

## PAPER

View Article Online  
View Journal | View IssueCite this: *RSC Adv.*, 2019, 9, 32210Received 3rd September 2019  
Accepted 2nd October 2019

DOI: 10.1039/c9ra07050h

rsc.li/rsc-advances

## Suzuki coupling-based synthesis of VATPase inhibitor archazolid natural product derived fragments†

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An archazolid natural product fragment that displays dose-dependent inhibition of the vacuolar-type ATPase (VATPase) has been synthesized by a high-yielding Suzuki coupling of two complex subunits. Similarly, a further simplified fragment was prepared and evaluated for VATPase inhibitory activity. This compound did inhibit the VATPase, as evidenced by growth inhibition of etiolated *Arabidopsis* seedlings, however at approximately 10× lower potency than the more complex fragment. Cyclooxygenase (COX) enzyme inhibition was not observed for either fragment.

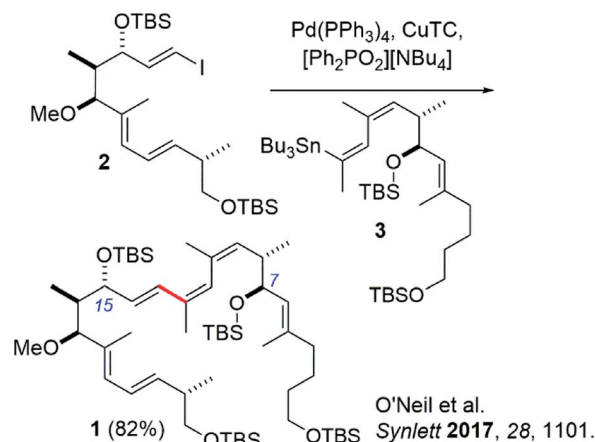
## Introduction

Recently our group reported the synthesis of an archazolid natural product fragment (**1**) that, after removal of the TBS protecting groups, displayed dose-dependent inhibition of the vacuolar-type ATPase (VATPase).<sup>1</sup> The VATPase has continued to emerge as a promising therapeutic target associated with several severe forms of cancer, as evidenced by a number of recent studies involving the archazolids.<sup>2–10</sup> Key to our synthesis of **1** was a high-yielding Stille coupling between iodide **2** and stannane **3** to complete the conjugated *Z,Z,E*-triene (Scheme 1).<sup>11</sup> This particular triene is unique to the archazolids and happens to link two important pharmacophoric elements, the C7- and C15 hydroxyl groups.<sup>12</sup>

While promising, others have commented on the drawbacks of Stille couplings due to the toxicity associated with organotin compounds.<sup>13,14</sup> In line with these recommendations, we set out to investigate a tin-free synthesis of our VATPase inhibitor lead compound. Herein we report a similarly effective Suzuki coupling strategy to synthesize compound **1**, in which tin has been replaced by a boronic acid derivative. We argue that this new approach represents to date the most direct, convergent, and a greener method for synthesizing the important triene region of this exciting class of compounds.

## Results and discussion

Tin featured not only in our Stille coupling, but also in our synthesis of vinyl iodide **2**,<sup>1</sup> which was prepared by palladium catalyzed hydrostannylation followed by iododestannylation (Scheme 2). To circumvent the use of tin in this instance, we opted instead to carry the TMS-protected alkynyl phosphonate **4**, prepared in a single step from known Weinreb amide **5**,<sup>15</sup> into a Horner–Wadsworth–Emmons (HWE) olefination<sup>16</sup> with aldehyde **6**.<sup>17</sup> This reaction delivered ketone **7** in 72% yield and >10 : 1 *E* : *Z* selectivity by NMR analysis. The ketone in **7** was diastereoselectively reduced with NaBH<sub>4</sub> and the resulting hydroxyl converted to the corresponding methyl ether by deprotonation with LiHMDS and alkylation with methyl iodide. Removal of the TMS group (K<sub>2</sub>CO<sub>3</sub>/MeOH) revealed the terminal



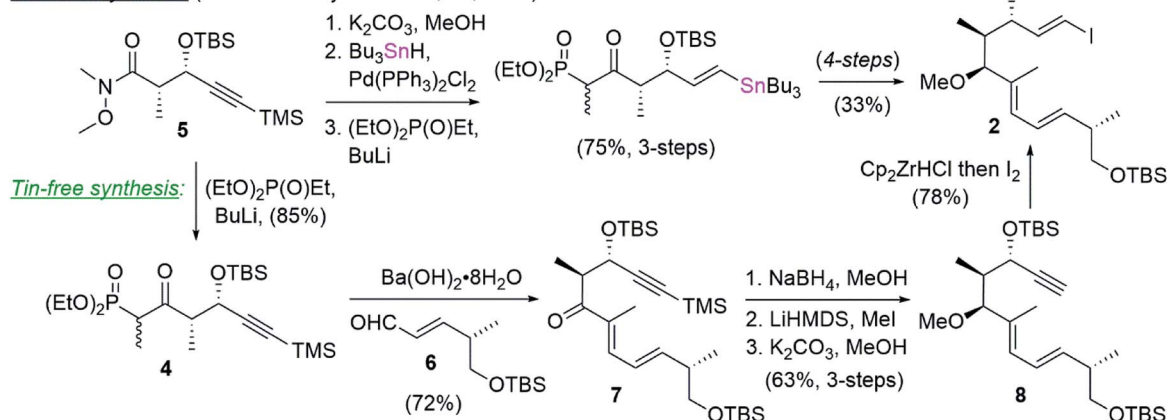
Scheme 1 Previous synthesis of archazolid-based VATPase inhibitor compound **1** by Stille coupling.

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† Electronic supplementary information (ESI) available: Copies of NMR spectra for compounds **1**, **2**, **4**, **7**, **8**, **10**, **13–15**, and **17–20**. VATPase and COX assay procedures and results. See DOI: 10.1039/c9ra07050h

*Previous synthesis* (O'Neil et al. *Synlett* **2017**, 28, 1101):



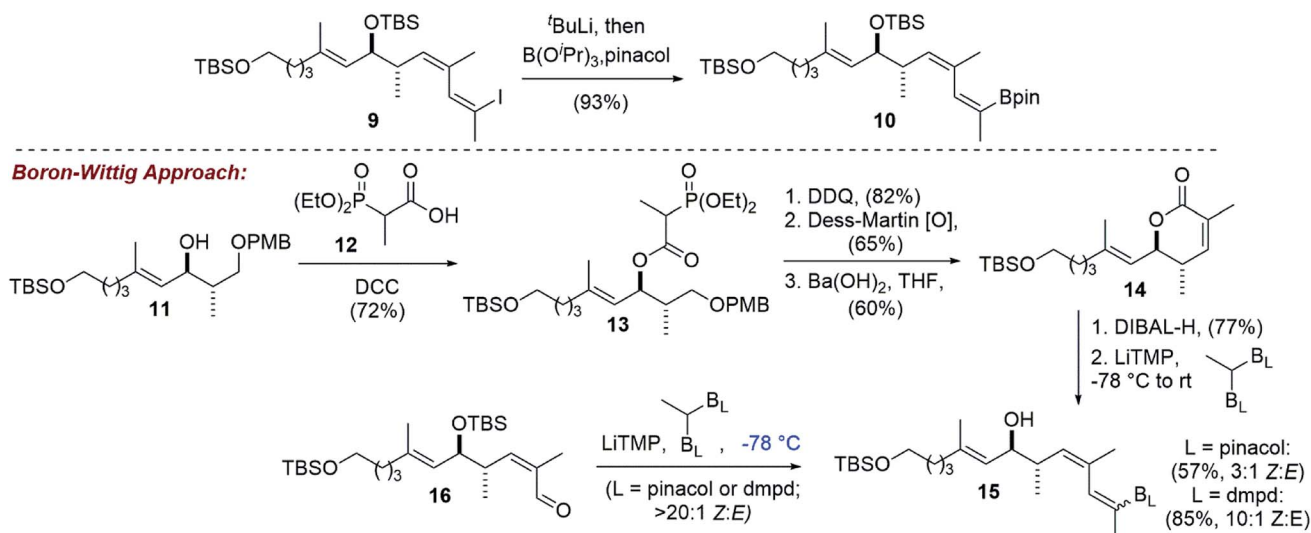
Scheme 2 An alternative tin-free synthesis of vinyl iodide 2.

alkyne in **8** and set the stage for vinyl iodide installation by treatment with Schwartz's reagent and trapping with iodine.<sup>18</sup> In this way, vinyl iodide coupling partner **2** was completed in comparable yields and one fewer step from compound **4** than had previously been described (*i.e.* 6-steps and 36% overall yield *vs.* 7-steps and 25% yield) while also avoiding the use of tin.

Adapting our vinyl stannane synthesis to incorporate a vinyl boronic ester was possible from advanced vinyl iodide **9** by trapping with B(<sup>i</sup>PrO)<sub>3</sub> rather than Bu<sub>3</sub>SnCl after lithium-halogen exchange (Scheme 3).<sup>19</sup> Treatment with pinacol then allowed for isolation of vinyl pinacol boronate **10** in 93% yield. In an attempt to reduce the step count of our vinyl boronic ester synthesis, we became interested in evaluating a potential boron-Wittig reaction. This chemistry was pioneered by Endo and coworkers<sup>20</sup> and more recently has been expanded upon by the Morken group.<sup>21,22</sup> To that end, intermediate **11** was acylated with phosphonate acid **12**<sup>23</sup> using DCC, giving ester **13** in 72%

yield. Removal of the PMB protecting group and oxidation of the resulting primary hydroxyl then allowed for an intramolecular HWE reaction. It was found that Ba(OH)<sub>2</sub> gave the best overall yields of lactone **14**, with some other reagents (*e.g.* KHMDS, DBU/LiCl) leading primarily to elimination. Reduction of **14** with DIBAL-H produced the corresponding lactol, that we thought could be converted directly to the desired *E*-vinyl boronic ester **15** by treatment with the lithium anion of a geminal bis(boronate). However, using Morken's procedure<sup>21</sup> for the conversion of aldehydes to tri-substituted vinyl pinacol boronates (LiTMP, −78 °C) using 1,1-bis(pinacolboronato) ethane, no reaction was observed.

We reasoned that the lactol was less reactive than an aldehyde in these reactions, and therefore repeated the experiment allowing the reaction to slowly warm to room temperature. Under these conditions, the vinyl boronate ester product **15** was indeed obtained, albeit as a 3 : 1 mixture of geometrical isomers



Scheme 3 Vinyl boronic ester synthesis by lithium-halogen exchange and an alternative boron-Wittig approach that gave primarily the undesired *Z*-vinyl boronate.



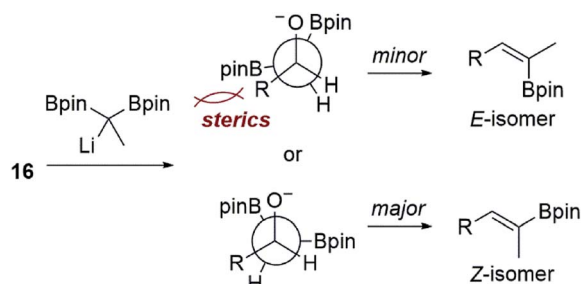
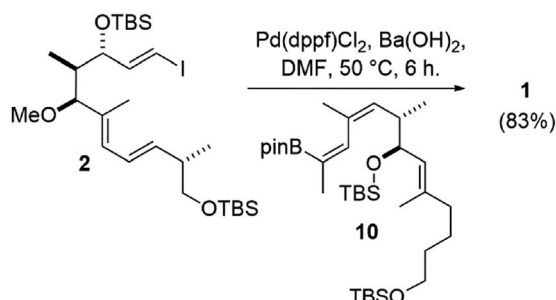
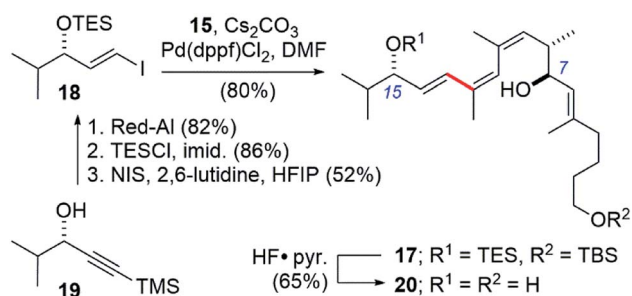


Fig. 1 Possible stereochemical rationale for the *E:Z* selectivity observed in our boron-Wittig reactions with the lactol derived from **13** or aldehyde **15** shown in Scheme 3.



Scheme 4 Synthesis of the archazolid conjugated triene by Suzuki coupling.



Scheme 5 Synthesis of a simplified archazolid fragment **20** containing the pharmacophoric C7- and C15-hydroxyls linked by the *Z,Z,E*-triene.

by NMR analysis. Using 2D-NMR techniques (*e.g.* COSY and NOESY), it was determined that the major product from this reaction was the undesired *Z*-vinyl boronate. Morken's group had reported that in some cases switching to the dimethylpentanediolato (dpmd) diboronate led to a reversal of stereoselectivity when compared to the pinacol diboronate.<sup>21</sup> Unfortunately, the reaction with 1,1-bis(dimethylpentanediolato)ethane was even more selective for the undesired *Z*-vinyl boronic ester (10 : 1 *Z* : *E*). When using aldehyde **16**, reactions that proceeded at the colder temperatures ( $-78^{\circ}\text{C}$ ) prescribed by Endo and Morken,<sup>20,21</sup> both diboronates gave exclusively the undesired *Z*-vinyl boronic ester products. We can perhaps rationalize the stereochemical outcome of these reactions by considering a steric clash between the *R* group from the substrate and one of the boronic esters after addition of the

lithiated diboronate and upon rotation into a conformation with the O- and B-groups *syn*-coplanar that is required for elimination (Fig. 1).<sup>20,22</sup>

Nonetheless, the *E/Z* isomers from the boron-Wittig reactions were separable by chromatography on silica. Combined with our lithium-halogen exchange approach, sufficient quantities of the desired *Z,E*-boronic esters **10** and **15** were obtained to then investigate a Suzuki coupling with vinyl iodide **2**.<sup>1</sup> Gratifyingly, it was found that the use of 10 mol% Pd(dppf)Cl<sub>2</sub> and Ba(OH)<sub>2</sub> as base<sup>24</sup> in DMF at 50 °C for 6 h gave the coupled product **1** in comparable yield to what was previously obtained from a Stille coupling<sup>1</sup> (83% for the Suzuki *vs.* 82% from Stille coupling, Scheme 4).

We also took this opportunity to prepare a further simplified archazolid fragment **17** (Scheme 5). The requisite vinyl iodide **18** was prepared from alkynol **19**, available in by enantioselective Noyori reduction<sup>25</sup> of the corresponding alkynone.<sup>26</sup> Red-Al reduction of the alkyne in **19** to the *trans*-alkene, TES protection of the alcohol, and iododesilylation of the TMS group gave **18** in 37% yield for the three steps. The Suzuki coupling with boronic ester **10** again proceeded efficiently, in this case using Pd(dppf)Cl<sub>2</sub> and Cs<sub>2</sub>CO<sub>3</sub> as base in DMF at room temperature,<sup>27</sup> giving the coupled product **17** in 80% yield.

Given that **17** contained an intact C7–C15 region of the archazolids, we suspected this compound might exhibit VAT-Pase inhibitory activity and opted to assay the desilylated compound **20** using our *Arabidopsis*-based method.<sup>28,29</sup> As shown in Fig. 2, while **20** did exhibit dose dependent growth inhibition of etiolated *Arabidopsis* as an indicator for impaired VATPase function, its activity was significantly lower ( $\sim 10\times$  less potent) than compound **1**. This data suggests that while the C7–C15 segment of the archazolids is important for VATPase binding, additional functionality present in compound **1** also contributes to its effectiveness as a VATPase inhibitor.

Compound **20** is similar the predicted cyclooxygenase (COX) enzyme inhibitor **Arca-1**<sup>30</sup> (Fig. 3). When tested using a commercial COX screening assay for inhibition of COX-1 and COX-2,<sup>31</sup> no measurable inhibition was observed at concentrations up to 200  $\mu\text{M}$ . This was also true for compound **1**, which we previously postulated could be due to its large size and/or lack of a carboxylic acid terminus.<sup>1</sup> The latter might also apply to compound **20**, however neither rationale would explain the modest reported COX inhibitory activity of archazolid A<sup>30</sup> which is both sterically large and lacks a carboxylic acid.

## Conclusions

We have devised and executed a high-yielding Suzuki coupling-based synthesis of the challenging yet biologically important conjugated triene region of the archazolid natural products. The vinyl iodide synthesis reported here represents an improvement over our previous approach in terms of step count, yield, and avoidance of hazardous tin compounds. Two different vinyl boronic ester syntheses were investigated. Ultimately it was found that while a boron-Wittig reaction did give some of the desired compound, the majority of product obtained was the undesired geometrical isomer. The isomers



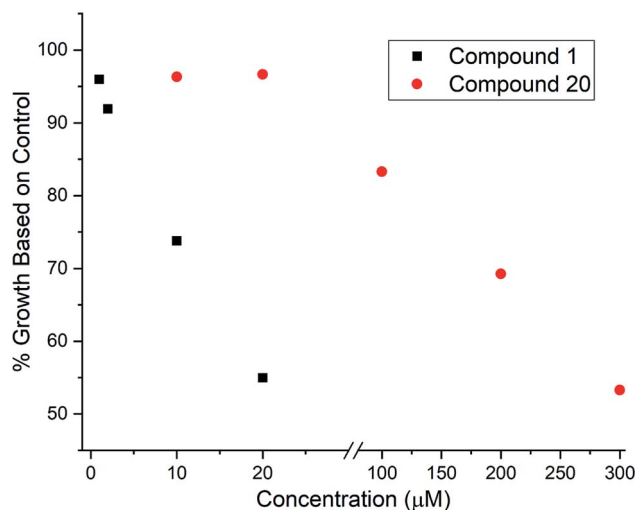


Fig. 2 VATPase assay results for compound **1** (after TBS removal) and compound **20** where % growth relative to control represents the average hypocotyl length for 40–60 *Arabidopsis* seedlings at the concentrations indicated relative to the average hypocotyl length of *Arabidopsis* seedlings grown in the absence of any inhibitors.

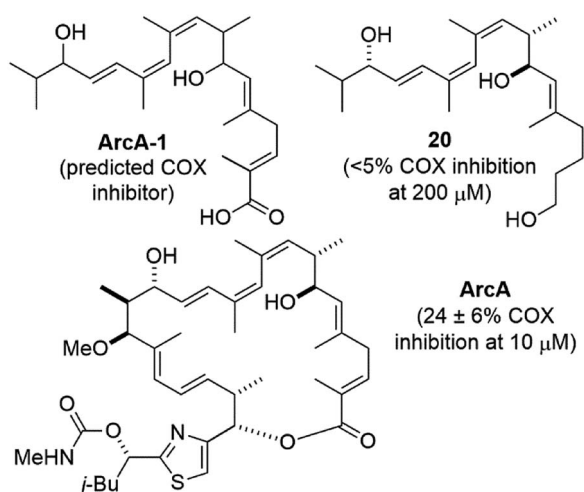


Fig. 3 Structures and cyclooxygenase (COX) inhibitory activity of proposed COX inhibitor **ArcA-1**,<sup>30</sup> archazolid A (**ArcA**), and compound **20**.

were, however, separable and combined with an alternative iodo-Wittig followed by lithium–halogen exchange-based synthesis, sufficient amounts of the correct boronic ester isomer were obtained to then conduct Suzuki couplings. In this way, an archazolid natural product fragment **1** that had previously exhibited dose dependent VATPase inhibition along with a further simplified fragment **20** were synthesized. Compound **20** also showed dose dependent VATPase inhibition in our *Arabidopsis* VATPase assay, however with approximately 10× less potency than compound **1**. The assay results support the importance of the C7–C15 region of the archazolids for VATPase inhibitory activity, but suggest additional functionality is needed for efficient VATPase inhibition. Compound **20** was also

assayed for COX inhibitory activity based on its similarity to a predicted COX inhibitor. However, like compound **1**, in our assay no measurable COX inhibition was observed for compound **20**. Further studies are underway to better understand the interactions of compounds **1** and **20** with VATPase and COX enzymes toward the design of more efficient inhibitors with therapeutic potential.

## Experimental section

### General information

All reactions were carried out under N<sub>2</sub> in flame-dried glassware. IR: Nicolet iS10 spectrometer, wavenumbers ( $\tilde{\nu}$ ) in cm<sup>−1</sup>. The solvents used were dried by passing the solvent through a column of activated alumina under nitrogen immediately prior to use. All reagents were purchased and used as received unless otherwise mentioned. All TLC analysis used 0.25 mm silica layer fluorescence UV<sub>254</sub> plates. Flash chromatography: SilaCycle silica gel P60 (230–400 mesh). NMR: spectra were recorded on a Varian Mercury 300, or Inova 500 spectrometer in the solvents indicated; chemical shifts ( $\delta$ ) are given in ppm, coupling constants ( $J$ ) in Hz. The solvent signals were used as references (C<sub>6</sub>D<sub>6</sub>:  $\delta_C \equiv 128.0$  ppm; residual C<sub>6</sub>H<sub>6</sub> in C<sub>6</sub>D<sub>6</sub>:  $\delta_H \equiv 7.16$  ppm; CDCl<sub>3</sub>:  $\delta_C \equiv 77.0$  ppm; residual CHCl<sub>3</sub> in CDCl<sub>3</sub>:  $\delta_H \equiv 7.26$  ppm).

**Diethyl ((4*S*,5*S*)-5-((*tert*-butyldimethylsilyl)oxy)-4-methyl-3-oxo-7-(trimethylsilyl)hept-6-yn-2-yl)phosphonate (**4**).** To a solution of diethyl ethylphosphonate (1.02 g, 6.15 mmol) in THF (14 mL) at −78 °C was added a solution of *n*-butyllithium (2.46 mL, 2.5 M in hexanes) and the mixture was stirred for 20 min. Weinreb amide **5**<sup>15</sup> (1.0 g, 2.8 mmol) was then added and the reaction was stirred for 30 min before quenching with aq. NH<sub>4</sub>Cl (50 mL) and extracting with EtOAc (2 × 50 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (1 : 1 hexanes : ethyl acetate) afforded phosphonate **4** (1.1 g, 85%) as an oil.

**Spectral data for the major diastereomer.** IR (ATR): 3036, 29 078, 1710, 1635, 1460, 1364, 1191, 1077, 910, 778 cm<sup>−1</sup>. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  4.24 (d,  $J = 8.1$  Hz, 1H), 4.13 (q,  $J = 6.4$  Hz, 2H), 4.11 (q,  $J = 6.4$  Hz, 2H), 3.70 (dq,  $J_{HP} = 26.0$  Hz,  $J_{HH} = 6.7$  Hz, 1H), 3.30 (m, 1H), 1.33 (d,  $J = 7.0$  Hz, 3H), 1.32 (t,  $J = 7.0$  Hz, 3H), 1.31 (t,  $J = 7.0$  Hz, 3H), 1.14 (d,  $J = 6.6$  Hz, 3H), 0.89 (s, 9H), 0.14 (s, 3H), 0.13 (s, 9H), 1.11 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  207.1, 105.0, 91.2, 65.5, 62.5 (t,  $J_{CP} = 6.4$  Hz, 1C), 54.2, 48.4, 47.5, 25.70, 25.67, 18.2, 16.4 (t,  $J_{CP} = 5.4$  Hz, 1C), 13.2, 10.6 ( $J_{CP} = 6.2$  Hz, 1C), −0.3, −0.4, −4.5, −5.1. HRMS-TOF (ESI<sup>+</sup>) calcd for C<sub>21</sub>H<sub>43</sub>O<sub>5</sub>PSi<sub>2</sub>Na<sup>+</sup> (M + Na): 485.2284. Found 485.2279.

**(5*S*,6*S*,8*E*,10*E*,12*S*)-2,2,3,3,6,8,12,15,15,16,16-Undecamethyl-5-((trimethylsilyl)ethynyl)-4,14-dioxo-3,15-disilaheptadeca-8,10-dien-7-one (**7**).** Ba(OH)<sub>2</sub>·8H<sub>2</sub>O (1.8 g, 5.73 mmol) was first activated by heating under vacuum at 130 °C for 1.5 h and then cooled to room temperature before adding THF (10 mL) and phosphonate **4** (1.1 g, 2.4 mmol) and the mixture was stirred for 30 min. Aldehyde **6**<sup>17</sup> (0.66 g, 2.9 mmol) was then added and the reaction was stirred for 8 h before quenching with aq. NaHCO<sub>3</sub>





(30 mL) and extracting with MTBE ( $2 \times 30$  mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (20 : 1 to 10 : 1 hexanes : ethyl acetate) afforded **7** (0.93 g, 72%) as an oil.

$[\alpha]_{\text{D}}^{20} = -2.8$  ( $c$  1.0,  $\text{CH}_2\text{Cl}_2$ ). IR (ATR) 3064, 2903, 1735, 1640, 1350, 1194, 1067, 910, 730  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.07 (d,  $J = 10.9$  Hz, 1H), 6.48 (ddd,  $J = 15.0, 10.9, 1.1$  Hz, 1H), 6.08 (dd,  $J = 15.2, 7.5$  Hz, 1H), 4.38 (d,  $J = 10.5$  Hz, 1H), 3.60–3.47 (m, 3H), 2.50 (p,  $J = 6.6$  Hz, 1H), 1.88 (s, 3H), 1.15 (d,  $J = 7.0$  Hz, 3H), 1.06 (d,  $J = 7.0$  Hz, 3H), 0.91 (s, 9H), 0.89 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H), 0.06 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  203.5, 146.2, 139.3, 134.7, 126.3, 106.1, 90.1, 67.4, 65.7, 46.8, 40.3, 25.9, 25.8, 18.3, 16.3, 14.6, 11.8,  $-0.4$ ,  $-4.5$ ,  $-5.1$ ,  $-5.3$ . HRMS-TOF (ESI+) calcd for  $\text{C}_{29}\text{H}_{56}\text{O}_3\text{Si}_3\text{Na}^+$  ( $M + \text{Na}$ ): 559.3435. Found 559.3428.

**(5S,6R,7S,8E,10E,12S)-2,2,3,3,6,8,12,15,15,16,16-Undecamethyl-5-((trimethylsilyl)ethynyl)-4,14-dioxo-3,15-disilaheptadeca-8,10-dien-7-ol**. To a solution of ketone **7** (0.2 g, 0.37 mmol) in MeOH (1.0 mL) and THF (1.0 mL) at  $0^\circ\text{C}$  was added  $\text{NaBH}_4$  (54 mg, 1.44 mmol) and the mixture was stirred and allowed to slowly warm to room temperature for 2 h. The reaction was quenched with brine (15 mL) and extracted with MTBE ( $2 \times 15$  mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (20 : 1 to 10 : 1 hexanes : ethyl acetate) afforded the alcohol (0.93 g, 72%) as an oil.

$[\alpha]_{\text{D}}^{20} = -4.6$  ( $c$  1.0,  $\text{CH}_2\text{Cl}_2$ ). IR (ATR) 3201, 2958, 2930, 2859, 1447, 1371, 1308, 1221, 1143, 1085, 1024, 755, 699  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  6.37 (ddd,  $J = 15.2, 10.8, 1.2$  Hz, 1H), 6.13 (dd,  $J = 11.0, 1.5$  Hz, 1H), 5.58 (dd,  $J = 15.2, 7.5$  Hz, 1H), 5.03 (d,  $J = 2.5$  Hz, 1H), 4.14 (dd,  $J = 9.0, 2.8$  Hz, 1H), 3.49 (dd,  $J = 9.6, 5.9$  Hz, 1H), 3.38 (dd,  $J = 9.6, 6.8$  Hz, 1H), 2.41 (hept,  $J = 6.7$  Hz, 1H), 2.12 (d,  $J = 2.9$  Hz, O–H), 2.00 (dq,  $J = 9.3, 6.9, 2.5$  Hz, 1H), 1.64 (s, 3H), 1.08 (d,  $J = 7.0$  Hz, 3H), 1.04 (d,  $J = 6.8$  Hz, 3H), 1.02 (s, 9H), 0.97 (s, 9H), 0.29 (s, 3H), 0.19 (s, 3H), 0.17 (s, 9H), 0.05 (s, 6H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  137.3, 137.0, 126.1, 107.6, 90.0, 79.6, 68.2, 65.0, 43.0, 40.2, 31.9, 26.1, 26.0, 23.0, 18.52, 18.45, 16.9, 14.3, 11.6, 11.5,  $-0.1$ ,  $-4.2$ ,  $-5.0$ ,  $-5.20$ ,  $-5.24$ . HRMS-TOF (ESI+) calcd for  $\text{C}_{29}\text{H}_{58}\text{O}_3\text{Si}_3\text{Na}^+$  ( $M + \text{Na}$ ): 561.3591. Found 561.3591.

**(6S,7E,9E,11S,12R,13S)-13-Ethynyl-11-methoxy-2,2,3,3,6,10,12,15,15,16,16-undecamethyl-4,14-dioxo-3,15-disilaheptadeca-7,9-diene (8)**. To a solution of the intermediate alcohol in THF (3.7 mL) at  $-78^\circ\text{C}$  was added a solution of  $\text{LiHMDS}$  (0.44 mL, 1.0 M in toluene) at  $-78^\circ\text{C}$  and the mixture was stirred for 20 min. Iodomethane (50  $\mu\text{L}$ , 0.74 mmol) was then added and the reaction was allowed to slowly warm to room temperature over 15 h before quenching with  $\text{NaHCO}_3$  (30 mL) and extracting with MTBE ( $2 \times 30$  mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. The crude methyl ether product was redissolved in MeOH (3.0 mL) and THF (1.0 mL) and the solution was cooled to  $0^\circ\text{C}$  before adding  $\text{K}_2\text{CO}_3$  (0.1 g, 0.72 mmol) and the mixture was slowly warmed to room temperature over 6 h. The reaction was quenched with aq.  $\text{NH}_4\text{Cl}$  (50 mL) and extracted

with MTBE ( $2 \times 30$  mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (20 : 1 to 10 : 1 hexanes : ethyl acetate) afforded **8** (0.11 g, 63% 3-steps) as an oil.

$[\alpha]_{\text{D}}^{20} = -3.4$  ( $c$  1.0,  $\text{CH}_2\text{Cl}_2$ ). IR (ATR) 2958, 2930, 2859, 1447, 1371, 1308, 1221, 1143, 1085, 1024, 755, 699  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  6.39 (dd,  $J = 15.2, 10.8$  Hz, 1H), 6.09 (d,  $J = 10.0$  Hz, 1H), 5.55 (dd,  $J = 15.2, 7.6$  Hz, 1H), 5.22 (t,  $J = 2.0$  Hz, 1H), 3.53 (d,  $J = 10.0$  Hz, 1H), 3.46 (dd,  $J = 9.7, 6.1$  Hz, 1H), 3.37 (dd,  $J = 9.7, 6.8$  Hz, 1H), 3.09 (s, 3H), 2.40 (p,  $J = 6.9$  Hz, 1H), 2.03 (d,  $J = 2.1$  Hz, 1H), 2.02 (m, 1H), 1.59 (d,  $J = 1.3$  Hz, 3H), 1.12 (d,  $J = 6.9$  Hz, 3H), 1.04 (s, 9H), 1.02 (d,  $J = 6.7$  Hz, 3H), 0.97 (s, 9H), 0.29 (s, 3H), 0.18 (s, 3H), 0.04 (s, 6H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  137.3, 133.6, 130.3, 125.5, 87.6, 85.7, 72.3, 67.8, 61.8, 55.2, 42.7, 39.9, 25.7, 18.2, 18.1, 16.4, 10.3, 10.0,  $-4.6$ ,  $-5.5$ ,  $-5.57$ ,  $-5.59$ . HRMS-TOF (ESI+) calcd for  $\text{C}_{27}\text{H}_{52}\text{O}_3\text{Si}_2\text{Na}^+$  ( $M + \text{Na}$ ): 503.3353. Found 503.3354.

**(6S,7E,9E,11S,12R,13S)-13-((E)-2-Iodovinyl)-11-methoxy-2,2,3,3,6,10,12,15,15,16,16-undecamethyl-4,14-dioxo-3,15-disilaheptadeca-7,9-diene (2)**. To a solution of alkyne **8** (0.1 g, 0.21 mmol) in THF (2.0 mL) was added zirconocene hydrochloride (30 mg, 0.1 mmol) and the mixture was stirred at room temperature for 20 min before adding additional zirconocene hydrochloride (30 mg, 0.1 mmol). After another 20 min at room temperature, iodine (66 mg, 0.26 mmol) was added and the solution was stirred for 30 min. The reaction was then diluted with hexanes (10 mL) and filtered through a pad of celite. The resulting solution was washed with sat. aq.  $\text{Na}_2\text{S}_2\text{O}_3$  ( $2 \times 15$  mL) and brine (15 mL). The organic phase was dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (10 : 1 hexanes : ethyl acetate) afforded **2** (0.1 g, 78%) as an oil.

$[\alpha]_{\text{D}}^{20} = -7.8$  ( $c$  1.0,  $\text{CH}_2\text{Cl}_2$ ). IR (ATR) 2955, 2928, 2865, 1450, 1370, 1310, 1235, 1121, 1065, 978, 884, 755, 699  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.55 (dd,  $J = 14.4, 6.0$  Hz, 1H), 6.29 (ddd,  $J = 15.2, 10.8, 1.2$  Hz, 1H), 6.19 (dd,  $J = 14.4, 1.3$  Hz, 1H), 5.89 (dd,  $J = 10.7, 1.5$  Hz, 1H), 5.60 (dd,  $J = 15.3, 7.4$  Hz, 1H), 4.62 (d,  $J = 6.0$  Hz, 1H), 3.51 (dd,  $J = 9.7, 6.4$  Hz, 1H), 3.43 (dd,  $J = 9.7, 6.9$  Hz, 1H), 3.31 (d,  $J = 9.9$  Hz, 1H), 3.11 (s, 3H), 2.40 (p,  $J = 6.7$  Hz, 1H), 1.62 (m, 1H), 1.59 (s, 3H), 1.03 (d,  $J = 6.8$  Hz, 3H), 0.92 (s, 9H), 0.89 (s, 9H), 0.63 (d,  $J = 7.0$  Hz, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  149.2, 137.3, 133.4, 130.3, 125.4, 87.9, 75.5, 73.2, 67.9, 55.5, 41.2, 39.7, 29.7, 18.4, 18.2, 16.5, 10.5, 8.9,  $-4.1$ ,  $-5.29$ ,  $-5.32$ . HRMS-TOF (ESI+) calcd for  $\text{C}_{27}\text{H}_{53}\text{IO}_3\text{Si}_2\text{Na}^+$  ( $M + \text{Na}$ ): 631.2476. Found 631.2476.

**(S,E)-2,2,3,3,7,11,11,12,12-Nonamethyl-5-((S,3Z,5E)-4-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-3,5-dien-2-yl)-4,10-dioxo-3,11-disila-tridec-6-ene (10)**. To a solution  $^t\text{BuLi}$  (0.1 mL, 1.7 M solution in pentane) in  $\text{Et}_2\text{O}$  (1.0 mL) at  $-78^\circ\text{C}$  was added iodide **9** (50 mg, 0.08 mmol) and the mixture was stirred for 5 min before adding triisopropoxyborate (30  $\mu\text{L}$ , 1.5 mmol) and the reaction was stirred for 30 min. Pinacol (20 mg, 2.0 mmol) was then added and the solution was warmed to room temperature and stirred for 15 h. The reaction was diluted with MTBE (20 mL) and washed with aq.  $\text{NH}_4\text{Cl}$  (20 mL),



water (20 mL), and brine (20 mL). The organic phase was dried over  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. Purification by flash column chromatography on silica (10 : 1 hexanes : ethyl acetate) afforded **10** (45 mg, 93%) as an oil.

$[\alpha]_D^{20} = +3.2$  (c 1.0,  $\text{CH}_2\text{Cl}_2$ ). IR (ATR) 3056, 2973, 1640, 1565, 1350, 1194, 1067, 910, 730  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.70 (s, 1H), 5.10 (dd,  $J = 9.1, 1.2$  Hz, 1H), 5.05 (d,  $J = 9.8$  Hz, 1H), 4.16 (dd,  $J = 9.0, 5.5$  Hz, 1H), 3.60 (t,  $J = 6.2$  Hz, 2H), 2.65 (ddd,  $J = 9.7, 6.9, 5.6$  Hz, 1H), 1.97 (s, 2H), 1.88 (d,  $J = 1.6$  Hz, 3H), 1.85 (d,  $J = 1.4$  Hz, 3H), 1.57 (d,  $J = 1.4$  Hz, 3H), 1.53–1.40 (m, 4H), 1.28 (s, 9H), 0.89 (s, 12H), 0.87 (d,  $J = 7.0$  Hz, 3H), 0.85 (s, 9H), 0.04 (s, 6H),  $-0.01$  (s, 3H),  $-0.04$  (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  138.1, 135.3, 133.4, 132.7, 127.2, 83.3, 72.9, 63.0, 39.4, 39.4, 32.5, 26.0, 25.90, 25.86, 24.8, 24.7, 24.0, 23.9, 23.0, 18.4, 18.2, 16.7, 16.0,  $-4.3$ ,  $-4.8$ ,  $-5.3$ . HRMS-TOF (ESI+) calcd for  $\text{C}_{34}\text{H}_{67}\text{BO}_4\text{Si}_2\text{Na}^+$  (M + Na): 629.4569. Found 629.4572.

**(2S,3R,E)-9-((tert-Butyldimethylsilyl)oxy)-1-((4-methoxybenzyl)oxy)-2,5-dimethylnon-4-en-3-yl 2-(diethoxyphosphoryl) propanoate (13).** To a solution of alcohol **11** (500 mg, 1.2 mmol) and phosphate **12** (249 mg, 1.2 mmol) in DCM (1.6 mL) at  $0^\circ\text{C}$  was added DCC (293 mg, 1.42 mmol) and the solution was allowed to warm to room temperature and stir for 24 h. The reaction mixture was filtered through celite, diluted with  $\text{H}_2\text{O}$  (10 mL), and extracted with DCM ( $2 \times 10$  mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. Purification by flash column chromatography on silica (4 : 1 to 1 : 1 to 1 : 2 hexanes : ethyl acetate) afforded ester **13** (604 mg, 82%) as an oil.

**Spectral data for the mixture of diastereomers.** IR (ATR) 2931, 2856, 1730, 1612, 1586, 1513, 1460, 1386, 1301, 1246, 1172, 1093, 1023, 962, 904, 834, 818, 774, 734, 661  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.25–7.22 (m, 4H), 6.86 (d,  $J = 8.7$  Hz, 4H), 5.61 (dd,  $J = 9.7, 6.5$  Hz, 1H), 5.57 (dd,  $J = 9.7, 6.7$  Hz, 1H), 5.09 (d,  $J = 9.7$  Hz, 2H), 4.41 (d,  $J = 10.2$  Hz, 2H), 4.37 (d,  $J = 10.2$  Hz, 2H), 4.16–4.07 (m, 8H), 3.80 (s, 6H), 3.59 (t,  $J = 5.9$  Hz, 4H), 3.42 (dd,  $J = 9.3, 5.8$  Hz, 1H), 3.35 (dd,  $J = 9.3, 6.1$  Hz, 1H), 3.30 (dd,  $J = 9.3, 6.3$  Hz, 1H), 3.31 (dd,  $J = 9.3, 6.1$  Hz, 1H), 2.95 (dq,  $J = 23.3, 7.4$  Hz, 2H), 2.16 (m, 12H), 2.11 (m, 2H), 2.02 (m, 4H), 1.72 (s, 6H), 1.47–1.36 (m, 8H), 1.33–1.27 (m, 6H), 0.93 (d,  $J = 7.0$  Hz, 3H), 0.92 (d,  $J = 7.0$  Hz, 3H), 0.88 (s, 18H), 0.03 (s, 12H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  159.1, 142.3, 130.6, 129.2, 120.4, 113.72, 113.70, 73.7, 72.7, 71.7, 62.9, 62.5, 55.3, 40.0, 39.5, 37.8, 32.41, 32.35, 26.0, 24.0, 18.4, 16.8, 12.7, 11.8,  $-5.3$ . HRMS-TOF (ESI+) calcd for  $\text{C}_{32}\text{H}_{57}\text{O}_8\text{PSiNa}^+$  (M + Na): 651.3458. Found 651.3458.

**(2S,3R,E)-9-((tert-Butyldimethylsilyl)oxy)-1-hydroxy-2,5-dimethylnon-4-en-3-yl-2-(diethoxyphosphoryl)propanoate.** To a solution of **13** (250 mg, 0.398 mmol) in a DCM :  $\text{H}_2\text{O}$  mixture (20 mL : 0.2 mL), DDQ (180 mg, 0.795 mmol) was added portion wise and stirred at room temperature for 1 h. The resulting solution was quenched with aqueous sodium bicarbonate (50 mL) and extracted with DCM ( $2 \times 50$  mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. Purification by flash column chromatography on silica (1 : 2 to 0 : 1 hexanes : ethyl acetate) afforded the corresponding alcohol (168 mg, 83%) as an oil.

**Spectral data for the mixture of diastereomers.** IR (ATR) 3406, 2928, 2856, 1471, 1455, 1384, 1360, 1253, 1100, 1081, 1030, 1002, 977, 935, 834, 773, 737, 661  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.43 (dd,  $J = 8.7, 8.7$  Hz, 1H), 5.39 (dd,  $J = 9.4, 9.4$  Hz, 1H), 5.11 (d,  $J = 9.2$  Hz, 1H), 5.06 (d,  $J = 9.8$  Hz, 1H), 4.17–4.09 (m, 8H), 3.75 (dd,  $J = 11.5, 3.3$  Hz, 1H), 3.64 (dd,  $J = 11.5, 3.8$  Hz, 1H), 3.58 (t,  $J = 6.1$  Hz, 4H), 3.50 (dd,  $J = 11.0, 4.9$  Hz, 1H), 3.48 (dd,  $J = 11.5, 4.5$  Hz, 1H), 2.99 (dq,  $J = 23.0, 7.5$  Hz, 2H), 2.00 (m, 12H), 1.83 (m, 2H), 1.73 (d,  $J = 1.2$  Hz, 3H), 1.71 (d,  $J = 1.2$  Hz, 3H), 1.70 (m, 2H), 1.65 (m, 2H), 1.48–1.41 (m, 4H), 1.39 (d,  $J = 7.0$  Hz, 3H), 1.35 (d,  $J = 7.0$  Hz, 3H), 1.34–1.28 (m, 4H), 0.91 (d,  $J = 7.0$  Hz, 3H), 0.89 (d,  $J = 7.0$  Hz, 3H), 0.87 (s, 18H), 0.02 (s, 12H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  169.3, 141.9, 122.3, 75.6, 75.1, 64.2, 62.9, 40.3, 39.4, 32.3, 26.0, 23.9, 18.3, 16.8, 16.4, 13.8, 11.7,  $-5.3$ . HRMS-TOF (ESI+) calcd for  $\text{C}_{24}\text{H}_{49}\text{O}_7\text{PSiNa}^+$  (M + Na): 531.2883. Found 531.2883.

**(5S,6S)-6-((E)-6-((tert-Butyldimethylsilyl)oxy)-2-methylhex-1-en-1-yl)-3,5-dimethyl-5,6-dihydro-2H-pyran-2-one (14).** To a solution of the alcohol (624 mg, 1.23 mmol) in DCM (6.13 mL) at  $0^\circ\text{C}$  was added  $\text{NaHCO}_3$  (515 mg, 6.13 mmol) followed by the portionwise addition of Dess–Martin periodinane (520 mg, 1.23 mmol) and the resulting mixture was stirred for 1 h. The solution then was diluted with DCM (20 mL) and stirred vigorously with sodium thiosulfate pentahydrate (50 mL) for 30 min. The layers were separated and the aqueous phase was extracted with DCM ( $2 \times 50$  mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. The crude aldehyde (371 mg, 60%) was used directly in the next reaction.

$\text{Ba}(\text{OH})_2 \cdot 8\text{H}_2\text{O}$  (340 mg, 1.1 mmol) was heated at  $120^\circ\text{C}$  for 1.5 hours under vacuum and then allowed to cool to room temperature. THF (7 mL) was added to the flask and the solution was stirred for 10 minutes before adding the aldehyde (181 mg, 0.36 mmol) and the resulting mixture was stirred at room temperature for 15 h. The reaction was quenched with aq.  $\text{NaHCO}_3$  (20 mL) and extracted with MTBE ( $2 \times 20$  mL). The combined organic extracts were dried over  $\text{MgSO}_4$ , filtered and concentrated *in vacuo*. Purification by flash column chromatography on silica (20 : 1 to 10 : 1 to 4 : 1 hexanes : ethyl acetate) afforded lactone **14** (72.2 mg, 57%) as an oil.

$[\alpha]_D^{20} = -2.8$  (c 1.0,  $\text{CH}_2\text{Cl}_2$ ). IR (ATR) 2952, 2928, 2856, 1716, 1460, 1359, 1253, 1226, 1199, 1154, 1134, 1099, 1005, 981, 834, 810, 773, 731, 661.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.34 (s, 1H), 5.22 (d,  $J = 9.0$  Hz, 1H), 4.68 (dd,  $J = 10.5, 9.0$  Hz, 1H), 3.57 (m, 2H), 2.45 (ddtt,  $J = 14.6, 7.2, 4.8, 2.4$  Hz, 1H), 2.03 (t,  $J = 5.4$  Hz, 2H), 1.87 (dd,  $J = 2.4, 1.5$  Hz, 3H), 1.67 (d,  $J = 1.5$  Hz, 3H), 1.50–1.41 (m, 3H), 0.98 (d,  $J = 7.3$  Hz, 3H), 0.85 (d,  $J = 6.0$  Hz, 1H), 0.85 (s, 9H), 0.00 (s, 6H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  165.96, 145.52, 143.82, 127.37, 121.50, 80.36, 62.86, 39.24, 34.59, 32.30, 25.95, 23.78, 18.31, 16.88, 15.94,  $-5.30$ . HRMS-TOF (ESI+) calcd for  $\text{C}_{20}\text{H}_{36}\text{O}_3\text{SiH}^+$  (M + H): 353.2512. Found 353.2516.

**(4Z,6S,7S,8E)-13-((tert-Butyldimethylsilyl)oxy)-4,6,9-trimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)trideca-2,4,8-trien-7-ol (15).** To a solution of lactone **14** (175 mg, 0.498 mmol) in DCM (5 mL) at  $-78^\circ\text{C}$  was added DIBAL-H (0.106 mL, 0.597 mmol) dropwise over 10 min and the resulting mixture was stirred for 1 hour. The reaction was quenched with the



addition of aq. Rochelle's salt (2.0 M, 20 mL) and the solution was stirred vigorously for 1 h. The layers were separated and the aqueous phase was extracted with DCM (2 × 20 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered and concentrated *in vacuo*. The resulting lactol product (141 mg, 80%) could be used without further purification.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 5.48 (s, 1H), 5.16 (m, 2H), 4.24 (t, *J* = 9.3 Hz, 1H), 3.61 (t, *J* = 6.0 Hz, 3H), 2.89 (s, 1H), 2.09 (m, 1H), 2.06 (m, 2H), 1.73 (m, 3H), 1.71 (d, *J* = 1.5 Hz, 3H), 1.50 (m, 3H), 0.89 (s, 9H), 0.86 (d, *J* = 7.1 Hz, 3H), 0.04 (s, 6H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 141.98, 132.03, 129.75, 12.65, 91.94, 69.63, 63.01, 39.38, 35.14, 32.41, 25.97, 23.96, 18.93, 18.35, 16.95, 16.38, −5.27.

To a solution of tetramethylpiperidine (137 mg, 0.97 mmol) in THF (0.5 mL) at −78 °C was added *n*-BuLi (0.388 mL, 2.5 M). The solution was allowed to warm to 0 °C before adding 1,1-bis(pinacolboronato)ethane (187 mg, 0.65 mmol). After 10 minutes, the lactol (114.6 mg, 0.32 mmol) was added and the solution was allowed to slowly warm to room temperature and stirred for 15 h. The solution was diluted with diethyl ether (10 mL), filtered through a silica plug, and concentrated *in vacuo*. Purification by flash column chromatography on silica (20 : 1 to 10 : 1 to 4 : 1 hexanes : ethyl acetate) afforded the vinyl boronate **15** (90 mg, 57%) as a 3 : 1 mixture of *Z* : *E* isomers.

**Spectral data for Z-15.** IR (ATR) 2977, 2933, 2879, 1460, 1305, 1268, 1215, 1142, 1105, 1016, 967, 846, 775, 736, 669. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 6.74 (s, 1H), 5.17–5.09 (m, 2H), 4.04 (dd, *J* = 8.9, 7.5 Hz, 1H), 3.61 (t, *J* = 5.9 Hz, 2H), 2.34 (m, 1H), 2.03 (m, 2H), 1.84 (s, 3H), 1.71 (s, 3H), 1.65 (s, 3H) 1.53–1.43 (m, 4H), 1.29 (s, 12H), 1.22 (d, *J* = 3.8 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 142.5, 139.7, 136.5, 130.3, 125.7, 83.1, 72.2, 63.1, 39.5, 32.5, 29.7, 26.0, 24.8, 24.0, 23.7, 18.4, 16.7, 16.2, 15.4, 10.4, −5.3. HRMS-TOF (ESI+) calcd for C<sub>28</sub>H<sub>53</sub>BO<sub>4</sub>SiNa<sup>+</sup> (M + Na): 515.3704. Found 515.3706.

**Spectral data for E-15.** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 6.68 (s, 1H), 5.13 (d, 9.24 Hz, 1H) 5.07 (d, *J* = 9.24 Hz, 1H), 4.01 (t, *J* = 8.46 Hz, 1H), 3.60 (m, 2H), 2.50 (m, 1H), 2.04 (d, *J* = 5.90 Hz, 2H), 1.88 (dd, *J* = 5.34, 1.34 Hz, 4H) 1.66 (s, 3H), 1.48 (m, 1H) 1.24 (d, *J* = 3.31 Hz, 3H), 1.21 (d, 4.15 Hz, 12H), 1.04 (d, *J* = 7.31 Hz, 2H), 0.89 (s, 9H), 0.84 (d, *J* = 6.73 Hz, 2H), 0.72 (q, *J* = 7.29 Hz, 1H) 0.04 (s, 6H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 140.12, 139.32, 136.49, 130.68, 126.10, 82.85, 72.41, 63.01, 40.19, 39.50, 32.45, 25.94, 24.81, 24.51, 24.08, 23.94, 23.23, 18.31, 16.80, 9.03, −5.30.

**Compound 1.** To a degassed solution of vinyl boronate **9** (60 mg, 0.1 mmol) and vinyl iodide **2** (61 mg, 0.1 mmol) in DMF (1 mL) were added Pd(dppf)Cl<sub>2</sub> (4 mg, 0.005 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (40 mg, 0.12 mmol) and the resulting solution was stirred at room temperature for 8 h. The reaction was diluted with MTBE (20 mL) and washed with water (20 mL). The layers were separated and the aqueous phase was extracted with MTBE (20 mL). The combined organic extracts were dried over MgSO<sub>4</sub> and concentrated *in vacuo*. Purification by flash column chromatography on silica (20 : 1 to 10 : 1 hexanes : ethyl acetate) afforded the coupled product **1** (77 mg, 80%) as an oil.

[α]<sub>D</sub><sup>20</sup> = −5.2 (c 0.5, CH<sub>2</sub>Cl<sub>2</sub>). IR (ATR) 3062, 2983, 1736, 1614, 1415, 1274, 1267, 1129, 1078, 930 cm<sup>−1</sup>. <sup>1</sup>H NMR (500 MHz,

C<sub>6</sub>D<sub>6</sub>): δ 6.80 (d, *J* = 16.0 Hz, 1H), 6.44 (ddd, *J* = 15.3, 10.7, 0.9 Hz, 1H), 6.17 (d, *J* = 10.4 Hz, 1H), 6.02 (s, 1H), 5.90 (dd, *J* = 16.0, 7.2 Hz, 1H), 5.58 (dd, *J* = 15.4, 8.0 Hz, 1H), 5.34 (dd, *J* = 8.4, 0.8 Hz, 1H), 5.29 (ddd, *J* = 9.8, 2.0, 1.0 Hz, 1H), 5.07 (d, *J* = 7.4 Hz, 1H), 4.29 (dd, *J* = 9.0, 6.0 Hz, 1H), 3.63 (d, *J* = 10.0 Hz, 1H), 3.58–3.53 (m, 2H), 3.47 (dd, *J* = 9.7, 6.2 Hz, 1H), 3.38 (dd, *J* = 9.7, 6.8 Hz, 1H), 3.18 (s, 3H), 2.71 (m, 1H), 2.42 (m, 1H), 1.96 (m, 2H), 1.91 (s, 3H), 1.86 (m, 1H), 1.89 (d, *J* = 1.0 Hz, 3H), 1.71 (d, *J* = 1.0 Hz, 3H), 1.59 (s, 3H), 1.50 (m, 2H), 1.39 (m, 2H), 1.08 (s, 6H), 1.03 (s, 6H), 1.02 (s, 3H), 1.01 (s, 6H), 1.00 (s, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.98 (s, 3H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.95 (s, 6H), 0.94 (d, *J* = 7.0 Hz, 3H), 0.93 (s, 3H), 0.19 (s, 3H), 0.17 (s, 3H), 0.13 (s, 6H), 0.08 (s, 6H), 0.05 (s, 6H). <sup>13</sup>C NMR (125 MHz, C<sub>6</sub>D<sub>6</sub>): δ <sup>13</sup>C NMR (126 MHz, C<sub>6</sub>D<sub>6</sub>) δ 137.8, 136.0, 134.9, 134.7, 133.4, 133.3, 133.0, 132.5, 130.9, 130.3, 126.3, 125.4, 73.8, 72.9, 68.5, 63.4, 63.4, 56.0, 43.7, 41.5, 40.6, 40.1, 33.1, 31.4, 30.3, 28.5, 26.7, 26.6, 26.5, 25.4, 24.8, 24.8, 24.0, 21.0, 19.1, 18.9, 18.8, 17.4, 17.2, 17.1, 16.2, 14.3, 11.2, 9.8, 8.7, −3.0, −3.6, −4.2, −4.3, −4.4, −4.7, −4.8, −4.9. HRMS (ESI+): calcd for C<sub>55</sub>H<sub>108</sub>O<sub>5</sub>Si<sub>4</sub>Na<sup>+</sup> (M + Na)<sup>+</sup>: 983.7172. Found 983.7179.

**(*S,E*)-4-Methyl-1-(trimethylsilyl)pent-1-en-3-ol.** Sodium bis(2-methoxyethoxy)aluminum hydride (2.65 mL, 3.07 M) was added dropwise to a solution of (*S*)-**19**<sup>26</sup> (1.0313 g, 6.05 mmol) in diethyl ether (15 mL) at 0 °C and the mixture was stirred to room temperature for 15 hours. The reaction was quenched with ethyl acetate (50 mL) and stirred vigorously with aq. Rochelle's salt (50 mL, 2.0 M) for 1 hour. The layers were separated and the aqueous phase was extracted with ethyl acetate (2 × 50 mL). The combined organic fractions were dried over MgSO<sub>4</sub>, filtered through cotton, and concentrated under vacuum. Purification by flash chromatography on silica (20 : 1 to 10 : 1 hexanes : ethyl acetate) gave the *trans*-alkene product (0.859 g, 4.98 mmol, 82.4%) as an oil.

[α]<sub>D</sub><sup>20</sup> = +20.2 (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>). IR (ATR): 3355, 3057, 3025, 2956, 2923, 1721, 1621, 1601, 1582, 1493, 1452, 1247, 1025, 989, 866, 835, 762, 742, 694. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 6.06 (dd, *J* = 9.5, 5.6 Hz, 1H), 5.88 (dd, *J* = 9.4, 1.3 Hz, 1H), 3.88 (s, 1H), 1.76 (o, *J* = 6.9 Hz, 1H), 0.94 (d, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 7.2 Hz, 3H), 0.10 (s, 9H). <sup>13</sup>C NMR (500 MHz, CDCl<sub>3</sub>): δ 146.98, 130.48, 79.61, 33.55, 18.35, 17.64, −1.26. HRMS (ESI+): calcd for C<sub>9</sub>H<sub>20</sub>OSiNa<sup>+</sup> (M + Na)<sup>+</sup>: 195.1181. Found 195.1180.

**(*S,E*)-Triethyl((4-methyl-1-(trimethylsilyl)pent-1-en-3-yl)oxy)silane.** Chlorotriethylsilane (0.117 mL, 0.696 mmol) was added to a solution of the alcohol (0.100 g, 0.580 mmol) and imidazole (0.0790 g, 1.16 mmol) in DCM (1.66 mL) at 0 °C and the resulting mixture was warmed to room temperature and stirred for 3 hours. The reaction was quenched with water (10 mL) and extracted with DCM (2 × 10 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered through cotton, and concentrated under vacuum. Purification by flash chromatography on silica (20 : 1 hexanes : ethyl acetate) gave the TES-protected alcohol (0.1453 g, 0.501 mmol, 86.3%) as an oil.

[α]<sub>D</sub><sup>20</sup> = +18.0 (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>). IR (ATR): 2954, 2911, 2876, 1620, 1459, 1414, 1259, 1059, 1004, 992, 872, 834, 721, 691. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 5.97 (dd, *J* = 18.7, 6.5 Hz, 1H), 5.75 (dd, *J* = 18.8, 1.1 Hz, 1H), 3.77 (ddd, *J* = 6.4, 1.0 Hz, 1H), 1.66 (o, *J* = 6.5 Hz, 1H), 0.96 (t, *J* = 8.0 Hz, 9H), 0.90 (d, *J* = 6.8, 3H), 0.85 (d, *J*





= 6.8 Hz, 3H), 0.59 (dq,  $J$  = 7.7, 2.5 Hz, 6H), 0.08 (s, 9H).  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  147.91, 129.98, 81.17, 34.35, 18.39, 18.18, 6.88, 5.00, -1.32. HRMS (ESI<sup>+</sup>): calcd for  $\text{C}_{15}\text{H}_{34}\text{OSi}_2\text{Na}^+$  ( $\text{M} + \text{Na}$ )<sup>+</sup>: 309.2046. Found 309.2045.

**(*S,E*)-Triethyl((1-iodo-4-methylpent-1-en-3-yl)oxy)silane (18).** *N*-Iodosuccinimide (0.169 g, 0.751 mmol) was added to the vinyl silane (0.144 g, 0.501 mmol) and 2,6-lutidine (0.081 mL, 0.701 mmol) in 1,1,1,3,3,3-hexafluoroisopropanol (2.00 mL) at 0 °C and the resulting mixture was stirred for 15 minutes. The reaction was quenched with water (5 mL) and extracted with DCM (2 × 10 mL). The combined organic extracts were washed with sodium thiosulfate (25 mL), hydrochloric acid (25 mL, 1 M), water (25 mL), and sodium bicarbonate (25 mL), then dried over  $\text{MgSO}_4$ , filtered through cotton, and concentrated under vacuum. Purification by flash chromatography on silica (20 : 1 hexanes : ethyl acetate) gave **18** (0.0885 g, 0.260 mmol, 52.0%) as an oil.

$[\alpha]_D^{20}$  = +8.2 ( $c$  0.5,  $\text{CH}_2\text{Cl}_2$ ). IR (ATR): 2955, 2910, 2875, 1607, 1459, 1414, 1384, 1364, 1238, 1182, 1162, 1118, 1103, 1071, 1004, 948, 828, 723.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.53 (dd,  $J$  = 14.4, 6.8 Hz, 1H), 6.20 (dd,  $J$  = 14.4, 1.1 Hz, 1H), 3.83 (ddd,  $J$  = 6.7, 5.7, 1.1 Hz), 1.69 (do,  $J$  = 6.8, 1.1 Hz, 1H), 0.97 (t,  $J$  = 8.0 Hz, 9H), 0.91 (d,  $J$  = 6.8, 3H), 0.87 (d,  $J$  = 6.8, 3H), 0.60 (q,  $J$  = 8.2 Hz, 6H).  $^{13}\text{C}$  NMR (500 MHz,  $\text{CDCl}_3$ ): 147.81, 80.18, 76.26, 34.34, 18.01, 17.82, 6.82, 4.90. HRMS (ESI<sup>+</sup>): calcd for  $\text{C}_{12}\text{H}_{25}\text{IOSiNa}^+$  ( $\text{M} + \text{Na}$ )<sup>+</sup>: 363.0617. Found 363.0612.

**(*5S,6E,8Z,10Z,12S,13S,14E*)-13-((*tert*-Butyldimethylsilyl)oxy)-3,3-diethyl-5-isopropyl-8,10,12,15,21,21,22,22-octamethyl-4,20-dioxa-3,21-disilatricosa-6,8,10,14-tetraene (17).** To a solution of vinyl boronate **E-15** (100 mg, 0.2 mmol) and vinyl iodide **18** (69 mg, 0.2 mmol) in degassed DMF (1 mL) was added Pd(dppf)  $\text{Cl}_2$  (4 mg, 0.004 mmol) and  $\text{Cs}_2\text{CO}_3$  (40 mg, 0.12 mmol) and the resulting solution was stirred for 15 h. The reaction mixture was diluted with MTBE (5 mL) and washed with water (20 mL). The aqueous phase was extracted with MTBE (2 × 20 mL). The combined organic extracts were dried with  $\text{MgSO}_4$  and concentrated *in vacuo*. Purification by flash column chromatography on silica (10 : 1 to 4 : 1 hexanes : ethyl acetate) afforded **17** (93 mg, 80%) as an oil. The product was unable to be purified away from a side product and this mixture was taken direction into the next reaction.

$[\alpha]_D^{20}$  = -3.2 ( $c$  0.5,  $\text{CH}_2\text{Cl}_2$ ). IR (ATR) 2955, 2930, 2875, 1460, 1352, 1344, 1254, 1143, 1103, 1004, 969, 835, 774, 741, 724, 666.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  6.37 (d,  $J$  = 15.7 Hz, 1H), 5.84 (s, 1H), 5.64 (dd,  $J$  = 15.7, 7.9 Hz, 1H), 5.16 (d, 9.8 Hz, 1H), 5.10 (d,  $J$  = 8.8 Hz, 1H), 4.02 (t,  $J$  = 8.8 Hz, 1H), 3.82 (t,  $J$  = 7.0 Hz, 1H), 3.60 (t,  $J$  = 5.9 Hz, 2H), 2.34 (m, 1H), 2.02 (m, 2H), 1.86 (s, 3H), 1.84 (s, 3H), 1.67 (m, 1H), 1.66 (s, 3H), 1.53–1.43 (m, 4H), 1.24 (d,  $J$  = 3.8 Hz, 3H), 0.93 (t,  $J$  = 7.9 Hz, 9H), 0.89 (s, 9H), 0.84 (d,  $J$  = 5.8 Hz, 3H), 0.82 (d,  $J$  = 5.8 Hz, 3H), 0.56 (q,  $J$  = 7.9 Hz, 6H) 0.04 (s, 6H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  139.8, 135.1, 132.4, 130.9, 129.0, 128.7, 125.7, 82.9, 72.3, 63.0, 40.5, 39.5, 35.1, 32.5, 26.0, 24.8, 24.6, 20.4, 18.4, 16.7, 16.4, 9.1, 6.9, 5.0, -5.3. HRMS (ESI<sup>+</sup>): calcd for  $\text{C}_{34}\text{H}_{66}\text{O}_3\text{Si}_2\text{Na}^+$  ( $\text{M} + \text{Na}$ )<sup>+</sup>: 601.4448. Found 601.4446.

**(*5E,7S,8S,9Z,11Z,13E,15S*)-5,8,10,12,16-Pentamethylheptadeca-5,9,11,13-tetraene-1,7,15-triol (20).** To a solution of **17** (77 mg, 0.053 mmol) in THF (1.2 mL) and

pyridine (0.3 mL) at 4 °C was added HF pyr (0.2 mL, 60% HF). The reaction mixture was kept at 4 °C for 15 h, and then quenched with aq.  $\text{NaHCO}_3$  (20 mL) and extracted with ethyl acetate (2 × 10 mL). The organic layers were dried over  $\text{MgSO}_4$  and concentrated *in vacuo*. Purification by flash column chromatography on silica (1 : 1 to 1 : 2 hexanes : ethyl acetate) afforded **20** (30.1 mg, 65%) as an oil.

$[\alpha]_D^{20}$  = -2.8 ( $c$  0.5,  $\text{CH}_2\text{Cl}_2$ ). IR (ATR) 3338, 2957, 2929, 2870, 1667, 1638, 1585, 1447, 1378, 1366, 1328, 1257, 1203, 1175, 1136, 1106, 1065, 1003, 973, 935, 858, 817, 769, 736, 697, 667.  $^1\text{H}$  NMR (500 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  6.84 (d,  $J$  = 15.8, 1H), 5.78 (dd,  $J$  = 15.8, 6.6 Hz, 1H), 5.73 (s, 1H), 5.27–5.24 (m, 2H), 4.12 (t,  $J$  = 8.0 Hz, 1H), 3.90 (t,  $J$  = 6.2 Hz, 1H), 3.40 (m, 2H), 2.60 (m, 1H), 1.89 (m, 2H), 1.81 (s, 3H), 1.78 (s, 3H), 1.57 (s, 3H), 1.40–1.34 (m, 5H), 1.03 (d,  $J$  = 6.2 Hz, 3H) 0.95 (dd,  $J$  = 11.6, 7.1 Hz, 6H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{C}_6\text{D}_6$ ):  $\delta$  138.5, 133.6, 132.8, 132.0, 130.5, 129.1, 77.7, 72.5, 62.1, 40.4, 39.1, 34.1, 32.1, 24.4, 23.7, 19.9, 18.5, 18.1, 16.8, 16.4. HRMS (ESI<sup>+</sup>): calcd for  $\text{C}_{22}\text{H}_{38}\text{O}_3\text{Na}^+$  ( $\text{M} + \text{Na}$ )<sup>+</sup>: 373.2719. Found 373.2711.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

Financial support from the Camille & Henry Dreyfus Foundation is gratefully acknowledged.

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