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Development of an end-game strategy towards apoptolidin: a sequential Suzuki coupling approach

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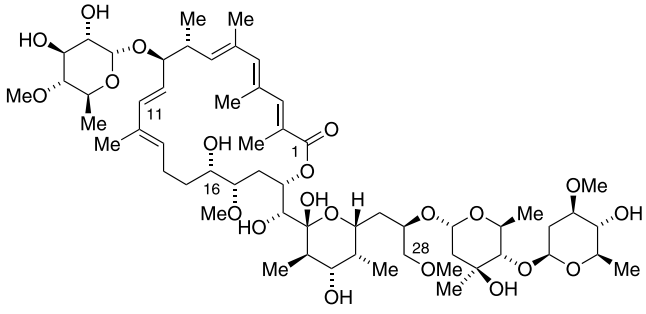
Abstract—An end-game strategy towards the synthesis of apoptolidin has been demonstrated in a model study, in which the C(1)–C(15) fragment was successfully assembled using three consecutive Suzuki coupling reactions.

1. Introduction and discussion

In the mid-1980's Seto and co-workers in Japan developed several immortalized cell lines transfected with oncogenes in order to screen natural product isolates for genotype selective anticancer agents.[1] In 1997, these investigations led to the isolation of apoptolidin from the *Nocardiopsis* sp. soil bacteria, a macrolide natural product that selectively induces apoptosis in cells transformed with the E1A oncogene.[2a] One year later the complete structure of apoptolidin was assigned based on NMR analysis and featured two sugar units located at C(9) and C(27) and an aglycone consisting of a 20-membered macrolactone (**1**).[2b] Apoptolidin was determined to induce apoptosis in cells transformed with the E1A oncogene while exhibiting cytostatic activity against normal cells. This unique pattern of cytotoxicity was later shown by workers at Stanford University to correlate with apoptolidin's ability to inhibit mitochondrial F_0F_1-ATPase.[3] Apoptolidin's remarkably selective cytotoxicity profile could prove useful in the development of new strategies for cancer treatment, as well as further the understanding of cellular events leading to apoptosis in cells.[4] Owing to its biological attributes and complex molecular architecture, apoptolidin has been the subject of extensive synthetic studies.[5–7] Previously, we reported a synthesis of the C(16)–C(28) fragment **2** (Scheme 2).[4f] In this paper we describe the successful development of an end-game strategy resulting in the completion of the C(1)–C(15) fragment of **1**.[5e,g]



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2. Synthetic design

The goal of our synthetic design was to develop a convergent route that integrates a novel synthesis of the polyene fragment imbedded in the 20-membered macrolactone, particularly the unique C(1)–C(7) highly substituted trienoate moiety. To that end, we propose strategic bond disconnections of apoptolidin leading to three major components: the lower portion as either a 1,1-geminal dibromide **3** or vinyliodide **4**; the C(7)–(11) boronate **5**; and the C(1)–C(5) dienoate boronate **7** (Scheme 1). Our plan was to form the C(11)–C(12) bond first via a Suzuki cross-coupling reaction between 1,1-dibromo olefin **3** (or vinyliodide **4**) and boronate **5**. Subsequently the aldehyde functionality at C(7) of the coupled product would be homologated to a 1,1-geminal dibromide, which would then be used in a second Suzuki cross-coupling reaction with the C(1)–C(5) boronate **7**. In the end, we would convert the remaining vinylbromides at C(6) and C(12), or the mono bromide at C(6) if vinyliodide **4** would have been used in the

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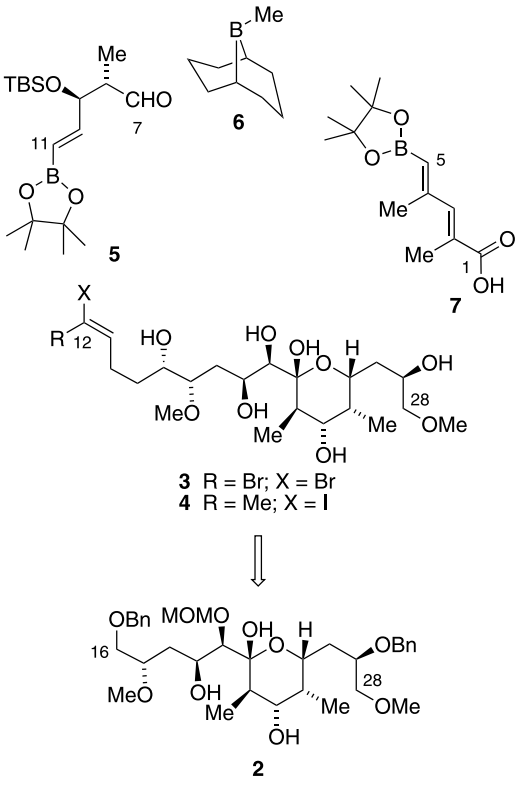
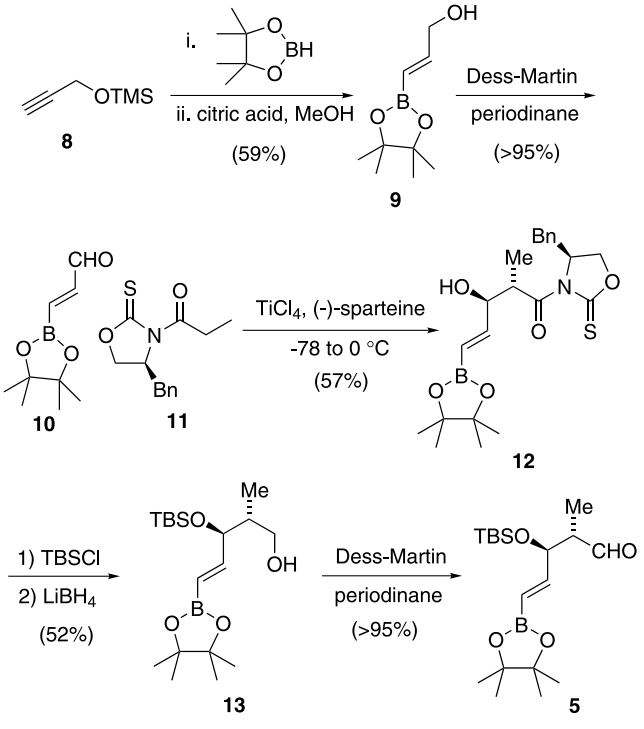


Scheme 1.

first Suzuki coupling reaction, to the requisite methyl groups via a final cross-coupling reaction using Me-9-B-BBN **6**.[8]

3. Results and discussion

The preparation of boronate **5** started with trimethylsilyl ether **8**[9a] (Scheme 2). Following a procedure developed by Vaultier,[9b] hydroboration of **8** using pinacolborane was followed by acidic methanolysis to afford allylic alcohol **9** in 59% yield for two steps. The oxidation of **9** to aldehyde **10** was then accomplished in near quantitative yield by Dess–Martin periodinane oxidation[10] following a modified work up protocol.[11] Aldol reaction between **10** and thioxazolidinone **11** furnished *syn* aldol product **12** in 57% yield (>99:1 diastereoselectivity determined by HPLC). The relatively low yield was presumably a reflection of the instability of aldehyde **10** under the reaction conditions.[12] The structure of adduct **12** was unambiguously confirmed by single crystal X-ray analysis.[13] The resulting hydroxyl group was protected as a TBS silylether (84%), and the auxiliary was reductively removed to furnish alcohol **13** in 61% yield. Finally, Dess–Martin oxidation gave rise to the C(7)–C(11) aldehyde **5**.

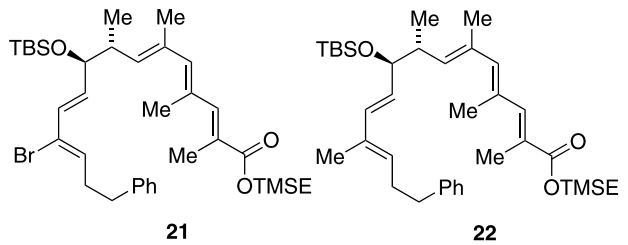


Scheme 2.

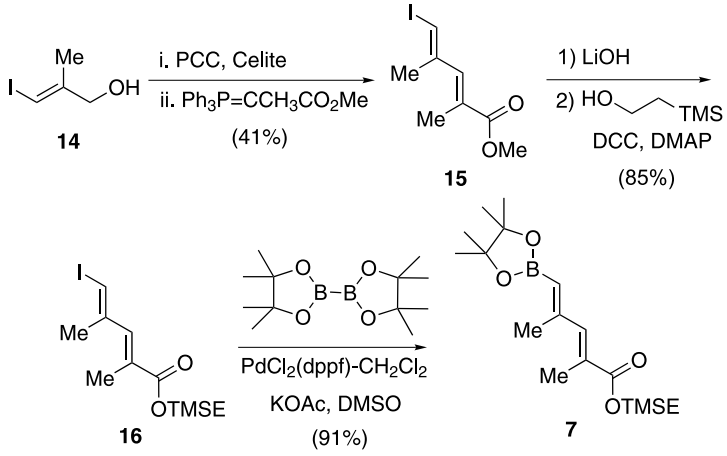
The synthesis of the C(1)–C(5) dienoate boronate **7** started with the known alcohol **14** (Scheme 4).[14] PCC oxidation, followed by Wittig olefination gave dienoate **15** in 41% yield for the two steps. The methyl ester was then exchanged for a trimethylsilylethyl ester (**16**) which was subsequently cross coupled with bis(pinacolato)diborane to give boronate **7** in 91% yield (Scheme 3).[15]

With the requisite C(7)–C(11) (**5**) and C(1)–C(5) (**7**) fragments in hand, we first set out to examine the possibility of using 1,1-dibromide **3** (Scheme 1) in the first Suzuki coupling reaction in order to form the C(11)–C(12) bond. To this end, dibromide **17** was used in a model study depicted in Scheme 4. Boronate **5** underwent Suzuki coupling with 1,1-geminal dibromide **17** in the presence of $Pd(PPh_3)_4$ and TlOEt[16] to give diene **18** in 70% yield. The aldehyde group was subsequently homologated to dibromide **19** using the ylide derived from Ramirez salt (PPh_3CHBr_3, *t*-BuOK).[17] Attempted Corey–Fuchs olefination[18] of **18** resulted in β-elimination of the OTBS group. A second Suzuki coupling reaction was then carried out between **19** and dienoate boronate **7** to afford the complete trienoate **20**.

What needed to be done at this stage was the conversion of the remaining C(6) and C(12) vinylbromides to the required methyl groups. After screening a variety of palladium mediated processes to no avail, using Me_4Sn,[19] MeMgBr,[20a] and $AlMe_3$[20b] as the methyl sources, we turned our attention again to Suzuki coupling reactions using Me-9-B-BBN, $CH_3B(OH)_2$,[21] and methyl pinacolborate[22] as the methyl sources.



Under standard reaction conditions [$Pd(PPh_3)_4$,TlOEt, THF–H_2O], the C(6) bromide underwent facile cross-



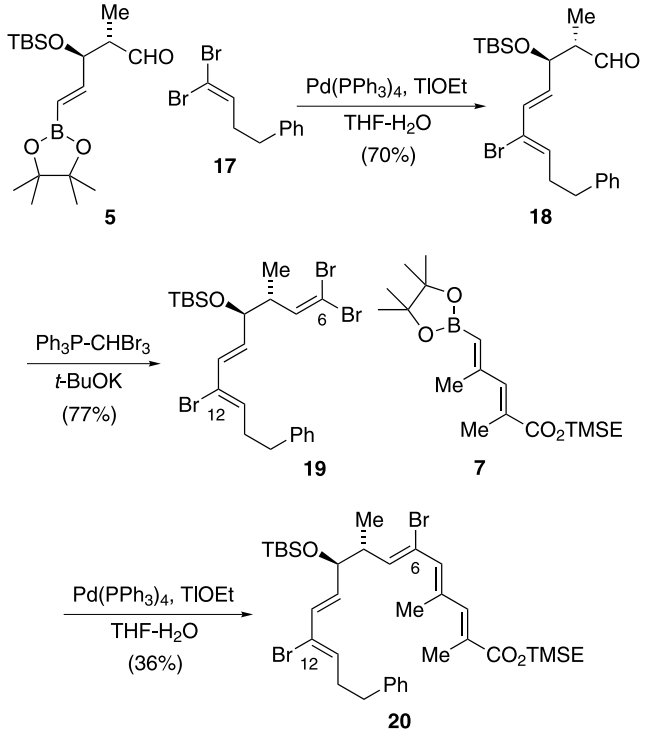
Scheme 3.

coupling, however, the more electron-rich but less sterically demanding C(12) bromide was found to be surprisingly resistant towards methylation, despite prolonged reaction times and heating. For example, when Me-9-B-BBN was used, **21** was isolated as the only product in 78% yield. With $CH_3B(OH)_2$, again only **21** was obtained in a comparable 74% yield. The only case where the bis-methylated product **22** was obtained was when methyl pinacolborate was used, however, as a 1:2 inseparable mixture with **21** (major product).

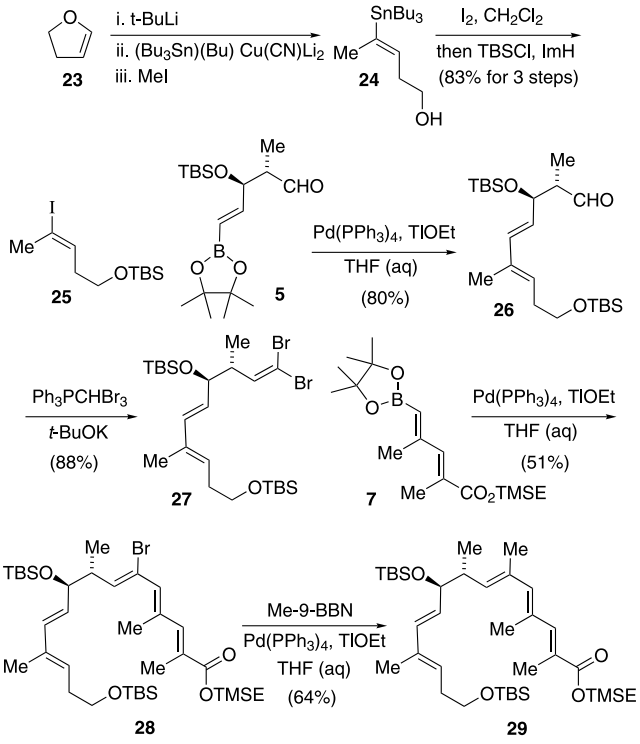
In light of the difficulty in effecting a cross-coupling reaction at the C(12) bromide, we elected to examine the possibility of using vinyliodide **4** (Scheme 1) in the first Suzuki coupling reaction to form the C(11)–C(12) bond, in which case the C(12) methyl group was already in place. Vinyliodide **25**, synthesized from dihydrofuran **23**,[23] was used in the model study described in Scheme 5. Boronate **5** underwent Suzuki coupling reaction with vinyliodide **25** in the presence of $Pd(PPh_3)_4$ and TlOEt to afford diene **26** in 80% yield. The aldehyde functionality was subsequently homologated to 1,1-geminal dibromide **27**. A second Suzuki coupling reaction was subsequently carried out between **27** and dienoate boronate **7** to furnish trienoate **28**. Finally, the C(6) bromide was uneventfully methylated using Me-9-B-BBN to afford the complete trienoate fragment **29** in high purity and good yield (64%).

4. Conclusion

In summary, the C(1)–C(15) polyene portion of apoptolidin has been synthesized, successfully demonstrating a tandem Suzuki coupling reaction based end-game strategy. The



Scheme 4.



Scheme 5.

application of this strategy to the synthesis of apoptolidin will be reported in due course.

5. Experimental

5.1. General

Unless indicated, all commercial reagents were used as received without further purification. All reactions were carried out under a nitrogen or argon atmosphere using dry glassware that had been flame-dried under a stream of nitrogen, unless otherwise noted. All reaction solvents were dried and/or purified before use. Reagent grade tetrahydrofuran was dried over 4 Å molecular sieves; dichloromethane and benzene were distilled from calcium hydride. Reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm E. Merck precoated silica gel plates. Visualization was accomplished with UV light and aqueous ceric ammonium molybdate solution or anisaldehyde stain followed by charring on a hot-plate. Flash chromatography was performed with the indicated solvents using silica gel 60 (particle size 230–400 mesh) with the indicated solvent system. Yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. Melting points were taken on a micro melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon-13 (^{13}C NMR) spectra were recorded on a 300 or 500 MHz spectrometer at ambient temperature. ^{1}H and ^{13}C NMR data are reported as δ values relative to tetramethylsilane (δ 0 ppm, $CDCl_3$) or residual non-deuterated solvent δ 7.26 ppm from $CHCl_3$, δ 7.16 ppm for C_6D_5H). For ^{13}C spectra, chemical shifts are reported relative to the δ 77.23 ppm resonance of $CDCl_3$ or the δ 128.39 resonance of C_6D_6. Infrared (IR) spectra were recorded as thin films or solutions in the indicated solvent. Mass spectra were obtained at the Laboratory for Biological Mass Spectrometry (Texas A&M University).

5.1.1. Trimethyl-prop-2-ynyloxy-silane 8.[9a] To a solution of propargyl alcohol (20 mL, 344 mmol) in ether (150 mL, reagent grade) at 0 °C was added TMSCl (66 mL, 516 mmol, reagent grade) and pyridine (50 mL, 619 mmol, reagent grade). The white slurry was stirred at ambient temperature for 43 h, diluted with petroleum ether (300 mL), and filtered through a bed of silica gel and rinsed with petroleum ether–ether (1 L, 10:1). Solvent was removed to give 34 g (77%) of **8** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.26 (d, J=1.2 Hz, 2H), 2.38 (t, J=1.5 Hz, 1H), 0.19 (s, 9H).

5.1.2. 3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-prop-2-en-1-ol 9. To a solution of **8** (20 g, 169 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added $BH_3\cdot SMe_2$ (16.9 mL, 169 mmol). The colorless solution was stirred at 0 °C for 1 h and then at ambient temperature for 3 h before a solution of 179 (10.8 g, 84.5 mmol) in CH_2Cl_2 (10 mL) was introduced via cannula. The reaction mixture was then heated to 50 °C and stirred sealed for 4 d. Solvent was removed and MeOH (60 mL) was added, followed by citric acid (17.7 g, 84.5 mmol). After 5 min, solvent was removed in vacuo and the residue was diluted with ether (700 mL) and washed with $NaHCO_3$ (4×60 mL, sat.). The aqueous layers were back extracted with ether (3×100 mL). The organic layers were combined and solvent was removed in vacuo. Flash chromatography of the residue (petroleum ether–ether: 2:1) gave 9.2 g (59%, 2 steps) of **9** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (dt, J=18.0, 4.5 Hz, 1H), 5.68 (dt, J=18.0, 1.8 Hz, 1H), 4.22 (m, 2H), 1.25 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.8, 83.2, 64.4, 24.7; HRMS (ESI) m/z 191.1462 [(M+Li)$^+$, calcd for $C_9H_{17}BO_3$ 191.1431].

5.1.3. 3-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-propenal 10. To a solution of **9** (4.3 g, 23.3 mmol) in CH_2Cl_2 (7 mL) was added Dess–Martin periodinane (11.9 g, 28 mmol). The white slurry was stirred for 1.5 h. Solvent was removed in vacuo and the residue was filtered through a fine fritted funnel and rinsed with petroleum ether–ether (330 mL, 10:1). Removal of solvent gave 4.2 g (>95%) of **10** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (d, J=7.5 Hz, 1H), 6.77 (dd, J=18.5, 8.0 Hz, 1H), 6.64 (d, J=18.5 Hz, 1H), 1.28 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.1, 147.0, 84.4, 24.7; HRMS (ESI) m/z 189.1272 [(M+Li)$^+$, calcd for $C_9H_{15}BO_3$ 189.1274]

5.1.4. 1-(4-Benzyl-2-thioxo-oxazolidin-3-yl)-3-hydroxy-2-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pent-4-en-1-one 12. To a solution of 1-(4-benzyl-2-thioxo-oxazolidin-3-yl)-propan-1-one (2.4 g, 9.7 mmol) in CH_2Cl_2 (20 mL) at 0 °C was slowly added titanium tetrachloride (9.7 mL, 9.7 mmol, 1.0 M in CH_2Cl_2). The resulting yellow slurry was stirred at 0 °C for 5 min, before (−)-sparteine (2.95 mL, 12.8 mmol) was introduced neat. The homogeneous solution was stirred at 0 °C for 20 min before being cooled to −78 °C. A solution of **10** (1.8 g, 9.9 mmol) in CH_2Cl_2 (20 mL) was added via cannula over 10 min. The reaction mixture was stirred at −78 °C for 1.5 h and then at 0 °C for another 30 min. The reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and filtered through a bed of Celite and rinsed with CH_2Cl_2. HPLC analysis of the crude product showed a diastereomeric ratio of >99:1. Flash chromatography of the residue (petroleum ether–ether: 4:1→1:1) gave 5.8 g (57%) of **12** as a white solid. Recrystallization from EtOAc gave a colorless needle crystalline suited for X-ray analysis. Mp 138–139 °C. $[\alpha]_D$=+62.3° (c 3.7, CH_2Cl_2); IR (CH_2Cl_2) 3595, 2986, 1696, 1358, 963 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19–7.33 (m, 5H), 6.55 (dd, J=18.0, 4.5 Hz, 1H), 5.76 (dd, J=18.0, 2.0 Hz, 1H), 4.92 (m, 1H), 4.78 (dq, J=7.0, 3.0 Hz, 1H), 4.63 (m, 1H), 4.30 (m, 2H), 3.24 (dd, J=13.5, 3.5 Hz, 1H), 2.74 (dd, J=13.5, 10.0 Hz, 1H), 1.25 (s, 12H), 1.24 (d, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.9, 177.3, 151.1, 135.1, 129.4, 129.0, 127.5, 83.4, 72.9, 70.2, 60.1, 42.1, 37.5, 24.8, 24.7, 10.5; HRMS (ESI) m/z 432.2016 [(M)$^+$, cald for $C_{22}H_{31}BNO_5S$ 432.2044].

5.1.5. 3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pent-4-en-1-ol 13. To a solution of **12** (1.6 g, 3.8 mmol) in CH_2Cl_2 (6 mL) at 0 °C was imidazole (772 mg, 11.3 mmol) and TBSCl (1.7 g, 11.3 mmol). The reaction mixture was stirred at 0 °C for 1 h and then at ambient temperature for 17 h. The mixture was quenched with water (10 mL). The aqueous

layer was separated and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography of the residue (petroleum ether–ether: 10:1) gave 2.5 g (84%) of the corresponding TBS ether as a colorless oil. $[\alpha]_D=+35.4°$ (*c* 0.48, CH_2Cl_2); IR (CH_2Cl_2) 2996, 1716, 1153 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.18–7.34 (m, 5H), 6.58 (dd, *J*= 18.0, 5.1 Hz, 1H), 5.63 (dd, *J*=18.0, 1.2 Hz, 1H), 4.76 (m, 2H), 4.56 (dt, *J*=4.8, 1.2 Hz, 1H), 4.27 (dd, *J*=9.3, 1.8 Hz, 1H), 4.18 (m, 1H), 3.28 (dd, *J*=12.9, 3.0 Hz, 1H), 2.73 (dd, *J*=13.2, 10.2 Hz, 1H), 1.23 (s, 12H), 1.18 (d, *J*=6.6 Hz, 3H), 0.87 (s, 9H), −0.05 (s, 3H), −0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.0, 175.0, 152.8, 135.3, 129.4, 128.9, 127.3, 83.1, 74.9, 69.8, 60.7, 43.8, 37.2, 25.7, 24.7, 24.6, 18.0, 11.0, −4.4, −5.4; HRMS (ESI) *m/z* 546.2881 $[(M+H)^+$, calcd for $C_{28}H_{45}BNO_5SSi$ 546.2792]. To a solution of thus obtained TBS ether (4.6 g, 8.4 mmol) in ether–MeOH (20 mL–155 μL) at 0 °C was added $LiBH_4$ (7.9 mL, 15.6 mmol, 2.0 M in ether). The reaction mixture was stirred at ambient temperature for 4.5 h, diluted with petroleum ether (100 mL), and filtered through a bed of silica gel and rinsed with petroleum ether–ether (600 mL, 1:2). Solvent was removed in vacuo. Flash chromatography of the residue (petroleum ether–ether: 5:1→2:1) gave 1.86 g (61%) of **13** as a colorless oil. $[\alpha]_D=-20.8°$ (*c* 0.48, CH_2Cl_2); IR (CH_2Cl_2) 3490, 2960, 1639, 856 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 6.59 (dd, *J*=17.5, 5.0 Hz, 1H), 5.64 (dd, *J*=17.5, 2.0 Hz, 1H), 4.30 (m, 1H), 3.60 (dd, *J*=11.0, 9.0 Hz, 1H), 3.44 (dd, *J*=10.5, 4.5 Hz, 1H), 1.98 (m, 1H), 1.25 (s, 12H), 0.88 (s, 9H), 0.80 (d, *J*=7.0 Hz, 3H), 0.04 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1, 83.2, 77.4, 65.7, 40.8, 25.8, 24.8, 24.7, 18.1, 12.1, −4.5, −5.2; HRMS (ESI) *m/z* 357.2636 $[(M)^+$, calcd for $C_{18}H_{37}BO_4Si$ 357.2646].

5.1.6. 3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-pent-4-enal 5. To a solution of **13** (890 mg, 2.49 mmol) in CH_2Cl_2 (10 mL) was added Dess–Martin periodinane (1.16 g, 2.75 mmol). The white slurry was stirred for 1.5 h. Solvent was removed in vacuo and the residue was filtered through a fine fritted funnel and rinsed with petroleum ether–ether (330 mL, 10:1). Removal of solvent gave 885 mg (>95%) of **5** as a colorless oil. $[\alpha]_D=+12.8°$ (*c* 5.08, CH_2Cl_2); IR (CH_2Cl_2) 2960, 1737, 1639, 1148 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 9.73 (d, *J*=1.0 Hz, 1H), 6.55 (dd, *J*=17.5, 5.0 Hz, 1H), 5.68 (dd, *J*=17.5, 1.5 Hz, 1H), 4.64 (m, 1H), 2.40 (m, 1H), 1.21 (s, 12H), 1.00 (d, *J*=2.0 Hz, 3H), 0.82 (s, 9H), −0.03 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.4, 152.2, 83.3, 73.5, 51.9, 25.8, 24.8, 24.7, 18.1, 7.9, −4.2, −5.2; HRMS (ESI) *m/z* 355.2476 $[(M)^+$, calcd for $C_{18}H_{35}BO_4Si$ 355.2476].

5.1.7. 5-Iodo-2,4-dimethyl-penta-2,4-dienoic acid methyl ester 15. To a solution of **14**[14] (9.3 g, 47 mmol) in CH_2Cl_2 (350 mL) at 0 °C was added Celite (21 g) and pyridinium chlorochromate (15 g, 70 mmol). The mixture was stirred at 0 °C for 3.5 h and filtered through a bed of silica gel and rinsed with ether (500 mL). Solvent was removed in vacuo to give a volatile brown crude oil. To a solution of the above-generated oil in CH_2Cl_2 (50 mL) at 0 °C was added $Ph_3P{=}C(CH_3)COOMe$ (10.6 g, 30 mmol). The solution was stirred at ambient temperature for 1.5 h. Solvent was removed and the residue was filtered through a bed of silica gel and rinsed with ether (500 mL). Solvent was removed to give a crude oil. Flash chromatography of the residue (petroleum ether–ether: 20:1) gave 5.1 g (41%) of **15** as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.03 (m, 1H), 6.39 (t, *J*=1.2 Hz, 1H), 3.74 (s, 3H), 1.98 (dd, *J*=1.2, 0.6 Hz, 3H), 1.93 (d, *J*=1.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 143.6, 138.9, 128.0, 85.4, 52.1, 24.5, 14.2; HRMS (ESI) *m/z* 272.9937 $[(M+Li)^+$, calcd for $C_8H_{11}IO_2$ 272.9964].

5.1.8. 5-Iodo-2,4-dimethyl-penta-2,4-dienoic acid 2-trimethylsilanyl-ethyl ester 16. To a solution of **15** (2.55 g, 9.6 mmol) in MeOH–H_2O (9–3 mL) was added lithium hydroxide (1.2 g, 48 mmol). The clear solution was stirred at ambient temperature for 6.5 h. Solvent was removed in vacuo and the residue was diluted with CH_2Cl_2 (20 mL) and water (10 mL). The biphasic mixture was then acidified with concentrated aqueous HCl to pH=3. The aqueous layer was separated and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography of the residue (petroleum ether–ether: 4:1) gave 2.4 g (99%) of the corresponding carboxylic acid as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.17 (s, 1H), 6.49 (s, 1H), 2.01 (d, *J*= 1.2 Hz, 3H), 1.94 (d, *J*=1.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 143.6, 140.9, 86.9, 24.4, 13.8. To a solution of the above carboxylic acid (470 mg, 1.86 mmol) in CH_2Cl_2 (4 mL) was added DMAP (cat.) and trimethylsilyl-ethyl alcohol (281 μL, 1.96 mmol). The mixture was cooled to 0 °C and DCC (404 mg, 1.96 mmol) was added. The reaction mixture was stirred at 0 °C for 80 min then at ambient temperature for 30 min. The white slurry was filtered and rinsed with ether (100 mL). Solvent was removed in vacuo. Flash chromatography of the residue (petroleum ether–ether: 20:1) gave 562 mg (86%) of **16** as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.37 (s, 1H), 4.22 (m, 2H), 1.97 (s, 3H), 1.91 (d, *J*=1.5 Hz, 3H), 1.01 (m, 2H), 0.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 143.7, 138.5, 128.4, 85.2, 63.2, 24.5, 17.3, 14.2, −1.5; HRMS (ESI) *m/z* 359.0515 $[(M+Li)^+$, calcd for $C_{12}H_{21}IO_2Si$ 359.0516].

5.1.9. 2,4-Dimethyl-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-penta-2,4-dienoic acid 2-trimethylsilanyl-ethyl ester 7. To a mixture of $PdCl_2$(dppf)–CH_2Cl_2 (34 mg, 0.04 mmol), KOAc (409 mg, 4.2 mmol), and bis(pinacolato)diboron (1 g, 4.2 mmol) flushed with argon was added a solution of **16** (490 mg, 1.4 mmol) in DMSO (5 mL) via cannula. The resulting dark reddish solution was heated to 80 °C and stirred in the dark under Ar for 10 min. It was cooled to ambient temperature, diluted with ether (250 mL), washed with water (30 mL), and dried over Na_2SO_4. Solvent was removed in vacuo. Flash chromatography of the residue (petroleum ether–ether: 15:1) gave 444 mg (91%) of **7** as a pale yellow solid; IR (CH_2Cl_2) 2991, 2249, 1706, 1265, 907 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.09 (s, 1H), 5.36 (s, 1H), 4.22 (m, 2H), 2.09 (s, 3H), 1.96 (d, *J*=1.5 Hz, 3H), 1.26 (s, 12H), 0.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 154.8, 142.9, 128.3, 83.0, 62.9, 24.8, 21.3, 17.3, 14.1, −1.5; ^{11}BNMR (96 MHz, $CDCl_3$, $BF_3\cdot OEt_2$ as reference) δ 95.9; HRMS (FAB) *m/z*

375.2139 [$(M+Na)^+$, calcd for $C_{18}H_{33}BO_4SiNa$ 375.2146].

5.1.10. 6-Bromo-3-(*tert*-butyl-dimethyl-silanyloxy)-2-methyl-9-phenyl-nona-4,6-dienal 18. To a solution of **5** (400 mg, 1.13 mmol) and **17** (109 mg, 0.376 mmol) in THF–H_2O (9–3 mL, degassed) was added $Pd(PPh_3)_4$ (44 mg, 0.0376 mmol). After 5 min, TlOEt (48 μL, 0.67 mmol) was introduced and the mixture was stirred in the dark for 90 min. A second batch of $Pd(PPh_3)_4$ (44 mg, 0.0376 mmol) was added and the mixture was stirred for another 1 h. The resulting dark slurry was filtered through a bed of Celite and rinsed with ether (300 mL). Solvent was removed in vacuo. Flash chromatography of the residue (petroleum ether–ether: 100:0→30:1→20:1) gave 115 mg (70%) of **18** as a colorless oil. $[\alpha]_D=-3.5°$ (*c* 0.57, CH_2Cl_2); IR (CH_2Cl_2) 2971, 2858, 1747, 840 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 9.72 (d, $J=1.5$ Hz, 1H), 7.89–7.30 (m, 5H), 6.19 (d, $J=15.0$ Hz, 1H), 6.01 (dd, $J=15.0$, 5.5 Hz, 1H), 5.96 (t, $J=7.0$ Hz, 1H), 4.68 (m, 1H), 2.74 (m, 2H), 2.59 (q, $J=7.0$ Hz, 2H), 2.46 (m, 1H), 1.07 (d, $J=7.0$ Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.3, 141.1, 133.8, 133.6, 130.2, 128.4, 128.3, 126.1, 124.8, 72.1, 52.6, 34.4, 33.3, 25.7, 18.1, 8.2, −4.2, −5.0; HRMS (ESI) *m/z* 437.1508 [$(M+H)^+$, calcd for $C_{22}H_{33}BrO_2Si$ 437.1511].

5.1.11. [4-Bromo-1-(3,3-dibromo-1-methyl-allyl)-7-phenyl-hepta-2,4-dienyloxy]-*tert*-butyl-dimethyl-silane 19. To a slurry of Ph_3P–$CHBr_3$ (1.47 g, 2.86 mmol) in THF (3 mL) at 0 °C was added *t*-BuOK (291 mg, 1.6 mmol). The bright yellow slurry was stirred at ambient temperature for 20 min and cooled to 0 °C. A solution of **18** (115 mg, 0.26 mmol) in THF (12 mL) was then introduced via cannula. The reaction mixture was stirred at 0 °C for 15 h and quenched with brine (10 mL). The aqueous layer was separated and extracted with ether (3×50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography of the residue (petroleum ether–ether: 30:1→1:1) gave 134 mg (77%) of **19** as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.17–7.29 (m, 5H), 6.28 (d, $J=9.5$ Hz, 1H), 6.15 (d, $J=15.0$ Hz, 1H), 5.96 (dd, $J=14.5$, 5.5 Hz, 1H), 5.94 (t, $J=7.0$ Hz, 1H), 4.23 (t, $J=5.0$ Hz, 1H), 2.75 (m, 2H), 2.61 (q, $J=7.5$ Hz, 2H), 2.56 (m, 1H), 0.97 (d, $J=7.0$ Hz, 3H), 0.89 (s, 9H), 0.04 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.3, 141.2, 134.4, 133.1, 129.8, 128.4, 128.4 (overlapping signal), 126.0, 125.2, 88.3, 74.1, 65.4, 44.9, 34.4, 33.4, 25.8, 18.2, 13.3, −4.4, −5.0; HRMS (ESI) *m/z* 597.0004 [$(M+Li)^+$, calcd for $C_{23}H_{33}Br_3OSi$ 597.0011].

5.1.12. 6,12-Dibromo-9-(*tert*-butyl-dimethyl-silanyloxy)-2,4,8-trimethyl-15-phenyl-pentadeca-2,4,6,10,12-pentaenoic acid 2-trimethylsilanyl-ethyl ester 20. To a solution of **19** (19 mg, 0.032 mmol) and **7** (58 mg, 0.163 mmol) in THF–H_2O (1.5–0.5 mL, degassed) was added $Pd(PPh_3)_4$ (4 mg, 0.00327 mmol). After 5 min, TlOEt (4.2 μL, 0.0589 mmol) was introduced and the mixture was stirred in the dark for 30 min. The resulting dark yellow slurry was filtered through a bed of Celite and rinsed with ether (100 mL). Solvent was removed in vacuo. Flash chromatography of the residue (petroleum ether–ether: 50:1→10:1→1:1) gave 8.4 mg (36%) of **20** as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.18–7.29 (m, 5H), 7.08 (s, 1H), 6.15 (d, $J=14.5$ Hz, 1H), 6.05 (s, 1H), 6.03 (dd, $J=14.5$, 6.0 Hz, 1H), 5.92 (t, $J=7.0$ Hz, 1H), 5.65 (dd, $J=9.0$, 1.0 Hz, 1H), 4.23 (m, 2H), 2.82 (m, 1H), 2.74 (m, 2H), 2.60 (q, $J=8.0$ Hz, 2H), 2.00 (s, 3H), 1.93 (d, $J=1.5$ Hz, 3H), 1.03 (d, $J=7.0$ Hz, 3H), 1.02 (m, 2H), 0.88 (s, 3H), 0.04 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 141.2, 141.0, 135.9, 135.6, 134.9, 133.6, 132.9, 129.7, 128.4, 128.4 (overlapping signal), 126.1, 125.2, 120.1, 75.1, 63.1, 43.9, 34.5, 33.3, 25.8, 18.2, 18.1, 17.4, 14.5, 14.2, −1.4, −4.3, −4.9; HRMS (ESI) *m/z* 743.2177 [$(M+Li)^+$, calcd for $C_{35}H_{54}Br_2O_3Si_2$ 743.2138].

5.1.13. 12-Bromo-9-(*tert*-butyl-dimethyl-silanyloxy)-2,4,6,8-tetramethyl-15-phenyl-pentadeca-2,4,6,10,12-pentaenoic acid 2-trimethylsilanyl-ethyl ester 21. To a solution of **20** (12.6 mg, 0.017 mmol) in THF (1.5 mL, degassed) was sequentially added $Pd(PPh_3)_4$ (4 mg, 0.0034 mmol), Me-9-B-BBN (204 μL, 0.51 mmol, 2.5 M in THF), TlOEt (18 μL, 0.255 mmol), and H_2O (0.3 mL, degassed). The yellow-brownish slurry was stirred in the dark for 19 h. The resulting dark slurry was filtered through a bed of Celite and rinsed with ether (100 mL). Solvent was removed in vacuo. Flash chromatography of the residue (petroleum ether–ether: 20:1) gave 9 mg (78%) of **21** as a colorless oil. It was further purification by HPLC (silica gel, 4 mL/min, 269 nm detection, 1% EtOAc/hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 7.18–7.29 (m, 5H), 7.13 (s, 1H), 6.06 (d, $J=14.5$ Hz, 1H), 6.03 (s, 1H), 5.94 (dd, $J=14.5$, 5.5 Hz, 1H), 5.88 (t, $J=7.0$ Hz, 1H), 5.19 (d, $J=10.0$ Hz, 1H), 4.23 (m, 2H), 3.99 (t, $J=5.5$ Hz, 1H), 2.73 (m, 2H), 2.60 (m, 2H), 2.31 (m, 1H), 2.01 (d, $J=1.0$ Hz, 3H), 1.81 (d, $J=1.0$ Hz, 3H), 1.77 (s, 3H), 1.03 (m, 2H), 0.91 (d, $J=6.5$ Hz, 3H), 0.88 (s, 9H), 0.04 (s, 9H), 0.00 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 142.6, 141.3, 136.3, 134.8, 133.2, 132.4, 132.2, 132.1, 128.7, 128.4, 128.3, 126.2, 126.0, 125.5, 76.1, 62.9, 40.6, 34.5, 33.3, 25.9, 23.6, 18.3, 18.0, 17.4, 15.5, 14.2, −1.4, −4.3, −4.9; HRMS (ESI) *m/z* 695.2927 [$(M+Na)^+$, calcd for $C_{36}H_{57}BrO_3Si_2Na$ 695.2922].

5.1.14. *tert*-Butyl-(4-iodo-pent-3-enyloxy)-dimethyl-silane 25. To a solution of CuCN (448 mg, 5 mmol) in THF–ether (6–10 mL) at −40 °C was added *n*-BuLi (4.85 mL, 10 mmol, 2.06 M in hexanes). After 5 min, cooling bath was removed and the mixture was stirred at ambient temperature for 15 min and cooled to −40 °C. Bu_3SnH (2.7 mL, 10 mmol) was then introduced and the mixture was stirred at −40 °C for 70 min. Separately, to a solution of dihydrofuran (378 μL, 5 mmol) in THF (5 mL) at −60 °C was added *t*-BuLi (3.5 mL, 6 mmol, 1.7 M in pentane). The mixture was stirred at −60 °C for 10 min and at 0 °C for 55 min before it was transferred to the above-generated mixture via cannula. The resulting orange solution was then stirred at 0 °C for 1.5 h. MeI (2.2 mL, 35 mmol) was added and the mixture was allowed to warm to ambient temperature in 1 h and stirred at ambient temperature for another 3 h. The resulting mixture was poured into a mixture of NH_4Cl (100 mL, sat.) and NH_3–H_2O (25 mL) at 0 °C and stirred for 30 min. The aqueous layer was separated and extracted with ether (3×100 mL). The combined organic layers were dried briefly over Na_2SO_4 and concentrated in vacuo. Removal of solvent

gave 196 as a colorless crude oil, which was used in the next step without further purification. To a solution of the above-generated alcohol **24** in CH_2Cl_2 (5 mL) at 0 °C was added a solution of I_2 (1.4 g, 5.4 mmol) in CH_2Cl_2 (45 mL) until brown color persisted. Imidazole (1 g, 14.8 mmol) was then added followed by TBSCl (2.23 g, 14.8 mmol). The resulting slurry was stirred at 0 °C for 20 min and quenched with $Na_2S_2O_3$ (25 mL) and stirred for 5 min. The aqueous layer was separated and extracted with ether (3×100 mL). The combined organic layers were dried briefly over Na_2SO_4 and concentrated in vacuo. Flash chromatography of the residue (petroleum ether–ether: 100:0→20:1) gave 1.35 g (83%, 3 steps) of **25** as a colorless oil. Observed physical properties were identical with those previously reported.[23] ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.14 (tq, J=8.0, 1.0 Hz, 1H), 3.59 (t, J=6.5 Hz, 2H), 2.35 (s, 3H), 2.22 (q, J=6.5 Hz, 2H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 95.3, 61.8, 34.2, 27.7, 25.9, 18.3, −5.3; HRMS (ESI) m/z 333.0731 [$(M+Li)^+$, calcd for $C_{11}H_{23}IOSi$ 333.0723].

5.1.15. 3,9-Bis-(*tert*-butyl-dimethyl-silanyloxy)-2,6-dimethyl-nona-4,6-dienal 26. To a solution of **25** (87 mg, 0.246 mmol) and **7** (53 mg, 0.164 mmol) in THF–H_2O (3–1 mL, degassed) was added $Pd(PPh_3)_4$ (19 mg, 0.0164 mmol). After 5 min, TlOEt (17 μL, 0.246 mmol) was introduced and the mixture was stirred in the dark for 35 min. The resulting reddish-brown slurry was filtered through a bed of Celite and rinsed with ether (200 mL). Solvent was removed in vacuo. Flash chromatography of the residue (petroleum ether–ether: 20:1) gave 56.3 mg (80%) of **26** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.74 (d, J=1.5 Hz, 1H), 6.18 (d, J=15.5 Hz, 1H), 5.48 (dd, J=15.5, 7.0 Hz, 1H), 5.45 (t, J=7.7 Hz, 1H), 4.54 (dd, J=6.5, 5.0 Hz, 1H), 3.62 (t, J=7.0 Hz, 2H), 2.46 (m, 1H), 2.34 (q, J=6.5 Hz, 2H), 1.71 (s, 3H), 1.04 (d, J=7.0 Hz, 3H), 0.86 (s, 9H), 0.85 (s, 9H), 0.02 (s, 6H), 0.01 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.8, 136.1, 134.3, 129.5, 126.6, 73.8, 62.6, 53.2, 32.1, 25.9, 25.8, 18.3, 18.1, 12.6, 8.5, −4.1, −5.0, −5.3, −5.3; HRMS (ESI) m/z 433.3149 [$(M+Li)^+$, calcd for $C_{23}H_{46}O_3Si_2$ 433.3146].

5.1.16. 1,1-Dibromo-4,10-bis-(*tert*-butyl-dimethyl-silanyloxy)-3,7-dimethyl-deca-1,5,7-triene 27. To a slurry of Ph_3P–$CHBr_3$ (579 g, 1.12 mmol) in THF (2 mL) at 0 °C was added *t*-BuOK (67 mg, 0.6 mmol). The bright yellow slurry was stirred at ambient temperature for 20 min and cooled to 0 °C. A solution of **26** (32 mg, 0.075 mmol) in THF (4 mL) was then introduced via cannula. The reaction mixture was stirred at 0 °C for 1 h and quenched with brine (10 mL). The aqueous layer was separated and extracted with ether (3× 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography of the residue (petroleum ether–ether: 30:1) gave 38.2 mg (88%) of **27**as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.27 (d, J=9.5 Hz, 1H), 6.13 (d, J=15.5 Hz, 1H), 5.46 (dd, J=15.5, 7.0 Hz, 1H), 5.44 (t, J=7.0 Hz, 1H), 4.11 (t, J=5.5 Hz, 1H), 3.63 (t, J=6.5 Hz, 2H), 2.53 (m, 1H), 2.35 (q, J=7.0 Hz, 2H), 1.72 (s, 3H), 0.96 (d, J=6.5 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.03 (s, 6H), 0.02 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.7, 135.5, 134.5, 128.8, 127.5, 87.8, 75.6, 62.7, 45.3, 32.1, 25.9, 25.8, 18.4, 18.2, 13.6, 12.7, −4.2, −4.9, −5.2, −5.3; HRMS (ESI) m/z 587.1530 [$(M+Li)^+$, calcd for $C_{24}H_{46}Br_2O_2Si_2$ 587.1563].

5.1.17. 6-Bromo-9,15-bis-(*tert*-butyl-dimethyl-silanyloxy)-2,4,8,12-tetramethyl-pentadeca-2,4,6,10,12-pentaenoic acid 2-trimethylsilanyl-ethyl ester 28. To a solution of **27** (38 mg, 0.0656 mmol) and **7** (115 mg, 0.32 mmol) in THF–H_2O (3–1 mL, degassed) was added $Pd(PPh_3)_4$ (7.6 mg, 0.00656 mmol). After 5 min, TlOEt (8 μL, 0.118 mmol) was introduced and the mixture was stirred in the dark for 30 min. The resulting yellow slurry was filtered through a bed of Celite and rinsed with ether (100 mL). Solvent was removed in vacuo. Flash chromatography of the residue (petroleum ether–ether: 50:1) gave 8.4 mg (36%) of **28** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (s, 1H), 6.13 (d, J=15.5 Hz, 1H), 6.04 (d, J=1.0 Hz, 1H), 5.65 (dd, J=9.0, 1.0 Hz, 1H), 5.53 (dd, J=15.5, 7.0 Hz, 1H), 5.42 (t, J=7.5 Hz, 1H), 4.23 (m, 2H), 4.10 (t, J=6.0 Hz, 1H), 3.62 (t, J=7.0 Hz, 2H), 2.78 (m, 1H), 2.34 (q, J=7.0 Hz, 2H), 2.00 (d, J=1.5 Hz, 3H), 1.92 (d, J=1.5 Hz, 3H), 1.72 (s, 3H), 1.02 (d, J=6.5 Hz, 3H), 1.01 (m, 2H), 0.87 (s, 9H), 0.86 (s, 9H), 0.04 (s, 9H), 0.02 (s, 6H), 0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 141.1, 136.4, 135.5, 135.4, 134.6, 133.8, 128.5, 128.3, 128.1, 119.7, 76.6, 63.0, 62.7, 44.3, 32.0, 25.9, 25.8, 18.4, 18.2, 18.1, 17.3, 14.8, 14.2, 12.6, −1.5, −4.1, −4.9, −5.3, −5.3; HRMS (ESI) m/z 733.3690 [$(M+Li)^+$, calcd for $C_{36}H_{67}BrO_4Si_3Li$ 733.3691].

5.1.18. 9,15-Bis-(*tert*-butyl-dimethyl-silanyloxy)-2,4,6,8,12-pentamethyl-pentadeca-2,4,6,10,12-pentaenoic acid 2-trimethylsilanyl-ethyl ester 29. To a solution of **28** (50 mg, 0.068 mmol) in THF (3 mL, degassed) was sequentially added $Pd(PPh_3)_4$ (8 mg, 0.0068 mmol), Me-9-B-BBN 189 (378 μL, 0.68 mmol, 1.8 M in THF), TlOEt (9 μL, 0.12 mmol), and H_2O (0.6 mL, degassed). The yellow slurry was stirred in the dark for 23 h. HPLC analysis of the reaction mixture showed complete consumption of starting material 200. The resulting dark slurry was filtered through a bed of Celite and rinsed with ether (100 mL). Solvent was removed in vacuo. Flash chromatography of the residue (petroleum ether–ether: 20:1) gave 36.6 mg (81%) of 201 as a colorless oil. Further purification by HPLC (silica gel, 4 mL/min, 269 nm detection, 0→3% gradient EtOAc/hexanes) gave 29 mg (64%) of analytically pure **29** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (s, 1H), 6.05 (d, J=16.0 Hz, 1H), 6.04 (s, 1H), 5.43 (dd, J=16.0, 7.0 Hz, 1H), 5.38 (t, J=7.0 Hz, 1H), 5.20 (dt, J=10.0, 1.5 Hz, 1H), 4.23 (m, 2H), 3.91 (t, J=6.0 Hz, 1H), 3.61 (t, J=7.0 Hz, 2H), 2.33 (q, J=7.0 Hz, 2H), 2.29 (m, 1H), 2.01 (d, J=1.5 Hz, 3H), 1.82 (d, J=1.0 Hz, 3H), 1.76 (s, 3H), 1.68 (s, 3H), 1.03 (m, 2H), 0.89 (d, J=7.0 Hz, 3H), 0.87 (s, 9H), 0.86 (s, 9H), 0.04 (s, 9H), 0.02 (s, 6H), 0.00 (s, 3H), −0.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 142.8, 134.9, 134.7, 134.6, 133.2, 133.1, 131.5, 129.2, 127.9, 126.2, 77.5, 62.8, 62.7, 40.8, 32.1, 25.9, 23.6, 18.3, 18.2, 18.0, 17.4, 15.4, 14.1, 12.6, −1.4, −4.1, −4.8, −5.2, −5.3; HRMS (ESI) m/z 685.4479 [$(M+Na)^+$, calcd for $C_{37}H_{70}O_4Si_3Na$ 685.4480].

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