New Applications of PhI(OAc)₂ in Synthesis: Total Synthesis and SAR Development of Potent Antitumor Natural Product Psymberin/irciniastatin A

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Experimental Procedures

tert-Butyl(6,6-diiodohex-5-enyloxy)dimethylsilane (10): To a solution of the alcohol 9 (5.2 g, 50 mmol, 1 equiv.) in dichloromethane (100 mL) was added triethylamine (7 mL, 50 mmol, 1 equiv.) and DMAP (1.22 g, 0.5 mmol) at 0 °C. A solution of TBSCl in dichloromethane (20 mL) was added dropwise. The reaction was stirred from 0 °C to room temperature overnight. The reaction mixture was diluted with EtOAc (100 ml), and washed with aqueous NH₄Cl (50 ml) and brine (30 ml), dried (Na₂SO₄) and concentrated under vacuum. The residue was purified with silica gel column chromatography (25% EtOAc/Hexane) to give the TBS protected alcohol as colorless oil (5 g, 48%). The resulting alcohol (5.2 g, 23 mmol) was dissolved in DMSO (50 mL) and treated with triethylamine (20 ml) and pyridine·SO₃ (25 g) at 0 °C. The reaction was stirred at room temperature with TLC monitoring. After the starting material was consumed, reaction was diluted with EtOAc (120 ml), washed with aqueous NH₄Cl (50 ml) and brine (30 ml), dried (MgSO₄) and concentrated under vacuum. The residue was purified with silica gel column chromatography (15% EtOAc/Hexane) to give the aldehyde (4.2 g, 80%). To a mixture of PPh₃ (20 g, 0.08mol), CHI₃ (25 g, 0.075 mol), and KOBu¹ (8 g, 0.075 mol) in THF (20 mL) was added a solution of the aldehyde (4.32 g, 0.02mol) in THF (10 ml). The reaction was stirred at room temperature with TLC monitoring. After the starting material was consumed, the reaction was quenched with water (25 ml), and extracted with EtOAc (100 ml), the organic layer was washed with brine (50 ml), dried (Na₂SO₄) and concentrated. The residue was purified with silica gel column chromatography (0% to 20
% EtOAc/Hexane) to give 10 (5 g, 50%). $^1$H NMR (500 MHz, CDCl$_3$) $d$ 6.94 (t, $J = 7.0$ Hz, 1H), 3.61 (t, $J = 6.0$ Hz, 2H), 1.94 (m, 2H), 1.50 (m, 4H), 0.89 (s, 9H), 0.05 (s, 6H).

tert-Butyl(6-iodohex-5-enyloxy)dimethylsilane (12) (Method A): To a solution of diiodide 10 (130 mg, 0.279 mmol), THF (4 mL) and MeOH (2 mL) at 0 °C was added AcOH (1 mL), followed by Zn-Cu couple (1 g). After the starting material was consumed judging by TLC, the reaction was quenched with saturated NaHCO$_3$ (10 ml) and extracted with EtOAc (20 ml), the organic layer was dried (Na$_2$SO$_4$) and concentrated. The residue was purified with silica gel column chromatography (0% to 20 % EtOAc/Hexane) to give 12 which was majorly the Z-isomer (68 mg, 72%). Z-isomer: $^1$H NMR (500 MHz, CDCl$_3$) $d$ 6.18 (d, $J = 5.5$ Hz, 1H), 6.17 (dt, $J = 6.0$, 12.0 Hz, 1H), 3.62 (t, $J = 6.0$ Hz, 2H), 2.16 (m, 2H), 1.57-1.48 (m, 4H), 0.90 (s, 9H), 0.05 (s, 6H).

General procedure for the preparation of vinyl iodide:

tert-Butyl(6-iodohex-5-enyloxy)dimethylsilane (12) (Method B): Alkyne 11 (8 g, 81.5 mmol, 1 equiv.) was dissolved in degassed anhydrous toluene (200 mL). To this solution was added Bu$_3$SnH (2.7 g, 163 mmol, 2 equiv.) and the mixture was heated in a preheated oil bath (90 °C) for 5 min before AIBN (2.7 g, 16.3 mmol, 0.2 equiv.) was added in one portion. The reaction mixture was heated to 100 °C for 12 hours before it was cooled to room temperature. Solvent was removed under vacuum and the residue was purified by silica gel column chromatography (100% hexane) to give the vinyl tributyltin compound (27 g, 85%). To a solution of this compound (13 g, 33.4 mmol) in dichloromethane (50 mL) was added a solution of I$_2$ in dichloromethane until the purple color persisted. The reaction mixture was stirred for another 30 minutes before it was quenched by addition of saturated Na$_2$SO$_3$ solution (100 ml). Brine was added to this mixture and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over
Na$_2$SO$_4$ and concentrated under vacuum. The residue was purified with silica gel column chromatography (0% to 20 % EtOAc/Hexane) to give the vinyl iodide 12 which was majorly the $E$-isomer (7.4 g, 99%). $E$-isomer: $^1$H NMR (500 MHz, CDCl$_3$) d 6.51 (dt, $J$ = 7.0, 14.5 Hz, 1H), 5.99 (dt, $J$ = 1.5, 14.5 Hz, 1H), 3.60 (t, $J$ = 6.0 Hz, 2H), 2.07 (m, 2H), 1.53-1.47 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H).

General procedure for the preparation of $N$-acyl enamine

$N$-(6-hydroxyhex-1-enyl)acetamide (4): An oven dried seal tube was charged with CuI (223 mg, 1.17 mmol, 0.1 equiv.), acetamide (1.38 g, 23.4 mmol, 2 equiv.), and Cs$_2$CO$_3$ (5.7 g, 17.6 mmol, 1.5 equiv.). The tube was filled with argon. Dimethyl ethylenediamine (252 μl, 2.34 mmol, 0.2 equiv.), vinyl iodide 12 (4.0 g, 11.7 mmol, 1 equiv.) and anhydrous toluene (15 mL) were then added under the atmosphere of argon. The tube was sealed and heated in a preheated oil bath at the temperature of 70 °C. The reaction mixture was stirred at this temperature for 20 hours. The reaction mixture was cooled to room temperature, diluted with EtOAc (50 ml), and filtered through a short pad of silica gel plug. After washing the silica gel with EtOAc three times (50 ml), the combined organic solvent was concentrated and purified by column chromatography (0% to 40 % EtOAc/Hexane) to give the TBS protected enamide as colorless oil (2.73 g, 86%). A solution of the protected enamide (1.22 g, 4.5 mmol) in THF (5 mL) was treated with TBAF (1.0 M in THF, 8 mL, 1.5 equiv.) at room temperature overnight. A short pad of silica gel was first treated with a mixture of acetone/hexane (1/1, containing 3% Et$_3$N) before the reaction mixture was filtered through this short pad of silica gel, followed by washing the silica column with acetone/hexane(1/1, 30 ml). The combined solution was concentrated to dryness, and the residue was purified by silica gel column (this silica gel column was first treated using the same condition as above) to give the hydroxyl enamide 4 (706 mg, 99%). $Z$-4: $^1$H NMR (500 MHz, CD$_3$CN) d 8.09 (broad, 1H), 6.63-6.59 (m, 1H), 4.68 (m, 1H), 3.54 (t, $J$ = 6.0 Hz, 2H), 2.83 (broad, 1H), 2.12-2.07 (m, 2H), 1.99 (s, 3H), 1.56-1.50(m, 2H), 1.47-1.40 (m, 2H); $^{13}$C NMR (125 MHz, CD$_3$CN) d 168.2, 121.6,
**N-(6-hydroxyhex-1-enyl)-2-phenylacetamide (15):** $^1$H NMR (500 MHz, CDCl$_3$) trans/cis-15 = 2/1. d 7.46-7.31 (m, 5H), 7.00 (broad, 1H, isomer I), 6.80-6.72 (m, 1H), 5.06 (m, 1H, isomer II), 4.76 (m, 1H, isomer I), 3.70 (s, 3H, isomer I), 3.65 (s, 3H, isomer II), 3.67-3.62 (m, 2H), 2.08-1.39 (m, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) d 168.6, 168.5, 134.9, 134.6, 130.0, 130.0, 129.6, 129.6, 128.0, 123.0, 121.7, 113.8, 111.9, 63.3, 63.1, 44.1, 44.1, 32.5, 31.7, 29.8, 26.3, 26.1, 25.6; HRMS(FAB) calecd for C$_{14}$H$_{20}$O$_2$N (M + H$^+$) 234.1494 found 234.1489.

**N-(6-hydroxyhex-1-enyl)cyclopropanecarboxamide (19):** $^1$H NMR (500 MHz, DMSO) trans/cis-19 = 2/1. d 9.92 (d, $J = 10.0$ Hz, 1H, isomer I), 9.53 (d, $J = 10.5$Hz, 1H, isomer II), 6.61-6.52 (m, 1H), 5.15-5.09 (m, 1H, isomer I), 4.57-4.52 (m, 1H, isomer II), 4.41-4.36 (m, 1H), 3.43-3.36 (m, 2H), 2.14-1.30 (m, 6H), 0.74-0.70(m, 4H); $^{13}$C NMR (125 MHz, DMSO) d 171.9, 171.0, 124.2, 122.3, 111.6, 110.7, 61.5, 61.4, 33.0, 32.8, 30.0, 26.9, 26.6, 26.1, 14.4, 14.1, 8.0, 7.6; HRMS(FAB) calecd for C$_{10}$H$_{18}$O$_2$N (M + H$^+$) 184.1338 found 184.1338.

**tert-Butyl 6-hydroxyhex-1-enylcarbamate (22):** $^1$H NMR (500 MHz, CDCl$_3$) trans-22. d 6.40 (dd, $J = 9.5$, 10.5 Hz, 1H), 6.31 (broad, 1H), 4.55 (dt, $J = 7.5$, 8.5 Hz, 1H), 3.66 (t, $J = 6.5$ Hz, 2H), 1.98 (m, 3H), 1.58 (m, 3H), 1.46 (s, 9H), 1.49-1.44 (m, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) d 152.9, 122.4, 107.8, 62.8, 31.9, 29.4, 28.3, 25.8, 25.2; MS (ES) calculated for C$_{11}$H$_{22}$NO$_3$ [M + H]$^+$: 216.16, found 216.18; C$_{11}$H$_{21}$NO$_3$Na [M + Na]$^+$: 238.14, found 238.14.
**Benzyl 6-hydroxyhex-1-enylcarbamate (24):** $^1$H NMR (500 MHz, CDCl$_3$) *trans*-24. d 7.36-7.31 (m, 5H), 6.45 (dd, $J = 9.0$, $11.0$ Hz, 1H), 6.83 (d, $J = 11.0$ Hz, 1H), 5.12 (s, 2H), 4.61 (dt, $J = 7.5$, $8.5$ Hz, 1H), 3.62 (m, 2H), 2.00-1.95 (m, 2H), 1.57-1.52 (m, 2H), 1.47-1.36 (m, 2H); MS (ES) calculated for C$_{14}$H$_{20}$NO$_3$ [M + H]$^+$: 250.14, found 250.14; C$_{14}$H$_{19}$NO$_3$Na [M + Na]$^+$: 272.13, found 272.20.

**N-(6-hydroxyhept-1-enyl)acetamide (29):** $^1$H NMR (500 MHz, CDCl$_3$) *trans/cis*-29 = 3/1. d 7.48 (broad, 1H, isomer I), 7.00 (broad, 1H, isomer II), 6.82-6.75 (m, 1H), 5.19-5.13 (m, 1H, isomer II), 4.80-4.75 (m, 1H, isomer I), 3.95-3.83 (m, 1H), 2.11 (s, 3H, isomer I), 2.08 (s, 3H, isomer II), 1.66-1.31 (m, 6H), 1.27 (d, $J = 6.0$ Hz, 3H, isomer I), 1.24 (d, $J = 6.0$ Hz, 3H, isomer II); $^{13}$C NMR (125 MHz, CDCl$_3$) d 167.5, 123.2, 122.0, 112.9, 111.0, 69.1, 68.4, 39.1, 37.9, 30.0, 29.7, 26.4, 26.2, 25.9, 24.5, 24.0, 23.8, 23.7, 7.8; HRMS(FAB) calculated for C$_9$H$_{18}$O$_2$N (M + H$^+$) 172.1338 found 172.1330.

**N-(6-hydroxyhept-1-enyl)cyclopropanecarboxamide (31):** $^1$H NMR (500 MHz, CDCl$_3$) *trans/cis*-31 = 3/1. d 7.59 (broad, 1H, isomer I), 7.16 (broad, 1H, isomer II), 6.85-6.79 (m, 1H), 5.19-5.14 (m, 1H, isomer II), 4.77-4.72 (m, 1H, isomer I), 3.97-3.83 (m, 1H), 2.14-2.08 (m, 1H), 1.57-1.31 (m, 6H), 1.27 (d, $J = 7.5$ Hz, 3H, isomer I), 1.24 (d, $J = 6.5$ Hz, 3H, isomer II), 1.10-1.06 m, 2H), 0.88-0.83 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) d 171.1, 123.4, 122.1, 112.2, 110.3, 69.0, 68.4, 39.1, 38.1, 30.0, 29.7, 26.5, 26.2, 25.9, 24.4, 24.0, 15.3, 8.3, 8.2; HRMS(FAB) calculated for C$_{11}$H$_{20}$O$_2$N (M + H$^+$) 198.1494 found 198.1498.

**N-(6-hydroxyhept-1-enyl)-2-phenylacetamide (33):** $^1$H NMR (500 MHz, CDCl$_3$) *trans/cis*-33 = 3/1. d 7.45-7.32 (m, 5H), 6.83-6.75 (m, 1H), 5.08-5.02 (m, 1H, isomer I), 4.78-4.73 (m, 1H, isomer II), 3.85-3.74 (m, 1H), 3.71 (s, 2H, isomer II), 3.67 (s, 2H, isomer I), 2.23 (broad, 1H), 2.10-2.03 (m, 2H), 2.23-1.19 (m, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) d 168.3, 134.6, 130.0, 129.6, 128.1, 123.0, 121.8, 113.7, 111.8, 68.7, 68.4, 54.2, 44.2, 44.1, 39.0, 38.1, 30.0, 29.7, 26.3, 25.8, 25.7, 24.3, 24.0; HRMS(FAB) calculated for C$_{15}$H$_{22}$O$_2$N (M + H$^+$) 248.1651 found 248.1650.
N-(6-hydroxy-6-methylhept-1-enyl)-2-phenylacetamide (35): $^1$H NMR (500 MHz, CDCl$_3$) trans/cis-35 = 3/1. d 7.46-7.31 (m, 5H), 6.90 (broad, 1H), 6.80-6.73 (m, 1H), 5.09-5.03 (m, 1H, major isomer I), 4.78-4.73 (m, 1H, minor isomer II), 3.70 (s, 2H, minor isomer II), 3.66 (s, 2H, major isomer I), 2.06-2.03 (m, 2H, major isomer I), 1.85-1.81 (m, 2H, minor isomer II), 1.52-1.22 (m, 10H); $^{13}$C NMR (125 MHz, CDCl$_3$) d 168.5, 168.3, 134.9, 134.6, 130.0, 129.9, 129.6, 128.1, 123.0, 121.8, 113.8, 111.9, 71.3, 44.2, 44.1, 43.6, 42.7, 30.5, 29.9, 29.7, 26.1, 24.9, 24.3; HRMS(FAB) caclcd for C$_{16}$H$_{24}$O$_2$N (M + H$^+$) 262.1807 found 262.1806.

N-(6-hydroxyhept-1-enyl)-N-methylacetamide (37): $^1$H NMR (500 MHz, CDCl$_3$) trans-37 d 6.53 (d, $J$ = 14.0 Hz, 1H), 4.96-4.88 (m, 1H), 3.73 (m, 1H), 2.98 (s, 3H), 2.12 (s, 3H), 2.02 (m, 2H), 1.47-1.34 (m, 4H), 1.12 (d, $J$ = 6.0 Hz, 3H); MS (ES) calculated for C$_{10}$H$_{20}$NO$_2$ [M + H$^+$]: 186.15, found 186.23.

General procedure for the oxidative cyclization of N-acyl enamine: To a stirred solution of substrate (0.2 mmol) in hexafluoroisopropanol (2 mL) under argon at 0 °C, methanol (4.0 mmol, 20 equiv.) was added followed with the addition of (diacetoxyiodo)benzene (146 mg, 0.44 mmol, 2.2 equiv.) in hexafluoroisopropanol (1 mL) dropwise. The reaction mixture was stirred at 0 °C for one hour before it was diluted with dichloromethane (20 ml). The diluted solution was passed through a short pad of silica gel and washed with EtOAc (40 ml). Solvent was removed under reduced pressure, and the residue was purified with silica gel flash column chromatography (0% to 40 % acetone/hexane) to give the desired product as a mixture of diastereomers.

N-(methoxy(tetrahydro-2H-pyran-2-yl)methyl)acetamide 6a: $^1$H NMR (500 MHz, CDCl$_3$) anti-6a d 6.30 (d, $J$ = 8.5 Hz, 1H), 5.04 (dd, $J$ = 2.0, 10.0 Hz, 1H), 4.09-4.01 (m, 1H), 3.61 (ddd, $J$ = 2.0, 2.0, 11.5 Hz, 1H), 3.52 (ddd, $J$ = 3.5, 10.0, 11.5 Hz, 1H), 3.41 (s, 3H), 2.12 (s, 3H), 1.93-1.85 (m, 1H), 1.61-1.51 (m, 4H), 1.34-1.27 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) d 171.4, 82.4, 78.7, 68.9, 56.4, 27.9, 26.3, 23.8, 23.1; HRMS(FAB) caclcd for C$_9$H$_{18}$O$_3$N (M + H$^+$) 188.1287 found 188.1281. $^1$H NMR (500 MHz, CDCl$_3$) syn-6a d 6.41 (d, $J$ = 9.0 Hz, 1H), 5.07 (dd, $J$ = 2.5, 10.0 Hz, 1H), 4.12-4.09 (m, 1H),
3.45 (dd, J = 2.0, 12.0, 12.0 Hz, 1H), 3.42 (s, 3H), 3.33 (dd, J = 2.0, 2.5, 11.5 Hz, 1H), 2.10 (s, 3H), 1.93-1.85 (m, 1H), 1.61-1.51 (m, 4H), 1.34-1.27 (m, 1H).

Acetamido(tetrahydro-2H-pyran-2-yl)methyl acetate (6b): \(^1\)H NMR (500 MHz, CDCl\(_3\)) d 6.75 (d, J = 9.0 Hz, 1H minor isomer I), 6.64 (d, J = 9.5 Hz, 1H, major isomer II), 6.56 (dd, J = 2.5, 9.5 Hz, 1H, minor isomer I), 6.33 (dd, J = 1.5, 10.0 Hz, 1H, major isomer II), 4.15-4.07 (m, 1H), 3.74-3.71 (m, 1H, minor isomer I), 3.66 (ddd, J = 2.0, 2.0, 11.5 Hz, 1H, major isomer II), 3.58-3.47 (m, 1H), 2.14 (s, 3H, minor isomer I), 2.12 (s, 3H, major isomer II), 2.09 (s, 3H, major isomer II), 2.06 (s, 3H, minor isomer I), 1.95-1.88 (m, 1H), 1.71-1.51 (m, 4H), 1.38-1.28 (m, 1H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) d 170.5, 170.4, 170.1, 170.0, 78.3, 77.7, 74.9, 69.6, 69.0, 27.7, 27.4, 26.1, 26.1, 23.7, 23.7, 23.1, 22.9, 21.6, 21.3; HRMS(FAB) calculated for C\(_{10}\)H\(_{18}\)O\(_4\)N (M + H\(^+\)) 216.1236 found 216.1232.

N-(tetrahydro-2H-pyran-2-yl)(2,2,2-trifluoroethoxy)methyl acetamide (6c): \(^1\)H NMR (500 MHz, CD\(_3\)CN) d 7.03-6.94 (m, 1H), 5.16 (dd, J = 4.5, 9.5 Hz, 1H, minor isomer I), 5.09 (dd, J = 4.5, 9.5 Hz, 1H, major isomer II), 4.05-3.94 (m, 3H), 3.48-3.31 (m, 2H), 2.17 (s, 3H), 1.89-1.81 (m, 1H), 1.67-1.45 (m, 4H), 1.33-1.25 (m, 1H).

N-(butoxy(tetrahydro-2H-pyran-2-yl)methyl)acetamide (13) (dr = 4/1): \(^1\)H NMR (500 MHz, CDCl\(_3\)) d 6.48 (d, J = 10.0 Hz, 1H minor isomer I), 6.32 (d, J = 9.0 Hz, 1H, major isomer II), 5.14 (dd, J = 2.5, 9.5 Hz, 1H, minor isomer I), 5.08 (dd, J = 2.0, 9.5 Hz, 1H, major isomer II), 4.13-4.05 (m, 1H), 3.70-3.31 (m, 4H), 2.10 (s, 3H, major isomer II), 2.07 (s, 3H, minor isomer I), 1.97-1.87 (m, 2H), 1.63-1.52 (m, 5H), 1.43-1.26 (m, 3H), 0.94 (t, J = 7.5 Hz, 3H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) d 171.3, 170.7, 81.2, 80.1, 79.8, 78.8, 69.6, 69.3, 68.9, 68.8, 32.0, 31.9, 28.1, 27.5, 26.3, 24.0, 23.9, 23.4, 23.1, 19.7, 14.3; HRMS(FAB) calculated for C\(_{12}\)H\(_{24}\)O\(_3\)N (M + H\(^+\)) 230.1756 found 230.1749.

N-(isopropoxy(tetrahydro-2H-pyran-2-yl)methyl)acetamide (14) (dr = 4/1): \(^1\)H NMR (500 MHz, CDCl\(_3\)) d 6.52 (broad, 1H, minor isomer I), 6.33 (d, J = 8.5 Hz, 1H major isomer II), 5.21 (dd, J = 3.0, 9.5 Hz, 1H, minor isomer I), 5.17 (dd, J = 2.5, 9.5 Hz, 1H,
major isomer II), 4.13-4.05 (m, 1H), 3.92-3.87 (m, 1H), 3.52-3.47 (m, 2H), 2.09 (s, 3H, major isomer II), 2.06 (s, 3H, minor isomer I), 1.96-1.26 (m, 6H), 1.26-1.16 (m, 6H); HRMS(FAB) cedia for C11H22O3N (M + H+) 216.1600 found 216.1601.

\[ \text{N-(methoxy(tetrahydro-2H-pyran-2-yl)methyl)-2-phenylacetamide (16) (dr = 3/1):} \]
\[ ^1H \text{NMR (500 MHz, CDCl}_3) d 7.42-7.32 (m, 5H), 6.29 (d, } J = 8.5 \text{ Hz, 1H), 5.01 (dd, } J = 2.0, 9.5 \text{ Hz, 1H), 3.97-3.94 (m, 1H), 3.69 (s, 2H), 3.55 (ddd, } J = 1.5, 2.0, 11.5 \text{ Hz, 1H), 3.43 (ddd, } J = 2.0, 11.5, 12.0 \text{ Hz, 1H), 3.35 (s, 2H), 1.82 (broad, 1H), 1.53-1.39 (m, 4H), 1.16-1.08 (m, 1H); } ^{13} \text{C NMR (125 MHz, CDCl}_3) d 172.4, 135.1, 129.8, 129.4, 127.8, 82.5, 78.6, 68.7, 56.3, 44.5, 27.7, 26.2, 23.0; \text{HRMS(FAB) cedia for C}_{15}\text{H}_{21}\text{O}_3\text{N (M + H)}^+ 264.1600 found 264.1590. \]

\[ \text{N-(isopropoxy(tetrahydro-2H-pyran-2-yl)methyl)-2-phenylacetamide (17) (dr = 3/1):} \]
\[ ^1H \text{NMR (500 MHz, CDCl}_3) d 7.41-7.30 (m, 5H), 6.40 (d, } J = 9.5 \text{ Hz, 1H minor isomer I), 6.27 (d, } J = 9.0 \text{ Hz, 1H, major isomer II), 5.21 (dd, } J = 3.0, 9.5 \text{ Hz, 1H, minor isomer I), 5.14 (dd, } J = 2.5, 9.5 \text{ Hz, 1H, major isomer II), 4.05-3.95 (m, 1H), 3.86-3.80 (m, 1H), 3.65 (s, 2H), 3.63 (s, 2H), 3.45-3.24 (m, 2H), 1.90-1.78 (m, 2H), 1.64-1.39 (m, 4H), 1.20 (d, } J = 6.0 \text{ Hz, 3H), 1.13 (d, } J = 6.0 \text{ Hz, 3H); } ^{13} \text{C NMR (125 MHz, CDCl}_3) d 172.0, 171.3, 135.2, 129.8, 129.7, 129.4, 127.7, 79.9, 79.6, 79.2, 79.0, 71.0, 70.1, 69.5, 68.7, 44.5, 44.5, 28.1, 27.4, 26.3, 26.2, 23.7, 23.7, 23.4, 23.0, 22.2, 22.1; \text{HRMS(FAB) cedia for C}_{17}\text{H}_{26}\text{O}_3\text{N (M + H)}^+ 292.1913 found 292.1912. \]

\[ \text{N-(hydroxy(tetrahydro-2H-pyran-2-yl)methyl)-2-phenylacetamide (18) (dr = 3.5/1):} \]
\[ ^1H \text{NMR (500 MHz, CDCl}_3) d 7.37-7.26 (m, 5H), 6.58 (broad, 1H), 5.23 (dd, } J = 3.5, 8.5 \text{ Hz, 1H minor isomer I), 5.14 (dd, } J = 3.5, 7.0 \text{ Hz, 1H, major isomer II), 3.99-3.91 (m, 1H), 3.59 (s, 2H, major isomer II), 3.58 (s, 2H, minor isomer I), 3.43-3.24 (m, 2H), 1.88-1.79 (m, 1H), 1.62-1.39 (m, 4H), 1.17-1.09 (m, 1H); } ^{13} \text{C NMR (125 MHz, CDCl}_3) d 172.9, 172.2, 134.8, 129.8, 129.8, 129.4, 127.8, 127.8, 78.8, 78.6, 76.6, 75.4, 69.2, 68.9, 44.1, 28.0, 27.1, 26.3, 26.2, 23.1, 23.0; \text{HRMS(FAB) cedia for C}_{14}\text{H}_{20}\text{O}_3\text{N (M + H)}^+ 250.1443 found 250.1434. \]
N-(methoxy(tetrahydro-2H-pyran-2-yl)methyl)cyclopropanecarboxamide (20) \((dr = 3.5/1)\): \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.60 (d, \(J = 9.5\) Hz, 1H, isomer I), 6.49 (d, \(J = 9.5\) Hz, 1H, isomer II), 5.04 (dd, \(J = 3.0, 10.0\) Hz, 1H, isomer I), 5.01 (dd, \(J = 2.0, 10.0\) Hz, isomer II), 4.08-4.02 (m, 1H), 3.59-3.56 (m, 1H), 3.51-3.45 (m, 1H), 3.35 (s, 3H, isomer I), 3.34 (s, 3H, isomer II), 1.89-0.77 (m, 10H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 175.2, 174.7, 82.3, 81.5, 79.7, 78.9, 69.6, 69.0, 56.8, 56.3, 27.8, 27.5, 26.3, 23.4, 23.1, 15.2, 8.1, 8.0; HRMS(FAB) calculated for \(\text{C}_{11}\text{H}_{20}\text{O}_{3}\text{N} (\text{M} + \text{H})^+\) 214.1443 found 214.1445.

N-(isopropoxy(tetrahydro-2H-pyran-2-yl)methyl)cyclopropanecarboxamide (21) \((dr = 4/1)\): \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.68 (d, \(J = 10.0\) Hz, 1H, isomer I), 6.49 (d, \(J = 9.0\) Hz, 1H, isomer II), 5.23 (dd, \(J = 3.0, 9.5\) Hz, 1H, isomer I), 5.19 (dd, \(J = 2.5, 10.0\) Hz, 1H, isomer II), 4.15-4.06 (m, 1H), 3.92-3.87 (m, 1H), 3.54-3.49 (m, 2H), 1.93-0.82 (m, 10H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 174.7, 80.1, 79.4, 79.3, 78.6, 70.7, 69.9, 69.6, 68.9, 28.2, 27.6, 26.3, 26.2, 23.8, 23.4, 23.1, 22.2, 15.3, 7.9, 7.8; HRMS(FAB) calculated for \(\text{C}_{13}\text{H}_{24}\text{O}_{3}\text{N} (\text{M} + \text{H})^+\) 242.1756 found 242.1746.

Benzyl methoxy(tetrahydro-2H-pyran-2-yl)methylcarbamate (25) \((dr = 4/1)\): \(^1\)H NMR (500 MHz, CDCl\(_3\)) trans-25. \(\delta\) 7.37-7.31 (m, 5H), 5.66 (d, \(J = 10.0\) Hz, 1H), 5.14 (m, 2H), 4.76 (dd, \(J = 2.0, 10.0\) Hz, 1H), 4.00 (m, 1H), 3.53 (m, 1H), 3.47-3.38 (m, 4H), 1.85 (m, 1H), 1.62-1.44 (m, 4H), 1.31 (m, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 156.6, 136.2, 128.5, 128.2, 128.0, 84.7, 78.2, 68.4, 66.9, 55.7, 27.3, 25.7, 22.6; MS (ES) calculated for \(\text{C}_{15}\text{H}_{22}\text{NO}_{4} [\text{M} + \text{H}]^+\): 280.15, found 280.20; \(\text{C}_{15}\text{H}_{21}\text{NO}_{4}\text{Na} [\text{M} + \text{Na}]^+\): 302.14, found 302.21.

N-(methoxy(tetrahydrofuran-2-yl)methyl)-2-phenylacetamide (27) \((dr > 10/1)\): \(^1\)H NMR (500 MHz, CDCl\(_3\)) trans-27. \(\delta\) 7.39-7.26 (m, 5H), 5.98 (d, \(J = 10.0\) Hz, 1H), 5.08 (dd, \(J = 2.0, 10.0\) Hz, 1H), 3.96 (dt, \(J = 2.0, 7.5\) Hz, 1H), 3.64 (s, 2H), 3.65 (m, 1H), 3.51 (m, 1H), 3.31 (s, 3H), 1.89 (m, 1H), 1.76 (m, 1H), 1.61 (m, 1H), 1.40 (m, 1H); MS (ES) calculated for \(\text{C}_{14}\text{H}_{20}\text{NO}_{3} [\text{M} + \text{H}]^+\): 250.14, found 250.16; \(\text{C}_{14}\text{H}_{21}\text{NO}_{4}\text{Na} [\text{M} + \text{Na}]^+\): 272.13, found 272.19.
(2-Phenylacetamido)(tetrahydrofuran-2-yl)methyl acetate (28) \((dr > 10/1)\): \(^1\)H NMR (500 MHz, CDCl\(_3\)) trans-28. \(\delta 7.38-7.25\) (m, 5H), 6.43 (dd, \(J = 2.0, 10.0\) Hz, 1H), 6.27 (d, \(J = 10.0\) Hz, 1H), 6.04 (dt, \(J = 2.0, 7.5\) Hz, 1H), 3.68-3.58 (m, 3H), 3.47 (dt, \(J = 6.5, 8.5\) Hz, 1H), 2.04 (s, 3H), 1.98 (m, 1H), 1.76 (m, 1H), 1.58 (m, 1H), 1.41 (m, 1H); MS (ES) calculated for C\(_{15}\)H\(_{20}\)NO\(_4\) \([\text{M + H}]^+\): 278.14, found 278.28; C\(_{15}\)H\(_{19}\)NO\(_4\)Na \([\text{M + Na}]^+\): 300.12, found 300.19.

\(N\)-(methoxy(6-methyltetrahydro-2H-pyran-2-yl)methyl)acetamide (30) \((dr = 4.6/1/1/4.6)\): \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 6.51\) (broad, 1H, isomer I), 6.37 (d, \(J = 8.5\) Hz, 1H isomer II), 6.23 (d, \(J = 8.0\) Hz, 1H, isomer III), 5.21 (dd, \(J = 5.0, 9.5\) Hz, 1H, isomer II or III, trans/anti), 5.06 (dd, \(J = 3.0, 10.0\) Hz, 1H, isomer I, cis/syn), 5.02 (dd, \(J = 1.5, 9.5\) Hz, 1H, isomer II or III, cis/anti), 4.00-3.96 (m, 1H), 3.81-3.78 (m, 1H), 3.66 (ddd, \(J = 1.5, 2.0, 12.0\) Hz, 1H), 3.58-3.52 (m, 1H), 3.41 (s, 3H), 2.11 (s, 3H, isomer II or III), 2.11 (s, 3H, isomer II or III), 1.98-1.16 (m, 6H), 1.25 (d, \(J = 6.5\) Hz, 3H, isomer I), 1.23 (d, \(J = 6.5\) Hz, 3H, isomer II or III), 1.22 (d, \(J = 6.5\) Hz, 3H, isomer II or III); HRMS(FAB) calculated for C\(_{10}\)H\(_{18}\)O\(_3\)N (M + H\(^+\)) 202.1443 found 202.1446. \(^1\)H NMR (500 MHz, CDCl\(_3\)) 2,6-trans-2,7-syn isomer which is contaminated with OAc attacked product. \(\delta 6.34\) (broad, 1H), 5.15 (dd, \(J = 3.5, 9.5\) Hz, 1H), 4.16-4.11 (m, 1H), 3.68-3.65 (m, 1H), 3.43 (s, 3H), 2.11 (s, 3H), 1.83-1.32 (m, 6H).

\(N\)-(methoxy(6-methyltetrahydro-2H-pyran-2-yl)methyl)cyclopropanecarboxamide (32) \((dr = 4/1/1/4)\): \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 6.69\) (d, \(J = 10.0\) Hz, 1H isomer I), 6.55 (d, \(J = 9.5\) Hz, 1H, isomer II), 6.39 (d, \(J = 9.5\) Hz, 1H, isomer III), 5.24 (dd, \(J = 5.0, 9.5\) Hz, 1H, isomer II or III, trans/anti), 5.06 (dd, \(J = 1.5, 10.0\) Hz, 1H, isomer I, cis/syn), 5.08 (dd, \(J = 3.0, 10.0\) Hz, 1H, isomer II or III, cis/anti), 4.01-3.96 (m, 1H), 3.84-3.81 (m, 1H), 3.70-3.67 (m, 1H), 3.60-3.54 (m, 1H), 3.41 (s, 3H), 1.92-0.83 (m, 14H); HRMS(FAB) calculated for C\(_{12}\)H\(_{22}\)O\(_3\)N (M + H\(^+\)) 228.1600 found 228.1609. \(^1\)H NMR (500 MHz, CDCl\(_3\)) 2,6-trans-2,7-syn isomer which is contaminated with OAc attacked product. \(\delta 6.49\) (d, \(J = 9.0\) Hz, 1H), 5.17 dd (\(J = 3.0, 9.5\) Hz, 1H), 4.29-4.25 (m, 1H), 3.71-3.68 (m, 1H), 3.42 (s, 3H), 1.86-0.84 (m, 11H), 1.28 (d, \(J = 6.5\) Hz).
N-(methoxy(6-methyltetrahydro-2H-pyran-2-yl)methyl)-2-phenylacetamide (34) (dr = 31/13): 1H NMR (500 MHz, CDCl3) d 7.43-7.31 (m, 5H), 6.49 (d, J = 9.5 Hz, 1H, isomer I), 6.39 (d, J = 9.5 Hz, 1H, isomer II), 6.18 (d, J = 9.0 Hz, isomer III), 5.18 (dd, J = 4.5, 9.0 Hz, 1H, isomer II or III, trans/anti), 5.05 (dd, J = 3.0, 9.5 Hz, 1H, isomer I, cis/syn), 4.96 (dd, J = 1.5, 9.5 Hz, 1H, isomer II or III, cis/anti), 3.90-3.85 (m, 1H), 3.76-3.70 (m, 1H), 3.69 (s, 2H), 3.68 (s, 2H), 3.59-3.57 (m, 1H), 3.47-3.41 (m, 1H), 3.38 (s, 3H, isomer II or III), 3.37 (s, 3H, isomer II or III), 3.36 (s, 3H, isomer I), 1.81-1.43 (m, 4H), 1.39-1.29 (m, 1H), 1.14 (d, J = 6.5 Hz, 3H, isomer II or III), 1.11 (d, J = 6.5 Hz, 3H, isomer I), 1.07 (d, J = 6.0 Hz, 3H, isomer II or III), 1.03-0.92 (m, 1H); HRMS(FAB) calcld for C16H24O3N (M + H+) 278.1756 found 278.1758. 1H NMR (500 MHz, CDCl3) 2,6-trans-2,7-syn isomer which was isolated pure. d 7.42-7.31 (m, 5H), 6.31 (d, J = 9.5 Hz, 1H), 5.11 (dd, J = 3.5, 10.0 Hz, 1H), 4.15-4.10 (m, 1H), 3.67 (s, 2H), 3.56-3.53 (m, 1H), 3.37 (s, 3H), 1.80-1.21 (m, 6H), 1.11 (d, J = 7.0 Hz).

N-(6,6-dimethyltetrahydro-2H-pyran-2-yl)(methoxy)methyl)-2-phenylacetamide (36) (dr = 4.3/1): 1H NMR (500 MHz, CDCl3) d 7.38-7.26 (m, 5H), 6.46 (d, J = 8.5 Hz, 1H, minor isomer I), 6.36 (d, J = 9.0 Hz, 1H, major isomer II), 4.96 (dd, J = 2.5, 9.5 Hz, 1H, minor isomer I), 4.87 (dd, J = 1.0, 9.5 Hz, major isomer II), 3.74-3.68 (m, 1H), 3.65 (s, 2H, major isomer II), 3.63 (s, 2H, minor isomer I), 3.33 (s, 3H, minor isomer I), 3.32 (s, 3H, major isomer II), 1.63-1.52 (m, 2H), 1.45-1.34 (m, 2H), 1.09-0.97 (m, 1H), 0.91-0.82 (m, 1H), 1.10 (s, 3H), 1.00 (s, 3H); 13C NMR (125 MHz, CDCl3) d 172.5, 171.8, 135.1, 130.1, 130.0, 129.9, 129.5, 127.9, 82.8, 81.5, 77.0, 72.5, 72.4, 72.0, 71.2, 57.1, 56.6, 44.5, 44.4, 44.2, 36.5, 36.2, 31.8, 31.7, 29.7, 27.7, 27.3, 26.7, 22.1, 21.9, 19.9, 19.4, 19.3; HRMS(FAB) calcld for C17H16O3N (M + H+) 292.1913 found 292.1906.

Ethyl 3-hydroxy-2,2-dimethylexta-4,5-dienoate (46): To a solution of ligand 52 (40 mg, 0.1 mmol) in acetonitrile (1.5 mL) was added BH3·THF complex (0.1 mL, 1 M solution in THF, 0.1 mmol) at room temperature and the mixture was stirred at 45 °C for
1 hour before being cooled to -78 °C. Ketene acetal 44 (0.126 mL, 0.6 mmol) was then added at -78 °C, followed by the addition of alkyne aldehyde (1 mmol) as a solution in acetonitrile (1 mL) over 4 hours via syringe pump. The reaction was stirred for another hour before quenched with pH 7 buffer (10 mL). The reaction mixture was warmed to room temperature and diluted with EtOAc (50 mL), the organic solution was washed with aq. NaHCO₃ (20 mL), dried over Na₂SO₄ and concentrated. The residue was purified by silica gel flash column chromatography to give a mixture of TMS protected hydroxyl ester (70%) and free hydroxyl ester (12%). The free hydroxyl ester 46: ¹H NMR (500 MHz, CDCl₃) δ 5.22 (dd, J = 6.5, 13.0 Hz, 1H), 4.86 (dd, J = 2.0, 2.5 Hz), 4.85 (dd, J = 2.0, 2.5 Hz, 1H), 4.23 (dd, J = 2.0, 2.5, 7.0 Hz, 1H), 4.16 (q, J = 7.5 Hz, 2H), 1.27 (t, J = 7.5 Hz, 3H), 1.21 (s, 3H), 1.20 (s, 3H); MS (ES) calculated for C₁₀H₁₇O₃ [M + H]⁺: 185.12, found 185.24.

(R)-Ethyl 5-(benzyloxy)-3-(tert-butyldimethylsilyloxy)-2,2-dimethylpentanoate (47): To a solution of ligand 52 (2.12 g, 5.4 mmol) in propynitrile (40 mL) was added BH₃·THF complex (5.4 mL, 5.4 mmol) at room temperature and the mixture was stirred at 45 °C for 1 hour before cooled to -78 °C. Ketene acetal 44 (7.71 g, 41 mmol) was then added at -78 °C, followed by the addition of aldehyde BnO(CH₂)₂CHO (4.43 g, 27 mmol) as a solution in propynitrile (10 mL) over 4 hours via syringe pump. The reaction was stirred for another 2 hours before quenched with pH 7 buffer (50 mL). The reaction mixture was warmed to room temperature and diluted with EtOAc (100 mL), the organic solution was washed with NaHCO₃ (30 mL), dried over Na₂SO₄ and concentrated. The residue was purified by silica gel flash column chromatography (0% to 30% EtOAc/Hexane) to give a mixture of TMS protected hydroxyl ester (65%) and free hydroxyl ester (30%). The TMS protected product was treated with 2.0 M HCl/Et₂O (2.0 eq.) at 0 °C for 1 hour at room temperature. The reaction was directly concentrated and purified by silica gel flash column chromatography (30% EtOAc/Hexane) to give the alcohol (7.16 g, 99%). To the solution of the alcohol (5.45 g, 19.4 mmol) in dichloromethane (30 mL) was added 2, 6-lutidine 4.66 mL, 40 mmol) at 0 °C. After
stirring for 5 minutes at 0 °C, TBSOTf (9.18 mL, 40 mmol) was added dropwise. The reaction mixture was allowed to stir at room temperature for 2 hours. After the reaction was complete judged by TLC, it was diluted with EtOAc (150 ml). The organic layer was washed with NaHCO₃ (50 ml), dried over Na₂SO₄ and concentrated. The residue was purified by silica gel flash column chromatography (10% EtOAc/hexane) to give the TBS protected product 47 (7.56 g, 99%) as an oil. [a]D²⁰ = + 41.85 (c = 1.0, dichloromethane). 

\[ \text{1HNMR (500 MHz, CDCl₃) d 7.36-7.26 (m, 5H), 4.48 (dd, } J = 12.0, 15.5 \text{ Hz, 2H), 4.14-4.03 (m, 3H), 3.55-3.46 (m, 2H), 1.80 (ddt, } J = 3.0, 7.5, 14.5 \text{ Hz, 1H), 1.66 (ddt, } J = 5.0, 15.0, 15.5 \text{ Hz, 1H), 1.22 (t, } J = 7.5 \text{ Hz, 3H), 1.15 (s, 3H), 1.09 (s, 3H), 0.86 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H); } \text{13C NMR (125 MHz, CDCl₃) d 177.2, 138.7, 128.5, 127.8, 127.7, 74.0, 73.0, 67.9, 60.6, 48.4, 34.2, 26.2, 22.1, 21.0, 20.4, 18.5, 14.3, -3.8, -4.0; MS (ES) calculated for } C_{22}H_{39}O_4Si [M + H]^+: 395.26, \text{ found 395.24; } C_{22}H_{38}NaO_4Si [M + Na]^+: 417.24, \text{ found 417.34.} \]

(R)-6-(Benzylxylo)-4-(tert-butyldimethylsilyloxy)-3,3-dimethylhexan-2-one (48): To a solution of compound 47 (7.56 g, 19.2 mmol) in anhydrous pentane (50 mL) was added trimethylsilyl methyl lithium (58 mL, 58.2 mmol) dropwise at 0 °C. The mixture was stirred at 0 °C for 4 hours with TLC monitoring (Et₂O/hexane 1/10). After the reaction is complete judged by TLC, to this suspension was added dry methanol (10 mL) and the resulting emulsion was stirred for another 1 hour at room temperature. The mixture was diluted with Et₂O/water (100 mL, 3/1). Aqueous layer was extracted with Et₂O (100 mL), dried over Na₂SO₄ and concentrated. The residue was purified by silica gel flash column chromatography (10% EtOAc/hexane) to give the methyl ketone 48 (5.81 g, 82%) as an oil. [a]D²⁰ = + 7.45 (c = 1.0, dichloromethane) ¹HNMR (500 MHz, CDCl₃) d 7.35-7.27 (m, 5H), 4.49 (d, } J = 12.0 \text{ Hz, 1H), 4.45 (d, } J = 12.0 \text{ Hz, 1H), 4.04 (dd, } J = 2.5, 7.5 \text{ Hz, 1H), 3.50-3.48 (m, 2H), 2.13 (s, 3H), 1.78-1.72 (m, 1H), 1.62-1.55 (m, 1H), 1.10 (s, 3H), 1.06 (s, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) d 213.7, 138.7, 128.6, 127.7, 74.1, 73.1, 67.7, 53.5, 34.5, 27.1, 26.2, 22.1, 20.3, 18.5, -3.8;
MS (ES) calculated for C_{21}H_{37}O_{3}Si [M + H]^+: 365.25, found 365.36; C_{21}H_{36}NaO_{3}Si [M + Na]^+: 387.23, found 387.09.

(R)-6-(2-(Benzyloxy)ethyl)-2,2,5,5,8,8,9,9-octamethyl-4-methylene-3,7-dioxa-2,8-disiladecane (49): To a solution of compound 48 (1.34 g, 3.6 mmol) in dichloromethane (15 mL) at 0 °C was added Et_3N (2 mL, 14.4 mmol) and then TMSOTf (1.3 mL, 7.2 mmol). The reaction was allowed to stir at room temperature for 1 hour. The reaction was diluted with hexane (75 ml), washed with aqueous NaHCO_3 (30 ml) and dried over Na_2SO_4. The solution was directly passed through a short pad of silica gel plug and washed EtOAc/hexane (1/20, 100 ml). The combined organic solution was concentrated to give compound 49 (1.58 g, 100%) as a light yellow oil. The crude 49 was used for the next step without further purification. ^1HNMR (500 MHz, CDCl_3) δ 7.33-7.25 (m, 5H), 4.48 (s, 2H), 4.11 (s, 1H), 3.95 (s, 1H), 3.87 (dd, J = 3.0, 8.0 Hz, 1H), 3.55-3.45 (m, 2H), 1.93-1.86 (m, 1H), 1.61-1.54 (m, 1H), 1.02 (s, 3H), 0.94 (s, 3H), 0.87 (s, 9H), 0.18 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^13C NMR (125 MHz, CDCl_3) δ 165.0, 139.0, 128.5, 127.8, 127.6, 88.2, 73.2, 72.9, 68.6, 45.4, 33.8, 26.4, 24.7, 19.8, 18.6, 0.28, -3.8.

(S)-methyl2-(tert-butoxycarbonylamino)-3-(3,4-dimethoxyphenyl)-2-methylpropanoate (51): To a solution of compound 50 (7.22 g, 30 mmol) and NaHCO_3 (8.8 g, 105 mmol) in DMF/BuOH (1/1, 50 mL) was added Boc_2O (16.4 g, 75 mmol). The mixture was stirred at 60 °C for 4 days before being cooled to room temperature and diluted with EtOAc (150 ml), washed with aq. 2 N HCl solution (80 ml), dried over Na_2SO_4 and concentrated to give a crude solid. The solid was then dissolved in DMF (30 mL), to this solution was added Me_4NOH (44 mL, 120 mmol) and MeI (8 mL, 120 mmol). The resulting solution was stirred for another 2 days. The reaction was quenched
by adding saturated NaHCO₃ (100 ml) and extracted with EtOAc (250 ml). Combined organic layer was washed with brine (50 ml) and dried over Na₂SO₄. After concentration the residue was purified by silica gel flash column chromatography (0% to 40% EtOAc/Hexane) to give methyl ester compound 51. ³¹HNMR (500 MHz, CDCl₃) δ 6.77 (d, J = 8.0 Hz, 1H), 6.63-6.60 (m, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.75 (s, 3H), 2.04 (s, 2H), 1.57 (s, 3H), 1.46 (s, 9H).

(S)-3-(3,4-Dimethoxyphenyl)-2-methyl-2-(4-methylphenylsulfonamido)propanoic acid (52): A solution of compound 51 (1.69 g, 4.78 mmol) in dichloromethane (3 mL) at 0 °C was treated with TFA (3 mL) and the reaction was allowed to stir at room temperature for 2 hours before being quenched by slow addition of aqueous NaHCO₃ solution (20 ml). The mixture was then extracted with dichloromethane (100 ml) and the combined organic layer was washed with 5 % aqueous NaHCO₃ (30 ml) and brine (30 ml). After being dried with Na₂SO₄, it was concentrated and the resulting crude product was taken to next step without further purification. To a solution of the crude substrate (4.78 mmol) in dichloromethane at 0 °C was added pyridine (2 mL, 18 mmol), followed by p-TsCl (1.72 g, 9 mmol) as a solution in dichloromethane (10 ml), the reaction was stirred at room temperature overnight. The mixture was diluted with dichloromethane (100 ml) and the combined organic layer was washed with 5 % aqueous NH₄Cl (40 ml), NaHCO₃ (40 ml), and brine (30 ml). After drying with Na₂SO₄, it was concentrated and purified by silica gel flash column chromatography (0% to 40% EtOAc/Hexane) to give sulfonamide (1.27 g 65% over 2 steps). To a solution of the sulfonamide (1.19 g, 2.9 mmol) in dioxane (8 mL) was added 2 N KOH solution (20 mL) and the reaction was stirred at 60 °C for 2 days. It was then evaporated under vacuum to remove dioxane and the remaining solution was washed with hexane (to remove dioxane). The aqueous layer was acidified to pH 1 with 4 N HCl solution and extracted with Et₂O/EtOAc (v/v = ¼, 100 ml). The organic layer was then dried and concentrated under vacuum to give compound 52 (1.1 g 96%), which was used as the catalyst without further purification. ³¹HNMR (500 MHz, CDCl₃) δ 7.71 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 8.5 Hz, 2H), 6.85-6.73 (m, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.19 (d, J = 13.5 Hz, 1H), 3.01 (d, J = 13.5 Hz,
1H), 2.38 (s, 3H), 2.03 (s, 3H), 1.44 (s, 3H); MS (ES) calculated for C_{19}H_{24}NO_{6}S [M + H]^+: 394.13, found 394.19.

(R)-ethyl-5-(benzyloxy)-2,2-dimethyl-3-((S)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyloxy)pentanoate (53): To determine the stereochemistry of the compound 47, a solution of the free alcohol 53a (28 mg, 0.1 mmol, prepared from 47 upon treatment with TBAF) in pyridine (1 ml) was added DMAP (6 mg) followed by (R)-(-)-alpha-methoxy-alpha-(trifluoromethyl)-phenylacetyl chloride (100 mg) at room temperature. The reaction was stirred at room temperature overnight before quenched with aqueous NaHCO₃ (10 ml). The mixture was extracted with EtOAc (20 ml), washed with aqueous NH₄Cl (20 ml) and brine (10 ml), dried (Na₂SO₄) and concentrated to give the crude 53 (40 mg) whose NMR was recorded without further purification. ¹HNMR (500 MHz, CDCl₃) δ 7.58-7.26 (m, 10H), 5.60 (dd, J = 2.5, 9.0 Hz, 1H), 4.45 (d, J = 12.0 Hz, 1H), 4.40 (d, J = 12.0 Hz, 1H), 4.06 (m, 2H), 3.51 (s, 3H), 3.42 (m, 2H), 1.90 9m, 2H), 1.21 (t, J = 7.5 Hz, 3H), 1.15 (s, 3H), 1.14 (s, 3H); MS (ES) calculated for C_{26}H_{32}F_{3}O_{6} [M + H]^+: 497.22, found 497.24; C_{26}H_{31}F_{3}NaO_{6} [M + Na]^+: 519.20, found 519.29.

(R)-3-((2R,3S,7R)-9-(benzyloxy)-7-(tert-butyldimethylsilyloxy)-3-hydroxy-6,6-dimethyl-5-oxononan-2-yl)-5-methyl-6,8-bis(triisopropylsilyloxy)isochroman-1-one (57): A mixture of aldehyde 43 (910 mg, 1.7 mmol) and silylenolether 49 (1.58 g, 3.6 mmol) was azeotropically condensed with toluene three times before dissolved in anhydrous dichloromethane (25 mL). The solution was cooled to -78 °C and freshly distilled BF₃.OEt₂ (2.2 mL, 18 mmol) was added dropwise. The reaction was allowed to
stir at -78 °C overnight. The reaction was quenched by adding saturated NaHCO₃ (30 mL) before being warmed up to room temperature. It was extracted with EtOAc (80 ml). Combined organic layer was washed with brine (20 ml) and dried over Na₂SO₄. After concentration the residue was purified by silica gel flash column chromatography (15% EtOAc/hexane) to give product 57 (1.15 g, 91%) as a colorless oil. [a] D²⁰ = + 28.59 (c = 0.1, dichloromethane); ¹HNMR (500 MHz, CDCl₃) δ 7.34-7.26 (m, 5H), 6.30 (s, 1H), 4.48 (d, J = 12.0 Hz, 1H), 4.44 (d, J = 12.0 Hz, 1H), 4.36 (ddd, J = 2.5, 5.0, 12.5 Hz, 1H), 4.31-4.27 (m, 1H), 4.05 (dd, J = 2.5, 7.5 Hz, 1H), 3.49 (dd, J = 5.5, 8.0 Hz, 2H), 3.24 (d, J = 2.0 Hz, 1H), 2.89 (dd, J = 2.5, 16.0 Hz, 1H), 2.78-2.71 (m, 2H), 2.08 (s, 3H), 1.83-1.69 (m, 2H), 1.62-1.54 (m, 5H), 1.35-1.25 (m, 6H), 1.18-1.05 (m, 42 H), 0.86 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). ¹³C NMR (125 MHz, CDCl₃) δ 217.4, 163.1, 159.0, 157.7, 141.4, 138.5, 128.6, 127.9, 118.3, 109.7, 78.3, 74.0, 73.2, 67.9, 67.5, 53.8, 42.9, 41.7, 34.7, 29.9, 26.2, 22.3, 20.2, 18.5, 18.3, 18.2, 17.9, 13.5, 13.4, 12.0, 9.6, -3.7, -3.8; MS (ES) calculated for C₅₂H₉₁O₈Si₃ [M + H]+: 927.60, found 927.73; C₅₂H₉₀NaO₈Si₃ [M + Na]+: 949.58, found 949.68.

(R)-3-((2R,3S,5R,7R)-9-(benzyloxy)-7-(tert-butyldimethylsilyloxy)-3,5-dihydroxy-6,6-dimethylnonan-2-yl)-5-methyl-6,8-bis(triisopropylsilyloxy)isochroman-1-one (58): To a solution of compound 57 (1.15 g, 1.54 mmol) in anhydrous THF (30 mL) was added catecholborane (20 mL, 1.0 M in THF, 20 mmol) at -78 °C. After stirring at 0 °C for 15 hours, the reaction was quenched by 10 mL anhydrous MeOH and aqueous solution of sodium potassium tartrate (50 mL). The mixture was further stirred at room temperature for 1 hour before ethyl acetate (50 mL) was added. The aqueous layer was extracted with EtOAc (80 ml). Combined organic layers were washed with brine (20 ml) and dried over Na₂SO₄. After concentration the residue was purified by silica gel flash column chromatography (15% EtOAc/hexane) to give the desired product 58 (1.05 g, 92%) (dr, 15/1). [a] D²⁰ = + 44.37 (c = 0.1, dichloromethane); ¹HNMR (500 MHz, CDCl₃)
d 7.37-7.28 (m, 5H), 6.30 (s, 1H), 4.87 (broad, 1H), 4.51 (d, J = 12.0 Hz, 1H), 4.48 (d, J = 12.0 Hz, 1H), 4.35 (dd, J = 2.5, 5.5, 12.5 Hz, 1H), 4.25 (broad, 1H), 4.14 (d, J = 10.0 Hz, 1H), 4.06 (d, J = 9.5 Hz, 1H), 3.66 (dd, J = 2.5, 7.5 Hz, 1H), 3.60-3.52 (m, 2H), 2.98 (dd, J = 3.0, 16.5 Hz, 1H), 2.80 (dd, J = 12.0, 16.0 Hz, 1H), 2.10 (s, 3H), 1.87-1.78 (m, 2H), 1.66-1.59 (m, 1H), 1.56 (s, 3H), 1.41 (d, J = 13.5 Hz, 1H), 1.35-1.25 (m, 7H), 1.17-1.11 (m, 36 H), 1.02 (s, 3H), 0.87 (s, 9H), 0.75 (s, 3H), 0.10 (s, 3H), 0.07 (s, 3H); 13C NMR (125 MHz, CDCl3) d 163.5, 158.9, 157.6, 141.8, 138.6, 128.6, 127.9, 118.4, 109.7, 81.3, 78.7, 77.9, 73.1, 72.7, 67.6, 43.1, 40.8, 35.0, 33.3, 29.9, 26.2, 23.5, 21.0, 18.4, 18.3, 18.2, 13.5, 13.4, 12.1, 9.9, -3.8, -4.1; MS (ES) calculated for C52H93O8Si3 [M + H]+: 929.62, found 929.68; C52H92NaO8Si3 [M + Na]+: 951.60, found 951.66.

(2S,3S,5R,7R)-7-(tert-butyldimethylsilyloxy)-10-iodo-6,6-dimethyl-2-((R)-5-methyl-1-oxo-6,8-bis(triisopropylsilyloxy)isochroman-3-yl)dec-9-en-3,5-diyl diacetate (59):

To a solution of compound 58 (2.14g, 2.3 mmol) in pyridine (4 mL) was added Ac2O (2 mL) and DMAP (35 mg, 0.287 mmol) at 0°C. The reaction mixture was allowed to stir at room temperature for 8 hours before it was diluted with EtOAc (80 ml). The mixture was washed with aq. 1N HCl (20 ml), aq. NaHCO3 (30 ml) and brine (20 ml) sequentially. After being dried over Na2SO4, it was concentrated and purified by silica gel flash column chromatography (0% to 25% EtOAc/hexane) to give 59a (1.82 g, 78 % one diastereomer) as an oil. 1HNMR (500 MHz, CDCl3) d 7.33-7.25 (m, 5H), 6.28 (s, 1H), 5.09 (m, 1H), 4.98-4.95 (m, 1H), 4.50 (d, J = 12.0 Hz, 1H), 4.46 (d, J = 12.0 Hz, 1H), 4.02 (dd, J = 2.5, 7.0, 12.0 Hz, 1H), 3.64 (dd, J = 2.0, 8.0 Hz, 1H), 3.53-3.50 (m, 2H), 2.92 (dd, J = 2.5, 16.0 Hz, 1H), 2.58 (dd, J = 12.0, 16.0 Hz, 1H), 2.09 (s, 3H), 2.08 (s, 3H), 2.00 (s, 3H), 2.04-2.00 (m, 1H), 1.95-1.87 (m, 1H), 1.73-1.58 (m, 2H), 1.35-1.25 (m, 6H), 1.16-1.10 (m, 39 H), 0.89 (s, 3H), 0.88 (s, 3H), 0.83 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H); 13C NMR (125 MHz, CDCl3) d 171.1, 170.7, 162.9, 158.9, 157.6, 141.2, 138.6, 128.5, 128.0, 127.8, 118.3, 109.9, 109.7, 78.2, 74.7, 74.0, 73.2, 71.7, 67.5, 42.9, 39.6,
33.7, 32.4, 30.5, 26.4, 21.4, 21.3, 20.7, 19.6, 18.7, 18.2, 13.5, 13.3, 11.8, 8.9, -3.7; MS (ES) calculated for C_{56}H_{97}O_{10}Si_{3} [M + H]^+: 1013.64, found 1013.70; C_{56}H_{96}NaO_{10}Si_{3} [M + Na]^+: 1035.62, found 1035.72. To a solution of compound 59a (1.82 g, 1.79 mmol) in EtOH (15 mL) was charged Pd/C (180 mg) and the flask was sealed with rubber stopper. The inner atmosphere was exchanged three times with H_2 before it was allowed to stir under H_2 (double layer balloon) overnight. The reaction mixture was filtered through a celite pad followed by washing with EtOH (50 mL). The combined organic solution was concentrated and purified by silica gel flash column chromatography (25% EtOAc/hexane) to give the alcohol 59b (1.65 g, 99%) as an oil: \(^1\)HNMR (500 MHz, CDCl_3) \(\delta\) 6.29 (s, 1H), 5.10-5.07 (m, 1H), 4.98 (dd, \(J = 2.0, 10.0\) Hz, 1H), 4.13 (ddd, \(J = 2.0, 6.0, 12.0,\) Hz), 3.8-3.75 (m, 1H), 3.71-3.66 (m, 1H), 3.66 (dd, \(J = 2.5, 8.5,\) Hz), 2.89 (dd, \(J = 2.5, 16.0\) Hz, 1H), 2.67 (dd, \(J = 12.0, 16.5\) Hz, 1H), 2.13-2.06 (m, 2H), 2.09 (s, 6 H), 2.03 (s, 3H), 1.87-1.71 (m, 3H), 1.65-1.58 (m, 2H), 1.56 (s, 3H), 1.35-1.25 (m, 6H), 1.15 (d, \(J = 7.0\) Hz, 3H), 1.12-1.09 (m, 36 H), 0.91 (s, 3 H), 0.90 (s, 9H), 0.84 (s, 3H), 0.11 (s, 3H), 0.08 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl_3) \(\delta\) 171.0, 163.0, 159.1, 157.7, 21.3, 20.8, 19.6, 18.7, 18.2, 13.5, 13.3, 11.9, 9.6, -3.6; MS (ES) calculated for C_{49}H_{91}O_{10}Si_{3} [M + H]^+: 923.59, found 923.65; C_{49}H_{90}NaO_{10}Si_{3} [M + Na]^+: 945.57, found 945.62. To a solution of compound 59b (1.15 g, 1.24 mmol) in dichloromethane (20 mL) was added Dess–Martin Periodinane (790 mg, 1.86 mmol) at 0 °C. The reaction mixture was allowed to stir at room temperature for 2 hours. After the reaction was complete, it was cooled to 0 °C and aqueous Na_2S_2O_3 (10 mL) was added. The mixture was stirred at room temperature for 15 minutes before being diluted with EtOAc (80 mL), washed with aqueous NaHCO_3 (30 mL) brine (20 mL), and dried over Na_2SO_4. The residue was purified by silica gel flash column chromatography (10% EtOAc/hexane) to give the aldehyde 59c (1.08 g, 95%) as a colorless oil. \(^1\)HNMR (500 MHz, CDCl_3) \(\delta\) 9.86 (s, 1H), 6.29 (s, 1H), 5.09-5.06 (m, 1H), 4.89 (dd, \(J = 2.0, 10.0\) Hz, 1H), 4.15 (dd, \(J = 4.0, 5.5\) Hz), 4.07 (ddd, \(J = 2.5, 7.0, 12.5\) Hz, 1H), 2.93 (dd, \(J = 2.5, 16.0\) Hz, 1H), 2.77 (ddd, \(J = 1.0, 4.0, 18.0\) Hz, 1H), 2.68-2.61 (m, 2H), 2.10 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H), 2.08-2.06 (m, 1H), 1.81-1.75 (m, 1H), 1.35-1.25 (m, 6H), 1.15 (d, \(J = 7.0\) Hz, 3H), 1.13-1.10 (m, 36 H), 0.88 (s, 3H), 0.87 (s, 9H), 0.08 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl_3) \(\delta\) 171.0, 163.0, 159.1, 157.7, 141.1, 118.4, 109.7, 77.9, 74.8, 73.8, 72.0, 60.0, 43.1, 40.0, 36.3, 32.7, 30.2, 26.4, 21.4, 21.3, 20.8, 19.6, 18.7, 18.2, 13.5, 13.3, 11.9, 9.6, -3.6; MS (ES) calculated for C_{49}H_{91}O_{10}Si_{3} [M + H]^+: 923.59, found 923.65; C_{49}H_{90}NaO_{10}Si_{3} [M + Na]^+: 945.57, found 945.62.
An aluminum foil wrapped round bottom flask containing CrCl₂ (2.28 g, 18.6 mmol) was flamed dried under high vacuum and then cooled to room temperature. The adapter was quickly replaced with a rubber stopper and an argon balloon was place on the top. Aldehyde 59c (1.14 g, 1.24 mmol) was azeotropically dried with toluene three times before putting under high vacuum. To a suspension of CrCl₂ (2.28 g, 18.6 mmol) in anhydrous THF (20 mL) was added a solution of aldehyde 59c (1.14 g, 1.24 mmol) and CH₃I (2.44 g, 6.2 mmol) in THF (20 mL plus 10 mL washing) at 0°C. Color should turn to reddish brown after 10 to 15 minutes. The reaction mixture was allowed to stir at room temperature overnight before it was diluted with EtOAc (30 ml) and water (20 ml) was added. The mixture was extracted with EtOAc (80 ml), washed with brine (20 ml) and dried over Na₂SO₄. After concentration the residue was purified by silica gel flash column chromatography (0% to 10% EtOAc/hexane) to give the vinyl iodide 59 (1.17 g, 90%, E/Z = 5/1) as a light yellow oil. ¹HNMR (500 MHz, CDCl₃) δ 6.52-3.46 (m, 1H), 6.28 (s, 1H), 6.06 (d, J = 14.5 Hz, 1H), 5.09-5.05 (m, 1H), 4.91 (dd, J = 1.5, 10.5 Hz, 1H), 4.07 (ddd, J = 2.5, 6.5, 12.0 Hz, 1H), 3.50 (dd, J = 4.0, 7.0 Hz, 1H), 2.90 (dd, J = 2.0, 16.0 Hz, 1H), 2.63 (dd, J = 12.0, 16.0 Hz, 1H), 2.38-2.32 (m, 1H), 2.25-2.19 (m, 1H), 2.12-2.10 (m, 1H), 2.08 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 1.99-1.96 (m, 1H), 1.78-1.72 (m, 1H), 1.34-1.24 (m, 6H), 1.15 (d, J = 7.0 Hz, 3H), 1.12-1.09 (m, 36 H), 0.89 (s, 9H), 0.88 (s, 3H), 0.85 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.0, 170.7, 162.8, 159.0, 157.7, 144.4, 141.0, 139.1, 118.3, 109.8, 109.7, 83.7, 78.1, 77.9, 77.1, 76.3, 74.4, 71.6, 43.4, 43.2, 40.2, 39.5, 32.7, 30.4, 26.3, 21.4, 21.3, 21.1, 20.9, 20.1, 18.5, 18.2, 18.1, 13.5, 13.3, 11.9, 9.2, -3.1, -3.9; MS (ES) calculated for C₅₀H₉₀I₀S₁₈ [M + H]⁺: 1045.50, found 1045.72.
(2S,3S,5R,7R)-7-(tert-butyldimethylsilyloxy)-10-((2S,3S)-2-(tert-butyldiphenylsilyloxy)-3-methoxy-5-methylhex-5-enamido)-6,6-dimethyl2-((R)-5-methyl-1-oxo-6,8-bis(triisopropylsilyloxy)isochroman-3-yl)dec-9-ene-3,5-diyldiacetate (60): To an oven dried seal tube was charged amide 40 (115 mg, 0.21 mmol), Cul (14 mg, 0.07 mmol), and Cs₂CO₃ (114 mg, 0.35 mmol) sequentially. Under Argon, dimethylethylene diamine (0.015 mL, 0.14 mmol) was then added followed by a solution of vinyl iodide 59 (110 mg, 0.105 mmol) in toluene (5 mL). The tube was filled with argon and quickly capped and sealed. The reaction was stirred vigorously at 70 °C for 20 hours. After the reaction was cooled to room temperature, it was diluted with EtOAc (30 ml) and filtered through a short pad of silica gel and washed with EtOAc (40 ml). The combined organic solution was concentrated and purified by silica gel flash column chromatography (0% to 30% EtOAc/hexane) to give the enamide 60 (105 mg Z isomer, 75%, and 15 mg E isomer, 11%) as an oil. Z isomer: ¹HNMR (500 MHz, CDCl₃) δ 8.17 (d, J = 11.0 Hz, 1H), 7.70-7.36 (m, 10H), 6.63 (dd, J = 11.0, 14.5 Hz, 1H), 6.28 (s, 1H), 5.09 (broad, 1H), 5.03 (m, 1H), 4.92 (d, J = 9.0 Hz, 1H), 4.70 (s, 1H), 4.67 (s, 1H), 4.39 (d, J = 2.0 Hz, 1H), 4.08 (m, 1H), 3.49 (m, 1H), 3.43 (dd, J = 3.5, 6.5 Hz, 1H), 3.14 (s, 3H), 2.92 (dd, J = 2.0, 16.0 Hz, 1H), 2.63 (dd, J = 12.5, 16.0 Hz, 1H), 2.38 (dd, J = 9.0, 14.5 Hz, 1H), 2.32 (m, 1H), 2.09 (s, 3H), 2.08 (s, 3H), 2.03 (s, 3H), 2.19-1.97 (m, 4 H), 1.75 (m, 2H), 1.57 (s, 3H), 1.35-1.23 (m, 6H), 1.17 (d, J = 6.5 Hz, 1H), 1.15 (s, 9H), 1.12-1.09 (m, 36 H), 0.90 (s, 9H), 0.87 (s, 3H), 0.86 (s, 3H), 0.02 (s, 3H), -0.02 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 170.8, 170.5, 167.9, 162.6, 158.7, 157.4, 142.1, 140.9, 136.0, 135.6, 132.6, 132.0, 130.2, 128.0, 127.8, 125.5, 122.8, 118.1, 112.7, 111.5, 109.6, 109.4, 82.0, 77.9, 75.0, 74.4, 71.5, 60.3, 57.8, 43.0, 39.1, 37.9, 33.6, 32.5, 30.3, 30.2, 29.6, 26.1, 22.4, 21.1, 21.0, 20.8, 20.0, 19.5, 18.3, 18.0, 17.9, 14.1, 13.2, 13.1, 11.6, 6.8, -3.1, -4.3; MS (FAB) calculated for C₇₄H₁₂₁NNaO₁₂Si₄ [M + Na]⁺: 1350.7864, found 1350.7864.
(3R)-3-((1R)-1-((4R)-6-((R)-5-(benzyloxy)-3-hydroxy-2-methylpentan-2-yl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-6,8-dihydroxy-5-methylisochroman-1-one (61): To a solution of diol 58 (75 mg, 0.1 mmol) in 2,2-dimethoxypropane (2 mL) was added PPTS (4 mg, 0.01 mmol) and the reaction was stirred at room temperature for 2 hours. The reaction was quenched by aqueous NaHCO₃ solution (20 ml) and extracted with EtOAc (40 ml). Organic layer was washed with brine (20 ml), dried and concentrated. The crude product was then treated with TBAF (0.1 M in THF, 5 mL) at 45 °C overnight. The reaction was then diluted with dichloromethane (30 ml), washed with aqueous NaHCO₃ solution (10 ml) and brine (10 ml), dried (Na₂SO₄) and concentrated. The crude product was purified by silica gel column chromatography (0% to 10% MeOH/DCM) to give 61 (31 mg, 57%). ³¹HNMR (500 MHz, CDCl₃) δ 11.12 (s, 1H), 7.34-7.25 (m, 5H), 6.32 (s, 1H), 4.54 (m, 1H), 4.53 (s, 2H), 4.07 (m, 1H), 4.02 (m, 1H), 3.87 (dd, J = 2.0, 12.0 Hz, 1H), 3.73-3.65 (m, 3H), 2.91-2.81 (m, 2H), 2.05 (s, 3H), 1.88 (m, 1H), 1.80 (m, 1H), 1.73-1.53 (m, 2H), 1.44 (s, 3H), 1.38 (s, 3H), 1.14 (d, J = 7.0 Hz, 3H), 0.90 (s, 3H), 0.89 (s, 3H); ¹³CNMR (125 MHz, CDCl₃) δ 170.6, 162.4, 161.7, 139.5, 138.3, 128.3, 127.7, 127.5, 113.4, 101.2, 98.9, 78.9, 75.1, 73.2, 69.3, 68.4, 60.5, 41.9, 39.6, 31.9, 30.1, 28.1, 27.8, 20.9, 20.4, 19.5, 14.2, 10.5, 9.9.

(4R)-6-(benzyloxy)-4-(tert-butyldimethylsilyloxy)-3,3-dimethylhexan-2-yl acetate (62): To a solution of ketone 48 (367 mg, 1 mmol) in MeOH (5 mL) was added NaBH₄ (76 mg, 2 mmol) at 0 °C and the reaction was stirred at room temperature for 2 hours. The reaction was quenched by aqueous NaHCO₃ solution (10 ml) and extracted with EtOAc (40 ml). Organic layer was washed with brine (10 ml), dried and concentrated. A portion of the crude product (175 mg, 0.47 mmol) was dissolved in dichloromethane (3 mL). To this solution was added DMAP (25 mg, 0.2 mmol), pyridine (0.2 mL) and Ac₂O (0.1 mL). The reaction mixture was stirred at room temperature overnight before it was diluted with EtOAc (50 ml), and then washed with NH₄Cl (20 ml) and brine (10 ml). The organic layer was dried (Na₂SO₄) and concentrated, the residue was purified by silica gel column chromatography (0% to 30% EtOAc/Hexane) to give 62 as a mixture (175 mg) of...
two isomers, one of which was separated and characterized and its stereochemistry was not determined. Isomer A: \(^1\)HNMR (500 MHz, CDCl\(_3\)) \(\delta 7.29-7.19 (m, 5 \text{ H}), 4.91 (d, J = 6.5 \text{ Hz}, 1\text{H}), 4.42 (d, J = 12.0 \text{ Hz}, 1\text{H}), 4.39 (d, J = 12.0 \text{ Hz}, 1\text{H}), 3.58 (dd, J = 2.5, 8.0 \text{ Hz}, 1\text{H}), 3.44 (m, 2\text{H}), 1.89 (m, 1\text{H}), 1.88 (s, 3\text{H}), 1.49 (m, 1\text{H}), 1.07 (d, J = 6.0 \text{ Hz}, 3\text{H}), 0.83 (broad, 12\text{H}), 0.76 (s, 3\text{H}), 0.00 (s, 3\text{H}), -0.03 (s, 3\text{H}); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta 170.4, 138.5, 128.3, 127.6, 127.4, 74.3, 74.0, 72.7, 67.7, 41.8, 33.1, 26.1, 21.2, 19.8, 18.7, 18.4, 15.0, -3.9, -4.0); MS (ES) calculated for C\(_{23}\)H\(_{41}\)O\(_4\)Si [M + H]+ 409.28, found 409.31.

(4\text{R})-4-(tert-butyldimethylsilyloxy)-7-iodo-3,3-dimethylhept-6-en-2-yl acetate (63):

To a solution of compound 62 (127 mg, 0.31 mmol) in EtOH (3 mL) was charged Pd/C (20 mg) and the flask was sealed with rubber stopper. The inner atmosphere was exchanged three times with hydrogen. Before it was allowed to stir under H\(_2\) (double layer balloon) overnight. The reaction mixture was filtered off a celite pad followed by washing with EtOH (30 mL). The combined organic solution was concentrated to give the crude alcohol as oil. To a solution of the crude alcohol (0.3 mmol) in dichloromethane (5 mL) was added Dess-Martin Periodinane (190 mg, 0.45 mmol) at 0 \(^\circ\)C. The reaction was allowed to stir at room temperature for 2 hours. After the reaction was complete, it was cooled to 0 \(^\circ\)C and aqueous Na\(_2\)S\(_2\)O\(_3\) (10 mL) was added. The mixture was stirred at room temperature for 15 minutes before being diluted with EtOAc (40 mL), washed with aqueous NaHCO\(_3\) (20 ml) brine (10 ml), and dried over Na\(_2\)SO\(_4\). The residue was purified by silica gel flash column chromatography (10% EtOAc/hexane) to give the aldehyde as colorless oil. An aluminum foil wrapped round bottom flask contained CrCl\(_2\) (276 mg, 2.25 mmol) was flamed dried under high vacuum and then cooled to room temperature. The adapter was quickly replaced by a rubber stopper and an argon balloon was place on the top. Aldehyde (80 mg, 0.25 mmol) was azeotropically condensed with toluene three times and then put under high vacuum. To a suspension of CrCl\(_2\) (276 mg, 2.25 mmol) in anhydrous THF (5 mL) was added a solution of aldehyde (80 mg, 0.25 mmol) and CHI\(_3\) (295 mg, 0.75 mmol) in THF (5 mL) at 0 \(^\circ\)C. Color should turn to reddish brown after 10
to 15 minutes. The reaction was allowed to stir at room temperature overnight. The reaction mixture was diluted with EtOAc (30 ml) and water (10 ml) was added. The mixture was extracted with EtOAc (50 ml), washed with brine (10 ml) and dried over Na₂SO₄. After concentration the residue was purified by silica gel flash column chromatography (0% to 10% EtOAc/hexane) to give the vinyl iodide 63 (94 mg, 71% over 3 steps, mixture of 4 isomer) as a light yellow oil.

\[ \text{N-((4R)-4-(tert-butyldimethylsilyloxy)-6-hydroxy-5,5-dimethylhept-1-enyl)acetamide (64):} \]

To an oven dried seal tube was charged acetamide (34 mg, 0.57 mmol), CuI (19 mg, 0.1 mmol), and Cs₂CO₃ (124 mg, 0.38 mmol) sequentially. Under argon, dimethyl-ethylenediamine (0.022 mL, 0.2 mmol) was then added followed by a solution of vinyl iodide 63 (84 mg, 0.19 mmol) in toluene. The tube was filled with argon and quickly capped and sealed. The reaction was stirred vigorously at 70°C for 20 hours. After the reaction was cooled to room temperature, it was diluted with EtOAc (30 ml) and filtered off a short pad of silica gel and washed with EtOAc (20 ml). The combined organic solution was concentrated and purified by silica gel flash column chromatography (0% to 10% acetone/hexane) to give the enamide (53 mg, 75%) as oil. The amide was then treated with NaOMe/MeOH (0.06 M, 1 mL) to remove the acetate to give 64 as 2 isomers. The major trans isomer: ¹HNMR (500 MHz, CDCl₃) δ 6.97 (d, J = 10.0 Hz, 1H), 6.71 (dd, J = 10.5, 14.5 Hz, 1H), 5.11 (m, 1H), 4.96 (m, 1H), 3.49 (dd, J = 4.5, 6.0 Hz, 1H), 2.33 (m, 1H), 2.10 (m, 1H), 2.03 (s, 3H), 2.02 (s, 3H), 1.13 (d, J = 6.5 Hz, 3H), 0.90 (s, 3H), 0.89 (s, 3H), 0.83 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H); MS (ES) calculated for C₂₁H₃₅O₃Si [M + H]⁺ 367.27, found 367.27.
**N-(((4R)-4-(tert-butyldimethylsilyloxy)-5,5,6-trimethyltetrahydro-2H-pyran-2-yl)(methoxy)methyl)acetamide (65):** Under an atmosphere of argon, a solution of compound 64 (31 mg, 0.094 mmol) in hexafluoroisopropanol (0.5 mL) at 0 °C was added MeOH (0.077 mL) and then a solution of (diacetoxyiodo)benzene (63 mg, 0.19 mmol) dropwise as a solution in hexafluoroisopropanol (0.5 mL). The reaction mixture was stirred at 0 °C for 4 hours. The reaction mixture was diluted with EtOAc (20 mL) and filtered through a short pad of silica gel. The filtrate was concentrated and then purified by silica gel flash column chromatography (0% to 50% EtOAc/Hexane) to give 65 (4 isomers, 1.5/2.2/1.0/2.1. Selected NMR data of 65: $^1$HNMR (500 MHz, CDCl$_3$) δ 5.15 (dd, $J$ = 2.5, 9.5 Hz, 1H, isomer III), 5.04 (dd, $J$ = 2.5, 9.5 Hz, 1H, isomer IV), 4.95 (dd, $J$ = 2.5, 9.5 Hz, 1H, isomer I), 4.93 (dd, $J$ = 2.0, 10.0 Hz, 1H, isomer II), 3.37 (s, 3H, isomer I), 3.36 (s, 3H, isomer II), 3.37 (s, 3H, isomer IV), 3.35 (s, 3H, isomer III). MS (ES) calculated for C$_{18}$H$_{38}$NO$_4$Si [M + H]$^+$ 360.26, found 360.21.

**N-(((S)-((2S,4R,6R)-6-((2S,3R)-3-(((R))-6,8-dihydroxy-5-methyl-1-oxoisochroman-3-yl)-2-hydroxybutyl)-4-hydroxy-5,5-dimethyltetrahydro-2H-pyran-2-yl)(methoxy)methyl)acetamide (67) and N-((R)-(2R,4R,6R)-6-((2S,3R)-3-(((R))-6,8-dihydroxy-5-methyl-1-oxoisochroman-3-yl)-2-hydroxybutyl)-4-hydroxy-5,5-dimethyltetrahydro-2H-pyran-2-yl)(methoxy)methyl)acetamide (epi-67):** These two compounds were prepared from 59 (40 mg, 0.04 mmol) followed the same procedure for the preparation of 65 from 63 except that the final product was obtained after deprotection of protecting groups with TBAF (0.1 M, 4 mL) at 50 °C overnight. The residue was carefully purified by prep TLC (acetone/DCM 1/1) to yield the desired compound 67 (6.2 mg, 32% overall) and epi-67 (5.3 mg, 27% overall). 67: $[\alpha]_D^{20}$ = +32.36 (MeOH, c = 0.08) $^1$HNMR (500 MHz, CDCl$_3$) δ 11.25 (broad, 1H), 6.30 (s, 1H), 5.82 (d, $J$ = 10.0 Hz, 1H), 5.38 (dd, $J$ = 7.0, 10.0 Hz, 1H), 4.53 (m, 1H), 3.94 (d, $J$ = 10.0 Hz, 1H), 3.91 (m, 1H), 3.84 (broad, 1H), 3.65 (dd, $J$ = 4.5, 9.5 Hz, 1H), 3.59 (d, $J$ = 9.5 Hz, 1H), 3.38 (s,
3H), 3.06 (dd, J = 3.0, 16.5 Hz, 1H), 2.83 (dd, J = 12.5, 17.0 Hz, 1H), 2.10 (s, 3H), 2.09 (s, 3H), 2.07-1.71 (m, 5H), 1.13 (d, J = 7.0 Hz, 3H), 1.00 (s, 3H), 0.93 (s, 3H); LCMS calculated for C_{25}H_{38}NO_{9} [M + H]^+ 496.3, found 496.3. **epi-67:** [α]D20 = +26.70 (MeOH, c = 0.1) HNMR (500 MHz, CDCl3) δ 11.21 (s, 1H), 6.32 (s, 1H), 6.05 (d, J = 10.0 Hz, 1H), 5.08 (dd, J = 2.5, 10.0 Hz, 1H), 4.58 (dt, J = 4.5, 11.0 Hz, 1H), 4.14 (broad, 1H), 4.09 (m, 1H), 3.74 (d, J = 12.5 Hz, 1H), 3.50 (dd, J = 4.5, 11.5 Hz, 1H), 3.32 (s, 3H), 3.29 (d, J = 10.0 Hz, 1H), 2.96-2.87 (m, 2H), 2.07 (s, 3H), 2.04 (s, 3H), 1.98-1.26 (m, 5H), 1.13 (d, J = 7.5 Hz, 3H), 0.96 (s, 3H), 0.88 (s, 3H); 13C NMR (125 MHz, CDCl3) δ 171.5, 171.1, 162.7, 161.6, 140.3, 113.7, 101.7, 86.8, 81.6, 79.9, 75.0, 73.3, 56.5, 52.8, 43.0, 39.6, 32.5, 32.3, 30.1, 28.7, 23.8, 22.6, 20.8, 14.2, 13.1, 11.0, 10.1; LCMS calculated for C_{25}H_{38}NO_{9} [M + H]^+ 496.3, found 496.3.

(R)-3-(((2R,3S,5R,7R)-7-(tert-butyldimethylsilyloxy)-10-((2S,3S)-2-(tert-butyl diphenylsilyloxy)-3-methoxy-5-methylhex-5-enamido)-3,5-dihydroxy-6,6-dimethyldece-9-en-2-yl)-5-methyl-1-oxo-8-(triisopropylsil yloxy)isochroman-6-yl acetate (68): Compound 60 (60 mg, 0.045 mmol) was treated with a solution of NaOMe in MeOH (0.06M, 1 mL) at room temperature for 5 hours before the reaction was quenched by water (1 ml). The mixture was then extracted with EtOAc (50 ml) thoroughly. The organic layer was washed with brine (10 ml), dried over Na2SO4 and concentrated. The crude was dissolved in dichloromethane (1 ml), pyridine (40 μl), DMAP (1 mg) and then Ac2O (20 μl) was added at 0 °C sequentially. The reaction mixture was allowed to stir at 0 °C for 2 hour before the addition aqueous NH4Cl (3ml) to quench the reaction. The aqueous layer was extracted with EtOAc (30 ml). Combine organic layers were washed with NH4Cl (10 ml) and brine (10 ml). After the organic layer was dried and concentrated, the residue was purified by PTLC (EtOAc/hexane 1/10, 1% NEt3) to give 68 (41 mg, 80% over two steps). NMR data of the major Z isomer: HNMR (500 MHz, CDCl3) δ 8.18 (d, J = 11.0 Hz, 1H), 7.70-7.37 (m, 10H), 6.66 (dd, J
= 11.5, 14.5 Hz, 1H), 6.53 (s, 1H), 5.03 (m, 1H), 4.85 (s, 1H), 4.71 (s, 1H), 4.67 (s, 1H), 4.40 (m, 2H), 4.25 (s, 1H), 4.15 (m, 1H), 4.06 (d, J = 9.0 Hz, 1H), 3.50-3.45 (m, 2H), 3.16 (s, 3H), 3.03 (dd, J = 3.0, 16.5 Hz, 1H), 2.86 (dd, J = 12.0, 16.5 Hz, 1H), 2.45 (m, 1H), 2.38 (dd, J = 9.0, 14.5 Hz, 1H), 2.33, (s, 3H), 2.28 (m, 1H), 2.10 (dd, J = 5.0, 14.5 Hz, 1H), 2.03 (s, 3H), 1.88 (m, 1H), 1.61 (s, 3H), 1.57 (s, 3H), 1.68-1.64 (m, 2H), 1.41-1.39 (m, 1H), 1.36-1.30 (m, 3H), 1.16 (s, 9H), 1.13-1.10 (m, 18H), 1.01 (s, 3H), 0.90 (s, 9H), 0.77 (s, 3H), 0.09 (s, 3H), 0.01 (s, 3H); ^13C NMR (125 MHz, CDCl3) d 169.2, 168.4, 165.1, 162.5, 156.8, 152.8, 142.0, 141.4, 123.3, 119.4, 114.7, 113.4, 111.8, 83.9, 79.4, 78.5, 77.6, 73.0, 72.3, 60.4, 58.1, 45.7, 42.8, 41.0, 38.2, 34.7, 33.3, 29.5, 25.9, 23.3, 22.6, 20.8, 17.9, 14.2, 13.1, 11.8, 9.7, 8.6, -3.6, -4.3; MS (FAB) calculated for C63H99NNaO11Si3 [M + Na]^+ 1152.6424, found 1154.6425.

(3R)-3-((2R,3S,5R,7R,E)-7-(tert-butyldimethylsilyloxy)-6-(methoxymethyl)-6-methyl-5,6-dihydro-2H-pyran-2-ylideneamino)-3,5-dihydroxy-6,6-dimethyldec-9-en-2-yl)-5-methyl-1-oxo-8-(triisopropylsilyloxy)isochroman-6-yl acetate (69) and (3R)-3-((2R,3S,5R,7R,E)-7-(tert-butyldimethylsilyloxy)-5-methyl-1-oxo-8-(triisopropylsilyloxy)isochroman-6-yl acetate (70): Under an atmosphere of argon, a solution of compound 68 (20 mg, 0.0177 mmol) in hexafluoroisopropanol (0.5 mL) at 0 °C was added MeOH (20 μl) and then a solution of (diacetoxyiodo)benzene (24 mg, 0.071 mmol) dropwise as a solution in hexafluoroisopropanol (0.1 mL). The reaction stirred from 0 °C to room temperature overnight. The reaction mixture was diluted with EtOAc (20 ml) and filtered through a short pad of silica gel. The filtrate was concentrated and then purified by PTLC (acetone/hexane 1/2) to give two major products 69 (8 mg, 40%) and 70 (4 mg, 20%). 69:
$^1$HNMR (500 MHz, CDCl$_3$) $d$ 7.81-7.74 (m, 4H), 7.41-7.32 (m, 6H), 7.02 (d, $J = 13.0$ Hz, 1H), 6.53 (s, 1H), 5.60 (m, 1H), 5.28 (dd, $J = 4.5$, 5.0 Hz, 1H), 5.02 (s, 1H), 4.39 (ddd, $J = 3.0$, 6.5, 12.5 Hz, 1H), 4.31 (s, 1H), 4.17 (d, $J = 11.0$ Hz, 1H), 4.11 (d, $J = 10.0$ Hz, 1H), 3.52 (dd, $J = 4.0$, 7.5 Hz, 1H), 3.28 (s, 3H), 3.21 (d, $J = 10.0$ Hz, 1H), 3.11 (d, $J = 10.0$ Hz, 1H), 3.04 (dd, $J = 3.0$, 16.0 Hz, 1H), 2.86 (dd, $J = 12.5$, 16.5 Hz, 1H), 2.55 (m, 1H), 2.42 (dd, $J = 4.5$, 17.5 Hz, 1H), 2.33 (s, 3H), 2.04 (s, 3H), 1.99 (dd, $J = 5.0$, 18.0 Hz, 1H), 1.89 (m, 1H), 1.65 (m, 1H), 1.36-1.30 (m, 3H), 1.25 (s, 3H), 1.14-1.09 (m, 30H), 1.03 (s, 3H), 0.89 (s, 9H), 0.78 (s, 3H), 0.11 (s, 3H), 0.09 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $d$ 168.4, 162.6, 156.8, 152.8, 148.0, 142.2, 142.1, 135.7, 133.4, 129.6, 127.4, 126.7, 119.4, 114.8, 113.3, 111.0, 84.6, 78.8, 77.7, 72.1, 59.5, 42.9, 40.8, 34.7, 34.2, 30.3, 29.7, 29.5, 26.7, 26.1, 23.6, 22.8, 21.0, 20.9, 19.7, 18.0, 13.1, 11.9, 9.7, -3.5, -4.1. MS (ES) calculated for C$_{63}$H$_98$NO$_{11}$ [M + H]$^+$: 1129.71, found 1129.68.

$^{70}$: $^1$HNMR (500 MHz, CDCl$_3$) $d$ 7.69-7.24 (m, 15H), 6.52, 6.51 (s, 1H), 5.19 (m, 1H), 4.43-4.38 (m, 3H), 4.26 (broad, 1H), 4.08 (broad, 1H), 3.97 (broad, 1H), 3.72, 3.70 (s, 1H), 3.52-3.48 (m, 2H), 3.34 (s, 3H), 3.33 (s, 3H), 3.29 (m, 1H), 3.22-3.00 (m, 6H), 2.92-2.85 (m, 1H), 2.31 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 1.84-1.44 (m, 3H), 1.37-1.31 (m, 3H), 1.13-1.10 (m, 30H), 0.90 (s, 9H), 0.80 (s, 3H), 0.77 (s, 3H), 0.74, 0.71 (d, $J = 6.5$ Hz, 3H), 0.04 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) $d$ 172.4, 172.2, 168.5, 162.7, 157.0, 152.9, 142.3, 136.3, 135.9, 132.8, 130.3, 130.1, 128.4, 128.0, 127.9, 127.6, 127.5, 113.3, 82.3, 79.1, 76.2, 75.5, 72.9, 72.2, 56.2, 43.3, 34.5, 30.4, 30.0, 29.6, 27.3, 25.9, 21.0, 19.6, 18.1, 16.8, 14.3, 13.3, 12.0, 9.8, -4.4, -4.9. MS (ES) calculated for C$_{62}$H$_{96}$NO$_{11}$ [M + H]$^+$: 1115.68, found 1115.67.

(S)-tert-butyl(2-methoxy-4-methylpent-4-enoxy)dimethylsilane (74): To a solution of compound 73 (8.87 g, 47.2 mmol) in anhydrous THF (150 mL) was added Cul (2.3 g, 11.8 mmol) and the resulting suspension was cooled to –15 °C. Vinylmagnesium bromide (180 mL, 0.5 M in THF, 94.4 mmol) was added dropwise through an addition funnel under N$_2$. The reaction mixture was allowed to stir at –15 °C for 3 hours with TLC monitoring before it was quenched by aqueous NH$_4$Cl (100 mL) and diluted with Et$_2$O.
(200 mL). The organic layer was washed with brine (50 ml), dried (Na$_2$SO$_4$) and concentrated. The residue was purified by silica gel flash column chromatography (0% to 5% EtOAc/hexane) to give alcohol 74a (8.9 g, 82 %) as an oil. $^1$HNMR (500 MHz, CDCl$_3$) δ 4.83(s, 1H), 4.78(s, 1H), 3.83-3.78 (m, 1H), 3.61(dd, $J$ = 3.5, 10.0 Hz, 1H), 3.46 (dd, $J$ = 7.0, 10.0 Hz, 1H), 2.37 (d, $J$ = 3.5 Hz, 1H), 2.17 (d, $J$ = 6.5 Hz, 2H), 1.77 (s, 3H), 0.90 (s, 3H), 0.07 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 142.6, 113.1, 69.8, 67.0, 41.8, 26.1, 22.8, 18.5, -5.2. To a solution of compound 74a (30 g, 130 mmol) in anhydrous dichloromethane (300 mL) was added freshly activated 4Å molecular sieves (5 g, powder), proton sponge (50 g, 234 mmol) and Me$_3$OBF$_4$ (23g, 156 mmol). The suspension was allowed to stir at room temperature overnight before it was diluted with dichloromethane (200 ml) and filtered. The filtrate was washed with water (50 ml), 1N aq. HCl (50 ml), NaHCO$_3$ (100 ml) and brine (50 ml). The organic layer was concentrated and the residue was purified by silica gel flash column chromatography (0% to 5% Et$_2$O/hexane) to give 74 (30g, 95%) as a volatile oil: $^1$HNMR (500 MHz, CDCl$_3$) δ 4.80 (s, 1H), 4.75 (s, 1H), 3.62 (dd, $J$ = 6.0, 10.5 Hz, 1H), 3.58 (dd, $J$ = 4.5, 10.5 Hz, 1H), 3.42 (s, 3H), 3.41-3.36 (m, 1H), 2.23 (dd, $J$ = 5.5, 14.5 Hz, 1H), 2.16 (dd, $J$ = 7.5, 14.5 Hz, 1H), 1.77 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 143.0, 112.6, 80.6, 65.1, 58.1, 40.0, 26.1, 23.1, 18.5, -5.1, -5.2. MS (ES) calculated for $C_{13}H_{29}O_2Si$ [M + H]$^+$: 245.19, found 245.18.

(2S)-5-(benzyloxy)-2-methoxy-4-methylpentanal (75): A solution of compound 74 (5 g, 20.4 mmol) in THF (50 mL) was treated with BH$_3$·THF (22.5 mL, 1.0 M in THF, 22.5 mmol) solution at 0 °C for 1 hour. To this solution was added aqueous NaOH (1N, 100 mL) solution followed immediately by aqueous 30 % H$_2$O$_2$ (11 mL). The ice bath was then removed and the mixture was allowed to stir at room temperature for another hour before being diluted with EtOAc (100 ml). The solution was washed with water (30 ml) and brine (30 ml), dried (MgSO$_4$) and concentrated. Silica gel flash column chromatography (20% EtOAc/hexane) of the residue gave compound 75a (4.7 g, 88%) as a pair of diastereomers. $^1$HNMR (500 MHz, CDCl$_3$) δ 3.68-3.26 (m, 5H, both isomers),
3.43 (s, 3H, isomer I), 3.42 (s, 3H, isomer II), 2.83 (br, 1H, isomer II), 2.66 (br, 1H, isomer I), 1.89-1.76 (m, 1H, both isomers), 1.56-1.36 (m, 2H, both isomers), 0.93 (d, \( J = 7.0 \) Hz, 3H, isomer I), 0.90 (d, \( J = 7.0 \) Hz, 3H, isomer II), 0.89 (s, 9H, isomer I), 0.88 (s, 9H, isomer II), 0.05 (s, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 81.1, 80.0, 68.6, 68.1, 65.5, 65.0, 58.1, 57.8, 36.6, 35.7, 33.7, 32.5, 26.0, 18.4, 18.0, 17.7, -5.2, -5.3. To a solution of compound 75a (1.9 g, 5.2 mmol) in anhydrous DMF (15 mL) was added NaH (380mg, 10 mmol) at 0 °C, after stirring for 15 minutes, BnBr (1.18 mL, 10 mmol) was added. The reaction was allowed to stir at room temperature for 2 hours. The reaction mixture was quenched by aqueous NH\(_4\)Cl (20 ml), extracted with EtOAc (80 ml), washed with aqueous NaHCO\(_3\) (30 ml) and brine (20 ml). The organic layer was dried (Na\(_2\)SO\(_4\)) and concentrated. The residue was purified by silica gel flash column chromatography (0% to 5% Et\(_2\)O/hexane) to give compound 75b (1.68 g, 92%) as an oil. \(^1\)HNMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.40-7.38 (m, 5H), 4.57 (s, 2H), 3.72-3.30 (m, 5H), 3.48 (s, 3H, isomer I), 3.46 (s, 3H, isomer II), 2.10-1.99 (m, 1H), 1.65-1.56 (m, 1H), 1.39-1.30 (m, 1H), 1.06 (d, \( J = 7.0 \) Hz, 3H, isomer I), 1.04 (d, \( J = 7.0 \) Hz, 3H, isomer II), 0.96 (s, 9H), 0.12 (s, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 139.0, 128.6, 127.8, 127.7, 127.6, 80.6, 80.0, 76.5, 75.9, 73.2, 73.1, 66.0, 65.8, 58.4, 58.1, 36.2, 36.1, 30.7, 30.3, 26.2, 18.6, 18.5, 17.4, -5.1. To a solution of compound 75b (1.68 g, 4.77 mmol) in THF (10 mL) was added TBAF (10 mL, 1.0 M in THF) at room temperature. The reaction mixture was allowed to stir at room temperature overnight before it was diluted with EtOAc (100 ml). The mixture was washed with water (30 ml) and brine (20 ml). The organic layer was dried (Na\(_2\)SO\(_4\)) and concentrated. The residue was purified by silica gel flash column chromatography (0% to 20% EtOAc/hexane) to give compound 75c (1.14 g, 99%) as an oil. \(^1\)HNMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.36-7.26 (m, 5H), 4.50 (s, 2H), 3.71-3.27 (m, 8H), 2.13-1.19 (m, 3H), 0.98 (d, \( J = 7.0 \) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 138.9, 138.8, 128.6, 127.8, 80.2, 79.7, 76.2, 76.0, 73.3, 64.3, 64.1, 57.4, 57.1, 35.3, 34.8, 30.6, 30.4, 18.0, 17.9. A solution of oxyl chloride (3 mL, 35 mmol) in dichloromethane (50 mL) at -78 °C was added DMSO (4.97 mL, 70 mmol) slowly. 5 minutes later, alcohol 75c (4.25 g, 17.8 mmol) in dichloromethane (30 mL) was added. Et\(_3\)N (9.7 mL, 70 mmol) was added at -78 °C in 45 minutes. The reaction mixture was allowed to stir at -78 °C for 15 minutes before the cold bath was removed. The reaction was kept stirring from -78 °C to room temperature.
at room temperature for 0.5 h. The reaction mixture was diluted with EtOAc (100 ml), washed with NaHCO₃ (20 ml), brine (20 ml), dried and concentrated. The residue was purified by silica gel flash column chromatography (10% EtOAc/hexane) to give aldehyde 75 (3.95 g, 94%) as a yellow oil. ¹H NMR (500 MHz, CDCl₃) δ 9.64 (d, J = 2.0 Hz, isomer I), 9.61 (d, J = 2.0 Hz, 1H, isomer II), 7.36-7.26 (m, 5H), 4.52-4.47 (m, 2H), 3.68-3.64 (m, 1H), 3.43 (s, 3H, isomer I), 3.39 (s, 3H, isomer II), 3.34-3.31 (m, 2H), 2.07-1.98 (m, 1H), 1.83-1.75 (m, 1H), 1.51-1.41 (m, 1H), 0.98 (d, J = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 204.0, 203.8, 138.7, 138.6, 128.5, 127.7, 127.6, 84.6, 84.1, 75.6, 75.2, 73.2, 73.0, 58.5, 58.3, 34.0, 33.7, 30.0, 29.8, 18.1, 16.9; MS (ES) calculated for C₁₄H₂₁O₃ [M + H]+: 237.15, found 237.12.

(2S,3S)-6-(benzyloxy)-2-(tert-butyldiphenylsilyloxy)-3-methoxy-5-methylhexanamide (76): To a solution of aldehyde 75 (4g, 17 mmol) in dichloromethane (100 mL) was added TMSCN (5.6 mL, 42.5 mmol) at 0 °C, AlCl₃ (2 g, 15 mmol) was added 5 minutes later. The reaction mixture was stirred from 0 °C to room temperature overnight. The reaction was quenched by adding aqueous NaHCO₃ solution (40 ml) and extracted with EtOAc (100 ml). The organic layer was washed with brine (20 ml), dried and concentrated. The residue was purified by silica gel flash column chromatography (20% acetone/hexane) to give 76a and 76b (3.88 g, 87%) as an inseparable mixture (76a/76b, 2/1). ¹H NMR (500 MHz, CDCl₃) δ 7.38-7.28 (m, 5H), 4.55-4.34 (m, 3H), 3.65-3.53 (m, 1H), 3.39-3.26 (m, 2H), 3.53, 3.51 (s, 3H, 76b), 3.46-3.45 (s, 3H, 76a) 2.01-1.43 (m, 3H), 1.00-0.97 (m, 3H); MS (ES) calculated for C₁₅H₂₂NO₃ [M + H]+: 264.16, found 264.10. To a solution of compound 76a/76b (1.23g, 4.68 mmol) in dichloromethane (15 mL) was added NEt₃ (1.15 mL, 8.24 mmol), DMAP (61 mg, 0.5 mmol) at 0 °C. To the solution was added TBDPSCI (1.82 mL, 7 mmol). The reaction mixture was stirred at room temperature overnight before being diluted with EtOAc (80 ml) and washed with aqueous NH₄Cl (20 ml), NaHCO₃ (20 ml) and brine (20 ml) sequentially. After being dried over Na₂SO₄, it was concentrated and purified by silica gel flash column chromatography (10% Et₂O/hexane) to give the protected
cyanohydrin. To a solution of this cyanohydrin in H₂O/THF (16 mL, 1/3) was added PdCl₂ (177 mg) followed by acetamide (1.18 g, 20 mmol). The reaction mixture was stirred vigorously at room temperature for 10 hours before it was diluted with EtOAc (80 ml) and washed with NaHCO₃ (20 ml) and brine (20 ml). After being dried over Na₂SO₄, it was concentrated and purified by silica gel flash column chromatography (20% EtOAc/hexane) to give isolated pure compound 76 (1.3 g, 53% over two steps) as the major product. ¹HNMR (500 MHz, CDCl₃) δ 7.71-7.31 (m, 15H), 6.58 (br, 1H), 5.35 (br, 1H), 4.47 (s, 1H), 4.44 (d, J = 2.5 Hz, 1H), 4.38, 4.34 (d, J = 2.0 Hz, 1H), 3.38 (m, 1H), 3.29, 3.26 (dd, J = 5.5, 9.0 Hz, 1H), 3.19, 3.13 (dd, J = 6.5, 9.0 Hz, 1H), 3.11 (s, 3H), 1.90, 1.83 (m, 1H), 1.59, 1.45 (m, 1H), 1.10, 1.04 (m, 1H), 1.13 (s, 9H), 0.88, 0.82 (d, J = 6.5 Hz, 3H); MS (ES) calculated for C₃₁H₄₂NO₄Si [M + H]⁺: 520.29, found 520.35.

(2S,3S)-6-(benzyloxy)-2-hydroxy-3-methoxy-5-methylhexanenitrile (77): To a solution of aldehyde 75 (100 mg, 0.42 mmol) and MgBr₂·Et₂O (568 mg, 2.2 mmol) in dichloromethane (10 mL) was added TMSCN (0.067 mL, 0.5 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for one hour before being quenched by sequential addition of TFA (4.2 mmol) and water (10 mL). The aqueous layer was extracted with EtOAc (50 mL) and the organic layer was washed with aqueous NaHCO₃ (20 mL) brine (20 mL), dried and concentrated. The residue was purified by silica gel flash column chromatography (30% EtOAc/Hexane) to give 77 (105 mg, 95%) as an inseparable mixture (10/1 at the new chiral center). NMR of the major 2 isomers (~1/1 ratio at the chiral center created by benzylxy substitution): ¹HNMR (500 MHz, CDCl₃) δ 7.38-7.28 (m, 5H), 4.54-4.48 (m, 2H), 4.40 (dd, J = 3.5, 9.0 Hz, 1H, isomer I), 4.34 (dd, J = 3.0, 9.0 Hz, 1H, isomer II), 3.61 (m, 1H, isomer I), 3.55 (m, 1H, isomer II), 3.52 (s, 3H, isomer I), 3.50 (s, 3H, isomer II), 3.36 (m, 1H, isomer I), 3.30 (m, 1H, isomer II), 2.02-1.87 (m, 1H, both isomer), 1.80-1.69 (m, 1H, both isomer), 1.57-1.42 (m, 1H, both isomer), 0.99 (d, J = 6.5 Hz, 3H, isomer II), 0.98 (d, J = 7.0 Hz, 3H, isomer I); MS (ES) calculated for C₁₅H₂₁NNaO₃ [M + Na]⁺: 286.14, found 286.20.
(1S,2S)-5-(benzyloxy)-1-cyano-2-methoxy-4-methylpentyl acetate (78): To a solution of 77 (105 mg, 0.4 mmol), PPh₃ (426 mg, 1.6 mmol), AcOH (0.1 mL, 1.6 mmol) in THF (4 mL) was added azodicarbonyldipiperidine (0.31 mL, 1.6 mmol) at room temperature, the reaction mixture was stirred for 5 hours before being concentrated directly. The residue was purified by column chromatography (0% to 40% EtOAc/Hexane) to give 78 (97 mg, 80%, 7/1 at the cyanohydrin chiral center). NMR of the major 2 isomers (~1/1 ratio at the chiral center created by benzyloxy substitution): 

1H NMR (500 MHz, CDCl₃) d 7.37-7.27 (m, 5H), 5.49 (d, J = 5.0 Hz, 1H, isomer I), 5.44 (d, J = 4.5 Hz, 1H, isomer II), 4.53-4.67 (m, 2H, both isomer), 3.61 (m, 1H, both isomer), 3.49 (s, 3H, isomer I), 3.46 (s, 3H, isomer II), 3.38-3.29 (m, 2H, both isomer), 2.16 (s, 3H, isomer I), 2.12 (s, 3H, isomer II), 2.01 (m, 1H, both isomer), 1.84-1.71 (m, 1H, both isomer), 1.60-1.23 (m, 2H, both isomer), 1.00 (d, J = 7.0 Hz, 3H, isomer I), 0.98 (d, J = 7.0 Hz, 3H, isomer II); MS (ES) calculated for C₁₇H₂₄NO₄ [M + H]⁺: 306.17, found 306.20. Selected NMR data of 78': 

1H NMR (500 MHz, CDCl₃) d 5.50 (d, J = 3.5 Hz, 1H, isomer I), 5.46 (d, J = 3.5 Hz, 1H, isomer II), 3.48 (s, 3H, isomer I), 3.43 (s, 3H, isomer II), 2.16 (s, 3H, isomer II), 2.15 (s, 3H, isomer I). MS (ES) calculated for C₁₇H₂₄NO₄ [M + H]⁺: 306.17, found 306.20.

(3R)-3-((2R,3S,5R,7R,E)-10-((2S,3S)-6-(benzyloxy)-2-(tert-butyldiphenylsilyloxy)-3-methoxy-5-methylhexanamido)-7-(tert-butyldimethylsilyloxy)-3,5-dihydroxy-6,6-dimethyldec-9-en-2-yl)-5-methyl-1-oxo-8-(triisopropylsilyloxy)isochroman-6-yl acetate (80): To an oven dried seal tube was charged amide 76 (500 mg, 0.99 mmol), CuI (31 mg, 0.16 mmol), and Cs₂CO₃ (326 mg, 1 mmol) sequentially. Under argon, dimethylethlenediamine (0.035 mL, 0.32 mmol) was then added followed by a solution of vinyl iodide 59 (346 mg, 0.33 mmol) in toluene (5 ml). The tube was filled with argon.
and quickly capped and sealed. The reaction was stirred vigorously at 70 °C for 20 hours. After the reaction was cooled to room temperature, it was diluted with EtOAc (10 ml) and filtered off a short pad of silica gel and washed with EtOAc (50 ml). The combined organic solution was concentrated and purified by silica gel column chromatography (0% to 10% acetone/hexane) to give the enamide 80a (450 mg, 95%) as an oil. The excess amide was recovered. For characterization purpose, a small amount of E/Z mixture was separated. E isomer: 1HNMR (500 MHz, CDCl₃) d 8.18 (d, J = 11.0 Hz, 1H), 7.69-7.30 (m, 15H), 6.62 (dd, J = 12.0, 13.5 Hz, 1H), 6.29 (s, 1H), 5.10 (broad, 1H), 5.03 (m, 1H), 4.92 (d, J = 9.0 Hz, 1H), 4.47 (s, 1H), 4.45 (dd, J = 5.0, 10.0 Hz, 1H), 4.37 (dd, J = 1.5, 19.5 Hz, 1H), 4.07 (ddd, J = 2.5, 6.5, 12.5 Hz, 1H), 3.42 (m, 2H), 3.27 (m, 1H), 3.19-3.08 (m, 4H), 2.92 (dd, J = 2.5, 16.5 Hz, 1H), 2.63 (dd, J = 12.5, 16.5 Hz, 1H), 2.30 (m, 1H), 2.15 (m, 2H), 2.12-1.72 (m, 13 H), 1.60 (m, 1H), 1.35-1.25 (m, 7H), 1.18-1.10 (m, 46 H), 0.90-0.80 (m, 18 H), 0.02 (s, 3H), -0.04 (s, 3H); 13C NMR (125 MHz, CDCl₃) d 171.1, 170.8, 168.4, 163.0, 159.0, 157.7, 141.2, 136.3, 135.9, 130.5, 128.5, 128.3, 128.1, 127.8, 127.7, 127.6, 123.1, 118.4, 110.0, 109.7, 82.1, 78.2, 76.4, 75.6, 74.7, 73.1, 73.0, 71.8, 43.3, 39.4, 33.9, 30.5, 27.3, 26.4, 21.5, 21.4, 21.1, 20.4, 18.6, 18.3, 18.2, 16.9, 13.5, 13.4, 11.9, 9.1, -2.8, -3.9; MS (FAB) calculated for C₈₁H₁₂₉NNaO₁₃Si₄ [M + Na]⁺: 1458.8439, found 1458.8439. Compound 80a (450 mg, 0.31 mmol) was treated with a solution of NaOMe in MeOH (0.06 M, 10 ml) at room temperature for 5 hours before the reaction was quenched by water (10 ml). The mixture was then extracted with EtOAc (100 ml) thoroughly. The organic layer was washed with brine (20 ml), dried over Na₂SO₄ and concentrated. The crude was dissolved in dichloromethane (8 ml). At 0 °C, pyridine (0.2 ml), DMAP (4 mg) and then Ac₂O (0.1 ml) was added sequentially. The reaction mixture was allowed to stir at 0 °C for 1 hour before aqueous NH₄Cl (10 ml) was added and the aqueous layer was extracted with EtOAc (80 ml). Combine organic layer was washed with NH₄Cl (15 ml) and brine (15 ml). After dried and concentrated, the residue was purified by silica gel flash column chromatography (0% to 15% acetone/hexane) to give 80 as a mixture (368 mg, 95%) of four isomers (E/Z isomers were separable on PTLC, hence a small part was separated for characterization purpose). The mixture was carried on to the next reaction directly. NMR data of the major E isomer: 1HNMR (500 MHz, CDCl₃) d 8.19 (d, J = 10.5 Hz, 1H), 7.69-7.26 (m, 15H), 6.65 (dd, J = 11.5, 13.5 Hz, 1H),
6.53 (s, 1H), 5.00 (m, 1H), 4.86 (s, 1H), 4.47 (s, 1H), 4.43-4.36 (m, 2H), 4.26 (s, 1H), 4.15 (d, \(J = 9.0\) Hz, 1H), 4.06 (d, \(J = 10.5\) Hz, 1H), 3.43 (m, 2H), 3.26 (m, 1H), 3.18 (m, 1H), 3.14-3.08 (m, 4H), 3.03 (d, \(J = 16.5\) Hz, 1H), 2.86 (dd, \(J = 12.5, 16.0\) Hz, 1H), 2.42 (m, 1H), 2.33 (s, 3H), 2.26 (m, 1H), 2.05-1.99 (m, 4H), 1.88 (m, 2H), 1.62 (m, 1H), 1.40-1.30 (m, 4H), 1.15-1.10 (m, 29 H), 1.01 (s, 3H), 0.89 (s, 9H), 0.92 (d, \(J = 7.0\) Hz, 3 H, isomer I), 0.86 (d, \(J = 7.0\) Hz, 3H, isomer II), 0.82 (s, 3H), 0.14 (s, 3H), 0.05 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(d\) 168.6, 168.4, 168.3, 162.7, 157.0, 153.0, 142.2, 136.2, 135.8, 130.5, 130.4, 128.4, 128.2, 128.0, 127.6, 127.5, 115.0, 113.5, 84.9, 81.6, 78.8, 77.8, 76.2, 75.5, 73.0, 72.9, 72.4, 43.0, 34.9, 33.1, 30.3, 30.0, 29.7, 27.2, 26.2, 23.7, 21.1, 19.7, 18.4, 18.3, 18.2, 16.8, 13.3, 12.0, 9.99, -3.3, -3.9; MS (FAB) calculated for C\(_{70}\)H\(_{107}\)NNaO\(_{12}\)Si\(_{3}\) [M + Na]\(^+\) 1260.6999, found 1260.7005.

(3R)-3-((2S,3S)-3-acetoxy-4-((2R,4R,6S)-4-(tert-butyldimethylsilyloxy)-6-((3S,6S)-6-((1S)-4-hydroxy-1-methoxy-3-methylbutyl)-9,9-dimethyl-5-oxo-8,8-diphenyl-2,7-dioxa-4-aza-8-siladecan-3-yl)-3,3-dimethyltetrahydro-2H-pyran-2-yl)butan-2-yl)-5-methyl-1-oxo-8-(triisopropylsilyloxy)isochroman-6-yl acetate (81): Under an atmosphere of argon, a solution of compound 80 (300 mg, 0.24 mmol) in hexafluoropropanol (4 mL) at 0 °C was added MeOH (0.2 mL) and then a solution of (diacetoxyiodo)benzene (320 mg, 0.96 mmol) dropwise as a solution in hexafluoropropanol (2 mL). The reaction mixture was stirred at room temperature for 70 hours before it was diluted with EtOAc (20 ml) and filtered through a short pad of
silica gel. The filtrate was concentrated and then purified by silica gel flash column chromatography (0% to 30% acetone/hexane) to give two crude fraction which was re-purified with EtOAc/toluene 1/10 to 1/2) to give cyclized benzyl ether 81a and epi-81a. (90 mg each, 60% combined). Another ~15% side product was obtained as a mixture, which was not fully characterized. 81a: 1H NMR (500 MHz, CDCl₃) δ 7.69-7.24 (m, 15H), 6.52, 6.51 (s, 1H), 5.19 (m, 1H), 4.43-4.38 (m, 3H), 4.26 (broad, 1H), 4.08 (broad, 1H), 3.97 (broad, 1H), 3.72, 3.70 (s, 1H), 3.52-3.48 (m, 2H), 3.34 (s, 3H), 3.33 (s, 3H), 3.29 (m, 1H), 3.22-3.00 (m, 6H), 2.92-2.85 (m, 1H), 2.31 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 1.84-1.44 (m, 3H), 1.37-1.31 (m, 3H), 1.13-1.10 (m, 30 H), 0.90 (s, 9H), 0.80 (s, 3H), 0.77 (s, 3H), 0.74, 0.71 (d, J = 6.5 Hz, 3H), 0.04 (s, 6H); 13C NMR (125 MHz, CDCl₃) δ 172.4, 172.2, 168.5, 162.7, 157.0, 152.9, 142.3, 136.3, 135.9, 132.8, 130.3, 130.1, 128.4, 128.0, 127.9, 127.6, 127.5, 113.3, 82.3, 79.1, 76.2, 75.5, 72.9, 72.2, 56.2, 43.3, 34.5, 30.4, 30.0, 29.6, 27.3, 25.9, 21.0, 19.6, 18.1, 16.8, 14.3, 13.3, 12.0, 9.8, -4.4, -4.9. MS (FAB) calculated for C₇₁H₁₀₉NO₁₃NaSi₃ [M + Na]⁺ 1290.7104, found 1290.7100.

To a solution of the above obtained cyclized benzyl ether 81a (48 mg, 0.038 mmol) in dichloromethane (1 mL) was added pyridine (0.30 mL), Ac₂O (0.15 mL) and DMAP (2.5 mg, 0.02 mmol) sequentially. The reaction mixture was stirred at room temperature overnight before aqueous NH₄Cl (5 ml) was added to quench the reaction. The aqueous layer was extracted with EtOAc (50 ml) thoroughly. The combine organic layer was washed with brine (10 ml), dried over Na₂SO₄ and concentrated. The residue was quickly purified by silica gel flash column chromatography (50% EtOAc/Hexane) and directly put to the next step. To a solution of acetate compound (20 mg, 0.015 mmol) in MeOH (2 mL) was charged Pd/C (5 mg) and the flask was sealed with rubber stopper. The inner atmosphere was exchanged three times with hydrogen before it was allowed to stir under H₂ (double layer H₂ balloon) overnight. The reaction mixture was filtered off a celite pad followed by washing with MeOH (30 ml). The combined organic solution was concentrated and purified by silica gel flash column chromatography (30% EtOAc/Hexane) to give the alcohol 81 (17.3 mg, 95%). epi-81 was obtained in the same sequence. Diasteromers of epi-81 could be isolated by PTLC, so for characterization purpose they are separated and NMR of each pure diastereomer was recorded (epi-81-I, epi-81-II). 81: 1H NMR (500 MHz, CDCl₃) δ 7.68-7.33 (m, 10 H), 6.52 (s, 1H), 5.39 (m,
1H), 5.07 (dm, J = 10.0 Hz, 1H), 4.49 (dd, J = 2.0, 10.0 Hz, 1H), 4.19 (broad, 1H), 4.11 (m, 1H), 3.55 (broad, 1H), 3.39, 3.38 (s, 3H), 3.34 (dm, J = 12.5 Hz, 1H), 3.23 (m, 2H), 3.13 (dm, J = 16.5 Hz, 1H), 2.99, 2.98 (s, 3H), 2.68-2.61 (m, 2H), 2.32 (s, 3H), 2.14 (m, 1H), 2.09 (m, 1H), 2.02 (s, 3H), 1.98, 1.97 (s, 3H), 1.77-1.39 (m, 6H), 1.37-1.30 (m, 3H), 1.18 (d, J = 7.0 Hz, 3H), 1.13-1.11 (m, 29 H), 0.88 (s, 9H), 0.82 (s, 3H), 0.77, 0.76 (s, 3H), 0.66, 0.61 (d, J = 7.0 Hz, 3H), 0.05 (s, 3H), 0.04 (s, 3H); 13C NMR (125 MHz, CDCl3) d 172.3, 172.1, 170.5, 168.7, 162.3, 157.0, 153.0, 141.8, 136.3, 135.7, 132.9, 132.8, 130.4, 130.3, 130.1, 128.0, 127.9, 119.6, 119.5, 114.6, 113.4, 83.0, 82.5, 81.7, 79.2, 71.4, 68.1, 67.3, 57.6, 56.5, 33.5, 32.4, 30.0, 27.3, 25.9, 21.3, 21.1, 19.6, 18.1, 18.0, 17.5, 17.2, 13.3, 11.9, 11.8, -4.4, -5.0; MS (FAB) calculated for C66H105NO14NaSi3 [M + Na]+ 1242.6741, found 1242.6745. For epi-81: 1H NMR (500 MHz, CDCl3) d 7.86 (d, J = 10.0 Hz, 1H), 7.73-7.34 (m, 10H), 6.52 (s, 1H), 5.34 (m, 1H), 4.90 (d, J = 10.0 Hz, 1H), 4.47, (d, J = 1.5 Hz, 1H), 4.08 (m, 1H), 3.65 (dm, J = 10.5 Hz, 1H), 3.42 (dd, J = 5.0, 11.0 Hz, 1H), 4.47 (d, J = 1.5 Hz, 1H), 4.08 (m, 1H), 3.65 (dm, J = 10.5 Hz, 1H), 3.42 (dd, J = 5.0, 11.0 Hz, 1H), 3.23 (s, 3H), 3.27-3.10 (m, 4H), 2.97 (s, 3H), 2.66 (dd, J = 12.0, 16.0 Hz, 1H), 2.34 (s, 3H), 2.30 (m, 1H), 2.01 (s, 3H), 1.97 (s, 3H), 1.78-1.42 (m, 8H), 1.36-1.28 (m, 3H), 1.16-1.10 (m, 31 H), 0.92 (s, 3H), 0.87 (s, 12H), 0.64 (d, J = 6.5 Hz, 3H), 0.05 (s, 3H), 0.01 (s, 3H). MS (FAB) calculated for C66H105NO14NaSi3 [M + Na]+ 1242.6741, found 1242.6745.

(2S,3S)-N-((S)-(2S,4R,6R)-6-((2S,3R)-3-((R)-6,8-dihydroxy-5-methyl-1-oxoisochroman-3-yl)-2-hydroxybutyl)-4-hydroxy-5,5-dimethyltetrahydro-2H-pyran-2-yl)(methoxy)methyl)-2-hydroxy-3-methoxy-5-methylhex-5-enamide (38): Substrate 81 was azeotropically condensed with toluene three times before use. To a solution of compound 81 (25 mg, 0.02 mmol) in anhydrous THF (1 mL) was charged with phenyl selenocynate (18 mg, 0.08 mmol) followed by Bu3P (0.025 mL, 0.1 mmol). The reaction
should turn to dark red immediately. The reaction was allowed to stir at room temperature for 2 hours. The reaction was quenched by adding MeOH (0.5 mL) and the mixture was stirred for additional 15 minutes before it was concentrated. The residue was purified by silica gel flash column chromatography (0% to 40% EtOAc/Hexane) to give a mixture of selenated product (The mixture was resulted from the liability of phenol acetate and TIPS group. Part of them was taken off under reaction conditions. However, this has no sequence since the phenol was not affected). The mixture was carried to the next step directly. To the above obtained selenide at 0 °C was added THF (2 mL) and then 30 % aqueous H$_2$O$_2$ (0.2 mL). The mixture was stirred at room temperature for 45 minutes and then at 50 °C for 1 to 2 hours. The reaction mixture was diluted with EtOAc (20 ml) and then washed with Na$_2$SO$_3$ thoroughly. After the organic phase was dried and concentrated, the residue was then dissolved in THF (1 mL), to this solution was added TBAF (0.1M, 0.3 mL). The reaction mixture was stirred at 50 °C for 20 hours and TLC showed only one compound had bright UV. The reaction mixture was treated with water (1 mL) and diluted with EtOAc (20 mL), the aqueous layer was separated and pH was adjusted to 6 with aqueous NaHSO$_4$ solution. The aqueous layer was then extracted with EtOAc (20 ml) thoroughly. Combined organic layer was washed with brine (5 ml), dried and concentrated. PTLC (5% MeOH/DCM) of the residue gave psymberin 38 (8.1 mg, 67% over three steps) as a light yellow glass. \([\alpha]_D^{20} = +19.5 \text{ (MeOH, c = 0.2)}\] 1HNMR (500 MHz, CDCl$_3$) $d$ 11.13 (s, 1H), 7.22 (broad, 1H), 7.12 (d, $J = 10.0$ Hz, 1H), 6.31 (s, 1H), 5.44 (dd, $J = 9.0, 10.0$ Hz, 1H), 4.81 (s, 1H), 4.80 (s, 1H), 4.54 (ddd, $J = 4.0, 4.0, 12.5$ Hz, 1H), 4.43 (dd, $J = 2.5, 3.0$ Hz, 1H), 4.40 (s, 1H), 4.17 (broad, 1H), 3.94 (dm, $J = 8.5$ Hz, 1H), 3.89 (m, 1H), 3.75 (m, 1H), 3.66 (dd, $J = 4.0, 10.5$ Hz, 1H), 3.53 (d, $J = 11.0$ Hz, 1H), 3.38 (s, 3H), 3.37 (s, 3H), 2.87 (dd, $J = 3.0, 16.0$ Hz, 1H), 2.80 (dd, $J = 12.5, 16.5$ Hz, 1H), 2.38 (dd, $J = 9.0, 14.5$ Hz, 1H), 2.18 (dd, $J = 4.5, 14.5$ Hz, 1H), 2.06 (m, 1H), 2.01 (s, 3H), 1.88 (m, 1H), 1.80 (m, 1H), 1.75 (s, 3H), 1.62 (m, 1H), 1.09 (d, $J = 7.5$ Hz, 3H), 0.96 (s, 3H), 0.91 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $d$ 173.8, 170.7, 162.5, 161.4, 142.2, 139.9, 113.6, 113.3, 101.7, 101.5, 82.2, 80.7, 79.6, 78.6, 74.0, 73.3, 71.6, 58.2, 56.5, 42.8, 39.0, 37.8, 32.3, 29.9, 28.6, 23.3, 22.9, 14.0, 10.7, 9.7; MS (ES) calculated for C$_{31}$H$_{47}$O$_{11}$Na [M + Na]$^+$ 632.30, found 632.23.
Preparation of compound epi-38: The same procedure for the synthesis of psymberin 38 was performed for compound epi-81. The only difference was that treatment with TBAF could not remove the acetate on the secondary alcohol in this case. After removal of silyl group by TBAF, a portion of the residue (2 mg) was dissolved in MeOH (1 mL) and aqueous LiOH (1N, 0.2 mL) was added. The reaction mixture was stirred at room temperature overnight. To this reaction was added water (2 ml) and EtOAc (10 ml), the aqueous layer was separated and pH was adjusted to 6 with aqueous NaHSO₄ solution. The aqueous layer was then extracted with EtOAc (30 ml) thoroughly. Combined organic layer was washed with brine (10 ml), dried and concentrated. PTLC (5% MeOH/DCM) of the residue gave epi-psymberin (epi-38, 2 mg, 99%) as a light yellow glass. [α]D²⁰ = -13.5 (MeOH, c = 0.1) ¹H NMR (500 MHz, CDCl₃) δ 11.24 (s, 1H), 7.37 (d, J = 9.5 Hz, 1H), 6.28 (s, 1H), 5.04 (dd, J = 2.5, 10.0 Hz, 1H), 4.83 (s, 1H), 4.80 (s, 1H), 4.56 (ddd, J = 3.5, 9.0, 13.0 Hz, 1H), 4.36 (d, J = 4.0 Hz, 1H), 4.12 (m, 1H), 3.80 (dm, J = 11.5 Hz, 1H), 3.73 (m, 1H), 3.49 (dd, J = 5.0, 11.0 Hz, 1H), 3.43 (s, 3H), 3.35 (s, 3H), 3.31 (d, J = 10.5 Hz, 1H), 2.95 (dd, J = 4.0, 16.5 Hz, 1H), 2.90 (dd, J = 12.0, 16.5 Hz, 1H), 2.33 (dd, J = 9.0, 14.5 Hz, 1H), 2.20 (m, 1H), 2.04 (s, 3H), 1.95 (m, 1H), 1.77 (s, 3H), 1.73 (m, 2H), 1.65 (m, 1H), 1.44 (m, 1H), 1.13 (d, J = 7.5 Hz, 3H), 0.96 (s, 3H), 0.88 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 172.8, 170.8, 162.5, 160.9, 142.1, 140.3, 113.5, 101.5, 86.5, 81.3, 80.8, 80.0, 74.8, 73.0, 71.3, 57.9, 56.5, 42.8, 39.4, 37.5, 32.3, 32.2, 28.4, 23.0, 22.4, 12.7, 10.8, 9.9; MS (ES) calculated for C₃₁H₄₇O₁₁Na [M + Na]⁺ 632.30, found 632.23.
Preparation of compounds 86 and 88: Under an atmosphere of argon, a solution of compound 82 (40 mg, 0.0476 mmol), prepared from vinyl iodide 59 followed the same procedure as the preparation of 80 from 59, in hexafluoroisopropanol (0.5 mL) at 0 °C was added MeOH (0.04 mL) and then a solution of (diacetoxyiodo)benzene (32 mg, 0.096 mmol) dropwise as a solution in hexafluoroisopropanol (0.5 mL). The reaction mixture was stirred at room temperature for 20 hours. The reaction mixture was diluted with EtOAc (30 ml) and filtered through a short pad of silica gel. The filtrate was concentrated and then purified by silica gel flash column chromatography (acetone/hexane 1/10 to 1/2) to give the crude product, which was treated with TBAF (0.1 M, 4 mL) at 50 °C overnight. The residue was carefully purified by PTLC (5% MeOH/DCM) to yield the desired compound 86 (8.6 mg, 36%) and epi-isomer 88 (8.4 mg, 35%) (86 and 88 combined yield of 71% over 2 steps). 86: \([\alpha]_D^{20} = +18.24\) (MeOH, c = 0.1) \(^1\)HNMR (500 MHz, CDCl\(_3\)) \(\delta\) 11.24 (s, 1H), 7.30-7.12 (m, 5H), 6.29 (s, 1H), 6.07 (broad, 1H), 5.85 (d, \(J = 11.0\) Hz, 1H), 5.35 (dd, \(J = 6.0, 9.5\) Hz, 1H), 4.52 (m, 1H), 3.97 (m, 1H), 3.91 (d, \(J = 10.0\) Hz, 1H), 3.85 (s, 1H), 3.64 (dd, \(J = 3.5, 8.0\) Hz, 1H), 3.59 (d, \(J = 11.0\) Hz, 1H), 3.35 (s, 3H), 2.98 (dd, \(J = 3.0, 11.5\) Hz, 1H), 2.83 (dd, \(J = 12.5, 16.5\) Hz, 1H), 2.62 (t, \(J = 7.0\) Hz, 2H), 2.38-2.22 (m, 2H), 2.04 (s, 3H), 2.01-1.55 (m, 7H), 1.11 (d, \(J = 7.0\) Hz, 3H), 0.99 (s, 3H), 0.83 (s, 3H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 174.5, 170.9, 162.7, 161.1, 141.6, 140.3, 128.9, 128.8, 126.5, 113.5, 102.4, 101.7, 82.9, 80.3, 79.9, 73.3, 72.2, 60.9, 56.6, 43.3, 38.6, 36.5, 32.8, 30.4, 28.8, 27.4, 14.6, 10.9, 10.1; LCMS calculated for C\(_{33}\)H\(_{46}\)NO\(_9\) [M + H]\(^+\) 600.3, found 600.3. 88: \([\alpha]_D^{20} = +25.10\) (MeOH, c = 0.1) \(^1\)HNMR (500 MHz, CDCl\(_3\)) \(\delta\) 11.21 (s, 1H), 7.30-7.15 (m, 5H), 6.31 (s, 1H), 6.07 (broad, 1H), 5.85 (d, \(J = 11.0\) Hz, 1H), 5.35 (dd, \(J = 6.0, 9.5\) Hz, 1H), 4.52 (m, 1H), 3.97 (m, 1H), 3.91 (d, \(J = 10.0\) Hz, 1H), 3.85 (s, 1H), 3.64 (dd, \(J = 3.5, 8.0\) Hz, 1H), 3.59 (d, \(J = 11.0\) Hz, 1H), 3.35 (s, 3H), 2.98 (dd, \(J = 3.0, 11.5\) Hz, 1H), 2.83 (dd, \(J = 12.5, 16.5\) Hz, 1H), 2.62 (t, \(J = 7.0\) Hz, 2H), 2.38-2.22 (m, 2H), 2.04 (s, 3H), 2.01-1.55 (m, 7H), 1.11 (d, \(J = 7.0\) Hz, 3H), 0.99 (s, 3H), 0.83 (s, 3H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 174.5, 170.9, 162.7, 161.1, 141.6, 140.3, 128.9, 128.8, 126.5, 113.5, 102.4, 101.7, 82.9, 80.3, 79.9, 73.3, 72.2, 60.9, 56.6, 43.3, 38.6, 36.5, 32.8, 30.4, 28.8, 27.4, 14.6, 10.9, 10.1; LCMS calculated for C\(_{33}\)H\(_{46}\)NO\(_9\) [M + H]\(^+\) 600.3, found 600.3.
1H), 6.01 (d, J = 10.0 Hz, 1H), 5.35 (broad, 1H), 5.11 (d, J = 2.5, 10.0 Hz, 1H), 4.57 (dt, J = 4.5, 11.5 Hz, 1H), 4.20 (m, 1H), 4.09 (d, J = 10.5 Hz, 1H), 3.76 (d, J = 12.0 Hz, 1H), 3.49 (dd, J = 5.0, 11.5 Hz, 1H), 3.31 (s, 3H), 2.94-2.85 (m, 2H), 2.65 (t, J = 8.0 Hz, 2H), 2.28 (t, J = 8.0 Hz, 2H), 2.02 (s, 3H), 2.00-1.94 (m, 2H), 1.78-1.59 (m, 5H), 1.13 (d, J = 7.0 Hz, 3H), 0.96 (s, 3H), 0.86 (s, 3H); 13C NMR (125 MHz, CDCl₃) δ 174.2, 171.0, 162.6, 161.4, 141.7, 140.4, 128.9, 126.5, 113.7, 102.1, 101.7, 86.8, 81.4, 79.9, 75.0, 734., 56.5, 43.0, 39.6, 36.3, 35.6, 32.5, 32.3, 30.1, 28.7, 27.4, 22.6, 13.1, 11.0, 10.1; LCMS calculated for C₃₃H₄₆NO₉ [M + H]⁺ 600.3, found 600.3.

Preparation of compound 87 and 89: These two compounds were prepared from 83 in the same way as described in the synthesis of compound 86 and 88. 87 (45% yield from 59): [α]D²⁰ = +21.32 (dichloromethane, c = 0.1) ¹H NMR (500 MHz, CDCl₃) δ 11.13 (s, 1H), 7.27-7.25 (m, 5H), 7.10 (d, J = 10.0 Hz, 1H), 6.30 (s, 1H), 5.48 (dd, J = 8.5, 10.0 Hz, 1H), 4.52 (ddd, J = 4.0, 4.5, 12.0 Hz, 1H), 4.39 (broad, 1H), 4.37 (s, 1H), 4.34 (d, J = 2.5 Hz, 1H), 3.93 (m, 1H), 3.89 (m, 1H), 3.76 (m, 1H), 3.68 (m, 1H), 3.55 (d, J = 10.0 Hz, 1H), 3.39 (s, 3H), 3.26 (s, 3H), 2.91 (dd, J = 8.0, 14.0 Hz, 1H), 2.86-2.78 (m, 3H), 2.08 (m, 1H), 2.01 (s, 3H), 1.86-1.75 (m, 3H), 1.61 (m, 1H), 1.09 (d, J = 7.0 Hz, 3H), 0.99 (s, 3H), 0.92 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 174.1, 170.9, 162.8, 161.3, 140.1, 138.7, 129.9, 128.7, 126.7, 113.6, 102.1, 101.8, 83.8, 82.3, 79.9, 78.7, 74.4, 73.6, 73.4, 71.8, 60.8, 58.7, 56.7, 43.1, 39.2, 36.3, 32.6, 30.2, 28.9, 23.5, 21.5, 14.6, 14.0, 10.9, 9.7; LCMS calculated for C₃₄H₄₈NO₁₁ [M + H]⁺ 646.3, found 646.4. 89 (20% yield from 59): ¹H NMR (500 MHz, CDCl₃) δ 11.28 (broad, 1H), 7.42 (d, J = 10.0 Hz, 1H), 7.35-7.21 (m, 5H), 6.34 (s, 1H), 5.11 (dd, J = 3.0, 10.0 Hz, 1H), 4.59 (m, 1H), 4.27 (d, J = 5.5 Hz, 1H), 4.18-4.13 (m, 2H), 3.84 (m, 1H), 3.77 (m, 1H), 3.52 (m, 1H), 3.42 (s, 3H), 3.34 (s, 3H), 2.98-2.89 (m, 4H), 2.09 (s, 3H), 1.99-1.86 (m, 5H), 1.17 (d, J = 7.0 Hz, 3H), 1.00 (s, 3H), 0.92 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 173.4, 162.7, 138.3, 130.1, 128.7, 126.8, 101.7, 86.6, 83.7, 81.7, 80.2, 77.2, 75.0, 73.1, 71.5, 58.4, 56.7, 43.0, 39.6, 35.9,
32.5, 28.6, 22.6, 12.9, 10.9, 10.0, 9.9; MS (ES) calculated for C_{34}H_{47}NNaO_{11} [M + Na]^+ 668.30, found 668.33.

Preparation of compound 90: Compound 90 was prepared from 81 with general deprotection procedure (TBAF, 50 °C). \(^1\)HNMR (500 MHz, CDCl\(_3\)) \(\delta\) 11.10 (broad, 1H), 7.07 (d, \(J = 10.0\) Hz, 1H), 6.39 (s, 1H), 5.43 (dd, \(J = 9.0, 9.5\) Hz, 1H), 4.54 (m, 1H), 4.40 (s, 1H), 4.29 (s, 1H), 3.95 (d, \(J = 11.0\) Hz, 1H), 3.87 (broad, 1H), 3.66 (m, 2H), 3.52 (d, \(J = 11.0\) Hz, 1H), 3.48 (dd, \(J = 4.5, 11.0\) Hz, 1H), 3.42 (dd, \(J = 7.0, 10.5\) Hz, 1H), 3.37 (s, 3H), 3.34 (s, 3H), 3.31 (d, \(J = 8.5\) Hz, 2H), 2.97-2.80 (m, 2H), 2.09 (s, 3H), 1.85-1.79 (m, 3H), 1.10 (d, \(J = 7.0\) Hz, 3H), 1.40-0.90 (m, 14H); MS (ES) calculated for C\(_{31}\)H\(_{50}\)NO\(_{12}\) [M + H]^+ 628.33, found 628.37.

Preparation of compound 92: To a solution of methyl isobutyrate (5g, 49 mmol) in THF (15 ml) was added slowly a solution of LDA (52 mmol, generated from n-BuLi and diisopropyl amine) in THF at -78 °C, the reaction mixture was stirred for 20 minutes. The resulting solution was treated with a solution of benzyl 3-bromopropyl ether (10 g, 43 mmol) in HMPA (10 ml) and stirred at -78 °C for 12 hours before aqueous HCl (1N, 50 ml) was added and the resulting mixture was extracted with ether (100 ml). Organic layer was washed with water, saturated NaHCO\(_3\), dried and concentrated, it was purified by silica gel flash column chromatography (0% to 10 % EtO/Hexane) to give the desired ester 92a (11.6 g, 80%). \(^1\)HNMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.36-7.26 (m, 5H), 4.49 (s, 2H), 3.65 (s, 3H), 3.45 (t, \(J = 6.5\) Hz, 2H), 1.62-1.52 (m, 4H), 1.18 (s, 6H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 178.3, 138.5, 128.3, 127.6, 127.5, 72.8, 70.5, 51.7, 42.0, 37.1, 25.3, 25.1. MS (ES) calculated for C\(_{12}\)H\(_{23}\)O\(_3\) [M + H]^+ 251.16, found 251.16. The above obtained
ester was transformed to the corresponding methyl ketone: To a solution of methyl ester (5 g, 18.9 mmol) in anhydrous pentane (50 ml) was added Trimethylsilyl methyl lithium (58 ml, 58.2 mmol) dropwise at 0 °C. The mixture was stirred at 0 °C for 4 h with TLC monitoring (Et₂O/Hexane 1/10). After the reaction is complete judged by TLC, to this suspension was added dry methanol (10 ml) and the resulting emulsion was stirred for another 1 h at room temperature. The mixture was diluted with Et₂O/water (50 ml). Aqueous layer was extracted with Et₂O (50 ml), dried over Na₂SO₄ and concentrated. The residue was purified by FC (EtOAc/Hexane 1/10) to give the methyl ketone 92b (5.81 g, 82%). ¹HNMR (500 MHz, CDCl₃) δ 7.36-7.26 (m, 5H), 4.49 (s, 2H), 3.44 (t, J = 6.5 Hz, 2H), 2.12 (s, 3H), 1.62-1.58 (m, 2H), 1.52-1.46 (m, 2H), 1.12 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 219.0, 138.9, 128.8, 128.0, 73.3, 71.0, 48.0, 36.8, 25.6, 25.5, 24.7. MS (ES) calculated for C₁₅H₂₃O₂ [M + H]⁺: 235.17, found 235.34; C₁₅H₂₂NaO₂ [M + Na]⁺: 257.15, found 257.32. The methyl ketone was transformed to the enol ether 92: To a solution of methyl ketone (1.64 g, 7 mmol) in DCM (20 ml) at 0 °C was added Et₃N (3.9 ml, 28 mmol) and then TMSOTf (2.52 ml, 14 mmol). The reaction was allowed to stir at room temperature for 1 h. The reaction was diluted with hexane, washed with aq. NaHCO₃ and dried over Na₂SO₄. The solution was directly passed through a short pad of silica gel plug with EtOAc/Hexane (1/20) washing. The combined organic solution was concentrated to give compound 92 (2.32 g, 100%) as a light yellow oil. The crude 92 was used for the next step without any further purification ¹HNMR (600 MHz, CDCl₃) δ 7.35-7.27 (m, 5H), 4.50 (s, 2H), 4.05 (d, J = 1.5 Hz, 1H), 3.98 (d, J = 1.0 Hz, 1H), 3.44 (t, J = 7.0 Hz, 2H), 1.57-1.51 (m, 2H), 1.41-1.38 (m, 2H), 1.02 (s, 6H), 0.20 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 165.2, 138.7, 128.3, 127.6, 127.4, 87.1, 72.7, 71.2, 39.3, 36.2, 26.1, 25.1, 0.1.
Preparation of compounds 91, 91a, 91b and 91c: These compounds were prepared from 92 and 43 through 93, 94 and 95 following the same synthetic sequence for the preparation of 38 and epi-38 from 49 and 43.

91: [a] D20 = +10.23 (dichloromethane, c = 0.2) 1HNMR (500 MHz, CDCl3) d 11.11 (broad, 1H), 6.32 (s, 1H), 5.44 (dd, J = 7.5, 10.0 Hz, 1H), 4.80 (broad, 2H), 4.50 (dt, J = 4.0, 12.0 Hz, 1H), 4.45 (d, J = 3.0 Hz, 1H), 3.99 (d, J = 9.5 Hz, 1H), 3.78 (m, 2H), 3.59 (d, J = 10.5 Hz, 1H), 3.39 (s, 3H), 3.36 (s, 3H), 2.84 (dd, J = 3.5, 16.5 Hz, 1H), 2.78 (dd, J = 12.0, 16.5 Hz, 1H), 2.39 (dd, J = 9.0, 14.5 Hz, 1H), 2.18 (dd, J = 3.5, 14.5 Hz, 1H), 1.98 (s, 3H), 1.75 (s, 3H), 1.85 (m, 2H), 1.72 (m, 2H), 1.57-1.41 (m, 3H), 1.09 (d, J = 7.0 Hz, 3H), 0.93 (s, 6H); 13 C NMR (125 MHz, CDCl3) d 174.1, 171.0, 162.7, 162.0, 142.5, 140.0, 113.9, 113.4, 101.7, 101.6, 83.1, 81.1, 80.3, 78.8, 74.4, 73.4, 73.2, 60.9, 58.2, 56.7, 43.1, 37.9, 33.5, 32.8, 32.5, 28.8, 27.7, 23.1, 22.0, 21.6, 14.6, 10.9, 9.6; LCMS calculated for C31 H48NO10 [M + H]+ 594.3, found 594.3.

91a: [a] D20 = +22.66 (dichloromethane, c = 0.1) 1HNMR (500 MHz, CDCl3) d 11.24 (broad, 1H), 7.43 (d, J = 10.0 Hz, 1H), 6.27 (s, 1H), 5.02 (dd, J = 2.5, 10.0 Hz, 1H), 4.83 (s, 1H), 4.81 (s, 1H), 4.55 (m, 1H), 4.37 (d, J = 4.5 Hz, 1H), 4.18 (m, 1H), 3.79 (m, 2H), 3.49 (s, 3H), 3.46 (m, 1H), 3.40 (s, 3H), 3.00 (dd, J = 4.0, 17.0 Hz, 1H), 2.94 (dd, J = 12.0, 16.5 Hz, 1H), 2.40 (dd, J = 9.0, 15.0 Hz, 1H), 2.25 (dd, J = 3.5, 15.0 Hz, 1H), 2.07 (s, 3H), 1.83 (s, 3H), 2.00 (m, 1H), 1.80-1.20 (m, 6H), 1.18 (d, J = 7.0 Hz, 3H), 0.99 (s, 3H), 0.92 (s, 3H); 13 C NMR (125 MHz, CDCl3) d 173.0, 162.6, 142.5, 140.4, 113.6, 101.6, 88.2, 81.7, 81.0, 80.2, 79.1, 73.4, 71.5, 58.1, 56.6, 43.0, 38.4, 37.7, 33.1, 32.9, 28.7, 27.5, 23.8, 23.2, 19.3, 10.9, 10.0; LCMS calculated for C31 H47NaNO10 [M + Na]+ 616.3, found 616.3.

91b: [a] D20 = +6.11 (dichloromethane, c = 0.2) 1HNMR (500 MHz, CDCl3) d 11.17 (broad, 1H), 7.11 (d, J = 10.0 Hz, 1H), 6.32 (s, 1H), 5.34 (dd, J = 8.0, 9.5 Hz, 1H), 4.83 (s, 1H), 4.78 (s, 1H), 4.59 (m, 1H), 4.44 (d, J = 4.0 Hz, 1H), 4.31 (broad, 1H), 4.10 (d, J = 9.5 Hz, 1H), 3.77-3.72 (m, 2H), 3.63 (d, J = 10.0 Hz, 1H), 3.42 (s, 3H), 3.41 (s, 3H), 3.38-3.35 (m, 1H), 2.97 (dd, J = 3.0, 16.5 Hz, 1H), 2.85 (dd, J = 12.5, 17.0 Hz, 1H), 2.28 (dd, J = 9.5, 14.5 Hz, 1H), 2.06 (d, J = 14.5 Hz, 1H), 2.00 (s, 3H), 1.95-1.44 (m, 7H), 1.75 (s, 3H), 1.15 (d, J = 7.0 Hz, 3H), 0.99 (s, 3H), 0.91 (s, 3H); 13 C NMR (125 MHz, CDCl3) d 172.6, 171.0, 162.6, 161.6, 142.3, 140.2, 113.7, 113.6, 102.0, 101.7, 82.9, 81.0, 80.8, 80.7, 73.6, 72.7, 71.5, 57.9, 56.7, 43.0, 37.4, 33.5, 32.8, 31.8, 30.1, 28.7, 27.5, 23.2, 23.1, 22.3, 10.8, 9.8; LCMS calculated for C31 H48 NO10 [M +
(S)-tert-butyl(2-methoxy-3-phenylpropoxy)dimethylsilane (97): This compound was prepared from compound 73 following the same procedure for the preparation of 74 from 73. 97: ¹HNMR (500 MHz, CDCl₃) δ 7.30-7.19 (m, 5H), 3.61 (dd, J = 5.5, 10.5 Hz, 1H), 3.58 (dd, J = 5.0, 10.5 Hz, 1H), 3.43 (m, 1H), 3.36 (s, 3H), 2.87 (dd, J = 5.5, 14.0 Hz, 1H), 2.75 (dd, J = 7.0, 14.0 Hz, 1H), 0.92 (s, 9H), 0.06 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 139.4, 129.9, 128.6, 126.6, 83.6, 64.5, 38.2, 26.4, 18.7, -4.9.

(2S,3S)-2-(tert-butyldiphenylsilyloxy)-3-methoxy-4-phenylbutanamide (100): This compound was prepared from 97 through 98 following a similar synthetic sequence for the preparation of 76 from 74. 98: ¹HNMR (500 MHz, CDCl₃) δ 9.69 (d, J = 2.0 Hz, 1H), 7.32-7.22 (m, 5H), 3.80 (m, 1H), 3.41 (s, 3H), 3.01 (dd, J = 5.0, 9.0 Hz, 1H), 2.92 (dd, J
= 8.5, 14.5 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) d 203.2, 136.4, 129.4, 128.5, 126.8, 86.4, 58.6, 36.4. 100: $^1$HNMR (500 MHz, CDCl$_3$) d 7.72-7.11 (m, 15H), 6.66 (broad, 1H), 6.07 (broad, 1H), 4.41 (d, $J = 2.0$ Hz, 1H), 3.53 (ddd, $J = 2.0, 4.5, 9.0$ Hz, 1H), 3.10 (s, 3H), 2.96 (dd, $J = 9.0$, 14.0 Hz, 1H), 2.77 (dd, $J = 4.5, 14.0$ Hz, 1H), 2.38 (s, 3H), 1.17 (s, 9H), 1.13 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) d 174.5, 139.2, 136.5, 136.1, 133.2, 132.9, 130.6, 130.6, 129.9, 129.5, 128.7, 128.6, 128.4, 128.3, 126.5, 85.7, 76.0, 59.0, 37.0, 27.5, 19.9.

(2S,3S)-\text{-}((2S,6R)-6-((2S,3R)-3-((R)-6,8-dihydroxy-5-methyl-1-oxoisochroman-3-yl)-2-hydroxybutyl)-5,5-dimethyltetrahydro-2H-pyran-2-yl)(methoxy)methyl)-2-hydroxy-3-methoxy-4-phenylbutanamide (96) and epi-96: These two compounds were prepared from 100 and 59 in the same way as described in the synthesis of 86 and 88. 96: $^1$HNMR (500 MHz, CDCl$_3$) d 11.13 (broad, 1H), 7.27-7.16 (m, 5H), 6.31 (s, 1H), 5.48 (dd, $J = 7.5$, 10.0 Hz, 1H), 4.50 (dt, $J = 4.0$, 11.5 Hz, 1H), 4.38 (d, $J = 3.0$ Hz, 1H), 3.98 (d, $J = 11.0$ Hz, 1H), 3.79 (m, 2H), 3.59 (d, $J = 10.0$ Hz, 1H), 3.38 (s, 3H), 3.27 (s, 3H), 2.91 (dd, $J = 8.5$, 14.0 Hz, 1H), 2.88-2.75 (m, 3H), 1.97 (s, 3H), 1.87-1.80 (m, 2H), 1.75-1.68 (m, 2H), 1.58-1.43 (m, 3H), 1.09 (d, $J = 7.5$ Hz, 3H), 0.94 (s, 3H), 0.93 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) d 174.0, 171.0, 162.7, 161.8, 140.0, 138.9, 138.8, 130.0, 129.9, 129.8, 128.7, 128.6, 113.8, 101.7, 83.8, 83.1, 80.1, 78.8, 74.2, 73.4, 73.3, 58.7, 58.2, 56.7, 43.1, 36.2, 33.5, 32.8, 32.3, 28.8, 27.7, 22.0, 21.7, 10.9, 9.7; LCMS calculated for C$_{34}$H$_{48}$NO$_{10}$ [M + H]$^+$ 630.3, found 630.3. epi-96: $^1$HNMR 500 MHz, CDCl$_3$ d 11.25 (broad, 1H), 7.44 (d, $J = 10.0$ Hz, 1H), 7.29-7.19 (m, 5H), 6.28 (s, 1H), 5.05 (dd, $J = 2.5$, 10.0 Hz, 1H), 4.53 (ddd, $J = 3.5$, 5.0, 12.5 Hz, 1H), 4.26 (d, $J = 5.0$ Hz, 1H), 4.13 (m, 1H), 3.73 (m, 2H), 3.40 (d, $J = 10.5$, Hz, 1H), 3.35 (s, 3H), 3.28 (s, 3H), 2.93-2.81 (m, 4H), 1.98 (s, 3H), 1.94 (m, 1H), 1.69-1.43 (m, 6H), 1.11 (d, $J = 7.5$ Hz, 3H), 0.92 (s, 3H), 0.85 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) d 173.4, 171.1, 162.5, 161.5, 140.3,
138.5, 130.1, 128.7, 126.8, 113.8, 102.0, 101.6, 88.3, 83.7, 81.8, 80.0, 79.1, 73.6, 71.5, 58.5, 56.6, 43.0, 38.3, 35.9, 33.1, 32.8, 28.7, 27.5, 23.8, 19.4, 10.9, 10.0; LCMS calculated for C_{34}H_{47}NNaO_{10} [M + Na]^+ 652.3, found 652.4.