this oxidant executes the transformation without inducing conjugation of the proximal olefin. Aldehyde **21**, which is too labile for chromatographic purification, must be used immediately in the critical aldol coupling to the CD-spiroketal (*vide infra*).

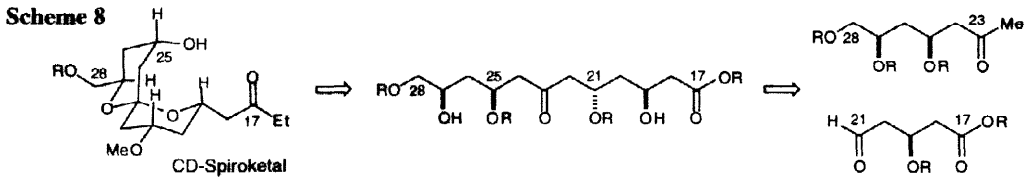
Scheme 7



(a) i. Bu_2BOTf, *i*-Pr_2NEt, CH_2Cl_2, -78 °C; ii. **6**, -78 °C; (b) CrO_3, pyridine, Celite, CH_2Cl_2; (c) $HF/CH_3CN/H_2O$; (d) TBSCl, imidazole, CH_2Cl_2; (e) MeLi, $CeCl_3$, THF, -78 °C; (f) TESOTf, 2,6-lutidine, CH_2Cl_2, -78 °C; (g) LDBB, THF, -78 °C; (h) Dess-Martin periodinane, pyridine, CH_2Cl_2.

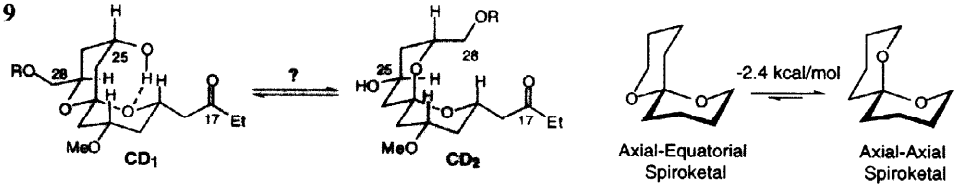
Synthesis of the CD Spiroketal. The CD spiroketal (C_{16}-C_{28}) contains a cluster of five stereogenic atoms arrayed on two spirofused pyran rings. Retrosynthetic unravelling of the CD spiroketal provides an acyclic dihydroxy ketone precursor which can be bisected at the C_{21}-C_{22} bond to give two fragments of similar size (Scheme 8).

Scheme 8



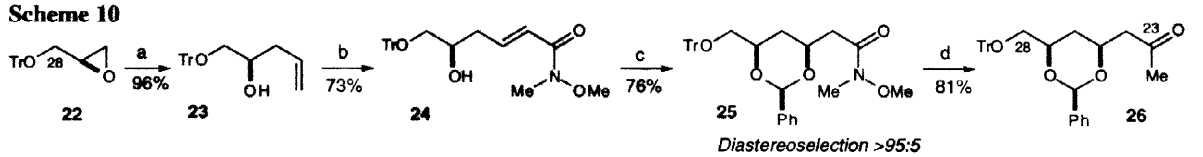
The configuration of the anomeric center (C_{23}) corresponds to a putatively disfavored axial-equatorial arrangement. In the absence of additional stabilizing interactions, the preferred 1,7-dioxaspirane conformation disposes each ring oxygen axial to its adjoining ring (Scheme 9). This "axial-axial" conformational bias is reinforced by the complementary equatorially disposed methylene substituents affording a significant bias (~2.4 kcal/mol) for the illustrated "axial-axial" conformer.[11] In the natural product, the CD spiroketal C_{23} configuration must be stabilized by additional factors which override the thermodynamic preference for the *bis*-axial configuration. Intramolecular hydrogen bonding can be an important influence in the stability of various spiroketal systems. This is particularly evident in systems containing a hydroxyl group and a spiro C-O bond in a 1,3 diaxial arrangement.[26] The axial C_{25}-hydroxyl substituent of the CD spiroketal can potentially participate in an intramolecular hydrogen bond with the axial C-O bond of the spiroketal (C_{23}) thereby stabilizing this particular spiroketal configuration (Scheme 9, CD_1). In addition to this phenomenon, constraints imposed by the macrocyclic structure may favor the observed axial-equatorial C_{23} configuration.

Scheme 9



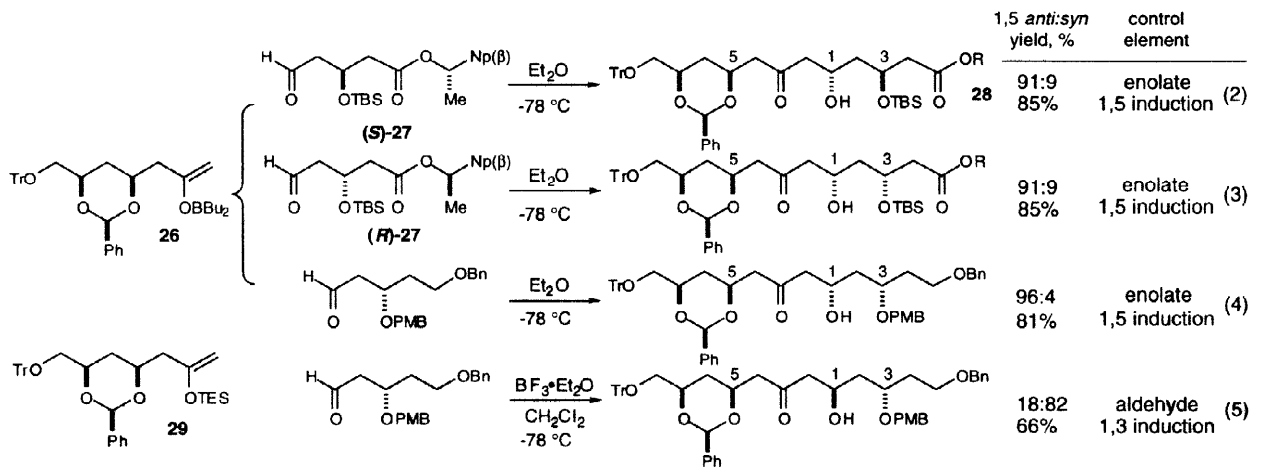
The synthesis of the acyclic precursor was initiated by the regioselective opening of (*R*)-trityl glycidol[27] (**22**) with divinylcuprate (Scheme 10). Carbinol **23** was conveniently homologated to α,β unsaturated amide **24** in a one-pot process involving ozonolysis of the alkene, reduction of the ozonide, and *in situ* Wittig olefination of the unpurified aldehyde with the requisite stabilized ylide reagent.[14] Base catalyzed intramolecular heteroconjugate addition (*vide supra*) of benzaldehyde hemiacetal alkoxide provided the protected 1,3 *syn* diol **25** as a single stereoisomer.[28] Organolithium addition afforded the desired methyl ketone fragment **26** (C_{28}-C_{22}) in 43% overall yield from (*R*)-trityl glycidol (4 steps).

Scheme 10



(a) Vinylmagnesium bromide, CuI, THF, -78 °C; (b) O_3, CH_2Cl_2, Ph_3P, -78 °C, then $Ph_3P{=}CHCO_2N(OMe)Me$, 73%; (c) KO*t*-Bu, PhCHO, 0 °C; (d) MeLi, THF, -78 °C.

With methyl ketone **26** in hand, we were poised to investigate the critical double stereodifferentiating[29] aldol coupling with aldehyde (*S*)-**27**[12] (Scheme 11). Control of the newly generated stereogenic center at C_{21} in the aldol addition reaction may be influenced, in principle, by remote stereocenters on both the aldehyde and enolate components. Our efforts to achieve this coupling have resulted in the discovery of a stereoselective aldol variant in which induction is controlled entirely by enolate stereochemistry. Addition of the dibutylboron enolate[21] of methyl ketone **26** to aldehyde (*S*)-**27** provides the 1,5 *anti* adduct **28**, which corresponds to the desired CD spiroketal stereoarray (eq. 2). The controlling element in this reaction is the enolate β stereocenter, as evidenced by the identical outcome of aldol addition to (*R*)-**27** (eq. 3). Additional experiments confirmed that the trend for 1,5-*anti* induction was general.[30] These results can be contrasted with the Mukaiyama aldol addition of the corresponding enolsilane **29**, in which the aldehyde β stereocenter is the primary source of induction (eq. 4 vs. eq. 5).[31]



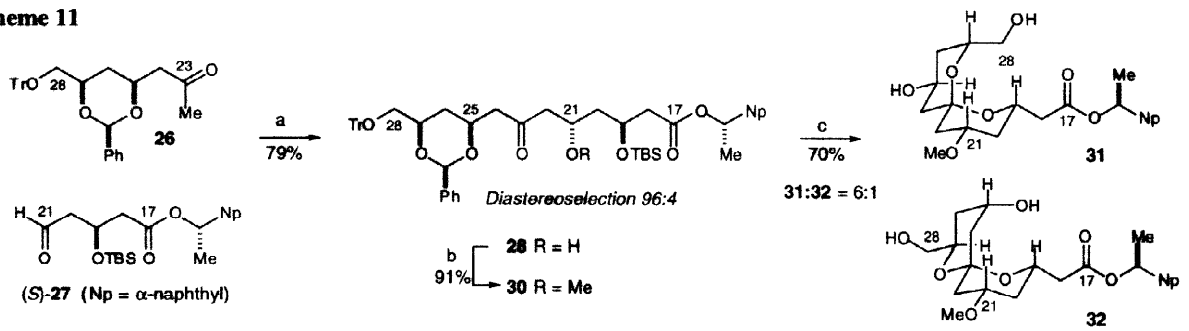
In preparative implementation of this process, reduction of the reaction temperature was found to further enhance the observed 1,5 *anti* selectivity. Thus aldol union of **26**, through its derived boron enolate, with aldehyde (*S*)-**27** at -110 °C proceeded with high diastereoselectivity (dr = 96:4). Methylation[32] of aldol adduct **28** afforded spirocyclization substrate **30**. Subsequent removal of the oxygen protecting groups positioned at C_{19}, C_{25}, C_{27}, and C_{28} and concomitant spirocyclization were achieved upon treatment of **30** with camphorsulfonic acid in a $MeOH/CH_2Cl_2$ solution (13 h, 25 °C).[33] Two separable isomeric spiroketal products **31** and

32 (ratio 6:1) were isolated in 70% yield. A byproduct which incorporated a second methyl ether at C_{25} was also identified (18%).[34] Diagnostic NOE experiments provided unequivocal stereochemical assignments for both spiroketal diastereomers.[35] The major isomer **31** possesses the undesired bis(axial) spirane ring fusion (CD_2, Scheme 9).

Formation of the desired axial-equatorial spiroketal **32** was accomplished by equilibration of the diaxial spiroketal **31** using either protic or Lewis acid catalysis. (eq. 6, Table 1).[26d,36] Equilibration of spiroisomer **31** with various Lewis acids led to preferential formation of the desired equatorial-axial spiroisomer **32**.

Presumably, the C_{25}-hydroxyl assists in these equilibrations[37] by participating in an internal chelate with the metal cation and the C_{27}-anomeric oxygen (structure **B**). Given that spiroketals **31** and **32** were prone to decomposition under these Lewis acidic conditions, magnesium trifluoroacetate offered the best compromise for maximizing both mass recovery (*ca.* 80%) and selectivity (2.6:1) for this equilibration.

Scheme 11



(a) Bu_2BOTf, *i*-Pr_2NEt, Et_2O, -110 °C, then (*S*)-**27**; (b) Me_3OBF_4, 2,6-di-*t*-butyl-4-methylpyridine; (c) CSA, $MeOH/CH_2Cl_2$.

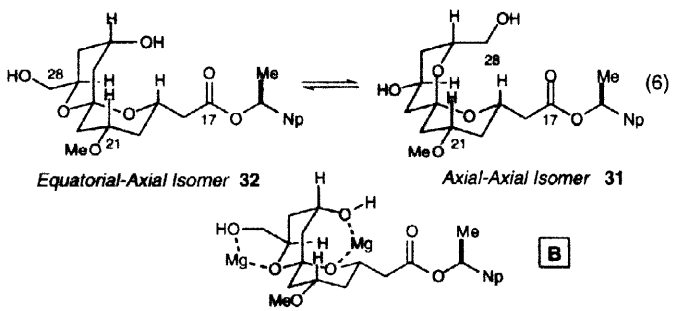
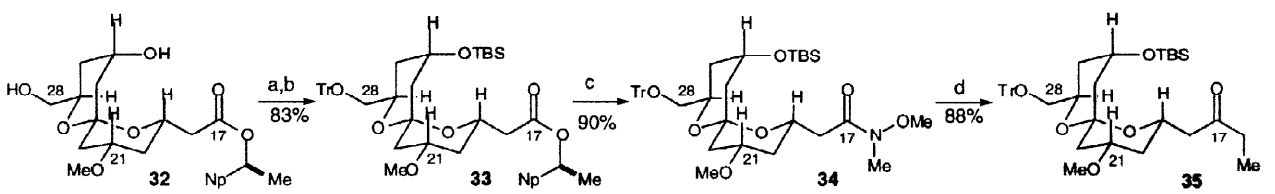


Table 1. CD spiroketal equilibration (eq. 6)

Conditions	Ratio (**32** : **31**)
CSA, $MeOH/CH_2Cl_2$, 24 h	1 : 6
CSA, CH_2Cl_2, 22 °C, 3 h	1 : 1
$ZnBr_2$, CH_2Cl_2, 22 °C, 1 h	2.3 : 1
$Mg(O_2CCF_3)_2$, CH_2Cl_2, 22 °C, 3 h	2.6 : 1
$ZnCl_2$, CH_2Cl_2, 22 °C, 3 h	4.3 : 1

Transformation of **32** to the CD-spiroketal ethyl ketone **35** (Scheme 12) was achieved by selective protection of the C_{28} hydroxyl of **32** as its derived trityl ether, TBS-silylation at C_{25}, and transformation of the C_{17} ester functionality to an ethyl ketone through the corresponding Weinreb amide **34**.[38] It is noteworthy that attempted transamidation of ester **33** under Lewis acidic conditions (MeONHMe•HCl, $AlMe_3$)[39] afforded none of the desired amide and led to appreciable epimerization of the spiroketal stereocenter to the unnatural diaxial configuration.

Scheme 12

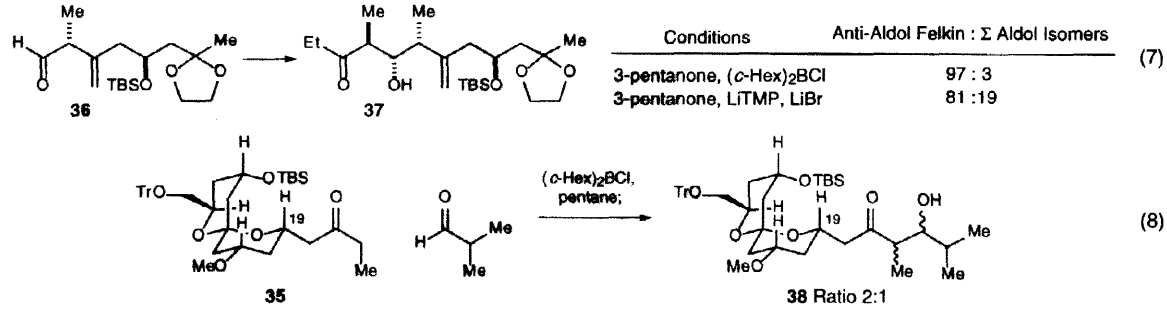


(a) TrCl, pyridine, 60 °C; (b) TBSOTf, 2,6-lutidine; (c) MeO(Me)NH•HCl, EtMgBr, THF, -10 °C; (d) EtMgBr, THF, 0 °C.

AB-CD Fragment Coupling. By employing an aldol addition of CD spiroketal ethyl ketone **35** to AB spiroketal aldehyde **21**, we planned to establish the stereocenters at C_{15} and C_{16} concomitant with the coupling of these two fragments. Ample precedent exists for establishment of the 1,2-*anti* relationship between C_{15} and C_{16} through the use of (*E*) boron enolates;[40] however, control of the incipient C_{15} hydroxyl configuration was

a concern. Because each reacting partner in this proposed aldol reaction has resident stereocenters which can potentially influence the stereochemical outcome of the reaction, the stereochemical preferences of each fragment were separately investigated.

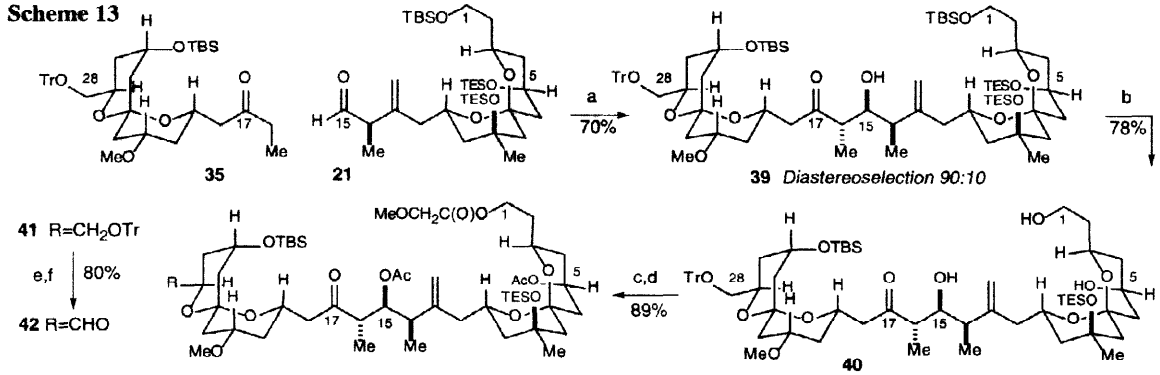
The relevant experiments are shown in equations 7 and 8. AB model aldehyde **36** underwent stereoselective aldol reactions with the boron and lithium enolates of 3-pentanone (eq. 7).[41] The reaction of the (*E*)-boron enolate prepared from dicyclohexylchloroborane and 3-pentanone with aldehyde **36** exhibited excellent selectivity for the desired *anti* aldol, Felkin addition product **37**. The (*E*)-lithium enolate derived from 3-pentanone and LiTMP/LiBr was somewhat less selective. In these experiments, it was essential to precisely control the stoichiometry of the boron Lewis acid; excess dicyclohexylchloroborane promoted the isomerization of the substrate to the corresponding α,β-unsaturated aldehyde.



In contrast, an investigation of the intrinsic diastereofacial bias of the (*E*) boron enolate derived from **35** indicated that remote chirality on **35** would play a subordinate role in the stereochemical outcome of the proposed aldol union (eq. 8). Stereoselective formation of the (*E*)-boron enolate of **35** using Brown's procedure[42] and subsequent aldol coupling with isobutyraldehyde gave an inseparable mixture of the two aldol products **38** (ratio 2:1). The products are presumably the two possible *anti*-aldol isomers. The absence of significant levels of 1,4 asymmetric induction arising from the C_{19} stereocenter implies that the (*E*)-boron enolate of ketone **35** would have a negligible facial bias in the projected double stereodifferentiating aldol fragment coupling.

Based on these results, the critical C_{15}-C_{16} bond construction was achieved by selective formation of the (*E*)-boron enolate of **35** using (*c*-Hex)$_2$BCl and triethylamine in pentane (Scheme 13). Addition of the unpurified aldehyde **21** to the enolate solution at -78 °C provided a mixture of aldol diastereomers (dr 90:10) favoring the desired stereoisomer in 70% overall yield. The desired isomer **39** could be obtained in 64% isolated yield over two steps (oxidation and aldol).

Scheme 13



(a) (*c*-Hex)$_2$BCl, Et_3N, pentane, 0 °C, 90 min, then -78 °C, add **21**; (b) HF•pyridine, THF, 0 °C; (c) $MeOAc_2O$, *i*-Pr_2EtN, CH_2Cl_2; (d) Ac_2O, DMAP, pyridine, 22 °C; (e) Me_2AlCl, CH_2Cl_2, -78 °C; (f) Dess-Martin periodinane, CH_2Cl_2.

At this point, incorporation of the C_5 and C_{15} acetate residues present in the altohyrtin structure was addressed. Selective desilylation of **39** at C_1 and C_5 using buffered HF•pyridine provided triol **40** (78%).[43] Selective monoacetylation at the C_1-hydroxyl using methoxyacetic anhydride was followed by bis(acylation) at C_5 and C_{15} with acetic anhydride to afford **41** (89%). The selection of the methoxyacetyl residue for interim protection of the C_1 terminus was made after difficulties were encountered in the selective hydrolysis of the

corresponding C_1 acetate. Optimal conditions (Et_3N, $MeOH/H_2O$)[44] promoted the slow (> 72 h) removal of the C_1 acetate. However, during this extended reaction time, deacetylation at C_1 was accompanied by β-elimination of the C_{15} acetate to give substantial amounts of the corresponding α,β unsaturated ketone.

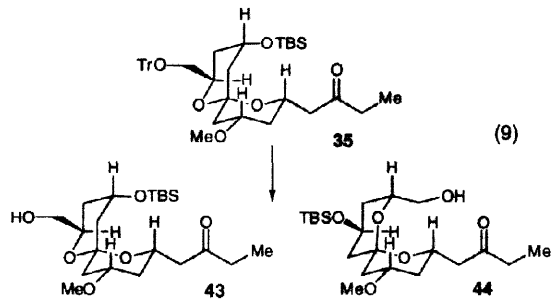
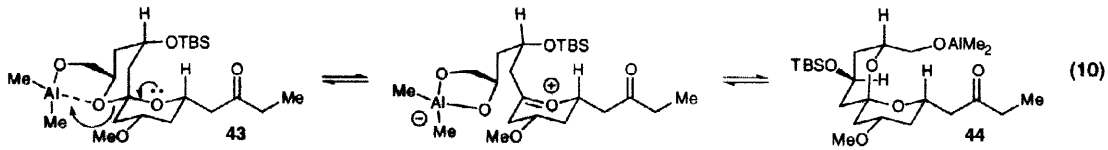


Table 2. Evaluation of trityl deprotection conditions

Entry	Conditions	43	44
1	Pd/C, cyclohexadiene, EtOH, 36 h	60%	-
2	$SnCl_2$, pyridine, EtOH, reflux, 24 h	-	51%
3	$ZnBr_2$, MeOH, r.t., 24 h	-	>90%
4	Me_2AlCl, CH_2Cl_2, 90 min quench satd. $NaHCO_3$	-	71%
5	Me_2AlCl, CH_2Cl_2, 90 min quench satd. Rochelle's Salt	83%	-

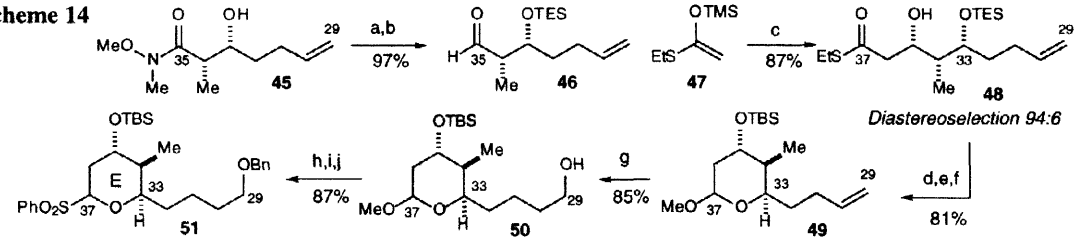


Refunctionalization of the C_{28} terminus in preparation for Wittig coupling was then undertaken. Removal of the C_{28} trityl ether proved to be a challenging transformation due to the lability of the equatorial-axial spiroketal center, which precluded the use of protic acids. This deprotection was modelled with the CD spiroketal ethyl ketone **35** (eq. 9, Table 2). Transfer hydrogenolysis of the trityl ether (entry 1)[45] proceeded slowly, and considerable unreacted starting material remained after 36 hours. Application of these conditions to the fully elaborated ABCD *bis*-spiroketal system resulted in competing saturation of the C_{13} disubstituted olefin. A range of Lewis acids[46,47] (entries 2 and 3) promoted trityl deprotection; however, in nearly all cases, isomerization of the spiroketal system to the bis(axial) configuration was observed. Dimethylaluminum chloride[48] was uniquely effective, promoting the efficient removal of the trityl ether at -78 °C with minimal epimerization at C_{23}. It was critical in these experiments to perform a work-up procedure which resulted in the removal of the organoaluminum salts prior to concentration of the crude product residue. If this procedure was not performed correctly, quantitative isomerization of the product was observed (entries 4 and 5). Presumably, the intermediate organoaluminum species can internally activate the spiroketal system toward isomerization via an oxocarbenium ion intermediate (eq. 10).

This deprotection reaction was applied to the *bis* spiroketal system **41** with complete fidelity to the model experiments (Scheme 13). The C_{28}-hydroxyl compound could be isolated in good yield under these conditions. Oxidation with Dess-Martin periodinane provided aldehyde **42**, a critical substrate for the Wittig fragment coupling (*vide infra*).

Synthesis of the E-Ring Sulfone. Synthesis of the C_{29}-C_{37} E-ring fragment was initiated from the enantiomerically pure boron aldol adduct **45**[12] (Scheme 14). Protection of the C_{33} hydroxy group and amide reduction afforded aldehyde **46** in 97% yield (2 steps). The *syn* stereotriad was completed by a Felkin selective addition of silylketene acetal **47** (87%, diastereoselection 94:6).[49,50] Use of the original Fukuyama conditions (Et_3SiH/Pd/C)[51] for the reduction of thioester **48** afforded predominantly the saturated aldehyde. To circumvent this problem, the reduction was conducted in the presence of Lindlar's catalyst and a sacrificial mono-

Scheme 14

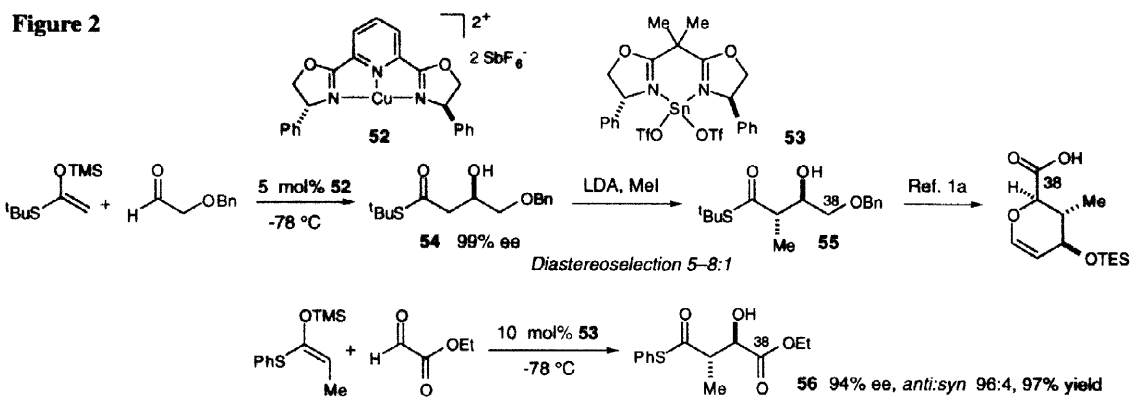


(a) TESOTf, 2,6-lutidine; (b) DIBAlH, -78 °C; (c) **47**, BF_3•Et_2O, CH_2Cl_2, -78°C; (d) Lindlar cat., Et_3SiH, 1-hexene, acetone; (e) CSA, MeOH; (f) TBSCl, imidazole, DMF; (g) 9-BBN, then H_2O_2; (h) TMSSPh, ZnI_2; (i) NaH, BnBr, Bu_4NI; (j) mCPBA, $NaHCO_3$.

substituted terminal olefin.[52] Given careful monitoring of the reaction, the aldehyde was obtained in 93% yield with minimal overreduction. Acid-catalyzed deprotection-acetalization followed by silyl protection of the remaining secondary alcohol afforded the E-ring methyl ketal **49** (81%, 3 steps). Hydroboration (9-BBN) then provided alcohol **50** (85%). Preparation of the E-ring phenylsulfone **51** was completed by successive anomeric sulfide formation (TMSSPh, ZnI_2),[53] C_{29} alcohol benzylation (NaH, BnBr, Bu_4NI, **90% from 50**), and sulfide oxidation (*m*CPBA, $NaHCO_3$, 97%).

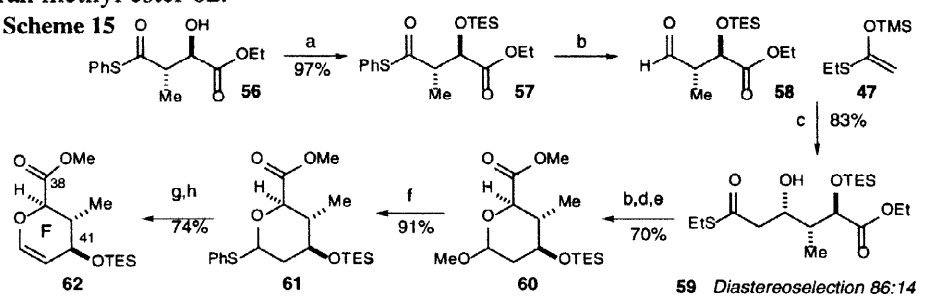
Synthesis of the F-Ring Dihydropyran. Our previously reported synthesis[1a] of the C_{38}-C_{43} F-ring fragment utilized a Cu(II)-catalyzed enantioselective acetate aldol reaction[54] for the construction of synthon **55** (Figure 2). Aldol adduct **54** was transformed via Fräter-Seebach alkylation (71% yield; dr = 5-8:1)[55] to the formal *anti* aldol product **55**, which was elaborated to a fully functionalized F-ring dihydropyran. Subsequent to these studies, the development of a Sn(II)-catalyzed, enantioselective *anti* aldol reaction in these laboratories[56] suggested an improved route to this fragment (Figure 2). Adduct **56** contains the required *anti* stereoarray and incorporates a C_{38} ester, potentially avoiding the oxidation state adjustment employed in the previous route from **55**.

Figure 2



In analogy to our previous F-ring synthesis, adduct **56** was TES-protected and reduced (Pd/C, Et_3SiH) to provide aldehyde **58** (Scheme 15). The use of Fukuyama conditions was demonstrated for the first time with *phenyl* thioesters and allowed the selective reduction of the thioester in the presence of the ethyl ester. A diastereoselective Mukaiyama aldol reaction (**47**, $BF_3{\cdot}OEt_2$) provided the desired C_{41} stereoisomer in 71% isolated yield, and a second Fukuyama reduction selectively converted ethyl thioester **59** to the corresponding β-hydroxy aldehyde. Treatment of this aldehyde with CSA in MeOH effected deprotection and internal ketalization as well as a fortuitous transesterification of the C_{38} ethyl ester to the corresponding methyl ester **60**. At this stage, a modified elimination sequence was employed in order to accommodate the epimerization-prone C_{39} stereocenter. Transformation to anomeric sulfide **61**,[53] oxidation, and sulfoxide thermolysis[57] provided F-ring dihydropyran methyl ester **62**.

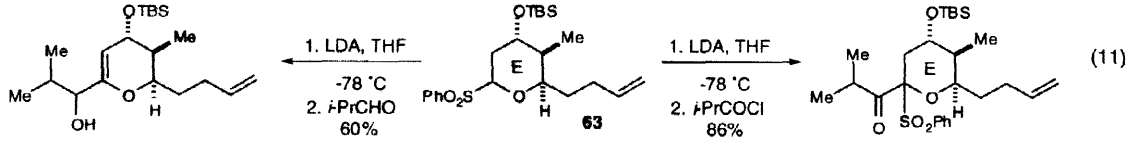
Scheme 15



(a) TESCl, imidazole; (b) Pd/C, Et_3SiH, acetone; (c) $BF_3{\cdot}OEt_2$, toluene, -93 °C; (d) CSA, $MeOH/CH_2Cl_2$ (1:1); (e) TESCl, imidazole; (f) TMSSPh, ZnI_2, 1,2-dichloroethane; (g) mCPBA, EtOAc, 0 °C; (h) benzene, 80 °C.

EF Bicycle Assemblage. Initial model studies indicated that addition of lithiated E-ring sulfone **63** to aldehydes resulted in elimination to an E-ring dihydropyran which could not be efficiently rehydrated (eq.

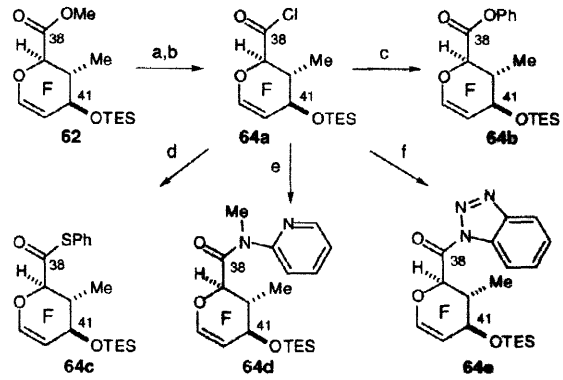
11).[58] In contrast, addition to simple acid chlorides was highly efficient and provided the intact sulfone coupling product without concomitant elimination (eq. 11).



(11)

The preparation of F-ring acid chloride **64a** was achieved via methyl ester cleavage (TMSOK, THF)[59] and treatment with the Ghosez reagent (Scheme 16).[60] This method for acid chloride formation was unique in its tolerance of the highly acid-sensitive dihydropyran intermediate. Additional acyl derivatives of the F-ring dihydropyran were prepared from **64a** by treatment with appropriate alcohols, thiols, or amines (Scheme 16).

Scheme 16

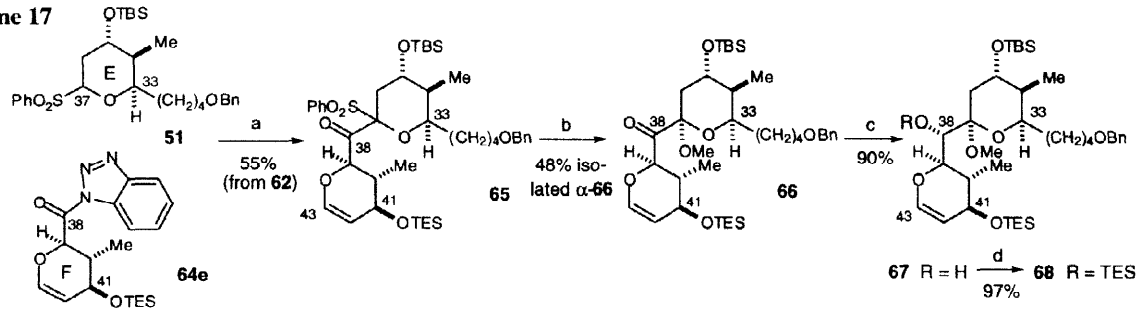


(a) TMSOK, THF, then pH 5.5 buffer; (b) 1-chloro-2,*N*,*N*-trimethyl-propenylamine; (c) PhOH, Et_3N, DMAP, CH_2Cl_2; (d) PhSH, pyridine, CH_2Cl_2; (e) 2-(methylamino)pyridine, pyridine, DMAP, CH_2Cl_2; (f) benzotriazole, pyridine, DMAP, CH_2Cl_2.

Acyl chloride **64a** was anticipated to be the most reactive F-ring derivative. As this intermediate could not be purified, an unpurified solution of **64a** in CH_2Cl_2 was added directly to the sulfone anion (in THF) at -78 °C.[61] This procedure, under various conditions of stoichiometry, led to irreproducible results and low yields (*ca.* 30%). Following the precedent of Beau,[58] we next examined the pure and stable acyl derivatives **64b** and **64c**. In reactions of these partners with the lithiated E-ring sulfone, both the sulfone and the ester or thioester were recovered unchanged. Two observations led us to conclude that these esters had been enolized by the sulfone anion: (1) the addition of either **64b** or **64c** decolorized the characteristically bright yellow lithiated sulfone solution; (2) in the attempted coupling of phenyl ester **64b** we were able to isolate a small amount of the ester as its C_{39} epimer. It is likely that the thermodynamic acidity of the C_{39} proton is greatly enhanced by the electron withdrawing effect of the enol ether function. Moreover, the relatively flat structure of the dihydropyran may increase the kinetic acidity of the sterically accessible C_{39} proton.

These experiments prompted us to investigate substituted amides as coupling partners for which enolization is precluded by allylic strain. While the pyridylamide **64d** was inert under the reaction conditions, the benzotriazole amide **64e** proved more reactive. Treatment of the sulfone anion with **64e** afforded the desired ketone in approximately 80% yield as a 60:40 mixture of sulfone anomers using a 20% excess of the anion.[62] Implementation of this acylation strategy (Scheme 17) provided the EF bicycle in 55% yield from **62** (4 steps).

Scheme 17

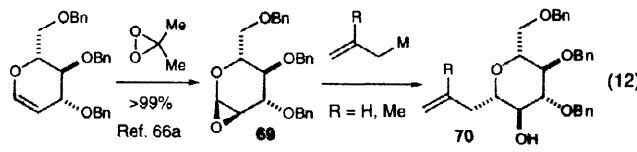


(a) LDA, THF, -78 °C, then **64e**; (b) i. ZnI_2, MeOH; ii. $MgBr_2{\cdot}Et_2O$, MeOH; (c) $KBHEt_3$, THF, -78 → -40 °C; (d) TESCl, imidazole, DMF.

Methanolysis of **65** provided ketone **66** in 48% isolated yield.[63] Of the hydride reducing agents surveyed, $KBHEt_3$ proved most effective in securing the desired alcohol stereochemistry at C_{38} (90%; dr >95:5). The observed stereoselectivity is presumably a consequence of Felkin induction from the C_{39} stereocenter. At this

juncture, single crystal X-ray analysis of alcohol **67** confirmed the structure of this advanced intermediate.[64] Silylation of the hindered secondary alcohol was achieved with TESCl in DMF to give **68**.

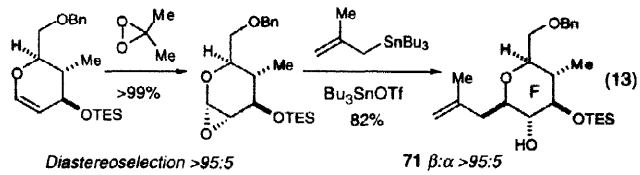
Addition of the C_{44}-C_{51} Sidechain. Concurrent with these studies, we investigated the feasibility of the projected late stage sidechain addition.[65] The synthesis plan called for stereoselective epoxidation of the F-ring dihydropyran followed by the stereoselective addition of a sidechain allyl metal to the resulting epoxide (see Scheme 1). The epoxidation was well precedented in Danishefsky's work with the similarly configured tri-*O*-benzyl glucal,[66a] and the Danishefsky 1,2-anhydrosugar **69** served as a convenient model for additions of simple allylmetals (Table 3, eq. 12). While allylmagnesium bromide effected a stereoselective and efficient epoxide opening to give β-*C*-glycoside **70** (Table 3, entry 3),[67] concerns about the compatiblity of allylic Grignards with more advanced intermediates led us to investigate alternative conditions. Allylstannanes (Table 2, entries 4-6) were subsequently identified as viable nucleophiles in Lewis acid mediated additions to **69**; tributyltin triflate proved the optimal Lewis acid with regard to both stereoselectivity and yield (Table 3, entry 6). This addition sequence was applicable in the analogous F-ring system (eq. 13).[68]



(12)

Table 3. Allyl metal additions to a model glycal epoxide (eq. 12)

Entry	Nucleophile	Conditions	β:α	Yield
1	Li	THF, -78 °C	n.d.	25%
2	$(CuCNLi)_2$	THF, -78→0 °C	>95:5	43%
3	MgBr	THF, -78 °C	>95:5	75%
4	Me, SnBu$_3$	TMSOTf CH_2Cl_2, -78 °C	4:1	51%
5	Me, SnBu$_3$	TESOTf CH_2Cl_2, -78 °C	7:1	56%
6	Me, SnBu$_3$	Bu_3SnOTf CH_2Cl_2, -78 °C	>95:5	63%

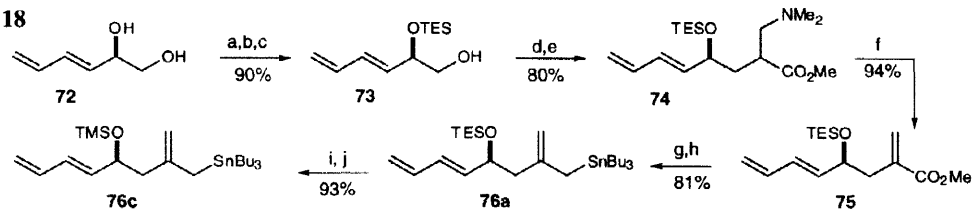


(13)

Diastereoselection >95:5 — 71 *β:α >95:5*

Synthesis of a fully functionalized sidechain allylstannane began with the known *(2S,3E)*-hexa-3,5-diene-1,2-diol (**72**)[69] (Scheme 18). A three-step sequence provided mono-silylated ether **73** in 90% overall yield without intervening purifications. While the corresponding tosylate and iodide were not reactive toward nucleophilic substitution, conversion of **73** to its unstable triflate derivative followed by immediate treatment with the lithium enolate of methyl-β-dimethylaminopropionate[70] provided **74** in 80% yield. Quaternization and elimination of the dimethylamino group were accomplished in a single reaction (MeI, Na_2CO_3, 94%).[71] Ester reduction (DIBAlH, 95%) gave the corresponding allylic alcohol. *In situ* mesylation and displacement with tributylstannyllithium[72] afforded TES-protected allylstannane **76a** in 85% yield. Basic deprotection and re-silylation then provided TMS-protected allylstannane **76c** in 93% yield.

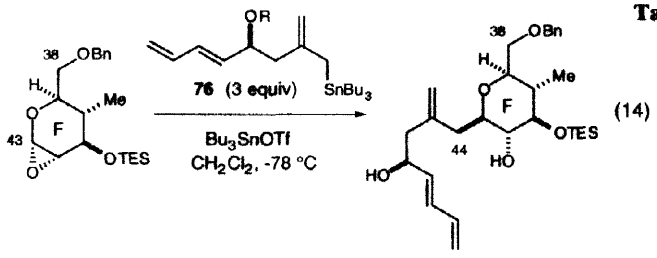
Scheme 18



(a) AcCl, 2,6-lutidine, CH_2Cl_2, -78 °C; (b) TESCl, imidazole, CH_2Cl_2; (c) DIBAlH, toluene, -78 °C; (d) Tf_2O, pyridine, CH_2Cl_2, -10 °C; (e) methyl-β-dimethylaminopropionate, LDA, THF, -78 °C; (f) MeI, Na_2CO_3, MeOH; (g) DIBAlH, CH_2Cl_2, -78 °C; (h) BuLi, MsCl, THF, -78 °C, then Bu_3SnLi; (i) NaOH, EtOH; (j) *N,O*-bis(trimethylsilyl)acetamide.

This final protecting group adjustment (**76a→76c**) represented a crucial transformation, as the efficiency of the sidechain addition was highly dependent on the identity of the allylstannane's hydroxyl protecting group (eq. 14, Table 4). All variations provided high β:α selectivities, but the isolated yields differed significantly. More sterically demanding alcohol protecting groups generally afforded lower yields (entries 1-3),[73] while the electronically deactivating acetate protecting group also gave poor results (entry 4). This steric effect was somewhat surprising given the apparently remote nature of the C_{47} hydroxyl and the unhindered environment

around the C_{43} center observed in the dihydropyran crystal structure. Use of higher concentrations of allylstannane improved the reaction efficiency (entry 5 vs. entry 3), supporting the interpretation that the rate of stannane addition must compete with the rate of nonproductive decomposition of the epoxide. Since the unreacted allylstannanes could be quantitatively recovered after flash chromatography, the use of multiple equivalents of stannane was regularly employed; the optimal protocol entailed treatment of the epoxide with tributyltin triflate and 16 equivalents of TMS-protected allylstannane **76c**.[74]



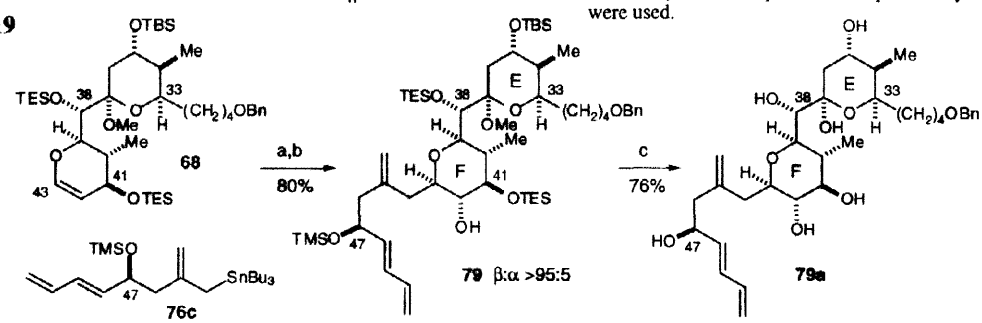
(14)

Table 4. Allylstannane structure vs. reaction efficiency

Entry	R	β:α	yield[a]
1	TES (**76a**)	>95:5	35%
2	MOP (**76b**)	>95:5	48%
3	TMS (**76c**)	>95:5	65%
4	Ac (**76d**)	>95:5	25%
5	TMS[b] (**76c**)	>95:5	75%

[a]Isolated yields are reported. [b]16 equiv of allylstannane were used.

Scheme 19



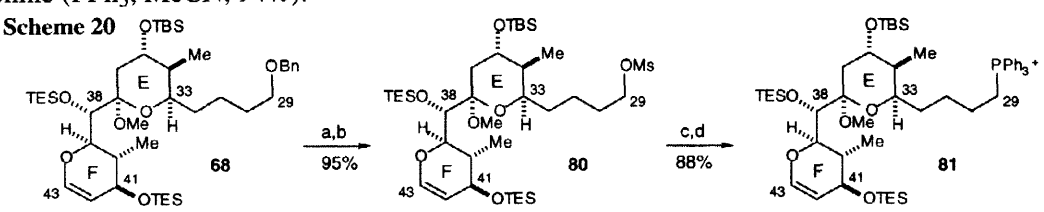
(a) Dimethyldioxirane, acetone, CH_2Cl_2, 0 °C; (b) 16 equiv **76c**, 2 equiv Bu_3SnOTf, CH_2Cl_2, -78 °C; (c) HF, H_2O, CH_3CN, 0 °C.

Application of this methodology in more complex systems was highly successful (Scheme 19). Epoxidation of bicycle **68** with dimethyldioxirane proceeded quantitatively (dr >95:5). Treatment of the epoxide with allylstannane **76c** and tributylstannyl triflate provided the desired adduct **79** in 80% yield as a single diastereomer. The excess allylstannane from this experiment was recovered quantitatively after chromatography.

At this juncture, acidic conditions were evaluated for the deprotection of the EF-bis(pyran) **79**. Prior experience had revealed that E-ring Δ-C_{36} dihydropyran formation was to be avoided since rehydration of this intermediate was problematic. Under the optimal conditions, treatment of **79** with aqueous HF resulted in removal of all four silyl protecting groups as well as hydrolysis of the C_{37} methyl ether to provide lactol **79a**. This experiment allayed concerns that the unwanted elimination to the dihydropyran would complicate the projected final deprotection sequence leading to the target structure.

Wittig Fragment Coupling and Elaboration. In accord with our plan to delay sidechain introduction to the latest possible stage, EF-bis(pyran) benzyl ether **68** was further elaborated to phosphonium salt **81** (Scheme 20). This key Wittig coupling partner was prepared via successive debenzylation (LDBB, 96%), mesylation (MsCl, Et_3N, 99%), sodium iodide substitution (NaI, acetone, 94%), and displacement by triphenylphosphine (PPh_3, MeCN, 94%).

Scheme 20



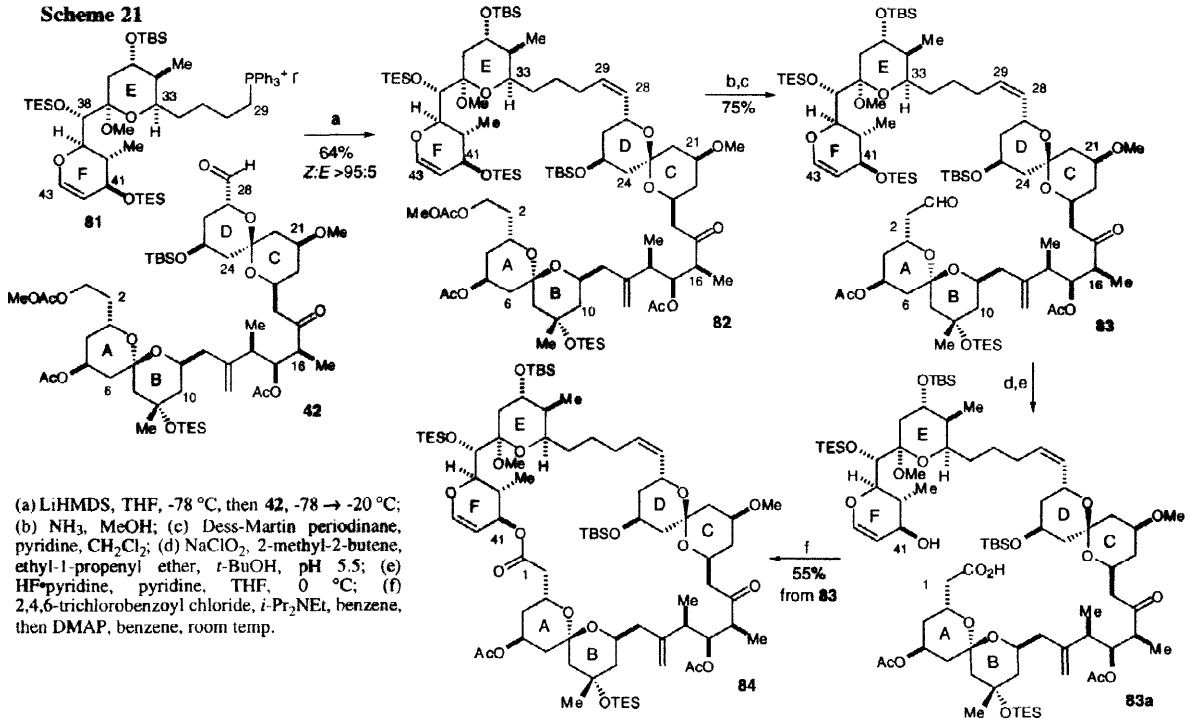
(a) LDBB, THF, -78 °C; (b) MsCl, Et_3N, CH_2Cl_2; (c) NaI, $NaHCO_3$, Na_2SO_3, acetone; (d) PPh_3, CH_3CN.

Deprotonation of **81** (1.26 equiv) with LiHMDS followed by addition of ABCD aldehyde **42** provided the desired Wittig product **82** in 64% yield (>95:5 *Z:E*).[75] Selective removal of the methoxyacetate C_1 protecting group was accomplished using NH_3/MeOH in 82% yield. While hydrolysis of the secondary acetates at C_5

and C_{15} was not observed, a minor byproduct resulting from β-elimination of the C_{15} ester was isolated (*vide supra*). The primary alcohol was oxidized to the aldehyde **83** using Dess-Martin periodinane (92% yield).

The two remaining major transformations, macrolactonization and sidechain addition, could, in principle, be carried out in either order. We first examined macrolactonization of the dihydropyran hydroxy acid **83a**, which was synthesized via modified Krause oxidation[76] of **83** and selective deprotection of the allylic C_{41} TES ether (HF•pyridine, pyridine, THF, 0 °C). As anticipated, this sterically unencumbered hydroxy acid readily underwent macrolactonization under Yamaguchi conditions[77] (room temperature, <3 h) to afford the dihydropyran macrolactone **84** (55% yield, 3 steps).

Scheme 21



(a) LiHMDS, THF, -78 °C, then **42**, -78 → -20 °C; (b) NH_3, MeOH; (c) Dess-Martin periodinane, pyridine, CH_2Cl_2; (d) $NaClO_2$, 2-methyl-2-butene, ethyl-1-propenyl ether, *t*-BuOH, pH 5.5; (e) HF•pyridine, pyridine, THF, 0 °C; (f) 2,4,6-trichlorobenzoyl chloride, *i*-Pr_2NEt, benzene, then DMAP, benzene, room temp.

Epoxidation of this advanced dihydropyran intermediate was expected to be challenging due to the presence of two additional olefins (C_{28}-C_{29} and C_{13}). While 1,1 disubstituted olefins are less reactive toward dioxiranes, *cis* olefins are known to react readily with dimethyldioxirane.[78] Overoxidation at the C_{28}-C_{29} olefin was thus identified as a potential problem. To examine this epoxidation, small scale experiments were designed in order to preserve this precious synthetic intermediate. Typically, 0.005 mg of macrolactone **84** were dissolved in 100 μL CH_2Cl_2 (0 °C). Approximately 20 equiv of a dilute solution of DMDO in acetone/CH_2Cl_2 (100 μL) were added, and the reaction was stirred at 0 °C. Reaction monitoring was achieved by removal of 1% aliquots from the reaction and subsequent electrospray ms analysis.[79] The results (Figure 3)

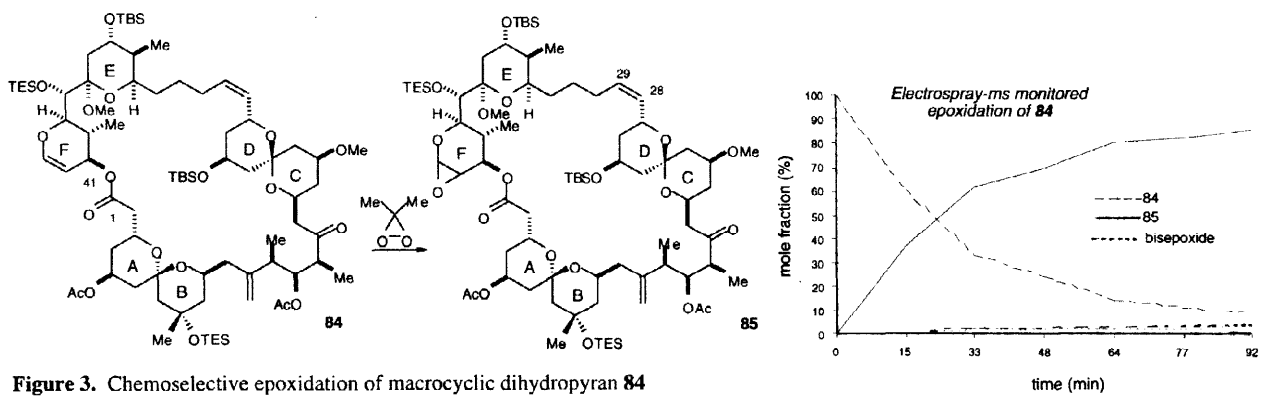


Figure 3. Chemoselective epoxidation of macrocyclic dihydropyran **84**

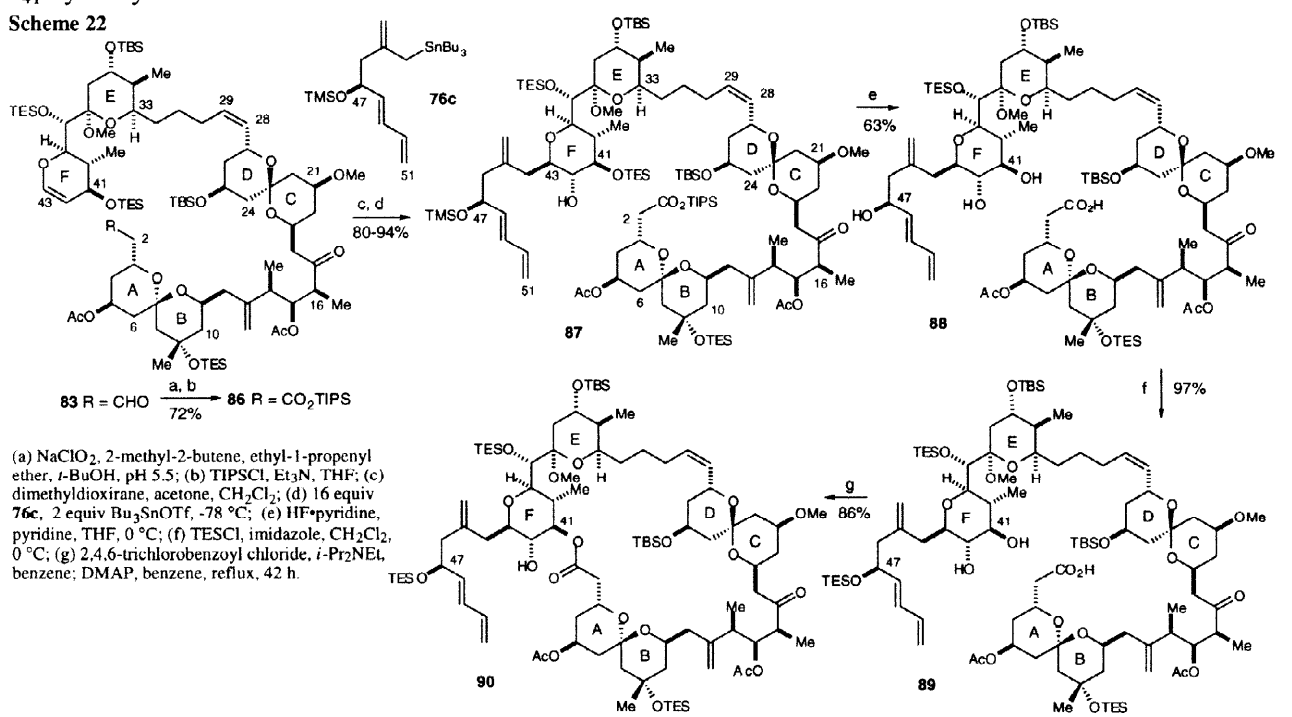
indicate that epoxidation occurred with almost complete chemoselectivity for the dihydropyran olefin despite the fact that the rate of epoxidation was significantly reduced relative to simpler systems.[80]

Preliminary attempts at sidechain addition to epoxide **85** (16 equiv **76c**, Bu_3SnOTf, CH_2Cl_2) resulted in a complex mixture of compounds, none of which incorporated the C_{44}-C_{51} sidechain by ms or NMR. Rather than pursue this disappointing result, we focused our attention on the alternative route involving addition of the sidechain prior to macrocyclization (Scheme 22). The C_1 oxidation sequence (*vide supra*) was again employed and followed by silylation of the resultant acid to give ester **86** (72% yield, 2 steps from **83**). Epoxidation of the C_{42}-C_{43} dihydropyran was accomplished with complete chemo- and stereoselectivity (as judged by ^1H NMR analysis) by addition of ~1.5 equiv of dimethyldioxirane (DMDO).[81] Immediate treatment of the resulting epoxide with allylstannane **76c** (16 equiv) and tributylstannyl triflate (2 equiv) afforded the desired adduct **87** in 80-94% isolated yield as a single diastereomer. The excess allylstannane was recovered in quantitative yield after column chromatography.

At this stage, the crucial regioslective diol macrolactonization (*vide supra*) was investigated. As a prelude to macrocycle formation, selective deprotection of ester **87** was implemented. Treatment of this intermediate with buffered HF•pyridine (THF, 0 °C), resulted in removal of the triisopropylsilyl (TIPS) ester, the C_{47} TMS ether, and the C_{41} TES ether while retaining the silyl protecting groups at C_9, C_{25}, C_{35}, and C_{38} (Scheme 22). Subjection of acid triol **88** to Yamaguchi macrolactonization conditions (2,4,6-trichlorobenzoyl chloride, *i*-Pr_2NEt, DMAP) provided a product tentatively identified as the desired macrocycle bearing a trichlorobenzoyl group at the C_{47} oxygen. To prevent this undesired acylation, selective protection of acid triol **88** at the C_{47} hydroxyl was performed prior to macrolactonization to give TES ether **89** (TESCl, imidazole, 0 °C, 97%).[82]

Exposure of **89** to modified Yamaguchi conditions provided a single regioisomeric lactone **90** in 86% yield. It is noteworthy that this macrocyclization was much less facile than cyclization of the corresponding dihydropyran hydroxy acid (Scheme 21), requiring high temperature (refluxing benzene) and syringe pump addition techniques (42 h) for optimal results. The regiochemical outcome of the reaction was established by observation of the coupling patterns among the C_{40}-C_{44} protons in the COSY spectrum (500 MHz, benzene-d_6). This allowed an unambiguous assignment of the $C_{41}H$ and $C_{42}H$ resonances; the large downfield shift of the $C_{41}H$ resonance (δ 4.84 for $C_{41}H$, δ 3.45 for $C_{42}H$) verified that macrolactonization had occurred at the C_{41} hydroxyl.

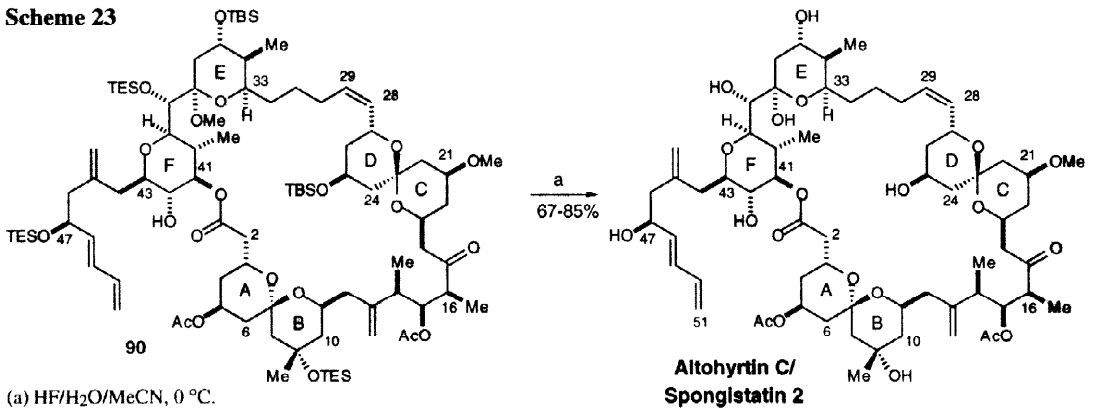
Scheme 22



(a) $NaClO_2$, 2-methyl-2-butene, ethyl-1-propenyl ether, *t*-BuOH, pH 5.5; (b) TIPSCl, Et_3N, THF; (c) dimethyldioxirane, acetone, CH_2Cl_2; (d) 16 equiv **76c**, 2 equiv Bu_3SnOTf, -78 °C; (e) HF•pyridine, pyridine, THF, 0 °C; (f) TESCl, imidazole, CH_2Cl_2, 0 °C; (g) 2,4,6-trichlorobenzoyl chloride, *i*-Pr_2NEt, benzene; DMAP, benzene, reflux, 42 h.

Deprotection ($HF/H_2O/MeCN$) provided synthetic altohyrtin C, which was isolated in 67-85% yield after reverse phase HPLC (Scheme 23). A detailed comparison of the natural and synthetic compounds was especially important in light of the stereochemical discrepancies which, in part, motivated the total synthesis. Thus the synthetic material was found to be identical to a sample of natural spongistatin 2[83] as judged by ^1H NMR (500 MHz, CD_3CN), COSY, HPLC, electrospray mass spectroscopy, and UV spectroscopy. Comparison of optical rotations confirmed that the synthetic and natural compounds possessed the same absolute stereochemistry (synthetic $[\alpha]^{24}_D$ +26.6 (*c* 0.04, MeOH); natural $[\alpha]^{24}_D$ +29.2 (*c* 0.12, MeOH)). Further, comparison of 1D ^1H NMR and 2D COSY spectra (500 MHz, DMSO-d_6) confirmed that the synthetic material was also identical to natural altohyrtin C.[84] We thus conclude that spongistatin 2 and altohyrtin C are identical compounds and speculate that the altohyrtin stereochemical assignment can be extended to the remaining members of the spongipyran family.[85]

Scheme 23



(a) $HF/H_2O/MeCN$, 0 °C.

Conclusion. The first total synthesis of a spongipyran macrolide, altohyrtin C/spongistatin 2, has been completed. The relative and absolute configurational assignment of Kobayashi and Kitagawa has been confirmed, and the spongistatin and altohyrtin families have been unified under a single structural identity. The synthesis required 32 steps (longest linear sequence) and produced the natural product in 0.9% overall yield for an average yield of 86% per step. A 1,5-*anti*, enolate-controlled methyl ketone aldol was developed to construct the CD-spiroketal and implemented for the first time in the synthesis of a natural product. The use of a Sn(II)-bis(oxazoline)-catalyzed, enantioselective *anti* aldol in a total synthesis was also demonstrated for the first time. A diastereoselective, Lewis acid mediated addition of allylstannanes to anomeric epoxides has been developed and successfully applied in a complex, late stage fragment coupling. As a result, the route to altohyrtin C reported here is, in principle, readily applicable to the sidechain congeners altohyrtin A (spongistatin 1) and altohyrtin B,[4b] with dihydropyran **86** serving as a common intermediate for the synthesis of these compounds and additional analogs.

Experimental Section

General. Melting points were determined with a Buchi SMP-20 melting point apparatus equipped with an Omega Model 450 AET thermocouple thermometer and are uncorrected. Infrared (IR) spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrophotometer. ^1H NMR spectra were recorded on Bruker DMX-500, AM-500 or AM-400 spectrometers. Chemical shifts are reported in ppm from tetramethylsilane or with the solvent resonance as the internal standard. ^{13}C NMR spectra were recorded on Bruker AM-500 (125 MHz) or AM-400 (100.6 MHz) spectrometers with proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane or with the solvent as the internal standard. Mass spectra were obtained on JEOL AX-505 and SX-102 high resolution magnetic sector mass spectrometers by the Harvard University Mass Spectrometry Laboratory. Optical rotations were measured on a Jasco DIP-0181 digital polarimeter with a mercury or sodium lamp, and are reported as follows: $[\alpha]$ t(°C) λ, (*c* (g/100 mL), solvent). Analytical thin layer chromatography (TLC) was performed on EM Reagent 0.25mm silica gel 60-F plates. Chromatography on silica gel was performed using a forced flow of the indicated solvent system (flash chromatography) on EM

Reagents Silica Gel 60 (230-400 mesh) or Waters Preparative C_{18} Silica Gel (125Å, 55-105 μm). Solvents used for extraction and chromatography were HPLC grade. Unless otherwise noted, all non-aqueous reactions and distillations were carried out under an atmosphere of dry nitrogen in glassware that had been either flame-dried under a stream of nitrogen or oven-dried (80 °C) overnight. pH 7.0 phosphate buffer (0.05 M), commercially available from Fisher Scientific, was used when pH 7.0 buffer is indicated. When necessary, solvents and reagents were dried prior to use. Deuterochloroform was stored over 4 Å molecular sieves. Toluene was distilled from potassium metal. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium or potassium metal and benzophenone ketyl. Dichloromethane (CH_2Cl_2), trimethylchlorosilane, oxalyl chloride, pentane, pyridine, 2,6-lutidine, triethylamine, diisopropylethylamine, and diisopropylamine were distilled from calcium hydride. Methanol (MeOH) was distilled from magnesium methoxide ($Mg(OMe)_2$). Boron trifluoride etherate was distilled from calcium hydride under reduced pressure. Di-*n*-butylboron trifluoromethanesulfonate (di-*n*-butylboron triflate) was prepared according to the procedure of Inoue and Mukaiyama as modified by Evans and co-workers. Trimethylsilylmethyl chloride and benzaldehyde were distilled immediately before use. (*S*)-2-Naphthyl ethanol was used as received and could be reutilized after recrystallization from hot hexanes. All other commercially available reagents were used as received.

[2'*S*,3*S*]-1-(2'-Naphthyl)ethyl-3-(*tert*-butyldimethylsiloxy)-5-triphenyl-methyloxy-pentanoate (1a). To a solution of 16.00 g (39.80 mmol) of alcohol **1** in 50 mL of CH_2Cl_2 under argon atmosphere was added 11.06 mL (79.60 mmol) of triethylamine followed by 12.20 g (43.78 mmol) of trityl chloride. The resultant yellow cloudy mixture was stirred for 12 h at room temperature, then concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (5% EtOAc/hexanes) gave 23.32 g (36.22 mmol, 91%) of trityl ether **1a** as a clear oil: $[\alpha]^{23}_{589}$ -33.1 (*c* 2.14, CH_2Cl_2); IR (neat) 3058, 2953, 2928, 2855, 1736 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.78-7.83 (m, 4H), 7.40-7.49 (m, 9H), 7.19-7.31 (m, 9H), 6.06 (q, 1H), 4.31 (m, 1H), 3.15 (m, 2H), 2.51 (dd, 1H. *J* = 5.8, 15.0 Hz), 2.46 (dd, 1H, *J* = 6.5, 15.0 Hz), 1.89 (m, 2H), 1.63 (d, 3H, *J* = 6.6 Hz), 0.71 (s, 9H), -0.10 (s, 3H), -0.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.7, 144.2, 138.9, 133.1, 132.9, 128.6, 128.3, 127.9, 127.7, 127.6, 126.8, 126.1, 125.9, 125.0, 124.0, 86.6, 72.3, 66.9, 60.4, 43.0, 37.6, 25.6, 22.2, 17.8, -4.9; exact mass (70eV, FAB/NaI) calculated for $C_{42}H_{48}O_4SiNa$: 667.3220; found: 667.3222; R_f = 0.67 (30% EtOAc / hexanes). Anal. Calcd. for $C_{42}H_{48}O_4Si$; C, 78.26; H, 7.45; found: C, 78.16; H, 7.52.

(3*S*)-3-(*tert*-Butyldimethylsiloxy)-5-triphenylmethyloxypentanal (2). To a -78 °C solution of 23.32 g (36.22 mmol) of **1a** in 360 mL of toluene was added dropwise 36.2 mL (54.33 mmol) of DIBAlH (1.5 M solution in toluene). After stirring for 2 h at -78 °C, the reaction was quenched by the addition of EtOAc (5.00 mL) followed by the slow addition of saturated Na/K tartrate solution (200 mL). After stirring at room temperature for 2 h, the aqueous solution was separated and extracted with 2 x 150 mL of Et_2O. The combined organic solutions were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (10% EtOAc / hexanes) gave 15.28 g (32.23 mmol, 89%) of aldehyde **2** as a clear oil: $[\alpha]^{23}_{589}$ +1.1 (*c* 0.89, CH_2Cl_2); IR (neat) 3086, 3058, 3033, 2953, 2527, 2880, 2855, 2738, 1725, 1692, 1638 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.76 (t, 1H, *J* = 2.4 Hz), 7.44-7.21 (m, 15H), 4.34 (qt, 1H), 3.15 (t, 2H, *J* = 6.4 Hz), 2.46 (m, 2H), 1.93 (m, 1H), 1.82 (m, 1H), 0.78 (s, 9H), 0.01 (s, 3H), -0.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 202.2, 144.1, 128.6, 127.8, 127.0, 86.7, 65.9, 60.2, 50.9, 38.0, 25.7, 17.9, -4.65, -4.73; exact mass (70eV, FAB/NaI) calculated for $C_{30}H_{38}O_3SiNa$: 497.2488; found: 497.2482; R_f = 0.59 (30% EtOAc / hexanes).

[2*E*,5*S*)-(*tert*-Butyldimethylsiloxy)-7-(triphenylmethyloxy)-[*N*-methoxy-*N*-methyl]-2-heptenamide (3). A solution of 15.28 g (32.23 mmol) of aldehyde **2** and 14.67 g (40.42 mmol) of *N*-methoxy-*N*-methyl-(triphenylphosphoranylidene)acetamide in 250 mL of CH_2Cl_2 was stirred at room temperature for 12 h. The solvent was removed *in vacuo* to provide a viscous yellow oil. Purification of the residue by flash chromatography on silica gel (30% EtOAc / hexanes) gave 16.93 g (30.29 mmol, 94%) of **3** as a clear oil: $[\alpha]^{23}_{589}$ -5.27 (*c* 1.29, CH_2Cl_2); IR (neat) 3086, 3058, 3033, 2930, 2884, 2856, 1666, 1634 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.45-7.41 (m, 6H), 7.31-7.29 (m, 6H), 7.25-7.21 (m, 3H), 6.95 (dt, 1H, *J* = 7.4, 15.4 Hz), 6.38 (d, 1H,

J = 15.4 Hz), 3.95 (qt, 1H), 3.67 (s, 3H), 3.24 (s, 3H), 3.17 (m, 1H), 3.09 (m, 1H), 2.34 (m, 2H), 1.80 (m, 2H), 0.78 (s, 9H), 0.00 (s, 3H), -0.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.4, 144.1, 143.8, 128.4, 127.5, 126.7, 120.7, 86.4, 68.9, 61.4, 60.6, 40.5, 37.3, 32.1, 25.6, 17.8, -4.6, -5.0; exact mass (70eV, FAB/NaI) calculated for $C_{34}H_{45}NO_4SiNa$: 582.3016; found: 582.2995; R_f = 0.53 (50% EtOAc / hexanes). Anal. Calcd. for $C_{34}H_{45}NO_4Si$; C, 72.98; H, 8.05; N, 2.50; found: C, 72.87; H, 8.15; N, 2.43.

[2*E*,5*S*]-5-Hydroxy-7-(triphenylmethyloxy)-*N*-methoxy-*N*-methyl-2-heptenamide (4). To a solution of 16.93 g (30.29 mmol) of silyl ether **3** in 150 mL of anhydrous THF at room temperature was added 66 mL (66.00 mmol) of tetrabutylammonium fluoride (1.0 M in THF). The resulting yellow solution was stirred at room temperature for 10 h before it was diluted with 200 mL of Et_2O. The mixture was washed with saturated NH_4Cl solution (2 x 100 mL) and brine (2 x 100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (40% EtOAc / hexanes) gave 12.47 g (28.17 mmol, 93%) of alcohol **4** as a pale yellow oil: $[\alpha]^{23}_{589}$ +9.0 (*c* 1.87, CH_2Cl_2); IR (neat) 3418, 3057, 2937, 1661, 1620 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41-7.45 (m, 6H), 7.29-7.33 (m, 6H), 7.23-7.26 (m, 3H), 6.95 (dt, 1H, J = 7.4, 15.4 Hz), 6.45 (d, 1H, J = 15.4 Hz), 3.95 (m, 1H), 3.68 (s, 3H), 3.39 (m, 1H), 3.24 (m, 1H), 3.23 (s, 3H), 2.98 (d, 1H, J = 3.1 Hz), 2.38 (m, 2H), 1.78 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.5, 143.7, 143.5, 128.4, 127.8, 127.0, 121.0, 87.1, 69.7, 62.0, 61.5, 40.2, 36.1, 32.2; exact mass (70eV, EI) calculated for $C_{28}H_{31}NO_4$: 445.2253; found: 445.2271; R_f = 0.16 (50% EtOAc / hexanes). Anal. Calcd. for $C_{28}H_{31}NO_4$; C, 75.50; H, 6.97; N, 3.14; found: C, 75.26; H, 6.98; N, 3.10.

[2*S*,4*S*,6*S*]-4-(*N*-methoxy-*N*-methyl-carboxamidomethyl)-6-[(2-triphenylmethyloxy)-ethyl]-2-phenyl-1,3-dioxane (5). To a solution of 5.00 g (11.23 mmol) of amide **4** in 112 mL of THF at 0 °C was added 1.25 mL (12.35 mmol) of freshly distilled benzaldehyde followed by 0.051 g (0.56 mmol) of *t*-BuOK. The resulting yellow solution was stirred for 15 min at 0 °C. This sequence was repeated again. After 25 min the reaction mixture was quenched with 100 mL of pH 7 phosphate buffer. The aqueous solution was separated and extracted with 3 x 100 mL of Et_2O. The combined organic solutions were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (30% EtOAc / hexanes) gave 5.13 g (9.32 mmol, 83%) of amide **5** as a white solid: mp 199-201 °C; $[\alpha]^{23}_{589}$ -21.0 (*c* 1.59, CH_2Cl_2); IR (CH_2Cl_2) 3058, 2938, 2877, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20-7.47 (m, 20H), 5.60 (s, 1H), 4.42 (m, 1H), 4.20 (m, 1H), 3.67 (s, 3H), 3.39 (m, 1H), 3.21 (s, 3H), 3.18 (m, 1H), 2.98 (dd, 1H, J = 5.6, 15.3 Hz), 2.54 (dd, 1H, J = 6.0, 15.3 Hz), 1.89 (m, 2H), 1.78 (dt, 1H, J = 13.0 Hz), 1.44 (dt, 1H, J = 11.2, 12.8 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 171.4, 144.3, 138.6, 128.7, 128.4, 128.0, 127.7, 126.8, 126.1, 100.4, 86.4, 73.7, 73.5, 61.4, 59.0, 38.2, 37.1, 36.3, 32.0; exact mass (70eV, EI) calculated for $C_{35}H_{37}NO_5$: 551.2672; found: 551.2662; R_f = 0.16 (30% EtOAc / hexanes).

[2*S*,4*S*,6*S*]-4-(Formylmethyl)-6-[(2-triphenylmethyloxyethyl)]-2-phenyl-1,3-dioxane (6). To a solution of 5.13 g (9.32 mmol) of amide **5** in 46 mL of CH_2Cl_2 at -78 °C was added dropwise 8.07 mL (12.12 mmol) of a 1.5 M solution of DIBAlH in toluene. The resulting solution was stirred at -78 °C for 45 min before it was quenched by the addition of 10 mL of EtOAc followed by 50 mL of saturated Na/K tartrate solution. After stirring at room temperature for 2 h, the aqueous solution was separated and extracted with Et_2O (2 x 150 mL). The combined organic solutions were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (20% EtOAc / hexanes) gave 4.36 g (8.85 mmol, 95%) of aldehyde **6** as a white solid: mp 48-49 °C; $[\alpha]^{23}_{589}$ -11.2 (*c* 3.78, CH_2Cl_2); IR (neat) 3086, 3058, 2946, 2917, 2874, 2731, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.86 (t, 1H, J = 1.7 Hz), 7.22-7.50 (m, 20H), 5.61 (s, 1H), 4.44 (m, 1H), 4.22 (m, 1H), 3.42 (ddd, 1H, J = 4.8, 8.7 Hz), 3.19 (dt, 1H, J = 5.3, 9.1 Hz), 2.80 (ddd, 1H, J = 2.1, 7.4, 16.9 Hz), 2.59 (ddd, 1H, J = 1.5, 5.0, 16.9 Hz), 1.95 (m, 1H), 1.88 (m, 1H), 1.66 (dt, 1H, J = 2.3, 13.0 Hz), 1.47 (dt, 1H, J = 11.2, 13.0 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 200.3, 144.2, 138.2, 128.6, 128.1, 127.7, 126.9, 126.0, 100.4, 86.5, 73.6, 71.8, 58.9, 49.3, 36.7, 36.2; exact mass (70eV, EI) calculated for $C_{33}H_{32}O_4$: 492.2300; found: 492.2287; R_f = 0.38 (30% EtOAc / hexanes).

Methyl-(2*S*)-3-(benzyloxy)-2-methyl-propanoate (9). To a solution of 20.00 g (56.65 mmol) of **8** in 150 mL of anhydrous MeOH was added 2.73 g (5.66 mmol) of dry $Sm(OTf)_3$, and the resulting clear solution was

stirred for 3 h at room temperature. The solvent was removed *in vacuo* to provide a clear oil. To this oil was added *n*-hexane which precipitated (*R*)-4-benzyl-2-oxazolidinone in 95% yield. Purification of the residue by flash chromatography on silica gel (10% EtOAc / hexanes) gave 11.43 g (54.95 mmol, 97%) of methyl ester **9** as a clear liquid: $[\alpha]^{23}_{589}$ +12.1 (*c* 10.10, $CHCl_3$); IR (neat) 3087, 3067, 3026, 1734 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.22 (m, 5H), 3.69 (s, 3H), 4.52 (s, 2H), 3.66 (dd, 1H, *J* = 7.3, 9.1 Hz), 3.04 (dd, 1H, *J* = 5.9, 9.1 Hz), 2.79 (dqd, 1H, *J* = 5.9, 7.1, 7.3 Hz), 1.18 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 175.0, 138.0, 128.1, 127.4, 72.9, 71.8, 51.5, 40.0, 13.8; exact mass (70eV, CI/NH_3) calculated for $C_{12}H_{20}NO_3$: 226.1443; found: 226.1450; Rf = 0.30 (15% EtOAc / hexanes).

[2*S*]-1-Benzyloxy-2-methyl-3-[(trimethylsilyl)methyl]-but-3-ene (10). In a 3-necked 250 mL round bottomed flask, powdered $CeCl_3.7H_2O$ (33.96 g, 91.15 mmol) was heated under vacuum (1 mm Hg) at 160 °C for 10 h with vigorous stirring, resulting in the formation of a white mobile solid. The reaction flask was flushed with nitrogen and allowed to cool to room temperature. 140 mL of THF was added to the vigorously stirred cerium (III) chloride, forming a uniform white suspension, which was left to stir for 2 h. During this time, a separate 3-necked 100 mL flask, fitted with a condenser and a pressure equalized dropping funnel, was charged with 2.21 g (91.15 mmol) of magnesium turnings, and the whole apparatus was flame dried under a flow of nitrogen. To this flask was added dropwise a solution of $ClCH_2TMS$ (12.72 mL, 91.15 mmol) in 50 mL of THF. This mixture was stirred for 1.5 h until almost all of the magnesium was dissolved. The cerium (III) chloride suspension was cooled to -78 °C. To this suspension was added dropwise the Grignard reagent, forming an off-white suspension which was stirred at -78 °C for 1 h. Ester **9** (6.32 g, 30.38 mmol) in 15 mL of THF was added dropwise over 5 min, and the resulting mixture was warmed gradually to room temperature. When consumption of starting ester was complete by TLC, the solution was cooled to -78 °C and quenched by the addition of 5% hydrochloric acid until pH 4.0 and then allowed to warm to room temperature. The aqueous solution was separated and extracted with Et_2O (2 x 100 mL). The combined organic solutions were washed with brine (2 x 50 mL) and saturated $NaHCO_3$ (2 x 50 mL), then dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to provide a slightly yellow liquid which was dissolved in 100 mL of CH_2Cl_2. To this solution was added 15.00 g of silica gel and 2 drops of 1% hydrochloric acid, and this mixture was stirred at room temperature until TLC indicated complete consumption of starting material. The silica gel was then removed by filtration and washed with 300 mL of CH_2Cl_2. The solvent was removed *in vacuo* to give a clear pale yellow liquid which was purified by flash chromatography on silica gel (2% EtOAc / hexanes) to afford 6.69 g (25.52 mmol, 84%) of allylsilane **10** as a clear liquid: $[\alpha]^{23}_{589}$ +6.2 (*c* 1.14, CH_2Cl_2); IR (neat) 3085, 3066, 3030, 2956, 2854, 2791, 1632 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35-7.25 (m, 5H), 4.63 (s, 1H), 4.60 (s, 1H), 4.53 (d, 1H, *J* = 12.1 Hz), 4.50 (d, 1H, *J* = 12.1 Hz), 3.52 (dd, 1H, *J* = 5.0, 9.1 Hz), 3.24 (dd, 1H, *J* = 8.1, 9.1 Hz), 2.29 (m, 1H), 1.58 (d, 1H, *J* = 0.9, 13.7 Hz), 1.53 (dd, 1H, *J* = 0.9, 13.7 Hz), 1.10 (d, 3H, *J* = 6.8 Hz), 0.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 149.7, 138.7, 128.3, 127.5, 127.4, 106.5, 75.0, 73.0, 41.0, 26.7, 17.2, -1.3; exact mass (70eV, CI/NH_3) calculated for $C_{16}H_{27}OSi$: 263.1831; found: 263.1836; Rf = 0.53 (10% EtOAc / hexanes).

2'-Methyl-2-[2*R*,5*R*]-2-hydroxyl-5-methyl-4-methylene-6-benzyloxy-hexyl-1,3-dioxolane (12). To a solution of 6.69 g (25.52 mmol) of allylsilane **10** in 70 mL of CH_2Cl_2 at -78 °C was added 3.28 mL (28.07 mmol) of $SnCl_4$ dropwise. The resulting solution was stirred at -78 °C for 1 h, then aldehyde **11** (3.98 g, 30.62 mmol) in 20 mL of CH_2Cl_2 was added dropwise. This mixture was stirred at -78 °C for 30 min and then quenched by the slow addition of 2 mL of Et_3N, followed by 100 mL of saturated NH_4Cl solution. The aqueous solution was separated and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic solutions were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (30% EtOAc / hexanes) gave 8.00 g (25.00 mmol, 98%) of homoallylic alcohol **12** as a clear oil: $[\alpha]^{23}_{589}$ +4.3 (*c* 1.85, CH_2Cl_2); IR (neat) 3518, 2981, 2930, 2881 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35-7.25 (m, 5H), 4.90 (s, 2H), 4.52 (d, 1H, *J* = 12.3 Hz), 4.48 (d, 1H, *J* = 12.3 Hz), 4.07 (m, 1H), 3.97 (m, 4H), 3.51 (s, 1H), 3.49 (dd, 1H, *J* = 6.5, 9.1 Hz), 3.32 (dd, 1H, *J* = 7.1, 9.1 Hz), 2.48 (s, 1H), 2.27 (dd, 1H, *J* = 7.1, 14.2 Hz), 2.13 (dd, 1H, *J* = 6.3, 14.2 Hz), 1.90 (dd, 1H, *J* = 1.7, 14.6 Hz), 1.74 (dd, 1H, *J* = 9.5, 14.8 Hz), 1.35 (s, 3H), 1.07 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 148.6,

138.4, 128.2, 127.5, 127.4, 111.6, 110.1, 74.5, 72.9, 66.2, 64.5, 64.2, 44.4, 43.5, 39.2, 24.0, 17.2; exact mass (70eV, CI/NH_3) calculated for $C_{19}H_{32}NO_4$: 338.2331; found: 338.2334; R_f = 0.26 (30% EtOAc / hexanes).

2'-Methyl-2-[2*S*,5*R*]-2-(4-nitrobenzoyl)-5-methyl-4-methylene-6-benzyloxy-hexyl-1,3-dioxolane (12a). To a mechanically stirred solution of 8.00 g (25.00 mmol) of alcohol **12**, 20.20 g (75.00 mmol) of triphenylphosphine and 11.70 g (70.00 mmol) of *p*-nitrobenzoic acid in 1 L of toluene at 0 °C was added dropwise 17.28 g (75.00 mmol) of di-*tert*-butylazodicarboxylate. After approximately 5 min the slightly orange solution became heterogeneous. This off-white suspension was then vigorously stirred at 0 °C for 12 h. The volatile components were then removed *in vacuo* and the residue purified by flash chromatography on silica gel (EtOAc/hexanes/Et_3N, 10/90/1) to provide 9.26 g (19.75 mmol, 79%) of ester **12a** as a pale yellow oil: $[\alpha]^{23}_{589}$ +4.1 (*c* 2.55, CH_2Cl_2); IR (neat) 3110, 3082, 3030, 2981, 2931, 2879, 1947, 1810, 1720, 1645, 1607 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.26 (dt, 2H, *J* = 2.0, 9.0 Hz), 8.17 (dt, 2H, *J* = 1.9, 9.0 Hz), 7.36-7.20 (m, 5H), 5.59 (m, 1H), 4.88 (d, 1H, J = 0.9 Hz), 4.87 (s, 1H), 4.48 (s, 2H), 3.92-3.79 (m, 4H), 3.46 (dd, 1H, *J* = 6.2, 9.2 Hz), 3.32 (dd, 1H, *J* = 6.9, 9.2 Hz), 2.54 (m, 1H), 2.48 (dd, 1H, *J* = 7.6, 14.6 Hz), 2.44 (dd, 1H, *J* = 5.8, 14.6 Hz), 2.14 (dd, 1H, *J* = 8.1, 15.0 Hz), 2.04 (dd, 1H, *J* = 3.3, 15.0 Hz), 1.32 (s, 3H), 1.08 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 164.0, 150.3, 147.4, 138.4, 136.2, 130.5, 128.2, 127.4, 123.4, 112.6, 108.6, 74.7, 72.9, 70.4, 64.5, 64.4, 42.5, 41.4, 39.1, 24.3, 16.9; εξαχτ mass (70eV, CI/NH_3) calculated for $C_{26}H_{32}NO_7$: 470.2179; found: 470.2192; R_f = 0.44 (30% EtOAc / hexanes). Anal. Calcd. for $C_{26}H_{31}NO_7$; C, 66.52; H, 6.61; N, 2.98; found: C, 66.60; H, 6.67; N, 2.99.

2'-Methyl-2-[2*S*,5*R*]-2-hydroxyl-5-methyl-4-methylene-6-benzyloxy-hexyl-1,3-dioxolane (13). To a solution of 9.26 g (19.75 mmol) of ester **12a** in 80 mL of MeOH was added 7 mL of water. To this solution was added 3.00 g (21.71 mmol) of K_2CO_3 and the resulting mixture was stirred at room temperature for 6 h. The volatiles were then removed *in vacuo*, and the residue purified by flash chromatography on silica gel (30% EtOAc / hexanes) to provide 6.26 g (19.55 mmol, 99%) of homoallylic alcohol **13** as a clear oil: $[\alpha]^{23}_{589}$ -2.0 (*c* 2.74, CH_2Cl_2); IR (neat) 3519, 3065, 3030, 2880, 1952, 1874, 1810, 1729, 1642, 1604 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.22 (m, 5H), 4.90 (m, 2H), 4.52 (d, 1H, *J* = 12.3 Hz), 4.48 (d, 1H, *J* = 12.3 Hz), 4.06 (m, 1H), 3.98 (m, 4H), 3.51 (s, 1H), 3.48 (dd, 1H, *J* = 6.2, 9.2 Hz), 3.32 (dd, 1H, *J* = 7.2, 9.2 Hz), 2.49 (m, 1H), 2.27 (dd, 1H, *J* = 7.3, 14.4 Hz), 2.12 (dd, 1H, *J* = 6.3, 14.4 Hz), 1.90 (dd, 1H, *J* = 1.8, 14.6 Hz), 1.74 (dd, 1H, *J* = 9.7, 14.6 Hz), 1.35 (s, 3H), 1.09 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 148.6, 138.4, 128.2, 127.44, 127.35, 111.6, 110.1, 74.5, 72.8, 66.4, 64.5, 64.2, 44.5, 43.2, 39.5, 24.0, 17.1; exact mass (70eV, CI/NH_3) calculated for $C_{19}H_{32}NO_4$: 338.2331; found: 338.2334; R_f = 0.26 (30% EtOAc / hexanes). Anal. Calcd. for $C_{19}H_{28}O_4$; C, 71.25; H, 8.75; found: C, 71.07; H, 8.81.

[4*S*,7*R*]-Hydroxyl-6-methylene-7-methyl-8-benzyloxy-octa-2-one (13a). To a solution of 6.26 g (19.55 mmol) of alcohol **13** in 100 mL of wet acetone was added 0.422 g (1.95 mmol) of pyridinium *p*-toluenesulfonate (PPTS). The resulting solution was refluxed for 5 h. The volatile components were then removed *in vacuo*. The residue was dissolved in 50 mL of Et_2O and washed with 25 mL of saturated aqueous $NaHCO_3$ and 25 mL of brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (30% EtOAc / hexanes) gave 5.29 g (19.16 mmol, 98%) of methyl ketone **13a** as a clear oil: $[\alpha]^{23}_{589}$ +18.2 (*c* 1.52, CH_2Cl_2); IR (neat) 3444, 3066, 3030, 2962, 2872, 1955, 1870, 1810, 1714, 1643 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.36-7.25 (m, 5H), 4.95 (d, 1H, *J* = 0.6 Hz), 4.92 (d, 1H, *J* = 1.1 Hz), 4.49 (s, 2H), 4.20 (m, 1H), 3.45 (dd, 1H, *J* = 7.4, 8.8 Hz), 3.36 (dd, 1H, *J* = 6.3, 8.8 Hz), 3.08 (d, 1H, *J* = 2.9 Hz), 2.60 (dd, H, *J* = 4.0, 17.1 Hz), 2.55 (dd, H, *J* = 8.2, 17.1 Hz), 2.50 (m, 1H), 2.21 (d, 2H, *J* = 6.4 Hz), 2.13 (s, 3H), 1.06 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 209.1, 148.5, 138.1, 128.2, 127.5, 127.4, 112.2, 74.5, 72.9, 66.3, 49.6, 42.7, 39.4, 30.6, 17.1; exact mass (70eV, CI/NH_3) calculated for $C_{17}H_{28}NO_3$: 294.2069; found: 294.2066; R_f = 0.19 (30% EtOAc / hexanes).

[4*S*,7*R*]-4-Triethylsiloxy-6-methylene-7-methyl-8-benzyloxy-octa-2-one (14). To a solution of 5.29 g (19.16 mmol) of methyl ketone **13a** in 77 mL of CH_2Cl_2 at -78 °C was added 4.46 mL (38.32 mmol) of 2,6-lutidine. To this solution was added dropwise 4.46 mL (21.07 mmol) of triethyltrifluoromethanesulfonate, and the resulting solution was stirred at -78 °C for 20 min. The solution was diluted with 120 mL of a 3:1 mixture of *n*-hexane/CH_2Cl_2 and then quenched by the addition of 25 mL of saturated aqueous $NaHCO_3$ solu-

tion. The aqueous solution was separated and extracted with 2 x 30 mL of CH_2Cl_2. The combined organic solutions were washed with 90 mL of 0.5 M aqueous $NaHSO_4$ solution. The aqueous phase was extracted with 20 mL of CH_2Cl_2, and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (5% EtOAc / hexanes) gave 7.25 g (18.58 mmol, 97%) of protected methyl ketone **14** as a pale green oil: $[\alpha]^{23}_{589}$ +17.7 (*c* 1.38, CH_2Cl_2); IR (neat) 3077, 3066, 3030, 2954, 2867, 1715, 1643 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35-7.25 (m, 5H), 4.87 (s, 1H), 4.83 (d, 1H, *J* = 1.0 Hz), 4.52 (d, 1H, *J* = 12.2 Hz), 4.48 (d, 1H, *J* = 12.2 Hz), 4.35 (m, 1H), 3.47 (dd, 1H, *J* = 6.1, 9.2 Hz), 3.31 (dd, 1H, *J* = 7.2, 9.2 Hz), 2.57 (dd, H, *J* = 4.6, 15.8 Hz), 2.51 (dd, H, *J* = 7.3, 15.8 Hz), 2.44 (m, 1H), 2.31 (dd, 1H, *J* = 5.1, 14.1 Hz), 2.15 (ddd, 1H, *J* = 0.6, 8.1, 14.1), 2.10 (s, 3H), 1.08 (d, 3H, *J* = 6.9 Hz), 0.93 (t, 9H, *J* = 7.7 Hz), 0.58 (q, 6H, *J* = 7.7 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 207.5, 148.2, 138.4, 128.1, 127.4, 127.3, 111.9, 74.3, 72.8, 67.7, 50.3, 43.6, 39.4, 31.3, 17.0, 6.7, 5.0; exact mass (70eV, CI/NH_3) calculated for $C_{23}H_{42}NO_3Si$: 408.2934; found: 408.2945; R_f = 0.63 (30% EtOAc / hexanes). Anal. Calcd. for $C_{23}H_{38}O_3Si$; C, 70.76; H, 9.74; found: C, 70.70; H, 9.84.

[2*R*,5*S*,9*RS*,10(4*S*,6*S*)]-1-[(Phenyl)-methoxy]-2-(methyl)-3-(methylene)-5-(triethylsiloxy)-9-(hydroxy)-10-[2-phenyl-4-(triphenylmethyloxy)-ethyl-1,3-dioxan-6-yl]-decan-7-one (15). To a solution of 3.625 g (9.29 mmol) of methyl ketone **14** in 20 mL of CH_2Cl_2 at -78 °C were added 2.3 mL (13.0 mmol) of diisopropylethylamine and 2.80 mL (11.25 mmol) of di-*n*-butyl-boron triflate. The resulting mixture was maintained at -78 °C for 45 min, producing a light yellow solution. To this enolate solution was added 4.13 g (8.40 mmol) of aldehyde **6** as a solution in 17 mL of CH_2Cl_2. The mixture was stirred at -78 °C for 2 h and quenched by the addition of 15 mL of a 1:1 mixture of pH 7 phosphate buffer and MeOH. The mixture was warmed to 0 °C and maintained at this temperature for an additional 15 min. A solution of 10 mL of 30% aqueous H_2O_2 in 10 mL of MeOH was added slowly, and the resulting solution was allowed to stir at 0 °C for 1 h. After removal of the organic solvents *in vacuo*, 50 mL of saturated aqueous $NaHCO_3$ was added, and the mixture was extracted with 3 x 60 mL of CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil. Purification by flash chromatography on silica gel (15% EtOAc / hexanes) gave 5.85 g (6.34 mmol, 79% based on aldehyde **6**) of a 1:1 mixture of aldol products **15** as a clear oil: IR (neat) 3527, 3086, 3060, 3032, 1707, 1641 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.48-7.20 (m, 25H), 4.86 (s, 1H), 5.55 (m, 1H), 4.82 (s, 1H), 4.49 (s, 2H), 4.37 (m, 2H), 4.16 (m, 2H), 3.47 (dd, 1H, *J* = 6.4, 9.1 Hz), 3.39 (m, 1H), 3.30 (dd, 1H, *J* = 7.1, 9.1 Hz), 3.14 (m, 1H), 2.48-2.64 (m, 4H), 2.43 (m, 1H), 2.32 (dd, 1H, *J* = 4.8, 14.2 Hz), 2.14 (dd, 1H, *J* = 8.5, 14.1 Hz), 1.92 (m, 1H), 1.88 (m, 1H), 1.67-1.56 (m, 3H), 1.53 (m, 1H), 1.41 (m, 1H), 1.08 (d, 3H, *J* = 6.9 Hz), 0.93 (t, 9H, *J* = 8.0 Hz), 0.59 (q, 6H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 211.0, 210.0, 200.3, 148.2, 144.3, 144.2, 138.7, 138.5, 138.4, 128.6, 128.4, 128.3, 128.1, 128.0, 127.7, 127.5, 126.8, 126.0, 112.1, 100.4, 100.2, 86.4, 75.6, 74.3, 73.8, 73.3, 72.9, 67.8, 65.7, 64.0, 59.1, 59.0, 51.0, 50.9, 50.3, 50.1, 43.7, 43.6, 42.4, 41.3, 39.6, 37.3, 36.9, 36.3, 17.2, 6.8, 4.9; exact mass (70 eV, FAB/NaI) calculated for $C_{56}H_{70}O_7SiNa$: 905.4789; found: 905.4840; R_f = 0.49 (30% EtOAc / hexanes). Anal. Calcd. for $C_{56}H_{70}O_7Si$; C, 76.19; H, 7.94; found: C, 76.07; H, 7.97.

[2*R*,5*S*,10(4*S*,6*S*)]-1-[(Phenyl)-methoxy]-2-(methyl)-3-(methylene)-5-(triethylsiloxy)-9-(hydroxy)-10-[2-phenyl-4-(triphenylmethyloxy)-ethyl-1,3-dioxan-6-yl]-8-decen-7-one (16). To a slurry of 6.00 g of celite in 120 mL of CH_2Cl_2 was added 2.06 mL (26.08 mmol) of pyridine, followed by 1.30 g (13.04 mmol) of CrO_3 (dried *in vacuo* prior to use). The resulting slurry was stirred at room temperature for 1 h producing a red heterogeneous mixture. To the reaction mixture was added a solution of 1.00 g (1.141 mmol) of aldol adducts **15** in 25 mL of CH_2Cl_2. This slurry was stirred vigorously for 1 h at room temperature. The dark red reaction mixture was then poured into 100 mL of a saturated aqueous solution of NH_4Cl and was extracted with 3 x 100 mL of EtOAc. The combined light-red extracts were filtered through a short plug of florisil, followed by further elution with 100 mL of EtOAc. The resulting colorless filtrate was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (10% EtOAc / hexanes) gave 0.773 g (0.878 mmol, 77%) of β-diketone **16** as a clear oil: $[\alpha]^{23}_{589}$ +22.2 (*c* 1.08, CH_2Cl_2); IR (neat) 3086, 3060, 3032, 2954 2912, 2875, 1954, 1811, 1704 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.48-7.20 (m, 25H), 5.59 (m, 1H), 5.57 (s, 1H), 4.91 (s, 1H), 4.88 (s, 1H), 4.53 (d, 1H, *J* = 12.2 Hz), 4.49 (d,

1H, J = 12.2 Hz), 4.32 (m, 2H), 4.19 (m, 1H), 3.50 (dd, 1H, J = 6.0, 9.2 Hz), 3.40 (m, 1H), 3.32 (dd, 1H, J = 7.3, 9.1 Hz), 3.18 (m, 1H), 2.72 (dd, 1H, J = 7.0, 14.8 Hz), 2.56 (dd, 1H, J = 4.1, 14.1 Hz), 2.46 (m, 1H), 2.45 (dd, 1H, J = 6.1, 14.8 Hz), 2.36 (dd, 1H, J = 5.1, 14.1 Hz), 2.27 (dd, 1H, J = 8.2, 14.1 Hz), 2.21 (dd, 1H, J = 7.8, 14.0 Hz), 1.88 (m, 2H), 1.66 (dt, 1H, J = 2.0, 13.0 Hz), 1.42 (dt, 1H, J = 11.3, 12.9 Hz), 1.09 (d, 3H, J = 6.9 Hz), 0.91 (t, 9H, J = 7.9 Hz), 0.55 (q, 6H, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 191.42, 191.35, 148.2, 144.3, 138.5, 138.5, 128.7, 128.3, 128.0, 127.9, 127.7, 127.5, 127.4, 126.9, 126.0, 112.2, 102.4, 100.3, 86.4, 74.5, 73.6, 73.5, 73.0, 68.7, 59.0, 45.7, 45.0, 44.1, 39.6, 36.9, 36.3, 17.2, 6.8, 4.9; exact mass (70 eV, FAB/NaI) calculated for $C_{56}H_{68}O_7SiNa$: 903.4632; found: 903.4630; R_f = 0.64 (30% EtOAc / hexanes). Anal. Calcd. for $C_{56}H_{68}O_7Si$; C, 76.36; H, 7.73; found: C, 76.30; H, 7.79.

[2*R*,2(3*R*),6*R*,8*S*,10*S*]-10-Hydroxy-8-[2-(hydroxy)ethyl]-2-[2-methylen-3-methyl-4-(phenylmethoxy)-butyl]-1,7-dioxaspiro[5.5]-undecan-4-one (17). To 10 mL of a 90:5 acetonitrile:conc. aqueous hydrofluoric acid (47%) mixture was added 5 mL of deionized water. This solution was added to 0.773 g (0.878 mmol) of β-diketone **16**, and the resulting yellow solution was stirred at room temperature for 48 h. The reaction was quenched by cautious addition of 20 mL of saturated aqueous $NaHCO_3$ and was then partitioned between 20 mL of water and 30 mL of EtOAc. The aqueous solution was extracted with 3 x 10 mL of EtOAc, and the combined organic extracts were washed with 30 mL of brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (70% EtOAc / hexanes) afforded 0.275 g (0.658 mmol, 75%) of spiroketal **17** as a clear oil: $[\alpha]^{23}_{589}$ -35.8 (*c* 5.79, CH_2Cl_2); IR (neat) 3517, 3086, 3060, 3031, 1722, 1645, 1606 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.37-7.25 (m, 5H), 4.98 (d, 1H, J = 0.7 Hz), 4.97 (s, 1H), 4.50 (d, 1H), 4.46 (d, 1H, J = 11.9 Hz), 4.05 (m, 2H), 3.76 (d, 1H, J = 10.4 Hz), 3.60 (m, 1H), 3.56 (m, 1H), 3.43 (dd, 1H, J = 6.7, 9.1 Hz), 3.32 (dd, 1H, J = 6.3, 9.1 Hz), 2.52 (m, 1H), 2.48 -2.43 (m, 2H), 2.41-2.35 (m, 3H), 2.21 (dd, 1H, J = 11.4, 14.2 Hz), 2.10 (br, 1H), 2.06 (dt, 1H, J = 2.3, 14.3 Hz), 1.72 (ddd, 1H, J = 2.1, 5.1, 13.7 Hz), 1.66 (dd, 1H, J = 3.5, 14.2 Hz), 1.63 (m, 2H), 1.46 (ddd, 1H, J = 2.8, 12.0, 13.6 Hz), 1.09 (d, 3H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 17.1, 37.4, 37.6, 38.3, 39.4, 43.4, 46.6, 51.4, 58.5, 62.3, 64.2, 68.0, 73.2, 75.2, 100.8, 112.7, 127.65, 127.70, 128.4, 137.9, 147.7, 204.2; exact mass (70 eV, FAB/NaI) calculated for $C_{24}H_{34}O_6SiNa$: 441.2230; found: 441.2253; calculated for $C_{24}H_{35}O_6Si$: 419.2433; found: 419.2416; R_f = 0.17 (70% EtOAc / hexanes).

[2*R*,2(3*R*),6*R*,8*S*,10*S*]-10-Hydroxy-8-[2-(*tert*-butyldimethylsiloxy)ethyl]-2-[2-methylen-3-methyl-4-(phenylmethoxy)-butyl]-1,7-dioxaspiro[5.5]-undecan-4-one (18). To a solution of 0.275 g (0.658 mmol) of spiroketone **17** in 5 mL of CH_2Cl_2 at room temperature was added 0.089 g (1.316 mmol) of imidazole and 0.149 g (0.990 mmol) of *tert*-butyldimethylsilyl chloride. A white suspension quickly formed, which was stirred at room temperature for 12 h. The reaction mixture was then diluted with 15 mL of CH_2Cl_2, and the combined organic extracts were washed with brine, filtered, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (30% EtOAc / hexanes) gave 0.336 g (0.631 mmol, 96%) of spiroketal **18** as a clear oil: $[\alpha]^{23}_{589}$ -28.2 (*c* 2.94, CH_2Cl_2); IR (neat) 3526, 3086, 3063, 3031, 2929, 2739, 2709, 1950, 1727, 1644 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36-7.25 (m, 5H), 5.01 (s, 2H), 4.49 (s, 2H), 4.14 (m, 1H), 4.04 (dt, 1H, J = 3.1, 10.5 Hz), 3.91 (m, 1H), 3.74 (d, 1H, J = 10.5 Hz), 3.68 (m, 2H), 3.43 (dd, 1H, J = 6.3, 9.1 Hz), 3.32 (dd, 1H, J = 6.6, 9.1 Hz), 2.46 (m, 1H), 2.44 -2.37 (m, 4H), 2.33 (dd, 1H, J = 8.6, 14.3 Hz), 2.21 (dd, 1H, J = 11.3, 14.4 Hz), 2.04 (dt, 1H, J = 2.3, 14.3 Hz), 1.76 (br d, 1H), 1.71-1.61 (m, 3H), 1.44 (m, 1H), 1.12 (d, 3H, J = 8.6 Hz), 0.86 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 204.2, 147.5, 138.4, 128.3, 127.5, 112.7, 100.7, 75.0, 73.0, 68.0, 64.2, 62.2, 59.5, 51.4, 46.6, 42.2, 39.5, 39.1, 38.8, 37.5, 26.0, 18.4, 16.7, -5.27, -5.32; exact mass (70 eV, FAB/NaI) calculated for $C_{30}H_{48}O_6SiNa$: 555.3118; found: 555.3094; R_f = 0.17 (30% EtOAc / hexanes). Anal. Calcd. for $C_{30}H_{48}O_6Si$; C, 67.67; H, 9.02; found: C, 67.65; H, 9.12.

[2*R*,2(3*R*),4*S*,6*R*,8*S*,10*S*]-8-[2-(*tert*-Butyldimethylsiloxy)ethyl]-2-[2-methylen-3-methyl-4-(phenylmethoxy)-butyl]-10-hydroxy-4-methyl-1,7-dioxaspiro[5.5]-undecan-4-ol (19). A 2-necked 50 mL flask containing 0.705 g (1.893 mmol) of powdered $CeCl_3 \cdot 7H_2O$ was heated under vacuum (1 mm Hg) at 160 °C for 12 h with vigorous stirring, resulting in the formation of a white mobile solid. The reaction flask was flushed with nitrogen and allowed to cool to room temperature. THF (5 mL) was added to the vigorously stirred cerium

(III) chloride to form a uniform white suspension which was allowed to stir at room temperature for 2 h. To the cooled mixture (-78 °C) was added dropwise 1.13 mL (1.17 mmol) of a 1.4 M solution of MeLi in THF to form an off-white suspension which was stirred at -78 °C for 1.5 h. To this suspension was added dropwise a solution of 0.336 g (0.631 mmol) of spiroketal **18** in 5 mL of THF, and the resulting mixture was stirred at -78 °C for 1 h. After this, the mixture was diluted with 20 mL of Et_2O, quenched by the slow addition of 10 mL of a saturated solution of NH_4Cl and allowed to warm to room temperature. The aqueous solution was separated and extracted with 2 x 20 mL of Et2O. The combined organic solutions were washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel (20% EtOAc / hexanes) afforded 0.300 g (0.548 mmol, 87%) of axial alcohol **19** as a clear oil: $[\alpha]^{23}_{589}$ -17.8 (*c* 2.20, CH_2Cl_2); IR (neat) 3518, 3086, 3064, 3031, 2930, 2739, 2710, 1644, 1604 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.36-7.25 (m, 5H), 4.98 (s, 2H), 4.51 (d, 1H, *J* = 12.2 Hz), 4.46 (d, 1H, *J* = 12.2 Hz), 4.30 (s, 1H), 4.08 (m, 1H), 3.99 (m, 2H), 3.93 (d, 1H), 3.76- 3.69 (m, 2H), 3.44 (dd, 1H, *J* = 5.7, 9.1 Hz), 3.28 (dd, 1H, *J* = 7.0, 9.1 Hz), 2.48 (m, 1H), 2.29 (dd, 1H, *J* = 3.8, 14.4 Hz), 2.22 (dd, 1H, *J* = 9.1, 14.3 Hz), 1.83-1.66 (m, 6H), 1.62 (dd, 1H, *J* = 3.4, 14.0 Hz), 1.48 (m, 1H, *J* = 13.8 Hz), 1.47 (d, 1H, *J* = 14.0 Hz), 1.29 (dd, 1H, *J* = 11.7, 13.4 Hz), 1.17 (s, 3H), 1.14 (d, 3H, *J* = 6.9 Hz), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 148.2, 138.6, 128.4, 127.61, 127.55, 112.4, 100.3, 75.2, 73.1, 67.8, 64.9, 64.5, 63.0, 60.1, 45.6, 43.8, 42.1, 40.0, 39.00, 38.97, 38.1, 30.1, 26.1, 18.5, 16.8; exact mass (70 eV, FAB/NaI) calculated for $C_{31}H_{52}O_6SiNa$: 571.3431; found: 571.3445; R_f = 0.37 (30% EtOAc / hexanes). Anal. Calcd. for $C_{31}H_{52}O_6Si$; C, 67.88; H, 9.49; found: C, 67.87; H, 9.60.

[2*R*,2(3*R*),4*S*,6*R*,8*S*,10*S*]-8-(2-*tert*-Butyldimethylsiloxy)ethyl]-2-[2-methylen-3-methyl-4-hydroxybutyl]-10-triethylsiloxy-4-triethylsiloxy-4-methyl-1,7-dioxaspiro[5.5]undecan-4-ol (20). To a -78 °C solution of **19** (0.692 g, 1.25 mmol) in CH_2Cl_2 (20 mL) were added 2,6-lutidine (0.436 mL, 3.75 mmol) and triethylsilyl trifluoromethanesulfonate (0.636 mL, 2.81 mmol). Upon completion, the reaction was diluted with saturated aqueous $NaHCO_3$ and Et_2O, then warmed to room temperature. The organic solution was separated, washed with saturated aqueous NH_4Cl and brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (150 g SiO_2, 10 % EtOAc/hexanes) to give 0.725 g of the silyl ether, which was used immediately in the following reaction. A solution of di-*tert*-butylbiphenyl (2.76 g, 10.38 mmol) in THF (20 mL) was treated with several small pieces of cut and crushed (with pliers) lithium wire (0.080 g, 11.42 mmol) at room temperature. The mixture was sonicated (with cooling to maintain temperature 10-25 °C) for 5 h to produce a deep green radical anion solution. In a separate flask, a solution of the benzyl ether (0.725 g, 0.930 mmol) in THF (15 mL) was cooled to -78 °C. The radical anion solution was added to the substrate portionwise (ca. 10 mL) until the green-blue color persisted. The solution was stirred for 15 min at -78 °C and carefully quenched with saturated aqueous NH_4Cl solution. The cold bath was removed and the mixture warmed to room temperature. The mixture was extracted with Et_2O (2 x 30 mL). The combined organic solutions were washed with saturated aqueous NH_4Cl (10 mL) and brine (10 mL), then dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (150 g SiO_2, 20 % EtOAc/ hexanes) to give 0.533 g (62% from **19**) of the alcohol **20**: $[\alpha]^{23}_{589}$ -39.2 (*c* 3.3, $CHCl_3$) IR (neat) 3460, 2957, 2878, 1636 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.99 (s, 1H), 4.92 (s, 1H), 4.23-4.17 (m, 1H), 4.13-4.07 (m, 1H), 4.03-3.99 (m, 1H), 3.76-3.62 (m, 2H), 2.45-2.37 (m, 1H), 2.27-2.22 (dd, *J* = 14.5, 6.8 Hz, 1H), 2.13-2.08 (dd, *J* = 14.5, 6.1 Hz, 1H), 1.92-1.90 (m, 1H), 1.82-1.73 (m, 2H), 1.67-1.45 (m), 1.27-1.24 (d, *J* = 14.1 Hz, 1H), 1.19 (s, 3H), 1.03-1.01 (d, *J* = 7.0 Hz, 3H), 0.96-0.92 (m, 18H), 0.88 (s, 9H), 0.60-0.54 (m, 12H), 0.04 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.4, 112.0, 97.3, 70.5, 65.9, 65.3, 64.8, 62.0, 60.3, 48.1, 44.8, 43.1, 43.0, 39.3, 38.7, 32.2, 25.9, 18.2, 16.2, 7.2, 6.9, 6.8, 4.8, -5.2; exact mass calcd for $C_{36}H_{74}O_6Si_3Na$: 709.4691; found 709.4690 (FAB, MNBA, added NaI); R_f=0.61 (20% EtOAc/ hexanes).

[2*R*,2(3*R*),4*S*,6*R*,8*S*,10*S*]-8-(2-*tert*-Butyldimethylsiloxy)ethyl]-2-[2-methylen-3-methyl-butan-4-al]-10-triethylsiloxy-4-triethylsiloxy-4-methyl-1,7-dioxaspiro[5.5]undecan-4-ol (21). A solution of Dess-Martin periodinane (0.061 g, 0.142 mmol) in CH_2Cl_2 (2 mL) was prepared under an inert atmosphere (weighed in dry box) and treated with pyridine (0.096 mL, 0.094 g, 1.19 mmol). After stirring for 5 min, a solution of alcohol **20** (0.092 g, 0.137 mmol) in CH_2Cl_2 (1 mL) was added. The clear, yellow solution was stirred for 40 min.

The solution was quenched with 1M $Na_2S_2O_3$/saturated aqueous $NaHCO_3$ (0.5 mL/0.5 mL). The mixture was extracted with Et_2O (2 x 10 mL). The combined organic solutions were washed with saturated aqueous $NaHCO_3$ (2 x 5 mL) and brine (5 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated. The residue (0.093 g, 100%) was used without further purification Partial data for the unpurified aldehyde **21**: IR (neat) ν 2955, 2872, 2717, 1722, 1639 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 9.61 (s, 1H) 5.13 (s, 1H), 4.86 (s, 1H), 4.36-4.31 (m, 2H), 3.96-3.94 (t, J = 3.4 Hz), 3.90-3.77 (m, 2H), 3.19-3.14 (q, J = 6.9 Hz, 1H), 2.41-2.36 (dd, J = 14.3, 6.4 Hz, 1H), 2.19-2.14 (dd, J = 14.3, 6.0 Hz, 1H), 2.02-1.94 (m, 1H), 1.75-1.63 (m, 4H), 1.45-1.34 (m, 1H), 1.22-1.21 (d, J = 6.9 Hz, 3H), 1.16-1.12 (d, J = 14.0 Hz, 1H), 1.10-0.96 (m, 27 H), 0.71-0.57 (m, 12H); ^{13}C NMR (101 MHz, C_6D_6) δ 199.9, 144.7, 115.0, 97.3, 70.7, 65.4, 65.1, 62.0, 60.6, 53.5, 48.4, 45.0, 43.2, 41.9, 39.8, 39.0, 32.3, 26.1, 18.4, 13.4, 7.5, 7.2, 7.1, 5.1, 1.3, -5.0, -5.1; R_f=0.60 (20% EtOAc/ hexanes).

[2*R*]-1-Triphenylmethoxy-2-hydroxy-4-pentene (23). A suspension of CuI (37.42 g, 197 mmol) in THF (480 mL) was cooled to -78 °C and treated with a solution of vinylmagnesium bromide (394.1 mL of a 1M solution in THF, 394.1 mmol) maintaining an internal temperature below -70 °C. After the addition was complete, the light-brown slurry was stirred for 1 h at -78 °C. A solution of **22** (31.16 g, 98.6 mmol) in THF (250 mL) was added via an addition funnel over 30 min. The resulting slurry was stirred at -78 °C for 90 min. The cold bath was removed and the mixture was warmed to -20 °C (mixture discolors to a dark brown color). A mixture of saturated aqueous NH_4Cl and NH_4OH (600 mL/600 mL) was cautiously added (vigorous evolution of ethylene gas). After foaming had subsided, Et_2O (1200 mL) was added and the mixture stirred for 12 h. The biphasic mixture was separated. The aqueous portion was extracted with Et_2O (2 x 500 mL). The combined organic solutions were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography (500 g SiO_2, 10% EtOAc / hexanes) afforded 32.54 g (96%) of alcohol **23** as a clear oil: $[\alpha]^{23}_{589}$ -1.0 (*c* 1.39, $CHCl_3$); IR (neat) 3578, 2925, 1956, 1820, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46-7.43 (m, 5H), 7.34-7.24 (m, 10H), 5.75 (m, 1H), 5.06 (m, 2H), 3.85 (m, 1H), 3.21-3.16 (dd, J = 9.2, 5.2 Hz, 1H), 3.12-3.07 (dd, J = 9.2, 6.8 Hz, 1H), 2.25 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 143.8, 134.3, 128.6, 127.8, 127.0, 117.5, 86.7, 70.2, 67.1, 38.1; exact mass (EI) calculated for $C_{24}H_{28}O_2N$: 362.2120; found 362.2131; R_f= 0.26 (15% EtOAc / hexanes).

[2*E*,5*R*]-5-Hydroxy-6-(triphenylmethyloxy)-*N*-methyl-*N*-methoxy-2-hexenamide (24). A solution of alkene **23** (25.37 g, 73.9 mmol) in dichloromethane (750 mL) was treated with several crystals of Sudan Red (ca. 20 mg). The pale red solution was cooled to -78 °C. Ozone was bubbled through the solution until the red color dissipated (40 min). The solution was purged with N_2 for 20 min. Triphenylphosphine (19.36 g, 73.9 mmol) was added and the cold bath removed. After stirring for 5 h at room temperature, *N*-methoxy-*N*-methyl-(triphenylphosphoranylidene)acetamide (26.83 g, 73.9 mmol) was added producing a slight exotherm (22 → 28 °C). The yellow solution was stirred for 14 h at ambient temperature. The solution was concentrated to an oil. The residue was initially purified by flash chromatography (1.25 kg SiO_2; 30 → 50% EtOAc/hexanes) to give the product **24** mixed with triphenylphosphine oxide. This material was concentrated to a paste and triturated with hexanes. The solid mass was washed with Et_2O/hexanes (1:1). The combined extracts were concentrated and chromatographed (750 g SiO2; 50% EtOAc/hexanes) to give 23.1 g (73%) of the product **24** as a white solid: $[\alpha]^{23}_{589}$ +2.0 (*c* 2.62, $CHCl_3$); IR (neat) 3405, 3059, 3006, 1661, 1623 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44-7.41 (m, 6H), 7.32-7.21 (m, 9H), 6.94-6.86 (dt, J = 7.3, 15.4 Hz, 1H), 6.96-6.42 (d, J = 15.4 Hz, 1H), 3.92-3.87 (m, 1H), 3.64 (s, 3H), 3.21 (s, 3H), 3.21-3.09 (m, 2H), 2.43-2.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 166.5, 143.7, 142.9, 128.5, 127.8, 127.1, 121.1, 86.7, 77.2, 69.7, 67.1, 61.6, 36.7, 32.3; exact mass (FAB) calculated for $C_{27}H_{29}O_4Na$: 454.1994; found 454.1998; R_f = 0.26 (15% EtOAc / hexanes).

[2*R* , 4*S* , 6*S*]-4-(*N*-methoxy-*N*-methyl-carboxamidomethyl)-6-[(triphenylmethyloxy)methyl]-2-phenyl-1,3-dioxane (25). A solution of the amide **24** (22.75 g, 52.78 mmol) in THF (530 mL) was cooled to 0 °C. The solution was treated with freshly distilled benzaldehyde (3 portions x 5.84 mL, 58 mmol) and potassium *tert*-butoxide (3 x 0.592 g, 5.28 mmol) at 1 h intervals. After stirring for an additional 30 min, saturated aqueous NH_4Cl solution (200 mL) was added. The mixture was extracted with Et_2O (2 x 500 mL). The combined

organic solutions were washed with saturated aqueous NH_4Cl (300 mL) and brine (300 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (1 kg SiO_2, 30→70% EtOAc/hexanes) to give 19.1 g (76%) of the benzylidene acetal **25** and 2.8 g (12%) of the starting carbinol **24**. $[\alpha]^{23}_{589}$ -10.2 (*c* 1.52, $CHCl_3$); IR (neat) 3008, 1659 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55-7.48 (m, 7H), 7.37-7.19 (m, 13H), 5.64 (s, 1H), 4.46-4.39 (m, 1H), 4.17-4.12 (m, 1H), 3.63 (s, 3H), 3.73-3.37 (dd, *J* = 5.8, 9.6 Hz, 1H), 3.17 (s, 3H), 3.10-3.06 (dd, *J* = 5.8, 9.6 Hz, 1H), 3.00-2.95 (m, 1H), 2.57-2.52 (dd, *J* = 15.6, 5.9 Hz, 1H), 1.84-1.81 (d, *J* = 13.0 Hz, 1H), 1.57-1.48 (q, *J* = 11.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 143.9, 138.5, 128.7, 128.5, 128.4, 128.0, 127.9, 127.7, 126.9, 126.0, 100.5, 86.3, 75.8, 73.3, 66.6, 61.3, 38.1, 33.79; exact mass calcd for $C_{34}H_{35}O_5NNa$: 560.2413; found 560.2397 (FAB, MNBA, added NaI); R_f=0.50 (60% EtOAc/ hexanes).

[2*R*,4*S*,6*S*]-4-(Propan-2-one)-6-[(triphenylmethyloxy)methyl]-2-phenyl-1,3-dioxane (26). A solution of the amide **25** (10.0 g, 18.69 mmol) in THF (180 mL) was cooled to -78 °C and treated with a solution of methyllithium in Et_2O (40.0 mL of a 1.4 **M** solution in Et_2O, 56 mmol) over 30 min. After stirring for 90 min at -78 °C, the solution was cautiously quenched by the addition of a saturated aqueous solution of NH_4Cl (40 mL). The cold bath was removed and the mixture warmed to room temperature. The mixture was extracted with Et_2O (2 x 150 mL). The combined organic solutions were washed with saturated aqueous NH_4Cl (100 mL) and brine (100 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (600 g SiO_2; 15→20% EtOAc/hexanes) to give 7.47 g (81%) of the methyl ketone **26** as a white foam. $[\alpha]^{23}_{589}$ +25.6 (*c* 1.96, $CHCl_3$); IR (neat) *v* 3070, 3022, 2917, 2869, 1716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54-7.22 (m, 20H), 5.59 (s, 1H), 4.39-4.35 (m, 1H), 4.15-4.12 (m, 1H), 3.38-3.34 (dd, *J* = 5.7, 9.5 Hz, 1H), 3.12-3.08 (dd, *J* = 5.7, 9.5 Hz, 1H), 2.92-2.86 (dd, *J* = 16.3, 7.2 Hz, 1H), 2.59-2.54 (dd, *J* = 16.3, 5.2 Hz, 1H) 2.21 (s, 3H), 1.76-1.73 (d, *J* = 12.9 Hz, 1H), 1.58-1.49 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.4, 143.9, 138.3, 128.6, 128.1, 127.7, 126.9, 125.9, 100.4, 86.4, 75.7, 72.8, 66.5, 49.4, 33.6, 31.1; exact mass calcd for $C_{33}H_{32}O_4Na$: 515.2199; found 515.2187 (FAB, MNBA, added NaI); R_f=0.24 (20% EtOAc/ hexanes).

(1*S*)-1-(-2-Napthyl)ethyl(3*S*,5*S*)-3-*tert*-Butyldimethylsilyloxy-5-hydroxy-8-[2-phenyl-4-(*R*)-triphenylmethyloxy)-methyl-1,3-dioxan-6-(*S*)-yl]-octan-7-on-1-oic acid (28). A solution of the methyl ketone **26** (7.15 g, 14.53 mmol) in Et_2O (250 mL) was slowly cooled to -78 °C (rapid cooling precipitates methyl ketone **26**). To this solution was added Hunig's base (2.76 mL, 16.27 mmol). After stirring for 5 min, neat Bu_2BOTf (3.81 mL) was added dropwise. The resulting white suspension was stirred for 45 min at -78 °C. The reaction mixture was cooled to -110 °C (internal temperature monitoring) by immersion in an Et_2O/liquid N_2 bath. A solution of the aldehyde (*S*)-**27** (6.50 g, 16.27 mmol) in Et_2O (50 mL) was added by cannula. After stirring for 45 min at -110 °C, the solution was warmed to -78 °C and stirred at this temperature for 45 min. The solution was quenched with a solution of MeOH/pH 7 phosphate buffer (5 mL/5 mL) and the -78 °C cold bath replaced with an ice bath. After warming to O °C, the biphasic mixture was treated with a mixture of MeOH/ 30% aqueous H_2O_2 (10 mL/10 mL) and the mixture stirred at 0 °C for 1 h. The mixture was warmed to room temperature and diluted with Et_2O (250 mL). The organic solution was washed with saturated aqueous $NaHCO_3$ (2 x 150 mL) and brine (150 mL). The aqueous washes were extracted with Et_2O (75 mL). The combined organic solutions were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (1 kg SiO_2, Gradient elution: 15→30% EtOAc/hexanes) to give 10.25 g (79%) of aldol product mixture and 1.04 g (15%) of starting methyl ketone **26**. The diastereoselectivity of the aldol addition process was determined to be 22:1 favoring the 1,5 *anti* product **28** (Zorbax, 20% EtOAc/hexanes, 1 mL/min). Data for the major isomer **28**: $[\alpha]^{25}_{589}$ -3.3 (*c* 1.47, $CHCl_3$); IR (neat) *v* 3507, 3046, 3015, 2851, 1728 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 7.71-7.61 (m, 11H), 7.45 (d, *J* = 8.5 Hz, 1H), 7.29-7.01 (m, 15H), 6.19-6.15 (q, *J* = 6.5 Hz, 1H), 5.44 (s, 1H), 4.64-4.55 (m, 1H), 4.42-4.32 (m, 1H), 4.20-4.08 (m, 1H), 3.91-3.80 (m, 1H), 3.46-3.43 (dd, *J* = 5.6, 9.6 Hz, 1H), 3.22 (br s), 2.64-2.54 (m, 2H), 2.45-2.41 (dd, *J* = 7.4, 16.0 Hz, 1H), 2.18-2.06 (m, 2H), 2.00-1.96 (dd, *J* = 4.8, 16.0 Hz, 1H), 1.62-1.46 (m, 2H), 1.51 (d, *J* = 6.5 Hz, 3H), 1.39-1.23 (m, 2H), 0.928 (s, 9H), 0.16 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.0, 169.9, 144.6, 139.5, 139.4, 133.8, 133.7, 129.2, 128.7, 128.6, 128.4, 128.2, 128.1, 127.2, 126.6, 126.3, 126.1, 125.5, 124.6,

100.9, 87.0, 77.5, 76.0, 72.9, 72.5, 67.2, 64.4, 51.2, 49.1, 43.6, 43.4, 33.6, 29.9, 26.0, 22.3, 18.2, -4.66; exact mass calcd for $C_{56}H_{64}O_8SiNa$: 915.4270; found 915.4271 (FAB, MNBA, added NaI); R_f=0.11 (20% EtOAc/ hexanes).

(1*S*)-1-(-2-Napthyl)ethyl(3*S*,5*S*)-3-*tert*-Butyldimethylsilyloxy-5-methoxy-8-[2-phenyl-4-(*R*)-triphenylmethyloxy)-methyl-1,3-dioxan-6-(*S*)-yl]-octan-7-on-1-oic acid (30). A suspension of trimethyloxonium tetrafluoroborate (2.93 g, 19.77 mmol) in dichloromethane (250 mL) at room temperature was treated with freshly distilled di-*tert*-butylmethylpyridine (5.40 g, 23.36 mmol). After the mixture was stirred for 20 min, a solution of aldol **28** in CH_2Cl_2 (80 mL) was rapidly added via cannula. The heterogeneous mixture was stirred for 50 min. The pale yellow suspension was treated with saturated aqueous $NaHCO_3$ (20 mL). The biphasic mixture was diluted with Et_2O (300 mL). The organic solution was washed with saturated aqueous $NaHCO_3$ (2 x 100 mL) and brine (100 mL). The solution was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (500 g SiO_2, 15% EtOAc/hexanes) to give 5.47 g (91%) of the methylated adduct **30** as a white foam: $[\alpha]^{25}_{589}$ -9.5 (*c* 1.34, $CHCl_3$); IR (neat) ν 3059, 2856, 1729 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78-7.62 (m, 11H), 7.46-7.44 (dd, *J* = 1.7, 8.4 Hz, 1H), 7.30-7.04 (m, 15H), 6.18 (q, *J* = 6.6 Hz, 1H), 5.51 (s, 1H), 4.54-4.47 (m, 1H), 4.20-4.16 (m, 1H), 3.99-3.95 (m, 1H), 3.92-3.83 (m, 1H), 3.47-3.43 (dd, *J* = 5.7, 9.6 Hz, 1H), 3.18 (dd, *J* = 4.5, 9.5 Hz, 1H), 3.13 (s, 3H) 2.67-2.44 (m, 4H), 2.23-2.18 (dd, *J* = 16, 6.0 Hz, 1H), 2.11 (dd, *J* = 5.1, 16.3 Hz, 1H), 1.82-1.71 (m, 2H), 1.50 (d, *J* = 6.5 Hz, 3H), 1.41-1.27 (m, 2H), 0.963 (s, 9H), 0.17 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.5, 170.3, 143.9, 138.9, 138.1, 133.1, 128.7, 128.6, 128.2, 128.1, 128.0, 127.7, 127.6, 126.9, 126.1, 126.0, 125.9, 125.0, 124.1, 100.4, 86.9, 75.8, 73.5, 72.6, 72.4, 66.5, 66.4, 56.3, 49.5, 48.4, 43.4, 42.5, 33.6, 29.2, 25.7, 22.1, 17.8, -4.5, -4.7; exact mass calcd for $C_{57}H_{66}O_8SiNa$: 929.4426; found 929.4415 (FAB, MNBA, added NaI); R_f=0.55 (30% EtOAc/ hexanes).

(1*S*)-1-(2-Napthyl)ethyl(2*S*,4*S*,6*R*,8*R*,10*R*)-10-hydroxy-8-(hydroxymethyl)-4-methoxy-1,7-dioxaspiro-[5.5]undecane-2-acetate (36) and (1*S*)-1-(2-Napthyl)ethyl(2*S*,4*S*,6*S*,8*R*,10*R*)-10-hydroxy-8-(hydroxymethyl)-4-methoxy-1,7-dioxaspiro[5.5]undecane-2-acetate (31). A solution of the ketone **30** (5.37 g, 5.91 mmol) in CH_2Cl_2/MeOH (10 mL/150 mL) was treated with camphorsulfonic acid (0.343 g, 1.48 mmol) at 0 °C. The colorless solution was stirred for 13 h with gradual warming to room temperature. The solution was neutralized with saturated aqueous $NaHCO_3$ (40 mL) and the mixture extracted with EtOAc (3 x 100 mL). The combined organic solutions were washed with saturated aqueous $NaHCO_3$ (2 x 75 mL) and brine (75 mL). The solution was dried over $MgSO_4$, filtered, and concentrated. An HPLC assay of the crude residue showed a 6.1 :1 ratio of spiroketal isomers (Zorbax column, 10% EtOAc/10% *i*-PrOH/80% hexanes; 0.5 mL/min). The residue was purified by flash chromatography (400 g SiO_2, 3% MeOH/CH_2Cl_2) to give a mixture of two spiroisomers **31** and **32** and 0.489 g (18%) of a *bis*-methyl ether byproduct. This material was rechromatographed (60 g SiO_2, 100% EtOAc→5%MeOH/EtOAc) to give pure **32** (0.201 g, 7.6%) and **31** (1.63 g, 62%). Data for **31** (unnatural spiroisomer): $[\alpha]^{25}_{589}$ -19.8 (*c* 1.31, $CHCl_3$); IR (neat) ν 3432, 3057, 2932, 1730, 1602 cm^{-1}; ^1H NMR (500 MHz, MeOD) δ 7.90-7.79 (m, 4H), 7.49-7.40 (m, 3H), 6.02 (q, *J* = 6.5 Hz, 1H), 4.35-4.30 (m, 1H), 3.95-3.89 (m, 1H), 3.67-3.60 (m, 1H), 3.44 (m, 2H), 2.52-2.50 (m, 2H), 2.38-2.34 (m, 1H), 2.03-1.99 (m, 1H), 1.83-1.80 (dd, *J* = 13.3, 3.9 Hz, 1H), 1.70-1.65 (m, 1H), 1.63-1.62 (d, *J* = 6.5 Hz, 3H), 1.50-1.46 (dd, *J* = 1.7, 10.0, 1H), 1.42-1.37 (m, 1H), 1.21-1.07 (t, *J* = 15.8 Hz, 1H), 1.04 (q, *J* = 14.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 138.9, 133.1, 133.0, 128.2, 128.0, 127.5, 126.2, 125.7, 124.5, 99.8, 73.1, 72.6, 72.3, 66.3, 64.0, 61.0, 55.4, 43.7, 41.8, 41.4, 36.8, 34.0, 21.7; exact mass calcd for $C_{25}H_{33}O_7$: 445.2226; found 445.2191 (CI, NH_3); R_f=0.17 (5% MeOH/ CH_2Cl_2). Data for **32** (natural spiroisomer): see below.

(1*S*)-1-(2-Napthyl)ethyl(2*S*,4*S*,6*S*,8*R*,10*R*)-10-hydroxy-8-(hydroxymethyl)-4-methoxy-1,7-dioxaspiro-[5.5]undecane-2-acetate (32). A solution of the spiroketal **31** (1.48 g, 3.31 mmol) in dichloromethane (120 mL) was treated with magnesium trifluoroacetate (9.93 mL of a 1M solution in Et_2O/2M in CF_3CO_2H, 9.93 mmol) at 0 °C. The orange solution was stirred for 6 h with warming to room temperature. The solution was neutralized with saturated aqueous EDTA solution (25 mL) and the mixture extracted with EtOAc (3 x 100 mL). The combined organic solutions were washed with saturated aqueous $NaHCO_3$ (2 x 60 mL) and brine

(60 mL). The solution was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (200 g SiO_2, 6% *i*-PrOH/CH_2Cl_2) to give 0.793 g (53%) of spiroisomer **32** and 0.349 g (24%) of spiroisomer **31**. Data for **32** (natural spiroisomer): $[\alpha]^{25}_{589}$ -51.1 (*c* 1.63, $CHCl_3$); IR (neat) *v* 3507, 2933, 1728 cm^{-1}; ^1H NMR (400 MHz, MeOD) δ 7.91-7.78 (m, 4H), 7.59-7.40 (m, 3H), 6.07 (q, *J* = 6.6 Hz, 1H), 4.11-3.99 (m, 1H), 3.93-3.91 (t, *J* = 3.2 Hz, 1H), 3.76-3.68 (m, 1H), 3.57-3.46 (m, 1H), 3.30-3.24 (m, 4H), 3.10-3.05 (dd, *J* = 11.7, 5.2 Hz, 1H), 2.66 (m, 2H), 2.24-2.20 (br d, *J* = 14.8 Hz, 1H), 2.09-1.98 (m, 1H), 1.62-1.61 (d, *J* = 6.6 Hz, 3H), 1.52-1.45 (m, 2H), 1.27-1.21 (m, 2H), 1.13-1.04 (q, *J* = 11.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 138.2, 133.0, 128.2, 127.5, 126.0, 125.6, 124.1, 99.1, 73.0, 67.4, 65.6, 65.4, 63.3, 55.5, 42.5, 41.0, 36.6, 34.5, 33.0, 21.6; exact mass calcd for $C_{25}H_{32}O_7$: 444.2148; found 444.2144 (EI); R_f=0.31 (5% MeOH/ CH_2Cl_2).

(1*S*)-1-(2-Napthyl)ethyl(2*S*,4*S*,6*S*,8*R*,10*R*)-10-hydroxy-8-(trityloxymethyl)-4-methoxy-1,7-dioxaspiro-[5.5]undecane-2-acetate (32a). A solution of the diol **32** (0.731 g, 1.64 mmol) in pyridine (8 mL) was treated with trityl chloride (freshly recrystallized from heptane, 2.22 g, 8.19 mmol) . The yellow solution was stirred at 60-65 °C for 4 h, cooled to room temperature, and stirred for an additional 12 h. The solution was diluted with water (30 mL) and extracted with EtOAc (2 x 75 mL). The combined organic solutions were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (150 g SiO_2, 50→60% EtOAc/hexanes) to give 0.986 g (89%) of the product **32a** as a yellow foam: $[\alpha]^{25}_{589}$ -20.6 (*c* 1.90, $CHCl_3$); IR (neat) *v* 3518, 3056, 2933, 1728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81-7.74 (m, 3H), 7.66-7.64 (m, 1H), 7.48-7.18 (m, 18H), 6.15 (q, *J* = 6.6 Hz, 1H), 4.16-4.03 (m, 2H), 3.89-3.86 (d, *J* = 12.0 Hz, 1H), 3.58-3.43 (m, 1H), 3.33 (s, 3H), 3.05-3.01 (dd, *J* = 9.4, 4.7 Hz, 1H), 2.96-2.93 (dd, *J* = 9.4, 4.4 Hz, 1H), 2.78-2.71 (dd, *J* = 16.7, 9.3 Hz, 1H), 2.66-2.61 (dd, *J* = 16.7, 3.3 Hz, 1H), 2.32-2.28 (d, *J* = 14.4 Hz, 1H), 2.12-2.03 (m, 2H), 1.69-1.62 (m, 2H), 1.63 (d, *J* = 6.6 Hz, 3H), 1.55-1.50 (dd, *J* = 14.4, 3.7 Hz, 1H), 1.43-1.37 (t, *J* = 11.5 Hz, 1H), 1.33-1.27 (q, *J* = 11.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.8, 144.1, 138.2, 132.9, 128.8, 127.6, 127.5, 126.8, 126.1, 126.0, 125.4, 125.4, 124.0, 99.4, 86.1, 73.1, 72.9, 67.5, 66.4, 64.6, 63.6, 55.5, 42.7, 41.1, 36.5, 34.9, 34.4, 21.7; exact mass calcd for $C_{44}H_{46}O_7Na$: 709.3129; found 709.3110 (FAB, MNBA, added NaI); R_f=0.50 (90% EtOAc/hexanes).

(1*S*)-1-(2-Napthyl)ethyl(2*S*,4*S*,6*S*,8*R*,10*R*)-10-*tert*-butyldimethylsiloxy-8-(trityloxymethyl)-4-methoxy-1,7-dioxaspiro[5.5]undecane-2-acetate (33). To a cold solution (-100 °C) of the spiroketal **32a** (0.986 g, 1.42 mmol) in CH_2Cl_2 (30 mL) was added 2,6-lutidine (0.245 mL, 0.228 g, 2.13 mmol) and *tert*-butyldimethylsilyl triflate (0.324 mL, 0.394 g, 1.49 mmol). The yellow solution was warmed to -78 °C and stirred 1 h at this temperature. The solution was quenched with saturated aqueous NH_4Cl (10 mL) and the cold bath removed. After warming to room temperature, the reaction mixture was extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (50 mL) and brine (30 mL). The solution was dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (100 g SiO_2, 10% EtOAc/hexanes) to give 1.06 g (93%) of silyl ether **33** as a white foam: $[\alpha]^{25}_{589}$ -20.2 (*c* 1.26, $CHCl_3$); IR (neat) *v* 3056, 2953, 2861, 1733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.81-7.77 (m, 3H), 7.48-7.43 (m, 6H), 7.27-7.18 (m, 13H), 6.07 (q, *J* = 6.5 Hz, 1H), 4.55-4.25 (m, 1H), 4.13-4.11 (t, *J* = 3.4 Hz, 1H), 3.90-3.86 (dt, *J* = 8.0, 2.1 Hz, 1H), 3.43-3.38 (m, 1H), 3.22 (s, 3H), 3.17-3.04 (m, 2H), 2.83-2.80 (dd, *J* = 15.5, 3.8 Hz, 1H), 2.58-2.52 (dd, *J* = 15.5, 9.9 Hz, 1H), 2.19-2.11 (m, 2H), 2.02-1.99 (dd, *J* = 12.3, 3.1 Hz, 1H), 1.73 (br d, *J* = 13.4 Hz, 1H), 1.68-1.65 (m, 1H), 1.63-1.62 (d, *J* = 6.5 Hz, 3H), 1.48-1.44 (dd, *J* = 14.3, 3.6 Hz, 1H), 1.37-1.32 (t, *J* = 11.9 Hz, 1H), 1.10 (q, *J* = 11.6 Hz, 1H), 0.761 (s, 9H), 0.01 (s, 3H), -0.05 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 144.1, 138.7, 133.1, 130.0, 128.8, 128.2, 128.0, 127.6, 127.5, 126.8, 126.1, 126.0, 125.3, 124.1, 120.1, 98.2, 86.1, 73.8, 72.5, 66.9, 66.5, 64.9, 64.3, 55.4, 43.2, 41.1, 36.6, 35.6, 35.5, 25.7, 21.9, 17.9, -4.8, -4.9; exact mass calcd for $C_{50}H_{60}O_7SiNa$: 823.4006; found 823.3975 (FAB, MNBA, added NaI); R_f=0.48 (30% EtOAc/hexanes).

2-[*N*-methoxy-*N*-methyl-]-(2*S*,4*S*,6*S*,8*R*,10*R*)-10-*tert*-butyldimethylsiloxy-8-(trityloxymethyl)-4-methoxy-1,7-dioxaspiro[5.5]undecane-2-acetamide (34). To a cooled (-10 °C) solution of the ester **33** (0.699 g, 0.873 mmol) in THF (15 mL) was added *N,O*-dimethyl hydroxylamine hydrochloride (0.153 g, 1.57 mmol). The resulting suspension was treated with a solution of ethyl magnesium bromide (4.71 mL of a 1M solution in

Et_2O, 4.71 mmol) maintaining an internal temperature of -10 °C to -5 °C during the addition. The pale yellow solution was stirred for 90 min at -10 °C. The solution was quenched with saturated aqueous NH_4Cl (5 mL). The cold bath was removed and the biphasic mixture stirred for 30 min. The solution was extracted with Et_2O (2 x 50 mL) and the combined organic solutions washed with saturated aqueous NH_4Cl (20 mL). The solution was dried over $MgSO_4$, filtered, and concentrated. the residue was purified by flash chromatography (60 g SiO_2, 15% EtOAc/hexanes then 50% EtOAc/hexanes) to give 0.018 g (3%) of ethyl ketone **35** and 0.540 g (90%) of the amide **34**: $[\alpha]^{25}_{589}$ -5.8 (*c* 1.26, CH_2Cl_2); IR (neat) *v* 3058, 2949, 2872, 1733, **1662** cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.44 (d, *J* = 7.2 Hz, 6H), 7.29-7.19 (m, 9H), 4.62-4.50 (m, 1H), 4.16-4.15 (t, *J* = 3.2 Hz, 1H), 4.02-3.97 (m, 1H), 3.65 (s, 3H), 3.55-3.45 (m, 1H), 3.33 (s, 3H), 3.21-3.10 (m, 5H), 2.87-2.72 (m, 2H), 2.37-2.34 (br d, *J* = 12 Hz, 1H), 2.24-2.20 (dd, *J* = 14.1, 2.8 Hz, 1H), 2.06-2.02 (dd, *J* = 11.7, 4.3 Hz, 1H), 1.85-1.82 (d, *J* = 13.4 Hz, 1H), 1.73-1.65 (m, 2H), 1.52-1.48 (dd, *J* = 3.6, 14.4, Hz, 1H), 1.39-1.33 (t, *J* = 11.9 Hz, 1H), 0.90 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 144.1, 128.8, 127.6, 126.8, 98.3, 86.1, 73.9, 67.2, 66.5, 65.0, 64.3, 61.2, 55.7, 43.4, 38.4, 37.1, 35.8, 35.7, 32.0, 25.8, 18.1, -4.8, -4.9; exact mass calcd for $C_{40}H_{55}O_7SiNNa$: 712.3646; found 712.3656 (FAB, MNBA, added NaI); R_f=0.35 (40% EtOAc/hexanes).

(2*S*,4*S*,6*S*,8*R*,10*R*)-10-*tert*-butyldimethylsiloxy-2-(buta-3-one)-8-(trityloxymethyl)-4-methoxy-1,7-dioxa-spiro[5.5]undecane (35).. A cooled solution (0 °C) of the amide **34** (0.896 g, 1.30 mmol) in THF (25 mL) was treated with a solution of ethylmagnesium bromide (6.51 mL of a 1 M solution in Et_2O, 6.51 mmol). The bright yellow solution was stirred at 0 °C for 90 min. The solution was treated with saturated aqueous NH_4Cl solution (10 mL) and the cold bath removed. After warming to room temperature, the mixture was extracted with Et_2O (2 x 60 mL). The combined organic solutions were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (75 g SiO_2, 15% EtOAc/hexanes) to give 0.785 g (95%) of the ethyl ketone **35** as a white foam: $[\alpha]^{25}_{589}$ -2.7 (*c* 2.18, CH_2Cl_2); IR (neat) *v* 3058, 2929, 2850, 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.44 (m, 6H), 7.29-7.19 (m, 9H), 4.59-4.55 (m, 1H), 4.15-4.13 (t, *J* = 3.4 Hz, 1H), 3.97-3.92 (m, 1H), 3.53-3.45 (m, 1H), 3.32 (s, 3H), 3.21-3.17 (dd, *J* = 8.8, 4.5 Hz, 1H), 3.10-3.06 (dd, *J* = 6.3, 8.8 Hz, 1H), 2.87-2.82 (dd, *J* = 17.2, 3.6 Hz, 1H), 2.70-2.64 (dd, *J* = 17.2, 8.9, 1H), 2.45-2.40 (q, *J* = 7.4 Hz, 2H), 2.24-2.14 (m, 2H), 2.05-2.01 (dd, *J* = 12.0, 3.6 Hz, 1H), 1.81-1.77 (br d, *J* = 13.4 Hz, 1H), 1.70-1.63 (m, 2H), 1.36-1.30 (t, *J* = 12.0, Hz, 1H), 1.06-1.03 (t, *J* = 7.4 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.034 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.3, 144.1, 128.8, 127.6, 126.8, 126.8, 98.2, 86.2, 73.8, 66.6, 65.0, 64.3, 55.5, 48.6, 43.2, 37.0, 36.9, 35.8, 35.7, 25.8, 18.1, 7.7,-4.8; exact mass calcd for $C_{40}H_{54}O_6SiNa$: 681.3587; found 681.3591 (FAB, MNBA, added NaI); R_f=0.41 (30% EtOAc/hexanes).

2'-Methyl-2-[2*S*,5*R*]-2-(*tert*-butyldimethylsiloxy-5-methyl-4-methylene-hexan-6-al)-1,3-dioxolane (36). A solution of di-*tert*-butylbiphenyl (9.76 g, 36.6 mmol) in THF (120 mL) was treated with several small pieces of cut and crushed (with pliers) lithium wire (0.330 g, 47.6 mmol) at room temperature. The mixture was sonicated (with cooling to maintain temperature 10-25 °C) for 5 h to produce a deep green solution of the radical anion solution. In a separate flask, a solution of benzyl ether **12** (0.720 g, 1.66 mmol) in THF (15 mL) was cooled to -78 °C. The radical anion solution was added portionwise (ca. 20 mL) until the green-blue color persisted. The solution was stirred for 30 min at -78 °C and carefully quenched with saturated aqueous NH_4Cl solution. The cold bath was removed and the mixture warmed to room temperature. The mixture was extracted with Et_2O (2 x 40 mL). The combined organic solutions were washed with saturated aqueous NH_4Cl (15 mL) and brine (10 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (50 g SiO_2, 100% Hexanes then 30 % EtOAc/ hexanes) to give 0.366 g (70%) of the desired alcohol and 0.139 g (27%) of a mixture of the desired product and deketalized product. Data for the alcohol: $[\alpha]^{23}_{589}$ +22.4 (*c* 2.8, $CHCl_3$) IR (neat) *v* 3446, 2964, 2861, 1641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.97 (s, 1H), 4.89 (s, 1H), 4.17-4.12 (m, 1H), 3.57-3.38 (m, 6H), 2.50-2.45 (dd, *J* = 14.1, 5.6 Hz, 1H), 2.36-2.28 (m, 2H), 2.08-1.94 (m, 2H), 1.84 (br s, 1H), 1.32 (s, 3H), 1.05-1.03 (d, *J* = 6.9 Hz, 3H), 0.991 (s, 9H), 0.15 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.9, 112.3, 109.3, 68.2, 66.3, 64.4, 64.1, 46.4, 44.9, 42.2, 26.1, 24.8, 18.2, 16.5, -4.0, -4.1; exact mass calcd for $C_{18}H_{37}O_4Si$: 345.2461 [M^+ +1]; found 345.2467 (CI); R_f=0.26 (25% EtOAc/ hexanes). A solution of Dess-Martin periodinane

(0.105 g, 0.248 mmol) in CH_2Cl_2 (2 mL) was prepared under an inert atmosphere (weighed in dry-box) and treated with pyridine (0.152 mL, 0.150 g, 1.90 mmol). After stirring for 5 min, a solution of the alcohol (0.066 g, 0.190 mmol) in CH_2Cl_2 (1 mL) was added. The clear, yellow solution was stirred for 40 min. The solution was quenched with 1M $Na_2S_2O_3$/saturated aqueousNaHCO$_3$ (0.5 mL/0.5 mL). The mixture was extracted with Et_2O (2 x 10 mL). The combined organic solutions were washed with saturated aqueous NaHCO$_3$ (2 x 5 mL) and brine (5 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated. The residue (0.060 g, 92%) was used without further purification Data for aldehyde **36**: $[\alpha]^{23}_{589}$ +31.67 (*c* 2.67, $CHCl_3$) IR (neat) *v* 2959, 2713, 1726, 1638 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 9.32 (s, 1H) 5.05 (s, 1H), 4.80 (s, 1H), 4.11-4.05 (m, 1H), 3.59-3.44 (m, 4H), 2.93-2.88 (dq, *J* = 2.3, 6.4 Hz, 1H), 2.52-2.47 (dd, *J* = 14.2, 4.4 Hz, 1H), 2.28-2.22 (dd, *J* = 14.2, 7.2 Hz, 1H), 2.03-1.93 (m, 2H), 1.27 (s, 3H), 1.05-1.03 (d, *J* = 6.4 Hz, 3H), 0.959 (s, 9H), 0.124 (s, 3H), 0.054 (s, 3H); ^{13}C NMR (101 MHz, C_6D_6) δ 148.9, 112.3, 109.3, 68.2, 66.3, 64.4, 64.1, 46.4, 44.9, 42.2, 26.1, 24.8, 18.2, 16.5, -4.0, -4.1; exact mass calcd for $C_{18}H_{35}O_4Si$: 343.2305; found 343.2300 (CI); R_f=0.39 (20% EtOAc/ hexanes).

2'-Methyl-2-[2*S*,5*R*,6*S*,7*S*]-2-(*tert*-butyldimethylsiloxy-4-methylene-5-methyl-6-hydroxy-7-methyl-non-8-one)-1,3-dioxolane (37). A solution of dicyclohexylboron chloride (0.112 mL, 0.112 g, 0.511 mmol) and triethylamine (0.071 mL, 0.052 g, 0.511 mmol) in pentane (11 mL) was cooled to 0 °C and treated with neat 3-pentanone (0.052 mL, 0.044 g, 0.511 mmol) producing a granular white precipitate (triethylamine hydrochloride). The mixture was stirred for 1 h at 0 °C and then cooled to -78 °C. A solution of the aldehyde **51** (0.060 g, 0.176 mmol) in pentane (1 mL) was added. The resulting white slurry was stirred at -78 °C for 90 min, quenched with MeOH/ pH 7 buffer (0.5 mL/0.5 mL), warmed to room temperature and treated with H_2O_2 (30% aqueous)/MeOH (0.5 mL/0.5 mL). After stirring for 45 min, the mixture was extracted with Et_2O (2 x 15 mL). The combined organic extracts were washed with saturated aqueous NaHCO$_3$ (2 x 10 mL) and brine (5 mL). The organic solution was dried over $MgSO_4$, filtered and concentrated. A small portion of the unpurified residue was silylated with trimethylsilyl imidazole (THF, 12 h, 22 °C) and assayed by gas chromatography. GC assay (DB 1701, oven temperature 190 °C, flow rate 16) showed a 97:3 ratio of isomers. t_r (major isomer) = 43.76 min. The residue was purified by flash chromatography (20 g SiO_2, 15% EtOAc/hexanes) to give 0.070 g (93%) of the aldol adduct **37**: $[\alpha]^{23}_{589}$ +29.9 (*c* 2.85, $CHCl_3$) IR (neat) *v* 3497, 2956, 2898, 1715, 1637 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 (s, 1H), 5.88 (s, 1H), 4.96-4.87 (m, 5H), 4.64-4.60 (dt, *J* = 8.3, 4.1 Hz, 1H), 3.74-3.66 (quintet, *J* = 7.2 Hz, 1H), 3.54-3.49 (q, *J* = 7.2 Hz, 2H), 3.40-3.36 (dd, *J* = 14.4, 4.2 Hz, 1H), 3.31-3.26 (m, 1H), 2.94-2.88 (dd, *J* = 14.4 Hz, 7.3, 1H), 2.85-2.81 (dd, *J* = 14.4, 3.9 Hz), 1.30 (s, 3H), 1.03-1.00 (m, 6H), 0.844 (s, 9H), 0.046 (s, 3H), 0.003 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 215.9, 148.4, 113.9, 108.8, 82.9, 73.6, 67.5, 64.3, 64.0, 47.4, 46.0, 44.0, 41.0, 36.5, 30.0, 25.8, 25.6, 24.5, 23.6, 17.9, 13.7, 11.5, 7.3, -4.4; exact mass calcd for $C_{23}H_{44}O_5SiNa$: 451.2856; found 451.2852 (FAB, MNBA, added NaI); R_f=0.39 (20% EtOAc/ hexanes).

2-[(2*S*,4*S*,6*R*,8*S*,10*S*)-8-[(3*R*,4*S*,5*S*)-7-[(2*S*,4*S*,6*R*,8*S*,10*S*)-10-(*tert*-Butyldimethylsiloxy)-4-methoxy-8-(trityloxymethyl)-1,7-dioxaspiro[5.5]undec-2-yl]-4-hydroxy-3,5-dimethyl-2-methylene-6-oxoheptyl]-4-(triethylsiloxy)-10-methyl-10-(triethylsiloxy)-1,7-dioxaspiro[5.5]undec-2-yl]1-(*tert*-butyldimethylsiloxy)-ethane (39). A solution of the ethyl ketone **35** (0.125 g, 0.202 mmol) in pentane (4.0 mL) was cooled to 0 °C and treated with dicyclohexylboron chloride (0.043 mL, 0.043 g, 0.202 mmol). After stirring for 10 min at 0 °C, triethylamine (0.028 mL, 0.020 g, 0.202 mmol) was added, producing a granular white precipitate. The heterogeneous mixture was stirred at 0 °C for 90 min. The enolate solution was cooled to -78 °C and treated with a solution of the unpurified aldehyde **21** (0.093 g, 0.137 mmol) in pentane (1.0 mL). The mixture was stirred at -78 °C for 4 h, the mixture was quenched with a solution of MeOH/pH 7 phosphate buffer (1 mL/1 mL) and the -78 °C bath replaced with an ice/water bath. Aqueous H_2O_2/pH 7 phosphate buffer (1 mL/1 mL) was added, and the mixture was stirred at 0 °C for 1 h. The mixture was extracted with Et_2O (3 x 15 mL). The combined organic solutions were washed with saturated aqueous NaHCO$_3$ (2 x 10 mL) and brine (10 mL). The solution was dried over $MgSO_4$, filtered, and concentrated. HPLC analysis of the unpurified product mixture showed a 9:1 mixture of aldol diastereomers (Zorbax column, 15 % EtOAc/ hexanes, 1.0 mL/ min; T_R Minor = 5.50 min, T_R Major = 7.18 min). The residue was purified by an initial flash

chromatography (20 g SiO_2, 15% EtOAc / hexanes) to give 0.194 g of a residue which was repurified by preparative HPLC (Zorbax column, 15% EtOAc/ hexanes, 20 mL/min) to give 0.118 g (64 % over two steps) of the major isomer **39**, 0.011 g (6 %) of a minor isomer, and unreacted ethyl ketone **35** (52 mg 74 % of theoretical). Data for aldol adduct **39**: $[\alpha]^{25}_{589}$ -9.3 (*c* 1.18, $CHCl_3$; IR (neat) υ 3514, 1713 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.43 (d, *J* = 7.4 Hz, 6H), 7.30-7.19 (m, 9H), 5.09 (s, 1H), 4.89 (s, 1H), 4.58-4.54 (m, 1H), 4.18-4.11 (m, 2H), 4.09-3.95 (m, 3H), 3.75-3.68 (m, 1H), 3.63-3.58 (m, 2H), 3.51-3.46 (m, 1H), 3.31 (s, 3H), 3.20-3.16 (dd, *J* = 8.9, 4.4 Hz, 1H), 3.11-3.07 (dd, *J* = 8.9, 6.3 Hz, 1H), 2.97-2.92 (dd, *J* = 18.1, 3.7 Hz, 1H), 2.87-2.81 (dd, *J* = 18.1, 9.0 Hz, 1H), 2.69-2.63 (m, 1H), 2.34-2.23 (m, 3H), 2.20-2.19 (dd, *J* = 14.3, 3.4 Hz, 1H), 2.04-2.00 (dd, *J* = 12.0, 3.4 Hz, 1H), 1.99-1.94 (dd, *J* = 14.3, 5.4 Hz, 1H), 1.82-1.47 (m, 12 H), 1.35-1.30 (t, *J* = 12.0 Hz, 1H), 1.28-1.24 (m, 1H), 1.98 (s, 3H), 1.04-1.02 (br d, *J* = 6.9 Hz, 6H), 0.96-0.92 (t, *J* = 7.9 Hz, 18 H), 0.885 (s, 9H), 0.878 (s, 9H), 0.594-0.526 (m, 12H), 0.656 (s, 3H), 0.032 (s, 9H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 213.2, 147.7, 144.1, 128.7, 127.6, 126.7, 113.6, 98.2, 97.2, 86.13, 77.2, 73.9, 73.7, 70.4, 66.5, 66.2, 65.0, 64.6, 64.4, 64.3, 62.1, 60.1, 55.5, 49.7, 48.1, 48.0, 45.1, 43.3, 43.1, 42.1, 40.5, 39.1, 38.6, 36.8, 35.8, 35.6, 32.1, 29.6, 25.8, 18.2, 18.1, 13.5, 11.7, 7.2, 6.9, 6.8, 4.7, –4.8, –4.9, –5.2, –5.3; MS (FAB) calculated for $C_{76}H_{126}O_{12}Si_4Na$ [M^++ Na], 1365; found 1365; R_f= 0.38 (20% EtOAc / hexanes).

2-[(2*S*, 4*S*, 6*R*, 8*S*, 10*S*)-8-[(3*R*, 4*S*, 5*S*)-7-[(2*S*, 4*S*, 6*R*, 8*S*, 10*S*)-10-(*tert*-Butyldimethylsiloxy)-4-methoxy-8-(trityloxymethyl)-1,7-dioxaspiro[5.5]undec-2-yl]-4-hydroxy-3,5-dimethyl-2-methylene-6-oxoheptyl]-4-hydroxy-10-methyl-10-(triethylsiloxy)-1,7-dioxaspiro[5.5]undec-2-yl]1-hydroxyethane (40). A solution of the *bis*-spiroketal **39** (143.7 mg, 0.107 mmol) in THF (1.85 mL) in a polyethylene vial was cooled to 0 °C and treated with a buffered solution of HF•pyridine (1.85 mL of a solution containing 7.7% HF-pyridine/10% pyridine/THF by volume). The solution was stirred at 0 °C for 7 h. The solution was cautiously quenched with saturated aqueous $NaHCO_3$ (4 mL) and the mixture was extracted with EtOAc (3 x 15 mL). The combined organic solutions were washed with saturated aqueous $NaHCO_3$ (2 x 10 mL) and brine (10 mL). The solution was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (2 x 12 cm silica gel, 70% ethyl acetate/hexanes) to give 102.4 mg (77%) of the desired triol **40** and 18 mg (14%) of a partially deprotected diol. Data for triol **40**: $[\alpha]^{25}_{589}$ +3.0 (*c* 1.38, $CHCl_3$); IR (neat) υ 3487, 2943, 1707, 1635 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.43 (d, *J* = 7.4 Hz, 6H), 7.29-7.19 (m, 9H), 5.11 (s, 1H), 5.01 (s, 1H), 4.61-4.49 (m, 1H), 4.23-4.18 (dt, *J* = 3.1, 10.4 Hz, 1H), 4.15-4.13 (t, *J* = 3.22 Hz, 1H), 4.08-3.91 (m, 3H), 3.83-3.78 (m, 1H), 3.71-3.67 (m, 1H), 3.66-3.64 (dd, *J* = 7.8 Hz, 1.7 Hz, 1H), 3.53-3.45 (m, 1H), 3.31 (s, 3H), 3.20-3.16 (dd, *J* = 8.9, 4.4 Hz, 1H), 3.12-3.08 (dd, *J* = 8.9, 6.3 Hz, 1H), 2.98-2.85 (m, 2H), 2.72-2.65 (m, 1H), 2.49-2.44 (m, 1H), 2.26-2.14 (m, 4H), 2.04-2.01 (m, 1H), 1.85-1.82 (d, *J* = 14.4 Hz, 1H), 1.79-1.56 (m, 11H), 1.37-1.30 (m, 2H), 1.26 (s, 3H), 1.05-1.03 (d, *J* = 7.0 Hz, 3H), 0.965-0.926 (t, *J* = 7.8 Hz, 9 H), 0.887 (s, 9H), 0.655-0.572 (two overlapping quartets, *J* = 7.8 Hz, 6H), 0.69 (s, 3H), 0.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 212.6, 148.1, 144.1, 128.8, 127.6, 126.8, 114.8, 98.8, 98.2, 86.1, 77.1, 73.9, 72.7, 70.3, 66.5, 66.3, 65.0, 64.8, 64.3, 64.2, 63.9, 60.1, 55.5, 49.7, 48.5, 47.8, 45.0, 43.3, 42.1, 40.7, 39.0, 37.1, 36.8, 35.8, 35.6, 31.9, 29.6, 25.9, 18.1, 12.9, 10.7, 7.2, 6.6, –4.8, –4.9; MS (FAB) calculated for $C_{64}H_{98}O_{12}Si_2Na$ [M^++ Na], 1137; found 1137; R_f= 0.31 (70% EtOAc / hexanes).

2-[(2*S*,4*S*,6*R*,8*S*,10*S*)-8-[(3*R*,4*S*,5*S*)-7-[(2*S*,4*S*,6*R*,8*S*,10*S*)-10-(*tert*-Butyldimethylsiloxy)-4-methoxy-8-(trityloxymethyl)-1,7-dioxaspiro[5.5]undec-2-yl]-4-hydroxy-3,5-dimethyl-2-methylene-6-oxoheptyl]-4-hydroxy-10-methyl-10-(triethylsiloxy)-1,7-dioxaspiro[5.5]undec-2-yl]ethylmethoxyacetate(40a). A solution of triol **40** (115.9 mg, 0.104 mmol) in CH_2Cl_2 (2.7 mL) was cooled to 0 °C and treated with Hunig's base (0.339 mL, 1.94 mmol) and methoxyacetic anhydride (0.134 mL, 0.972 mmol). After stirring for 22 h, the solution was diluted with Et_2O (20 mL) and washed with saturated aqueous NH_4Cl solution (2 x 7.5 mL). The aqueous washes were extracted with Et_2O (2 x 10 mL). The combined organic solutions were dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (2 x 12 cm silica gel, 40% EtOAc/CH_2Cl_2) to give 113.1 mg (92%) of the methoxyacetate **40a** as a white foam. $[\alpha]^{25}_{589}$ +3.1 (*c* 0.39, $CHCl_3$); IR (neat) υ 3497, 2933, 1753, 1712, 1641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45-7.44 (d, *J* = 7.4 Hz, 6H), 7.29-7.20 (m, 9H), 5.08 (s, 1H), 4.99 (s, 1H), 4.57-4.55 (m, 1H), 4.31-4.26 (m, 2H) 4.16-4.10 (m, 2H), 4.00 (s, 2H), 4.01-3.95 (m, 1H), 3.90-3.84 (m, 2H), 3.65-3.63 (dd, *J* = 9.2, 2.0 Hz, 1H), 3.51-3.45

(m, 1H), 3.42 (s, 3H), 3.31 (s, 3H), 3.19-3.17 (dd, J = 8.8, 4.3 Hz, 1H), 3.11-3.08 (dd, J = 8.8, 6.3 Hz, 1H), 2.98-2.95 (dd, J = 10.1, 5.9 Hz, 1H), 2.90-2.85 (dd, J = 18.1, 9.0 Hz, 1H), 2.71-2.66 (dq, J = 9.0, 7.2 Hz, 1H), 2.41-2.37 (br q, J = 6.7 Hz, 1H), 2.25-2.17 (m, 2H), 2.19-2.17 (d, J = 6.9 Hz, 2H), 2.04-2.01 (dd, J = 12.6, 6.4 Hz, 1H), 1.87-1.43 (m, 13H), 1.34-1.26 (m, 2H), 1.24 (s, 3H), 1.06-1.05 (d, J = 6.9 Hz, 3H), 1.01-1.00 (d, J = 6.9 Hz, 3H), 0.95-0.91 (t, J = 8.0 Hz, 9H), 0.886 (s, 9H) 0.586-0.541 (q, J = 8.0 Hz, 6H), 0.068 (s, 3H), 0.036 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 212.7, 170.0, 148.1, 144.1, 128.8, 127.6, 126.8, 114.5, 99.0, 98.2, 86.1, 73.9, 72.9, 70.0, 69.7, 66.5, 66.3, 65.0, 64.9, 64.3, 64.1, 61.7, 61.6, 59.3, 55.5, 49.7, 48.4, 47.2, 45.3, 41.9, 40.8, 39.4, 37.2, 36.8, 35.8, 35.6, 34.2, 31.9, 25.9, 18.1, 13.0, 10.8, 7.2, 6.8, –4.8, –4.9; MS (FAB) calculated for $C_{67}H_{102}O_{14}Si_2Na$ [M^++ Na], 1209; found 1209; R_f = 0.55 (40% EtOAc / CH_2Cl_2).

2-[(2*S*,4*S*,6*R*,8*S*,10*S*)-8-[(3*R*,4*S*,5*S*)-7-[(2*S*,4*S*,6*R*,8*S*,10*S*)-10-(*tert*-Butyldimethylsiloxy)-4-methoxy-8-(trityloxymethyl)-1,7-dioxaspiro[5.5]undec-2-yl]-4-hydroxy-3,5-dimethyl-2-methylene-6-oxoheptyl]-4-hydroxy-10-methyl-10-(triethylsiloxy)-1,7-dioxaspiro[5.5]undec-2-yl]ethylmethoxyacetate,diacetate (41). A solution of diol **40a** (113.1 mg, 0.095 mmol) in pyridine (5.95 mL) was treated with acetic anhydride (0.267 mL, 2.83 mmol) and DMAP (115.3 mg, 0.944 mmol). The bright orange solution was stirred for 3 h at room temperature. The solution was diluted with EtOAc (20 mL) and washed with saturated aqueous NH_4Cl (10 mL), 1M HCl (10 mL), and brine (10 mL). The aqueous solutions were extracted with EtOAc (10 mL). The combined organic solutions were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography (2 x 12 cm silica gel, linear gradient, 30-40% EtOAc/hexanes) to give 106.8 mg (89%) of the *bis*-acetate **41** as a clear, colorless oil. $[\alpha]^{25}_{589}$ -5.4 (*c* 0.95, $CHCl_3$); IR (neat) υ 2930, 1735, 1631 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.44 (d, J = 7.4 Hz, 6H), 7.29-7.20 (m, 9H), 5.23-5.21 (dd, J = 9.6, 2.8 Hz, 1H), 5.10 (br s, 1H), 5.00 (s, 1H), 4.84 (s, 1H), 4.57-4.55 (m, 1H), 4.30-4.22 (m, 2H) 4.16-4.10 (m, 3H), 4.14-4.13 (t, J = 3.2 Hz), 4.01 (s, 2H), 3.47-3.44 (m, 1H), 3.44 (s, 3H), 3.30 (s, 3H), 3.19-3.17 (dd, J = 8.9, 4.7 Hz, 1H), 3.12-3.09 (dd, J = 8.9, 6.3 Hz, 1H), 2.95-2.89 (m, 2H), 2.74-2.70 (dd, J = 18.1, 9.0 Hz, 1H), 2.39-2.37 (m, 1H), 2.36-2.27 (m, 2H), 2.18-2.14 (m, 2H), 2.04 (s, 3H), 2.04-2.01 (m, 1H), 1.91 (s, 3H), 1.84-1.46 (m, 13H), 1.33-1.21 (m, 2H), 1.25 (s, 3H), 1.08-1.06 (d, J = 6.9, 3H), 1.06-1.05 (d, J = 6.9 Hz, 3H), 0.94-0.91 (t, J = 8.0 Hz, 9H), 0.879 (s, 9H) 0.585-0.508 (q, J = 8.0 Hz, 6H), 0.063 (s, 3H), 0.020 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 209.7, 170.9, 170.0, 169.3, 146.9, 144.1, 128.8, 127.9, 127.6, 126.8, 113.4, 98.2, 96.7, 86.1, 74.1, 73.7, 70.5, 69.7, 67.0, 66.5, 66.1, 64.9, 64.5, 64.3, 61.8, 61.2, 59.2, 55.5, 49.6, 47.7, 45.0, 43.4, 41.6, 38.7, 38.5, 36.9, 35.7, 35.4, 34.2, 34.0, 32.0, 29.6, 25.8, 22.6, 21.5, 20.7, 18.1, 14.0, 13.4, 11.9, 7.2, 6.8, -4.8, -4.9; MS (FAB) calculated for $C_{71}H_{106}O_{16}Si_2Na$: 1293; found 1293; R_f = 0.44 (40% EtOAc / hexanes).

2-[(2*S*,4*S*,6*R*,8*S*,10*S*)-8-[(3*R*,4*S*,5*S*)-7-[(2*S*,4*S*,6*R*,8*S*,10*S*)-10-(*tert*-Butyldimethylsiloxy)-4-methoxy-8-(hydroxymethyl)-1,7-dioxaspiro[5.5]undec-2-yl]-4-hydroxy-3,5-dimethyl-2-methylene-6-oxoheptyl]-4-hydroxy-10-methyl-10-(triethylsiloxy)-1,7-dioxaspiro [5.5] undec-2-yl] ethylmethoxyacetate, diacetate (41a). A solution of the trityl ether **41** (63 mg, 0.05 mmol) in CH_2Cl_2 (6.9 mL) was cooled to -78 °C and treated with a solution of Me_2AlCl (0.248 mL of a 1M solution in hexanes, 0.248 mmol). After stirring for 30 min, an additional portion of Me_2AlCl (0.248 mL) was added and the solution was stirred for another 30 min. The bright yellow solution was quenched with THF/saturated aqueous Rochelle's salt (10.4 mL/ 3.6 mL). The biphasic mixture was stirred at room temperature for 30 min and extracted with Et_2O (2 x). The organic solution was washed saturated aqueous Rochelle's salt (1 x), 1M HCl (1 x), water (1 x) and brine (1 x). The solution was dried over $MgSO_4$, filtered and partially concentrated (volume reduced to ca. 0.1 mL). The crude residue was purified by flash chromatography (2 x 12 cm silica gel, 75% EtOAc/hexanes) to give 45.8 mg (89%) of the carbinol **41a** as a colorless foam. $[\alpha]^{25}_{589}$ -11.8 (*c* 0.44, $CHCl_3$); IR (neat) *v* 3487, 2953, 1733 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.24-5.22 (dd, J = 9.7, 2.7 Hz, 1H), 5.06 (br s, 1H), 4.99 (s, 1H), 4.84 (s, 1H), 4.43-4.40 (m, 1H), 4.29-4.22 (m, 2H), 4.10-4.09 (t, J = 3.2 Hz), 4.05-3.86 (m, 5H), 3.69-3.66 (dd, J = 11.5, 3.1 Hz, 1H), 3.53-3.45 (m, 2H), 3.44 (s, 3H), 3.30 (s, 3H), 2.95-2.90 (m, 1H), 2.90-2.85 (dd, J = 17.8, 3.6 Hz, 1H), 2.74-2.69 (dd, J = 17.8, 9.0 Hz), 2.43-2.38 (m, 1H), 2.33-2.28 (dd, J = 14.5, 8.5 Hz, 1H), 2.18-2.10 (m, 3H), 2.03-1.99 (m, 1H), 2.03 (s, 3H), 1.91 (s, 3H), 1.84-1.18 (m, 15 H), 1.09-1.07 (d, J = 6.9 Hz, 3H), 1.06-1.04 (d, J = 6.9 Hz, 3H), 0.94-0.91 (t, J = 8.0 Hz, 9H), 0. 87 (s, 9H), 0.57-0.52 (q, J = 8.0 Hz, 6H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.7, 170.9, 170.1, 169.3, 146.9, 113.5, 98.2, 96.7,

74.0, 70.5, 69.7, 67.0, 66.4, 66.3, 65.8, 64.5, 64.2, 61.8, 61.2, 59.2, 55.5, 49.3, 47.8, 47.6, 45.1, 43.1, 41.7, 38.6, 38.5, 36.7, 35.6, 34.2, 34.0, 32.0, 29.6, 25.8, 21.5, 20.7, 18.1, 13.3, 11.9, 7.2, 6.8, -4.9. Mass calcd for $C_{51}H_{90}O_{15}Si_2Na$: 1051; found 1051 (FAB, MNBA, added NaI); R_f=0.18 (60% EtOAc/hexanes).

2-[(2*S*,4*S*,6*R*,8*S*,10*S*)-8-[(3*R*,4*S*,5*S*)-7-[(2*S*,4*S*,6*R*,8*S*,10*S*)-10-(*tert*-Butyldimethylsiloxy)-4-methoxy-8-(formyl)-1,7-dioxaspiro[5.5]undec-2-yl]-4-hydroxy-3,5-dimethyl-2-methylene-6-oxoheptyl]-4-hydroxy-10-methyl-10-(triethylsiloxy)-1,7-dioxaspiro[5.5]undec-2-yl]ethylmethoxyacetate,diacetate (42). To a room temperature solution of **41a** (45.8 mg, 0.045 mmol) in 5 mL of CH_2Cl_2 was added, via cannula, a suspension of Dess-Martin periodinane (75.6 mg, 0.178 mmol) and pyridine (0.083 mL, 1.02 mmol) in 2 mL of CH_2Cl_2. The reaction was stirred for 1.6 h, then diluted with saturated aqueous $NaHCO_3$ (2 mL), saturated aqueous $Na_2S_2O_3$ (2 mL), and Et_2O (2 mL) and stirred for 30 min. The mixture was extracted with Et_2O (2 x). The combined organic solutions were washed with saturated aqueous $NaHCO_3$ (1 x) and brine (1 x), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (2 x 12 cm silica gel, linear gradient, 20-30% acetone/hexanes) provided 41.6 mg (90%) of a clear oil. $[\alpha]^{23}_{589}$ -11.1 (*c* 0.98, CH_2Cl_2); IR (neat) 2955, 2931, 1737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 5.24-5.21 (dd, *J* = 9.5, 2.3 Hz, 1H), 5.02 (br s, 1H), 4.99 (s, 1H), 4.84 (s, 1H), 4.84-4.80 (m, 1H), 4.28-4.23 (m, 2H), 4.16 (m, 1H), 4.01 (s, 2H), 4.03-3.92 (m, 3H), 3.50-3.43 (m, 1H), 3.44 (s, 3H), 3.31 (s, 3H), 2.93-2.87 (m, 2H), 2.78-2.71 (dd, *J* = 18.2, 9.6 Hz, 1H), 2.40-2.38 (m, 1H), 2.34-2.14 (m, 4H), 2.11-2.07 (dd, *J* = 12.0, 4.2 Hz, 1H), 2.03 (s, 3H), 1.91 (s, 3H), 1.86-1.36 (m, 15 H), 1.20 (s, 3H), 1.08-1.07 (d, *J* = 6.8 Hz, 3H), 1.05-1.04 (d, *J* = 7.0 Hz, 3H), 0.94-0.90 (t, *J* = 8.0 Hz, 9H), 0. 85 (s, 9H), 0.57-0.51 (q, *J* = 8.0 Hz, 6H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 209.6, 202.7, 171.0, 170.2, 169.4, 147.0, 113.7, 98.6, 96.9, 74.1, 73.5, 71.1, 70.6, 69.8, 67.1, 66.6, 64.5, 63.6, 62.0, 61.3, 59.4, 55.7, 49.5, 47.8, 47.7, 45.2, 43.3, 41.8, 38.64, 38.60, 36.9, 35.2, 34.3, 34.1, 33.2, 32.1, 25.9, 21.6, 20.8, 18.2, 13.5, 12.0, 7.3, 6.9, -4.9; Mass calcd. for $C_{52}H_{90}O_{16}Si_2Na$: 1049; found: 1049 (FAB, *m*-nitrobenzyl alcohol, NaI added).

(2*S*,4*S*,6*S*8*R*,10*R*)-10-*tert*-butyldimethylsiloxy-8-(hydroxymethyl)-4-methoxy--2-(buta-3-one)-1,7-dioxaspiro[5.5]undecane (43). A solution of trityl ether **35** (0.045 g, 0.073 mmol) in CH_2Cl_2 (5 mL) was cooled to -78 °C and treated with a solution of Me_2AlCl (0.364 mL of a 1 M solution in hexanes, 0.364 mmol). The resulting bright yellow solution was stirred at -78 °C for 40 min. The solution was quenched at -78 °C with saturated aqueous Rochelle's salt/THF (0.200 mL/ 0.600 mL), resulting in rapid decolorization. The cold bath was removed and additional portions of Rochelle's salt (3 mL) and Et_2O (3 mL) were added. The biphasic mixture was stirred for 4 hrs. The mixture was extracted with Et_2O (2 x 5 mL) and the combined organic solutions treated again with saturated aqueous Rochelle's salt (2 mL). The mixture was stirred for 1 h. The mixture was extracted with Et_2O (2 x 5 mL). The combined organic solutions were washed with 1M HCl (2 x 5 mL), water (5 mL), and brine (5 ML). The organic solution was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (5 g SiO_2, 70% EtOAc/hexanes) to give 0.025 g (83%) of carbinol **43** as a clear, colorless oil: $[\alpha]^{25}_{589}$ -23.6 (*c* 1.26, $CHCl_3$); IR (neat) *v* 3466, 2943, 2892, 1712 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.43-4.40 (m, 1H), 4.11-4.08 (t, *J* = 3.7 Hz, 1H), 3.94-3.90 (m, 1H), 3.68-3.65 (dd, *J* = 11.6, 3.15 Hz, 1H), 3.51-3.44 (m, 2H) 3.31 (s, 3H), 2.84-2.79 (dd, *J* = 17.1, 3.7 Hz, 1H), 2.65-2.61 (dd, *J* = 14.6, 3.8), 2.42-2.38 (q, *J* = 7.3 Hz, 2H), 2.02-1.99 (ddd, *J* = 12.2, 4.4, 1.5 Hz, 1H), 1.69-1.63 (m, 2H), 1.49-1.46 (m, 2H), 1.35-1.30 (t, *J* = 11.9 Hz, 1H), 1.04-1.02 (t, *J* = 7.4 Hz, 3H), 0.84 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.1, 98.2, 73.8, 66.6, 66.3, 65.8, 64.2, 55.5, 48.5, 43.1, 39.8, 37.0, 36.8, 35.7, 34.2, 25.8, 18.0, 7.6, -4.9; exact mass calcd for $C_{21}H_{40}O_6Na$: 439.2492; found 439.2476 (FAB, MNBA, added NaI); R_f=0.15 (60% EtOAc/hexanes).

(2*S*,4*S*,6*R*8*R*,10*R*)-10-*tert*-Butyldimethylsiloxy-8-(hydroxymethyl)-4-methoxy-2-(buta-3-one)-1,7-dioxaspiro[5.5]undecane (44). A solution of trityl ether **35** (0.010 g, 0.016 mmol) in EtOH (1.0 mL) and pyridine (0.013 mL, 0.013 g, 0.160 mmol) was treated with anhydrous $SnCl_2$ (0.031 g, 0.160 mmol). The heterogeneous mixture was heated to reflux for 24 h. The yellow mixture was cooled to room temperature, diluted with EtOAc (5 mL) and washed with saturated aqueous NH_4Cl (2 mL) and brine (2 mL). The organic solution was dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (10 g SiO_2, 40% EtOAc/hexanes) to give 0.004 g (51%) of carbinol **44** as a clear, colorless oil: $[\alpha]^{25}_{589}$ +26.9 (*c*

0.58, $CHCl_3$); IR (neat) ν 3464, 2928, 2856, 1715 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.44-4.41 (m, 1H), 4.16-4.13 (m, 1H), 4.05-4.04 (m, 1H), 3.63-3.55 (m, 3H), 3.31 (s, 3H), 2.74-2.68 (dd, J = 15.7, 7.4 Hz, 1H), 2.66-2.61 (m, 1H), 2.49-2.41 (m, 3H), 2.08-2.04 (m, 1H), 1.81-1.77 (dd, J = 13.4, 4.1 Hz), 1.72-1.60 (m, 2H), 1.50-1.46 (m, 1H), 1.15-1.04 (m, 2H), 1.06-1.02 (t, J = 7.3 Hz, 3H), 0.88 (s, 9H), 0.041 (s, 3H), 0.036 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.2, 99.6, 72.5, 71.3, 65.9, 65.8, 63.5, 55.4, 48.4, 44.0, 39.8, 37.4, 37.2, 34.6, 25.7, 18.0, 7.5, -4.8, -4.9; exact mass calcd for $C_{21}H_{40}O_6Na$: 439.2492; found 439.2489 (FAB, MNBA, added NaI); R_f=0.20 (60% EtOAc/hexanes).

(2*S*, 3*R*)-*N*-Methoxy-*N*,2-dimethyl-3-(triethylsiloxy)-6-heptenamide (45a). To a solution of ca. 27 g (134 mmol) alcohol **45** in 500 mL of CH_2Cl_2 at -78°C, was added 25 mL (218 mmol) of 2,6-lutidine followed by 39.3 mL (174 mmol) of triethylsilyl trifluoromethanesulfonate. The reaction was allowed to warm to -20 °C over 1 h and cooled to -78 °C. The solution was poured into a mixture of Et_2O and saturated aqueous $NaHCO_3$ (500 mL/100 mL). The aqueous solution was separated and extracted with 200 mL of Et_2O, and the organic solutions were washed with 3 x 200 mL of 1M $NaHSO_4$. The combined aqueous washes were extracted with 200 mL of Et_2O. The combined organic solutions were washed with saturated aqueous $NaHCO_3$ and brine, then dried over Na_2SO_4. The volatiles were removed under reduced pressure and the residue was filtered through a short plug of silica gel (15% EtOAc in hexanes) and used directly in the next reaction. The product could be purified by flash chromatography on silica gel (15% EtOAc in hexanes) to give amide **45a**. $[\alpha]^{23}_D$ +3.9 (*c* 2.0, $CHCl_3$); IR (neat) ν 3077, 2955, 2912, 2877, 1664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81-5.71 (m, 1H), 4.99-4.87 (m, 2H), 3.91 (dt, J = 8, 5 Hz, 1H), 3.65 (s, 3H), 3.14 (s, 3H), 2.95 (s(br), 1H), 2.11-2.05 (m, 2H), 1.59-1.45 (m, 2H), 1.14 (d, J = 7 Hz, 3H), 0.94 (t, J = 8 Hz, 9H). 0.60 (q, J = 8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 138.5, 114.1, 73.3, 61.2, 40.8, 35.0, 31.9, 28.7, 14.4, 6.8, 5.0. R_f 0.3 (15 % EtOAc/hexanes); exact mass calcd for $C_{16}H_{34}SiNO_3$: 316.2308; found: 316.2310 (CI, NH_3 atmosphere).

(2*S*, 3*R*)-2-dimethyl-3-(triethylsiloxy)-6-heptenal (46). To a -78 °C solution of the total sample of unpurified amide **45a** (*ca.* 134 mmol) in 1 L of THF was added 52 mL (290 mmol) of DIBAlH over 20 min. The reaction was stirred at -73 °C for 3 h followed by the addition of 14 mL of EtOAc. The resulting solution was cannulated into a 0 °C mixture of Et_2O and 1 M Rochelle's salt (1 L/1 L) and stirred at room temperature for 3 h. The aqueous solution was separated and extracted with 2 x 500 mL of Et_2O. The combined organic solutions were washed with brine and dried over $MgSO_4$. The volatiles were removed under reduced pressure (only 10 min under high vacuum) and the residue was purified by flash chromatography on silica gel (20-30% CH_2Cl_2 in hexanes) to afford 33.47 g (97% for 2 steps) of aldehyde **46**. $[\alpha]^{23}_D$ +57.6 (*c* 2.3, $CHCl_3$); IR (neat) ν 2955, 2912, 2877, 1727, 1641 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.77 (s, 1H), 5.83-5.75 (m, 1H), 5.05-4.96 (m, 2H), 4.14 (dt, J = 7, 4 Hz, 1H), 2.48-2.43 (m, 1H), 2.15-2.00 (m, 2H), 1.65-1.53 (m, 2H), 1.06 (d, J = 7 Hz, 3H), 0.95 (t, J = 8 Hz, 9H), 0.59 (q, J = 8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.0, 137.7, 114.8, 71.5, 51.2, 33.6, 29.8, 7.6, 6.7, 5.0; R_f 0.3 (20 % CH_2Cl_2/hexanes); exact mass calcd for $C_{14}H_{28}SiO_2$: 274.2202; found: 274.2216 (CI, NH_3 atmosphere).

***S*-Ethyl-(3*S*, 4*R*, 5*R*)-3-Hydroxy-4-methyl-5-(triethylsiloxy)-8-nonenethioate (48).** To a -78 °C solution of 35.0 g (136.5 mmol) of aldehyde **46** in 1 L of CH_2Cl_2 was added 26.5 g (150.1 mmol) of silyl ketene thioacetal **47**, followed by 18.5 mL (150.1 mmol) of freshly distilled BF_3•Et_2O over 15 min. The reaction was stirred at -78 °C for 2 h, after which 3.8 mL of Et_3N, 1 L of Et_2O and 500 mL of saturated aqueous $NaHCO_3$. were added. The resulting mixture was allowed to warm to room temperature and diluted with 1 L of Et_2O. The aqueous solution was separated and extracted with 200 mL of Et_2O. The combined organic solutions were washed with brine and dried over Na_2SO_4. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography on silica gel (6-15% EtOAc in hexanes) to afford 42.8 g (87%) of thioester **48** as a 95:5 mixture of isomers. HPLC analysis of the unpurified product showed a 94:6 mixture of isomers (Zorbax; 5% EtOAc/hexanes; 1 mL/min; major 10.6 min, minor 8.2 min). $[\alpha]^{23}_D$ -22.9 (*c* 2.56, $CHCl_3$); IR (neat) ν 3518, 3077, 2955, 2911, 2877, 1686, 1641 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.81-5.73 (m, 1H), 5.02-4.94 (m, 2H), 4.25-4.21 (m, 1H), 3.89-3.87 (m, 1H), 3.20 (d, J = 1 Hz, 1H), 2.92-2.85 (m, 2H), 2.78 (dd, J = 15, 7 Hz, 1H), 2.68 (dd, J = 13, 5 Hz, 1H), 2.01-1.95 (m, 2H), 1.67-1.55 (m, 3H), 1.24 (t, J

= 7 Hz, 3H), 0.96 (t, J = 8 Hz, 9H), 0.91 (d, J = 7 Hz, 3H), 0.61 (q, J = 8 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 137.7, 114.7, 76.1, 71.4, 49.2, 39.8, 33.4, 29.7, 23.2, 14.5, 6.7, 6.4, 5.2; Rf 0.3 (10 % EtOAc/hexanes); exact mass calcd for $C_{18}H_{37}SiSO_3$: 361.2233; found: 361.2247 (FAB, MNBA, added NaI).

(3*S*, 4*R*, 5*R*)-3-Hydroxy-4-methyl-5-(triethylsiloxy)-8-nonenal (48a). To a solution of thioester **48** (24.5 g, 67.9 mmol) in 600 mL of acetone was added 163 mL (102 mmol) of Et_3SiH followed by 42 mL (340 mmol) of 1-hexene and 4.34 g (2.04 mmol) of Lindlar catalyst. The reaction was stirred vigorously at room temperature for 30 min (monitored by TLC every 10 min) and stopped by filtering the reaction over a pad of celite. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography on silica gel (15-25% EtOAc in hexanes) to afford 19 g (93%) of aldehyde **48a** contaminated with a trace of saturated product (reduction of the olefin). $[\alpha]^{23}_D$ -21.5 (*c* 3.5, $CHCl_3$); IR (neat) ν 3466, 2956, 2912, 2878, 1725, 1641 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82-5.72 (m, 1H), 5.03-4.93 (m, 2H), 4.36-4.32 (m, 1H), 3.95-3.91 (m, 1H), 3.30 (s, 1H), 2.69 (ddd, J = 17, 9, 2 Hz, 1H), 2.49 (dd, J = 17, 4 Hz, 1H), 2.01-1.92 (m, 2H), 1.71-1.52 (m, 3H), 0.96 (t, J = 8 Hz, 9H), 0.91 (d, J = 7 Hz, 3H), 0.62 (q, J = 8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1, 137.6, 114.9, 76.6, 70.1, 49.1, 39.7, 33.4, 29.7, 6.7, 6.0, 5.2; Rf 0.35 (15 % EtOAc/hexanes); exact mass calcd for $C_{16}H_{32}SiO_3$+NH_4: 318.2464; found: 318.2480 (CI, NH_3 atmosphere).

(4*S*, 5*R*, 6*R*)-6-(3-butenyl)-5-methyl-4-hydroxy-2-methoxy-tetrahydro-2H-pyran (48b). To a solution of aldehyde **48a** (31 g, 103 mmol) in a mixture of CH_2Cl_2 (350 mL) and MeOH (150 mL) at room temperature was added 479 mg of CSA in one portion. The reaction was monitored by TLC and after completion 2 g of $NaHCO_3$ were added followed by 500 mL of Et_2O and 300 mL of saturated aqueous $NaHCO_3$. The resulting mixture was poured into a separatory funnel containing 500 mL of Et_2O. The organic solution was separated and washed with 300 mL of water. The combined aqueous solutions were extracted with 300 mL of Et_2O, and the combined organic solutions were washed with saturated aqueous $NaHCO_3$ and brine, then dried over Na_2SO_4. The volatiles were removed under reduced pressure to afford 30.2 g of unpurified oil. 11.7 g of this crude material was purified by flash chromatography (10-20 % Et_2O in CH_2Cl_2) to afford 7.46 g (93%) of the mixed methyl ketal. $[\alpha]^{23}_D$ (major isomer) +131.5 (*c* 1.91, $CHCl_3$); IR (neat) ν 3540, 3076, 2938, 2833, 1641 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (major isomer) 5.86-5.76 (m, 1H), 5.04-4.93 (m, 2H), 4.74 (d, J = 4 Hz, 1H), 4.07-4.03 (m, 1H), 3.73-3.70 (m, 2H), 3.32 (s, 3H), 2.27-2.18 (m, 1H), 2.11-2.01 (m, 1H), 1.92 (dt, J = 15, 4 Hz, 1H), 1.73-1.58 (m, 3H), 1.43-1.34 (m, 1H), 0.86 (d, J = 7 Hz, 3H); δ (minor isomer) 5.88-5.78 (m, 1H), 5.05-4.94 (m, 2H$_2$), 4.64 (dd, J = 9, 4 Hz, 1H), 3.97-3.96 (m, 1H), 3.92-3.88 (m, 1H), 3.50 (s, 3H), 2.29-2.20 (m, 1H), 2.16-2.06 (m, 1H), 1.79-1.65 (m, 3H), 1.57-1.51 (m, 1H), 1.44-1.36 (m, 1H), 0.92 (d, J = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (major isomer) 138.2, 114.6, 99.0, 70.1, 64.3, 54.7, 38.0, 31.6, 30.5, 30.1, 10.4; δ (minor isomer) 138.3, 114.6, 99.9, 71.6, 71.5, 56.2, 38.4, 34.1, 31.4, 30.2, 10.8; Rf (major isomer) 0.45, (minor isomer) 0.2 (10 % Et_2O/CH_2Cl_2); exact mass calcd for $C_{11}H_{20}O_3$+NH_4: 218.1756; found: 218.1752 (CI, NH_3 atmosphere).

(4*S*, 5*R*, 6*R*)-6-(but-3-enyl)-5-methyl-4-(*tert*-Butyldimethylsiloxy)-2-methoxy-tetrahydro-2H-pyran (49). To a solution of alcohol **48b** (18.5 g, 90% pure) in 140 mL of DMF was added 14.3 g (209.7 mmol) of imidazole at room temperature. The resulting solution was placed at 0 °C, and 16 g (106.2 mmol) of *tert*-butyldimethylsilyl chloride was added in one portion. The ice bath was removed, the solution was stirred at room temperature for 20.5 h and poured into a mixture of 600 mL of Et_2O and 100 mL of saturated aqueous $NaHCO_3$. The organic solutions were washed with water (6 x 100 mL), and the combined aqueous solutions were extracted with Et_2O (100 mL). The combined organic solutions were washed with 50 mL of 1 N HCl, 100 mL of saturated aqueous $NaHCO_3$, 100 mL of brine, then dried over $MgSO_4$. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography (5-10% EtOAc/hexanes) to afford 18.2 g (92%, 2 steps) of the protected mixed methyl ketal **49**. major isomer: $[\alpha]^{23}_D$ +98.4 (*c* 1.38, $CHCl_3$); IR (neat) ν 3078, 2951, 2935, 2878, 1642 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89-5.81 (m, 1H), 5.07-4.95 (m, 2H), 4.63 (dd, J = 4, 3 Hz, 1H), 4.18-4.14 (m, 1H), 3.68 (q, J = 4 Hz, 1H), 3.33 (s, 3H), 2.27-2.20 (m, 1H), 2.21-2.05 (m, 1H), 1.90 (dt, J = 14, 4 Hz, 1H), 1.65-1.54 (m, 3H), 1.42-1.35 (m, 1H), 0.89 (s, 9H), 0.89 (d, J = 7 Hz, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 114.5, 97.8,

69.9, 66.6, 54.8, 39.3, 33.9, 30.6, 30.2, 25.6, 17.9, 11.0, -4.7, -5.0; R$_f$ 0.3 (4 % EtOAc/hexanes); exact mass calcd for $C_{17}H_{34}SiO_3Na$: 337.2175; found: 337.2175 (FAB, NBA, NaI added).

(4*S*, 5*R*, 6*R*)-6-(4-hydroxy-butyl)-5-methyl-4-(*tert*-Butyldimethylsiloxy)-2-methoxy-tetrahydro-2H-pyran (50). To a 0 °C solution of 11.0 g (35.0 mmol) of olefin **49** in 250 mL of THF was added, via cannula, 17.3 g (69.9 mmol) of 9-BBN in 200 mL of THF over 30 min. After 1 h the ice bath was removed, and the clear solution was stirred at room temperature for 1 h, then cooled to 0 °C. The reaction was stopped by adding 70 mL of a 1:1 mixture of THF:EtOH followed by 70 mL of pH 7 buffer and 70 mL of 30% H_2O_2 (T < 10 °C). The ice bath was removed, and the resulting clear solution was stirred at room temperature for 5 h. The reaction was poured into a mixture of 1 L of Et_2O and 300 mL of water. The organic solution was separated and washed with 200 mL of 5% aqueous $Na_2S_2O_3$. The combined aqueous solutions were extracted with EtOAc (2 x 200 mL), and the combined organic solutions were washed with 200 mL of saturated aqueous $NaHCO_3$ and 200 mL of brine, then dried over $MgSO_4$. The volatiles were removed under reduced pressure, and the residue was purified by flash chromatography (25-30% EtOAc in CH_2Cl_2) to afford 9.1 g (85%) of alcohol **50** as a colorless oil. IR (neat) ν 3418, 2934, 2884, 2858 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63-4.59 (m, 1H), 4.16-4.11 (m, 1H), 3.90-3.87 (m, 1H$_{min}$), 3.69-3.64 (m, 3H$_{maj}$), 3.49 (s, 3H$_{min}$), 3.32 (s, 3H$_{maj}$), 1.90 (dt, J = 14, 4 Hz, 1H$_{maj}$), 1.66-1.28 (m, 9H), 0.89-0.87 (m, 12H), 0.05 (s, 3H$_{min}$), 0.04 (s, 3H$_{maj}$), 0.03 (s, 3H$_{min}$), 0.01 (s, 3H$_{maj}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 100.3, 97.8, 72.3, 72.0, 69.9, 66.8, 62.7, 56.1, 54.8, 39.3, 38.6, 34.7, 33.7, 32.6, 31.9, 31.0, 25.6, 22.3, 22.2, 17.9, 10.9, 10.7, -4.7, -5.0; R$_f$ 0.3 (30 % EtOAc/CH_2Cl_2); exact mass calcd for $C_{17}H_{36}SiO_4$+NH_4: 350.2727; found: 350.2730 (CI, NH_3 atmosphere).

(4*S*, 5*R* , 6*R*)-6-(4-benzyloxybutyl)-5-methyl-4-(*tert*-Butyldimethylsiloxy)-2-phenylthio-tetrahydro-2H-pyran (50a). To a solution of 6.00 g (18.04 mmol) of methyl ketal **50** in 90 mL of 1,2-dichloroethane was added, at room temperature, 10.25 mL (54.13 mmol) of TMSSPh followed by 11.5 g (36.08 mmol) of ZnI_2 in one portion. The slightly exothermic reaction was placed in an ice bath for 10 min and then stirred at room temperature for 1 h. The white heterogeneous mixture was poured into a mixture of EtOAc/saturated aqueous $NaHCO_3$ (1L/500 mL). The aqueous solution was separated extracted with 2 x 150 mL of EtOAc and the combined organic solutions were washed with 1N HCl (2 x 200 mL), 200 mL of saturated aqueous $NaHCO_3$, 200 mL of brine and dried over $MgSO_4$. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography (20-30% EtOAc/hexanes) to afford 7.02 g (95%) of the primary alcohol as a colorless oil. To a solution of 6.8 g (16.55 mmol) of the alcohol in 160 mL of DMF at -20°C was added 730 mg (18.21 mmol) of NaH (60% in oil) immediately followed by 2.0 mL (16.55 mmol) of benzyl bromide and 6.1 g (16.55 mmol) of Bu_4NI. The reaction was allowed to warm to 0 °C where an extra 264 mg (0.4 eq.) of NaH and 0.393 mL (0.2 equiv.) of benzyl bromide were added. The heterogeneous mixture was stirred 4 h at 0 °C, 13 h at 10 °C, and 4 h at room temperature, then diluted at 0 °C with 150 mL of Et_2O and quenched with 5 mL of saturated aqueous $NaHCO_3$. The resulting solution was poured into an Et_2O/saturated aqueous $NaHCO_3$ mixture (1 L/200 mL). The organic solution was separated and washed with water (4 x 200 mL), and the combined aqueous solutions were extracted with Et_2O (2 x 200 mL). The combined organic solutions were washed with 200 mL of brine and dried over $MgSO_4$. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography (5-8% EtOAc in hexanes) to afford 7.42 g (90%) of the benzyl ether **50a** as a colorless oil. **β-Anomer (Major):** $[\alpha]^{23}_D$ -3.4 (*c* 1.77, $CHCl_3$); IR (neat) ν 3062, 3030, 2952, 2931, 2857 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48-7.16 (m, 10H), 5.18 (dd, J = 12, 2 Hz, 1H), 4.49 (s, 2H), 3.97-3.94 (m, 1H), 3.86-3.85 (m, 1H), 3.47-3.44 (m, 2H), 1.94-1.88 (m, 1H), 1.69-1.29 (m, 8H), 0.89 (d, J = 7 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 135.1, 130.1, 128.5, 128.2, 127.5, 127.3, 126.4, 80.3, 75.0, 72.8, 71.4, 70.2, 38.3, 34.5, 32.2, 29.5, 25.7, 22.6, 17.9, 10.7, -5.0, -5.1; R$_f$ 0.25 (5 % EtOAc/hexanes); exact mass calcd for $C_{29}H_{44}SiSO_3$+Na: 523.2678; found: 523.2687 (FAB, MNBA NaI added).

(4*S*, 5*R* , 6*R*)-6-(4-benzyloxybutyl)-5-methyl-4-(*tert*-Butyldimethylsiloxy)-2-phenylsulfone-tetrahydro-2H-pyran (51). To a solution of 5.4 g (10.78 mmol) of thioglycoside **50a** in 100 mL of ethyl acetate at 0 °C was added 4.53 g (53.9 mmol) of $NaHCO_3$ followed by 6.29 g (23.72 mmol) of *m*-CPBA (65 % pure). The reaction was stirred for 2 h at 0 °C, then diluted with 100 mL of Et_2O and quenched with 10 mL of saturated

aqueous $NaHCO_3$. The resulting heterogeneous mixture was poured into an Et_2O/saturated aqueous $NaHCO_3$ mixture (600 mL/100 mL). The organic solution was separated and washed with 100 mL of 5% aqueous $Na_2S_2O_3$ and 2 x 100 mL of 1N NaOH. The combined aqueous solutions were extracted with 100 mL of Et_2O, and the combined organic solutions were washed with brine and dried over $MgSO_4$. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography (15% EtOAc in hexanes) to afford 5.54 g (97%) of the sulfone **51** as a mixture of anomers. **β-Anomer (Major).** $[\alpha]^{23}_D$ +41.6 (*c* 1.23, $CHCl_3$); IR (neat) *v* 3064, 2935, 2857 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94-7.91 (m, 2H), 7.60-7.28 (m, 8H), 4.71 (dd, *J* = 11, 3 Hz, 1H), 4.48 (s, 2H), 3.96-3.95 (m, 1H), 3.80-3.78 (m, 1H), 3.38-3.31 (m, 2H), 1.96 (td, *J* = 12, 3 Hz, $1H_{ax}$), 1.89 (dt, *J* = 13, 3 Hz, 1H), 1.59-1.11 (m, 7H), 0.88 (s, 9H), 0.78 (d, *J* = 7 Hz, 3H), 0.07 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 136.5, 133.5, 129.5, 128.5, 128.3, 127.5, 127.4, 88.2, 75.5, 72.8, 70.2, 70.1, 38.3, 31.7, 29.4, 26.6, 25.7, 22.2, 17.9, 10.4, -5.0, -5.1; R_f 0.4 (15 % EtOAc/hexanes); exact mass calcd for $C_{29}H_{44}SiSO_5$+Na: 555.2576; found: 555.2584 (FAB, MNBA, added NaI). **α-Anomer (Minor).** $[\alpha]^{23}_D$ +62.6 (*c* 1.50, $CHCl_3$); IR (neat) *v* 2930, 2857 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91-7.89 (m, 2H), 7.56-7.29 (m, 8H), 4.48 (dd, *J* = 11, 3 Hz, 1H), 4.46 (s, 2H), 4.09 (dt, *J* = 12, 4 Hz, 1H), 3.63 (td, *J* = 9, 5 Hz, 1H), 3.23 (t, *J* = 7 Hz, 2H), 2.31 (dt, *J* = 13, 4 Hz, 1H), 1.95-1.79 (m, 2H), 1.50-1.22 (m, 6H), 0.90 (s, 9H), 0.83 (d, *J* = 7 Hz), 0.10 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 136.9, 133.5, 129.3, 128.6, 128.3, 127.5, 127.5, 85.3, 77.3, 72.8, 69.9, 69.3, 40.8, 31.0, 29.0, 26.2, 25.6, 21.6, 17.9, 12.9, -4.3, -4.9; R_f 0.35 (15 % EtOAc/hexanes); exact mass calcd for $C_{29}H_{44}SiSO_5$+Na: 555.2576; found: 555.2566 (FAB, MNBA, added NaI).

Ethyl (3*S*, 2*R*)-2-triethylsiloxy-3-methyl-4-oxo-4-phenylthiobutanoate (57). To a solution of 2.73 g (10.2 mmol) of **56** in 72 mL of CH_2Cl_2 was added 3.47 g (51.0 mmol) of imidazole. After cooling to 0 °C, chlorotriethylsilane (4.3 mL, 25.5 mmol) was added dropwise. After 15 min, the reaction was quenched by adding pH 7 buffer, diluted with Et_2O, and warmed to room temperature. The aqueous solution was separated and washed with Et_2O (2x). The combined organic solutions were washed with brine, dried over Na_2SO_4, filtered and concentrated. Flash chromatography (2% EtOAc/hexanes, then 4% EtOAc/hexanes) afforded 3.78 g (9.89 mmol, 97%) of **57** as a clear oil. IR (neat) 2956, 2877, 2361, 2343, 1752, 1736, 1702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 5H), 4.44 (d, *J* = 8.0 Hz, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 3.16 (dq, *J* = 8.0, 7.1 Hz, 1H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.21 (d, *J* = 7.1 Hz, 3H), 0.94 (t, *J* = 8.1 Hz, 9H), 0.59 (q, *J* = 8.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 171.5, 134.3, 129.3, 129.1, 127.7, 74.3, 61.0, 52.6, 14.1, 13.4, 6.6, 4.5; R_f 0.50 (10% EtOAc/hexanes); Anal. Calcd for $C_{16}H_{24}O_4SSi$: C, 59.65, H, 7.90; found: C, 59.71, H, 7.88; exact mass calcd. for $C_{19}H_{34}O_4SSiN$: 400.1978; found: 400.1990 (FAB, *m*-nitrobenzyl alcohol, NaI added).

Ethyl (4*S*, 2*R*, 3*R*)-6-ethylthio-2-triethylsiloxy-3-methyl-4-hydroxy-6-oxohexanoate (59). To a solution of **57** (1.96 g, 5.14 mmol) in 52 mL of acetone was added 5.8 mL (36.0 mmol) of triethylsilane. The reaction was stirred for 5 min, and 0.547 g (0.514 mmol) of Pd/C was added in two portions. After stirring for 35 min, the reaction was filtered through a pad of celite, which was then rinsed several times with fresh Et_2O, and the volatiles were removed *in vacuo*. Flash chromatography (3% EtOAc/hexanes, then 6% EtOAc/hexanes) afforded *ca.* 1.40 g of aldehyde **58**, which was used directly in the next step. IR (neat) 2957, 2878, 1753, 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.73 (d, *J* = 1.1 Hz, 1H), 4.45 (d, *J* = 4.8 Hz, 1H), 4.22 (dq, *J* = 3.6, 8.0 Hz, 1H), 4.20 (dq, *J* = 3.6, 8.0 Hz, 1H), 2.76 (ddq, *J* = 1.1, 4.8, 7.1 Hz, 1H), 1.28 (t, *J* = 8.0 Hz, 3H), 1.13 (d, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.63 (q, *J* = 8.0 Hz, 6H);.^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 171.9, 73.1, 61.3, 50.5, 14.1, 10.0, 6.6, 4.5; R_f 0.33 (10% EtOAc/hexanes); exact mass calcd. for $C_{13}H_{30}O_4SiN$: 292.1944; found: 292.1945 (FAB, *m*-nitrobenzyl alcohol, NaI added). To a solution of 1.40 g of unpurified aldehyde **58** in 52 mL of toluene at –93 °C was added dropwise 1.70 mL (7.71 mmol) of silyl thioketene acetal **47**. The reaction was stirred for 5 min, and 0.76 mL (6.17 mmol) of BF_3•OEt_2 was added dropwise over 15 min. After stirring a further 15 min, the reaction was quenched by adding 2 mL of triethylamine and diluted with saturated aqueous $NaHCO_3$, followed by EtOAc at –93 °C. The aqueous solution was separated and washed with EtOAc (2 x). The combined organic solutions were washed with brine, dried over Na_2SO_4, filtered and concentrated. ^1H NMR analysis of the unpurified reaction mixture showed an 86:14 mixture of diastereomers. Flash chromatograpy (12% Et_2O/pentane, then 15% Et_2O/pentane) afforded 1.38 g (3.65 mmol,

71% from **57**) of the Felkin diasteromer **59** as a yellow oil. $[\alpha]^{23}_D$ +13.9 (*c* 1.16, CH_2Cl_2); IR (neat) 3516, 2957, 2937, 2914, 2878, 1750, 1735, 1687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.36 (dddd, *J* = 1.5, 3.1, 4.6, 8.6 Hz, 1H), 4.24-4.16 (m, 3H), 2.88 (q, *J* = 7.6 Hz, 2H), 2.78 (dd, J = 8.7, 15.0 Hz, 1H), 2.54 (dd, J = 4.6, 15.0 Hz, 1H), 1.96 (ddq, *J* = 3.1, 3.2, 7.1 Hz, 1H), 1.29 (t, *J* = 7.6 Hz, 3H), 1.23 (t, *J* = 7.6 Hz, 3H), 1.02 (d, *J* = 7.1 Hz, 3H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.63 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.1, 172.7, 76.6, 68.3, 61.1, 48.8, 40.5, 23.4, 14.6, 14.2, 10.0, 6.6, 4.4; R_f 0.24 (15% Et_2O/pentane); Anal. Calcd, for $C_{17}H_{34}O_5SSi$: C, 53.93, H, 9.05; found: C, 54.17, H, 9.08; exact mass calcd. for $C_{17}H_{38}O_5SSiN$: 396.2240; found: 396.2246 (FAB, *m*-nitrobenzyl alcohol, NaI added).

Methyl (4*S*, 2*R*, 3*R*)-4-triethylsiloxy-6-methoxy-3-methyltetrahydro-2H-pyran-2-carboxylate (60). To a solution of **59** (1.29 g, 3.41 mmol) in 38 mL of acetone was added triethylsilane (4.1 mL, 25.5 mmol). After stirring for 5 min, 0.365 g of 10% Pd/C was added in one portion. The reaction was stirred for 3 h, then filtered through a pad of celite and concentrated. The residual oil was dissolved in 50 mL of MeOH and 50 mL of CH_2Cl_2, and 0.20 g of camphorsulfonic acid was added. After 30 min of stirring, a further 3.0 g of camphorsulfonic acid was added, and the reaction was stirred for 7 days, when ^1H NMR of an aliquot confirmed complete transesterification. The reaction was then diluted with EtOAc, and quenched by adding saturated $NaHCO_3$. The aqueous solution was separated and extracted with EtOAc (3 x). The combined organic solutions were washed with brine, dried over Na_2SO_4, filtered and concentrated. Filtration through a silica plug (15% EtOAc/hexanes, then 70% EtOAc/hexanes) yielded 0.87 g (4.26 mmol) of a volatile, yellow oil contaminated with residual solvent. The oil was dissolved in 21 mL of CH_2Cl_2, and 1.16 g (17.0 mmol) of imidazole was added. The solution was then cooled to 0 °C, and 1.1 mL (6.40 mmol) of chlorotriethylsilane was added dropwise. After 5 min, the reaction was quenched by adding pH 7 buffer and diluted with Et_2O. The aqueous solution was separated and extracted with Et_2O (2 x). The combined organic solutions were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (8% EtOAc/hexanes) afforded 0.760 g (2.39 mmol, 70% from **59**) of a clear oil. $[\alpha]^{23}_D$ –45.7 (*c* 0.470, CH_2Cl_2); IR (neat) 2956, 2913, 2877, 1755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.90 (dd, *J* = 1.7, 3.4 Hz, 1H), 3.97 (d, *J* = 10.4, 1H), 3.77 (s, 3H), 3.69 (ddd, *J* = 4.7, 4.7, 9.8 Hz, 1H), 3.33 (s, 3H), 1.96 (ddd, *J* = 3.7, 4.6, 8.4 Hz, 1H), 1.80-1.68 (m, 2H), 0.95 (t, *J* = 8.0 Hz, 9H). 0.58 (q, *J* = 8.0 Hz, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 170.9, 99.6, 73.9, 69.1, 55.1, 52.1, 41.1, 39.2, 12.9, 6.8, 5.0; P_f 0.33 (10% EtOAc/hexanes); Anal. Calcd, for $C_{15}H_{30}O_5Si$: C, 56.57; H, 9.50; found: C, 58.50; H, 9.74; exact mass calcd. for $C_{15}H_{34}O_5SiN$: 336.2206; found: 336.2208 (FAB, *m*-nitrobenzyl alcohol, NaI added).

Methyl (4*S*, 2*R*, 3*R*)-4-triethylsiloxy-6-phenylthio-3-methyltetrahydro-2H-pyran-2-carboxylate (61). To a solution of **60** (760 mg, 2.39 mmol) in 12.5 mL of 1,2-dichloroethane was added 1.35 mL (7.17 mmol) of phenylthiotrimethylsilane. ZnI_2 (1.53 g, 4.80 mmol) was added in one portion, and the reaction was cooled to 0 °C for 10 min. The bath was then removed, and the reaction was stirred for 90 min, then quenched with saturated $NaHCO_3$ and diluted with EtOAc. The aqueous solution was separated and washed with EtOAc (2 x). The combined organic solutions were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (5% EtOAc/hexanes) afforded 861mg (2.17 mmol, 91%) of **61** as a clear oil. $[\alpha]^{23}_D$ –122.6 (*c* 0.530, CH_2Cl_2). IR (neat) 2955, 2912, 2877, 1754 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 1.4, 7.1 Hz, 2H), 7.28 (dd, *J* = 5.2, 7.1 Hz, 2H), 7.23 (dd, *J* = 1.4, 5.2 Hz, 1H), 5.81(dd, *J* = 4.0, 4.4 Hz, 1H), 4.45 (d, *J* = 8.4, 1H), 3.76 (s, 3H), 3.74 (ddd, *J* = 4.4, 9.0, 12.7 Hz, 1H), 2.16 (ddd, *J* = 4.0, 4.4, 9.3 Hz, 1H), 2.05 (ddd, *J* = 4.4, 9.3, 12.7 Hz, 1H), 1.94 (ddq, *J* = 8.4, 9.0, 6.8 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.96 (t, *J* = 8.0 Hz, 9H). 0.61 (q, *J* = 8.0 Hz, 6H); ^{13}C (100 MHz, $CDCl_3$) δ 170.9, 134.7, 130.6, 128.9, 126.9, 82.8, 72.1, 69.7, 52.0, 40.6, 38.6, 13.7, 6.8, 4.9; P_f 0.51 (10% EtOAc/hexanes); Anal. Calcd, for $C_{20}H_{32}O_4SSi$: C, 60.58; H, 8.14; found: C, 60.55; H, 8.21; exact mass calcd. for $C_{20}H_{36}O_4SSiN$: 414.2134; found: 414.2127 (FAB, *m*-nitrobenzyl alcohol, NaI added).

Methyl (4*S*, 2*R* , 3*R*)-4-triethylsiloxy-6-(phenylsulfinyl)-3-methyltetrahydro-2H-pyran-2-carboxylate (61a). To a 0 °C solution of **61** (330 mg, 0.83 mmol) in 8.3 mL of EtOAc was added 210 mg (2.50 mmol) of $NaHCO_3$. After stirring several min, 207 mg (0.874 mmol) of *meta*-chloroperoxybenzoic acid was added in one portion, and the reaction was stirred at 0 °C for 45 min. The reaction was quenched by adding saturated

$NaHCO_3$, and diluted with Et_2O. The organic solution was separated and washed with 1 N NaOH. The combined aqueous solutions were then washed with EtOAc (2 x). The combined organic solutions were washed with 0.5 M $Na_2S_2O_3$ and brine, then dried over Na_2SO_4, filtered, and concentrated. ^1H NMR of the unpurified mixture showed a 7:1 ratio of diastereomers. Flash chromatography (15% EtOAc/hexanes) yielded 325 mg (0.70 mmol, 84% from **61**) of a clear, viscous oil which was used immediately in the next reaction. Major Diastereomer: $[\alpha]^{23}_D$ +37.0 (*c* 1.51, CH_2Cl_2); IR (neat) 2954, 2912, 2877, 1752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 1.9, 6.7 Hz, 2H), 7.53-7.50 (m, 3H), 5.02 (dd, *J* = 3.8, 8.5 Hz, 1H), 4.27 (d, *J* = 4.3, 1H), 3.91 (ddd, *J* = 3.2, 4.8, 5.7 Hz, 1H), 3.70 (s, 3H), 2.32 (ddd, *J* = 5.7, 8.5, 10.7 Hz, 1H), 2.17 (ddd, *J* = 3.8, 4.8, 10.7 Hz, 1H), 1.37 (ddq, *J* = 3.2, 4.3, 7.1 Hz, 3H) 1.07 (d, *J* = 7.1 Hz, 3H), 0.81 (t, *J* = 8.0 Hz, 9H). 0.45 (dq, *J* = 4.0, 8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 141.0, 130.9, 129.0, 124.3, 91.2, 77.3, 68.7, 51.8, 38.4, 26.1, 15.0, 6.6, 4.5; P_f 0.30 (30% EtOAc/hexanes).

Methyl (4*S*, 2*R*, 3*R*)-4-triethylsiloxy-3-methyl-3,4-dihydro-2H-pyran-2-carboxylate (62). A solution of 81.8 mg (0.20 mmol) of **61** in 20 mL benzene was refluxed at 80 °C for 90 min, then cooled to room temperature, quenched with saturated $NaHCO_3$, and diluted with Et_2O. The aqueous solution was separated and washed with Et_2O (2 x). The combined organic solutions were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (3% EtOAc/hexanes) afforded 49.7 mg (0.17 mmol, 88%) of **62** as a clear oil. $[\alpha]^{23}_D$ +39.1 (*c* 0.725, CH_2Cl_2; IR (neat) 2955, 2913, 2878, 1765, 1741, 1648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.43 (d, *J* = 6.2 Hz, 1H), 4.81 (ddd, *J* = 1.3, 5.0, 6.2 Hz, 1H), 4.36 (d, *J* = 8.4, 1H), 3.71 (m, 4H), 2.41 (dddq, *J* = 1.3, 2.1, 3.3, 7.1 Hz, 1H), 1.02 (d, *J* = 7.1 Hz, 3H), 0.93 (t, *J* = 7.8 Hz, 9H). 0.61 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 143.0, 102.5, 75.5, 64.8, 51.7, 37.6, 16.0, 6.7, 4.9. R_f 0.68 (20% EtOAc/hexanes); Anal. Calcd, for $C_{14}H_{26}O_4Si$: C, 58.70; H, 9.15; found: C, 58.93; H, 9.28; exact mass calcd. for $C_{14}H_{30}O_4SiN$: 304.1944; found: 304.1949 (FAB, *m*-nitrobenzyl alcohol, NaI added).

(4*S*, 2*R*, 3*R*)-4-Hydroxy-3-methyl(3,4-dihydro-2H-pyran-2-yl) benzotriazolyl ketone (64e). To a solution of potassium trimethylsilanoate (63.6 mg, 0.494 mmol) in 0.70 mL of THF was added **62** (70.6 mg, 0.247 mmol) in 1.0 mL of THF via cannula (0.7 mL THF rinse). The reaction was stirred for 60 min, then quenched by adding pH 5.5 buffer and diluted with EtOAc. The aqueous solution was separated and extracted with EtOAc (2 x). The aqueous solution was then acidified to pH 4.5 with 1 N HCl and extracted with CH_2Cl_2 (3 x). The combined organic solutions were stirred over $MgSO_4$ for 5 min, then filtered and concentrated to afford 72.8 mg of a carboxylic acid. ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (br. s, 1H), 6.42 (d, *J* = 6.2 Hz, 1H), 4.84 (ddd, *J* = 1.1, 5.0, 6.2 Hz, 1H), 4.37 (d, *J* = 3.8 Hz, 1H), 3.76 (dd, *J* = 3.5, 5.0 Hz, 1H), 2.43 (dddq, *J* = 1.1, 3.5, 3.8, 5.8 Hz), 0.95 (d, J = 5.8 Hz, 3H), 0.93 (t, J = 7.8 Hz, 9H), 0.56 (q, J = 7.8 Hz, 9H). The unpurified acid was dissolved in 2.7 mL of CH_2Cl_2, and 71 μL (0.535 mmol) of 1-chloro-*N*,*N*-2-trimethylpropenylamine was added via syringe. After stirring for 60 min, this was cannulated into a solution of 134 mg (1.12 mmol) benzatriazole, 165 μL (1.66 mmol) pyridine, and *ca.* 20 mg DMAP in 1 mL CH_2Cl_2. The reaction was stirred at room temperature for 3 h, then quenched by adding saturated aqueous $NaHCO_3$ and diluted with Et_2O. The aqueous solution was separated and washed with fresh Et_2O (2x). The combined organic solutions were washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was filtered through a short silica plug (CH_2Cl_2 eluent) to yield 80.0 mg of amide **64e**. $[\alpha]^{23}_D$ -39.1 (*c* 3.25, $CHCl_3$); IR (neat) *v* 2956, 2911, 2877, 1755, 1646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8 Hz, 1H), 8.10 (d, *J* = 8 Hz, 1H), 7.65-7.61 (m, 1H), 7.51-7.47 (m, 1H), 6.65 (d, *J* = 6 Hz, 1H), 5.64 (d, *J* = 2 Hz, 1H), 4.91 (td, *J* = 6, 2 Hz, 1H), 3.70, dd, *J* = 5, 2 Hz, 1H), 3.04-2.98 (m, 1H), 1.20 (d, *J* = 7 Hz, 3H), 0.56 (t, *J* = 8 Hz, 9H), 0.16 (q, *J* = 8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 145.4, 143.5, 131.1, 130.1, 126.0, 119.8, 114.4, 101.9, 64.2, 39.0, 15.9, 6.2, 4.3; R_f 0.3 (5 % EtOAc/hexanes); R_f 0.80 (CH_2Cl_2); exact mass calcd for $C_{19}H_{27}SiN_3O_3$+NH_4: 391.2165; found: 391.2164 (CI, NH_3 atmosphere).

(2*R*, 3*S*, 4*S*)-4-(*tert*-Butyldimethylsiloxy)-6-[(2*R*, 3*S*, 4*S*)-3,4-dihydro-3-methyl-4-(triethylsiloxy)-2H-pyran-2-(oxo)methyl] tetrahydro-6-phenylsulfone-3-methyl-2-(4-benzyloxybutyl)-2H-pyran (65). To a solution of **51** (145 mg, 0.272 mmol) in 1.8 mL of THF at –78 °C was added 0.50 mL of freshly prepared LDA (1 mL THF, 140 μL (1.0 mmol) diisopropylamine, 0.68 mL BuLi (1.50 M in hexanes), 0 °C, 10 min). The solution gradually turned bright yellow, and was stirred at –78 °C for 1 h. Amide **64e** was then added via

cannula in 0.6 mL of THF (0.4 mL THF rinse). The reaction was stirred for a further 30 min at –78 °C, then quenched by adding saturated NH_4Cl, diluted with Et_2O and warmed to room temperature. The organic solutions were separated washed with 1 N NaOH. The combined aqueous solutions were washed with Et_2O (2x). The combined organic solutions were washed with brine, dried over $MgSO_4$, filtered and concentrated. ^1H NMR analysis of the unpurified residue indicated a 1.3:1 mixture of sulfone anomers. Flash chromatography (10% EtOAc/hexanes) afforded 104.2 mg (0.132 mmol, 55%) of **65** as a viscous oil. **β-Sulfone-anomer (Major).** $[\alpha]^{23}_D$ +58.1 (*c* 2.18, $CHCl_3$); IR (neat) *v* 2953, 2877, 1737, 1648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80-7.78 (m, 2H), 7.58-7.27 (m, 8H), 6.27 (d, *J* = 6 Hz, 1H), 5.33-5.31 (m, 1H), 4.60 (t, *J* = 6 Hz, 1H), 4.56 (s, 2H), 4.06 (d, *J* = 2 Hz, 1H), 3.84 (q, *J* = 3 Hz, 1H), 3.59-3.55 (m, 3H), 2.73 (dd, *J* = 16, 3 Hz, 1H), 2.49-2.44 (m, 1H), 2.24 (dd, *J* = 16, 4 Hz, 1H), 1.83-1.40 (m, 7H), 0.97 (s, 9H), 0.93 (d, *J* = 7 Hz, 3H), 0.90 (t, *J* = 8 Hz, 9H), 0.85 (d, *J* = 7 Hz, 3H), 0.59-0.47 (m, 6H), 0.17 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.0, 143.7, 138.5, 137.2, 133.4, 130.7, 128.5, 128.2, 127.5, 127.4, 100.1, 99.8, 78.6, 72.8, 72.1, 70.2, 68.8, 64.5, 37.8, 37.4, 32.5, 29.7, 28.8, 25.7, 22.5, 18.1, 17.0, 11.0, 6.6, 4.8, -4.9, -5.2; R_f 0.4 (15 % EtOAc/hexanes); exact mass calcd for $C_{42}H_{66}Si_2SO_8$+Na: 809.3915; found: 809.3890 (FAB, MNBA, added NaI). **α-Sulfone-anomer (Minor).** $[\alpha]^{23}_D$ +143.9 (*c* 3.13, $CHCl_3$); IR (neat) *v* 2952, 2877, 2858, 1733, 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98-7.96 (m, 2H), 7.69-7.28 (m, 8H), 6.22 (dd, *J* = 6, 1 Hz, 1H), 5.12 (d, *J* = 11 Hz, 1H), 4.70 (dd, *J* = 6, 2 Hz, 1H), 4.65-4.62 (m, 1H), 4.54 (s, 2H), 4.17-4.14 (m, 1H), 3.68 (d, *J* = 3 Hz, 1H), 3.52 (t, *J* = 6 Hz, 2H), 2.81 (dd, *J* = 14, 3 Hz, 1H), 2.28-2.22 (m, 1H), 1.72-1.20 (m, 8H), 1.04 (d, *J* = 7 Hz, 3H), 0.99 (t, *J* = 8 Hz, 9H), 0.79 (s, 9H), 0.64 (q, *J* = 8 Hz, 6H), 0.00 (s, 3H), -0.02 (d, *J* = 7 Hz, 3H), -0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 142.7, 138.5, 134.9, 134.3, 131.4, 128.4, 128.3, 127.5, 127.4, 106.8, 98.1, 76.9, 73.6, 72.9, 70.1, 69.2, 69.1, 36.6, 36.4, 32.3, 29.8, 28.3, 25.4, 22.3, 17.8, 14.2, 8.8, 6.8, 5.0, -5.4, -5.5; R_f 0.37 (15 % EtOAc/hexanes); exact mass calcd for $C_{42}H_{66}Si_2SO_8$+Na: 809.3915; found: 809.3903 (FAB, MNBA, added NaI).

(2*R*, 3*S*, 4*S*, 6*R*)-4-(*tert*-Butyldimethylsiloxy)-6-[(2*R*, 3*S*, 4*S*)-3,4-dihydro-3-methyl-4-(triethylsiloxy)-2H-pyran-2-(oxo)methyl] tetrahydro-6-methoxy-3-methyl-2-(4-benzyloxybutyl)-2H-pyran (α-66). To a solution of 3.0 g (3.81 mmol) of sulfone **65** (1:1 mixture of anomers) in 150 mL of acetonitrile at room temperature was added 1.5 g of $NaHCO_3$ and 1.5 g of Na_2SO_3 followed by 40 mL of a solution of ZnI_2 (51 g; 160 mmol) in MeOH. The mixture was stirred at room temperature for 3 h 30 min, then poured into an Et_2O/H_2O mixture (1.5 L/200 mL), and 20 mL of 1 N HCl were added to dissolve the ZnI_2. The organic solution was washed with 200 mL of 0.1 N HCl and 3 x 200 mL of H_2O. The combined aqueous solutions were extracted with Et_2O (2 x 200 mL), and the combined organic solutions were washed with saturated aqueous $NaHCO_3$, brine and dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography (Gradient 5% to 15% EtOAc in hexanes) to afford 1.18 g of an inseparable mixture of methyl ketal **α-66** and 237 mg of elimination product. The α-sulfone-anomer was found to be inert to these methanolysis conditions. 1.16 g were recovered unchanged and treated with a MeOH solution of $MgBr_2 \cdot Et_2O$ (20 g, 77.4 mmol in 130 mL of MeOH) followed by 1 g of $NaHCO_3$. The mixture was stirred 18 h at 70 °C, cooled to room temperature and poured into a Et_2O/H_2O mixture (1.5 L/200 mL). The organic solution was washed with H_2O (3 x 200 mL), and the combined aqueous solutions were extracted with Et_2O (2 x 100 mL). The combined organic solutions were washed with saturated aqueous $NaHCO_3$ and brine, then dried over $MgSO_4$. The volatiles were removed under reduced pressure, and the residue was purified by flash chromatography (5% EtOAc in hexanes) to afford 614 mg of an inseparable mixture of mixed methyl ketal **α-66** contaminated with 304 mg of **β-66** and elimination product. Combined yield: 1.25 g (48 %) of methyl ketal **α-66**. $[\alpha]^{23}_D$ +59.2 (*c* 2.0, $CHCl_3$); IR (neat) *v* 2935, 2877, 1743, 1648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.26 (m, 5H), 6.49 (d, *J* = 6 Hz, 1H), 4.84 (d, *J* = 3 Hz, 1H), 4.72-4.69 (m, 1H), 4.52 (s, 2H), 4.51-4.24 (m, 1H), 3.78 (q, *J* = 3 Hz, 1H), 3.73 (t, *J* = 4 Hz, 1H), 3.50 (t, *J* = 7 Hz, 2H), 3.12 (s, 3H), 2.64-2.60 (m, 1H), 1.99 (dd, *J* = 15, 4 Hz, 1H), 1.80 (dd, *J* = 15, 2 Hz, 1H), 1.73-1.36 (m, 7H), 1.02 (d, *J* = 7 Hz, 3H), 0.93 (t, *J* = 8 Hz, 9H), 0.89 (d, *J* = 7 Hz, 3H), 0.89 (s, 9H), 0.56 (q, *J* = 8 Hz, 6H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.6, 143.7, 138.5, 128.2, 127.5, 127.4, 101.5, 100.4, 79.7, 77.1, 72.8, 70.1, 67.2, 65.4, 50.0, 38.0, 37.5, 32.1, 30.7,

29.7, 25.6, 22.7, 17.9, 16.7, 10.7, 6.7, 4.9, -4.9, -5.3; R_f 0.35 (10 % EtOAc/hexanes); exact mass calcd for $C_{37}H_{64}Si_2O_7$+Na: 699.4088; found: 699.4075 (FAB, MNBA, added NaI).

(2*R*, 3*S*, 4*S*, 6*R*)-4-(*tert*-Butyldimethylsiloxy)-6-[(*S*)-[(2*R*, 3*S*, 4*S*)-3,4-dihydro-3-methyl-4-(triethylsiloxy)-2H-pyran-2-yl] (hydroxy) methyl] tetrahydro-6-methoxy-3-methyl-2-(4-benzyloxybutyl)-2H-pyran (67). To a -78 °C solution of 0.303 g (0.447 mmol) of ketone **66** in 8 mL of THF was added 1.77 mL (1.77 mmol) of a 1.0 M solution of $KBH(Et)_3$ in THF. The reaction was allowed to warm to -40 °C over 30 min and stirred at this temperature for 1 h. The solution was cooled to -78 °C, and 7 mL of a pH 7 buffer/MeOH (1/6, v/v) solution was added. The resulting clear solution was warmed to 0 °C, and 3 mL of a 30% H_2O_2/MeOH (1/2, v/v) solution was added. The ice bath was removed, and the reaction was stirred for 1 h at room temperature. The solution was diluted with 80 mL of Et_2O and 20 mL of water, the phases were separated (10 mL of brine was added to break the emulsion), and the organic solution was washed with 10 mL of half-saturated aqueous Na_2SO_3 solution. The aqueous solution was extracted with 2 x 20 mL of EtOAc, and the combined organic solutions were washed with brine and dried over $MgSO_4$. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography (9% EtOAc in hexanes or 5% EtOAc in CH_2Cl_2 for the mixed fraction of anomers) to afford 280 mg (90%) of alcohol **67**. ^{1}H NMR analysis of the unpurified product of the reaction showed only one isomer of the C_{38} alcohol (>95:5 diastereoselection). $[\alpha]^{23}_D$ +66.9 (*c* 3.39, $CHCl_3$); IR (neat) *v* 3473, 2953, 2936, 2877, 1653 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.28 (m, 5H), 6.34 (d, *J* = 6 Hz, 1H), 4.65 (dd, *J* = 6, 2 Hz, 1H), 4.51 (s, 2H), 4.15-4.12 (m, 1H), 3.98 (d, *J* = 8 Hz, 1H), 3.94 (d, *J* = 10 Hz, 1H), 3.81-3.80 (m, 2H), 3.49, (t, *J* = 6 Hz, 2H), 3.17 (s, 3H), 2.50 (d, *J* = 5 Hz, 1H), 2.04 (dd, *J* = 15, 4 Hz, 1H), 2.03-1.97 (m, 1H), 1.68-1.35 (m, 8H), 1.04 (d, *J* = 7 Hz, 3H), 0.98 (t, *J* = 8 Hz, 9H), 0.89 (s, 9H), 0.84 (d, *J* = 7 Hz, 3H), 0.64 (q, *J* = 8 Hz, 6H), 0.05 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 138.6, 128.2, 127.5, 127.3, 104.7, 100.5, 76.7, 72.7, 71.1, 70.2, 70.1, 69.2, 66.9, 47.5, 37.9, 37.3, 32.3, 30.0, 29.8, 25.7, 22.6, 17.8, 14.7, 10.0, 6.7, 5.0, -4.7, -5.2; R_f 0.2 (10 % EtOAc/hexanes); exact mass calcd for $C_{37}H_{66}Si_2O_7$+Na: 701.4245; found: 701.4241 (FAB, MNBA, added NaI).

(2*R*, 3*S*, 4*S*, 6*R*)-4-(*tert*-Butyldimethylsiloxy)-6-[(*S*)-[(2*R*, 3*S*, 4*S*)-3,4-dihydro-3-methyl-4-(triethylsiloxy)-2H-pyran-2-yl] (triethylsiloxy) methyl] tetrahydro-6-methoxy-3-methyl-2-(4-benzyloxybutyl)-2H-pyran (68). To a solution of alcohol **67** (980 mg, 1.44 mmol) in 7.2 mL of DMF were added 392 mg (5.76 mmol) of imidazole and 725 μL (4.32 mmol) of chlorotriethylsilane. The reaction was stirred for 5 h at room temperature, and excess chlorotriethylsilane was destroyed with 250 μL of MeOH. The solution was poured into an Et_2O/saturated aqueous $NaHCO_3$ mixture (80 mL/20 mL). The organic solution was separated and washed with 4 x 20 mL of water. The combined aqueous solutions were extracted with 20 mL of Et_2O. The combined organic solutions were washed with saturated aqueous NaCl and dried over $MgSO_4$. The volatiles were removed under reduced pressure and the residue was purified by flash chromatography (4% EtOAc in hexanes) to afford 1.11 g (97%) of silyl ether **68**. $[\alpha]^{23}_D$ +53.1 (*c* 1.87, $CHCl_3$); IR (neat) *v* 2953, 2876, 1655 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.27 (m, 5H), 6.33 (d, *J* = 6 Hz, 1H), 4.59 (dd, *J* = 6, 2 Hz, 1H), 4.52 (s, 2H), 4.07-4.04 (m, 1H), 4.00 (dt, *J* = 9, 1 Hz, 1H), 3.89 (s, 1H), 3.86 (d, *J* = 11 Hz, 1H), 3.77-3.76 (m, 1H), 3.52-3.45 (m, 2H), 3.10 (s, 3H), 2.04 (dd, *J* = 15, 4 Hz, 1H), 1.87-1.78 (m, 1H), 1.70-1.31 (m, 8H), 1.02 (d, *J* = 7 Hz, 3H), 0.99 (t, *J* = 8 Hz, 9H), 0.98 (t, *J* = 8 Hz, 9H), 0.88 (s, 9H), 0.86 (d, *J* = 7 Hz, 3H), 0.72-0.65 (m, 6H), 0.64 (q, *J* = 8 Hz, 6H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 138.6, 128.2, 127.5, 127.4, 104.7, 101.1, 77.9, 72.7, 70.5, 70.5, 70.4, 70.3, 67.0, 46.8, 38.1, 36.7, 32.5, 29.9, 25.7, 22.8, 17.9, 14.6, 10.4, 7.1, 6.8, 5.6, 5.1, -4.6, -5.2; R_f 0.2 (3 % EtOAc/hexanes); Anal. calcd. for $C_{43}H_{80}O_7Si_3$: C, 65.11; H, 10.17; found: C, 64.96; H, 10.10.

(3*S*, 2*R*, 4*R*, 5*R*, 6*R*)-4-Triethylsiloxy-5-methyl-2-(2-methylprop-2-enyl)-6-[(phenylmethoxy)methyl]-tetrahydro-2H-pyran-3-ol (71). To a 0 °C solution of 35.8 mg (0.103 mmol) ((4*S*, 2*R*, 3*R*)-4-triethylsiloxy-3-methyl(3,4-dihydro-2H-pyran-2-yl))(phenylmethoxy)methane[1a] in 1 mL of CH_2Cl_2 was added a solution of dimethyldioxirane in acetone (prepared according to Murray, R. W.; Singh, M. *Org. Synth.* **1997**, *74*, 91-100) via cannula until TLC indicated complete consumption of starting material. The reaction was concentrated under a vigorous stream of nitrogen. The residue was dissolved in 2 mL of CH_2Cl_2, and cooled to -78 °C. Methallyltributyltin (0.118 mL, 0.309 mmol) was added via syringe. A solution of tributyltin triflate (91.2

mg, 0.208 mmol) in 1.5 mL of CH_2Cl_2 was then added rapidly via cannula. After 10 min, the reaction was quenched by addition of 0.500 mL of Et_3N. The mixture was diluted with saturated aqueous $NaHCO_3$ and Et_2O and allowed to warm to room temperature. The aqueous solution was extracted once with EtOAc. The combined organic solutions were washed once with brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (2 x 14 cm silica gel, linear gradient 0-20% EtOAc/hexanes) afforded 39.4 mg (82%) of a clear oil. $[\alpha]^{23}_{589}$ +8.9 (*c* 1.68, CH_2Cl_2); IR (neat) 3940, 2954, 2911, 2875, 1648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 5H), 4.83 (s, 1H), 4.81 (s, 1H), 4.61 (d, *J* = 12.2 Hz, 1H), 4.55 (d, *J* = 12.2 Hz, 1H), 3.66 (dd, *J* = 11.0, 2.3 Hz, 1H), 3.52 (dd, *J* = 11.0, 5.2 Hz, 1H), 3.34 (app dt, *J* = 8.5, 3.5 Hz, 1H), 3.26-3.18 (m, 3H), 2.56 (dd, *J* = 14.5, 3.2 Hz, 1H), 2.28 (dd, *J* = 14.5, 8.4 Hz, 1H), 2.03 (d, *J* = 3.0 Hz), 1.81 (s, 3H), 1.69 (ddq, *J* = 6.6, 3.4, 3.4 Hz, 1H), 0.98 (t, *J* = 8.0 Hz, 9H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.67 (q, *J* = 8.0 Hz, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.6, 138.6, 128.3, 127.6, 127.4, 112.3, 80.9, 80.5, 78.0, 76.2, 73.4, 70.9, 40.7, 39.6, 23.1, 13.3, 7.0, 5.5; exact mass calcd. for $C_{24}H_{40}O_4SiNa$: 443.2594; found: 443.2585 (FAB, *m*-nitrobenzyl alcohol, NaI added).

(3*E*)(2*R*)-2-Triethylsiloxyhexa-3,5-dien-1-ol (73). To a -78 °C solution of diol **72** (151.8 mg, 1.33 mmol) in 32 mL of CH_2Cl_2 were added 2,6-lutidine (0.310 mL, 2.66 mmol) and acetyl chloride (0.100 mL, 1.40 mmol). The reaction was stirred for 1 h, then quenched with pH 7 phosphate buffer, diluted with EtOAc, and warmed to room temperature. The organic solution was separated and washed once with brine. The combined aqueous solutions were extracted once with EtOAc. The combined organic solutions were dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in 32 mL of CH_2Cl_2. Imidazole (453.3 mg, 6.66 mmol) was added, and the resulting solution was cooled to 0 °C. Chlorotriethylsilane (0.335 mL, 2.00 mmol) was added via syringe, and the reaction was stirred for 10 min, then diluted with pH 7 phosphate buffer and Et_2O and warmed to room temperature. The organic solution was separated and washed once with brine. The combined aqueous solutions were extracted once with Et_2O. The combined organic solutions were dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in 15 mL of toluene and cooled to -78 °C. DIBAlH (0.593 mL, 3.33 mmol) was added via syringe, and the reaction was stirred for 10 min, then quenched by addition of EtOAc. The solution was diluted with saturated aqueous sodium/potassium tartrate, allowed to warm to room temperature, and stirred vigorously for 12 h. The aqueous solution was separated and extracted with EtOAc (3 x). The combined organic solutions were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (3 x 12 cm silica gel, 7% ethyl acetate/hexanes) provided 271.5 mg (90%) of a clear oil. $[\alpha]^{23}_{589}$ -12.2 (*c* 0.87, CH_2Cl_2); IR (neat) 3423, 2955, 2913, 2877, 1605 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.32 (ddd, *J* = 16.6, 10.4, 10.4 Hz, 1H), 6.24 (dd, *J* = 15.0, 10.6 Hz, 1H), 5.62 (dd, *J* = 14.8, 6.9 Hz, 1H), 5.21 (d, *J* = 16.3 Hz, 1H), 5.10 (d, *J* = 9.6 Hz, 1H), 4.25 (dd, *J* = 10.9, 6.7 Hz, 1H), 3.53 (ddd, *J* = 11.2, 7.6, 4.1 Hz, 1H), 3.45 (ddd, *J* = 11.3, 6.6, 5.2 Hz, 1H), 2.02 (t, *J* = 7.0 Hz, 1H), 0.96 (t, *J* = 7.9 Hz, 9H), 0.62 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1, 133.1, 132.3, 117.8, 73.6, 66.9, 6.7, 4.9; exact mass calcd. for $C_{12}H_{24}O_2Si(NH_4)$: 246.1889 found: 246.1886 (CI).

Methyl (5*E*)(4*S*)-2-[(dimethylamino)methyl]-4-triethylsiloxyocta-5,7-dienoate (74). To a -10 °C solution of **73** (127.9 mg, 0.56 mmol) in 1.5 mL of CH_2Cl_2 were added pyridine (0.068 mL, 0.84 mmol) and trifluoromethanesulfonic anhydride (0.099 mL, 0.59 mmol). The reaction was stirred for 30 min, then diluted (5 x by volume) with hexanes. The resulting suspension was filtered through Celite, and the volume was reduced to ~0.5 mL by rotary evaporation at 0 °C. The remaining solution was cooled to -78 °C and further concentrated under a stream of nitrogen. In a separate flask, diisopropylamine (0.147 mL, 1.12 mmol) and 2 mL of THF were cooled to 0 °C. A 2.57 M solution of *n*-BuLi in hexanes (0.429 mL, 1.10 mmol) was added via syringe. After 15 min stirring, the reaction was cooled to -78 °C, and methyl-β-dimethylaminopropionate (0.192 mL, 1.12 mmol) was added via syringe. The solution was stirred for 30 min, after which a solution of the triflate in 1.6 mL of THF and 0.6 mL of HMPA was added via cannula. After 30 min stirring, the reaction was quenched by addition of saturated aqueous NH_4Cl, diluted with Et_2O, and warmed to room temperature. The organic solution was separated, washed once with brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (3 x 12 cm silica gel, 45% ethyl acetate/hexanes) provided 152.6 mg (80%) of **74** as a mixture of diastereomers. IR (neat) 2953, 2913, 2877, 2820, 2769, 1740, 1605 cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$) δ 6.29 (ddd, *J* = 16.9, 10.4, 10.4 Hz, 1H [major]), 6.13 (dd, *J* = 15.2, 10.5 Hz, 1H [major]), 5.62 (dd, *J* = 15.2, 6.6 Hz, 1H [major]), 5.18 (dd, *J* = 16.9, 1.5 Hz, 1H [minor]), 5.17 (d, *J* = 16.9 Hz, 1H [major]), 5.06 (d, *J* = 10.0 Hz, 1H [major]), 4.14 (dd, *J* = 11.9, 7.2 Hz, 1H [major]), 3.67 (s, 3H [major]), 3.66 (s, 3H [minor]), 2.80 (dddd, *J* = 10.0, 9.0, 6.4, 3.7 Hz, 1H [major]), 2.66 (dddd, *J* = 9.7, 9.1, 5.5, 4.0 Hz, 1H [minor]), 2.57 (dd, *J* = 11.7, 9.5 Hz, 1H [minor]), 2.56 (dd, *J* = 11.9, 9.0 Hz, 1H [major]), 2.22 (dd, *J* = 15.0, 8.6 Hz, 1H [major]), 1.90 (ddd, *J* = 13.7, 9.2, 5.7, 1H [minor]), 1.80 (ddd, *J* = 13.8, 10.0, 4.5, 1H [major]), 1.65 (ddd, *J* = 13.8, 7.9, 3.7, 1H [major]), 0.93 (t, *J* = 7.9 Hz, 9H), 0.57 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.9, 136.7, 136.4, 136.2, 130.9, 130.6, 117.1, 71.3, 62.4, 62.3, 51.4, 45.7, 45.6, 40.6, 40.4, 38.9, 38.8, 6.8, 4.9; exact mass calcd. for $C_{18}H_{35}O_3NSi$: 341.2386; found: 341.2387 (EI).

Methyl (5*E*)(4*S*)-4-triethylsiloxy-2-methyleneocta-5,7-dienoate (75). To a suspension of **74** (488.3 mg, 1.43 mmol) and Na_2CO_3 (759 mg, 7.16 mmol) in 25 mL of MeOH was added methyl iodide (0.891 mL, 14.32 mmol) via syringe. The reaction was protected from light and stirred at room temperature for 8.5 h, then diluted with pH 7 phosphate buffer and Et_2O. The organic solution was separated and washed once with brine. The combined aqueous solutions were extracted once with Et_2O, and the combined organic solutions were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (3.5 x 12 cm silica gel, linear gradient 1-2% ethyl acetate/hexanes) provided 398 mg (94%) of a clear oil. $[\alpha]^{23}_{589}$ +13.3 (*c* 0.98, CH_2Cl_2); IR (neat) 2953, 2913, 2877, 1722, 1631, 1604 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.30 (ddd, *J* = 16.9, 10.3, 10.3 Hz, 1H), 6.20 (d, 1H, *J* = 1.5 Hz), 6.14 (dd, *J* = 15.2, 10.5 Hz, 1H), 5.66 (dd, *J* = 15.2, 6.6 Hz, 1H), 5.59 (d, 1H, *J* = 0.9 Hz), 5.17 (d, *J* = 16.9 Hz, 1H), 5.06 (d, *J* = 10.1 Hz, 1H), 4.34 (app. q, *J* = 6.5 Hz, 1H), 3.75 (s, 3H), 2.50 (d, *J* = 6.6 Hz, 2H), 0.92 (t, *J* = 7.9 Hz, 9H), 0.56 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 167.6, 136.6, 136.44, 136.39, 130.3, 128.2, 116.9, 71.5, 51.7, 41.3, 6.7, 4.8; exact mass calcd. for $C_{16}H_{28}O_3Si$: 296.1808; found: 296.1804 (EI).

(5*E*)(4*S*)-4-Triethylsiloxy-2-methyleneocta-5,7-dien-1-ol (75a). To a -78 °C solution of ester **75** (378 mg, 1.28 mmol) in 10 mL CH_2Cl_2 was added DIBAlH (0.91 mL, 5.11 mmol) followed by 5 mL CH_2Cl_2. The reaction was stirred for 20 min, then quenched by addition of EtOAc. The solution was diluted with saturated aqueous sodium/potassium tartrate, allowed to warm to room temperature, and stirred vigorously for 12 h. The aqueous solution was separated and extracted with EtOAc (2 x). The combined organic solutions were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (3.5 x 12 cm silica gel, 15% ethyl acetate/hexanes) provided 327.4 mg (95%) of a clear oil. $[\alpha]^{23}_{589}$ +16.2 (*c* 1.25, CH_2Cl_2); IR (neat) 3351, 2955, 2912, 2877, 1654, 1605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.30 (ddd, *J* = 16.9, 10.3, 10.3 Hz, 1H), 6.14 (dd, *J* = 15.2, 10.5 Hz, 1H), 5.68 (dd, *J* = 15.2, 7.1 Hz, 1H), 5.19 (dd, *J* = 16.8, 1.2 Hz, 1H), 5.10-5.07 (m, 2H), 4.88 (s, 1H), 4.31 (dd, *J* = 12.2, 6.2 Hz, 1H), 4.06 (d, *J* = 5.8 Hz, 2H), 2.89 (t, *J* = 6.0 Hz, 1H), 2.36 (d, *J* = 5.7 Hz, 2H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.60 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 145.3, 136.3, 136.0, 130.7, 117.3, 113.9, 73.2, 66.7, 42.6, 6.7, 4.8; Anal. calcd. for $C_{15}H_{28}O_2Si$: C, 67.12; H, 10.52; found: C, 67.10; H, 10.44; exact mass calcd. for $C_{15}H_{28}O_2Si(NH_4)$: 286.2202; found: 286.2214 (CI).

1-((1*E*)-Buta-1,3-dienyl)(1*S*)-5,5-dibutyl-1-triethylsiloxy-3-methylene-5-stannanonane (76a). To a -78 °C solution of **75a** (171.5 mg, 0.64 mmol) in 5 mL of THF was added a 2.57 M solution of *n*-BuLi in hexanes (0.274 mL, 0.70 mmol). The resulting light orange solution was stirred for 20 min, after which methanesulfonyl chloride (0.055 mL, 0.70 mmol) was added to give a colorless solution which was stirred for 40 min at -78 °C. A -78 °C solution of Bu_3SnLi (0.96 mmol, prepared according to Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481-1487) in 2.6 mL THF was then added via cannula. The resulting bright yellow solution was stirred for 25 min, then quenched by addition of water and Et_2O. The mixture was warmed to room temperature, and the organic solution was separated, dried over K_2CO_3, filtered, and concentrated. Reverse phase flash chromatography (2 cm x 12 cm C_{18} silica gel, 10% CH_2Cl_2/MeOH) provided 294 mg (85%) of a clear oil. $[\alpha]^{23}_{589}$ +1.4 (*c* 0.61, CH_2Cl_2); IR (neat) 2956, 2928, 2875, 1626 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.36-6.27 (m, 2H), 5.83 (dd, *J* = 14.4, 6.6 Hz, Sn satellites visible, 1H), 5.17-5.11 (m, 1H), 4.97-4.94 (m, 1H), 4.83-4.79 (m, 1H), 4.74-4.71 (m, 1H), 4.47 (dd, *J* = 13.0, 6.5 Hz, 1H), 2.45 (dd, *J* = 13.4, 6.9 Hz, 1H), 2.29 (dd, *J* = 13.4, 6.2 Hz, 1H), 2.00 (dd, *J* = 20.1, 11.3 Hz, 2H), 1.63-1.53 (m, 6H), 1.40-1.33 (m, 6H), 1.06 (t, *J* = 7.9 Hz, 9H), 1.01-0.90 (m, 15H), 0.67 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (100.6 MHz, C_6D_6) δ 146.5, 137.7, 137.0, 130.4,

116.8, 108.3, 73.0, 48.0, 29.6, 27.8, 20.1, 13.9, 13.9, 9.8, 7.2, 5.5; Anal. calcd. for $C_{27}H_{54}OSiSn$: C, 59.75; H, 10.04; found: C, 59.83; H, 9.98.

(5*E*)(4*S*)-2-(2,2-Dibutyl-2-stannahexyl)octa-1,5,7-trien-4-ol (76a'). To a room temperature solution of **76a** (194 mg, 0.359 mmol) in 8 mL of ethanol were added 2 mL of a 2 N aqueous NaOH solution. After 17 h stirring, the reaction was poured into a 1:1 mixture of water and Et_2O. The mixture was shaken, and the organic solution was separated, washed once with brine, dried over Na_2SO_4, filtered, and concentrated to give 156.6 mg of a clear oil. The unpurified product was used directly in the next reaction, but could be purified by reverse phase flash chromatography (2 cm x 12 cm C_{18} silica gel, 10% CH_2Cl_2/MeOH). $[\alpha]^{23}_{589}$ +20.4 (*c* 1.02, CH_2Cl_2); IR (neat) 3407, 2957, 2926, 2872, 2853, 1626 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 6.39-6.25 (m, 2H), 5.70 (dd, 1H, *J* = 14.5, 5.8 Hz), 5.14-5.08 (m, 1H), 4.98-4.94 (m, 1H), 4.73 (m, 1H), 4.62 (m, 1H), 4.30-4.24 (m, 1H), 2.23-2.15 (m, 2H), 1.84 (dd, *J* = 24.9, 11.5 Hz, 2H), 1.62 (app. dd, *J* = 7.4, 3.1 Hz), 1.59-1.43 (m, 6H), 1.34 (sextet, *J* = 7.3 Hz, 6H), 1.10-0.75 (m, 6H), 0.93 (t, *J* = 7.3 Hz, 9H); ^{13}C NMR (100.6 MHz, C_6D_6) δ 146.7, 137.0, 136.9, 130.6, 116.9, 108.6, 69.9, 47.1, 29.5, 27.7, 19.3, 13.9, 9.8.

1-((1*E*)-Buta-1,3-dienyl)(1*S*)-5,5-dibutyl-1-trimethylsiloxy-3-methylene-5-stannanonane (76c). Alcohol **76a'** (156.6 mg) was combined with *N*,*O*-bis(trimethylsilyl acetamide (0.266 mL, 1.08 mmol). The resulting solution was stirred for 14 h, then concentrated and purified by reverse phase flash chromatography (2 cm x 12 cm C_{18} silica gel, 7% CH_2Cl_2/MeOH) to give 166 mg (93%, 2 steps) of a clear oil. $[\alpha]^{23}_{589}$+3.4 (*c* 0.83, CH_2Cl_2); IR (neat) 2957, 2927, 2873, 1628, 1605 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 6.35-6.25 (m, 2H), 5.79 (dd, 1H, *J* = 14.1, 6.4 Hz), 5.17-5.09 (m, 1H), 4.99-4.92 (m, 1H), 4.82-4.77 (m, 1H), 4.73-4.68 (m, 1H), 4.43 (dd, *J* = 12.8, 6.3 Hz, 1H), 2.40 (dd, *J* = 13.4, 7.3 Hz, 1H), 2.26 (dd, *J* = 13.4, 5.0 Hz, 1H), 1.99 (dd, *J* = 24.9, 11.4 Hz, 2H), 1.67-1.47 (m, 6H), 1.36 (sextet, *J* = 7.3 Hz, 6H), 1.11-0.86 (m, 6H), 0.94 (t, *J* = 7.3 Hz, 9H), 0.18 (s, 9H); ^{13}C NMR (100.6 MHz, C_6D_6) δ 146.6, 137.7, 137.0, 130.3, 116.8, 108.2, 72.9, 47.7, 29.6, 27.8, 20.0, 13.9, 9.8, 0.4; Anal. calcd. for $C_{24}H_{48}OSiSn$: C, 57.57; H, 9.67; found: C, 57.69; H, 9.68.

2-((5*E*)(4*S*)-4-Trimethylsiloxy-2-methyleneocta-5,7-dienyl)-6-((1*S*){(4*S*, 2*R*, 5*R*)-2-methoxy-4-*tert*-butyldimethylsiloxy-5-methyl-6-[4-(phenylmethoxy)butyl]tetrahydro-2H-pyran-2-yl}triethylsiloxymethyl)(3*S*, 2*R*, 4*R*, 5*R*)-4-triethylsiloxy-5-methyltetrahydro-2H-pyran-3-ol (79). To a 0 °C solution of dihydropyran **68** (3.6 mg, 0.0045 mmol) in 0.500 mL CH_2Cl_2 was added dimethyldioxirane/acetone solution (Murray, R. W.; Singh, M. *Org. Synth.* **1997**, *74*, 91-100) until TLC indicated complete consumption of starting material. The reaction was concentrated under a steady stream of nitrogen. The residue was combined with a solution of allylstannane **76c** (37.5 mg, 0.075 mmol) in 0.250 mL of CH_2Cl_2, and the resulting solution was cooled to -78 °C. A solution of tributyltin triflate in 0.250 mL of CH_2Cl_2 was added rapidly via cannula. After 20 min stirring, the reaction was quenched by addition of 0.250 mL triethylamine, diluted with saturated aqueous $NaHCO_3$ and Et_2O, and warmed to room temperature. The organic solution was separated, washed with brine (1 x), dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (1.5 x 10 cm, linear gradient 2-4% ethyl acetate/hexanes) provided 3.7 mg (80%) of a clear oil (34.2 mg, 0.069 mmol of **76c** was recovered). $[\alpha]^{23}_{589}$ +27.2 (*c* 0.19, CH_2Cl_2); IR (neat) 3467, 2959, 2933, 2876, 1605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 5H), 6.29 (ddd, *J* = 16.8, 10.3, 10.3 Hz, 1H), 6.13 (dd, *J* = 14.9, 10.6 Hz, 1H), 5.66 (dd, *J* = 15.1, 6.1 Hz, 1H), 5.15 (d, *J* = 16.7 Hz, 1H), 5.03 (d, *J* = 10.0 Hz, 1H), 4.91 (s, 1H), 4.84 (s, 1H), 4.50 (s, 2H), 4.24 (dd, *J* = 12.8, 6.5 Hz, 1H), 4.02-4.00 (m, 1H), 3.71 (s, 1H), 3.70 (m, 1H), 3.47 (dt, *J* = 9.1, 3.3 Hz, 1H), 3.20 (app. t, *J* = 9.1 Hz, 1H), 3.16 (d, *J* = 10.6 Hz, 1H), 3.09 (dt, *J* = 8.8, 2.9 Hz, 1H), 3.05 (s, 3H), 2.52 (dd, *J* = 14.3, 2.9 Hz, 1H), 2.28 (d, *J* = 6.5 Hz, 2H), 2.15 (dd, *J* = 14.0, 7.5 Hz, 1H), 2.01 (dd, *J* = 15.4, 3.8 Hz, 1H), 1.96 (d, *J* = 3.2 Hz, 1H), 1.68-1.25 (m, 9H), 0.99 (t, *J* = 7.9 Hz, 9H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.93 (d, *J* = 6.5 Hz, 3H), 0.87 (s, 9H), 0.80 (d, *J* = 7.2 Hz, 3H), 0.67 (q, *J* = 7.9 Hz, 6H), 0.60 (dq, *J* = 8.0, 1.9 Hz, 6H), 0.08 (s, 9H), 0.01 (s, 3H), -0.01 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 143.6, 138.8, 137.2, 136.7, 129.8, 128.4, 127.6, 127.5, 116.5, 115.0, 101.2, 81.0, 78.3, 78.2, 75.8, 72.9, 72.1, 70.8, 70.6, 70.5, 66.9, 46.8, 45.7, 39.4, 39.3, 38.3, 32.6, 30.0, 29.9, 25.9, 22.9, 18.1, 13.9, 10.4, 7.2, 7.1, 5.7, 0.3, -4.3, -4.9; Mass calcd. for $C_{55}H_{102}O_9Si_4Na$: 1041; found: 1041 (FAB, *m*-nitrobenzyl alcohol, NaI added).

2-((5*E*)(4*S*)-4-Hydroxy-2-methyleneocta-5,7-dienyl)-6-((1*S*){(4*S* , 2*R* , 5*R*)-4-hydroxy-2-methoxy-5-methyl-6-[4-(phenylmethoxy)butyl]tetrahydro-2H-pyran-2-yl}hydroxymethyl)(3*S*, 2*R* , 4*R* , 5*R*) - 5-

methyltetrahydro-2H-pyran-3,4-diol (79a). To a 0 °C solution of **79** in 0.500 mL acetonitrile was added 0.100 mL of a freshly prepared HF/water/acetonitrile solution (0.5 mL of 48% aqueous HF, 0.9 mL of water, and 8.6 mL of acetonitrile). The resulting solution was stirred at 0 °C for 1 h, after which an additional 0.100 mL HF/water/acetonitrile solution was added. After 13 h stirring, an additional 0.050 mL HF/water/acetonitrile solution was added, and the reaction was stirred for 3 h, then diluted with saturated aqueous $NaHCO_3$ and CH_2Cl_2. The aqueous solution was separated and extracted with CH_2Cl_2 (2 x). The combined organic solutions were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (1 cm x 10 cm silica gel, 5% MeOH/CH_2Cl_2) provided 2.6 mg (76%) of a clear oil. $[\alpha]^{23}_{365}$ +44.2 (*c* 0.13, CH_2Cl_2); IR (neat) 3403, 2935, 1642, 1604 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6) δ 7.35-7.25 (m, 5H), 6.29 (ddd, *J* = 16.9, 10.3, 10.3 Hz, 1H), 6.14 (dd, *J* = 15.0, 10.7 Hz, 1H), 5.69 (dd, *J* = 15.2, 5.9 Hz, 1H), 5.25 (s, 1H), 5.14 (dd, *J* = 17.0, 1.5 Hz, 1H), 5.00 (app. d, *J* = 10.8 Hz, 1H), 4.89 (d, *J* = 5.2 Hz, 1H), 4.81 (d, *J* = 4.9 Hz, 1H), 4.77 (d-like, *J* = 5.1 Hz, 2H), 4.73 (d, *J* = 5.4 Hz, 1H), 4.52 (d, *J* = 8.1 Hz, 1H), 4.44 (d, *J* = 7.9 Hz, 1H), 4.43 (s, 2H), 4.13 (m, 2H), 3.60 (dd-like, *J* = 6.5, 3.2 Hz, 1H), 3.45 (d, *J* = 10.6 Hz, 1H), 3.42 (t, *J* = 6.5 Hz, 2H), 3.21 (t-like, *J* = 9.7 Hz, 1H), 3.16 (d, *J* = 8.2 Hz), 2.91 (dt, *J* = 9.3, 5.5 Hz, 1H), 2.82 (dt, *J* = 9.3, 5.5 Hz, 1H), 2.63 (br d, *J* = 15.0 Hz), 2.22 (dd, *J* = 14.0, 6.7 Hz, 1H), 2.06 (dd, *J* = 13.3, 6.5 Hz, 1H), 1.94 (dd, *J* = 15.0, 10.3 Hz, 1H), 1.81 (dd, *J* = 14.3, 2.9 Hz, 1H), 1.68 (m), 1.57 (m, 1H), 1.54 (m, 2H), 1.49 (m, 1H), 1.38 (m, 2H), 1.25 (m, 2H), 0.81 (d, *J* = 6.5 Hz, 3H), 0.72 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, C_6D_6) δ 143.4, 139.3, 136.9, 136.7, 131.0, 117.4, 115.6, 99.6, 80.9, 78.5, 77.4, 75.9, 73.0, 72.9, 71.2, 71.0, 70.3, 67.2, 44.1, 39.6, 38.1, 37.9, 33.5, 32.6, 30.2, 23.5, 12.2, 10.8; exact mass calcd. for $C_{33}H_{50}O_9Na$: 613.3353; found: 613.3347 (FAB, *m*-nitrobenzyl alcohol, NaI added).

4-{6-[(1*S*)((4*S*,3*R*)-4-Triethylsiloxy-3-methyl(3,4-dihydro-2H-pyran-2-yl))triethylsiloxymethyl](4*S*,3*R*, 6*R*)-4-*tert*-butyldimethylsiloxy-6-methoxy-3-methyltetrahydro-2H-pyran-2-yl}butan-1-ol (68a). To a -78 °C solution of **68** (390.7 mg, 0.493 mmol) in 2.7 mL of THF was added a THF solution of lithium di-*tert*-butyl biphenylide via cannula until a deep green color persisted. The reaction was diluted with saturated aqueous NH_4Cl and Et_2O and warmed to room temperature. The organic solution was separated, washed with saturated aqueous $NaHCO_3$ (1 x) and brine (1 x), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (3 x 12 cm silica gel, linear gradient, 0-10% ethyl acetate/hexanes) provided 333.2 mg (96%) of a clear oil. $[\alpha]^{23}_{589}$ +57.6 (*c* 0.73, CH_2Cl_2); IR (neat) 3338, 2954, 2877, 1656 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 6.33 (d, *J* = 6.1 Hz, 1H), 4.63 (dd, *J* = 6.2, 1.3 Hz, 1H), 4.27-4.25 (m, 1H), 4.05 (d, *J* = 11.3 Hz, 1H), 4.05 (s, 1H), 3.91 (app. d, *J* = 8.6 Hz), 3.88-3.87 (m, 1H), 3.38 (t, *J* = 6.4 Hz, 2HOH), 3.13 (s, 3H), 2.44 (dd, *J* = 15.2, 3.7 Hz, 1H), 2.14 (app. d quintets, *J* = 13.0, 6.7 Hz, 1H), 1.97 (br d, *J* = 15.2 Hz, 1H), 1.71-1.34 (m), 1.45 (quintet, *J* = 6.7 Hz, 2H), 1.40-1.21 (m, 2H), 1.09 (d, *J* = 6.4 Hz, 3H), 1.09 (t, 9H, *J* = 7.9 Hz), 1.06 (s, 9H), 1.02 (t, *J* = 7.9 Hz, 9H), 0.95 (d, *J* = 7.2 Hz, 3H), 0.79 (dq, *J* = 7.9, 4.9 Hz, 6H), 0.62 (q, *J* = 7.9 Hz, 6H), 0.17 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100.6 MHz, C_6D_6) δ 144.0, 105.2, 101.7, 78.2, 71.3, 71.0, 70.6, 67.5, 62.6, 47.0, 38.8, 37.3, 33.3, 33.1, 30.7, 26.1, 22.9, 18.3, 15.2, 10.7, 7.4, 7.2, 6.1, 5.6, -4.3, -4.8; exact mass calcd. for $C_{36}H_{74}O_7Si_3Na$: 725.4640; found: 725.4639 (FAB, *m*-nitrobenzyl alcohol, NaI added).

(2*R*,3*S*,4*S*,6*R*)-4-(*tert*-Butyldimethylsiloxy)-6-[(*S*)-[(2*R*,3*S*,4*S*)-3,4-dihydro-3-methyl-4-(triethylsiloxy)-2H-pyran-2-yl](triethylsiloxy)methyl]tetrahydro-6-methoxy-3-methyl-2-(4-methanesulfonyloxybutyl)-2H-pyran (80). To a 0 °C solution of **68a** (287.6 mg, 0.410 mmol) in 7 mL of CH_2Cl_2 were added triethylamine (0.234 mL, 1.68 mmol) and methanesulfonyl chloride (0.048 mL, 0.62 mmol). After 30 min stirring, the reaction was diluted with saturated aqueous $NaHCO_3$ and Et_2O and warmed to room temperature. The organic solution was separated, washed with saturated aqueous $NaHCO_3$ (1 x) and brine (1 x), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (3 x 12 cm silica gel, 30% ethyl acetate/hexanes) provided 316.5 mg (99%) of a clear oil. $[\alpha]^{23}_{589}$ +52.7 (*c* 1.16, CH_2Cl_2); IR (neat) 2954, 2877, 1656 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 6.32 (dd, *J* = 6.2, 1.1 Hz, 1H), 4.64 (dd, *J* = 6.2, 1.6 Hz, 1H), 4.22-4.18 (m, 1H), 4.05 (s, 1H), 4.04 (d, *J* = 11.3 Hz, 1H), 3.92 (dt, *J* = 8.5, 1.5 Hz, 1H), 3.87-3.84 (m, 1H), 3.84 (t, *J* = 6.4 Hz), 3.14 (s, 3H), 2.42 (dd, *J* = 15.2, 3.8 Hz, 1H), 2.17-2.09 (m, 1H), 2.16 (s, 3H), 1.97 (dd, *J* = 14.9, 1.8 Hz), 1.57-1.41 (m, 5H), 1.25-1.14 (m, 2H), 1.11-1.06 (m, 12H), 1.06 (s, 9H), 1.02 (t, *J* = 7.9 Hz, 9H), 0.91 (d, *J* = 7.2 Hz, 3H), 0.78 (dq, *J* = 7.9, 3.2 Hz, 6H), 0.62 (q, *J* = 7.9 Hz, 6H), 0.17 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100.6

MHz, C_6D_6) δ 143.9, 105.3, 101.8, 78.1, 71.2, 71.0, 70.5, 69.2, 67.2, 47.0, 38.8, 37.2, 36.7, 32.6, 30.7, 29.6, 26.1, 22.5, 18.3, 15.2, 10.6, 7.4, 7.2, 6.1, 5.6, -4.3, -4.8; exact mass calcd. for $C_{37}H_{76}O_9SSi_3Na$: 803.4416; found: 803.4430 (FAB, *m*-nitrobenzyl alcohol, NaI added).

(2*R*,3*S*,4*S*,6*R*)-4-(*tert*-Butyldimethylsiloxy)-6-[(*S*)-[(2*R*,3*S*,4*S*)-3,4-dihydro-3-methyl-4-(triethylsiloxy)-2H-pyran-2-yl](triethylsiloxy)methyl]tetrahydro-6-methoxy-3-methyl-2-(4-iodobutyl)-2H-pyran (80a). To a solution of mesylate **80** (163.2 mg, 0.209 mmol) in 6 mL of acetone were added $NaHCO_3$ (42 mg), Na_2SO_3 (29 mg) and NaI (156.8 mg, 1.05 mmol). The mixture was heated at reflux for 14 h, then cooled to room temperature and poured into a 1:1 mixture of water and Et_2O. The organic solution was separated, washed with saturated aqueous $Na_2S_2O_3$ (1 x), saturated aqueous $NaHCO_3$ (1 x) and brine (1 x), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (2 x 12 cm silica gel, 10% ethyl acetate/hexanes) provided 158.9 mg (94%) of a clear oil. $[\alpha]^{23}_{589}$ +46.4 (*c* 1.14, CH_2Cl_2); IR (neat) 2935, 2876, 1656 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 6.32 (dd, *J* = 6.2, 1.3 Hz, 1H), 4.64 (dd, *J* = 6.2, 1.6 Hz, 1H), 4.21-4.18 (m, 1H), 4.04 (s, 1H), 4.04 (d, *J* = 11.4 Hz, 1H), 3.92 (dt, *J* = 8.6, 1.6 Hz, 1H), 3.86 (br dd, *J* = 5.8, 2.8 Hz, 1H), 3.13 (s, 3H), 2.79-2.72 (m, 2H), 2.42 (dd, *J* = 15.2, 3.8 Hz, 1H), 2.19-2.09 (m, 1H), 1.97 (dd, *J* = 15.2, 1.5 Hz, 1H), 1.58-1.45 (m, 5H), 1.23-1.12 (m, 2H), 1.10-1.06 (m, 12H), 1.06 (s, 9H), 1.02 (t, *J* = 7.9 Hz, 9H), 0.91 (d, *J* = 7.2 Hz, 3H), 0.78 (dq, *J* = 7.9, 3.7, 6H), 0.62 (q, *J* = 7.9 Hz, 6H), 0.17 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100.6 MHz, C_6D_6) δ 143.9, 105.2, 101.8, 78.1, 71.2, 70.9, 70.5, 67.2, 47.0, 38.8, 37.2, 33.9, 32.0, 30.7, 27.5, 26.1, 18.3, 15.2, 10.6, 7.5, 7.2, 6.3, 6.1, 5.6, -4.3, -4.8; exact mass calcd. for $C_{36}H_{73}O_6Si_3INa$: 835.3657; found: 835.3653 (FAB, *m*-nitrobenzyl alcohol, NaI added).

[4-[2*R*,3*S*,4*S*,6*R*)-4-(*tert*-Butyldimethylsiloxy)-6-[(*S*)-[2*R*,3*S*,4*S*)-3,4-dihydro-3-methyl-4-(triethylsiloxy)-2H-pyran-2-yl]-(triethylsiloxy)methyl]tetrahydro-6-methoxy-3-methyl-2H-pyran-2-yl]butyl]triphenylphosphoniumiodide (81). A solution of iodide **80a** (158.9 mg, 0.196 mmol) and triphenylphosphine (515 mg, 1.96 mmol) in 7 mL CH_3CN was heated at reflux for 44 h, then cooled to room temperature and concentrated. Flash chromatography (2 x 12 cm silica gel, 30% CH_3CN/ethyl acetate, then 100% CH_3CN) provided 197.5 mg (94%) of a pale yellow solid. Trace amounts of water were removed by lyophilizing the solid from benzene (4 x) to give a pale yellow powder (96% mass recovery). $[\alpha]^{23}_{365}$ +104.6 (*c* 0.50, MeOH); IR (neat) 2954, 2877, 1656 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.91-7.86 (m, 6H), 7.33-7.24 (m, 9H), 6.34 (d, *J* = 6.5 Hz, 1H), 4.64 (dd, *J* = 6.2, 1.4 Hz, 1H), 4.26 (m, 1H), 4.20 (s, 1H), 4.17 (m, 2H), 4.12 (d, *J* = 11.4 Hz, 1H), 3.94 (br d, *J* = 8.6 Hz, 1H), 3.90 (m, 1H), 3.30 (s, 3H), 2.47 (dd, *J* = 15.2, 3.7 Hz, 1H), 2.22-2.12 (m, 1H), 2.09 (m, 1H), 2.01 (d, *J* = 15.2 Hz, 1H), 1.86 (m, 1H), 1.64-1.52 (m, 4H), 1.32 (m, 1H), 1.21 (t, *J* = 6.5 Hz, 3H), 1.10 (t, *J* = 7.9 Hz, 9H), 1.06 (s, 9H), 1.02 (t, *J* = 7.9 Hz, 9H), 1.00 (d, *J* = 7.1 Hz, 3H), 0.87-0.80 (m, 6H), 0.62 (q, *J* = 7.9 Hz, 6H), 0.17 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100.6 MHz, C_6D_6) δ 144.0, 134.7, 134.5, 134.4, 130.4, 130.3, 119.4, 118.6, 105.2, 101.8, 78.3, 71.5, 71.2, 70.7, 67.1, 48.1, 39.0, 37.3, 33.2, 30.8, 26.3, 18.4, 15.4, 11.0, 7.6, 7.2, 6.2, 5.6, -4.3, -4.5; exact mass calcd. for $C_{54}H_{88}O_6Si_3P^+$: 947.5626; found: 947.5613 (FAB, *m*-nitrobenzyl alcohol, NaI added).

(3*S*,4*S*,5*R*)-1-[(2*S*,4*S*,6*R*,8*R*,10*S*)-10-(*tert*-Butyldimethylsiloxy)-8-[(1*Z*)-5-[(2*R*,3*S*,4*S*,6*R*)-4-(*tert*-butyldimethylsiloxy)-6-[(*S*)-[(2*R*,3*S*,4*S*)-3,4-dihydro-3-methyl-4-triethylsiloxy)-2H-pyran-2-yl](triethylsiloxy)-methyl]tetrahydro-6-methoxy-3-methyl-2H-pyran-2-yl]-1-pentenyl]-4-methoxy-1,7-dioxaspiro[5.5]undec-2-yl]-4-hydroxy-6-[[2*S*,4*S*,6*R*,8*S*,10*S*)-10-hydroxy-8-(2-methoxyacetyloxyethyl)-4-methyl-4-(triethylsiloxy)-1,7-dioxaspiro[5.5]undec-2-yl]methyl]-3,5-dimethyl-6-hepten-2-one4,6^{10}-diacetate (82). To a -78 °C solution of **81** (54.2 mg, 0.05 mmol) in 0.44 mL of THF was added 0.153 mL (0.050 mmol) of a 0.33 M solution of lithium hexamethyldisilazide (prepared from 0.211 mL of hexamethyldisilazane and 0.710 mL of a 1.41 M solution of *n*-BuLi in hexanes) in THF. The resulting dark orange solution was stirred at -78 °C for 1h. A solution of aldehyde **42** (41 mg, 0.040 mmol) in 0.150 mL of THF was then added dropwise via cannula to give a yellow-orange solution. The reaction was stirred 5 min, then warmed to -24 °C and stirred 40 min to give a red solution. The reaction was quenched by addition of saturated aqueous NH_4Cl and saturated aqueous $Na_2S_2O_3$, diluted with Et_2O, and warmed to room temperature. The organic solution was separated, washed with saturated aqueous $NaHCO_3$ (1 x) and brine (1 x), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (2 x 12 cm silica gel, linear gradient, 10-30% acetone/hexanes) provided

4.6 mg (11%) of recovered **42** and 43.2 mg (64%) of a clear oil. $[\alpha]^{23}_{589}$ +4.4 (*c* 0.77, CH_2Cl_2); IR (CH_2Cl_2) 2957, 2935, 2876, 1737, 1728, 1606 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.33 (dd, *J* = 5.9, 0.9 Hz, 1H), 5.75 (dd, *J* = 10.5, 8.3 Hz, 1H), 5.62-5.59 (m, 1H), 5.60 (dd, 9.7, 2.5, 1H), 5.51 (dt, *J* = 10.7, 7.2, 1H), 5.17 (s, 1H), 4.99 (br s, 1H), 4.95 (s, 1H), 4.64 (dd, *J* = 6.2, 1.4 Hz, 1H), 4.38-4.32 (m, 2H), 4.27-4.26 (m, 1H), 4.19-4.10 (m, 3H), 4.06 (d, *J* = 11.3 Hz, 1H), 4.06 (s, 1H), 4.03-3.92 (m, 2H), 3.88 (m, 1H), 3.83 (dd, *J* = 20.8, 16.3 Hz, 2H), 3.27-3.22 (m, 1H), 3.23 (s, 3H), 3.14 (s, 3H), 3.12-3.05 (m, 1H), 3.04 (s, 3H), 2.89 (dq, *J* = 9.8, 7.0 Hz, 1H), 2.74 (dd, *J* = 18.4, 10.0, 1H), 2.54-2.49 (m, 2H), 2.45 (dd, *J* = 15.2, 3.8 Hz, 1H), 2.37 (m, 4H), 2.18-2.08 (m, 3H), 1.98 (dd, 15.3, 1.4, 1H), 1.96-1.91 (m, 1H), 1.92 (s, 3H), 1.88-1.55 (m, 11H), 1.78 (s, 3H), 1.49 (br d, 14.2), 1.46-1.37 (m, 5H), 1.25 (dd, *J* = 14.9, 4.3, 1H), 1.21-0.97 (m, 40H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.06 (s, 9H), 1.02 (s, 9H), 0.88-0.75 (m, 6H), 0.64-0.57 (m, 12H), 0.17 (s, 3H), 0.09 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.6, 170.8, 170.0, 169.1, 147.0, 143.9, 131.0, 130.8, 128.7, 113.4, 104.7, 101.2, 98.1, 96.8, 77.9, 74.2, 73.7, 70.6, 70.53, 70.49, 70.41, 69.7, 67.2, 67.0, 66.1, 64.6, 64.4, 62.5, 61.8, 61.2, 59.2, 55.4, 49.9, 47.7, 47.6, 46.8, 45.1, 43.6, 41.6, 38.9, 38.6, 38.2, 37.0, 36.7, 34.9, 34.2, 34.0, 32.4, 32.0, 31.8, 29.9, 29.6, 29.3, 28.1, 26.2, 25.8, 25.7, 21.4, 20.6, 17.9, 14.7, 13.4, 12.0, 10.4, 7.11, 7.09, 6.8, 5.6, 5.2, -4.6, -5.0, -5.1; Mass calcd. for $C_{88}H_{162}O_{21}Si_5Na$: 1718; found: 1718 (FAB, *m*-nitrobenzyl alcohol, NaI added).

(3*S*,4*S*,5*R*)-1-[(2*S*,4*S*,6*R*,8*R*,10*S*)-10-(*tert*-Butyldimethylsiloxy)-8-[(1*Z*)-5-[(2*R*,3*S*,4*S*,6*R*)-4-(*tert*-butyldimethylsiloxy)-6-[(*S*)-[(2*R*,3*S*,4*S*)-3,4-dihydro-3-methyl-4-triethylsiloxy)-2H-pyran-2-yl](triethylsiloxy)-methyl]tetrahydro-6-methoxy-3-methyl-2H-pyran-2-yl]-1-pentenyl]-4-methoxy-1,7-dioxaspiro[5.5]undec-2-yl]-4-hydroxy-6-[[2*S*,4*S*,6*R*,8*S*,10*S*)-10-hydroxy-8-(2-hydroxyethyl)-4-methyl-4-(triethylsiloxy)-1,7-dioxaspiro[5.5]undec-2-yl]methyl]-3,5-dimethyl-6-hepten-2-one4,6^{10}-diacetate (82a). To a solution of methoxyacetate **82** (15.2 mg, 0.009 mmol) in 3.7 mL of MeOH was added 3.7 mL of a saturated solution of ammonia in MeOH (prepared by bubbling ammonia through 10 mL of 0 °C MeOH for 15 min). The reaction was stirred at room temperature for 3.5 h, then concentrated and purified by flash chromatography (1 x 12 cm silica gel, linear gradient 20-40% ethyl acetate/hexanes) to give 11.8 mg (82%) of a clear oil. $[\alpha]^{23}_{365}$ +30.9 (*c* 0.14, CH_2Cl_2); IR (CH_2Cl_2) 3502, 2956, 2877, 1712, 1651 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.33 (dd, *J* = 6.0, 0.9 Hz, 1H), 5.74 (dd, *J* = 10.8, 8.2 Hz, 1H), 5.62-5.58 (m, 1H), 5.59 (dd, 9.7, 2.7, 1H), 5.51 (dt, *J* = 10.8, 7.3, 1H), 5.17 (s, 1H), 5.01 (br s, 1H), 4.93 (s, 1H), 4.64 (dd, *J* = 6.2, 1.4 Hz, 1H), 4.27-4.15 (m, 4H), 4.06 (d, *J* = 11.4 Hz, 1H), 4.06 (s, 1H), 3.94-3.91 (m, 2H), 3.89 (m, 1H), 3.84-3.78 (m, 1H), 3.68 (m, 1H), 3.26-3.21 (m, 1H), 3.15 (s, 3H), 3.09 (dd, *J* = 18.4, 2.8 Hz, 1H), 3.04 (s, 3H), 2.89 (dq, *J* = 9.7, 7.0 Hz, 1H), 2.77 (dd, *J* = 18.4, 9.9, 1H), 2.58 (m, 1H), 2.49 (dd, *J* = 14.8, 8.6 Hz), 2.45 (dd, *J* = 15.1, 3.8 Hz, 1H), 2.39-2.28 (m, 4H), 2.18-2.08 (m, 3H), 1.99 (br d, *J* = 15.4 Hz, 1H), 1.94-1.91 (m, 1H), 1.92 (s, 3H), 1.78 (s, 3H), 1.76-1.71 (m, 3H), 1.67-1.36 (m), 1.29 (dd, *J* = 11.9, 3.4 Hz, 1H), 1.25 (m, 1H), 1.25 (dd, *J* = 14.9, 4.3, 1H), 1.15-1.11 (m, 6H), 1.12 (t, *J* = 8.0 Hz, 9H), 1.07 (s, 9H), 1.05-0.97 (m, 9H), 1.03 (s, 9H), 1.02 (t, *J* = 8.0 Hz, 9H), 0.85-0.77 (m, 6H), 0.70 (q, *J* = 7.9 Hz, 6H), 0.62 (q, *J* = 7.9 Hz, 6H), 0.17 (s, 3H), 0.09 (m, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 209.4, 170.1, 168.9, 147.9, 144.0, 132.2, 130.9, 127.5, 113.4, 105.2, 101.8, 98.3, 96.9, 78.2, 74.8, 73.8, 71.3, 71.03, 71.00, 70.6, 67.7, 67.2, 66.6, 65.2, 64.4, 64.3, 62.3, 60.4, 55.1, 51.1, 48.3, 47.9, 47.0, 45.3, 44.5, 42.7, 39.3, 38.9, 38.8, 38.05, 37.97, 37.3, 35.0, 34.4, 33.0, 32.3, 30.8, 28.7, 26.9, 26.2, 26.1, 21.3, 20.5, 18.4, 15.2, 13.8, 12.3, 10.8, 7.6, 7.5, 7.2, 7.1, 6.2, 5.6, -4.3, -4.8, -4.9; Mass calcd. for $C_{85}H_{158}O_{19}Si_5Na$: 1646; found: 1646 (FAB, *m*-nitrobenzyl alcohol, NaI added).

(3*S*,4*S*,5*R*)-1-[(2*S*,4*S*,6*R*,8*R*,10*S*)-10-(*tert*-Butyldimethylsiloxy)-8-[(1*Z*)-5-[(2*R*,3*S*,4*S*,6*R*)-4-(*tert*-butyldimethylsiloxy)-6-[(*S*)-[(2*R*,3*S*,4*S*)-3,4-dihydro-3-methyl-4-triethylsiloxy)-2H-pyran-2-yl](triethylsiloxy)-methyl]tetrahydro-6-methoxy-3-methyl-2H-pyran-2-yl]-1-pentenyl]-4-methoxy-1,7-dioxaspiro[5.5]undec-2-yl]-4-hydroxy-6-[[2*S*,4*S*,6*R*,8*S*,10*S*)-10-hydroxy-8-(formylmethyl)-4-methyl-4-(triethylsiloxy)-1,7-dioxaspiro[5.5]undec-2-yl]methyl]-3,5-dimethyl-6-hepten-2-one4,6^{10}-diacetate (83). To a room temperature solution of alcohol **82a** (11.8 mg, 0.0073 mmol) in 0.200 mL of CH_2Cl_2 was added, via cannula, a suspension of Dess-Martin periodinane (11 mg, 0.026 mmol) and pyridine (0.087 mL of a 1 M solution in CH_2Cl_2, 0.087 mmol) in 0.100 mL of CH_2Cl_2. The reaction was stirred for 1 h, then diluted with saturated aqueous $NaHCO_3$ (0.25 mL), saturated aqueous $Na_2S_2O_3$ (0.50 mL), and Et_2O (1 mL). The mixture was stirred for 25 min and poured into 20 mL 1:1 Et_2O:EtOAc. The organic solution was separated, washed with

saturated aqueous $Na_2S_2O_3$ (1 x), saturated aqueous $NaHCO_3$ (1 x) and brine (1 x), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (1 x 12 cm silica gel, 30% ethyl acetate/hexanes) provided 10.8 mg (92%) of a clear oil. $[\alpha]^{23}_{365}$ +15.3 (*c* 0.26, CH_2Cl_2); IR (CH_2Cl_2) 2956, 2930, 2877, 1727, 1651, 1606 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 9.70 (m, 1H), 6.33 (d, *J* = 6.0 Hz, 1H), 5.77-5.73 (m, 1H), 5.63-5.60 (m, 1H), 5.61 (dd, *J* = 9.9, 2.4 Hz, 1H), 5.51 (dt, *J* = 10.8, 7.4 Hz, 1H), 5.17 (s, 1H), 4.97 (br s, 1H), 4.93 (s, 1H), 4.64 (dd, *J* = 6.0, 1.3 Hz, 1H), 4.43 (m, 1H), 4.28-4.26 (m, 1H), 4.18 (m, 2H), 4.07 (d, *J* = 11.4 Hz, 1H), 4.06 (s, 1H), 3.95-3.92 (m, 2H), 3.89 (m, 1H), 3.27-3.21 (m, 1H), 3.15 (s, 3H), 3.09 (dd, *J* = 18.4, 2.8 Hz, 1H), 3.04 (s, 3H), 2.91 (dq, *J* = 10.0, 6.9 Hz, 1H), 2.76 (dd, *J* = 18.4, 9.9, 1H), 2.62 (m, 1H), 2.48-2.42 (m, 2H), 2.40-2.27 (m, 5H), 2.20-2.09 (m, 3H), 2.09-1.97 (m, 1H), 1.97 (m, 1H), 1.95-1.93 (m, 1H), 1.93 (s, 3H), 1.91 (br d, *J* = 8.4 Hz, 1H), 1.78 (s, 3H), 1.78-1.72 (m), 1.66 (m), 1.61-1.55 (m), 1.46-1.31 (m, 6H), 1.21 (dd, *J* = 15.3, 4.3, 1H), 1.18-1.16 (m, 6H), 1.12 (t, *J* = 7.9 Hz, 9H), 1.07 (s, 9H), 1.03 (s, 9H), 1.02 (t, *J* = 8.0 Hz, 9H), 1.01-0.94 (m, 9H), 0.86-0.77 (m, 6H), 0.62 (q, *J* = 7.9 Hz, 6H), 0.58 (q, *J* = 7.9 Hz, 6H), 0.17 (s, 3H), 0.10 (s, 3H), 0.09 (m, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 209.6, 199.7, 170.1, 168.7, 147.9, 144.0, 132.2, 130.9, 113.5, 105.2, 101.8, 98.3, 97.0, 78.2, 74.6, 73.8, 71.3, 71.0, 70.7, 70.6, 67.7, 66.8, 66.6, 65.3, 64.5, 62.3, 60.2, 55.1, 51.1, 49.2, 47.9, 47.8, 47.0, 45.5, 44.5, 42.8, 39.3, 38.9, 38.6, 38.4, 38.0, 37.3, 35.0, 34.4, 33.0, 32.1, 30.8, 30.1, 28.7, 26.9, 26.2, 26.1, 21.3, 20.5, 18.4, 15.2, 13.7, 12.0, 10.8, 7.53, 7.49, 7.22, 7.17, 6.2, 5.6, -4.3, -4.8, -4.9; Mass calcd. for $C_{85}H_{156}O_{19}Si_5Na$: 1644; found: 1644 (FAB, *m*-nitrobenzyl alcohol, NaI added).

(1*S*,3*S*,9*S*,14*S*,17*S*,18*S*,27*S*,29*S*,31*S*,33*S*,36*S*,37*S*,41*S*,43*S*,47*S*,5*R*,15*R*,25*R*,38*R*)-3-Acetyloxy-15,31-dimethoxy-18,36,38,43,47-pentamethyl-39-methylene-8,12,45,46,48,49,50-heptaoxa-7,35-dioxo-14,43-bis(triethylsiloxy)-17,27-bis(*tert*-butyldimethylsiloxy)heptacyclo[39.3.1.1<1,5>.1<9,13>.1<15,19>. 1<25,29>.1<29,33>]pentaconta-10,23-dien-37-ylacetate (84). To aldehyde **83** (5.7 mg, 0.0035 mmol) was added 0.178 mL (0.036 mmol) of a 2-methyl-2-propene stock solution (0.2 M in *t*-BuOH) and 0.178 mL (0.018 mmol) of an ethyl 1-propenyl ether stock solution (0.1 M in *t*-BuOH) followed by 0.036 mL (0.018 mol) of a $NaClO_2$ stock solution (0.5 M in pH 5 phosphate buffer; prepared from 56.5 mg of $NaClO_2$ in 1.0 mL of buffer). Two additional portions of 3 equivalents of $NaClO_2$ solution were added after 1 and 2.5 h. After 3.5 h total stirring at room temperature, the reaction was diluted with an EtOAc/H_2O mixture (20 mL/5 mL). The aqueous solution was extracted with EtOAc (10 mL) and CH_2Cl_2 (2 x 10 mL). The combined organic solutions were dried over Na_2SO_4 for 15 min, filtered, and concentrated. The residue was used directly for the next reaction without purification. To a 0 °C solution of the carboxylic acid (0.0035 mmol) in 0.285 mL of THF was added 0.071 mL of a HF•pyridine/THF solution (4 mL of HF•pyr, 8 mL of pyridine, and 32 mL of THF). The solution was stirred at 0° C for 3 h and diluted with a EtOAc/H_2O mixture (20 mL/5 mL). The aqueous solution was extracted with EtOAc (10 mL) and CH_2Cl_2 (2 x 10 mL). The combined organic solutions were dried over Na_2SO_4 for 15 min, filtered, and concentrated. The residue was used directly in the next reaction without purification. To a solution of the seco acid (0.0035 mmol) in 0.350 mL of benzene was added diisopropylethylamine (0.012 mL, 0.07 mmol) followed by 2,4,6-trichlorobenzoyl chloride (0.011 mL, 0.07 mmol). This solution was stirred at room temperature for 3 h, after which a solution of DMAP (21.4 mg, 0.175 mmol) in 7.2 mL of benzene was added rapidly via cannula. After 3 h the cloudy solution was poured into a Et_2O/saturated aqueous $NaHCO_3$ mixture. The organic solution was separated and washed with 1 N HCl, saturated aqueous $NaHCO_3$, and brine, then dried over Na_2SO_4 for 15 min. The volatiles were removed under reduced pressure, and the residue was purified by flash chromatography (10% acetone/hexanes) to afford 2.9 mg (55%, 3 steps) of macrolactone **84**. Partial data for **84**: ^1H NMR (500 MHz, C_6D_6) δ 6.40 (dd, *J* = 5.9, 0.9 Hz, 1H), 5.78 (t-like, *J* = 4.6 Hz, 1H), 5.69 (d, *J* = 10.2 Hz, 1H), 5.57 (d, *J* = 8.9 Hz, 1H), 5.46-5.40 (m, 2H), 5.07 (s, 1H), 4.99 (br s, 1H), 4.93 (s, 1H), 4.80 (dd, *J* = 6.1, 1.7 Hz, 1H), 4.65 (t, *J* = 10.8 Hz, 1H), 4.42 (app. d, *J* = 9.2 Hz, 1H), 4.35 (t, *J* = 10.7 Hz, 1H), 4.32 (d, *J* = 10.7 Hz, 1H), 4.20 (s, 1H), 4.14 (t, *J* = 10.5 Hz, 1H), 3.97 (m, 1H), 3.87-3.86 (m, 1H,), 3.50 (s, 3H), 3.37-3.27 (m, 3H), 3.10 (dq, *J* = 6.7, 3.6 Hz), 3.08 (d, *J* = 6.2 Hz, 1H), 3.05 (d, *J* = 4.8 Hz, 1H), 3.04 (s, 3H), 3.00 (dd, *J* = 17.7, 2.5 Hz, 1H), 2.73 (dd, *J* = 18.2, 9.9 Hz, 1H), 2.54 (br d, *J* = 14.1 Hz, 1H), 2.49 (dd, *J* = 15.1, 4.0 Hz, 1H), 2.47-2.45 (m, 1H), 2.41 (dd, *J* = 13.2, 9.8 Hz, 1H), 2.33 (dd, *J* = 14.1, 11.2 Hz, 1H), 2.22 (dd, *J* = 12.5, 3.4 Hz, 1H), 2.08-2.02 (m, 3H), 1.98 (s, 3H), 1.95-1.86 (m, 1H), 1.85 (s, 3H), 1.79-1.69 (m), 1.60 (d, *J* = 13.0 Hz, 1H)), 1.54-1.51 (m), 1.40 (d, *J* =

6.9 Hz, 3H), 1.38-1.29 (m), 1.27 (d, J = 6.7 Hz, 3H), 1.23 (d, J = 6.7 Hz, 3H), 1.22-1.17 (m), 1.15 (t, J = 8.0 Hz, 9H), 1.06 (s, 9H), 1.02 (s, 9H), 1.00 (t, J = 7.9 Hz, 9H), 0.89-0.80 (m, 6H), 0.57 (dq, J = 7.8, 2.1 Hz, 6H), 0.12 (s, 3H), 0.101 (s, 3H), 0.098 (s, 3H), 0.096 (s, 3H); Mass calcd. for $C_{79}H_{140}O_{19}Si_4Na$: 1528; found: 1528 (FAB, *m*-nitrobenzyl alcohol, NaI added).

Triisopropylsilyl-2-[(2*S*,4*S*,6*R*,8*S*,10*S*)-8-[(3*R*,4*S*,5*S*)-7-[(2*S*,4*S*,6*R*,8*S*,10*S*)-10-(*tert*-butyldimethylsiloxy)-8-[(1*Z*)-5-(2*R*,3*S*,4*S*,6*R*)-4-(*tert*-Butyldimethylsiloxy)-6-[(*S*)-[(2*R*,3*S*,4*S*)-3,4-dihydro-3-methyl-4-(triethylsiloxy)-2H-pyran-2-yl](triethylsiloxy)methyl]tetrahydro-6-methoxy-3-methyl-2H-pyran-2-yl]-1-pentenyl]-4-methoxy-1,7-dioxaspiro[5.5]undec-2-yl]-4-hydroxy-3,5-dimethyl-2-methylene-6-oxoheptyl]-4-hydroxy-10-methyl-10-(triethylsiloxy)-1,7-dioxaspiro[5.5]undec-2-yl]ethanoate, diacetate (86). To a room temperature solution of aldehyde **83** (26.6 mg, 0.0164 mmol) in 0.328 mL of *t*-butanol were added 2-methyl-2-butene (0.035 mL, 0.328 mmol) and ethyl propenyl ether (0.018 mL, 0.164 mmol). A 0.5 M solution of $NaClO_2$ in pH 5 phosphate buffer (0.493 mL, 0.246 mmol) was then added via syringe. The reaction was stirred for 1 h, after which an additional 0.250 mL of $NaClO_2$ solution was added. Another 0.250 mL of $NaClO_2$ solution was added 1 h later. After 3.5 h total stirring, the reaction was diluted with EtOAc (20 mL) and water (5 mL). The aqueous solution was separated and extracted with EtOAc (1 x 10 mL) and CH_2Cl_2 (2 x 10 mL). The combined organic solutions were dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in a 0.4 M solution of triethylamine in THF (0.493 mL, 0.197 mmol). A 0.4 M solution of chlorotriisopropylsilane in THF (0.246 mL, 0.099 mmol) was added via syringe. After 30 min stirring, an additional 0.250 mL of triethylamine solution and 0.125 mL of chlorotriisopropylsilane solution were added. After 1 h total stirring, the reaction was diluted with 2.5 mL of a 1 M solution of Et_3NHOAc in THF and stirred for 1 min, then diluted with water (10 mL), saturated aqueous $NaHCO_3$ (2 mL), and Et_2O. The organic solution was separated, washed with water (1 x), dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (2 x 12 cm, linear gradient 5-10% acetone/hexanes) provided 21.3 mg (72%) of a clear oil. $[\alpha]^{23}_{365}$ +23.6 (*c* 0.42, CH_2Cl_2); IR (CH_2Cl_2) 2954, 1728, 1606 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.33 (d, J = 5.7 Hz, 1H), 5.75 (dd, J = 10.8, 8.2 Hz, 1H), 5.63-5.60 (m, 1H), 5.61 (dd, J = 9.8, 2.4 Hz, 1H), 5.51 (dt, J = 10.9, 7.3 Hz, 1H), 5.15 (s, 1H), 5.06 (br s, 1H), 4.96 (s, 1H), 4.64 (dd, J = 6.4, 1.3 Hz, 1H), 4.49 (m, 1H), 4.30-4.27 (m, 2H), 4.19 (br t, 1H), 4.07 (d, J = 11.3 Hz, 1H), 4.06 (s, 1H), 3.94-3.88 (m, 2H), 3.25 (m, 1H), 3.15 (s, 3H), 3.10 (dd, J = 18.7, 2.4 Hz, 1H), 3.05 (s, 3H), 2.95 (dq, J = 10.0, 6.8 Hz, 1H), 2.92 (dd, J = 15.8, 3.8 Hz, 1H), 2.76 (dd, J = 18.6, 10.0, 1H), 2.68 (m, 1H), 2.56-2.50 (m, 1H), 2.53 (dd, J = 15.8, 10.0 Hz, 1H), 2.46 (dd, J = 15.3, 3.5 Hz, 1H), 2.43-2.29 (m, 2H), 2.31 (septet, J = 7.4 Hz, 2H), 2.18-2.09 (m, 4H), 1.99 (br d, J = 14.6 Hz, 1H), 1.95-1.92 (m, 1H), 1.92 (s, 3H), 1.81-1.72 (m, 3H), 1.77 (s, 3H), 1.67-1.54 (m), 1.46-1.33 (m, 3H), 1.33-1.23 (m, 2H), 1.31 (d, J = 6.8 Hz, 3H), 1.20 (d, J = 6.8 Hz, 3H), 1.14-1.11 (m, 27H), 1.07 (s, 9H), 1.06-0.97 (m, 30H), 1.04 (s, 9H), 1.02 (m, 2H), 0.88-0.77 (m, 6H), 0.69-0.55 (m, 12H), 0.18 (s, 3H), 0.10 (s, 3H), 0.09 (m, 6H); ^{13}C NMR (125 MHz, C_6D_6) δ 209.6, 170.6, 170.2, 168.7, 147.8, 144.0, 132.2, 130.9, 113.8, 105.2, 101.7, 98.3, 97.1, 78.2, 74.7, 73.8, 71.2, 70.9, 70.62, 70.56, 67.7, 66.8, 66.5, 65.2, 64.3, 62.3, 61.6, 55.1, 51.2, 47.8, 47.0, 45.5, 44.5, 42.9, 42.7, 39.3, 38.8, 38.7, 38.1, 38.0, 37.2, 34.8, 34.4, 33.0, 32.0, 30.7, 28.7, 26.9, 26.2, 26.1, 21.3, 20.5, 18.4, 18.0, 15.2, 13.7, 12.2, 12.0, 10.8, 7.6, 7.5, 7.3, 7.2, 6.2, 5.6, -4.3, -4.8, -4.9; Mass calcd. for $C_{94}H_{177}O_{20}Si_6Na$: 1816; found: 1816 (FAB, *m*-nitrobenzyl alcohol, NaI added).

Triisopropylsilyl(2*R*,4*S*,6*S*,8*S*,10*S*)-8-[2-[(1*R*,2*S*,3*S*)-5-[(2*S*,4*S*,6*R*,8*R*,10*S*)-10-(*tert*-butyldimethylsiloxy)-8-(1*Z*)-5-[(2*R*,3*S*,4*S*,6*R*)-4-(*tert*-butyldimethylsiloxy)tetrahydro-6-methoxy-3-methyl-6-[(*S*)-[2*R*,3*S*,4*R*,5*R*,6*R*)-tetrahydro-5-hydroxy-3-methyl-6-[(4*S*,5*E*)-2-methylene-4-(trimethylsiloxy)-5,7-octadienyl]-4-(triethylsiloxy)-2H-pyran-2-yl](triethylsiloxy)methyl]-2H-pyran-2-yl]-1-pentenyl]-4-methoxy-1,7-dioxaspiro[5.5]undec-2-yl]-2-hydroxy-1,3-dimethyl-4-oxopentyl]allyl]-4-hydroxy-10-methyl-10-(triethylsiloxy)-1,7-dioxaspiro[5.5]undecane-2-acetate,4,8²-diacetate (87). Dimethyldioxirane/acetone solution (prepared according to Murray, R. W.; Singh, M. *Org. Synth.* **1997**, *74*, 91-100) was diluted in CH_2Cl_2 to a concentration of ~0.004 M (measured by addition to a known quantity of tri-*O*-benzyl glucal). The resulting solution (0.900 mL, ~0.0037 mmol) was added via syringe to a 0 °C solution of dihydropyran **86** (3.6 mg, 0.002 mmol) in 0.600 mL of CH_2Cl_2. After 5 min stirring, the reaction was concentrated under a steady stream of nitrogen. To the residue was added a solution of allylstannane **76c** (16.03 mg, 0.032 mmol) in 0.111

mL of CH_2Cl_2, and the resulting solution was cooled to -78 °C. A solution of tributyltin trifluoromethanesulfonate (1.76 mg, 0.004 mmol) in 0.111 mL CH_2Cl_2 was added rapidly via syringe. The reaction was stirred for 20 min, then quenched by addition of triethylamine (0.100 mL), diluted with saturated aqueous $NaHCO_3$ and Et_2O, and warmed to room temperature. The organic solution was separated, washed with brine (1 x), dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (1 x 12 cm, linear gradient 15-30% ethyl acetate/hexanes) provided 3.8 mg (94%) of a clear oil (unreacted **76c** was recovered quantitatively). $[\alpha]^{23}_{365}$ +5.7 (*c* 0.42, CH_2Cl_2); IR (CH_2Cl_2) 3686, 3602, 2937, 2876, 1781, 1728, 1606 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.34-6.30 (m, 2H), 5.79 (dd, *J* = 14.4, 6.2 Hz, 1H), 5.76 (m, 1H), 5.64-5.61 (m, 1H), 5.62 (dd, *J* = 9.7, 2.2 Hz, 1H), 5.51 (dt, *J* = 10.7, 7.2 Hz, 1H), 5.17-5.12 (m, 1H), 5.16 (s, 1H), 5.07 (s, 1H), 5.06 (m, 1H), 5.03 (s, 1H), 4.98-4.96 (m, 1H), 4.96 (s, 1H), 4.49 (m, 1H), 4.41 (dd, *J* = 13.0, 6.0 Hz, 1H), 4.31-4.22 (m, 2H), 4.19 (br t, *J* = 10.3 Hz, 1H), 4.13-3.88 (m, 2H), 3.94 (s, 1H), 3.40-3.37 (m, 1H), 3.37 (d, *J* = 10.5 Hz, 1H), 3.32 (dt, *J* = 8.6, 3.6 Hz, 1H), 3.28-3.22 (m, 1H), 3.25 (app. t, *J* = 8.9 Hz), 3.16 (s, 3H), 3.10 (dd, *J* = 18.4, 2.7 Hz, 1H), 3.05 (s, 3H), 3.01-2.95 (m, 1H), 2.93 (dd, *J* = 15.9, 3.9 Hz, 1H), 2.78-2.68 (m, 3H), 2.61 (dd, *J* = 13.6, 7.8 Hz, 1H), 2.56-2.33 (m), 2.16-2.12 (m, 1H), 2.10 (br d, *J* = 13.9 Hz, 2H), 1.96-1.92 (m, 1H), 1.92 (s, 3H), 1.87-1.81 (m, 2H), 1.77 (s, 3H), 1.67-1.55 (m), 1.42-1.17 (m), 1.32 (d, *J* = 6.8 Hz, 3H), 1.21 (d, *J* = 6.8 Hz, 3H), 1.16-0.97 (m, 54H), 1.11 (s, 9H), 1.05 (s, 9H), 1.00 (d, *J* = 7.4 Hz, 3H), 0.84-0.78 (m, 6H), 0.74 (dq, *J* = 7.9, 4.0 Hz, 6H), 0.66-0.57 (m, 6H), 0.26 (s, 3H), 0.18 (s, 9H), 0.16 (s, 3H), 0.10 (m, 6H); ^{13}C NMR (100.6 MHz, C_6D_6) δ 209.6, 170.6, 170.2, 168.7, 147.8, 144.4, 137.6, 137.0, 132.1, 130.9, 130.3, 116.8, 115.2, 113.8, 101.6, 98.3, 97.1, 81.1, 78.8, 78.4, 76.1, 74.7, 73.7, 73.0, 71.3, 71.2, 70.6, 67.5, 66.8, 66.5, 65.2, 64.3, 62.3, 61.6, 55.1, 51.2, 47.78, 47.75, 46.9, 45.9, 45.5, 44.5, 42.9, 42.7, 40.03, 39.9, 39.3, 38.9, 38.7, 38.1, 37.9, 34.8, 34.4, 33.0, 32.0, 30.6, 30.4, 30.2, 30.1, 20.5, 18.4, 18.0, 14.4, 13.7, 12.2, 12.0, 10.7, 7.6, 7.5, 7.4, 7.3, 7.1, 6.1, 6.0, 5.9, 5.2, 0.4, -4.1, -4.6, -4.8, -4.9; Mass calcd. for $C_{106}H_{198}O_{22}Si_7Na$: 2043; found: 2043 (FAB, *m*-nitrobenzyl alcohol, NaI added).

(2*R*,4*S*,6*S*,8*S*,10*S*)-8-[2-[(1*R*,2*S*,3*S*)-5-[(2*S*,4*S*,6*R*,8*R*,10*S*)-10-(*tert*-Butyldimethylsiloxy)-8-(1*Z*)-5-[(2*R*,3*S*,4*S*,6*R*)-4-(*tert*-butyldimethylsiloxy)tetrahydro-6-methoxy-3-methyl-6-[(*S*)-[2*R*,3*S*,4*R*,5*R*,6*R*)-tetrahydro-5-hydroxy-3-methyl-6-[(4*S*,5*E*)-2-methylene-4-(hydroxy)-5,7-octadienyl]-4-(hydroxy)-2H-pyran-2-yl]-(triethylsiloxy)methyl]-2H-pyran-2-yl]-1-pentenyl]-4-methoxy-1,7-dioxaspiro[5.5]undec-2-yl]-2-hydroxy-1,3-dimethyl-4-oxopentyl]allyl]-4-hydroxy-10-methyl-10-(triethylsiloxy)-1,7-dioxaspiro[5.5]undecane-2-acetate,4, 8²-diacetate (88). To a 0 °C solution of ester **87** (14.9 mg, 0.0074 mmol) in 0.600 mL of THF was added 0.150 mL of a freshly prepared solution of buffered HF•pyridine (2 mL HF•pyridine, 4 mL pyridine, and 16 mL THF). The resulting solution was stirred at 0 °C for 22 h, then diluted with water and warmed to room temperature. The mixture was extracted with EtOAc (2 x 10 mL) and CH_2Cl_2 (2 x 10 mL). The combined organic solutions were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (1 x 12 cm silica gel, 40 mL of 30% acetone/hexanes, then 40 mL of 30% acetone/hexanes+1% acetic acid) provided 7.8 mg (63%) of acid **88**. $[\alpha]^{23}_{365}$ +33.6 (*c* 0.38, CH_2Cl_2); IR (neat) 3452, 2954, 1781, 1733 (br) cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.40-6.31 (m, 2H), 5.79-5.71 (m, 2H), 5.67 (app d, *J* = 10.0 Hz, 1H), 5.57 (br t, *J* = 9.1 Hz, 1H), 5.49 (app dd, *J* = 17.5, 8.2 Hz, 1H), 5.18 (d-like, *J* = 16.0 Hz, 1H), 5.14 (s, 1H), 5.12 (s, 1H), 5.04 (s, 1H), 5.01 (d, *J* = 9.2 Hz, 1H), 4.96 (m, 2H), 4.40 (m, 2H), 4.31-4.27 (m, 2H), 4.20 (br t, *J* = 10.5 Hz, 1H), 3.98 (br s, 1H), 3.93 (s, 1H), 3.89 (m, 1H), 3.40 (d, *J* = 10.5 Hz, 1H), 3.40 (m, 1H), 3.30 (t, *J* = 8.9 Hz, 1H), 3.26-3.18 (m, 1H), 3.20 (s, 3H), 3.16-3.11 (m, H), 3.09-3.04 (m, 1H), 3.02 (s, 3H), 2.91 (dd, *J* = 18.7, 10.0 Hz, 1H), 2.78 (m, 1H), 2.69-2.65 (m, 2H), 2.58 (br d, *J* = 14.1 Hz, 1H), 2.50-2.36 (m), 2.12 (m, 1H), 2.07 (d-like, *J* = 13.8 Hz, 1H), 1.93 (s, 3H), 1.91-1.84 (m), 1.81 (s, 3H), 1.70 (t, *J* = 12.0 Hz, 1H), 1.64-1.57 (m), 1.55-1.48 (m), 1.38 (d, *J* = 6.9 Hz, 3H), 1.33 (d, *J* = 6.9 Hz, 3H), 1.17 (t, *J* = 8.0 Hz, 9H), 1.12 (d, *J* = 6.3 Hz, 3H), 1.09 (s, 9H), 1.04 (t, *J* = 7.6 Hz, 9H), 1.03 (s, 9H), 0.96 (s, 3H), 0.92-0.80 (m, 6H), 0.63 (q, *J* = 7.9 Hz, 6H), 0.22 (s, 3H), 0.12 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100.6 MHz, C_6D_6) δ 209.3, 170.3, 168.6, 147.6, 143.4, 136.9, 136.7, 132.0, 130.3, 127.3, 127.1, 116.7, 115.5, 113.5, 101.4, 98.0, 97.0, 79.1, 78.6, 78.5, 75.1, 74.6, 73.5, 71.2, 71.1, 71.0, 70.5, 67.2, 66.6, 66.1, 64.9, 63.7, 62.1, 61.4, 54.8, 53.3, 51.4, 47.5, 46.7, 45.9, 45.1, 44.0, 42.7, 39.0, 38.7, 38.4, 38.3, 38.0, 37.7, 37.3, 34.0, 32.6, 31.8, 30.8, 30.4, 29.2, 28.3, 26.1, 25.92, 25.89, 21.1, 20.3, 18.2, 18.1, 13.8, 13.7, 11.9, 10.6, 7.39, 7.36, 7.0, 6.9, 5.8, -4.4, -4.9, -5.06; -5.13;

Mass calcd. for $C_{94}H_{170}O_{22}Si_5Na$ (Na_2): 1699 (1722); found: 1699 (1722) (FAB, *m*-nitrobenzyl alcohol, NaI added).

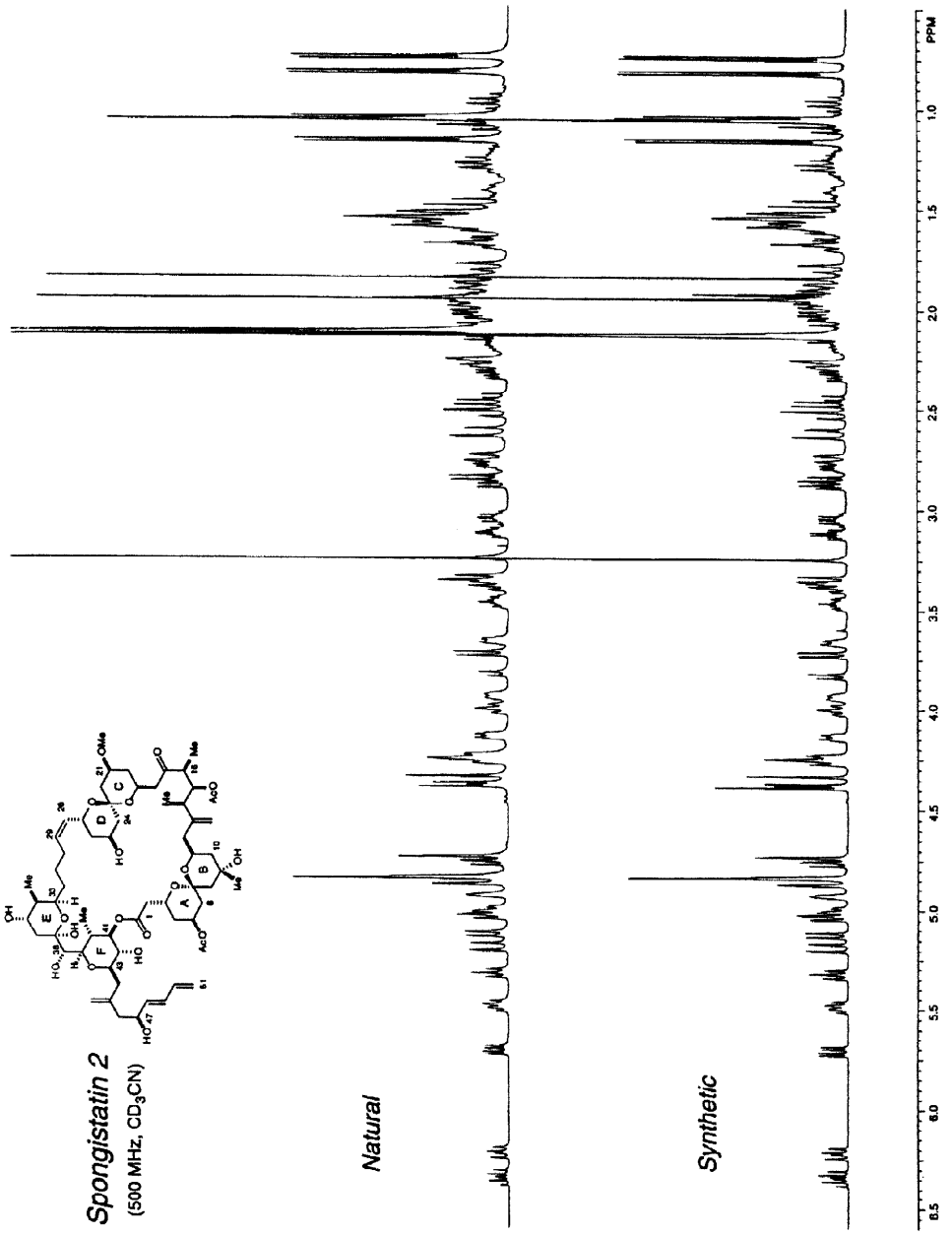
(2*R*,4*S*,6*S*,8*S*,10*S*)-8-[2-[(1*R*,2*S*,3*S*)-5-[(2*S*,4*S*,6*R*,8*R*,10*S*)-10-(*tert*-Butyldimethylsiloxy)-8-(1*Z*)-5-[(2*R*,3*S*,4*S*,6*R*)-4-(*tert*-butyldimethylsiloxy)tetrahydro-6-methoxy-3-methyl-6-[(*S*)-[2*R*,3*S*,4*R*,5*R*,6*R*)-tetrahydro-5-hydroxy-3-methyl-6-[(4*S*,5*E*)-2-methylene-4-(triethylsiloxy)-5,7-octadienyl]-4-(hydroxy)-2H-pyran-2-yl](triethylsiloxy)methyl]-2H-pyran-2-yl]-1-pentenyl]-4-methoxy-1,7-dioxaspiro[5.5]undec-2-yl]-2-hydroxy-1,3-dimethyl-4-oxopentyl]allyl]-4-hydroxy-10-methyl-10-(triethylsiloxy)-1,7-dioxaspiro[5.5]undecane-2-acetate,4, 8²-diacetate (89). To a solution of acid **88** (1.1 mg, 0.0007 mmol) in 0.070 mL of CH_2Cl_2 was added a 0.1 M solution of imidazole in CH_2Cl_2 (0.045 mL, 0.0045 mmol). The resulting solution was cooled to 0 °C, and a 0.1 M solution of chlorotriethylsilane in CH_2Cl_2 (0.020 mL, 0.0020 mmol) was added. 5 additional portions of imidazole solution (0.100 mL) and chlorotriethylsilane solution (0.080 mL) were added at 30 min intervals. After 4.2 h total reaction time, saturated aqueous NH_4Cl and CH_2Cl_2 were added, and the mixture was warmed to room temperature. The aqueous solution was separated and extracted with CH_2Cl_2 (2 x). The combined organic solutions were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (0.7 x 12 cm silica gel, 20 mL of 30% acetone/hexanes, then 50 mL of 20% acetone/hexanes+1% acetic acid) provided 1.2 mg (97%) of a clear oil. $[\alpha]^{23}_{365}$ +23.1 (*c* 0.08, CH_2Cl_2); IR (CH_2Cl_2) 3775-3600, 2995, 2956, 1738, 1726, 1712 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.40-6.32 (m, 2H), 5.85 (dd, *J* = 14.1, 6.5 Hz, 1H), 5.74 (app. t, *J* = 9.3 Hz, 1H), 5.65 (dd, *J* = 9.7, 3.1 Hz, 1H), 5.58-5.50 (m, 2H), 5.18 (d, *J* = 15.9 Hz, 1H), 5.13 (m, 2H), 5.08 (s, 1H), 5.01-4.98 (m, 3H), 4.46-4.44 (m, 2H), 4.29 (m, 2H), 4.19 (br t, *J* = 9.7 Hz, 1H), 3.97 (m, 1H), 3.94 (s, 1H), 3.89 (m, 1H), 3.41-3.39 (m, 1H), 3.40 (d, *J* = 10.4 Hz, 1H), 3.26-3.23 (m, 1H), 3.23 (s, 3H), 3.17-3.14 (m, 1H), 3.11-3.07 (m, 1H), 3.04 (s, 3H), 2.89 (dd, *J* = 18.4, 10.0 Hz, 1H), 2.78-2.76 (m, 1H), 2.63 (dd, *J* = 13.7, 7.1 Hz, 1H), 2.56-2.49 (m), 2.42-2.38 (m), 2.19 (m, 1H), 2.10 (m, 1H), 1.96 (s, 3H), 1.90-1.85 (m), 1.81 (s, 3H), 1.77-1.53 (m), 1.36 (d, *J* = 6.6 Hz, 3H), 1.29 (d, *J* = 6.9 Hz, 3H), 1.17 (t, *J* = 7.9 Hz, 9H), 1.12-1.10 (m, 3H), 1.10 (s, 9H), 1.08 (t, *J* = 7.9 Hz, 9H), 1.05 (t, *J* = 7.9 Hz, 9H), 1.03 (s, 9H), 0.98 (m, 6H), 0.88-0.79 (m, 6H), 0.70 (q, *J* = 7.9 Hz, 6H), 0.64 (q, *J* = 7.9 Hz, 6H), 0.25 (s, 3H), 0.14 (s, 3H), 0.10 (m, 6H); ^{13}C NMR (100.6 MHz, C_6D_6) δ 209.6, 170.5, 169.1, 147.8, 144.0, 137.7, 137.0, 132.2, 130.9, 130.4, 127.2, 116.9, 115.5, 113.8, 101.7, 98.3, 97.3, 78.94, 78.85, 75.8, 75.0, 73.8, 72.9, 71.2, 70.8, 67.2, 65.2, 64.0, 62.4, 55.1, 51.4, 47.9, 47.0, 46.2, 45.3, 44.2, 42.8, 39.3, 39.2, 38.7, 38.1, 37.9, 35.0, 34.3, 32.8, 32.1, 30.6, 29.5, 28.4, 26.4, 26.2, 26.1, 21.4, 20.6, 18.4, 14.0, 13.9, 12.4, 10.8, 7.6, 7.2, 6.1, 5.4, -4.1, -4.6, -4.8, -4.9; Mass calcd. for $C_{94}H_{170}O_{22}Si_5Na$ (Na_2): 1813 (1836); found: 1813 (1836) (FAB, *m*-nitrobenzyl alcohol, NaI added).

(1*S*,3*S*,5*R*,9*R*,10*R*,11*R*,13*R*,14*S*,15*R*,17*S*,18*S*,19*R*,23*Z*,25*R*,27*S*,29*R*,31*S*,33*S*,36*S*,37*S*,38*R*,41*S*,43*S*,49*S*)-17,27-Bis(*tert*-butyldimethylsiloxy)-3,10,37-trihydroxy-15,21-dimethoxy-18,36,38,43,49-pentamethyl-39-methylene-11-[(4*S*,5*E*)-2-methylene-4-(triethylsiloxy)-5,7-octadienyl]-14,43-bis(triethylsiloxy)-8,12,45,-46,47,48,50-heptaoxaheptacyclo[39.3.1.1^{1,5}.1^{9,13}.1^{15,19}.1^{25,29}.1^{29,33}]-pentacont-23-ene-7,35-dione-3,37-diacetate (90). Hydroxy acid **89** (4.7 mg, 0.0026 mmol) was dissolved in a 0.4 M solution of diisopropylethylamine in benzene (0.197 mL, 0.079 mmol). A 0.4 M solution of 2,4,6-trichlorobenzoyl chloride (0.131 mL, 0.053 mmol) was added via syringe, and the resulting solution was stirred at room temperature for 3 h. The reaction was diluted with 1.49 mL benzene and added via syringe pump to a refluxing solution of 4-dimethylaminopyridine (16 mg, 0.131 mmol) in 2.9 mL benzene over 24 h. The anhydride flask was rinsed twice with 0.750 mL benzene; each rinse was added via syringe pump to the refluxing reaction over 9 h. The resulting cloudy white suspension was cooled to room temperature and diluted with saturated aqueous $NaHCO_3$, then stirred to give a clear biphasic mixture. The aqueous solution was separated and extracted with EtOAc (2 x). The combined organic solutions were washed once with brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (1 x 6 cm, 30% ethyl acetate/hexanes) provided 4.4 mg (86%) of a clear oil. $[\alpha]^{23}_{365}$ +71.5 (*c* 0.20, CH_2Cl_2); IR (neat) 3490, 2953, 2877, 1737 (br), 1642 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 6.35-6.28 (m, 2H), 5.82 (dd, *J* = 14.2, 6.6 Hz, 1H), 5.77 (dd, *J* = 10.9, 7.0 Hz, 1H), 5.63 (d, *J* = 10.2 Hz, 1H), 5.47 (m, 1H), 5.38 (m, 1H), 5.17-5.12 (m, 3H), 5.10 (s, 1H), 5.06 (s, 1H), 4.98 (d, *J* = 9.0 Hz, 1H), 4.93 (m, 2H), 4.84 (m, 1H), 4.51 (t, *J* = 11.1 Hz, 1H), 4.43 (m, 1H), 4.41-4.37 (m, 2H), 4.3 (t, *J* = 10.5 Hz,

1H), 4.01 (s, 1H), 3.94 (m, 2H), 3.53 (d, J = 10.4 Hz, 1H), 3.45 (m, 2H), 3.38 (s, 3H), 3.28-3.25 (m, 2H), 3.15 (app dd, J = 10.5, 6.9 Hz), 3.10-3.05 (m, 3H), 3.04 (s, 3H), 2.91-2.84 (m, 2H), 2.74-2.69 (m, 1H), 2.63 (dd, J = 13.3, 7.0 Hz, 1H), 2.54-2.50 (m, 4H), 2.40-2.36 (m, 2H), 2.35-2.28 (m, 2H), 2.19 (m, 1H), 2.15-2.06 (m, 2H), 2.03-2.01 (m), 1.98 (s, 3H), 1.95-1.86 (m), 1.85 (s, 3H), 1.83-1.59 (m), 1.52 (m), 1.47-1.44 (m), 1.40 (d, J = 6.9 Hz, 3H), 1.35 (d, J = 6.8 Hz, 3H), 1.21 (t, J = 7.9 Hz, 9H), 1.13 (d, J = 7.1 Hz, 3H), 1.11 (s, 9H), 1.09 (m, 3H), 1.07 (t, J = 8.0 Hz, 9H), 1.03 (t, J = 8.0 Hz, 9H), 1.00 (m, 12H), 0.92-0.80 (m, 6H), 0.69 (q, J = 7.9 Hz, 6H), 0.60 (q, J = 7.9 Hz, 6H), 0.23 (s, 3H), 0.15 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100.6 MHz, C_6D_6) δ 209.0, 171.5, 170.4, 168.5, 148.0, 143.7, 137.8, 137.0, 132.7, 130.3, 129.9, 127.6, 116.8, 115.6, 113.5, 101.7, 98.5, 97.0, 81.1, 79.7, 78.5, 74.9, 73.9, 73.5, 73.0, 71.8, 71.4, 70.3, 67.1, 66.5, 66.1, 65.2, 63.7, 63.3, 60.5, 55.2, 52.3, 47.6, 47.5, 46.6, 45.6, 43.9, 40.9, 39.8, 39.3, 38.4, 38.0, 36.7, 36.0, 34.3, 32.7, 32.3, 30.4, 27.9, 26.2, 26.1, 21.4, 20.6, 18.4, 14.4, 14.2, 12.9, 10.8, 7.6, 7.5, 7.22, 7.17, 6.2, 5.4, 5.3, -4.1, -4.7, -4.9; Mass calcd. for $C_{94}H_{170}O_{22}Si_5Na$: 1797; found: 1797 (FAB, *m*-nitrobenzyl alcohol, NaI added).

Altohyrtin C (Spongistatin 2). To a 0 °C solution of macrolactone **90** (3.8 mg, 0.002 mmol) in 0.600 mL of acetonitrile was added 0.05 mL of a freshly prepared HF/water/acetonitrile solution (0.5 mL of 48% aqueous HF, 0.9 mL of water, and 8.6 mL of acetonitrile). The resulting solution was stirred at 0 °C for 24 h, then diluted with saturated aqueous $NaHCO_3$ and CH_2Cl_2. The aqueous solution was separated and extracted with CH_2Cl_2 (2 x). The combined organic solutions were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (0.7 cm x 5 cm silica gel, 5% MeOH/CH_2Cl_2) provided 2.5 mg of a solid residue, which was further purified by HPLC (Zorbax ODS C_{18}, 27.5% water/MeOH, 1 mL/min) to give 1.6 mg (67%) of a white solid. $[\alpha]^{23}_{589}$ +26.6 (*c* 0.04, MeOH); UV λ_{max} = 226 nm; HPLC retention time 8.5 min (Zorbax ODS C_{18} 4.6 mm x 25 cm, 27.5% water/MeOH, 1 mL/min, UV detection, λ = 226 nm), 1.4 min (HP ODS Hypersil C_{18} 2.1 x 100 mm, 25% water/MeOH, 0.400 mL/min, APCI-ms detection); ^{1}H NMR (500 MHz, CD_3CN) δ 6.35 (ddd, J = 16.9, 10.3, 10.3 Hz, 1H), 6.22 (dd, J = 15.0, 10.5 Hz, 1H), 5.71 (dd, J = 15.2, 6.3 Hz, 1H), 5.49 (dd-like, J = 17.9, 8.5 Hz, 1H), 5.33 (t, J = 10.2 Hz, 1H), 5.19 (d-like, J = 17.7 Hz, 1H), 5.13 (dd, J = 10.6, 1.8 Hz, 1H), 5.04 (d-like, J = 9.9 Hz, 1H), 5.00 (dd, J = 10.0, 3.2 Hz, 1H), 4.93 (m, 1H), 4.87 (s, 1H), 4.84 (m, 3H), 4.76 (t-like, J = 10.1 Hz), 4.74 (m, 1H), 4.39-4.37 (m, 2H), 4.34 (s, 1H), 4.25 (m, 3H), 4.14 (dt, J = 9.1, 3.2 Hz, 1H), 4.00 (t, J = 10.9 Hz), 3.94 (m, 1H), 3.84 (d, J = 9.4 Hz), 3.73 (d, J = 10.2 Hz, 1H), 3.66 (m, 1H), 3.47 (tt, 11.5, 4.1 Hz, 1H), 3.41-3.34 (m, 2H), 3.25 (s, 3H), 3.12 (dt, J = 9.1, 5.4 Hz, 1H), 3.05 (dq, J = 10.6, 6.9 Hz, 1H), 2.90-2.84 (m, 2H), 2.79 (br dd, J = 13.5, 7.1 Hz, 1H), 2.75 (br d, J = 14.5 Hz), 2.62 (d-like, J = 18.2 Hz), 2.53 (dd, J = 16.1, 1.7 Hz, 1H), 2.46 (dd, J = 16.1, 10.5 Hz, 1H), 2.33 (dd, J = 13.9, 6.4 Hz, 1H), 2.27 (m, 2H), 2.20-2.16 (m, 2H), 2.08-1.96 (m, 4H), 1.95 (s, 3H), 1.94-1.88 (m, 2H), 1.85 (s, 3H), 1.80 (d-like, J = 15.2 Hz, 1H), 1.70-1.65 (m, 2H), 1.62-1.39 (m, 10H), 1.32-1.23 (m, 3H), 1.17 (d, J = 6.9 Hz, 3H), 1.10 (d, J = 12.2 Hz, 1H), 1.07 (s, 3H), 1.05 (d, J = 6.9 Hz, 3H), 0.97 (app. q, J = 11.8 Hz, 2H), 0.82 (d, J = 7.2 Hz, 3H), 0.75 (d, J = 6.6 Hz, 3H); Mass calcd. for $C_{63}H_{96}O_{21}Na$: 1211.6; found: 1211.5 (electrospray); 1211.5 (atmospheric pressure CI). **Natural sample** (spongistatin 2 provided by Professor G.R. Pettit). $[\alpha]^{23}_{589}$ +29.2 (*c* 0.12, MeOH); UV λ_{max} = 226 nm; HPLC retention time 8.5 min (Zorbax ODS C_{18} 4.6 mm x 25 cm, 27.5% water/MeOH, 1 mL/min, UV detection, λ = 226 nm), 1.4 min (HP ODS Hypersil C_{18} 2.1 x 100 mm, 25% water/MeOH, 0.400 mL/min, APCI-ms detection); ^{1}H NMR (500 MHz, CD_3CN) δ 6.35 (ddd, J = 16.9, 10.3, 10.3 Hz, 1H), 6.22 (dd, J = 15.1, 10.6 Hz, 1H), 5.71 (dd, J = 15.2, 6.3 Hz, 1H), 5.49 (dd-like, J = 17.9, 8.5 Hz, 1H), 5.33 (t, J = 10.2 Hz, 1H), 5.19 (d-like, J = 17.5 Hz, 1H), 5.13 (dd, J = 10.7, 1.6 Hz, 1H), 5.04 (d-like, J = 10.2 Hz, 1H), 5.00 (dd, J = 10.0, 3.0 Hz, 1H), 4.93 (m, 1H), 4.87 (s, 1H), 4.84 (m, 3H), 4.76 (t-like, J = 10.1 Hz), 4.74 (m, 1H), 4.39-4.37 (m, 2H), 4.34 (s, 1H), 4.25 (m, 3H), 4.14 (dt, J = 8.8, 3.0 Hz, 1H), 4.00 (t, J = 10.8 Hz), 3.94 (m, 1H), 3.83 (d, J = 9.4 Hz), 3.72 (d, J = 10.3 Hz, 1H), 3.66 (m, 1H), 3.47 (tt, 11.5, 4.3 Hz, 1H), 3.41-3.34 (m, 2H), 3.25 (s, 3H), 3.12 (dt, J = 9.1, 5.2 Hz, 1H), 3.05 (dq, J = 10.6, 6.8 Hz, 1H), 2.90-2.84 (m, 2H), 2.79 (br dd, J = 13.5, 6.8 Hz, 1H), 2.75 (br d, J = 14.9 Hz), 2.62 (d-like, J = 18.6 Hz), 2.53 (dd, J = 16.0, 1.5 Hz, 1H), 2.46 (dd, J = 16.1, 10.5 Hz, 1H), 2.33 (dd, J = 13.8, 6.4 Hz, 1H), 2.27 (m, 2H), 2.23-2.13 (m, 2H), 2.08-1.96 (m, 4H), 1.95 (s, 3H), 1.94-1.86 (m, 2H), 1.85 (s, 3H), 1.80 (d-like, J = 15.3 Hz, 1H), 1.70-1.65 (m, 2H), 1.62-1.39 (m, 10H), 1.35-1.20 (m, 3H), 1.17 (d, J = 6.9 Hz, 3H), 1.10 (d, J = 12.1 Hz, 1H), 1.07

(s, 3H), 1.05 (d, J = 6.9 Hz, 3H), 0.97 (app. q, J = 11.8 Hz, 2H), 0.82 (d, J = 7.2 Hz, 3H), 0.75 (d, J = 6.7 Hz, 3H); Mass calcd. for $C_{63}H_{96}O_{21}Na$: 1211.6; found: 1211.4 (electrospray); 1211.7 (atmospheric pressure CI).



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80. Information concerning the stereoselectivity of this epoxidation was not obtained from these small scale experiments. Epoxidation of a simple F ring acetate proceeded with 3:1 selectivity for the desired isomer. See also: Park, T. K.; Kim, I. J.; Hu, S.; Bilodeau, M. T.; Randolph, J. T.; Kwon, O.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 11488-11500.

81. In this system, overoxidation to give a mixture of diepoxides (presumably stereoisomers at C_{28}-C_{29}) was observed if dioxirane stoichiometry was not appropriately controlled.

82. The initial product of the reaction is the corresponding C_1 TES ester, which is cleaved during purification on silica gel.

83. Professor G. R. Pettit is gratefully acknowledged for providing a natural sample of spongistatin 2.

84. We thank Professor Motomasa Kobayashi for providing NMR spectra of natural altohyrtin C.

85. This conclusion was subsequently corroborated by Kishi's total synthesis of altohyrtin A/spongistatin 1. See reference 1b.