JOC Article

Metal-Catalyzed Coupling Reactions on an Olefin Template: The Total Synthesis of (13*E*,15*E*,18*Z*,20*Z*)-1-Hydroxypentacosa-13,15,18,20-tetraen-11-yn-4-one 1-Acetate

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The naturally occurring ant venom (13*E*,15*E*,18*Z*,20*Z*)-1-hydroxypentacosa-13,15,18,20-tetraen-11-yn-4-one 1-acetate was synthesized stereospecifically using a series of metal-mediated cross-coupling reactions. The use of the difunctional olefin template (*E*)-1-chloro-2-iodoethylene as the central, pseudosymmetrical building block facilitated a fully convergent and, thus, efficient strategy to prepare this polyunsaturated natural product.

Introduction

The ability to build an olefin into the structure of target molecules continues to be a challenge that is hampered by a number of factors. Elimination-based olefination reactions routinely suffer poor stereospecificity during the elimination portion of the overall transformation. This encompasses, for example, Julia, Peterson, Wittig, and Horner−Wadsworth−Emmons reactions that bring the olefin carbons together during olefin formation.[1] While these methods are nicely convergent, they all involve reactive intermediates (i.e., anions or ylides) implying that the partners cannot have reactive functional groups present, at least without first employing suitable protecting group chemistry.

Olefins can be prepared also using metal-catalyzed coupling reactions that are stereospecific, such as the Suzuki[2] or Stille[3] transformations. In only a few instances do these reactions provide mixtures of olefin stereoisomers when starting with stereochemically pure olefinic halides and organometallic coupling partners.[4] The challenge for such approaches then is to build the requisite stereochemistry into the coupling partners and rely on the coupling reaction to provide the correct stereochemistry in the product. This means that the difficulty has shifted to preparing the appropriate functionalized coupling precursors stereochemically pure. Installing cross coupling handles (i.e., the halide or the organometal center) at a later stage in a synthesis can be a challenge due to chemoselectivity concerns when installing such reactive functional groups. Alternatively, if the functionality is built in at an earlier stage, one must then be concerned about carrying such reactive moieties through a number of steps to get to the metal-mediated coupling step.

We have been working at developing a modular synthetic approach to the synthesis of olefin-containing molecules that is based primarily on coupling reactions that utilize small, densely functionalized olefin building blocks (templates).[5] In this strategy, the functional groups have a defined stereochemistry and are differentiated from each other in terms of their reactivity toward transition metal catalysis. This affords a number of advantages. The coupling reactions can all be done one after another, ideally in a one-pot operation with a single catalyst, which makes this approach convergent. Further, the compactness and unobtrusiveness of these templates makes them strong candidates for general utility across a wide variety of structurally diverse targets. We have successfully demonstrated this strategy with model substrates in the past,[5] and we are now beginning to apply this strategy to the total synthesis of natural products.[6] The subject of this report is the total synthesis of compound **1**,[7] a potent ant toxin, using this methodology (Figure 1). Compound **2**[8] is key to this synthesis because it allows for the independent preparation of **3** and **4** and then joins them in successive Pd-catalyzed couplings without the need for any functional group protection.

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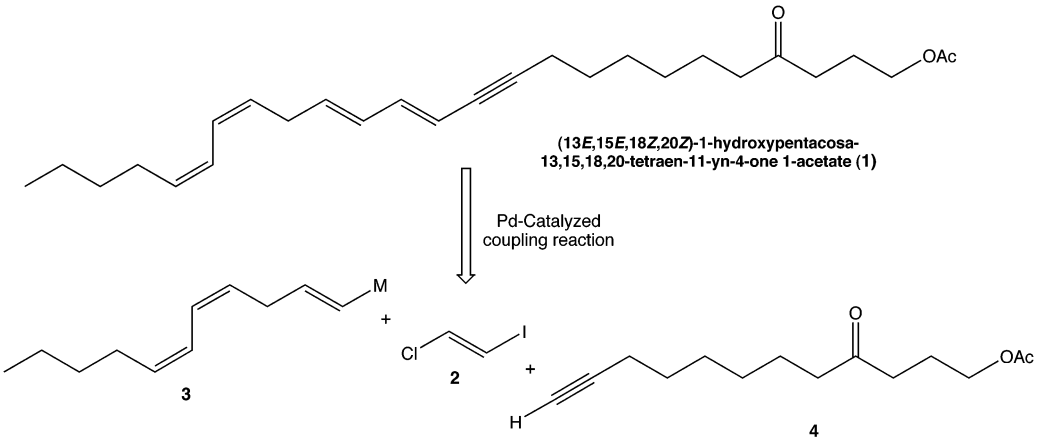
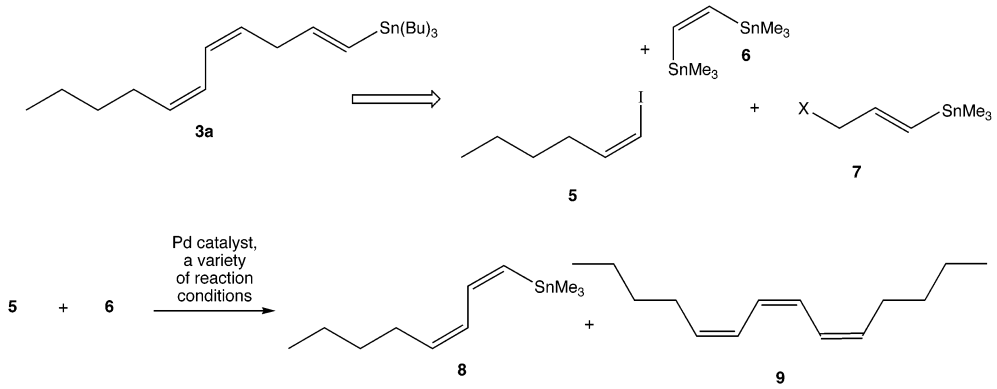


FIGURE 1. Structure of retrosynthetic analysis of (13*E*,15*E*,18*Z*,20*Z*)-1-hydroxypentacosa-13,15,18,20-tetraen-11-yn-4-one 1-acetate (**1**).

SCHEME 1



Compound **1** is interesting from a bioactivity point of view. Most long-chain ant toxins are derivatives of 4-oxo-2,5-dienyl acetates that when acted upon by esterase and oxidase enzymes stored in the poison gland of the ant are transformed into highly electrophilic 4-oxo-2,5-dienals. Thus, compound **1** represents a new polyfunctionalized long-chain derivative and is a prime target for total synthesis.

Results and Discussion

Preparation of the Left-Hand Piece (3). In our original approach to subunit **3**, we envisioned making an sp^2-sp^3 bond using a similar olefin template strategy to the one being used to piece the entire structure together (vide supra). We have had experience with template **7b** that undergoes smooth chemo- and stereoselective Pd-catalyzed allylic substitution followed by Stille coupling to yield trans olefin products.[5] With this in mind, we set out to prepare **5** and react it with *cis*-1,2-ditrimethylstanylethylene (**6**,[9] Scheme 1). Compound **5**[10] was prepared readily, however, we could not selectively mono couple template **6** and significant biscoupled product **9** was produced that could not be separated from **8** during purification. This result demonstrates clearly the merit in the creation and utilization of olefin templates that possess different functional groups. Significant over coupling of olefin building blocks with two or more of the same functional group has been reported to be a significant problem as well by others.[11] Varying the reaction conditions by adding excess **6** or adding compound **5** to **6** dropwise did not prevent over coupling from occurring.

We have also had experience coupling boronic acids to allylic acetates[12] and reasoned that, given the difficulty using the tin reagent above, we could adjust the route to include **10** as a viable synthetic intermediate instead (Scheme 2). We began this study using **11** as a simple and readily available model substrate. With a variety of allylic leaving groups (i.e., **7a**−**c**), we were only able to obtain the homo coupled product (**12**). We tried the same reactions using the zinc analogue of **11** and we did obtain coupling between the two partners. Surprisingly, however, coupling occurred at the tin substituted end of the Pd π-allyl complex leading to structures resembling **13** rather than the desired linear structure.

After these model studies, it was clear to us that we could not establish readily the desired sp^2-sp^3 bond using this strategy. However, we did not want to use classical

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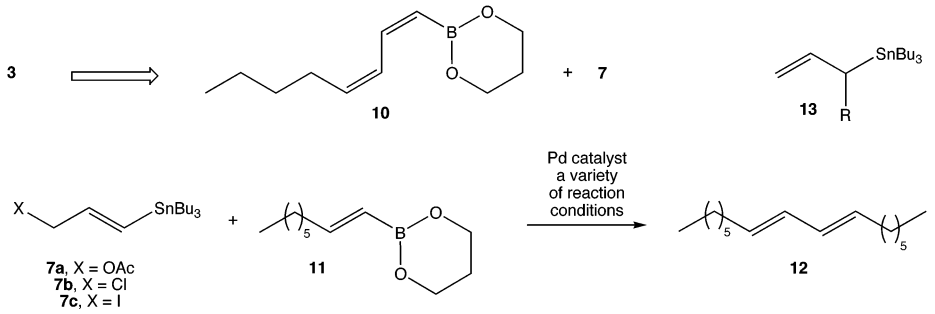
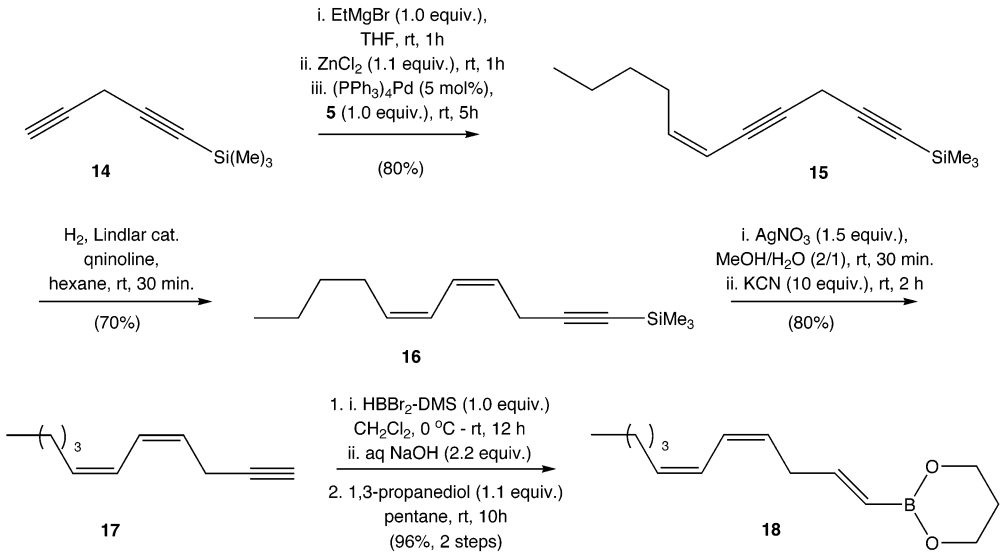
SCHEME 2



SCHEME 3



olefination reactions (vide supra) as they most certainly would lead to inseparable isomers. With this in mind, we settled on the route outlined in Scheme 3. While we were no longer relying on metal coupling reactions to set the carbon framework, the reactions that yield the two additional olefins are nonetheless stereospecific. Thus, Negishi coupling[13] between **5** and **14** provided ene diyne **15** that was chemo- and stereoselectively reduced to yield **16**. Removal of the TMS group and hydroboration yielded the requisite boronic acid that was directly esterified to provide **18** as one single stereoisomer (by ^{13}C NMR spectroscopy).

Preparation of the Right-Hand Piece (4). In our initial approach to **4**, we envisioned the addition of an organometallic reagent derived from a precursor resembling **19** to aldehyde **20**, both of which were prepared very efficiently in our laboratory (Scheme 4). However, all attempts to generate the Mg Grignard from either the corresponding Cl (**19a**) or I (**19b**) failed. The corresponding lithium species was generated by lithium−iodide exchange between **19b** and *t*-BuLi, but while addition to **20** was achieved on a small scale, the reaction could not be scaled up reliably. We are certain that the exchange took place on the basis of controlled quenching studies with **19b**, which returned a 72% recovery of the corresponding alkane. While nearby coordinating functionality, such as the protected alcohol in this case, can make carbonyl additions difficult, we suspected that the problem resided primarily with the alkyne group. We tried the addition to a variety of relatively simply aldehydes (e.g., isovaleraldehyde) and all exhibited sluggish reactivity and low yields. There must be an intramolecular interaction taking place between the alkyne and the lithiate that diminishes its nucleophilicity.

With these results in hand, we redesigned the approach to **4** such that the alkyne portion was not part of the nucleophile and there was no potential coordinating functionality present during nucleophilic addition. We have tried to generate organomagnesium or organolithium species with neighboring alkoxy substituents before, and this has proven to be problematic. Thus, we opted to use allylmagnesium bromide as the nucleophile and adjust the oxidation state of the alkene later. Terminal alkyne **22** is not available commercially, but internal alkyne **21** is and in a mechanistically interesting transformation **21** was isomerized into **22** simply by treating it with NaH in warm ethylenediamine.[14] Silylation of the terminal alkyne using Denmark's procedure[15] provided **23** that upon oxidation yielded aldehyde **24**. Grignard addition and oxidation gave **26** that was hydroborated selectively to provide **27**. Capping the alcohol with acetyl chloride completed the synthesis of **4**.

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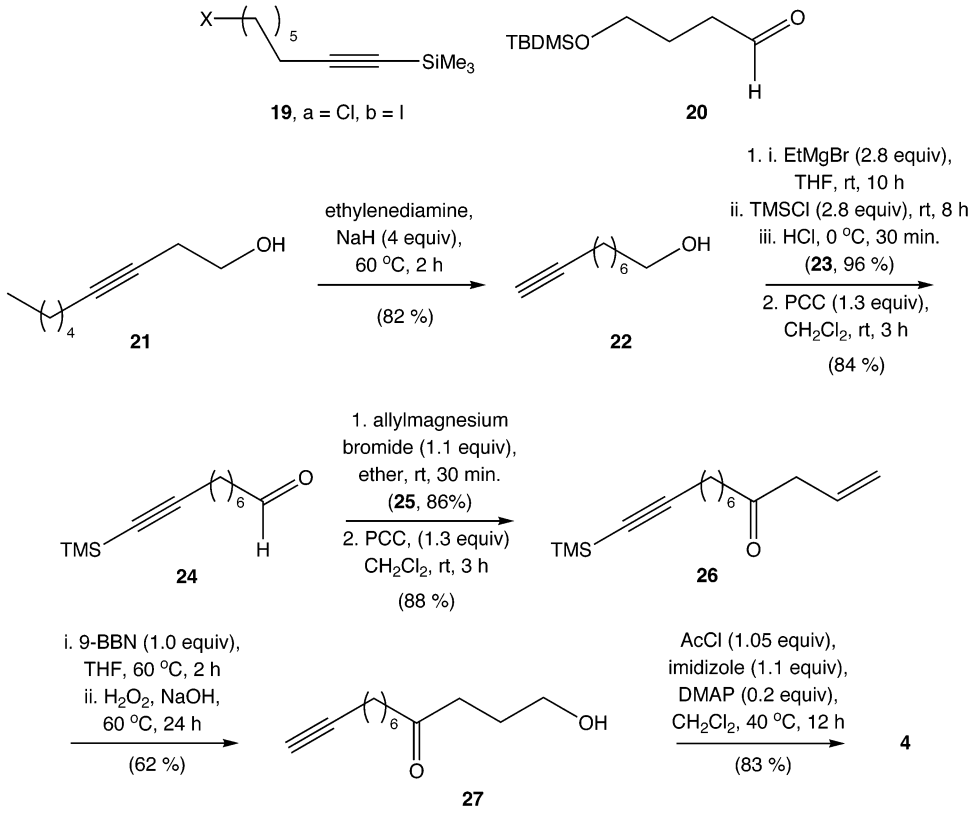
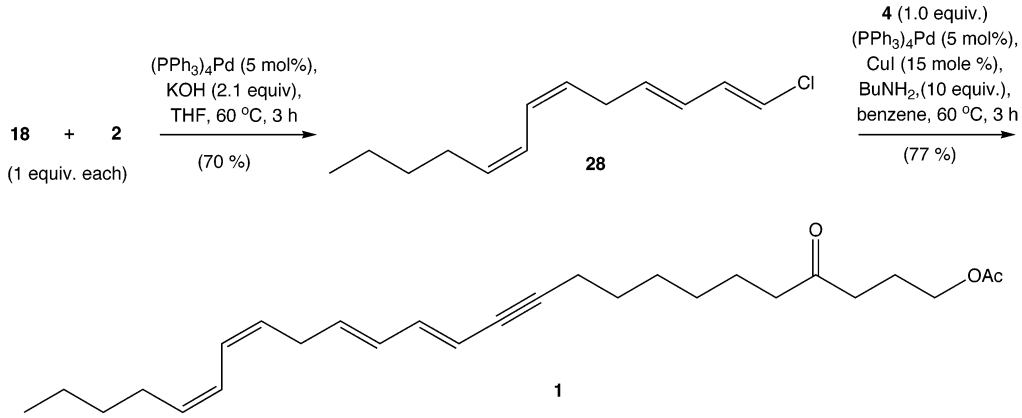
SCHEME 4



SCHEME 5



The Final Coupling of the Left- (3) and Right-Hand (4) Pieces. What was left to do now was to "stitch" the left- and right-hand pieces together using template **2**. Selective Suzuki coupling between **18** and the iodide of **2** provided polyene chloride **28** in good recovery. The desired coupling is in competition with dimerization of **18**, which accounted for the rest of the mass balance in this transformation. When (*E*)-1,2-diiodoethylene was used as the template, no desired coupling was observed and homo coupling of **18** was quantitative. Sonogashira coupling between **28** and the right-hand piece (**4**) proceeded smoothly providing the natural product. In summary, (13*E*,15*E*,18*Z*,20*Z*)-1-hydroxypentacosa-13,15,18,20-tetraen-11-yn-4-one 1-acetate (**1**) has been synthesized in a completely stereoselective fashion using a series of metal-catalyzed coupling reactions. The spectral data recorded for **1** are identical in all respects to the data reported by Daloze and co-workers.[16] Key in this approach was the use of a pseudosymmetrical olefin template, that is (*E*)-1-chloro-2-iodoethylene (**2**), to stitch the structure together. The use of late transition metal catalysis meant that protecting group chemistry could be avoided and the final steps of this modular and convergent approach provided the final target directly. This synthesis represents the first total synthesis of this natural product.

Experimental Section

***(E)*-1-Chloro-2-iodoethene (2).** To a cooled solution (−10 °C) of ICl (10 g, 60.60 mmol) in 70 mL of hydrochloric acid (6 N) was bubbled acetylene gas for 6 h. After being warmed to

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rt, the reaction mixture was extracted (3×) with pentane and the pooled organic layers were washed with saturated $Na_2S_2O_3$. The combined organic layers were dried over anhydrous $MgSO_4$ and filtered, and the filtrate was concentrated in vacuo providing 6.8 g of **2** (59%) as a yellow liquid (R_f = 0.8 in pentane): ^{1}H NMR ($CDCl_3$) δ 6.69 (d, J = 13.2 Hz, 1H), 6.50 (d, J = 13.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 76.4 (−), 24.8 (−). The NMR spectral data are identical to the literature.[8]

(*Z*)-11-(Trimethylsilyl)-7,10-diynyl-5-undecene (15). To 0.28 g of Mg (1.2 equiv, 11.42 mmol) in 20 mL of THF was added 1.04 g of bromoethane (1.0 equiv, 9.5 mmol), and the reaction was stirred at rt for 2 h. The resultant Grignard was added to a flask containing 1.3 g of **14** (1.0 equiv, 9.52 mmol), and the solution was stirred at rt for 1 h. To this mixture was added 21 mL of a 0.5 M solution of $ZnCl_2$ in THF (1.1 equiv, 10.47 mmol), and the mixture was stirred for 1 h at rt. At this time, 2 g of **5** (1.0 equiv, 9.52 mmol) and 0.55 g of $(PPh_3)_4Pd$ (0.05 equiv, 0.476 mmol) were added, and the reaction mixture was stirred for 5 h at rt. The reaction mixture was then passed through a short silica gel pad to remove metal salts and the filtrate concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (R_f = 0.4; 50% ether in pentane) providing 1.66 g of **15** (80%) as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 5.89 (m, 1H), 5.43 (d, J = 10.8 Hz, 1H), 3.36 (s, 2H), 2.29 (m, 2H), 1.38 (m, 4H), 0.92 (t, J = 7.2 Hz, 3H), 0.17 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 147.0 (−), 109.2 (−), 100.1 (+), 86.9 (+), 85.1 (+), 77.8 (+), 31.0 (+), 29.8 (+), 22.2 (+), 14.5 (−), 11.7 (+), 0.2 (−); IR (neat) 2184 cm^{-1}; HRMS *m*/*z* calcd for $C_{14}H_{22}Si$ 218.1491, found 218.1475.

(*Z*,*Z*) 1-(Trimethylsilyl)-4,6-undecadien-1-yne (16). Compound **15** (0.16 g, 1.0 equiv, 0.735 mmol) was dissolved in 24 mL of hexane and hydrogenated with H_2 (1 atm) in the presence of 0.11 g of quinoline (0.85 mmol, 1.1 equiv, 0.10 mL) and 24 mg of Lindlar catalyst (5% Pd on $CaCO_3$) at rt for 30 min. The reaction mixture was concentrated in vacuo, and the crude product was purified by column chromatography on silica gel (R_f = 0.3; pentane) providing 70 mg of **16** (70%) as a yellow liquid: ^{1}H NMR ($CDCl_3$) δ 6.30 (t, J = 10.8 Hz, 1H), 6.20 (t, J = 10.8 Hz, 1H), 5.53 (m, 1H), 5.45 (m, 1H), 3.13 (d, J = 14.8 Hz, 2H), 2.23 (m, 2H), 1.36 (m, 4H), 0.92 (t, J = 6.8 Hz, 3H), 0.18 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 134.3 (−), 130.3 (−), 126.5 (−), 122.4 (−), 104.9 (+), 84.5 (+), 31.7 (+), 27.3 (+), 22.3 (+), 18.7 (+), 17.0 (−), 0.2 (−); IR (neat) 2176 cm^{-1}; HRMS *m*/*z* calcd for $C_{14}H_{24}Si$ 220.1647, found 220.1657.

(*Z*,*Z*)-4,6-Undecadien-1-yne (17). To a solution of 1.0 g of **16** (1.0 equiv, 4.54 mmol) in 8 mL of methanol was added a solution of 1.16 g of $AgNO_3$ (1.5 equiv, 6.82 mmol) in 4.2 mL of water. The mixture was stirred for 30 min at rt, after which time a KCN solution (3 g, 10.0 equiv, 45.45 mmol) in 2.4 mL of water was added. After being stirred for 2 h at rt, the reaction was diluted with ether, and the organic and aqueous layers were separated. The aqueous layer was extracted with ether, and the combined organic layers were dried over anhydrous $MgSO_4$ and filtered, and the filtrate was concentrated in vacuo. The crude product was purified by column chromatography on silica gel (R_f = 0.9; 5% ethyl acetate in hexane) providing 538 mg of **17** (80%) as a yellow liquid: ^{1}H NMR ($CDCl_3$) δ 6.35 (t, J = 10.8 Hz, 1H), 6.19 (t, J = 10.8 Hz, 1H), 5.61 (m, 1H), 5.44 (m, 1H), 3.08 (d, J = 7.2 Hz, 2H), 2.19 (m, 2H), 2.00 (t, J = 2.8 Hz, 1H), 1.36 (m, 4H), 0.91 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 136.2 (−), 127.5 (−), 124.2 (−), 122.3 (−), 82.4 (+), 68.3 (+), 31.7 (+), 27.3 (+), 22.3 (+), 17.1 (+), 15.7 (−); IR (neat) 2176 cm^{-1}; HRMS *m*/*z* calcd for $C_{11}H_{16}$ 148.1252, found 148.1240.

2-(1*E*,4*Z*,6*Z*)-1.4,6-Undecatrienyl-1,3,2-dioxaborinane (18). To a solution of **17** (100 mg, 1.0 equiv, 0.676 mmol) in 5 mL of dichloromethane was added 0.68 mL of $HBBr_3{\cdot}S(CH_3)_2$ (1.0 equiv, 0.676 mmol) at 0 °C. After being stirred for 12 h at rt, 1.5 mL of a 1 M aqueous NaOH solution (60 mg, 2.2 equiv, 1.49 mmol) was added. The precipitated product was filtered, and the solid was washed with 10 mL of water and dried in vacuo providing 126 mg of the intermediate boronic acid (96%) as a white solid: ^{1}H NMR ($CDCl_3$) δ 6.97 (m, 1H), 6.37 (t, J = 10.8 Hz, 1H), 6.24 (t, J = 10.8 Hz, 1H), 5.57 (d, J = 18.0 Hz, 1H), 5.49 (m, 2H), 3.10 (m, 2H), 2.19 (m, 2H), 1.36 (m, 4 H), 0.92 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 156.4 (−), 139.2 (−), 134.4 (−), 128.7 (−), 125.0 (−), 123.1 (−), 33.6 (+), 31.8 (+), 27.3 (+), 22.4 (+), 14.7 (−).

To a solution of 47.5 μL of propane-1,3-diol (1.1 equiv, 0.624 mmol) and 3 mL of pentane was added 110 mg of the above boronic acid (1 equiv, 0.567 mmol). The mixture was stirred for 10 h at rt, and when the reaction was judged complete, it was stirred with anhydrous Na_2SO_4 for 30 min and filtered, and the filtrate was concentrated in vacuo. The crude product was purified by column chromatography on silica gel (R_f = 0.3; 40% ether in hexane) providing 130 mg of product (100%) as a pale yellow liquid: ^{1}H NMR ($CDCl_3$) δ 6.52 (td, J = 17.6, 7.6 Hz, 1H), 6.34 (t, J = 10.8 Hz, 1H), 6.22 (t, J = 10.8 Hz, 1H), 5.47 (m, 2H), 5.37 (d, J = 17.6 Hz, 1H), 4.01 (t, J = 4.8 Hz, 4H), 3.00 (t, J = 7.6 Hz, 2H), 2.18 (m, 2H), 1.96 (quint, J = 5.4 Hz, 2H), 1.36 (m, 4H), 0.90 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 147.1 (−), 132.6 (−), 127.3 (−), 124.9 (−), 122.1 (−), 61.7 (+), 33.5 (+), 31.8 (+), 27.4 (+), 27.2 (+), 14.7 (−); HRMS *m*/*z* calcd for $C_{14}H_{23}BO_2$ 234.1794, found 234.1781.

8-Nonan-1-ol (22). To a flask containing 70 mL of ethylenediamine was added 5.7 g of NaH (60% in mineral oil, 4.0 equiv, 142.64 mmol), and this was stirred at rt for 1 h and then at 60 °C for 1 h. After the mixture was cooled to −45 °C, 5 g of 3-nonyn-1-ol (**21**) (1.0 equiv, 35.66 mmol) was added and the solution stirred at 60 °C for 1 h. Upon cooling to 0 °C, 30 mL of 1 M HCl was added, and the organic and aqueous layers were separated. The aqueous layer was extracted with ether (2×), and the combined organic layers were dried over anhydrous $MgSO_4$. The suspension was filtered and the filtrate concentrated in vacuo. Purification by column chromatography on silica gel (R_f = 0.5; 50% ether in pentane) provided 4.1 g of **22** (82%) as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 3.51 (t, J = 6.4 Hz, 2H), 3.03 (br. s, 1H), 2.08 (m, 2H), 1.86 (s, 1H), 1.43 (m, 4H), 1.27 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 84.5 (+), 68.2 (+), 62.5 (+), 32.6 (+), 28.8 (+), 28.6 (+), 28.3 (+), 25.6 (+), 18.3 (+). The NMR data are in agreement with the literature.[15]

9-Trimethylsilyl-8-nonan-1-ol (23). To 3.16 g of magnesium turnings (3.6 equiv, 130 mmol) in 70 mL of THF was added 10.91 g of 2-bromoethane (2.8 equiv, 100 mmol). After the mixture was stirred for 4 h at rt, the resulting Grignard solution was added to **22** (5 g, 1.0 equiv, 35.71 mmol) in 70 mL of THF. After the mixture was stirred for 16 h at rt, 10.85 g of trimethylsilyl chloride (2.80 equiv, 100 mmol) was added at 0 °C, and the resulting solution was stirred at rt for 8 h. The reaction mixture was then treated with 50 mL of hydrochloric acid (1 M), stirred for 30 min, and then quenched with a solution of saturated sodium bicarbonate. The layers were separated, and the aqueous layer was extracted with ether (2×). The combined organic layers were dried over anhydrous $MgSO_4$ and filtered, and the filtrate was concentrated in vacuo. Purification by column chromatography on silica gel (R_f = 0.5; 40% ether in pentane) provided 7.24 g of **23** (96%) as a pale yellow liquid: ^{1}H NMR ($CDCl_3$) δ 3.63 (t, J = 6.8 Hz, 2H), 2.21 (t, J = 7.2 Hz, 2H), 1.56 (m, 4H), 1.36 (m, 6H), 0.15 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 107.6 (+), 84.4 (+), 63.0 (+), 32.7 (+), 28.9 (+), 28.7 (+), 28.5 (+), 25.6 (+), 19.8 (+), 0.2 (−); MS (EI, 70 eV) *m*/*z* (relative intensity) 212 (100).

9-Trimethylsilyl-1-non-8-ynal (24). To a suspension of 8.40 g of PCC (1.3 equiv, 38.94 mmol) in 400 mL of dichloromethane was added 6.35 g of **23** (1.0 equiv, 29.95 mmol). After being stirred for 3 h at rt, the reaction was diluted with pentane and passed through a short pad of silica, and the filtrate was then concentrated in vacuo. Purification by column chromatography on silica gel (R_f = 0.7, 33% ether in pentane) provided 5.30 g of **24** (84%) as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 9.77 (s, 1H), 2.43 (dt, J = 6.4, 1.2 Hz, 2H), 2.22 (t, J = 7.2 Hz, 2H), 1.64 (m, 2H), 1.53 (m, 2H), 1.36 (m, 4H), 0.15 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 207.8 (−), 107.3 (+), 84.5 (+), 43.8 (+), 28.6 (+), 28.4 (+), 28.3 (+), 21.9 (+), 19.7 (+), 0.0 (−); MS

(EI, 70 eV) *m/z* (relative intensity) 211 (M + 1, 10), 75 (100). Anal. Calcd for $C_{12}H_{22}OSi$: C, 68.51; H, 10.54. Found: C, 68.78; H, 10.82.

12-(Trimethylsilyl)-1-octenen-11-yn-4-ol (25). To a solution of **24** (5 g, 1.0 equiv, 23.80 mmol) in 110 mL of ether was added 26.2 mL of a 1 M solution of allylmagnesium bromide in ether (1.1 equiv, 26.19 mmol). After being stirred at rt for 30 min, the mixture was quenched with water and the layers were separated. The aqueous layer was extracted with ether (2×), and the combined organic layers were dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated in vacuo. Purification by column chromatography on silica gel (R_f = 0.5; 34% ether in pentane) provided 5.11 g of **25** (86%) as a colorless liquid: ^{1}H NMR ($CDCl_3$) δ 5.82 (m, 1H), 5.14 (d, J = 13.2 Hz, 2H), 4.62 (m, 1H), 2.19 (m, 4H), 1.31 (m, 10H), 0.13 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 138.8 (−), 118.1 (+), 107.6 (+), 84.3 (+), 72.4 (−), 42.0 (+), 36.8 (+), 29.1 (+), 28.7 (+), 28.6 (+), 25.5 (+), 19.8 (+), 0.1 (−); IR (neat) 3385, 2176 cm^{-1}; HRMS *m/z* calcd for $C_{15}H_{28}OSi$ 251.1817, found 251.1831.

12-(Trimethylsilyl)-4-dodec-1-en-11-ynone (26). To a suspension of 4.1 g of PCC (1.3 equiv, 18.09 mmol) in 200 mL of dichloromethane was added 3.5 g of **25** (1.0 equiv, 13.88 mmol), and the mixture was stirred for 3 h at rt. The reaction mixture was then diluted with pentane and passed through a short pad of Celite, and the filtrate was then concentrated in vacuo. Purification by column chromatography on silica gel (R_f = 0.9; 34% ether in pentane) provided 3.09 g of **26** (88%) as a slightly yellow liquid: ^{1}H NMR ($CDCl_3$) δ 5.89 (m, 1H), 5.16 (m, 2H), 3.16 (d, J = 7.2 Hz, 2H), 2.44 (t, J = 7.6 Hz, 2H), 2.21 (t, J = 7.6 Hz, 2H), 1.59 (m, 2H), 1.51 (m, 2H), 1.34 (m, 2H), 1.34 (m, 2H), 0.06 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 208.76 (+), 128.1 (−), 118.7 (+), 107.5 (+), 84.4 (+), 47.8 (+), 42.2 (+), 28.6 (+), 28.5 (+), 28.4 (+), 23.5 (+), 19.8 (+), 0.0 (−); IR (neat) 2174, 1714 cm^{-1}; MS (EI, 70 eV) *m/z* (relative intensity) 250 (2), 235 (14), 209 (88), 73 (100). Anal. Calcd for $C_{15}H_{26}$-OSi: C, 71.93; H, 10.46. Found: C, 72.29; H, 10.36.

4-Hydroxy-4-dodec-11-ynone (27). To a solution of **26** (280 mg, 1.0 equiv, 1.12 mmol) in 2 mL of THF was added 2.52 mL of 9-BBN (1 M solution, 1.0 equiv, 1.12 mmol) at 0 °C. After being stirred at 60 °C for 2 h, the reaction mixture was quenched with water. At this time, 2 mL of 3 N aqueous NaOH was added followed by 2 mL of 35% H_2O_2, and the mixture was stirred for 24 h at 60 °C. The mixture was extracted with ether (3×), the pooled organic layers were dried over anhydrous $MgSO_4$ and filtered, and the filtrate was concentrated in vacuo. The crude product was then purified by column chromatography on silica gel (R_f = 0.75; 17% ether in pentane) providing 0.14 g of **27** (64%) as a pale yellow liquid: ^{1}H NMR ($CDCl_3$) δ 3.42 (t, J = 6.0 Hz, 2H), 2.94 (br s, 1H), 2.43 (t, J = 6.8 Hz, 2H), 2.32 (t, J = 7.2 Hz, 2H), 2.06 (m, 2H), 1.89 (s, 1H), 1.71 (t, J = 6.4 Hz, 2H), 1.46 (m, 2H), 1.32 (m, 2H), 1.19 (m, 2H), 1.29 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 211.7 (+), 84.5 (+), 68.2 (+), 62.2 (+), 42.8 (+), 39.5 (+), 28.6 (+), 28.4 (+), 28.2 (+), 26.5 (+), 23.7 (+), 18.3 (+); IR (neat) 3473, 1707 cm^{-1}.

1-Acetoxy-4-dodec-11-ynone (4). To a round-bottom flask was added 0.27 mL of acetyl chloride (1.05 equiv, 3.75 mmol), 0.27 g of imidazole (1.1 equiv, 3.93 mmol), 87 mg of DMAP (0.2 equiv, 0.71 mmol), and 0.7 g of **7** (1.0 equiv, 3.57 mmol) in 35 mL of dichloromethane. The mixture was refluxed for 12 h and quenched with saturated sodium bicarbonate, and the layers were separated. The aqueous layer was extracted with ether (2×), the combined organic layers were dried over anhydrous $MgSO_4$ and filtered, and the filtrate was concentrated in vacuo. The crude product was purified by column chromatography on silica gel (R_f = 0.5; 50% ether in pentane) providing 0.70 g of **4** (83%) as a yellow liquid: ^{1}H NMR ($CDCl_3$) δ 4.04 (t, J = 6.4 Hz, 2H), 2.46 (t, J = 7.2 Hz, 2H), 2.39 (t, J = 7.2 Hz, 2H), 2.15 (m, 2H), 2.01 (s, 3H), 1.91 (m, 3H), 1.58 (m, 2H), 1.53 (m, 2H), 1.39 (m, 2H), 1.31 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 209.8 (+), 170.9 (+), 84.5 (+), 68.2 (+), 63.6 (+), 42.7 (+), 38.9 (+), 28.6 (+), 28.4 (+), 28.2 (+), 23.6 (+), 22.8 (+), 21.6 (−), 18.3 (+); IR (neat) 1738, 1714 cm^{-1}; HRMS *m/z* calcd for $C_{14}H_{23}O_3$ 239.1647, found 239.1640.

(1*E*,3*E*,6*Z*,8*Z*)-1-Chlorotrideca-1,3,6,8-tetraene (28). To a solution of 100 mg of **18** (1.0 equiv, 0.43 mmol) in 2 mL of THF was added 80 mg of **2** (1.0 equiv, 0.43 mmol), 25 mg of $(PPh_3)_4Pd$ (0.05 equiv, 0.021 mmol), and 1 mL of a 1 M KOH solution (2.1 equiv, 0.90 mmol). The mixture was stirred at 60 °C for 3 h, cooled to rt, diluted with pentane, and dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated in vacuo, and the crude product was purified by column chromatography on silica gel (R_f = 0.9; hexane) providing 63 mg of **28** (70%) as a yellow liquid: ^{1}H NMR ($CDCl_3$) δ 6.40 (dd, J = 13.2, 10.8 Hz, 1H), 6.34 (m, 1H), 6.24 (m, 1H), 6.11 (d, J = 13.2 Hz, 1H), 6.00 (m, 1H), 5.73 (dt, J = 15.2, 7.6 Hz, 1H), 5.49 (m, 1H), 5.44 (m, 1H), 2.97 (t, J = 7.2 Hz, 2H), 2.19 (m, 2H), 1.36 (m, 4H), 0.91 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 133.6 (−), 133.4 (−), 133.3 (−), 128.5 (−), 127.5 (−), 125.0 (−), 123.1 (−), 119.0 (−), 31.8 (+), 30.5 (+), 27.3 (+), 22.3 (+), 13.9 (−).

(13*E*,15*E*,18*Z*,20*Z*)-1-Hydroxypentacosa-13,15,18,20-tetraen-11-yn-4-one 1-Acetate (1). To a solution of 40 mg of **28** (1.0 equiv, 0.19 mmol) in 2 mL of benzene was added 0.14 g mg of *n*-butylamine (10.0 equiv, 0.19 mL, 1.9 mmol), 11 mg of $(PPh_3)_4Pd$ (0.05 equiv, 0.0095 mmol), 6 mg of CuI (0.15 equiv, 0.28 mmol), and 54 mg of **27** (1.2 equiv, 0.228 mmol). After the mixture was heated at 60 °C for 3 h, the solvent was removed in vacuo and the crude product was purified by column chromatography on silica gel (R_f = 0.4; 20% acetone in hexane), providing 60 mg of **1** (77%) as a yellow liquid: ^{1}H NMR ($CDCl_3$) δ 6.45 (dd, J = 15.5, 10.5 Hz, 1H), 6.29 (t, J = 10.5 Hz, 1H), 6.20 (t, J = 10.5 Hz, 1H), 6.07 (dd, J = 15.5, 10.5 Hz, 1H), 5.72 (dt, J = 15.5, 7.0 Hz, 1H), 5.48 (d, J = 15.5 Hz, 1H), 5.43 (m, 2H), 4.05 (t, J = 7.0 Hz, 2H), 2.96 (t, J = 7.0 Hz, 2H), 2.46 (t, J = 7.2 Hz, 2H), 2.41 (t, J = 7.2 Hz, 2H), 2.29 (td, J = 7.0, 2.0 Hz, 2H), 2.16 (quart, J = 7.2 Hz, 2H), 2.04 (s, 3H), 1.89 (quint, J = 6.8 Hz, 2H), 1.56 (m, 2H), 1.51 (m, 2H), 1.38 (m, 2H), 1.35 (m, 2H), 1.29 (m, 4H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 209.9 (+), 171.9 (+), 140.1 (−), 133.9 (−), 133.0 (−), 130.1 (−), 128.0 (−), 124.4 (−), 123.7 (−), 109.9 (−), 92.3 (+), 80.0 (+), 63.7 (+), 42.8 (+), 38.9 (+), 31.8 (+), 30.7 (+), 29.7 (+), 28.7 (+), 28.6 (+), 27.3 (+), 23.7 (+), 22.8 (+), 22.3 (+), 21.0 (−), 19.6 (+), 14.5 (−); HRMS *m/z* calcd for $C_{27}H_{40}O_3$ 412.2977, found 412.2955; UV spectrum [λ_{max} (MeOH) 240, 269, 278 nm].

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Supporting Information Available: Proton and/or carbon NMR spectra are included for compounds **15**−**17**, **23**, **25**, **27**, **28**, **4**, and **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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