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Total Synthesis of Dermostatin A

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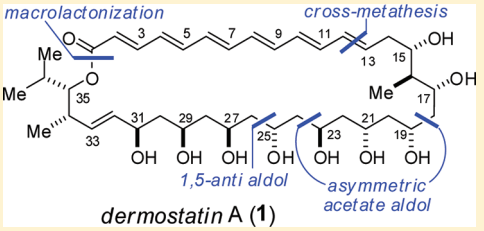
Supporting Information

ABSTRACT: The concise total synthesis of dermostatin A is described. Highlights include a two-directional application of the asymmetric acetate aldol method developed in our lab, a novel diastereotopic-group-selective acetal isomerization for terminus differentiation, and a selective cross-metathesis reaction between a terminal olefin and a trienal. A study of the scope and viability of similar cross-metathesis reactions is also described. The synthesis is convergent and utilizes fragments of roughly equal complexity.



INTRODUCTION

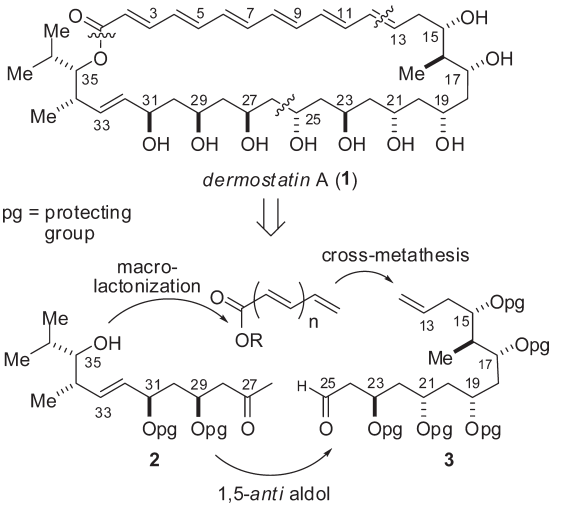
The oxopolyene macrolides are a structurally complex class of natural products that possess a hydrophilic skipped polyol domain and a hydrophobic polyene domain.[1] They display diverse biological activities, including antifungal activity against a variety of human pathogens, and their combination of biological activity and structural complexity has rendered them popular targets for synthesis.[2] Among the synthetic challenges posed by these molecules are the stereocontrolled synthesis of the polyol and polyene fragments as well as the fragment couplings required to produce the full-length carbon chain. We have described a method for the construction of acetate aldol subunits with control of absolute stereochemistry,[3] and in this article we describe a two-directional application of this method to the synthesis of dermostatin A (**1**) along with a novel terminus differentiation. Our synthesis also utilizes an alkene cross-metathesis reaction[4] between an electron-deficient triene and a terminal olefin,[2p] and we describe the scope of this reaction herein as well.

Dermostatin A (**1**, Scheme 1) is one of the more complex oxopolyene macrolides. It was first isolated nearly 50 years ago,[5] and its structure, devoid of stereochemical assignment, was determined about 10 years later by a combination of UV and NMR spectroscopy, mass spectrometry, and chemical derivatization and degradation.[6] In 1997, Rychnovsky et al.[7] published the full stereochemical assignment of dermostatins A and B by means of extensive NMR studies using the acetonide analysis method developed in his lab. Subsequently, Sinz and Rychnovsky[8] reported the total synthesis of dermostatin A.

RESULTS AND DISCUSSION

We wished to synthesize dermostatin A in a convergent fashion by a route that utilizes the stereoselective coupling of fragments of roughly equal complexity. The 1,5-*anti* aldol reaction developed by Evans and Paterson and co-workers[9] was deemed an expeditious approach because, in addition to coupling

Scheme 1. Initial Retrosynthetic Disconnection



the two fragments, it provides a product with 1,5-oxygenation bearing an anti relationship and a ketone at the 3-position. Reduction of the ketone directed[10] by the hydroxyl group of the aldol product allows for the creation of either hydroxyl stereochemistry at the 3-position of this stereotriad, thus providing added flexibility. An analysis of the connectivity and stereochemistry of the linear polyol chain suggests disconnection at the C-25−C-26 bond to provide two fragments, **2** and **3**, which are of approximately equal complexity and can be coupled by a 1,5-*anti* aldol reaction (Scheme 1).

A more detailed retrosynthesis is shown in Scheme 2. Late-stage macrocyclization[11] would be preceded by installation of the full polyene via a vinylogous Horner−Wadsworth−Emmons reaction between phosphonate **4** and aldehyde **5**. Synthesis of **5**

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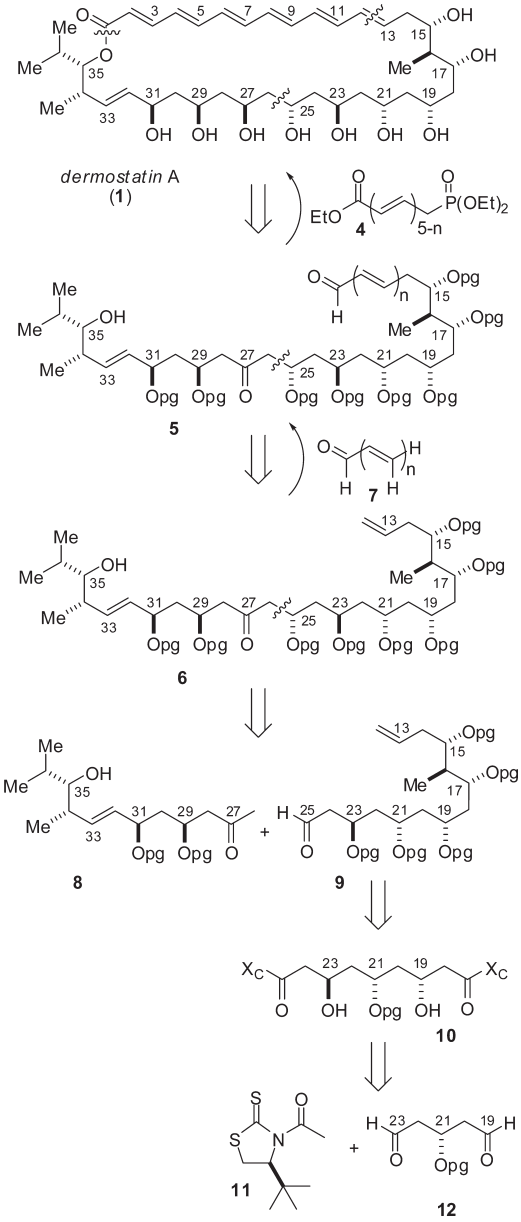
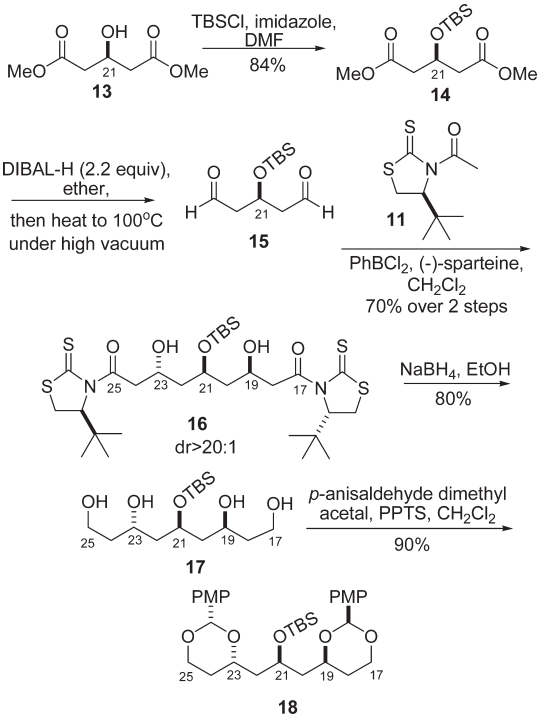
Scheme 2. Retrosynthesis



Scheme 3. Preparation of Bis-acetal 18



was envisioned via a selective olefin cross-metathesis reaction with terminal alkene **6** and an electron-deficient polyene: either a diene, triene, or tetraene (**7**, n = 2−4) depending on the suitability of these substrates in this reaction. Synthesis of **6** would be accomplished by aldol condensation of ketone **8** and aldehyde **9**. This disconnection also offers the advantage of using a common precursor in our synthesis of RK-397, ketone **8**.[2P] We envisioned the synthesis of aldehyde **9** by a two-directional strategy using our previously developed asymmetric acetate aldol method with reagent **11**.[3] This strategy would proceed via a bis-aldol reaction on an achiral dialdehyde to produce a 1,3- 1,5-, or 1,7-stereodiad with the two stereocenters bearing the same absolute stereochemistry. An examination of the structure of **9** suggests the use of a 3-hydroxyglutaraldehyde derivative centered on C-21 (**12**), wherein the double aldol addition would set the stereochemistry at C-23 and C-19. This would provide a pseudo-*C*2-symmetric product (**10**), which requires terminus differentiation in order to establish the stereocenter at C-21.[12] The implementation of this strategy is described below.

Our synthesis began with the protection [*tert*-butyldimethylsilyl chloride (TBSCl) and imidazole] and reduction (diisobutylaluminium hydride, DIBAL-H) of glutarate ester **13**, which provides the glutaraldehyde product as a complex mixture due to reversible hydration and cyclizaton to a lactol, followed by polymerization (Scheme 3). Dehydration of this polymeric material by heating to 100 °C at reduced pressure (∼2 mmHg) cleanly provided the monomeric dialdehyde (**15**) with only traces of oligomers detectable by NMR.[13] Subjection of **15** to our standard acetate aldol reaction conditions[3] [$PhBCl_2$, (−)-sparteine, *N*-acetylthiazolidinethione **11**[14]] provided the desired product (**16**) in 70% yield after chromatography. Analysis of the ^1H NMR spectrum of the crude reaction mixture indicated that the product is formed as a >20:1 diastereomeric mixture. Reduction to tetraol **17** ($NaBH_4$, 80%) was followed by treatment with pyridinium *p*-toluenesulfonate (PPTS) and *p*-anisaldehyde dimethyl acetal to provide bis-acetal **18** in 90% yield.

Compound **18** is pseudo-*C*2-symmetric, and the central carbon (C-21) is not stereogenic. A diastereotopic-group-selective differentiation[12] of the termini is required in order to set this stereocenter and differentiate the termini for subsequent elaboration. This was accomplished by a stereoselective acetal isomerization reaction that was induced by deprotection of the *tert*-butyldimethylsilyl (TBS) ether of **18** [tetrabutylammonium fluoride (TBAF), 87%] to provide alcohol **19**, followed by treatment with PPTS in toluene at 80 °C (Scheme 4). Under these conditions we obtained a 90:10 mixture of the desired internal acetal (**20**, wherein acetal B migrates) to starting terminal acetal (**19**) from which the desired acetal could be isolated in 82% yield. The isomeric internal acetal (**21**, wherein

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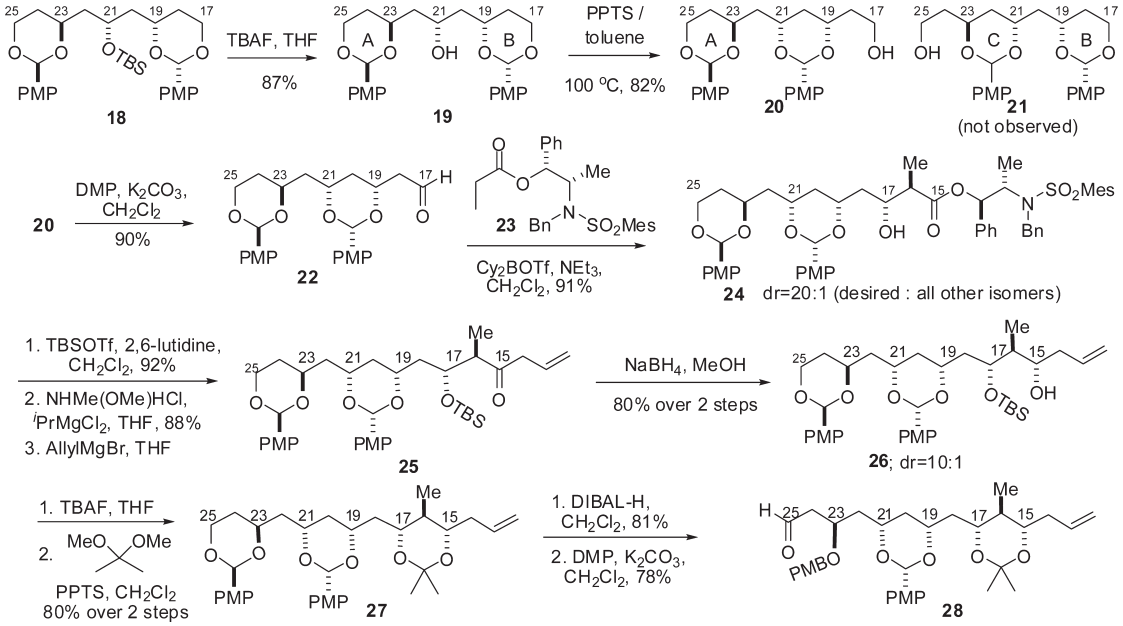
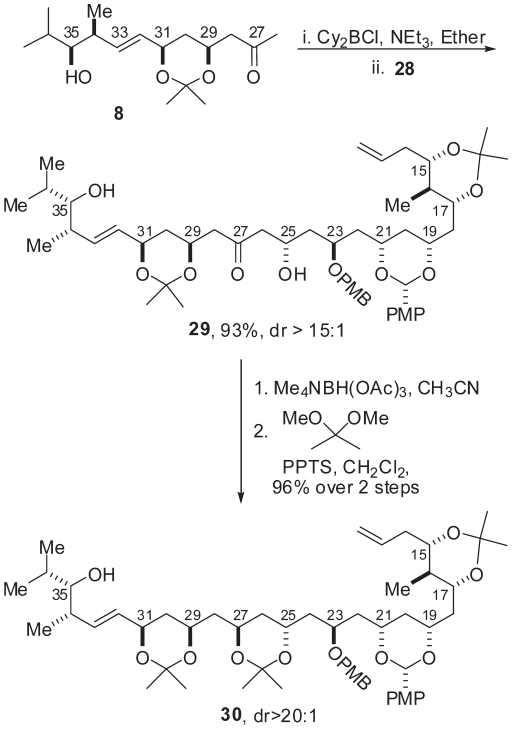
Scheme 4. Preparation of Aldehyde 28



acetal A migrates) was not observed, presumably because of the axial substituent that would be present at the 4-position of the newly formed 1,3-dioxane (acetal C). The A-value for substituents at the 4-position of a 1,3-dioxane is significantly higher than that in cyclohexane due to the decreased bond lengths and angles of the oxygen, thereby leading to the high selectivity in this reaction.[15] This reaction not only sets the stereocenter at C-21 to the desired configuration but also provides material wherein the termini are differentiated; C-17 bears a primary alcohol while C-25 is part of a *p*-methoxyphenyl (PMP) acetal. Oxidation of the C-17 alcohol [Dess−Martin periodinane (DMP), 90%] provides aldehyde **22**, which was subjected to an *anti*-selective aldol reaction using the Masamune reagent (**23**)[16] to provide ester **24** (91%, 20:1 desired/all other isomers). Protection of the hydroxyl group of **24** [*tert*-butyldimethylsilyl triflate (TBSOTf), 2,6-lutidine, 92%], conversion to the Weinreb amide via the Merck procedure[17] (MeNHOMe·HCl, *i*-PrMgCl; 88%), and allylation (allylMgBr) provided ketone **25**, which was reduced with $NaBH_4$ to provide the desired alcohol [**26**, 80% over two steps, diastereomeric ratio (dr) = 10:1].[8] Deprotection of the TBS ether (TBAF) and acetonide formation (2,2-dimethoxypropane, PPTS; 80% for two steps) provided **27**. Compound **27** was then treated with DIBAL-H to cleave the terminal PMP acetal selectively (81%). Oxidation of the resulting primary alchol (DMP, 78%) provided aldehyde **28** for use in the fragment coupling.

With aldehyde **28** in hand, we turned our attention to fragment coupling using the 1,5-*anti* aldol method developed by Evans and Paterson and co-workers.[9] Methyl ketone **8**, prepared in nine steps from isobutyraldehyde in 9% overall yield and previously used in our synthesis of RK-397,[18] and aldehyde **28** were subjected to the aldol reaction under the Paterson conditions[9] (Cy_2BCl, NEt_3) to provide aldol product **29** (93%, dr = 15:1, Scheme 5). *Anti*-selective reduction of the C-27 ketone, directed by the hydroxyl group at C-25 [$Me_4NBH(OAc)_3$, dr > 20:1],[19] and protection of the resulting

Scheme 5. Completion of Polyol Portion of Dermostatin A



diol as the acetonide (2,2-dimethoxypropane, PPTS; 96% for two steps) provided **30**, which contains the full polyol portion of the molecule with the C-35 hydroxyl group unprotected.

With the successful completion of the synthesis of the polyol domain of dermostatin A, we turned our attention to installation of the polyene domain to complete the total synthesis. We envisioned this occurring via the cross-metathesis of the terminal alkene of compound **30** with an unsaturated polyenal or

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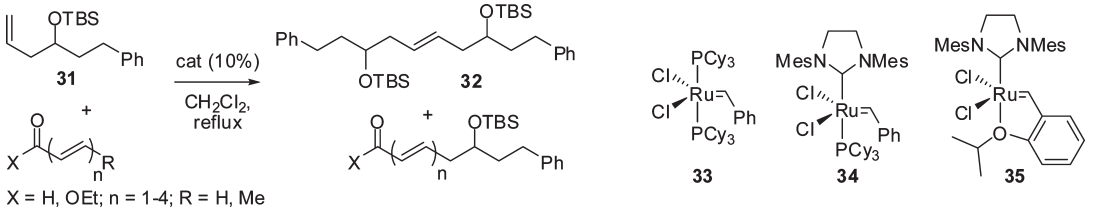
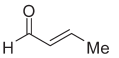
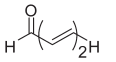
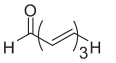
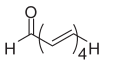
Scheme 6. Cross-Metathesis with Electron-Deficient Polyenes



polyenoate in order to construct the polyene in minimal steps. In our previous synthesis of RK-397, we employed the cross-metathesis of a trienal with a terminal alkene resembling **30**;[2p] however, the presence of a hexaene in dermostatin A as compared to the pentaene of RK-397 presents a greater challenge. Grubbs and co-workers[4a] have described a general model for selectivity in olefin cross-metathesis reactions wherein they place alkenes into one of four reactivity types, according to their ability to undergo homodimerization with a particular catalyst and whether that dimerization is reversible.[4] Cross-metathesis will then be selective for olefins of two different reactivities and less so when the olefins are of similar reactivity. To assess the viability of various cross-metathesis substrates, we undertook a model study with terminal alkene **31**,[20] which mimics our terminal alkene substrate and falls into the highest reactivity type for all common Ru metathesis catalysts (type 1, according to Grubbs' nomenclature).[21] We studied the cross-metathesis of **31** with alkenes, dienes, trienes, and tetraenes conjugated to an aldehyde or ester as shown in Scheme 6.[22] These compounds are of different reactivity types (we speculated types 1−3, depending on the choice of catalyst), and as such, we suspected they would require different catalysts and conditions to promote selective cross-metathesis with **31**. The problems we anticipated included the reticence of electron-deficient olefins to participate in metathesis reactions and, in the case of dienes−tetraenes, issues of selectivity with respect to metathesis of the terminal versus internal olefins. Reactions were run with a 10% catalyst loading in dichloromethane at reflux at a concentration of 0.1 M with 2.0 equiv of the α,β-unsaturated alkene. We then studied each substrate pair with each catalyst and noted the following general trends. In many cases we observed incomplete consumption of **31**, indicating that the reactions had stalled after some time, presumably due to catalyst inactivation or decomposition. In some reactions, conversion of **31** to the corresponding dimer (**32**) was prominent; thus, while consumption of **31** was high, conversion to the desired product was low. At times, complex mixtures of products were observed, again with consumption of **31**. Our results with each aldehyde-derived substrate and catalysts **33**−**35** are shown in Table 1.

For the cross-metathesis of acrolein and crotonaldehyde, we found that these electron-deficient substrates failed with the less active first-generation Grubbs catalyst (**33**).[23] In the case of acrolein, the reaction stalled at low conversion, and in the case of crotonaldehyde, most of **31** was converted to dimer **32** (36% conversion to **32**, which consumes 72% of **31**) and provided the desired product in only 16% yield. The more active second-generation Grubbs catalyst (**34**)[24] or the phosphine-free variant (**35**) described by Hoveyda and co-workers[25] and by Blechert and co-workers[26] provided superior results. In the case of crotonaldehyde, catalysts **34** and **35** were essentially equivalent;

Table 1. Cross-Metathesis of 31 with Enal and Polyenal Substrates (Scheme *6*)

Entry	Substrate (2 equiv)	Cat	Consumption of **31**	Dimer (**32**)	Yield[a]	Comments
1	 **36**	**33**	7%	3%	ND	
2		**34**	56%	trace	(54%)	
3		**35**	92%	trace	75%	
4[b]	 **37**	**33**	91%	36%	16%	
5		**34**	>98%	trace	91%	
6		**35**	>98%	trace	94%	
7	 **38**	**33**	12%	trace	ND	
8[c]		**34**	46%	ND	ND	2.2:1[d]
9[c]		**36**	66%	trace	ND	1.2:1[d]
10	 **39**	**33**	86%	trace	72%	4:1 E:Z[e]
11		**34**	32%	trace	ND	
12		**35**	33%	trace	ND	
13	 **40**	**33**	37%	trace	ND	Complex mixtures by NMR
14		**34**	41%	ND	ND	
15		**35**	30%	ND	ND	

[a] Isolated yield; numbers in parentheses are conversions as determined by NMR. [b] 3.0 equiv of **37** were used. [c] Conducted at room temperature. [d] Ratio of terminal to internal olefin metathesis. [e] Isomeric at the alkene distal to the aldehyde.

both provided complete consumption of **31** and cleanly provided the desired product in 91% and 94% yields, respectively. Acrolein required the more active catalyst, **35**, to proceed to complete conversion, presumably because it is less reactive than crotonaldehyde, and provided the product in a yield of 75%.

We were unable to obtain satisfactory results with dienal **38**[18] due to either reactivity or selectivity problems. In the case of the least reactive first-generation Grubbs catalyst (**33**), the reaction cleanly proceeded to the desired product but consistently stalled at about 12% conversion. The more reactive catalysts (**34** and **35**) provided higher conversion but suffered from poor selectivity for the terminal alkene (2.2:1 ratio of terminal to internal metathesis with catalyst **34**, and 1.2:1 ratio with catalyst **35**).

In contrast, we were pleased to find that trienal **39**[18] is a competent substrate, but only with the least active of the catalysts. In this substrate, it appears that the electron-withdrawing aldehyde

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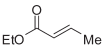
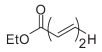
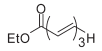
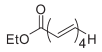
is sufficiently removed from the terminal alkene that it is reactive enough for the first-generation Grubbs catalyst while the internal alkenes are not. The product is formed as a 4:1 mixture of *E*- to *Z*-olefin isomers at the distal (ε,ζ) alkene. A variety of conditions were studied; however, we were unable to improve this ratio. Surprisingly, reactions with the more reactive catalysts stalled after 32−33% consumption of **31** and were not clean. Similarly, reactions with tetraenal substrate **40** provided complex mixtures by NMR with all catalysts under all conditions studied and stalled after low consumption of **31** (30−41%).

Table 2. Cross-Metathesis of 31 with Enoate and Polyenoate Substrates (Scheme *6*)

Entry	Substrate	Equivs	Cat	Consumption of **31**	Dimer (**32**)	Yield[a]	Comments
1	 **41**	1.3	**33**	89%	32%	(26%)	
2		1.3	**34**	>98%	trace	86%	
3		1.3	**35**	>98%	2%	92%	
4	 **42**	1.3	**33**	86%	36%	(8%)	
5		2.0	**34**	>98%	trace	92%	
6		1.3	**35**	>98%	trace	70%	
7	 **43**	2.0	**33**	82%	ND	ND	Several unidentified side products
8		2.0	**34**	65%	ND	ND	
9		2.0	**35**	98%	ND	ND	
10	 **44**	1.5	**33**	96%	2%	84%	5:1 *E*/*Z*[b]
11		2.0	**34**	55%	8%	ND	
12		2.0	**35**	10%	trace	ND	
13	 **45**	2.0	**33**	67%	2%	(62%)	
14		2.0	**34**	17%	trace	ND	Complex mixtures by NMR
15		2.0	**35**	22%	trace	ND	

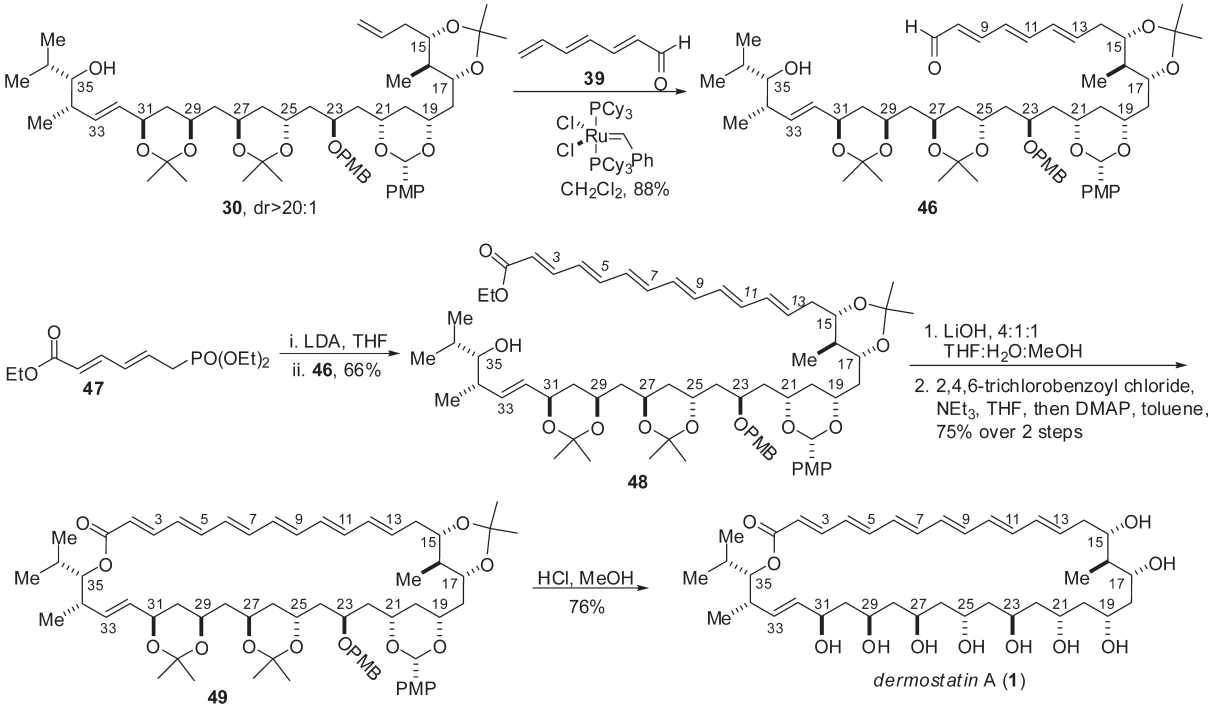
[a] Isolated yield; numbers in parentheses are conversions as determined by NMR. [b] Isomeric at the alkene distal to the ester.

Similar results were obtained with the ester-derived substrates (Table 2). In the case of ethyl acrylate or ethyl crotonate, again, the less active first-generation Grubbs catalyst (**33**) provided significant amounts of dimer **32** (32%, which consumes 64% of **31**, and 36%, which consumes 72% of **31**; Table 2, entries 1 and 4, respectively). The more reactive catalysts (**34** and **35**) provided the desired product in 70−92% yield (Table 2, entries 2, 3, 5 and 6). Dienoate **43**[27] did not provide satisfactory results with any of the catalysts studied: while the consumption of **31** was high in many reactions, several unidentified side products were observed, and we were unable to devise conditions that provided clean reactions.

As in the case of trienal **39**, cross-metathesis with trienoate **44**[18] provided good conversion and high yields with the first-generation Grubbs catalyst (96% consumption of **31**, 84% yield) and a 5:1 ratio of *E*- to *Z*-olefin isomers at the distal (ε,ζ) alkene. The more active catalysts stalled at lower conversion, again presumably due to catalyst inactivation or decomposition.[28] The tetraenoate substrate provided slightly better results than the tetraenal. With the first-generation Grubbs catalyst, we observed a 62% conversion to the desired product by NMR; however, we were unable to isolate the product cleanly by flash chromatography. The more active catalysts stalled at low conversion.

With these results in hand, we settled on cross-metathesis between trienal **39**[18] and terminal alkene **30**. Using the first-generation Grubbs catalyst, the reaction proceeded as expected, and the desired trienal (**46**) was isolated in 82% yield as a 4:1 mixture of isomers at the olefin distal to the aldehyde (C-12−C-13; Scheme 7). Horner−Wadsworth−Emmons olefination with the doubly vinylogous reagent **47**[29] proceeded uneventfully to provide conjugated hexaenoate **48**, from which isomerically

Scheme 7. Completion of the Synthesis of Dermostatin A (1)



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pure material was isolated in 66% yield. Due to the potential photoreactivity of the conjugated hexaenoate, the products of this and subsequent reactions were protected from exposure to light by conducting reactions in glassware wrapped with aluminum foil and by performing chromatography in dimmed lighting. Hydrolysis to the seco acid (LiOH) and cyclization (Yamaguchi conditions)[30] provided the fully protected macrolide in 75% yield for the two steps. The final deprotection proved challenging. Although the acetonide and *p*-methoxybenzylidine acetal functionalities were easily hydrolyzed under mildly acidic conditions, the PMB ether was more stable and resistant to removal. Attempts to deprotect under various acidic conditions (acidic Dowex resin, acidic Amberlyst 15 resin, and pTsOH in MeOH) led to partial deprotection or decomposition at longer reaction times. Conditions with trimethylsilyl triflate (TMSOTf), *N*-trimethylsilylimidazole (TMSI), and BCl_3 also failed to effect deprotection without decomposition. Ultimately, the use of concentrated HCl in MeOH (12 h at room temperature) was found to be effective,[31,2p] and purification by flash chromatography followed by reverse-phase HPLC provided synthetic dermostatin A (**1**) in 76% yield. Synthetic dermostatin A exhibited spectroscopic and physical properties identical to those reported for the natural material [^{1}H and ^{13}C NMR, circular dichroism (CD), and high-resolution mass spectrometry (HRMS)].

CONCLUSIONS

In conclusion, the synthesis of dermostatin A is described; a key step is the acetate aldol method developed in our group with glutaradehyde **15** in a two-directional chain synthesis approach, illustrating the robustness of this method. Other key steps include a diastereotopic-group-selective acetal isomerization and a cross-metathesis reaction between a terminal alkene and a trienal. The synthesis is convergent and utilizes fragments of roughly equal complexity in an efficient fashion.

EXPERIMENTAL SECTION

General Information. All air- and moisture-sensitive reactions were conducted under a dry nitrogen atmosphere in oven-dried glassware, using standard syringe/cannula transfer techniques. Dichlorophenylborane (97%) was purchased from Aldrich, distilled under nitrogen, and then stored in a resealable container bearing a Teflon valve at −26 °C under a nitrogen atmosphere until used. (−)-Sparteine was distilled and stored under a nitrogen atmosphere at −26 °C until used. 2,2-Dimethoxypropane was predried with $MgSO_4$ and passed through a plug of basic alumina and was used immediately. Acrolein, crotonaldehyde, ethyl acrylate, and ethyl crotonate were distilled under nitrogen prior to use. Triethylamine was distilled from CaH_2 under nitrogen. Dichloromethane was distilled from CaH_2 under nitrogen. Toluene was distilled from CaH_2 under nitrogen. Tetrahydrofuran (THF) and Et_2O were distilled from sodium benzophenone ketyl under nitrogen. All other starting materials were used as received. In order to avoid hydrolysis, flash chromatography of the acetate aldol adducts was performed on neutral silica gel [Mallinckrodt Silicar silica gel 150, 60−200 mesh (75−250 μm)] following the procedure of Still et al.[32] All other flash chromatography was performed by use of Sorbent Technologies 60 Å silica gel (32−63 mm). ^{1}H NMR spectra were recorded at 500 or 400 MHz, with $CDCl_3$ (internal reference 7.24 ppm) as solvent. ^{13}C NMR spectra were obtained at 100 MHz with $CDCl_3$ (internal reference 77.23 ppm) as solvent. Infrared spectra were recorded as thin films on NaCl plates. Melting points were determined in capillaries and are uncorrected. Optical rotations were determined on a digital polarimeter at 28 °C (ambient temperature). Exact mass was obtained by electrospray ionization in positive ion mode (M + H or M + Na or M + Li) or in negative ion mode (M + Cl) as indicated.

*Dimethyl 3-(tert-Butyldimethylsilyloxy)pentanedioate (**14**).* To a cooled (0 °C) solution of 3-hydroxypentanedioic acid dimethyl ester (**13**; 10.44 g, 59.26 mmol, 1.0 equiv) and imidazole (5.23 g, 76.8 mmol, 1.3 equiv) in *N*,*N*-dimethylformamide (DMF) (20 mL) was added TBSCl (9.4 g, 62 mmol, 1.1 equiv) in one portion. The reaction was allowed to stir for 14 h, warming slowly to room temperature, and then diluted with 100 mL of Et_2O and washed with H_2O (15 mL) and brine (2 × 10 mL). The combined aqueous phases were extracted with ether (10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Distillation under reduced pressure (113−121 °C at ca. 1 mmHg) afforded the diester **14** (14.40 g, 49.56 mmol, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.53 (quintet, J = 6.0 Hz, 1H), 3.65 (s, 6H), 2.49−2.58 (m, 4H), 0.82 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 66.3, 51.6, 42.4, 25.6, 17.8, −5.0. IR (cm^{-1}) 2925, 2946, 2913, 1730, 1432. HRMS m/z calcd for $C_{13}H_{26}O_5Si + Na^+$, 313.1441; found, 313.1431.

*3-(tert-Butyldimethylsilyloxy)pentanedial (**15**).* A solution of ester **14** (5.0 g, 17.22 mmol, 1.0 equiv) in ether (80 mL) was cooled to −78 °C. DIBAL-H (45 mL, 0.95 M in hexanes, 43 mmol, 2.5 equiv) was added dropwise via a cannula over 50 min. The solution was stirred for 1 h at −78 °C and then quenched by addition of dry acetone (1 mL) followed by saturated potassium sodium tartrate (80 mL). The mixture was stirred vigorously for 3 h at room temperature. The phases were separated, and the aqueous phase was extracted with ether (6 × 30 mL). The combined organic phases were dried ($MgSO_4$), concentrated under reduced pressure, and heated at 100 °C for 40 min under vacuum (ca. 2 mmHg) to give the largely monomeric dialdehyde **15**[13a] as a red oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (t, J = 2.0 Hz, 2H), 4.70 (quintet, J = 6.0 Hz, 1H), 2.60−2.70 (m, 4H), 0.83 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6, 63.4, 51.0, 25.6, 17.9, −4.7. Upon prolonged standing exposed to the atmosphere, the dialdehyde undergoes reversible partial hydration and polymerization.[13a] The ^{1}H NMR spectrum of such polymerized material displays broad indiscernible signals. Thus, the dialdehyde prepared as above was used in the next aldol reaction immediately.

*(3R,7R)-1,9-Bis[(S)-4-tert-butyl-2-thioxothiazolidin-3-yl]-5-(tert-butyldimethylsilyloxy)-3,7-dihydroxynonane-1,9-dione (**16**).* To a 250 mL round-bottom flask were added the *N*-acetyl thiazolidinethione **11**[14] (7.66 g, 35.26 mmol, 2.05 equiv) and CH_2Cl_2 (50 mL). The flask was cooled to 0 °C and $PhBCl_2$ (4.7 mL, 35.26 mmol, 2.05 equiv) was then added dropwise to provide an orange-colored solution. After the solution was stirred for 3 min, (−)-sparteine (0.12 mL, 0.50 mmol, 2.6 equiv) was added dropwise, at which point the solution turned yellow and cloudy. After being stirred for about a minute, the solution turned translucent but remained yellow. The ice bath was then removed, and the reaction was allowed to warm to room temperature and stir for 30 min. The reaction was then cooled to 0 °C, and the dialdehyde (3.96 g, 17.22 mmol, 1.0 equiv) in 4 mL of CH_2Cl_2 was added dropwise via cannula over a period of about 10 min. The flask containing the aldehyde was rinsed with 2 × 0.8 mL of CH_2Cl_2, which was also added to the reaction via cannula. The reaction was stirred for 15 h at 0 °C and then warmed to room temperature and stirred for 1 h. The reaction was placed in an ice bath, quenched by the addition of hexanes (50 mL) and H_2O_2 (30%, 20 mL), warmed to room temperature, and stirred rapidly for 15 min at room temperature. (Note that rapid stirring is required at this step. If the rate of stirring is too slow, incomplete oxidation of the borane occurs, and boron species are observed in the product.) The solution was diluted with 1:1 hexanes/CH_2Cl_2 (80 mL), and the layers were separated. The organic layer was washed with distilled water and brine. The combined aqueous layer was then extracted with 1:1 hexanes/CH_2Cl_2 (80 mL) and washed with distilled water and brine.

The combined organics were dried over anhydrous $MgSO_4$, filtered, and concentrated at reduced pressure to provide an orange oil. Analysis of this material by ^{1}H NMR provided a diastereomeric ratio (dr) value of >20:1. The product was purified by flash chromatography on neutral silica gel (20:1 to 5:1 hexanes/EtOAc) to provide the aldol adduct **16** as a translucent yellow oil (8.0 g, 12.1 mmol, 70% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.33 (d, J = 7.8 Hz, 1H), δ 5.31 (d, J = 7.8 Hz, 1H), 4.34−4.20 (m, 2H), 4.17−4.07 (m, 1H), 3.56−3.26 (m, 8H), 3.10 (d, J = 11.8 Hz, 1H), 1.87−1.73 (m, 2H), 1.73−1.58 (m, 2H), 1.01 (s, 9H), 0.86 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.3, 205.2, 173.0, 172.6, 72.4, 72.3, 67.8, 46.1, 45.7, 43.7, 42.1, 38.2, 30.8, 30.7, 27.1, 26.1, 18.2, −4.3, −4.5. IR (cm^{-1}) 3421, 2951, 2897, 1642. $[\alpha]^{28}_D$ = +182.5 (c 0.06, EtOH). HRMS m/z calcd for $C_{29}H_{52}N_2O_5S_4Si + Na^+$, 687.2420; found, 687.2445.

*(3S,7S)-5-(tert-Butyldimethylsilyloxy)nonane-1,3,7,9-tetraol (**17**).* To a cooled (0 °C) yellow solution of compound **16** (7.50 g, 11.28 mmol, 1.00 equiv) in ethanol (50 mL) was added $NaBH_4$ (2.56 g, 67.66 mmol, 6.00 equiv) in five portions over 10 min. The reaction was warmed to room temperature and stirred until the yellow solution became colorless. The reaction was quenched by addition of excess solid NH_4Cl (50 g) and stirred for 2.5 h. This mixture was filtered through Celite (washing with 1:1 EtOAc/MeOH) and concentrated under reduced pressure to give a cloudy, viscous residue indicative of incomplete borate methanolysis. The residue was dissolved in methanol (500 mL) and NH_4Cl (20 g) was added. Distillation of 450 mL of MeOH removed trimethylborate azeotropically. The remainder was diluted with EtOAc, filtered, and concentrated under reduced pressure. The residue was taken up in EtOAc, filtered through Celite, and concentrated under reduced pressure. The product was then purified by flash chromatography on silica gel (EtOAc to 10:1 EtOAc/MeOH) to provide tetraol **17** (2.90 g, 9.02 mmol, 80%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34−4.07 (m, 2H), 4.01−3.90 (m, 1H), 3.90−3.73 (m, 3H), 3.0−3.50 (br s, 4H), 1.89−1.77 (m, 2H), 1.77−1.58 (m, 6H), 0.87 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.0, 69.6, 69.0, 61.6, 43.8, 42.2, 39.3, 39.1, 26.0, 18.1, −4.4, −4.5. IR (cm^{-1}) 3367, 2921, 2856. $[\alpha]^{28}_D$ = +9.7 (c 1.11, CH_2Cl_2). HRMS m/z calcd for $C_{15}H_{34}O_5Si + H^+$, 323.2248; found, 323.2244.

*{1,3-Bis[(2S,4S)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]propan-2-yloxy}(tert-butyl)dimethylsilane (**18**).* To a cooled (0 °C) solution of tetraol **17** (2.50 g, 7.76 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) was added *p*-anisaldehyde dimethyl acetal (3.31 mL, 19.41 mmol, 2.5 equiv) dropwise by syringe. PPTS (1.95 g, 7.76 mmol, 1.0 equiv) was then added in one portion and the solution was warmed to room temperature, and stirred for 3 h. The reaction was then filtered through a short plug of silica with a layer of Celite on top with CH_2Cl_2 as the eluent and concentrated at reduced pressure. Flash chromatography on silica gel (5:1 hexanes/EtOAc) provided analytically pure **18** as a colorless oil (3.67 g, 6.60 mmol, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.32 (m, 4H), 6.84−6.76 (m, 4H), 5.45 (s, 1H), 5.42 (s, 1H), 4.33−4.18 (m, 3H), 4.05−3.88 (m, 4H), 3.76 (s, 3H), 3.75 (s, 3H), 1.96−1.73 (m, 4H), 1.69−1.59 (m, 2H), 1.51−1.42 (m, 2H), 0.88 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 159.8, 131.6, 131.5, 127.4, 127.3, 113.7, 113.6, 100.9, 100.8, 73.9, 73.5, 67.3, 67.2, 65.0, 55.4, 44.4, 43.8, 32.2, 32.1, 26.1, 18.3, −4.0, −4.4. IR (cm^{-1}) 2950, 2856, 1622, 1516. $[\alpha]^{28}_D$ = +79.3 (c 0.33, CH_2Cl_2). HRMS m/z calcd for $C_{31}H_{46}O_7Si + H^+$, 559.3085; found, 559.3106.

*1,3-Bis[(2S,4S)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]propan-2-ol (**19**).* To a solution of acetal **18** (3.50 g, 6.28 mmol, 1.0 equiv) in THF (8 mL) was added a solution of TBAF (12.56 mL, 1 M solution in THF, 2.0 equiv). The reaction mixture was stirred for 6 h at room temperature and then was quenched with 20 mL of H_2O. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (4:5 hexanes/EtOAc) to give alcohol **19** as a white foam (2.50 g, 5.65 mmol, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44−7.32 (m, 4H), 6.90−6.80 (m, 4H), 5.47 (s, 1H), 5.46 (s, 1H), 4.26−4.17 (m, 3H), 4.17−4.06 (m, 2H), 3.99−3.88 (m, 2H), 3.77 (s, 3H), 3.76 (s, 3H), 3.40 (br s, 1H), 1.96−1.76 (m, 3H), 1.76−1.58 (m, 3H), 1.54−1.40 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 160.0, 131.6, 130.9, 127.5, 127.4, 113.9, 113.7, 101.3, 101.2, 78.0, 74.0, 67.3, 67.1, 55.5, 43.9, 43.4, 31.8, 31.6. IR (cm^{-1}) 3510, 2950, 2913, 1614, 1511. $[\alpha]^{28}_D$ = +181.6 (c 0.07, CH_2Cl_2). HRMS m/z calcd for $C_{25}H_{32}O_7 + H^+$, 445.2220; found, 445.2215.

*2-[(2S,4S,6S)-2-(4-Methoxyphenyl)-6-{[(2S,4S)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]methyl}-1,3-dioxan-4-yl]ethanol (**20**).* To a solution of alcohol **19** (1.50 g, 3.39 mmol, 1.0 equiv) in toluene (15 mL) was added *p*-anisaldehyde dimethyl acetal (577 μL, 3.39 mmol, 1.0 equiv) dropwise by syringe. PPTS (804 mg, 3.39 mmol, 1.0 equiv) was then added in one portion, and the solution was heated to 90 °C and stirred for 3 h. A sample of the reaction mixture was analyzed by ^{1}H NMR and was found to provide alcohol **20**/alcohol **19** > 85:15. The reaction was then quenched with 5 mL of saturated $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (25:1 CH_2Cl_2/acetone) to give alcohol **20** as a white solid (1.23 g, 2.78 mmol, 82%). Also, 180 mg (12%) of alcohol **19** was recovered and could be reused. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.36 (m, 4H), 6.92−6.84 (m, 4H), 5.51 (s, 1H), 5.47 (s, 1H), 4.26−4.18 (m, 1H), 4.18−4.10 (m, 2H), 4.10−4.02 (m, 1H), 3.99−3.88 (m, 1H), 3.87−3.79 (m, 2H), 3.79 (s, 6H), 2.16 (br t, 1H), 1.90−1.73 (m, 5H), 1.60−1.46 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 160.0, 131.6, 131.4, 127.5, 127.4, 113.8, 113.7, 101.1, 100.7, 76.3, 73.1, 72.7, 67.2, 60.7, 55.5, 42.8, 38.2, 37.4, 32.0. IR (cm^{-1}) 3420, 2946, 2913, 1610, 1511. $[\alpha]^{28}_D$ = +101.7 (c 0.10, CH_2Cl_2). HRMS m/z calcd for $C_{25}H_{32}O_7 + H^+$, 445.2220; found, 445.2211.

*2-[(2R,4R,6R)-2-(4-Methoxyphenyl)-6-{[(2S,4S)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]methyl}-1,3-dioxan-4-yl]acetaldehyde (**22**).* To a cooled solution (0 °C) of alcohol **20** (1 g, 2.26 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added solid K_2CO_3 (468 mg, 3.39 mmol, 1.5 equiv), followed by Dess−Martin periodinane (1.44 g, 3.39 mmol, 1.5 equiv). The resulting solution was allowed to warm to room temperature and stirred for 15 h. The mixture was diluted with 10 mL of CH_2Cl_2, 10 mL of saturated aqueous $NaHCO_3$, and 10 mL of saturated aqueous $Na_2S_2O_3$ and stirred for 15 min. The aqueous phase was extracted with Et_2O (2 × 20 mL) and the combined organic layers were washed with 3 mL of saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and brine and then dried over $MgSO_4$ and filtered through Celite. After evaporation, the crude residue was purified by flash chromatography on silica gel (15:1 CH_2Cl_2/EtOAc) to give aldehyde **22** as a clear, colorless oil (910 mg, 2.07 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (t, J = 1.7 Hz, 1H), 7.46−7.34 (m, 4H), 6.93−6.83 (m, 4H), 5.54 (s, 1H), 5.48 (s, 1H), 4.43−4.33 (m, 1H), 4.24−4.10 (m, 3H), 3.99−3.88 (m, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 2.77 (ddd, J = 2.2, 7.3, 16.8 Hz, 1H), 2.57 (ddd, J = 1.7, 5.1, 16.8 Hz, 1H), 1.86−1.71 (m, 3H), 1.71−1.62 (m, 1H), 1.53−1.40 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6, 160.1, 160.0, 131.6, 131.1, 127.5, 127.5, 113.8, 101.1, 100.8, 73.1, 72.6, 72.0, 67.1, 55.5, 49.6, 42.8, 37.2, 31.9. IR (cm^{-1}) 2954, 2913, 1728, 1615, 1511. $[\alpha]^{28}_D$ = +188.4 (c 0.06, CH_2Cl_2). HRMS m/z calcd for $C_{25}H_{30}O_7 + H^+$, 443.2064; found, 443.2071.

*(2R,3R)-[(1R,2S)-2-(N-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl] 3-Hydroxy-4-[(2S,4S,6R)-2-(4-methoxyphenyl)-6-{[(2S,4S)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]methyl)-1,3-dioxan-4-yl]-2-methylbutanoate (**24**).* Dicyclohexylborontriflate[33] (5.40 mmol in 6 mL of CH_2Cl_2, 2.60 equiv) was added dropwise to a −78 °C solution of **23**[16]

(2.48 g, 5.18 mmol, 2.50 equiv) and Et_3N (0.96 mL, 6.89 mmol, 3.33 equiv) in CH_2Cl_2 (30 mL).[34] After 2 h, aldehyde **22** (910 mg, 2.07 mmol, 1.0 equiv) in 3 mL of CH_2Cl_2 was added dropwise via cannula. The flask containing the aldehyde was rinsed with 2 × 0.5 mL of CH_2Cl_2, which was also added to the reaction via cannula. The reaction was stirred for an additional hour at −78 °C and then warmed to room temperature and stirred for 2 h. The reaction was quenched by the addition of pH 7 buffer (12 mL), MeOH (30 mL), and hydrogen peroxide (4 mL of a 30% solution). The resulting mixture was vigorously stirred overnight and then diluted with water (30 mL) and CH_2Cl_2 (40 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated at reduced pressure. The product was determined to be a 20:1 mixture of diastereomers by ^{1}H NMR analysis of the crude reaction mixture. Flash chromatography on silica gel (3:1 hexanes/EtOAc) provided alcohol **24** (1.76 g, 1.90 mmol, 92%) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48−7.36 (m, 4H), 7.34−7.27 (m, 2H), 7.25−7.13 (m, 6H), 6.95−6.83 (m, 8H), 5.82 (d, J = 3.9 Hz, 1H), 5.51 (s, 1H), 5.47 (s, 1H), 4.76 (d, A of AB, J = 16.7 Hz, 1H), 4.58 (d, B of AB, J = 16.7 Hz, 1H), 4.30−4.19 (m, 1H), 4.18−3.90 (m, 6H), 3.79 (s, 3H), 3.77 (s, 3H), 3.41 (d, J = 2.5 Hz, OH), 2.63−2.52 (m, 1H), 2.49 (s, 6H), 2.26 (s, 3H), 1.81−1.60 (m, 5H), 1.60−1.40 (m, 3H), 1.15 (d, J = 7 Hz, 3H), 1.10 (d, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 160.1, 160.0, 142.7, 140.4, 138.8, 138.6, 133.6, 132.3, 131.5, 131.0, 128.5, 128.5, 128.0, 127.7, 127.4, 127.4, 127.2, 126.0, 113.8, 113.7, 101.1, 100.6, 78.4, 73.0, 72.7, 72.3, 67.1, 57.0, 55.5, 48.4, 45.8, 42.7, 39.1, 37.5, 31.9, 23.1, 21.1, 13.4, 13.0. IR (cm^{-1}) 3448, 3064, 2942, 2852, 1740, 1614, 1511. $[\alpha]^{28}_D$ = +107.5 (c 0.14, CH_2Cl_2). HRMS m/z calcd for $C_{53}H_{63}NO_{11}S$ + H^+, 922.4194; found, 922.4216.

*(4S,5S,6R)-6-(tert-Butyldimethylsilyloxy)-7-[(2R,4R,6R)-2-(4-methoxyphenyl)-6-{[(2S,4S)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]methyl}-1,3-dioxan-4-yl]-5-methylhept-1-en-4-ol (**26**).* To a solution of alcohol **24** (1.70 g, 1.84 mmol, 1.0 equiv) and 2,6-lutidine (0.96 mL, 8.30 mmol, 4.50 equiv) in dichloromethane (3 mL) was added triethylsilyl triflate (TESOTf) (1.27 mL, 5.53 mmol, 3.00 equiv) at 0 °C. The reaction was warmed to room temperature and stirred for 4 h, and then the reaction was diluted with dichloromethane (20 mL) and quenched with saturated $NaHCO_3$ (5 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated at reduced pressure. Flash chromatography on silica gel (4:1 hexanes/EtOAc) provided the ester (1.68 g, 1.62 mmol, 88%) as a white foam. ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.44−7.38 (m, 2H), δ 7.38−7.33 (m, 2H), δ 7.32−7.26 (m, 2H), 7.23−7.12 (m, 4H), 7.12−7.07 (m, 2H), 6.91−6.80 (m, 8H), 5.72 (d, J = 5.0 Hz, 1H), 5.47 (s, 1H), 5.38 (s, 1H), 4.74 (d, A of AB, J = 16.4 Hz, 1H), 4.48 (d, B of AB, J = 16.4 Hz, 1H), 4.24−4.17 (m, 1H), 4.15−3.98 (m, 4H), 3.97−3.84 (m, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 2.66−2.56 (m, 1H), 2.41 (s, 6H), 2.22 (s, 3H), 1.84−1.74 (m, 2H), 1.72−1.65 (m, 2H), 1.50−1.35 (m, 2H), 1.28−1.17 (m, 2H), 1.15 (d, J = 7.0 Hz, 3H), 1.07 (d, J = 7.10 Hz, 3H), 0.84 (s, 9H), 0.01 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 160.0, 160.0, 142.7, 140.5, 138.6, 138.4, 133.3, 132.3, 131.6, 131.6, 128.6, 128.5, 128.0, 127.9, 127.5, 127.4, 126.6, 113.8, 113.7, 101.1, 100.4, 78.4, 73.6, 73.1, 72.6, 70.5, 67.2, 56.9, 55.5, 48.3, 45.2, 42.8, 40.1, 37.6, 32.0, 26.1, 23.1, 21.1, 18.2, 14.2, 12.5, −4.3, −4.4. IR (cm^{-1}) 2921, 2855, 1732, 1614, 1511. $[\alpha]^{28}_D$ = +88.7 (c 0.04, CH_2Cl_2). HRMS m/z calcd for $C_{59}H_{77}NO_{11}SSi$ + H^+, 1036.5059; found, 1036.5041.

To a slurry of the above ester (1.60 g, 1.54 mmol, 1.0 equiv) and *N*,*O*-dimethylhydroxylamine hydrochloride (1.66 g, 16.98 mmol, 11.0 equiv) in THF (30 mL) was added isopropylmagnesium chloride (2 M solution in Et_2O, 15.5 mL, 30.88 mmol, 20 equiv) at −20 °C over 20 min and under vigorous stirring. The reaction mixture was then stirred at −20 °C for 1 h and warmed to 5 °C over 1 h. The cooling bath was then removed and the mixture was allowed to warm to room temperature where the slurry turned into a homogeneous brown solution, which was then cooled to 0 °C and quenched with saturated NH_4Cl solution (10 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure. Flash chromatography on silica gel (3:4 hexanes/EtOAc) provided the amide (825 mg, 1.25 mmol, 81%) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.38 (m, 4H), 6.93−6.84 (m, 4H), 5.51 (s, 1H), 5.50 (s, 1H), 4.24−4.08 (m, 5H), 3.95 (m, 1H), 3.79 (s, 6H), 3.58 (s, 3H), 3.48−3.35 (m, 1H), 3.12 (s, 3H), 2.04−1.93 (m, 1H), 1.87−1.72 (m, 3H), 1.68−1.60 (m, 1H), 1.55−1.48 (m, 2H), 1.48−1.38 (m, 1H), 1.07 (d, J = 7.0 Hz, 3H), 0.85 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.6, 160.0, 159.8, 131.7, 131.6, 127.5, 127.3, 113.8, 113.6, 101.2, 100.2, 73.2, 72.9, 72.7, 71.6, 67.2, 61.4, 55.5, 55.5, 42.9, 40.6, 39.3, 38.2, 32.0, 26.0, 18.2, 13.8, −4.4, −4.8. IR (cm^{-1}) 2933, 2852, 1659, 1614, 1516, 1242. $[\alpha]^{28}_D$ = +17.7 (c 1.30, CH_2Cl_2). HRMS m/z calcd for $C_{36}H_{55}NO_9Si$ + H^+, 674.3718; found, 674.3691.

In a 25 mL flask were placed the above amide (800 mg, 1.21 mmol, 1.0 equiv) and THF (6 mL). The reaction mixture was cooled to 0 °C with an ice bath. To the solution was added a 1 M solution of allylmagnesium bromide in Et_2O (1.46 mL, 1.46 mmol, 1.2 equiv) dropwise over 2 min. The reaction mixture was stirred for 30 min. The reaction was then quenched with saturated aqueous NH_4Cl solution (2 mL) and was transferred to a separatory funnel. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organics were washed with brine (5 mL), dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure, providing the expected ketone (775 mg, >99%) as a translucent yellow oil, which was used immediately.

To a cooled (−50 °C, acetonitrile−dry ice bath) solution of the above ketone (775 mg, 1.212 mmol, 1.0 equiv) in methanol (6 mL) was added $NaBH_4$ (230 mg, 6.060 mmol, 5.0 equiv) in a single portion. After 15 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl solution (6 mL). The mixture was warmed to room temperature and was diluted with CH_2Cl_2 (20 mL) and H_2O (6 mL). The mixture was transferred to a separatory funnel, and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure. The product was determined to be a 10:1 mixture of diastereomers by ^{1}H NMR analysis of the crude reaction mixture. Flash chromatography on silica gel (3:1 hexanes/EtOAc) provided alcohol **26** (620 mg, 0.95 mmol, 78% over 2 steps) as a translucent yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46−7.36 (m, 4H), 6.94−6.78 (m, 4H), 5.93−5.75 (m, 1H), 5.50 (s, 1H), 5.49 (s, 1H), 5.19−5.07 (m, 2H), 4.27−4.19 (m, 1H), 4.17−3.94 (m, 5H), 3.80 (s, 3H), 3.79 (s, 3H), 3.55−3.45 (m, 1H), 2.45 (br s, OH), 2.48−2.35 (m, 1H), 2.13−2.00 (m, 1H), 1.90−1.65 (m, 7H), 1.54−1.46 (m, 1H), 1.46−1.32 (m, 1H), 0.89 (s, 9H), 0.86 (d, J = 6.9 Hz, 3H), 0.06 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 159.9, 135.2, 131.7, 131.6, 127.5, 127.5, 118.3, 113.8, 113.7, 101.1, 100.6, 74.2, 73.3, 72.8, 72.7, 71.4, 67.2, 55.5, 43.4, 42.9, 39.9, 39.6, 37.7, 32.0, 26.1, 18.2, 12.1, −4.2, −4.3. IR (cm^{-1}) 3488, 2942, 2854, 1616, 1517. $[\alpha]^{28}_D$ = +76.5 (c 3.30, CH_2Cl_2). HRMS m/z calcd for $C_{37}H_{56}O_8Si$ + H^+, 657.3817; found, 657.3796.

*(4S,5S,6R)-4-Allyl-6-{[(2R,4R,6R)-2-(4-methoxyphenyl)-6-{[(2S,4S)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]methyl}-1,3-dioxan-4-yl]methyl}-2,2,5-trimethyl-1,3-dioxane (**27**).* To a solution of alcohol **26** (500 mg, 0.76 mmol, 1.0 equiv) in THF (4 mL) was added a solution of tetrabutylammonium fluoride (1.52 mL, 1 M solution in THF, 2.0 equiv). The reaction mixture was stirred for 6 h at room temperature and then quenched with 5 mL of H_2O. The layers were separated and the

aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure to provide the expected diol as a translucent yellow oil, which was used immediately.

To a cooled (0 °C) solution of the above diol in CH_2Cl_2 (3 mL) was added 2,2-dimethoxypropane (1 mL, 8.16 mmol, 1.1 equiv, predried with $MgSO_4$ and passed through a plug of basic alumina) dropwise by syringe. PPTS (90 mg, 0.38 mmol, 0.5 equiv) was then added in one portion, and the solution was warmed to room temperature and stirred for 3 h. The reaction was then filtered through a short plug of silica with a layer of Celite on top, with CH_2Cl_2 as the eluent, and concentrated at reduced pressure. Flash chromatography on silica gel (4:1 hexanes/EtOAc) provided analytically pure **27** as a colorless oil (355 mg, 0.61 mmol, 80% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47−7.37 (m, 4H), 6.94−6.83 (m, 4H), 5.97−5.82 (m, 1H), 5.52 (s, 1H), 5.50 (s, 1H), 5.10−4.97 (m, 2H), 4.27−4.20 (m, 1H), 4.20−4.04 (m, 3H), 4.00−3.89 (m, 1H), 3.79 (s, 6H), 3.58−3.46 (m, 2H), 2.42−2.31 (m, 1H), 2.23−2.10 (m, 1H), 1.93−1.81 (m, 2H), 1.81−1.70 (m, 4H), 1.65−1.46 (m, 1H), 1.46−1.37 (m, 2H), 1.36 (s, 3H), 1.35 (s, 3H), 0.77 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 159.9, 135.1, 131.8, 131.6, 127.5, 127.5, 116.6, 113.8, 113.7, 101.1, 100.4, 98.0, 74.2, 73.5, 73.2, 72.5, 70.8, 67.2, 55.5, 43.0, 39.3, 38.7, 37.6, 36.9, 32.0, 30.3, 19.7, 12.3. IR (cm^{-1}) 3064, 2942, 2913, 1614, 1511. $[\alpha]^{28}_D$ = +73.0 (c 3.20, CH_2Cl_2). HRMS m/z calcd for $C_{34}H_{46}O_8 + H^+$, 583.3265; found, 583.3269.

*(R)-4-[(2R,4R,6R)-6-{[(4R,5S,6S)-6-Allyl-2,2,5-trimethyl-1,3-dioxan-4-yl]-methyl}-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]-3-(4-methoxybenzyloxy)-butanal (**28**).* To a cooled (0 °C) solution of **27** (350 mg, 0.60 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added DIBAL-H (1.09 mL, 0.99 M in hexanes, 1.08 mmol, 1.8 equiv) dropwise over 5 min. The resulting solution was stirred for 10 min at 0 °C and then allowed to warm to room temperature. After an additional 4 h, the reaction was quenched by addition of saturated potassium sodium tartrate (5 mL) and stirred vigorously for 2 h. The aqueous phase was saturated with NaCl and the phases were separated. The aqueous phase was extracted with 1:1 CH_2Cl_2/Et_2O (3 × 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography on silica gel (3:2 hexanes/EtOAc) gave the alcohol (281 mg, 0.48 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.30 (m, 2H), 7.27−7.22 (m, 2H), 6.90−6.77 (m, 4H), 5.99−5.80 (m, 1H), 5.41 (s, 1H), 5.10−4.98 (m, 2H), 4.56 (d, A of AB, J = 11.1 Hz, 1H), 4.46 (d, B of AB, J = 11.1 Hz, 1H), 4.14−4.04 (m, 1H), 4.04−3.93 (m, 2H), 3.78 (s, 3H), 3.85−3.74 (m, 1H), 3.72 (s, 3H), 3.74−3.64 (m, 1H), 3.61−3.47 (m, 2H), 2.41−2.33 (m, 1H), 2.32 (br s, OH), 2.23−2.11 (m, 1H), 2.00−1.83 (m, 2H), 1.83−1.64 (m, 4H), 1.63−1.52 (m, 1H), 1.39 (s, 3H), 1.49−1.27 (m, 2H), 1.37 (s, 3H), 0.77 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 159.5, 135.1, 131.5, 130.5, 129.9, 127.4, 116.6, 114.1, 113.6, 101.3, 98.1, 74.2, 73.6, 73.5, 73.2, 71.8, 70.9, 60.1, 55.5, 55.4, 41.6, 39.2, 38.0, 37.6, 36.9, 36.4, 30.3, 19.7, 12.3. IR (cm^{-1}) 3452, 3077, 2995, 2929, 1614, 1516. $[\alpha]^{28}_D$ = +51.8 (c 4.50, CH_2Cl_2). HRMS m/z calcd for $C_{34}H_{48}O_8 + H^+$, 585.3421; found, 585.3428.

To a cooled solution (0 °C) of the above alcohol (170 mg, 0.29 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) was added solid K_2CO_3 (60 mg, 0.43 mmol, 1.5 equiv), followed by Dess−Martin periodinane (184 mg, 0.43 mmol, 1.5 equiv). The resulting solution was allowed to warm to room temperature and stirred for 15 h. The mixture was diluted with 3 mL of CH_2Cl_2, 3 mL of saturated aqueous $NaHCO_3$, and 3 mL of saturated aqueous $Na_2S_2O_3$ and stirred for 15 min. The aqueous phase was extracted with Et_2O (2 × 10 mL), and the combined organic layers were washed with 3 mL of saturated aqueous $Na_2S_2O_3$, saturated aqueous $NaHCO_3$, and brine. The organics were then dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure. Flash chromatography on silica gel (5:2 hexanes/EtOAc) provided aldehyde **28** (139 mg, 0.24 mmol, 82%). R_f 0.29 (2:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (t, J = 2.4 Hz, 1H), 7.40−7.31 (m, 2H), 7.30−7.20 (m, 2H), 6.92−6.80 (m, 4H), 5.99−5.83 (m, 1H), 5.43 (s, 1H), 5.13−4.99 (m, 2H), 4.59 (d, A of AB, J = 11.2 Hz, 1H), 4.47 (d, B of AB, J = 11.2 Hz, 1H), 4.34−4.24 (m, 1H), 4.17−3.98 (m, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 3.63−3.48 (m, 2H), 2.76−2.60 (m, 2H), 2.44−2.34 (m, 1H), 2.24−2.12 (m, 1H), 1.97−1.85 (m, 1H), 1.85−1.68 (m, 3H), 1.65−1.55 (m, 1H), 1.41 (s, 3H), 1.51−1.28 (m, 2H), 1.39 (s, 3H), 0.79 (d, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.5, 159.8, 159.5, 135.1, 131.4, 130.2, 129.8, 127.3, 116.5, 114.1, 113.6, 100.3, 98.0, 77.6, 77.2, 76.9, 74.2, 73.5, 72.9, 71.9, 70.8, 70.3, 55.4, 55.3, 49.1, 42.2, 39.1, 38.0, 37.6, 36.7, 30.3, 19.7, 12.3. IR (cm^{-1}) 3072, 2991, 1929, 2905, 1724, 1618, 1511. $[\alpha]^{28}_D$ = +56.3 (c 1.90, CH_2Cl_2). HRMS m/z calcd for $C_{34}H_{46}O_8 + H^+$, 583.3265; found, 583.3274.

*(4S,6S)-7-[(2R,4R,6R)-6-{[(4R,5S,6S)-6-Allyl-2,2,5-trimethyl-1,3-dioxan-4-yl]methyl}-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]-4-hydroxy-1-{(4S,6R)-6-[(3S,4S,E)-4-hydroxy-3,5-dimethylhex-1-enyl]-2,2-dimethyl-1,3-dioxan-4-yl}-6-(4-methoxybenzyloxy)heptan-2-one (**29**).* To a cooled (−10 °C) solution of ketone **8**[18] (105 mg, 0.35 mmol, 1.5 equiv) in Et_2O (1.5 mL) was added NEt_3 (110 μL, 0.79 mmol, 3.35 equiv) dropwise by syringe. Chlorodicyclohexylborane (706 μL, 1.0 M in hexanes, 0.71 mmol, 3.0 equiv) was then added by cannula over 10 min, resulting in the formation of a white precipitate. The resulting mixture was stirred for 40 min at −10 °C and then cooled to −78 °C. A solution of aldehyde **28** (137 mg, 0.235 mmol, 1.0 equiv) in Et_2O (1 mL) was added dropwise by cannula over 5 min. The flask originally containing the aldehyde was rinsed with Et_2O (2 × 0.6 mL), and this solution was also added to the reaction by cannula. The resulting mixture was stirred for 3 h at −78 °C and 28 h at −26 °C. The reaction was quenched by the addition of pH 7 buffer (3 mL), MeOH (6 mL), and hydrogen peroxide (3 mL of a 30% solution). The resulting mixture was then warmed to room temperature and vigorously stirred for 3 h. The reaction mixture was transferred to a separatory funnel and diluted with brine (5 mL) and CH_2Cl_2 (20 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were diluted with Et_2O (60 mL), washed with 1 M NaOH aqueous solution (2 × 5 mL) and brine (1 × 5 mL), and then dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure. The product was determined to be a >15:1 mixture of diastereomers by ^{1}H NMR analysis of the crude reaction mixture. Flash chromatography on silica gel (3:2 hexanes/EtOAc) provided diol **29** (193 mg, 0.22 mmol, 93%) as a white viscous oil. ^{1}H NMR (100 MHz, $CDCl_3$) δ 7.36−7.30 (m, 2H), 7.27−7.20 (m, 2H), 6.89−6.78 (m, 4H), 5.96−5.81 (m, 1H), 5.63 (ddd, J = 0.8, 7.4, 15.7 Hz, 1H), 5.45 (ddd, J = 1, 6.2, 15.7 Hz, 1H), 5.39 (s, 1H), 5.08−4.98 (m, 2H), 4.58 (d, A of AB, J = 11.0 Hz, 1H), 4.47 (d, B of AB, J = 11.0 Hz, 1H), 4.37−4.32 (m, 3H), 4.12−4.01 (m, 2H), 4.01−3.91 (m, 1H), 3.77 (s, 3H), 3.72 (s, 3H), 3.60−3.46 (m, 2H), 3.42 (br s, 1H, OH), 3.13 (t, J = 3.9 Hz, 1H), 2.68 (dd, J = 7.3, 16.1 Hz, 1H), 2.54 (br d, 2H), 2.37 (dd, J = 5.2, 16.1 Hz, 1H), 2.44−2.27 (m, 2H), 2.22−2.10 (m, 1H), 1.93−1.83 (m, 1H), 1.80−1.62 (m, 5H), 1.61−1.54 (m, 2H), 1.55−1.20 (m, 5H), 1.44 (s, 3H), 1.39 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H), 1.00 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 7.3 Hz, 3H), 0.77 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2, 159.9, 159.6, 135.5, 135.2, 131.6, 130.8, 130.5, 130.1, 127.4, 116.6, 114.1, 113.7, 100.3, 99.1, 98.1, 79.9, 74.3, 73.6, 73.2, 72.6, 72.4, 70.9, 70.6, 65.7, 64.9, 55.5, 55.4, 51.5, 49.9, 41.8, 40.8, 39.5, 39.2, 38.1, 37.7, 37.2, 36.9, 30.8, 30.3, 30.3, 20.0, 19.9, 19.7, 17.3, 14.0, 12.3. IR (cm^{-1}) 3480, 2936, 2897, 1705, 1612, 1511. $[\alpha]^{28}_D$ = +37.2 (c 2.90, CH_2Cl_2). HRMS m/z calcd for $C_{51}H_{76}O_{12}$ + Cl^-, 915.5030; found, 915.5015.

*(3S,4S,E)-6-[(4R,6R)-6-{[(4R,6S)-6-{(R)-3-[(2R,4R,6R)-6-{[(4R,5S,6S)-6-Allyl-2,2,5-trimethyl-1,3-dioxan-4-yl]methyl}-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]-2-(4-methoxybenzyloxy)propyl}-2,2-dimethyl-1,3-dioxan-4-yl]methyl}-2,2-dimethyl-1,3-dioxan-4-yl]-2,4-dimethylhex-5-en-3-ol (**30**).* To a solution of diol **29** (190 mg, 0.22 mmol, 1.0 equiv) in 5 mL of CH_3CN at −30 °C was added $(CH_3)_4NHB(OAc)_3$ (909 mg,

3.46 mmol, 16 equiv) as a solution in 2 mL of AcOH over a period of 10 min. The mixture was warmed to −25 °C and stirred for 48 h and then quenched with 5 mL of half-saturated aqueous sodium potassium tartrate. The reaction mixture was warmed to room temperature, diluted with 5 mL of EtOAc, and neutralized with saturated sodium carbonate. The reaction mixture was then transferred to a separatory funnel and diluted with saturated sodium carbonate (5 mL) and EtOAc (20 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with 5 mL of saturated aqueous $NaHCO_3$ and brine before being dried over $MgSO_4$, filtered through Celite, and concentrated at reduced pressure to provide the triol as a yellow oil (ca. 190 mg, >99%), which was used immediately in the next step.

To the above triol in CH_2Cl_2 (2 mL) was added dropwise 2,2-dimethoxypropane (1 mL, 8.16 mmol, 37.8 equiv, predried with $MgSO_4$ and passed through a plug of basic alumina). PPTS (51 mg, 0.22 mmol, 1.0 equiv) was then added in one portion and the solution was stirred for 15 h at room temperature The reaction was then filtered through a short plug of silica with a layer of Celite on top, with Et_2O as the eluent, and concentrated at reduced pressure. The product was determined to be a >20:1 mixture of diastereomers by ^1H NMR analysis of the crude reaction mixture. Flash chromatography on silica gel (3:1 hexanes/EtOAc) provided analytically pure **30** as a white foam (191 mg, 0.21 mmol, 96% over two steps). ^1H NMR (400 MHz, $CDCl_3$) δ 7.39−7.33 (m, 2H), 7.26−7.20 (m, 2H), 6.89−6.79 (m, 4H), 5.95−5.81 (m, 1H), 5.64 (ddd, J = 0.7, 7.3, 15.7 Hz, 1H), 5.50 (ddd, J = 0.9, 6.1, 15.7 Hz, 1H), 5.41 (s, 1H), 5.09−4.97 (m, 2H), 4.51 (d, A of AB, J = 10.9 Hz, 1H), 4.45 (d, B of AB, J = 10.9 Hz, 1H), 4.35−4.26 (m, 1H), 4.10−3.91−3.81 (m, 5H), 3.60−3.46 (m, 1H), 3.78 (s, 3H), 3.72 (s, 3H), 3.53 (m, 2H), 3.13 (q, J = 5.5 Hz, 1H), 2.41−2.28 (m, 2H), 2.22−2.11 (m, 1H), 1.90−1.50 (m, 10H), 1.50−1.21 (m, 6H), 1.42 (s, 3H), 1.39 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H), 1.01 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.7 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H), 0.76 (d, J = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 159.4, 135.1, 131.7, 131.2, 130.9, 129.7, 127.4, 116.6, 114.0, 113.6, 100.5, 100.2, 98.7, 98.0, 79.9, 76.9, 74.2, 73.6, 73.2, 72.1, 72.0, 70.9, 70.2, 65.5, 63.7, 63.0, 55.5, 55.4, 42.5, 42.4, 39.5, 39.2, 39.0, 38.0, 37.6, 37.2, 36.9, 30.8, 30.4, 30.3, 25.1, 20.0, 19.9, 19.7, 17.3, 14.0, 12.3. IR (cm^{-1}) 3501, 2987, 2942, 1614, 1516, 1458. $[\alpha]^{28}_D$ = +36.3 (c 5.00, CH_2Cl_2). HRMS m/z calcd for $C_{54}H_{82}O_{12}$ + H^+, 923.5879; found, 923.5907.

*(2E,4E,6E)-8-[(4S,5S,6R)-6-{[(2R,4R,6R)-6-[(2S,4S)-4-Hydroxy-7-{(4S,6R)-6-[(3S,4S,E)-4-hydroxy-3,5-dimethylhex-1-enyl]-2,2-dimethyl-1,3-dioxan-4-yl}-2-(4-methoxybenzyloxy)-6-oxoheptyl]-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]methyl}-2,2,5-trimethyl-1,3-dioxan-4-yl]-octa-2,4,6-trienal (**46**).* Alcohol **30** (226 mg, 0.25 mmol, 1.0 equiv) and trienal **39**[18] (132 mg, 1.02 mmol, 4.16 equiv) were dissolved in CH_2Cl_2 (10 mL). Grubbs catalyst first generation (10 mg, 0.01 mmol, 0.05 equiv) was added in one portion, and the resulting solution was heated to reflux for 24 h. The reaction was cooled to room temperature, and the solvent was removed under reduced pressure. Purification by flash column chromatography on silica gel (1:1 hexanes/EtOAc) provided analytically pure aldehyde **46** as a yellow foam (216 mg, 0.22 mmol, 88%). ^1H NMR (400 MHz, $CDCl_3$) δ 9.54 (d, J = 8.0, 1H), 7.41−7.33 (m, 2H), 7.33−7.21 (m, 2H), 7.09 (dd, J = 11.5, 15.5 Hz, 1H), 6.91−6.80 (m, 4H), 6.65 (dd, J = 11.3, 15.0 Hz, 1H), 6.32 (dd, J = 11.1, 15.0 Hz, 1H), 6.21 (dd, J = 10.5, 15.0 Hz, 1H), 6.17−6.05 (m, 2H), 5.64 (ddd, J = 0.7, 7.3, 15.6 Hz, 1H), 5.49 (ddd, J = 0.7, 6.1, 15.7 Hz, 1H), 5.42 (s, 1H), 4.53 (d, A of AB, J = 10.9 Hz, 1H), 4.46 (d, B of AB, J = 10.9 Hz, 1H), 4.37−4.26 (m, 1H), 4.10−3.90 (m, 5H), 3.93−3.83 (m, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.63−3.51 (m, 2H), 3.15 (t, J = 5.70 Hz, 1H), 2.59−2.41 (m, 1H), 2.40−2.23 (m, 2H), 1.90−1.25 (m, 16H), 1.42 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H), 1.32 (s, 3H), 1.32 (s, 3H), 1.02 (d, J = 6.8 Hz, 3H), 0.92 (d, J = 6.7 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.7, 159.8, 159.4, 152.5, 143.2, 138.3, 135.1, 131.7, 131.2, 131.0, 130.9, 129.6, 128.4, 127.3, 114.0, 113.6, 100.4, 100.2, 98.7, 98.1, 79.9, 74.1, 73.5, 72.3, 72.1, 70.9, 70.2, 65.5, 63.7, 63.0, 55.5, 55.4, 42.5, 42.3, 39.5, 39.2, 39.0, 38.1, 37.2, 36.9, 36.8, 30.8, 30.4, 30.3, 25.1, 20.0, 19.8, 19.7, 17.3, 14.0, 12.3. IR (cm^{-1}) 3510, 2983, 2933, 1736, 1679, 1614, 1511, 1377. $[\alpha]^{28}_D$ = +22.6 (c 6.30, CH_2Cl_2). HRMS m/z calcd for $C_{59}H_{86}O_{13}$ + Na^+, 1025.5960; found, 1025.5926.

*(2E,4E,6E,8E,10E,12E)-Ethyl 14-[(4S,5S,6R)-6-{[(2R,4R,6R)-6-{(R)-3-[(4S,6R)-6-{[(4R,6R)-6-[(3S,4S,E)-4-Hydroxy-3,5-dimethylhex-1-enyl]-2,2-dimethyl-1,3-dioxan-4-yl]methyl}-2,2-dimethyl-1,3-dioxan-4-yl]-2-(4-methoxybenzyloxy)propyl}-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]methyl}-2,2,5-trimethyl-1,3-dioxan-4-yl]tetradeca-2,4,6,8,10,12-hexaenoate (**48**).* To a cooled (−78 °C) solution of diisopropylamine (32.3 μL, 0.23 mmol, 3.70 equiv) in THF (1 mL) was added dropwise over 2 min n-BuLi (142 μL, 1.55 M in hexanes, 0.22 mmol, 3.50 equiv). The resulting cloudy mixture was allowed to warm to room temperature and stirred for 10 min and was then cooled to −78 °C. Phosphonate **47**[29] (60.8 mg, 0.22 mmol, 3.50 equiv) in 1 mL of THF was added to the above LDA solution by cannula over 5 min to give a bright yellow solution, which was stirred for 30 min before aldehyde **46** (63 mg, 0.06 mmol, 1.0 equiv) was added via cannula as a solution in 0.8 mL of THF (plus 0.8 mL of THF rinse). After 30 min at −78 °C, the solution was warmed to room temperature and stirred for 10 h. Then the reaction was quenched with 3 mL of saturated aqueous $NaHCO_3$ and diluted with 5 mL of Et_2O. The aqueous material was extracted with Et_2O (3 × 5 mL) and the combined organic layers was washed with 5 mL of brine, dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure. Flash chromatography on silica gel (2:1 hexanes/EtOAc) provided ester **48** (46.7 mg, 0.04 mmol, 66%) as a yellow foam. ^1H NMR (400 MHz, $CDCl_3$) δ 7.40−7.34 (m, 2H), 7.28 (dd, J = 3.3, 15.1 Hz, 1H), 7.29−7.22 (m, 2H), 6.90−6.79 (m, 4H), 6.58 (dd, J = 11.3, 14.8 Hz, 1H), 6.42 (dd, J = 10.7, 14.9 Hz, 1H), 6.40−6.23 (m, 5H), 6.16 (dd, J = 10.0, 14.5 Hz, 1H), 6.13 (dd, J = 10.4, 14.7 Hz, 1H), 5.93−5.80 (m, 1H), 5.83 (d, J = 15.2 Hz, 1H), 5.62 (ddd, J = 0.7, 6.6, 15.0 Hz, 1H), 5.49 (ddd, J = 0.7, 6.3, 15.5 Hz, 1H), 5.41 (s, 1H), 4.51 (d, A of AB, J = 10.8 Hz, 1H), 4.44 (d, B of AB, J = 10.8 Hz, 1H), 4.37−4.27 (m, 1H), 4.18 (q, J = 7.0 Hz, 2H), 4.10−3.90 (m, 5H), 3.93−3.82 (m, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 3.62−3.47 (m, 2H), 3.14 (q, J = 5.5 Hz, 1H), 2.51−2.40 (m, 1H), 2.40−2.31 (m, 1H), 2.31−2.20 (m, 1H), 1.90−1.20 (m, 16H), 1.55 (s, 3H), 1.43 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.01 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.7 Hz, 3H), 0.87 (d, J = 6.9 Hz, 3H), 0.76 (d, J = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 159.8, 159.4, 144.6, 141.0, 137.6, 136.0, 135.1, 132.7, 132.5, 131.7, 131.2, 131.1, 130.9, 129.9, 129.7, 127.4, 120.6, 114.0, 113.6, 100.5, 100.2, 98.7, 98.1, 79.9, 77.6, 74.4, 73.5, 73.2, 72.1, 72.0, 70.9, 70.2, 65.5, 63.7, 62.9, 60.4, 55.5, 55.4, 42.5, 42.3, 39.5, 39.2, 39.0, 38.1, 37.2, 36.9, 30.8, 30.4, 30.3, 25.1, 20.0, 19.9, 19.7, 17.3, 14.5, 14.0, 12.3. IR (cm^{-1}) 3501, 2987, 2933, 1716, 1621, 1565, 1516. $[\alpha]_D$ = 47.922 (c 0.19, CH_2Cl_2). HRMS m/z calcd for $C_{67}H_{96}O_{14}$ + H^+, 1125.6872; found, 1125.6858.

*Protected Dermostatin A (**49**).* To a solution of ester **48** (35 mg, 0.03 mmol, 1.0 equiv) in 6 mL of 4:1:1 THF/H_2O/MeOH was added LiOH (2 mL, 1 M in H_2O, 2.00 mmol, 64.5 equiv). This suspension was stirred for 5 h and then diluted with 3 mL of water and 10 mL of EtOAc. The aqueous material was extracted with EtOAc (5 × 10 mL) and the combined organic layers were washed with 5 mL of brine, dried over $MgSO_4$, filtered through Celite, and concentrated under reduced pressure to provide the crude hydroxy acid as a pale yellow oil.

To the above hydroxy acid in 4 mL of THF was added triethylamine (44.3 μL, 0.32 mmol, 10.25 equiv), followed by 2,4,6-trichlorobenzoyl chloride (33.9 μL, 0.22 mmol, 7.00 equiv). The reaction mixture was stirred for 15 h and then filtered through a short plug of Celite (prewashed with copious amounts of dry THF) and rinsed with excess THF. The filtrate was concentrated under reduced pressure and

dissolved in 12 mL of toluene (0.002 M solution). This solution was added, via syringe pump over 6 h, to 70 mL of toluene containing 4-(dimethylamino)pyridine (DMAP) (77.5 mg, 0.63 mmol, 20 equiv) at room temperature. After addition was complete, the syringe was rinsed with 2 mL of toluene and this was also added to the reaction. The reaction mixture was stirred for 12 h and then was concentrated under reduced pressure. Rapid flash chromatography on silica gel (3:1 hexanes/EtOAc) provided protected dermostatin A **49** and its isomeric compounds (ca. 25 mg, 0.02 mmol, 75% over two steps) as a yellow foam. Rapid olefin isomerization prevented further isolation, via HPLC, of a single, pure product that was not contaminated with varying amounts of isomeric structures. HRMS m/z calcd for $C_{65}H_{90}O_{13} + Cl^-$, 1113.6075; found, 1113.6040.

*Dermostatin A (**1**).* To a solution of protected dermostatin A (**49**) (ca. 15 mg of pure **49**, 0.01 mmol, 1.0 equiv) in 10 mL of MeOH was added concentrated HCl (70 μL, 0.84 mmol, 60.0 equiv). The reaction was stirred for 12 h and then was neutralized by use of polymer-bound piperidine (440 mg, ca. 1.68 mmol, ca. 120 equiv). The polymer was removed by filtration and the filtrate was concentrated under reduced pressure. The resulting crude yellow solid was purified by flash chromatography on silica gel (EtOAc to EtOAc/MeOH 3:1) to afford dermostatin A (**1**) and partially deprotected **49**. The partially deprotected macrolactone was resubjected to the reaction conditions described above to afford ca. 8.0 mg of dermostatin A (**1**). After silica gel chromatography, the synthetic dermostatin A (**1**) was further purified by reversed-phase analytical HPLC (Alltima C18 5u, 250 mm × 10.0 mm with a guard column 33 mm × 7 mm. MeOH/H_2O 5:1, flow 1.8 mL/min, UV detector at 390 nm; retention time 37.8 min). The HPLC purification was repeated twice to obtain pure synthetic dermostatin A (**1**) (7.6 mg, 10.6 μmol, 76%) as a yellow powder. ^{1}H NMR (500 MHz, CD_3OD) δ 7.30 (dd, J = 11.5, 15.1 Hz, 1H, H3), 6.70 (dd, J = 11.3, 14.5 Hz, 1H, H5), 6.52 (dd, J = 11.2, 14.5 Hz, 1H, H7), 6.44−6.12 (m, 7H, H4, H6, H8, H9, H10, H11, and H12), 5.88 (d, J = 15.0 Hz, 1H, H2), 5.84−5.79 (m, 1H, H13), 5.58 (dd, J = 5.4, 15.8 Hz, 1H, H33), 5.48 (dd, J = 5.1, 16.0 Hz, 1H, H32), 4.84−4.79 (m, 1H, H35), 4.27−4.24 (m, 1H, H15), 4.14−4.10 (m, 1H, H31), 4.10−3.89 (m, 6H, H19, H21, H23, H25, H27, and H29), 3.56−3.54 (m, 1H, H17), 2.62−2.59 (m, 1H, H34), 2.48−2.34 (m, 2H, H14 and H14′), 1.90−1.13 (m, 16H, H36, H16, H18, H18′, H20, H20′, H22, H22′, H24, H24′, H26, H26′, H28, H28′, H30, and H30′), 1.01 (d, J = 6.9 Hz, 3H, H39), 0.94 (d, J = 6.7 Hz, 3H, H37/H38), 0.87 (d, J = 6.9 Hz, 3H, H40), 0.85 (d, J = 6.4 Hz, 3H, H37/H38). ^{13}C NMR (100 MHz, CD_3OD) δ 169.2, 147.1, 143.2, 139.6, 137.7, 136.1, 134.7, 133.8, 133.7, 133.5, 133.3(2), 132.8, 131.1, 121.4, 82.4, 72.5, 71.9, 71.3, 71.0, 70.6, 69.8, 69.6, 65.2, 64.7, 48.0, 47.6, 47.4, 46.1, 45.8, 44.8, 43.8, 38.7, 37.5, 30.9, 30.8, 20.4, 19.1, 11.4, 10.6. IR (cm^{-1}) 3354, 2942, 1565, 1430, 1131, 1246. $[\alpha]_D$ = −99.162 (c 0.22, MeOH). Circular dichroism: positive Cotton effect (max λ = 226 nm, min λ = 206 nm). HRMS m/z calcd for $C_{40}H_{64}O_{11} + H^+$, 719.4375; found, 719.4392.

*(2E,4E,6E)-Ethyl Nona-2,4,6,8-tetraenoate (**45**).* To a cooled (0 °C) suspension of sodium hydride (776 mg, 19.4 mmol, 1.2 equiv) in THF (75 mL) was added triethyl phosphonoacetate (3.85 mL, 19.4 mmol, 1.2 equiv) slowly by syringe. Rapid hydrogen gas evolution occurred as the sodium hydride was consumed. After the mixture was stirred at 0 °C for 30 min, a solution of **39**[18] (1.75 g, 16.2 mmol, 1.0 equiv) in THF (6 mL) was added by cannula and the resulting red solution was heated to reflux. After 16 h, the reaction was quenched by the addition of saturated sodium bicarbonate (10 mL). The phases were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered through Celite, and concentrated under reduced pressure. Flash chromatography on silica gel (20:1 hexanes/EtOAc) provided tetraenoate **45** as a white, flaky solid (1.84 g, 10.3 mmol, 64%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (dd, J = 26.5, 11.5 Hz, 1H), 6.55 (dd, J = 14.5, 10.5 Hz, 1H), 6.34−6.26 (m, 4H), 5.86 (d, J = 15.5 Hz, 1H), 5.32 (d, J = 15.0 Hz, 1H), 5.21 (d, J = 9.5 Hz, 1H), 4.19 (q, J = 7.0 Hz, 2H), 1.28 (t, J = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 144.5, 140.5, 137.6, 136.8, 132.5, 130.7, 121.2, 120.1, 60.6, 14.6. IR (cm^{-1}) 3016, 2991, 1703, 1263, 1156, 1013. HRMS m/z calcd for $C_{11}H_{14}O_2 + Li^+$, 185.1148; found, 185.1159.

*(2E,4E,6E)-Nona-2,4,6,8-tetraenal (**40**).* To a cooled (−78 °C) solution of **45** (500 mg, 2.81 mmol, 1.0 equiv) in CH_2Cl_2 (7 mL) was slowly added diisobutylaluminum hydride (5.9 mL, 1 M in hexanes, 5.9 mmol, 2.1 equiv) by cannula. The ice bath was removed and the reaction was stirred for 4 h, at which point it was at room temperature. The reaction was diluted with Et_2O (7 mL) and quenched by sequential addition of water (0.5 mL), 1 M sodium hydroxide (1 mL), and additional water (0.5 mL), resulting in the formation of a white precipitate. This suspension was stirred for 30 min, then magnesium sulfate was added, and the mixture was stirred for an additional 5 min. The solution was filtered through Celite and concentrated under reduced pressure to provide the desired tetraenol (355 mg, 2.61 mmol, 93%) as a white solid. A portion of this material was used directly in the next reaction without further purification.

To a cooled (0 °C) solution of the tetraenol (28 mg, 0.21 mmol, 1.0 equiv) in CH_2Cl_2 (2 mL) was added Dess−Martin periodinane (96 mg, 0.23 mmol, 1.1 equiv) in one portion. The suspension was slowly warmed to room temperature and stirred overnight. The mixture was then filtered through a plug of silica over a pad of Celite, washed with CH_2Cl_2 (5 mL), and then quenched with saturated 1:1 sodium thiosulfate/sodium bicarbonate (10 mL) and allowed to stir for 1 h. The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 3 mL); the combined organic layers were washed with sodium bicarbonate (2 × 3 mL) and brine (1 × 3 mL). The organic layer was dried over magnesium sulfate, filtered through Celite, and concentrated under reduced pressure. Flash chromatography on silica gel (CH_2Cl_2) provided tetraenal **40** as a yellow oil (22.5 mg, 0.17 mmol, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.55 (d, J = 8.0 Hz, 1H), 7.12 (dd, J = 15.5, 11.0 Hz, 1H), 6.68 (dd, J = 14.5, 11.0 Hz, 1H), 6.50−6.30 (m, 4H), 6.14 (dd, J = 15.0, 8.0 Hz, 1H), 5.37 (d, J = 16.5 Hz, 1H), 5.26 (d, J = 10.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.8, 151.9, 142.5, 139.2, 136.7, 132.1, 131.5, 130.6, 121.2. IR (cm^{-1}) 1676, 1591, 1140, 1021. HRMS m/z calcd for $C_9H_{10}O + Li^+$, 141.0886; found, 141.0879.

General Metathesis Procedure. Reactions were carried out in a coldfinger apparatus in which there was no ground glass joint between the condenser and reaction flask. This was done in order to prevent evaporation of the solvent while the reaction was carried out under nitrogen at reflux overnight. To a solution of alkene **31**[20] (50 mg, 0.17 mmol, 1.0 equiv) and metathesis partner (1−3 equiv) in CH_2Cl_2 (1.72 mL) was quickly added the ruthenium metathesis catalyst (0.1 equiv) with brief exposure to atmosphere. The reaction was heated at reflux overnight. The suspension was then cooled to room temperature, filtered through a silica plug over a pad of Celite, washed with CH_2Cl_2, and concentrated under reduced pressure. Flash chromatography on silica gel (40:1 hexanes/EtOAc) provided the product.

(E)-5-(tert-Butyldimethylsilyloxy)-7-phenylhept-2-enal (Table 1, Entries 3−6). Product was a colorless oil (51.2 mg, 0.16 mmol, 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.47 (d, J = 8.0 Hz, 1H), 7.25−7.21 (m, 2H), 7.16−7.11 (m, 3H), 6.84 (dt, J = 15.0, 7.5 Hz, 1H), 6.10 (dd, J = 15.0, 7.5 Hz, 1H), 3.87 (quintet, J = 6.0 Hz, 1H), 2.68−2.62 (m, 1H), 2.60−2.44 (m, 3H), 1.80−1.69 (m, 2H), 0.86 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 155.2, 142.1, 135.2, 128.7, 128.5, 126.2, 70.8, 40.7, 39.3, 32.0, 22.3, 18.3, −4.16, −4.24. IR (cm^{-1}) 3027, 2929, 2857, 1697, 1471, 1255, 1090, 776. HRMS m/z calcd for $C_{19}H_{30}O_2Si + Na^+$, 341.1907; found, 341.1893.

(E)-Ethyl 5-(tert-Butyldimethylsilyloxy)-7-phenylhept-2-enoate (Table 2, Entries 2, 3, 5, and 6). Product was a colorless oil (43.7 mg, 0.12 mmol, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28−7.24 (m, 2H), 7.17−7.15 (m, 3H), 6.95 (dt, J = 15.5, 7.5 Hz, 1H), 5.82 (d, J = 15.5 Hz, 1H), 4.17

(q, J = 7.5 Hz), 3.83 (quintet, J = 6.0 Hz, 1H), 2.71−2.65 (m, 1H), 2.61−2.55 (m, 1H), 2.43−2.34 (m, 2H), 1.77−1.73 (m, 2H), 1.27 (t, J = 7.5 Hz, 3H), 0.89 (s, 9H), 0.5 (s, 3H), 0.4 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 145.9, 142.4, 128.65, 128.56, 126.1, 123.7, 71.1, 60.4, 40.4, 39.3, 32.0, 26.1, 18.3, 14.5, −4.2, −4.3. IR (cm^{-1}) 3027, 2930, 2857, 1721, 1257, 1092, 836. HRMS m/z calcd for $C_{21}H_{34}O_3Si + H^+$, 363.2350; found, 363.2350.

(2E,4E,6E)-9-(tert-Butyldimethylsilyloxy)-11-phenylundeca-2,4,6-trienal (Table 1, Entry 10). Product was a colorless oil (46 mg, 0.12 mmol, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.54 (d, J = 8.0 Hz, 1H), 7.28−7.24 (m, 2H), 7.18−7.15 (m, 3H), 7.10 (dd, J = 15.0, 11.0 Hz, 1H), 6.63 (dd, J = 15.0, 10.5 Hz, 1H), 6.34 (dd, J = 15.0, 11.0 Hz, 1H), 6.24−6.10 (m, 2H), 6.02 (dd, J = 22.5, 7.5 Hz, 1H), 3.80 (quintet, J = 6.0 Hz, 1H), 2.73−2.65 (m, 1H), 2.62−2.54 (m, 1H), 2.41−2.31 (m, 2H), 1.76−1.72 (m, 2H), 0.90 (s, 9H), 0.50 (s, 3H), 0.3 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.9, 152.6, 143.1, 142.5, 138.6, 132.2, 131.1, 128.6, 128.5, 126.0, 71.6, 41.2, 39.3, 32.1, 18.4, −4.1, −4.3. IR (cm^{-1}) 3026, 2929, 2856, 1682, 1614, 1255, 1112, 836. HRMS m/z calcd for $C_{23}H_{34}O_2Si + Na^+$, 393.2220; found, 393.2202.

(2E,4E,6E)-Ethyl 9-Hydroxy-11-phenylundeca-2,4,6-trienoate (Table 2, Entry 10). To a solution of alkene **31**[20] (100 mg, 0.34 mmol, 1.0 equiv) and trienoate **45** (79 mg, 0.52 mmol, 1.5 equiv) in CH_2Cl_2 (3.44 mL) in a coldfinger was quickly added the ruthenium catalyst **33** (28 mg, 0.03 mmol, 0.1 equiv) with brief exposure to atmosphere. The reaction was heated to reflux and allowed to stir overnight. The suspension was then cooled to room temperature, filtered through a silica plug over a pad of Celite, washed with CH_2Cl_2 (5 mL), and concentrated under reduced pressure. The crude mixture was then taken up in acetonitrile and transferred to a plastic, conical vial and then concentrated again under reduced pressure. To a cooled (0 °C) solution of this crude mixture (143 mg, 0.34 mmol, 1.0 equiv) and acetonitrile (3.45 mL) was added hydrofluoric acid (48% in water, 0.2 mL, 14 equiv). After being stirred at 0 °C for 5 min, the reaction was allowed to come to room temperature and was stirred overnight. The reaction was then diluted with $CHCl_3$ (5 mL), the layers were separated, and the aqueous layer was extracted with $CHCl_3$ (3 × 3 mL). The combined organic layers were then dried over magnesium sulfate, filtered through Celite, and concentrated under reduced pressure. Flash chromatography on silica gel (5:1 hexanes/EtOAc) yielded the alcohol as a yellow oil (87 mg, 0.29 mmol, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29−1.23 (m, 2H), 7.18−7.14 (m, 3H), 6.49 (dd, J = 14.5, 11.0 Hz, 1H), 6.23−6.15 (m, 2H), 5.92−5.82 (m, 2H), 4.17 (q, J = 7.5 Hz, 2H), 3.70−3.66 (m, 1H), 2.82−2.75 (m, 1H), 2.69−2.62 (m, 1H), 2.42−2.24 (m, 1H), 1.80−1.73 (m, 2H), 1.91 (br s, 1H), 1.28−1.23 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 144.7, 142.0, 140.6, 135.5, 132.9, 129.0, 128.6, 126.1, 120.9, 70.5, 60.5, 41.4, 38.8, 32.2, 14.5. IR (cm^{-1}) 3454, 3025, 2930, 1708, 1617, 1262, 1136. HRMS m/z calcd for $C_{19}H_{24}O_3 + Na^+$, 323.1617; found, 323.1619.

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org/.

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