Investigation of an Acrylate Lynchpin Approach toward the Synthesis of Stolonidiol

Thomas Barton, Dionicio Siegel*

Department of Chemistry and Biochemistry, The University of Texas at Austin, Austin, TX 78712, USA
Fax +1(512)4716835; E-mail: dsiegel@cm.utexas.edu

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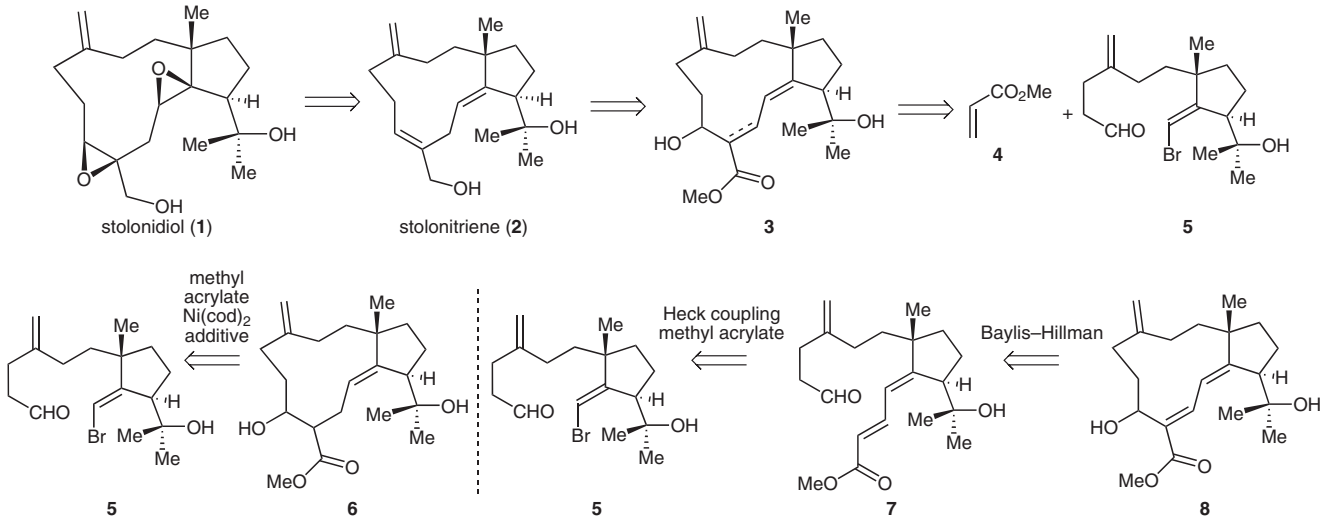
Abstract: An acrylate lynchpin approach toward the synthesis of stolonidiol has been investigated. To access the key macrocyclization precursor we adapted the silylcupration reaction of alkynes, facilitating attack of the intermediate vinylcuprate on a trisubstituted epoxide. With all of the required carbons of stolonidiol in place, macrocyclization reactions to provide the 11-membered ring were attempted using either a nickel-mediated cyclization of a bromo aldehyde, intercepting methyl acrylate, or an intramolecular Baylis–Hillman cyclization.

Key words: stolonidiol, epoxides, silylcupration, macrocyclization, acrylate lynchpin approach

Stolonidiol (**1**) induces the biosynthesis of choline acetyltransferase (ChAT) mRNA at concentrations of 27 nM resulting in an increased biosynthesis of acetylcholine.[1] Owing to limited access from the marine soft coral *Clavularia* sp., the mode of action leading to this transcriptional regulation is currently unknown.[2] Neurogenesis, producing newborn cells, in the mature brain occurs continuously in the hippocampal dentate gyrus and stimulation of the developing cells by the actions of acetylcholine has been strongly implicated in the production and the survival of neural progenitors during early development and adulthood.[3–5] The new cells' contacts with cholinergic projections are associated with the growth and development of fledgling cells.[6] In the absence of these contacts, as seen in Alzheimer's disease, neurogenesis is attenuated.[7,8] Importantly, cholinergic agonists have been shown to increase the rate of neurogenesis.[9] Fortification of the cholinergic system by increasing ChAT activity has the potential to favorably shift the balance of cell production and cell loss, slowing cognitive decline or possibly reversing existing degeneration.[10] Structure–activity relationships (SAR) for stolonidiol, based on compounds that could be prepared from the natural product, demonstrated that compounds without epoxide functionality lack the ability to potently induce ChAT activity, providing evidence for potential covalent modification of protein targets.[1] Yamada and co-workers, the group which isolated stolonidiol from *Clavularia viridis*, achieved the sole synthesis of stolonidiol to date.[11] Work toward the synthesis of the functionalized cyclopentane core of stolonidiol has also been reported.[12,13]

Our synthetic studies have investigated an acrylate lynchpin approach to stolonidiol utilizing either a nickel-mediated conjugate addition/aldol sequence with methyl acrylate or a Heck reaction, also with methyl acrylate, followed by an intramolecular Baylis–Hillman macrocyclization to form the 11-membered ring (Scheme 1). These approaches should provide efficient sequences toward the



Scheme 1 Acrylate lynchpin strategy for the formation of the fully functionalized bicyclic ring system, **6** and **8**, of stolonidiol

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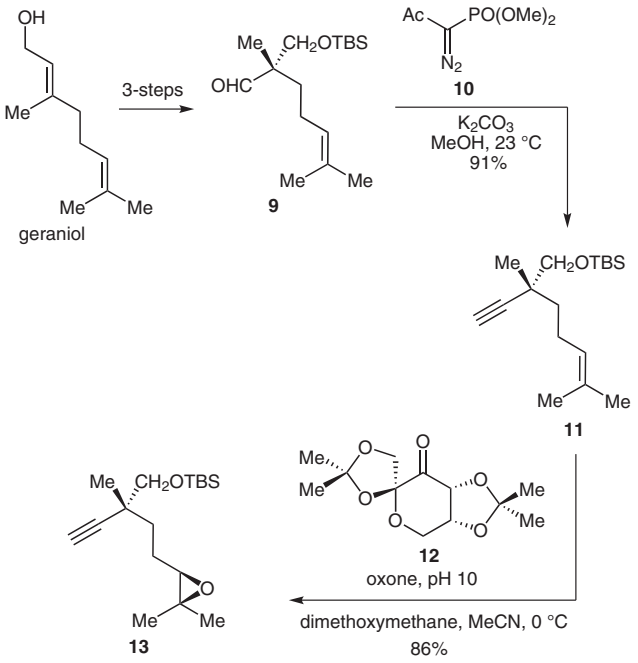
assembly of the appropriately functionalized bicyclic ring system **6** and **8**. In addition, the formation of both cyclization precursors can be traced back to single compound, bromo aldehyde **5**.

To examine the acrylate lynchpin strategies, a synthesis of bromo aldehyde **5** was required. Proceeding from geraniol, optically active aldehyde **9** was prepared over three steps on a 50-gram scale (Scheme 2).[14] Alkynylation of aldehyde **9** using the Bestmann–Ohira reagent **10** (1.5 equiv) with potassium carbonate in methanol at 23 °C provided alkyne **11** in 91% yield.[15,16] Epoxidation of the trisubstituted olefin of alkyne **11** using the Shi catalyst **12** (1.1 equiv) with slow addition of aqueous, buffered Oxone® solution resulted in the formation of epoxyalkyne **13** in a 9:1 ratio of diastereomers.[17–19]

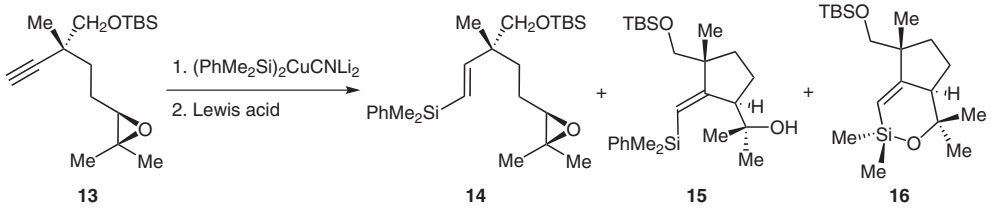
Using dilithium bis(dimethyl(phenyl)silyl)cyanocuprate to induce the cyclization of epoxyalkyne **13** to form the desired cyclopentane led predominantly to hydrosilylation of the alkyne, generating vinylsilane **14** with none of the cyclized products **15** or **16** (Table 1). Challenges in inducing cyclization following silylcupration reactions have been previously noted by Fleming and co-workers.[20] A variety of conditions, summarized in Table 1, were examined and the addition of boron trifluoride–diethyl ether complex was found to promote the formation of cyclized products, generating vinylsilanes **15** and **16**.

The ratio of vinylsilanes **15** and **16** changed depending on the amount of boron trifluoride–diethyl ether complex employed. The optimized procedure for our purposes entailed the addition of a tetrahydrofuran solution of epoxyalkyne **13** to 1.15 equivalents of dilithium bis[dimethyl(phenyl)silyl]cyanocuprate in tetrahydrofuran [prepared by adding 2.3 equiv of a deep red dimeth-



Scheme 2 Synthesis of epoxide **13** from geraniol

Table 1 Optimization of Conditions for the Silylcupration Reaction of Epoxyalkyne **13** to Cyclopentane **15**[a]

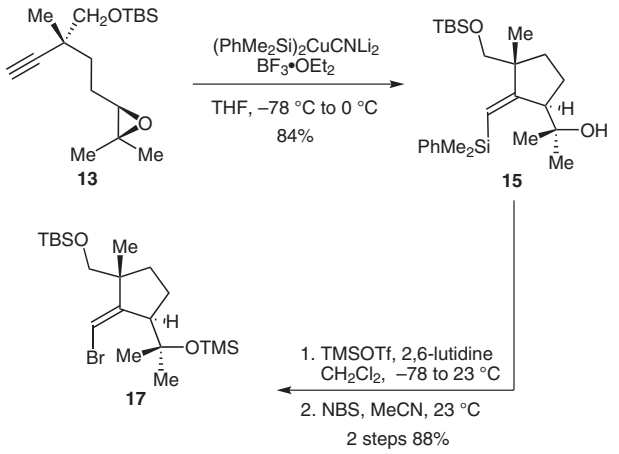


Entry	Lewis acid (equiv)	Temp (°C) of Lewis acid addition	Time (h) after addition	Yield (%) of **14**/**15**/**16**
1	–	0	6	82: 0: 0
2	TMSCl (1.5)	0	6	32: 0: 0
3	TMSOTf (1.5)	0	6	28: 0: 0
4	Me_3Al (1.5)	0	6	46: 0: 0
5	$BF_3{\cdot}OEt_2$ (1.5)	0	6	31:32:12
6	$BF_3{\cdot}OEt_2$ (2.0)	0	2	8:14:51
7	$BF_3{\cdot}OEt_2$ (2.0)	–78	2	21:11:45
8	$BF_3{\cdot}OEt_2$ (2.0)	0	18	6:17:65
9	$BF_3{\cdot}OEt_2$ (5.0)	0	18	5:81: 0
10	$BF_3{\cdot}OEt_2$ (5.0)	0	6	7:64: 0
11	$BF_3{\cdot}OEt_2$ (3.0)	0	12	5:84: 0

[a] Conditions: All reactions were performed in THF (0.1 M). The epoxyalkyne **13** was added at –78 °C and warmed to 0 °C. TLC (hexanes–EtOAc, 9:1) indicated that starting material was consumed within 2 h at 0 °C, at which point the Lewis acid was introduced, where indicated.

yl(phenyl)silyllithium solution to CuCN (1.15 equiv) suspended in THF at 0 °C, followed by stirring for 20 min, which gave a brown solution] at –78 °C and warming to 0 °C for 2 hours, followed by the addition of boron trifluoride–diethyl ether complex (3 equiv) and stirring at 0 °C for 12 hours, generating **15** in 84% yield. Notably, this reaction proved reliable on a 15-gram scale.

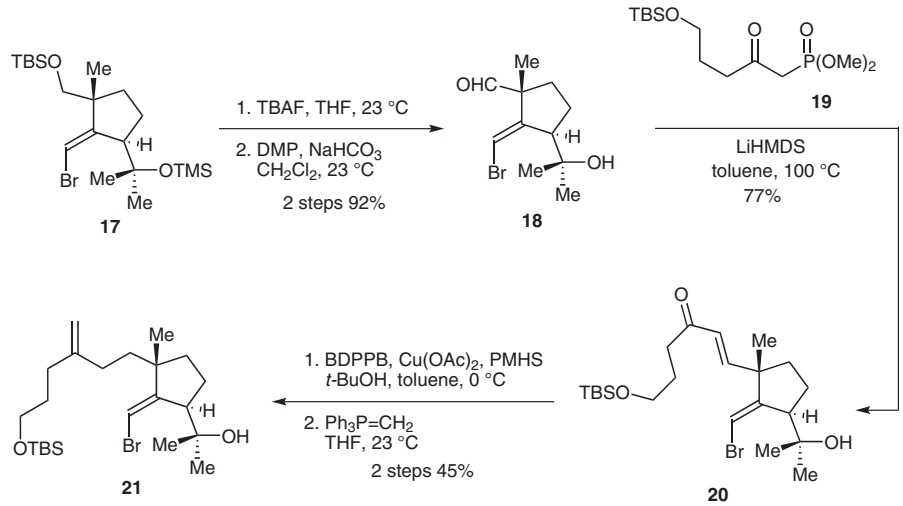
Protection of the tertiary alcohol of **15** was necessary[21] and achieved in dichloromethane using trimethylsilyl trifluoromethanesulfonate (3.0 equiv) and 2,6-lutidine (6.0 equiv) at –78 °C with warming to 23 °C (Scheme 3). Addition of solid *N*-bromosuccinimide (2.0 equiv) to a solution of the resulting trimethylsilyl ether in acetonitrile provided bromide **17** with retention of the olefin geometry (confirmed by X-ray crystallography of the *p*-bromobenzoate derived from the parent alcohol by treatment with *p*-bromobenzoyl chloride and pyridine).[22] The corresponding vinyl iodide of **17** could also be prepared in 62% yield using *N*-iodosuccinimide.



Scheme 3 Synthesis of bromide **17** from epoxyalkyne **13**

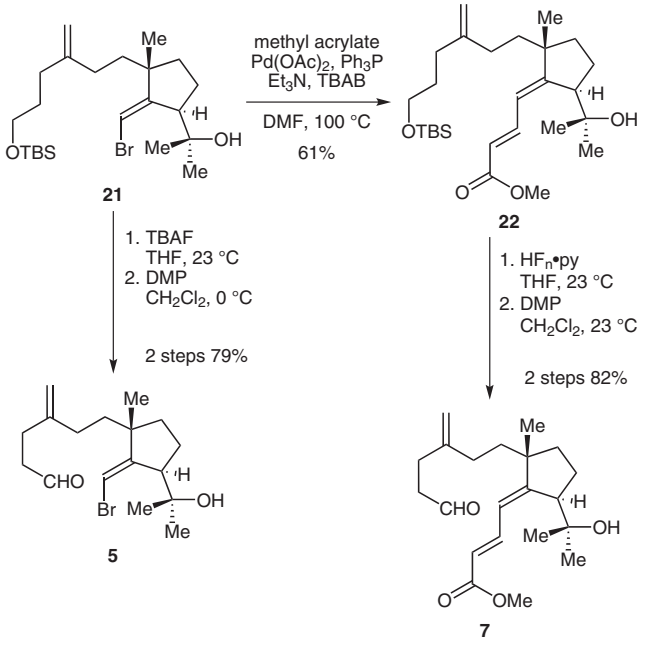
Bromo diene **21** was prepared over a five-step sequence from bromide **17** as outlined in Scheme 4. Cleavage of the silyl groups using tetrabutylammonium fluoride (2.5 equiv) in tetrahydrofuran at 23 °C followed by oxidation of the resulting diol using Dess–Martin periodinane gave aldehyde **18** on a 10-gram scale. Horner–Wadsworth–Emmons olefination of aldehyde **18** using lithium hexamethyldisilazide and the known ketophosphonate **19** in toluene heated to 100 °C provided enone **20** in 77% yield.[23] Conjugate reduction of enone **20** was achieved by combining copper(II) acetate monohydrate (5 mol%), 1,2-bis(diphenylphosphino)benzene (BDPPB, 5 mol%), and *tert*-butyl alcohol (1.5 equiv) in toluene (0.2 M), providing a clear blue solution, followed by addition of polymethylhydrosiloxane (PMHS, 1.5 equiv), transitioning the color of the solution to bright yellow; after 30 minutes, enone **20** was introduced in a toluene solution and after 18 hours the reaction mixture was worked up to provided the corresponding saturated ketone.[24] Wittig methylenation of the ketone with methylenetriphenylphosphorane in tetrahydrofuran at 23 °C provided bromo diene **21** in 46% yield over two steps.

The *tert*-butyldimethylsilyl group of bromo diene **21** was removed with tetrabutylammonium fluoride (1.5 equiv) in tetrahydrofuran, which was followed by oxidation of the primary alcohol with Dess–Martin periodinane (1.1 equiv) in dichloromethane, generating the desired bromo aldehyde **5** in 53% yield over two steps (Scheme 5). Heck reaction using bromo diene **21** was accomplished using methyl acrylate (8 equiv), triethylamine (10 equiv), triphenylphosphane (20 mol%), and tetrabutylammonium bromide (1 equiv) in degassed *N*,*N*-dimethylformamide followed by the addition of palladium(II) acetate (0.2 equiv).[25] After combination of the components was complete, the reaction mixture was placed in a 100 °C oil bath and stirred for 16 hours yielding, after purification, dienoate **22** (Scheme 5). Subjecting this material to deprotection with fluoride and oxidation with Dess–Martin periodinane afforded dienoate aldehyde **7** in 82% yield over two steps.

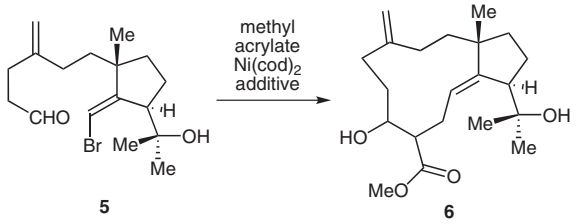


Scheme 4 Synthesis of bromo diene **21** from bromide **17**

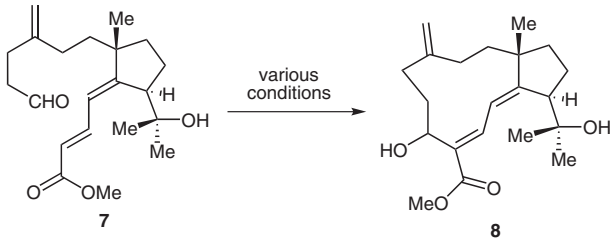
Access to bromo aldehyde **5** allowed examination of the nickel-catalyzed conjugate addition/aldol sequence to form the 11-membered ring of stolonidiol (Scheme 6). Following conditions reported by Subburaj and Montgomery,[26] bis(cyclooctadiene)nickel (20 mol%) was transferred in a glovebox to a flame-dried flask and suspended in tetrahydrofuran. A solution of the bromo aldehyde **5** in tetrahydrofuran was added to the nickel solution, turning the yellow solution orange, followed by the addition of methyl acrylate (2 equiv). To the resulting deep red solution, dimethylzinc (1.0 M soln, 2 equiv) was added and the reaction mixture was stirred at 23 °C, transitioning the color to brown after 30 minutes. This procedure gave rise to no discernable conjugate addition product. Variation of the acrylate species, reductants (alkylzincs, boranes), reaction times, and temperature failed to generate the desired product. The corresponding iodo aldehyde of **5** showed similar reactivity under these conditions.



Scheme 5 Synthesis of the cyclization precursors bromo aldehyde **5** and dienoate **7**



Scheme 6 Attempted nickel-catalyzed conjugate addition/intramolecular aldol reaction of bromo aldehyde **5**



Scheme 7 Attempted Baylis–Hillman macrocyclization of dienoate **7**

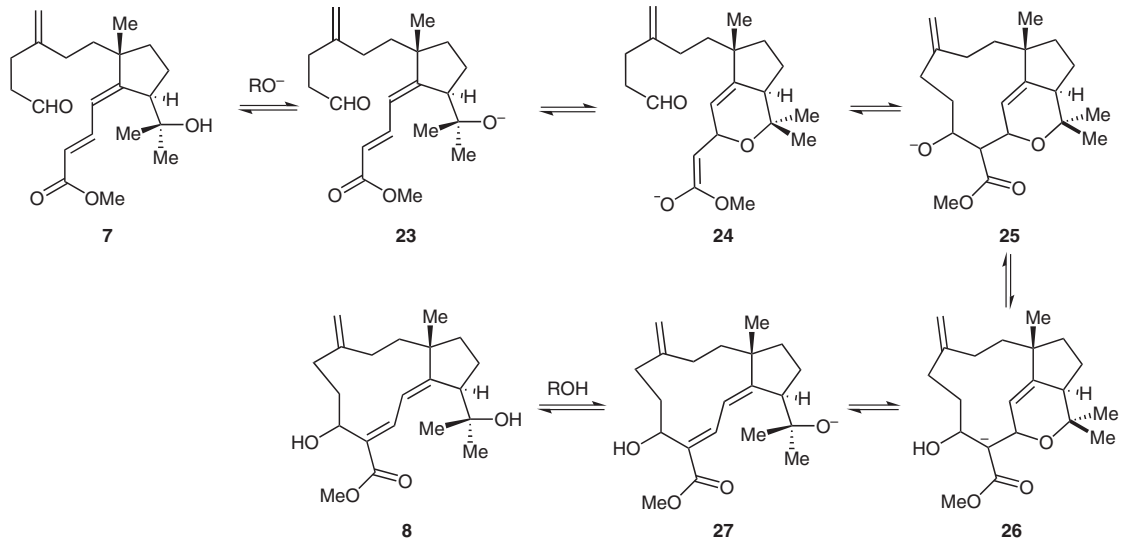
Intramolecular Baylis–Hillman ring closures using dienoate **7** were examined under a variety of conditions (Scheme 7), including the use of triphenyl- and tributylphosphane, 1,4-diazabicyclo[2.2.2]octane, and the anion of thiophenol, none of which generated the desired macrocycle. Intermolecular examples of the reaction with dienoates have been shown previously.[27]

In addition to the typical nucleophiles used in the reaction, the tertiary alkoxide of **7**, anion **23**, was examined in an effort to promote the ring closure (Scheme 8). Attempts at macrocyclization using this approach did not succeed; only the conjugate addition product (protio quench of anion **24**) was isolated.

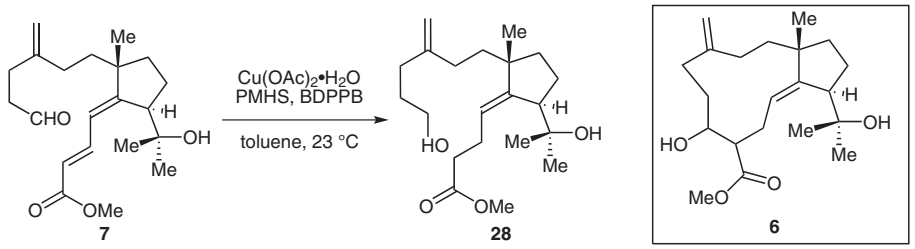
From the same scaffold, a reductive aldol pathway was investigated. Copper hydride reagents were examined to induce conjugate reduction of the dienoate **7**, which would provide an enolate that could be used to engage the aldehyde in an intramolecular aldol reaction.[28,29] Use of Stryker's reagent gave no reaction. Switching to the same copper hydride/phosphane system used earlier (see Scheme 4), conjugate reduction was effected but the desired accompanying cyclization did not occur, only reduction of the aldehyde to form alcohol **28** after prolonged reaction (Scheme 9).

In summary, we have reported an efficient route to construct the cyclopentane ring of (–)-stolonidiol and all of the carbons of the natural product with appropriate functionalization. The use of boron trifluoride–diethyl ether complex to promote the silylcuprate-mediated cyclization of epoxyalkyne **13** was key in accessing the cyclization precursors. With access to the key intermediates for macrocyclizations, **5** and **7**, the strategies employed to date have failed to successfully form the large 11-membered ring. Future efforts using these same types of substrates will employ related aldol and Horner–Wadsworth–Emmons strategies for the late-stage cyclizations.

All reactions were run under an atmosphere of argon or nitrogen using anhydrous conditions, unless otherwise indicated. Toluene, CH_2Cl_2, Et_2O, and THF were purified using a solvent purification system. All other reagents were used directly from the supplier without further purification, unless noted. Analytical thin-layer chromatography (TLC) was carried out using commercial 0.2-mm silica gel plates (silica gel 60, F254, EMD Chemicals). Infrared spectra were recorded using neat thin-film technique. High-resolution mass spectra (HRMS) are reported as *m/z*; accurate masses are reported for the molecular ion $[M + Na]^+$, $[M + H]^+$, or $[M^+]$. Nuclear magnetic resonance spectra (^1H and ^{13}C NMR) were recorded at 400 MHz (^1H) and 100 MHz (^{13}C). For $CDCl_3$ the chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvent: $CHCl_3$, δ H (7.26 ppm); $CDCl_3$, δ C (77.0 ppm). Coupling constants are reported in hertz (Hz). Data for ^1H NMR spectra are reported as follows: chemical shift (ppm, ref-



Scheme 8 Proposed internal-alkoxide-induced Baylis–Hillman macrocyclization of **7**



Scheme 9 Conjugate reduction/aldol cyclization strategy

erenced to protium), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, m = multiplet), coupling constant (in Hz), integration.

***tert*-Butyl{[(*R*)-2-ethynyl-2,6-dimethylhept-5-en-1-yl]oxy}dimethylsilane (11)**

The aldehyde **9**[14] (3.66 g, 12.86 mmol, 1.0 equiv) was dissolved in anhyd MeOH (120 mL) and the solution was cooled to 0 °C. Solid K_2CO_3 (4.44 g, 32.2 mmol, 2.5 equiv) was added, followed by neat Bestmann–Ohira reagent (dimethyl 1-diazo-2-oxopropylphosphonate, **10**) (3.70 g, 19.3 mmol, 1.5 equiv). The reaction mixture was allowed to warm to 23 °C and was stirred for 14 h. Over this period the solution changed from a clear yellow to green. The reaction mixture was poured into pentane (200 mL), and the organic layer was separated and washed with H_2O (400 mL) then brine (200 mL). The organic extract was dried (Na_2SO_4) and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (hexanes–EtOAc, 100:1) to provide **11** as a clear oil; yield: 3.20 g (91%).

R_f = 0.73 (hexanes–EtOAc, 9:1).

IR (neat): 2111, 1103, 851 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 5.07 (t, *J* = 8.6 Hz, 1 H), 3.49 (d, *J* = 9.4 Hz, 1 H), 3.41 (d, *J* = 9.4 Hz, 1 H), 2.08–2.02 (m, 2 H), 2.03 (s, 1 H), 1.63 (s, 3 H), 1.57 (s, 3 H), 1.51–1.44 (m, 1 H), 1.35–1.27 (m, 1 H), 1.12 (s, 3 H), 0.84 (s, 9 H), 0.00 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.5, 124.5, 89.2, 69.5, 69.4, 37.2, 25.9, 25.7, 23.8, 23.6, 18.4, 17.7, –5.3.

HRMS (EC-CI$^+$): *m*/*z* $[M - H]^+$ calcd for $C_{17}H_{31}OSi$: 279.2144; found: 279.2148.

***tert*-Butyl{[(*R*)-2-{2-[(*R*)-3,3-dimethyloxiran-2-yl]ethyl}-2-methylbut-3-yn-1-yl]oxy}dimethylsilane (13)**

Alkyne **11** (3.04 g, 10.8 mmol, 1.0 equiv) dissolved in dimethoxymethane–MeCN (2:1, 160 mL) was added to a 3-neck 1-L flask, followed by aq $Na_2B_4O_7$ soln (0.5 M with 4 mM Na_2EDTA, 105 mL), solid Bu_4NHSO_4 (0.294 g, 0.867 mmol, 0.08 equiv), and the Shi catalyst **12** (3.08 g, 11.9 mmol, 1.1 equiv). Then Oxone® (16.66 g, 27.1 mmol, 2.5 equiv) dissolved in a 4 mM Na_2EDTA soln (100 mL) in one addition funnel, and K_2CO_3 (14.98 g, 108 mmol, 10.0 equiv) in H_2O (100 mL) in a second addition funnel, were added simultaneously at 0 °C over 1.5 h. After the addition, the reaction mixture was diluted with pentane (300 mL) and H_2O (300 mL). The organic phase was collected and the aqueous layer was extracted with pentane (2 × 250 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure; NMR spectroscopy showed a 9:1 ratio of diastereomers. The crude material was purified by silica gel chromatography (hexanes–EtOAc, 99:1 to hexanes–EtOAc, 95:5) to afford **13** as a clear, colorless oil; yield: 2.79 g (86%).

R_f = 0.42 (hexanes–EtOAc, 9:1).

IR (neat): 1251, 1100 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.55 (d, *J* = 9.5 Hz, 1 H), 3.46 (d, *J* = 9.5 Hz, 1 H), 2.73 (t, *J* = 6.1 Hz, 1 H), 2.09 (s, 1 H), 1.74–1.55 (m, 4 H), 1.31 (s, 3 H), 1.28 (s, 3 H), 1.17 (s, 3 H), 0.89 (s, 9 H), 0.05 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 88.6, 69.9, 69.5, 64.5, 58.4, 37.1, 33.6, 25.9, 25.0, 24.7, 23.6, 18.7, 18.3, –5.3.

HRMS (EC-CI$^+$): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{33}O_2Si$: 297.2250; found: 297.2251.

Dimethyl(phenyl)silyllithium[20c]

A 50-mL flask equipped with a large stir bar was dried in an oven overnight. Lithium wire (0.540 g, 78.0 mmol, 2.0 equiv) was cut into 0.5-cm sections and added to the flask. The flask was then equipped with septa, evacuated, and backfilled with argon three times before placing the contents under argon. Anhyd THF (30 mL) was added to the flask which was placed in a 0 °C bath before $PhMe_2SiCl$ (6.0 mL, 39 mmol, 1.0 equiv) was added. After 15 min of stirring, the clear solution developed a red color. After 30 min, the solution obtained a dark red color. The flask was stirred at 0 °C for 2 h then placed in a –4 °C freezer to stand for 12 h. Such a solution proved stable at –4 °C for 2–3 weeks maintaining a titer of 0.5 M.

2-[(1*R*,3*R*,*E*)-3-{[(*tert*-Butyldimethylsilyl)oxy]methyl}-2-{[dimethyl(phenyl)silyl]methylene}-3-methylcyclopentyl]propan-2-ol (15)

Solid CuCN (1.04 g, 11.6 mmol, 1.15 equiv) was added to a flame-dried flask then purged with argon and flame-dried again under reduced pressure. The CuCN was suspended in THF (90 mL) and the flask was placed in a 0 °C bath. Dimethyl(phenyl)silyllithium (0.5 M in THF; 46.6 mL, 23.3 mmol, 2.3 equiv) was added via syringe. The reaction mixture was allowed to stir at 0 °C until all the CuCN had dissolved (indicated by the red color from $PhMe_2SiLi$ turning to a darker red-brown opaque solution, ~20 min). The reaction mixture was cooled to –78 °C, and epoxyalkyne **13** (3.0 g, 10.1 mmol, 1.0 equiv) was added as a solution in THF (20 mL) via cannula. The reaction mixture was warmed to 0 °C and allowed to stir for 2 h. Neat $BF_3{\cdot}OEt_2$ (3.73 mL, 30.4 mmol, 3.0 equiv) was added and the mixture was allowed to stir for 12 h, then poured into sat. NH_4Cl soln (100 mL) and extracted with Et_2O (2 × 100 mL). The combined organic extracts were washed with brine (150 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (hexanes–EtOAc, 99:1 to hexanes–EtOAc, 95:5) to provide **15** as a yellow oil; yield: 3.68 g (84%).

R_f = 0.52 (hexanes–EtOAc, 9:1).

IR (neat): 1599, 1249, 1093 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.50 (dd, *J* = 6.2, 2.7 Hz, 2 H), 7.32–7.30 (m, 3 H), 5.62 (d, *J* = 1.5 Hz, 1 H), 3.28 (d, *J* = 9.3 Hz, 1 H), 3.14 (d, *J* = 9.3 Hz, 1 H), 2.65 (dd, *J* = 8.2, 1.2 Hz, 1 H), 1.87–1.79 (m, 2 H), 1.47–1.44 (m, 2 H), 1.13 (s, 3 H), 1.05 (s, 3 H), 0.98 (s, 3 H), 0.87 (s, 9 H), 0.41 (s, 3 H), 0.35 (s, 3 H), 0.01 (s, 3 H), 0.00 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 140.4, 133.8, 128.7, 127.8, 121.7, 72.7, 72.5, 54.8, 50.5, 34.6, 29.1, 27.4, 27.2, 26.0, 23.0, 18.3, –0.3, –1.2, –5.4.

HRMS (EC-CI$^+$): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{45}O_2Si_2$: 433.2958; found: 433.2958.

***tert*-Butyl{[(1*R*,3*R*,*E*)-2-{[dimethyl(phenyl)silyl]methylene}-1-methyl-3-{2-[(trimethylsilyl)oxy]propan-2-yl}cyclopentyl]-methoxy}dimethylsilane**

To a soln of the tertiary alcohol **15** (3.50 g, 8.09 mmol, 1.0 equiv) in CH_2Cl_2 (80 mL) was added 2,6-luitdine (5.65 mL, 48.5 mmol, 6.0 equiv) and the solution was cooled to –78 °C in a dry ice–acetone bath. Neat TMSOTf (4.38 mL, 24.2 mmol, 3.0 equiv) was then added dropwise via syringe and the reaction mixture was stirred for 30 min before the cooling bath was removed and the solution was allowed to warm to 23 °C. Excess TMSOTf was quenched by the addition of MeOH (5 mL) and the mixture was concentrated under reduced pressure. The crude material was purified by silica gel chromatography (hexanes) to provide the TMS ether as a clear, colorless oil; yield: 3.92 g (96%).

R_f = 0.82 (hexanes).

IR (neat): 1604, 1250, 1033, 837 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.49 (m, 2 H), 7.31–7.30 (m, 3 H), 5.51 (s, 1 H), 3.34 (d, *J* = 10.2 Hz, 1 H), 3.24 (d, *J* = 9.2 Hz, 1 H), 2.32–2.30 (m, 1 H), 1.85–1.81 (m, 1 H), 1.74–1.70 (m, 2 H), 1.58–1.53 (m, 1 H), 1.14 (s, 3 H), 1.11 (s, 3 H), 1.03 (s, 3 H), 0.89 (s, 9 H), 0.34 (s, 3 H), 0.33 (s, 3 H), 0.05 (s, 9 H), 0.02 (s, 3 H), 0.01 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 140.2, 133.9, 128.7, 127.6, 118.7, 76.6, 72.8, 56.2, 49.6, 34.7, 30.3, 30.3, 30.2, 26.9, 26.0, 23.7, 18.4, 2.7, –0.5, –0.6, –5.4.

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $C_{28}H_{52}O_2Si_3Na$: 527.3181; found: 527.3169.

{[(1*R*,3*R*,*E*)-2-(Bromomethylene)-1-methyl-3-{2-[(trimethylsilyl)oxy]propan-2-yl}cyclopentyl]methoxy}(*tert*-butyl)dimethylsilane (17)

The vinylsilane (3.92 g, 7.76 mmol, 1.0 equiv) was dissolved in MeCN–CH_2Cl_2 (20:1, 78 mL) and solid NBS (2.76 g, 15.5 mmol, 2.0 equiv) was added in a single portion. The reaction mixture was stirred at 23 °C for 2 h and excess NBS was quenched with sat. aq $Na_2S_2O_3$ soln (50 mL) and sat. aq $NaHCO_3$ soln (50 mL). The organic layer was collected and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (150 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (hexanes) to provide **17** as a pale yellow oil; yield: 3.21 g (92%).

R_f = 0.76 (hexanes).

IR (neat): 1612, 1250, 1106, 1030, 837 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.18 (d, *J* = 1.3 Hz, 1 H), 3.30 (d, *J* = 11.3 Hz, 1 H), 3.29 (d, *J* = 11.6 Hz, 1 H), 2.69 (d, *J* = 8.2 Hz, 1 H), 1.95–1.83 (m, 2 H), 1.73–1.59 (m, 2 H), 1.39 (s, 3 H), 1.34 (s, 3 H), 1.12 (s, 3 H), 0.88 (s, 9 H), 0.11 (s, 9 H), 0.027 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.5, 101.8, 78.2, 77.3, 71.7, 57.2, 49.6, 36.9, 30.5, 30.4, 26.8, 25.9, 24.1, 18.3, 2.7, –5.3, –5.4.

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{41}BrO_2Si_2Na$: 471.1741; found: 471.1726.

2-[(1*R*,3*R*,*E*)-2-(Bromomethylene)-3-(hydroxymethyl)-3-methylcyclopentyl]propan-2-ol

Vinyl bromide **17** (1.0 g, 2.24 mmol, 1.0 equiv) was dissolved in THF (22 mL) at 23 °C and 1.0 M TBAF in THF (5.56 mL, 5.56 mmol, 2.5 equiv) was added in a single portion. The reaction mixture was stirred for 18 h, then diluted with sat. aq NH_4Cl soln (30 mL). The mixture was extracted with EtOAc (2 × 30 mL) and the combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (hexanes–EtOAc, 9:1 to hexanes–EtOAc, 4:1) to provide the diol as a viscous, clear yellow oil; yield: 0.574 g (98%).

R_f = 0.31 (hexanes–EtOAc, 1:1).

IR (neat): 3370, 1611, 1037, 949 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.22 (d, *J* = 1.7 Hz, 1 H), 3.45 (d, *J* = 10.9 Hz, 1 H), 3.37 (d, *J* = 10.9 Hz, 1 H), 2.93 (dd, *J* = 6.1, 1.4 Hz, 1 H), 1.89–1.77 (m, 4 H), 1.38 (s, 3 H), 1.28 (s, 3 H), 1.19 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 102.4, 75.1, 71.7, 55.9, 49.9, 36.8, 30.0, 28.9, 27.1, 23.7.

HRMS (ESI$^+$): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{19}BrO_2Na$: 285.0441; found: 285.0463.

(1*R*,3*R*,*E*)-2-(Bromomethylene)-3-(2-hydroxypropan-2-yl)-1-methylcyclopentanecarbaldehyde (18)

The diol (0.480 g, 1.82 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C. Solid $NaHCO_3$ (0.460 g, 5.47 mmol, 3.0 equiv) was added followed by Dess–Martin periodinane (0.851 g, 2.00 mmol, 1.1 equiv) in portions over 30 min. After an addition-

al 30 min, the excess periodinane was quenched by addition of sat. aq $Na_2S_2O_3$ soln (20 mL) followed by 10 min of vigorous stirring. The mixture was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (hexanes–EtOAc, 20:1 to hexanes–EtOAc, 10:1) to provide **18** as a viscous, clear yellow oil; yield: 0.438 g (92%).

R_f = 0.44 (hexanes–EtOAc, 1:1).

IR (neat): 3481, 1722, 1684, 1094 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.29 (s, 1 H), 6.11 (s, 1 H), 2.92 (d, *J* = 7.8 Hz, 1 H), 2.17–2.12 (m, 1 H), 2.06–1.97 (m, 2 H), 1.81–1.77 (m, 1 H), 1.39 (s, 3 H), 1.31 (s, 3 H), 1.30 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.8, 151.2, 105.8, 74.7, 58.7, 55.0, 34.6, 30.5, 29.4, 27.6, 20.7.

HRMS (CI^+): *m*/*z* [M – OH]$^+$ calcd for $C_{11}H_{16}BrO$: 243.0385; found: 243.0388.

(*E*)-1-[(1*S*,3*R*,*E*)-2-(Bromomethylene)-3-(2-hydroxypropan-2-yl)-1-methylcyclopentyl]-6-[(*tert*-butyldimethylsilyl)oxy]hex-1-en-3-one (20)

The ketophosphonate **19**[23] (0.560 g, 1.72 mmol, 1.5 equiv) was dissolved in toluene (10.0 mL) and 1.0 M LiHMDS in toluene (1.72 mL, 1.72 mmol, 1.5 equiv) was added. The mixture was stirred for 20 min then aldehyde **18** (0.300 g, 1.14 mmol, 1.0 equiv) was added at 23 °C as a solution in toluene (1.0 mL). The reaction mixture was placed in a 100 °C oil bath for 18 h. After cooling, the mixture was diluted with sat. aq NH_4Cl soln (20 mL) and extracted with EtOAc (2 × 20 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (hexanes–EtOAc, 20:1 to hexanes–EtOAc, 10:1) to provide **20** as a viscous, clear yellow oil; yield: 0.407 g (77%).

R_f = 0.47 (hexanes–EtOAc, 4:1).

IR (neat): 3488, 1666, 1617, 1256, 1099, 835 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.79 (d, *J* = 16.0 Hz, 1 H), 6.07 (d, *J* = 15.7 Hz, 1 H), 6.00 (d, *J* = 1.7 Hz, 1 H), 3.63 (t, *J* = 6.2 Hz, 2 H), 2.91–2.89 (m, 1 H), 2.63 (t, *J* = 7.1 Hz, 1 H), 2.04–1.75 (m, 6 H), 1.61 (s, 1 H), 1.38 (s, 3 H), 1.38 (s, 3 H), 1.30 (s, 3 H), 0.88 (s, 9 H), 0.03 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.8, 155.4, 153.7, 124.7, 105.8, 74.6, 62.2, 55.0, 50.5, 39.9, 37.0, 30.6, 29.3, 27.5, 27.0, 26.0, 24.1, 18.3, –5.2.

HRMS (ESI^+): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{40}BrO_3Si$: 459.1946; found: 459.1928.

1-[(1*S*,3*R*,*E*)-2-(Bromomethylene)-3-(2-hydroxypropan-2-yl)-1-methylcyclopentyl]-6-[(*tert*-butyldimethylsilyl)oxy]hexan-3-one

Solid $Cu(OAc)_2 \cdot H_2O$ (4.34 mg, 5 mol%) and 1,2-bis(diphenylphosphino)benzene (9.72 mg, 5 mol%) were combined in a flask equipped with a septum and the flask was evacuated and backfilled with argon three times; then, the solids were suspended in toluene (2 mL) at 23 °C. *t*-BuOH (0.062 mL, 0.653 mmol, 1.5 equiv) was added to the heterogeneous mixture which was allowed to stir until a faint blue color persisted. Neat polymethylhydrosiloxane (0.041 mL, 0.653 mmol, 1.5 equiv) was added and the reaction mixture was stirred until it turned bright yellow. At this point the reaction mixture became homogeneous. Enone **20** (0.200 g, 0.435 mmol, 1.0 equiv) was added as a solution in toluene (2 mL) and the reaction mixture was stirred for 18 h. After concentration under reduced pressure, the crude material was purified by silica gel chromatography (hexanes–EtOAc, 9:1) to provide the desired ketone as a clear, pale yellow oil; yield: 0.128 g (64%).

R_f = 0.52 (hexanes–EtOAc, 4:1).

IR (neat): 3480, 1713, 1257, 1096, 836 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.10 (d, *J* = 1.7 Hz, 1 H), 3.61 (t, *J* = 6.1 Hz, 2 H), 2.90–2.88 (m, 1 H), 2.48 (t, *J* = 7.5 Hz, 2 H), 2.44–2.28 (m, 2 H), 1.86–1.56 (m, 9 H), 1.37 (s, 3 H), 1.27 (s, 3 H), 1.17 (s, 3 H), 0.88 (s, 9 H), 0.03 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.9, 157.2, 102.8, 74.9, 62.2, 55.6, 47.5, 39.2, 39.0, 38.1, 37.7, 30.4, 29.1, 27.8, 27.1, 26.9, 26.0, 18.4, –5.2.

HRMS (ESI^+): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{42}BrO_3Si$: 461.2081; found: 461.2083.

2-[(1*R*,3*S*,*E*)-2-(Bromomethylene)-3-{6-[(*tert*-butyldimethylsilyl)oxy]-3-methylenehexyl}-3-methylcyclopentyl]propan-2-ol (21)

Solid methyltriphenylphosphonium bromide (0.495 g, 1.38 mmol, 5.0 equiv) was suspended in THF (2.0 mL) at 23 °C and 1.8 M *n*-BuLi in hexanes (0.755 mL, 1.36 mmol, 4.9 equiv) was added. A color change to bright red was observed and the reaction mixture became homogeneous over 20 min. To this clear red-yellow solution, the ketone (0.128 g, 0.277 mmol, 1.0 equiv) in THF (1 mL) was added dropwise. During addition the reaction mixture became opaque. After the mixture was stirred for 12 h, excess anion was quenched by careful addition of sat. aq NH_4Cl soln (10 mL) and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (hexanes–EtOAc, 10:1) to provide **21** as a clear yellow oil; yield: 0.092 g (72%).

R_f = 0.78 (hexanes–EtOAc, 4:1).

IR (neat): 3472, 1644, 1613, 1256, 1101, 835 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.10 (d, *J* = 1.7 Hz, 1 H), 4.70 (s, 2 H), 3.60 (t, *J* = 6.5 Hz, 2 H), 2.91–2.89 (m, 1 H), 2.07–1.50 (m, 12 H), 1.37 (s, 3 H), 1.27 (s, 3 H), 1.18 (s, 3 H), 0.89 (s, 9 H), 0.05 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.8, 149.8, 108.8, 102.4, 75.0, 62.9, 55.7, 48.1, 43.1, 38.1, 32.4, 31.7, 31.0, 30.4, 28.9, 27.8, 27.2, 26.0, 18.4, –5.1.

HRMS (ESI^+): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{43}BrO_2SiNa$: 481.2110; found: 481.2109.

6-[(1*S*,3*R*,*E*)-2-(Bromomethylene)-3-(2-hydroxypropan-2-yl)-1-methylcyclopentyl]-4-methylenehexan-1-ol

Vinyl bromide **21** (15 mg, 0.033 mmol, 1.0 equiv) was dissolved in THF (0.500 mL) at 23 °C and 1.0 M TBAF in THF (0.050 mL, 0.05 mmol, 1.5 equiv) was added. The reaction mixture was stirred for 2 h and diluted with 1 M pH 7 phosphate buffer (10 mL). The resulting solution was extracted with EtOAc (2 × 5 mL) and the combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (hexanes–EtOAc, 9:1 to hexanes–EtOAc, 4:1) to provide the diol as a viscous, clear yellow oil; yield: 10 mg (89%).

R_f = 0.42 (hexanes–EtOAc, 1:1).

IR (neat): 3393, 1643, 1613, 1383, 1057 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.10 (d, *J* = 1.7 Hz, 1 H), 4.73 (s, 2 H), 3.66 (t, *J* = 6.5 Hz, 2 H), 2.91–2.89 (m, 1 H), 2.11–1.91 (m, 4 H), 1.84–1.66 (m, 6 H), 1.58–1.48 (m, 2 H), 1.37 (s, 3 H), 1.27 (s, 3 H), 1.18 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.7, 149.6, 109.0, 102.3, 74.9, 62.7, 55.6, 48.0, 43.0, 38.1, 32.4, 31.5, 30.7, 30.3, 28.9, 27.8, 27.1.

HRMS (ESI^+): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{29}BrO_2Na$: 367.1250; found: 367.1246.

6-[(1*S*,3*R*,*E*)-2-(Bromomethylene)-3-(2-hydroxypropan-2-yl)-1-methylcyclopentyl]-4-methylenehexanal (5)

The diol (10 mg, 0.029 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (0.500 mL) and the flask was placed in a 0 °C bath. Solid $NaHCO_3$ (7 mg, 0.087 mmol, 3.0 equiv) was then added. Dess–Martin periodinane (14 mg, 0.032 mmol, 1.1 equiv) was added as a solid in a single portion. After 30 min of stirring, excess periodinane was quenched by addition of sat. aq $Na_2S_2O_3$ soln (2 mL) followed by 10 min of vigorous stirring. The mixture was extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (hexanes–EtOAc, 9:1 to hexanes–EtOAc, 4:1) to provide **5** as a viscous, clear yellow oil; yield: 8.6 mg (60%).

R_f = 0.69 (hexanes–EtOAc, 1:1).

IR (neat): 3433, 1721, 1643, 1266, 1094 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.78 (t, *J* = 1.3 Hz, 1 H), 6.10 (d, *J* = 1.3 Hz, 1 H), 4.78 (s, 1 H), 4.69 (s, 1 H), 2.91–2.89 (m, 1 H), 2.57 (dt, *J* = 7.5, 1.3 Hz, 2 H), 2.34 (t, *J* = 7.5 Hz, 2 H), 2.01–1.67 (m, 6 H), 1.56–1.52 (m, 2 H), 1.37 (s, 3 H), 1.27 (s, 3 H), 1.18 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.0, 157.6, 147.9, 109.4, 102.3, 74.8, 55.6, 48.0, 42.9, 41.8, 38.1, 31.9, 30.3, 28.9, 28.2, 27.8, 27.1.

HRMS (ESI^+): *m*/*z* [M + Na + H]$^+$ calcd for $C_{17}H_{27}BrO_2Na$: 366.1128; found: 366.1121.

Methyl (2*E*,4*E*)-4-[(2*S*,5*R*)-2-{6-[(*tert*-Butyldimethylsilyl)oxy]-3-methylenehexyl}-5-(2-hydroxypropan-2-yl)-2-methylcyclopentylidene]but-2-enoate (22)

To a soln of vinyl bromide **21** (0.120 g, 0.263 mmol, 1.0 equiv) in DMF (2.0 mL), Ph_3P (14 mg, 0.052 mmol, 0.2 equiv), TBAB (84 mg, 0.263 mmol, 1.0 equiv), methyl acrylate (0.237 mL, 2.61 mmol, 10.0 equiv), and Et_3N (0.294 mL, 2.08 mmol, 8.0 equiv) were added. The reaction mixture was sparged with argon and stirred for 20 min. Solid $Pd(OAc)_2$ (12 mg, 0.052 mmol, 0.20 equiv) was added and the reaction mixture was sparged with argon again; the flask was placed in an oil bath heated to 100 °C for 16 h. The mixture was cooled and diluted with H_2O (10 mL), then extracted with EtOAc (10 mL). The organic layer was washed with brine (4 × 15 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (hexanes–EtOAc, 20:1 to hexanes–EtOAc, 4:1) to provide **22** as a clear yellow oil; yield: 74 mg (61%).

R_f = 0.28 (hexanes–EtOAc, 4:1).

IR (neat): 3468, 1719, 1705, 1629, 1604, 1100, 835 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.69 (dd, *J* = 15.0, 11.2 Hz, 1 H), 6.19 (dd, *J* = 11.2, 1.4 Hz, 1 H), 5.79 (d, *J* = 15.0 Hz, 1 H), 4.68 (s, 2 H), 3.72 (s, 3 H), 3.59 (t, *J* = 6.5 Hz, 2 H), 3.06–3.03 (m, 1 H), 2.04–1.91 (m, 3 H), 1.84–1.76 (m, 3 H), 1.69–1.57 (m, 4 H), 1.51–1.46 (m, 2 H), 1.29 (s, 3 H), 1.19 (s, 3 H), 1.16 (s, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 166.1, 149.8, 144.1, 122.9, 118.7, 108.7, 77.3, 74.2, 62.8, 54.1, 51.5, 46.9, 43.0, 36.8, 32.4, 31.7, 31.0, 30.1, 28.5, 27.4, 26.8, 26.0, 18.4, –5.1.

HRMS (ESI^+): *m*/*z* [M + Na]$^+$ calcd for $C_{27}H_{48}O_4SiNa$: 487.3214; found: 487.3214.

Methyl (2*E*,4*E*)-4-[(2*S*,5*R*)-2-(6-Hydroxy-3-methylenehexyl)-5-(2-hydroxypropan-2-yl)-2-methylcyclopentylidene]but-2-enoate

To a soln of TBS ether **22** (40 mg, 0.086 mmol, 1.0 equiv) in THF (1.0 mL) at 23 °C was slowly added neat HF·py (70% HF; 0.039 mL, 0.430 mmol, 5.0 equiv) and the resulting cloudy solution was stirred for 8 h. Sat. aq $NaHCO_3$ soln (3 mL) was carefully added to the reaction mixture. The resulting mixture was then extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (15 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (hexanes–EtOAc, 4:1 to hexanes–EtOAc, 1:1) to provide the diol as a pale yellow oil; yield: 29 mg (98%).

R_f = 0.25 (hexanes–EtOAc, 1:1).

IR (neat): 3420, 1717, 1700, 1628, 1275, 1145 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.69 (dd, *J* = 15.0, 11.2 Hz, 1 H), 6.19 (d, *J* = 11.2 Hz, 1 H), 5.80 (d, *J* = 15.0 Hz, 1 H), 4.71 (s, 2 H), 3.72 (s, 3 H), 3.64 (t, *J* = 6.5 Hz, 2 H), 3.05 (t, *J* = 4.1 Hz, 1 H), 2.09–1.96 (m, 3 H), 1.89–1.76 (m, 3 H), 1.71–1.64 (m, 4 H), 1.51–1.45 (m, 2 H), 1.29 (s, 3 H), 1.18 (s, 3 H), 1.16 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 166.0, 149.6, 144.0, 122.8, 118.6, 109.0, 74.1, 62.7, 54.0, 51.4, 46.8, 42.9, 36.8, 32.4, 31.5, 30.6, 30.0, 28.4, 27.4, 26.7.

HRMS (ESI^+): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{34}O_4Na$: 373.2349; found: 373.2349.

Methyl (2*E*,4*E*)-4-[(2*S*,5*R*)-5-(2-Hydroxypropan-2-yl)-2-methyl-2-(3-methylene-6-oxohexyl)cyclopentylidene]but-2-enoate (7)

To a soln of the diol (15 mg, 0.043 mmol, 1.0 equiv) in CH_2Cl_2 (0.500 mL) at 23 °C was added solid $NaHCO_3$ (14 mg, 0.171 mmol, 4.0 equiv) in a single portion. Solid Dess–Martin periodinane (20 mg, 0.047 mmol, 1.1 equiv) was added in small portions over 20 min. After 10 min, the reaction mixture was diluted with sat. aq $Na_2S_2O_3$ soln (5 mL) followed by 10 min of vigorous stirring. The mixture was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude material was purified by silica gel chromatography (hexanes–EtOAc, 9:1 to hexanes–EtOAc, 4:1) to provide **7** as a viscous, clear yellow oil; yield: 12 mg (83%).

R_f = 0.38 (hexanes–EtOAc, 1:1).

IR (neat): 3489, 1717, 1629, 1604, 1274, 1143 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.76 (t, *J* = 1.7 Hz, 1 H), 7.69 (dd, *J* = 15.0, 11.2 Hz, 1 H), 6.19 (dd, *J* = 11.2, 1.7 Hz, 1 H), 5.80 (d, *J* = 15.0 Hz, 1 H), 4.75 (s, 1 H), 4.67 (s, 1 H), 3.72 (s, 3 H), 3.06–3.04 (m, 1 H), 2.55 (dt, *J* = 7.5, 1.7 Hz, 2 H), 2.32 (t, *J* = 7.5 Hz, 2 H), 2.04–1.96 (m, 1 H), 1.89–1.83 (m, 1 H), 1.81–1.75 (m, 1 H), 1.70–1.66 (m, 1 H), 1.52–1.48 (m, 4 H), 1.29 (s, 3 H), 1.19 (s, 3 H), 1.17 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.0, 167.9, 165.8, 147.9, 143.9, 122.8, 118.7, 109.4, 74.2, 54.0, 51.4, 46.7, 42.8, 41.8, 36.8, 31.9, 30.0, 28.4, 28.1, 27.3, 26.7.

HRMS (CI^+): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{33}O_4$: 349.2379; found: 349.2373.

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