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Synthesis of the Conjugated Tetraene Acid Side Chain of Mycolactone E by Suzuki–Miyaura Cross-Coupling Reaction of Alkenyl Boronates

Yuan Wang[a] and Wei-Min Dai*[a]

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The conjugated tetraene acid side chain of mycolactone E has been synthesized by the cross-coupling reaction of a trisubstituted triene bromide with a trisubstituted alkenyl boronate catalyzed by $Pd(OAc)_2$–Aphos-Y under mildly basic conditions [$K_3PO_4 \cdot 3H_2O$, H_2O, tetrahydrofuran (THF), 35 °C, 18 h]. The conjugated tetraene product was obtained in 85 % yield without geometrical isomer(s) under the catalytic conditions. These results demonstrated that the coupling of alkenyl halides with alkenyl boronates catalyzed by $Pd(OAc)_2$–Aphos-Y in combination with Cu^I-catalyzed regio- and stereoselective alkyne borylation offers an efficient synthetic tool for accessing conjugated polyene molecules.

Introduction

Mycolactone E (**1**, Figure 1)[1] was isolated from a frog pathogen *Mycobacterium liflandii* in 2005, and its structure including the absolute stereochemistry of the acid side chain was determined from a total synthesis by Kishi.[2] First reported in 1999,[3] the mycolactone family of polyketide toxins features more than five distinct structural types of acid side chain that append to a common 12-membered macrocyclic core.[4–6] Mycolactone E is one of the members isolated from aquatic mycobacteria related to *Mycobacterium ulcerans*, the causative agent of the severe human skin disease known as Buruli ulcer.[7] Mycolactone A/B, C, and D are produced by different strains of *M. ulcerans* collected from ulcer patients and exhibit cytotoxic and immunosuppressive properties.[7,8a] Mycolactone E exerts cytotoxicity similar to that of mycolactone A/B but with 100-fold less potency, presumably owing to the absence of the C12′ hydroxy group on the acid side chain.[1a] At present, the molecular target and mechanisms of action of the mycolactones remain unknown. A recent study suggests that *M. ulcerans* adopts a biofilm-like structure in vitro and in vivo with an abundant extracellular matrix that serves as the reservoir of the mycolactone toxin.[8b] It is proposed that biofilm changes may confer selective advantages for the development of Buruli ulcer pathogenesis.

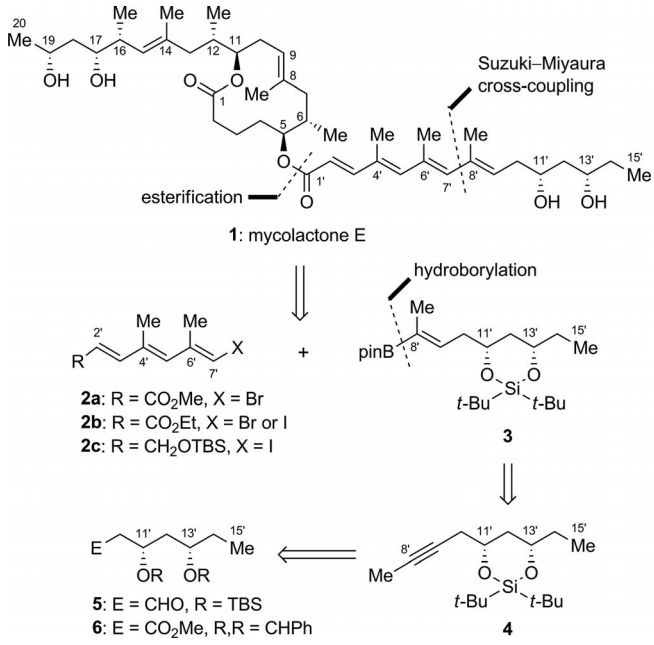

Figure 1. Structure of mycolactone E and our retrosynthetic bond disconnection of the acid side chain by Suzuki–Miyaura cross-coupling.

Kishi and co-workers used an 18-step linear sequence for the synthesis of the tetraene acid side chain of mycolactone E in 7.8% overall yield.[2] Starting from (*S*)-1,2-epoxybutane, the chiral aldehyde **5** (Figure 1) was prepared in seven steps and it was then transformed into the acid side chain through three cycles of iterative Horner–Wadsworth–Emmons olefination in another 11 steps. We envisioned a convergent synthesis of the tetraene acid by the Suzuki–Miyaura cross-coupling[9] of the triene bromide **2a** with the trisubstituted alkenyl boronate **3** under the catalysis of our $Pd(OAc)_2$–Aphos-Y catalyst system.[10] The similar triene halides **2b**[11] and **2c**[12] were used in the Cu^I-catalyzed Stille and Pd-catalyzed Negishi cross-coupling reactions for the synthesis of the pentaene acid side chain of mycolactone A/B. Our requisite alkenyl boronate **3** could be prepared from

[a] Laboratory of Advanced Catalysis and Synthesis, Department of Chemistry, The Hong Kong University of Science and Technology,
Clear Water Bay, Kowloon, Hong Kong SAR, P. R. China
E-mail: chdai@ust.hk
http://ihome.ust.hk/~chdai/index.html

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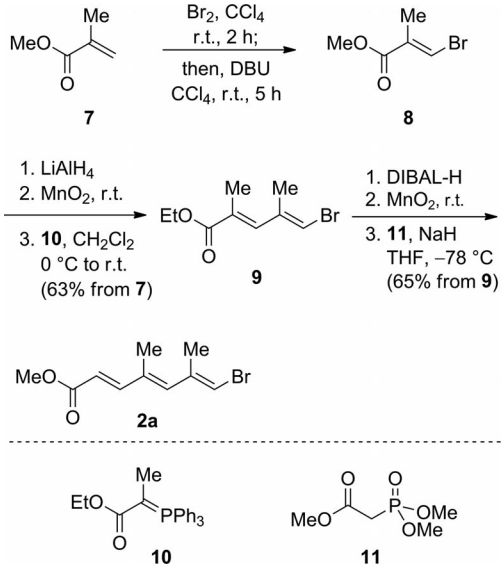
the Cu^I-catalyzed regio- and stereoselective borylation[13,14] of the alkyne **4**. To the best of our knowledge, homopropargyl silyl ethers such as **4** have not been reported for the Cu^I-catalyzed borylation. We were interested in expanding the substrate scope of the borylation chemistry and utilizing it in our polyene synthesis. Finally, the alkyne **4** would be derived from the chiral ester **6**, which could be obtained from the intramolecular conjugate addition of the hemiacetal-derived alkoxide.[15] We report here on the results of the Cu^I-catalyzed regio- and stereoselective borylation of the alkyne **4** and the subsequent cross-coupling of the triene bromide **2a** with the trisubstituted alkenyl boronate **3** catalyzed by $Pd(OAc)_2$–Aphos-Y. Our current work demonstrates that the combination of the Cu^I-catalyzed borylation and the Suzuki–Miyaura cross-coupling catalyzed by $Pd(OAc)_2$–Aphos-Y under mild conditions offers an efficient method for the synthesis of conjugated polyene molecules.

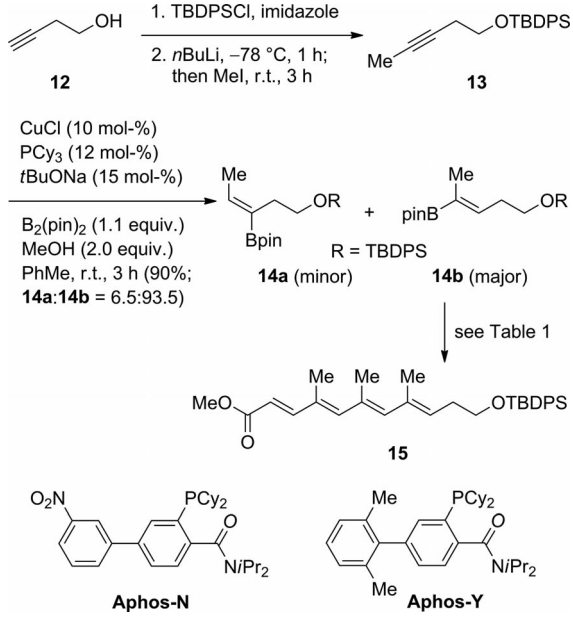
Results and Discussion

The triene halides **2b** (X = Br, I) were previously prepared as mixtures of geometric isomers from 2,4-dimethylfuran in 18.8 and 6% overall yields for three steps, respectively.[11a] Alternatively, the triene iodide **2b** (X = I) was synthesized from diethyl methylmalonate in a 10-step sequence.[11b] As shown in Scheme 1, we used a simple and efficient route to access the triene bromide **2a**. From dimethyl acrylate **7**, bromination followed by DBU-mediated elimination gave the known alkenyl bromide **8**.[16] The latter, without purification, was subjected to $LiAlH_4$ reduction of the ester moiety, MnO_2 oxidation of the allyl alcohol, and Wittig olefination of the aldehyde with the ylide **10** to afford the known diene bromide **9** in 63% overall yield from **7**.[17] The reduction of the ester moiety in **9** by diisobutylaluminum hydride (DIBAL-H) and MnO_2 oxidation of the resultant allyl alcohol formed the aldehyde, which underwent the Horner–Wadsworth–Emmons olefination with trimethyl phosphonoacetate **11** to furnish **2a** in 65% overall yield from **9**. Our synthesis of the triene bromide **2a** is both operationally simple, with only two column chromatographic purifications, and high-yielding with high geometric purity. As the triene bromide **2a** is prone to photoisomerization, the sample of **2a** should be covered with aluminum foil and kept as a solution for storage. If necessary, the trace geometric isomer of **2a** could be removed before the subsequent coupling reactions.

The regioselectivity of the Cu^I-catalyzed borylation of internal alkynes is highly dependent on the propargylic functionality. For homopropargylic substrates, only benzyl ether was reported.[13] We examined borylation of the *tert*-butyldiphenylsilyl protected (TBDPS-protected) homopropargylic substrate **13** (Scheme 2) to assess the regioselectivity of the borylation. The silylation of but-3-yn-1-ol (**12**) with TBDPSCl and imidazole (95%) followed by methylation of the lithium acetylide (90%) gave **13**. The hydroboration of **13** with pinacolborane (HBpin) without a catalyst or in the presence of 5 mol-% of Cp_2ZrHCl in CH_2Cl_2 at room temperature for 24 h failed to give any product.[18] Fortunately, the borylation[13d] of **13** with bis(pinacolato)diboron [$B_2(pin)_2$] catalyzed by Cu^I–PCy_3 in the presence of *t*BuONa and MeOH in PhMe provided the alkenyl boronates **14a** and **14b** in 90% combined yield and in a diastereomeric ratio of 6.5:93.5 in favor of the desired regioisomer **14b**. A similar yield and regioselectivity for the borylation of **13** were obtained by using $PCy_3{\cdot}HBF_4$ as the ligand precursor. Compared with those for the benzyl-protected analogue, which gave a 12:88 ratio of the two regioisomeric alkenyl boronates in a combined yield of 72%,[13d] the silyl ether **13** afforded both higher chemical yield and higher regioselectivity under the same borylation conditions.



Scheme 1. Synthesis of the trienyl bromide **2a**.



Scheme 2. Synthesis of the model tetraene ester **15**.

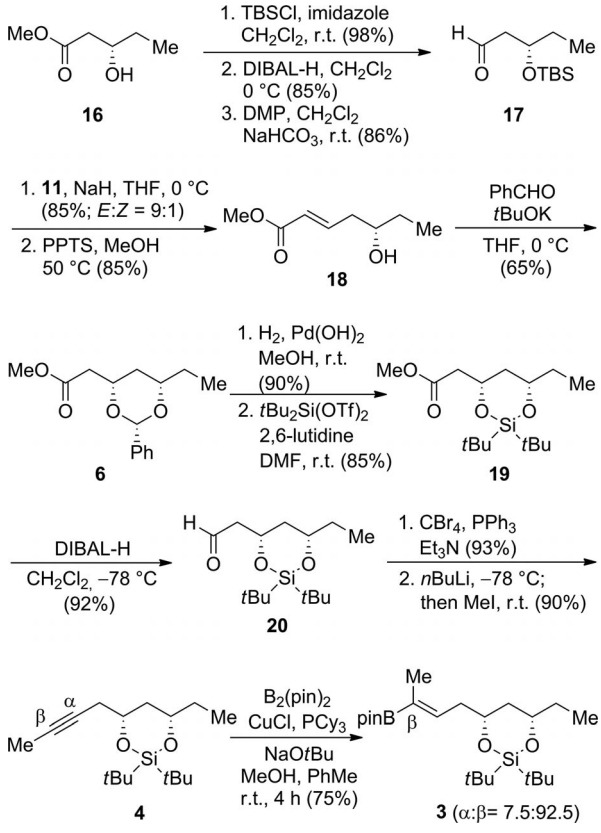
The cross-coupling of both trisubstituted alkenyl halides and alkenyl boronates such as **2a** and **14b** generally requires temperatures of 45–80 °C.[17,19] When TlOEt or Tl_2CO_3 was used as the base, the coupling could proceed at room temperature.[20] In our previous work, we demonstrated that Aphos ligands such as Aphos-N (Scheme 2) in combination with $Pd(OAc)_2$ and K_3PO_4 could be used for the cross-coupling of alkenyl bromides with alkenyl boronic acids at room temperature.[21] Similarly, the $Pd(OAc)_2$–Aphos-Y system could effectively catalyze the *B*-alkyl Suzuki–Miyaura cross-coupling of highly functionalized coupling partners at room temperature.[10c,10e] Here, we used the $Pd(OAc)_2$–Aphos-Y catalyst system for the coupling reaction of **2a** and **14b**. Some optimization results are listed in Table 1. With 5 mol-% $Pd(OAc)_2$ and 7.5 mol-% Aphos-Y, the coupling reaction occurred at room temperature in the presence of $K_3PO_4{\cdot}3H_2O$ as the base in tetrahydrofuran (THF) for 48 h and furnished the desired product **15** in 46% yield with 50% recovery of the triene bromide **2a** (Table 1, Entry 1). When a mixture of THF/H_2O (9:1) was used as the solvent, the coupling reaction proceeded at room temperature, but it was slow; after the reaction mixture was heated at 35 °C for another 24 h, the tetraene product **15** was obtained in 73% yield, and 20% of **2a** was recovered (Table 1, Entry 2). When a stronger base, Cs_2CO_3, was employed in THF/H_2O (9:1), the conversion of the triene bromide **2a** increased with increasing reaction temperature, but the substrate **2a** was not completely consumed (Table 1, Entries 3–5). These results suggest that the inexpensive and mild base, K_3PO_4, was sufficient for the coupling reaction. On other hand, we observed the formation of palladium black during the reaction in THF/H_2O (9:1), which is unique for the coupling reaction of alkenyl boronates, as the same solvent system could be used for coupling reaction of boronic acids.[10d] This led us to suspect that high water content in the reaction system may deteriorate the catalytic species. Finally, when only 18 equivalents of water were used, the coupling reaction of **2a** with **14b** proceeded in the presence of $K_3PO_4{\cdot}3H_2O$ as the base at 35 °C for 18 h to afford the product **15** in 90% yield (Table 1, Entry 6).

Table 1. Optimization of Suzuki–Miyaura cross-coupling of **2a** with **14b**.[a]

Entry	Base	Solvent(s)	*T* [°C]	*t* [h]	Yield [%][e]
1	$K_3PO_4{\cdot}3H_2O$	THF	r.t.	48	46 (50)
2	K_3PO_4	THF/H_2O[b]	r.t.; 35	18 + 24[d]	73 (20)
3	Cs_2CO_3	THF/H_2O[b]	r.t.	48	50 (44)
4	Cs_2CO_3	THF/H_2O[b]	35	18	59 (35)
5	Cs_2CO_3	THF/H_2O[b]	50	18	72 (20)
6	$K_3PO_4{\cdot}3H_2O$	THF/H_2O[c]	35	18	90 (4)

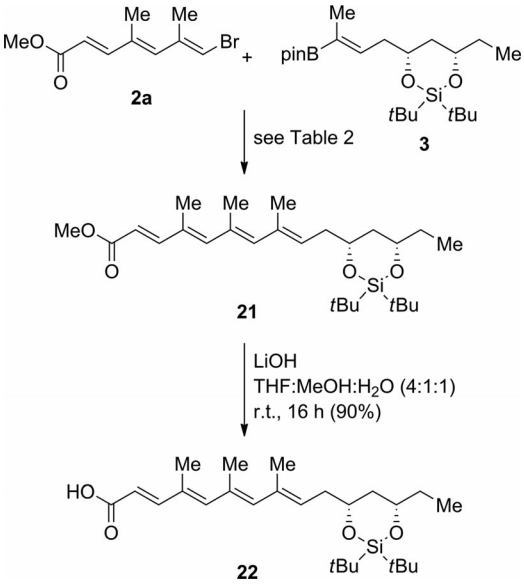
[a] Reaction conditions: 1 equiv. **2a**, 1.1 equiv. **14b**, 5 mol-% $Pd(OAc)_2$, 7.5 mol-% Aphos-Y, 3 equiv. base in the specified solvent(s). [b] THF/H_2O 9:1 (v/v). [c] 18 equiv. H_2O used. [d] At room temp. for 18 h followed by 35 °C for 24 h. [e] Isolated yield of the tetraene ester **15**. The numbers in the parentheses are the amount of triene bromide **2a** recovered. Room temp. is 20–25 °C.

Next, we synthesized the fully functionalized alkenyl boronate **3** as shown in Scheme 3. The known methyl (*S*)-hydroxypentanoate **16**, readily available from the asymmetric hydrogenation of the corresponding β-keto ester,[22] was protected as the *tert*-butyldimethyl silyl (TBS) ether followed by DIBAL-H reduction and Dess–Martin periodinane oxidation to form the aldehyde **17**. The latter underwent the Horner–Wadsworth–Emmons olefination with **11**, after separation of the minor *Z* isomer and removal of the TBS protecting group, to give the isomerically pure hydroxy ester **18**. At this stage, the thermodynamically controlled intramolecular conjugate addition of the hemiacetal-derived alkoxide formed from **18** and benzaldehyde was performed to provide the cyclic acetal **6** in 65% isolated yield as a single diastereomer.[15] Manipulation of the protecting group was performed by cleavage of the cyclic acetal in **6** under hydrogenolysis conditions [H_2, $Pd(OH)_2$, MeOH] and formation of the cyclic silyl ether of the resultant 1,3-diol to form **19**. The controlled DIBAL-H reduction of the ester **19** gave the aldehyde **20**, which was transformed into the alkyne **4** by the Corey–Fuchs protocol.[23] Finally, the Cu^I–PCy_3-catalyzed borylation[13d] of **4** furnished the trisubstituted alkenyl boronate **3** in 75% combined yield and in a 7.5:92.5 ratio for the two regioisomers. The regioselectivity is similar to that for the borylation of the alkyne **13** as given in Scheme 2. Also, by using $PCy_3{\cdot}HBF_4$ as the ligand precursor, a similar yield and regioselectivity for the borylation of **4** were obtained.



Scheme 3. Synthesis of the alkenylboronate **3**.

With the successful synthesis of the trisubstituted alkenyl boronate **3**, the stage was now set for its cross-coupling with the triene bromide **2a** (Scheme 4). Some results are summarized in Table 2. Table 2, Entries 1 and 2, obtained for the coupling reactions catalyzed by $Pd(OAc)_2$–Aphos-Y in mixed THF/H_2O (v/v 9:1), are similar to those for the coupling of **2a** with **14b** (Table 1, Entries 4 and 5). For example, after 18 h at 50 °C in the presence of Cs_2CO_3 as the base, the desired tetraene ester **21** was isolated in 73% yield, and 21% of **2a** was recovered (Table 2, Entry 2). For the coupling of **2a** and **3** in THF in the presence of $K_3PO_4{\cdot}3H_2O$ and 18 equivalents of H_2O at 35 °C for 18 h, the product **21** formed in 85% isolated yield with only 6% of **2a** unreacted (Table 2, Entry 3). Finally, the hydrolysis of the methyl ester **21** with LiOH in THF/MeOH/H_2O at room temperature furnished the tetraene acid **22** in 90% yield. Our synthesized sample of **22** has $[\alpha]_D^{26}$ = +42.4 (c = 0.65, $CHCl_3$) and is free of geometric isomers as confirmed by ^1H NMR analysis (see Supporting Information).



Scheme 4. Synthesis of the mycolactone E acid side chain **22**.

Table 2. Cross-coupling of triene bromide **2a** with alkenyl boronate **3**.[a]

Entry	Base	Solvents	T [°C]	t [h]	Yield [%][d]
1	Cs_2CO_3	THF/H_2O[b]	35	18	46 (50)
2	Cs_2CO_3	THF/H_2O[b]	50	18	73 (21)
3	$K_3PO_4{\cdot}3H_2O$	THF/H_2O[c]	35	18	85 (6)

[a] Reaction conditions: 1 equiv. **2a**, 1.1 equiv. **3**, 5 mol-% $Pd(OAc)_2$, 7.5 mol-% Aphos-Y, 3 equiv. base in the specified solvents. [b] THF/H_2O (v/v) 9:1. [c] 18 equiv. H_2O used. [d] Isolated yield of the tetraene ester **21**. The numbers in the parentheses are the amount of triene bromide **2a** recovered.

Conclusions

We have established a convergent synthesis of the tetraene acid side chain of mycolactone E by a 14-step longest linear sequence in 9.5% overall yield. Both $Pd(OAc)_2$ and the Aphos-Y ligand are stable to air and easy to handle. Their combination offers a robust catalyst system that enables the cross-coupling of trisubstituted alkenyl halides and trisubstituted boronates at 35 °C. The mild basic conditions without the use of Tl^I species are advantageous over the common catalysts (or precatalysts) such as [$PdCl_2(PPh_3)_2$],[17] $Pd(PPh_3)_4$,[19b] [$PdCl_2$(DPEphos)],[19c] and [$PdCl_2$(dppf)] (dppf = 1,1′-bis(diphenylphosphino)ferrocene).[19a,20f] Both SPhos and XPhos along with $Pd(OAc)_2$ catalyze coupling reactions between disubstituted and trisubstituted partners in the temperature range 23–45 °C.[24] Therefore, by taking advantage of the recently advanced Cu^I-catalyzed regio- and stereoselective alkyne borylation,[13,14] polyenes possessing two or more sequentially connected trisubstituted double bonds can be synthesized in high isomeric purity under mild and nontoxic conditions through a combination of Cu and Pd catalysis as mentioned above.

Experimental Section

General Methods: NMR spectra were recorded with a 400 MHz instrument with samples in $CDCl_3$ or CD_3COCD_3; residual $CHCl_3$ or acetone signals were used as the internal reference for ^1H (δ = 7.26 or 2.05 ppm, respectively) and ^{13}C (δ = 77.0 or 2.05 ppm, respectively). IR spectra were recorded with an FTIR spectrophotometer. Mass spectra (MS) were measured by the CI+ or CI– method. Silica gel plates (60 F-254, 0.25 mm, E. Merck) were used for thin-layer chromatography, and UV light or 7% ethanolic phosphomolybdic acid and heating were used for the visualization. Silica gel 60 (particle size 0.040–0.063 mm, E. Merck) was used for flash column chromatography, yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials. Dry THF and PhMe were freshly distilled from sodium and benzophenone under a nitrogen atmosphere. Dry MeOH obtained from a solvent purification system was used. THF, MeOH, and H_2O were degassed before use in Cu- and Pd-catalyzed reactions.

Methyl (2*E*,4*E*,6*E*)-7-Bromo-4,6-dimethylhepta-2,4,6-trienoate (2a): To a solution of ethyl (2*E*,4*E*)-5-bromo-2,4-dimethylpenta-2,4-dienoate (**9**, 305.0 mg, 1.31 mmol) in dry CH_2Cl_2 (20 mL) cooled in an ice/water bath (0 °C) was added DIBAL-H (3.3 mL, 1.0 M in hexane, 3.3 mmol), and the mixture was stirred at the same temperature for 2 h. The reaction was quenched by the careful addition of saturated aqueous sodium potassium tartrate (Rochelle's salt, 20 mL), and the resultant mixture was vigorously stirred at room temperature for 1 h. The mixture was diluted with water and CH_2Cl_2, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure to give (2*E*,4*E*)-5-bromo-2,4-dimethylpenta-2,4-dien-1-ol, which was used directly in the following step.

To a solution of the above alcohol in dry CH_2Cl_2 (10 mL) was added activated MnO_2 (2.30 g, 26.2 mmol) at room temperature, and the mixture was stirred for 1 h at the same temperature. The reaction mixture was filtered through a pad of Celite, which was washed with CH_2Cl_2. The combined filtrate was concentrated under reduced pressure to give (2*E*,4*E*)-5-bromo-2,4-dimethylpenta-2,4-dienal (200.0 mg, 81% from **9**), which was used directly in the next step.

To a suspension of NaH (127.0 mg, 60 wt.-% in mineral oil, 3.17 mmol) in dry THF (20 mL) cooled to –78 °C in a dry ice/acetone bath was added dropwise trimethyl phosphonoacetate (0.51 mL, 3.17 mmol), and the mixture was stirred for 15 min at the same temperature. A solution of the above aldehyde (200.0 mg, 1.06 mmol) in dry THF (20 mL) was added at –78 °C. After stirring for 2 h at the same temperature, the reaction mixture was quenched with saturated NH_4Cl and further diluted with water. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 2.4% EtOAc in hexane) to give the triene bromide **2a** (208.0 mg, 80%) as a colorless oil. R_f = 0.40 (5% EtOAc in hexane). IR (film): $\tilde{\nu}$ = 1718, 1620, 1312, 1170 cm^{-1}. ^1H NMR (400 MHz, CD_3COCD_3): δ = 7.32 (d, J = 16.0 Hz, 1 H), 6.48 (s, 1 H), 6.38 (s, 1 H), 5.97 (d, J = 15.2 Hz, 1 H), 3.70 (s, 3 H), 2.00 (d, J = 1.2 Hz, 3 H), 1.96 (d, J = 1.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 167.6, 149.8, 139.4, 139.0, 134.9, 118.7, 110.9, 51.6, 20.1, 14.0 ppm. HRMS (CI+): calcd. for $C_{10}H_{13}BrO_2$ $[M]^+$ 244.0099; found 244.0099; calcd. for $C_{10}H_{13}{}^{81}BrO_2$ $[M + 2]^+$ 246.0079; found 246.0089.

(*E*)-2-(4-{[(*tert*-Butyldiphenyl)silyl]oxy}-1-methylbut-1-enyl)-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (14b): A flame-dried 25 mL two-neck flask was charged with CuCl (13.0 mg, 0.13 mmol), NaO*t*Bu (19.0 mg, 0.19 mmol), bis(pinacolato)diboron (378.0 mg, 1.49 mmol), and tricyclohexylphosphine (42.0 mg, 0.15 mmol) in a glovebox. Then, the loaded flask was evacuated and backfilled with argon three times. A solution of *tert*-butyl[(pent-3-ynyl)oxy]diphenylsilane (**13**, 403.0 mg, 1.25 mmol) in dry toluene (12 mL) and dry MeOH (0.10 mL, 2.50 mmol) were added with a syringe. The resultant mixture was stirred at room temperature for 3 h. The reaction was quenched with MeOH. The mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 3.2% EtOAc in hexane) to give **14b** and the inseparable regioisomer **14a** (503.0 mg, 90%, **14a**/**14b** = 6.5:93.5) as a colorless oil. R_f = 0.31 (5% EtOAc in hexane). IR (film): $\tilde{\nu}$ = 2977, 2933, 2860, 1634, 1371, 1304, 1109 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.75–7.71 (m, 4 H), 7.46–7.38 (m, 6 H), 6.54 (q, J = 6.8 Hz, 0.065 H, vinyl proton of **14a**), 6.36 (tq, J = 7.2, 1.6 Hz, 0.935 H, vinyl proton of **14b**), 3.76 (t, J = 7.2 Hz, 2 H), 2.51–2.45 (m, 2 H), 1.71 (d, J = 1.6 Hz, 3 H), 1.29 (s, 12 H), 1.10 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.9, 135.5 (×4), 133.9 (×2), 129.5 (×2), 127.5 (×4), 83.0 (×2), 62.9, 32.1, 26.8 (×3), 24.7 (×4), 19.1, 13.9 ppm. HRMS (CI–): calcd. for $C_{27}H_{38}BO_3Si$ $[M – H]^-$ 449.2683; found 449.2681; calcd. for $C_{27}H_{41}BNO_3Si$ $[M – H + NH_3]^-$ 466.2949; found 466.2939.

Methyl (2*E*,4*E*,6*E*,8*E*)-11-{[(*tert*-Butyldiphenyl)silyl]oxy}-4,6,8-trimethylundeca- 2,4,6,8-tetraenoate (15): A flame-dried 10 mL process vial was charged with $Pd(OAc)_2$ (2.5 mg, 1.1×10^{-2} mmol), Aphos-Y (8.6 mg, 1.7×10^{-2} mmol), and $K_3PO_4 \cdot 3H_2O$ (176.0 mg, 0.66 mmol). The loaded vial was sealed with a cap containing a silicon septum and then evacuated through a needle under vacuum and backfilled with argon (this sequence was repeated five times). A solution of the triene bromide **2a** (52.0 mg, 0.22 mmol) and the alkenyl boronate **14b** (113.0 mg, 0.25 mmol) in degassed THF (2.2 mL) was added through a syringe followed by degassed water (71 μL, 18 equiv.) through another syringe. The resultant mixture was heated to 35 °C with stirring for 18 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography (silica gel, 3.2% EtOAc in hexane) to give the coupling product **15** (90.0 mg, 86%) as a pale yellow oil. R_f = 0.27 (5% EtOAc in hexane). IR (film): $\tilde{\nu}$ = 2956, 2933, 2858, 1723, 1621, 1430, 1109 cm^{-1}. ^1H NMR (400 MHz, CD_3COCD_3): δ = 7.73–7.70 (m, 4 H), 7.47–7.40 (m, 6 H), 7.35 (d, J = 15.6 Hz, 1 H), 6.43 (s, 1 H), 6.04 (s, 1 H), 5.87 (d, J = 15.6 Hz, 1 H), 5.56 (t, J = 6.8 Hz, 1 H), 3.78 (t, J = 6.8 Hz, 2 H), 3.69 (s, 3 H), 2.45 (dt, J = 6.8, 6.8 Hz, 2 H), 2.02 (s, 3 H), 1.99 (s, 3 H), 1.78 (s, 3 H), 1.05 (s, 9 H) ppm. ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 167.8, 151.2, 145.4, 138.8, 136.3 (×4), 134.9 (×2), 134.6, 133.0, 132.6, 130.6 (×2), 129.6, 128.5 (×4), 116.8, 64.2, 51.5, 32.6, 27.2 (×3), 19.7, 18.9, 17.2, 14.1 ppm. HRMS (CI–): calcd. for $C_{31}H_{40}O_3Si$ $[M]^-$ 488.2747; found 488.2729.

Methyl (5*S*)-5-Hydroxyhept-2-enoate (18): To a suspension of sodium hydride (684.0 mg, 60 wt.-% in mineral oil, 17.1 mmol) in THF (40 mL) cooled to 0 °C in an ice/water bath was added trimethyl phosphonoacetate (2.7 mL, 17.1 mmol) dropwise. The mixture was stirred at the same temperature for 15 min, a solution of the chiral aldehyde **17** (1.23 g, 5.69 mmol) in dry THF (30 mL) was added, and the mixture was stirred at the same temperature for 2 h. The reaction was quenched with saturated aqueous NH_4Cl and further diluted with water. The organic layer was separated, and the aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 2.4% EtOAc in hexane) to give the unsaturated ester (1.32 g, 85%; *E*/*Z* = 9:1) as a colorless oil. The minor *Z* isomer was separated during column chromatography and an isomerically pure enoate was obtained. $[\alpha]_D^{26}$ = –8.5 (c = 1.20, $CHCl_3$). R_f = 0.35 (4.8% EtOAc in hexane). IR (film): $\tilde{\nu}$ = 2957, 1729, 1659, 1256, 1171 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.97 (dt, J = 15.6, 7.6 Hz, 1 H), 5.84 (dt, J = 15.6, 1.6 Hz, 1 H), 3.72 (s, 3 H), 3.74–3.68 (m, 1 H), 2.39–2.28 (m, 2 H), 1.50–1.43 (m, 2 H), 0.89–0.85 (m, 12 H), 0.039 (s, 3 H), 0.037 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9, 146.4, 122.8, 72.4, 51.4, 39.7, 29.9, 25.8 (×3), 18.1, 9.6, –4.6 (×2) ppm. HRMS (CI–): calcd. for $C_{14}H_{27}O_3Si$ $[M – H]^-$ 271.1729; found 271.1726.

To a solution of the above ester (1.32 g, 4.84 mmol) in MeOH (20 mL) was added pyridinium *p*-toluenesulfonate (PPTS; 607.0 mg, 2.42 mmol) at room temperature. The resultant mixture was heated at 50 °C for 3 d under a nitrogen atmosphere. The reaction was quenched with saturated aqueous $NaHCO_3$, and the reaction mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 20% EtOAc in hexane) to give the alcohol **18** (650.0 mg, 85%) as a colorless oil. $[\alpha]_D^{26}$ = +21.6 (c = 0.50, $CHCl_3$). R_f = 0.43 (33.3% EtOAc in hexane). IR (film): $\tilde{\nu}$ = 3400 (br), 2962, 2933, 1725, 1658, 1438, 1275, 1170 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.99 (dt, J = 15.6, 7.6 Hz, 1 H), 5.91 (dt, J = 15.6, 1.6 Hz, 1 H), 3.72 (s, 3 H), 3.73–3.67 (m, 1 H), 2.45–2.28 (m, 2 H), 1.69 (br s, 1 H), 1.60–1.43 (m, 2 H), 0.96 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 145.5, 123.4, 71.9, 51.5, 39.7, 29.9, 9.8 ppm. HRMS (CI+): calcd. for $C_8H_{15}O_3$ $[M + H]^+$ 159.1021; found 159.1024.

Methyl (2*S*,4*S*,6*S*)-{6-Ethyl-2-phenyl[1,3]dioxan-4-yl}acetate (6):[15a] To a solution of alcohol **18** (650.0 mg, 4.11 mmol) in dry THF (40 mL) cooled to 0 °C in an ice/water bath was added freshly distilled benzaldehyde (0.46 mL, 4.52 mmol) followed by *t*BuOK (46.0 mg, 0.41 mmol), and the resultant yellow solution was stirred for 15 min at 0 °C. This addition/stirring sequence was repeated

twice, and the reaction was quenched with pH 7 phosphate buffer. The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 3.2% EtOAc in hexane) to give the acetal **6** (706.0 mg, 65%) as a colorless oil. $[\alpha]_D^{27}$ = –1.3 (*c* = 1.25, $CHCl_3$). R_f = 0.29 (9.1% EtOAc in hexane). IR (film): $\tilde{\nu}$ = 2964, 1741, 1348, 1138, 1037, 1022 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.52–7.47 (m, 2 H), 7.38–7.28 (m, 3 H), 5.56 (s, 1 H), 4.34–4.28 (m, 1 H), 3.80–3.74 (m, 1 H), 3.71 (s, 3 H), 2.75 (ABqd, *J* = 15.6, 7.2 Hz, 1 H), 2.53 (ABqd, *J* = 16.0, 6.4 Hz, 1 H), 1.76–1.38 (m, 4 H), 1.00 (t, *J* = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 138.6, 128.6, 128.1 (×2), 126.1 (×2), 100.6, 77.9, 73.2, 51.7, 40.8, 36.1, 28.7, 9.5 ppm. HRMS (CI+): calcd. for $C_{15}H_{20}O_4$ $[M]^+$ 264.1362; found 264.1364.

Methyl (4*S*,6*S*)-{2,2-Di-*tert*-butyl-6-ethyl[1,3,2]dioxasilinan-4-yl}acetate (19): To a solution of acetal **6** (706.0 mg, 2.67 mmol) in dry MeOH (40 mL) at room temperature was added $Pd(OH)_2$ (747.0 mg, 5.34 mmol). The resultant mixture was then stirred under an atmosphere of H_2 (balloon) until all of the starting materials were consumed as checked by TLC analysis (ca. 3 h). The reaction mixture was filtered through a pad of Celite, which was washed with MeOH. The combined filtrate was concentrated under reduced pressure to afford the crude *syn*-diol (423.0 mg, 90%) as a colorless oil, which could be used without further purification. An analytic sample was obtained by flash column chromatography (silica gel, 40% EtOAc in hexane). $[\alpha]_D^{25}$ = +4.9 (*c* = 0.95, $CHCl_3$). R_f = 0.14 (33.3% EtOAc in hexane). IR (film): $\tilde{\nu}$ = 3584 (br), 2963, 1734, 1440, 1166 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.30–4.24 (m, 1 H), 4.00–3.70 (br s, 1 H, OH), 3.82–3.76 (m, 1 H), 3.70 (s, 3 H), 3.55–3.20 (br s, 1 H, OH), 2.50–2.48 (m, 2 H), 1.62–1.44 (m, 4 H), 0.92 (t, *J* = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 73.5, 69.1, 51.8, 41.6, 41.5, 30.5, 9.6 ppm. HRMS (CI+): calcd. for $C_8H_{17}O_4$ $[M + H]^+$ 177.1127; found 177.1127.

To a solution of the above *syn*-diol (423.0 mg, 2.40 mmol) in anhydrous *N*,*N*-dimethylformamide (DMF) (25 mL) cooled to 0 °C in an ice/water bath was added dropwise 2,6-lutidine (0.70 mL, 5.98 mmol) and $tBu_2Si(OTf)_2$ (0.94 mL, 2.88 mmol), and the mixture was stirred for 1 h at the same temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ (25 mL) and extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 3.2% EtOAc in hexane) to afford the cyclic silyl ether **19** (645.0 mg, 85%) as a colorless oil. $[\alpha]_D^{24}$ = +0.72 (*c* = 1.00, $CHCl_3$). R_f = 0.58 (9.1% EtOAc in hexane). IR (film): $\tilde{\nu}$ = 2937, 2860, 1745, 1470, 1136 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.52–4.50 (m, 1 H), 4.00–3.93 (m, 1 H), 3.67 (s, 3 H), 2.53 (ABqd, *J* = 14.8, 7.6 Hz, 1 H), 2.40 (ABqd, *J* = 14.8, 6.0 Hz, 1 H), 1.65 (dt, *J* = 13.6, 2.0 Hz, 1 H), 1.49–1.43 (m, 3 H), 0.99 (s, 9 H), 0.95 (s, 9 H), 0.92 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 74.8, 70.6, 51.5, 43.7, 40.8, 31.5, 27.4 (×3), 27.0 (×3), 22.7, 19.5, 9.4 ppm. HRMS (CI+): calcd. for $C_{16}H_{33}O_4Si$ $[M + H]^+$ 317.2148; found 317.2150.

(4*S*,6*S*)-{2,2-Di-*tert*-butyl-6-ethyl[1,3,2]dioxasilinan-4-yl}acetaldehyde (20): To a solution of ester **19** (645.0 mg, 2.04 mmol) in dry CH_2Cl_2 (30 mL) cooled to –78 °C in an acetone/dry ice bath was added DIBAL-H (2.45 mL, 1.0 M in hexane, 2.45 mmol) dropwise over a period of 20 min. After stirring at the same temperature for 0.5 h, the reaction mixture was quenched by the careful addition of saturated aqueous sodium potassium tartrate (Rochelle's salt, 30 mL), and the resultant mixture was vigorously stirred at room temperature for 0.5 h. The mixture was diluted with water and CH_2Cl_2, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 4.8% EtOAc in hexane) to give the aldehyde **20** (537.0 mg, 92%) as a colorless oil. $[\alpha]_D^{23}$ = + 3.2 (*c* = 0.75, $CHCl_3$). R_f = 0.32 (9.1% EtOAc in hexane). IR (film): $\tilde{\nu}$ = 2964, 2937, 2860, 1729, 1472, 1152, 1122, 1019 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.85 (t, *J* = 2.4 Hz, 1 H), 4.64–4.58 (m, 1 H), 4.03–3.97 (m, 1 H), 2.57 (ABqdd, *J* = 15.6, 8.0, 2.8 Hz, 1 H), 2.46 (ABqdd, *J* = 15.6, 4.4, 2.0 Hz, 1 H), 1.65 (dt, *J* = 14.0, 2.4 Hz, 1 H), 1.54–1.43 (m, 3 H), 1.01 (s, 9 H), 0.96 (s, 9 H), 0.93 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.9, 74.8, 69.7, 52.1, 41.2, 31.4, 27.4 (×3), 27.1 (×3), 22.7, 19.6, 9.4 ppm. HRMS (CI+): calcd. for $C_{15}H_{31}O_3Si$ $[M + H]^+$ 287.2042; found 287.2046.

(4*R*,6*S*)-4-(But-2-ynyl)-2,2-di-*tert*-butyl-6-ethyl[1,3,2]dioxasilinane (4): To a stirred solution of CBr_4 (2.50 g, 7.52 mmol) in CH_2Cl_2 (20 mL) cooled to 0 °C in an ice/water bath was added PPh_3 (1.97 g, 7.52 mmol), and the mixture was stirred for 1 h at the same temperature. A solution of aldehyde **20** (537.0 mg, 1.88 mmol) in CH_2Cl_2 (5 mL) was added at 0 °C, and the mixture was stirred at room temperature for 1 h. The reaction mixture was diluted with Et_2O and filtered through a pad of Celite, which was washed with Et_2O. The combined filtrate was evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 2.0% EtOAc in hexane) to give the dibromoalkene (773.0 mg, 93%) as a white solid. $[\alpha]_D^{23}$ = + 5.3 (*c* 1.10, $CHCl_3$). R_f = 0.77 (4.8% EtOAc in hexane). IR (film): $\tilde{\nu}$ = 2963, 2935, 2858, 1472, 1219, 1142 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.56 (t, *J* = 7.2 Hz, 1 H), 4.16–4.10 (m, 1 H), 3.97–3.90 (m, 1 H), 2.34–2.20 (m, 2 H), 1.61–1.40 (m, 4 H), 1.01 (s, 9 H), 0.97 (s, 9 H), 0.93 (d, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.3, 89.6, 74.8, 72.1, 41.2, 40.8, 31.5, 27.5 (×3), 27.1 (×3), 22.7, 19.6, 9.5 ppm. HRMS (CI+): calcd. for $C_{16}H_{31}{}^{79}Br_2O_2Si$ $[M + H]^+$ 441.0460; found 441.0458; calcd. for $C_{16}H_{31}{}^{81}Br^{79}BrO_2Si$ $[M + 2 + H]^+$ 443.0440; found 443.0429; calcd. for $C_{16}H_{31}{}^{81}Br_2O_2Si$ $[M + 4 + H]^+$ 445.0420; found 445.0419.

To a solution of the above dibromoalkene (761.0 mg, 1.73 mmol) in dry THF (30 mL) cooled to –78 °C in an acetone/dry ice bath was added *n*BuLi (1.73 mL, 2.5 M in hexane, 4.33 mmol), and the mixture was stirred at the same temperature for 1 h. MeI (0.54 mL, 8.66 mmol) was added at –78 °C, and the resultant mixture was warmed to room temperature and stirred for 3 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl and extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 2% EtOAc in hexane) to give the alkyne **4** (461.0 mg, 90%) as a colorless oil. $[\alpha]_D^{24}$ = –25.6 (*c* = 0.86, $CHCl_3$). R_f = 0.34 (hexane). IR (film): $\tilde{\nu}$ = 2964, 2936, 2859, 1472, 1130 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.13–4.07 (m, 1 H), 3.99–3.93 (m, 1 H), 2.47–2.40 (m, 1 H), 2.29–2.21 (m, 1 H), 1.84 (dt, *J* = 14.0, 2.0 Hz, 1 H), 1.77 (t, *J* = 2.8 Hz, 3 H), 1.51–1.42 (m, 3 H), 1.01 (s, 9 H), 0.97 (s, 9 H), 0.94 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 77.6, 75.7, 74.9, 72.7, 40.2, 31.6, 28.7, 27.5 (×3), 27.1 (×3), 22.7, 19.7, 9.5, 3.5 ppm. HRMS (CI–): calcd. for $C_{17}H_{31}O_2Si$ $[M - H]^-$ 295.2093; found 295.2094.

(*E*,4*S*,6*R*)-2,2-Di-*tert*-butyl-4-ethyl-6-{3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-but-2-enyl}[1,3,2]dioxasilinane (3): A flame-dried 25 mL two-neck flask was charged with CuCl (16.0 mg,

0.16 mmol), NaO*t*Bu (22.0 mg, 0.23 mmol), bis(pinacolato)diboron (475.0 mg, 1.87 mmol), tricyclohexylphosphine (53.0 mg, 0.19 mmol) in a glove box. Then, the loaded flask was evacuated and backfilled with argon three times. A solution of alkyne **4** (461.0 mg, 1.56 mmol) in dry toluene (15 mL) and dry MeOH (0.13 mL, 3.25 mmol) were added with a syringe. The resultant mixture was stirred at room temperature for 3 h. The reaction was quenched with MeOH. The mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, 3.2% EtOAc in hexane) to give the major product **3** and the inseparable minor regioisomer (496.0 mg, 75%, *dr* = 92.5:7.5) as a colorless oil. $[\alpha]_D^{22}$ = –5.0 (*c* = 2.75, $CHCl_3$). R_f = 0.32 (5.0% EtOAc in hexane). IR (film): $\tilde{\nu}$ = 2966, 2936, 2859, 1634, 1472, 1371, 1304, 1142 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.52 (q, *J* = 6.8 Hz, 0.075 H, vinyl proton of the minor regioisomer), 6.36 (td, *J* = 7.2, 1.6 Hz, 0.925 H, vinyl proton of **3**), 4.15–4.07 (m, 1 H), 3.94–3.86 (m, 1 H), 2.48–2.20 (m, 2 H), 1.70 (d, *J* = 0.4 Hz, 3 H), 1.60 (dt, *J* = 14.0, 2.0 Hz, 1 H), 1.47–1.34 (m, 3 H), 1.25 (s, 12 H), 1.00 (s, 9 H), 0.96 (s, 9 H), 0.92 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.7, 83.1 (×2), 75.0, 73.4, 40.9, 38.0, 31.6, 27.5 (×3), 27.2 (×3), 24.8 (×2), 24.7 (×2), 22.7, 19.6, 14.2, 9.5 ppm. HRMS (CI–): calcd. for $C_{23}H_{44}BO_4Si$ $[M - H]^-$ 423.3102; found 423.3102; calcd. for $C_{23}H_{47}BNO_4Si$ $[M + NH_2]^-$ 440.3367; found 440.3342; calcd. for $C_{23}H_{48}BNO_4Si$ $[M + NH_3]^-$ 441.3446; found 441.3323.

Methyl (2*E*,4*E*,6*E*,8*E*,4′*R*,6′*S*)-10-{2′,2′-Di-*tert*-butyl-6′-ethyl-[1′,3′,2′]dioxasilinan-4′-yl}-4,6,8-trimethyldeca-2,4,6,8-tetraenoate (21): A flame-dried 10 mL process vial was charged with $Pd(OAc)_2$ (2.2 mg, 1.0×10^{-2} mmol), Aphos-Y (7.6 mg, 1.5×10^{-2} mmol), and $K_3PO_4 \cdot 3H_2O$ (160.0 mg, 0.60 mmol). The loaded vial was sealed with a cap containing a silicon septum and then evacuated through a needle under vacuum and backfilled with argon (this sequence was repeated five times). A solution of the triene bromide **2a** (50.0 mg, 0.20 mmol) and the alkenyl boronate **3** (96.0 mg, 0.22 mmol) in degassed THF (2 mL) was added with a syringe followed by degassed water (64.8 μL, 18 equiv.) with another syringe. The resultant mixture was heated to 35 °C with stirring for 18 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography (silica gel, 3.2% EtOAc in hexane) to give the coupling product **15** (46.0 mg, 85%) as a pale yellow oil. $[\alpha]_D^{24}$ = +27.6 (*c* = 0.25, $CHCl_3$). R_f = 0.28 (5.0% EtOAc in hexane). IR (film): $\tilde{\nu}$ = 2961, 2934, 2858, 1720, 1617, 1470, 1436, 1305, 1167 cm^{-1}. ^1H NMR (400 MHz, CD_3COCD_3): δ = 7.35 (d, *J* = 15.6 Hz, 1 H), 6.44 (s, 1 H), 6.06 (s, 1 H), 5.87 (d, *J* = 15.2 Hz, 1 H), 5.63 (t, *J* = 7.2 Hz, 1 H), 4.24–4.18 (m, 1 H), 4.05–3.98 (m, 1 H), 3.69 (s, 3 H), 2.36 (dd, *J* = 6.8, 6.8 Hz, 2 H), 2.05 (s, 3 H), 2.00 (d, *J* = 0.8 Hz, 3 H), 1.82 (s, 3 H), 1.77 (dt, *J* = 14.0, 2.0 Hz, 1 H), 1.53–1.44 (m, 3 H), 1.03 (s, 9 H), 0.99 (s, 9 H), 0.95 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 167.8, 151.3, 145.4, 139.0, 134.5, 133.0, 132.6, 129.2, 116.8, 76.1, 74.9, 51.5, 42.1, 38.4, 32.3, 28.0 (×3), 27.6 (×3), 23.3, 20.2, 19.0, 17.4, 14.1, 9.8 ppm. HRMS (CI–): calcd. for $C_{27}H_{46}O_4Si$ $[M]^-$ 462.3165; found 462.3171.

(2*E*,4*E*,6*E*,8*E*,4′*R*,6′*S*)-10-{2′,2′-Di-*tert*-butyl-6′-ethyl[1′,3′,2′]-dioxasilinan-4′-yl}-4,6,8-trimethyldeca-2,4,6,8-tetraenoic Acid (22): To a solution of the methyl ester **21** (26.0 mg, 5.0×10^{-2} mmol) in a mixture of THF/MeOH/H_2O (2.5 mL, v/v/v 4:1:1) cooled in an ice/water bath was added an aqueous solution of LiOH (0.38 mL, 0.38 mmol, 1.0 M in H_2O). The resultant solution was protected from light and stirred for 16 h at room temperature. The reaction was quenched by the addition of saturated aqueous NH_4Cl (5 mL). The reaction mixture was diluted with EtOAc (5 mL), and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried with anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by preparative TLC to give the acid **22** (20.0 mg, 90%). $[\alpha]_D^{26}$ = +42.4 (*c* = 0.65, $CHCl_3$). R_f = 0.45 (20% EtOAc in hexane). IR (film): $\tilde{\nu}$ = 2963, 2935, 2858, 2362, 2338, 1684, 1613, 1308, 1282, 1211, 1140 cm^{-1}. ^1H NMR (400 MHz, CD_3COCD_3): δ = 7.34 (d, *J* = 15.6 Hz, 1 H), 6.42 (s, 1 H), 6.05 (s, 1 H), 5.85 (d, *J* = 15.6 Hz, 1 H), 5.62 (t, *J* = 7.2 Hz, 1 H), 4.23–4.17 (m, 1 H), 4.05–3.98 (m, 1 H), 2.36 (dd, *J* = 6.8, 6.8 Hz, 2 H), 2.04 (s, 3 H), 2.00 (s, 3 H), 1.81 (s, 3 H), 1.76 (br d, *J* = 14.0 Hz, 1 H), 1.53–1.44 (m, 3 H), 1.02 (s, 9 H), 0.99 (s, 9 H), 0.95 (t, *J* = 7.2 Hz, 3 H) ppm (the carboxylic acid O*H* proton was not observed). ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 168.1, 151.4, 145.1, 138.9, 134.5, 133.0, 132.7, 129.1, 117.2, 76.0, 74.8, 42.1, 38.4, 32.3, 28.0 (×3), 27.6 (×3), 23.3, 20.2, 19.0, 17.4, 14.1, 9.8 ppm. HRMS (CI–): calcd. for $C_{26}H_{44}O_4Si$ $[M]^-$ 448.3009; found 448.3012.

Supporting Information (see footnote on the first page of this article): Procedures for the synthesis of **9**, **13**, and **17** and copies of original ^1H and ^{13}C NMR spectra of the compounds shown in Schemes 1–4.

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