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Strategic use of nickel(0)-catalyzed enyne–epoxide reductive coupling toward the synthesis of (−)-cyatha-3,12-diene

Brian A. Sparling, Graham L. Simpson, Timothy F. Jamison *

Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge, MA 02139, USA

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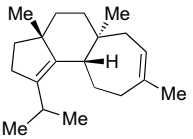
ABSTRACT

Various situations are explored in which the nickel(0)-catalyzed enyne–epoxide reductive coupling was utilized to access key intermediates toward the total synthesis of (−)-cyatha-3,12-diene (**1**). Enantioenriched 3,5-dien-1-ols with a variety of functionality were obtained in a straightforward manner from easily accessible 1,3-enynes and terminal epoxides.

1. Introduction

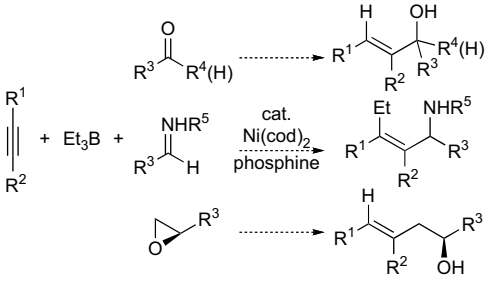
The cyathanes are diterpenoid fungal metabolites having a structurally unique fused, angular tricyclic core composed of contiguous five-, six-, and seven-membered rings.[1] Many cyathanes are known to have pronounced antifungal and antibacterial properties, and some potently induce nerve growth factor (NGF) production in human nerve cells.[2,3] In 1979, Ayer et al. hypothesized that tricycle **1** was the common biological precursor of all cyathane metabolites;[4] 22 years after the initial proposal, this compound was isolated from the basidiomycete *Hericium erinaceum* YB4-6237 and named (−)-cyatha-3,12-diene (**1**).[5] Its potential role in cyathane biosynthesis along with its unknown biological properties and low abundance in nature makes cyatha-3,12-diene an attractive target for total synthesis.



1; (−)-cyatha-3,12-diene

Various strategies have been employed toward the synthesis of cyathane natural products; however, all of such approaches rely on stepwise installation of the central three rings.[6] A possible alternative to these strategies is a transannular Diels–Alder (TADA) reaction to form the characteristic cyathane core from a 14-membered macrocyclic triene in a single step. While a TADA reaction has not been utilized in the synthesis of fused 5,6,7-ring systems, it has been successfully implemented in the synthesis of tricyclic systems bearing three fused six-membered rings and a fused 5,6,6-ring system.[7,8]

A focus of our research program has been the catalytic, multicomponent coupling reaction involving cis addition across an alkyne.[9] Generally, we have found that use of a low-valent nickel catalyst, an electron-rich trialkylphosphine ligand, and triethylborane as a stoichiometric reductant affords reductive or alkylative alkyne coupling in a variety of functional contexts to form (*E*)-trisubstituted or tetrasubstituted olefins (Scheme 1). Specifically, alkynes have been coupled to electrophilic double bonds including aldehydes,[10] ketones,[11] and imines[12] in the presence of triethylborane to form allylic alcohols and allylic amines. Asymmetric variants of such couplings have also been developed using chiral phosphine ligands,[13] and enantioenriched α-oxyaldehydes have been shown to couple with high diastereoselectivity to form *anti*-1,2-diols.[14]



Scheme 1.

Regioselective addition across the alkyne has been a challenge for these intermolecular coupling reactions and several solutions have been implemented. The presence of a trimethylsilyl group on

* Corresponding author. Tel.: +1 617 253 1830; fax: +1 617 253 3297.
E-mail address: tfj@mit.edu (T.F. Jamison).

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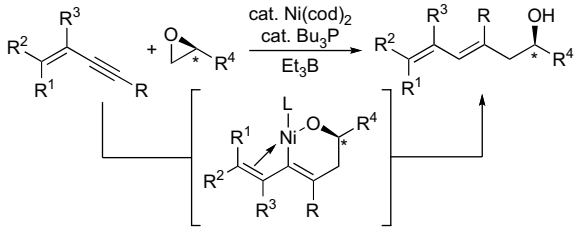
the alkyne terminus or the presence of conjugated aryl groups and olefins[10b] directs coupling to the terminal end of the alkyne. In the olefin case, transient interaction of the conjugated π-bond with the metal center may direct the addition (Scheme 2). With this potential to afford high regioselectivity and stereoselectivity, we have implemented alkyne reductive coupling strategies toward the synthesis of complex natural products, such as (−)-terpestacin[15] and members of the amphidinolide T class.[16]



Scheme 2.

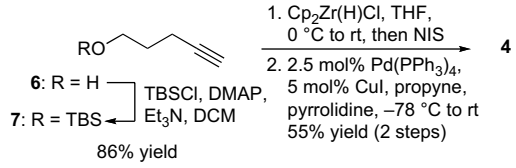
Aside from alkyne additions to electrophilic double bonds, we have also expanded the scope of the reductive coupling to include additions to the electrophilic single bonds of terminal epoxides to afford homoallylic alcohols (Schemes 1 and 2).[17] Addition occurs regioselectively to the terminal end of the epoxide and retention of epoxide configuration is observed in the product alcohol. An oxanickelacycle is proposed to be an intermediate during the fragment coupling,[18] and the use of a 1,3-enyne may impart regioselectivity in the key bond-forming step.[10b] As such a coupling would afford substrates bearing 3,5-dien-1-ol functionality in a straightforward manner, we sought to use this transformation to rapidly access the core of (−)-cyatha-3,12-diene.

A retrosynthetic analysis leading to the target (**1**) is presented in Scheme 3. Tricyclic ketone **2** was selected as a key intermediate, possessing the key trans-6,7 ring junction (C5 and C6), and it may be accessed directly from 14-membered macrocyclic triene **3** via a TADA reaction. The two adjacent stereocenters at C12 and C13, though not present in the natural product, are the means by which the naturally occurring enantiomer **1** will be prepared. The sterically demanding TIPS group as shown should occupy a pseudoequatorial position in the macrocycle and provide the only conformation in which the methyl group of the 1,3-diene at C6 can avoid a severe steric interaction with the groups at C13.[19] To examine the conformational effects of the TIPS group, the C12 epimer of **3** would be made as well. The 3,5-dien-1-ol present in **3** can be conveniently accessed from the nickel(0)-catalyzed reductive coupling of enyne **4** and known epoxide **5**.

Reported herein are the efforts toward the synthesis of **1**, with a focus on the application of the nickel(0)-catalyzed enyne–epoxide reductive coupling in various strategic contexts.

2. Results and discussion

The synthesis of enyne **4** commenced with the protection of commercially available 4-pentyn-1-ol (**6**) to its TBS ether **7** in 86% yield (Scheme 4). Hydrozirconation of **7** using Schwartz's reagent[20] in THF followed by quenching with NIS furnished the



Scheme 4.

corresponding trans-substituted vinyl iodide. This iodide was then coupled with propyne using Sonogashira conditions[21] to reliably yield enyne **4** in multigram quantities in 55% yield over two steps.

Terminal epoxide **5** was synthesized in two steps from commercially available β-citronellene based upon an established route that utilized diastereoselective iodolactonization.[22]

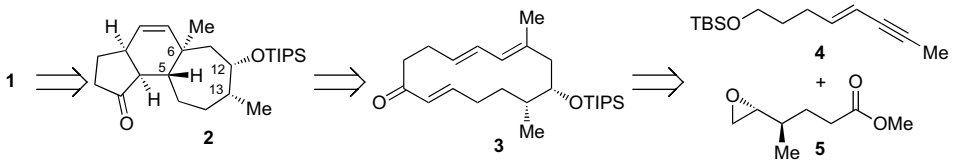
With enyne **4** and epoxide **5** readily available in multigram quantities, the pivotal reductive coupling step was investigated (Table 1). The presence of a phosphine catalyst was necessary for conversion to the diene **8**, and a catalyst to phosphine ratio of 1:2 gave the best results (entry 2). Long reaction times were needed to give appreciable yield, presumably due to the unreactive nature of the epoxide. In entries 2 and 3, a significant amount of **5** was recovered from the reaction. It is believed that the methyl substitution adjacent to the terminal epoxide in **5** lowered the reactivity toward coupling. None of the enyne was recovered from the reaction. In the presence of a nickel(0) catalyst and an electron-rich phosphine, alkynes are known to readily dimerize and cyclotrimerize.[23] Mixtures of such polymerization products were recovered in all these reactions.

Interestingly, when a 1:4 catalyst to phosphine ratio was used (entry 3), 5% yield of lactone **9** was observed along with the expected product **8**. Reductive elimination of the coupling product from the nickel catalyst may yield an unstable borinate ester, which under extended exposure to reaction conditions formed this cyclized product. When the reaction time was extended to 128 h (entry 4), indeed 32% of lactone **9** was isolated. Earlier quenching of the reaction would preclude formation of byproduct **9**.

In addition to a shorter reaction time, it was also found that the yield of the reductive coupling product could be improved by several means. By increasing the catalyst loading to 20 mol %, it was found that only a small excess of enyne **4** was necessary to generate a similar yield. Sequential addition of the epoxide and then enyne also provided a boost in yield. Perhaps the byproducts of enyne homocoupling adversely affected the reaction through catalyst sequestration. In summary, the reductive coupling optimization led to reliable gram-scale production of highly functionalized intermediate **8** in 48% yield (Scheme 5).

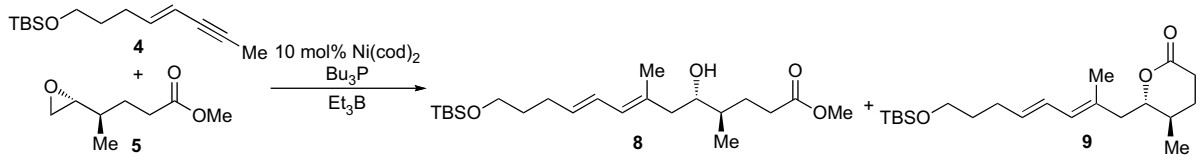
However, at this point difficulty was encountered in the selective removal of the TBS group at a step later in the synthesis. Therefore an alternative, more labile protecting group was needed. Accordingly, the triethylsilyl (TES) protecting group was selected. Enyne **10** bearing a TES group was synthesized using the aforementioned route in 47% yield over three steps from 4-pentyn-1-ol.

Using the optimized conditions of the reductive coupling of **4** and **5** afforded only 26% yield of the diene **11** from **5** and **10**, prompting further optimization efforts (Table 2). By slowing down the addition time of the enyne from less than 1 min to 1 h (entries 1–3), the yield was improved to 41%. Further, cod was chosen as



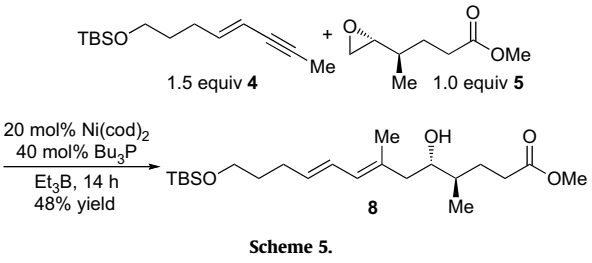
Scheme 3.

Table 1
Reductive coupling of enyne **4** and epoxide **5**

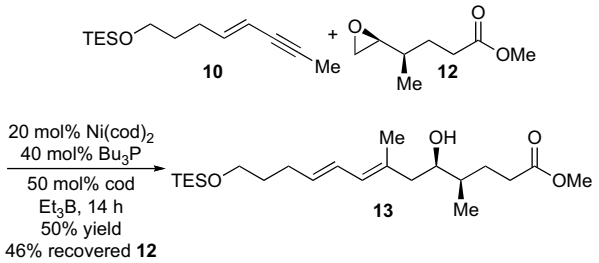


Entry	Bu_3P (mol %)	Time (h)	Yield of **8** (%)	Yield of **9** (%)	Recovered **5** (%)
1[a]	0	60	0	0	n.d.
2[a]	20	60	25	0	26
3[a]	40	60	23	5	38
4[b]	20	128	19	32	20

[a] A mixture of **4** (3 equiv) and **5** (1 equiv) was added over <1 min to a stirring slurry of $Ni(cod)_2$, Bu_3P, and Et_3B.
[b] A mixture of **4** (1.5 equiv) and **5** (1 equiv) was added over <1 min to a stirring slurry of $Ni(cod)_2$, Bu_3P, and Et_3B. After 24 h, **4** (1.5 equiv) was added.



Scheme 5.



Scheme 6.

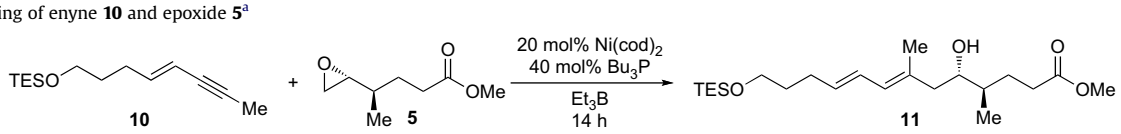
a stabilizing additive (entries 4–6). The presence of cod may hinder sequestration of the catalyst by enyne polymerization byproducts. Using 50 mol % cod as an additive (entry 4) improved the yield of the reaction to 49% with 50% recovery of epoxide **5**. The coupling of enyne **10** and epoxide **12** was also performed, which afforded similar results for this epoxide diastereomer, yielding diene **13** in 50% yield with 46% recovery of epoxide **12** (Scheme 6).

Diene **11** was then elaborated to macrocyclic triene **3** (Scheme 7). Reduction of **11** to the corresponding diol and treatment with excess TIPSOTf afforded the tris-silyl ether **14** in 79% yield over the two steps. Stirring a solution of **14** with Amberlyst-15 acidic resin for 45 min selectively removed the 1° TES group, which was oxidized using Swern conditions to give aldehyde **15** in 80% yield over two steps. Alternatively, exposure of **14** to Collins reagent afforded **15** directly via selective oxidative deprotection, albeit in only 60% yield at 88% conversion.[24]

Nucleophilic addition of deprotonated methyl dimethyl phosphonate to aldehyde **15** followed by Dess–Martin periodinane (DMP) oxidation installed β-ketophosphonate functionality, affording **16** in 54% yield over two steps. From **16**, selective deprotection of the 1° TIPS protecting group and subsequent oxidation afforded Horner–Wadsworth–Emmons cyclization precursor bearing terminal β-ketophosphonate and aldehyde groups. After screening several conditions, modified Still–Gennari conditions[25] provided optimal amounts of macrocyclic triene **3** in 34% over three steps. Major byproducts of this reaction not only included the *Z* isomer of **3** but also 28-membered ring dimers bearing variable olefin geometries. In addition to problems with this macrocyclization, purified **3** did not convert to tricycle **2** under a variety of thermal and Lewis acid-promoted TADA reaction conditions (Table 3). Heating a toluene solution of **3** to 200 °C in a sealed tube only provided isomers that were products of [1,5]-hydride shift (entry 2). In reactions involving Lewis acid promotion (entries 3–5), only decomposition was observed above the noted temperature thresholds.

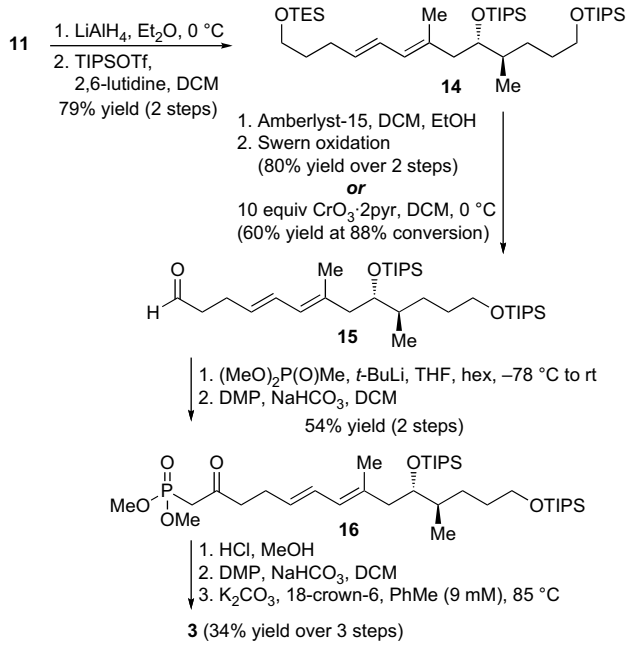
In addition to the above route, several other enyne–epoxide coupling systems were explored. To minimize functional group interconversion, it would be advantageous to install the β-ketophosphonate prior to the reductive coupling. With this in mind, β-ketophosphonate-enyne **18** was synthesized (Scheme 8). TBS-protected enyne **4** was converted to its alcohol using acidic methanol and oxidized using Swern conditions to yield aldehyde **17** in 81% yield over two steps. Exposure of **17** to a cold solution of

Table 2
Reductive coupling of enyne **10** and epoxide **5**[a]



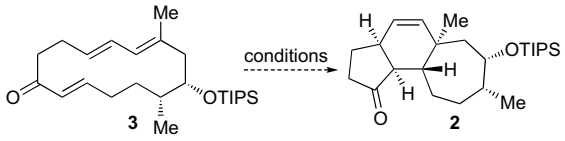
Entry	Addition time of **10** (min)	Additive	Yield of **11** (%)	Recovered **5** (%)
1	<1	None	26	73
2	45	None	28	63
3	60	None	41	39
4	60	50 mol % cod	49	50
5	60	100 mol % cod	44	30
6	60	150 mol % cod	41	41

[a] Compound **5** (1 equiv) was added to a stirring slurry of $Ni(cod)_2$, Bu_3P, Et_3B, and an additive. Compound **10** was then added over the specified amount of time.



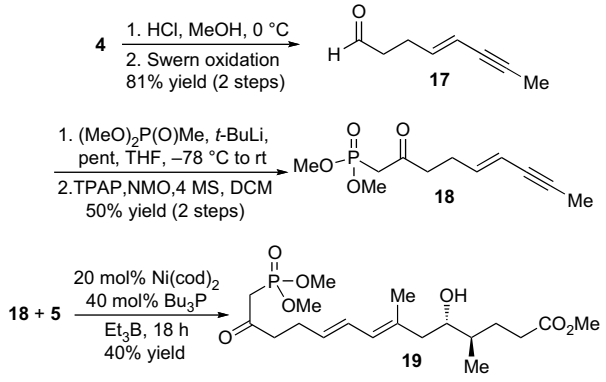
Scheme 7.

Table 3
Attempted TADA reaction of triene **3**



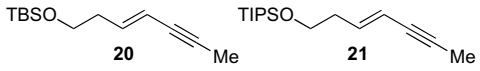
Entry	Conditions	Result
1	PhMe, 180 °C	No reaction
2	PhMe, 200 °C	Some isomerization
3	Et_2AlCl, DCM, hept, −78 °C to 40 °C	Decomposition
4	$BF_3{\cdot}OEt_2$, PhMe, −78 °C to 30 °C	Decomposition
5	$SnCl_4$, DCM, −78 °C to rt	Decomposition

tert-butyl lithium and dimethyl methylphosphonate and subsequent oxidation with TPAP/NMO afforded the target enyne **18** in 50% yield over two steps. The reductive coupling of **18** and epoxide **5** gave 40% yield of the coupling product **19**.

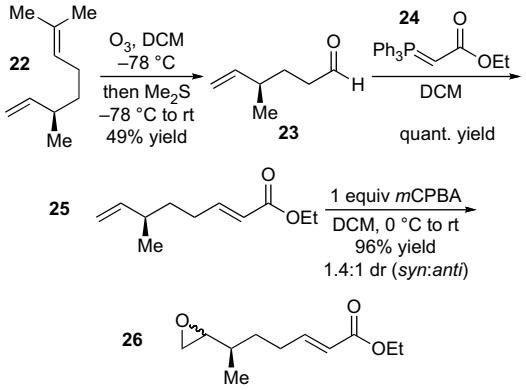


Scheme 8.

Further, a route involving an intramolecular Diels–Alder (IMDA) reaction[26] was pursued in which the direct product of the reductive coupling reaction would be the precursor triene. TBS-protected enyne **20** was synthesized in 27% yield over three steps from 3-butyn-1-ol using the identical enyne synthesis methodology as above. The TIPS analog **21** was also synthesized in 27% over three steps.

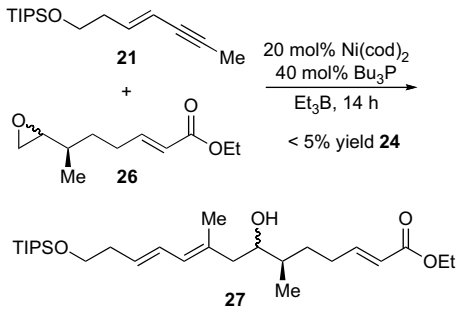


To make the requisite epoxide **26** bearing an α,β-unsaturated ester, β-citronellene (**22**) was converted to the known aldehyde **23**[22] in 49% yield through monitored ozonolysis followed by dimethylsulfide workup (Scheme 9). Wittig-type coupling of **23** with commercially available phosphorane **24** provided dienyl ester **25** in quantitative yield. Regioselective epoxidation was observed when **25** was treated with *m*-CPBA, affording **26** in multigram quantities and in 96% yield.



Scheme 9.

With enynes **20**–**21** and epoxide **26** readily available, the key reductive coupling reaction was investigated. Quite unfortunately and unexpectedly, the reductive coupling of **21** and **26** under optimized conditions only afforded a trace amount of product triene **27** with recovery of enyne polymerization byproducts and unreacted epoxide **26** (Scheme 10).



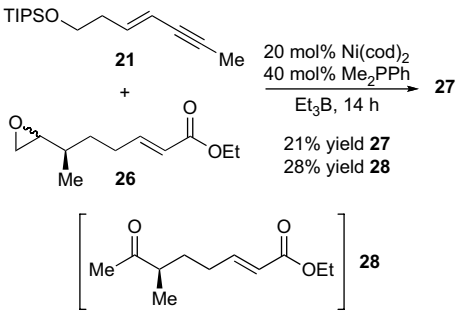
Scheme 10.

This result prompted a reinvestigation of the reductive coupling reaction. Perhaps if a different phosphine was used, the formation of **27** could be favored over polymerization of **21**. Electron-rich trialkylphosphines, aside from facilitating reductive coupling of terminal epoxides and 1,3-enynes, are also good ligands for cyclotrimerization of alkynes, especially in the 2:1 to 10:1 ratio range of phosphine ligand to nickel(0) compound.[27] Since using an electron-poor phosphine ligand would be inhibitory to the reductive coupling process, decreasing the phosphine cone angle, while keeping the electronic nature of the ligand approximately equivalent, was

judged as the means by which reductive coupling would be favored over enyne homocoupling.

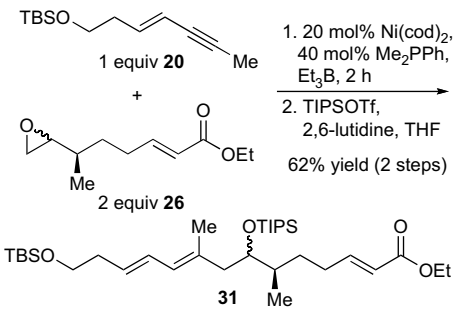
Accordingly, Me_2PPh was selected as a possible ligand in this reductive coupling. This phosphine has similar electronic properties to Bu_3P; however, it has a smaller cone angle (122° vs 132°).[28] Additionally, Me_2PPh has been shown to be effective in key alkyne–epoxide reductive cyclizations in our syntheses of pumiliotoxins 209F and 251D.[29]

Gratifyingly, the reductive coupling of **21** and **26** with the use of Me_2PPh proceeded in 21% yield of triene **27** (Scheme 11). Ketone **28** was also isolated from the reaction, which formed from metal-mediated rearrangement of epoxide **26**. Especially noteworthy was the appearance of **21** in the crude reaction mixture by ^1H NMR. In any of the prior enyne–epoxide reductive couplings, unreacted enyne was not recovered; mixtures of homocoupling products were invariably isolated. Unfortunately, the dr of **27** could not be determined due to similarities of the ^1H signals of both diastereomers and overlap of peaks in the spectrum.



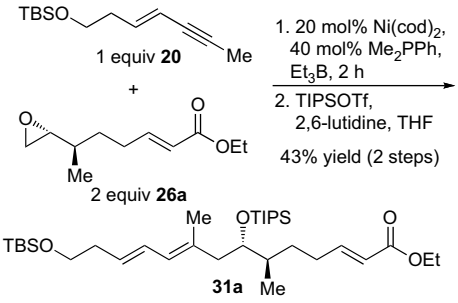
Scheme 11.

A similar yield was seen when enyne **20** was coupled with **26** under standard reductive coupling conditions to form triene **29** (Table 4, entry 1). In addition to triene **29**, regioisomer **30** was also isolated. When the reaction was run for shorter periods of time (entries 2–3), the yield of **29** not only increased, but also greater regioselectivity was observed. Slow decomposition of the product during the reaction may account for the decrease in yield. It appears that rearrangement of epoxide **26** to ketone **28** becomes a competing process when using Me_2PhP. With this in mind, the yield was increased further by using a 2:1 ratio of epoxide **26** to enyne **20** (Scheme 12). In this case, it was difficult to isolate the product triene **29** from byproduct ketone **28**. This problem was circumvented by treatment of an isolated mixture of **28** and **29** with TIPSOTf to afford the TIPS-protected triene **31** in 62% yield over two steps.



Scheme 12.

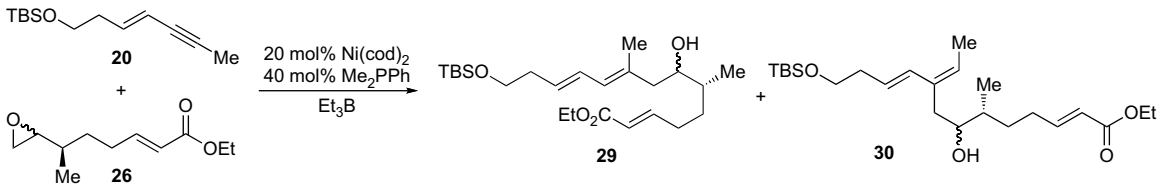
Interestingly, when diastereomerically pure epoxide **26a** (synthesized in two steps from epoxide **5**) was used in a reductive coupling with enyne **20** with identical procedures to those found in Scheme 12, only a 43% yield of coupling product **31a** was observed (Scheme 13). This seems to suggest that the two diastereomers of **26** react at different rates in the reductive coupling reaction.



Scheme 13.

Initial screening of IMDA reaction conditions with **31a** failed to produce even trace amounts of cyclization products. In order to activate the substrate further, aldehyde **32** was prepared from **31a** by DIBAL-H reduction followed by DMP oxidation. Under a variety of thermal, Lewis acid-promoted, and iminium-based IMDA reaction conditions,[30] **32** failed to cyclize to **33** (Table 5). Heating at 300 °C in a sealed tube (entry 2) or at 200 °C in a microwave reactor (entry 3) caused decomposition, and the use of several Lewis acids promoted deprotection of the 1° TBS group (entries 5–6). Perhaps the lack of reactivity of this and similar systems stems from inability to attain the *s-cis* diene conformation due to severe steric strain.

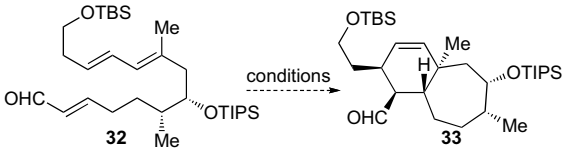
Table 4
Reductive coupling of enyne **20** and epoxide **26**[a]



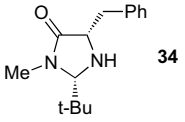
Entry	Reaction time (h)	Recovered **20** (%)	Yield of **28** (%)	Yield of **29** (%)	Yield of **30** (%)
1	15	31[b]	40	27	12
2	4	36	41	39	13
3	2	55	32	51	9

[a] Compound **26** (1 equiv) was added to a stirring slurry of $Ni(cod)_2$, Me_2PPh, and Et_3B. Compound **20** (1.5 equiv) was then added over 30 min.
[b] Minor homocoupling products of **20** were observed as well.

Table 5
Attempted IMDA reaction of trienal **32**



Entry	Conditions	Result
1	PhMe, 175 °C	No reaction
2	$C_6H_3Cl_3$, 330 °C	Decomposition
3	DMSO, μW, 200 °C, 10 min	Decomposition
4	$MeAlCl_2$, DCM, hex, −78 °C to rt	Decomposition
5	$BF_3{\cdot}OEt_2$, DCM, −78 °C to −15 °C	1° TBS deprotection
6	$SnCl_4$, DCM, −78 °C to −30 °C	1° TBS deprotection
7	**34**, 98:2 MeCN/H_2O	No reaction
8	**34**, $CDCl_3$	Decomposition



34

3. Conclusion

Within the context of studies directed toward the total synthesis of (−)-cyatha-3,12-diene, the nickel(0)-catalyzed enyne–epoxide reductive coupling has been shown to be effective in a variety of contexts. Variations to the size and nature of both coupling partners are well-tolerated, including the α,β-unsaturated ester and β-ketophosphonate functionalities. Within a single step, a wide diversity of valuable intermediates containing a 3,5-dien-1-ol was made.

4. Experimental

4.1. General information

Unless otherwise noted, all reactions were performed under an argon atmosphere with rigid exclusion of moisture from reagents and glassware. THF was freshly distilled over sodium/benzophenone ketyl. DCM was distilled from calcium hydride. Anhydrous pyrrolidine was used as purchased from Aldrich. $Ni(cod)_2$ was purchased from Strem Chemicals, Inc., stored under nitrogen atmosphere, and used without further purification. Analytical thin-layer chromatography (TLC) was performed using EM Science silica gel 60 F_{254} plates and developed using UV light (254 nm) and aqueous ceric ammonium molybdate (CAM) stain. Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle silica gel (230–400 mesh). ^1H and ^{13}C NMR spectra were recorded on a Varian Inova 500 MHz spectrometer in $CDCl_3$ and analyzed using iNMR version 0.6.2. Chemical shifts in ^1H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and br=broad), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in parts per million from the central peak of $CDCl_3$ (77.23 ppm) on the δ scale. IR spectra were recorded on a Perkin–Elmer 2000 FT-IR. High resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEXII 3 Fourier Transform Mass Spectrometer by Ms. Li Li of the Massachusetts Institute of Technology, Department of Chemistry Instrumentation Facility.

4.2. Preparation of enynes and epoxides

*4.2.1. tert-Butyldimethyl(pent-4-ynyloxy)silane (**7**)*

TBSCl (18.84 g, 125 mmol, 1.05 equiv) was added to a stirring solution of 4-pentyn-1-ol (10.00 g, 119 mmol, 1 equiv), Et_3N (24.05 g, 238 mmol, 2 equiv), and DMAP (2.91 g, 23.8 mmol, 0.2 equiv) in DCM (100 mL) at 0 °C. The solution was allowed to stir overnight and warmed to room temperature. The solution was subsequently diluted to 250 mL DCM and washed four times with water (200 mL each). The aqueous layers were combined and washed with DCM (100 mL). The DCM layers were combined and washed with brine (100 mL). Drying over $MgSO_4$, filtration, and concentration in vacuo afforded a clear oil. The oil was distilled at 10 Torr, 72 °C to give **7** as a clear oil (20.50 g, 86% yield). ^1H NMR (500 MHz, $CDCl_3$, δ): 3.70 (t, J=6.0 Hz, 2H), 2.28 (dt, J_t=7.1 Hz, J_d=2.7 Hz, 2H), 1.93 (t, J=2.7 Hz, 1H), 1.73 (m, 2H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 99.9, 84.4, 61.6, 31.7, 26.1, 18.5, 15.0, −5.1. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{11}H_{22}O_2Si$, 221.1332; found, 221.1379.

*4.2.2. (E)-tert-Butyldimethyl(oct-4-en-6-ynyloxy)silane (**4**)*

To a stirring slurry of Schwartz's reagent (13.61 g, 52.8 mmol, 1.05 equiv) in THF (140 mL) at 0 °C was added **7** (10.00 g, 50.2 mmol, 1 equiv). The solution was warmed to room temperature, and after 100 min, the creamy white solution turned dark green. NIS (11.87 g, 52.8 mmol, 1.05 equiv) was then dropwise added, and the solution turned from green to bright orange to deep red to brown black. The solution was stirred for 90 min. Volatiles were then removed in vacuo to yield a brown-gray residue. The residue was retaken in hexane (100 mL), passed through a plug of silica gel (90 mL), and rinsed with hexane to give a total eluent volume of 500 mL. The solvent was then removed in vacuo to give a yellow oil. The yellow oil was retaken in DCM (200 mL), washed with 1 N NaOH (75 mL), and washed with brine (75 mL). Drying over $MgSO_4$, filtration, and concentration in vacuo yielded 15.39 g of a yellow oil. This oil was added to a solution of CuI (447 mg, 2.35 mmol, 0.05 equiv) and $Pd(PPh_3)_4$ (1.36 g, 1.18 mmol, 0.025 equiv) in pyrrolidine (48 mL) at −78 °C. Propyne (7.5 mL, 240 mmol, 5 equiv) was bubbled through the solution and it was stirred overnight while warming to room temperature. The solution was subsequently diluted with Et_2O (200 mL) and added to ice-cold 1 M HCl (200 mL). The layers were separated, and the organic layer was washed twice with 1 M HCl (75 mL each) and dried over $MgSO_4$. The solution was then passed through a pad of silica (100 mL) and washed with Et_2O to afford a total eluent volume of 700 mL. Concentration in vacuo yielded an orange residue, which was retaken in hexane (200 mL) and passed through a pad of silica (100 mL) and washed with hexane to afford a total eluent volume of 700 mL. Concentration in vacuo yielded a pale yellow oil. The oil was distilled at 2.2 Torr, 102 °C to yield **4** as a clear oil (6.62 g, 55% yield over two steps). ^1H NMR (300 MHz, $CDCl_3$, δ): 6.05 (m, 1H), 5.45 (d, J=17.4 Hz, 1H), 3.61 (t, J=6.3 Hz, 2H), 2.15 (m, 2H), 1.94 (d, J=2.2 Hz, 3H), 1.60 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 143.0, 110.3, 84.4, 78.6, 62.5, 32.1, 29.5, 26.2, 18.5, 4.4, −5.1. IR (NaCl, thin film, cm^{-1}): 2929, 2857, 1744, 1472, 1361, 1256, 1103, 955, 837, 776. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{14}H_{26}OSi$, 261.1645; found, 261.1654.

*4.2.3. (R)-Methyl 4-((R)-oxiran-2-yl)pentanoate (**7**)*

Synthesized according to a literature procedure.[22]

*4.2.4. (E)-Triethyl(oct-4-en-6-ynyloxy)silane (**10**)*

Using the identical procedure for the synthesis of **7**, the reaction of TESCl (31.4 mL, 187 mmol) and 4-pentyn-1-ol (15.00 g, 178 mmol) with Et_3N (49.6 mL, 357 mmol) and DMAP (4.35 g, 35.7 mmol) in DCM (600 mL) afforded triethyl(pent-4-ynyloxy)silane as a clear oil

after distillation at 2.8 Torr, 57 °C (35.32 g, >99% yield). Using the identical procedure for the synthesis of **4**, the reaction of triethyl(pent-4-ynyloxy)silane (14.86 g, 74.9 mmol), Schwartz's reagent (20.27 g, 78.7 mmol), and NIS (9.83 g, 78.7 mmol) in THF (245 mL) afforded the corresponding vinyl iodide. The reaction of this oil and propyne (12 mL, 244 mmol) with $Pd(PPh_3)_4$ (1.41 g, 1.23 mmol) and CuI (464 mg, 2.44 mmol) in pyrrolidine (49 mL) afforded **10** as a clear oil after distillation at 2.8 Torr, 87 °C (8.48 g, 47% yield over two steps). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 6.05 (dt, J_d=15.8 Hz, J_t=7.4 Hz, 1H), 5.45 (dq, J_d=15.8 Hz, J_q=2.1 Hz, 1H), 3.61 (t, J=6.4 Hz, 2H), 2.15 (m, 2H), 1.94 (d, J=2.1 Hz, 3H), 1.61 (m, 2H), 0.96 (t, J=7.9 Hz, 9H), 0.60 (q, J=7.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 143.0, 110.3, 84.4, 78.5, 62.2, 32.2, 29.5, 7.0, 6.6, 4.6. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{14}H_{26}OSi$, 261.1645; found, 261.1650.

4.2.5. (R)-Methyl 4-((S)-oxiran-2-yl)pentanoate (**12**)

Synthesized according to a literature procedure.[22]

4.2.6. (E)-Oct-4-en-6-ynal (**17**)

Concentrated HCl (0.3 mL) was added dropwise to a solution of **4** (1.80 g, 7.55 mmol) in MeOH (30 mL). After stirring for 1 h, saturated aqueous $NaHCO_3$ (50 mL) was added. Volatiles were removed in vacuo and the resulting solution was extracted thrice with EtOAc (50 mL each). The aqueous layer was saturated with NaCl and the extraction procedure was repeated. The EtOAc layers were combined, dried over Na_2SO_4, and concentrated in vacuo to afford a crude oil (958 mg). DMSO (710 μL, 10 mmol, 2.3 equiv) was added dropwise to a solution of oxalyl chloride (623 μL, 7.5 mmol, 1.75 equiv) in DCM (25 mL) at −78 °C, and the resulting solution was stirred for 15 min. A portion of this oil (531 mg, 4.28 mmol, 1 equiv) in DCM (3 mL) was added dropwise to this solution and stirred for 30 min. Et_3N (1.52 g, 15 mmol, 3.5 equiv) was added dropwise, and the solution was warmed to room temperature over 1 h. The solution was diluted with water (30 mL) and extracted with DCM (4×25 mL). The organic extracts were combined, washed with water (30 mL), brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo to yield an oil. Flash column chromatography (300 mL silica, 8:2 hexane/EtOAc) afforded **17** (485 mg, 81% yield over two steps). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 9.77 (t, J=1.3 Hz, 1H), 6.02 (dt, J_d=15.8 Hz, J_t=7.0 Hz, 1H), 5.49 (dq, J_d=15.8 Hz, J_q=1.6 Hz, 1H), 2.55 (dt, J_t=6.7 Hz, J_d=1.3 Hz, 2H), 2.41 (dt, J_d=7.0 Hz, J_t=6.7 Hz, 2H), 1.92 (d, J=1.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 201.5, 140.4, 111.6, 85.4, 76.9, 43.0, 25.5, 4.3. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_8H_{10}O$, 145.0624; found, 145.0629.

4.2.7. (E)-Dimethyl 2-oxonon-5-en-7-ynylphosphonate (**18**)

A solution of *t*-BuLi in pentane (1.7 M, 9.36 mL, 15.92 mmol, 4 equiv) was added dropwise over 10 min to THF (117 mL) at −78 °C. Dimethyl methylphosphonate (2.47 g, 19.9 mmol, 5 equiv) was added dropwise over 10 min and the solution was stirred for 45 min to give a colorless solution. A solution of **17** (485 mg, 3.98 mmol, 1 equiv) in THF (3 mL) was added dropwise over 10 min and the solution was stirred at −78 °C for 2 h. Brine (40 mL) was added by syringe and the solution was warmed to room temperature over 1 h. Volatiles were removed in vacuo, and the residue was diluted with water (100 mL) and extracted thrice with EtOAc (75 mL each). The organic extracts were combined, washed with brine (100 mL), dried over Na_2SO_4, and concentrated in vacuo to yield a residue. The residue, NMO (932 mg, 7.96 mmol, 2 equiv), and 4 Å MS (2 g) were taken up in DCM (45 mL). TPAP (70 mg, 0.2 mmol, 0.05 equiv) was added and the solution was stirred for 16 h. The solution was then filtered through a plug of silica (100 mL) and rinsed with EtOAc. The eluent was concentrated in vacuo to yield a residue. Flash column chromatography (200 mL silica, 1:9 hexane/EtOAc) afforded **18** (486 mg, 50% yield over two steps). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 5.99 (dt, J_d=15.8 Hz, J_t=7.1 Hz, 1H), 5.48 (dq, J_d=15.8 Hz, J_q=1.6 Hz, 1H), 3.80 (d, J_{H-P}=11.3 Hz, 6H), 3.09 (d, J_{H-P}=22.8 Hz, 2H), 2.71 (t, J=7.3 Hz, 2H), 2.37 (dt, J_d=7.3 Hz, J_t=7.1 Hz, 2H), 1.92 (d, J=1.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ) 200.5 (J_{C-P}=6.2 Hz), 140.4, 111.2, 84.9, 74.9, 53.0 (J_{C-P}=6.4 Hz), 42.9, 41.3 (J_{C-P}=128.0 Hz), 26.5, 4.1. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{11}H_{17}O_4P$, 267.0757; found, 267.0751.

4.2.8. (E)-tert-Butyl(hept-3-en-5-ynyloxy)dimethylsilane (**20**)

Using the identical procedure for the synthesis of **7**, the reaction of TBSCl (10.45 g, 69.4 mmol) and 3-butyn-1-ol (5.0 mL, 66.1 mmol) with Et_3N (18.5 mL, 132 mmol) and DMAP (1.61 g, 13.2 mmol) in DCM (220 mL) afforded (but-3-ynyloxy)(*tert*-butyl)dimethylsilane as a clear oil after distillation at 5 Torr, 39 °C (8.74 g, 72% yield). Using the identical procedure for the synthesis of **4**, the reaction of (but-3-ynyloxy)(*tert*-butyl)dimethylsilane (4.00 g, 21.7 mmol), Schwartz's reagent (5.87 g, 22.8 mmol), and NIS (2.85 g, 22.8 mmol) in THF (72 mL) afforded the corresponding vinyl iodide. The reaction of this oil and propyne (5 mL, 71 mmol) with $Pd(PPh_3)_4$ (412 mg, 0.36 mmol) and CuI (136 mg, 0.71 mmol) in pyrrolidine (14 mL) afforded **20** as a clear oil after distillation at 5 Torr, 98 °C (1.81 g, 37% yield over two steps). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 6.04 (dt, J_d=15.9 Hz, J_t=7.2 Hz, 1H), 5.50 (dq, J_d=15.9 Hz, J_q=2.2 Hz, 1H), 3.64 (t, J=6.7 Hz, 2H), 2.30 (dt, J_d=7.2 Hz, J_t=6.7 Hz, 1H), 1.94 (d, J=2.2 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 139.7, 111.9, 84.7, 78.5, 62.6, 36.8, 26.1, 18.5, 4.4, −5.1. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{13}H_{24}OSi$, 247.1489; found, 247.1487.

4.2.9. (E)-(Hept-3-en-5-ynyloxy)tri-iso-propylsilane (**21**)

Using the identical procedure for the synthesis of **7**, the reaction of TIPSCl (8.02 g, 41.6 mmol) and 3-butyn-1-ol (3.0 mL, 39.6 mmol) with Et_3N (11 mL, 79.3 mmol) and DMAP (0.97 g, 7.9 mmol) in DCM (132 mL) afforded (but-3-ynyloxy)tri-*iso*-propylsilane as a clear oil (8.40 g, >99% yield). Using the identical procedure for the synthesis of **4**, the reaction of (but-3-ynyloxy)tri-*iso*-propylsilane (3.67 g, 17.3 mmol), Schwartz's reagent (4.67 g, 18.1 mmol), and NIS (2.27 g, 18.1 mmol) in THF (60 mL) afforded the corresponding vinyl iodide. The reaction of this oil and propyne (1.5 g, 40 mmol) with $Pd(PPh_3)_4$ (206 mg, 0.18 mmol) and CuI (68 mg, 0.36 mmol) in pyrrolidine (7.1 mL) afforded **21** as a clear oil (1.13 g, 27% yield over two steps). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 6.08 (dt, J_d=15.9 Hz, J_t=7.2 Hz, 1H), 5.51 (dq, J_d=15.9 Hz, J_q=2.1 Hz, 1H), 3.71 (t, J=6.8 Hz, 2H), 2.34 (dt, J_d=7.2 Hz, J_t=6.8 Hz, 1H), 1.94 (d, J=2.1 Hz, 3H), 1.05–1.10 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 139.8, 111.8, 84.7, 78.5, 62.9, 37.0, 18.2, 12.2, 4.4. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{16}H_{30}OSi$, 289.1958; found, 289.1954.

4.2.10. (R,E)-Ethyl 6-methylocta-2,7-dienoate (**25**)

β-Citronellene (10.8 mL, 59 mmol, 1 equiv) was taken up in DCM (120 mL) and cooled to −78 °C while bubbling oxygen through the solution. Ozone was then bubbled through the solution (~0.7 mmol/min) for 75 min. Oxygen and then argon were bubbled through the solution for 10 min each. Me_2S (10.9 mL, 148 mmol, 2.5 equiv) was added, and the solution was allowed to stir overnight and warmed to room temperature. The solution was then concentrated at 40 Torr to yield a white residual oil. Short-path distillation of the oil at 40 Torr, 59–61 °C afforded aldehyde **23**[22] as a clear oil (3.27 g). To a solution of **23** (3.27 g, 29.2 mmol, 1 equiv) in DCM (97 mL) was added (carbethoxymethylene)-triphenyl phosphorane (10.16 g, 29.2 mmol, 1 equiv). The solution was stirred overnight and then concentrated in vacuo to an oily, white residue. Flash column chromatography (300 mL, 95:5 hexane/EtOAc) afforded **25** as a clear oil (5.32 g, 49% yield over two steps). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 6.96 (dt, J_d=15.6 Hz, J_t=6.9 Hz, 1H), 5.82 (d, J=15.6 Hz, 1H), 4.94–5.00 (m, 2H), 4.19 (q, J=7.1 Hz, 2H), 2.14–2.21 (m, 3H), 1.45 (m, 2H), 1.29 (t, J=7.1 Hz, 3H), 1.01 (d,

J=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 168.8, 149.3, 143.8, 121.4, 113.5, 60.2, 37.4, 34.8, 30.0, 20.3, 14.4. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{11}H_{18}O_2$, 205.1199; found, 205.1205.

4.2.11. (R,E)-Ethyl 6-(oxiran-2-yl)hept-2-enoate (**26**)

To a solution of **25** (1.09 g, 6.0 mmol, 1 equiv) in DCM (12 mL) at 0 °C was portionwise added *m*-CPBA (≤77% purity, 1.34 g, 29.2 mmol, 1 equiv). The solution was stirred overnight and warmed to room temperature. The solution was then diluted with EtOAc (50 mL) and treated with saturated aqueous $NaHCO_3$ (25 mL) and 1 M NaOH (25 mL). The layers were separated and the aqueous layer was washed thrice with EtOAc (50 mL each). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to yield a clear oil. Flash column chromatography (150 mL silica, 8:2 hexane/EtOAc) afforded **26** as a clear oil (1.14 g, 96% yield, 1.4:1 dr *syn*(**26a**)/*anti*(**26b**)). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 6.90–6.98 (m, 1H), 5.79–5.85 (m, 1H), 4.17 (q, J=7.1 Hz, 2H), 2.76 (**26b**, m, 2H), 2.70 (**26a**, m, 2H), 2.53 (**26b**, m, 1H), 2.46 (**26a**, m, 1H), 2.20–2.31 (m, 2H), 1.71 (**26a**, m, 1H), 1.56 (**26b**, m, 1H), 1.45 (**26a**, m, 1H), 1.35 (**26b**, m, 1H), 1.30–1.34 (**26a**, m, 1H), 1.27 (t, J=7.1 Hz, 3H), 1.03 (**26a**, d, J=6.8 Hz, 3H), 0.97 (**26b**, d, J=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 166.8, 166.7, 149.0, 149.0, 121.8, 121.7, 60.4, 60.3, 57.0, 56.7, 46.9, 45.8, 36.0, 35.6, 33.2, 31.9, 29.8, 29.8, 18.1, 17.0, 16.0, 14.4. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{11}H_{18}O_3$, 221.1148; found, 221.1147.

4.3. Optimized reductive coupling procedures

4.3.1. (4R,5S,7E,9E)-Methyl 13-(tert-butyldimethylsilyloxy)-5-hydroxy-4,7-dimethyltrideca-7,9-dienoate (**8**)

In a glovebox, a 10 mL teardrop flask was charged with $Ni(cod)_2$ (70 mg, 0.25 mmol, 0.2 equiv) and Bu_3P (126 μL, 0.51 mmol, 0.4 equiv). The flask was sealed with a rubber septum and electrical tape. Outside the box and under a positive pressure of argon, Et_3B (0.74 mL, 5.1 mmol, 4 equiv), **5** (198 mg, 1.25 mmol, 1 equiv), and **4** (452 mg, 1.90 mmol, 1.5 equiv) were sequentially added. The black reaction mixture was stirred overnight for 14 h. The reaction mixture was then exposed to air, diluted with EtOAc (5 mL), and stirred vigorously for 2 h, whereupon the solution turned from black to clear yellow. The solution was then concentrated in vacuo to a yellow oil. Flash column chromatography (100 mL silica, 95:5 hexane/EtOAc→9:1 hexane/EtOAc) afforded **8** as a slight yellow oil (241 mg, 48% yield). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 6.25 (dd, J_1=15.0 Hz, J_2=10.8 Hz, 1H), 5.88 (d, J=10.8 Hz, 1H), 5.63 (dt, J_d=15.0 Hz, J_t=7.4 Hz, 1H), 3.67 (s, 3H), 3.61 (t, J=6.4 Hz, 2H), 3.55 (m, 1H), 1.40–2.43 (m, 14H), 0.92 (d, J=6.6 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 174.5, 133.5, 132.7, 128.4, 126.5, 72.3, 62.6, 51.7, 44.4, 38.1, 32.6, 32.1, 29.3, 27.6, 26.1, 16.6, 15.2, 14.3, −5.2. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{22}H_{42}O_4Si$, 421.2745; found, 421.2734.

4.3.2. (4R,5S,7E,9E)-Methyl 5-hydroxy-4,7-dimethyl-13-(triethylsilyloxy)trideca-7,9-dienoate (**11**)

In a glovebox, a 10 mL teardrop flask was charged with $Ni(cod)_2$ (35 mg, 0.13 mmol, 0.2 equiv) and Bu_3P (63 μL, 0.25 mmol, 0.4 equiv). The flask was sealed with a rubber septum and electrical tape. Outside the box and under a positive pressure of argon, Et_3B (0.37 mL, 2.5 mmol, 4 equiv), cod (39 μL, 0.32 mmol, 0.5 equiv), and **5** (106 mg, 0.67 mmol, 1 equiv) were added sequentially. Compound **10** (226 mg, 0.95 mmol, 1.5 equiv) was added dropwise over approximately 1 h. The black reaction mixture was stirred overnight for 14 h. The reaction mixture was diluted with EtOAc (5 mL), exposed to air, and then stirred vigorously for 30 min, whereupon the solution turned from black to clear yellow. The solution was then concentrated in vacuo to a yellow-green oil. Flash column chromatography (150 mL silica, 95:5→9:1 hexane/EtOAc) afforded **11** as a clear oil (132 mg, 49% yield) along with **7** (53 mg, 50% recovery). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 6.24 (dd, J_1=15.0 Hz, J_2=10.8 Hz, 1H), 5.87 (d, J=10.8 Hz, 1H), 5.62 (dt, J_d=15.0 Hz, J_t=7.4 Hz, 1H), 3.65 (s, 3H), 3.60 (t, J=6.5 Hz, 2H), 3.53 (m, 1H), 2.41 (m, 1H), 2.31 (m, 1H), 2.24 (m, 1H), 2.14 (m, 2H), 2.00 (m, 1H), 1.87 (m, 1H), 1.74 (s, 3H), 1.55–1.64 (m, 1H), 1.49 (m, 1H), 0.94 (t, J=8.0 Hz, 9H), 0.91 (d, J=6.8 Hz, 3H), 0.58 (q, J=8.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 174.6, 133.6, 132.7, 128.6, 126.5, 72.3, 62.4, 51.8, 44.5, 38.2, 32.7, 32.2, 29.4, 27.7, 16.7, 15.3, 7.0, 4.6. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{22}H_{42}O_4Si$, 421.2745; found, 421.2749.

4.3.3. (4R,5R,7E,9E)-Methyl 5-hydroxy-4,7-dimethyl-13-(triethylsilyloxy)trideca-7,9-dienoate (**13**)

Using the optimized procedure for the synthesis of **11**, the reaction of **10** (1.13 g, 4.74 mmol, 1.5 equiv) and **12** (503 mg, 3.18 mmol, 1 equiv) with $Ni(cod)_2$ (174 mg, 0.63 mmol, 0.2 equiv), Bu_3P (316 μL, 1.26 mmol, 0.4 equiv), Et_3B (1.85 mL, 12.64 mmol, 4 equiv), and cod (194 μL, 1.58 mmol, 0.5 equiv) afforded **13** as a clear oil (631 mg, 50% yield) along with recovered **12** (230 mg, 46% recovery). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 6.26 (dd, J_1=15.0 Hz, J_2=10.8 Hz, 1H), 5.88 (d, J=10.8 Hz, 1H), 5.64 (dt, J_d=15.0 Hz, J_t=7.0 Hz, 1H), 3.68 (s, 3H), 3.64 (m, 1H), 3.62 (t, J=6.5 Hz, 2H), 2.32–2.42 (m, 2H), 2.08–2.22 (m, 4H), 1.87 (m, 1H), 1.76 (s, 3H), 1.61–1.66 (m, 2H), 1.54 (m, 2H), 0.96 (t, J=8.0 Hz, 9H), 0.93 (d, J=6.5 Hz, 3H), 0.60 (q, J=8.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 174.6, 133.5, 132.8, 128.3, 126.6, 71.6, 62.4, 51.8, 45.0, 37.8, 32.7, 32.3, 29.4, 28.5, 16.7, 13.9, 7.0, 4.6. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{22}H_{42}O_4Si$, 421.2745; found, 421.2750.

4.3.4. (4R,5S,7E,9E)-Methyl 14-(dimethoxyphosphoryl)-5-hydroxy-4,7-dimethyl-13-oxotetradeca-7,9-dienoate (**19**)

In a glovebox, a 10 mL teardrop flask was charged with $Ni(cod)_2$ (9 mg, 33 μmol, 0.2 equiv) and Bu_3P (14 μL, 66 μmol, 0.4 equiv). The flask was sealed with a rubber septum and electrical tape. Outside the box and under a positive pressure of argon, Et_3B (97 μL, 0.66 mmol, 4 equiv) was added followed by a mixture of **5** (26 mg, 0.16 mmol, 1 equiv) and **18** (42 mg, 0.17 mmol, 1.1 equiv). The solution was stirred for 18 h. The solution was diluted with Et_2O, exposed to air for 1 h, and was subjected directly to flash column chromatography (EtOAc→99:1 EtOAc/MeOH) to yield **19** (26 mg, 40% yield). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 6.28 (dd, J_1=15.1 Hz, J_2=11.2 Hz, 1H), 5.87 (d, J=11.2 Hz, 1H), 5.59 (dt, J_d=15.1 Hz, J_t=7.2 Hz, 1H), 3.80 (d, J_{H-P}=11.2 Hz, 6H), 3.76–3.79 (m, 1H), 3.68 (s, 3H), 3.52–3.57 (br m, 1H), 3.10 (d, J_{H-P}=22.8 Hz, 2H), 2.74 (t, J=7.3 Hz, 2H), 2.42–2.48 (br m, 2H), 2.40 (t, J=6.4 Hz, 2H), 2.22–2.28 (br m, 2H), 1.77 (s, 3H), 1.99–2.05 (br m, 2H), 1.85–1.92 (br m, 1H), 0.93 (d, J=6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 201.3 (J_{C-P}=6.1 Hz), 174.6, 133.9, 131.2, 128.1, 127.5, 72.4, 53.3 (J_{C-P}=6.4 Hz), 51.8, 44.5, 43.9, 41.6 (J_{C-P}=128.1 Hz), 38.2, 32.1, 27.7, 26.8, 16.8, 15.3. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{19}H_{33}O_7P$, 427.1856; found, 427.1854.

4.3.5. (R,2E,9E,11E)-Ethyl 7-hydroxy-6,9-dimethyl-14-(tri-isopropylsilyloxy)tetradeca-2,9,11-trienoate (**27**)

In a glovebox, a 10 mL teardrop flask was charged with $Ni(cod)_2$ (14 mg, 0.050 mmol, 0.2 equiv) and Me_2PhP (14 μL, 0.10 mmol, 0.4 equiv). The flask was sealed with a rubber septum and electrical tape. Outside the box and under a positive pressure of argon, Et_3B (0.15 mL, 1.0 mmol, 4 equiv) and **26** (50 mg, 0.25 mmol, 1 equiv) were added sequentially. Compound **21** (101 mg, 0.34 mmol, 1.5 equiv) was added dropwise over 30 min. The black reaction mixture was stirred overnight. The reaction mixture was diluted with EtOAc (5 mL), exposed to air, and then stirred vigorously for 1 h, whereupon the solution turned from black to clear yellow. The solution was then concentrated in vacuo to a brown oil. Flash column chromatography (100 mL silica, 95:5 hexane/EtOAc→8:2

hexane/EtOAc) afforded **27** (25 mg, 21% yield) as a clear oil along with **28** (14 mg, 28% yield) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 6.98 (dt, J_d=15.7 Hz, J_t=6.6 Hz, 1H), 6.31 (dd, J_1=15.1 Hz, J_2=11.5 Hz, 1H), 5.89 (d, J=11.5 Hz, 1H), 5.84 (d, J=15.7 Hz, 1H), 5.67 (dt, J_d=15.1 Hz, J_t=7.5 Hz, 1H), 4.19 (q, J=7.1 Hz, 2H), 3.73 (t, J=6.8 Hz, 2H), 3.64 (m, 1H), 3.54 (br m, 1H), 2.36 (dt, J_t=6.8 Hz, J_d=7.0 Hz, 2H), 2.20 (m, 2H), 2.11 (m, 1H), 1.90 (m, 1H), 1.84 (m, 1H), 1.77 (s, 3H), 1.36 (m, 1H), 1.29 (t, J=7.1 Hz, 3H), 1.03–1.10 (m, 22H), 0.93 (d, J=6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ) 166.7, 166.7, 149.4, 149.3, 133.1, 133.1, 130.1, 130.0, 128.4, 128.2, 128.0, 128.0, 121.4, 121.4, 72.3, 72.1, 71.6, 63.3, 60.2, 60.2, 45.7, 44.9, 44.4, 38.0, 37.5, 36.8, 35.9, 33.1, 31.5, 30.7, 30.1, 29.7, 18.1, 16.6, 15.9, 15.1, 14.4, 13.9, 13.8, 12.1. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{27}H_{50}O_4Si$, 489.3371; found, 489.3380.

4.4. (2*E*,6*R*,7*S*,9*E*,11*E*)-Ethyl 14-(*tert*-butyldimethyl silyloxy)-6,9-dimethyl-7-(tri-*iso*-propylsilyloxy)tetradeca-2,9,11-trienoate (31a)

In a glovebox, a 10 mL teardrop flask was charged with $Ni(cod)_2$ (62 mg, 0.23 mmol, 0.2 equiv) and Me_2PhP (64 μL, 0.45 mmol, 0.4 equiv). The flask was sealed with a rubber septum and electrical tape. Outside the box and under a positive pressure of argon, Et_3B (0.66 mL, 4.5 mmol, 4 equiv) and **26a** (446 mg, 2.25 mmol, 2 equiv) were added sequentially. Compound **20** (300 mg, 1.13 mmol, 1 equiv) was added dropwise over approximately 30 min. The black reaction mixture was stirred for 2 h. The reaction mixture was diluted with EtOAc (5 mL), exposed to air, and then stirred vigorously for 1 h, whereupon the solution turned from black to clear yellow. The solution was then concentrated in vacuo to a brown oil. Flash column chromatography (500 mL silica, 95:5 hexane/EtOAc→8:2 hexane/EtOAc) afforded a crude mixture containing **29a**, which was retaken in THF (10 mL). To this solution was added TIPSOTf (0.39 mL, 1.5 mmol) and 2,6-lutidine (0.27 mL, 2.3 mmol). The solution was stirred overnight. Water (5 mL) was added and the layers were separated. The aqueous layer was washed thrice with EtOAc (5 mL each). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo to yield a clear oil. Flash column chromatography (400 mL silica, 97:3 hexane/EtOAc) afforded **31a** as a clear oil (284 mg, 43% yield). ^{1}H NMR (500 MHz, $CDCl_3$, δ): 6.97 (dt, J_d=15.5 Hz, J_t=6.8 Hz, 1H), 6.25 (dd, J_1=15.1 Hz, J_2=11.8 Hz, 1H), 5.82 (d, J=15.5 Hz, 1H), 5.80 (d, J=11.8 Hz, 1H), 5.55 (dt, J_d=15.1 Hz, J_t=7.1 Hz, 1H), 4.19 (q, J=7.1 Hz, 2H), 3.92 (dt, J_t=6.6 Hz, J_d=2.5 Hz, 1H), 3.64 (t, J=6.8 Hz, 2H), 2.26–2.34 (m, 3H), 2.17 (m, 2H), 2.11 (m, 1H), 1.73 (s, 3H), 1.62 (m, 1H), 1.52 (m, 1H), 1.27 (t, J=7.1 Hz, 3H), 1.02–1.10 (m, 28H), 0.95 (d, J=7.1 Hz, 3H), 0.90 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 167.4, 150.2, 134.0, 129.4, 129.0, 128.1, 121.8, 74.4, 63.8, 60.8, 45.4, 37.7, 37.3, 32.1, 31.3, 26.6, 19.0, 17.5, 16.0, 15.0, 13.7, 13.4, −4.5. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{33}H_{64}O_4Si_2$, 603.4235; found, 603.4226.

4.5. Elaboration of reductive coupling products

*4.5.1. (8E,10E,13S,14R)-3,3-Diethyl-19,19-di-iso-propyl-11,14,20-trimethyl-13-(tri-iso-propylsilyloxy)-4,18-dioxa-3,19-disilahenicosa-8,10-diene (**14**)*

To a solution of **11** (402 mg, 1.01 mmol, 1 equiv) in Et_2O (26 mL) at 0 °C was added dropwise a solution of $LiAlH_4$ in Et_2O (1 M, 2.0 mL, 2.02 mmol, 2 equiv). The solution was stirred for 35 min at 0 °C. Water (76 μL), 15% (w/w) aqueous NaOH (76 μL), and water (230 μL) were sequentially added. The solution was allowed to warm to room temperature and stir for an additional 10 min. The solution was then filtered, rinsed with Et_2O, and concentrated in vacuo. Flash column chromatography (200 mL Florisil, 8:2 hexane/EtOAc→7:3 hexane/EtOAc) afforded 286 mg of the intermediate diol. To a solution of this intermediate (286 mg, 0.80 mmol, 1 equiv) in DCM (6 mL) were added TIPSOTf (0.68 mL, 2.5 mmol, 3.1 equiv) and 2,6-lutidine (0.63 mL, 5.4 mmol, 6.8 equiv). The solution was stirred for 4 h. Water (9 mL) was then added and the solution was stirred for 10 min. The solution was then acidified with 1 N HCl (3 mL) and extracted thrice with DCM (10 mL each). The organic extracts were combined, washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash column chromatography (200 mL silica, 98:2 hexane/EtOAc) afforded 547 mg (79% yield over two steps) of **14** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 6.21 (dd, J_1=15.0 Hz, J_2=10.8 Hz, 1H), 5.81 (d, J=10.8 Hz, 1H), 5.54 (dt, J_d=15.0 Hz, J_t=7.4 Hz, 1H), 3.92 (dt, J_t=6.6 Hz, J_d=2.5 Hz, 1H), 3.68 (t, J=6.5 Hz, 2H), 3.62 (t, J=6.5 Hz, 2H), 2.15 (m, 4H), 1.73 (s, 3H), 1.56–1.70 (m, 5H), 1.46 (m, 2H), 1.10–1.19 (m, 4H), 1.05–1.07 (m, 36H), 0.97 (t, J=8.0 Hz, 9H), 0.94 (d, J=6.8 Hz, 3H), 0.61 (q, J=8.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 133.6, 132.0, 127.7, 127.1, 75.2, 64.0, 62.5, 43.8, 38.4, 32.9, 31.6, 29.4, 28.0, 18.5, 18.3, 17.2, 15.5, 13.2, 12.2, 7.0, 4.6. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{39}H_{82}O_3Si_3$, 705.5464; found, 705.5476.

*4.5.2. (4E,6E,9S,10R)-7,10-Dimethyl-9,13-bis(tri-iso-propylsilyloxy)trideca-4,6-dienal (**15**)*

In a glovebox, CrO_3 (123 mg, 1.23 mmol, 10 equiv) was placed in a 20 mL screw-top vial. The vial was sealed with a septum and electrical tape. Outside the box and under a positive pressure of argon, DCM (1.8 mL) and pyridine (199 μL, 2.46 mmol, 20 equiv) were added to yield a heterogeneous orange slurry, which was stirred for 30 min. This solution was added to a solution of **14** (84 mg, 0.12 mmol, 1 equiv) in DCM (1 mL) at 0 °C. The red solution was stirred for 11 h. The solution was then diluted with DCM (10 mL) and washed with 1 N HCl (2 mL), saturated aqueous $NaHCO_3$ (4 mL), water (4 mL), and brine (2 mL). The organic layer was then dried over Na_2SO_4 and passed through a pad of SiO_2 (20 mL), rinsing with EtOAc to give a total eluent volume of 50 mL. The eluent was concentrated in vacuo to an orange oil. Flash column chromatography (35 mL silica, 98:2 hexane/EtOAc) afforded 36 mg (60% yield based on recovered **14**) of **15** as a clear oil along with 10 mg (12% recovery) of **14** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 9.78 (t, J=1.0 Hz, 1H), 6.25 (dd, J_1=15.0 Hz, J_2=10.8 Hz, 1H), 5.80 (d, J=10.8 Hz, 1H), 5.52 (dt, J_t=6.8 Hz, J_d=15.0 Hz, 1H), 3.92 (dt, J_t=5.9 Hz, J_d=1.9 Hz, 1H), 3.67 (t, J=6.2 Hz, 2H), 2.54 (m, 2H), 2.43 (m, 2H), 2.15 (m, 2H), 1.73 (s, 3H), 1.60 (m, 2H), 1.44 (m, 2H), 1.16 (m, 1H), 1.04–1.07 (m, 42H), 0.94 (d, J=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 202.3, 135.0, 129.5, 128.1, 127.1, 75.1, 64.0, 43.8, 43.7, 38.5, 31.5, 28.1, 25.7, 18.5, 18.3, 17.3, 15.3, 13.1, 12.2. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{33}H_{66}O_3Si_2$, 589.4443; found, 589.4426.

*4.5.3. Dimethyl (5E,7E,10S,11R)-8,11-dimethyl-2-oxo-10,14-bis-(tri-iso-propylsilyloxy)tetradeca-5,7-dienylphosphonate (**16**)*

To a solution of dimethyl methylphosphonate (626 μL, 5.86 mmol, 5 equiv) in THF (26.6 mL) cooled to −78 °C was added a solution of *n*-BuLi in hexane (2.5 M, 1.87 mL, 4.69 mmol, 4 equiv). The solution was stirred for 30 min at −78 °C. A solution of **15** (664 mg, 1.17 mmol, 1 equiv) in THF (2 mL) was slowly added followed by two THF rinses (1 mL each). The solution was allowed to stir overnight while warming to room temperature. The yellow solution was poured onto aqueous pH 7 phosphate buffer (20 mL) and diluted with EtOAc (20 mL). The layers were separated and the aqueous layer was washed thrice with EtOAc (10 mL each). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was retaken in DCM (11.7 mL), and DMP (1.49 g, 3.52 mmol, 3 equiv) and $NaHCO_3$ (984 mg, 11.7 mmol, 10 equiv) were added. After stirring for 20 min, saturated aqueous $Na_2S_2O_3$ (15 mL) was added. After stirring for 1 h, the layers were separated and the aqueous layer was washed four times with EtOAc (10 mL each). The organic extracts were combined and dried over Na_2SO_4. Filtration and concentration in

vacuo yielded a yellow oil. Flash column chromatography (110 mL silica, 3:7 hexane/EtOAc→1:3 hexane/EtOAc) afforded 630 mg (54% yield over 2 steps) of **16** as a slightly yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 6.22 (dd, J_1=15.0 Hz, J_2=10.8 Hz, 1H), 5.77 (d, J=10.8 Hz, 1H), 5.48 (dt, J_d=15.0 Hz, J_t=7.5 Hz, 1H), 3.90 (dt, J_t=6.3 Hz, J_d=2.6 Hz, 1H), 3.67 (t, J=6.5 Hz, 3H), 3.78 (d, J_{H-P}=11.2 Hz, 4H), 3.66 (t, J=6.5 Hz, 2H), 3.09 (d, J_{H-P}=22.7 Hz, 2H), 2.70 (t, J=7.6 Hz, 2H), 2.37 (m, 2H), 2.13 (m, 2H), 1.71 (s, 3H), 1.60 (m, 2H), 1.43 (m, 2H), 1.11–1.17 (m, 1H), 1.02–1.06 (m, 42H), 0.92 (d, J=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 201.4 (J_{C-P}=6.4 Hz), 134.7, 129.7, 127.9, 127.2, 75.1, 64.0, 53.2 (J_{C-P}=6.4 Hz), 44.2, 43.7, 42.0 (J_{C-P}=127.8 Hz), 38.4, 31.5 (m), 28.1 (m), 26.9, 18.4, 18.2, 17.3, 15.4, 13.1, 12.2. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{36}H_{73}O_6PSi_2$, 711.4576; found, 711.4602.

4.5.4. (2E,6R,7S,9Z,11E)-6,9-Dimethyl-7-(tri-iso-propylsilyloxy)-cyclotetradeca-2,9,11-trienone (3)

To a solution of **16** (106 mg, 0.15 mmol) in MeOH (5 mL) cooled to 0 °C was added concentrated HCl (three drops). The solution was stirred for 30 min at 0 °C and then for 45 min at room temperature. Water (2 mL) and saturated aqueous $NaHCO_3$ (6 mL) were added. The solution was extracted four times with Et_2O (5 mL each). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo to give a clear oil. Flash column chromatography (30 mL silica, 1:9 hexane/EtOAc) afforded 66 mg (83% yield) of the intermediate primary alcohol as a clear oil. To a solution of this alcohol (183 mg, 0.34 mmol, 1 equiv) in DCM (18.7 mL) were added DMP (437 mg, 1.03 mmol, 3 equiv) and $NaHCO_3$ (288 mg, 3.43 mmol, 10 equiv). After stirring for 100 min, saturated aqueous $Na_2S_2O_3$ (10 mL) and saturated aqueous $NaHCO_3$ (10 mL) were added. The layers were separated and the aqueous layer was washed four times with DCM (10 mL each). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo to yield a white residue. Flash column chromatography (75 mL silica, 4:96 hexane/EtOAc→2:98 hexane/EtOAc) afforded 163 mg (90% yield) of the intermediate aldehyde as a clear oil. To a solution of this aldehyde (47 mg, 88 μmol, 1 equiv) in PhMe (9.5 mL) were added oven-dried K_2CO_3 (61 mg, 0.44 mmol, 5 equiv) and 18-crown-6 (116 mg, 0.44 mmol, 5 equiv). After 45 min of stirring, the solution was submerged into an oil bath preheated to 85 °C, and the solution was stirred overnight at that temperature. The reaction mixture was then cooled to room temperature and washed twice with saturated aqueous NH_4Cl (5 mL each) and once with brine (5 mL). The aqueous extracts were combined and washed twice with EtOAc (10 mL each). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated in vacuo to yield a yellow oil. Flash column chromatography (30 mL silica, 99:1 hexane/EtOAc) afforded a complex mixture of olefin isomers and dimers, but 16 mg (45% yield, 34% over three steps) of **3** was isolated. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 6.74 (m, 1H), 6.21 (dd, J_1=15.3 Hz, J_2=10.5 Hz, 1H), 6.06 (d, J=16.0 Hz, 1H), 5.79 (d, J=10.5 Hz, 1H), 5.56 (dt, J_d=15.3 Hz, J_t=7.0 Hz, 1H), 4.01 (m, 1H), 2.63 (m, 2H), 2.30–2.40 (m, 4H), 2.12 (m, 1H), 1.71 (s, 3H), 1.58 (m, 1H), 1.48 (m, 1H), 1.41 (m, 1H), 1.28 (m, 1H), 1.02–1.06 (m, 21H), 0.95 (d, J=6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 200.0, 148.1, 133.8, 131.3, 131.0, 127.3, 127.1, 74.9, 45.7, 39.3, 35.2, 30.3, 27.6, 27.3, 18.5, 16.9, 16.9, 13.1. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{25}H_{44}O_2Si$, 427.3003; found, 427.3019.

4.5.5. (2E,6R,7S,9E,11E)-14-(tert-Butyldimethylsilyloxy)-6,9-dimethyl-7-(tri-iso-propylsilyloxy)tetradeca-2,9,11-trienal (32)

To a solution of **31a** (244 mg, 0.42 mmol, 1 equiv) in PhMe (1.8 mL) cooled to −78 °C was added dropwise a PhMe solution of DIBAL-H (1 M, 1.05 mL, 1.05 mmol, 2.5 equiv). The solution was warmed to room temperature while stirring for 2 h. The solution was diluted with Et_2O (5 mL) and treated with saturated aqueous Rochelle's salt (5 mL). The mixture was stirred vigorously for 45 min and the layers were separated. The aqueous layer was washed twice with Et_2O (5 mL each). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to a clear oil. Flash column chromatography (75 mL silica, 3:1 hexane/EtOAc) afforded 154 mg (68% yield) of the intermediate allylic alcohol as a clear oil. To a solution of this alcohol (133 mg, 0.25 mmol, 1 equiv) in DCM (12 mL) were added DMP (209 mg, 0.49 mmol, 2 equiv) and $NaHCO_3$ (207 mg, 2.47 mmol, 10 equiv). The solution was stirred for 2 h and then treated with saturated aqueous $Na_2S_2O_3$ (5 mL). The layers were separated and the aqueous layer was washed twice with DCM (5 mL each). The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo to a clear oil. Flash column chromatography (80 mL silica, 4:1 hexane/EtOAc) afforded 126 mg (94% yield, 64% yield over two steps) of **32** as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 9.49 (d, J=7.9 Hz, 1H), 6.83 (dt, J_d=15.5 Hz, J_t=7.1 Hz, 1H), 6.25 (dd, J_1=15.0 Hz, J_2=10.9 Hz, 1H), 6.13 (dd, J_1=15.5 Hz, J_2=7.9 Hz, 1H), 5.80 (d, J=10.9 Hz, 1H), 5.55 (dt, J_d=15.0 Hz, J_t=7.1 Hz, 1H), 3.95 (dt, J_t=6.2 Hz, J_d=2.0 Hz, 1H), 3.65 (t, J=6.7 Hz, 2H), 2.43 (m, 1H), 2.32 (m, 2H), 2.22 (m, 2H), 1.73 (s, 3H), 1.59 (m, 2H), 1.39 (m, 1H), 1.08 (m, 1H), 1.05–1.08 (m, 21H), 0.98 (d, J=6.8 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, δ): 194.4, 159.4, 133.5, 133.2, 129.1, 128.5, 127.8, 75.0, 63.3, 44.6, 37.1, 36.8, 31.2, 31.1, 29.1, 26.2, 18.5, 17.2, 15.9, 13.1, −5.0. HRMS-ESI (m/z): $[M+Na]^+$ calcd for $C_{31}H_{60}O_3Si_2$, 559.3973; found, 559.3985.

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