3-Boronoacrolein as an Exceptional Heterodiene in the Highly Enantio- and Diastereoselective Cr(III)-Catalyzed Three-Component [4+2]/Allyboration

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Supporting Information

General information……………………………………………………………………………………2
Experimental procedures…………………………………………………………………………3

Synthesis of (2S, 4S)-2-ethoxy-4-hydroxy-3,4-dihydro-2H-pyran 5…………………………3
Synthesis of (2S, 4S)-2-ethoxy-4-acetoxy-3,4-dihydro-2H-pyran 6………………………5
Synthesis of (2S, 4S)-2-ethoxy-4-benzyloxy-3,4-dihydro-2H-pyran 7………………5
Synthesis of compound 8a-f……………………………………………………………………6
Synthesis of compound 8g and 8h……………………………………………………………11
Synthesis of compound 9……………………………………………………………………..13
Synthesis of compound 10……………………………………………………………………14
Synthesis of (5R, 6S)-6-acetoxy-5-hexadecanolide 2……………………………………15
Reproductions of \(^1\)H and \(^{13}\)C NMR spectra………………………………………………16
Chiral HPLC analysis……………………………………………………………………………..32
General Information

Catalyst 1 was prepared according to the procedure of Jacobsen.1 Boronate 3 was prepared according to our previously published procedure and purified by Kugelrohr distillation (< 0.5 mm Hg) (94%).2 Toluene and CH₂Cl₂ were distilled from CaH₂. Ethyl vinyl ether was stirred over KOH for 30 min. before distillation. All aldehydes were purified by Kugelrohr distillation prior to use. BaO (Acros) was used as supplied (90% tech powder). Powdered 4 Å molecular sieves (< 5 micron, Aldrich) were dried in a vacuum oven (138°C) prior to use. Unless otherwise stated, all reagents were purchased from Aldrich and used as received. Analytical thin layer chromatography was performed on Merck Silica Gel 60 F254 plates and were visualized with UV light and 1% KMnO₄(aq). NMR spectra were recorded on Varian INOVA-300, INOVA-400 or INOVA-500 MHz instruments. The residual solvent protons (¹H) or the solvent carbon (¹³C) were used as internal standards. ¹H NMR data are presented as follows: chemical shift in ppm (ppm) downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; dq, doublet of quartets; dd, doublet of doublets; m, multiplet. High resolution mass spectrum were recorded by the University of Alberta mass spectrum service laboratory using either electron impact (EI) or electrospray (ES) ionization techniques. Infrared spectra were obtained on a Nicolet Magna-IR 750 with frequencies expressed in cm⁻¹. Optical Rotations were measured using a 1mL cell with a 1dm length on a P.E. 241 polarimeter. Melting point were determined in a capillary tube in Gallenkamp melting point apparatus and are uncorrected.
Experimental procedures

Synthesis of (2S, 4S)-2-ethoxy-4-hydroxy-3,4-dihydro-2H-pyran 5 (Method A)

A mixture of 3-boronoacrolein pinacolate 3 (364mg, 2.00mmol) and ethyl vinyl ether (1.9mL, 20.00mmol) was placed in an oven dried 10ml RBF with stirbar. To this solution was added 1 (9.6 mg, 0.01mmol) and powdered 4Å MS (300mg). The reaction was allowed to stir for 14 h at ambient temperature then filtered through celite and concentrated in vacuo to give crude 4. 

$^1$H NMR (500 MHz, CDCl$_3$): δ 6.22 (dd, $J$=6.2, 2.1 Hz, 1H), 4.98 (dd, $J$=3.8, 2.9Hz, 1H), 4.82 (dd, $J$=6.2, 4.4Hz 1H), 3.82 (dq, $J$=9.7, 7.1Hz, 1H), 3.56 (dq, $J$=9.7, 7.1Hz, 1H), 1.99 (m, 2H), 1.76 (m, 1H), 1.16-1.23 (m, 15H).

The Diels-Alder cycloadduct 4 was dissolved in THF (10mL) and cooled to 0°C. An aqueous solution of 3M NaOAc (1.0mL, 3.00mmol) was added dropwise and the temperature maintained below 5°C. Hydrogen peroxide (0.61mL, 6.55mmol) was added and the mixture was stirred at 0°C for 1 hr. Water (10mL) was then added and the aqueous layer extracted with ether (2 × 30mL). The ether layers were combined, washed with saturated solutions of NH$_4$Cl (15mL) and NaCl (15mL), then dried over anhydrous MgSO$_4$. Filtration and concentration in vacuo gave the crude product 5, which was purified by flash column chromatography (deactivated silica-gel, pentane:ether (4:1)) to provide 5 (234mg, 81%) as a clear oil. [α]$_D$$_{3}$$^3$ +136.0° (c=1.0, CHCl$_3$); IR (CH$_2$Cl$_2$, cast, cm$^{-1}$): 3553, 3431, 1646, 1297; $^1$H NMR (500 MHz, CDCl$_3$): δ 6.24 (d, $J$=6.2 Hz, 1H), 5.22 (dd, $J$=2.2, 2.2Hz, 1H), 5.16 (m, 1H), 3.95 (m, 1H), 3.80 (dq, $J$=9.7, 7.1Hz, 1H), 3.52 (dq, $J$=9.7, 7.1Hz, 1H), 3.04 (d, $J$=11.2Hz, 1H), 2.24 (m, 1H), 2.02 (m, 1H), 1.21 (t,
$J=7.1\text{Hz, 3H})$; $^{13}\text{C NMR (125 MHz, CDCl}_3): [140.8, 105.9, 96.6, 64.2, 58.6, 35.0, 15.2; HRMS(EI, m/z) Calcd for C$_7$H$_{12}$O$_3$: 144.07864. Found: 144.07827.

Assay of enantiomeric excess: Chiral HPLC analysis (Chiralpak AD-RH, 50% isopropanol/water, 0.300mL/min, 210.8nm), $t_R$(major)=8.60 in., $t_R$(minor)=10.64min.) 96% ee.

**Synthesis of (2S, 4S)-2-ethoxy-4-hydroxy-3,4-dihydro-2H-pyran 5 (Method B)**

A mixture of 3-boronoacrolein pinacolate 3 (364mg, 2.00mmol) and ethyl vinyl ether (1.9mL, 20.00mmol) was placed in an oven dried 10ml RBF with stirbar. To this solution was added 1 (2.8 mg, 0.003mmol) and powdered BaO (600mg). The reaction was allowed to stir for 14 h at ambient temperature then filtered through celite and concentrated *in vacuo* to give crude 4.

The Diels-Alder cycloadduct 4 was dissolved in THF (10mL) and cooled to 0°C. An aqueous solution of 3M NaOAc (1.0mL, 3.00mmol) was added dropwise and the temperature maintained below 5°C. Hydrogen peroxide (0.61mL, 6.55mmol) was added and the mixture stirred at 0°C for 1 h. Water (10mL) was added and the aqueous layer was extracted with ether (2 ¥ 30mL). The ether layers were combined, washed with saturated solutions of NH$_4$Cl (15mL) and NaCl (15mL), then dried over anhydrous MgSO$_4$. Filtration and concentration *in vacuo* gave the crude product 5, which was purified by flash column chromatography (deactivated silica-gel, pentane:ether (4:1)) to provide 5 (234mg, 81%) as a clear oil.
Assay of enantiomeric excess: Chiral HPLC analysis (chiralpak AD-RH, 50% isopropanol/water, 0.300mL/min, 210.8nm), $t_R$(major)=8.60min., $t_R$(minor)=10.64min.) 96% ee.

**Synthesis of (2S, 4S)-2-ethoxy-4-acetoxy-3,4-dihydro-2H-pyran 6**

To a 25ml RBF was added 5 (186mg, 1.29mmol), 2,6-lutidine (0.20ml, 1.96mmol) and DMAP (15.7mg, 0.129mmol) in dry CH$_2$Cl$_2$ (4mL). The mixture was cooled to 0°C and acetic anhydride was added via a syringe (0.12mL, 1.29mmol). The reaction mixture was stirred at 0°C for 1 hr and further stirred at ambient temperature overnight. Water (10mL) and ether (30mL) was added to the solution. The phases were separated and the aqueous layer was extracted with ether (20mL). The combined organic layers were washed with a saturated solution of NaCl, dried over anhydrous MgSO$_4$, filtered, concentrated and purified by flash column chromatography (deactivated silica-gel, hexane:ether (9:1)) to provide 6 (233mg, 96%) as a clear oil. $[\alpha]^\text{D}$_3+37.0° (c=1.0, CHCl$_3$); IR (CH$_2$Cl$_2$, cast, cm$^{-1}$): 3071, 2929, 1730, 1650, 1244; $^1$H NMR (300MHz, CDCl$_3$): δ 6.42 (dd, $J$=6.3, 1.0 Hz, 1H), 5.30 (m, 1H), 5.06 (dd, $J$=5.2, 2.9Hz, 1H), 4.96(m, 1H), 3.90 (dq, $J$=9.7, 7.1Hz, 1H), 3.58 (dq, $J$=9.7, 7.1Hz, 1H), 2.06-2.30 (m, 2H), 2.05 (s, 3H), 1.21 (t, $J$=7.1Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 170.9, 144.2, 100.7, 96.6, 64.5, 62.7, 33.0, 21.3, 15.0; HRMS (EI, m/z) Calcd for C$_9$H$_{14}$O$_4$: 186.08920. Found: 186.08969.

**Synthesis of (2S,4S)-2-Ethoxy-4-benzyloxy-3,4-dihydro-2H-pyran 7**

To a solution of 5 (570mg, 3.95mmol) in DMF (10mL) cooled in an ice-water bath was added NaH (95%, 131mg, 5.20mmol). The mixture was stirred at 0°C for 30 min. then
benzyl bromide (0.57mL, 4.8mmol) was added dropwise. The reaction mixture was slowly warmed to ambient temperature and stirred overnight. The mixture was added to water (25mL) and ether (50mL) and the phase were separated. The aqueous layer was extracted with ether (25mL), and the combined organic layers were washed with a saturated solution of NaCl, dried over anhydrous MgSO₄, concentrated and purified by flash column chromatography (deactivated silica-gel, hexane:ether (95 : 5)) to provide 7 (878mg, 95%) as a clear oil. [α]D +22.8° (c=1.0, CHCl₃); IR (CH₂Cl₂, cast, cm⁻¹): 3064, 2976, 1646, 1229; ¹H NMR (400MHz, CDCl₃): δ 7.10-7.20 (m, 5H), 6.30 (dd, Jₙ=6.3, 1.3 Hz, 1H), 4.99 (dd, J=7.7, 2.5Hz, 1H), 4.93 (dd, J=7.2, 1.9Hz, 1H), 4.56 (d, J=1.3Hz, 2H), 4.18 (m, 1H), 3.88 (dq, J=9.7, 7.1Hz, 1H), 3.58 (dq, J=9.7, 7.1Hz, 1H), 2.22 (m, 1H), 2.05 (m, 1H), 1.25 (t, J=7.1Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 143.0, 138.6, 128.3, 127.6, 127.5, 102.8, 98.2, 69.7, 67.9, 64.5, 34.3, 15.1; HRMS (EI, m/z) Calcd for C₁₄H₁₈O₃: 234.12560. Found: 234.12579.

**Synthesis of compound 8a**

A mixture of 3-boronoacrolein pinacolate 3 (364mg, 2.00mmol) and ethyl vinyl ether (1.9mL, 20.00mmol) was placed in an oven dried 10ml RBF with stirbar. To this solution was added 1 (9.6 mg, 0.01mmol) and powdered 4Å MS (300mg). After stirred for 14 h at ambient temperature, benzaldehyde (0.41mL, 4.00mmol) was added to the reaction mixture. The reaction mixture was allowed to stir at 40°C for 24 h, then diluted with ethyl acetate and filtered through celite. The ethyl acetate solution was then stirred for 30 min. with a saturated solution of NaHCO₃. The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 ✕ 20mL). The combined organic layers
were washed with saturated NaCl, dried over anhydrous MgSO$_4$, filtered, and concentrated to afford 8a as a crude product. Purification by flash column chromatography (deactivated silica-gel, hexane:ether (9:1)) led to the pure product 8a (384mg, 82%) as a clear oil. $[^{23}$D$]+24.9^\circ$ (c=1.0, CHCl$_3$); IR (CH$_2$Cl$_2$, cast, cm$^{-1}$): 3451, 3035, 2877, 1640, 1257; $^1$H NMR (500MHz, CDCl$_3$): $\delta$ 7.26-7.40 (m, 5H), 5.75 (m, 1H), 5.40 (m, 1H), 4.78 (dd, $J$=5.9, 5.9Hz, 1H), 4.56 (dd, $J$=7.4, 1.5Hz, 1H), 4.36 (m, 1H), 3.96 (dq, $J$=9.7, 7.1Hz, 1H), 3.58 (dq, $J$=9.7, 7.1Hz, 1H), 3.11 (s, 1H), 2.13 (m, 2H), 1.25 (t, $J$=7.1Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 139.8, 128.3, 128.0, 127.2, 125.4, 124.8, 98.5, 78.7, 76.8, 64.5, 31.1, 15.3; HRMS (ESI, m/z) Calcd for C$_{14}$H$_{18}$O$_3$Na: 257.115364. Found: 257.115200.

**Synthesis of compound 8b**

A mixture of 3-boronoacrolein pinacolate 3 (364mg, 2.00mmol) and ethyl vinyl ether (1.9mL, 20.00mmol) was placed in an oven dried 10ml RBF with stirbar. To this solution was added 1 (9.6 mg, 0.01mmol) and powdered 4Å MS (300mg). After stirred for 14 h at ambient temperature, 4-nitrobenzaldehyde (604mg, 4.00mmol) was added to the reaction mixture. The reaction mixture was allowed to stir at ambient temperature for 24 h, then diluted with ethyl acetate and filtered through celite. The ethyl acetate solution was then stirred for 30 min. with a saturated solution of NaHCO$_3$. The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 ¥ 20mL). The combined organic layers were washed with saturated NaCl, dried over anhydrous MgSO$_4$, filtered, and concentrated to afford 8b as a crude product. Purification by flash column chromatography (deactivated silica-gel, hexane:ether (9:1)) led to the pure product 8b.
(512mg, 92%) as a brown solid. Mp 102-103°C; [\(\alpha\)]\textsc{D}\textsubscript{23} +23.0° (c=1.0, CHCl\textsubscript{3}); IR (CH\textsubscript{2}Cl\textsubscript{2}, cast, cm\textsuperscript{-1}): 3442, 2977, 1604, 1519, 1431; \(^1\)H NMR (500MHz, CDCl\textsubscript{3}): \(\delta\) 8.21 (d, \(J=8.7\)Hz, 2H), 7.58 (d, \(J=8.7\)Hz, 2H), 5.95 (m, 1H), 5.48 (m, 1H), 4.79 (dd, \(J=6.3, 3.9\)Hz, 1H), 4.75 (dd, \(J=4.9, 4.9\)Hz, 1H), 4.39 (m, 1H), 3.83 (dq, \(J=9.6, 7.1\)Hz, 1H), 3.52 (dq, \(J=9.6, 7.1\)Hz, 1H), 3.39 (d, \(J=3.9\)Hz, 1H), 2.22 (m, 2H), 1.25 (t, \(J=7.1\)Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\textsubscript{3}): \(\delta\) 147.8, 147.5, 127.8, 125.6, 124.7, 123.4, 98.1, 77.8, 75.6, 64.7, 30.8, 15.3; HRMS (EI, \(m/z\)) Calcd for C\textsubscript{14}H\textsubscript{16}O\textsubscript{3}N: 278.10284. Found: 278.10265.

**Synthesis of compound 8c**

A mixture of 3-boronoacrolein pinacolate 3 (364mg, 2.00mmol) and ethyl vinyl ether (1.9mL, 20.00mmol) was placed in an oven dried 10ml RBF with stirbar. To this solution was added 1 (9.6 mg, 0.01mmol) and powdered 4Å MS (300mg). After stirred for 14 h at ambient temperature, \(p\)-anisaldehyde (0.49mL, 4.00mmol) was added to the reaction mixture. The reaction mixture was allowed to stir at 45°C for 24 h, then diluted with ethyl acetate and filtered through celite. The ethyl acetate solution was then stirred for 30 min. with a saturated solution of NaHCO\textsubscript{3}. The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 \(\times\) 20mL). The combined organic layers were washed with saturated NaCl, dried over anhydrous MgSO\textsubscript{4}, filtered, and concentrated to afford 8c as a crude product. Purification by flash column chromatography (deactivated silica-gel, hexane:ether (9:1)) led to the pure product 8c (428mg, 81%) as a clear oil. [\(\alpha\)]\textsc{D}\textsubscript{23} +24.3° (c = 1.0, CHCl\textsubscript{3}); IR (CH\textsubscript{2}Cl\textsubscript{2}, cast, cm\textsuperscript{-1}): 3442, 2977, 1604, 1519, 1431; \(^1\)H NMR (500MHz, CDCl\textsubscript{3}): \(\delta\) 7.32 (d, \(J=8.1\)Hz, 2H), 6.85 (d, \(J=8.1\)Hz, 2H), 5.76 (m, 1H), 5.38 (m, 1H), 4.79 (dd, \(J=7.7, 5.3\)Hz, 1H), 4.50 (d,
$J=7.7\text{Hz}, 1\text{H})$, 4.29 (m, 1H), 4.01 (dq, $J=9.6, 7.1\text{Hz}, 1\text{H})$, 3.80 (s, 3H), 3.59 (dq, $J=9.6, 7.1\text{Hz}, 1\text{H})$, 3.18 (br s, 1H), 2.23 (m, 2H), 1.23 (t, $J=7.1\text{Hz}, 3\text{H})$; $^{13}\text{C NMR (125 MHz, CDCl}_3$): $\delta$ 159.4, 131.9, 128.5, 125.4, 124.7, 113.7, 98.5, 78.8, 76.4, 64.5, 55.2, 31.1, 15.2; HRMS (EI, $m/z$) Calcd for C$_{15}$H$_{20}$O$_4$: 264.13617. Found: 264.13670.

**Synthesis of compound 8d**

A mixture of 3-boronoacrolein pinacolate 3 (364mg, 2.00mmol) and ethyl vinyl ether (1.9mL, 20.00mmol) was placed in an oven dried 10ml RBF with stirbar. To this solution was added 1 (9.6 mg, 0.01mmol) and powdered 4Å MS (300mg). After stirred for 14 h at ambient temperature, isovaleraldehyde (0.43mL, 4.00mmol) was added to the reaction mixture. The reaction mixture was allowed to stir at 45°C for 24 h, then diluted with ethyl acetate and filtered through celite. The ethyl acetate solution was then stirred for 30 min. with a saturated solution of NaHCO$_3$. The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 ¥ 20mL). The combined organic layers were washed with saturated NaCl, dried over anhydrous MgSO$_4$, filtered, and concentrated to afford 8d as a crude product. Purification by flash column chromatography (deactivated silica-gel, hexane:ether (9:1)) led to the pure product 8d (347mg, 81%) as a clear oil. 

$[\alpha]_D^{23}+98.0^\circ$ (c = 1.0, CHCl$_3$); IR (CH$_2$Cl$_2$, cast, cm$^{-1}$): 3446, 3041, 1467, 1293; $^1\text{H NMR (300MHz, CDCl}_3$): $\delta$ 5.82 (m, 1H), 5.66 (m, 1H), 4.79 (dd, $J=5.5, 5.5\text{Hz}, 1\text{H})$, 4.10 (m, 1H), 3.96 (dq, $J=9.6, 7.1\text{Hz}, 1\text{H})$, 3.50-3.66 (m, 2H), 2.42 (d, $J=5.7\text{Hz}, 1\text{H})$, 2.23 (m, 2H), 1.86 (m, 1H), 1.52 (m, 1H), 1.22-1.38 (m, 4H), 0.96 (d, $J=7.8\text{Hz}, 3\text{H})$, 0.93 (d, $J=7.8\text{Hz}, 3\text{H})$; $^{13}\text{C NMR (125 MHz, CDCl}_3$): $\delta$ 126.6, 124.7, 98.4, 77.7, 71.4, 64.2, 41.9,
31.1, 24.4, 23.6, 21.8, 15.1; HRMS (ESI, m/z) Calcd for $\text{C}_{12}\text{H}_{22}\text{O}_3\text{Na}$: 237.14612 Found: 237.14607.

**Synthesis of compound 8e**

A mixture of 3-boronoacrolein pinacolate 3 (364mg, 2.00mmol) and ethyl vinyl ether (1.9mL, 20.00mmol) was placed in an oven dried 10ml RBF with stirbar. To this solution was added 1 (9.6 mg, 0.01mmol) and powdered 4Å MS (300mg). After stirred for 14 h at ambient temperature, tert-butyl(dimethylsilyloxy)acetaldehyde (0.76mL, 4.00mmol) was added to the reaction mixture. The reaction mixture was allowed to stir at 45°C for 24 h, then diluted with ethyl acetate and filtered through celite. The ethyl acetate solution was then stirred for 30 min. with a saturated solution of NaHCO$_3$. The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 × 20mL). The combined organic layers were washed with saturated NaCl, dried over anhydrous MgSO$_4$, filtered, and concentrated to afford 8e as a crude product. Purification by flash column chromatography (deactivated silica-gel, hexane:ether (9:1)) led to the pure product 8e (496mg, 82%) as clear oil. $[^1]D$ +34.5° (c = 1.0, CHCl$_3$); IR (CH$_2$Cl$_2$, cast, cm$^{-1}$): 3324, 3038, 2857, 1317; $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 5.82 (m, 1H), 5.66 (m, 1H), 4.76 (dd, $J$=6.2, 4.7Hz, 1H), 4.42 (m, 1H), 3.93 (dq, $J$=9.6, 7.1Hz, 1H), 3.60-3.76 (m, 3H), 3.50 (dq, $J$=9.6, 7.1Hz, 1H), 2.62 (d, $J$=5.9Hz, 1H), 2.23 (m, 2H), 1.25 (t, $J$=7.1Hz, 3H), 0.86 (s, 9H), 0.02 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 126.8, 124.5, 98.4, 73.9, 73.2, 64.4, 63.2, 31.0, 25.9, 18.2, 15.1, -5.4, -5.5; HRMS (ESI, m/z) Calcd for $\text{C}_{15}\text{H}_{30}\text{O}_4\text{NaSi}$: 325.18056 Found: 325.18041.
Synthesis of compound 8f

A mixture of 3-boronoacrolein pinacolate 3 (364mg, 2.00mmol) and ethyl vinyl ether (1.9mL, 20.00mmol) was placed in an oven dried 10ml RBF with stirbar. To this solution was added 1 (9.6 mg, 0.01mmol) and powdered 4Å MS (300mg). After stirred for 14 h at ambient temperature, undecanal (0.82mL, 4.00mmol) was added to the reaction mixture. The reaction mixture was allowed to stir at 45°C for 24 h, then diluted with ethyl acetate and filtered through celite. The ethyl acetate solution was then stirred for 30 min. with a saturated solution of NaHCO₃. The organic layer was separated and the aqueous layer extracted with ethyl acetate (2 ¥ 20mL). The combined organic layers were washed with saturated NaCl, dried over anhydrous MgSO₄, filtered, and concentrated to afford 8f as a crude product. Purification by flash column chromatography (deactivated silica-gel, hexane:ether (9:1)) led to the pure product 8f (530mg, 89%) as a clear oil. [ ObjectOutputStream[\x2044]\x2044] [3] D +54.7° (c = 1.0, CHCl₃); IR (CH₂Cl₂, cast, cm⁻¹): 3451, [ ObjectOutputStream[\x2044]\x2044] [3] D +54.7° (c = 1.0, CHCl₃); IR (CH₂Cl₂, cast, cm⁻¹): 3454, 3040, 2854, 1209; ¹H NMR (300MHz, CDCl₃): δ 5.82 (m, 1H), 5.66 (m, 1H), 4.76 (dd, J=5.5, 5.5Hz, 1H), 4.16 (m, 1H), 3.96 (dq, J=9.5, 7.1Hz, 1H), 3.46-3.62 (m, 2H), 2.42 (d, J=5.7Hz, 1H), 2.23 (m, 2H), 1.20-1.60 (m, 21H), 0.88 (t, J=6.8Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 126.7, 124.7, 98.5, 77.2, 73.3, 64.3, 33.0, 31.9, 31.1 29.7, 29.6, 29.6, 29.5, 29.3, 25.6, 22.6, 15.1, 14.0; HRMS (EI, m/z) Calcd for C₁₉H₃₄O₃: 298.25079, Found: 298.25044.

Synthesis of compound 8g

A mixture of 3-boronoacrolein pinacolate 3 (364mg, 2.00mmol) and ethyl vinyl ether (1.9mL, 20.00mmol) was placed in an oven dried 10ml RBF with stirbar. To this
solution was added 1 (9.6 mg, 0.01mmol) and powdered 4Å MS (300mg). After 14 h at ambient temperature, the ethyl vinyl ether was evaporated in vacuo. The residue was dissolved in CH₂Cl₂ (1mL) and 4-nitrocinamaldehyde (708mg, 4.00mmol) was added to the solution. The reaction was allowed to stir at 40°C for 24 h, then diluted with ethyl acetate and filtered through celite. The ethyl acetate solution was stirred for 30 min. with a saturated solution of NaHCO₃. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 20mL). The combined organic layers were washed with saturated NaCl then dried over anhydrous MgSO₄, filtered, and concentrated to afford 8g as a crude product. Purification by flash column chromatography (deactivated silica-gel, hexane:ether (9:1)) led to the pure product 8g (495mg, 81%) as a brown solid. Mp 99-100°C; [α]D²³ +55.0° (c = 1.0, CHCl₃); IR (CH₂Cl₂, cast, cm⁻¹): 3426, 1650, 1596, 1432, 1210; ¹H NMR (500MHz, CDCl₃): δ 8.18 (d, J=8.7Hz, 2H), 7.50 (d, J=8.7Hz, 2H), 6.80 (d, J=16.0Hz, 1H), 6.45 (dd, J=16.0, 5.2Hz, 1H), 5.86 (m, 1H), 5.65 (m, 1H), 4.80 (dd, J=6.4, 3.8Hz, 1H), 4.30 (m, 2H), 3.95 (dq, J=9.6, 7.1Hz, 1H), 3.57 (dq, J=9.6, 7.1Hz, 1H), 3.02 (br s, 1H), 2.15-2.35 (m, 2H), 1.25 (t, J=7.1Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 146.9, 143.1, 133.2, 129.9, 127.0, 125.2, 125.2, 123.9, 98.1, 77.1, 74.3, 64.7, 30.9, 15.2; HRMS (ESI, m/z) Calcd for C₁₆H₁₉O₅NNa: 328.116093. Found: 328.116463.

**Synthesis of compound 8h**

A mixture of 3-boronoacrolein pinacolate 3 (364mg, 2.00mmol) and ethyl vinyl ether (1.9mL, 20.00mmol) was placed in an oven dried 10ml RBF with stirbar. To this solution was added 1 (9.6 mg, 0.01mmol) and powdered 4Å MS (300mg). After 14 h at
ambient temperature, the ethyl vinyl ether was evaporated in vacuo. The residue was dissolved in CH$_2$Cl$_2$ (1mL) and trans-2-methyl-2-butenal (0.39mL, 4.00mmol) was added to the solution. The reaction was allowed to stir at 50°C for 48 h, then diluted with ethyl acetate and filtered through celite. The ethyl acetate solution was stirred for 30 min. with a saturated solution of NaHCO$_3$. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 ¥ 20mL). The combined organic layers were washed with saturated NaCl then dried over anhydrous MgSO$_4$, filtered, and concentrated to afford 8h as a crude product. Purification by flash column chromatography (deactivated silica-gel, hexane:ether (9:1)) led to the pure product 8h (261mg, 61%) as a clear oil. [$\alpha$]$^D_{23}$ +57.1° (c = 1.0, CHCl$_3$); IR (CH$_2$Cl$_2$, cast, cm$^{-1}$): 3462, 3041, 1650, 1256; $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 5.80 (m, 1H), 5.46-5.62 (m, 2H), 4.78 (dd, $J$=6.2, 5.0Hz, 1H), 4.22 (m, 1H), 3.86-4.02 (m, 2H), 3.58 (dq, $J$ =9.6, 7.1Hz, 1H), 2.80 (br s, 1H), 2.23 (m, 2H), 1.62-1.66 (m, 6H), 1.23 (t, $J$=7.1Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 133.8, 126.0, 124.4, 124.2, 98.6, 79.9, 76.0, 63.4, 31.1, 15.2, 13.1, 11.6; HRMS (ESI, m/z) Calcd for C$_{12}$H$_{20}$O$_3$Na: 235.13047 Found: 235.12994.

**Synthesis of compound 9**

Compound 8f (596mg, 2.00mmol) was dissolved in ether (10mL) and Pd/C (10%wt, 30mg) was added. The reaction was stirred under an atmosphere of H$_2$ for 4 h, then filtered through celite, and the celite washed with ether. The ether was evaporated to give crude 9. Purification by flash column chromatography (deactivated silica-gel, hexane:ether (9:1)) led to the isolation of 9 (541mg, 90%) as a clear oil. [$\alpha$]$^D_{23}$ +39.0° (c=1.0, CHCl$_3$); IR (CH$_2$Cl$_2$, cast, cm$^{-1}$): 3465, 2924, 1442, 1255; $^1$H NMR (300MHz,
CDCl$_3$): 4.42 (dd, $J$=9.3, 2.1Hz, 1H), 3.86 (dq, $J$=9.5, 7.1Hz, 1H), 3.42-3.60 (m, 2H), 3.25 (m, 1H), 2.52 (d, $J$=3.9Hz, 1H), 1.76-1.96 (m, 2H), 1.22-1.58 (m, 25H), 0.88 (t, $J$=6.8Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 102.2, 79.1, 73.8, 64.1, 32.7, 31.8, 31.2, 29.6, 29.5, 29.5, 26.5, 25.3, 22.6, 21.9, 15.2, 14.0 (Note: two missing alkane CH$_2$ carbon peaks are overlapping with others); HRMS (EI, $m/z$) Calcd for C$_{18}$H$_{36}$O$_3$: 300.26645, Found: 300.26580.

**Synthesis of compound 10**

To a stirred solution of 9 (284mg, 0.95mmol) in CH$_2$Cl$_2$ (10mL) was added Et$_3$N (0.27mL, 1.5mmol) and the solution was stirred at 0°C for 30 min. Methanesulfonyl chloride (90mL, 1.14mmol) was added and the solution stirred for additional 30 min. Saturated NH$_4$Cl solution (12mL) was then added to the solution. The organic layer was separated and the aqueous layer extracted with ether (30mL). The organic layers were combined, dried over anhydrous MgSO$_4$ and concentrated. The crude mesylate was used for the next reaction without further purification.

To the crude mesylate was added cesium acetate (640mg, 3.3mmol), 18-Crown-6 (600mg, 2.3mmol) and toluene (10mL). The reaction was allowed to stir at 100°C for 24 h. The solution was cooled to ambient temperature and concentrated. The residual oil was purified by flash column chromatography (deactivated silica-gel, hexane:ether (19: 1)) to give compound 10 (201mg, 62%) as a clear oil. [$^2$H]$_3$D$_3$ +14.1° (c=1.0, CHCl$_3$); IR (CH$_2$Cl$_2$, cast, cm$^{-1}$): 2926, 1743, 1441, 1201; $^1$H NMR (300MHz, CDCl$_3$): 4.95 (m, 1H), 4.36 (dd, $J$=9.2, 2.1Hz, 1H), 3.82 (dq, $J$=9.5, 7.1Hz, 1H), 3.50 (dq, $J$=9.5, 7.1Hz, 1H), 3.42 (m, 1H), 2.02 (s, 3H), 1.22-1.96 (m, 27H), 0.88 (t, $J$=6.8Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$): δ 102.2, 79.1, 73.8, 64.1, 32.7, 31.8, 31.2, 29.6, 29.5, 29.5, 26.5, 25.3, 22.6, 21.9, 15.2, 14.0 (Note: two missing alkane CH$_2$ carbon peaks are overlapping with others); HRMS (EI, $m/z$) Calcd for C$_{18}$H$_{36}$O$_3$: 300.26645, Found: 300.26580.
CDCl₃): δ 170.4, 102.2, 76.6, 75.5, 63.9, 31.8, 31.1, 30.4, 29.5, 29.4, 29.2, 26.6, 25.0, 22.6, 21.8, 21.0, 15.1, 14.0 (Note: two missing alkane CH₃ carbon peaks are overlapping with others); HRMS (ESI, m/z) Calcd for C₁₈H₃₈O₄Na: 365.26623, Found: 365.26664.

**Synthesis of (5R, 6S)-6-acetoxy-5-hexadecanolide 2**

To a stirred solution of 10 (126mg, 0.37mmol) and m-chloroperoxybenzoic acid (pure, 182mg, 0.48mmol) in CH₂Cl₂ (2mL) at 0°C, was added dropwise BF₃-OEt₂ (50µL, 0.40mmol) The mixture was stirred for 10min. followed by 1.5h at ambient temperature. The mixture was then cooled to 0°C and Et₃N (0.26mL, 1.85mmol) was added slowly. The solution was allowed to stir at 0°C for 2h, then poured into a mixture of saturated solution of NaHCO₃ and Na₂S₂O₃. The mixture was extracted with ether (3×15mL), the organic layers were combined, dried over MgSO₄ and concentrated. The residual oil was purified by flash chromatography (hexane:ether (4:1)) to give 2 (102mg, 88%) as a clear oil. The spectral data are in full accord with the literature data.³ [α]₂₃D −35.1° (c=1.1, CHCl₃), Lit.³ [α]D −34.5° (c=1.11, CHCl₃); IR (CH₂Cl₂, cast, cm⁻¹), 2924, 1744, 1466, 1229; ¹H NMR (300MHz, CDCl₃): 4.98 (m, 1H), 4.35 (m, 1H), 2.62 (m, 1H), 2.45 (m, 1H), 2.06 (s, 3H), 1.20-1.95 (m, 22H), 0.88 (t, J=6.6Hz, 3H); ¹³C NMR (125 MHz, CDCl₃): δ 170.7, 170.3, 80.4, 74.2, 31.8, 29.6, 29.5, 29.5, 29.4, 29.3, 29.2, 25.2, 23.4, 22.6, 20.9, 18.2, 14.0; HRMS (ESI, m/z) Calcd for C₁₈H₃₈O₄: 313.23734, Found: 313.23744.


Reproductions of $^1$H and $^{13}$C NMR spectra

![Compound 4](image)

$^1$H(500 MHz) NMR in CDCl$_3$
Compound 5

$^1$H (500MHz) and $^{13}$C (125MHz) NMR in CDCl$_3$
Compound 6

$^1$H (300MHz) and $^{13}$C (125MHz) NMR in CDCl$_3$
Compound 7

$^1$H (400MHz) and $^{13}$C (125MHz) NMR in CDCl$_3$
Compound 8a

$^1$H (500MHz) and $^{13}$C (125MHz) NMR in CDCl$_3$
Compound 8b

$^1$H (500MHz) and $^{13}$C (125MHz) NMR in CDCl$_3$
$^1$H (500MHz) and $^{13}$C (125MHz) NMR in CDCl$_3$
Compound 8d

$^1$H (300MHz) and $^{13}$C (125MHz) NMR in CDCl$_3$
Compound 8e

$^1$H (300MHz) and $^{13}$C (125MHz) NMR in CDCl$_3$
Compound 8f

$^{1}H$ (300MHz) and $^{13}C$ (125MHz) NMR in CDCl$_3$
Compound 8g

$^1$H (500MHz) and $^{13}$C (125MHz) NMR in CDCl$_3$
Compound 8h

$^1$H (300MHz) and $^{13}$C (125MHz) NMR in CDCl$_3$
Compound 9

\(^1\text{H} (300\text{MHz})\) and \(^{13}\text{C} (125\text{MHz})\) NMR in CDCl\textsubscript{3}
Compound 10

$^{1}H$ (300MHz) and $^{13}C$ (125MHz) NMR in CDCl$_3$
Compound 2

$^1$H (300MHz) and $^{13}$C (125MHz) NMR in CDCl$_3$

Chiral HPLC analysis (chiralpak AD-RH)
Racemic

Chiral HPLC Analysis (Chiralpak AD-RH)
BaO, 0.25% catalyst

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Acq. Operator : xuri
Inj Volume : 1 µl
Method : D:\TEMP\METHODS\XURI\CHIRAL1.M
Last changed : 5/10/03 12:27:05 PM by xuri
(modified after loading)
chiral HPLC with 50% isopropanol/H2O for 15 minutes; DAD detector; flow rate of 0.300 ml/min

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**Area Percent Report**

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Sorted By : Signal
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Dilution : 1.0000
Sample Amount : 1.00000 [ng/µl] (not used in calc.)

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*** End of Report ***

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