JOC The Journal of Organic Chemistry

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Study of the Total Synthesis of (−)-Exiguolide

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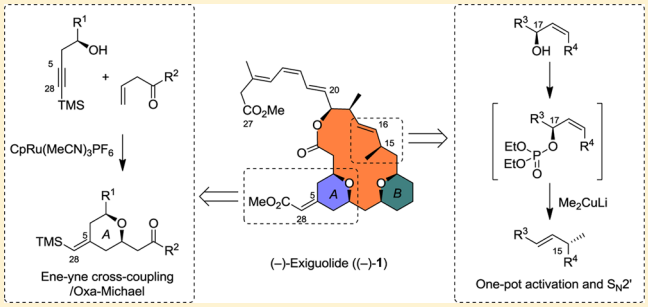
Supporting Information

ABSTRACT: In this article, we disclose the various routes and strategies we had to explore before finally achieving the total synthesis of (−)-exiguolide ((−)-**1**). Two first types of approaches were set, both relying on the Trost's domino ene−yne coupling/oxa-Michael reaction that we choose for its ability to control the geometry of the methylacrylate-bearing tetrahydropyrane ring *B*. In our first approach, we expected to assemble the two main fragments (C14−C21 and C1−C13) by creating the C13−C14 bond through a palladium(0)-catalyzed cross-coupling, but this step failed, unfortunately. In the second approach, which was more linear, we created the C16−C17 bond through condensation of a lithium acetylide on a Weinreb amide, and we assembled the C1−C5 and C6−C21 subunits through Trost's domino ene−yne coupling/oxa-Michael reaction. These two approaches served us to design an ameliorated third strategy, which finally led to the total synthesis of (−)-exiguolide.



INTRODUCTION

In 2006, the Ikegami group reported the isolation of (−)-exiguolide ((−)-**1**) from the marine sponge *Geodia exigua*.[1] This macrolide displays a number of salient motifs, which renders this target quite attractive and challenging for synthetic chemists. (−)-Exiguolide ((−)-**1**) is a 16-membered macrolactone bearing five C−C double bonds and seven stereogenic centers. The macrocycle is fused with two tetrahydropyran rings *A* and *B*, ring *A* bearing a methoxycarbonylmethylidene function at C5 with a *Z* configuration. The control of the geometry of this double bond represents a synthetic challenge; furthermore, Scheidt et al.[2] demonstrated that 28-(*E*)-exiguolide has only minimal activity against a series of cell lines, thus indicating Z-enoate geometry is essential for the biological activity. When the molecule was discovered, biological tests were performed that revealed its ability to inhibit the fertilization of sea urchin gametes,[1] a property indicating that **1** might possess relevant anticancer activity.[3] More recent studies showed that **1** is indeed endowed with antiproliferative activity on various cell lines such as NCI-H460 human lung large cell carcinoma, on A549 human lung adenocarcinoma cell lines significantly, and moderate growth inhibition against PC3 prostate cancer cells, MDA-MB-231 breast cancer, and BxPC3 pancreatic cancer cells.[4,2]

Several total syntheses of exiguolide (**1**) have been published since its discovery as well as a study of the synthesis of its tetrahydropyranes.[5] In 2008, Lee et al. reported the synthesis of *ent*-exiguolide ((+)-**1**), the enantiomer of the naturally occurring compound thus establishing the right absolute configuration for this product.[6] The strategy designed for this approach featured the macrocyclization by ring closing metathesis through formation of the C16−C17 double bond. The installation of methoxycarbonylmethylidene function at C5 was made by using a Horner−Wadsworth−Emmons reaction, which required a stoichiometric amount of a chiral phosphonoacetate to finally deliver a *Z*/*E* mixture of products with a relatively poor selectivity (5.8/1). This confirmed that the construction of this structural motif is challenging and that a better solution deserved to be found. The publication of our own total synthesis of (−)-exiguolide ((−)-**1**),[7] happened in 2010 concomitantly with that of Fuwa and Sasaki.[8] In their approach, a cross-metathesis reaction was used to assemble the two main fragments, and the control of the geometry of the methyl acrylate function of tetrahydropyrane ring *A* was again made through a Horner−Wadsworth−Emmons. Since, the same authors performed the synthesis of a series of analogues.[4] In 2011, Scheidt et al. described the third total synthesis of exiguolide (**1**). To achieve it, they used an interesting Prins cyclization and again the same Horner−Wadsworth−Emmons to build the methyl acrylate function of tetrahydropyrane ring *A* (67%, *Z*/*E*: 7/1).[2]

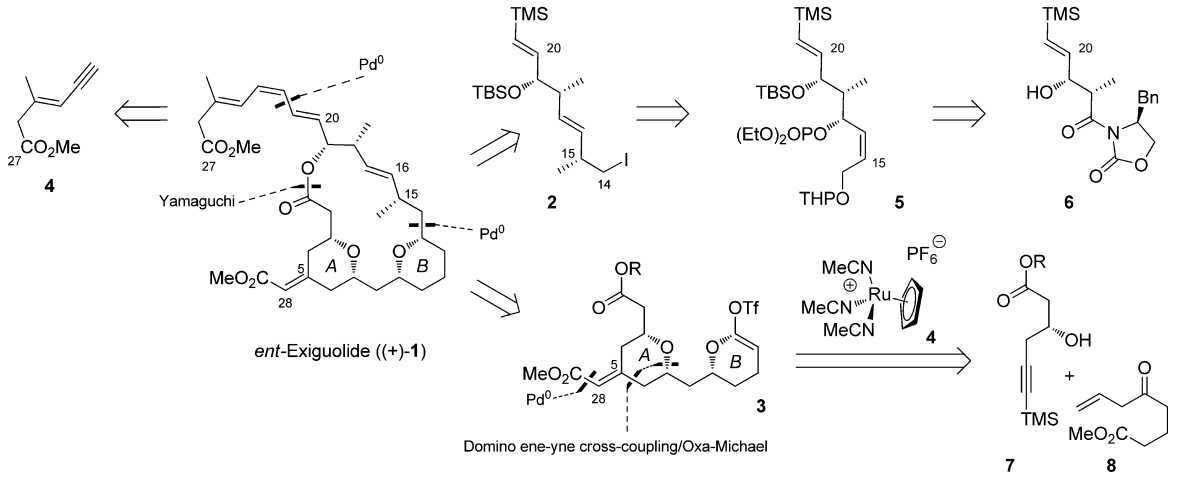
RESULTS AND DISCUSSION

1. First Approach. When we started our study, the right absolute configuration of (−)-exiguolide ((−)-**1**) was still undetermined. Unfortunately we had targeted the wrong enantiomer when we started our study of the total synthesis of **1**. As a consequence the configurations of the various stereogenic centers of our various fragments are inverted all along the first and second approaches. Our strategy relied on the Trost's domino ene−yne coupling/oxa-Michael reaction

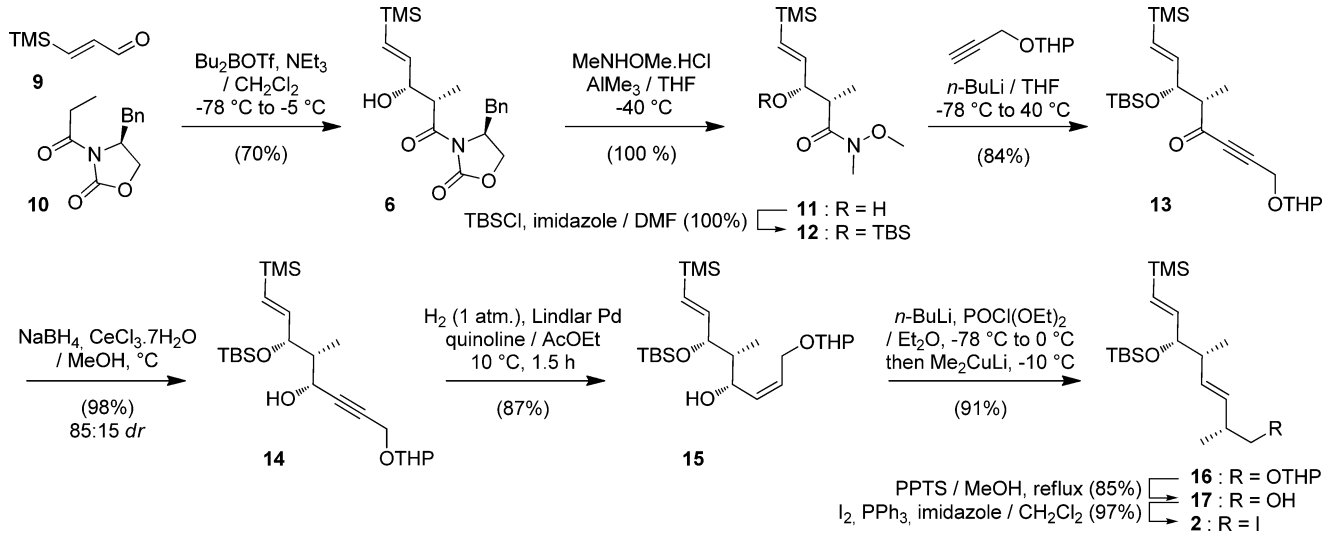
Received: May 30, 2012
Published: July 31, 2012

dx.doi.org/10.1021/jo301066p | J. Org. Chem. 2012, 77, 6728−6742

Scheme 1. First Retrosynthetic Plan toward *ent*-Exiguolide ((+)-1)



Scheme 2. Synthesis of Fragment 2



catalyzed by the cationic Ru^{II} complex $[CpRu(MeCN)_3]PF_6$ (**4**).[9] This reaction allows building the tetrahydropyrane ring of fragment **2** while coupling fragments **7** (yne) and **8** (ene), allowing a full control of the geometry of the vinylsilane precursor of the acrylate double bond (C5−C28) (Scheme 1). In this first approach we planned to assemble fragments **2** and **3** through a Pd^0-catalyzed cross-coupling. We envisioned controlling the allylic stereogenic center at C15 in intermediate **2** by substitution of the asymmetric allylic phosphate **5** by a methylcuprate through an S_N2' process.

1.2. Synthesis of Fragment 2. The synthesis of fragment **2** (Scheme 2) started with a classical *syn* Evans aldol reaction[10] that implied aldehyde **9** and propionyloxazolidinone (*S*)-**10** and that led to known alcohol (+)-**6**.[11] The latter was transformed into the corresponding Weinreb amide[12] **11** and then protected as silanyl ether **12** before being finally condensed with a lithium acetylide to furnish ketone **13**. Under Luche's conditions,[13] the reduction of the ketone function of **13** occurred diastereoselectively (85:15) furnishing propargylic alcohol **14**. Then, a semihydrogenation promoted by the Lindlar catalyst[14] conducted at 10 °C led very cleanly to the *Z* alkene **15**.

Then we investigated conditions for the diastereoselective conjugated substitution of activated *Z* allylic alcohol **15**. Here, the *Z* configuration of the double bond is important, because such geometry blocks allylic bond rotations for obvious steric reasons (Scheme 3). Hence, the leaving group remains blocked at one side of the average plane defined by the carbons of the allylic system, and as a consequence its conjugated substitution

Scheme 3. S_N2' Substitution of Z Vs E Allylic Alcohols

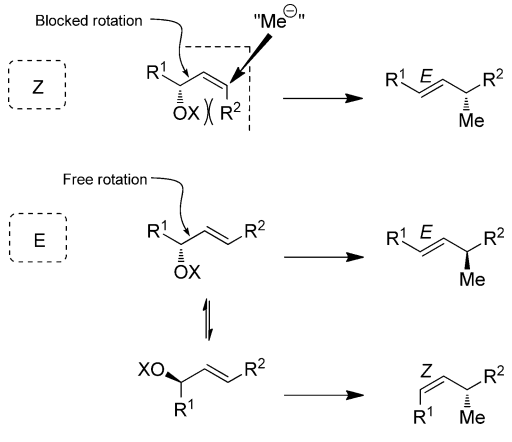


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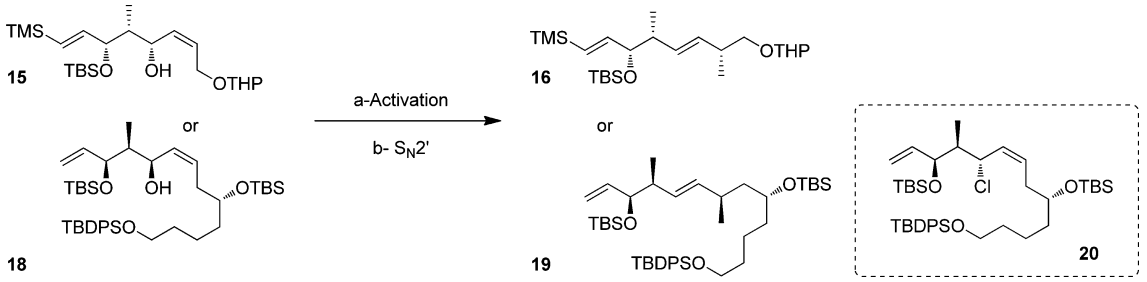
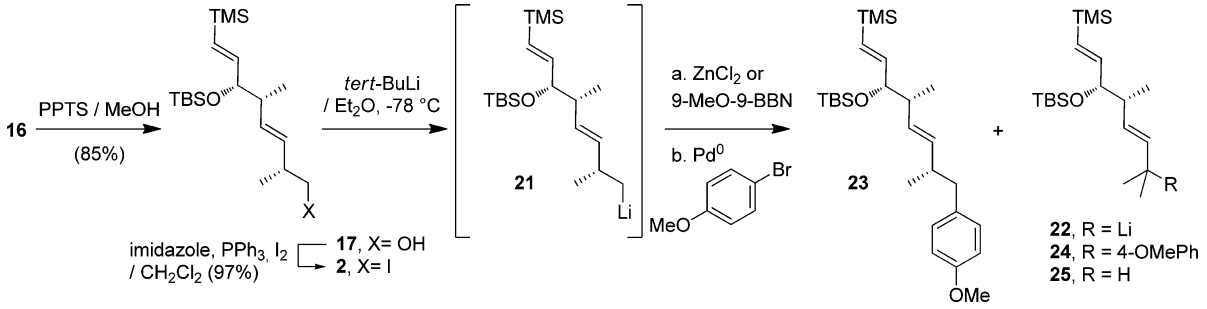
Table 1. S_N2' Conditions



entry	solvent	activation method	nucleophile	yield[a]
1	THF	**15**, *n*-BuLi, C_6F_6COCl, −78 to 0 °C	2MeLi, CuI, −78 to 0 °C	**16**, 46%[b]
2	THF	**15**, *n*-BuLi, $(EtO)_2POCl$, −78 to 0 °C	Me_2Zn, CuCN·2LiCl, −30 to −10 °C	**16**, 52%[c]
3	Et_2O	**15**, *n*-BuLi, $(EtO)_2POCl$, −78 to 0 °C	Me_2Zn, CuCN·2LiCl, −30 to −10 °C	**16**, 7%[c]
4	THF	**15**, *n*-BuLi, $(EtO)_2POCl$, −78 °C	2MeLi, CuI, −78 °C	**16**, traces[c]
5	THF	**15**, *n*-BuLi, $(EtO)_2POCl$, −78 to 0 °C	2MeLi, CuI, −78 to 0 °C	**16**, 61−69%[c]
6	Et_2O	**15**, *n*-BuLi, $(EtO)_2POCl$, −78 to RT	2MeLi, CuI, −10 °C	**16**, 88−91%[c]
7	Et_2O	18, *n*-BuLi, $(EtO)_2POCl$, −78 to 0 °C	2MeLi, CuI, −10 °C to RT	**19**, 97%[c] 85:15 *dr*[c,d]
8	Et_2O	18, KHMDS, $(EtO)_2POCl$, −78 to 0 °C	2MeLi, CuI, −10 °C to RT	**19**, 96%[c] >95:5 *dr*[c,d]

[a]Isolated yields. [b]Yield after PPTS promoted THP removal. [c]One-pot procedure. [d]*dr* estimated by ^1H NMR.

Scheme 4. Tests Coupling on Fragment 2



through antiperiplanar attack of the nucleophile gives one sole stereoisomer. The same reaction conducted on an *E* allylic system would deliver a mixture of *E* and *Z* isomers having opposite absolute configurations at the newly formed stereogenic center. We tried to activate alcohol **15** through the corresponding mesylate, perfluorobenzoate or phosphate. Unfortunately, classical conditions (MsCl, NEt_3/CH_2Cl_2; $POCl(OEt)_2$, NaH/THF; $POCl(OEt)_2$, DMAP/pyridine; C_6F_6COCl, NEt_3/CH_2Cl_2[15]) failed to afford synthetically useful yields of activated allylic alcohol. However, using *n*-BuLi as base, we succeeded in introducing the C_6F_6CO leaving group (71%), but the substitution of this leaving group led to **16** in unsatisfactory yields. So, considering that activated allylic alcohols are sensitive species, we chose to investigate one-pot conditions, and we also focused our attention on the cheaper diethylphosphate leaving group. The results are presented in Table 1. The cuprate nucleophile was prepared separately just prior to use. We observed that methylcuprate formed from MeLi (entries 1, 4−8) gave better yields than the one prepared from Me_2Zn (entries 2, 3). The solvent of the reaction appeared to be important too, Et_2O giving better yields than THF (entries 6−8). One must notice that with the allylic alcohol **18**[7] that we synthesized in our final strategy of synthesis,[16] the use of *n*-BuLi led to *dr* erosion of the S_N2' reaction (entry 7). This was surprising because only *E* products (**19** and its stereoisomer at C15) were formed, indicating that the allylic bond rotation remained well blocked in the *Z* allylic system. Hence, apparently this is another process that accounts for this *dr* erosion.

So, we hypothesized that the inversion of configuration occurred at the alcohol position (C17) before the methylcuprate addition. LiCl is formed when *n*-BuLi was used as the base to install the phosphate leaving group, LiCl is soluble in Et_2O, and the Cl^- anions may perform a S_N2 (nonconjugated) of the phosphate with inversion of configuration at C17, leading then to *Z*-allylchloride **20**. In the next step, the latter can undergo a S_N2' reaction with Me_2CuLi, thus accounting for the formation of the isomer of **19**. To circumvent this problem, we used KHMDS as the base to prepare the allylic phosphate intermediate, the byproduct being this time insoluble KCl. Under these optimized conditions, the subsequent S_N2' step delivered **19** in a 96% yield and as the sole detectable isomer (entry 8). Curiously, with starting allylic alcohol **15**, no isomer of **16** was detected, which indicates that no inversion by formation of allylic chloride occurred in that case. To explain this, we may imagine that the OTHP protective group in **15** has the possibility of chelating lithium ions that the OTBS group in **18** does not have, which could have important consequences on the environment of the leaving group. Then, with **16** in hand, the THP protecting group was removed, leading to alcohol **17**, which was then transformed into iodide **2**. In order to validate our strategy, we chose to perform Pd^0-catalyzed coupling tests involving **2** (Scheme 4). For this aim, the Negishi and the Suzuki protocols were envisioned, which means that iodide **2**

dx.doi.org/10.1021/jo301066p | *J. Org. Chem.* 2012, 77, 6728−6742

Scheme 5. Synthesis of Fragment 7 and 8

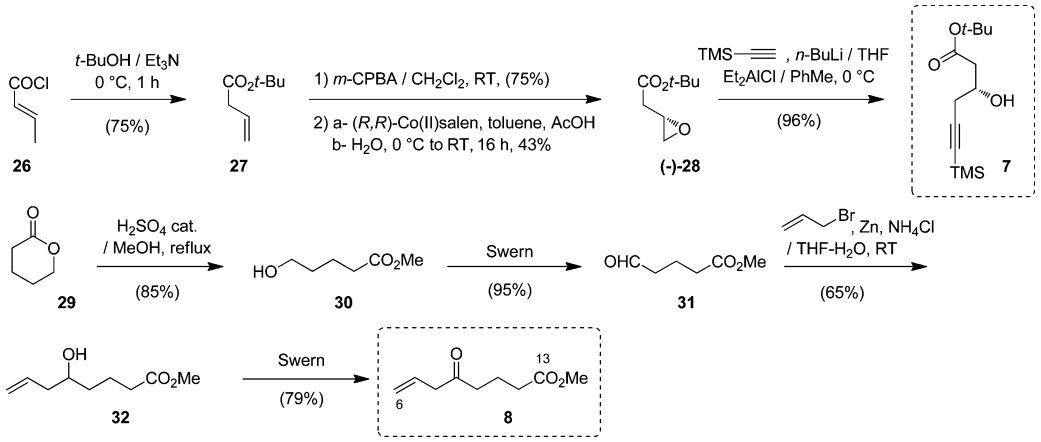
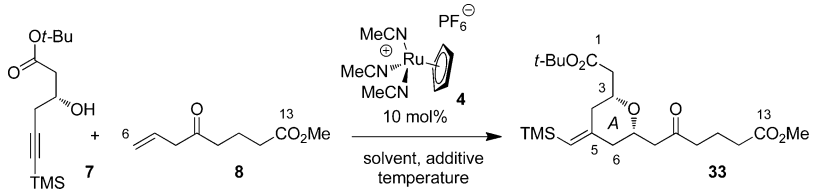


Table 2. Trost Coupling Optimization



entry	solvent	additive	temperature	time (h)	yields (%)	*dr syn/anti*
1	acetone		RT	19	69	>2/1
2	CH_2Cl_2		RT	72	37	<2/1
3	CH_3CN		reflux	18	0	
4	MeOH		RT	72	46	4/1
5	*t*-BuOH		reflux	18	0	
6	acetone		reflux	2	63	4/1
7	acetone	CSA (38 mol %)	RT	3	59[a]	n.d.
8	acetone	AcOH (16 mol %)	RT	2	63[b]	n.d.
9	acetone	AcOH (3 mol %)	RT	2	78	>9/1

[a]Desilylated product (53%). [b]Inseparable mixture of desired product **33** (58%) and its corresponding desilylated analogue (7%).

had to undergo a lithium−halogen exchange reaction and then a transmetalation step prior to coupling. Following the Negishi protocol,[17] lithium derivative **21** was transmetalated as a zinc derivative. Then $Pd_2(dba)_3$, DpePhos or PPh_3, and 4-bromoanisol were added, and the reaction medium was refluxed overnight. But here, the only product we isolated was deiodinated product **25**. The Suzuki protocol was performed using 9-MeO-9-BBN to transmetallate **21**, and then $PdCl_2(dppf)$, K_2CO_3, and 4-bromoanisol were added. After refluxing overnight in THF, we isolated a mixture of desired **23** along with **24**, an unexpected isomeric coupling product (**23**/**24**: 1/1, 52%). Coupling product **24** unambiguously accounts for the formation of the allyl-lithium derivative **22**.

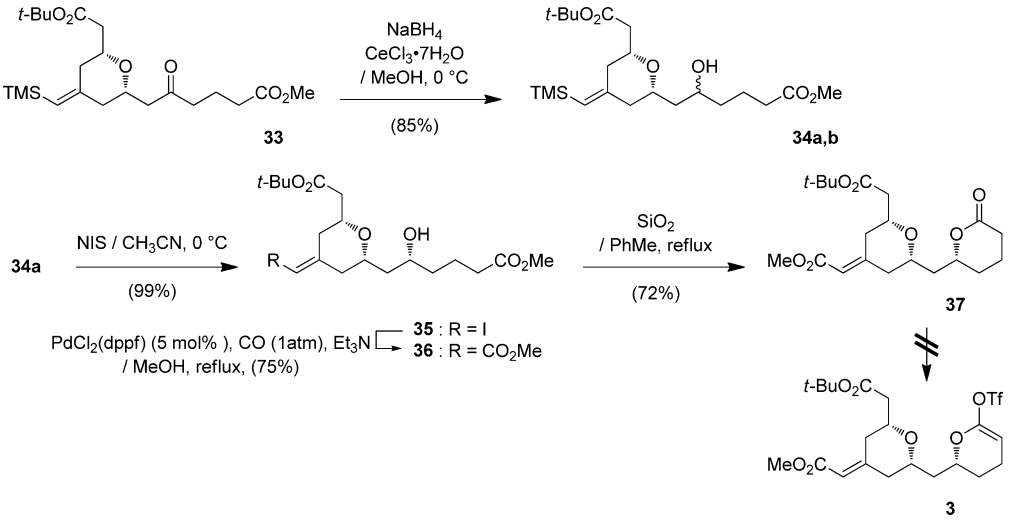
It is likely that the latter arose in the course of the metal/halogen exchange step through a process in which lithium derivative **21**, acting here as a base, would deprotonate **25** at its more acidic position delivering allylic lithium **22**, and regenerating then **25**. Considering the rather important amount of product **24** formed here, the above process could be catalytic in **25**. To initiate this process, only little amounts of **25** would be necessary, the latter could come from the quench of **21** with trace amounts of water present in THF. Despite this slightly disappointing result, we considered that this part of our strategy was validated, particularly since other methods could be used to obtain the desired C14−C21 metalated fragments. Then we started the study of the synthesis of triflate **3**.

1.3. Synthesis of Fragment 3. Commercially available methacryloyle chloride **26** was readily transformed into *β*,*γ*-unsaturated ester **27** in a very straightforward manner via the corresponding ketene (Scheme 5).[7,18] Then, a reaction with *m*-CPBA led to racemic epoxide **28**, and a Jacobsen hydrolytic kinetic resolution of racemate **28** using the (*R*,*R*)-salen-Co(III) complex[19] led to (−)-**28**. The epoxide function of (−)-**28** was opened by attack of an aluminum acetylide leading to the desired homopropargylic alcohol **7**. For the synthesis of *β*,*γ*-unsaturated ketone **8**, we started from lactone **29**, which was opened into its corresponding seco-ester **30**.[20] A Swern[21] oxidation led to aldehyde **31**, which under Luche's conditions,[22] led to homoallylic alcohol **32**.[23] Fragment **8**[24] was finally obtained by Swern oxidation of **32**.

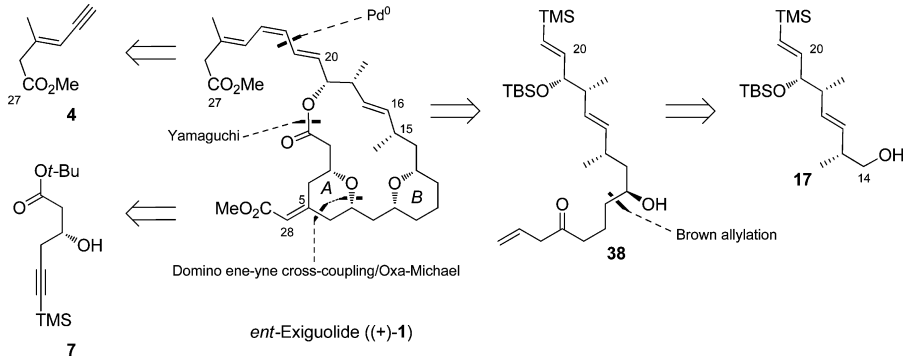
With yne and ene fragments (**7** and **8**) in hand, we searched for suitable Trost domino ene−yne/oxa-Michael conditions. Those originally reported by Trost (Table 2, entry 1) only led to a mixture of **33** and its isomer at C3 (2/1) with 69% yield after 19 h of reaction. Other solvents, CH_2Cl_2, MeCN, MeOH or *t*-BuOH (entries 2−5), led to no reaction or only poor yield and *dr*. With Trost standard conditions in refluxing acetone (entry 6), we observed a faster reaction (2 h) delivering **33** in 63% yield and with a *dr* enhanced to 4/1. We added then

dx.doi.org/10.1021/jo301066p | J. Org. Chem. 2012, 77, 6728−6742

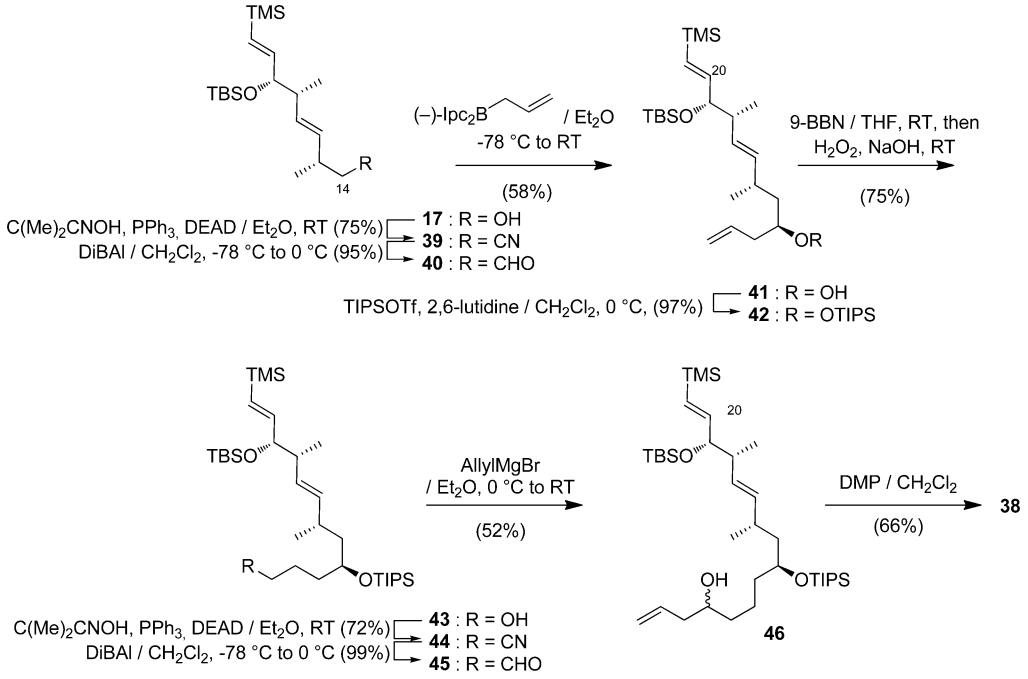
Scheme 6. Toward Triflate 3



Scheme 7. First Retrosynthetic Plan toward *ent*-Exiguolide ((+)-1)



Scheme 8. Synthesis of Ene Fragment 38



various additives such as Lewis acids or Brønsted acids and discovered conditions (entries 7, 8) in which the reaction rate was markedly accelerated, giving good yields of products, which had unfortunately lost their TMS groups. Finally, we set

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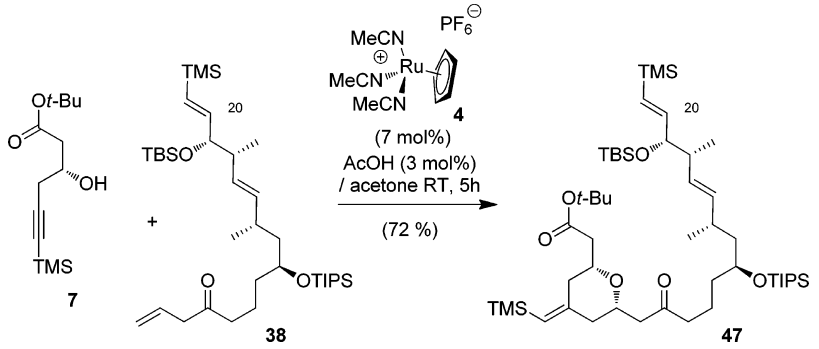
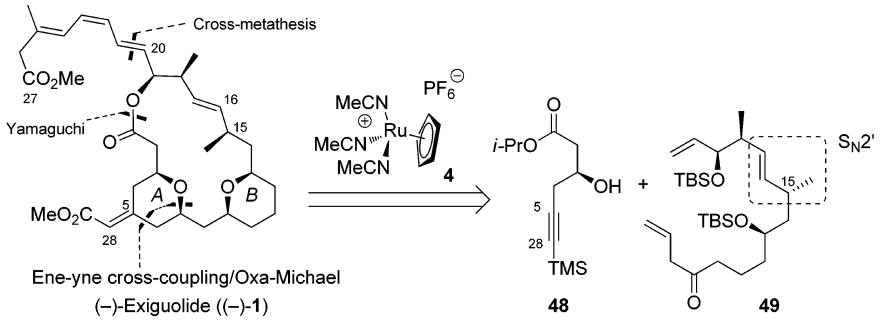
Scheme 9. Assemblage of "Yne" 7 and "Ene" 38 through Optimized Trost Reaction Conditions



Scheme 10. Third Strategy



efficient modified Trost conditions (entry 9) in which the addition of 3 mol % of AcOH allowed the formation of **33** in 78% yield, after only 2 h of reaction (10 times faster than under standard conditions), and with furthermore a dramatic amelioration of the *dr* that climbed from 2/1 to more than 9/1. The effect of Brønsted acid is likely to help the hydrolysis of the intermediate ruthenium enolate that is formed in the course of the oxa-Mikael step, thus allowing the catalyst to perform the ene−yne coupling step with a faster rate.

Having key intermediate **33** in hand, we transformed it into alcohol **34** under Luche reduction conditions (Scheme 6). Here unfortunately, the best observed *dr* was 2/1 (*syn*/*anti*). Desired *syn* product **34a** was treated with NIS, which led to the substitution of the TMS group leading to iodide derivative **35**. We were delighted to obtain methyl acrylate **36** with a full control of the double geometry through Pd^0-catalyzed carbonylation in methanol, thus resolving one of the most challenging problems of this total synthesis. Lactone **37** was readily obtained through a smooth acidic treatment with SiO_2. Compound **37** is a triester, but the most deprotonable of the three ester functions should be the lactone. However we failed in transforming lactone **37** neither into triflate **3** nor into the corresponding phosphate despite numerous conditions tried (LDA, KHMDS or *n*-BuLi as base, and $PfNTf_2$ or $POCl(OEt)_2$ as electrophile even with HMPA as cosolvent). Therefore this disappointing result prompted us to rethink our strategy of synthesis.

2. Second Approach. We designed a new strategy, still relying on the Trost ene−yne coupling that would be used this time for assembling the two main fragments of the molecule, namely, ene **38** and yne **7** (Scheme 7).

2.1. Synthesis of Fragment ***38****.* Starting from the alcohol **17** prepared during our first approach, we designed an iterative strategy for the introduction of carbons C13 to C6. A first carbon was added by substitution of the hydroxyl function of **17** by a cyanide ion under Mutsunobu conditions,[25] which led to nitrile **39** (Scheme 8). Then nitrile **39** was reduced into aldehyde **40** selectively. A Brown allylation[26] of **40** was used to control the C13 stereogenic center but it gave alcohol **41** in only a 58% yield. The alcohol function was protected as a TIPS ether (**42**) prior to the hydroboration/oxidation step that delivered alcohol **43**. Iteratively, alcohol **43** was homologated to give nitrile **44**, reduced into aldehyde **45**, transformed into homoallylic alcohol **46** and finally oxidized into β,γ-unsaturated ketone **38** using Dess−Martin periodinane.[27]

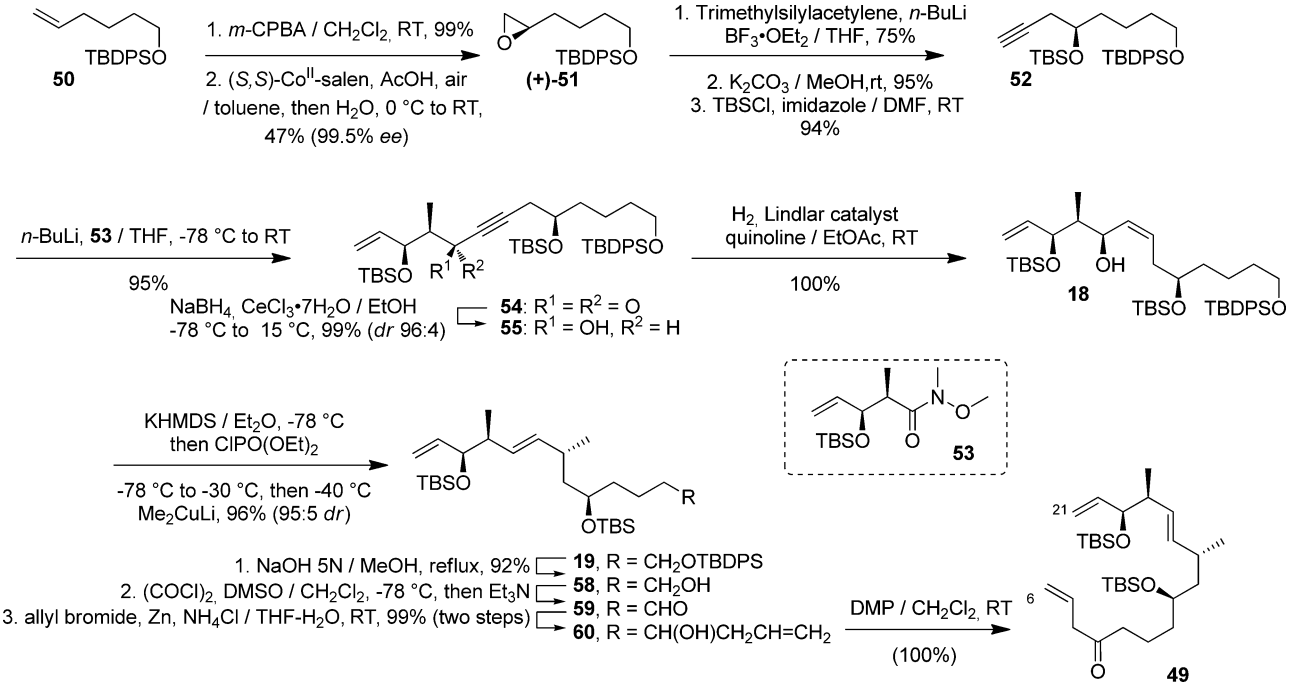
We were delighted to see that the Trost reaction under our optimized conditions allowed a fast cross-coupling of fragment **38** and **7**, with a high yield (72%) and an improved *dr* (>9/1) (Scheme 9), delivering **47**, which is a very advanced fragment containing almost all the carbons of the target and most of its asymmetric centers.

Nevertheless, the global yield of this rather linear and long sequence was too low to be compatible with the requirements of an elegant and efficient total synthesis. Furthermore we met trouble in having an acceptable selectivity in the transformation of the TMS group at C28 into the corresponding iodide derivative, the TMS at C21 being unexpectedly very reactive. So we decided to bring various improvements and modifications to this second strategy, which at the end led to the third and last strategy. Meanwhile, Lee et al. had published their synthesis of *ent*-exiguolide ((+)-**1**),[6] thus establishing the absolute configuration of natural (−)-exiguolide ((−)-**1**); hence, this time in the third strategy we targeted the right enantiomer of **1**.

3. Third and Final Approach. In a final effort we designed a more accurate and more efficient strategy toward (−)-**1**, the naturally occurring enantiomer of exiguolide. Among the steps we wanted to keep were the Trost ene−yne coupling, the installation of the Me at C15 by an S_N2' reaction, and the Evans aldol reaction for the starting material. One of the most

dx.doi.org/10.1021/jo301066p | J. Org. Chem. 2012, 77, 6728−6742

Scheme 11. Synthesis of Ene Key Fragment 49



important modifications that we choose to bring was to introduce the side chain through cross-metathesis, rendering the TMS at C21 no longer required in this strategy. But this latter choice was not the best.

We commenced with the synthesis of the C6−C21 fragment **49** (Scheme 10). First, we accessed the enantio-enriched epoxide (+)-**51** using the Jacobsen hydrolytic kinetic resolution (HKR)[19] on the corresponding racemic epoxide *rac*-**51** obtained by *m*-CPBA epoxidation of alkene **50**. Alkyne **52** was furnished by reaction of epoxide (+)-**51** with lithium trimethylsilylacetylide, followed by removal of the TMS alkyne protective group and protection of the alcohol function. The lithium acetylide of **52** was then condensed with known Weinreb amide **53**.[28] This efficient cross-coupling step afforded propargylic ketone **54** in 95% yield. The ketone function of **54** was reduced into alcohol **55** with a good diastereoselectivity using Luche conditions.[13] The semireduction of the alkyne function of **55**, using the Lindlar catalyst, led to *Z* allylic alcohol **18**. As already mentioned above in section 2.1, our S_N2' one-pot-two-step strategy was used for the control of the allylic C15 stereogenic center allowing the direct transformation of the *Z* allylic alcohol **18** into the desired alkene **19** in high yield (96%) and a very good transfer of chirality (*dr* around 95:5 by ^{1}H NMR spectroscopy). Next, the TBDPS protective group was selectively removed under basic conditions[29] affording alcohol **58**, which was oxidized into aldehyde **59** under Swern conditions.[21] The latter was transformed using the Luche[22] procedure into homoallylic alcohol **60** and readily oxidized by Dess−Martin periodinane[27] into *β*,*γ*-unsaturated ketone **49**, the key "ene" coupling partner of the Ru^{II}-catalyzed Trost's ene−yne coupling (53.4% over 11 steps from (+)-**51**).

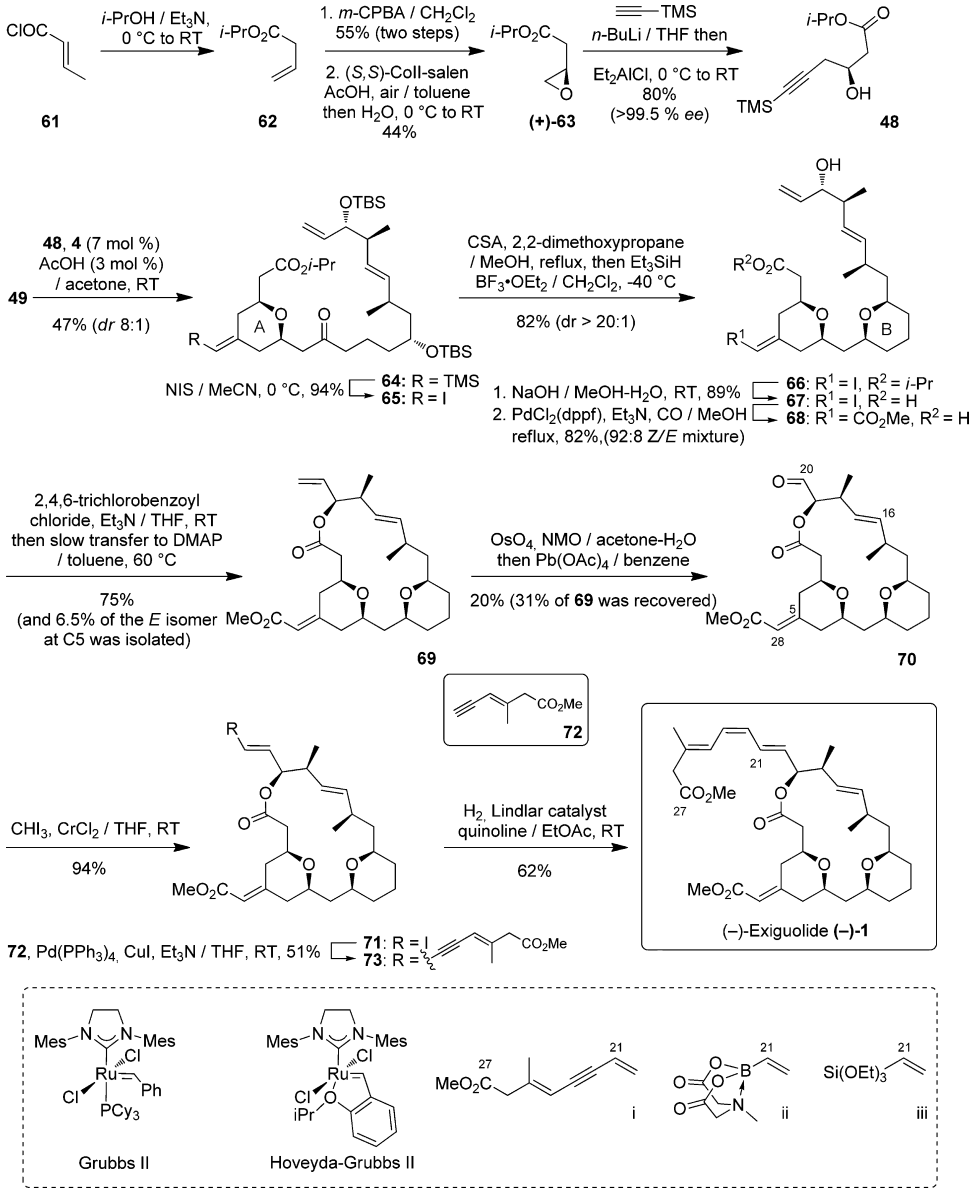
On the other hand, the known "yne" partner **48**[30] was accessed from *trans*-crotonoyl chloride **61**, which was transformed into *β*,*γ*-unsaturated ester **62** (Scheme 11).[31] An epoxidation by *m*-CPBA furnished *rac*-**63**, which was enantio-enriched by using the Jacobsen HKR method furnishing (+)-**63**.[19] Finally, **48** was cleanly obtained after reaction with an aluminum acetylide nucleophile;[32] the more classical reaction of the corresponding lithium acetylide in the presence of BF_3 led to decomposition.

We have shown above that a catalytic amount of acetic acid accelerated the domino ene−yne coupling/Michael reaction promoted by **4**, and in this case, these conditions allowed a remarkable enhancement of the diastereoselectivity. The same conditions of cross-coupling of alkyne **48** with alkene **49** led to tetrahydropyran **64** in a 47% yield as a 8:1 mixture of diastereomers easily separated by HPLC. Anyway, this result compares favorably with the 34% yield (*dr* not given) obtained by Trost for his bryostatin 16 synthesis on a comparable substrate. Furthermore one should notice that in our case, the reaction was regioselective as the C20−C21 terminal double bond was not engaged in the cross-coupling. The TMS group of **64** being particularly acid sensitive, we performed its iodolysis leading to **65**, prior to the acid-promoted removal of the two TBS protective groups and subsequent cyclization into the hemiketal precursor of cycle *B*. The crude mixture of hemiketals was subsequently reduced by Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ at −40 °C, affording compound **66** (*dr* >20:1) now featuring the two tetrahydropyran rings *A* and *B*. After saponification we obtained carboxylic acid **67**. Then, the methoxycarbonyl function was cleanly installed at C28 by a Pd^0-catalyzed carbonylation[33] of iodinated derivative **67** furnishing the desired (*Z*)-*α*,*β*-unsaturated methylester **68** (92:8 *Z*/*E* mixture). We proceeded then to the macrolactonization step using the Yamaguchi conditions[34] and obtained macrolactone **69** in a good 74% yield (9.2% over 17 steps). The order of these steps (saponification−carbonylation−macrolactonization) is rather unusual, but it was the only way we found to make the carbonylation reaction working in a reproducible manner.

For the last step of the synthesis, it was first envisioned to introduce the C21−C27 side chain directly by a cross-metathesis reaction[35] on alkene **69**. Unfortunately, none on the catalysts (Grubbs II and Hoveyda−Grubbs II (Scheme

dx.doi.org/10.1021/jo301066p | J. Org. Chem. 2012, 77, 6728−6742

Scheme 12. Endgame Leading to (−)-Exiguolide (1)



12)), cross-coupling partners (*i*, *ii*,[36] *iii*,[37] and allylic alcohol (Scheme 12)), and solvents (CH_2Cl_2, toluene, rt or reflux) we tried gave any product; in all cases, the starting material **69** was totally recovered, and not even dimers of **69** were formed. We then reconsidered our retrosynthetic analysis, and we thought it reasonable to expect selectivity from the OsO_4 catalyzed dihydroxylation reaction[38] in favor of the C20−C21 double bond, which is not electron-deficient and is the less hindered of the three alkene functions of compound **69**. Surprisingly we observed a poor selectivity and identified various diols and tetra-ols, some resulting from the unexpected dihydroxylation of the α,β-unsaturated ester at C5−C28, the C16−C17 double bond remaining untouched. A mild reaction with $Pb(OAc)_4$[39] finally delivered aldehyde **70** from this mixture of diols with 20% yield over two steps and partial recovery of the starting material **69** (31%). The Takai−Utimoto[40] olefination reaction on aldehyde **70** furnished vinylic iodide derivative (−)-**71** in high yield, the enantiomer of which was previously described by Lee.[6] In the two final steps of this synthesis, we followed the Lee's strategy. Thus we introduced the C22−C27 side chain by Sonogashira cross-coupling of **71** with alkyne **72**,[6,41] which furnished dienyne **73**. The final step of semihydrogenation led to the targeted (−)-exiguolide (**1**), the characterization data of which are identical with those reported for the naturally occurring compound ($[\alpha]_D^{20}$ −95.0 (*c* 0.28, $CHCl_3$), lit.[1] $[\alpha]_D^{20}$ −92.5 (*c* 0.069, $CHCl_3$)). We also performed the biological evaluation of synthetic (−)-exiguolide ((−)-**1**) by testing its cytotoxicity on KB cancer cells and found an IC_{50} value of 3.39 μM with 100 and 2% of growth cell inhibition at 10^{-5} and 10^{-6} M, respectively.

CONCLUSION

No less than three approaches have been necessary to finally achieve the total synthesis of (−)-exiguolide ((−)-**1**). However, this long lasting effort gave us the occasion of developing new relevant methodologies of synthesis, namely, the one-pot formation and S_N2' substitution of *Z*-allylic phosphates, and to apply them to total synthesis of natural product. We also performed a study of the ene−yne Trost coupling reaction, which led us to set optimized conditions for this powerful

dx.doi.org/10.1021/jo301066p | J. Org. Chem. 2012, 77, 6728−6742

transformation. Our total synthesis approach of **1** is robust, so relying on it we are currently developing the synthesis of analogues in the exiguolide series. The installation of the C20−C27 side chain was the weakness of our final approach, so we are also currently designing a new strategy to solve this problem.

EXPERIMENTAL SECTION

(*S*)-4-Benzyl-3-((2*S*,3*S*,*E*)-3-hydroxy-2-methyl-5-(trimethylsilyl)pent-4-enoyl)oxazolidin-2-one (6). To a solution of (*R*)-4-benzyl-3-propionyloxazolidin-2-one (3.88 g, 16.6 mmol) in CH_2Cl_2 (35 mL) at −78 °C was added slowly a 1.0 M solution of Bu_2BOTf in CH_2Cl_2 (16.6 mL, 16.6 mmol). Et_3N (3.2 mL, 22.8 mmol) was added. The resulting yellow solution was stirred for 30 min at −78 °C, and then 30 min at 0 °C. The mixture was then recooled to −78 °C, and acrylaldehyde **9** (17.5 mmol) in CH_2Cl_2 (10 mL) was added slowly. The resulting yellow solution was slowly warmed to −50 °C over 1.5 h. Stirring was continued at 0 °C for 30 min, and then at room temperature for 1.5 h. The solution was then quenched by addition of a pH 7.2 phosphate buffer solution (100 mL) added in one portion. To this vigorously stirred mixture was added H_2O_2 (30%, 25 mL) while the temperature was maintained below 5 °C. The addition of H_2O_2 was continued until the internal temperature was no longer affected by the addition of oxidant. The resulting mixture was stirred for 30 min while slowly warming to room temperature. This mixture was then poured in a saturated aqueous $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, filtered and concentrated under a vacuum to a yellow oil. The crude oil was purified by flash column chromatography (Toluene/EtOAc, 10/1) to give aldol **6** as a white solid (4.45 g, 70%): R_f = 0.30 (Heptane/EtOAc, 2/1); mp 85−87 °C; $[\alpha]_D^{20}$ = +62.6 (*c* 1.04, $CHCl_3$); IR (film) ν 3511, 2953, 1783, 1693, 1376, 1193, 830, 693 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36−7.28 (m, 3H), 7.21 (d, *J* = 7.0 Hz, 2H), 6.01 (s, 2H), 4.74−4.69 (m, 1H), 4.52−4.50 (m, 1H), 4.25−4.19 (m, 2H), 3.90−3.85 (m, 1H), 3.27 (dd, *J* = 13.5, 3.3 Hz, 1H), 2.92 (d, *J* = 3.2 Hz, 1H), 2.80 (dd, *J* = 13.4, 9.5 Hz, 1H), 1.22 (d, *J* = 7.1 Hz, 3H), 0.08 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 177.0, 153.2, 144.5, 135.2, 131.4, 129.6, 129.2, 127.6, 73.7, 66.4, 55.3, 42.5, 38.0, 10.7, −1.2; LRMS (ESI, TOF) *m*/*z* (%) 256.1 (13) [M − $C_6H_{12}OSi$ + Na]$^+$, 384.1 (100) [M + Na]$^+$, 745.2 (16) [2M + Na]$^+$; HRMS (ESI, TOF) *m*/*z* calcd for $C_{19}H_{27}NO_4{}^{23}NaSi$ [M + Na]$^+$ 384.1607, found 384.1609.

(2*S*,3*S*,*E*)-3-Hydroxy-*N*-methoxy-*N*,2-dimethyl-5-(trimethylsilyl)pent-4-enamide (11). To a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (3.79 g, 38.8 mmol) in THF (60 mL) at 0 °C was added a 2.0 M solution of trimethylaluminium in heptane (19.1 mL, 38.2 mmol). After the end of the gaseous evolution, the solution was allowed to warm to room temperature for 50 min. To this solution cooled at −40 °C was added a solution of aldol **6** (4.677 g, 12.94 mmol, 1.0 equiv) in THF (30 mL). The solution was allowed to warm to +15 °C over 2 h and stirred at this temperature for an additional 1 h period. Then the solution was cooled to −20 °C, quenched with a saturated aqueous Rochelle salt solution (50 mL), and then stirred during 1 h and extracted with EtOAc. The organic layer was washed with NH_4Cl and water, dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. Purification by column chromatography (Heptane/EtOAc, 2/1 then 1/1) gave pure Weinreb amide **11** as a light yellow liquid (3.179 g, 100%). Further elution (EtOAc 100%) allowed recovery of (*S*)-4-benzyloxazolidin-2-one 2.180 g, 95%): R_f = 0.19 (Heptane/EtOAc, 2/1); $[\alpha]_D^{20}$ = +28.4 (*c* 1.36, $CHCl_3$); IR (film) ν 3266, 2953, 1751, 1407, 1246, 836, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.02 (d, *J* = 18.9 Hz, 1H), 5.96 (dd, *J* = 18.9, 3.7 Hz, 1H), 4.43 (s, 1H), 3.87 (s, 1H), 3.72 (s, 3H), 3.21 (s, 3H), 2.97 (s, 1H), 1.14 (d, *J* = 7.0 Hz, 3H), 0.08 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 177.8, 145.2, 130.8, 73.7, 61.8, 39.3, 10.6, −1.1; LRMS (ESI, TOF) *m*/*z* (%) 268.1 (100) [M + Na]$^+$, 513.2 (92) [2M + Na]$^+$; HRMS (ESI, TOF) *m*/*z* calcd for $C_{11}H_{23}NO_3{}^{23}NaSi$ [M + Na]$^+$ 268.1345, found 268.1358.

(2*S*,3*S*,*E*)-3-(*tert*-Butyldimethylsilyloxy)-*N*-methoxy-*N*,2-dimethyl-5-(trimethylsilyl)pent-4-enamide (12). To a solution of Weinreb amide **11** (3.169 g, 12.91 mmol) and imidazole (1.58 g, 23.2 mmol) in DMF (25 mL) at room temperature was added *tert*-butylchlorodimethylsilane (2.92 g, 19.4 mmol). The solution was stirred for 3.5 h and then quenched with water (20 mL) and extracted with Et_2O. The organic layer was washed with saturated aqueous NH_4Cl and water, dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. Purification by column chromatography (Heptane/EtOAc, 10/1) gave pure Weinreb amide **12** as a colorless oil (4.645 g, 100%): R_f = 0.20 (Heptane/EtOAc, 10/1); $[\alpha]_D^{20}$ = −12.9 (*c* 1.36, $CHCl_3$); IR (film) ν 2955, 2857, 1663, 1247, 1059, 992, 833, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.98 (dd, *J* = 18.6, 6.1 Hz, 1H), 5.79 (d, *J* = 18.6 Hz, 1H), 4.18 (dd, *J* = 8.6, 6.4 Hz, 1H), 3.63 (s, 3H), 3.12 (s, 3H), 2.95 (s, 1H), 1.17 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.02 (s, 9H), 0.00 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.9, 147.8, 130.4, 77.8, 61.6, 42.7, 32.2, 26.0, 25.8, 18.4, 14.6, −1.2, −4.0, −4.6; LRMS (ESI, TOF) *m*/*z* (%) 360.5 (21) [M + H]$^+$, 382.5 (100) [M + Na]$^+$, 742.0 (13) [2M + Na]$^+$; HRMS (ESI, TOF) *m*/*z* calcd for $C_{17}H_{38}NO_3Si_2$ [M + H]$^+$ 360.2390, found 360.2378.

(5*S*,6*S*,*E*)-6-(*tert*-Butyldimethylsilyloxy)-5-methyl-1-(tetrahydro-2*H*-pyran-2-yloxy)-8-(trimethylsilyl)oct-7-en-2-yn-4-one (13). To a solution of 2-(prop-2-ynyloxy)tetrahydro-2*H*-pyran (1.1 mL, 7.5 mmol) in THF (40 mL), at −78 °C was added a 1.6 M solution of *n*-BuLi in hexanes (4.7 mL, 7.5 mmol). After a 5 min period at room temperature, the reaction medium was recooled to −78 °C, and a solution of Weinreb amide **12** (1.351 g, 3.76 mmol) in THF (8 mL) was added. The light yellow solution was allowed to warm to room temperature over a 3 h period to an orange solution and then heated at 45 °C for 1.5 h. The solution was quenched with saturated aqueous NH_4Cl solution (50 mL) and extracted with Et_2O. The organic layer was washed with saturated aqueous NH_4Cl and water, dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. Purification by column chromatography (Heptane/EtOAc, 10/1) and drying under a vacuum to remove excess of 2-(prop-2-ynyloxy)tetrahydro-2*H*-pyran gave pure propargylic ketone **13** as a colorless oil (1.392 g, 84%): R_f = 0.46 (Heptane/EtOAc, 4/1); IR (film) ν 2951, 2856, 2212, 1680, 1248, 1121, 1030, 833, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.97 (dd, *J* = 18.6, 5.5 Hz, 1H), 5.87 (d, *J* = 18.6 Hz, 1H), 4.82 (t, *J* = 3.4 Hz, 1H), 4.67−4.64 (m, 1H), 4.43 (s, 2H), 3.86−3.81 (m, 1H), 3.57−3.53 (m, 1H), 2.64 (qd, *J* = 6.9, 4.3 Hz, 1H), 1.86−1.53 (m, 6H), 1.13 (d, *J* = 6.7 Hz, 3H), 0.87 (s, 9H), 0.07 (s, 9H), 0.03 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 189.3, 146.6, 131.3, 97.3, 89.0, 84.9, 75.8, 62.2, 54.8, 54.0, 30.3, 25.9, 25.4, 19.0, 18.3, 9.6, −1.3, −3.9, −4.9; LRMS (ESI, TOF) *m*/*z* (%) 461.2 (100) [M + Na]$^+$; HRMS (ESI, TOF) *m*/*z* calcd for $C_{23}H_{42}O_4{}^{23}NaSi_2$ [M + Na]$^+$ 461.2519, found 461.2523.

(4*R*,5*R*,6*S*,*E*)-6-(*tert*-Butyldimethylsilyloxy)-5-methyl-1-(tetrahydro-2*H*-pyran-2-yloxy)-8-(trimethylsilyl)oct-7-en-2-yn-4-ol (14). To a solution of propargylic ketone **13** (6.912 g, 15.75 mmol) and $CeCl_3{\cdot}7H_2O$ (7.04 g, 18.9 mmol) in MeOH (100 mL) at −78 °C was added $NaBH_4$ (655.6 mg, 17.3 mmol, 1.1 equiv) by small portions over 30 min. The solution was allowed to warm to 0 °C over 45 min, and solid K_2CO_3 (6.53 g, 47.3 mmol, 3.0 equiv) was added. The mixture was stirred 2 h at room temperature and then quenched by addition of water and extracted with CH_2Cl_2. The organic layer was washed with water, dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. Column chromatography purification (Heptane/EtOAc, 10/1) followed by preparative HPLC (Heptane/EtOAc, 10/1) allowed the separation of the major alcohol diastereomer **14** (5.625 g, 81%) and the minor diastereomer (416.6 mg, 6%): R_f = 0.26 (Heptane/EtOAc, 4/1); IR (film) ν 3432, 2951, 2855, 2357, 1247, 1019, 833, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.05 (dd, *J* = 18.6, 6.1 Hz, 1H), 5.82 (d, *J* = 18.9 Hz, 1H), 4.81 (t, *J* = 3.2 Hz, 1H), 4.54−4.52 (m, 1H), 4.34−4.26 (m, 3H), 3.86−3.81 (m, 1H), 3.54−3.50 (m, 1H), 2.57 (d, *J* = 2.4 Hz, 0.5H), 2.56 (d, *J* = 2.4 Hz, 0.5H), 1.87−1.50 (m, 7H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.89 (s, $9H_3$), 0.07 (s, $9H_3$), 0.06 (s, $3H_2$), 0.00 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 147.6, 131.2, 96.9, 86.4, 81.5, 78.7, 65.6, 62.2, 62.1, 54.4,

dx.doi.org/10.1021/jo301066p | *J. Org. Chem.* 2012, 77, 6728−6742

45.4, 30.4, 26.0, 25.5, 19.24, 19.21, 18.3, 9.3, −1.3, −3.7, −4.8; LRMS (ESI, TOF) *m/z* (%) 463.3 (100) $[M + Na]^+$; HRMS (ESI, TOF) *m/z* calcd for $C_{23}H_{44}O_4{}^{23}NaSi_2$ $[M + Na]^+$ 463.2676, found 463.2664.

(2*Z*,4*S*,5*R*,6*S*,7*E*)-6-(*tert*-Butyldimethylsilyloxy)-5-methyl-1-(tetrahydro-2*H*-pyran-2-yloxy)-8-(trimethylsilyl)octa-2,7-dien-4-ol (15). To a solution of propargylic alcohol **14** (3.057 g, 6.94 mmol) in EtOAc (80 mL) at room temperature was added Lindlar palladium catalyst (452 mg) and freshly distilled quinoline (640 μL). The solution was purged and placed under hydrogen atmosphere (1 atm) at 0 °C and then stirred strongly at 10 °C for 1.5 h. The mixture was filtered on a thin silica pad and washed with EtOAc. The organic layer was concentrated under a vacuum. Purification by column chromatography (Heptane/EtOAc, 10/1) afforded allylic alcohol **15** as a colorless oil (2.672 g, 87%): R_f = 0.33 (Heptane/EtOAc, 4/1); IR (film) ν 3469, 2952, 2856, 2363, 1620, 1248, 1022, 833, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.044 (dd, *J* = 18.9, 6.3 Hz, 0.5H), 6.040 (dd, *J* = 18.9, 6.3 Hz, 0.5H), 5.82 (d, *J* = 18.6 Hz, 1H), 5.75−5.59 (m, 2H), 4.67−4.61 (m, 2H), 4.36 (dd, *J* = 12.5, 5.5 Hz, 0.5H), 4.25−4.23 (m, 1H), 4.21−4.16 (m, 1H), 4.07 (dd, *J* = 12.7, 5.1 Hz, 0.5H), 3.88−3.83 (m, 1H), 3.55−3.48 (m, 1H), 2.91 (d, *J* = 2.1 Hz, 0.5H), 2.83 (d, *J* = 2.1 Hz, 0.5H), 1.85−1.51 (m, 7H), 0.97 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 9H), 0.06 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 147.9, 135.7, 134.8, 130.8, 127.7, 127.1, 98.5, 97.5, 79.8, 79.6, 70.4, 70.1, 63.6, 62.8, 62.33, 62.26, 45.3, 45.1, 30.8, 30.7, 26.0, 25.6, 19.5, 18.3, 8.0, 7.9, −1.3, −3.6, −4.7; LRMS (ESI, TOF) *m/z* (%) 465.2 (100) $[M + Na]^+$; HRMS (ESI, TOF) *m/z* calcd for $C_{23}H_{46}O_4{}^{23}NaSi_2$ $[M + Na]^+$ 465.2832, found 465.2809.

***tert*-Butyl((1*E*,3*S*,4*R*,5*E*,7*R*)-4,7-dimethyl-8-(tetrahydro-2*H*-pyran-2-yloxy)-1-(trimethylsilyl)octa-1,5-dien-3-yloxy)-dimethylsilane (16).** To a solution of allylic alcohol **15** (1.476 g, 3.33 mmol) in Et_2O (3.5 mL) at −78 °C was added a 1.6 M solution of *n*-BuLi in hexanes (2.9 mL, 4.7 mmol), followed by diethyl chlorophosphate (725 μL, 5.0 mmol), and this reaction mixture was stirred 1 h at 0 °C. A solution of Me_2CuLi in Et_2O (extemporaneously prepared by the addition of a 1.6 M solution of MeLi in Et_2O (4.6 mL, 7.3 mmol, 2.2 equiv) to a suspension of CuI (698.3 mg, 3.7 mmol, 1.1 equiv) in Et_2O (3 mL) at 0 °C) was added at −10 °C to the solution of allylic phosphate. After 40 min of stirring at −10 °C, the reaction was quenched by addition of a saturated aqueous NH_4Cl solution (5 mL) and of aqueous NH_3 (5 mL). The mixture became dark blue and was then extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous NH_4Cl and water, dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. Purification by column chromatography (Heptane/CH_2Cl_2, 2/1, then Heptane/EtOAc, 10/1) gave diene **16** (1.343 g, 91%) as a colorless oil: R_f = 0.61 (Heptane/EtOAc, 4/1); IR (film) ν 2954, 2856, 1621, 1248, 1032, 833, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.92 (dd, J = 18.7, 5.9 Hz, 1H), 5.71 (d, J = 18.9 Hz, 1H), 5.43 (dd, J = 15.6, 7.0 Hz, 0.5H), 5.42 (dd, J = 15.6, 7.0 Hz, 0.5H), 5.34 (dd, J = 15.6, 6.7 Hz, 0.5H), 5.31 (dd, J = 15.6, 6.7 Hz, 0.5H), 4.59−4.56 (m, 1H), 3.88−3.83 (m, 2H), 3.64 (dd, J = 9.5, 5.8 Hz, 0.5H), 3.51−3.45 (m, 1.5H), 3.29 (dd, J = 9.5, 5.8 Hz, 0.5H), 3.14 (dd, J = 9.2, 7.6 Hz, 0.5H), 2.44−2.37 (m, 1H), 2.20−2.14 (m, 1H), 1.86 1.50 (m, 6H), 1.02 (d, J = 6.8 Hz, 1.5H), 1.01 (d, J = 6.8 Hz, 1.5H), 0.94 (d, J = 6.7 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 9H), 0.02 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 148.2, 132.9, 132.8, 132.3, 132.2, 129.7, 99.2, 98.6, 79.8, 72.9, 72.5, 62.3, 62.2, 43.3, 37.0, 36.9, 30.8, 26.1, 25.7, 19.7, 19.6, 18.5, 17.5, 17.4, 15.43, 15.40, −1.1, −4.0, −4.7; LRMS (ESI, TOF) *m/z* (%) 463.2 (100) $[M + Na]^+$; HRMS (ESI, TOF) *m/z* calcd for $C_{24}H_{48}O_3{}^{23}NaSi_2$ $[M + Na]^+$ 463.3040, found 463.3052.

(2*R*,3*E*,5*R*,6*S*,7*E*)-6-(*tert*-Butyldimethylsilyloxy)-2,5-dimethyl-8-(trimethylsilyl)octa-3,7-dien-1-ol (17). A solution of diene **16** (73.5 mg, 0.17 mmol) and PPTS (4.2 mg, 0.02 mmol) in MeOH (5 mL) was refluxed for 1.5 h. Some solid $NaHCO_3$ was added to neutralize the reaction mixture, which was then filtered and washed with EtOAc, and concentrated under a vacuum. Purification by column chromatography (Heptane/EtOAc, 20/1) gave dienol **17** (50.7 mg, 85%): R_f = 0.35 (Heptane/EtOAc, 4/1); $[\alpha]_D{}^{20}$ = +6.5 (*c* 1.07, $CHCl_3$); IR (film) ν 3350, 2955, 2857, 1620, 1461, 1248, 1028, 832, 773 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.92 (dd, *J* = 18.6, 6.1 Hz, 1H), 5.73 (d, *J* = 18.6, Hz, 1H), 5.40 (dd, *J* = 15.6, 8.2 Hz, 1H), 5.15 (dd, *J* = 15.6, 8.2 Hz, 1H), 3.88 (dd, *J* = 6.1 Hz, 1H), 3.47−3.42 (m, 1H), 3.25 (t, *J* = 9.5 Hz, 1H), 2.32−2.21 (m, 2H), 1.55 (s, 1H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 9H), 0.03 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 147.5, 134.9, 132.8, 130.8, 79.8, 67.1, 43.8, 40.2, 26.1, 18.5, 16.6, 16.2, −1.2, −4.0, −4.7; LRMS (ESI, TOF) *m/z* (%) 379.3 (100) $[M + Na]^+$; HRMS (ESI, TOF) *m/z* calcd for $C_{19}H_{40}O_2{}^{23}NaSi_2$ $[M + Na]^+$ 379.2448, found 379.2465.

***tert*-Butyl((1*E*,3*S*,4*R*,5*E*,7*R*)-8-iodo-4,7-dimethyl-1-(trimethylsilyl)octa-1,5-dien-3-yloxy)dimethylsilane (2).** To a solution of dienol **17** (495.0 mg, 1.39 mmol) and imidazole (624 mg, 9.2 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added a solution of PPh_3 (910 mg, 3.5 mmol) and I_2 (881 mg, 3.5 mmol) prepared 10 min before in CH_2Cl_2 (10 mL) at 0 °C. The yellow solution was stirred 16 h at room temperature, and then 70−200 μm silica (1.5 g) was added. The solvent was removed giving a powder, and purification by column chromatography (Heptane/EtOAc, 20/1) gave iodide **2** (629.0 mg, 97%): R_f = 0.68 (Heptane/EtOAc, 10/1); $[\alpha]_D{}^{20}$ = +18.9 (*c* 0.92, $CHCl_3$); IR (film) ν 2953, 2927, 2855, 1620, 1461, 1360, 1247, 832, 773, 691, 670, 612 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.93 (dd, *J* = 18.6, 6.1 Hz, 1H), 5.73 (d, *J* = 18.6 Hz, 1H), 5.45 (dd, *J* = 15.6, 7.6 Hz, 1H), 5.25 (dd, *J* = 15.6, 7.3 Hz, 1H), 3.89 (dd, *J* = 5.8, 5.5 Hz, 1H), 3.17 (dd, *J* = 9.5, 5.5 Hz, 1H), 3.06 (dd, *J* = 9.5, 7.3 Hz, 1H), 2.35−2.27 (m, 1H), 2.23−2.16 (m, 1H), 1.09 (d, *J* = 6.4 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 9H), 0.02 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 147.9, 133.9, 132.8, 130.1, 79.7, 43.3, 38.9, 26.1, 21.0, 18.5, 15.9, 15.5, −1.1, −3.9, −4.6; LRMS (ESI, TOF) *m/z* (%) 489.2 $[M + Na]^+$; HRMS (ESI, TOF) *m/z* calcd for $C_{19}H_{39}IO^{23}NaSi_2$ $[M + Na]^+$ 489.1482, found 489.1483.

***tert*-Butyl((1*E*,3*S*,4*R*,5*E*,7*S*)-8-(4-methoxyphenyl)-4,7-dimethyl-1-(trimethylsilyl)octa-1,5-dien-3-yloxy)dimethylsilane (23). *tert*-Butyl((1*E*,3*S*,4*R*,5*E*)-7-(4-methoxyphenyl)-4,7-dimethyl-1-(trimethylsilyl)octa-1,5-dien-3-yloxy)dimethylsilane (24).** To a solution of iodide **2** (91.7 mg, 0.20 mmol) in Et_2O (3 mL) at −78 °C was added a 1.7 M solution of *t*-BuLi in pentane (250 μL, 0.4 mmol), followed 10 min later by the addition of a 1.0 M solution of *B*-methoxy-9-borabicyclo[3.3.1]nonane in hexane (462 μL, 0.46 mmol) and THF (3 mL). The solution was allowed to warm to room temperature, and then an aqueous solution of K_3PO_4 (200 μL, 3.0 M, 0.6 mmol) was added, followed by the addition of 4-bromoanisol (49.2 μL, 0.4 mmol) and $PdCl_2$(dppf) (7.2 mg, 0.01 mmol). Et_2O was removed, and the mixture was refluxed for 3 h and then stirred at room temperature for 63 h. The reaction was quenched with water and extracted with Et_2O. The organic layer was washed with brine and water, dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. Purification by column chromatography (Heptane/CH_2Cl_2, 10/1, then 5/1) gave a nonseparable mixture of product **23** and the isomer byproduct **24** (1:1, 45.8 mg, 52%). Data for the 1:1 mixture of **23** and **24**: R_f = 0.31 (Heptane/CH_2Cl_2, 5/1); ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.8 Hz, 2H, H^{Ar}), 7.05 (d, *J* = 8.6 Hz, 2H, H^{Ar}), 6.84−6.80 (m, 4H, H^{Ar}), 5.95 (dd, *J* = 18.3, 5.8 Hz, 1H, H^2), 5.92 (dd, *J* = 18.3, 5.8 Hz, 1H, H^2), 5.74 (d, *J* = 18.5 Hz, 1H, H^1), 5.71 (d, *J* = 18.7 Hz, 1H, H^1), 5.56 (d, *J* = 15.7 Hz, 1H, H^5), 5.37 (d, *J* = 7.8 Hz, 1H, H^6), 5.35−5.33 (m, 2H, H^5, H^6), 3.89 (t, *J* = 5.9 Hz, 1H, H^3), 3.86 (t, *J* = 5.6 Hz, 1H, H^3), 3.79 (s, 6H, OCH_3), 2.62 (dd, *J* = 13.0, 5.7 Hz, 1H, H^{8a}), 2.38 (dd, *J* = 12.9, 8.1 Hz, 1H, H^{8a}), 2.36−2.28 (m, 1H, H^7), 2.26−2.19 (m, 1H, H^4), 2.19−2.12 (m, 1H, H^4), 1.33 (s, 6H, H^{8b}), 0.98 (d, *J* = 6.7 Hz, 3H, H^9 or H^{10}), 0.94 (d, *J* = 6.9 Hz, 3H, H^9 or H^{10}), 0.91 (d, *J* = 6.6 Hz, 3H, H^9 or H^{10}), 0.89 (s, 18H, $SiMe_2C(CH_3)_3$), 0.05 (s, 9H, $Si(CH_3)_3$), 0.04 (s, 9H, $Si(CH_3)_3$), 0.02 (s, 3H, $Si^tBu(CH_3)_2$), 0.00 (s, 3H, $Si^tBu(CH_3)_2$), −0.01 (s, 3H, $Si^tBu(CH_3)_2$), −0.03 (s, 3H, $Si^tBu(CH_3)_2$).

***tert*-Butyl((1*E*,3*S*,4*R*,5*E*)-4,7-dimethyl-1-(trimethylsilyl)octa-1,5-dien-3-yloxy)dimethylsilane (25).** To a solution of iodide **2** (38.7 mg, 0.08 mmol) in Et_2O (0.6 mL) at −78 °C was added a 1.7 M solution of *t*-BuLi in pentane (100 μL, 0.2 mmol). Ten minutes later, a solution of $ZnCl_2$ in THF (180 μL, 0.5 M, 0.09 mmol) was added. The reaction mixture was allowed to warm to room temperature, and then 40 min later 4-bromoanisol (16 μL, 0.12 mmol) was added followed

dx.doi.org/10.1021/jo301066p | *J. Org. Chem.* 2012, 77, 6728−6742

by a solution of $Pd_2(dba)_3$ (2.3 mg, 2.5 μmol) and PPh_3 (3.3 mg, 0.012 mmol) in THF (0.5 mL). Et_2O was removed, and the mixture was refluxed for 19 h. The reaction was quenched by addition of water and extracted with AcOEt. The organic layer was washed with water, dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. The crude oil contained 4-bromoanisol and product **25**: R_f = 0.62 (Heptane/CH_2Cl_2, 5/1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (dd, *J* = 18.7, 5.9 Hz, 1H), 5.71 (d, *J* = 18.7 Hz, 1H), 5.35−5.25 (m, 2H), 3.86 (dd, *J* = 6.1, 5.6 Hz, 1H), 2.25−2.18 (m, 1H), 2.18−2.10 (m, 1H), 0.95 (d, *J* = 6.7 Hz, 6H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.90 (s, 9H), 0.05 (s, 9H), 0.02 (s, 3H), −0.02 (s, 3H).

(3*S*)-*tert*-Butyl 3,4-Epoxybutanoate ((−)-28). To a solution of *tert*-butyl but-3-enoate **27** (10 g, 70.4 mmol) in CH_2Cl_2 (100 mL) was added *m*-CPBA (24.0 g, 97.4 mmol, 1.4 equiv) in one portion at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The white precipitate was filtered off, and the filtrate concentrated under a vacuum. The residue was distilled under a vacuum using a bulb to bulb Büchi oven affording the racemic epoxyde **28** as a colorless oil (8.2 g, 75%). To a flask open to air and charged with (*S*,*S*)-Co(II) salen (19.5 mg, 0.03 mmol) in toluene (2 mL) was added AcOH (20 μL, 0.4 mmol). The solution, initially red, turned brown within a few seconds and was stirred in open air for 45 min before being concentrated under a vacuum. Racemic epoxyde **28** (998.2 mg, 6.3 mmol, 1 equiv) was added neat, the mixture was cooled to 0 °C, and water (63 μL, 3.5 mmol, 0.55 equiv) was added dropwise, while the temperature was controlled, which must stay below 15 °C. After the end of the addition, the reaction mixture was allowed to warm to room temperature (water bath was used to ensure temperature remained around 20 °C). The solution was stirred in air for 18 h and was then directly distilled under a vacuum in a bulb to bulb Büchi oven affording enantiomerically enriched (*ee* determined at the next step on product **7**) (*S*)-epoxyde (−)-**28** (389 mg, 43%) as a colorless oil: bp 26−30 °C/0.01 mbar; $[\alpha]_D^{20}$ = −4.15 (*c* 0.92, $CHCl_3$); IR (film) ν 2977, 2930, 1726, 1367, 1256, 1151 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.28−3.22 (m, 1H), 2.83 (t, *J* = 4.5 Hz, 1H), 2.57−2.53 (m, 2H), 2.48 (d, *J* = 6.0 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 81.5, 48.5, 46.9, 39.5, 28.3; MS (EI) *m*/*z* 145 (M − Me), 139, 102; HRMS (ESI, TOF) *m*/*z* calcd for $C_8H_{14}O_3{}^{23}Na$ $[M + Na]^+$ 181.0841, found 181.0858.

(5*R*)-*tert*-Butyl 3-Hydroxy-6-(trimethylsilyle)hex-5-ynoate (7). To a solution of trimethylsilylacetylene (450 μL, 3.2 mmol) in toluene (5 mL) was added at 0 °C a 1.6 M solution of *n*-BuLi in hexanes (2.0 mL, 3.2 mmol). The reaction mixture was stirred for 30 min, and a 1.0 M solution of Et_2AlCl in heptane (3.2 mL, 3.2 mmol) was added, and then stirring was continued for 40 min. Epoxyde (−)-**28** (389 mg, 2.46 mmol) was then added, and the reaction was stirred for 2 h before being quenched by addition of water and extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated under a vacuum. Purification by column chromatography (Heptane/EtOAc, 4/1) gave homopropargylic alcohol **7** (504 mg, 80%) as a colorless oil: $[\alpha]_D^{20}$ = −25.5 (*c* 1.41, $CHCl_3$); IR (film) ν 3449, 2961, 2359, 2175, 1726, 1248, 1147, 837 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm) 4.15−4.07 (m, 1H), 3.13 (d, *J* = 3.0 Hz, 1H), 2.62−2.55 (m, 1H), 2.50−2.39 (m, 3H), 1.47 (s, 9H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 102.4, 87.6, 81.4, 66.7, 41.1, 28.1, 27.7, 28.1, 27.7, 0.0; MS (EI) *m*/*z* 257 (M + H), 201, 183, 167, 161, 145, 140; HRMS (ESI, TOF) *m*/*z* calcd for $C_{13}H_{24}O_3{}^{23}NaSi$ $[M + Na]^+$ 279.1392, found 279.1376. Determination of enantiomeric excess by chiral HPLC: column AD-H 5 μm (4.6 × 150 mm), hexane/*iso*-propanol, 98/2, 1 mL/min; $t_R(R)$ = 5.578 min; $t_R(S)$ = 5.995 min.

Methyl 5-Hydroxypentanoate (30). To a flask charged with δ-valerolactone (15.0 g, 150.0 mmol) in MeOH (300 mL) was added concentrated sulphuric acid (0.8 mL, 15.0 mmol), and the reaction mixture was refluxed for 21 h. Solid $NaHCO_3$ was added, and the solution was filtered and partially concentrated under a vacuum. Water was added, and the mixture was extracted with EtOAc, dried over Na_2SO_4, filtered and concentrated under a vacuum. It yielded the expected hydroxyester **30** (16.93 g, 85%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.65 (t, *J* = 6.2 Hz, 2H), 2.37 (t, *J* = 7.3 Hz, 2H), 1.80 (br s, 1H), 1.78−1.68 (m, 2H), 1.65−1.55 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 62.4, 51.7, 33.8, 32.2, 21.2.

Methyl 5-Oxopentanoate (31). To a solution of oxalylchloride (1.4 mL, 15.0 mmol) in CH_2Cl_2 (15 mL) at −78 °C was added dropwise a solution of DMSO (2.3 mL, 29.9 mmol) in CH_2Cl_2 (15.mL). The reaction mixture was stirred for 10 min, and then a solution of alcohol **30** (1.80 g, 13.6 mmol) in CH_2Cl_2 (15 mL) was added, and the reaction mixture was stirred for 30 min. Et_3N (10.1 mL, 72.5 mmol) was added, and the reaction mixture was allowed to warm to room temperature. The reaction mixture was then hydrolyzed with saturated aqueous NH_4Cl and extracted with EtOAc. The organic phase was dried over Na_2SO_4, filtered and concentrated under a vacuum. The residue was distilled bulb to bulb under a vacuum yielding aldehyde **31** (1.68 g, 95%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H (ppm) 9.78 (t, *J* = 1.3 Hz, 1H, C*H*O), 3.68 (s, 3H, CO_2CH_3), 2.54 (dt, *J* = 7.3, 1.3 Hz, 2H, H^4), 2.38 (t, *J* = 7.3 Hz, 2H, H^2), 1.96 (quint, *J* = 7.2 Hz, 2H, H^3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (ppm) 201.7, 173.5, 43.1, 33.1, 17.5.

Methyl 5-Hydroxyoct-7-enoate (32). A flask fitted with a reflux condenser was charged with a saturated aqueous NH_4Cl solution (8.0 mL), THF (1.5 mL) and aldehyde **31** (1.04 g, 8.0 mmol). Allylbromide (1.4 mL, 16.1 mmol) was added, followed by Zn dust (1.17 g, 17.9 mmol), which led to a very exothermic evolution. After 20 min the reaction was completed, and the mixture was diluted with water and 2 N HCl and extracted with EtOAc. The organic phase was dried over Na_2SO_4, filtered, concentrated under a vacuum, and purified by column chromatography (Heptane/EtOAc, 4/1) giving homoallylic alcohol **32** (900 mg, 65%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89−5.75 (m, 1H), 5.16−5.11 (m, 2H), 3.67 (s, 3H), 3.67−3.62 (m, 1H), 2.36 (t, *J* = 7.3 Hz, 2H), 2.20−2.10 (m, 1H), 1.86−1.66 (m, 3H), 1.55−1.43 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 134.8, 118.5, 70.4, 51.8, 42.1, 36.3, 34.1, 21.2; MS (ESI, TOF) *m*/*z* 195 (M + Na); HRMS (ESI, TOF) *m*/*z* calcd for $C_9H_{16}O_3{}^{23}Na$ $[M + Na]^+$ 195.0997, found 195.0996.

Methyl 5-Oxooct-7-enoate (8). A solution of oxalylchloride (0.84 mL, 0.6 mmol, 1.17 equiv) in CH_2Cl_2 (20 mL) was cooled to −78 °C, and a solution of DMSO (1.4 mL, 19.7 mmol) in CH_2Cl_2 (20 mL) was added dropwise. The reaction mixture was stirred for 10 min, and then a solution of alcohol **32** (1.41 g, 8.2 mmol) in CH_2Cl_2 (15 mL) was added dropwise. The solution was stirred for 20 min before introduction of Et_3N (6.0 mL, 43.0 mmol). The mixture was stirred at −78 °C for 4 h before being poured into a saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, filtered, concentrated under a vacuum and purified by column chromatography (Heptane/EtOAc, 9/1) giving homoallylic ketone **8** (1.10 g, 79%) as a colorless oil: IR (film) ν 2952, 2359, 1732, 1713, 1638, 1435, 1198, 1169 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98−5.85 (m, 1H), 5.21−5.11 (m, 2H), 3.68 (s, 3H), 3.17 (dt, *J* = 7.2, 1.7 Hz, 2H), 2.53 (t, *J* = 7.5 Hz, 2H), 2.34 (d, *J* = 7.5 Hz, 2H), 1.96−1.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.0, 173.8, 130.7, 119.1, 51.2, 48.0, 41.2, 33.2, 19.0; MS (EI) *m*/*z* 170 (M^+), 129, 101; Anal. Calcd for $C_9H_{14}O_3$ C 63.51; H 8.29, found C 63.50; H 8.45.

Methyl 6-((2*S*,6*R*,*Z*)-6-(2-*tert*-Butoxy-2-oxoethyl)-4-((trimethylsilyl)methylene)tetrahydro-2*H*-pyran-2-yl)-5-oxohexanoate (33). To a solution of homoallylic ketone **8** (654.0 mg, 3.85 mmol) and homopropargylic alcohol **7** (1.568 g, 6.1 mmol) in acetone (4 mL) were added $[CpRu(MeCN)_3]PF_6$ (127.8 mg, 0.29 mmol) and AcOH (7 μL, 0.12 mmol). The reaction mixture was stirred at room temperature for 1.5 h. The solvents were then evaporated under a vacuum, and the residue was purified by HPLC (Heptane/EtOAc, 8/1, 23 bar, 30 mL/min) giving tetrahydropyran **33** (1.28 g, 78%) as a colorless oil: $[\alpha]_D^{20}$ = +15.3 (*c* 1.05, $CHCl_3$); IR (film) ν 2933, 2358, 2339, 1702, 1407, 918 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.28 (s, 1H), 3.84−3.78 (m, 1H), 3.70−3.65 (m, 1H), 3.66 (s, 3H), 2.64 (dd, *J* = 8.2, 15.4 Hz, 1H), 2.52 (t, *J* = 8.2 Hz, 1H), 2.49−2.48 (m, 1H), 2.46−2.45 (m, 1H), 2.41 (dd, *J* = 4.7, 15.4 Hz, 1H), 2.34−2.30 (m, 3H), 2.18 (d, *J* = 12.9 Hz, 1H), 2.05 (t, *J* = 12.0 Hz, 1H), 1.91−1.84 (m, 4H), 1.44 (s, $9H_3$), 0.10 (s, $9H_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.2, 173.9, 170.2, 151.9, 124.6, 80.8, 75.2, 75.1, 51.7, 49.4, 45.2, 42.9, 42.6, 39.3, 33.2, 28.3, 18.8, 0.5; MS (EI) *m*/*z* 426

dx.doi.org/10.1021/jo301066p | *J. Org. Chem.* 2012, 77, 6728−6742

(M^+), 370, 282, 226, 181, 129, 101; Anal. Calcd for $C_{22}H_{38}O_6Si$ C 61.94; H 8.98. Found C 62.46; H 9.14.

(5*R*)-Methyl 6-((2*S*,6*R*,*Z*)-6-(2-*tert*-Butoxy-2-oxoethyl)-4-((trimethyl-silyl)methylene)tetrahydro-2*H*-pyran-2-yl)-5-hydroxyhexanoate (34a). (5*S*)-Methyl 6-((2*S*,6*R*,*Z*)-6-(2-*tert*-Butoxy-2-oxoethyl)-4-((trimethyl-silyl)methylene)tetrahydro-2*H*-pyran-2-yl)-5-hydroxyhexanoate (34b). To a solution of tetrahydropyran **33** (845.0 mg, 1.98 mmol) and $CeCl_3{\cdot}7H_2O$ (734.7 mg, 1.97 mmol) in MeOH (5 mL) was added $NaBH_4$ (81.5 mg, 2.2 mmol, 1.1 equiv) at 0 °C in small portions. The reaction mixture was stirred at 0 °C for 1 h and then diluted with water and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated under a vacuum. HPLC purification (Heptane/EtOAc, 5/1, 36 bar, 20 mL/min) allowed separation of diastereomer **34a** (460 mg, 54%) and diastrereoisomer **34b** (263 mg, 31%). Data for **34a**: $[\alpha]_D^{20}$ = +22.9 (*c* 0.94, $CHCl_3$); IR (film) ν 3524, 2949, 2358, 2339, 1728, 1622, 1366, 1246, 1153, 1131 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.26 (s, 1H), 3.86−3.81 (m, 1H), 3.79−3.68 (m, 1H), 3.66 (s, 3H), 3.64−3.57 (m, 1H), 2.51 (dd, *J* = 8.0 Hz, 15.3 Hz, 1H), 2.42−2.39 (m, 2H), 2.33 (t, *J* = 7.4 Hz, 1H), 2.11 (d, *J* = 6.5 Hz, 2H), 1.94 (t, *J* = 12.5 Hz, 2H), 1.81−1.65 (m, 2H), 1.62−1.56 (m, 2H), 1.54−1.37 (m, 2H), 1.46 (s, 9H), 0.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 170.3, 151.9, 124.5, 81.3, 80.4, 75.1, 71.6, 51.6, 45.8, 42.8, 42.6, 39.4, 36.9, 34.2, 28.3, 21.1, 0.5; MS (ESI, TOF) *m*/*z* 451 ([M + Na]$^+$); HRMS (ESI, TOF) *m*/*z* calcd for $C_{22}H_{40}O_6{}^{23}NaSi$ [M + Na]$^+$ 451.2492, found 451.2524. Data for **34b**: $[\alpha]_D^{20}$ = +18.1 (*c* 1.28, $CHCl_3$); IR (film) ν 3484, 2949, 2359, 1729, 1622, 1247, 1152, 1132 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.26 (s, 1H), 3.88−3.80 (m, 1H), 3.74−3.63 (m, 1H), 3.68 (s, 3H), 2.82 (d, *J* = 4.6 Hz, 1H), 2.53−2.42 (m, 2H), 2.39 (d, *J* = 5.0 Hz, 1H), 2.36−2.31 (m, 2H), 2.18 (t, *J* = 11.6 Hz, 1H), 2.07 (d, *J* = 13.1 Hz, 1H), 1.93 (t, *J* = 12.4 Hz, 1H), 1.84−1.73 (m, 1H), 1.72−1.56 (m, 4H), 1.55−1.40 (m, 2H), 1.46 (s, 9H), 0.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 170.5, 152.4, 124.4, 81.1, 76.4, 75.2, 68.4, 51.6, 45.2, 42.7, 41.9, 39.4, 36.4, 34.2, 28.3, 21.6, 0.5; MS (ESI, TOF) *m*/*z* 451 ([M + Na]$^+$); HRMS (ESI, TOF) *m*/*z* calcd for $C_{22}H_{40}O_6{}^{23}NaSi$ [M + Na]$^+$ 451.2492, found 451.2476.

(5*R*)-Methyl 6-((2*S*,6*R*,*Z*)-6-(2-*tert*-Butoxy-2-oxoethyl)-4-(iodomethylene)tetrahydro-2*H*-pyran-2-yl)-5-hydroxyhexanoate (35). A solution of **34a** (90 mg, 0.21 mmol) in CH_3CN (3 mL) was protected from light and cooled to 0 °C, and then NIS (78.6 mg, 0.35 mmol) was added, and the reaction was stirred at 0 °C for 25 min. The reaction mixture was hydrolyzed by addition of a solution of sodium thiosulfate and extracted with EtOAc. The organic layer was dried over Na_2SO_4, filtered and concentrated under a vacuum. Column chromatography (Heptane/EtOAc, 4/1) gave the desired vinyl iodide **35** (100 mg, 99%) as a colorless oil: $[\alpha]_D^{20}$ = +49.1 (*c* 1.07, $CHCl_3$); IR (film) ν 3521, 2947, 1726, 1367, 1264, 1151, 1134 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.99 (s, 1H), 3.86−3.70 (m, 2H), 3.66 (s, 3H), 3.61−3.53 (m, 1H), 3.47 (m, 1H), 2.70 (dt, *J* = 1.8, 13.7 Hz, 1H), 2.52 (dd, *J* = 15.6, 6.5 Hz, 1H), 2.45 (dd, *J* = 4.3, 15.3 Hz, 1H), 2.39−2.36 (m, 1H), 2.33 (t, *J* = 7.4 Hz, 2H), 2.07 (t, *J* = 12.2 Hz, 1H), 1.88 (t, *J* = 12.5 Hz, 1H), 1.80−1.57 (m, 5H), 1.53−1.39 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 170.1, 145.1, 81.5, 79.5, 74.7, 74.4, 71.3, 51.7, 43.2, 42.33, 42.30, 40.9, 36.9, 34.1, 28.3, 21.1; MS (ESI, TOF) *m*/*z* 505 ([M + Na]$^+$); HRMS (ESI, TOF) *m*/*z* calcd for $C_{19}H_{31}IO_6{}^{23}Na$ [M + Na]$^+$ 505.1063, found 505.1082.

(5*R*)-Methyl 6-((2*S*,6*R*,*Z*)-6-(2-*tert*-Butoxy-2-oxoethyl)-4-(2-methoxy-2-oxoethylidene)tetrahydro-2*H*-pyran-2-yl)-5-hydroxyhexanoate (36). To a solution of vinyl iodode **35** (75 mg, 0.16 mmol) in MeOH (3 mL) were added $PdCl_2$(dppf) (5.9 mg, 8.1 μmol) and Et_3N (43 μL, 0.31 mmol). The reaction flask was purged with CO, and the reaction mixture was refluxed under vigorous stirring for 45 min. After cooling to room temperature, the reaction mixture was concentrated under a vacuum. Column chromatography (Heptane/EtOAc, 2/1) gave the desired ester **36** (48 mg, 75%) as a brown oil: IR (film) ν 3526, 2948, 1714, 1650, 1149 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.70 (s, 1H), 3.85 (dd, *J* = 1.9, 13.7 Hz, 1H), 3.84−3.78 (m, 3H), 3.69 (s, 3H), 3.66 (s, 3H), 3.48 (s, 1H), 2.53−2.43 (m, 3H), 2.33 (t, *J* = 7.3 Hz, 3H), 2.16 (d, *J* = 6.4 Hz, 3H), 1.89 (t, *J* = 12.5 Hz, 1H), 1.80−1.58 (m, 8H), 1.54−1.39 (m, 6H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 170.0, 166.6, 155.5, 115.1, 81.2, 79.5, 74.5, 71.1, 51.5, 51.0, 42.6, 42.2, 36.6, 34.9, 33.9, 28.0, 20.9; MS (ESI, TOF) *m*/*z* 437 ([M + Na]$^+$); HRMS (ESI, TOF) *m*/*z* calcd for $C_{21}H_{34}O_8{}^{23}Na$ [M + Na]$^+$ 437.2151, found 437.2144.

***tert*-Butyl 2-((2*R*,6*S*,*Z*)-4-(2-Methoxy-2-oxoethylidene)-6-(((*R*)-6-oxotetrahydro-2*H*-pyran-2-yl)methyl)tetrahydro-2*H*-pyran-2-yl)acetate (37).** To a solution of alcohol **36** (66 mg, 0.16 mmol) in toluene (3 mL) was added silica (59.4 mg). The suspension was refluxed for 26 h and then filtered and concentrated under a vacuum. Column chromatography purification (Heptane/EtOAc, 2/1) gave lactone **37** (44 mg, 72%) as a colorless oil: $[\alpha]_D^{20}$ = +48.5 (*c* 0.70, $CHCl_3$); IR (film) ν 2949, 1714, 1650, 1366, 1239, 1150 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.70 (s, 1H), 4.54−4.46 (m, 1H), 3.85 (d, *J* = 13.9 Hz, 1H), 3.79−3.66 (m, 1H), 3.69 (s, 3H), 3.62−3.55 (m, 1H), 2.62−2.51 (m, 1H), 2.50−2.38 (m, 3H), 2.25−2.16 (m, 2H), 2.11−1.70 (m, 7H), 1.66−1.50 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 170.1, 166.8, 156.0, 115.3, 80.8, 74.6, 74.1, 51.2, 42.6, 42.3, 41.5, 35.1, 29.6, 29.5, 28.2, 27.2, 18.7; MS (ESI, TOF) *m*/*z* 405 ([M + Na]$^+$); HRMS (ESI, TOF) *m*/*z* calcd for $C_{20}H_{30}O_7{}^{23}Na$ [M + Na]$^+$ 405.1889, found 405.1889.

(3*S*,4*E*,6*R*,7*S*,8*E*)-7-(*tert*-Butyldimethylsilyloxy)-3,6-dimethyl-9-(trimethylsilyl)nona-4,8-dienenitrile (39). To a solution of alcohol **17** (584.9 mg, 1.64 mmol) in Et_2O (9 mL) at room temperature was added PPh_3 (1.720 g, 6.6 mmol), and then DEAD (1.0 mL, 6.6 mmol), and acetone cyanohydrin (375 μL, 4.1 mmol). The solution was then stirred for 5 h at room temperature, quenched by addition of water and extracted with CH_2Cl_2. The organic phase was washed with water, dried over anhydrous Na_2SO_4 and filtered. DEAD (0.2 mL, 1.3 mmol, 0.8 equiv) was added to consume the excess of PPh_3, and then the organic layer was concentrated under a vacuum. The crude oil was purified by column chromatography (Heptane/EtOAc, 40/1) to give nitrile **39** (451.0 mg, 75%): R_f = 0.42 (Heptane/EtOAc, 10/1); $[\alpha]_D^{20}$ = +2.6 (*c* 1.06, $CHCl_3$); IR (film) ν 2956, 2856, 1458, 1248, 1107, 836, 775, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.91 (dd, *J* = 18.7, 6.0 Hz, 1H), 5.73 (d, *J* = 18.6 Hz, 1H), 5.50 (dd, *J* = 15.6, 7.3 Hz, 1H), 5.32 (dd, *J* = 15.6, 7.0 Hz, 1H), 3.89 (dd, *J* = 5.5, 5.2 Hz, 1H), 2.56−2.48 (m, 1H), 2.34 (dd, *J* = 16.5, 6.1 Hz, 1H), 2.27 (dd, *J* = 16.5, 7.0 Hz, 1H), 2.24−2.18 (m, 1H), 1.14 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 9H), 0.02 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 147.6, 134.2, 131.6, 130.3, 118.8, 79.5, 43.1, 33.8, 26.1, 25.2, 20.0, 18.4, 15.3, −1.1, −4.0, −4.7; LRMS (ESI, TOF) *m*/*z* (%) 388.2 (100) [M + Na]$^+$; HRMS (ESI, TOF) *m*/*z* calcd for $C_{20}H_{39}NO^{23}NaSi_2$ [M + Na]$^+$ 388.2468, found 388.2476.

(3*S*,4*E*,6*R*,7*S*,8*E*)-7-(*tert*-Butyldimethylsilyloxy)-3,6-dimethyl-9-(trimethylsilyl)nona-4,8-dienal (40). To a solution of nitrile **39** (446.5 mg, 1.22 mmol) in CH_2Cl_2 (10 mL) at −78 °C was added a 1.0 M solution of di-*iso*-butylaluminium hydride in heptane (2.4 mL, 2.4 mmol). The solution was allowed to warm to 0 °C over 1.75 h and stirred at this temperature for 30 min. The solution was quenched at 0 °C by adding a saturated aqueous solution of Rochelle salt, stirred for 2.5 h, and extracted with CH_2Cl_2. The organic layer was washed with water, dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum to give aldehyde **40** (425.5 mg, 95%): R_f = 0.46 (Heptane/EtOAc, 10/1); $[\alpha]_D$ = +21.0 (*c* 1.03, $CHCl_3$); IR (film) ν 2954, 2928, 2856, 1729, 1247, 833, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.71 (s, 1H), 5.90 (dd, *J* = 18.6, 5.9 Hz, 1H), 5.71 (d, *J* = 18.6 Hz, 1H), 5.40 (dd, *J* = 15.6, 7.3 Hz, 1H), 5.32 (dd, *J* = 15.6, 6.7 Hz, 1H), 3.86 (dd, *J* = 5.5, 5.2 Hz, 1H), 2.75−2.67 (m, 1H), 2.40 (ddd, *J* = 15.9, 7.0, 1.8 Hz, 1H), 2.31 (ddd, *J* = 15.9, 7.0, 2.1 Hz, 1H), 2.21−2.14 (m, 1H), 1.04 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 9H), 0.01 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.8, 147.8, 133.7, 132.6, 130.1, 79.6, 50.6, 43.2, 31.8, 26.1, 20.8, 18.4, 15.5, −1.2, −4.0, −4.7; LRMS (ESI, TOF) *m*/*z* (%) 391.2 (51) [M + Na]$^+$, 423.3 (100) [M + MeOH + Na]$^+$; HRMS (ESI, TOF) *m*/*z* calcd for $C_{20}H_{40}O_2{}^{23}NaSi_2$ [M + Na]$^+$ 391.2465, found 391.2472.

(4*S*,6*S*,7*E*,9*R*,10*S*,11*E*)-10-(*tert*-Butyldimethylsilyloxy)-6,9-dimethyl-12-(trimethylsilyl)dodeca-1,7,11-trien-4-ol (41). To a solution of (−)Ipc_2BOMe (772.4 mg, 2.4 mmol, 2.2 equiv) in Et_2O (5 mL) at 0 °C was added a 1.0 M solution of allylmagnesium bromide in Et_2O (2.4 mL, 2.4 mmol, 2.2 equiv). The solution was allowed to

dx.doi.org/10.1021/jo301066p | J. Org. Chem. 2012, 77, 6728−6742

warm to room temperature and stirred for 1.5 h leading to the formation of a white precipitate. After cooling down to −78 °C, a solution of aldehyde **40** (368.7 mg, 1.22 mmol, 1.0 equiv) in Et_2O (10 mL) at 0 °C was added, and the resulting solution was stirred at −78 °C for 1 h, 30 min at 0 °C, and then 45 min at room temperature. The solution was cooled at 0 °C and quenched by addition of H_2O_2 30% (6 mL) and 2 N aqueous NaOH (6 mL). The resultant mixture was stirred at room temperature for 16 h and then extracted with Et_2O. The organic layer was washed with water, dried over anhydrous Na_2SO_4, filtered and concentrated under a vacuum. HPLC purification (Heptane/EtOAc, 30/1; 40 mL/min) allowed separation of the two diastereomers (*dr* 93/7, by ^1H NMR) and gave homoallylic alcohol **41** (261.5 mg, 58%): R_f = 0.36 (Heptane/EtOAc, 10/1); $[\alpha]_D^{20}$ = +18.0 (*c* 1.12, $CHCl_3$); IR (film) ν 3380, 2954, 2924, 2857, 1462, 1248, 833, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.95 (dd, *J* = 18.6, 5.8 Hz, 1H), 5.86−5.78 (m, 1H), 5.75 (d, *J* = 18.9 Hz, 1H), 5.38 (dd, *J* = 15.6, 7.6 Hz, 1H), 5.22 (dd, *J* = 15.6, 8.2 Hz, 1H), 5.13 (d, *J* = 4.6 Hz, 1H), 5.10 (s, 1H), 3.90 (dd, *J* = 5.2, 4.9 Hz, 1H), 3.72−3.67 (m, 1H), 2.39−2.31 (m, 1H), 2.27−2.12 (m, 3H), 1.46−1.33 (m, 2H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 9H), 0.02 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 147.6, 135.5, 135.1, 132.0, 129.9, 118.0, 79.6, 68.7, 44.2, 43.3, 42.5, 33.9, 26.1, 21.9, 18.5, 15.9, −1.1, −4.0, −4.7; LRMS (ESI, TOF) *m*/*z* (%) 433.3 (100) $[M + Na]^+$; HRMS (ESI, TOF) *m*/*z* calcd for $C_{23}H_{46}O_2{}^{23}NaSi_2$ $[M + Na]^+$ 433.2934, found 433.2947.

(5*S*,6*R*,9*S*,11*S*,*E*)-11-Allyl-13,13-diisopropyl-2,2,3,3,6,9,14-heptamethyl-5-((*E*)-2-(trimethylsilyl)vinyl)-4,12-dioxa-3,13-disilapentadec-7-ene (42). To a solution of homoallylic alcohol **41** (240.6 mg, 0.59 mmol) and 2,6-lutidine (140 μL, 1.2 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added TIPSOTf (190 μL, 0.7 mmol). The solution was stirred at 0 °C for 2 h, quenched at 0 °C with water and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous NH_4Cl, dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. Purification by column chromatography (Heptane/CH_2Cl_2, 30/1) gave triene **42** (323.5 mg, 97%): R_f = 0.48 (Heptane/CH_2Cl_2, 10/1); $[\alpha]_D^{20}$ = +13.2 (*c* 1.12, $CHCl_3$); IR (film) ν 2954, 2865, 2358, 1462, 1248, 1060, 835, 774, 676 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.93 (dd, *J* = 18.6, 5.8 Hz, 1H), 5.91−5.82 (m, 1H), 5.71 (d, *J* = 18.9 Hz, 1H), 5.35 (dd, *J* = 15.6, 6.7 Hz, 1H), 5.26 (dd, *J* = 15.6, 7.0 Hz, 1H), 5.05 (d, *J* = 3.4 Hz, 1H), 5.02 (s, 1H), 3.94−3.89 (m, 1H), 3.86 (t, *J* = 5.5 Hz, 1H,), 2.34−2.12 (m, 4H), 1.73−1.34 (m, 5H), 1.06 (s, 18H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 9H), 0.02 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 148.1, 135.9, 135.1, 130.9, 129.7, 116.9, 79.8, 70.4, 44.1, 43.1, 41.8, 33.2, 32.1, 26.1, 22.9, 21.1, 18.4, 15.4, 12.9, −1.1, −4.0, −4.6; LRMS (ESI, TOF) *m*/*z* (%) 589.4 (100) $[M + Na]^+$; HRMS (ESI, TOF) *m*/*z* calcd for $C_{32}H_{66}O_2{}^{23}NaSi_3$ $[M + Na]^+$ 589.4268, found 589.4270.

(4*S*,6*S*,7*E*,9*R*,10*S*,11*E*)-10-(*tert*-Butyldimethylsilyloxy)-6,9-dimethyl-4-(triisopropylsilyloxy)-12-(trimethylsilyl)dodeca-7,11-dien-1-ol (43). A solution of triene **42** (173.7 mg, 0.31 mmol) and solid 9-BBN (41.1 mg, 0.4 mmol) in THF (2 mL) was stirred at room temperature for 17.5 h. Solid 9-BBN dimer (11.2 mg, 0.05 mmol) was added, and the solution was stirred at room temperature for 4 h, and then it was heated at 40 °C for 2 h. Then H_2O_2 30% (1 mL), 3 N aqueous NaOH (1 mL) and EtOH (1 mL) were added, and the mixture was stirred at room temperature for 1 h. After extraction by CH_2Cl_2, the organic phase was washed with saturated aqueous $Na_2S_2O_3$ and water, dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. Purification by column chromatography (Heptane/CH_2Cl_2, 30/1 then 10/1 and Heptane/EtOAc 20/1 then 10/1) gave alcohol **43** (134.0 mg, 75%): R_f = 0.62 (Heptane/EtOAc, 1/1); $[\alpha]_D^{20}$ = 0.00 (*c* 1.05, $CHCl_3$); IR (film) ν 3328, 2928, 2864, 1462, 1248, 1056, 835, 774, 675 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.93 (dd, *J* = 18.6, 5.8 Hz, 1H), 5.72 (d, *J* = 18.6 Hz, 1H), 5.36 (dd, *J* = 15.6, 7.0 Hz, 1H), 5.28 (dd, *J* = 15.6, 6.7 Hz, 1H), 3.99−3.95 (m, 1H), 3.87 (t, *J* = 5.5 Hz, 1H), 3.67−3.59 (m, 2H), 2.42−2.40 (m, 0.5H), 2.18−2.10 (m, 2H), 1.89−1.86 (m, 0.5H), 1.65−1.38 (m, 9H), 1.07 (s, 18H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 9H), 0.02 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 148.1, 137.2, 135.9, 130.9, 129.7, 79.8, 70.4, 63.5, 43.3, 43.0, 33.4, 33.0, 29.5, 27.4, 26.1, 22.9, 20.7, 18.5, 18.4, 15.3, 12.8, −1.1, −4.0, −4.6; LRMS (ESI, TOF) *m*/*z* (%) 607.4 (100) $[M + Na]^+$; HRMS (ESI, TOF) *m*/*z* calcd for $C_{32}H_{68}O_3{}^{23}NaSi_3$ $[M + Na]^+$ 607.4374, found 607.4365.

(5*S*,7*S*,8*E*,10*R*,11*S*,12*E*)-11-(*tert*-Butyldimethylsilyloxy)-7,10-dimethyl-5-(triisopropylsilyloxy)-13-(trimethylsilyl)trideca-8,12-dienenitrile (44). To a solution of alcohol **43** (166.0 mg, 0.28 mmol) and PPh_3 (297.6 mg, 1.1 mmol, 4.0 equiv) in Et_2O (2 mL) at room temperature was added DEAD (185 μL, 1.2 mmol), and acetone cyanohydrin (80 μL, 0.9 mmol). The reaction mixture was then stirred for 15 h at room temperature, concentrated and then purified by column chromatography (Heptane/CH_2Cl_2, 10/1, 6/1 and 2/1) to give nitrile **44** (122.0 mg, 72%): R_f = 0.11 (Heptane/CH_2Cl_2, 10/1); $[\alpha]_D^{20}$ = +0.1 (*c* 1.09, $CHCl_3$); IR (film) ν 2954, 2928, 2865, 1462, 1248, 836, 775, 677 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.92 (dd, *J* = 18.6, 5.9 Hz, 1H), 5.72 (d, *J* = 18.6 Hz, 1H), 5.35 (dd, *J* = 15.6, 7.0 Hz, 1H), 5.26 (dd, *J* = 15.6, 7.0 Hz, 1H), 3.96−3.92 (m, 1H), 3.87 (t, *J* = 5.5 Hz, 1H), 2.39−2.31 (m, 2H), 2.18−2.09 (m, 2H), 1.81−1.40 (m, 9H), 1.05 (s, 18H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 9H), 0.02 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 148.0, 135.7, 131.1, 129.8, 79.8, 69.8, 43.8, 43.0, 35.4, 33.5, 26.1, 20.8, 20.3, 18.4, 17.7, 15.4, 12.9, −1.1, −4.0, −4.6; LRMS (ESI, TOF) *m*/*z* (%) 616.4 (100) $[M + Na]^+$; HRMS (ESI, TOF) *m*/*z* calcd for $C_{33}H_{67}NO_2{}^{23}NaSi_3$ $[M + Na]^+$ 616.4377, found 616.4388.

(5*S*,7*S*,8*E*,10*R*,11*S*,12*E*)-11-(*tert*-Butyldimethylsilyloxy)-7,10-dimethyl-5-(triisopropylsilyloxy)-13-(trimethylsilyl)trideca-8,12-dienal (45). To a solution of nitrile **44** (117.2 mg, 0.20 mmol) in CH_2Cl_2 (2 mL) at −78 °C was added a 1.0 M solution of diisobutylaluminium hydride in heptane (395 μL, 0.4 mmol). The solution was allowed to warm to 0 °C over 1.5 h and was stirred at 0 °C for 2 h. The solution was quenched at 0 °C by addition of a saturated aqueous Rochelle salt solution, stirred for 1.5 h and extracted with CH_2Cl_2. The organic phase was washed with water, dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum to give aldehyde **45** (118 mg, 100%): R_f = 0.52 (Heptane/EtOAc, 7/1); $[\alpha]_D^{20}$ = +6.3 (*c* 1.08, $CHCl_3$); IR (film) ν 2954, 2928, 2865, 1731, 1462, 1248, 1059, 836, 775, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.76 (s, 1H), 5.92 (dd, *J* = 18.6, 5.8 Hz, 1H), 5.72 (d, *J* = 18.6 Hz, 1H), 5.36 (dd, *J* = 15.6, 6.7 Hz, 1H), 5.27 (dd, *J* = 15.6, 7.0 Hz, 1H), 3.93−3.86 (m, 2H), 2.44−2.40 (m, 1H), 2.19−2.13 (m, 2H), 1.76−1.35 (m, 10H), 1.05 (s, 18H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 9H), 0.02 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.8, 148.1, 135.8, 131.0, 129.8, 79.8, 70.3, 44.3, 43.9, 43.0, 36.2, 33.4, 26.1, 20.9, 18.4, 17.0, 15.4, 12.9, −1.1, −4.0, −4.6; LRMS (ESI, TOF) *m*/*z* (%) 619.5 (5) $[M + Na]^+$, 651.5 (100) $[M + MeOH + Na]^+$; HRMS (ESI, TOF) *m*/*z* calcd for $C_{34}H_{72}O_4{}^{23}NaSi_3$ $[M + MeOH + Na]^+$ 651.4636, found 651.4639.

(8*S*,10*S*,11*E*,13*R*,14*S*,15*E*)-14-(*tert*-Butyldimethylsilyloxy)-10,13-dimethyl-8-(triisopropylsilyloxy)-16-(trimethylsilyl)-hexadeca-1,11,15-trien-4-ol (46). To a solution of crude aldehyde **45** (0.20 mmol) in Et_2O (2 mL) at 0 °C was added a 1.0 M solution of allylmagnesium bromide in Et_2O. The solution was stirred at 0 °C for 2.25 h and at room temperature for 1 h, and then quenched by addition of a saturated aqueous NH_4Cl solution (60 μL). A white precipitate appeared, and the mixture was filtered over a silica pad. The crude product was purified by column chromatography (Heptane/EtOAc, 25/1, 20/1 and 15/1) to give homoallylic alcohol **46** (65.4 mg, 52%): R_f = 0.37 (Heptane/EtOAc, 7/1); IR (film) ν 2928, 2864, 1462, 1248, 1058, 993, 835, 774, 675 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.93 (dd, *J* = 18.6, 5.9 Hz, 1H), 5.87−5.79 (m, 1H), 5.71 (d, *J* = 18.6 Hz, 1H), 5.36 (dd, *J* = 15.6, 6.7 Hz, 1H), 5.27 (dd, *J* = 15.6, 6.7 Hz, 1H), 5.15 (br s, 1H), 5.12 (s, 1H), 3.89−3.85 (m, 2H), 3.65 (br s, 1H), 2.34−2.28 (m, 1H), 2.21−2.11 (m, 3H), 1.73−1.38 (m, 12H), 1.05 (s, 18H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 9H), 0.02 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 148.1, 136.0, 135.9, 130.8, 129.7, 118.3, 79.8, 70.8, 70.7, 44.1, 43.0, 42.0, 37.3, 37.0, 33.4, 26.1, 21.1, 20.4, 18.4, 15.4, 13.0, −1.1, −4.0, −4.6; LRMS (ESI, TOF) *m*/*z* (%) 661.5 (100) [M +

dx.doi.org/10.1021/jo301066p | *J. Org. Chem.* 2012, 77, 6728−6742

Na]$^+$; HRMS (ESI, TOF) m/z calcd for $C_{36}H_{74}O_3{}^{23}NaSi_3$ [M + Na]$^+$ 661.4844, found 661.4844.

(8*S*,10*S*,11*E*,13*R*,14*S*,15*E*)-14-(*tert*-Butyldimethylsilyloxy)-10,13-dimethyl-8-(triisopropylsilyloxy)-16-(trimethylsilyl)-hexadeca-1,11,15-trien-4-one (38). To a solution of homoallylic alcohol **46** (59.4 mg, 0.093 mmol) in CH_2Cl_2 (1 mL) at room temperature was added Dess−Martin periodinane (59.1 mg, 0.14 mmol). The solution was stirred for 2 h, and then more Dess−Martin periodinane (31.0 mg, 0.073 mmol) was added. The solution was stirred for another 1.5 h, quenched by addition of a saturated aqueous $NaHCO_3$ solution and $Na_2S_2O_3$, and then extracted with CH_2Cl_2. The organic phase was washed with saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$, dried over anhydrous Na_2SO_4, filtered, and concentrated under a vacuum. The crude product was purified by column chromatography (Heptane/Et_2O, 50/1 and 40/1) to give homoallylic ketone **38** (38.9 mg, 66%): R_f = 0.21 (Heptane/Et_2O, 40/1); $[\alpha]_D{}^{20}$ = +3.7 (c 0.30, $CHCl_3$); IR (film) ν 2955, 2865, 1720, 1462, 1248, 1060, 882, 837, 775, 678 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.96−5.88 (m, 2H), 5.71 (d, J = 18.6 Hz, 1H), 5.36 (dd, J = 15.7, 6.8 Hz, 1H), 5.27 (dd, J = 15.7, 6.8 Hz, 1H), 5.18 (d, J = 10.1 Hz, 1H), 5.13 (d, J = 17.1 Hz, 1H), 3.90−3.84 (m, 2H), 3.16 (d, J = 7.0 Hz, 2H), 2.49−2.38 (m, 2H), 2.19−2.12 (m, 2H), 1.69−1.36 (m, 9H), 1.05 (s, 18H), 0.94 (s, 3H), 0.92 (s, 3H), 0.89 (s, 9H), 0.04 (s, 9H), 0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 208.8, 148.1, 135.9, 130.9, 129.7, 118.8, 79.9, 70.5, 47.8, 44.0, 43.0, 42.8, 36.4, 33.4, 26.1, 21.0, 18.7, 18.4, 15.4, 12.9, −1.1, −3.9, −4.6; LRMS (ESI, TOF) m/z (%) 659.5 (100) [M + Na]$^+$; HRMS (ESI, TOF) m/z calcd for $C_{36}H_{72}O_3{}^{23}NaSi_3$ [M + Na]$^+$ 659.4687, found 659.4695.

***tert*-Butyl-2-((2*R*,6*S*,*Z*)-6-((6*S*,8*S*,9*E*,11*R*,12*S*,13*E*)-12-(*tert*-butyldimethylsilyloxy)-8,11-dimethyl-2-oxo-6-(triisopropylsilyloxy)-14-(trimethylsilyl)tetradeca-9,13-dienyl)-4-((trimethylsilyl)methylene)tetrahydro-2*H*-pyran-2-yl)acetate (47).** A solution of homoallylic ketone **38** (38.9 mg, 0.061 mmol), homoallylic alcohol **7** (25.0 mg, 0.1 mmol), $[CpRu(MeCN)_3]PF_6$ (1.9 mg, 4.3 μmol) and AcOH (0.1 μL, 1.8 μmol) in acetone (200 μL) was stirred at room temperature for 5.5 h. The mixture was then filtered over a silica pad, and the crude oil was purified by column chromatography (Heptane/Et_2O, 50/1 and 40/1, then Heptane/EtOAc, 30/1 and 20/1) to give tetrahydropyran **47** (39.1 mg, 72%): R_f = 0.49 (Heptane/EtOAc, 10/1); $[\alpha]_D{}^{20}$ = +9.4 (c 0.89, $CHCl_3$); IR (film) ν 2953, 2865, 1731, 1623, 1462, 1366, 1248, 1062, 993, 834, 774, 675 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (dd, J = 18.6, 5.8 Hz, 1H), 5.71 (d, J = 18.9 Hz, 1H), 5.36 (dd, J = 15.8, 6.7 Hz, 1H), 5.28 (s, 1H), 5.27 (dd, J = 15.3, 7.0 Hz, 1H), 3.89−3.79 (m, 3H), 3.70−3.65 (m, 1H), 2.66 (dd, J = 15.6, 7.6 Hz, 1H), 2.50−2.37 (m, 5H), 2.33 (dd, J = 14.7, 6.1 Hz, 1H), 2.20−2.13 (m, 3H), 2.03 (t, J = 12.2 Hz, 1H), 1.88 (t, J = 12.2 Hz, 1H), 1.65−1.36 (m, 9H), 1.44 (s, 9H), 1.05 (s, 18H), 0.94 (s, 3H), 0.92 (s, 3H), 0.89 (s, 9H), 0.10 (s, 9H), 0.04 (s, 9H), 0.02 (s, 3H), −0.02 (s, 3H$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 208.8, 170.2, 152.0, 148.1, 135.9, 130.8, 129.7, 124.5, 80.7, 79.8, 75.1, 70.6, 49.1, 45.1, 44.2, 44.0, 43.0, 39.3, 36.5, 33.3, 28.2, 26.1, 21.0, 18.6, 18.4, 15.4, 12.9, 0.4, −1.1, −4.0, −4.6; LRMS (ESI, TOF) m/z (%) 915.6 (100) [M + Na]$^+$; HRMS (ESI, TOF) m/z calcd for $C_{49}H_{96}O_6{}^{23}NaSi_4$ [M + Na]$^+$ 915.6182, found 915.6149.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

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■ ACKNOWLEDGMENTS

We thank CNRS for its financial support. We thank Dr. Yves Janin (Institut Pasteur, Paris) for all the fruitful scientific discussions we used to have.

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