Pergamon

Tetrahedron 58 (2002) 1817–1834

TETRAHEDRON

Ring closing metathesis for the formation of medium ring ethers: the total synthesis of (−)-isolaurallene

Michael T. Crimmins,* Kyle A. Emmitte and Allison L. Choy

Venable and Kenan Laboratories of Chemistry, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-3290, USA

Received 25 September 2001; accepted 29 October 2001

Abstract—The total synthesis of the marine metabolite (−)-isolaurallene is described. Two approaches to the core nine-membered ether are presented both of which are based on a ring closing metathesis to close the cyclic ether. © 2002 Published by Elsevier Science Ltd.

Marine organisms are a rich source of structurally diverse and biologically significant metabolites. The *laurencia*, *gymnodinium*, and *ciguatera* red algae produce a range of topographically unique structures which are characterized by the presence of one or more medium-sized (seven, eight or nine-membered) ether rings.[1] The fascinating structures of naturally occurring medium ring ethers have stimulated the imagination of synthetic chemists and many unique and interesting approaches to their construction have been designed.[2] While eight-membered ring ethers (oxocenes) have received more attention than the homologous oxonenes, the nine-membered ethers are found in the polyether ladder toxins brevetoxin A,[3] ciguatoxin,[4] gambieric acid A,[5] the eunicellins[6] and in the simpler metabolites obtusenyne,[7] neolaurallene **2**[8] and isolaurallene **1** (Fig. 1).[9] Previous synthetic approaches to nine-membered ethers have been limited by their infrequent occurrence and because of the challenges associated with their stereoselective assembly.[10] Isolaurallene **1** was isolated from *laurencia nipponica* yamada collected in Izumihama near Hiroo on the Pacific Coast of Hokkaido by Kurata and

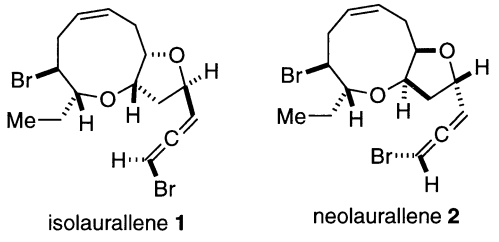
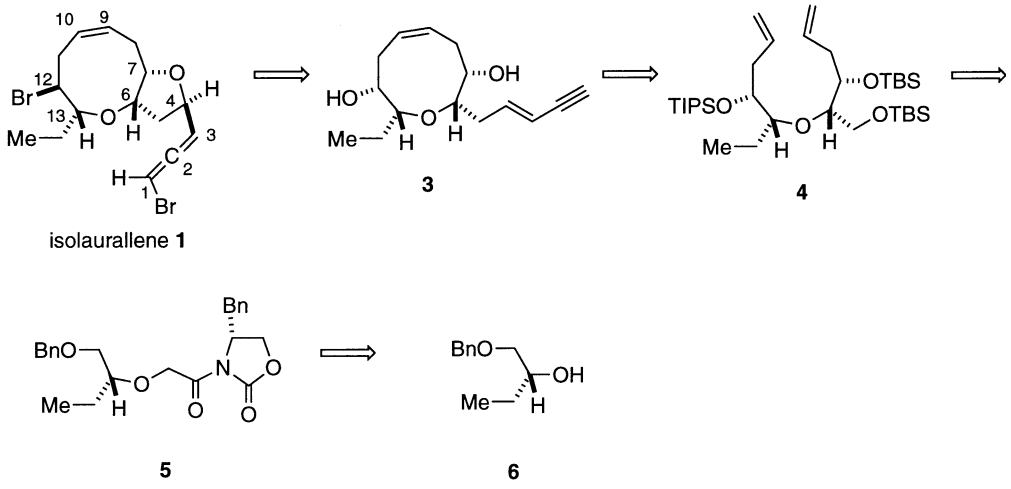


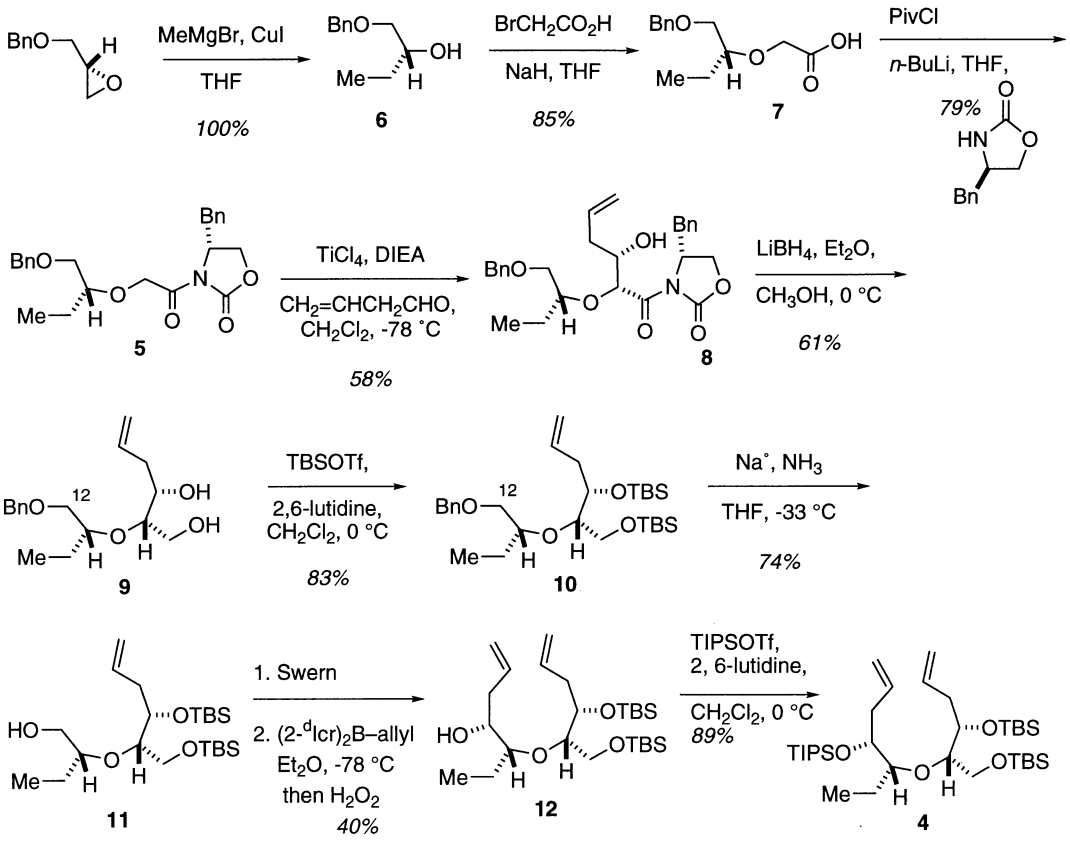
Figure 1.



Scheme 1.

Keywords: marine natural products; isolaurallene; metathesis; asymmetric aldol; asymmetric alkylation; oxonene.
* Corresponding author. Tel.: +919-966-5177; fax: +919-962-2388; e-mail: crimmins@email.unc.edu

0040–4020/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0040-4020(02)00040-6



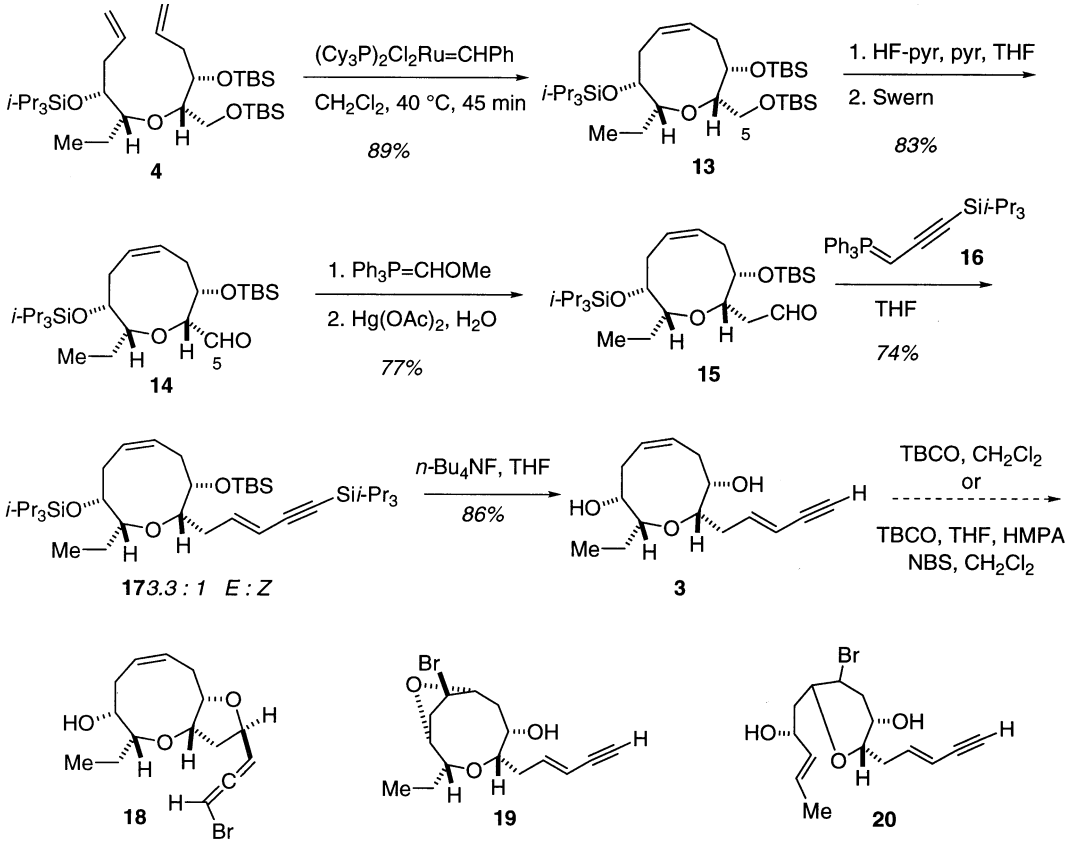
Scheme 2.

coworkers. The structure was assigned based on spectroscopic studies and later confirmed by single crystal X-ray crystallography.[9] The closely related metabolite, neolaurallene **2**, was subsequently isolated and its structure was also elucidated by X-ray studies.[8] The core of the structure of isolaurallene is a nine-membered ether to which is fused a bromoallene substituted tetrahydrofuran. The molecule contains five stereogenic tetrahedral carbons and a stereogenic allene.

As part of a program directed toward the development of a general strategy for the enantioselective construction of medium ring ether metabolites, an approach to the synthesis of isolaurallene was designed. The initial synthetic plan centered on the construction of the bromoallene and the tetrahydrofuran ring through a bromonium ion cyclization on an enyne such as **3** (Scheme 1). A similar biomimetic closure of the tetrahydrofuran had been accomplished in the conversion of prelaureatin to laurallene by Murai[11] and had been reproduced in our recent laurallene synthesis.[2] The assembly of the core nine-membered ether was to be accomplished through a ring closing metathesis reaction of an α,ω-diene that contained the resident stereogenic centers for the Δ-5-oxonene. Because of a report by Grubbs[12] on the limited effectiveness of cyclic constraints in the preparation of eight-membered diethers, the ring closing metathesis was to be accomplished with the aid of an acyclic rather than a cyclic conformational constraint.[13] Our previous success in the utilization of the *gauche* effect in the constructions of eight-membered cyclic ethers led to the selection of diene **4** as the metathesis substrate.[14] It was anticipated that diene **4** would undergo rapid closure to the oxonene because of the gearing effect created by two synergistic *gauche* effects at C6–C7 and C12–C13.[13] The assembly of diene **4** would hinge on an asymmetric aldol addition[15] of the chlorotitanium enolate of oxazolidinone **5** with 3-butenal[16] to establish the C6 and C7 stereogenic centers. The oxazolidinone **5** was to be prepared from the alcohol **6**, ultimately derivable from (*R*)-benzyl glycidyl ether.

1. Preparation of diene 4

The metathesis substrate **4** was prepared as illustrated in Scheme 2. (*R*)-Benzylglycidyl ether was exposed to methylmagnesium bromide and copper iodide to afford a quantitative yield of the secondary alcohol **6**. Alkylation of the sodium alkoxide of **6** with sodium bromoacetate provided the glycolic acid derivative **7** in excellent yield. The carboxylic acid **7** was converted to its mixed pivalic anhydride and the resultant anhydride was treated with lithio(*S*)-4-benzyl-2-oxazolidinone to provide the *N*-acyloxazolidinone **5** in 79% overall yield. Treatment of acyl oxazolidinone **5** with $TiCl_4$ and diisopropylethyl amine followed by addition of 3-butenal[16] gave the desired aldol adduct **8** in 58% yield accompanied by 20% of a mixture of two other diastereomers. A variety of conditions were explored to improve the yield and selectivity of the aldol addition, but all other combinations of Lewis acids and amine bases investigated gave inferior results. While the dibutylboryl enolate[17] gave high selectivity, the yield was



Scheme 3.

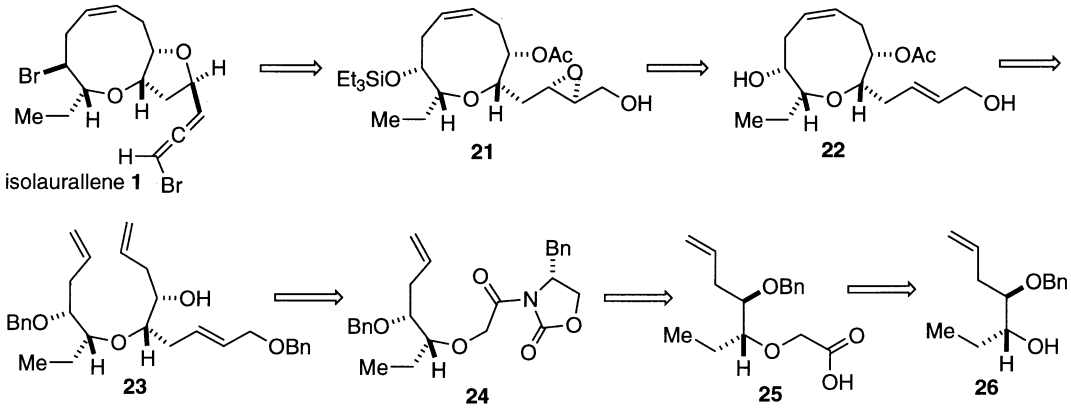
only about 10%. The major aldol isomer was readily separated by chromatography and exposed to lithium borohydride to reductively remove the chiral auxiliary. The resultant diol **9** was protected as its bis-silyl ether **10** in 83% yield.

To complete the preparation of diene **4**, a stereoselective allylation was required at C12. To that end, the benzyl ether at C12 needed to be removed. Carefully controlled conditions were required to allow removal of the benzyl ether without concommitant nucleophilic cleavage of the primary TBS ether. When a solution of the benzyl ether in THF was treated with sodium metal followed by careful addition of small amounts of ammonia, good yields of the primary alcohol could be obtained without removal of the primary TBS ether. The primary alcohol **11** was exposed to Swern conditions[18] and the resultant crude aldehyde was treated with Brown's allyl borane reagent[19] derived from (+)-2-carene, to generate the homoallylic alcohol **12** in 40% overall yield along with 12% of the diastereomeric alcohol. Finally protection of the secondary alcohol as its TIPS ether provided the required diene **4**.

With the desired diene in hand, the critical olefin metathesis reaction was investigated (Scheme 3). Heating a 0.003 M solution of diene **4** and 5 mol% of the Grubbs ruthenium alkylidine $[(Cy_3P)_2Cl_2Ru{=}CHPh]$[20] in dichloromethane for only 45 min cleanly produced the Δ-5-oxonene **13** in 89% yield. Clearly, the substituents on the α,ω-diene chain displayed a dramatic effect on the rate of the ring closing metathesis reaction. Whether the rate enhancement is a result of a transition state conformation where the ring oxygen is *gauche* to each of the adjacent oxygen substituents or a conformation where there is an *anti* relationship of the ring and the adjacent oxygens is unclear.

The next phase of the synthesis required conversion of the metathesis product **13** to the enyne **3** to allow investigation of the biomimetic bromonium ion cyclization of the enyne to introduce the necessary bromoallene moiety. As such, a one carbon extension at C5 was needed in preparation for the attachment of the enyne. Selective removal of the C5 silyl ether was achieved with buffered HF–pyridine and the resultant alcohol was oxidized under Swern conditions to deliver the aldehyde **14** in 83% overall yield. The C5 homologation was then accomplished by condensation of aldehyde **14** with methoxymethylenetriphenylphsophorane followed by immediate hydrolysis of the intermediate enol ether with aqueous mercuric acetate. The aldehyde **15**, obtained in 77% yield from aldehyde **14**, was treated without delay with phosphorane **16** to produce the enyne **17** as a 3.3:1 mixture of *E* and *Z* diastereomers. Cleavage of the two silyl ethers (n-Bu_4NF, THF) delivered the diol **3** poised for testing the closure of the tetrahydrofuran ring.

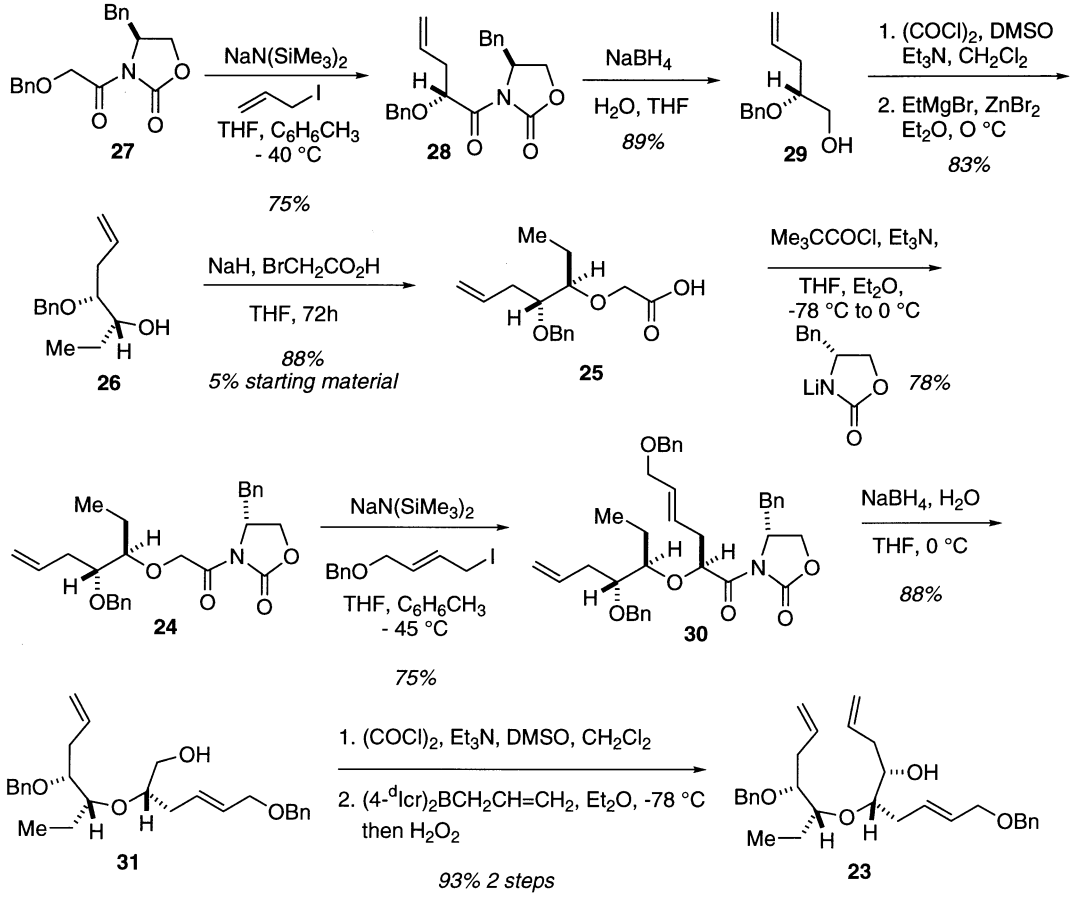
With the necessary enyne in hand, the biomimetic cyclization was attempted under a variety of conditions. Unfortunately, none of the desired bromoallene could be detected using either NBS or tetrabromocyclohexadienone as the electrophilic bromine source.[11] A complex mixture of products was isolated in each case. The ^1H NMR data provided evidence for loss of the ring olefin in all the



Scheme 4.

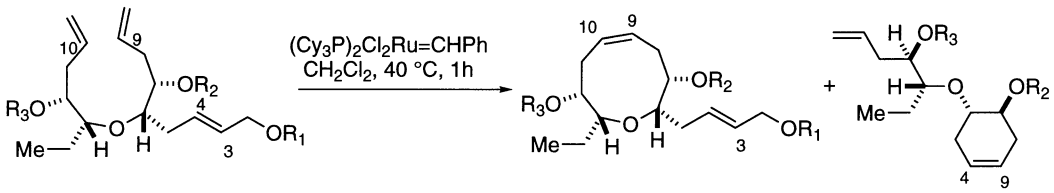
products and cleavage of one of the C–O ring bonds in many of the products. Thus, possible products of the reactions were ethers **19** and **20** and similar products.

With the failure of the biomimetic cyclization, a more conservative approach was considered. Scheme 4 outlines a modified strategy for the construction of isolaurallene where the tetrahydrofuran would be incorporated by an opening of epoxide **21** thus allowing the control of the stereochemistry at C4. The bromoallene would be elaborated subsequent to the cyclization. Epoxide **21** would arise from the corresponding allylic alcohol which might be derived from a regioselective ring closing metathesis of triene **23**. The opportunity to test the effectiveness of acyclic conformational constraints on the relative rates of ring closing metathesis in a complex substrate of this type was very appealing. The triene **23** could be constructed in much the same manner as diene **4** above, but another strategic opportunity presented itself. Since a relatively low diastereoselectivity had been observed in the aldol addition of oxazolidinone **5** with 3-butenal, and since a homologation at C5 was required after the removal of the auxiliary, an alternate approach was considered. An intriguing possibility was that the triene **23** could be derived from an

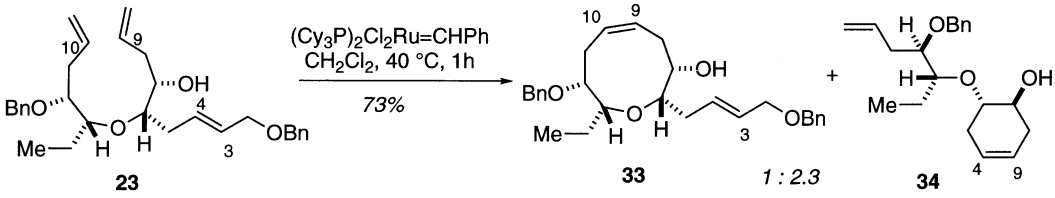


Scheme 5.

Table 1.



Entry	R_1	R_2	R_3	Yield **33** (%)	Yield **34** (%)
1	Bn	H	Bn	22	51
2	Bn	Me_3Si	Bn	38	57
3	Bn	Ac	Bn	42	42
4	Et_3Si	Ac	Bz	54	45
5	Et_3Si	Ac	PNBz	43	48
6	Et_3Si	Ac	*i*-Pr_3Si	35	49



Scheme 6.

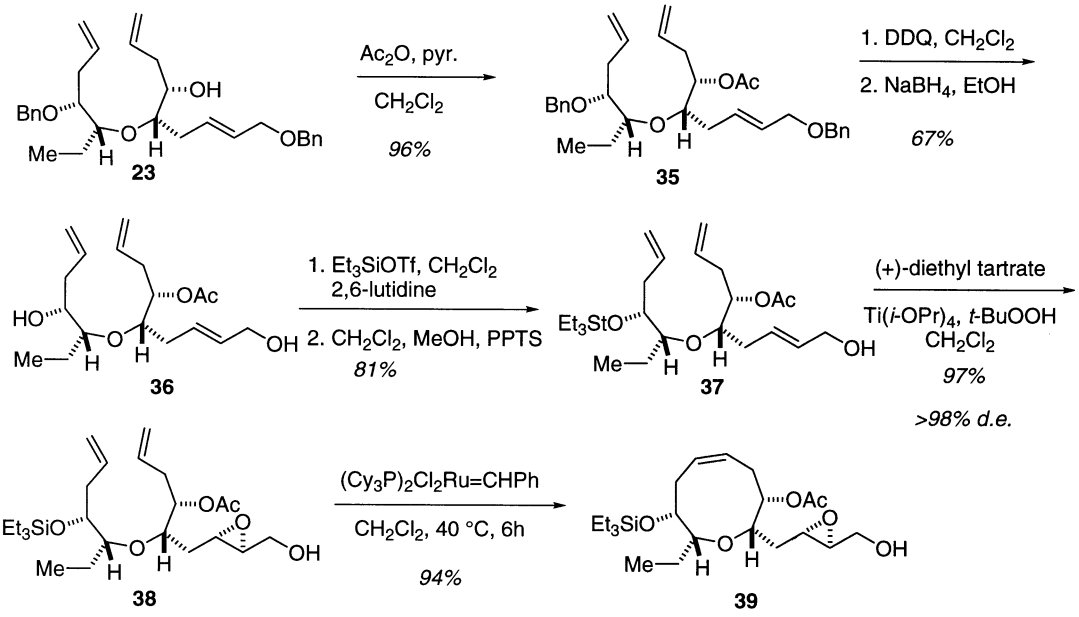
asymmetric glycolate alkylation of oxazolidinone **24** with an allylic halide which would incorporate nearly all the required carbons for the bromoallene side chain. Furthermore, the oxazolidinone **24** was derivable form the same glycolic acid derivative **25** employed in our recent synthesis of (−)-laurencin.[21] Glycolic acid **25** was available from the alcohol **26**.

2. Synthesis of triene 23

The synthesis of triene **23** is illustrated in Scheme 5. Strategically, the pivotal step in the construction of the triene was the alkylation of oxazolidinone **24** to attach the four carbon unit which would ultimately become the bromoallene. Thus, an efficient source of the alcohol **26** was needed. The known oxazolidinone **27** was alkylated with allyl iodide ($NaN(SiMe_3)_2$, THF, −78 to −40°C) to provide the oxazolidinone **28**.[22] Reductive removal of the auxiliary furnished the primary alcohol **29**.[23] The primary alcohol **29** was oxidized under Swern conditions, and the intermediate aldehyde was treated immediately, without purification, with ethylmagnesium bromide according to Asami's procedure[24] to deliver the chelation controlled adduct **26** in 83% overall yield. Alkylation of the alcohol **26** proved surprisingly difficult. High concentration and long reaction times were required to achieve reproducible yields of the glycolic acid **25**. The acid **25** was converted to its mixed pivalic anhydride and exposed in situ to lithio-(*R*)-4-benzyl-2-oxazolidinone producing the *N*-acyl oxazolidinone **24** in good yield. Enolization of the glycolyl-oxazolidinone **24** as described earlier for **28** followed by addition of *trans*-1-iodo-4-benzyloxy-2-butene[25] resulted in highly diastereoselective (>98:2) alkylation to give the α,α′-disusbstituted ether **30**. The auxiliary was reductively removed ($NaBH_4$, THF, H_2O)[23] to furnish the alcohol **31**. The final stereogenic center was introduced by oxidation of the primary alcohol and immediate exposure of the aldehyde to 1.8 equiv. of Brown's chiral allylborane reagent $[(4\text{-}^{d}Ipc)_2BCH_2CH{=}CH_2]$[19] generating the desired triene **23** in 93% yield and 96:4 diastereomeric ratio. It was necessary to use excess reagent in the asymmetric allylation reaction, since use of a stoichiometric amount resulted in significantly diminished yields.

3. Investigation of the metathesis of triene 23

The closure of the oxonene ring through a ring closing metathesis reaction was the next crucial transformation. The triene **23** could form three possible products upon ring closing metathesis: (1) a *cis* α,α′-disubstituted nine-membered oxonene (C9–C10 metathesis), (2) a *trans* α,α′-disubstituted eight-membered oxocene (C4–C10 metathesis) or (3) a cyclohexene (C9–C4 metathesis). Previous studies in our laboratory had indicated that the metathesis of dienes to form *trans* α,α′-disubstituted eight-membered oxocene ethers was significantly slower than *cis* isomers.[13] Thus, it seemed likely that given the rapid formation of the oxonene **13** from diene **4** discussed earlier, formation of the *cis* α,α′-disubstituted nine-membered oxonene should be favored over the *trans* α,α′-disubstituted eight-membered oxocene. The major question was whether the two *gauche* effects in the nine-membered ring formation would override the usual higher rate of cyclohexene formation. When diene **23** was exposed to the Grubbs catalyst in dichloromethane, rapid conversion to a 2.3:1 mixture of cyclohexene **34** to oxonene **33** was observed. While the selectivity of the reaction was less than desired, it was encouraging that the oxonene **33** was formed to some extent. It was reasoned that one possible explanation for the selectivity was the rates of insertion of the



Scheme 7.

alkylidine into the corresponding alkenes to form the C9 and C10 alkylidines. The C9 carbene could proceed to **34** while the C10 carbene could give rise to the oxonene **33**. Thus two effects were considered: if the rates of insertion into the C9 and C10 alkenes could be biased toward C10, more oxonene would be formed and if the rate of insertion into the C3–C4 alkene could be slowed, the cyclohexene formation might be minimized. In an attempt to influence the rates of insertion into the C9 and C3–C4 alkenes, a series of differentially protected forms of triene **23** were prepared (Scheme 6). Table 1 shows the specific protecting groups employed and the ratios of the oxonene **33** and cyclohexene **34** products.

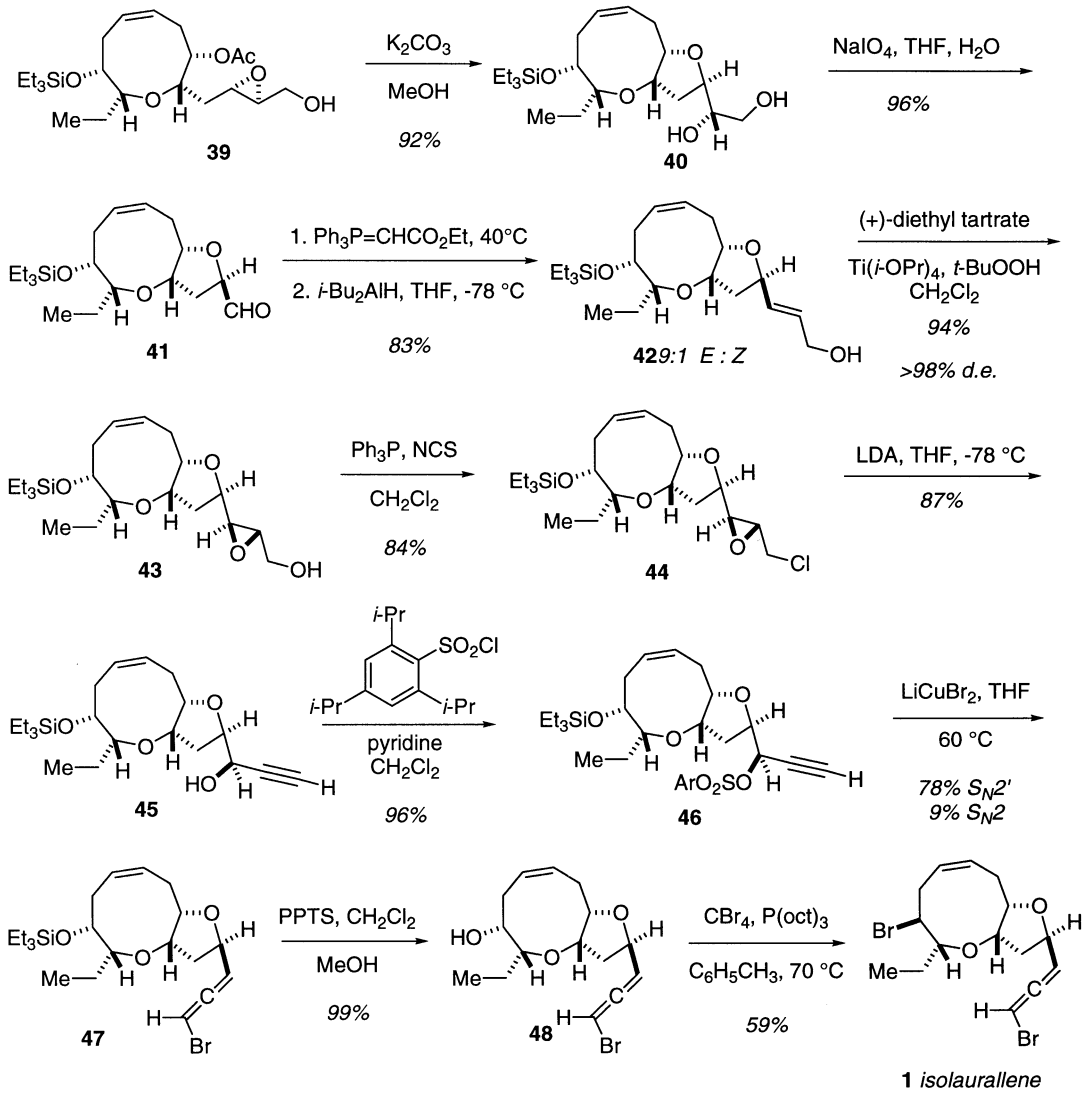
While exclusive formation of the oxonene **33** could not be achieved, some influence on the selectivity was noted, particularly when more electron withdrawing groups were used as protecting groups for the C2 and C7 hydroxyl groups. Since greater selectivity was still needed for formation of the oxonene, another approach was required. An obvious solution was to completely eliminate the possibility of cyclohexene formation by removing the C3–C4 alkene from the molecule. Given that epoxidation at C3–C4 was required to allow formation of the tetrahydrofuran, a simple reordering of the steps by executing the epoxidation prior to the ring closing metathesis should solve the selectivity problem.

4. Closure of the isolaurallene oxonene core

Alcohol **23** was readily protected as the acetate **35** (Scheme 7). Oxidative cleavage of the two benzyl ethers also resulted in oxidation of the C2 alcohol to the corresponding aldehyde.[26] Immediate reduction of the aldehyde with sodium borohydride provided diol **36** in 92% yield. Protection of the diol **36** as the bis-triethylsilyl ether was accomplished in quantitative yield with triethylsilyl triflate and subsequent selective deprotection of the primary silyl ether was accomplished through exposure to catalytic PPTS in a mixture of ethanol and dichloromethane (1:5). The allylic alcohol **37** was subjected to standard Sharpless catalytic asymmetric epoxidation conditions[27] providing the epoxy alcohol **38** in 97% yield as a single diastereomer by ^{1}H NMR analysis. Exposure of diene **38** to standard ring closing metathesis conditions (5 mol% [$(Pcy_3)_2Cl_2Ru{=}CHPh$], CH_2Cl_2 (0.003 M), 40°C) resulted in a 94% yield of the desired oxonene **39** in only 6 h.

5. Completion of isolaurallene

Completion of the synthesis required closure of the tetrahydrofuran ring, attachment of the bromoallene unit and incorporation of the secondary bromide at C12. Hydrolysis of the acetate of **39** by exposure to potassium carbonate in methanol resulted in concomitant closure of the tetrahydrofuran ring and the resultant diol **40** was converted to the aldehyde **41** by periodate cleavage (Scheme 8). Attempts to carry out stereoselective additions to aldehyde **41** to provide a propargylic alcohol proved unsuccessful. For example, addition of ethynyl magnesium bromide to aldehyde **41** gave a 1:1 mixture of diastereomers. Use of chiral additives and other metals were also ineffective. As an alternative, reaction of the aldehyde with carbethoxymethylenetriphenylphosphorane and subsequent reduction of the unsaturated ester with i-Bu_2AlH gave the allylic alcohol **42**. Since a highly stereocontrolled introduction of an acetylenic alcohol was needed to facilitate the installation of the required bromoallene, once again the Sharpless epoxidation[27] was utilized to produce the epoxy alcohol **43** with essentially complete control of stereochemistry. Conversion of the epoxy alcohol to the chloride **44** set the stage for the elimination of the chloroepoxide to the propargylic alcohol **45** according to the method of Yadav.[28] The propargylic alcohol **45** was produced in >98:2 diastereoselectivity by virtue of the highly selective Sharpless epoxidation. The bromoallene was introduced by



Scheme 8.

conversion of the acetylenic alcohol to the trisylate **46** followed by S_N2' displacement with $LiCuBr_2$[29] to provide the bromoallene **47** in good yield. The desired isomer **47** was accompanied by 9% of a direct S_N2 product and 9% of the isomeric bromoallene. Finally, conversion of bromoallene **47** to isolaurallene was achieved by removal of the silyl ether and treatment of the secondary alcohol **48** with CBr_4–trioctylphosphine[30] to give synthetic (−)-isolaurallene in 58% overall yield. The structure of synthetic (−)-isolaurallene was confirmed by comparison of ^{13}C, ^1H NMR, $[\alpha]_D$, to those reported for the natural product.[9]

6. Experimental

6.1. Materials and methods

General. Infrared (IR) spectra were obtained using a Perkin–Elmer 283 infrared spectrometer. Proton and carbon nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were recorded on the following instruments: Bruker model WM250 (^1H at 250 MHz), Bruker model DRX 300 (^1H at 300 MHz; ^{13}C at 75 MHz), Bruker model DRX 400 (^1H at 400 MHz; ^{13}C at 100 MHz), and Bruker model DRX 500 (^1H at 500 MHz; ^{13}C at 125 MHz). Optical rotations were determined using a Perkin–Elmer 241 polarimeter. Elemental analysis was performed by Atlantic Microlab, Inc. Thin layer chromatography (TLC) was conducted on silica gel F_{254} TLC plates purchased from Scientific Adsorbents, Inc. Flash chromatography was carried out using silica gel (32–63 μm) purchased from Scientific Adsorbents, Inc. Diethyl ether, tetrahydrofuran (THF), and dichloromethane were dried by being passed through a column of activated neutral alumina under nitrogen immediately prior to use. Alkylamines and toluene were distilled from calcium hydride immediately prior to use. Dimethyl sulfoxide (DMSO) was distilled under reduced pressure from calcium hydride and stored over 4 Å molecular sieves. All air and water sensitive reactions were performed in flasks flame dried under a positive flow of nitrogen and conducted under a nitrogen or argon atmosphere.

6.1.1. (2*R*)-1-(Benzyloxy)-2-butanol (6). Copper(I) iodide (0.46 g, 2.44 mmol) and 90 mL of THF were placed in a

250 mL 1-neck flask and cooled to −78°C. Methylmagnesium bromide (3.0 M in ether, 40.6 mL, 121.8 mmol) was added slowly dropwise via an addition funnel, followed by the dropwise addition of commercially available (*R*)-benzyl glycidyl ether (4.0 g, 24.4 mmol). After complete addition, the mixture was stirred at −78°C for 30 min. The reaction was quenched at −78°C by the addition of saturated NH_4Cl and then warmed to 25°C. The mixture was filtered through Celite, the Celite was washed with ether, and the combined washes were concentrated in vacuo. Ether was added and the layers were separated. The organic layer was washed with saturated NH_4Cl until the washings were colorless. The organic layer was then washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The alcohol **6** was obtained in quantitative yield and was used without further purification. ^{1}H NMR ($CDCl_3$) δ 7.32 (m, 5H), 4.53 (s, 2H), 3.72 (m, 1H), 3.49 (dd, J=9.5, 2.9 Hz, 1H), 3.30 (dd, J=9.5, 7.9 Hz, 1H), 2.28 (d, J=3.7 Hz, 1H), 1.44 (m, 2H), 0.93 (t, J=7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 137.9, 128.4, 127.68, 127.65, 74.2, 73.2, 71.7, 26.0, 9.8. IR (film) 3640–3120 (br), 2920, 1090 cm^{-1}. $[\alpha]_D^{25}$=−8.7 (*c* 0.23, CH_2Cl_2).

6.1.2. (*R*)-1-(Benzyloxymethyl)propyl-1-oxyacetic acid (7). Sodium hydride (60% dispersion in mineral oil, 1.33 g, 33.2 mmol) in a 100 mL 1-neck flask was washed three times with dry hexanes and suspended in 50 mL of THF. The mixture was cooled to 0°C. Alcohol **6** (5.44 g, 30.2 mmol) in 10 mL of dry THF was added dropwise over 15 min. The resulting mixture was stirred at 0°C for 15 min, warmed to 25°C for 15 min and then recooled to 0°C. In a second flask, sodium hydride (60% dispersion in mineral oil, 1.33 g, 33.2 mmol) was washed three times with dry hexanes, suspended in 50 mL of THF, and cooled to 0°C. Bromoacetic acid (4.19 g, 30.2 mmol) dissolved in 50 mL of THF was transferred via cannula into the second flask, and the mixture was stirred at 0°C for 5 min. The sodium alkoxide of the alcohol was then transferred via cannula into the flask containing the sodium carboxylate of bromoacetic acid. The resultant mixture was warmed to 25°C and stirred for 3 h. The reaction was quenched with water, and the THF was removed in vacuo. The aqueous layer was washed with ether, acidified with conc. H_2SO_4, and then extracted three times with ether. The extracts were washed with water, dried over Na_2SO_4, filtered, and concentrated in vacuo. The alkoxyacetic acid **7** was obtained in 85% yield and was used without further purification. ^{1}H NMR ($CDCl_3$) δ 7.33 (m, 5H), 4.61 (ABq, J=12.0 Hz, $\Delta\nu_{AB}$=9.0 Hz, 2H), 4.17 (ABq, J=17.1 Hz, $\Delta\nu_{AB}$=67.9 Hz, 2H), 3.49 (m, 3H), 1.51 (m, 2H), 0.91 (t, J=7.7 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 172.3, 136.5, 128.6, 128.2, 128.0, 82.7, 73.7, 71.8, 68.4, 24.4, 9.6. IR (film) 3700–2500 (br), 2920, 1760, 1110 cm^{-1}. $[\alpha]_D^{25}$=−25.7 (*c* 0.21, CH_2Cl_2). Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.32; H, 7.72.

6.1.3. (4*R*)-3-[1-Oxo-2-[(*R*)-1-(benzyloxymethyl)propyl-1-oxy]]-4-benzyl-1,3-oxazolidinone (5). A solution of the alkoxyacetic acid **7** (16.5 g, 69.0 mmol) and triethylamine (10.6 mL, 75.9 mmol) in 275 mL of ether was cooled to −78°C. Pivaloyl chloride (8.49 mL, 69.0 mmol) was added via syringe over 5 min and the resultant mixture was warmed to 0°C and stirred for 1 h. In a separate flask (*R*)-4-benzyl-2-oxazolidinone (12.3 g, 69.0 mmol) in 125 mL of THF was cooled to −78°C and *n*-BuLi (1.6 M in hexanes, 43.1 mL, 69.0 mmol) was added via syringe over 5 min. After addition was complete, the mixture was stirred at −78°C for 15 min. The solution of mixed anhydride was recooled to −78°C and the lithiated oxazolidinone was then transferred via cannula into the mixed anhydride. After stirring for 15 min at −78°C, the mixture was warmed to 0°C for 1 h. The reaction was quenched with water and warmed to 25°C. The aqueous layer was extracted with ether and the combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography provided 21.6 g (79%) of acyloxazolidinone **5**: ^{1}H NMR ($CDCl_3$) δ 7.22 (m, 10H), 4.86 (ABq, J=18.1 Hz, $\Delta\nu_{AB}$=22.5 Hz, 2H), 4.48 (ABq, J=12.0 Hz, $\Delta\nu_{AB}$=9.8 Hz, 2H), 4.43 (m, 1H), 4.04 (dd, J=8.9, 2.8 Hz, 1H), 3.81 (dd, J=8.9, 8.6 Hz, 1H), 3.59 (m, 3H), 3.23 (dd, J=13.4, 3.2 Hz, 1H), 2.69 (dd, J=13.4, 9.4 Hz, 1H), 1.60 (m, 2H), 0.98 (t, J=7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 170.8, 153.3, 138.4, 135.1, 129.3, 128.9, 128.3, 127.4, 127.3, 126.9, 81.5, 73.7, 72.9, 70.6, 66.9, 54.7, 37.6, 24.7, 9.9. IR (film) 2920, 1780, 1720, 1390, 1260, 1210, 1120, 700 cm^{-1}. $[\alpha]_D^{25}$=−52.5 (*c* 0.29, CH_2Cl_2).

6.1.4. (4*R*)-3-[(2*R*,3*S*)-1-Oxo-2-[(*R*)-1-(benzyloxymethyl)-propyl-1-oxy]-3-hydroxy-5-hexenyl]-4-benzyl-1,3-oxazolidinone (8). A solution of the acyloxazolidinone **5** (8.46 g, 21.3 mmol) in 142 mL of dichloromethane was cooled to −78°C. Titanium tetrachloride (2.50 mL, 22.3 mmol) was added slowly dropwise via syringe and the mixture was stirred for 15 min at −78°C. Diisopropylethylamine (9.30 mL, 53.2 mmol) diluted with 10 mL of dichloromethane was added via addition funnel over the course of 1 h. After complete addition, the mixture was stirred at −78°C for 1 h. A solution of freshly prepared 3-butenal (117 mmol) in dichloromethane was added slowly dropwise via addition funnel and the reaction was then stirred for 1.5 h at −78°C. The reaction was quenched at −78°C with 140 mL of half-saturated NH_4Cl and warmed to 25°C. The solution was filtered through Celite, and the salts were washed with dichloromethane. The aqueous layer was extracted with dichloromethane and the combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography afforded 5.81 g (58%) of alcohol **8**: ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 10H), 5.86 (m, 1H), 5.43 (d, J=4.0 Hz, 1H), 5.07 (m, 2H), 4.60 (m, 1H), 4.50 (ABq, J=12.0 Hz, $\Delta\nu_{AB}$=9.0 Hz, 2H), 4.14 (dd, J=17.0, 9.0 Hz, 1H), 4.08 (dd, J=9.0, 3.0 Hz, 1H), 3.98 (m, 1H), 3.76 (m, 1H), 3.53 (app d, J=4.8 Hz, 2H), 3.28 (dd, J=13.5, 3.3 Hz, 1H), 3.03 (d, J=7.3 Hz, 1H), 2.41 (m, 2H), 1.59 (m, 3H), 0.94 (t, J=7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 171.0, 153.3, 137.7, 135.2, 134.6, 129.4, 128.9, 128.4, 128.0, 127.7, 127.3, 117.1, 79.9, 78.3, 73.5, 72.9, 72.0, 66.6, 55.6, 38.3, 37.4, 25.4, 9.7. IR (film) 3700–3140 (br), 2920, 1780, 1710, 1390, 1210, 1100, 700 cm^{-1}. $[\alpha]_D^{25}$=−27.2 (*c* 0.25, CH_2Cl_2). Anal. Calcd for $C_{27}H_{33}O_6N_1$: C, 69.36; H, 7.11. Found: C, 68.79; H, 7.22.

6.1.5. (2*S*,3*S*)-2-[(*R*)-1-(Benzyloxymethyl)propyl-1-oxy]-5-hexen-1,3-diol (9). A solution of alcohol **8** (15.8 g, 33.8 mmol) and anhydrous methanol (3.00 mL, 74.1 mmol) in 338 mL of ether was cooled to 0°C. Lithium borohydride (2.0 M in THF, 37.0 mL, 74.3 mmol) was added

dropwise and the mixture was stirred for 2 h at 0°C. The reaction was quenched by the addition of 15% NaOH and warmed to 25°C. The aqueous layer was extracted several times with ether, and the combined extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography gave 7.55 g (76%) of diol **9**: ^{1}H NMR ($CDCl_3$) δ 7.31 (m, 5H), 5.89 (m, 1H), 5.09 (m, 2H), 4.56 (s, 2H), 3.90 (d, J=2.9 Hz, 1H), 3.73 (m, 3H), 3.47 (m, 4H), 2.33 (m, 1H), 2.18 (m, 1H), 1.98 (m, 1H), 1.54 (m, 2H), 0.88 (t, J=7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 137.4, 134.6, 128.4, 127.80, 127.76, 117.1, 82.6, 80.9, 73.4, 72.3, 71.4, 62.3, 37.4, 25.3, 9.7. IR (film) 3700–3100 (br), 2920, 1090 cm^{-1}. $[\alpha]_D^{25}$=+1.7 (c 0.19, CH_2Cl_2).

6.1.6. (2*S*,3*S*)-2-[(*R*)-1-(Benzyloxymethyl)propyl-1-oxy]-5-hexen-1,3-diol bis(*tert*-butyldimethylsilyl ether) (10). A solution of the diol **9** (2.53 g, 8.59 mmol) in 17 mL of dichloromethane was cooled to 0°C. Freshly distilled 2,6-lutidine (3.00 mL, 25.8 mmol) was added dropwise, followed by the dropwise addition of *tert*-butyldimethylsilyl trifluoromethanesulfonate (4.70 mL, 20.5 mmol). The reaction was stirred at 0°C for 1 h and then quenched with water. The aqueous layer was extracted twice with dichloromethane and the combined extracts were washed three times with 10% H_2SO_4, once with saturated $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography gave 3.75 g (83%) of compound **10**: ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5H), 5.73 (m, 1H), 4.97 (m, 2H), 4.51 (s, 2H), 3.84 (dd, J=10.3, 2.4 Hz, 1H), 3.80 (m, 1H), 3.59 (m, 2H), 3.42 (m, 2H), 3.41 (dd, J=5.3, 3.4 Hz, 1H), 2.41 (m, 1H), 1.95 (m, 1H), 1.55 (m, 2H), 0.91 (t, J=7.3 Hz, 3H), 0.87 (s, 9H), 0.85 (s, 9H), 0.02 (s, 6H), −0.003 (s, 3H), −0.013 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 138.5, 136.6, 128.3, 127.6, 127.5, 116.3, 82.6, 79.4, 73.3, 72.7, 72.1, 62.7, 36.5, 25.91, 25.87, 25.4, 18.2, 18.0, 9.8, −4.4, −5.3, −5.4. IR (film) 2940, 1253, 1098 cm^{-1} $[\alpha]_D^{25}$=−6.0 (c 0.30, CH_2Cl_2). Anal. Calcd for $C_{29}H_{54}O_4Si_2$: C, 66.61; H, 10.41. Found: C, 66.52; H, 10.42.

6.1.7. (2*S*,3*S*)-2-[(*R*)-1-(Hydroxymethyl)propyl-1-oxy]-5-hexen-1,3-diol bis(*tert*-butyl dimethylsilyl ether) (11). A solution of benzyl ether **10** (2.70 g, 5.16 mmol) in 171 mL of THF was cooled to −78°C in a flask fitted with a dry ice condenser. Chunks of sodium metal (0.470 g, 20.5 mmol) were added to the flask and the cold bath was removed. Anhydrous ammonia gas was condensed into the flask and the mixture was allowed to stir at reflux at −33°C. Ammonia was added until the mixture became a faint copper color, but not yet blue. Reaction progress was monitored by TLC and the reaction was quenched with sodium benzoate when most of the starting material had been consumed. The flask was purged with air to evaporate all of the ammonia. Ether was then added and the organic layer was washed with water, saturated NH_4Cl, water, and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography afforded a 48% yield of alcohol **11** and 61% brsm of unreacted benzyl ether **10**. Yields were improved when the scale was reduced. ^{1}H NMR ($CDCl_3$) δ 5.83 (m, 1H), 5.04 (m, 2H), 3.78 (m, 2H), 3.54 (m, 5H), 3.16 (m, 1H), 2.42 (m, 1H), 2.10 (m, 1H), 1.47 (m, 2H), 0.90 (m, 21H), 0.07 (s, 3H), 0.06 (s, 3H), 0.03 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 135.0, 117.2, 81.2, 80.8, 72.1, 64.9, 62.9, 37.6, 25.88, 25.86, 24.7, 18.2, 18.1, 10.0, −4.4, −4.7, −5.4, −5.5. IR (film) 3700–3100 (br), 2940, 1090 cm^{-1}. $[\alpha]_D^{25}$=−5.2 (c 0.13, CH_2Cl_2). Anal. Calcd for $C_{22}H_{48}O_4Si_2$: C, 61.05; H, 11.18. Found: C, 61.76; H, 11.28.

6.1.8. (4*R*,5*R*)-5-[(1*S*,2*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-(*tert*-butyldimethylsilyloxymethyl)-4-pentenyl-1-oxy]-1-hepten-4-ol (12). A solution of oxalyl chloride (2.0 M in dichloromethane, 2.80 mL, 5.60 mmol) in 5 mL of dichloromethane was cooled to −78°C. Dimethyl sulfoxide (0.80 mL, 11 mmol) was added very slowly in order to keep the reaction temperature below −65°C. After complete addition, the mixture was stirred for 15 min. A solution of alcohol **11** (2.21 g, 5.11 mmol) in 20 mL of dichloromethane was added slowly dropwise (keeping the internal temperature below −65°C). The resultant mixture was stirred for 15 min at −78°C. Triethylamine (3.60 mL, 25.8 mmol) was added slowly to maintain the temperature below −50°C and the mixture was warmed to 25°C. After stirring for 15 min at 25°C, the reaction was quenched with water. The organic layer was washed with 10% HCl, water, saturated $NaHCO_3$, water, and brine. The organic layer was dried with Na_2SO_4, filtered, and concentrated in vacuo. Ether was added and the solution was filtered through Celite. The aldehyde was obtained in 94% yield (2.06 g) and was used immediately in the next reaction without further purification. ^{1}H NMR ($CDCl_3$) δ 9.65 (d, J=3.0 Hz, 1H), 5.79 (m, 1H), 5.03 (m, 2H), 4.04 (m, 1H), 3.85 (m, 2H), 3.64 (dd, J=10.8, 7.3 Hz, 1H), 3.42 (m, 1H), 2.43 (m, 1H), 2.03 (m, 1H), 1.67 (m, 2H), 0.97 (t, J=7.5 Hz, 3H), 0.86 (s, 9H), 0.85 (s, 9H), 0.03 (s, 12H).

2-Icr$_2$BOMe was prepared according to the procedure of Brown.[19] A solution of 2-Icr$_2$BOMe (2.16 g, 6.80 mmol) in 2 mL of ether was cooled to −78°C. Allylmagnesium bromide (1.0 M in ether, 6.10 mL, 6.10 mmol) was added dropwise via syringe and the mixture was stirred at −78°C for 15 min. The mixture was then warmed to 25°C and stirred vigorously for 1 h. The mixture was recooled to −78°C and the aldehyde from above (2.06 g, 4.78 mmol) diluted with 6 mL of ether was added dropwise. The slurry was stirred at −78°C for 3 h. The reaction was quenched at −78°C with 2.7 mL of 3N NaOH and 5.4 mL of 30% H_2O_2. The solution was heated at reflux at 34°C for 2 h to ensure complete oxidation. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography afforded 0.90 g (40%) of the desired diastereomeric alcohol **12** and 0.280 g (12%) of the undesired diastereomeric alcohol. ^{1}H NMR ($CDCl_3$) δ 5.85 (m, 2H), 5.06 (m, 4H), 3.84 (dd, J=11.6, 5.0 Hz, 1H), 3.74 (dd, J=10.1, 2.8 Hz, 1H), 3.54 (m, 3H), 3.33 (d, J=3.7 Hz, 1H), 3.22 (dd, J=11.7, 6.2 Hz, 1H), 2.35 (m, 2H), 2.13 (m, 2H), 1.60 (m, 1H), 1.44 (m, 1H), 0.92 (t, J=7.7 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), 0.02 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 135.2, 135.1, 117.1, 116.6, 82.6, 81.8, 72.5, 71.7, 62.4, 37.7, 37.5, 25.9, 25.8, 23.9, 18.2, 18.1, 9.5, −4.4, −4.6, −5.4, −5.5. IR (film) 3460 (br), 2940, 1090 cm^{-1}. $[\alpha]_D^{25}$=−7.6 (c 0.23, CH_2Cl_2). Anal. Calcd for $C_{25}H_{52}O_4Si_2$: C, 63.50; H, 11.08. Found: C, 63.74; H, 11.02.

6.1.9. (4*R*,5*R*)-5-[(1*S*,2*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-(*tert*-butyldimethylsilyloxymethyl)-4-pentenyl-1-oxy]-1-hepten-4-(triisopropylsilyl ether) (4). A solution of

alcohol **12** (0.960 g, 2.03 mmol) in 4 mL of dichloromethane was cooled to 0°C. Freshly distilled 2,6-lutidine (0.36 mL, 3.1 mmol) was added dropwise, followed by the dropwise addition of triisopropylsilyl trifluoromethanesulfonate (0.66 mL, 2.4 mmol). The mixture was stirred at 0°C for 3 h and then quenched at 0°C with water. The aqueous layer was extracted twice with dichloromethane and the combined extracts were washed three times with 10% H_2SO_4, and once with saturated $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography afforded 1.05 g (82%) of diene **4**: 400 MHz ^{1}H NMR ($CDCl_3$) δ 5.92 (m, 1H), 5.75 (m, 1H), 5.01 (m, 4H), 3.87 (m, 2H), 3.70 (dt, J=9.6, 3.8 Hz, 1H), 3.59 (dd, J=10.4, 7.4 Hz, 1H), 3.48 (ddd, J=9.9, 3.9, 2.4 Hz, 1H), 3.42 (ddd, J=7.1, 4.3, 2.7 Hz, 1H), 2.40 (m, 2H), 2.10 (m, 1H), 1.94 (m, 1H), 1.70 (m, 1H), 1.32 (m, 1H), 1.04 (m, 21H), 0.99 (t, J=7.4 Hz, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.02 (s, 6H), 0.01 (s, 6H). ^{13}C NMR ($CDCl_3$) δ 137.2, 136.6, 116.5, 116.0, 84.1, 82.6, 73.3, 72.8, 63.1, 36.6, 36.3, 25.9, 25.8, 21.7, 18.3, 18.25, 18.21, 18.0, 12.7, 11.2, −4.4, −4.5, −5.4, −5.5. IR (film) 2920, 1090 cm^{-1}. $[\alpha]_D^{25}$=+9.9 (*c* 0.31, CH_2Cl_2). Anal. Calcd for $C_{34}H_{72}O_4Si_3$: C, 64.90; H, 11.53. Found: C, 65.07; H, 11.60.

6.1.10. (2*S*,3*S*,8*R*,9*R*)-9-Ethyl-8-(triisopropyloxy)-3-(*tert*-butyldimethylsilyloxy)-2-(*tert*-butyldimethylsilyloxymethyl)-Δ5,6-oxonene (13). A solution of diene **4** (0.900 g, 1.43 mmol) in 475 mL of dichloromethane (0.003 M) was heated to reflux and then 0.082 g of $(Cy_3P)_2Cl_2Ru$=CHPh (7 mol%) was added in one portion. The mixture was heated at reflux for 45 min, and then cooled to 25°C. After dilution with dichloromethane, air was bubbled through the mixture for 8 h. The solution was concentrated and the residue was purified by flash chromatography to give 0.770 g (89%) of oxonene **13**: 400 MHz ^{1}H NMR ($CDCl_3$) δ 5.67 (m, 1H), 5.38 (m, 1H), 4.01 (m, 1H), 3.75 (ddd, J=10.6, 4.7, 2.7 Hz, 1H), 3.69 (m, 2H), 3.57 (m, 1H), 3.29 (dt, J=6.0, 2.7 Hz, 1H), 3.00 (m, 1H), 2.89 (dd, J=22.5, 11.3 Hz, 1H), 1.91 (m, 1H), 1.83 (m, 2H), 1.45 (m, 1H), 1.04 (m, 21H), 0.91 (t, J=7.5 Hz, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H), 0.01 (s, 6H). ^{13}C NMR (CD_2Cl_2) δ 130.1, 126.7, 83.9, 80.3, 72.2, 71.7, 64.5, 32.7, 32.1, 26.18, 26.16, 22.7, 18.6, 18.51, 18.46, 18.4, 13.0, 11.1, −4.0, −4.8, −5.21, −5.24. IR (film) 2940, 1250, 1090 cm^{-1}. $[\alpha]_D^{25}$=+28.5 (*c* 0.38, CH_2Cl_2). Anal. Calcd for $C_{32}H_{68}O_4Si_3$: C, 63.94; H, 11.40. Found: C, 64.03; H, 11.50.

6.1.11. (2*S*,3*S*,8*R*,9*R*)-9-Ethyl-8-(triisopropyloxy)-3-(*tert*-butyldimethylsilyloxy)-2-(formyl)-Δ5,6-oxonene (14). To a solution of oxonene **13** (0.204 g, 0.34 mmol) in 6 mL of THF in a Nalgene container was added 5 mL of freshly prepared buffered pyridinium hydrofluoride stock solution (stock solution was prepared from 1.0 g of pyridinium hydrofluoride, 4 mL of pyridine, and 16 mL of THF). The resultant mixture was stirred at 25°C for 3 h, and then quenched by the dropwise addition of saturated $NaHCO_3$. The aqueous layer was extracted several times with dichloromethane and the combined extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography gave 0.068 g of starting material and 0.082 g (50%, 83% brsm) of the alcohol: 400 MHz ^{1}H NMR ($CDCl_3$) δ 5.52 (m, 2H), 3.90 (m, 2H), 3.80 (m, 1H), 3.65 (dd, J=11.1, 6.2 Hz, 1H), 3.55 (m, 1H), 3.30 (dt, J=6.8, 3.6 Hz, 1H), 2.98 (m, 2H), 2.25 (m, 1H), 1.98 (m, 1H), 1.83 (m, 2H), 1.57 (m, 1H), 1.05 (m, 21H), 0.89 (t, J=7.5 Hz, 3H), 0.87 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 128.3, 127.9, 79.7, 76.3, 72.2, 70.7, 62.0, 31.8, 31.5, 25.8, 22.1, 18.22, 18.18, 18.0, 12.8, 10.5, −4.4, −4.9. IR (film) 3650–3125 (br), 2943, 2865, 1463, 1253, 1081 cm^{-1}. $[\alpha]_D^{25}$=+3.5 (*c* 0.12, CH_2Cl_2).

A solution of oxalyl chloride (2.0 M in dichloromethane, 0.39 mL, 0.79 mmol) in 5 mL of dichloromethane was cooled to −78°C. Dimethyl sulfoxide (0.11 mL, 1.6 mmol) was added very slowly to keep the reaction temperature below −65°C. After complete addition, the mixture was stirred for 15 min. The alcohol from above (0.350 g, 0.720 mmol) was diluted with 5 mL of dichloromethane and added slowly dropwise (keeping the internal temperature below −65°C). The resultant mixture was stirred for 15 min at −78°C. Triethylamine (0.50 mL, 3.6 mmol) was added dropwise slowly and the mixture was warmed to 25°C. After stirring for 15 min at 25°C, the reaction was quenched with water. The organic layer was washed with 10% HCl, water, saturated $NaHCO_3$, water, and brine. The organic layer was dried with Na_2SO_4, filtered, and concentrated in vacuo. Ether was added and the solution was filtered through Celite. The organic layer was dried over sodium sulfate, filtered and concentrated to provide 0.350 g (100%) of aldehyde **14**: ^{1}H NMR ($CDCl_3$) δ 9.74 (d, J=2.0 Hz, 1H), 5.60 (m, 1H), 5.40 (m, 1H), 4.19 (m, 1H), 3.99 (m, 1H), 3.40 (dd, J=2.9, 1.8 Hz, 1H), 3.01 (m, 3H), 2.04 (m, 2H), 1.88 (m, 1H), 1.51 (m, 1H), 1.06 (m, 21H), 0.92 (t, J=7.5 Hz, 3H), 0.82 (s, 9H), 0.02 (s, 3H), −0.03 (s, 3H).

6.1.12. ((2*S*,3*S*,8*R*,9*R*)-9-Ethyl-8-(triisopropyloxy)-3-(*tert*-butyldimethylsilyloxy)-2-(2-oxo-ethyl)-Δ5,6-oxonene (15). A suspension of (methoxymethyl)triphenyl-phosphonium bromide (0.740 g, 2.16 mmol) in 4 mL of THF was cooled to 0°C. Potassium *tert*-butoxide (1.0 M in THF, 2.10 mL, 2.10 mmol) was added to give a ruby red solution. This solution was stirred for 5 min at 0°C and then aldehyde **14** (0.350 g, 0.720 mmol) in 5 mL of THF was added. The reaction was stirred at 0°C for 10 min and then quenched at 0°C with saturated $NaHCO_3$. The solution was diluted with ether and warmed to 25°C. The organic layer was separated and concentrated in vacuo. Purification by flash chromatography afforded 0.310 g (85%) of the vinyl ether as a 4.2:1 ratio of *E*/*Z* isomers. 400 MHz ^{1}H NMR ($CDCl_3$) δ 6.34 (d, J=13.0 Hz, 1H), 5.95 (dd, J=6.3, 0.6 Hz, 0.24H), 5.67 (dt, J=10.9, 6.9 Hz, 1.24H), 5.39 (dt, J=10.9, 6.3 Hz, 1.24H), 4.88 (dd, J=13.0, 8.7 Hz, 1H), 4.59 (dd, J=9.3, 6.3 Hz, 0.24H), 4.20 (dd, J=9.3, 2.3 Hz, 0.24H), 4.05 (m, 0.24H), 3.95 (m, 1H), 3.57 (ddd, J=10.6, 4.8, 2.7 Hz, 0.24H), 3.53 (m, 5.48H), 3.29 (m, 1.24H), 2.99 (m, 2.72H), 1.92 (m, 1.48H), 1.80 (m, 2.48H), 1.42 (m, 1H), 1.04 (m, 26.04H), 0.87 (m, 14.88H), 0.03 (m, 7.44H). ^{13}C NMR ($CDCl_3$) δ 148.7, 147.2, 130.5, 126.2, 106.3, 102.0, 78.9, 75.4, 74.6, 73.5, 71.7, 71.4, 59.5, 55.6, 32.4, 31.6, 26.0, 25.9, 21.2, 18.30, 18.25, 18.10, 18.07, 12.4, 10.8, 10.7, −4.2, −4.3, −4.5.

The vinyl ether from above (0.290 g, 0.570 mmol) was diluted with 15 mL of THF and 1.5 mL of water. Mer-

cury(II) acetate (0.550 g, 1.72 mmol) was added in one portion and the mixture was stirred at 25°C for 1 h. The reaction was quenched by the addition of 30 mL of freshly prepared saturated potassium iodide and stirred for 10 min. The aqueous layer was extracted three times with ether and the combined extracts were washed with 30 mL of saturated potassium iodide. Concentration followed by purification of the residue by flash chromatography gave 0.260 g (91%) of aldehyde **15**: ^{1}H NMR ($CDCl_3$) δ 9.82 (t, J=2.0 Hz, 1H), 5.54 (m, 2H), 3.92 (m, 2H), 3.77 (dt, J=9.5, 3.7 Hz, 1H), 3.24 (dt, J=6.6, 4.1 Hz, 1H), 2.96 (m, 2H), 2.77 (ddd, J=17.2, 6.3, 1.5 Hz, 1H), 2.50 (ddd, J=17.2, 5.1, 2.2 Hz, 1H), 1.86 (m, 3H), 1.48 (m, 1H), 1.04 (m, 21H), 0.87 (m, 12H), 0.05 (s, 3H), −0.003 (s, 3H).

6.1.13. (2*S*,3*S*,8*R*,9*R*)-9-Ethyl-8-(triisopropyloxy)-3-(*tert*-butyldimethylsilyloxy)-2-(2-penten-4-yn-5-triisopropylsilyl-1-yl)-Δ5,6-oxonene (17). A suspension of the phosphonium salt **16** (0.420 g, 0.790 mmol) and 5 mL of THF were cooled to 0°C. Potassium *tert*-butoxide (1.0 M in THF, 0.73 mL, 0.73 mmol) was added and the mixture was stirred at 0°C for 20 min and then stirred at 25°C for 20 min. The ylide solution was cooled to −78°C and aldehyde **15** (0.260 g, 0.520 mmol) in 5 mL of THF was added dropwise. The mixture was stirred at −78°C for 5 min, −50°C for 15 min, 0°C for 1.5 h, and then at 25°C for 15 min. The reaction was quenched by the addition of saturated $NaHCO_3$ and the aqueous layer was extracted with ether until the extracts were colorless. The combined extracts were concentrated in vacuo. Purification of the residue by flash chromatography afforded 0.260 g (74%) of alkene **17** as a 3.3:1 ratio of *E*/*Z* isomers. 400 MHz ^{1}H NMR ($CDCl_3$) δ 6.16 (m, 1H), 6.06 (m, 0.3H), 5.62 (dt, J=10.8, 6.7 Hz, 1.3H), 5.53 (m, 1.3H), 5.42 (dt, J=10.8, 6.5 Hz, 1.3H), 3.93 (m, 1.3H), 3.65 (dt, J=9.7, 3.5 Hz, 1.3H), 3.42 (m, 2.6H), 2.93 (m, 2.6H), 2.66 (m, 0.3H), 2.55 (m, 0.3H), 2.39 (m, 2H), 1.85 (m, 3.9H), 1.43 (m, 1.3H), 1.06 (m, 54.6H), 0.90 (m, 15.6H), 0.04 (m, 7.8H). ^{13}C NMR (CD_2Cl_2) δ 143.2, 142.9, 129.8, 127.0, 126.8, 112.1, 110.7, 106.4, 104.1, 96.1, 89.3, 82.2, 81.5, 77.5, 73.4, 72.5, 71.8, 71.7, 35.4, 33.7, 32.8, 32.5, 31.9, 30.1, 26.2, 22.42, 22.37, 18.9, 18.9, 18.8, 18.5, 18.4, 18.3, 13.0, 12.9, 11.7, 11.1, 11.0, −3.7, −3.9, −4.7. IR (film) 2944, 2865, 1463, 1078 cm^{-1}.

6.1.14. (2*S*,3*S*,8*R*,9*R*)-9-Ethyl-8-(hydroxy)-3-(hydroxy)-2-(2-penten-4-yn-1-yl)-Δ5,6-oxonene (3). A solution of silyl acetylene **17** (0.170 g, 0.250 mmol) in 8 mL of THF was cooled to 0°C. Tetrabutylammonium fluoride (1.0 M in THF, 0.82 mL, 0.82 mmol) was added and the solution was stirred at 0°C for 1 h and then warmed to 25°C and stirred for 1.5 h. An additional 0.25 mL of tetrabutylammonium fluoride was then added and the solution was stirred for another 1.5 h at 25°C. The reaction was quenched with brine and the aqueous layer was extracted three times with ethyl acetate. The combined extracts were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography afforded 0.053 g (86%) of diol **3** as a 6.7:1 mixture of *E*/*Z* isomers. 400 MHz ^{1}H NMR ($CDCl_3$) δ 6.17 (m, 1H), 6.01 (m, 0.15H), 5.52 (m, 3.45H), 3.84 (ddd, J=9.9, 6.2, 2.7 Hz, 1.15H), 3.75 (ddd, J=9.9, 6.2, 2.6 Hz, 1.15H), 3.18 (m, 1.3H), 3.09 (m, 3.15H), 2.79 (d, J=2.3 Hz, 1H), 2.71 (m, 3.6H), 2.44 (m, 1H), 2.36 (m, 2.3H), 1.87 (m, 1.3H), 1.67 (m, 1.15H), 0.87 (t, J=7.5 Hz, 3.45H). ^{13}C NMR (C_6D_6) for *E* isomer δ 142.1, 127.9, 127.6, 112.0, 88.4, 86.0, 82.5, 77.2, 72.1, 71.2, 37.1, 33.3, 33.2, 25.9, 10.1. ^{13}C NMR ($CDCl_3$) for *E* isomer δ 141.7, 127.8, 127.4, 111.5, 88.5, 86.0, 82.1, 76.6, 72.0, 71.1, 36.8, 32.9, 32.9, 25.6, 10.0. IR (film) 3650–3125 (br), 2930, 1041 cm^{-1}.

6.1.15. (4*S*)-4-Benzyl-3-[(2*R*)-2-benzyloxy-pent-4-enoyl]-oxazolidin-2-one (28). Into a flask fitted with a low-temperature thermometer was added sodium bis(trimethylsilyl)amide (1.0 M in toluene, 124 mL, 124 mmol). 200 mL of THF was added and the flask was cooled to −78°C. (*S*)-(+)-4-Benzyl-3-benzyloxyacetyl-2-oxazolidinone **27** (28.0 g, 86.0 mmol) in 100 mL of THF was added via cannula at such a rate so as to maintain the internal temperature below −60°C. After stirring for 30 min at −78°C, allyl iodide (39.0 mL, 427 mmol) was added via syringe. After 10 min the reaction was warmed to −45°C and stirred at that temperature for 3.5 h. The reaction was quenched by the addition of saturated NH_4Cl and warmed to room temperature. The THF was removed in vacuo and the remaining solution extracted twice with 50% ethyl acetate/hexanes. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography provided 23.6 g (75%) of acyl oxazolidinone **28**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.16 (m, 10H), 5.92 (ddt, J=17.8, 10.1, 6.3 Hz, 1H), 5.19–5.08 (m, 3H), 4.60 (m, 1H), 4.55 (AB, J_{AB}=12.0 Hz, $\Delta\nu_{AB}$=46.6 Hz, 2H), 4.15 (d, J=11.1 Hz, 2H), 3.25 (dd, J=13.0, 3.8 Hz, 1H), 2.69–2.50 (m, 2H), 2.67 (dd, J=13.0, 10.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.2, 37.9, 55.0, 66.7, 72.6, 76.7, 118.2, 127.4, 127.8, 128.2, 128.3, 128.9, 129.3, 133.0, 135.0, 137.5, 153.0, 172.2; IR (film) 1775, 1705, 1390, 1210, 1105 cm^{-1}; $[\alpha]^{24}_D$=+94.4 (c 1.79, CH_2Cl_2). Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.19; H, 6.23; N, 3.81.

6.1.16. (2*R*)-2-Benzyloxy-pent-4-en-1-ol (29). Acyl oxazolidinone **28** (0.555 g, 1.52 mmol) and anhydrous methanol (0.074 mL, 1.8 mmol) in 15 mL of diethyl ether were cooled to 0°C. Lithium borohydride (2.0 M in THF, 0.91 mL, 1.8 mmol) was added dropwise via syringe. After stirring 1.5 h the reaction was quenched by the dropwise addition of 15 mL of 10% NaOH and warmed to room temperature. After 20 min the reaction was extracted twice with ethyl acetate, and the combined organic layers were dried over Na_2SO_4. Purification by flash chromatography gave 0.259 g (89%) of primary alcohol **29** which was identical to that previously reported:[31] ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.39–7.23 (m, 5H), 5.81 (ddt, J=17.8, 9.6, 7.3 Hz, 1H), 5.18–5.03 (m, 2H), 4.59 (AB, J_{AB}=12.3 Hz, $\Delta\nu_{AB}$=34.2 Hz, 2H), 3.75–3.48 (m, 3H), 2.47–2.23 (m, 2H), 1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.3, 64.0, 71.5, 79.1, 117.5, 127.7, 128.5, 134.0, 138.2; IR (film) 3700–3100 (br), 2920, 2860, 1090, 910 cm^{-1}; $[\alpha]^{24}_D$=−14.0 (c 0.75, CH_2Cl_2).

6.1.17. (3*R*,4*R*)-4-Benzyloxy-hept-6-en-3-ol (26). Into a flask equipped with a mechanical stirrer and low-temperature thermometer was added 150 mL of dichloromethane and oxalyl chloride (2.0 M in CH_2Cl_2, 31.6 mL, 63.2 mmol). After cooling to −78°C, DMSO (9.00 mL, 127 mmol) in 9.0 mL of dichloromethane was added dropwise via addition funnel. After stirring for 10 min, alcohol

29 (11.04 g, 57.44 mmol) in 15.0 mL of CH_2Cl_2 was added via addition funnel. After 15 min, triethyl amine (40.0 mL, 287 mmol) was added dropwise via addition funnel. The cooling bath was removed and the reaction allowed to warm to room temperature. The reaction mixture was poured into 600 mL of diethyl ether, and the organic layer was washed with water, cold 1 M HCl, saturated $NaHCO_3$, water, and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The aldehyde was used immediately without further purification.

Into a flask equipped with a mechanical stirrer was added anhydrous zinc bromide (14.23 g, 63.19 mmol) and 200 mL of diethyl ether. The reaction was cooled to 0°C with vigorous stirring. The crude aldehyde (10.93 g, 57.44 mmol) in 50 mL of diethyl ether was added via cannula. After 5 min, ethyl magnesium bromide (1.0 M in diethyl ether, 345 mL, 345 mmol) was added rapidly via cannula. After 1 h, the reaction was quenched by the careful addition of saturated NH_4Cl. 10% HCl was added until all of the salts had dissolved and the reaction mixture was poured into a separatory funnel. The layers were separated and the aqueous layer extracted with 50% ethyl acetate/hexanes. The combined organic extracts were washed with saturated $NaHCO_3$, brine, and dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography provided 10.47 g (83%) of secondary alcohol **26** which was identical to that previously reported:[32] ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.38–7.24 (m, 5H), 5.86 (ddt, J=17.8, 8.7, 7.3 Hz, 1H), 5.18–5.04 (m, 2H), 4.59 (AB, J_{AB}=11.9 Hz, $\Delta\nu_{AB}$=55.2 Hz, 2H), 3.46 (m, 1H), 3.34 (dt, J=6.2, 5.0 Hz, 1H), 2.53–2.27 (m, 2H), 2.23 (d, J=5.0 Hz, 1H), 1.64–1.37 (m, 2H), 0.95 (t, J=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.0, 26.2, 34.8, 72.2, 73.8, 81.2, 117.4, 127.76, 127.83, 128.4, 134.3, 138.2; IR (film) 3630–3160 (br), 2930, 2870, 1060, 905 cm^{-1}; $[\alpha]^{24}_D$=−32.4 (c 5.88, CH_2Cl_2).

6.1.18. [(1*R*,2*R*)-2-Benzyloxy-1-ethyl-pent-4-enyloxy]-acetic acid (25). Sodium hydride (60% dispersion in mineral oil, 3.98 g, 24.5 mmol) was washed twice with hexanes, suspended in 4 mL THF, and cooled to 0°C. Alcohol **26** (3.59 g, 16.3 mmol) in 2 mL of THF was added dropwise via syringe, and the reaction allowed to warm to room temperature, where it was allowed to stir for 1 h. In a second flask, sodium hydride (60% dispersion in mineral oil, 3.98 g, 24.5 mmol) was washed twice with hexanes, suspended in 5 mL THF, and cooled to 0°C. Bromoacetic acid (2.49 g, 17.9 mmol) in 3 mL of THF was added via syringe, and the mixture was stirred for 10 min. The sodium alkoxide of alcohol **5** was then transferred via cannula into the flask containing the sodium carboxylate of bromoacetic acid. The resultant mixture was allowed to warm to room temperature and stirred for 84 h. The reaction was quenched by the slow addition of water, extracted twice with diethyl ether, and dried over Na_2SO_4. The aqueous layer was acidified by the addition of 10% H_2SO_4, and extracted three times with ethyl acetate. The ether extracts were concentrated in vacuo and purified by flash chromatography to give 0.174 g (5%) of recovered alcohol **5**. The ethyl acetate extracts were dried over Na_2SO_4, concentrated in vacuo, and purified by flash chromatography to provide 3.99 g (88%) of acid **25**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.39–7.22 (m, 5H), 5.83 (m, 1H), 5.17–5.04 (m, 2H), 4.65 (AB, J_{AB}=10.5 Hz, $\Delta\nu_{AB}$=34.2 Hz, 2H), 4.12 (AB, J_{AB}=17.3 Hz, $\Delta\nu_{AB}$=62.4 Hz, 2H), 3.57 (m, 1H), 3.31 (m, 1H), 2.54 (m, 1H), 2.18 (m, 1H), 1.56 (m, 1H), 1.48 (m, 1H), 0.92 (t, J=7.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.6, 22.9, 33.7, 68.2, 72.2, 79.3, 83.4, 118.3, 128.2, 128.3, 128.5, 132.7, 136.6, 172.6; IR (film) 3700–2200 (br), 1735, 1240, 1115, 910 cm^{-1}; $[\alpha]^{24}_D$=−50.0 (c 2.17, CH_2Cl_2).

6.1.19. (4*S*)-4-Benzyl-3-[2-((1*R*,2*R*)-2-benzyloxy-1-ethyl-pent-4-enyloxy)-acetyl]-oxazolidin-2-one (24). To a solution of carboxylic acid **25** (3.98 g, 14.3 mmol) in 60 mL of diethyl ether was added triethyl amine (2.20 mL, 15.8 mmol) via syringe, and the mixture was cooled to −78°C. Pivaloyl chloride (1.80 mL, 14.6 mmol) was added dropwise via syringe. After 5 min, the mixture was warmed to 0°C, where it was stirred for 1 h and subsequently recooled to −78°C. In a separate flask (*S*)-(+)-4-benzyl-2-oxazolidinone (2.54 g, 14.3 mmol) was dissolved in 25 mL of THF and cooled to −78°C. *n*-Butyl lithium (1.6 M in hexanes, 9.40 mL, 15.0 mmol) was added dropwise via syringe, and the mixture was stirred for 15 min. The lithiated oxazolidinone was added via cannula to the mixed anhydride, and the reaction stirred for an additional 10 min before being warmed to 0°C, where stirring continued for 1 h. The reaction was quenched by the addition of water and extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography gave 4.87 g (78%) of acyl oxazolidinone **24**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.13 (m, 10H), 5.89 (ddt, 1H, J=17.2, 10.0, 7.0 Hz), 5.16–5.02 (m, 2H), 4.81 (AB, 2H, J_{AB}=17.6 Hz, $\Delta\nu_{AB}$=31.6 Hz), 4.60 (AB, 2H, J_{AB}=11.8 Hz, $\Delta\nu_{AB}$=51.4 Hz), 4.40 (m, 1H), 4.08 (dd, 1H, J=8.8, 2.8 Hz), 3.98 (dd, 1H, J=8.8, 8.8 Hz), 3.59 (m, 1H), 3.39 (m, 1H), 3.25 (dd, 1H, J=13.6, 3.2 Hz), 2.71 (dd, 1H, J=13.6, 9.6 Hz), 2.51 (m, 1H), 2.27 (m, 1H), 1.69 (m, 1H), 1.55 (m, 1H), 0.98 (t, 3H, J=7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.2, 23.3, 34.5, 37.7, 54.6, 67.0, 71.4, 71.9, 80.9, 84.0, 117.1, 127.22, 127.24, 127.3, 128.2, 128.9, 129.4, 134.8, 135.1, 139.0, 153.3, 170.4; IR (film) 2925, 1780, 1720, 1390, 1260, 1130 cm^{-1}; $[\alpha]^{25}_D$=−69.0 (c 0.58, CH_2Cl_2). Anal. Calcd for $C_{26}H_{31}NO_5$: C, 71.37; H, 7.14; N, 3.20. Found: C, 71.39; H, 7.19; N, 3.24.

6.1.20. (4*R*)-4-Benzyl-3-[(2*S*,4*E*)-6-benzyloxy-2-((1*R*,2*R*)-2-benzyloxy-1-ethyl-pent-4-enyloxy)-hex-4-enoyl]-oxazolidin-2-one (30). Into a 500 mL 3-neck flask fitted with a low-temperature thermometer and addition funnel was added sodium bis(trimethylsilyl)amide (0.75 M in toluene, 21.2 mL, 15.9 mmol). 60 mL of THF was added and the flask was cooled to −78°C. Oxazolidinone **24** (4.64 g, 10.6 mmol) in 10 mL of THF was added dropwise via addition funnel at such a rate so as to maintain the reaction temperature below −60°C. After stirring for 30 min at −78°C, *trans*-4-benzyloxymethyl-1-iodide-2-butene (16.28 g, 56.51 mmol) in 10 mL THF was added dropwise via addition funnel. After 10 min the reaction was warmed to −45°C and stirred at that temperature for 2 h. The reaction was quenched by the addition of half-saturated NH_4Cl and warmed to room temperature. The THF was removed in vacuo and the remaining solution extracted twice with 50% ethyl acetate/hexanes. The combined organic extracts

were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash chromatography provided 4.75 g (75%) of acyl oxazolidinone **30**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.03 (m, 15H), 5.96–5.80 (m, 2H), 5.71 (m, 1H), 5.35 (dd, J=6.3, 4.8 Hz, 1H), 5.13–5.03 (m, 2H), 4.52 (AB, J_{AB}=12.6 Hz, $\Delta\nu_{AB}$=61.8 Hz, 2H), 4.48 (s, 2H), 4.05 (m, 1H), 3.98 (d, J=5.7 Hz, 2H), 3.78 (dd, J=9.0, 3.3 Hz, 1H), 3.53 (m, 1H), 3.40 (m, 1H), 3.23–3.11 (m, 2H), 2.61–2.42 (m, 4H), 2.20 (ddd, J=15.0, 7.8, 5.1 Hz, 1H), 1.66 (m, 1H), 1.49 (m, 1H), 1.02 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.6, 23.9, 33.8, 37.1, 37.9, 54.6, 66.2, 69.9, 70.6, 72.0, 79.5, 81.7, 84.6, 117.2, 126.0, 127.0, 127.2, 127.4, 127.7, 128.28, 128.33, 128.8, 129.3, 130.1, 134.1, 135.3, 138.4, 139.4, 153.0, 172.4; IR (film) 3040, 2930, 1780, 1715, 1390, 1105 cm^{-1}; $[\alpha]^{24}_D$=−71.3 (c 1.15, CH_2Cl_2); Anal. Calcd for $C_{37}H_{43}NO_6$: C, 74.35; H, 7.25; N, 2.34. Found: C, 74.53; H, 7.21; N, 2.38.

6.1.21. (2*S*,4*E*)-6-Benzyloxy-2-((1*R*,2*R*)-2-benzyloxy-1-ethyl-pent-4-enyloxy)-hex-4-en-1-ol (31). A 500 mL flask was equipped with an additon funnel and a solution of acyl oxazolidinone **30** (7.25 g, 12.1 mmol) in 120 mL of THF was cooled to 5°C. Sodium borohydride (1.84 g, 48.6 mmol) in 38 mL of water was added dropwise via additon funnel. The reaction was allowed to warm to room temperature. After 3.5 h, additional sodium borohydride (0.920 g, 24.3 mmol) was added in a single portion. After another 2 h of stirring, the solution was cooled to 5°C and 75 mL of 10% HCl was added dropwise via addition funnel. The solution was allowed to warm to room temperature, where it was stirred for 20 min. The reaction was poured into ethyl acetate, and the layers were separated. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$ and brine, and dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography provided 4.53 g (88%) of alcohol **31**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.25 (m, 10H), 5.90 (m, 1H), 5.79–5.61 (m, 2H), 5.17–5.07 (m, 2H), 4.64 (AB, J_{AB}=11.4 Hz, $\Delta\nu_{AB}$=21.0 Hz, 2H), 4.51 (s, 2H), 3.99 (d, J=4.5 Hz, 2H), 3.63–3.37 (m, 6H), 2.49 (m, 1H), 2.36–2.14 (m, 3H), 1.65 (m, 1H), 1.43 (m, 1H), 0.93 (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.7, 23.6, 34.6, 35.3, 65.5, 70.6, 72.0, 72.8, 80.0, 80.3, 81.2, 117.4, 127.5, 127.7, 127.8, 128.0, 128.3, 128.4, 129.1, 129.9, 134.0, 137.8, 138.3; IR (film) 3700–3140 (br), 2920, 1455, 1360, 1065 cm^{-1}; $[\alpha]^{24}_D$=−22.0 (c 1.29, CH_2Cl_2); Anal. Calcd for $C_{27}H_{36}O_4$: C, 76.38; H, 8.55. Found: C, 76.15; H, 8.77.

6.1.22. (4*S*,5*S*,7*E*)-9-Benzyloxy-5-((1*R*,2*R*)-2-benzyloxy-1-ethyl-pent-4-enyloxy)-nona-1,7-dien-4-ol (23). Into a 25 mL flask was added 7 mL of dichloromethane and oxalyl chloride (2.0 M in dichloromethane, 0.44 mL, 0.88 mmol). The solution was cooled to −78°C, and DMSO (0.12 mL, 1.7 mmol) was added dropwise via syringe. After 15 min alcohol **31** (0.247 g, 0.582 mmol) in 3 mL of dichloromethane was added dropwise via syringe. After 25 min triethyl amine (0.41 mL, 2.9 mmol) was added dropwise via syringe. The cold bath was removed, and the solution was allowed to warm to room temperature. The reaction was poured into ethyl acetate and washed with water, 1 M HCl, saturated $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Filtration through a plug of silica with 30% ethyl acetate/hexanes and concentration in vacuo provided an aldehyde, which was used immediately in the next reaction.

Into a 50 mL flask was added the methoxyborane derived from 3-carene (1 M in diethyl ether, 1.20 mL, 1.20 mmol) and 8 mL diethyl ether. The solution was cooled to 0°C, and allylmagnesium bromide (0.84 M in diethyl ether, 1.25 mL, 1.05 mmol) was added dropwise via syringe. The solution was warmed to room temperature, where it was stirred for 1 h. The solution was cooled to −78°C, and aldehyde from above (0.246 g, 0.582 mmol) in 5 mL of diethyl ether was added dropwise via syringe. After 2 h the reaction was quenched by the dropwise addition of 1 mL of methanol, and the solution was warmed to room temperature. 10 mL of THF, 5 mL of 10% NaOH, and 10 mL of 30% H_2O_2 were added in succession. The solution was allowed to stir for 3 h and poured into 50% ethyl acetate/hexanes and water. The layers were separated, and the aqueous layer was extracted with 50% ethyl acetate/hexanes. The combined organics were washed with saturated Na_2SO_3 and dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography provided 0.251 g (93%) of secondary alcohol **23**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.22 (m, 10H), 5.94–5.60 (m, 4H), 5.14–4.98 (m, 4H), 4.60 (AB, J_{AB}=12.0 Hz, $\Delta\nu_{AB}$=17.1 Hz, 2H), 4.49 (s, 2H), 3.98 (d, J=5.7 Hz, 2H), 3.68 (d, J=3.3 Hz, 1H), 3.60–3.45 (m, 3H), 3.19 (dt, J=6.6, 5.4 Hz, 1H), 2.46–2.06 (m, 6H), 1.62 (m, 1H), 1.40 (m, 1H), 0.88 (t, J=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.8, 22.8, 34.4, 34.5, 37.5, 70.7, 71.9, 72.6, 72.9, 79.5, 81.1, 81.3, 116.7, 117.3, 127.5, 127.7, 127.9, 128.30, 128.33, 129.1, 130.0, 134.4, 135.0, 138.1, 138.3; IR (film) 3660–3160 (br), 3040, 2920, 1455, 1365, 1065 cm^{-1}; $[\alpha]^{24}_D$=−10.3 (c 0.68, CH_2Cl_2); Anal. Calcd for $C_{30}H_{40}O_4$: C, 77.55; H, 8.68. Found: C, 77.45; H, 8.71.

6.1.23. (1*S*,2*S*,4*E*)-Acetic acid 1-allyl-6-benzyloxy-2-((1*R*,2*R*)-2-benzyloxy-1-ethyl-pent-4-enyloxy)-hex-4-enyl ester (35). Into a 50 mL flask was placed alcohol **23** (0.647 g, 1.39 mmol) in 14 mL of dichloromethane. Pyridine (1.13 mL, 14.0 mmol) was added via syringe. 4-Dimethylaminopyridine (0.017 g, 0.14 mmol) was added followed by dropwise addition of acetic anhydride (0.66 mL, 7.0 mmol) via syringe. The reaction was allowed to stir overnight and was poured into diethyl ether. The solution was washed with 1 M HCl, saturated $NaHCO_3$, and brine. The organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography provided 0.678 g (96%) of acetate ester **35**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.22 (m, 10H), 5.88 (m, 1H), 5.76–5.58 (m, 3H), 5.14–4.97 (m, 4H), 4.94 (dt, J=9.2, 4.0 Hz, 1H), 4.57 (AB, J_{AB}=23.6 Hz, $\Delta\nu_{AB}$=12.0 Hz, 2H), 4.49 (s, 2H), 3.97 (d, J=5.6 Hz, 2H), 3.50 (m, 1H), 3.41–3.34 (m, 2H), 2.44–2.18 (m, 6H), 2.02 (s, 3H), 1.64 (m, 1H), 1.40 (m, 1H), 0.88 (t, J_{AB}=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.5, 21.1, 22.2, 33.3, 33.8, 34.1, 70.6, 72.0, 72.4, 73.2, 77.7, 79.1, 80.3, 116.6, 117.5, 127.5, 127.7, 127.9, 128.26, 128.34, 129.4, 129.8, 134.0, 135.8, 138.3, 138.6, 170.5; IR (film) 2940, 1740, 1440, 1370, 1240, 1065 cm^{-1}; $[\alpha]^{24}_D$=+17.9 (c 1.43, CH_2Cl_2); Anal. Calcd for $C_{32}H_{42}O_5$: C, 75.86; H, 8.36. Found: C, 75.93; H, 8.41.

6.1.24. (1*S*,2*S*,4*E*)-Acetic acid 1-allyl-2-((1*R*,2*R*)-1-ethyl-2-hydroxy-pent-4-enyloxy)-6-oxo-hex-4-enyl ester (36). Into a 50 mL flask was placed dibenzyl ether **35** (0.257 g, 0.507 mmol) in 10 mL of dichloromethane. 1 mL of aqueous pH 7 buffer was added followed by DDQ (0.921 g, 4.06 mmol). The reaction was allowed to stir overnight. The reaction was quenched by the slow addition of saturated $NaHCO_3$. The mixture was poured into ethyl acetate, and the layers were separated. The organic layer was washed with brine, and the combined aqueous layers extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography provided 0.124 g (75%) of (1*S*,2*S*,4*E*)-acetic acid 1-allyl-2-((1*R*,2*R*)-1-ethyl-2-hydroxy-pent-4-enyloxy)-6-oxo-hex-4-enyl ester, which was used immediately in the next reaction.

Into a 100 mL flask was placed (1*S*,2*S*,4*E*)-acetic acid 1-allyl-2-((1*R*,2*R*)-1-ethyl-2-hydroxy-pent-4-enyloxy)-6-oxo-hex-4-enyl ester (0.838 g, 2.59 mmol) in 20 mL of ethanol. The solution was cooled to 0°C, and sodium borohydride (0.0490 g, 1.30 mmol) was added in a single portion. After 30 min the reaction was quenched by the dropwise addition of 10% HCl. The mixture was poured into ethyl acetate, and the layers were separated. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated $NaHCO_3$ and brine, and dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatrography provided 0.773 g (92%) of diol **36**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.93–5.61 (m, 4H), 5.14–5.00 (m, 4H), 4.96 (m, 1H), 4.07 (s, 2H), 3.61 (m, 1H), 3.55 (dt, *J*=6.3, 5.1 Hz, 1H), 3.29 (dt, *J*=5.4, 5.4 Hz, 1H), 2.49–2.10 (m, 7H), 2.04 (s, 3H), 1.69–1.38 (m, 3H), 0.88 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.2, 21.1, 23.0, 33.7, 34.2, 37.6, 63.4, 71.3, 73.5, 77.4, 81.9, 117.3, 117.9, 127.7, 132.3, 133.4, 134.9, 170.5; IR (film) 3700–3120 (br), 2940, 1730, 1435, 1375, 1240 cm^{-1}; $[\alpha]^{24}_D$=+9.4 (*c* 1.66, CH_2Cl_2); Anal. Calcd for $C_{18}H_{30}O_5$: C, 66.23; H, 9.26. Found: C, 65.40; H, 9.33.

6.1.25. (1*S*,2*S*,4*E*)-Acetic acid 1-allyl-2-((1*R*,2*R*)-1-ethyl-2-triethylsilanyloxy-pent-4-enyloxy)-6-triethylsilanyloxy-hex-4-enyl ester. Into a 50 mL flask was placed diol **36** (0.281 g, 0.861 mmol) in 9 mL of dichloromethane, and the solution was cooled to 0°C. 2,6-Lutidine (0.46 mL, 3.9 mmol) was added via syringe followed by the dropwise addition of triethylsilyl trifluoromethanesulfonate (0.45 mL, 2.0 mmol) via syringe. The reaction was allowed to warm to room temperature and was stirred for 1 h. The reaction was poured into dichloromethane and washed with brine. The aqueous layer was extracted with dichloromethane, and the combined organic layers were dried over Na_2SO_4. Concentration in vacuo and purification via flash chromatography yielded 0.463 g (97%) of the silyl ether: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91–5.53 (m, 4H), 5.11–4.90 (m, 5H), 4.09 (d, *J*=4.5 Hz, 2H), 3.75 (ddd, *J*=9.9, 3.6, 3.0 Hz, 1H), 3.41 (dt, *J*=6.0, 4.2 Hz, 1H), 3.20 (ddd, *J*=9.3, 3.6, 3.3 Hz, 1H), 2.46–2.20 (m, 5H), 2.08 (m, 1H), 2.03 (s, 3H), 1.67 (m, 1H), 1.32 (m, 1H), 1.03–0.85 (m, 21H), 0.57 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.5, 5.0, 6.7, 6.8, 11.3, 21.1, 21.4, 33.1, 34.1, 35.9, 63.4, 72.2, 73.2, 77.8, 83.0, 116.4, 117.5, 126.5, 132.3, 134.0, 136.5, 170.4; IR (film) 2950, 1745, 1460, 1375, 1240, 1060 cm^{-1}; $[\alpha]^{24}_D$=+33.7 (*c* 1.70, CH_2Cl_2); Anal. Calcd for $C_{30}H_{58}O_5Si_2$: C, 64.93; H, 10.53. Found: C, 65.14; H, 10.60.

6.1.26. (1*S*,2*S*,4*E*)-Acetic acid 1-allyl-2-((1*R*,2*R*)-1-ethyl-2-triethylsilanyloxy-pent-4-enyloxy)-6-hydroxy-hex-4-enyl ester (37). Into a 50 mL flask was placed triene from above (1.018 g, 1.835 mmol) in 15 mL of dichloromethane and 3 mL of ethanol. The solution was cooled to 5°C. Catalytic PPTS (0.046 g, 0.18 mmol) was added, and the reaction was allowed to stir for 2 h. The reaction was quenched with saturated $NaHCO_3$ and poured into dichloromethane and brine. The layers were separated, and the aqueous layer was extracted with dichloromethane. Concentration in vacuo and purification via flash chromatography gave 0.709 g (88%) of alcohol **37**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91–5.60 (m, 4H), 5.13–4.90 (m, 5H), 4.07 (s, 2H), 3.75 (ddd, *J*=9.9, 3.6, 2.7 Hz, 1H), 3.44 (dt, *J*=4.2, 3.9 Hz, 1H), 3.19 (ddd, *J*=9.3, 3.9, 3.0 Hz, 1H), 2.46–2.21 (m, 5H), 2.09 (m, 1H), 2.05 (s, 3H), 1.66 (m, 1H), 1.46–1.23 (m, 2H), 0.93 (t, *J*=7.9 Hz, 9H), 0.93 (t, *J*=7.9 Hz, 3H), 0.56 (q, *J*=7.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.0, 6.9, 11.3, 21.2, 21.4, 33.2, 34.3, 35.9, 63.6, 72.2, 73.2, 77.7, 83.1, 116.5, 117.6, 128.1, 132.2, 133.9, 136.5, 170.6; IR (film) 3660–3120 (br), 2960, 1745, 1375, 1240, 1100 cm^{-1}; $[\alpha]^{24}_D$=+44.1 (*c* 1.20, CH_2Cl_2); Anal. Calcd for $C_{24}H_{44}O_5Si$: C, 65.41; H, 10.06. Found: C, 65.45; H, 10.20.

6.1.27. (1*S*)-Acetic acid 1-[(1*S*)-1-((1*R*,2*R*)-1-ethyl-2-triethylsilanyloxy-pent-4-enyloxy)-2-((2*S*,3*S*)-3-hydroxymethyl-oxiranyl)-ethyl]-but-3-enyl ester (38). Into a 25 mL flask was placed 4 Å molecular sieves (0.029 g) and 2.5 mL of dichloromethane. The solution was cooled to −20°C, and (+)-diethyl tartrate (0.0047 mL, 0.027 mmol) and Ti(O*i*-Pr)$_4$ (0.0056 mL, 0.019 mmol) were added successively. After 10 min *t*-BuOOH (7.4 M in dichloromethane, 0.074 mL, 0.55 mmol) was added dropwise via syringe. After 30 min alcohol **37** (0.120 g, 0.273 mmol) in 1 mL of dichloromethane was added dropwise via syringe. The reaction was allowed to stir for 40 h. The reaction was warmed to 0°C, and 0.2 mL of 30% NaOH saturated with NaCl was added dropwise via syringe. The solution was warmed to room temperature and stirred for 30 min. After filtering the suspension through Celite, the solution was dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography provided 0.121 g (97%) of epoxy alcohol **38**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89–5.65 (m, 2H), 5.11–4.96 (m, 5H), 3.89 (d, *J*=12.4 Hz, 1H), 3.76 (dt, *J*=8.4, 4.0 Hz, 1H), 3.68–3.57 (m, 2H), 3.30 (dt, *J*=8.0, 4.0 Hz, 1H), 3.11 (ddd, *J*=7.0, 4.8, 2.4 Hz, 1H), 2.94 (dt, *J*=4.0, 2.8 Hz, 1H), 2.44 (dddd, *J*=14.8, 4.8, 3.2, 1.6 Hz, 1H), 2.32 (m, 1H), 2.20 (m, 1H), 2.09 (m, 1H), 2.02 (s, 3H), 1.79–1.60 (m, 4H), 1.38 (m, 1H), 0.94 (t, *J*=7.6 Hz, 3H), 0.93 (t, *J*=8.0 Hz, 9H), 0.58 (q, *J*=8.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.0, 6.9, 11.0, 21.1, 21.6, 32.5, 32.8, 36.3, 53.1, 59.2, 61.5, 72.8, 75.4, 83.2, 116.6, 117.5, 134.0, 136.2, 170.4; IR (film) 3720–3140 (br), 2960, 1745, 1420, 1235, 1095 cm^{-1}; $[\alpha]^{24}_D$=−0.26 (*c* 2.91, CH_2Cl_2).

6.1.28. (2*S*,3*S*,8*R*,9*R*)-Acetic acid 9-ethyl-2-((2*S*,3*S*)-3-hydroxymethyl-oxiranylmethyl)-8-triethylsilanyloxy-2,3,4,7,8,9-hexahydro-oxonin-3-yl ester (39). Into a 250 mL

flask fitted with a reflux condenser was added epoxy alcohol **38** (0.121 g, 0.265 mmol) and 88 mL of dichloromethane. The solution was degassed by rapidly bubbling nitrogen through the stirring solution for 30 min. The solution was heated to reflux, and the Grubbs' catalyst (0.0110 g, 0.0134 mmol) was added. After 6 h the solution was cooled to room temperature and allowed to stir open to the atmosphere overnight. Concentration in vacuo and purification by flash chromatography gave 0.107 g (94%) of cyclic ether **39**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63–5.51 (m, 2H), 4.90 (dt, J=9.6, 4.0 Hz, 1H), 3.90–3.77 (m, 2H), 3.69–3.59 (m, 2H), 3.18 (m, 1H), 2.98–2.83 (m, 4H), 2.13–1.60 (m, 6H), 2.03 (s, 3H), 1.52 (m, 1H), 0.94 (t, J=8.0 Hz, 9H), 0.86 (t, J=7.6 Hz, 3H), 0.60 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.0, 6.9, 10.4, 21.2, 22.9, 28.0, 32.2, 33.6, 53.3, 58.6, 61.5, 70.8, 73.5, 75.8, 82.9, 126.8, 128.9, 170.7; IR (film) 3700–3120 (br), 2950, 1735, 1450, 1370, 1240, 1065 cm^{-1}; $[\alpha]^{24}_D$=−17.7 (c 1.35, CH_2Cl_2).

6.1.29. (1*S*)-1-((2*R*,3a*S*,5*R*,6*R*,10a*S*)-5-Ethyl-6-triethylsilanyloxy-2,3,3a,5,6,7,10,10a-octahydro-furo[3,2-*b*]oxonin-2-yl)-ethane-1,2-diol (40). Into a 25 mL flask was placed acetate ester **39** (0.104 g, 0.243 mmol) in 7 mL of methanol. Finely ground potassium carbonate (0.101 g, 0.731 mmol) was added in a single portion. The solution was stirred for 2 h, and poured into dichloromethane and half-saturated NH_4Cl. The layers were separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography provided 0.086 g (92%) of diol **40**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52–5.39 (m, 2H), 4.17 (dt, J=9.8, 4.9 Hz, 1H), 4.05 (dt, J=11.4, 4.9 Hz, 1H), 3.82–3.72 (m, 3H), 3.66 (m, 1H), 3.55 (m, 1H), 3.01–2.83 (m, 3H), 2.42 (s, 1H), 2.23 (s, 1H), 2.15–1.93 (m, 4H), 1.69 (m, 1H), 1.57 (m, 1H), 0.96 (t, J=7.9 Hz, 9H), 0.86 (t, J=7.6 Hz, 3H), 0.61 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.1, 7.0, 10.5, 23.7, 28.9, 32.9, 35.9, 63.8, 71.2, 72.8, 78.3, 82.2, 82.5, 86.3, 127.3, 128.0; IR (film) 3720–3090 (br), 2930, 1455, 1240, 1135, 1040 cm^{-1}; $[\alpha]^{24}_D$=−16.2 (c 0.79, CH_2Cl_2); Anal. Calcd for $C_{20}H_{38}O_5Si$: C, 62.14; H, 9.91. Found: C, 61.93; H, 9.99.

6.1.30. (2*R*,3a*S*,5*R*,6*R*,10a*S*)-5-Ethyl-6-triethylsilanyloxy-2,3,3a,5,6,7,10,10a-octahydro-furo[3,2-*b*]oxonine-2-carbaldehyde (41). Into a 25 mL flask was placed diol **40** (0.0860 g, 0.223 mmol), 4 mL of THF, 2.7 mL of water, and 1.3 mL of aqueous pH 7 buffer. Sodium periodate (0.0950 g, 0.444 mmol) was added in a single portion, and the mixture was stirred for 45 min. The reaction was poured into 10% $Na_2S_2O_3$ and ethyl acetate. The layers were separated, and the organic layer was washed with brine. The combined aqueous layers were extracted with ethyl acetate, and the combined organic layers were dried over Na_2SO_4. The solution was concentrated in vacuo and used immediately in the next reaction.

6.1.31. (2*E*)-3-((2*R*,3a*S*,5*R*,6*R*,10a*S*)-5-Ethyl-6-triethylsilanyloxy-2,3,3a,5,6,7,10,10a-octahydro-furo[3,2-*b*]oxonin-2-yl)-acrylic acid ethyl ester. Into a 25 mL flask equipped with a reflux condenser was placed aldehyde **41** (0.0790 g, 0.223 mmol) in 7 mL of dichloromethane. Carbethoxymethylenetriphenylphosphorane (0.0930 g, 0.267 mmol) was added, and the solution was heated to reflux for 16 h. The solution was cooled and concentrated in vacuo. Purification by flash chromatography gave 0.0910 g (96%) of (2*E*)-3-((2*R*,3a*S*,5*R*,6*R*,10a*S*)-5-ethyl-6-triethylsilanyloxy-2,3,3a,5,6,7,10,10a-octahydro-furo[3,2-*b*]oxonin-2-yl)-acrylic acid ethyl ester: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (dd, J=15.6, 5.2 Hz, 1H), 5.99 (dd, J=15.6, 1.6 Hz, 1H), 5.52–5.42 (m, 2H), 4.75 (ddt, J=7.0, 6.8, 1.4 Hz, 1H), 4.16 (q, J=6.8 Hz, 2H), 4.09 (dt, J=11.2, 4.4 Hz, 1H), 3.82–3.74 (m, 2H), 3.01–2.87 (m, 3H), 2.22 (ddd, J=13.2, 6.4, 2.4 Hz, 1H), 2.14 (dt, J=12.0, 4.2 Hz, 1H), 2.08 (dt, J=12.8, 4.9 Hz, 1H), 1.89 (ddd, J=12.8, 8.8, 6.4 Hz, 1H), 1.69 (m, 1H), 1.56 (m, 1H), 1.26 (t, J=7.2 Hz, 3H), 0.95 (t, J=8.0 Hz, 9H), 0.85 (t, J=7.6 Hz, 3H), 0.61 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.1, 7.0, 10.5, 14.2, 23.6, 28.8, 32.9, 41.0, 60.4, 71.2, 75.9, 81.9, 82.2, 86.2, 120.4, 127.4, 128.0, 147.9, 166.5; IR (film) 2940, 1760, 1465, 1305, 1270, 1170, 1065 cm^{-1}; $[\alpha]^{24}_D$=−16.2 (c 0.79, CH_2Cl_2); Anal. Calcd for $C_{23}H_{40}O_5Si$: C, 65.05; H, 9.49. Found: C, 65.21; H, 9.67.

6.1.32. (2*E*)-3-((2*R*,3a*S*,5*R*,6*R*,10a*S*)-5-Ethyl-6-triethylsilanyloxy-2,3,3a,5,6,7,10,10a-octahydro-furo[3,2-*b*]oxonin-2-yl)-prop-2-en-1-ol (42). Into a 25 mL flask was added (2*E*)-3-((2*R*,3a*S*,5*R*,6*R*,10a*S*)-5-ethyl-6-triethylsilanyloxy-2,3,3a,5,6,7,10,10a-octahydro-furo[3,2-*b*]oxonin-2-yl)-acrylic acid ethyl ester (0.0910 g, 0.215 mmol) and 5 mL of THF. The solution was cooled to −78°C, and (i-Bu)$_2$AlH (1.0 M in hexanes, 0.87 mL, 0.87 mmol) was added dropwise via syringe. The reaction was stirred for 2.5 h and quenched by the dropwise addition of 1 mL of methanol. After the solution was allowed to warm to room temperature, 6 mL of saturated potassium/sodium tartrate was added dropwise by pipet. After 30 min, the mixture was poured into ethyl acetate and brine. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography provided 0.0680 g (83%) of allylic alcohol **42**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.86 (ddt, J=15.4, 5.2, 0.8 Hz, 1H), 5.65 (ddt, J=15.4, 7.2, 1.4 Hz, 1H), 5.51–5.41 (m, 2H), 4.62 (m, 1H), 4.15–4.05 (m, 3H), 3.82–3.74 (m, 2H), 3.01–2.87 (m, 3H), 2.18–2.03 (m, 3H), 1.83 (ddd, J=13.0, 8.8, 6.0 Hz, 1H), 1.67 (m, 1H), 1.56 (m, 1H), 1.40 (s, 1H), 0.97 (t, J=8.0 Hz, 9H), 0.86 (t, J=7.4 Hz, 3H), 0.61 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.2, 7.0, 10.5, 23.7, 29.0, 32.9, 41.7, 63.0, 71.3, 81.6, 82.6, 86.2, 127.6, 127.8, 131.0, 131.7; IR (film) 3700–3110 (br), 2940, 1460, 1360, 1245, 1065 cm^{-1}; $[\alpha]^{24}_D$=−10.4 (c 0.83, CH_2Cl_2); Anal. Calcd for $C_{21}H_{38}O_4Si$: C, 65.92; H, 10.01. Found: C, 65.87; H, 10.17.

6.1.33. [(2*S*,3*S*)-3-((2*R*,3a*S*,5*R*,6*R*,10a*S*)-5-Ethyl-6-triethylsilanyloxy-2,3,3a,5,6,7,10,10a-octahydro-furo[3,2-*b*]-oxonin-2-yl)-oxiranyl]-methanol (43). Into a 25 mL flask was placed 4 Å molecular sieves (0.050 g) and 4 mL of dichloromethane. The solution was cooled to −20°C, and (+)-diethyl tartrate (0.0074 mL, 0.043 mmol) and Ti(Oi-Pr)$_4$ (0.0089 mL, 0.030 mmol) were added successively. After 10 min t-BuOOH (7.4 M in dichloromethane, 0.12 mL, 0.89 mmol) was added dropwise via syringe. After 30 min alcohol **42** (0.165 g, 0.432 mmol) in 2 mL of dichloromethane was added dropwise via syringe. The reaction was allowed to stir for 40 h. The reaction was warmed to 0°C, and 0.3 mL of 30% NaOH saturated with NaCl was added dropwise via syringe. The solution was warmed to

room temperature and stirred for 30 min. After filtering the suspension through Celite, the solution was dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography provided 0.161 g (94%) of epoxide **43**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.53–5.38 (m, 2H), 4.20 (m, 1H), 4.02 (dt, J=11.1, 4.5 Hz, 1H), 3.93 (m, 1H), 3.84 (m, 1H), 3.76 (ddd, J=10.2, 5.4, 3.0 Hz, 1H), 3.64 (ddd, J=12.8, 7.7, 2.1 Hz, 1H), 3.20 (m, 1H), 3.03–2.83 (m, 3H), 3.00 (m, 1H), 2.22–2.00 (m, 4H), 1.78–1.49 (m, 3H), 0.95 (t, J=7.8 Hz, 9H), 0.86 (t, J=7.5 Hz, 3H), 0.61 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.1, 7.0, 10.5, 23.6, 28.8, 32.9, 37.8, 55.9, 57.3, 60.9, 71.2, 75.1, 82.1, 82.3, 86.0, 127.5, 127.8; IR (film) 3740–3140 (br), 2960, 1460, 1270, 1245, 1060 cm^{-1}; $[\alpha]^{27}_D$=−36.7 (c 0.64, CH_2Cl_2).

6.1.34. [(2*R*,3a*S*,5*R*,6*R*,10a*S*)-2-((2*S*,3*R*)-3-Chloromethyl-oxiranyl)-5-ethyl-2,3,3a,5,6,7,10,10a-octahydro-furo-[3,2-*b*]oxonin-6-yloxy]-triethyl-silane (44). Into a 25 mL flask equipped with a reflux condenser was placed epoxy alchohol **43** (0.0630 g, 0.158 mmol) and 5 mL of dichloromethane. Triphenylphosphine (0.050 g, 0.19 mmol) was added followed by *N*-chlorosuccinimide (0.026 g, 0.19 mmol), and the solution was heated to reflux for 1 h. The solution was cooled and poured into half-saturated brine with dichloromethane. The layers were separated, and the aqueous layer was extracted with dichloromethane. The organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography provided 0.0550 g (84%) of epoxy chloride **44**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.53–5.38 (m, 2H), 4.23 (dt, J=7.4, 3.3 Hz, 1H), 4.01 (dt, J=11.1, 4.5 Hz, 1H), 3.84 (m, 1H), 3.77 (m, 1H), 3.56 (d, J=5.4 Hz, 2H), 3.30 (dt, J=5.4, 2.1 Hz, 1H), 3.02–2.80 (m, 4H), 2.23–2.00 (m, 4H), 1.78–1.39 (2H), 0.95 (t, J=8.0 Hz, 9H), 0.85 (t, J=7.5 Hz, 3H), 0.62 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.1, 7.0, 10.5, 23.6, 28.8, 32.9, 37.7, 44.3, 54.7, 60.5, 71.2, 74.5, 82.0, 82.4, 85.9, 127.5, 127.9; IR (film) 2960, 1465, 1250, 1070, 980 cm^{-1}; $[\alpha]^{25}_D$=−33.9 (c 0.74, CH_2Cl_2); Anal. Calcd for $C_{21}H_{37}ClO_4Si$: C, 60.48; H, 8.94. Found: C, 60.27; H, 8.89.

6.1.35. (1*R*)-1-((2*R*,3a*S*,5*R*,6*R*,10a*S*)-5-Ethyl-6-triethyl-silanyloxy-2,3,3a,5,6,7,10,10a-octahydro-furo[3,2-*b*]oxo-nin-2-yl)-prop-2-yn-1-ol (45). Into a 50 mL flask was added 8 mL of THF and diisopropylamine (0.34 mL, 2.4 mmol), and the solution was cooled to −40°C. Butyl lithium (1.6 M in hexanes, 1.43 mL, 2.29 mmol) was added dropwise via syringe. After 15 min chloride **44** (0.119 g, 0.286 mmol) in 4 mL of THF was added dropwise via syringe. The solution was warmed to −30°C, where it was maintained for 30 min. The reaction was quenched by the addition of half-saturated NH_4Cl, and the solution was warmed to room temperature. The mixture was poured into ethyl acetate, and the layers were separated. The organic layer was washed with brine, and the combined aqueous layers were extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography gave 0.0950 g (87%) of propargylic alcohol **45**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.55–5.38 (m, 2H), 4.28 (dd, J=14.0, 6.3 Hz, 1H), 4.17 (dd, J=6.0, 1.8 Hz, 1H), 4.06 (dt, J=11.1, 4.5 Hz, 1H), 3.86–3.73 (m, 2H), 3.02–2.85 (m, 3H), 2.43 (d, J=2.4 Hz, 1H), 2.39 (s, 1H), 2.23–2.00 (m, 4H), 1.78–1.48 (m, 2H), 0.95 (t, J=8.0 Hz, 9H), 0.86 (t, J=7.5 Hz, 3H), 0.62 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.1, 7.0, 10.5, 23.6, 28.6, 32.9, 36.9, 64.7, 71.3, 73.8, 80.1, 82.0, 82.2, 82.3, 86.2, 127.3, 128.1; IR (film) 3700–3160 (br), 3320, 2960, 1465, 1270, 1245 cm^{-1}; $[\alpha]^{25}_D$=−22.5 (c 0.64, CH_2Cl_2); Anal. Calcd for $C_{21}H_{36}O_4Si$: C, 66.27; H, 9.53. Found: C, 65.52; H, 9.45.

6.1.36. 2,4,6-Triisopropyl-benzenesulfonic acid (1*R*)-1-((2*R*,3a*S*,5*R*,6*R*,10a*S*)-5-ethyl-6-triethylsilanyloxy-2,3,3a,5,6,7,10,10a-octahydro-furo[3,2-*b*]oxonin-2-yl)-prop-2-ynyl ester (19). Into a 25 mL flask equipped with a reflux condenser was placed alcohol **45** (0.0840 g, 0.221 mmol) and 5 mL of dichloromethane. 4-Dimethylaminopyridine (0.0940 g, 0.769 mmol) and 2,4,6-triisopropylbenzenesulfonyl chloride (0.167 g, 0.551 mmol) were added, and the solution was heated to reflux for 2.5 h. The solution was cooled to room temperature and filtered through a plug of silica gel washing with dichloromethane. The filtrate was condensed in vacuo, and purification by flash chromatography provided 0.137 g (96%) of trisylate **46**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (s, 2H), 5.52–5.37 (m, 2H), 5.07 (dd, J=5.2, 2.0 Hz, 1H), 4.38 (dd, J=12.8, 7.2 Hz, 1H), 4.17–4.00 (m, 3H), 3.84–3.72 (m, 2H), 2.98–2.82 (m, 4H), 2.30–2.15 (m, 2H), 2.26 (d, J=2.0 Hz, 1H), 2.11–2.02 (m, 2H), 1.67 (m, 1H), 1.55 (m, 1H), 1.25 (m, 18H), 0.95 (t, J=8.0 Hz, 9H), 0.85 (t, J=7.4 Hz, 3H), 0.61 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.1, 7.0, 10.6, 23.6, 23.8, 24.6, 24.7, 28.5, 29.7, 32.9, 34.2, 36.8, 71.2, 71.4, 77.2, 77.8, 82.2, 82.6, 86.4, 123.6, 127.2, 128.1, 130.5, 150.7, 153.7; IR (film) 3300, 2970, 1605, 1460, 1355, 1185, 1070 cm^{-1}; $[\alpha]^{25}_D$=−34.0 (c 0.72, CH_2Cl_2); Anal. Calcd for $C_{36}H_{58}O_6SSi$: C, 66.83; H, 9.04. Found: C, 66.68; H, 8.94.

6.1.37. [(2*R*,3a*S*,5*R*,6*R*,10a*S*)-2-((3*R*)-3-Bromo-propa-1,2-dienyl)-5-ethyl-2,3,3a,5,6,7,10,10a-octahydro-furo-[3,2-*b*]oxonin-6-yloxy]-triethyl-silane (47). Into a 50 mL flask was added lithium bromide (0.260 g, 2.99 mmol) and cuprous bromide (0.428 g, 2.98 mmol) and 12 mL of THF. The solution was allowed to stir at room temperature for 20 min. Into a separate 25 mL flask equipped with a reflux condenser was placed trisylate **46** (0.0680 g, 0.105 mmol) in 3 mL of THF. The $LiCuBr_2$ solution (0.25 M in THF, 2.1 mL, 0.53 mmol) was added via syringe, and the solution was heated to reflux for 8.5 h. The mixture was cooled to room temperature and quenched by the addition of saturated NH_4Cl. The mixture was extracted with diethyl ether, and the organic layer was washed with brine. The combined aqueous layers were extracted with diethyl ether. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash chromatography provided 0.0042 g (9%) of a propargylic bromide S_N2 addition byproduct and 0.0361 g (78%) of an 8:1 mixture of isomeric bromallenes in favor of the desired diastereomer **47**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.05 (dd, J=5.7, 1.7 Hz, 1H), 5.54–5.40 (m, 2H), 5.36 (dd, J=5.7, 5.7 Hz, 1H), 4.77 (m, 1H), 4.03 (dt, J=11.4, 4.5 Hz, 1H), 3.85 (m, 1H), 3.76 (ddd, J=10.1, 5.4, 2.9 Hz, 1H), 3.03–2.84 (m, 3H), 2.27–2.00 (m, 4H), 1.77–1.50 (m, 2H), 0.95 (t, J=8.0 Hz, 9H), 0.87 (t, J=7.5 Hz, 3H), 0.61 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 5.1, 7.0, 10.5, 23.8, 28.6, 33.0, 40.3, 71.2, 73.6, 73.7, 81.2, 82.0, 86.0, 101.8, 127.5, 127.9, 201.5; IR (film)

2950, 1975, 1465, 1250, 1200,1110, 1065 cm^{-1}; $[\alpha]^{25}_D$= −120.5 (*c* 0.51, CH_2Cl_2).

6.1.38. (2*R*,3a*S*,5*R*,6*R*,10a*S*)-2-((3*R*)-3-Bromo-propa-1,2-dienyl)-5-ethyl-2,3,3a,5,6,7,10,10a-octahydro-furo[3,2-*b*]-oxonin-6-ol. Into a 25 mL flask was placed silyl ether **47** (0.0650 g, 0.147 mmol) and PPTS (0.0810 g, 0.322 mmol) in 3 mL of dichloromethane and 1 mL of methanol. The solution was stirred for 1 h and quenched with saturated $NaHCO_3$. The mixture was poured into brine and dichloromethane, and the layers were separated. The aqueous layer was extracted with dichloromethane, and the combined organic layers were dried over Na_2SO_4. Concentration in vacuo and purification by flash chromatography provided 0.0480 g (99%) of (2*R*,3a*S*,5*R*,6*R*, alcohol **48**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (dd, *J*=5.6, 2.0 Hz, 1H); 5.58–5.44 (m, 2H), 5.36 (dd, *J*=5.6, 5.6 Hz, 1H), 4.73 (m, 1H), 4.08 (dt, *J*=11.2, 4.4 Hz, 1H), 3.94 (m, 1H), 3.71 (s, 1H), 3.04 (m, 1H), 2.90 (dd, *J*=11.2, 11.2 Hz, 1H), 2.76 (dd, *J*=10.4, 10.4 Hz, 1H), 2.32 (dt, *J*=11.6, 5.6 Hz, 1H), 2.22–2.04 (m, 3H), 1.75–1.58 (m, 2H), 1.48 (s, 1H), 0.88 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 10.2, 23.7, 28.8, 33.0, 40.1, 69.9, 73.5, 73.9, 81.0, 81.6, 84.8, 101.5, 127.5, 127.9, 201.5; IR (film) 3800–3120 (br), 2940, 1970, 1465, 1200, 1135, 1060 cm^{-1}; $[\alpha]^{26}_D$= −139.7 (*c* 0.48, CH_2Cl_2).

6.1.39. (2*R*,3a*S*,5*R*,6*S*,10a*S*)-6-Bromo-2-((3*R*)-3-bromo-propa-1,2-dienyl)-5-ethyl-2,3,3a,5,6,7,10,10a-octahydro-furo[3,2-*b*]oxonine (isolaurallene) (1). Into a 25 mL flask was placed alcohol **48** (0.0455 g, 0.138 mmol) and carbon tetrabromide (0.229 g, 0.691 mmol). The flask was purged with nitrogen for 10 min. 3 mL of freshly distilled toluene was added, and the solution was degassed by bubbling nitrogen through the solution for 15 min. Trioctylphosphine (0.62 mL, 0.83 mmol) was added dropwise via syringe, and the solution was stirred for 5 min. The flask was placed in an oil bath preheated to 70°C and stirred there for 3 h. The solution was cooled to room temperature and concentrated in vacuo to an approximate volume of 1 mL. The solution was pipeted directly onto a silica column, and purification by flash chromatography provided 0.0320 g (59%) of the natural product isolaurallene **1**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.07 (dd, *J*=5.5, 1.5 Hz, 1H), 5.75 (ddd, *J*=10.8, 10.8, 5.3 Hz, 1H), 5.65 (ddd, *J*=10.8, 10.8, 5.3 Hz, 1H), 5.40 (dd, *J*=5.5, 5.5 Hz, 1H), 4.72 (ddt, *J*=12.5, 6.5, 1.5 Hz, 1H), 4.15–4.08 (m, 2H), 3.94 (q, *J*=5.0 Hz, 1H), 3.42–3.31 (m, 2H), 2.75 (q, *J*=11.5 Hz, 1H), 2.35 (ddd, *J*=14.5, 4.8, 2.3 Hz, 1H), 2.20 (ddd, *J*=11.2, 11.2, 4.8 Hz, 1H), 2.10 (dd, *J*=6.5, 5.0 Hz, 2H), 1.88–1.73 (m, 2H), 0.92 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 7.6, 23.8, 29.2, 32.2, 40.2, 52.3, 73.7, 73.9, 80.9, 82.8, 85.0, 101.4, 126.7, 128.5, 201.6; IR (film) 2940, 1965, 1450, 1195, 1170, 1050 cm^{-1}; $[\alpha]^{24}_D$=−117.8 (*c* 0.09, $CHCl_3$).

Acknowledgements

This work was supported by a grant from the National Institutes of Health (GM 60567). We thank Dr Kazuya Kurata for providing spectra of (−)-isolaurallene for comparison and we are especially grateful to Professor Akio Murai for assistance in obtaining the spectral data.

References

1. Faulkner, D. *J. Nat. Prod. Rep.* **1999**, *16*, 155–198. Faulkner, D. *J. Nat. Prod. Rep.* **1998**, *15*, 113–158. Faulkner, D. *J. Nat. Prod. Rep.* **1997**, *14*, 259–302. Faulkner, D. *J. Nat. Prod. Rep.* **1996**, *13*, 75–125 and earlier reviews in the same series. Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897–1909.
2. For recent approaches to the synthesis of eight-membered ring ethers, see: Crimmins, M. T.; Tabet, E. A. *J. Am. Chem. Soc.* **2000**, *122*, 5473–5476 and references therein.
3. Pawlak, J.; Tempesta, M. S.; Golik, J.; Zagorski, M. G.; Lee, M. S.; Nakanishi, K.; Iwashita, T.; Gross, M. L.; Tomer, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 1144–1150.
4. Murata, M.; Legrand, A. M.; Ishibashi, Y.; Yasumoto, T. *J. Am. Chem. Soc.* **1989**, *111*, 8929–8931. Murata, M.; Legrand, A. M.; Ishibashi, Y.; Fukui, M.; Yasumoto, T. *J. Am. Chem. Soc.* **1990**, *112*, 4380–4386.
5. Nagai, H.; Torigoe, K.; Satake, M.; Murata, M.; Yasumoto, T.; Hirota, H. *J. Am. Chem. Soc.* **1992**, *114*, 1102–1103. Nagai, H.; Murata, M.; Torigoe, K.; Satake, M.; Yasumoto, T. *J. Org. Chem.* **1992**, *57*, 5448–5453.
6. Uchio, Y.; Kodama, M.; Usui, S.; Fukazawa, Y. *Tetrahedron Lett.* **1992**, *33*, 1317–1320.
7. King, T. J.; Imre, S.; Oztunc, A.; Thomson, R. H. *Tetrahedron Lett.* **1979**, 1453–1454. Howard, B. M.; Schulte, G. R.; Fenical, W.; Solheim, B.; Clardy, J. *Tetrahedron* **1980**, *36*, 1747–1751. Norte, M.; Gonzalez, A. G.; Cataldo, F.; Rodriguez, M. L.; Brito, I. *Tetrahedron* **1991**, *47*, 9411–9418.
8. Notaro, G.; Piccialli, V.; Sica, D.; Mayol, L.; Giordano, F. *J. Nat. Prod.* **1992**, *55*, 626–632.
9. Kurata, K.; Furusaki, A.; Suehiro, K.; Katayama, C.; Suzuki, T. *Chem. Lett.* **1982**, 1031–1034.
10. For approaches to nine-membered ring ethers see: Fujiwara, K.; Awakura, D.; Tsunashima, M.; Nakamura, A.; Honma, T.; Murai, A. *J. Org. Chem.* **1999**, *64*, 2616–2617 and references therein.
11. Ishihara, J.; Shimada, Y.; Kanoh, N.; Takasugi, Y.; Fukuzawa, A.; Murai, A. *Tetrahedron* **1997**, *53*, 8371–8382.
12. Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108–2109.
13. A preliminary communication on the synthesis of isolaurallene has appeared, see: Crimmins, M. T.; Emmitte, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 1533–1534. For a discussion of conformational effects on rates of ring closing metathesis of medium ring ethers see: Crimmins, M. T.; Emmitte, K. A. *Synthesis* **2000**, 899–903. Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653–5660. Crimmins, M. T.; Choy, A. L. *J. Org. Chem.* **1997**, *62*, 7548–7549. For other applications of ring closing metathesis in the synthesis of medium ring ethers see: Clark, J. S.; Hamelin, O. *Angew. Chem., In. Ed. Engl.* **2000**, *39*, 372–374 and references therein.
14. Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, NY, 1994, pp 609–610.
15. Crimmins, M. T.; King, B. W. *J. Am. Chem. Soc.* **1998**, *120*, 9084–9085. Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *65*, 894–902.
16. Crimmins, M. T.; Kirincich, S. J.; Wells, A. J.; Choy, A. L. *Synth. Commun.* **1998**, *28*, 3675–3679.
17. Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129.
18. Swern, D.; Mancuso, A. J.; Huang, S.-L. *J. Org. Chem* **1978**, *43*, 2480–2482.

19. Brown, H. C.; Randad, R. S.; Bhat, K. S.; Zaidlewicz, M.; Racherla, U. S. *J. Am. Chem. Soc.* **1990**, *112*, 2389–2392.
20. Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110.
21. Crimmins, M. T.; Emmitte, K. A. *Org. Lett.* **1999**, *1*, 2029–2032.
22. Crimmins, M. T.; Emmitte, K. A.; Katz, J. D. *Org. Lett.* **2000**, *2*, 2165–2167.
23. Prashad, M.; Har, D.; Kim, H.-Y.; Repic, O. *Tetrahedron Lett.* **1998**, *39*, 7067–7070.
24. Asami, M.; Kimura, R. *Chem. Lett.* **1985**, 1221–1222.
25. Sugiyama, H.; Yokokawa, F.; Shioiri, T.; Katagiri, N.; Oda, O.; Ogawa, H. *Tetrahedron Lett.* **1998**, *39*, 7067–7070.
26. Schreiber, S. L.; Ikemoto, N. *J. Am. Chem. Soc.* **1992**, *114*, 2524–2536.
27. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.
28. Yadav, J. S.; Deshpande, P. K.; Sharma, G. V. M. *Tetrahedron* **1990**, *55*, 4235–4237.
29. Elsevier, C. J.; Vermeer, P.; Gedanken, A.; Runge, W. *J. Org. Chem.* **1985**, *50*, 364–367. Montmury, M.; Goré, J. *Synth. Commun.* **1980**, 873. Grese, T. A.; Hutchinson, K. D.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *58*, 2468–2477.
30. Tsushima, K.; Murai, A. *Tetrahedron Lett.* **1992**, *33*, 4345–4348.
31. Mulzer, J.; Angermonn, A.; Muench, W. *Liebigs Ann. Chem.* **1986**, *5*, 825–838.
32. Mulzer, J.; Angermonn, A. *Tetrahedron Lett.* **1983**, *24*, 2843–2846.