Titanium-Mediated Fragment Union Processes in Complex Molecule Synthesis: Development of a Branched Reaction Pathway of High Step Economy for the Synthesis of Complex and Diverse Polyketides

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Received 19 October 2007; revised 20 November 2007

Abstract: We describe a synthetic pathway to structurally complex and diverse polyketides based, in part, on regio- and stereoselective titanium-mediated coupling reactions. The sequences described allow for rapid assembly of polyketide-inspired architecture while providing significant flexibility for the establishment of diverse stereochemical relationships and substitution patterns along the carbon backbone (including stereodefined alkenes and 1,3-dienes, saturated and unsaturated lactones, hemiketals, α,β-unsaturated carbonyls, and spiroketals).

Keywords: polyketides, diversity-oriented synthesis, alkyne complexes, titanium, cross-coupling, regioselectivity

Introduction

Natural products of polyketide biosynthetic origin display an impressive array of potent and diverse biological activities (Figure 1). Members of this class have therapeutic importance based on their known function as antibiotics, anticancer agents, antifungals, antiparasitics, immunosuppressants, and cardiovascular agents.[1] This impressive functional diversity is a direct result of the large structural diversity observed throughout this natural product class.

The biological activity of polyketide-derived natural products is a function of their intricate structure,[2] whereby conformational preferences lead to the defined projection of an array of functional groups in space.[3] Conformational preferences of polyketides are, in turn, a function of stereochemistry, substitution, and oxidation state of the carbons that define their skeletons.[4] All of these structural features are varied in nature by modular type 1 polyketide synthases (PKS1). Within this pathway, iterative Claisen condensation and diverse functionalization serve as the basis for chain elongation and structural variation.[5] Post PKS1 modifications, performed by tailoring enzymes, provide an additional mechanism for the generation of molecular complexity and structural diversity via functionalization processes including glycosylation, cyclization, methylation, and oxidation.[6a]

The polyketide biosynthetic pathway represents an elegant example of a system well equipped for the synthesis of a large collection of structurally diverse small molecules by iterative carbon–carbon bond formation.[6] This strategy is in sharp contrast to the numerous biosynthetic pathways that access complexity and diversity through oligomerization by carbon–heteroatom bond formation (biopolymers including DNA, RNA, proteins, and carbohydrates).[7]

Synthetic pathways of great efficiency have been developed to prepare novel biopolymers. Mirroring biosynthetic pathways, these synthetic accomplishments embrace carbon–heteroatom bond formation to achieve oligomerization.[8] The development of a general pathway for the synthesis of complex and diverse polyketide-based chemotherapeutic agents represents a synthetically more challenging problem. Whereas significant contributions in synthetic methodology have been made to enable the total syntheses of numerous members of this natural product class,[9] chemistry to define synthetic pathways to collections of complex and diverse polyketide-like molecules is underdeveloped.[10]

New synthetic methods and strategies are required to address the combined requirements of diversity, complexity, and efficiency for a unified synthetic pathway to polyketide-like molecules. Here, we describe a flexible synthetic pathway of great step economy[11] for the synthesis of complex and diverse polyketides based, in part, on titanium-mediated coupling reactions between a variety of substituted π-systems.

Background

Advances in acyclic stereocontrol have provided a means to mimic the basic C–C bond-forming strategy used in PKS1[12] and have enabled numerous total syntheses of polyketides (Scheme 1).[9] The synthetic oligomerization of propionate and acetate units can be accomplished through the use of aldol or allylmetal chemistry and typically proceeds via the intermediacy of protected β-hydroxy carbonyls (i.e., **8** and **9**; R^2, R^3 = protecting groups). Based on contributions of numerous investigators over the last thirty years, these C–C bond-forming reactions can predictably deliver complex stereochemically dense polyketides in a selective manner.[13]

Whereas these advances have provided a general stereocontrolled pathway to complex polyketide targets, they typically rely on extensive protecting group manipula-

SYNTHESIS 2008, No. 4, pp 0627–0648
Advanced online publication: 08.02.2008
DOI: 10.1055/s-2008-1032160; Art ID: E19707SS

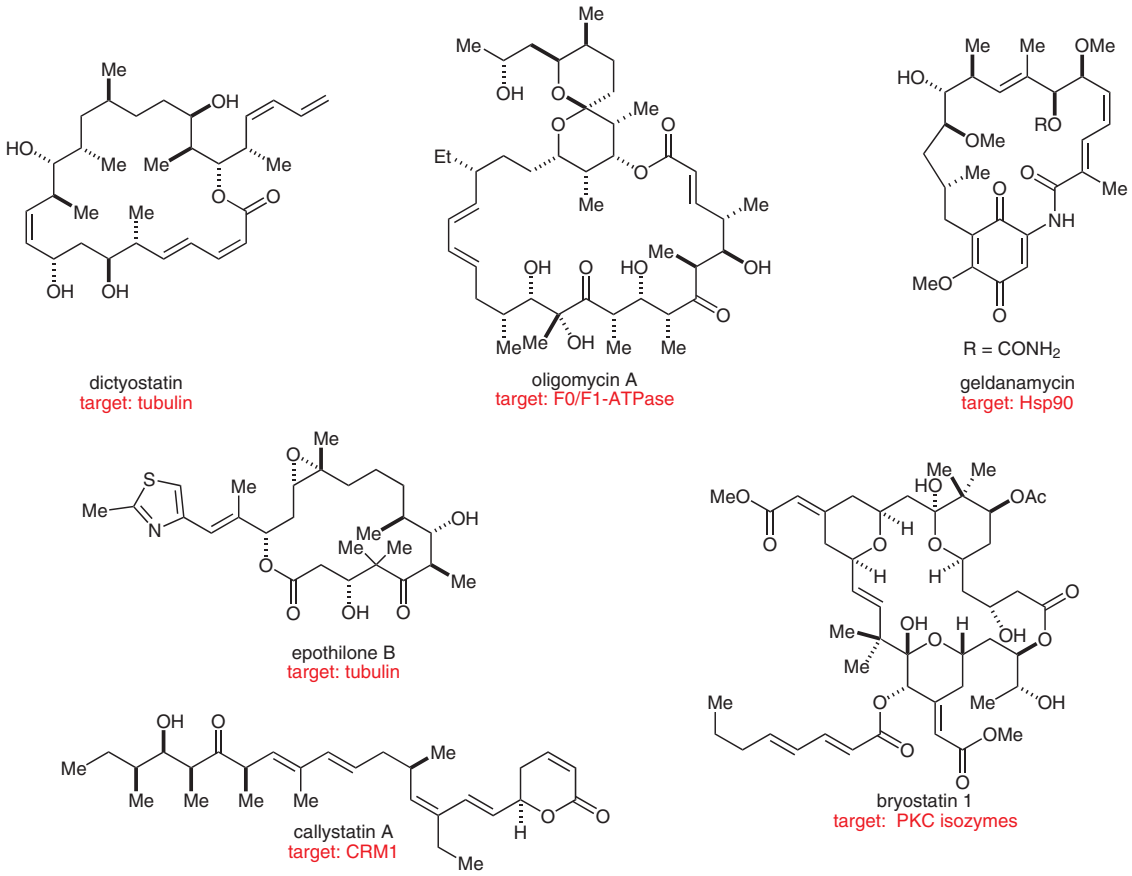


Figure 1 Natural products from polyketide biosynthetic origin and their known biological targets

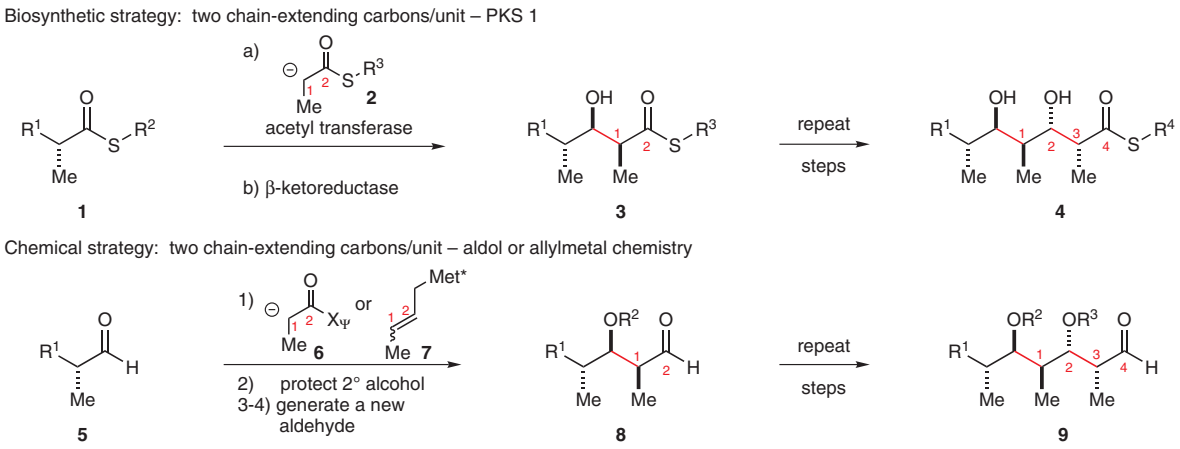
tions and suffer from the requirement of multistep carbonyl redox processes to accomplish chain elongation.[14]

Aside from issues regarding efficiency (step economy),[11] these methods have not yet defined a unified iterative homologation procedure that allows for facile incorporation of diverse skeletal motifs commonly found embedded within polyketide skeletons (i.e., stereodefined alkenes and dienes, 1,5-diols, tertiary alcohols, and epoxides). Although such structural motifs (outside of the common 1,3-polyol) can be installed using a variety of synthetic methods, they typically require deviation from a simple idealized modular pathway, and often require the use of numerous additional functional group manipulations — factors that ultimately further decrease step economy and complicate synthetic pathways required for the installation of each unique structural motif.

Convergent assembly of polyketides by aldol-based bond construction provides a powerful pathway to these complex targets. Selectivity in these processes are a complex function of: (1) the relative and absolute stereochemistry of each coupling partner, (2) the nature and position of protecting groups on each coupling partner, and (3) the type, and geometry, of the metal enolate employed.[15] As a further complication, these reactions are typically incompatible with free hydroxy groups.

Although convergent aldol bond construction has proved useful for target-oriented synthesis, where stereochemical control can be engineered as a function of the aforementioned variables, the use of these processes for the efficient modular synthesis of diverse polyketide-like molecules is anticipated to be inherently limiting. This statement is not meant to detract from the examples of polyketide library synthesis reported where collections of polyols can be accessed through such a strategy,[16] but rather to emphasize that development of a synthetic pathway of high step economy to a variety of polyketides that differ in substitution, oxidation state, and stereochemistry would represent a significant advance.

The goal of defining synthetic sequences useful for the efficient preparation of complex and diverse polyketide-like molecules requires the development of new synthetic methods. Such methods need to be capable of illuminating a pathway that provides diversity in stereochemistry, oxidation state, and substitution along the carbon backbone while maintaining high step economy.[17] These considerations served as the foundation to drive the development of the chemistry described herein.



Scheme 1 Stepwise oligomerization for polyketide synthesis

Results and Discussion

We describe a flexible synthetic pathway of high step economy for the preparation of complex and diverse polyketide-like small molecules (Scheme 2). The pathways described (a–h), proceed from a tris-homopropargylic alcohol **10** in just one to ten steps without protecting group manipulations.

At the outset of our studies, we focused on the following considerations:

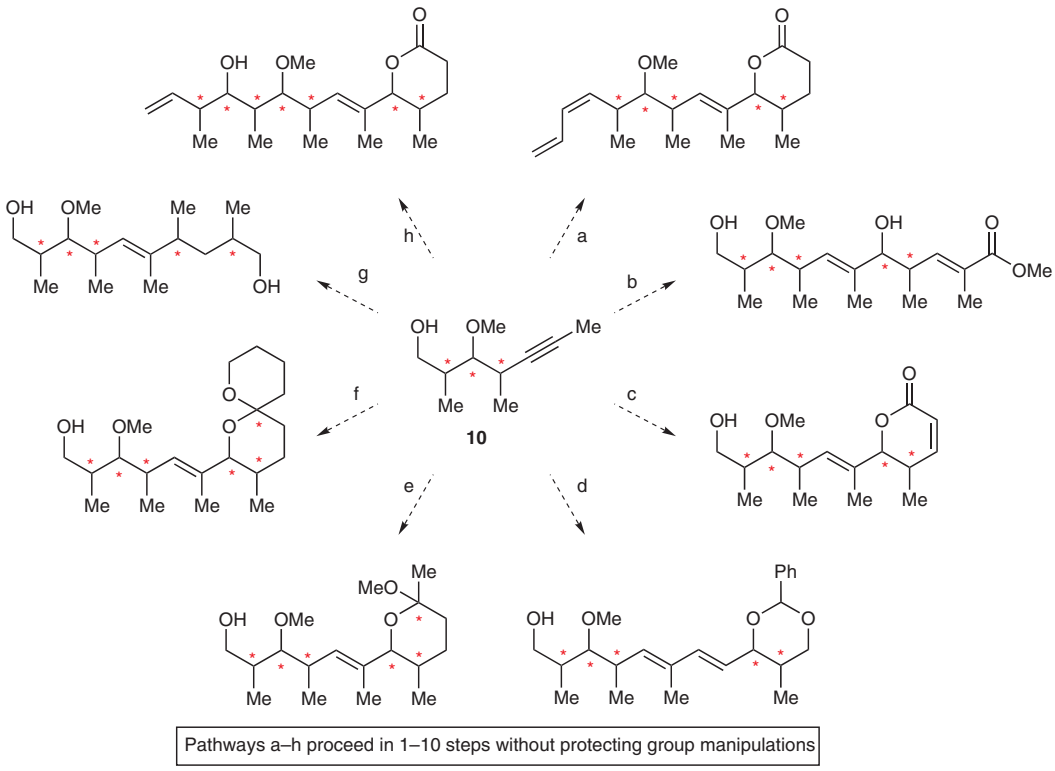
(1) To minimize dependence on complex protecting group manipulations, common to modern strategies for polyketide synthesis, we targeted the development and use of convergent C–C bond-forming processes that are tolerant of free hydroxy groups.

(2) To provide flexibility in the structural motif around which a C–C bond is formed during modular assembly, we planned on developing a suite of regio- and stereoselective cross-coupling reactions between a variety of functionalized π-systems (alkyne–aldehyde, alkyne–alkyne, alkyne–nitrile, alkyne–imine, etc.).

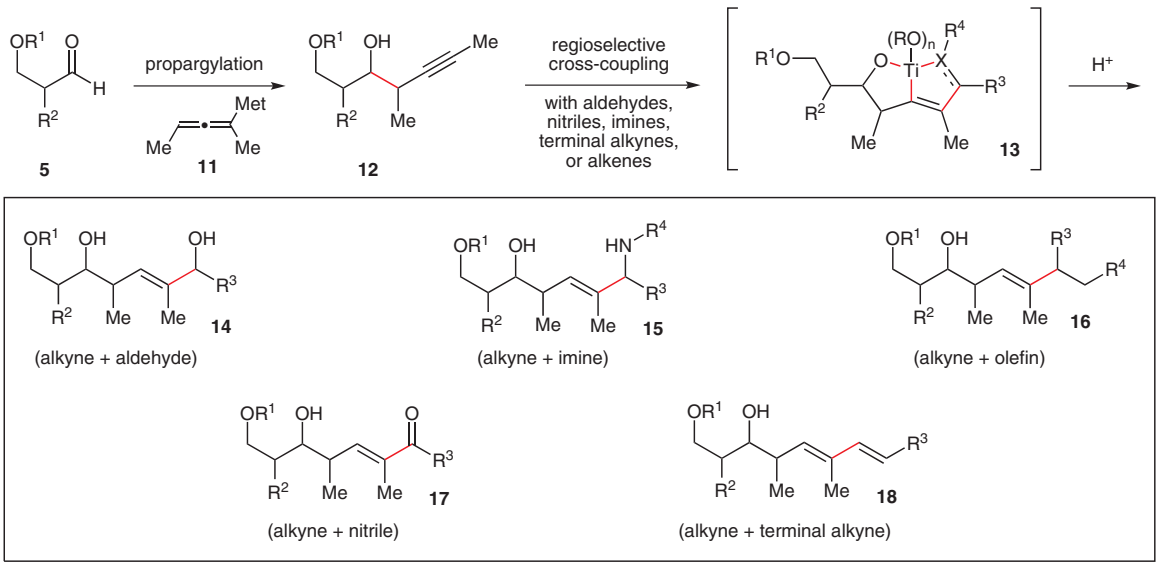
Biographical Sketches

Lark J. Perez was born in Southampton, NY in 1982. During his undergraduate studies at Long Island University, Southampton College, he performed natural product research with Prof. D. John Faulkner at The Scripps Institute of Oceanography before receiving his B.S. in 2003. He is currently a Ph.D. student in the research group of Prof. Glenn C. Micalizio at Yale University studying the utility of titanium alkoxide mediated processes in organic synthesis.

Glenn C. Micalizio was born in East Orange, NJ in 1973, and raised in Paramus, NJ. After receiving a B.S. degree in 1996 from Ramapo College of NJ, he studied with Professor William R. Roush at the University of Michigan, and received a Ph.D. in 2001 based on his research focused on methods development and application to natural product synthesis. Following his doctoral studies, he relocated to Harvard University, where he was appointed as a Helen Hay Whitney Postdoctoral Fellow in the laboratory of Professor Stuart L. Schreiber. Here, his studies were focused on the development of synthetic methods for application to diversity-oriented synthesis. After completion of his postdoctoral studies in 2003, he moved to Yale University and began an appointment as an Assistant Professor in the Department of Chemistry. His current research interests are focused on the development of new synthetic methods to facilitate the synthesis and discovery of complex molecules of therapeutic relevance. A topic of great current interest is the design of new reactions for site- and stereoselective convergent coupling via carbon–carbon bond formation.



Scheme 2 Synthesis of complex polyketides without protecting group manipulations



Scheme 3 Titanium alkoxide mediated cross-coupling of tris-homopropargylic alcohols with π-electrophiles

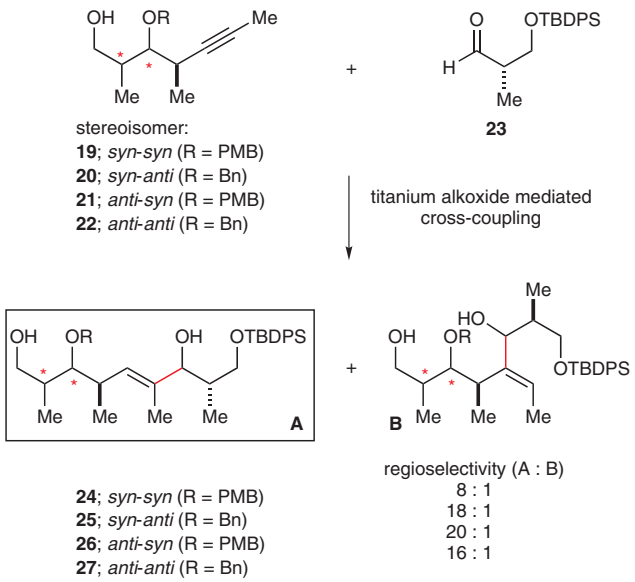
(3) To avoid the requirement of hydroxy group oxidation state manipulations, often coupled to complex protecting group strategies, we targeted the preparation of aldehydes from alkenes rather than primary alcohols.

At the core of our design was the application of alkoxide-directed, titanium-mediated, cross-coupling reactions of functionalized π-systems. As illustrated in Scheme 3, combination of this flexible fragment union process with well-known propargylation reactions would allow for stereochemical flexibility at every chiral center of **12**, as well as provide a convenient branch point for convergent synthesis of ene-1,5-diols (**12** → **14**), ene-1,5-amino alcohols (**12** → **15**), stereodefined trisubstituted alkenes (**12** → **16**), α,β-unsaturated ketones (**12** → **17**), and 1,3-dienes (**12** → **18**).

We have demonstrated previously the utility of penta-2,3-diene-based allenylmetal reagents for the diastereoselective propargylation of chiral aldehydes.[18] Based on the

pioneering work of Marshall,[19] we have defined reaction conditions for the selective preparation of all stereoisomers of homopropargylic alcohol **12**.

We have also reported titanium alkoxide mediated C–C bond-forming processes for the coupling of homopropargylic alcohols **12** with aldehydes[20] and terminal alkynes.[21] These studies revealed that regioselection in the alkyne functionalization process is a complex function of: (1) relative stereochemistry, (2) pairing of absolute stereochemistry of each coupling partner, and (3) the presence and position of a tethered alkoxide on the internal alkyne. Interestingly, we found that with each stereoisomeric series studied (internal alkynes containing *syn-syn*, *syn-anti*, *anti-syn*, and *anti-anti* stereotriads), highest site-selectivities in cross-coupling reactions with chiral aldehydes were observed with tris-homopropargylic alcohol containing substrates (**19**–**22**; Scheme 4). Detailed experimental procedures and comprehensive data regarding regioselection as a function of stereochemistry and position of tethered hydroxy group are available.[20b]



Scheme 4 Regioselective cross-coupling of internal alkynes and aldehydes for polypropionate assembly. *Reaction conditions*: (i) *n*-BuLi, toluene, –78 °C, (ii) $ClTi(O\textit{i}\text{-}Pr)_3$, cyclopentylmagnesium chloride, –78 to –40 °C, (iii) aldehyde, $BF_3{\cdot}OEt_2$, –78 °C.

Step 1: Flexibility in the Titanium-Mediated Fragment Union Process

To explore the versatility of titanium-mediated cross-coupling processes between chiral internal alkynes and diverse π-electrophiles we examined the reaction of tris-homopropargylic alcohol **28** with a variety of coupling partners. The results of these initial studies are illustrated in Scheme 5.

Alkyne–Aldehyde Cross-Coupling. Coupling of the *syn-anti* tris-homopropargylic alcohol **28** with the simple chiral aldehyde *ent*-**23** proceeds with high levels of site selectivity, consistent with our previous studies. In short, formation of the titanium–alkyne complex, followed by addition of the chiral aldehyde and protonation of the presumed intermediate oxatitanacyclopentene provides ene-1,5-diol **29**. Although diastereoselection was not ideal (ds 2:1), these initial studies demonstrated that we could achieve high levels of site selectivity (≥20:1) in the functionalization of alkyne **28**.

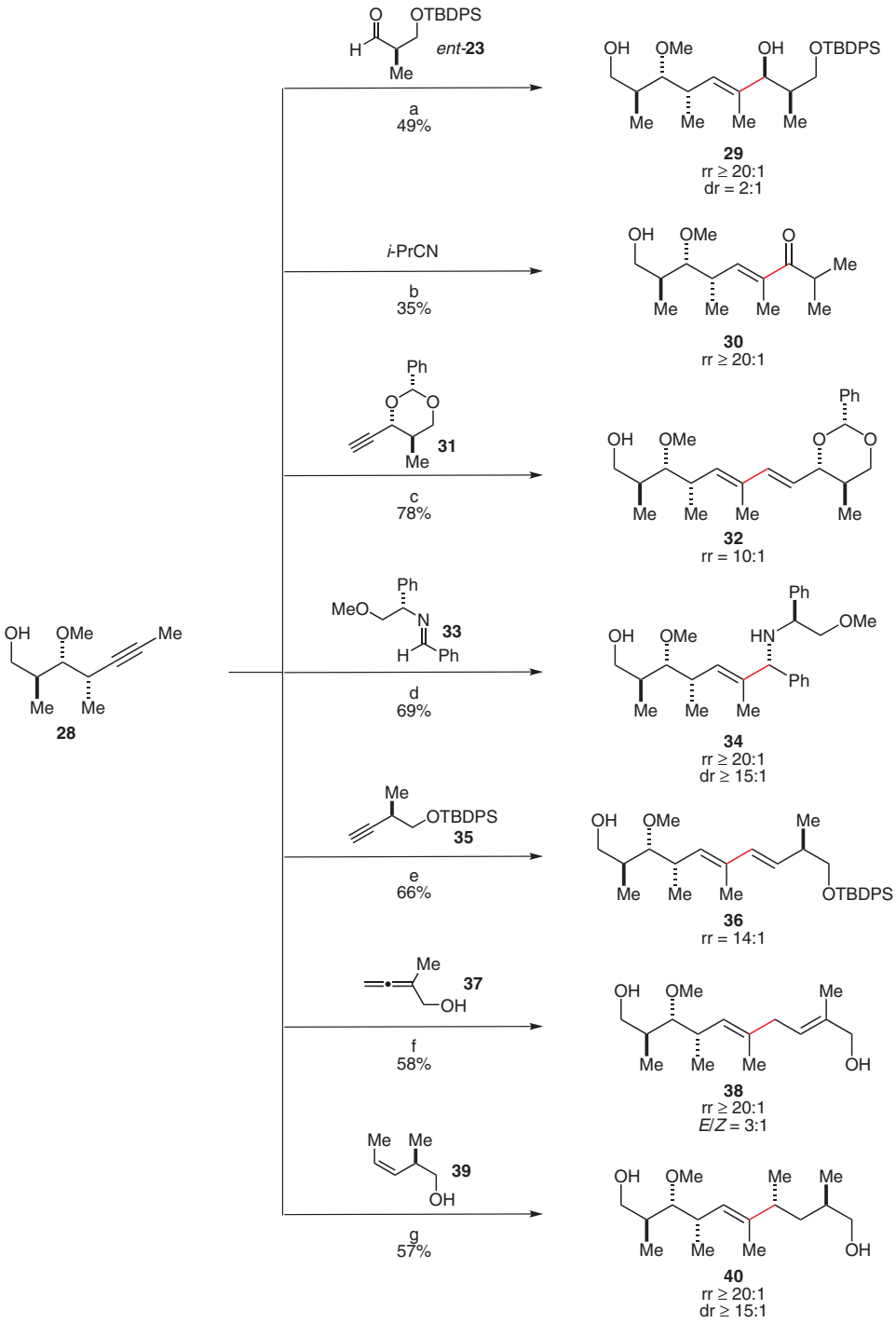
Alkyne–Nitrile Cross-Coupling. Although one has the potential of adding a variety of polarized π-bonds to the preformed metal–alkyne complex of **28**, we observed some limitations. For example, nitrile–alkyne cross-coupling proceeds to deliver the enone **30** as a single regioisomer, but does so with poor efficiency (35% yield). Nevertheless, this process represents a potential pathway for alkoxide-directed hydroacylation[22] of an internal alkyne and presents an interesting branch point in the pathway.

Alkyne–Alkyne Cross-Coupling. Whereas the efficiency of nitrile–alkyne coupling is a barrier for application in the context of synthesis, alkyne–alkyne cross-coupling reactions provide an efficient convergent route to substituted 1,3-dienes embedded within the polyketide skeleton. Deprotonation of the tris-homopropargylic alcohol **28**, followed by formation of the titanium–alkyne complex, addition of a terminal alkyne **31**, and protonation of the presumed metallacyclopentadiene provides the trisubstituted 1,3-diene **32** (rr 10:1), as a single stereoisomer. In this case, high site- and stereoselectivity is observed in the functionalization of both π-systems.

Alkyne–Imine Cross-Coupling. Enabling the convergent synthesis of stereodefined unsaturated 1,5-amino alcohols, alkyne–imine cross-coupling[23] provides a unique process for functionalization of **28**. Formation of the chiral titanium–imine complex derived from **33**, followed by addition of the lithium alkoxide of **28**, and protonation of the presumed azatitanacyclopentene affords the chiral allylic amine **34** in 69% yield (rr ≥ 20:1; dr ≥ 15:1).

Alkyne–Alkyne, Alkyne–Allene and Alkyne–Alkene Cross-Coupling. Interestingly, minor modification of the substitution and/or nature of the π-system used in the functionalization of alkyne **28** can deliver products that contain structural motifs that deviate from the common methylation patterns seen in natural products of polyketide biosynthetic origin. For example, cross-coupling of alkyne **28** with the chiral alkyne **35** or allene **37** provides stereodefined dienes **36** and **38**, each bearing a 1,3,5,8-tetramethylation pattern.[24] Similarly, titanium-mediated cross-coupling of internal alkyne **28** with the chiral homoallylic alcohol **39** provides the diol **40** (rs ≥ 20:1, ds ≥ 15:1), a structure bearing a 1,3,5,6,8-pentamethylation pattern.[25]

The sum of these experiments demonstrates that titanium alkoxide based cross-coupling reactions of stereodefined



Scheme 5 Titanium alkoxide mediated cross-coupling of tris-homopropargylic alcohols with diverse π–electrophiles. *Reaction conditions*: (a) (i) *n*-BuLi, Ti(O*i*-Pr)$_4$, toluene, (ii) cyclopentylmagnesium chloride, –78 to –30 °C, (iii) BF_3·OEt_2, *ent*-**23**, –78 to –30 °C; (b) (i) *n*-BuLi, toluene, Ti(O*i*-Pr)$_4$, (ii) cyclopentylmagnesium chloride, –78 to –40 °C, (iii) *i*-PrCN, –40 to –10 °C; (c) (i) *n*-BuLi, toluene, Ti(O*i*-Pr)$_4$, (ii) cyclopentylmagnesium chloride, –78 to –30 °C, (iii) **31**, –78 to –20 °C; (d) (i) **33**, Ti(O*i*-Pr)$_4$, Et_2O, (ii) cyclopentylmagnesium chloride, –78 to –30 °C, (iii) lithium alkoxide of **28**, Et_2O, –30 °C to r.t.; (e) (i) *n*-BuLi, toluene, Ti(O*i*-Pr)$_4$, (ii) cyclopentylmagnesium chloride, –78 to –30 °C, (iii) **35**, –78 to –20 °C; (f) (i) *n*-BuLi, toluene, Ti(O*i*-Pr)$_4$, (ii) cyclopentylmagnesium chloride, –78 to –30 °C, (iii) lithium alkoxide of **37**, –78 to 0 °C; (g) (i) *n*-BuLi, toluene, Ti(O*i*-Pr)$_4$, (ii) cyclopentylmagnesium chloride, –78 to –30 °C, (iii) lithium alkoxide of **39**, –78 to –20 °C.

tris-homopropargylic alcohol **28** with a variety of substituted π-systems provides a convenient and convergent route to diverse, highly functionalized acyclic systems. In all cross-coupling reactions described, site selectivity is ≥10:1 with respect to both of the π-systems involved. In the reactions of alkyne **28** with carbonyl electrophiles, stereoselectivity varies, but high diastereoselection is possible in the double asymmetric coupling reaction of **28** with chiral imine **33** (dr ≥ 15:1).

Step 2: Forward Synthetic Analysis

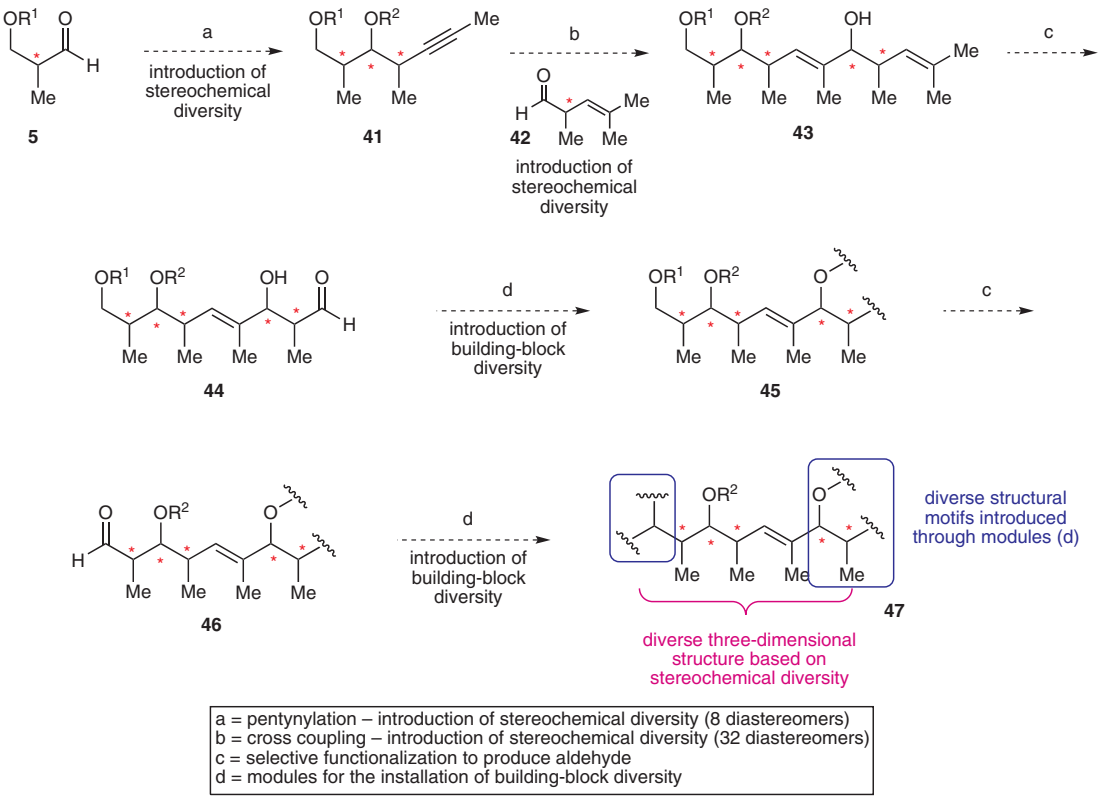
With a workable strategy in place for the synthesis of diverse polyketide architecture from a stereodefined internal alkyne (i.e., Scheme 5), we sought to define a flexible pathway for the bidirectional elaboration of one of these central acyclic polyketide scaffolds. With this goal in mind, we aimed to: (1) increase molecular complexity, (2) access structural diversity (judged by stereochemistry and substitution), and (3) maximize step economy by minimizing the use of protecting group manipulations. Scheme 6 illustrates the general strategy that was pursued to accomplish these goals.

Pentynylation of chiral aldehyde **5** was anticipated to provide a stereochemically flexible route to the internal alkynes **41**. Coupling of these with chiral aldehyde **42** would deliver a stereodefined collection of allylic alcohols **43**. Conversion of these addition products into aldehydes **44** would then be followed by modular diversification through a parallel sequence of reactions to install building block diversity. Ideally, this functionalization would provide a means to append structural motifs that are commonly found in natural products of polyketide biosynthetic origin (α,β-unsaturated carbonyls, lactones, hemiketals, and spiroketals). Next, conversion into a set of new complex aldehydes **46** could be followed by a second branch point for the installation of additional elements of structural diversity. Such a pathway was envisioned to provide access to the extensively functionalized and diverse set of compounds **47**.

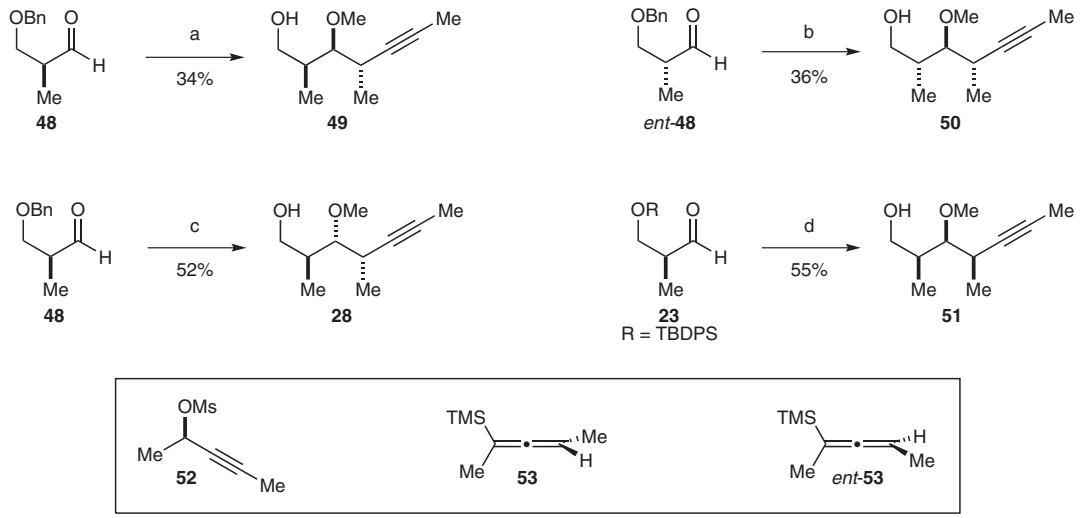
Alkyne–Aldehyde Coupling

As depicted in Scheme 7, all diastereomers of the required tris-homopropargylic alcohol can be prepared via a straightforward three-step sequence. Double asymmetric propargylation[26] of aldehyde **48**, *ent*-**48**, or **23**, followed by methylation and deprotection provides diastereoselective access to the *anti-syn*, *anti-anti*, *syn-anti*, and *syn-syn* isomeric tris-homopropargylic alcohols **28** and **49**–**51**.

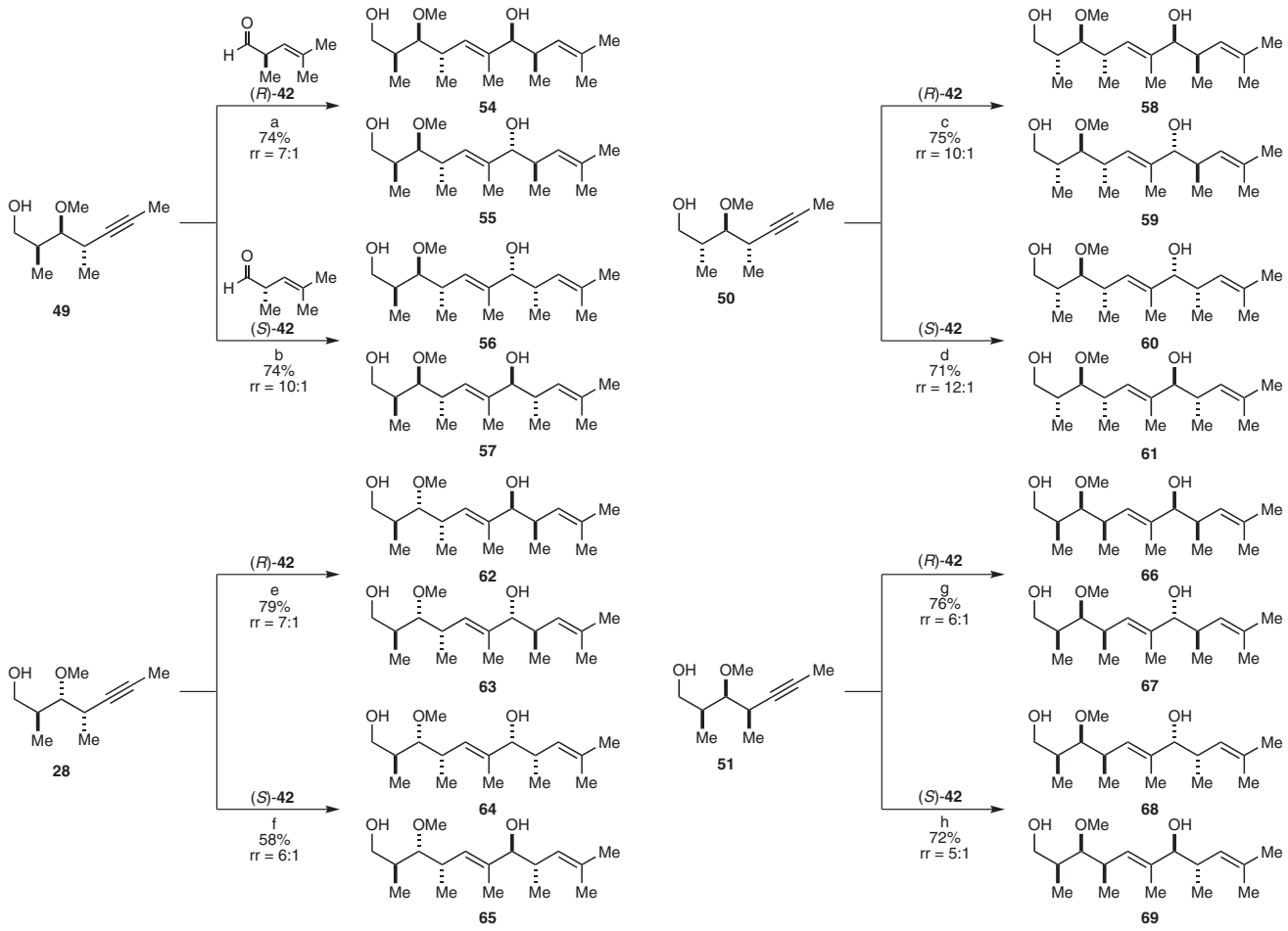
Each of the stereoisomerically pure alkynes **28** and **49**–**51** can be effectively coupled to either enantiomer of a β,γ-unsaturated aldehyde, (*R*)-**42** and (*S*)-**42** (Scheme 8). These reactions are uniformly regioselective, provide access to the desired polyketide backbone, and occur with exclusive chemoselectivity. Furthermore these examples demonstrate the mild nature of the reaction conditions employed. In no case did we find evidence for racemization



Scheme 6 Synthetic strategy for the development of a general synthetic pathway to complex and diverse polyketides



Scheme 7 Preparation of stereoisomeric alkyne coupling partners. *Reaction conditions*: (a) (1) $Pd(PPh_3)_4$, **52**, THF, Et_2Zn, 0 °C to r.t., 60%, ds 9:1, (2) NaH, MeI, DMF, 95%, (3) BBr_3, CH_2Cl_2, –78 °C, 66%; (b) (1) $TiCl_4$, **53**, CH_2Cl_2, –78 °C, 70%, ds 5:1, (2) NaH, MeI, DMF, 99%; (3) BBr_3, CH_2Cl_2, –78 °C, 62%; (c) (1) $TiCl_4$, **53**, CH_2Cl_2, –78 °C, 82%, ds 20:1, (2) NaH, MeI, DMF, 95%, (3) BBr_3, CH_2Cl_2, –78 °C, 67%; (d) (1) $TiCl_4$, *ent*-**53**, CH_2Cl_2, –78 °C, 75%, ds 15:1, (2) NaH, MeI, DMF, 99%, (3) TBAF, THF, 79%.



Scheme 8 Regioselective coupling of hydroxyalkynes **28** and **49**–**51** with β,γ-unsaturated aldehydes **42** and *ent*-**42**. *Reaction conditions*: (a) (i) alkyne, *n*-BuLi, $Ti(O\textit{i}\text{-}Pr)_4$, toluene, (ii) *c*-$C_5H_9MgCl$, –78 °C to –40 °C, (iii) $BF_3{\cdot}OEt_2$, aldehyde, –78 °C to –30 °C, ds 3:1; (b) same as above, ds 3:1; (c) same as above, ds 2:1; (d) same as above, ds 2:1; (e) same as above, ds 2:1; (f) same as above, ds 2:1; (g) same as above, ds 2:1; (h) same as above, ds 2:1.

of the potentially sensitive chiral β,γ-unsaturated aldehyde **42**.

Consistent with our earlier studies, these double asymmetric alkyne–aldehyde coupling reactions proceed with Felkin selectivity, yet do so with relatively low levels of facial selectivity; in many of the cases, selectivity is on the order of 2–3:1. Although this level of diastereoselection leaves significant room for improvement, at this point, we remained focused on the development of the pathway and did not shift attention toward enhancing levels of facial selectivity in this cross-coupling reaction. Rather, simple flash column chromatography could typically be used to deliver pure samples of each diastereomer.

Homologation of the Diene

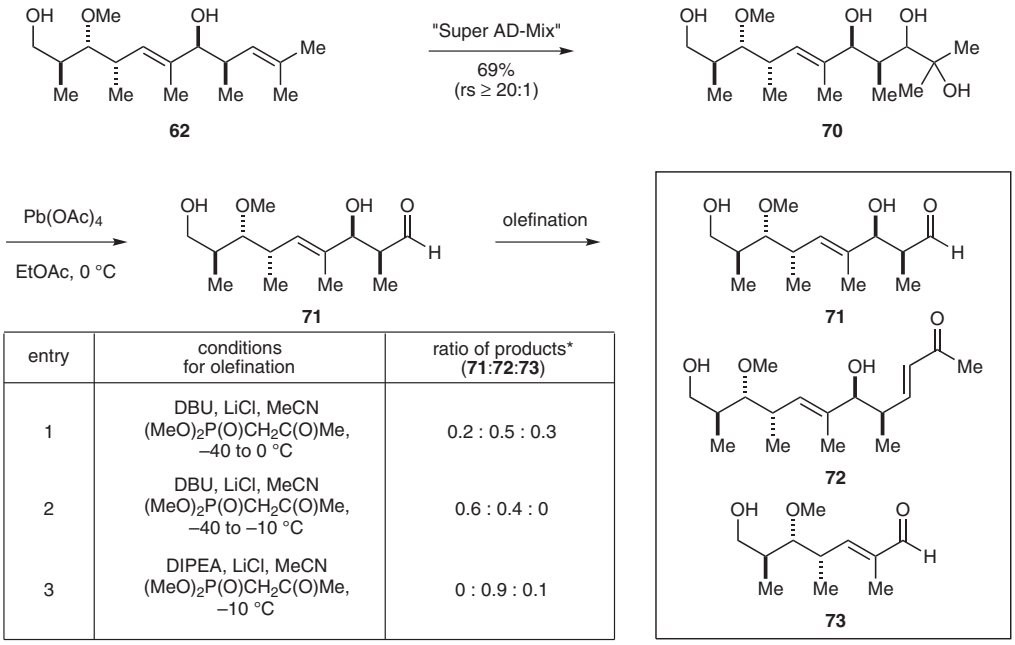
With the collection of dienes in hand **54**–**69**, we selected a single isomer **62** to probe subsequent functionalization reactions. As illustrated in Scheme 9, regioselective dihydroxylation of the less sterically congested trisubstituted alkene can be achieved with the Sharpless asymmetric dihydroxylation reaction.[27] Although use of either AD-mix-α or AD-mix-β provided similar levels of site selectivity, best results were obtained with super AD-mix-β (**62** → **70**; 69%; rr ≥ 20:1). Interestingly, attempts to use standard dihydroxylation conditions (OsO_4, NMO, acetone, H_2O) led only to products of bisfunctionalization.

Selective oxidative cleavage of tetraol **70** delivers the sensitive β-hydroxy aldehyde **71**. Initial attempts to functionalize **71** via olefination processes were not highly effective due to the propensity of the aldehyde to undergo retro-aldol-based fragmentation (Scheme 9).

Fortunately, we found that Horner–Wadsworth–Emmons (HWE) olefination, conducted by the procedure described by Masamune and Roush[28] (DBU, LiCl, MeCN) provided a glimpse of success for the realization of a reaction process to homologate the β-hydroxyaldehyde. Initially, we were able to access **72** as the major product, yet this was found along with a significant amount of starting aldehyde and retro-aldol product (**71**/**72**/**73** = 0.2:0.5:0.3; determined by ^{1}H NMR of the crude reaction mixture) (Scheme 9, entry 1). Running the reaction at lower temperatures (–40 to –10 °C) suppressed formation of the retro-aldol product, but the reaction rate for the desired HWE olefination dropped significantly. In this case, a substantial amount of starting material could be isolated. After significant experimentation, suitable conditions were found to successfully functionalize the sensitive β-hydroxy aldehyde (**71** → **72**). Key to this success was the use of *N*,*N*-diisopropylethylamine as base, and maintaining a temperature of –10 °C throughout the reaction.

Based on the functionality present in **71**, and the flexibility of the Horner–Wadsworth–Emmons olefination, a variety of structural motifs common to natural products of polyketide biosynthetic origin can be readily installed (Scheme 10). For example, α,β-unsaturated esters **74** can be introduced by direct HWE of **71** [$(MeO)_2P(O)CH_2CO_2Me$, DIPEA, LiCl, MeCN, –10 °C, 58%]. Alternatively, a sequence of HWE olefination, followed by chemoselective dissolving metal reduction[29] and acid promoted cyclization (average yield/step = 58%) defines a convenient pathway to saturated lactones **75**.

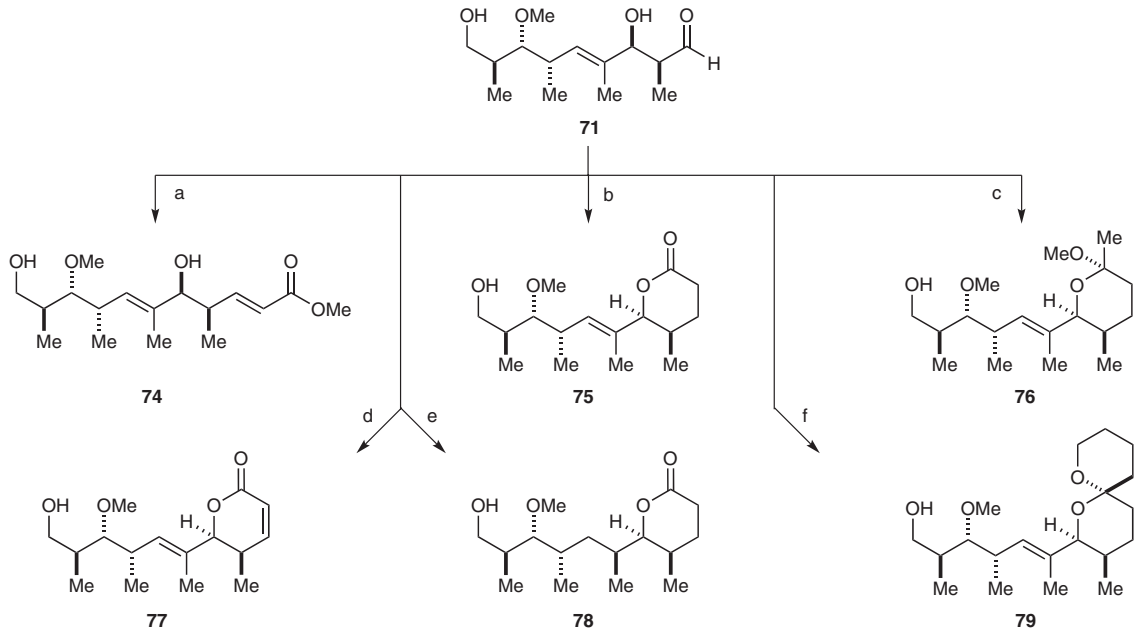
Methyl hemiketals are accessible by a similar homologation procedure. For example, HWE olefination of **71** [$(MeO)_2P(O)CH_2C(O)Me$, DIPEA, LiCl, MeCN, –10 °C,



entry	conditions for olefination	ratio of products* (**71**:**72**:**73**)
1	DBU, LiCl, MeCN $(MeO)_2P(O)CH_2C(O)Me$, –40 to 0 °C	0.2 : 0.5 : 0.3
2	DBU, LiCl, MeCN $(MeO)_2P(O)CH_2C(O)Me$, –40 to –10 °C	0.6 : 0.4 : 0
3	DIPEA, LiCl, MeCN $(MeO)_2P(O)CH_2C(O)Me$, –10 °C	0 : 0.9 : 0.1

* Ratio of products determined by ^{1}H-NMR integration of the crude reaction mixture.

Scheme 9 Optimization of the Horner–Wadsworth–Emmons reaction of the β-hydroxy aldehyde **71**



Scheme 10 A simple branched reaction pathway from the complex β-hydroxy aldehyde **71**. *Reaction conditions*: (a) DIPEA, LiCl, $(MeO)_2P(O)CH_2CO_2Me$, MeCN, –10 °C, 58% (2 steps); (b) (1) DIPEA, LiCl, $(MeO)_2P(O)CH_2CO_2Me$, MeCN, –10 °C, 58% (2 steps) (2) Mg, MeOH, (3) CSA, CH_2Cl_2, 57% (2 steps); (c) (1) DIPEA, LiCl, $(MeO)_2P(O)CH_2C(O)Me$, MeCN, –10 °C, 50% (2 steps); (2) $[CuH(PPh_3)]_6$, benzene, (3) PPTS, MeOH, 37% (2 steps); (d) (1) KHMDS, 18-crown-6, $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, THF, –78 °C, (2) CSA, CH_2Cl_2, 43% (3 steps); (e) (1) DIPEA, LiCl, $(MeO)_2P(O)CH_2CO_2Me$, MeCN, –10 °C, 58% (2 steps), (2) $Rh[(nbd)(dppb)]BF_4$, H_2 (52 bar), CH_2Cl_2, 62%; (f) (1) DIPEA, LiCl, $(MeO)_2P(O)CH_2C(O)(CH_2)_4OTES$, MeCN, –10 °C, 51% (2 steps) (2) $[CuH(PPh_3)]_6$, benzene, (3) CSA, MeOH–CH_2Cl_2, 56% (2 steps).

50%], followed by chemoselective conjugate reduction with Stryker's reagent ($[CuH(PPh_3)]_6$, benzene),[30] and acid-catalyzed cyclization of the crude reduction product (PPTS, MeOH; average yield/step = 61%) provides **76**.

Unsaturated lactones such as **77** can be prepared simply by application of Still's modification of the HWE[31] [$(CF_3CH_2O)_2P(O)CH_2CO_2Me$, KHMDS, 18-crown-6, THF, –78 °C], followed by acid-promoted cyclization (CSA, CH_2Cl_2; average yield/step = 66%). Alternatively, HWE reaction of **71**, to afford **74** (described previously), followed by hydroxy-directed hydrogenation ($Rh[(nbd)(dppb)]BF_4$, H_2 (52 bar), CH_2Cl_2)[32] provides **78** in 62% yield. In this case the saturated lactone, containing a central deoxypropionate motif, is accessed through a process that reduces each alkene and promotes cyclization.

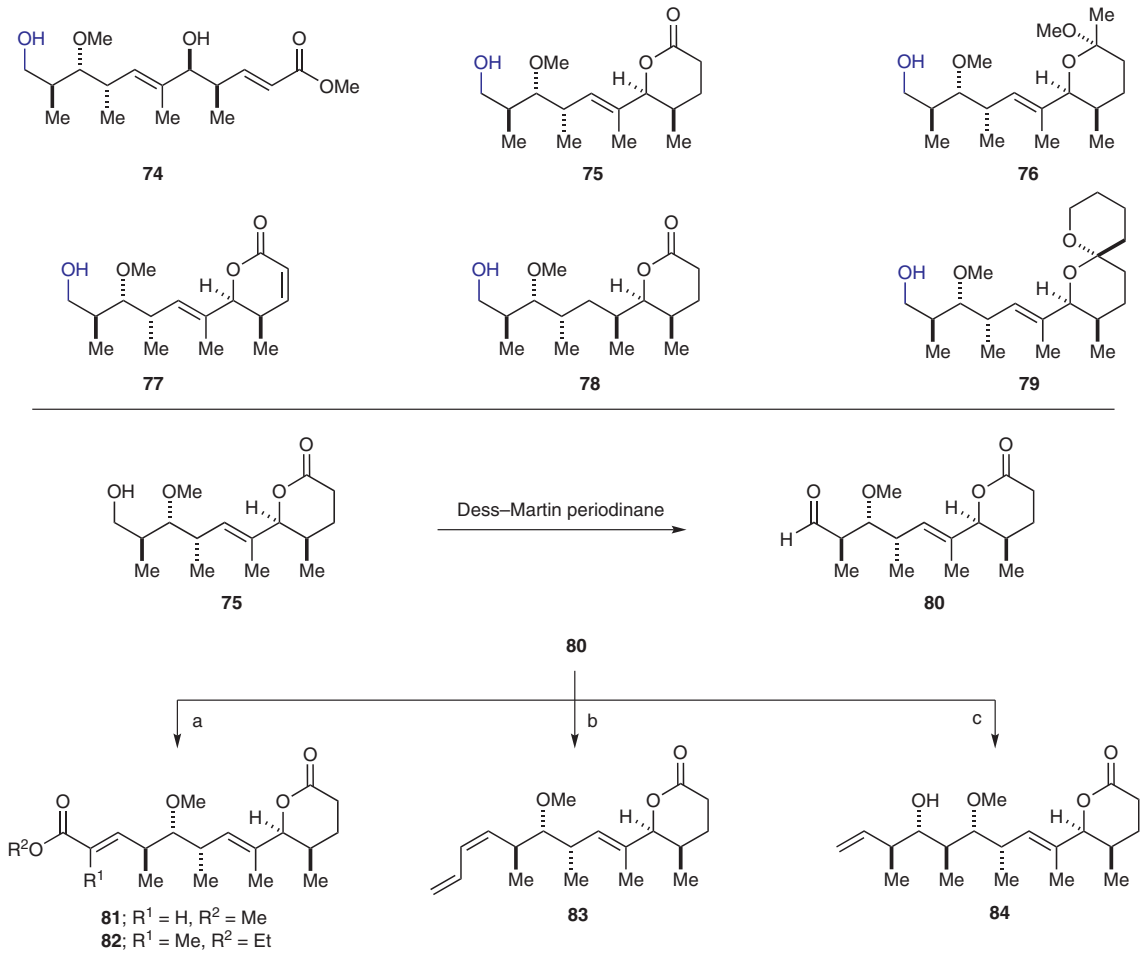
Finally, spiroketals, structural motifs found in a large variety of polyketides that possess anticancer and antibiotic activities, can be installed by a similarly simple sequence of transformations. For example, HWE of **71** [$(MeO)_2P(O)CH_2C(O)(CH_2)_4OTES$, DIPEA, LiCl, MeCN, –10 °C; 51%], followed by conjugate reduction ($[CuH(PPh_3)]_6$, benzene), and acid-promoted cyclization (CSA, MeOH–CH_2Cl_2; average yield/step = 75%), provides the complex spirocyclic polyketide **79**.

Overall, the sequence of simple functionalization reactions described provides a means to convert the propionate-like diene **62** into a collection of complex molecules that possess a variety of structural motifs present in known polyketide-derived natural products. Importantly, in all cases **74**–**79**, these stereodefined complex species were prepared in six steps or less from alkyne **28**, without the need for protecting group manipulations.

Homologation of the Primary Alcohol

The collection of polyketide-like molecules **74**–**79** prepared from alkyne–aldehyde coupling, followed by HWE and functionalization (Scheme 11), all contain a single primary hydroxy group. As such, the potential exists to incorporate additional chemoselective operations as a means to further enhance molecular complexity and structural diversity in the collection of polyketide-like molecules produced from this pathway.

For example, Dess–Martin oxidation of **75** provides the chiral aldehyde **80**, which, upon chemoselective functionalization can be elaborated to a number of new synthetic polyketides (Scheme 11). Wittig homologation of **80** provides the α,β-unsaturated esters **81** or **82** in 62% and 68% yield, respectively. Installation of a *Z*-diene, a structural motif found in the potent anticancer agents discodermolide and dictyostatin, can also be achieved. As depicted, allylation of **80** [4,4,5,5-tetramethyl-2-[(*E*)-3-(trimethylsilyl)allyl]-1,3,2-dioxaborolane, toluene, 4 Å MS], followed by base induced Peterson elimination (KH, THF),[33] and final acidification (CSA, CH_2Cl_2) provides diene **83** in 46% yield over three steps.



Scheme 11 Subsequent functionalization of complex aldehyde **80**. *Reaction conditions*: (a) R^1 = H, R^2 = Me, Ph_3PCHCO_2Me, CH_2Cl_2, 62% (2 steps), R^1 = Me, R^2 = Et, $Ph_3PC(Me)CO_2Et$, CH_2Cl_2, 68% (2 steps); (b) (1) TMS-allyl pinacol borane, 4 Å MS, toluene, (2) KH, THF, (3) CSA, CH_2Cl_2, 46% (4 steps); (c) (*E*)-(*R*,*R*)-DIPT-crotylboronate, 4 Å MS, toluene, –78 °C to r.t., 89% (dr = 4:1, 2 steps).

Alternatively, extension of the polypropionate backbone can be accomplished by reaction of **80** with well-known crotylmetal reagents. For example, treatment with a diisopropyl tartrate modified (*E*)-crotylboronate[34] provides the product of mismatched double asymmetric crotylation **84** in 89% yield (dr 4:1).

Conclusion

We have developed a synthesis strategy for the generation of complex and diverse polyketides from a tris-homopropargylic alcohol and defined a highly branched synthetic network for diversity oriented synthesis (Figure 2). This pathway can be characterized by:

(1) *Initial titanium-mediated fragment union between a simple alkyne (**28**; **B3**, Figure 2) and a diverse array of functionalized π-systems (including aldehydes, imines, terminal alkynes, alkenes, and allenes; **B3** → **D1**–**D7**).*

(2) *Selective oxidation of the coupled product to a complex aldehyde for subsequent homologation*. In the proof-of-concept example provided, site-selective alkene oxidation of a diene product derived from alkyne–aldehyde coupling, provided a sensitive β-hydroxy aldehyde. This intermediate was employed in chain-elongation processes, without the need for protecting group manipulations, by applying a variety of Horner–Wadsworth–Emmons reaction conditions (**C9** → **E1**–**E6**).

(3) *Subsequent chain elongation accomplished from advanced intermediates by selective functionalization of the remaining primary free hydroxy*. Conversion into a new densely functionalized aldehyde provides an opportunity to employ a wealth of well-known bond-construction processes to further extend the growing polyketide backbone (**E4** → **F1**–**F4**).

This pathway is notable for its high step economy, providing complex and diverse products **74**–**84** in ten steps or less (longest linear sequence) from a simple alkyne, while avoiding the use of a single protecting group manipulation. This extensive minimization of standard protecting group manipulations is rare to synthetic sequences commonly employed to access such architectures, and represents an important characteristic of the pathway described.

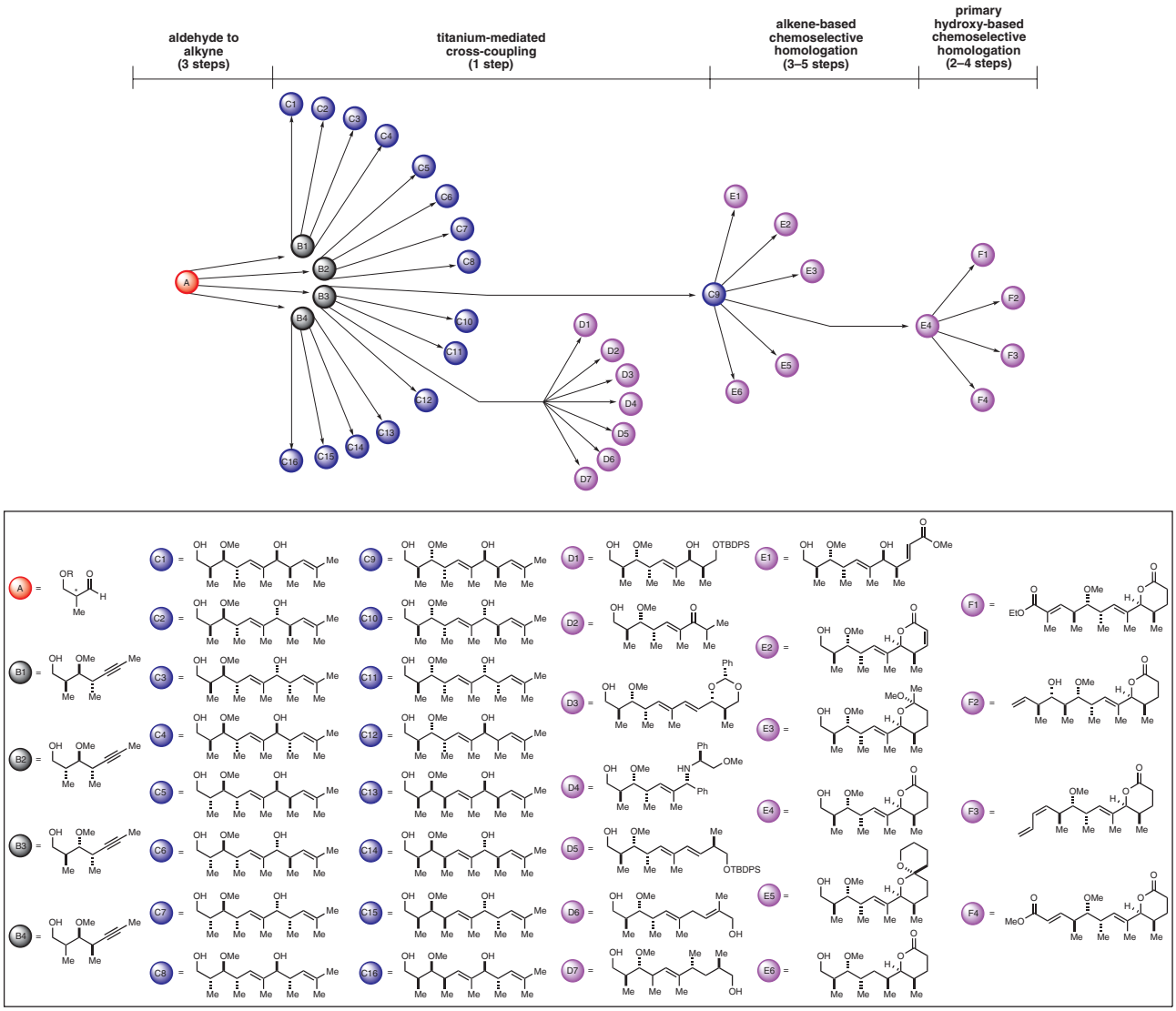


Figure 2 A divergent pathway for the synthesis of stereochemically and structurally complex polyketides

Overall, we believe that this study represents a step toward the realization of a broad network of reaction processes that could be employed in the efficient synthesis of large collections of complex and diverse polyketide-like molecules. Such accomplishments are required to investigate the broad medical potential of polyketide-based architecture, unbound by the laborious and serendipitous process of natural product isolation, or the limitations of combinatorial biosynthesis.[35]

All reactions were conducted in flame-dried glassware under nitrogen using anhydrous solvents. Toluene was dried by distillation over Na/benzophenone ketyl. CH_2Cl_2 and Et_2O were used after passing through activated alumina columns. MeCN, EtOAc, and THF were purchased from Aldrich Chemical Company in Sure/Seal containers and were used as received. All chiral aldehydes were obtained from a Dess–Martin periodinane oxidation of the corresponding primary alcohol and were used without purification except where indicated. All other commercially available reagents were used as received.

^{1}H NMR data was recorded at 500 MHz or 400 MHz using a Bruker AM-500, a Bruker Avance DPX-500 or a Bruker AM-400 instrument. ^{1}H NMR chemical shifts are relative to residual $CHCl_3$ (δ = 7.26). ^{13}C NMR data was recorded at 126 MHz or 101 MHz using a Bruker AM-500, a Bruker Avance DPX-500 or a Bruker AM-400 instrument. ^{13}C NMR chemical shifts are reported relative to the central line of $CDCl_3$ (δ = 77.0). IR spectra were recorded using a Midac Spectrometer M-series. LRMS was performed on a Waters Micromass ZQ instrument using electrospray ionization (EI). Optical rotations were measured on a Perkin Elmer Model 341 polarimeter using a 1-mL capacity microcell with a 10-cm path length.

Chromatographic purifications were performed using 60 Å, 35–75 μm particle size silica gel from Silicycle. All compounds purified by chromatography were sufficiently pure for use in subsequent experiments, unless indicated otherwise. Semi-preparative HPLC normal phase separations were performed using a HPLC system composed of two Dynamax SD-1 pumps, a Rheodyne injector and a Shimadzu RID-10A refractive index detector or a Dynamax UV-1 Absorbance detector at 254 nm.

9-(*tert*-Butyldiphenylsiloxy)-3-methoxy-2,4,6,8-tetramethylnon-5-ene-1,7-diols 29a and 29b

To a soln of alkyne **28** (102.3 mg, 0.601 mmol) in toluene (6.0 mL) at r.t. was added sequentially 2.5 M *n*-BuLi in hexanes (240 μL, 0.601 mmol) and Ti(O*i*-Pr)$_4$ (360 μL, 1.202 mmol) and the mixture

was cooled to –78 °C. At –78 °C the pale yellow mixture was treated with 2.0 M cyclopentylmagnesium chloride in Et_2O (1.2 mL, 2.404 mmol), it was allowed to warm to –40 °C over 35 min and then stirred at –40 °C for 1 h before it was recooled to –78 °C. At –78 °C $BF_3{\cdot}OEt_2$ (150 μL, 1.202 mmol) was added and the mixture was stirred for 15 min before the addition of aldehyde *ent*-**23** (1.8 mL, 1.803 mmol, 1.0 M in toluene) dropwise via syringe. The mixture was allowed to warm to –30 °C over 1.5 h and it was quenched by the addition of sat. NH_4Cl (5 mL) and diluted with Et_2O (5 mL). The reaction was allowed to quench for 1 h and was extracted with Et_2O (2 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Chromatography [silica gel, 50 mL, 30% EtOAc–hexanes (100 mL) and EtOAc (100 mL)] gave **29a** and **29b** (147.4 mg, 49%); 31:1 mixture of regioisomers; 2:1 mixture of diastereomers. Further purification by normal-phase HPLC (UV detection, gradient of 30% EtOAc–hexanes to 80% EtOAc–hexanes over 20 min) provided characterization samples of **29a** and **29b**.

(*E*)-(2*S*,3*R*,4*S*,7*R*,8*S*)-9-(*tert*-Butyldiphenylsiloxy)-3-methoxy-2,4,6,8-tetramethylnon-5-ene-1,7-diol (29a)
Clear, colorless oil; $[\alpha]_{589}^{20}$ –1.3 (*c* 5.2, $CHCl_3$).

IR (thin film, NaCl): 3421, 2962, 2931, 2859, 1472, 1457, 1428, 1113, 1085, 1008, 824, 741, 703, 614 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$): δ = 7.64–7.62 (m, 4 H), 7.43–7.38 (m, 6 H), 5.31 (ddd, *J* = 10.1, 1.3, 1.3 Hz, 1 H), 4.14 (s, 1 H), 3.68 (ddd, *J* = 10.7, 3.8, 3.8 Hz, 1 H), 3.64 (d, *J* = 5.4 Hz, 2 H), 3.46–3.42 (m, 1 H), 3.42 (s, 3 H), 2.90 (dd, *J* = 6.9, 4.7 Hz, 1 H), 2.82 (t, *J* = 5.4 Hz, 1 H), 2.71–2.64 (m, 1 H), 2.55 (s, 1 H), 1.88–1.82 (m, 1 H), 1.77–1.71 (m, 1 H), 1.52 (d, *J* = 1.3 Hz, 3 H), 1.08 (s, 9 H), 1.01 (d, *J* = 6.6 Hz, 3 H), 1.00 (d, *J* = 7.3 Hz, 3 H), 0.90 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 135.6, 135.5 134.8, 133.3, 133.1, 129.8, 129.7, 128.6, 127.7, 91.9, 77.8, 67.9, 65.5, 61.7, 37.8, 37.2, 35.9, 26.8, 19.2, 16.5, 15.5, 13.3, 10.4.

LRMS (EI): *m*/*z* $[M + Na]^+$ calcd for $C_{30}H_{46}NaO_4Si$: 521.3; found: 521.2.

(*E*)-(2*S*,3*R*,4*S*,7*S*,8*S*)-9-(*tert*-Butyldiphenylsiloxy)-3-methoxy-2,4,6,8-tetramethylnon-5-ene-1,7-diol (29b)
Clear, colorless oil; $[\alpha]_{589}^{20}$ +8.8 (*c* 2.3, $CHCl_3$).

IR (thin film, NaCl): 3421, 2962, 2931, 2859, 1457, 1438, 1112, 1086, 1008, 824, 741, 703 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 6.6 Hz, 4 H), 7.47–7.38 (m, 6 H), 5.23 (d, *J* = 10.1 Hz, 1 H), 4.01 (s, 1 H), 3.90 (d, *J* = 8.8 Hz, 1 H), 3.76 (m, 2 H), 3.66 (dd, *J* = 10.1, 8.5 Hz, 1 H), 3.54 (dd, *J* = 11.0, 5.4 Hz, 1 H), 3.49 (s, 3 H), 2.97 (dd, *J* = 6.6, 5.0 Hz, 1 H), 2.88 (s, 1 H), 2.75–2.68 (m, 1 H), 1.97–1.89 (m, 1 H), 1.87–1.81 (m, 1 H), 1.65 (d, *J* = 0.9 Hz, 3 H), 1.06 (s, 9 H), 1.04 (d, *J* = 6.9 Hz, 3 H), 0.99 (d, *J* = 6.6 Hz, 3 H), 0.61 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 135.6, 135.3, 132.8, 132.7, 131.4, 129.9, 127.8, 91.7, 84.0, 69.6, 65.7, 61.8, 37.7, 37.2, 35.9, 26.8, 19.1, 16.8, 16.2, 15.6, 13.5, 11.2.

LRMS (EI): *m*/*z* $[M + Na]^+$ calcd for $C_{30}H_{46}NaO_4Si$: 521.3; found: 521.4.

(*E*)-(6*S*,7*R*,8*S*)-9-Hydroxy-7-methoxy-2,4,6,8-tetramethylnon-4-en-3-one (30)
To a soln of internal alkyne **28** (15.3 mg, 0.09 mmol) in toluene (900 μL) was added sequentially 2.5 M *n*-BuLi in hexanes (36 μL, 0.09 mmol) and $Ti(O\textit{i}\text{-}Pr)_4$ (33 μL, 0.112 mmol). The resulting pale yellow mixture was cooled to –78 °C and was treated with 1.9 M cyclopentylmagnesium chloride in Et_2O (118 μL, 0.225 mmol). This soln was allowed to warm to –40 °C over 45 min and it was stirred at –40 °C for 1 h. To the resulting dark brown mixture *i*-PrCN (24 μL, 0.27 mmol) was added dropwise down the side of the flask and the reaction was allowed to warm to –10 °C over 55 min. The reaction was quenched with sat. NH_4Cl (2 mL), diluted with Et_2O (2 mL) and stirred for 1 h. The mixture was extracted with Et_2O (2 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Chromatography [silica gel, 15 mL, 30% EtOAc–hexanes (30 mL), 50% EtOAc–hexanes (30 mL), and 80% EtOAc–hexanes (30 mL)] gave **30** (7.6 mg, 35%) as a clear, colorless oil; ≥20:1 mixture of regioisomers; $[\alpha]_{589}^{20}$ –9.0 (*c* 0.2, $CHCl_3$).

IR (thin film, NaCl): 3466, 2969, 2932, 2876, 1666, 1461, 1381, 1236, 1119, 1088, 1046, 919, 734 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 6.48 (d, *J* = 9.8 Hz, 1 H), 3.71 (ddd, *J* = 10.1, 5.7, 3.8 Hz, 1 H), 3.62–3.56 (m, 1 H), 3.50 (s, 3 H), 3.30 (dddd, *J* = 6.9, 6.9, 6.9, 6.9 Hz, 1 H), 3.07 (t, *J* = 5.7 Hz, 1 H), 2.91–2.84 (m, 1 H), 2.58 (t, *J* = 5.4 Hz, 1 H), 1.81 (s, 3 H), 1.81–1.78 (m, 1 H), 1.11 (d, *J* = 6.6 Hz, 3 H), 1.09 (d, *J* = 6.9 Hz, 3 H), 1.08 (d, *J* = 6.9 Hz, 3 H), 1.05 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 206.2, 143.8, 135.1, 90.3, 65.7, 61.7, 37.9, 36.9, 33.9, 19.6, 19.5, 15.3, 14.9, 11.9.

LRMS (EI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{26}NaO_3$: 265.2; found: 265.1.

(5*E*,7*E*)-(2*S*,3*R*,4*S*)-3-Methoxy-2,4,6-trimethyl-8-[(2*R*,4*S*,5*R*)-5-methyl-2-phenyl-1,3-dioxan-4-yl]octa-5,7-dien-1-ol (32)
To a soln of alkyne **28** (14.9 mg, 0.087 mmol) in toluene (870 μL) was added sequentially 2.5 M *n*-BuLi in hexanes (35 μL, 0.087 mmol) and $Ti(O\textit{i}\text{-}Pr)_4$ (52 μL, 0.175 mmol). The resulting pale yellow mixture was cooled to –78 °C and was treated with 2 M cyclopentylmagnesium chloride in Et_2O (175 μL, 0.351 mmol) dropwise via syringe. The reaction was allowed to warm to –40 °C over 45 min and it was stirred at –40 °C for 1.25 h and then recooled to –78 °C. To the resulting dark brown soln terminal alkyne **31** (614 μL, 0.061 mmol, 0.1 M in toluene) was added and the reaction was allowed to warm to –20 °C over 2 h. The reaction was quenched with sat. NH_4Cl (2 mL) and diluted with Et_2O (2 mL) and stirred for 1 h. The biphasic mixture was extracted with Et_2O (2 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Chromatography [silica gel, 20 mL, 30% EtOAc–hexanes (50 mL) and EtOAc (50 mL)] gave **32** (18 mg, 78%) as a clear, colorless oil; 10:1 mixture of regioisomers. Further purification by normal-phase HPLC (UV detection (254nm), gradient of 20% EtOAc–hexanes to 50% EtOAc–hexanes over 30 min) provided a characterization sample of **32**; $[\alpha]_{589}^{20}$ –4.2 (*c* 0.3, $CHCl_3$).

IR (thin film, NaCl): 3447, 2966, 2932, 2360, 2337, 1734, 1456, 1274, 1114, 1027 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.52–7.49 (m, 2 H), 7.38–7.30 (m, 3 H), 6.31 (dd, *J* = 15.5, 7.6 Hz, 1 H), 5.60 (dd, *J* = 15.5, 7.6 Hz, 1 H), 5.55 (s, 1 H), 5.34 (d, *J* = 10.1 Hz, 1 H), 4.18 (dd, *J* = 11.7, 5.0 Hz, 1 H), 3.92 (dd *J* = 9.8, 7.9 Hz, 1 H), 3.74–3.68 (m, 1 H), 3.58–3.47 (m, 2 H), 3.47 (s, 3 H), 2.96 (dd, *J* = 6.3, 5.4 Hz, 1 H), 2.82–2.76 (m, 2 H), 1.98–1.91 (m, 1 H), 1.76 (s, 3 H), 1.05 (d, *J* = 6.6 Hz, 3 H), 1.03 (d, *J* = 6.9 Hz, 3 H), 0.78 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 138.5, 138.4, 136.8, 132.3, 128.9, 128.3, 128.2, 126.2, 125.0, 101.3, 91.6, 84.9, 73.1, 65.7, 61.8, 37.4, 36.4, 34.5, 16.1, 15.5, 12.7, 12.5.

LRMS (EI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{34}NaO_4$: 397.3; found: 397.3.

(*E*)-(2*S*,3*R*,4*S*,7*S*)-3-Methoxy-7-{[(*S*)-2-methoxy-1-phenylethyl]amino}-2,4,6-trimethyl-7-phenylhept-5-en-1-ol (34)
To a soln of imine **33** (60.8 mg, 0.254 mmol) in Et_2O (1.5 mL, 0.17 M) at r.t. was added $Ti(O\textit{i}\text{-}Pr)_4$ (68.1 μL, 0.229 mmol) and the resulting mixture was cooled to –78 °C before the addition of 2 M cy-

clopentylmagnesium chloride in Et_2O (229 μL, 0.458 mmol). The reaction was allowed to stir with warming to –30 °C over 45 min and then it was stirred at –30 °C for 3 h. To the resulting dark brown soln was added, via canula, the lithium alkoxide of the trishomopropargyl alcohol **28** [generated through the reaction of 2.5 M *n*-BuLi in hexanes (51 μL, 0.127 mmol) with **28** (21.6 mg, 0.127 mmol) in Et_2O (420 μL, 0.3 M)]. The resulting mixture was allowed to warm from –30 °C to r.t. over 2 h and allowed to stir at r.t. for 1 h before quenching with sat. NH_4Cl. The mixture was diluted with Et_2O (5 mL) and it was stirred at r.t. for 1 h. The mixture was extracted with Et_2O (2 × 20 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was subjected to chromatography [silica gel, 25 mL, 30% EtOAc–hexanes (25 mL), 50% EtOAc–hexanes (25 mL), 80% EtOAc–hexanes (25 mL), and EtOAc (50 mL)] to give **34** (27.3 mg, 69%) as a clear, colorless oil; 20:1 mixture of regioisomers; dr 15:1; $[\alpha]_{589}^{20}$ +22.7 (*c* 0.9, $CHCl_3$).

IR (thin film, NaCl): 3443, 2963, 2926, 2877, 1453, 1114, 701 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.18 (m, 10 H), 5.17 (d, *J* = 10.1 Hz, 1 H), 4.00 (s, 1 H), 3.90 (t, *J* = 6.6 Hz, 1 H), 3.82 (ddd, *J* = 8.5, 4.4, 4.4 Hz, 1 H), 3.66–3.60 (m, 1 H), 3.52 (s, 3 H), 3.45 (d, *J* = 6.9 Hz, 2 H), 3.36 (s, 3 H), 2.98 (dd, *J* = 7.3, 4.4 Hz, 1 H), 2.87 (t, *J* = 5.7 Hz, 1 H), 2.80–2.72 (m, 1 H), 2.36 (s, 1 H), 1.97–1.91 (m, 1 H), 1.45 (s, 3 H), 1.15 (d, *J* = 7.3 Hz, 3 H), 1.06 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 142.8, 140.6, 134.5, 131.9, 128.3, 128.0, 127.6, 127.3, 126.8, 126.5, 91.9, 78.1, 65.4, 65.4, 61.9, 59.0, 58.8, 37.6, 36.5, 16.8, 15.8, 11.6.

LRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{38}NO_3$: 412.3; found: 412.5.

(5*E*,7*E*)-(2*S*,3*R*,4*S*,9*R*)-10-(*tert*-Butyldiphenylsiloxy)-3-methoxy-2,4,6,9-tetramethyldeca-5,7-dien-1-ol (36)

To a soln of alkyne **28** (18 mg, 0.106 mmol) in toluene (1.1 mL) was added sequentially 2.5 M *n*-BuLi in hexanes (42 μL, 0.106 mmol) and $Ti(O\textit{i}\text{-}Pr)_4$ (63 μL, 0.212 mmol). The resulting pale yellow mixture was cooled to –78 °C and was treated with 2 M cyclopentylmagnesium chloride in Et_2O (210 μL, 0.424 mmol) dropwise via syringe. The reaction was allowed to warm to –40 °C (45 min) and stirred for 1.25 h at –40 °C; it was then recooled to –78 °C. To the resulting dark brown soln terminal alkyne **35** (850 μL, 0.085 mmol, 0.1 M in toluene) was added and the reaction was allowed to warm to –20 °C over 2 h. The reaction was quenched with sat. NH_4Cl (2 mL) and diluted with Et_2O (2 mL) and stirred for 1 h. The biphasic mixture was extracted with Et_2O (2 × 20 mL). The combined organic extracts were dried (Na_2SO_4), and concentrated in vacuo. Chromatography [silica gel, 20 mL, 30% EtOAc–hexanes (50 mL) and EtOAc (50 mL)] gave **36** (27.7 mg, 66%) as a clear, colorless oil; mixture of regioisomers 14:1 . Further purification by normal-phase HPLC (UV detection, gradient of 10% EtOAc–hexanes to 50% EtOAc–hexanes over 30 min) provided a characterization sample of **36**; $[\alpha]_{589}^{20}$ –4.6 (*c* 2.9, $CHCl_3$).

IR (thin film, NaCl): 3432, 2961, 2931, 2858, 1589, 1428, 1112, 965, 824, 702 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.68–7.65 (m, 4 H), 7.42–7.35 (m, 6 H), 6.04 (d, *J* = 15.8 Hz, 1 H), 5.52 (dd, *J* = 15.8, 7.3 Hz, 1 H), 5.21 (d, *J* = 9.5 Hz, 1 H), 3.74 (ddd, *J* = 11.0, 4.4, 4.4 Hz, 1 H), 3.58–3.49 (m, 3 H), 3.49 (s, 3 H), 2.96 (dd, *J* = 6.6, 5.0 Hz, 1 H), 2.82–2.75 (m, 2 H), 2.48–2.42 (m, 1 H), 1.82–1.77 (m, 1 H), 1.72 (d, *J* = 1.3 Hz, 3 H), 1.10–1.03 (m, 18 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 135.6, 134.4, 134.0, 134.0, 133.8, 132.9, 130.6, 129.5, 127.6, 91.9, 68.7, 65.7, 61.8, 39.4, 37.3, 36.3, 26.8, 19.3, 16.8, 16.4, 15.6, 12.7.

LRMS (EI): *m*/*z* $[M + Na]^+$ calcd for $C_{31}H_{46}NaO_3Si$: 517.3; found: 517.6.

(2*E*,5*E*)-(7*S*,8*R*,9*S*)-8-Methoxy-2,5,7,9-tetramethyldeca-2,5-diene-1,10-diol (38)

To a soln of internal alkyne **28** (79.6 mg, 0.467 mmol) in toluene (4.7 mL) was added sequentially 2.5 M *n*-BuLi in hexanes (188 μL, 0.467 mmol) and $Ti(O\textit{i}\text{-}Pr)_4$ (210 μL, 0.701 mmol). The resulting pale yellow mixture was cooled to –78 °C and was treated with 2 M cyclopentylmagnesium chloride in Et_2O (700 μL, 1.40 mmol). This soln was allowed to warm to –30 °C over 1 h and stirred at –30 °C for 1 h before recooling to –78 °C. In a separate flask the allene **37** (27.5 mg, 0.327 mmol) in toluene (820 μL) at –78 °C was treated with 2.5 M *n*-BuLi in hexanes (130 μL, 0.327 mmol) and stirred for 15 min while warming to –30 °C. The resulting soln was transferred via canula to the cooled (–78 °C) soln of the titanium–alkyne complex. The mixture was allowed to stir with warming to 0 °C over 130 min and it was quenched with sat. NH_4Cl (5 mL), diluted with Et_2O (5 mL), and stirred for 1 h. The mixture was extracted with Et_2O (2 × 20 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Chromatography [silica gel, 50 mL, 30% EtOAc–hexanes (100 mL) and EtOAc (100 mL)] gave **38** (69.5 mg, 58%) as a clear, colorless oil; 20:1 mixture of regioisomers; ratio *E*/*Z* 3:1. Further purification by normal-phase HPLC (RI detection, isocratic at 70% EtOAc–hexanes) provided a characterization sample of **38**; $[\alpha]_{589}^{20}$ –15.1 (*c* 1.1, $CHCl_3$).

IR (thin film, NaCl): 3381, 2966, 2932, 2361, 2340, 1717, 1457, 1086, 1026 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.41 (dddd, *J* = 7.6, 7.6, 1.3, 1.3 Hz, 1 H), 5.02 (ddd, *J* = 9.8, 1.3, 1.3 Hz, 1 H), 4.03 (d, *J* = 4.4 Hz, 2 H), 3.73–3.68 (m, 1 H), 3.56–3.50 (m, 1 H), 3.46 (s, 3 H), 2.93 (dd, *J* = 6.6, 5.4 Hz, 1 H), 2.85 (t, *J* = 5.0 Hz, 1 H), 2.72–2.61 (m, 3 H), 1.83–1.78 (m, 1 H), 1.68 (s, 3 H), 1.61 (d, *J* = 1.3 Hz, 3 H), 1.48 (t, *J* = 4.4 Hz, 1 H), 1.03 (d, *J* = 6.9 Hz, 3 H), 0.99 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 136.1, 133.4, 128.3, 123.8, 91.8, 68.9, 65.9, 61.5, 37.7, 37.1, 35.9, 16.6, 16.4, 15.5, 13.7.

LRMS (EI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{28}NaO_3$: 279.2; found: 279.2.

(*E*)-(2*S*,3*R*,4*S*,7*R*,9*R*)-3-Methoxy-2,4,6,7,9-pentamethyldec-5-ene-1,10-diol (40)

To a soln of internal alkyne **28** (48.9 mg, 0.287 mmol) in toluene (2.9 mL) was added sequentially 2.5 M *n*-BuLi in hexanes (115 μL, 0.287 mmol) and $Ti(O\textit{i}\text{-}Pr)_4$ (130 μL, 0.431 mmol). The resulting pale yellow mixture was cooled to –78 °C and was treated with 2 M cyclopentylmagnesium chloride in Et_2O (430 μL, 0.861 mmol). This soln was allowed to warm to –30 °C over 1 h and was stirred at –30 °C for 1 h before recooling to –78 °C. In a separate flask the alkene **39** (14.4 mg, 0.144 mmol) in toluene (240 μL) at –78 °C was treated with 2.5 M *n*-BuLi in hexanes (60 μL, 0.144 mmol) and stirred for 15 min while warming to –30 °C. The resulting soln was transferred via canula to the cooled (–78 °C) soln of the titanium–alkyne complex. The mixture was allowed to stir with warming to –20 °C over 70 min and then it was stirred at –20 °C for 2 h. The reaction was quenched with sat. NH_4Cl (5 mL), diluted with Et_2O (5 mL) and stirred for 1 h. The mixture was extracted with Et_2O (2 × 20 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Chromatography [silica gel, 50 mL, 30% EtOAc–hexanes (100 mL) and EtOAc (100 mL)] gave **40** (22.4 mg, 57%) as a clear colorless oil; 20:1 mixture of regioisomers; dr 15:1. Further purification by normal-phase HPLC (RI detection, isocratic at 70% EtOAc–hexanes) provided a characterization sample of **40**; $[\alpha]_{589}^{20}$ –0.8 (*c* 1.1, $CHCl_3$).

IR (thin film, NaCl): 3364, 2962, 2927, 2873, 2361, 2337, 1489, 1261, 1084, 1024, 800 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.03 (d, *J* = 9.5 Hz, 1 H), 3.74–3.70 (m, 1 H), 3.57–3.48 (m, 2 H), 3.48 (s, 3 H), 3.44–3.39 (m, 1 H), 2.92 (dd, *J* = 6.6, 5.0 Hz, 1 H), 2.82 (s, 1 H), 2.68–2.61 (m, 1 H), 2.22–2.15 (m, 1 H), 1.84–1.77 (m, 1 H), 1.61–1.54 (m, 1 H), 1.54 (s, 3 H), 1.34–1.14 (m, 3 H), 1.04 (d, *J* = 7.3 Hz, 3 H), 0.99 (d, *J* = 6.6 Hz, 3 H), 0.95 (d, *J* = 6.9 Hz, 3 H), 0.91 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 138.9, 127.6, 92.1, 68.1, 65.9, 61.7, 40.2, 38.4, 37.3, 35.8, 33.5, 19.5, 17.1, 16.4, 15.5, 12.6.

LRMS (EI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{32}O_3Na$: 295.2; found: 295.2.

(*R*)-2,4-Dimethylpent-3-enal [(*R*)-42]; Typical Procedure

To a soln of (*R*)-2,4-dimethylpent-3-en-1-ol (390 mg, 3.4 mmol) in anhyd CH_2Cl_2 (22 mL) at 0 °C was added Dess–Martin periodinane (2.9 g, 6.8 mmol) and the mixture was stirred vigorously for 10 min to effect dissolution. To this cloudy mixture at 0 °C was added dropwise via addition funnel CH_2Cl_2 saturated with H_2O over 2 h. At this time the reaction was complete by TLC and the mixture was concentrated in vacuo to a volume of ca. 2 mL. The slurry was suspended in 50% Et_2O–hexanes (30 mL), washed with sat. $NaHCO_3$/10% $Na_2S_2O_3$ soln (1:1, 50 mL) and brine, dried (Na_2SO_4), and concentrated in vacuo. The resulting oil (380 mg, quant.) was used without purification in the subsequent step.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.49 (d, *J* = 1.9 Hz, 1 H), 4.95 (dt, *J* = 9.1, 1.6 Hz, 1 H), 3.28–3.20 (m, 1 H), 1.78 (d, *J* = 0.9 Hz, 3 H), 1.70 (d, *J* = 0.9 Hz, 3 H), 1.15 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 201.6, 137.1, 120.6, 46.5, 25.8, 18.4, 14.1

3-Methoxy-2,4,6,8,10-pentamethylundeca-5,9-diene-1,7-diols 54 and 55; Typical Procedure

To a soln of the tris-homopropargyl alcohol **49** (98.5 mg, 0.58 mmol) in toluene (5.8 mL, 0.1 M) at r.t., 2.5 M *n*-BuLi in hexanes (232 μL, 0.58 mmol) and $Ti(O\textit{i}\text{-}Pr)_4$ (345 μL, 1.16 mmol) were added sequentially. The resulting light yellow, clear soln was cooled to –78 °C and treated with 1.9 M cyclopentylmagnesium chloride in Et_2O(1.22 mL, 2.31 mmol) dropwise via syringe. The resulting mixture was allowed to warm to –40 °C over 35 min and stirred at –40 °C for 1 h and then re-cooled to –78 °C. The dark brown mixture was treated with $BF_3{\cdot}OEt_2$ (147 μL, 1.16 mmol) and allowed to stir for 15 min before the addition of the freshly prepared aldehyde (*R*)-**42** (1.7 mL, 1.74 mmol, 1.0 M in toluene) dropwise via syringe. The reaction was allowed to warm to –30 °C (1.5 h), quenched with sat. NH_4Cl (5 mL), diluted with Et_2O (5 mL), and stirred at r.t. for 1 h. The biphasic mixture was extracted with Et_2O (2 × 20 mL) and the organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Chromatography [silica gel, 50 mL, 30% EtOAc–hexanes (100 mL) and 100% EtOAc (100 mL)] gave **54** and **55** (121.7 mg, 74%); 7:1 mixture of regioisomers; major regioisomer dr 2:1. Further purification by chromatography [silica gel, 40 mL, 30% EtOAc–hexanes (10 mL), 50% EtOAc–hexanes (80 mL), and 80% EtOAc–hexanes (80 mL); gave the diastereomeric diols **54** and **55**.

(*E*)-(2*S*,3*S*,4*S*,7*S*,8*R*)-3-Methoxy-2,4,6,8,10-pentamethylundeca-5,9-diene-1,7-diol (54)

Clear, colorless oil; $[\alpha]_{589}^{20}$ –4.2 (*c* 1.6, $CHCl_3$).

IR (thin film, NaCl): 3389, 2965, 2926, 2872, 1435, 1376, 1261, 1089, 1027, 932, 796 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.32 (d, *J* = 9.8 Hz, 1 H), 4.81 (dt *J* = 9.8, 1.3 Hz, 1 H), 3.69 (d, *J* = 8.2 Hz, 1 H), 3.57 (dd, *J* = 10.7, 6.9 Hz, 1 H), 3.46 (dd, *J* = 10.7, 5.4 Hz, 1 H), 3.41 (s, 3 H), 3.06 (dd, *J* = 4.7, 4.7 Hz, 1 H), 2.64–2.58 (m, 1 H), 2.53–2.47 (m, 1 H), 2.37 (s, 1 H), 1.94–1.88 (m, 1 H), 1.60 (d, *J* = 1.0 Hz, 3 H), 1.57 (d, *J* = 1.3 Hz, 3 H), 1.54 (d, *J* = 1.3 Hz, 3 H), 0.96 (d, *J* = 6.6 Hz, 3 H), 0.90 (d, *J* = 6.9 Hz, 3 H), 0.88 (d, *J* = 7.8 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 136.2, 130.2, 129.6, 127.7, 87.7, 82.5, 66.0, 60.3, 37.5, 36.4, 34.3, 25.7, 18.3, 17.8, 17.3, 12.0, 11.5.

LRMS (EI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{32}NaO_3$: 307.2; found: 307.7.

(*E*)-(2*S*,3*S*,4*S*,7*R*,8*R*)-3-Methoxy-2,4,6,8,10-pentamethylundeca-5,9-diene-1,7-diol (55)

Clear, colorless oil; $[\alpha]_{589}^{20}$ +4.6 (*c* 1.2, $CHCl_3$).

IR (thin film, NaCl): 3376, 2964, 2926, 2870, 1576, 1473, 1378, 1261, 1089, 1028, 933, 797 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.42 (dd, *J* = 9.4, 1.3 Hz, 1 H), 4.95 (dt, *J* = 9.8, 1.3 Hz, 1 H), 3.63 (dd, *J* = 10.4, 6.6 Hz, 1 H), 3.55 (d, *J* = 9.1 Hz, 1 H), 3.50 (dd, *J* = 10.4, 5.0 Hz, 1 H), 3.41 (s, 3 H), 3.09 (dd, *J* = 5.7, 4.7 Hz, 1 H), 2.73–2.68 (m, 1 H), 2.56–2.51 (m, 1 H), 1.88–1.84 (m, 1 H), 1.79 (s, 1 H), 1.73 (d, *J* = 1.3 Hz, 3 H), 1.67 (d, *J* = 1.3 Hz, 3 H), 1.64 (d, *J* = 1.6 Hz, 3 H), 0.98 (d, *J* = 6.9 Hz, 3 H), 0.94 (d, *J* = 6.9 Hz, 3 H), 0.78 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 134.9, 134.7, 131.8, 127.3, 87.2, 82.7, 66.3, 60.5, 37.9, 36.8, 34.9, 26.0, 18.3, 18.1, 17.4, 11.8, 11.0.

LRMS (EI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{32}NaO_3$: 307.2; found: 307.7.

(*E*)-(2*S*,3*S*,4*S*,7*R*,8*S*)-3-Methoxy-2,4,6,8,10-pentamethylundeca-5,9-diene-1,7-diol (56)

Clear, colorless oil; $[\alpha]_{589}^{20}$ +24.9 (*c* 0.5, $CHCl_3$).

IR (thin film, NaCl): 3387, 2967, 2928, 2872, 1455, 1376, 1091, 1027, 933 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.44 (d, *J* = 9.5 Hz, 1 H), 4.89 (dt, *J* = 9.8, 1.6 Hz, 1 H), 3.76 (dd, *J* = 7.9, 3.4 Hz, 1 H), 3.60–3.49 (m, 2 H), 3.44 (s, 3 H), 3.09 (dd, *J* = 5.0, 5.0 Hz, 1 H), 2.71–2.64 (m, 1 H), 2.60–2.52 (m, 1 H), 1.90–1.84 (m, 2 H), 1.63 (d, *J* = 1.3 Hz, 3 H), 1.62 (d, *J* = 1.6 Hz, 3 H), 1.58 (d, *J* = 1.3 Hz, 3 H), 1.48 (d, *J* = 3.5 Hz, 1 H), 1.00 (d, *J* = 6.9 Hz, 3 H), 0.99 (d, *J* = 6.6 Hz, 3 H), 0.95 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 136.5, 130.7, 129.8, 127.5, 87.8, 82.4, 66.2, 60.5, 37.9, 36.5, 34.6, 25.8, 18.4, 17.8, 17.2, 12.3, 11.9.

LRMS (EI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{32}NaO_3Na$: 307.2; found: 307.2.

(*E*)-(2*S*,3*S*,4*S*,7*S*,8*S*)-3-Methoxy-2,4,6,8,10-pentamethylundeca-5,9-diene-1,7-diol (57)

Clear, colorless oil; $[\alpha]_{589}^{20}$ –3.2 (*c* 0.6, $CHCl_3$).

IR (thin film, NaCl): 3376, 2964, 2926, 2870, 1576, 1473, 1378, 1261, 1089, 1028, 933 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.41 (d, *J* = 10.1 Hz, 1 H), 4.95 (dt, *J* = 10.1, 1.2 Hz, 1 H), 3.62–3.54 (m, 2 H), 3.55 (d, *J* = 9.5 Hz, 1 H), 3.43 (s, 3 H), 3.11 (dd, *J* = 5.4, 5.4 Hz, 1 H), 2.75–2.71 (m, 1 H), 2.54–2.49 (m, 1 H), 1.95–1.89 (m, 2 H), 1.77 (s, 1 H), 1.73 (d, *J* = 1.3 Hz, 3 H), 1.67 (d, *J* = 1.3 Hz, 3 H), 1.64 (d, *J* = 1.3 Hz, 3 H), 0.95 (d, *J* = 6.9 Hz, 3 H), 0.95 (d, *J* = 6.9 Hz, 3 H), 0.76 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 134.8, 134.8, 131.4, 127.4, 87.5, 82.6, 66.3, 60.4, 37.6, 36.9, 34.7, 26.0, 18.3, 18.1, 17.4, 11.8, 11.1.

LRMS (EI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{32}NaO_3$: 307.2; found: 307.2.

(*E*)-(2*R*,3*S*,4*S*,7*S*,8*R*)-3-Methoxy-2,4,6,8,10-pentamethylundeca-5,9-diene-1,7-diol (58)

Clear, colorless oil; $[\alpha]_{589}^{20}$ –5.1 (*c* 0.6, $CHCl_3$).

IR (thin film, NaCl): 3430, 2965, 2927, 2872, 1452, 1376, 1096, 1029, 984 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.32 (d, *J* = 9.8 Hz, 1 H), 4.86 (dt, *J* = 9.5, 1.3 Hz, 1 H), 3.75 (d, *J* = 7.6 Hz, 1 H), 3.63 (dd, *J* = 10.7, 3.8 Hz, 1 H), 3.59 (dd, *J* = 10.7, 5.9 Hz, 1 H), 3.49 (s, 3 H), 2.97 (dd, *J* = 7.6, 3.8 Hz, 1 H), 2.68–2.62 (m, 1 H), 2.56–2.50 (m, 1 H), 1.80–1.74 (m, 1 H), 1.63 (d, *J* = 1.3 Hz, 3 H), 1.59 (d, *J* = 0.9 Hz, 3 H), 1.54 (d, *J* = 1.3 Hz, 3 H), 0.96 (d, *J* = 6.6 Hz, 6 H), 0.89 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 136.6, 130.6, 128.1, 127.6, 91.3, 82.1, 66.6, 61.5, 38.2, 36.4, 35.2, 25.7, 18.0, 17.8, 17.0, 15.0, 12.0.

LRMS (EI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{32}NaO_3$: 307.2; found: 307.3.

(*E*)-(2*R*,3*S*,4*S*,7*R*,8*R*)-3-Methoxy-2,4,6,8,10-pentamethylundeca-5,9-diene-1,7-diol (59)

Clear, colorless oil; $[\alpha]_{589}^{20}$ +42.1 (*c* 0.6, $CHCl_3$).

IR (thin film, NaCl): 3429, 2966, 2927, 2871, 1452, 1376, 1096, 1029, 984 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.39 (d, *J* = 9.7 Hz, 1 H), 4.93 (d, *J* = 9.7 Hz, 1 H), 3.64–3.52 (m, 3 H), 3.49 (s, 3 H), 2.97 (dd, *J* = 7.8, 3.8 Hz, 1 H), 2.74–2.68 (m, 1 H), 2.56–2.49 (m, 1 H), 2.10 (s, 1 H), 1.74 (s, 3 H), 1.74–1.70 (m, 1 H), 1.68 (s, 3 H), 1.63 (s, 3 H), 1.06 (d, *J* = 6.9 Hz, 3 H), 0.87 (d, *J* = 7.3 Hz, 3 H), 0.77 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 135.1, 135.1, 130.6, 127.4, 91.3, 82.9, 66.8, 61.4, 38.3, 36.7, 35.4, 26.0, 18.3, 18.0, 17.4, 14.9, 10.8.

LRMS (EI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{32}NaO_3$: 307.2; found: 307.3.

(*E*)-(2*R*,3*S*,4*S*,7*R*,8*S*)-3-Methoxy-2,4,6,8,10-pentamethylundeca-5,9-diene-1,7-diol (60)

Clear, colorless oil; $[\alpha]_{589}^{20}$ +53.9 (*c* 0.8, $CHCl_3$).

IR (thin film, NaCl): 3435, 2966, 2927, 2871, 1452, 1376, 1096, 1029, 984 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.35 (d, *J* = 9.8 Hz, 1 H), 4.85 (dt, *J* = 9.8, 1.3 Hz, 1 H), 3.72 (d, *J* = 8.5 Hz, 1 H), 3.61 (dd, *J* = 10.7, 4.1 Hz, 1 H), 3.58 (dd, *J* = 10.7, 5.9 Hz, 1 H), 3.49 (s, 3 H), 2.95 (dd, *J* = 8.5, 3.2 Hz, 1 H), 2.65–2.59 (m, 1 H), 2.56–2.50 (m, 1 H), 1.74–1.68 (m, 1 H), 1.62 (d, *J* = 0.9 Hz, 3 H), 1.59 (d, *J* = 1.3 Hz, 3 H), 1.54 (d, *J* = 1.3 Hz, 3 H), 1.03 (d, *J* = 6.9 Hz, 3 H), 0.98 (d, *J* = 6.6 Hz, 3 H), 0.80 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 136.9, 130.5, 128.7, 127.5, 91.0, 82.9, 66.9, 61.4, 38.4, 36.4, 35.1, 25.8, 18.0, 17.8, 17.5, 14.6, 11.4.

LRMS (EI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{32}NaO_3$: 307.2; found: 307.3.

(*E*)-(2*R*,3*S*,4*S*,7*S*,8*S*)-3-Methoxy-2,4,6,8,10-pentamethylundeca-5,9-diene-1,7-diol (61)

Clear, colorless oil; $[\alpha]_{589}^{20}$ –7.9 (*c* 0.4, $CHCl_3$).

IR (thin film, NaCl): 3420, 2966, 2928, 2871, 1452, 1376, 1097, 1030, 984 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.39 (d, *J* = 9.5 Hz, 1 H), 4.95 (d, *J* = 9.5 Hz, 1 H), 3.65 (dd, *J* = 10.4, 3.8 Hz, 1 H), 3.59 (dd, *J* = 10.7, 5.4 Hz, 1 H), 3.56 (d, *J* = 9.1 Hz, 1 H), 3.48 (s, 3 H), 2.98 (dd, *J* = 7.6, 3.8 Hz, 1 H), 2.75–2.69 (m, 1 H), 2.54–2.49 (m, 1 H), 1.99 (s, 1 H), 1.84–1.79 (m, 1 H), 1.73 (s, 3 H), 1.67 (s, 3 H), 1.63 (s, 3 H), 1.01 (d, *J* = 6.9 Hz, 3 H), 0.89 (d, *J* = 7.6 Hz, 3 H), 0.77 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 135.2, 134.8, 129.9, 127.3, 91.1, 82.5, 66.6, 61.4, 37.9, 36.9, 35.3, 26.0, 18.3, 17.9, 17.5, 15.1, 11.1.

LRMS (EI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{32}NaO_3$: 307.2; found: 307.3.

(*E*)-(2*S*,3*R*,4*S*,7*S*,8*R*)-3-Methoxy-2,4,6,8,10-pentamethylundeca-5,9-diene-1,7-diol (62)

Clear, colorless oil; $[\alpha]_{589}^{20}$ –27.8 (*c* 0.5, $CHCl_3$).

IR (thin film, NaCl): 3393, 2963, 2928, 2871, 1457, 1375, 1094, 1023, 935 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.16 (d, *J* = 9.8 Hz, 1 H), 4.86 (dt, *J* = 9.8, 1.3 Hz, 1 H), 3.75–3.68 (m, 2 H), 3.52–3.48 (m, 1 H), 3.46 (s, 3 H), 2.92 (dd, *J* = 7.3, 4.7 Hz, 1 H), 2.79 (dd, *J* = 5.9, 5.0 Hz, 1 H), 2.67–2.61 (m, 1 H), 2.55–2.49 (m, 1 H), 1.80–1.74 (m, 1 H), 1.62 (d, *J* = 1.3 Hz, 3 H), 1.58 (d, *J* = 1.3 Hz, 3 H), 1.55 (d, *J* = 1.3 Hz, 3 H), 1.46 (d, *J* = 3.8 Hz, 1 H), 1.03 (d, *J* = 6.9 Hz, 3 H), 0.94 (d, *J* = 6.6 Hz, 3 H), 0.93 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 135.9, 130.9, 129.8, 127.4, 91.9, 81.7, 65.6, 61.8, 37.3, 36.5, 35.9, 25.8, 17.9, 16.7, 16.3, 15.7, 12.4.

LRMS (EI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{32}NaO_3$: 307.2; found: 307.7.

(*E*)-(2*S*,3*R*,4*S*,7*R*,8*R*)-3-Methoxy-2,4,6,8,10-pentamethylundeca-5,9-diene-1,7-diol (63)

Clear, colorless oil; $[\alpha]_{589}^{20}$ +32.3 (*c* 1.0, $CHCl_3$).

IR (thin film, NaCl): 3382, 2962, 2928, 2871, 1460, 1388, 1094, 1024 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.24 (d, *J* = 9.8 Hz, 1 H), 4.93 (d, *J* = 9.8 Hz, 1 H), 3.75–3.69 (m, 1 H), 3.53–3.47 (m, 1 H), 3.46 (s, 3 H), 2.92 (dd, *J* = 6.6, 5.0 Hz, 1 H), 2.81 (t, *J* = 5.4 Hz, 1 H), 2.73–2.67 (m, 1 H), 2.56–2.50 (m, 1 H), 1.79 (d, *J* = 1.6 Hz, 1 H), 1.79–1.73 (m, 1 H), 1.74 (d, *J* = 0.9 Hz, 3 H), 1.67 (d, *J* = 0.9 Hz, 3 H), 1.63 (d, *J* = 1.3 Hz, 3 H), 1.03 (d, *J* = 7.3 Hz, 3 H), 1.02 (d, *J* = 6.9 Hz, 3 H), 0.73 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 135.3, 134.6, 132.5, 127.1, 91.9, 82.7, 61.7, 65.7, 37.3, 36.9, 36.0, 26.0, 18.4, 17.4, 16.1, 15.6, 11.0.

LRMS (EI): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{32}NaO_3$: 307.2; found: 307.2.

(*E*)-(2*S*,3*R*,4*S*,7*R*,8*S*)-3-Methoxy-2,4,6,8,10-pentamethylundeca-5,9-diene-1,7-diol (64)

Clear, colorless oil; $[\alpha]_{589}^{20}$ +2.6 (*c* 1.2, $CHCl_3$).

IR (thin film, NaCl): 3418, 2964, 2928, 2873, 1669, 1457, 1376, 1085, 1023, 803 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.13 (d, *J* = 10.4 Hz, 1 H), 4.77 (dt, *J* = 9.8, 1.3 Hz, 1 H), 3.72 (dd, *J* = 11.0, 3.2 Hz, 1 H), 3.67 (d, *J* = 8.5 Hz, 1 H), 3.46 (s, 3 H), 3.44 (dd, *J* = 11.0, 5.0 Hz, 1 H), 2.88 (dd, *J* = 7.6, 4.4 Hz, 1 H), 2.67–2.61 (m, 1 H), 2.56–2.50 (m, 1 H), 1.75–1.70 (m, 1 H), 1.59 (d, *J* = 1.3 Hz, 3 H), 1.58 (d, *J* = 1.3 Hz, 3 H), 1.54 (d, *J* = 1.3 Hz, 3 H), 1.53 (s, 1 H), 1.05 (d, *J* = 7.3 Hz, 3 H), 1.01 (d, *J* = 6.6 Hz, 3 H), 0.97 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 136.3, 130.8, 130.8, 127.3, 92.2, 82.7, 65.4, 61.9, 36.9, 36.5, 36.1, 25.9, 17.8, 17.4, 16.7, 15.8, 11.5.

LRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{33}O_3$: 285.2; found: 285.2.

(*E*)-(2*S*,3*R*,4*S*,7*S*,8*S*)-3-Methoxy-2,4,6,8,10-pentamethylundeca-5,9-diene-1,7-diol (65)

Clear, colorless oil; $[\alpha]_{589}^{20}$ –4.2 (*c* 0.6, $CHCl_3$).

IR (thin film, NaCl): 3388, 2966, 2928, 2872, 1457, 1375, 1091, 1027 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.23 (dd, *J* = 9.2, 1.3 Hz, 1 H), 4.94 (dt, *J* = 9.8, 1.3 Hz, 1 H), 3.73 (dt, *J* = 11.0, 3.5 Hz, 1 H), 3.55–3.52 (m, 2 H), 3.49 (s, 3 H), 2.97 (dd, *J* = 6.6, 5.1 Hz, 1 H), 2.83 (t, *J* = 5.7 Hz, 1 H), 2.74–2.69 (m, 1 H), 2.55–2.49 (m, 1 H), 1.86–1.80

(m, 1 H), 1.78 (d, *J* = 1.6 Hz, 1 H), 1.76 (d, *J* = 1.3 Hz, 3 H), 1.73 (d, *J* = 1.3 Hz, 3 H), 1.66 (d, *J* = 1.3 Hz, 3 H), 1.04 (d, *J* = 7.3 Hz, 3 H), 0.99 (d, *J* = 6.6 Hz, 3 H), 0.78 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 135.1, 134.5, 131.7, 126.9, 91.7, 82.3, 65.8, 61.8, 37.2, 36.9, 35.9, 26.0, 18.3, 17.5, 16.2, 15.6, 11.3.

LRMS (EI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{32}NaO_3$: 307.2; found: 307.2.

(*E*)-(2*S*,3*S*,4*R*,7*S*,8*R*)-3-Methoxy-2,4,6,8,10-pentamethylundeca-5,9-diene-1,7-diol (66)

Clear, colorless oil; $[\alpha]_{589}^{20}$ –33.0 (*c* 1.0, $CHCl_3$).

IR (thin film, NaCl): 3396, 2966, 2928, 2872, 1457, 1375, 1091, 1027 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.08 (d, *J* = 9.8 Hz, 1 H), 4.79 (dt, *J* = 9.8, 1.3 Hz, 1 H), 3.67 (dd, *J* = 8.5, 3.5 Hz, 1 H), 3.59–3.53 (m, 2 H), 3.47 (s, 3 H), 3.07 (dd, *J* = 9.5, 2.2 Hz, 1 H), 2.59–2.50 (m, 1 H), 1.82–1.75 (m, 1 H), 1.61 (d, *J* = 1.3 Hz, 3 H), 1.59 (d, *J* = 1.3 Hz, 3 H), 1.56 (d, *J* = 1.3 Hz, 3 H), 1.43 (d, *J* = 3.5 Hz, 1 H), 1.03 (d, *J* = 6.6 Hz, 3 H), 0.97 (d, *J* = 6.6 Hz, 3 H), 0.76 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 136.0, 130.7, 130.6, 127.3, 86.7, 82.8, 66.4, 61.3, 38.2, 36.5, 36.0, 25.8, 17.9, 17.8, 17.5, 11.4, 10.1.

LRMS (EI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{32}NaO_3$: 307.2; found: 307.2.

(*E*)-(2*S*,3*S*,4*R*,7*R*,8*R*)-3-Methoxy-2,4,6,8,10-pentamethylundeca-5,9-diene-1,7-diol (67)

Clear, colorless oil; $[\alpha]_{589}^{20}$ +12.8 (*c* 1.2, $CHCl_3$).

IR (thin film, NaCl): 3386, 2963, 2926, 2873, 1457, 1375, 1262, 1091, 1027, 933 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.15 (d, *J* = 9.8 Hz, 1 H), 4.94 (dt, *J* = 9.5, 1.3 Hz, 1 H), 3.58–3.55 (m, 2 H), 3.52 (d, *J* = 8.8 Hz, 1 H), 3.47 (s, 3 H), 3.11 (dd, *J* = 9.1, 2.5 Hz, 1 H), 2.67–2.62 (m, 1 H), 2.53–2.49 (m, 1 H), 1.90–1.85 (m, 1 H), 1.76 (s, 1 H), 1.73 (d, *J* = 1.3 Hz, 3 H), 1.67 (d, *J* = 1.3 Hz, 3 H), 1.63 (d, *J* = 1.3 Hz, 3 H), 1.02 (d, *J* = 6.6 Hz, 3 H), 0.84 (d, *J* = 6.9 Hz, 3 H), 0.77 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 135.0, 134.3, 131.6, 127.1, 86.6, 82.4, 66.5, 61.2, 38.3, 36.9, 35.9, 26.0, 18.3, 17.6, 17.5, 11.2, 10.6.

LRMS (EI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{32}NaO_3$: 307.2; found: 307.7.

(*E*)-(2*S*,3*S*,4*R*,7*R*,8*S*)-3-Methoxy-2,4,6,8,10-pentamethylundeca-5,9-diene-1,7-diol (68)

Clear, colorless oil; $[\alpha]_{589}^{20}$ +20.0 (*c* 0.8, $CHCl_3$).

IR (thin film, NaCl): 3395, 2967, 2927, 2871, 1457, 1374, 1090, 1027 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.09 (dt, *J* = 10.0, 0.9 Hz, 1 H), 4.86 (dt, *J* = 9.8, 1.3 Hz, 1 H), 3.72 (dd, *J* = 7.6, 3.5 Hz, 1 H), 3.60–3.56 (m, 2 H), 3.47 (s, 3 H), 3.09 (dd, *J* = 9.1, 2.5 Hz, 1 H), 2.61–2.50 (m, 2 H), 1.86–1.81 (m, 1 H), 1.64 (d, *J* = 1.3 Hz, 3 H), 1.59 (d, *J* = 1.6 Hz, 3 H), 1.56 (d, *J* = 1.3 Hz, 3 H), 1.45 (d, *J* = 3.8 Hz, 1 H), 0.98 (d, *J* = 6.6 Hz, 3 H), 0.94 (d, *J* = 6.6 Hz, 3 H), 0.83 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 135.7, 130.9, 129.7, 127.5, 86.7, 81.9, 66.5, 61.2, 38.3, 36.5, 35.8, 25.7, 17.9, 17.6, 16.8, 12.2, 10.4.

LRMS (EI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{32}NaO_3$: 307.2; found: 307.2.

(*E*)-(2*S*,3*S*,4*R*,7*S*,8*S*)-3-Methoxy-2,4,6,8,10-pentamethylundeca-5,9-diene-1,7-diol (69)

Clear, colorless oil; $[\alpha]_{589}^{20}$ –2.4 (*c* 0.5, $CHCl_3$).

IR (thin film, NaCl): 3386, 2966, 2927, 2872, 1457, 1419, 1375, 1091, 1027 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.15 (dd, *J* = 9.7, 0.9 Hz, 1 H), 4.93 (dt, *J* = 9.8, 1.6 Hz, 1 H), 3.59–3.50 (m, 3 H), 3.45 (s, 3 H), 3.08 (dd, *J* = 8.8, 2.5 Hz, 1 H), 2.65–2.60 (m, 1 H), 2.55–2.50 (m, 1 H), 1.79–1.74 (m, 1 H), 1.72 (d, *J* = 1.3 Hz, 3 H), 1.66 (d, *J* = 1.3 Hz, 3 H), 1.63 (d, *J* = 1.3 Hz, 3 H), 1.05 (d, *J* = 6.6 Hz, 3 H), 0.81 (d, *J* = 6.9 Hz, 3 H), 0.74 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 135.1, 134.4, 132.1, 127.2, 86.6, 82.7, 66.4, 61.2, 38.4, 36.9, 36.0, 26.0, 18.3, 17.6, 17.3, 10.9, 10.3.

LRMS (EI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{32}NaO_3$: 307.2; found: 307.2.

(*E*)-(2*S*,3*R*,4*S*,7*S*,8*S*,9*R*)-3-Methoxy-2,4,6,8,10-pentamethylundec-5-ene-1,7,9,10-tetraol (70)

To a soln of diene **62** (406 mg, 1.43 mmol) in *t*-BuOH (7.1 mL) the following were added sequentially: $(DHQD)_2PHAL$ (55.7 mg, 0.072 mmol), methanesulfonamide (136.0 mg, 1.43 mmol), K_2CO_3 (593.0 mg, 4.29 mmol), and $K_3Fe(CN)_6$ (1.41 g, 4.29 mmol). To the resulting suspension H_2O (7.1 mL) was added followed by OsO_4 (205 μL, 2% soln in H_2O, 0.014 mmol). The resulting biphasic mixture was stirred for 24 h at r.t. and quenched with solid Na_2SO_3 and stirred at r.t. for 1 h. The mixture was diluted with EtOAc (200 mL), washed with 1 M $KHSO_4$ (20 mL), sat. $NaHCO_3$ (20 mL), and brine (20 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was passed through a plug of silica gel (30 mL) eluting with EtOAc (40 mL) and 10% MeOH–EtOAc (60 mL) to yield tetraol **70** (314 mg, 69%); 2:1 mixture of diastereomers. The mixture was used in subsequent reactions without further purification.

^{13}C NMR (126 MHz, $CDCl_3$): δ = 134.6, 127.9, 91.9, 81.2, 80.9, 72.9, 65.5, 61.8, 37.3, 36.0, 35.6, 30.8, 25.2, 16.5, 15.2, 14.1, 5.9.

(3*E*,7*E*)-(5*R*,6*S*,9*S*,10*R*,11*S*)-6,12-Dihydroxy-10-methoxy-5,7,9,11-tetramethyldodeca-3,7-dien-2-one (72)

To a soln of tetraol **70** (42.7 mg, 0.134 mmol) in EtOAc (540 μL) at 0 °C was added $Pb(OAc)_4$ (62.4 mg, 0.141 mmol) in one portion. The resulting mixture was allowed to stir for 5 min and was filtered through a plug of silica gel (7 mL) eluting with EtOAc (3 × 10 mL). The eluent was concentrated in vacuo to yield a clear colorless oil (35 mg, 99%) and was used without purification in the subsequent step. LiCl (6.8 mg, 0.161 mmol) was flame-dried in a 10-mL flask equipped with a magnetic stir bar and was suspended in MeCN (140 μL) upon cooling. Dimethyl 2-oxopropylphosphonate (22 μL, 0.161 mmol) was added to the resulting suspension followed by DIPEA (23 μL, 0.134 mmol) and the mixture was allowed to stir at r.t. for 30 min before cooling to –10 °C. The previously generated crude aldehyde in MeCN (1.3 mL) was added to the cooled reaction via syringe and the mixture was stirred at –10 °C for 16 h. The reaction was quenched with 0.1 M HCl (1 mL), was extracted with Et_2O (3 × 15 mL); the combined organic extracts were washed with sat. $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by chromatography [silica gel, 30 mL, EtOAc (120 mL)] to give **72** (20.1 mg, 50%) as a clear, colorless oil; $[\alpha]_{589}^{20}$ –7.5 (*c* 0.2, $CHCl_3$).

IR (thin film, NaCl): 3405, 2964, 2929, 2874, 2361, 2340, 1671, 1623, 1457, 1363, 1258, 1092, 1025, 982 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.67 (dd, *J* = 16.1, 7.9 Hz, 1 H), 6.05 (dd, *J* = 16.1, 0.9 Hz, 1 H), 5.28 (d, *J* = 9.8 Hz, 1 H), 3.89 (dd, *J* = 6.9, 3.5 Hz, 1 H), 3.72 (ddd, *J* = 8.8, 5.0, 3.8 Hz, 1 H), 3.57–3.51 (m, 1 H), 3.49 (s, 3 H), 2.95 (dd, *J* = 6.6, 4.7 Hz, 1 H), 2.75 (t, *J* = 5.0 Hz, 1 H), 2.72–2.65 (m, 1 H), 2.58–2.52 (m, 1 H), 2.22 (s, 3 H), 1.81–1.76 (m, 1 H), 1.61 (d, *J* = 1.3 Hz, 3 H), 1.56 (s, 1 H), 1.10 (d, *J* = 6.9 Hz, 3 H), 1.05 (d, *J* = 6.9 Hz, 3 H), 0.97 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 198.5, 149.8, 135.1, 130.8, 130.5, 91.4, 80.1, 65.5, 61.8, 40.5, 37.3, 35.8, 26.8, 16.4, 15.6, 14.9, 12.2.

LRMS (EI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{30}NaO_4$: 321.2; found: 321.3.

Methyl (2*E*,6*E*)-(4*R*,5*S*,8*S*,9*R*,10*S*)-5,11-Dihydroxy-9-methoxy-4,6,8,10-tetramethylundeca-2,6-dienoate (74)

To a soln of tetraol **70** (33.4 mg, 0.105 mmol) in EtOAc (420 μL) at 0 °C was added $Pb(OAc)_4$ (48.8 mg, 0.110 mmol) in one portion. The resulting mixture was allowed to stir for 5 min and was filtered through a plug of silica gel (7 mL) eluting with EtOAc (3 × 10 mL). The eluent was concentrated in vacuo to yield a clear colorless oil (26 mg, 98%) and was used without purification in the subsequent step. LiCl (5.3 mg, 0.126 mmol) was flame dried in a 10-mL flask equipped with a magnetic stir bar and was suspended in MeCN (105 μL) upon cooling. Trimethyl phosphonoacetate (17 μL, 0.126 mmol) was added to the resulting suspension followed by DIPEA (18 μL, 0.105 mmol) and the mixture was allowed to stir at r.t. for 30 min before cooling to 0 °C. The previously generated crude aldehyde in MeCN (1.1 mL) was added to the cooled reaction via syringe and the mixture was stirred at 0 °C for 20 h. The reaction was quenched with 0.1 M HCl (1 mL), was extracted with Et_2O (3 × 15 mL); the combined organic extracts were washed with sat. $NaHCO_3$ (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by chromatography [silica gel, 20 mL, 50% EtOAc–hexanes (50 mL), 80% EtOAc–hexanes (50 mL), and EtOAc (50 mL)] to give **74** (19.1 mg, 58%) as a clear, colorless oil; $[\alpha]_{589}^{20}$ –31.9 (*c* 0.2, $CHCl_3$).

IR (thin film, NaCl): 3426, 2968, 2935, 2879, 1720, 1453, 1385, 1275, 1113, 1027, 714 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.85 (dd, *J* = 15.9, 8.1 Hz, 1 H), 5.80 (dd, *J* = 15.9, 1.3 Hz, 1 H), 5.27 (d, *J* = 10.4 Hz, 1 H), 3.88 (dd, *J* = 7.1, 3.5 Hz, 1 H), 3.76–3.71 (m, 1 H), 3.71 (s, 3 H), 3.57–3.50 (m, 1 H), 3.48 (s, 3 H), 2.95 (dd, *J* = 7.1, 4.8 Hz, 1 H), 2.80 (t, *J* = 5.6 Hz, 1 H), 2.72–2.64 (m, 1 H), 2.57–2.50 (m, 1 H), 1.82–1.74 (m, 1 H), 1.60 (d, *J* = 1.3 Hz, 3 H), 1.58 (s, 1 H), 1.09 (d, *J* = 6.8 Hz, 3 H), 1.05 (d, *J* = 7.1 Hz, 3 H), 0.97 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 166.9, 151.1, 135.0, 130.7, 120.5, 91.6, 80.3, 65.6, 61.8, 51.5, 40.4, 37.3, 35.9, 16.3, 15.7, 14.8, 12.4.

LRMS (EI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{30}NaO_5$: 337.2; found: 337.3.

(5*R*,6*S*)-6-[(*E*)-(3*S*,4*R*,5*S*)-6-Hydroxy-4-methoxy-1,3,5-trimethylhex-1-enyl)-5-methyl-tetrahydro-2*H*-pyran-2-one (75)

To a soln of **74** (167.1 mg, 0.531 mmol) in MeOH (4.4 mL) at r.t. was added Mg turnings (129 mg, 5.3 mmol) and the mixture was stirred vigorously for 1.5 h at which time it had become white and cloudy with little remaining Mg solids. The mixture was diluted with EtOAc (50 mL) and passed through a plug of silica gel (40 mL) eluting with EtOAc (50 mL) and the eluent was concentrated in vacuo. The residue was resuspended in CH_2Cl_2 (5.3 mL) at r.t. and CSA (6.2 mg, 0.026 mmol) was added. The mixture was stirred at r.t. for 39 h and was loaded directly onto a chromatography column [silica gel, 70 mL, 50% EtOAc–hexanes (70 mL), 80% EtOAc–hexanes (70 mL), and EtOAc (100 mL)] to give **75** (86.1 mg, 57%) as a clear, colorless oil; $[\alpha]_{589}^{20}$ –10.0 (*c* 0.5, $CHCl_3$).

IR (thin film, NaCl): 3421, 2966, 2933, 2875, 2831, 1692, 1461, 1242, 1093, 1017 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.47 (d, *J* = 10.1 Hz, 1 H), 4.66 (app s, 1 H), 3.76 (ddd, *J* = 11.0, 4.4, 4.4 Hz, 1 H), 3.54–3.49 (m, 1 H), 3.50 (s, 3 H), 2.98 (dd, *J* = 7.3, 4.4 Hz, 1 H), 2.79 (dd, *J* = 6.9, 4.4 Hz, 1 H), 2.78–2.70 (m, 1 H), 2.57 (dd, *J* = 8.2, 6.6 Hz, 1 H), 2.28–2.20 (m, 1 H), 2.14–2.05 (m, 1 H), 1.80–1.67 (m, 2 H), 1.62 (s, 3 H), 1.08 (d, *J* = 7.3 Hz, 3 H), 1.05 (d, *J* = 6.6 Hz, 3 H), 0.81 (d, *J* = 7.3 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.5, 129.5, 128.9, 91.9, 84.3, 65.4, 62.1, 37.2, 36.4, 28.4, 26.7, 26.1, 16.7, 15.8, 13.9, 12.4.

LRMS (EI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{28}NaO_4$: 307.2; found: 307.2.

(*E*)-(2*S*,3*R*,4*S*)-3-Methoxy-6-[(2*S*,3*R*,6*S*)-6-methoxy-3,6-dimethyl-tetrahydro-2*H*-pyran-2-yl)-2,4-dimethylhept-5-en-1-ol (76)

In a glove box, $[CuH(PPh_3)]_6$ (64.9 mg, 0.033 mmol) was added to **72** (26.7 mg, 0.090 mmol) in a 10-mL flask equipped with a magnetic stir bar. The resulting solids were dissolved in benzene (2.2 mL, containing 0.02% H_2O by volume, degassed using three iterations of the freeze–pump–thaw method) and the rust colored soln was stirred at r.t. for 16 h. The reaction vessel was opened to air to quench and was allowed to stir exposed to the ambient atmosphere for 2 h. The resulting brown turbid mixture was passed through a short plug of silica gel (5 mL) eluting with EtOAc (20 mL) and the eluent was concentrated in vacuo. The crude residue was resuspended in MeOH (900 μL) and was treated with 0.25 M PPTS in CH_2Cl_2 (36 μL, 0.009 mmol). The resulting mixture was stirred at r.t. for 24 h and was quenched with sat. $NaHCO_3$ (1 mL). The mixture was extracted with EtOAc (2 × 30 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue using chromatography (silica gel, 20 mL, 50% EtOAc–hexanes) gave **76** [10.4 mg, 37% (2 steps)] as a clear, colorless oil; $[\alpha]_{589}^{20}$ –3.8 (*c* 1.0, $CHCl_3$).

IR (thin film, NaCl): 3420, 2963, 2933, 2875, 1717, 1457, 1378, 1226, 1118, 1088, 1054, 864 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.34 (dt, *J* = 9.8, 1.3 Hz, 1 H), 3.96 (app s, 1 H), 3.76 (ddd, *J* = 7.9, 4.4, 3.5 Hz, 1 H), 3.54–3.49 (m, 1 H), 3.50 (s, 3 H), 3.14 (s, 3 H), 2.96 (dd, *J* = 7.3, 4.7 Hz, 1 H), 2.92 (dd, *J* = 6.3, 4.7 Hz, 1 H), 2.72–2.66 (m, 1 H), 2.09–2.01 (m, 1 H), 1.89–1.78 (m, 2 H), 1.67–1.59 (m, 1 H), 1.54 (s, 3 H), 1.54–1.50 (m, 1 H), 1.44–1.39 (m, 1 H), 1.30 (s, 3 H), 1.07 (d, *J* = 6.9 Hz, 3 H), 1.03 (d, *J* = 6.9 Hz, 3 H), 0.70 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 132.8, 126.1, 98.2, 92.4, 73.8, 65.7, 61.8, 47.8, 37.2, 35.9, 29.9, 28.4, 26.3, 23.9, 16.6, 15.6, 14.0, 11.2.

LRMS (EI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{34}NaO_4$: 337.2; found: 338.2.

(5*R*,6*S*)-6-[(*E*)-(3*S*,4*R*,5*S*)-6-Hydroxy-4-methoxy-1,3,5-trimethylhex-1-enyl)-5-methyl-5,6-dihydro-2*H*-pyran-2-one (77)

To a soln of **70** (19.6 mg, 0.062 mmol) in EtOAc (250 μL) at 0 °C was added $Pb(OAc)_4$ (28.6 mg, 0.065 mmol) in one portion. The mixture was stirred at 0 °C for 5 min and was filtered through a plug of silica gel (5 mL) eluting with EtOAc (30 mL). The eluent was concentrated in vacuo and was used in the subsequent reaction without purification. Bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl)phosphonate (52 μL, 0.246 mmol) was added to a soln of 18-crown-6 (316.9 mg, 0.984 mmol, freshly recrystallized from MeCN, 2:1 MeCN/18-crown-6 complex) in THF (1.2 mL) and the mixture was cooled to –78 °C and treated with 0.6 M $KN(TMS)_2$ in toluene (330 μL, 0.197 mmol). The mixture was stirred for 20 min at –78 °C before the addition of the freshly prepared aldehyde (620 μL, 0.1 M in THF). The reaction was stirred at –78 °C for 4 h and was quenched with sat. NH_4Cl (2 mL), extracted with Et_2O (3 × 15 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was passed through a plug of silica gel (10 mL) eluting with 80% EtOAc–hexanes to give the α,β-unsaturated ester as a mixture. The mixture of α,β-unsaturated esters (13.4 mg, 0.043 mmol) was dissolved in CH_2Cl_2 (420 μL), treated with CSA (0.5 mg, 0.002 mmol) and allowed to stir at r.t. for 19 h. The reaction was loaded directly onto a column (silica gel, 20 mL, 80% EtOAc–hexanes) to give **77** as a clear colorless oil [7.4

mg, 43% (3 steps)]. The isolated product was contaminated with a small amount of an inseparable impurity and was fully characterized following conversion into the corresponding TBDPS ether.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.00 (dd, *J* = 9.8, 6.3 Hz, 1 H), 6.00 (d, *J* = 9.5 Hz, 1 H), 5.61 (ddd, *J* = 10.1, 1.3, 1.3 Hz, 1 H), 4.78 (app s, 1 H), 3.76 (ddd, *J* = 10.7, 4.1, 4.1 Hz, 1 H), 3.54–3.45 (m, 1 H), 3.50 (s, 3 H), 2.99 (dd, *J* = 7.3, 4.4 Hz, 1 H), 2.82 (dd, *J* = 6.6, 4.1 Hz, 1 H), 2.80–2.72 (m, 1 H), 2.60–2.54 (m, 1 H), 1.80–1.74 (m, 1 H), 1.64 (s, 3 H), 1.08 (d, *J* = 6.9 Hz, 3 H), 1.06 (d, *J* = 6.9 Hz, 3 H), 0.87 (d, *J* = 7.3 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 164.3, 151.4, 129.7, 128.5, 119.9, 91.9, 81.8, 65.3, 61.9, 37.3, 36.3, 31.5, 16.6, 15.7, 13.6, 11.8.

(5*R*,6*S*)-6-[(*E*)-(3*S*,4*R*,5*S*)-6-(*tert*-Butyldiphenylsiloxy)-4-methoxy-1,3,5-trimethylhex-1-enyl]-5-methyl-5,6-dihydro-2*H*-pyran-2-one

To a soln of **77** (4.4 mg, 0.016 mmol) in CH_2Cl_2 (150 μL) the following were added sequentially: 0.5 M Et_3N in CH_2Cl_2 (40 μL, 0.019 mmol), 0.5 M TBDPSCl in CH_2Cl_2 (34 μL, 0.017 mmol), and 0.002 M DMAP in CH_2Cl_2 (60 μL, 0.002 mmol). The reaction vessel was sealed under argon and was stirred at r.t. for 36 h. The crude residue was loaded onto a plug of silica gel (10 mL) and eluted with 20% EtOAc–hexanes (20 mL) and 30% EtOAc–hexanes (20 mL) to give the TBDPS ether of **77** (8.0 mg, 99%) as a clear, colorless oil. Further purification by HPLC (UV detection (254 nm), 15% to 30% EtOAc–hexanes over 25 min) provided an analytical sample.

$[\alpha]_{589}^{20}$ –31.5 (*c* 0.4, $CHCl_3$).

IR (thin film, NaCl): 2962, 2930, 2857, 2361, 2337, 1733, 1489, 1387, 1247, 1106, 823, 702 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.66–7.64 (m, 4 H), 7.42–7.33 (m, 6 H), 6.98 (dd, *J* = 9.4, 6.3 Hz, 1 H), 5.99 (d, *J* = 9.4 Hz, 1 H), 5.64 (d, *J* = 9.4 Hz, 1 H), 4.73 (app s, 1 H), 3.68–3.62 (m, 2 H), 3.36 (s, 3 H), 3.00 (dd, *J* = 6.0, 6.0 Hz, 1 H), 2.63–2.58 (m, 1 H), 2.53–2.47 (m, 1 H), 1.88–1.82 (m, 1 H), 1.52 (s, 3 H), 1.05 (m, 12 H), 0.96 (d, *J* = 6.9 Hz, 3 H), 0.87 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 164.4, 151.5, 135.7, 133.9, 133.9, 130.7, 129.5, 127.9, 127.5, 119.9, 87.4, 82.0, 65.1, 61.2, 39.0, 34.9, 31.8, 26.9, 19.3, 15.6, 15.1, 13.4, 11.9.

LRMS (EI): *m*/*z* [M + Na]$^+$ calcd for $C_{32}H_{44}NaO_4Si$: 543.3; found: 543.5.

(5*R*,6*S*)-6-[(1*S*,3*S*,4*R*,5*S*)-6-Hydroxy-4-methoxy-1,3,5-trimethylhexyl]-5-methyl-tetrahydro-2*H*-pyran-2-one (78)

The α,β-unsaturated ester **74** (24.2 mg, 0.077 mmol) was dissolved in degassed CH_2Cl_2 (3.8 mL, degassed by bubbling through with dry argon gas for 10 min), and was transferred to a glass sleeve for the Parr hydrogenation apparatus containing Rh[(nbd)(dppb)]BF_4 (16.3 mg, 0.023 mmol). The mixture was placed under an atmosphere of H_2 (52 bar) and was allowed to react at r.t. for 6 h. The crude mixture was filtered through a plug of silica gel eluting with EtOAc and was concentrated to provide **78** (13.4 mg, 62%) as a clear colorless oil; 19:1 mixture of isomers. An analytical sample (dr >20:1) was obtained by HPLC purification (RI detector, 80% EtOAc–hexanes, 8 mL/min).

$[\alpha]_{589}^{20}$ +7.0 (*c* 0.7, $CHCl_3$).

IR (thin film, NaCl): 3447, 2965, 2932, 2878, 1734, 1457, 1381, 1248, 1098, 983 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.88 (dd, *J* = 10.1, 2.5 Hz, 1 H), 3.68 (ddd, *J* = 11.0, 6.9, 3.5 Hz, 1 H), 3.58 (ddd, *J* = 11.0, 8.2, 4.1 Hz, 1 H), 3.54 (s, 3 H), 3.01 (dd, *J* = 8.5, 2.8 Hz, 1 H), 2.91 (dd, *J* = 7.9, 3.2 Hz, 1 H), 2.52 (dd, *J* = 8.5, 6.6 Hz, 1 H), 2.22–2.15 (m, 1 H), 2.11–2.01 (m, 2 H), 1.91–1.76 (m, 3 H), 1.71–1.59 (m, 2 H), 0.96 (d, *J* = 6.9 Hz, 3 H), 0.93 (d, *J* = 6.6 Hz, 3 H), 0.89 (d, *J* = 6.9 Hz, 3 H), 0.89 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.8, 88.6, 87.5, 67.0, 61.4, 38.5, 38.1, 33.4, 32.8, 26.9, 26.7, 26.2, 15.7, 15.2, 15.1, 11.5.

LRMS (EI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{30}NaO_4$: 309.2; found: 309.2.

(*E*,*E*)-(8*R*,9*S*,12*S*,13*R*,14*S*)-9,15-Dihydroxy-13-methoxy-8,10,12,14-tetramethyl-1-(triethylsiloxy)pentadeca-6,10-diene-5-one and (*E*)-(2*S*,3*R*,4*S*)-3-Methoxy-6-[(2*S*,3*R*)-3-methyl-1,7-dioxaspiro[5.5]undec-2-yl]-2,4,6-trimethylhex-5-en-1-ol (79)

To a soln of **70** (25.5 mg, 0.08 mmol) in EtOAc (320 μL) at 0 °C was added $Pb(OAc)_4$ (37.3 mg, 0.084 mmol) in one portion. The mixture was stirred at 0 °C for 5 min and was filtered through a plug of silica gel (5 mL) eluting with EtOAc (30 mL). The eluent was concentrated in vacuo and was used in the subsequent reaction without purification. LiCl (4.1 mg, 0.096 mmol) was flame dried in a 10-mL flask equipped with a magnetic stir bar and was suspended in MeCN (100 μL) upon cooling. Dimethyl 6-(triethylsiloxy)-2-oxohexylphosphonate (32.5 mg, 0.096 mmol) was added to the resulting suspension followed by DIPEA (14 μL, 0.08 mmol) and the mixture was allowed to stir at r.t. for 30 min and then cooled to –20 °C. The previously generated crude aldehyde in MeCN (800 μL) was added to the cooled reaction via syringe and the mixture was stirred at –20 °C for 15.5 h. The reaction was quenched with sat. $NaHCO_3$ (1 mL) and extracted with EtOAc (4 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by chromatography [silica gel, 30 mL, 80% EtOAc–hexanes (120 μL)] to give the α,β-unsaturated ketone (19.4 mg, 51%) as a clear, colorless oil.

$[\alpha]_{589}^{20}$ +8.0 (*c* 1.9, $CHCl_3$).

IR (thin film, NaCl): 3421, 2958, 2876, 2361, 2340, 1684, 1457, 1096, 1017, 744 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.68 (dd, *J* = 16.1, 8.2 Hz, 1 H), 6.06 (d, *J* = 16.1 Hz, 1 H), 5.26 (d, *J* = 9.8 Hz, 1 H), 3.87 (dd, *J* = 6.9, 2.8 Hz, 1 H), 3.71 (ddd, *J* = 10.7, 4.1, 4.1 Hz, 1 H), 3.60 (dd, *J* = 6.3, 6.3 Hz, 2 H), 3.56–3.50 (m, 1 H), 3.48 (s, 3 H), 2.94 (dd, *J* = 6.9, 5.0 Hz, 1 H), 2.80 (t, *J* = 5.4 Hz, 1 H), 2.69–2.64 (m, 1 H), 2.56–2.50 (m, 3 H), 1.82–1.74 (m, 2 H), 1.68–1.60 (m, 2 H), 1.60 (s, 3 H), 1.59–1.50 (m, 2 H), 1.08 (d, *J* = 6.6 Hz, 3 H), 1.05 (d, *J* = 6.9 Hz, 3 H), 0.94 (app t, *J* = 7.9 Hz, 12 H), 0.58 (q, *J* = 7.9 Hz, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 200.4, 148.6, 135.1, 130.7, 129.5, 91.4, 80.4, 65.4, 62.5, 61.7, 40.5, 39.8, 37.3, 35.8, 32.3, 20.6, 16.4, 15.6, 14.9, 12.2, 6.8, 4.4.

LRMS (EI): *m*/*z* [M + Na]$^+$ calcd for $C_{26}H_{50}NaO_5Si$: 493.3; found: 493.3.

$[CuH(PPh_3)]_6$ (17.3 mg, 0.009 mmol) was added to the α,β-unsaturated ketone (11.2 mg, 0.024 mmol) in a glove box. The resulting solids were dissolved in benzene (600 μL, containing 0.02% H_2O by volume, degassed using 3 iterations of the freeze–pump–thaw method) and the rust colored soln was stirred at r.t. for 11.5 h. The reaction vessel was opened to air to quench and was allowed to stir exposed to the ambient atmosphere for 1 h. The resulting brown turbid mixture was passed through a short plug of silica gel (1 mL) eluting with 10% EtOAc–hexanes (2 mL), 50% EtOAc–hexanes (2 mL), EtOAc (2 mL), and 10% MeOH–EtOAc (2 mL). The 50% EtOAc–hexanes and EtOAc fractions were concentrated in vacuo. The residue was dissolved in MeOH–CH_2Cl_2 (1:1, 240 μL) at r.t. and 0.25 M CSA in CH_2Cl_2 (19 μL, 0.005 mmol) was added. The mixture was stirred at r.t. for 1 h, was diluted with CH_2Cl_2 (480 μL), and allowed to stir for 20 h. The mixture was diluted with CH_2Cl_2 (10 mL), was quenched with sat. $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were

dried (Na_2SO_4) and concentrated in vacuo. Purification was achieved by chromatography [silica gel, 10 mL, 10% EtOAc–hexanes (15 mL), 30% EtOAc–hexanes (30 mL), and 50% EtOAc–hexanes (30 mL)] to give **79** (4.5 mg, 56%) as a clear, colorless oil.

$[\alpha]_{589}^{20}$ –10.9 (*c* 0.4, $CHCl_3$).

IR (thin film, NaCl): 3447, 2935, 2870, 1473, 1086, 1004, 877 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.39 (dd, *J* = 10.1, 1.3 Hz, 1 H), 4.05 (app s, 1 H), 3.77 (dd, *J* = 11.0, 3.5 Hz, 1 H), 3.56–3.50 (m, 3 H), 3.50 (s, 3 H), 2.97 (dd, *J* = 6.9, 5.0 Hz, 1 H), 2.74–2.68 (m, 1 H), 2.12–2.04 (m, 1 H), 1.94–1.85 (m, 2 H), 1.85–1.78 (m, 1 H), 1.69–1.64 (m, 1 H), 1.60–1.38 (m, 7 H), 1.55 (d, *J* = 1.0 Hz, 3 H), 1.07 (d, *J* = 6.9 Hz, 3 H), 1.03 (d, *J* = 6.6 Hz, 3 H), 0.70 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 133.0, 126.1, 95.8, 92.5, 72.7, 65.8, 61.8, 60.6, 37.2, 35.9, 35.8, 29.9, 28.8, 26.1, 25.4, 18.8, 16.6, 15.6, 13.9, 11.2.

LRMS (EI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{36}NaO_4$: 363.3; found: 360.3.

Methyl (2*E*,7*E*)-(4*S*,5*S*,6*S*)-5-Methoxy-4,6-dimethyl-8-[(2*S*,3*R*)-3-methyl-6-oxo-tetrahydro-2*H*-pyran-2-yl]nona-2,7-dienoate (81)

To a soln of **75** (20.2 mg, 0.071 mmol) in CH_2Cl_2 (470 μL) at 0 °C was added Dess–Martin periodinane (60.2 mg, 0.142 mmol). To the resulting vigorously stirred mixture was added CH_2Cl_2 (890 μL, saturated with H_2O) via syringe pump over 1 h. At this time the reaction was complete by TLC and the mixture was concentrated in vacuo to yield a thick white slurry (ca. 100 μL). This slurry was diluted with Et_2O (30 mL), quenched with sat. $NaHCO_3$–10% $Na_2S_2O_3$ (1:1, 20 mL), and extracted with Et_2O (20 mL). The Et_2O was washed with brine (10 mL), and dried (Na_2SO_4). The crude aldehyde (20.0 mg, quant.) was used without purification in the subsequent reaction after azeotropic removal of H_2O by concentration from benzene. The crude residue was resuspended in CH_2Cl_2 (180 μL) and was treated with methyl (triphenylphosphoranylidene)acetate (30.8 mg, 0.092 mmol). The resulting mixture was sealed under N_2 and allowed to stir at r.t. for 24 h. The resulting mixture was diluted with 10% EtOAc–hexanes and loaded directly onto a column and chromatographed [silica gel, 25 mL, 30% EtOAc–hexanes (70 mL) and 50% EtOAc–hexanes (70 mL)] to give **81** (14.9 mg, 62%) as a clear, colorless oil.

$[\alpha]_{589}^{20}$ –36.9 (*c* 0.6, $CHCl_3$).

IR (thin film, NaCl): 2966, 2933, 2875, 2831, 1725, 1738, 1461, 1241, 1093, 1074, 933.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.00 (dd, *J* = 15.8, 8.5 Hz, 1 H), 5.73 (d, *J* = 16.1 Hz, 1 H), 5.42 (d, *J* = 10.1 Hz, 1 H), 4.66 (app s, 1 H), 3.71 (s, 3 H), 3.48 (s, 3 H), 2.89 (dd, *J* = 8.8, 3.2 Hz, 1 H), 2.58 (dd, *J* = 8.2, 6.3 Hz, 2 H), 2.57–2.45 (m, 2 H), 2.31–2.24 (m, 1 H), 2.14–2.06 (m, 1 H), 1.76–1.69 (m, 1 H), 1.58 (s, 3 H), 1.13 (d, *J* = 6.9 Hz, 3 H), 1.01 (d, *J* = 6.6 Hz, 3 H), 0.85 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.5, 166.9, 150.8, 129.8, 128.5, 121.2, 89.9, 84.3, 61.9, 51.4, 40.1, 36.9, 28.3, 26.6, 26.1, 17.6, 17.1, 13.9, 12.4.

LRMS (EI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{30}NaO_5$: 361.2; found: 361.3.

Ethyl (2*E*,7*E*)-(4*S*,5*R*,6*S*)-5-Methoxy-2,4,6-trimethyl-8-[(2*S*,3*R*)-3-methyl-6-oxo-tetrahydro-2*H*-pyran-2-yl)nona-2,7-dienoate (82)

To a soln of **75** (14 mg, 0.049 mmol) in CH_2Cl_2 (330 μL) at 0 °C was added Dess–Martin periodinane (41.6 mg, 0.098 mmol). To the resulting vigorously stirring mixture was added CH_2Cl_2 (610 μL, saturated with H_2O) via syringe pump over 1 h. At this time the reaction was complete by TLC and the mixture was concentrated in vacuo to yield a thick white slurry (ca. 100 μL). This slurry was diluted with Et_2O (30 mL), quenched with sat. $NaHCO_3$–10% $Na_2S_2O_3$ (1:1, 20 mL), and extracted with Et_2O (20 mL). The Et_2O extract was washed with brine (10 mL) and dried (Na_2SO_4). The crude aldehyde (13.6 mg, quant.) was used without purification in the subsequent reaction after azeotropic removal of H_2O by concentration from benzene. The crude residue was resuspended in CH_2Cl_2 (250 μL) and was treated with [1-(ethoxycarbonyl)ethylidene]triphenylphosphorane (21.4 mg, 0.064 mmol). The resulting mixture was sealed under N_2 and allowed to stir at r.t. for 24 h. The resulting mixture was diluted with 10% EtOAc–hexanes and loaded directly onto a column and chromatographed [silica gel, 25 mL, 30% EtOAc–hexanes (70 mL) and 50% EtOAc–hexanes (70 mL)] to give 82 (12.1 mg, 68%) as a clear, colorless oil.

$[\alpha]_{589}^{20}$ –13.6 (*c* 0.1, $CHCl_3$).

IR (thin film, NaCl): 2966, 2932, 2834, 1734, 1707, 1457, 1367, 1301, 1237, 1094, 1074 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 6.82 (dd, *J* = 9.8, 1.6 Hz, 1 H), 5.40 (dt, *J* = 10.1, 1.6 Hz, 1 H), 4.65 (app s, 1 H), 4.18 (dddd, *J* = 9.8, 4.4, 2.8, 2.5 Hz, 2 H), 3.47 (s, 3 H), 2.88 (dd, *J* = 7.9, 3.5 Hz, 1 H), 2.69–2.64 (m, 1 H), 2.60–2.49 (m, 3 H), 2.25–2.19 (m, 1 H), 2.12–2.04 (m, 1 H), 1.78 (d, *J* = 1.6 Hz, 3 H), 1.76–1.70 (m, 1 H), 1.54 (d, *J* = 1.3 Hz, 3 H), 1.29 (t, *J* = 7.3 Hz, 3 H), 1.06 (d, *J* = 6.9 Hz, 3 H), 1.01 (d, *J* = 6.6 Hz, 3 H), 0.87 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.5, 168.3, 143.5, 129.9, 129.5, 127.6, 89.6, 84.7, 61.6, 60.4, 36.8, 36.7, 28.7, 26.7, 26.1, 17.4, 16.8, 14.3, 13.8, 12.7, 12.6.

LRMS (EI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{34}NaO_5$: 389.2; found: 389.3.

(5*R*,6*S*)-6-[(1*E*,8*Z*)-(3*S*,4*S*,5*S*)-4-Methoxy-1,3,5-trimethylnona-1,6,8-trienyl]-5-methyl-tetrahydro-2*H*-pyran-2-one (83)

To a soln of **75** (20.3 mg, 0.071 mmol) in CH_2Cl_2 (475 μL) at 0 °C was added Dess–Martin periodinane (60.6 mg, 0.143 mmol). To the resulting vigorously stirring mixture was added CH_2Cl_2 (890 μL, saturated with H_2O) via syringe pump over 1 h. At this time the reaction was complete by TLC and the mixture was concentrated in vacuo to yield a thick white slurry (ca. 100 μL). This slurry was diluted with Et_2O (30 mL), quenched with sat $NaHCO_3$–10% $Na_2S_2O_3$ (1:1, 20 mL) and extracted with Et_2O (20 mL). The Et_2O extract was washed with brine (10 mL) and dried (Na_2SO_4). The crude aldehyde (20.2 mg, quant.) was used without purification in the subsequent reaction after azeotropic removal of H_2O by concentration from benzene. Molecular sieves (4 Å powdered, 8.6 mg) were flame dried in a 10-mL flask equipped with a stir bar and upon cooling 0.6 M 4,4,5,5-tetramethyl-2-[(*E*)-3-(trimethylsilyl)allyl]-1,3,2-dioxaborolane in toluene (140 μL) was added. The freshly prepared aldehyde was added as a soln in toluene (720 μL, with a 300 μL wash) and the reaction was heated to 60 °C for 21 h, was quenched with 1.5 M NaOH (2 mL), stirred vigorously for 20 min, and extracted with Et_2O (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification was achieved by chromatography [silica gel, 20 mL, 30% EtOAc–hexanes (40 mL), 50% EtOAc–hexanes (40 mL), and 80% EtOAc–hexanes (40 mL)] to give the TMS allylated product as a mixture of diastereomers (16.7 mg, 59%). To a soln of KH (1.6 mg, 0.040 mmol, weighed out neat in a glove box) in THF (400 μL) at –78 °C was added the freshly prepared TMS allylated product prepared above (16 mg, 0.040 mmol) as a soln in THF (400 μL, with a 400 μL wash). The mixture was stirred with warming to 0 °C over 2 h, was stirred at 0 °C for 30 min and was quenched with anhyd MeOH (1 mL) and diluted with H_2O (2 mL) and Et_2O (10 mL). The Et_2O layer was separated and discarded and the aqueous layer was acidified with 1 M HCl (10 mL) and extracted with Et_2O (2 × 20 mL). The combined organic

extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The resulting residue was resuspended in CH_2Cl_2 (2.0 mL), treated with 0.1 M CSA in CH_2Cl_2 (80 μL, 0.008 mmol), sealed under N_2 and stirred for 18 h at r.t.. The mixture was loaded directly onto column and chromatographed (silica gel, 30 mL, 50% EtOAc–hexanes) to give **83** (9.7 mg, 78%) as a clear, colorless oil; 19:1 mixture of isomers.

$[\alpha]_{589}^{20}$ +10.0 (*c* 0.4, $CHCl_3$).

IR (thin film, NaCl): 2962, 2928, 2871, 1734, 1472, 1237, 1092, 1001, 668 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 6.66 (ddd, *J* = 16.7, 11.0, 11.0 Hz, 1 H), 6.00 (t, *J* = 11.0 Hz, 1 H), 5.53 (t, *J* = 10.4 Hz, 1 H), 5.39 (dd, *J* = 9.8, 1.3 Hz, 1 H), 5.15 (d, *J* = 17.0 Hz, 1 H), 5.03 (d, *J* = 10.4 Hz, 1 H), 4.64 (app s, 1 H), 3.48 (s, 3 H), 2.84 (dd, *J* = 8.5, 2.5 Hz, 1 H), 2.81–2.74 (m, 1 H), 2.61–2.50 (m, 3 H), 2.26–2.20 (m, 1 H), 2.10–2.02 (m, 1 H), 1.75–1.67 (m, 1 H), 1.53 (s, 3 H), 1.06 (d, *J* = 7.3 Hz, 3 H), 1.01 (d, *J* = 6.6 Hz, 3 H), 0.88 (d, *J* = 7.3 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.6, 134.0, 132.6, 129.8, 129.7, 129.1, 116.9, 90.1, 84.7, 61.8, 36.9, 35.8, 28.7, 26.8, 26.1, 19.1, 17.0, 13.9, 12.7.

LRMS (EI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{30}NaO_3$: 329.2; found: 329.5.

(5*R*,6*S*)-6-[(*E*)-(3*S*,4*R*,5*S*,6*S*,7*S*)-6-Hydroxy-4-methoxy-1,3,5,7-tetramethylnona-1,8-dienyl]-5-methyl-tetrahydro-2*H*-pyran-2-one (84)

To a soln of **75** (22.8 mg, 0.08 mmol) in CH_2Cl_2 (530 μL) at 0 °C was added Dess–Martin periodinane (67.9 mg, 0.16 mmol). To the resulting vigorously stirring mixture was added CH_2Cl_2 (1.0 mL, saturated with H_2O) via syringe pump over 1 h. At this time the reaction was complete by TLC and the mixture was concentrated in vacuo to yield a thick white slurry (ca. 100 μL). This slurry was diluted with Et_2O (30 mL), quenched with sat. $NaHCO_3$–10% $Na_2S_2O_3$ (1:1, 20 mL), and extracted with Et_2O (20 mL). The Et_2O extract was washed with brine (10 mL) and dried (Na_2SO_4). The crude aldehyde (22.5 mg, quant.) was used without purification in the subsequent reaction after azeotropic removal of H_2O by concentration from benzene. Molecular sieves (4 Å powdered, 10 mg) were flame dried in a 10-mL flask equipped with a stir bar and upon cooling 0.4 M diisopropyl (4*R*,5*R*)-2-[(*E*)-but-2-enyl]-1,3,2-dioxaborolane-4,5-dicarboxylate in toluene (400 μL) was added. The mixture was cooled to –78 °C and the freshly prepared aldehyde was added as a soln in toluene (800 μL, with a 400 μL wash). The reaction was allowed to warm to r.t. while stirring for 15.5 h, was quenched with 1.5 M NaOH, stirred vigorously for 20 min, and extracted with Et_2O (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification was achieved by chromatography [silica gel, 20 mL, 30% EtOAc–hexanes (40 mL), 50% EtOAc–hexanes (40 mL), and 80% EtOAc–hexanes (40 mL)] to give **84** (24.1 mg, 89%) as a clear, colorless oil; 4:1 mixture of diastereomers. An analytical sample was obtained by normal-phase HPLC (RI Detector, 38% EtOAc–hexenes, 8 mL/min).

$[\alpha]_{589}^{20}$ –6.8 (*c* 0.2, $CHCl_3$).

IR (thin film, NaCl): 3482, 2965, 2929, 2361, 2340, 1540, 1457, 1239, 1074, 1002, 668 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.86 (ddd, *J* = 17.3, 10.1, 7.9 Hz, 1 H), 5.45 (d, *J* = 9.8 Hz, 1 H), 5.10–5.03 (m, 2 H), 4.66 (app s, 1 H), 3.62 (d, *J* = 9.1 Hz, 1 H), 3.53 (s, 1 H), 3.50 (s, 3 H), 3.07 (dd, *J* = 8.2, 3.8 Hz, 1 H), 2.84–2.77 (m, 1 H), 2.58 (dd, *J* = 8.2, 6.3 Hz, 2 H), 2.28–2.20 (m, 2 H), 2.14–2.05 (m, 1 H), 1.78–1.68 (m, 2 H), 1.64 (s, 3 H), 1.04 (d, *J* = 6.6 Hz, 3 H), 1.03 (d, *J* = 7.3 Hz, 3 H), 0.84 (d, *J* = 6.6 Hz, 3 H), 0.84 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.5, 142.6, 129.7, 129.4, 114.4, 91.9, 84.4, 74.0, 62.4, 41.8, 36.1, 35.7, 28.4, 26.7, 26.0, 16.8, 16.5, 14.1, 12.5, 11.3.

LRMS (EI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{34}NaO_4$: 361.2; found: 361.3.

Acknowledgment

We gratefully acknowledge financial support of this work by the American Cancer Society (RSG-06-117-01), the American Chemical Society (PRF-45334-G1), the Arnold and Mabel Beckman Foundation, Boehringer Ingelheim, Eli Lilly & Co., and the National Institutes of Health – NIGMS (GM80266). The authors also wish to thank Raul Navarro for assistance in the synthesis of **28** and **53**. Finally, L.J.P. acknowledges support from Novartis in the form of a graduate student fellowship.

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