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

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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 towards 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 5-, 6-, and 7-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 hypothesized that tricycle 1 was the common biological precursor of all cyathane metabolites.⁴ Twenty-two 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.
Various strategies have been employed towards the synthesis of cyathane natural products; however, all of such approaches rely on stepwise installation of the central three rings. 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 6-membered rings and a fused 5,6,6 ring system.

A focus of our research program has been the catalytic, multi-component coupling reaction involving cis addition across an alkyne. 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, ketones, and imines 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, and enantioenriched α-oxyaldehydes have been shown to couple with high diastereoselectivity to form anti-1,2-diols.

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 the alkyne terminus or the presence of conjugated aryl groups and olefins direct 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 towards the synthesis of complex natural products, such as (−)-terpestacin and members of the amphidinolide T class.

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). 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, and the use of a 1,3-enyne may impart regioselectivity in the key bond-forming step. 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 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 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 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. 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 and known epoxide 5.

Reported herein are efforts towards 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\textsuperscript{20} in THF followed by quenching with NIS furnished the corresponding trans-substituted vinyl iodide. This iodide was then coupled with propyne using Sonogashira conditions\textsuperscript{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.\textsuperscript{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 phosphate 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 towards 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.\textsuperscript{23} Mixtures of such polymerization products were recovered in all these reactions.

Interestingly, when a 1:4 catalyst to phosphate ratio was used (entry 3), 5% yield of lactone 9 was observed along with 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 hours (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 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 one minute to one hour (entries 1–3), the yield was improved to 41%. Further, cod was chosen as 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 and 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% over the 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 conditions²⁵ 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-enzyme 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 t-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.

Further, a route involving an intramolecular Diels–Alder (IMDA) reaction²⁶ 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 known aldehyde 23²² 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 mCPBA, affording 26 in multigram quantities and in 96% yield.

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).
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. 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$_2$PPh was selected as a possible ligand in this reductive coupling. This phosphine has similar electronic properties to Bu$_3$P; however, it has a smaller cone angle (122° vs. 132°). Additionally, Me$_2$PPh has been shown to be effective in key alkyne-epoxide reductive cyclizations in our syntheses of pumiliotoxins 209F and 251D.

Gratifyingly, the reductive coupling of 21 and 26 with the use of Me$_2$PPh 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 $^1$H 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 $^1$H signals of both diastereomers and overlap of peaks in the spectrum.

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$_2$PhP. 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 the two steps.

Interestingly, when diasteriomerically-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 31 react at different rates in the reductive coupling reaction.

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, 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.

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-

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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 were 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). $^1$H 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 $^1$H 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 ppm 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 APEX II 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)—TBSCI (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$_3$N (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 warm 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). $^1$H 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$_2$Si, 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, 52.8 mmol, 1 equiv). The solution was warmed to room temperature, and after 100 min, the creamy white solution turned a 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-grey residue. The residue was retaken in hexane (100 mL) and passed through a plug of silica gel (90 mL), rinsing 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 then redissolved 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 ºC. 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 Et2O (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 MgSO4. The solution was then passed through a pad of silica (100 mL), washing with Et2O 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), washing 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 ºC to yield 4 as a clear oil (6.62 g, 55% yield over 2 steps). 1H NMR (300 MHz, CDCl3, 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); 13C NMR (125 MHz, CDCl3, 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 C14H26OSi, 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-ynoxy)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 Et3N (49.6 mL, 357 mmol) and DMAP (4.35 g, 35.7 mmol) in DCM (600 mL) afforded triethyl(pent-4-ynoxy)silane as a clear oil after distillation at 2.8 torr, 57 ºC (35.32 g, > 99% yield). Using the identical procedure for the synthesis of 4, the reaction of triethyl(pent-4-ynoxy)silane (14.86 g, 74.9 mmol), Schwartz’s reagent (20.27 g, 78.7 mmol), CuI (464 mg, 2.44 mmol) in pyrrolidine (49 mL) afforded 10 as a clear oil after distillation at 2.8 torr, 87 ºC (8.48 g, 47% yield over 2 steps). 1H NMR (500 MHz, CDCl3, δ): 6.05 (dt, Jd = 15.8 Hz, Jf = 7.4 Hz, 1H), 5.45 (dq, Jdf = 15.8 Hz, Jdf = 2.1 Hz, 1H), 3.61 (t, Jdf = 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); 13C NMR (125 MHz, CDCl3, 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 C14H26OSi, 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 NaHCO3 (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 Na2SO4, 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 ºC, 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. Et3N (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 MgSO4, 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 2 steps). 1H NMR (500 MHz, CDCl3, δ): 9.77 (t, J = 1.3 Hz, 1H), 6.02 (dt, Jd = 15.8 Hz, Jf = 7.0 Hz N (1.52 g, 15 mmol, 3.5 equiv) was added dropwise, and the solution was stirred for 30 min. Et3N (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 MgSO4, 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 2 steps).
Hz, 1H), 5.49 (dq, Jd = 15.8 Hz, Jq = 1.6 Hz, 1H), 2.55 (dt, Jl = 6.7 Hz, Jd = 1.3 Hz, 2H), 2.41 dt, Jd = 7.0 Hz, Jl = 6.7 Hz, 2H), 1.92 (d, J = 1.6 Hz, 3H). 13C NMR (125 MHz, CDCl3, 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 C8H16O, 145.0624; found, 145.0629.

4.2.7. (E)-Dimethyl 2-oxanon-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 Na2SO4, and concentrated in vacuo to yield a residue. Flash column chromatography (200 mL silica, 1:9 hexane/EtOAc) afforded 18 (486 mg, 50% yield over 2 steps). 1H NMR (500 MHz, CDCl3, δ): 5.99 (dt, Jd = 15.8 Hz, Jl = 7.1 Hz, 1H), 5.48 (dq, Jd = 15.8 Hz, Jl = 1.6 Hz, 1H), 3.80 (d, Jdh = 11.3 Hz, 6H), 3.09 (d, Jdh = 22.8 Hz, 2H), 2.71 (t, J = 7.3 Hz, 2H), 2.37 (dt, Jd = 7.3 Hz, Jl = 7.1 Hz, 2H), 1.92 (d, J = 1.6 Hz, 3H). 13C NMR (125 MHz, CDCl3, δ): 200.5 (JC=P = 6.2 Hz), 140.4, 111.2, 84.9, 74.9, 53.0 (JC=P = 6.4 Hz), 42.9, 41.3 (JC=P = 128.0 Hz), 26.5, 4.1. HRMS-ESI (m/z): [M+Na]+ calcd for C11H17O4P, 267.0757; found, 267.0751.

4.2.8. (E)-tert-Butyld(hept-3-en-5-ynyloxy)dimethylsilane (20)—Using the identical procedure for the synthesis of 7, the reaction of TBSCI (10.45 g, 69.4 mmol) and 3-butyne-1-ol (5.0 mL, 66.1 mmol) with Et3N (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(PPh3)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 2 steps). 1H NMR (500 MHz, CDCl3, δ): 6.04 (dt, Jd = 15.9 Hz, Jl = 7.2 Hz, 1H), 5.50 (dq, Jd = 15.9 Hz, Jl = 2.2 Hz, 1H), 3.64 (t, J = 6.7 Hz, 2H), 2.30 (dt, Jd = 7.2 Hz, Jl = 6.7 Hz, 1H), 1.94 (d, J = 2.2 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H). 13C NMR (125 MHz, CDCl3, 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 C13H24OSi, 247.1489; found, 247.1487.

4.2.9. (E)-(Hept-3-en-5-ynylxy)tri-iso-propylsilane (21)—Using the identical procedure for the synthesis of 7, the reaction of TIPSCI (8.02 g, 41.6 mmol) and 3-butyne-1-ol (3.0 mL, 39.6 mmol) with Et3N (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(PPh3)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 2 steps). 1H NMR (500 MHz, CDCl3, δ): 6.08 (dt, Jd = 15.9 Hz, Jl = 7.2 Hz, 1H), 5.51 (dq, Jd = 15.9 Hz, Jl = 7.2 Hz, 1H), 2.55 (dt, Jd = 7.0 Hz, Jl = 6.7 Hz, 2H), 1.92 (d, J = 1.6 Hz, 3H). 13C NMR (125 MHz, CDCl3, 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 C13H24OSi, 247.1489; found, 247.1487.

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4.3. Optimized Reductive Coupling Procedures

4.3.1. (4R,5S,7E,9E)-Methyl 13-(tert-butyldimethylsilyl oxy)-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$_3$P (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$_3$B (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 was stirred overnight for 14 h. The reaction 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) afforded 8 as a slight yellow oil (241 mg, 19% yield, 77% purity, 1.34 g, 29.2 mmol, 1 equiv). The solution was stirred overnight, a small amount of argon, and then the solution was allowed to stir overnight, warming 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 (6.01 g, 24% yield) as a clear oil.

4.3.2. (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. Ozono 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$_2$S (10.9 mL, 148 mmol, 2.5 equiv) was added, and the solution was allowed to stir overnight, warming 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 (3.27 g) as a clear oil (3.27 g). To a solution of 23 (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, warming to room temperature. The solution was then concentrated at 40 torr to yield a white residual oil. Flash column chromatography (300 mL, 95:5 hexane/EtOAc) afforded 26 as a clear oil (1.14 g, 96% yield, 1.4:1 dr). To a solution of 26 as a clear oil (5.32 g, 49% yield) in DCM (12 mL) at 0 °C was portionwise added CPBA (23 ml, 1.25 mmol, 1 equiv), and Bu$_3$S (0.51 mmol, 0.40 equiv). The solution was stirred overnight, warming to room temperature. The solution was then concentrated at 40 torr to yield a white residual oil. Flash column chromatography (150 mL silica, 8:2 hexane/EtOAc) afforded 26 as a clear oil (1.41 g, 96% yield, 1.4:1 dr syn (26a):anti (26b)). 

4.3.3. (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 mCPBA (≤77% purity, 1.3 g, 29.2 mmol, 1 equiv). The solution was stirred overnight, warming to room temperature. The solution was then concentrated at 40 torr, and treated with saturated aqueous NaHCO$_3$ (25 mL) and 1 M NaOH (25 mL). Chemically and separated, 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)). 

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NMR (125 MHz, CDCl₃, 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_{3}Si, 421.2745; found, 421.2743.

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 Bu₃P (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, Et₂B (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. 10 (226 mg, 0.95 mmol, 1.5 equiv) was added dropwise over approximately 1 h. The black reaction was stirred overnight for 14 h. The reaction 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). 1H NMR (500 MHz, CDCl₃, δ): 6.24 (dd, J₁ = 15.0 Hz, J₂ = 10.8 Hz, 1H), 5.87 (d, J = 10.8 Hz, 1H), 5.62 (dt, J₂ = 15.0 Hz, J₃ = 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, 2H), 2.14 (m, 2H), 2.00 (m, 1H), 1.86 (m, 1H), 1.74 (s, 3H), 1.50–1.64 (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); 13C NMR (125 MHz, CDCl₃, δ): 174.6, 133.9, 131.2, 128.1, 127.5, 72.4, 53.3.

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), Bu₃P (316 µL, 1.26 mmol, 0.4 equiv), Et₂B (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). 1H NMR (500 MHz, CDCl₃, δ): 6.26 (dd, J₁ = 15.0 Hz, J₂ = 10.8 Hz, 1H), 5.88 (d, J = 10.8 Hz, 1H), 5.64 (dt, J₃ = 15.0 Hz, J₄ = 7.0 Hz, 1H), 3.68 (s, 3H), 3.64 (m, 1H), 3.62 (t, J = 6.5 Hz, 2H), 3.08–2.22 (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); 13C NMR (125 MHz, CDCl₃, δ): 174.6, 133.5, 132.8, 128.3, 126.6, 71.6, 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_{3}Si, 421.2745; found, 421.2749.

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 Bu₃P (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, Et₂B (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 Et₂O, 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). 1H NMR (500 MHz, CDCl₃, δ): 6.28 (dd, J₁ = 15.1 Hz, J₂ = 11.2 Hz, 1H), 5.87 (d, J = 11.2 Hz, 1H), 5.59 (dt, J₃ = 15.1 Hz, J₄ = 7.2 Hz, 1H), 3.80 (d, J₄ = 11.2 Hz, 6H, 3.76–3.79 (m, 1H), 3.68 (s, 3H), 3.52–3.57 (br m, 1H), 3.10 (d, J₅ = 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), 2.09 (d, J = 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); 13C NMR (125 MHz, CDCl₃, δ): 201.3 (J_C-P = 6.1 Hz), 174.6, 133.9, 131.2, 128.1, 127.5, 72.4, 53.3.
4.4. Elaboration of Reductive Coupling Products

4.4.1. (8E,10E,13S,14R)-3,3-Diethyl-19,19-di-iso-propyl-11,14,20-trimethyl-13-(tri-iso-propylsilyloxy)-4,18-dioxo-3,19-disilahenicosa-8,10-diene (14)—To a brown 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\(_3\), \(\delta\)): 6.97 (dt, \(J_d = 15.5\) Hz, \(J_1 = 6.8\) Hz, 1H), 6.25 (dd, \(J_d = 15.1\) 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, \(J_1 = 7.1\) 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, \(J_d = 6.8\) Hz, \(J_1 = 7.0\) 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\(_3\), \(\delta\)): 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\(_4\)Si\(_2\), 603.4235; found, 603.4226.

4.4.2. (10E,12S)-3,3-Diethyl-15,15-di-iso-propyl-11,14,17-trimethyl-14-(tri-iso-propylsilyloxy)-4,18-dioxo-3,19-disilahenicosa-8,10-diene (21)—To a brown oil. Flash column chromatography (500 mL silica, 95:5 hexane/EtOAc) afforded 21 as a clear oil (284 mg, 43% yield). \(^1\)H NMR (500 MHz, CDCl\(_3\), \(\delta\)): 6.97 (dt, \(J_d = 15.5\) Hz, \(J_1 = 6.8\) Hz, 1H), 6.25 (dd, \(J_d = 15.1\) 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, \(J_1 = 7.1\) 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, \(J_d = 6.8\) Hz, \(J_1 = 7.0\) 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\(_3\), \(\delta\)): 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\(_4\)Si\(_2\), 603.4235; found, 603.4226.
solution of 11 (402 mg, 1.01 mmol, 1 equiv) in Et₂O (26 mL) at 0 °C was added dropwise a solution of LiAlH₄ in Et₂O (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, 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, rinsing with Et₂O, and concentrated in vacuo. Flash column chromatography (200 mL florisorl, 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) was 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 MgSO₄, filtered, and concentrated in vacuo. Flash column chromatography (200 mL silica, 98:2 hexane/EtOAc) afforded 547 mg (79% yield over 2 steps) of 14 as a clear oil. ¹H NMR (500 MHz, CDCl₃, δ): 6.21 (dd, J₁ = 15.0 Hz, J₂ = 10.8 Hz, 1H), 5.81 (d, J = 10.8 Hz, 1H), 5.54 (dt, J₃ = 15.0 Hz, J₄ = 7.4 Hz, 1H), 3.92 (dt, J₅ = 6.6 Hz, J₆ = 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, 3H), 0.97 (t, J = 8.0 Hz, 9H), 0.94 (d, J = 6.8 Hz, 3H), 0.61 (q, J = 8.0 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃, 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, 15.3, 12.2, 7.0, 4.6. HRMS-ESI (m/z): [M+Na]⁺ calcd for C₃₉H₆₂O₃S₁₃ 705.5464; found, 705.5476.

4.4.2. (4E,6E,9S,10R)-7,10-Dimethyl-9,13-bis(tri-iso-propylsilyloxy)trideca-4,6-dienal (15)—In a glovebox, CrO₃ (123 mg, 1.23 mmol, 10 equiv) in DCM (1 mL) at 0 °C. The solution was then diluted with DCM (10 mL) and washed with 1 N HCl (2 mL), saturated aqueous NaHCO₃ (4 mL), water (4 mL), and brine (2 mL). The organic layer was then dried over Na₂SO₄ and passed through a pad of SiO₂ (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. ¹H NMR (500 MHz, CDCl₃, δ): 9.78 (t, J = 1.0 Hz, 1H), 6.25 (dd, J₁ = 15.0 Hz, J₂ = 10.8 Hz, 1H), 5.80 (d, J = 10.8 Hz, 1H), 5.52 (dt, J₃ = 6.8 Hz, J₄ = 15.0 Hz, 1H), 3.92 (dt, J₅ = 5.9 Hz, J₆ = 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); ¹³C NMR (125 MHz, CDCl₃, 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 589.4443; found, C₃₃H₆₆O₃Si₂ 589.4426.

4.4.3. 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 Na₂SO₄, 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 NaHCO₃ (984 mg, 11.7 mmol, 10 equiv) were added. After stirring for 20 min, saturated aqueous Na₂S₂O₃ (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 Na₂SO₄. 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. ¹H NMR (500 MHz, CDCl₃, δ): 6.22 (dd, J₁ = 15.0 Hz, J₂ = 10.8 Hz, 1H), 5.77 (d, J = 10.8 Hz, 1H), 5.48 (dt, J₃ = 15.0 Hz, J₄ = 7.5 Hz, 1H), 3.90 (dt, J₅ = 6.3 Hz, J₆ = 2.6 Hz, 1H), 3.67 (t, J = 6.5 Hz, 3H), 3.78 (d, J₇₋₈ = 11.2 Hz, 4H), 3.66 (t, J = 6.5 Hz, 2H), 3.09 (d, J₉₋₁₀ = 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); ¹³C NMR (125 MHz, CDCl₃, δ): 201.4 (J_C₋₆ = 6.4 Hz), 134.7, 129.7, 127.9, 127.2, 75.1, 64.0, 53.2 (J_C₋₆ = 6.4 Hz), 44.2, 43.7, 42.0 (J_C₋₆ = 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 C₃₆H₇₃O₆PSi₂, 711.4576; found, 711.4602.

4.4.4. (2E,6R,7S,9Z,11E)-6,9-Dimethyl-7-(tris-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 (3 drops). The solution was stirred for 30 min at 0 °C, and then 45 min at room temperature. Water (2 mL) and saturated aqueous NaHCO₃ (6 mL) were added. The solution was extracted four times with Et₂O (5 mL each). The organic extracts were combined, dried over Na₂SO₄, 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) was added DMP (437 mg, 1.03 mmol, 3 equiv) and 18-crown-6 (116 mg, 0.44 mmol, 5 equiv). After stirring for 100 min, saturated aqueous Na₂S₂O₃ (10 mL) and saturated aqueous NaHCO₃ (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 Na₂SO₄, 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) was added oven-dried K₂CO₃ (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 was then cooled to room temperature and washed twice with saturated aqueous NH₄Cl (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 Na₂SO₄, 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 3 steps) of 3 was isolated. ¹H NMR (500 MHz, CDCl₃, δ): 6.74 (m, 1H), 6.21 (dd, J₁ = 15.3 Hz, J₂ = 10.5 Hz, 1H), 6.06 (d, J = 16.0 Hz, 1H), 5.79 (d, J = 10.5 Hz, 1H), 5.56 (dt, J₃ = 15.3 Hz, J₄ = 7.0 Hz, 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); ¹³C NMR (125 MHz, CDCl₃, 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 C₂₃H₄₄O₂Si, 427.3003; found, 427.3019.

4.4.5. (2E,6R,7S,9E,11E)-14-(tert-Butyldimethylsilyloxy)-6,9-dimethyl-7-(tri-propylsilyloxy)cyclotetradeca-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 Et₂O (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 Et₂O (5 mL each). The organic extracts were combined, dried over MgSO₄, 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) was added DMP (209 mg, 0.49 mmol, 2 equiv) and NaHCO₃ (207 mg, 2.47 mmol, 10 equiv). The solution was stirred for 2 h and then treated with saturated aqueous Na₂S₂O₃ (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 MgSO₄, 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 2 steps) of 32 as a clear oil.

**1H NMR** (500 MHz, CDCl₃, 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), 1.05–1.08 (m, 21H), 0.98 (d, J = 6.8 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H); **13C NMR** (125 MHz, CDCl₃, δ): 194.4, 159.4, 133.5, 133.2, 129.1, 128.5, 127.8, 75.0, 63.3, 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]⁺ calcld for C₃₁H₆₀O₃Si₂, 559.3973; found, 559.3985.

**Acknowledgments**

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**References and Notes**


18. The crystal structure of a nickelacycle has been recently reported, formed from the oxidative cyclization of an alkyne and an aldehyde with nickel(0): Ogoshi S, Arai T, Ohashi M, Kurosawa H. Chem Commun 2008:1347–1349.


Tetrahedron. Author manuscript; available in PMC 2010 April 18.
Scheme 1.
Scheme 2.
Scheme 3.
Scheme 4.

1. Cp₂Zr(H)Cl, THF, 0 °C to rt, then NIS
2. 2.5 mol% Pd(PPh₃)₄, 5 mol% Cul, propyne, pyrrolidine, 78 °C to rt
55% yield (2 steps)

6: R = H
7: R = TBS
86% yield
Scheme 5.

TBSO\textsuperscript{-} + \textsuperscript{1.5 equiv 4} + \textsuperscript{1.0 equiv 5} \rightarrow \textsuperscript{8}

\[
\begin{align*}
20 \text{ mol\% Ni(cod)}_2 & \\
40 \text{ mol\% Bu}_3\text{P} & \\
\text{Et}_3\text{B, 14 h} & \\
48\% \text{ yield}
\end{align*}
\]
Scheme 6.
Scheme 7.

1. LiAlH₄, Et₂O, 0 °C
2. TIPSOTf,
   2,6-lutidine, DCM
79% yield (2 steps)

1. Amberst-15, DCM, EtOH
2. Swern oxidation
   (80% yield over 2 steps)

or

10 equiv CrO₃pyr, DCM, 0 °C
(60% yield at 88% conversion)

1. (MeO)₂P(O)(O)Me, t-BuLi, THF, hex, 78 °C to rt
2. DMP, NaHCO₃, DCM
54% yield (2 steps)

1. HCl, MeOH
2. DMP, NaHCO₃, DCM
3. K₂CO₃, 18-crown-6, PhMe (9 mM), 85 °C
3 (34% yield over 3 steps)
Scheme 8.

1. HCl, MeOH, 0 %C
2. Swern oxidation
81% yield (2 steps)

1. (MeO)₂P(O)Me, t-BuLi,
pent, THF, 78 %C to rt
2. TPAP, NMO, 4% MS, DCM
50% yield (2 steps)

20 mol% Ni(cod)₂
40 mol% Bu₃P
Et₃B, 18 h
40% yield

Tetrahedron. Author manuscript; available in PMC 2010 April 18.
Scheme 9.

**Scheme 9.**

Chemical reactions and structures are depicted, including reactions with ozone (O₃, DCM, 78% yield), methyl disulfide (Me₂S, 49% yield), and peroxydisulfate (1 equiv mCPBA, DCM, 96% yield and 1.4:1 dr (syn:anti)).
Scheme 10.
Scheme 11.
Scheme 12.

1. 20 mol% Ni(cod)$_2$, 40 mol% Me$_2$PPh, Et$_3$B, 2 h
2. TIPSOTf, 2,6-lutidine, THF

62% yield (2 steps)
Scheme 13.

1. 20 mol% Ni(cod)$_2$, 40 mol% Me$_2$PPh, Et$_3$B, 2 h

2. TIPSOTf, 2,6-lutidine, THF

43% yield (2 steps)
Reducive coupling of enyne 4 and epoxide 5.

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Bu3P (mol%)</th>
<th>Time (h)</th>
<th>Yield 8 (%)</th>
<th>Yield 9 (%)</th>
<th>Recovered 5 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
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<td>60</td>
<td>0</td>
<td>0</td>
<td>n.d.</td>
</tr>
<tr>
<td>2a</td>
<td>20</td>
<td>60</td>
<td>25</td>
<td>0</td>
<td>26</td>
</tr>
<tr>
<td>3a</td>
<td>40</td>
<td>60</td>
<td>23</td>
<td>5</td>
<td>38</td>
</tr>
<tr>
<td>4b</td>
<td>20</td>
<td>128</td>
<td>19</td>
<td>32</td>
<td>20</td>
</tr>
</tbody>
</table>

*a* A mixture of 4 (3 equiv) and 5 (1 equiv) was added over < 1 min to a stirring slurry of Ni(cod)2, Bu3P, and Et3B.

*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, Bu3P, and Et3B. After 24 h, 4 (1.5 equiv) was added.
Table 2

Reductive coupling of enyne 10 and epoxide 5.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Addition time of 10 (min)</th>
<th>Additive</th>
<th>Yield 11 (%)</th>
<th>Recovered 5 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;1</td>
<td>None</td>
<td>26</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>45</td>
<td>None</td>
<td>28</td>
<td>63</td>
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<tr>
<td>3</td>
<td>60</td>
<td>None</td>
<td>41</td>
<td>39</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>50 mol% cod</td>
<td>49</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>100 mol% cod</td>
<td>44</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>150 mol% cod</td>
<td>41</td>
<td>41</td>
</tr>
</tbody>
</table>

\(^a\) 5 (1 equiv) was added to a stirring slurry of Ni(cod)\(_2\), Bu\(_3\)P, Et\(_3\)B, and an additive. 10 was then added over the specified amount of time.
### Table 3

Attempted TADA reaction of triene 3.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe, 180 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>PhMe, 200 °C</td>
<td>Some isomerization</td>
</tr>
<tr>
<td>3</td>
<td>Et₂AlCl, DCM, hept, −78 °C to 40 °C</td>
<td>Decomposition</td>
</tr>
<tr>
<td>4</td>
<td>BF₃·OEt₂, PhMe, −78 °C to 30 °C</td>
<td>Decomposition</td>
</tr>
<tr>
<td>5</td>
<td>SnCl₄, DCM, −78 °C to rt</td>
<td>Decomposition</td>
</tr>
</tbody>
</table>
Table 4

Reductive coupling of enyne 20 and epoxide 26.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction time (h)</th>
<th>Recovered 20 (%)</th>
<th>Yield 28 (%)</th>
<th>Yield 29 (%)</th>
<th>Yield 30 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>31\textsuperscript{b}</td>
<td>40</td>
<td>27</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>36</td>
<td>41</td>
<td>39</td>
<td>13</td>
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<tr>
<td>3</td>
<td>2</td>
<td>55</td>
<td>32</td>
<td>51</td>
<td>9</td>
</tr>
</tbody>
</table>

\textsuperscript{a} 26 (1 equiv) was added to a stirring slurry of Ni\textsubscript{(cod)}\textsubscript{2}, Me\textsubscript{2}PPh, and Et\textsubscript{3}B. 20 (1.5 equiv) was then added over 30 min.

\textsuperscript{b} Minor homocoupling products of 20 were observed as well.
Table 5

Attempted IMDA reaction of trienal 32.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe, 175 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>2</td>
<td>C₆H₅Cl₂, 330 °C</td>
<td>Decomposition</td>
</tr>
<tr>
<td>3</td>
<td>DMSO, µW, 200 °C, 10 min</td>
<td>Decomposition</td>
</tr>
<tr>
<td>4</td>
<td>MeAlCl₂, DCM, hex, −78 °C to rt</td>
<td>Decomposition</td>
</tr>
<tr>
<td>5</td>
<td>BF₃·OEt₂, DCM, −78 °C to −15 °C</td>
<td>1° TBS deprotection</td>
</tr>
<tr>
<td>6</td>
<td>SnCl₄, DCM, −78 °C to −30 °C</td>
<td>1° TBS deprotection</td>
</tr>
<tr>
<td>7</td>
<td>34, 98:2 MeCN:Η₂Ο</td>
<td>No reaction</td>
</tr>
<tr>
<td>8</td>
<td>34, CDCl₃</td>
<td>Decomposition</td>
</tr>
</tbody>
</table>