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Total synthesis of the polyene macrolide dermostatin A

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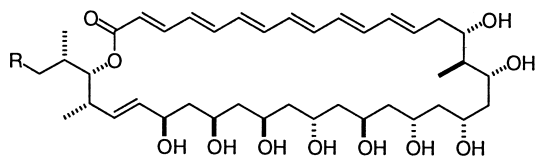
Dedicated to Professor Yoshi Kishi for his elegant work in natural product synthesis

Abstract—Herein we provide full details of studies which culminated in the first total synthesis of the polyene macrolide dermostatin A, confirming our earlier stereochemical assignment. A highly convergent synthesis was developed, featuring the cyanohydrin acetonide method for polyol construction and a Stille approach to polyene introduction. The strategies and tactics developed en route should be of value for the preparation of other members of the polyene macrolide class, as well as analogs of the dermostatins.

1. Introduction

The polyene macrolides are a class of natural products that are characterized by a lipophilic conjugated polyene unit and a hydrophilic skipped polyol unit. By virtue of their important biological activity and structural complexity, the polyene macrolides have attracted much interest from synthetic chemists, particularly toward the development of approaches to the 1,3-skipped polyol segments.[1] We have been engaged in the development of broadly applicable methods for the stereochemical elucidation and total synthesis of highly oxygenated natural products.[2] Pursuant to the these goals, a recent report from this group described the new strategy of 2D-^{13}C acetonide analysis for the stereochemical assignment of polyol containing natural products, which allowed for the rapid stereochemical elucidation of the dermostatins.[3] In this paper, we present a full report of our studies which led to the total synthesis of dermostatin A (**1**).[4]



Dermostatin A (**1**), R = H
Dermostatin B (**2**), R = CH_3

Dermostatin A (**1**) and B (**2**) are polyene macrolides that were isolated nearly 40 years ago from the mycelium of *Streptomyces virdigreseus* Thirum.[5] UV–Vis studies led to the erroneous conclusion that dermostatin was an oxopentaene macrolide.[6] This was later corrected by Rinehart and Pandey, who showed that dermostatin is in fact an oxohexaene antibiotic.[7] Rinehart also showed that dermostatin is comprised of two distinct components, dermostatin A and B, which differ by the presence of an additional methylene unit at C38. By a combination of spectroscopic experiments and chemical derivitization, the Rinehart group was able to elucidate the flat structures of dermostatin A and B.

The dermostatins have drawn attention on the basis of their range of biological activities. The dermostatins exhibit potent antifungal activity (comparable to amphotericin B) against a large number of human pathogens,[8] and have been used clinically as a treatment for deep vein mycoses.[9] In an evaluation of a variety of polyene macrolides as potential HIV treatments, dermostatin A and B showed the highest anti-proliferative activity against HIV in H9 cells.[10] An efficient synthesis of dermostatin A could facilitate analog production and the elucidation of its mode of biological activity.[11]

2. Retrosynthesis

The central synthetic challenges posed by the dermostatins are the complex polyol region and conjugated hexaene. Previous syntheses of other polyene macrolides by this group have employed an iterative construction of the polyene segment; we sought to develop a novel Stille-coupling approach for polyene installation, which would allow for a convergent, late-stage introduction of the highly sensitive polyene unit. Thus, retrosynthetic removal of polyene segment **4** gave rise to the C13–C38 polyol subtarget **3** (Scheme 1). The utility of cyanohydrin acetonide alkylations for the construction of complex protected polyols has been demonstrated in a number of total syntheses.[12] In the present context, the sequential connection of cyanohydrin acetonide fragments **5** and **7** with

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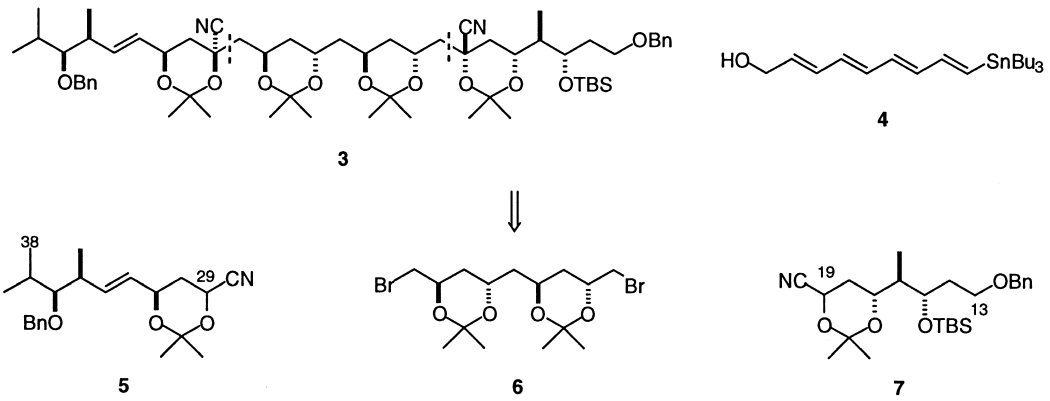


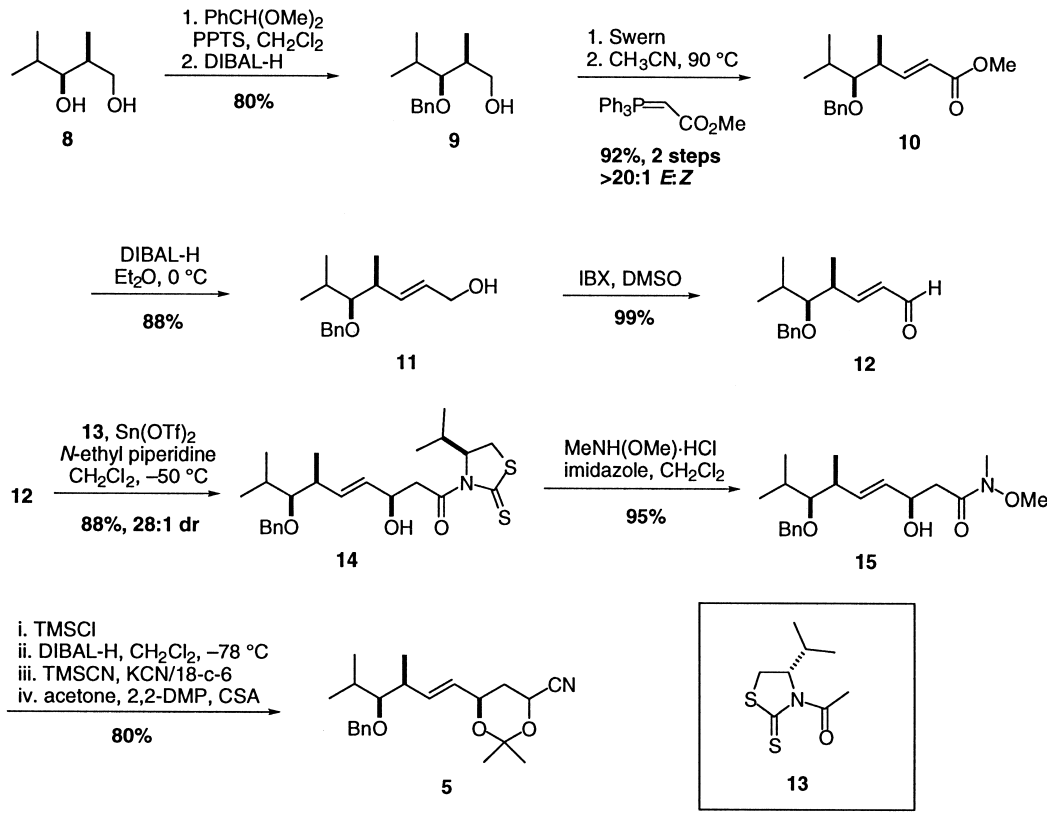
Scheme 1. Retrosynthesis of dermostatin A.

the C_2-symmetric bis-electrophile **6** would provide the fully protected polyol fragment **3**. We anticipated that an intramolecular Horner–Wadsworth–Emmons macrolactonization would generate the macrolide under sufficiently mild conditions.

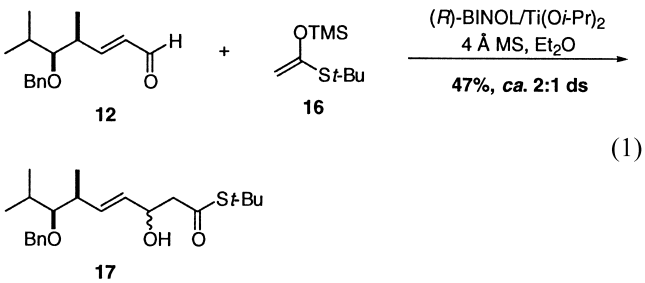
3. Results and discussion

3.1. Synthesis of the C29–C38 cyanohydrin acetonide 5

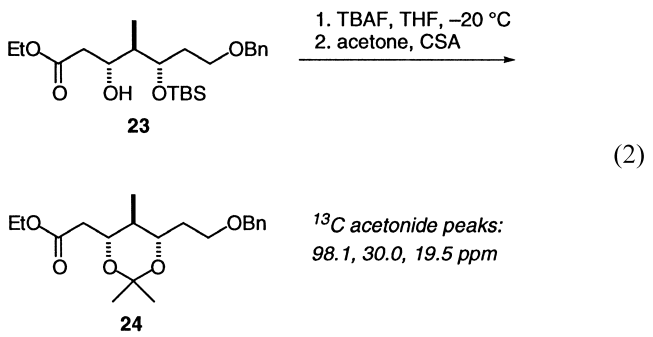
Synthesis of the C29–C38 fragment **5** commenced from known diol **8**,[12] available by standard aldol methodology (Scheme 2). Selective protection of **8** by benzylidene acetal formation and reductive cleavage at the less hindered site with DIBAL-H gave alcohol **9**. The requisite (*E*)-olefin was then installed, by Swern oxidation and Wittig olefination in refluxing acetonitrile. This gave enoate **10** in 92% yield, as single geometric isomer. Reduction with DIBAL-H and oxidation with the IBX reagent[13] gave enal **12** in 87% overall yield. Generation of the C31-allylic alcohol required a diastereoselective acetate aldol addition. A variety of strategies involving asymmetric catalysis gave disappointingly low selectivity. For example, Keck's BINOL–Ti(IV) catalyzed aldol addition[14] produced **17** with modest efficiency, and poor diastereoselection (Eq. (1)). The acetate aldol method of Nagao appeared to represent a highly practical solution.[15] A drawback of Nagao protocol is the requirement of excess aldehyde; we found that this could be obviated by generation of the tin-enolate over an extended period and at a high concentration. By this modified procedure, adduct **14** was isolated in 88% yield, with 28:1 diastereoselectivity. The observed facial selectivity was consistent with the model put forth by Nagao



Scheme 2. Synthesis of C29–C38 fragment **5**.



(1)



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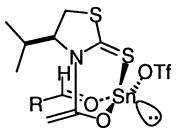


Figure 1. Stereochemical rationale for $Sn(OTf)_2$ mediated aldol.

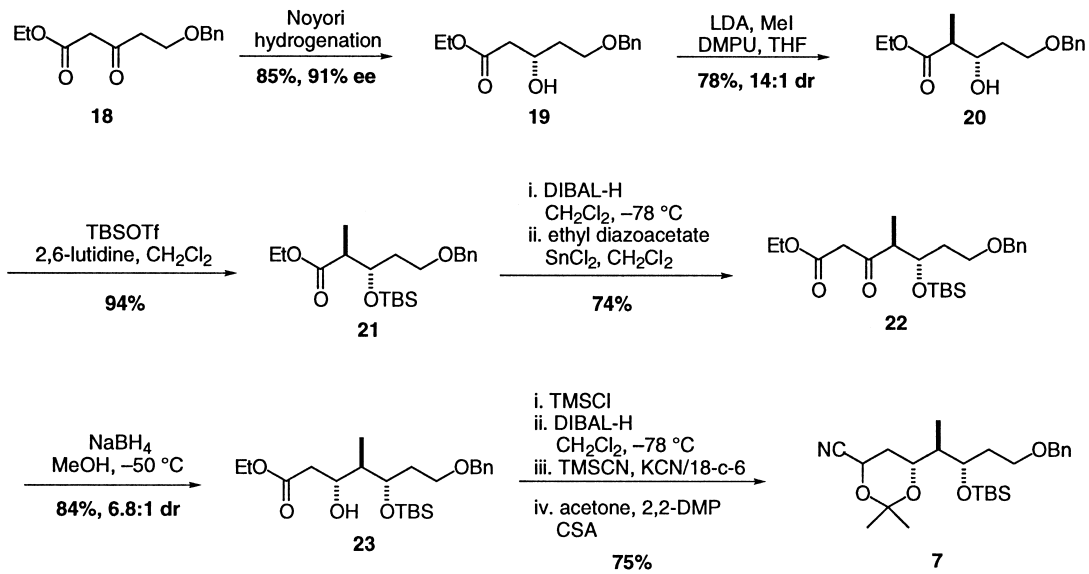
(Fig. 1).[16] Aldol adduct **14** was converted to Weinreb amide **15** under mild conditions. A reaction sequence (with no purification of intermediates) involving silylation of the C31-alcohol, reduction by DIBAL-H, and cyanohydrin acetonide formation provided **5** in 80% yield.

3.2. Synthesis of C13–C19 cyanohydrin acetonide 7

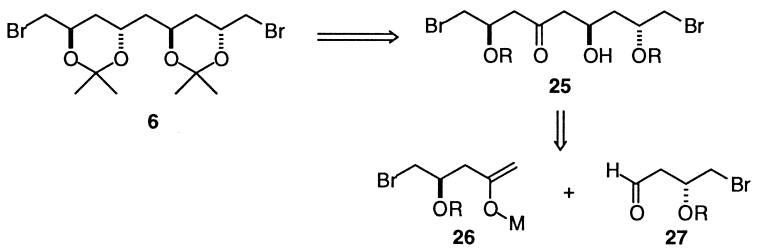
Synthesis of the C13–C19 cyanohydrin acetonide **7** followed the route outlined in Scheme 3. Noyori asymmetric hydrogenation of β-keto ester **18** gave β-hydroxy ester **19**.[17] According to the method Frater and Seebach,[18] formation of the corresponding dilithio anion with excess LDA and quenching with iodomethane produced **20** in 78% yield with 14:1 diastereoselectivity. Treatment with TBSOTf and 2,6-lutidine gave silyl ether **21**. DIBAL-H reduction and Roskamp homologation[19] gave β-keto ester **22**. Selective reduction with $NaBH_4$ provided diol **23** with good selectivity. In this reduction, optimal results were obtained at −50°C with methanol as solvent. Increased temperatures resulted in concomitant ester reduction and attenuated selectivity. Nonpolar, aprotic solvents such as THF also gave reduced selectivity. Proof of stereochemistry was achieved by conversion of the major isomer to acetonide **24** (Eq. (2)). Completion of the C13–C19 fragment by the method described above gave **7** in 75% yield.

3.3. Synthesis of C20–C28 fragment 6

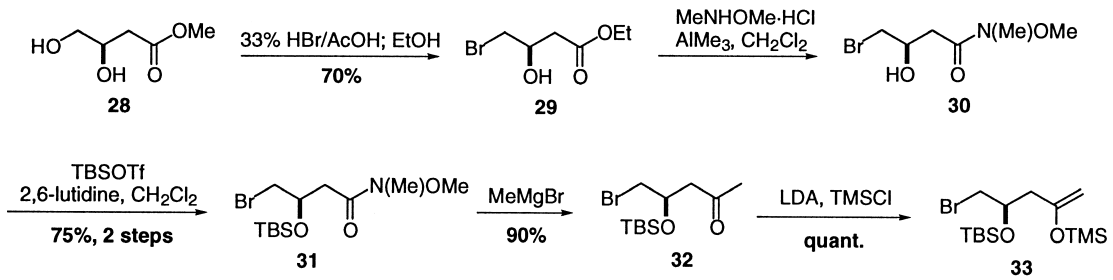
After exploring various approaches to the synthesis of the C20–C28 fragment, we chose to pursue a strategy that would rely on a Mukaiyama aldol reaction to forge the C24–C25 bond (Scheme 4). This approach would take advantage of the C_2-symmetry of **6**, and would allow for synthesis of the two fragments **26** and **27** from a common intermediate. From aldol adduct **25**, 1,3-*anti* reduction and protecting group exchange would provide **6**. The choice of acetonides as protecting groups was dictated by two considerations. First, cyanohydrin acetonide alkylations have been shown to proceed smoothly with 4-iodomethyl- and 4-bromomethyl-2,2-dimethyl-1,3-dioxanes, whereas alkylations of some β-silyloxy alkyl halides have been less successful.[20] Equally important is the beneficial effect of cyclic protecting groups on macrocyclizations. We were intrigued by the possibility of carrying reactive alkyl bromides through the entire sequence, which would have obvious benefits in terms of overall efficiency. Central to our



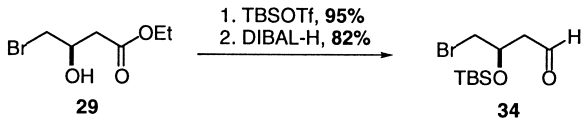
Scheme 3. Synthesis of the C13–C19 fragment **7**.



Scheme 4. Aldol approach to C20–C28 fragment **6**.



Scheme 5. Synthesis of enol silane **33**.



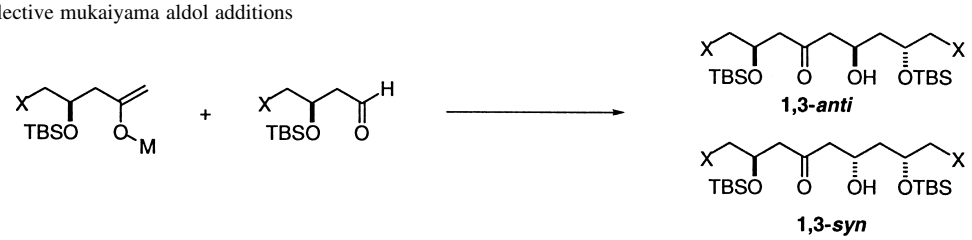
Scheme 6. Synthesis of aldehyde **34**.

strategy would be the development of an efficient 1,3-*anti* selective Mukaiyama aldol coupling.

Mukaiyama aldol precursors **33** and **34** are readily available from [D]-malic acid (Scheme 5). Diol **28**[21] was converted to the corresponding bromohydrin[22] upon treatment with HBr in acetic acid, and in situ Fischer esterification gave ester **29**. Weinreb amide **31** was obtained in 75% yield by exposure of **29** to Weinreb's salt and Me_3Al, followed by silylation with TBSOTf. Conversion of **31** to methyl ketone **32**, and subsequent treatment with LDA/TMSCl provided enol silane **33** (Scheme 5). Notably, none of the product arising from 5-*exo-tet O*-alkylation was observed. The aldehyde coupling partner **34** was prepared by silylation of **29** and reduction with DIBAL-H (Scheme 6).

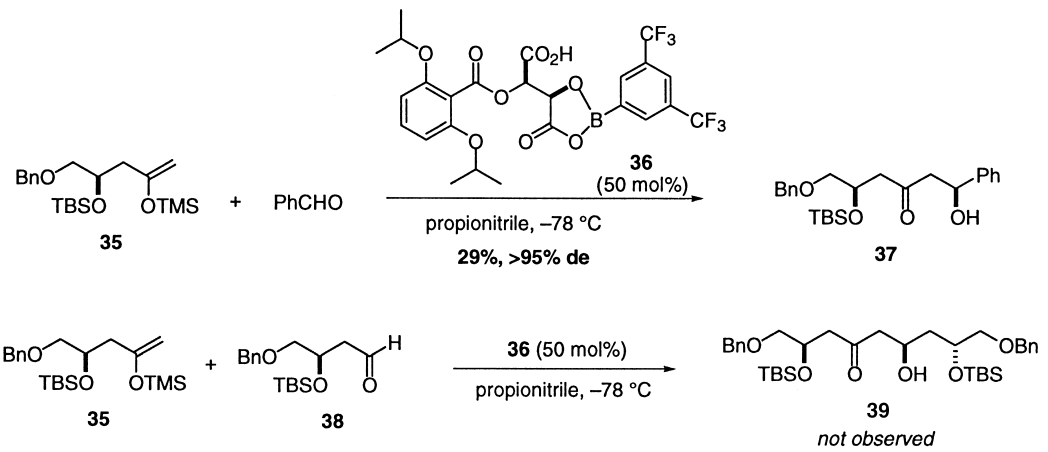
Recent studies have revealed that useful levels of 1,3-*anti* selectivity can be realized in the Mukaiyama aldol additions to β-alkoxy aldehydes. Reetz has shown that the appropriate combination of β-alkoxy group and bidendate Lewis acid can lead to high diastereoselectivity via chelation control.[23] In our hands, such a strategy failed due to facile solvolytic deprotection of β-alkoxy (benzyl or *p*-methoxybenzyl) groups under the reaction conditions. Thus, guided by Evans' comprehensive studies of polar effects in Mukaiyama aldol additions,[24] we elected to use more stable β-silyloxy aldehydes. Use of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 (entry 1, Table 1) resulted in 3.3:1 selectivity in favor of the desired 1,3-*anti* isomer. A more comprehensive Lewis acid screen with a variety of aldehydes and enol silanes (X=Cl, OBn) failed to reveal more selective conditions. Evans has recently reported chelation controlled additions to β-silyloxy aldehydes mediated by cationic aluminum

Table 1. 1,3-*anti* Selective mukaiyama aldol additions



Entry	X=	M=	Lewis acid	Solvent	1,3-*anti*/1,3-*syn*[a]
1	Br	TMS	$BF_3{\cdot}OEt_2$	CH_2Cl_2	3.3:1
2	Cl	TMS	$BF_3{\cdot}OEt_2$	CH_2Cl_2	3.2:1
3	Cl	TMS	$BF_3{\cdot}OEt_2$	Toluene	3.3:1
4	Cl	TMS	Me_2AlCl	CH_2Cl_2	2.5:1
5	OBn	TMS	$BF_3{\cdot}OEt_2$	CH_2Cl_2	2.3:1
6	Cl	(+)-DIPCl	None	Et_2O	1:2.0
7	Cl	(−)-DIPCl	None	Et_2O	<5:>95

[a] Determined by ^1H NMR analysis of the acylated (Ac_2O, pyridine, DMAP), unpurified reaction mixture.



Scheme 7. Use of Yamamoto's CAB catalyst.

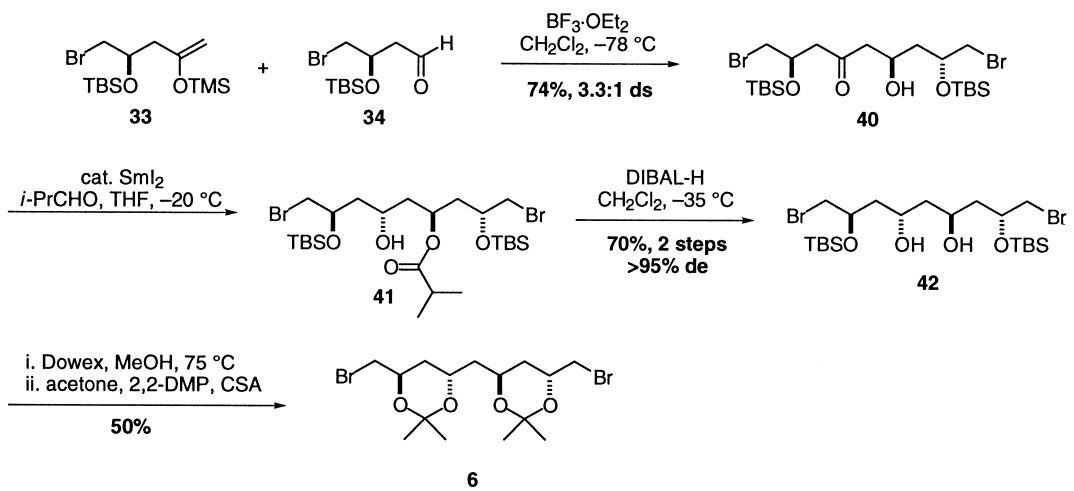
Lewis acids.[25] For our purpose, use of Me_2AlCl failed to improve selectivity (entry 4). Interestingly, the chiral boron enolate-derived from (+)-DIPCl led to a 2:1 mixture favoring the undesired 1,3-*syn* isomer, while the (−)-DIPCl derived enolate was completely selective for the 1,3-*syn* isomer (entries 6 and 7).[26] This may reflect an intrinsic preference for 1,5-*anti* additions of β-silyloxy ketone derived boron enolates; however, both Evans and Paterson have postulated that in the absence of a Lewis basic ketone β-alkoxy substituent, 1,5-*anti* induction plays a minor role.[27]

Chiral Lewis acids were also examined, in an effort to improve the moderate 1,3-*anti* selectivity (Scheme 7). Of the catalysts screened, including Corey's trytophan derived oxazaborolidine[28] and Yamamoto's chiral aclyoxyborane catalysts,[29] only catalyst **36**[30] showed any promise. Exposure of enol silane **35** and benzaldehyde to boronic ester **36** (50 mol%) in propionitrile provided adduct **37** as a single isomer, albeit in poor yield. Under the same conditions, however, catalyst **36** failed to promote addition of **35** to aldehyde **38**.

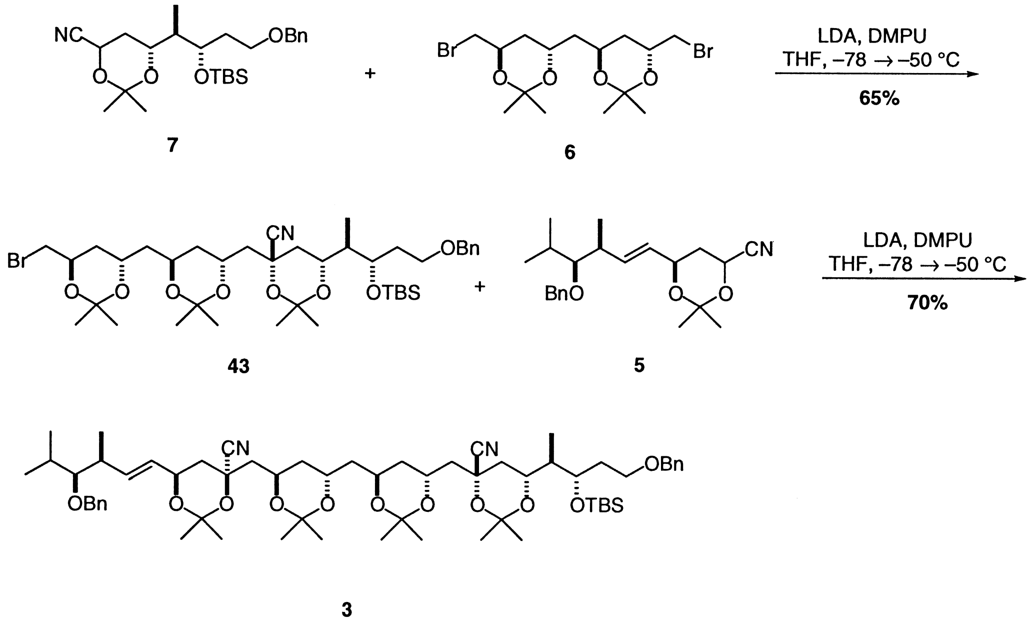
Of the Mukaiyama aldol conditions screened, the $BF_3{\cdot}OEt_2$ mediated addition of enol silane **33** to aldehyde **34** proved to be the most efficient (Scheme 8). Conversion of adduct **40** to the desired bis-acetonide required 1,3-*anti* selective ketone reduction and protecting group interchange. Directed reduction of **40** according to the Evans protocol[31] ($Me_4NBH(OAc)_3$, CH_3CN, AcOH) provided **42** directly, with moderate levels of selectivity (ca. 8:1). Yields for this transformation were compromised by the problematic separation of diastereomers, as **42** suffered extensive decomposition on prolonged exposure to silica gel. Thus, the more mild and much more selective Tischenko reduction was employed.[32] Under optimized conditions, treatment of **40** with catalytic SmI_2 and isobutyraldehyde, followed by reductive ester cleavage with DIBAL-H gave **42** in 70% yield for two steps, as a single diastereomer. The success of this transformation in the presence of reducible primary alkyl bromides is noteworthy. Conversion to bis-acetonide **6** was achieved upon exposure to Dowex resin in refluxing methanol, followed by acid catalyzed ketalization.

3.4. Fragment couplings and elaboration to dermostatin A

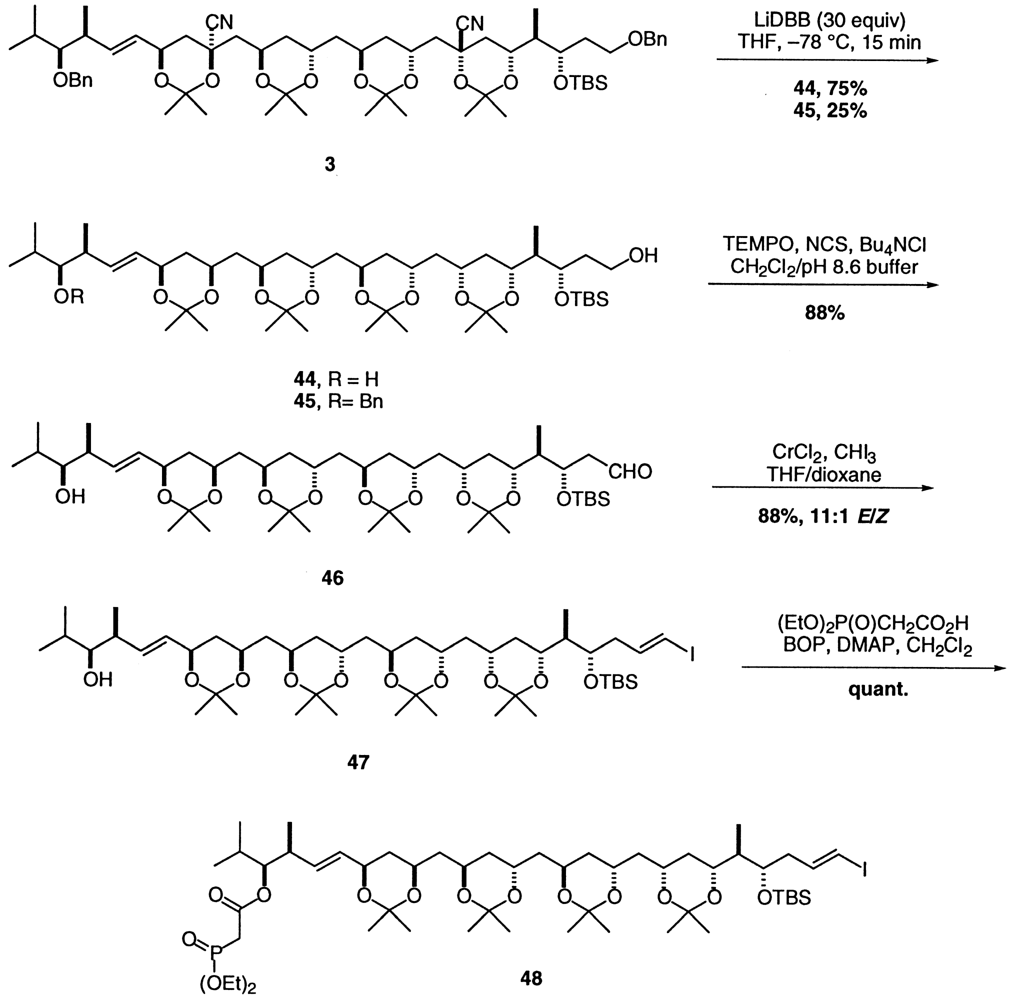
With the requisite fragments in hand, our attention shifted to fragment couplings. In the event, treatment of a mixture of **6** (2.2 equiv.) and **7** with LDA in the presence of DMPU provided the monoalkylation product **43** in 65% yield (Scheme 9). Notably, no undesired bis-alkylation was



Scheme 8. Optimized synthesis of bis-electrophile **6**.



Scheme 9. Fragment couplings via cyanohydrin method.

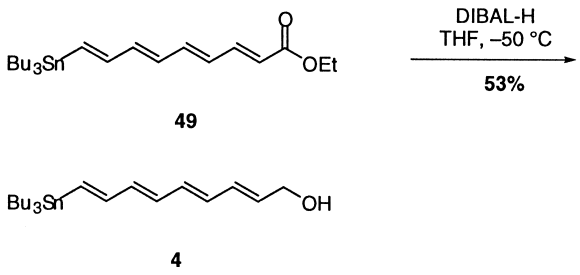


Scheme 10. Reductive decyanation and elaboration.

observed, and excess **6** could be readily recovered. A second alkylation under identical reaction conditions, this time with C29–C38 fragment **5** provided the C13–C38 dermostatin polyol **3** in 70% yield.

To set the stage for polyene installation, it was necessary to deprotect the C13 and C35–benzyl ethers, and set stereochemistry at C19 and C29 (Scheme 10). Toward this end, exposure of **3** to a large excess of lithium di-*tert*-butylbiphenylide effected reductive decyanation of both nitriles with concomitant removal of both benzyl ethers, giving rise to **44** in 75% yield.[33] Optimized conditions called for short reaction time and a careful low temperature quench; deviation from this protocol, or use of standard Birch conditions (Li/NH_3) resulted in much lower yields. Partial deprotection product **45** was also isolated in 25% yield; this material could be recycled. Selective oxidation of the primary alcohol was readily accomplished via Einhorn's modified TEMPO oxidation, generating aldehyde **46** in 88% yield, with complete selectivity for the less hindered alcohol.[34] Exposure of **46** to $CrCl_2$ and CHI_3 in THF/dioxane gave vinyl iodide **47** in excellent yield, with 11:1 *E*/*Z* selectivity.[35] Upon esterification with diethylphosphonoacetic acid to give **48**, we were poised to attempt the critical Stille coupling.[36]

The insightful studies of Farina pointed to appropriate reaction conditions for the crucial cross coupling.[37] Oxidative dimerization of the vinyl stannane can be minimized by use of a 'ligandless' palladium(0) catalyst.[38] Various additives such as copper salts,[39] trifurylphosphine, and triphenylarsine are now well known to facilitate Stille couplings by accelerating the transmetalation step.[37] A non-coordinating tertiary amine base such as Hunig's base has often been used to prevent decomposition of acid labile products. Thus, addition of a suspension of $Pd_2(dba)_3{\cdot}CHCl_3$ and triphenylarsine to a mixture of vinyl iodide **48**, vinyl stannane **4** (prepared as depicted in Eq. (3), from the known ester **49**)[40] and Hunig's base in THF gave polyene **50** in 77% yield (Scheme 11). The compatibility of the Stille conditions with the phosphonate ester and unprotected primary alcohol of the unstable polyene highlights the outstanding functional group tolerance of the modern Stille coupling. Oxidation of the allylic alcohol by treatment with the Dess–Martin periodinane[41] under buffered conditions gave aldehyde **51**.



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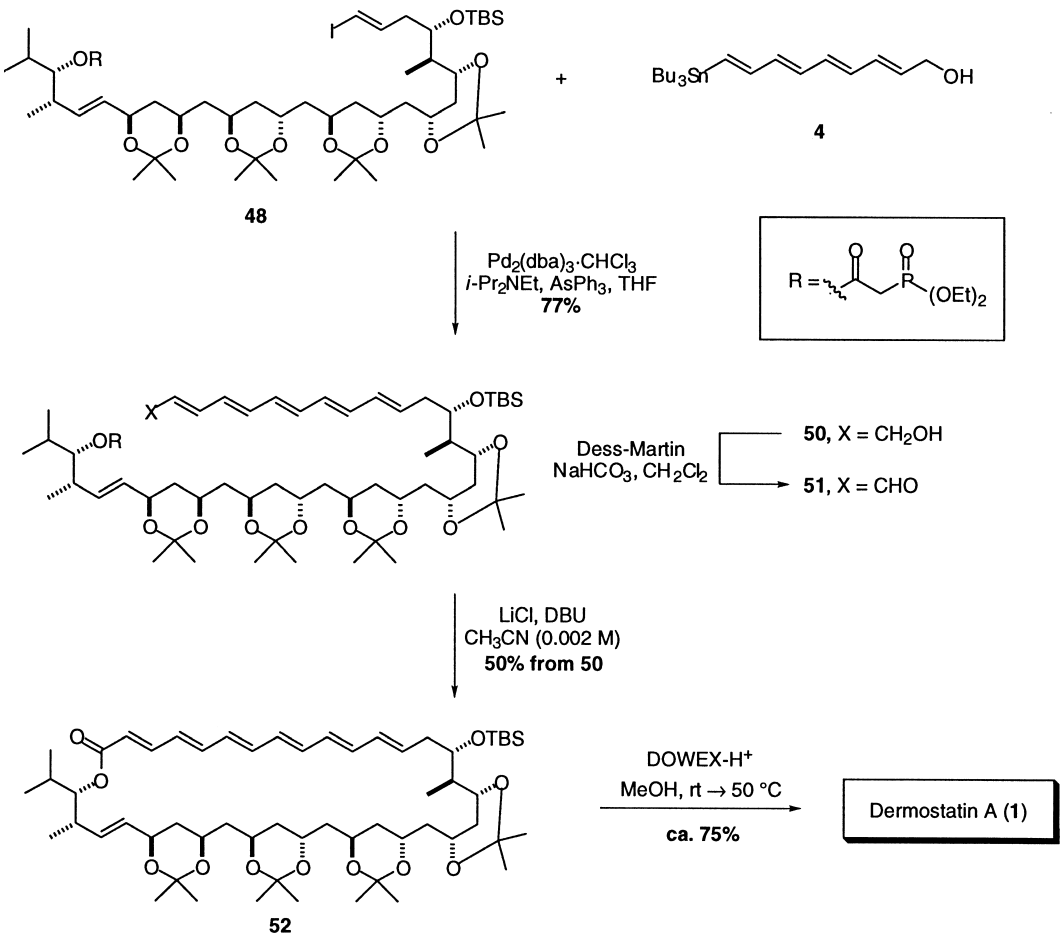

Scheme 11. Completion of dermostatin A.

With pentaenal **51** in hand, completion of the total synthesis required only macrocyclization and global deprotection. Attempts to effect cyclization under conditions originally described by Nicolaou[42] (K_2CO_3, 18-crown-6, toluene, 70°C) led to decomposition, while the milder conditions favored by Paterson[43] ($Ba(OH)_2$ in wet THF) returned starting material unchanged. To our relief, treatment of **51** with LiCl and DBU in acetonitrile (Masamune–Roush[44] conditions) smoothly provided macrolide **52**, in 50% yield from **50**. Exposure of **52** to Dowex acidic resin in methanol at ambient temperature effected removal of the four acetonide protecting groups and partial deprotection of the C15 TBS–ether, which was driven to completion by gentle heating. Analysis of the unpurified deprotection by ^{1}H NMR indicated the presence of dermostatin A with >80% purity. Purification by reverse-phase HPLC provided synthetic dermostatin A (**1**), which was indistinguishable from natural dermostatin A by a variety of analytical methods (^{1}H NMR in CD_3OD and d_6-DMSO, high-resolution mass spectrometry, circular dichroism, and analytical HPLC).

4. Conclusion

The first total synthesis of the polyene macrolide dermostatin A has been accomplished, which serves to confirm our stereochemical assignment. Particularly noteworthy transformations included a highly efficient acetate aldol addition, and application of Einhorn's chemoselective oxidation to a highly functionalized molecule. A novel Stille coupling strategy allowed for the high-yielding, convergent installation of a sensitive polyene. Our synthetic plan proved to be well considered, as the natural product was synthesized in just eight steps from the fully protected polyol **3**. The strategy and tactics outlined above should prove useful for the synthesis of analogs of the dermostatins, as well as other members of the polyene macrolide class.

5. Experimental

5.1. General experimental details

Unless otherwise noted, all reactions were carried out under an atmosphere of dry argon or nitrogen using flame dried glassware and standard syringe/septa techniques. THF, Et_2O, CH_2Cl_2, and toluene were degassed with argon, then dried by vacuum filtration through activated alumina according to the method described by Grubbs.[46] Triethylamine, diisopropylethylamine, disopropylamine, *N*-ethylpiperidine, propionitrile, trimethylsilyl chloride, and acetonitrile were distilled from CaH_2 under argon at atmospheric pressure. 2,6-Lutidine was distilled from CaH_2 under reduced pressure. Benzaldehyde was distilled under reduced pressure. Stannous triflate was handled under an inert atmosphere (glove box). All other commercial reagents were used as received. Indicated molarity of *n*-BuLi was determined by titration with diphenylacetic acid and 2,2′-bipyridyl. ^{1}H NMR spectra were recorded on Bruker instruments, at 400 or 500 MHz. ^{13}C NMR spectra were recorded on Bruker instruments, at 100 or 125 MHz. ^{1}H and ^{13}C NMR chemical shifts are reported as δ values in ppm and are referenced either to residual solvent peaks or tetramethylsilane. Coupling constants refer to apparent multiplicities, indicated as follows: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); dd (doublet of doublets); etc. Mass spectra were measured on a MicroMass Analytical 7070E, a MicroMass AutoSpec E, or a MicroMass LCT Electrospray spectrometer. Combustion analyses were performed by M-H-W laboratories, Phoenix, Arizona. Flash chromatography was performed with Bodman or Fisher silica gel 60 (230–400 Mesh). MPLC was performed with an Isco CYGNET instrument. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Infrared spectra were recorded on a MIDAC Grams/Prospect FT-IR.

5.1.1. (2*S*,3*S*)-1-Benzyloxy-2,4-dimethyl-pentan-3-ol (9). To a solution of diol **8**[45] (1.50 g, 11.4 mmol) in CH_2Cl_2 (60 mL) were added benzaldehyde dimethylacetal (2.23 mL, 14.8 mmol) and CSA (132 mg, 0.568 mmol). After 24 h, Et_3N (1 mL) was added, and the mixture was concentrated. Flash chromatography (25% CH_2Cl_2/hexanes) provided the benzylidene acetal, which was taken forward. The acetal was dissolved in toluene (60 mL), cooled to 0°C, and DIBAL-H (31 mL, 1.0 M in hexanes, 31 mmol) was added. After 1 h, the 0°C bath was removed, and the mixture was stirred at room temperature for 12 h. The mixture was cooled to 0°C, then quenched by the addition of MeOH. After gas evolution ceased, 10% aq. acetic acid was added, and the mixture was stirred rapidly until clear phase separation was observed. The organic phase was washed with sat. aq. $NaHCO_3$, dried over Na_2SO_4, and concentrated to yield **9** (1.58 g, 7.12 mmol, 80%) as a colorless oil. Analytical data matched were consistent with those reported for the enantiomer:[45] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.25 (m, 5H), 4.64 (ABq, J=11.3 Hz, $\Delta\nu$=25.3 Hz, 2H), 3.66–3.58 (m, 2H), 2.38 (s, 1H), 1.73–1.67 (m, 1H), 1.07 (d, J=6.7 Hz, 3H), 0.95 (d, J=7.0 Hz, 3H), 0.95 (d, J=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 128.3, 127.6, 127.5, 85.7, 74.6, 66.4, 37.7, 19.7, 19.5, 10.9; IR (NaCl, film) 3390, 3089, 1470, 1384, 1361 cm^{-1}; $[\alpha]_D$=+9.2 (*c* 0.77, CH_2Cl_2).

5.1.2. (4*S*,5*S*)-5-Hydroxy-4,6-dimethyl-hept-2-enoic acid methyl ester (10). To a cooled (−60°C) solution of oxalyl chloride (7.1 mL, 2.0 M in CH_2Cl_2, 14.2 mmol) in CH_2Cl_2 (5 mL) was added DMSO (2.0 mL, 42.6 mmol) dropwise. The mixture was stirred for 20 min, then a solution of benzyl ether **9** (2.10 g, 9.46 mmol) in CH_2Cl_2 (8 mL+2 mL rinse) was added dropwise via cannula over 15 min. After an additional 15 min, Et_3N (8.0 mL, 56.8 mmol) was added and the mixture was brought to room temperature. The mixture was diluted with H_2O and extracted with CH_2Cl_2 (2×). The combined organic phases were washed (1 M $NaHSO_4$, sat. aq. $NaHCO_3$), dried over Na_2SO_4, and concentrated. The crude oil was dissolved in CH_3CN (57 mL) and methyl (triphenylphosphoranilydene) acetate (4.75 g, 14.2 mmol) was added. The flask was equipped with a reflux condenser and the mixture was heated at 90°C. After 18 h, the solution was allowed to cool to room temperature and then was concentrated. Flash chromatography (10% EtOAc/hexanes) provided enoate **10** as a colorless oil (2.40 g, 8.70 mmol 92% over steps). ^{1}H NMR analysis revealed a >20:1 *E*/*Z* ratio: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 7.01 (dd, J=15.6, 8.0 Hz,

1H), 5.85 (dd, J=16.0, 1.2 Hz, 1H), 4.56 (ABq, J=11.2 Hz, $\Delta\nu$=11.2 Hz, 2H), 3.74 (s, 3H), 3.10 (t, J=5.8 Hz, 1H), 2.68–2.59 (m, 1H), 1.89–1.82 (m, 1H), 1.13 (d, J=6.8 Hz, 3H), 0.97 (d, J=6.4 Hz, 3H), 0.96 (d, J=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1, 152.5, 138.6, 128.2, 127.8, 127.4, 120.0, 87.7, 75.1, 51.4, 39.8, 31.2, 20.2, 17.4, 14.7; IR (NaCl, film) 2964, 1722, 1652, 1456, 1274, 1066 cm^{-1}; Anal. calcd for $C_{17}H_{24}O_3$: C, 73.85, H, 8.75. Found: C, 73.63, H, 8.89; $[\alpha]_D$=+9.1 (c 0.35, $CHCl_3$).

5.1.3. (4*S*,5*S*)-4,6-Dimethyl-hept-2-ene-1,5-diol (11). To a cooled (−78°C) solution of ester **10** (0.225 g, 0.82 mmol) in Et_2O (4 mL) was added DIBAL-H (2.45 mL, 1.0 M in hexanes, 2.45 mmol) dropwise. After 30 min, the reaction mixture was placed in a 0°C bath. After an additional 45 min, the reaction was quenched by the addition of 10% aq. AcOH and allowed to warm to room temperature. The aqueous phase was extracted twice with Et_2O, and the combined organic phases were washed with H_2O, sat. aq. $NaHCO_3$ (2×), sat. aq. NaCl, then were dried over $MgSO_4$ and concentrated. Purification by flash chromatography (20% EtOAc/hexanes) afforded allylic alcohol **11** (0.170 g, 0.685 mmol, 84%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 5.74–5.62 (m, 2H), 4.57 (ABq, J=11.7 Hz, $\Delta\nu$=5.0 Hz, 2H), 4.08 (d, J=4.1 Hz, 2H), 3.00 (t, J=5.5 Hz, 1H), 2.47 (ddd, J=13.1, 13.1, 6.8 Hz, 1H), 1.88–1.85 (m, 1H), 1.08 (d, J=6.8 Hz, 3H), 0.96 (d, J=6.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.0, 136.6, 128.3, 128.1, 127.6, 127.4, 88.7, 75.2, 63.8, 39.6, 31.0, 20.4, 17.6, 15.7; IR (NaCl, film) 3363, 3064, 1456, 1397, 1094 cm^{-1}; Anal. calcd for $C_{16}H_{24}O_2$: C, 77.38, H, 9.74. Found: C, 77.67, H, 9.85; $[\alpha]_D$=+5.86 (c 1.4, $CHCl_3$).

5.1.4. (4*S*,5*S*)-5-Hydroxy-4,6-dimethyl-hept-2-enal (12). Alcohol **11** (0.533 g, 2.15 mmol) was dissolved in DMSO (3 mL). A separate flask was charged with the IBX reagent (1.20 g, 4.30 mmol) and DMSO (8 mL) was added. The initial suspension was stirred for 20 min, resulting in a homogeneous solution. This solution was then added to the solution of the alcohol via cannula. After 2 h, the reaction was quenched by the addition of H_2O. The resulting cloudy suspension was filtered through a course fritted funnel, then was extracted with Et_2O (3×). The combined organic phases were dried over $MgSO_4$ and concentrated. Purification by flash chromatography (20% EtOAc/hexanes) provided aldehyde **12** (0.527 g, 2.13 mmol, 99%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (d, J=8.0 Hz, 1H), 7.35–7.25 (m, 5H), 6.84 (dd, J=15.6, 7.6 Hz, 1H), 6.12 (ddd, J=15.6, 7.6, 1.2 Hz, 1H), 4.57 (ABq, J=11.2 Hz, $\Delta\nu$=28.3 Hz, 2H), 3.15 (t, J=5.6 Hz, 1H), 2.76 (app dsextet, J=6.8, 1.2 Hz, 1H), 1.86 (app octet, J=6.8 Hz, 1H), 1.16 (d, J=6.8 Hz, 3H), 0.99 (d, J=6.8 Hz, 3H), 0.98 (d, J=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.1, 161.8, 138.4, 131.8, 128.4, 127.7, 127.6, 87.6, 75.0, 40.1, 31.3, 20.2, 17.9, 14.3; IR (NaCl, film) 1688, 1650, 1457, 1363, 1097 cm^{-1}; HRMS (CI) calcd for $C_{16}H_{22}O_2$ 246.1620, found 246.1619 $[M]^+$; $[\alpha]_D$=+9.40 (c 0.36, CH_2Cl_2).

5.1.5. (3*R*,6*S*,7*S*)-1-((4*S*)-4-Isopropyl-2-thioxo-thiazolidin-3-yl)-6,8-dimethyl-non-4-en-1-one (14). To stannous triflate (1.84 g, 4.42 mmol) was added CH_2Cl_2 (3 mL), and the resulting suspension was cooled to −50°C (cryobath). *N*-Ethylpiperidine (0.607 mL, 4.42 mmol) was added dropwise. A solution of thiazolidinethione **13** (0.747 g, 3.68 mmol) in CH_2Cl_2 (1 mL+1 mL rinse) was added dropwise via cannula. The mixture was then held at −50°C for 4 h. After cooling the enolate mixture to −78°C, a solution of aldehyde **12** (0.830 g, 3.35 mmol) in CH_2Cl_2 (7 mL+3 mL rinse) was added dropwise via cannula. After 2 h at −78°C, the mixture was placed in a −50°C cryobath and held at this temperature for 12 h. The reaction was quenched by the addition of pH 7 phosphate buffer, and allowed to warm to ambient temperature. The aqueous phase was extracted with CH_2Cl_2 (2×), and the combined organic phases were washed sequentially with 1 M HCl, pH 7 buffer, and sat. aq. NaCl, then dried over Na_2SO_4. Flash chromatography afforded a 28:1 mixture of separable diastereomers **14** (1.33 g total, 2.95 mmol, 88%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 5.75 (dd, J=15.6, 8.0 Hz, 1H), 5.57 (dd, J=15.6, 6.1 Hz, 1H), 5.14 (dd, J=6.7, 6.7 Hz, 1H), 4.64–4.60 (m, 1H), 4.58 (ABq, J=11.2 Hz, $\Delta\nu$=15.2 Hz, 2H), 3.63 (dd, J=17.6, 3.0 Hz, 1H), 3.50 (dd, J=11.5, 8.0 Hz, 1H), 3.29 (dd, J=17.6, 8.9 Hz, 1H), 3.03–3.00 (m, 2H), 2.51–2.44 (m, 1H), 2.42–2.37 (m, 1H), 1.90–1.81 (m, 1H), 1.11 (d, J=7.8 Hz, 3H), 1.07 (d, J=6.8 Hz, 3H), 0.99 (d, J=7.0 Hz, 3H), 0.96 (d, J=6.7 Hz, 3H), 0.96 (d, J=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.9, 172.6, 139.0, 135.8, 129.7, 128.2, 127.6, 127.3, 88.7, 75.2, 71.3, 68.7, 45.3, 39.6, 31.0, 30.8, 30.6, 20.3, 19.1, 17.8, 17.6, 15.5; IR (NaCl, film) 3430, 1693, 1466, 1363, 1164 cm^{-1}; HRMS (CI, NH_3) calcd for $C_{24}H_{35}NO_3S_2$ 449.2048, found 449.2040 $[M+H]^+$; $[\alpha]_D$=+213.4 (c 3.0, CH_2Cl_2).

5.1.6. (3*R*,6*S*,7*S*)-3,7-Dihydroxy-6,8-dimethyl-non-4-enoic acid methoxy-methyl-amide (15). To a solution of aldol adduct **14** (0.517 g, 1.15 mmol) in CH_2Cl_2 (6 mL) were added imidazole (0.391 g, 5.75 mmol), followed by *N*,*O*-dimethyl hydroxylamine hydrochloride (0.280 g, 2.88 mmol). The resulting suspension was capped with a glass stopper and stirred for 18 h, then diluted with sat. aq. NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 (2×), and the combined organic phases were dried over Na_2SO_4 and concentrated. Flash chromatography (40% EtOAc/hexanes) provided the thiazolidinethione chiral auxiliary as a white solid (0.169 g, 1.05 mmol, 91% recovery) and the Weinreb amide **15** as a colorless oil (0.382 g, 1.09 mmol, 95%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.27 (m, 5H), 5.75 (ddd, J=15.5, 8.0, 1.0 Hz, 1H), 5.55 (dd, J=15.5, 5.5 Hz, 1H), 4.57 (ABq, J=11.2 Hz, $\Delta\nu$=19.1 Hz, 2H), 4.55–4.52 (m, 1H), 3.80 (br s, 1H), 3.65 (s, 3H), 3.18 (s, 3H), 3.01 (t, J=5.8 Hz, 1H), 2.69–2.66 (m, 1H), 2.57 (dd, J=16.5, 9.1 Hz, 1H), 2.50–2.43 (m, 1H), 1.90–1.81 (m, 2H), 1.09 (d, J=6.8 Hz, 3H), 0.96 (d, J=6.8 Hz, 3H), 0.95 (d, J=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 138.8, 135.1, 130.1, 129.9, 128.0, 127.3, 127.1, 88.7, 75.2, 61.3, 39.8, 38.5, 32.0, 31.2, 20.6, 17.7, 16.0; IR 3443, 2963, 1647, 1454, 1385, 1108 cm^{-1}; HRMS (CI/NH_3) calcd for $C_{20}H_{32}NO_4$ 350.2331, found 350.2320 $[M+H]^+$; $[\alpha]_D$=+23.3 (c 1.85, CH_2Cl_2).

5.1.7. (6*R*)-((4*S*,3*S*)-4-Hydroxy-3,5-dimethyl-hex-1-enyl)-2,2-dimethyl-[1,3]dioxane-4-carbonitrile (5). To a solution of Weinreb amide **15** (0.895 g, 2.56 mmol) in CH_2Cl_2 (20 mL) were added Et_3N (0.890 mL, 6.38 mmol),

TMSCl (0.487 mL, 3.83 mmol), and a catalytic quantity of DMAP. The reaction mixture was stirred for 2.5 h, then the reaction was quenched by the addition of sat. aq. $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (2×), and the combined organic phases were dried over Na_2SO_4 and concentrated. The crude oil was filtered through a plug of silica gel (30% EtOAc/hexanes), then was concentrated. To a cooled (−78°C) solution of the crude silyl ether in CH_2Cl_2 (20 mL) was added DIBAL-H (3.85 mL, 1.0 M in hexanes, 3.85 mmol) dropwise over 10 min. After 1 h, the reaction was quenched by dropwise addition of methyl formate (0.8 mL). The mixture was then added via cannula to a cooled (0°C), rapidly stirred solution of Rochelle's salt. The resulting mixture was stirred rapidly at room temperature until the cloudy mixture became clear, at which time it was diluted with H_2O and extracted with CH_2Cl_2 (2×). The combined organic phases were washed (10% aq. HOAc, sat. aq. $NaHCO_3$ (2×), brine), then dried over Na_2SO_4 and concentrated. The crude aldehyde was dissolved in CH_2Cl_2 (5 mL), and TMSCN (0.528 mL, 3.84 mmol) was added, followed by a few crystals of KCN/18-crown-6 complex. After 12 h, acetone (16 mL), 2,2-dimethoxypropane (8 mL), H_2O (75 μL), and *dl*-CSA (50 mg, 0.22 mmol) were added sequentially. After 24 h, Et_3N (0.5 mL) was added, and the mixture was concentrated. Purification by flash chromatography (10% EtOAc/hexanes) gave cyanohydrin acetonides **5** (0.730 g, 0.204 mmol, 80%), both as colorless oils. Analytical data for the less polar diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5H), 5.76 (ddd, J=15.6, 7.9, 0.9 Hz, 1H), 5.46 (ddd, J=15.6, 6.3, 0.9 Hz, 1H), 4.85 (dd, J=6.4, 2.1 Hz, 1H), 4.63–4.55 (m, 1H), 4.57 (ABq, J=11.2 Hz, $\Delta\nu$=12.0 Hz, 2H), 3.01 (t, J=5.7 Hz, 1H), 2.47 (ddd, J=13.4, 13.2, 6.6 Hz, 1H), 1.95 (ddd, J=13.6, 11.5, 6.5 Hz, 1H), 1.87–1.80 (m, 1H), 1.78 (dt, J=13.6, 2.5 Hz, 1H), 1.71 (s, 3H), 1.41 (s, 3H), 1.09 (d, J=6.8 Hz, 3H), 0.96 (d, J=6.7 Hz, 3H), 0.95 (d, J=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 137.5, 128.3, 127.8, 127.7, 127.5, 119.9, 100.9, 88.5, 75.2, 66.5, 58.7, 39.6, 33.3, 31.0, 30.0, 21.8, 20.3, 17.7, 15.2; IR (NaCl, film) 3055, 2306, 1605, 1422, 1264 cm^{-1}; HRMS (CI) calcd for $C_{22}H_{35}N_2O_3$ 375.2647, found 375.2633 $[M+NH_4]^+$; $[\alpha]_D$=−25.6 (*c* 0.6, CH_2Cl_2). Analytical data for the more polar diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.26 (m, 5H), 5.72 (dd, J=15.6, 8.0 Hz, 1H) 5.44 (dd, J=15.6, 6.3 Hz, 1H), 4.77 (dd, J=11.9, 2.4 Hz, 1H), 4.55 (ABq, J=11.2 Hz, $\Delta\nu$=18.8 Hz, 2H), 4.30–4.27 (m, 1H), 2.99 (t, J=5.8 Hz, 1H), 2.46 (ddd, J=13.6, 13.6, 6.9 Hz, 1H), 1.90–1.76 (m, 3H), 1.47 (s, 3H), 1.46 (s, 3H), 1.07 (d, J=6.8 Hz, 3H), 0.96 (d, J=6.2 Hz, 3H), 0.95 (d, J=5.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 137.2, 128.1, 127.7, 127.4, 127.2, 117.5, 100.0, 88.6, 68.9, 59.0, 39.7, 34.7, 31.2, 29.8, 20.5, 19.4, 18.0, 15.4; IR (NaCl, film) 3032, 2253, 1464, 1384, 911 cm^{-1}; HRMS (CI/NH_3) calcd for $C_{22}H_{35}N_2O_3$ 375.2647, found 375.2636 $[M+NH_4]^+$; $[\alpha]_D$=+27.2 (*c* 0.6, CH_2Cl_2).

5.1.8. (2*S*,3*S*)-5-Benzyloxy-3-(*tert*-butyl-dimethylsilanyloxy)-2-methyl-pentanoic acid ethyl ester (21). To a cooled (−78°C) solution of ester **20**[17,45] (2.32 g, 8.72 mmol) in CH_2Cl_2 (30 mL) were added 2,6-lutidine (3.05 mL, 26.2 mmol), followed by TBSOTf (4.0 mL, 17.4 mmol). The mixture was held at −78°C for 2 h, then was quenched by the addition of sat. aq. NH_4Cl, and the mixture was allowed to warm to room temperature. The phases were separated and the aqueous phase extracted with CH_2Cl_2. The combined organic phases were washed (1 M aq. $NaHSO_4$, sat. aq. $NaHCO_3$, sat. aq. NaCl), and dried over Na_2SO_4 and concentrated. Flash chromatography (4% EtOAc/hexanes) provided **21** as a colorless oil (3.13 g, 8.25 mmol, 95%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.27 (m, 5H), 4.48 (s, 2H), 4.18–4.07 (m, 3H), 3.54 (app t, J=6.8 Hz, 2H), 2.64 (ddd, J=13.3, 7.0, 7.0 Hz, 1H), 1.83–1.77 (m, 2H), 1.24 (t, J=7.2 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 138.6, 128.3, 127.5, 127.4, 72.8, 70.7, 66.5, 60.2, 45.7, 33.1, 25.8, 18.0, 14.2, 11.6, −4.7, −4.9; IR (NaCl, film) 2956, 1736, 1256, 1104, 837 cm^{-1}; HRMS (CI) calcd for $C_{21}H_{37}O_4Si$ 381.2461, found 381.2459 $[M+H]^+$; $[\alpha]_D$=+16.5 (*c* 0.85, CH_2Cl_2).

5.1.9. (4*S*,5*S*)-7-Benzyloxy-5-(*tert*-butyl-dimethylsilanyloxy)-4-methyl-3-oxo-heptanoic acid ethyl ester (22). A solution of ester **21** (1.57 g, 4.13 mmol) in CH_2Cl_2 (20 mL) was cooled to −78°C, and DIBAL-H (6.2 mL, 1.0 M in CH_2Cl_2, 6.2 mmol) was added dropwise over 10 min. After 1 h, the reaction was quenched by dropwise addition of methyl formate (0.5 mL). After 5 min, the reaction mixture was quickly poured into a cooled (0°C), rapidly stirred solution of Rochelle's salt (50 mL). The resulting mixture was stirred rapidly at room temperature until the cloudy mixture became clear, at which time it was diluted with H_2O and extracted with CH_2Cl_2 (2×). The combined organic phases were dried over Na_2SO_4, concentrated, and redissolved in CH_2Cl_2 (10 mL). In a separate flask, $SnCl_2$ (0.391 g, 2.06 mmol) was suspended in CH_2Cl_2 (7 mL) and ethyl diazoacetate (0.87 mL, 8.26 mmol) was added. The crude aldehyde solution obtained above was then added via cannula over 10 min (with a 3 mL rinse). After 18 h, the mixture was concentrated. Purification by flash chromatography (10% EtOAc/hexanes) afforded β-keto ester **22** (1.29 g, 3.06 mmol, 74%) as a colorless oil: ^{1}H NMR (keto form) (500 MHz, $CDCl_3$) δ 7.34–7.26 (m, 5H), 4.51–4.45 (m, 2H), 4.20–4.13 (m, 2H), 3.61–3.53 (m, 2H), 3.61–3.53 (m, 5H), 2.88 (ddd, J=11.0, 5.5, 5.5 Hz, 1H), 1.85–1.72 (m, 2H), 1.26 (t, J=5.7 Hz, 3H), 1.09 (d, J=5.6 Hz, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.6, 179.8, 138.4, 128.3, 127.6, 127.5, 89.6, 72.9, 71.2, 65.8, 59.9, 51.6, 49.8, 33.6, 25.8, 14.0, 11.9, −4.8, −4.9; IR (NaCl, film) 3030, 1746, 1721, 1253, 1099, 836 cm^{-1}; HRMS (electrospray) calcd for $C_{23}H_{38}O_5SiNa$ 445.2386, found 445.2386 $[M+Na]^+$; $[\alpha]_D$=+40.6 (*c* 1.6, CH_2Cl_2).

5.1.10. (3*R*,4*R*,5*S*)-7-Benzyloxy-5-(*tert*-butyl-dimethylsilanyloxy)-3-hydroxy-4-methyl-heptanoic acid ethyl ester (23). To a cooled (−50°C, cryobath) solution of β-keto ester **22** (40 mg, 0.01 mmol) in methanol (1 mL) was added $NaBH_4$ (11 mg, 0.28 mmol) in a single portion. After 2 h, the reaction was quenched by the addition of sat. aq. NH_4Cl. The mixture was diluted with CH_2Cl_2 and H_2O. The phases were separated and the aqueous phase extracted with CH_2Cl_2. The combined organic phases were dried with Na_2SO_4, and concentrated in vacuo. Flash chromatography (10% EtOAc/hexanes) afforded **23** as a colorless oil, a 6.8:1 mixture of diastereomers (34 mg, 0.08 mmol, 84%). Further purification by MPLC (15% EtOAc/hexanes) afforded

diastereomerically pure material. Data for the major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.27 (m, 5H), 4.52 (d, J=12.0 Hz, 1H), 4.49 (d, J=12.0 Hz, 1H), 4.17 (qd, J=7.5, 1.0 Hz, 2H), 4.13–4.10 (m, 1H), 3.89 (td, J=7.3, 2.0 Hz, 1H), 3.61–3.52 (m, 2H), 2.60 (dd, J=16.1, 1.8 Hz, 1H), 2.37 (dd, J=16.1, 9.5 Hz, 1H), 1.85 (dddd, J=14.0, 7.4, 7.4, 2.9 Hz, 1H), 1.79–1.75 (m, 1H), 1.71–1.66 (m, 1H), 1.27 (app. td, J=7.5, 1.0 Hz, 3H), 0.88 (s, 9H), 0.85 (d, J=7.0 Hz, 3H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.15, 138.43, 128.3, 127.6, 127.5, 73.0, 70.3, 69.9, 67.5, 60.6, 43.9, 39.3, 32.4, 25.8, 18.0, 14.2, 10.6, −4.6, −4.7; IR (NaCl, film) 3480, 1726, 1370, 1255, 1098 cm^{-1}; HRMS (CI/isobutane) calcd for $C_{23}H_{41}O_5Si$ 425.2723, found 425.2719 $[M+H]^+$; $[\alpha]_D$=+1.8 (c 1.0, CH_2Cl_2).

5.1.11. (6*R*)-6-[(1*R*,2*S*)-4-Benzyloxy-2-(*tert*-butyl-dimethyl-silanyloxy)-1-methyl-butyl]-2,2-dimethyl-[1,3]-dioxan-4-carbonitrile (7). To a solution of β-hydroxy ester **23** (0.425 g, 1.0 mmol) in CH_2Cl_2 (12 mL) were added Et_3N (0.35 mL, 2.5 mmol), TMSCl (0.19 mL, 1.5 mmol) and 4-dimethylaminopyridine (12 mg, 0.10 mmol) in succession. After 3 h, the reaction was quenched by the addition of sat. aq. $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2, and the organic phase was dried over Na_2SO_4 and concentrated. The resulting crude silyl ether was dissolved in CH_2Cl_2 (5 mL) and the solution was cooled to −78°C. DIBAL-H (1.4 mL, 1.0 M in CH_2Cl_2, 1.4 mmol) was added dropwise. After 1.5 h, the reaction was quenched at −78°C by dropwise addition of methyl formate (0.2 mL). After 5 min, the reaction mixture was poured quickly into a cooled (0°C), rapidly stirred solution of Rochelle's salt. The resulting mixture was stirred rapidly at room temperature until the cloudy mixture became clear, at which time it was diluted with H_2O and extracted with CH_2Cl_2 (2×). The combined organic phases were dried over Na_2SO_4 and concentrated. The resulting crude aldehyde was dissolved in CH_2Cl_2. TMSCN (0.28 mL, 2.0 mmol) was added, followed by a crystal of KCN/18-crown-6 complex, and the reaction mixture was capped with a glass stopper. After 12 h, H_2O (0.018 mL, 1.0 mmol), acetone (4 mL) and 2,2-dimethoxypropane (2 mL) were added, followed by a catalytic quantity of *dl*-camphor sulfonic acid. After 18 h, Et_3N (0.5 mL) was added, and the mixture was concentrated. Flash chromatography (10% EtOAc/hexanes) readily separated the diastereomers, providing cyanohydrin acetonides **7** as clear oils (0.342 g combined, 0.77 mmol, 77% over four steps). Analytical data for the less polar diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 4.84 (dd, J=4.9, 4.2 Hz, 1H), 4.89 (s, 2H), 4.11 (ddd, J=8.9, 3.5, 3.5 Hz, 1H), 4.03–3.96 (m, 1H), 3.59–3.51 (m, 2H), 1.88–1.84 (m, 2H), 1.79–1.72 (m, 2H), 1.69–1.61 (m, 1H), 1.60 (s, 3H), 1.33 (s, 3H), 0.88 (s, 9H), 0.86 (d, J=7.1 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 128.1, 127.2, 127.2, 119.8, 100.7, 72.7, 68.6, 67.4, 66.8, 43.7, 32.1, 32.0, 29.6, 26.0, 21.9, 18.2, 9.6, −4.2, −4.3; IR (NaCl, film) 3062, 2955, 2357, 1472, 1383, 1122, 836 cm^{-1}; HRMS (CI) calcd for $C_{25}H_{42}NO_4Si$ 448.2884, found 448.2883 $[M+H]^+$; $[\alpha]_D$=−19.2 (c 5.55, CH_2Cl_2). Analytical data for the more polar diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.27 (m, 5H), 4.73 (dd, J=11.9, 2.5 Hz, 1H), 4.49 (s, 2H), 4.08–4.06 (m, 1H), 3.73 (ddd, J=10.5, 9.5, 1.9 Hz, 1H), 3.59–3.50 (m, 2H), 1.85 (dt, J=12.9, 2.3 Hz, 1H), 1.78–1.63 (m, 4H), 1.38 (d, J=11.1 Hz, 6H), 0.89 (s, 9H), 0.85 (d, J=7.0 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.34, 128.1, 127.2 (2), 117.7, 99.6, 72.8, 69.1, 68.7, 67.4, 59.4, 43.9, 32.7, 32.3, 29.6, 26.0, 19.2, 18.2, 9.7, −4.3, −4.4; IR (NaCl, film) 3089, 2253, 1472, 1382, 1259, 1101 cm^{-1}; HRMS (CI/NH_3) calcd for $C_{25}H_{42}NO_4Si$ 448.2884, found 448.2874 $[M+H]^+$; $[\alpha]_D$=−27.0 (c 1.9, CH_2Cl_2).

5.1.12. (3*R*)-4-Bromo-3-(*tert*-butyl-dimethyl-silanyloxy)-*N*-methoxy-*N*-methyl-butyramide (31). To a cooled (0°C) suspension of *N*,*O*-dimethyl hydroxylamine hydrochloride (7.42 g, 76.1 mmol) in CH_2Cl_2 (75 mL) was added Me_3Al (38.3 mL, 2.0 M in hexanes, 76.6 mmol) cautiously via syringe (gas evolution). The mixture was stirred at 0°C for 10 min, then at room temperature for 30 min. The reaction mixture was cooled to 0°C, and a solution of alcohol **29**[22] (5.00 g, 23.7 mmol) in CH_2Cl_2 (40 mL+10 mL rinse) was added dropwise via cannula. The reaction mixture was allowed to warm slowly to room temperature. After being stirred for 18 h, the reaction mixture was cooled to −15°C, carefully quenched by dropwise addition of 0.5 M aq. HCl (150 mL), and stirred vigorously until clean phase separation was achieved. The aqueous phase was extracted twice with CH_2Cl_2, and the combined organic phases were washed sat. aq. $NaHCO_3$, dried over Na_2SO_4, and concentrated. The resulting crude Weinreb amide was dissolved in CH_2Cl_2 (100 mL) and the mixture was cooled to −78°C. 2,6-Lutidine (5.5 mL, 47 mmol) was added, followed by TBSOTf (7.1 mL, 31 mmol). After 1.5 h, the reaction mixture was placed in a 0°C bath, stirred at this temperature for 30 min, then was quenched by the addition of sat. aq. NH_4Cl. The aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were washed with 1 M aq. $NaHSO_4$ (2×), sat. aq. $NaHCO_3$ (2×), then dried over Na_2SO_4 and concentrated. Purification by flash chromatography (15% EtOAc/hexanes) afforded Weinreb amide **31** (5.77 g, 17.8 mmol, 75% over two steps) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.42–4.35 (m, 1H), 3.70 (s, 3H), 3.48 (dd, J=10.4, 4.0 Hz, 1H), 3.44 (dd, J=10.4, 5.6 Hz, 1H), 3.17 (s, 3H), 2.80 (dd, J=15.4, 7.0 Hz, 1H), 2.68 (dd, J=15.4, 5.0 Hz, 1H), 0.88 (s, 9H), 0.12 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 68.5, 61.4, 38.5, 38.2, 32.0, 25.7, 18.0, −4.7, −4.8; IR (NaCl, film)1663, 1463, 1254, 1088 cm^{-1}; HMRS (CI) calcd for $C_{12}H_{27}BrNO_3Si$ 340.0944, found 340.0936 $[M+H]^+$; $[\alpha]_D$=+33.3 (c 1.65, $CHCl_3$).

5.1.13. (4*R*)-5-Bromo-4-(*tert*-butyl-dimethyl-silanyloxy)-pentan-2-one (32). A solution of Weinreb amide **31** (2.0 g, 5.88 mmol) in THF (39 mL) was cooled to −25°C, and MeMgBr (4.9 mL, 3.0 M in Et_2O, 14.7 mmol) was added dropwise. After 45 min, a second portion of MeMgBr (0.8 mL, 3.0 M in Et_2O, 2.4 mmol) was added, and the mixture was stirred for an additional 50 min, at which time the reaction was quenched by the dropwise addition of sat. aq. NH_4Cl. The mixture was allowed to warm to room temperature, and the aqueous phase was extracted with Et_2O (2×). The combined organic phases were dried over $MgSO_4$ and concentrated. Purification by flash chromatography provided methyl ketone **32** (1.56 g, 5.30 mmol, 90%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.35–4.31 (m,

1H), 3.41 (dd, J=10.3, 4.1 Hz, 1H), 3.36 (dd, J=10.3, 5.9 Hz, 1H), 2.78 (dd, J=16.5, 5.0 Hz, 1H), 2.71 (dd, J=16.5, 7.0 Hz, 1H), 2.17 (s, 3H), 0.87 (s, 9H), 0.11 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.6, 67.9, 49.2, 37.8, 31.5, 25.7, 18.0, −4.7, −4.9; IR (NaCl, film) 1719, 1469, 1361, 1255, 837 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{22}BrO_2Si$ 293.0562, found 293.0565 $[M-H]^+$; $[\alpha]_D$=+31.9 (c 2.0, CH_2Cl_2).

5.1.14. (4*R*)-5-Bromo-4-(*tert*-butyl-dimethyl-silanyloxy)-2-trimethylsilanyloxy-pent-1-ene (33). To a cooled (0°C) solution of i-Pr_2NH (0.70 mL, 5.04 mmol) in THF (27 mL) was added n-BuLi (2.50 mL, 1.70 M in hexanes, 4.23 mmol). After 10 min, the mixture was cooled to −78°C and a solution of ketone **32** (1.19 g, 4.03 mmol) in THF (3 mL+3 mL rinse) was added dropwise via cannula. The resulting mixture was stirred for 2 min, then TMSCl (0.83 mL, 6.44 mmol) was added dropwise. The reaction mixture was held at −78°C for 1.5 h, then allowed to warm to room temperature. After 40 min at room temperature, pentane was added (100 mL), and the resulting cloudy white suspension was poured into a separatory funnel containing ice cold sat. aq. $NaHCO_3$. The layers were separated, and the organic phase was dried over Na_2SO_4. The resulting silyl enol ether **33** was taken on directly: ^{1}H NMR (400 MHz, C_6D_6) δ 4.16–4.09 (m, 3H), 3.32 (dd, J=10.4, 4.4 Hz, 1H), 3.26 (dd, J=10.4, 5.6 Hz, 1H), 2.35 (dd, J=13.6, 6.4 Hz, 1H), 2.30 (dd, J=13.6, 6.0 Hz, 1H), 1.00 (s, 9H), 0.13 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H).

5.1.15. (3*R*)-4-Bromo-3-(*tert*-butyl-dimethyl-silanyloxy)-butyraldehyde (34). To a cooled (−78°C) solution of ester **29**[22] (7.17 g, 34.0 mmol) in CH_2Cl_2 (75 mL) were added 2,6-lutidine (8.3 mL, 71 mmol), followed by TBSOTf (11 mL, 48 mmol). After 2 h, the mixture was placed in a 0°C bath, and was held at this temperature for 20 min. At this point the reaction was quenched by the addition of sat. aq. NH_4Cl and the mixture was allowed to warm to room temperature. The aqueous phase was extracted with CH_2Cl_2 (2×), and the combined organic phases were washed with 1 M $NaHSO_4$, sat. aq. $NaHCO_3$ (2×), and H_2O, then dried over Na_2SO_4 and concentrated. Purification by flash chromatography (20% CH_2Cl_2/hexanes, then 3% EtOAc/hexanes) afforded the silyl ether (10.49 g, 6.81 mmol, 95%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32–4.29 (m, 1H), 4.17–4.10 (m, 2H), 3.42 (dd, J=10.4, 4.8 Hz, 1H), 3.39 (dd, J=10.4, 6.4 Hz, 1H), 2.71 (dd, J=15.6, 4.8 Hz, 1H), 2.53 (dd, J=15.6, 7.2 Hz, 1H), 1.27 (t, J=8.0 Hz, 3H), 0.87 (s, 9H), 0.12 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 69.0, 60.6, 41.1, 37.1, 25.6, 17.9, 14.2, −4.6, −5.0; IR (NaCl, film) 1732, 1472, 1377, 1265 cm^{-1}; HRMS (CI) calcd for $C_{11}H_{22}BrO_3Si$ 309.0522, found 309.0523 $[M-CH_3]^+$; $[\alpha]_D$=+23.6 (c 2.35, CH_2Cl_2). To a cooled (−78°C) solution of the silyl ether obtained above (1.40 g, 4.30 mmol) in CH_2Cl_2 (22 mL) was added DIBAL-H (6.45 mL, 1.0 M in hexanes, 6.45 mmol), dropwise over 10 min. After 80 min, the reaction was quenched at −78°C by dropwise addition of methyl formate (1.5 mL). The reaction mixture was then added via cannula to a rapidly stirred, 0°C solution of Rochelle's salt. The resulting cloudy suspension was stirred rapidly at room temperature for 3 h, at which point a clear phase separation was apparent. The aqueous phase was then extracted with CH_2Cl_2 (2×) and the combined organic phases were dried over Na_2SO_4 and concentrated. Purification by flash chromatography (8% EtOAc/hexanes) afforded aldehyde **34** (989 mg, 3.53 mmol, 82%), as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.79 (t, J=1.8 Hz, 1H), 4.39–4.36 (m, 1H), 3.42 (dd, J=10.4, 4.3 Hz, 1H), 3.35 (dd, J=10.4, 6.6 Hz, 1H), 2.81 (ddd, J=16.7, 4.6, 1.3 Hz, 1H), 2.70 (ddd, J=16.7, 6.9, 2.3 Hz, 1H), 0.86 (s, 9H), 0.11 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.5, 67.6, 49.7, 37.2, 25.9, 18.2, −4.3, −4.6; IR (NaCl, film) 2725, 1727, 1257, 838 cm^{-1}; HRMS (CI) calcd for $C_{10}H_{22}BrO_2Si$ 281.0573 found 281.0573 $[M+H]^+$; $[\alpha]_D$=+23.1 (c 4.8, CH_2Cl_2).

5.1.16. (2*R*,6*R*,8*R*)-1,9-Dibromo-2,8-bis-(*tert*-butyl-dimethyl-silanyloxy)-6-hydroxy-nonan-4-one (40). To a cooled (−78°C) solution of crude enol silane **33** obtained above and aldehyde **34** (0.989 g, 3.54 mmol) in CH_2Cl_2 (35 mL) was added $BF_3{\cdot}OEt_2$ (0.67 mL, 5.28 mmol) dropwise. The reaction mixture was allowed to stir at −78°C for 1.5 h, at which point the reaction was quenched by addition of sat. aq. $NaHCO_3$, and allowed to warm to room temperature. The aqueous phase was extracted with CH_2Cl_2 (2×), and the combined organic phases were dried over Na_2SO_4 and concentrated. Purification by flash chromatography (2% EtOAc/hexanes then 8% EtOAc/hexanes) afforded a diastereomeric mixture of aldol adducts **40** (1.50 g, 2.62 mmol, 74%) as a slightly yellow oil. Acylation (Ac_2O, pyridine, DMAP) of a small portion of the mixture of diastereomers and integration of the acetate peaks revealed diastereoselectivity of 3.3:1. Diastereomerically pure **40** was obtained by MPLC purification (10% EtOAc/hexanes): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.35–4.32 (m, 1H), 4.26–4.22 (m, 1H), 4.15 (dddd, J=8.1, 5.1, 5.1, 3.1 Hz, 1H), 3.42–3.33 (m, 4H), 3.22 (br s, 1H), 2.81 (dd, J=16.5, 4.8 Hz, 1H), 2.71 (dd, J=16.5, 6.9 Hz, 1H), 2.62 (dd, J=17.7, 3.6 Hz, 1H), 2.56 (dd, J=17.7, 8.4 Hz, 1H), 1.74 (ddd, J=13.8, 10.5, 2.9 Hz, 1H), 1.64–1.60 (m, 1H), 0.90 (s, 9H), 0.87 (s, 9H), 0.12 (s, 6H), 0.11 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 68.6, 67.8, 63.8, 51.1, 49.0, 41.5, 37.9, 37.5, 26.8, 25.7, 18.0, 17.9, −4.6, −4.7, −4.8 (2); IR (NaCl, film) 3534, 1709, 1472, 1256, 1076 cm^{-1}; HRMS (electrospray) calcd for $C_{21}H_{44}O_4Si_2Br_2Na$ 597.1055, found 597.1042 $[M+Na]^+$; $[\alpha]_D$=+25.8 (c 2.7, CH_2Cl_2).

5.1.17. (2*R*,4*S*,6*S*,8*R*)-1,9-Dibromo-2,8-bis-(*tert*-butyl-dimethyl-silanyloxy)-nonane-4,6-diol (42). To a cooled (−25°C) solution of **40** (1.36 g, 2.36 mmol) and isobutyraldehyde (1.07 mL, 11.8 mmol) was added SmI_2 (11.8 mL, 0.10 M in THF, 1.18 mmol). After 10 min, more SmI_2 was added (5.0 mL, 0.5 mmol). After an additional 10 min, the reaction was quenched by the addition of sat. aq. $NaHCO_3$. The mixture was diluted with H_2O, and the aqueous phase was extracted with Et_2O (2×). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated. The crude reduction product was dissolved in CH_2Cl_2 (15 mL). The mixture was cooled to −78°C, and DIBAL-H (11.8 mL, 1.0 M in toluene, 11.8 mmol) was added. After 10 min, the reaction mixture was placed in a −35°C cryobath. After 40 min, the reaction mixture was warmed to 0°C, then quenched by the careful addition of Rochelle's salt. The mixture was rapidly stirred until a clear phase separation was apparent. The organic phase was dried

over Na_2SO_4 and concentrated. Rapid purification by flash chromatography (30% EtOAc/hexanes) provided **42** (0.933 g, 1.65 mmol, 70% for two steps) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.24–4.18 (m, 4H), 3.52 (s, 2H), 3.44–3.38 (m, 4H), 1.88–1.82 (m, 2H), 1.77–1.72 (m, 2H), 1.61 (t, J=5.5 Hz, 2H), 0.90 (s, 18H), 0.13 (s, 6H), 0.12 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 70.3, 65.4, 43.4, 40.9, 36.3, 25.7, 18.0, −4.6, −4.9; IR (NaCl, film) 3428, 1362, 1256, 1080, 837 cm^{-1}; HRMS (electrospray) calcd for $C_{21}H_{46}Br_2O_4Si_2Na$ 599.1199, found 599.1181 $[M+Na]^+$; $[\alpha]_D$=+20.3 (c 0.86, CH_2Cl_2).

5.1.18. C20–C28 fragment (6). To a solution of diol **42** (0.481 g, 0.833 mmol) in MeOH (25 mL) was added Dowex-50WX8-100 acidic resin (0.800 g), and the resultant suspension was heated to reflux. After 2 h, the mixture was allowed to cool to room temperature, and was filtered through a fritted funnel to remove the resin. The filtrate was concentrated, and the resulting oil was azeotroped with hexanes (2×) and with benzene. The resulting pale orange solid was dried for 2 h under high vacuum, then was dissolved in acetone (10 mL) and 2,2-dimethoxypropane (4 mL). *dl*-Camphor sulfonic acid (40 mg, 0.17 mmol) was then added. After the mixture was stirred for 5 days at room temperature, triethylamine (0.5 mL) was added and the reaction mixture was concentrated. Purification by flash chromatography (10% EtOAc/hexanes) provided bis-acetonide **6** (0.182 g, 0.425 mmol, 51%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.03–3.98 (m, 4H), 3.37 (dd, J=10.4, 6.3 Hz, 2H), 3.34 (dd, J=10.4, 5.5 Hz, 2H), 1.71–1.66 (m, 4H), 1.57 (dd, J=7.3, 5.4 Hz, 2H), 1.36 (s, 6H), 1.35 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 100.9, 68.8, 62.7, 41.6, 37.2, 35.3, 24.7, 24.6; IR (NaCl, film) 2988, 1382, 1224, 1130, 649 cm^{-1}; HRMS (CI/NH_3) calcd for $C_{15}H_{27}O_4Br_2$ 429.0277, found 429.0269 $[M+H]^+$; $[\alpha]_D$=+29.0 (c 0.84, $CHCl_3$).

5.1.19. C20–C38 fragment (43). To a solution of bis-acetonide **6** (0.410 g, 0.95 mmol) and cyanohydrin acetonide **7** (0.178 g, 0.39 mmol) in THF (1.5 mL) was added DMPU (0.24 mL, 1.99 mmol), and the mixture was cooled to −78°C. Freshly prepared LDA (0.60 mL, 1.0 M in THF, 0.60 mmol) was added dropwise. After 10 min, the reaction mixture was placed in a −50°C cryobath. After 45 min, another portion of LDA (0.20 mL, 1.0 M in THF, 0.20 mmol) was added, followed 30 min later by another addition of LDA (0.20 mL, 1.0 M in THF, 0.20 mmol), at which point TLC indicated disappearance of cyanohydrin acetonide **7**. The reaction was then quenched by addition of sat. aq. NH_4Cl, and the mixture was allowed to warm to room temperature. The aqueous phase was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated. Purification by flash chromatography (8% EtOAc/hexanes then 10% EtOAc/hexanes) provided adduct **43** (0.20 g, 0.25 mmol, 65%), in addition to dibromide **6** (0.172 g, 0.41 mmol, 75% recovery): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.26 (m, 5H), 4.48 (s, 2H), 4.19–4.10 (m, 2H), 4.40–3.94 (m, 2H), 3.60–3.49 (m, 3H), 3.39–3.33 (m, 2H), 2.04 (dd, J=14.4, 8.4 Hz, 1H), 1.92 (dd, J=12.2, 2.8 Hz, 1H), 1.90–1.85 (m, 1H), 1.78–1.56 (m, 10H), 1.61 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H), 0.87 (s, 9H), 0.85 (d, J=7.0 Hz, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 128.3, 127.4, 127.3, 122.4, 100.9, 100.7, 100.6, 72.7, 68.6, 68.3, 67.5, 66.9, 62.8, 62.7, 61.8, 46.7, 43.8, 41.7, 39.2, 37.3, 35.9, 35.3, 31.9, 30.7, 25.9, 24.8, 24.7, 24.6, 24.5, 21.3, 18.0, 9.5, −4.6 (2); IR (NaCl, film) 3054, 2988, 2309, 1383, 1266, 1225, 896 cm^{-1}; HRMS (electrospray) calcd for $C_{40}H_{66}NO_8$-BrSiNa 818.3639, found 818.3609 $[M+Na]^+$; $[\alpha]_D$=−3.1 (c 0.45, $CHCl_3$).

5.1.20. C13–C38 fragment (3). A solution of cyanohydrin acetonide **5** (82.0 mg, 0.228 mmol) and bromide **43** (91.0 mg, 0.114 mmol) in THF (0.46 mL) was cooled to −78°C, and DMPU (69 μL, 0.57 mmol) was added. Freshly prepared LDA (250 μL, 1.0 M in THF, 0.25 mmol) was added dropwise over 5 min. The reaction mixture was then transferred to a cryobath set at −50°C, and was stirred at this temperature for 2.5 h. Another portion of LDA (70 μL, 0.070 mmol) was added, and the reaction mixture was stirred for an additional 30 min, then was quenched at −50°C by addition of MeOH (100 μL). The mixture was allowed to warm to room temperature and was diluted with H_2O and extracted twice with CH_2Cl_2. The combined organic phases were washed with sat. aq. NaCl, dried over Na_2SO_4 and concentrated. Flash chromatography (8% EtOAc/hexanes then 10% EtOAc/hexanes) provided polyol **3** as a colorless oil (86.0 mg, 0.80 mmol, 70%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.26 (m, 10H), 5.75 (dd, J=15.6, 8.1 Hz, 1H), 5.43 (dd, J=15.6, 6.1 Hz, 1H), 4.59–4.55 (m, 1H), 4.57 (s, 2H), 4.48 (s, 2H), 4.14–4.10 (m, 3H), 4.01–3.95 (m, 3H), 3.58–3.51 (m, 2H), 3.00 (dd, J=5.8, 5.5 Hz, 1H), 2.46 (ddd, J=13.4, 13.4, 6.6 Hz, 1H), 2.09–1.31 (m, 18H), 1.72 (s, 3H), 1.62 (s, 3H), 1.42 (s, 3H), 1.35 (s, 6H), 1.33 (s, 3H), 1.31 (s, 3H), 1.30 (s, 3H), 1.08 (d, J=6.5 Hz, 3H), 0.96 (d, J=6.6 Hz, 3H), 0.95 (d, J=6.4 Hz, 3H), 0.88 (s, 9H), 0.86 (d, J=7.5 Hz, 3H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.91, 138.7, 137.0, 128.3, 128.2, 128.1, 127.6, 127.5, 127.4 (2), 122.4, 122.2, 101.0, 100.7, 100.6 (2), 88.6 (2), 75.2, 72.7, 68.5, 68.3, 68.0, 67.5, 67.3, 67.2, 62.7, 61.7 (2), 46.7, 46.6, 43.8, 41.7, 39.8, 39.2, 38.0, 35.9, 31.9, 31.0, 30.9, 30.7, 25.8 (2), 24.6 (2), 24.5, 24.4, 21.6, 21.3, 20.4, 18.0, 17.6, 15.6, 9.5, 4.64 (2); IR (NaCl, film) 3066, 2253, 1462, 1384, 1216, 757 cm^{-1}; LRMS (electrospray) calcd for $C_{62}H_{99}N_2O_{11}SiNa$ 1095.7, found 1095.7 $[M+Na]^+$; $[\alpha]_D$=−4.9 (c 2.4, CH_2Cl_2).

5.1.21. Diol (44). An approximately 0.35 M solution of lithium di-*tert*-butyl biphenylide in THF was prepared in the following manner: to a solution of di-*tert*-butylbiphenyl (0.90 g, 3.4 mmol) in THF (7.5 mL) was added a crystal of 2,2′-bipyridine. *n*-BuLi was added dropwise until a deep red color persisted. The red solution was then cooled to 0°C and 1.5 cm of lithium wire was added. The resulting deep green suspension was stirred for 5 h at 0°C. In a separate flask, a solution of **3** (11.4 mg, 0.011 mmol) in THF (1 mL) was cooled to −78°C. A portion of the LiDBB solution (0.9 mL, ~0.32 mmol) was added dropwise, resulting in a deep green reaction mixture. After 20 min, the reaction was quenched at −78°C by dropwise addition of a solution of 5:1 THF/MeOH (1 mL) and the colorless mixture was allowed to warm to room temperature. The mixture was diluted with H_2O and extracted twice with CH_2Cl_2. The combined organic phases were washed with sat. aq. NH_4Cl, dried over Na_2SO_4, and concentrated. Flash chromatography (15% CH_2Cl_2/hexanes then 40% EtOAc/hexanes) provided diol

44 (6.8 mg, 0.008 mmol, 75%) in addition to benzyl ether **45** (2.6 mg, 0.003 mmol, 25%), both as colorless oils. Analytical data for the desired diol **44**: ^{1}H NMR (500 MHz, C_6D_6) δ 5.66 (dd, J=15.6, 7.6 Hz, 1H), 5.55 (d, J=15.6, 5.6 Hz, 1H), 4.33 (ddd, J=9.0, 3.6, 3.6 Hz, 1H), 4.28–4.21 (m, 2H), 4.18–4.13 (m, 2H), 4.06–3.96 (m, 2H), 3.71 (t, J=5.8 Hz, 2H), 3.54–3.50 (m, 1H), 2.99 (t, J=5.8 Hz, 1H), 2.28–2.24 (m, 1H), 2.07–2.00 (m, 2H), 1.90–1.84 (m, 1H), 1.68–1.53 (m, 1H), 1.54 (s, 3H), 1.46 (s, 3H), 1.45 (s, 3H), 1.44 (s, 3H), 1.44–1.36 (m, 6H), 1.42 (s, 3H), 1.41 (s, 3H), 1.34 (s, 3H), 1.27 (s, 3H), 1.22–1.10 (m, 6H), 1.00 (s, 9H), 0.99 (d, J=6.7 Hz, 3H), 0.92 (d, J=6.6 Hz, 3H), 0.84 (d, J=6.1 Hz, 3H), 0.79 (d, J=6.9 Hz, 3H) 0.15 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 134.4, 131.4, 100.5 (2), 98.7, 98.5, 79.8, 70.9, 70.5, 70.2, 70.0, 66.2, 66.0, 63.5, 63.4, 63.3, 60.8, 45.2, 43.3, 43.1, 40.4 (2), 39.5 (2), 37.9, 36.5, 35.6, 31.3 (2), 31.0, 30.8, 26.5 (2), 25.7, 25.4, 20.3, 20.2, 20.1, 18.7, 17.4, 15.3, 9.8, −3.8, −4.0; IR (NaCl, film) 3446, 3053, 1645, 1385, 1265 cm^{-1}; HRMS (electrospray) calcd for $C_{46}H_{86}O_{11}SiNa$ 865.5837, found 865.5859 $[M+Na]^+$; $[\alpha]_D$=1.8 (c 0.90, CH_2Cl_2).

5.1.22. Aldehyde (46). To a solution of alcohol **44** (12.0 mg, 14.2 μmol) in CH_2Cl_2 (1 mL) was added freshly prepared pH 8.6 buffer (1 mL; 0.5 M $NaHCO_3$/0.05 M Na_2CO_3). *N*-Chlorosuccinimide (ca. 1 mg), TEMPO (one crystal), and Bu_4NCl (ca. 1 mg) were added sequentially. The resulting mixture was stirred vigorously at room temperature. After 2 h, the reaction mixture was diluted with CH_2Cl_2, dried over Na_2SO_4, and concentrated. Purification by flash chromatography (15% EtOAc/hexanes then 30% EtOAc/hexanes) provided aldehyde **46** (10.5 mg, 12.5 μmol, 88%) as a colorless oil. This unstable aldehyde was immediately taken forward: ^{1}H NMR (500 MHz, C_6D_6) δ 9.70 (dd, J=3.0, 1.6 Hz, 1H), 5.68 (dd, J=15.7, 7.7 Hz, 1H), 5.57 (dd, J=15.7, 5.4 Hz, 1H), 4.67 (app dt, J=8.5, 3.8 Hz, 1H), 4.29–4.13 (m, 7H), 3.39–3.35 (m, 1H), 2.98 (t, J=5.8 Hz, 1H), 2.35 (ddd, J=15.6, 8.5, 3.0 Hz, 1H), 2.25 (dd, J=13.6, 6.7 Hz, 1H), 2.20 (ddd, J=15.6, 3.7, 1.6 Hz, 1H), 1.86–1.82 (m, 1H), 1.72–1.62 (m, 4H), 1.65 (s, 3H), 1.59–1.52 (m, 5H), 1.55 (s, 3H), 1.46 (s, 3H), 1.44 (s, 3H), 1.41 (s, 3H), 1.39–1.33 (m, 6H), 1.34 (s, 3H), 1.22 (s, 3H), 1.04 (d, J=6.7 Hz, 3H), 0.96 (s, 9H), 0.92 (d, J=6.6 Hz, 3H), 0.79 (d, J=6.8 Hz, 3H), 0.76 (d, J=7.0 Hz, 3H), 0.11 (s, 3H), 0.08 (s, 3H).

5.1.23. Vinyl iodide (47). Chromous chloride (57.0 mg, 0.46 mmol) was suspended in THF (300 μL), which had been degassed by an argon sparge. In a separate flask, aldehyde **46** (28.0 mg, 0.033 mmol) was dissolved in dioxane (1.8 mL), and to this solution was added iodoform (113 mg, 0.29 mmol). Both flasks were then briefly degassed by an argon sparge. The aldehyde/iodoform solution was added to the suspension of chromous chloride via cannula, and the resulting mixture was stirred at room temperature in the absence of light. After 3.5 h, the reaction was quenched by the addition of sat. aq. NH_4Cl, diluted with H_2O, and extracted twice with EtOAc. The combined organic phases were washed successively with sat. aq. NaCl, 0.5 M aq. $Na_2S_2O_3$, again with sat. aq. NaCl, then dried over $MgSO_4$. Purification by flash chromatography (5% EtOAc/hexanes then 30% EtOAc/hexanes) provided vinyl iodide **47** (28.0 mg, 0.29 mmol, 88%) as an amorphous solid. Analysis of the ^{1}H NMR spectrum revealed an E/Z ratio of 11:1: ^{1}H NMR (500 MHz, C_6D_6) δ 6.60 (dt, J=14.4, 7.3 Hz, 1H), 5.90 (d, J=14.4 Hz, 1H), 5.67 (dd, J=15.6, 7.7 Hz, 1H), 5.56 (dd, J=15.6, 5.6 Hz, 1H), 4.26–4.22 (m, 3H), 4.19–4.14 (m, 3H), 4.07–3.97 (m, 2H), 3.52–3.47 (m, 1H), 2.98 (t, J=5.6 Hz, 1H), 2.25 (ddd, J=13.5, 13.5, 6.7 Hz, 1H), 2.09–1.93 (m, 5H), 1.83–1.78 (m, 2H), 1.73–1.67 (m, 2H), 1.65–1.56 (m, 3H), 1.55 (s, 3H), 1.47 (s, 3H), 1.46 (s, 3H), 1.44 (s, 3H), 1.43 (s, 3H), 1.42–1.36 (m, 3H), 1.40 (s, 3H), 1.34 (s, 3H), 1.25 (s, 3H), 1.03 (d, J=6.7 Hz, 3H), 1.00 (s, 9H), 0.92 (d, J=6.7 Hz, 3H), 0.90–0.83 (m, 3H), 0.79 (d, J=6.9 Hz, 3H), 0.77 (d, J=7.1 Hz, 3H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 144.7, 134.3, 131.5, 128.5, 100.5 (2), 98.7, 98.4, 79.7, 76.6, 71.3, 70.8, 70.2, 66.2, 66.0, 63.5, 63.3, 63.2, 45.1, 43.3 (2), 43.2, 40.4 (2), 40.0, 39.5 (2), 39.3, 38.0, 35.4, 31.3, 31.0, 30.8, 26.5, 25.7, 25.5, 20.3, 20.2, 20.1, 18.7, 17.3, 15.3, 10.0, −3.7, −4.0; IR (NaCl, film) 3430, 3054, 2987, 1422, 1264 cm^{-1}; HRMS (electrospray) calcd for $C_{47}H_{85}IO_{10}SiNa$ 987.4855, found 987.4830 $[M+Na]^+$; $[\alpha]_D$=+6.9 (c 1.0, CH_2Cl_2).

5.1.24. Phosphonate ester (48). To a solution of **47** (20.0 mg, 0.021 mmol) in CH_2Cl_2 (600 μL) was added DMAP (46 mg, 0.38 mmol) followed by BOP reagent (128 mg, 0.29 mmol). To this mixture was added (diethylphosphono)acetic acid (57.0 mg, 0.29 mmol) as a solution in CH_2Cl_2 (500 μL). The resulting mixture was stirred at room temperature for 48 h, at which point it was diluted with EtOAc. The organic phase was washed with sat. aq. $NaHCO_3$ and brine, then dried over Na_2SO_4 and concentrated. Purification by flash chromatography (50% EtOAc/hexanes) provided phosphonate ester **49** (25.0 mg, 0.021 mmol, ~100%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.51 (ddd, J=14.4, 7.5, 7.5 Hz, 1H), 5.97 (d, J=14.4 Hz, 1H), 5.54–5.46 (m, 2H), 4.71 (dd, J=7.5, 4.8 Hz, 1H), 4.31–4.27 (m, 1H), 4.20–4.14 (m, 2H), 3.94–3.91 (m, 9H), 3.71–3.61 (m, 1H), 2.97 (d, J=21.6 Hz, 2H), 2.49–2.44 (m, 1H), 2.28–2.01 (m, 3H), 1.89–1.80 (m, 4H), 1.72–1.70 (m, 1H), 1.58–1.45 (m, 17H), 1.43 (s, 3H), 1.39 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H), 1.34 (s, 6H), 1.33 (s, 6H), 1.00 (d, J=6.7 Hz, 3H), 0.89 (d, J=7.7 Hz, 6H), 0.88 (s, 9H), 0.80 (d, J=7.0 Hz, 3H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6 (d, $J_{3\text{-}P}$=6.2 Hz), 144.3, 139.2, 133.3, 131.6, 100.3 (2), 98.5, 98.1, 82.2, 76.0, 70.9, 70.0 (2), 65.7, 65.3, 63.0, 62.9, 62.7, 62.5 ($J_{3\text{-}P}$=6.2 Hz), 62.5 ($J_{3\text{-}P}$=6.2 Hz), 43.9, 42.3, 42.2, 42.1, 39.0, 38.7 (2), 38.5, 36.8, 34.3, 34.2 ($J_{2\text{-}P}$=134 Hz), 30.2, 30.1, 29.6, 25.8, 24.9 (2), 24.8 (2), 19.8, 19.7, 19.6, 18.0, 16.3 ($J_{4\text{-}P}$=6.2 Hz), 16.3 ($J_{4\text{-}P}$=6.2 Hz), 16.2, 15.7, 9.6, −4.3, −4.7; IR (NaCl, film) 3054, 1727, 1632, 1422, 1381 cm^{-1}; $[\alpha]_D$=+9.3 (c 0.40, CH_2Cl_2).

5.1.25. 9-Tributylstannyl-nona-2,4,6,8-tetraen-1-ol (4). To a cooled (−78°C) solution of ester **49**[40] (130 mg, 0.278 mmol) in THF (3 mL) was added DIBAL-H (1.11 mL, 1.0 M in toluene, 1.11 mmol) dropwise. After 90 min, the reaction was quenched by dropwise addition of MeOH (750 μL), then was diluted with Et_2O and Rochelle's salt, and stirred rapidly at room temperature. The layers were separated, and the organic phase was diluted with hexanes and dried over Na_2SO_4. Purification by flash chromatography (5% EtOAc/hexanes with 2% Et_3N, then 15% EtOAc/hexanes with 2% Et_3N) afforded **4** (63 mg,

0.15 mmol, 53%) as a yellow oil. This light sensitive compound was stored at −20°C, protected from light, in deoxygenated benzene: ^{1}H NMR (500 MHz, C_6D_6) δ 6.82 (dd, J=23.3, 12.1 Hz, 1H), 6.45 (d, J=23.3 Hz, 1H), 6.33–6.14 (m, 5H), 5.63–5.55 (m, 1H), 3.85 (t, J=6.9 Hz, 2H), 1.68–1.54 (m, 6H), 1.38 (sextet, J=9.2 Hz, 6H), 1.03–0.99 (m, 6H), 0.94 (t, J=9.2 Hz, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 148.1, 136.6, 135.3, 133.9, 133.8, 133.5, 132.8, 131.3, 63.5, 29.9 (t, J_{Sn-C}=10.3 Hz), 28.1 (t, J_{Sn-C}=26.8 Hz), 14.3, 10.3 (t, J_{Sn-C}=170.7 Hz).

5.1.26. Polyene (50). To a dry flask containing vinyl iodide **48** (9.0 mg, 7.9 μmol) and vinyl stannane **4** (18.0 mg, 0.042 mmol) was added THF (700 μL) and *i*-Pr_2NEt (5.0 μL, 0.05 mmol). The mixture was then degassed by an argon sparge for 5 min. A separate flask was charged with $Pd_2(dba)_3$·$CHCl_3$ (6.5 mg, 0.0063 mmol) and triphenylarsine (12.0 mg, 0.039 mmol), and the mixture was suspended in THF (300 μL). The contents of this flask were then degassed by an argon sparge for 5 min. The contents of the flask containing the palladium catalyst were added to the reaction flask via cannula, and the resulting mixture was stirred at room temperature, protected from light. After 3 h, the reaction mixture was loaded directly onto a Pasteur pipet silica gel column. Purification by chromatography (10% EtOAc/hexanes, 2% Et_3N then 65% EtOAc/hexanes, 2% Et_3N) afforded polyene **50** (7.0 mg, 6.0 μmol, 77%) as a yellow oil. This highly sensitive compound was immediately taken forward: ^{1}H NMR (500 MHz, C_6D_6) δ 6.38–6.16 (m, 8H), 5.95–5.91 (m, 1H), 5.66–5.57 (m, 3H), 4.94 (dd, J=7.3, 5.0 Hz, 1H), 4.31–4.15 (m, 7H), 4.08–3.75 (m, 9H), 2.82 (d, J=21.6 Hz, 2H), 2.59–2.30 (m, 8H), 2.10–1.82 (m, 8H), 1.63–1.58 (m, 6H), 1.55 (s, 6H), 1.49–1.43 (m, 3H), 1.47 (s, 3H), 1.46 (s, 3H), 1.45 (s, 3H), 1.44 (s, 3H), 1.36 (s, 6H), 1.09 (d, J=6.7 Hz, 3H), 1.06 (t, J=6.7 Hz, 6H), 1.04 (s, 9H), 0.95 (d, J=6.7 Hz, 3H), 0.91 (d, J=7.2 Hz, 3H), 0.86 (d, J=6.9 Hz, 3H), 0.15 (s, 3H), 0.14 (s, 3H).

5.1.27. Macrolactone (52). Compound **50** (4.5 mg, 3.9 μmol) was dissolved in CH_2Cl_2 (1 mL) and $NaHCO_3$ (7.0 mg, 83.0 μmol) was added, followed by the Dess–Martin periodinane (7.1 mg, 20.0 μmol). The reaction mixture was stirred at room temperature, protected from light. After 1.5 h, the reaction mixture was loaded directly onto a Pasteur pipet silica gel column. Rapid filtration (60% EtOAc/hexanes, 2% Et_3N) afforded aldehyde **51**, which was used immediately in the next step. A separate dry flask had been charged with LiCl (8.8 mg, 0.21 mmol) and heated at 140°C overnight under high vacuum. After allowing the flask to cool to room temperature, a solution of aldehyde **51** in CH_3CN (1 mL+1 mL rinse) was added via cannula. After 15 min, DBU (13 μL, 0.09 mmol) was added dropwise. The mixture was then stirred at room temperature, protected from light. After 36 h, the reaction mixture was diluted with EtOAc, washed with pH 7 phosphate buffer, dried over Na_2SO_4, and concentrated. Flash chromatography (8% EtOAc/hexanes, 1% Et_3N) gave macrolactone **52** (2.0 mg, 2.0 μmol, 50%) as a yellow film: ^{1}H NMR (500 MHz, C_6D_6) δ 7.57 (dd, J=15.1, 11.3 Hz, 1H), 6.25–5.95 (m, 10H), 5.81–5.67 (m, 3H), 5.11 (dd, J=9.7, 1.6 Hz, 1H), 4.41–3.87 (m, 8H), 3.71–3.66 (m, 1H), 2.66–2.33 (m, 2H), 2.15–1.78 (m, 5H), 1.60 (s, 3H), 1.57–1.51 (m, 6H), 1.52 (s, 3H), 1.50–1.43 (m, 4H), 1.47 (s, 3H), 1.41 (s, 3H), 1.38 (s, 3H), 1.36 (s, 6H), 1.36–1.28 (m, 2H), 1.27 (s, 3H), 1.09 (d, J=6.8 Hz, 3H), 1.04 (s, 9H), 1.00 (d, J=6.3 Hz, 3H), 0.93 (d, J=7.0 Hz, 3H), 0.70 (d, J=6.6 Hz, 3H), 0.17 (s, 3H), 0.16 (s, 3H); HRMS (electrospray) calcd for $C_{58}H_{94}O_{11}SiNa$ 1017.6463, found 1017.6446 $[M+Na]^+$.

5.1.28. Synthetic dermostatin A (1). Macrolactone **52** (0.9 mg, 0.9 μmol) was dissolved in MeOH (1 mL), and Dowex 50WX8-100 acidic resin (10.0 mg) was added. The suspension was stirred at room temperature, protected from light. After 24 h, a small aliquot was removed and analzyed by electrospray mass spectrometry, which indicated complete deprotection of the acetonide protecting groups and partial deprotection of the C_{35}-OTBS group. The mixture was then heated to 50°C. After 2 h, the mixture was allowed to cool to room temperature, and the resin was removed by filtration through a cotton plug. Et_3N (3 drops) was added, and the mixture was concentrated. ^{1}H NMR analysis of the crude mixture indicated the presence of dermostatin A, with >80% purity. Purification by HPLC (C18 reversed-phase, isocratic 80% MeOH/H_2O at 3 mL/min, detector UV 390 nm) provided pure dermostatin A (0.5 mg, 77%) as a yellow film: ^{1}H NMR (500 MHz, CD_3OD) δ 7.30 (dd, J=15.0, 11.6 Hz, 1H), 6.70 (dd, J=14.8, 10.9 Hz, 1H), 6.52 (dd, J=14.6, 10.8 Hz, 1H), 6.44–6.12 (m, 7H), 5.88 (d, J=15.0 Hz, 1H), 5.84–5.79 (m, 1H), 5.58 (dd, J=15.9, 6.2 Hz, 1H), 5.48 (dd, J=15.9, 4.7 Hz, 1H), 4.84–4.79 (m, 1H), 4.27–4.24 (m, 1H), 4.13–3.89 (m, 7H), 3.56–3.54 (m, 1H), 2.62–2.59 (m, 1H), 2.48–2.34 (m, 2H), 1.90–1.13 (m, 16H), 1.00 (d, J=6.9 Hz, 3H), 0.95 (d, J=6.7 Hz, 3H), 0.87 (d, J=7.0 Hz, 3H), 0.96 (d, J=6.3 Hz, 3H); HRMS (electrospray) calcd for $C_{40}H_{64}O_{11}Na$ 743.4346, found 743.4324 $[M+Na]^+$; Analytical HPLC: Microsorb C18 reversed-phase column, detector λ=390 nm, isocratic 80/20 MeOH/H_2O, t_r=12.02 min. Absolute stereochemistry was confirmed by circular dichroism in MeOH: synthetic dermostatin A matched natural dermostatin A, each showing a positive Cotton effect (max λ=230 nm, min λ=208 nm).

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