Supporting Information
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Supporting Information

General methods

$^1$H and $^{13}$C NMR spectra were recorded on a JEOL JNM-LD400 spectrometer operating at either 400 MHz ($^1$H) or 100 MHz ($^{13}$C) or on a JEOL AL-300 operating at either 300 MHz ($^1$H) or 75 MHz ($^{13}$C). Chemical shifts are reported in δ units and are referenced to the solvent, i.e., 7.26/77.1 for CDCl$_3$, 7.15/128.0 for C$_6$D$_6$. Multiplicities are indicated as: br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sept (septet) or m (multiplet). Coupling constants ($J$) are reported in Hertz (Hz). Infrared spectra were recorded on a Jasco FT-IR410 spectrometer. Electron impact mass spectra were performed on a Hitachi M-80B mass spectrometer. Fast atom bombardment mass spectra were performed on a JEOL JMS-SX102A. Electrospray ionization mass spectra were recorded on an Applied Biosystems API QSTAR pulsar i as high resolution, using poly(ethylene glycol) as internal standard. Thin-layer chromatography (TLC) was performed on silica gel 60 F$_{254}$ (Merck 1.05715.0009) plates. Flash column chromatography was performed on a PSQ100B silica gel (Fuji Silysia Co., Ltd., Japan) or on a Silica Gel 60 N (spherical, neutral) 63-210 μm (Kanto Chemical Co., Inc., Japan) and PSQ100B was usually used. THF and Et$_2$O were purchased from Wako Pure Chemical Industries Ltd. in anhydrous grade. CH$_2$Cl$_2$ was distilled from CaH$_2$ immediately before use. DMSO was distilled from CaH$_2$ and stored over activated MS 4A. Pyridine, Et$_3$N, diisopropylethylamine, and diisopropylamine were distilled from CaH$_2$ and stored over KOH. TiCl$_4$ was distilled from a small amount of pure copper turnings. Other reagents were used as received. All moisture sensitive reactions were performed under a static argon atmosphere in flame-dried glassware.
Synthesis of 5

To a solution of isovaleric acid (16.9 mL, 155 mmol) in distilled CH₂Cl₂ (517 mL) was added distilled Et₃N (26.0 mL, 186 mmol) and pivaroyl chloride (21.0 mL, 171 mmol) at 0 °C, and then the mixture was allowed to warm to rt and stirred for 3 h. The reaction mixture was quenched with a saturated aqueous solution of NH₄Cl. The aqueous layer was extracted two times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtrated, and concentrated under reduced pressure to afford crude isovaleric pivaroic anhydride.

To a solution of oxazolidinethione (18.3 g, 102 mmol) in THF (630 mL) was added n-BuLi (2.63 M in hexane, 46.4 mL) at −78 °C, and then the resulting mixture was stirred at that temperature for 1.5 h. To the resulting mixture was added crude isovaleric pivaroic anhydride in THF (30.0 mL) at −78 °C, and stirred at that temperature for 2 h. Then the resulting mixture was allowed to warm to rt and stirred for 15 h 20 min. The reaction mixture was quenched with a saturated aqueous solution of NH₄Cl. The aqueous layer was extracted two times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtrated, and concentrated under reduced pressure. Purification by recrystallize from hexane/EtOAc gave 23.5 g of 5 (87% yield for the two steps) as a white needles: mp: 76.5-77.0 °C; [α]D²⁴ −86.6 (c 1.03, CHCl₃); Rf 0.55 (hexane/EtOAc = 3:1); ¹H NMR (400 MHz, CDCl₃) δ 7.40-7.21 (m, 5H), 5.70 (dd, J = 3.6, 8.9 Hz, 1H), 4.79 (dd, J = 8.9, 9.1 Hz, 1H), 4.44 (dd, J = 3.6, 9.1 Hz, 1H), 3.29 (dd, J = 6.2, 16.4 Hz, 1H), 3.08 (dd, J = 7.5, 16.4 Hz, 1H), 2.24-2.10 (m, 1H), 0.918 (d, J = 6.7 Hz, 3H), 0.888 (d, J = 6.7 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 185.6, 173.0, 138.8, 129.2, 128.9, 126.0, 73.8, 62.2, 45.9, 25.2, 22.5, 22.2; IR (neat, cm⁻¹) 2956, 1706, 1461, 1419, 1389; HR-FABMS calcd for C₁₄H₁₈NO₂S: 264.1058, found: 264.1057.
Asymmetric aldol reaction

To a solution of 5 (8.27 g, 31.4 mmol) in distilled CH$_2$Cl$_2$ (63.0 mL) was added TiCl$_4$ (4.80 mL, 34.5 mmol) dropwise at 0 °C, and then the mixture was stirred at that temperature for 25 min. To the yellow suspension was added diisopropylethylamine (6.02 mL, 34.5 mmol). The dark red solution was stirred at 0 °C for 35 min. After the reaction mixture was cooling to −78 °C, the mixture was stirred at that temperature for 40 min. To the resulting mixture was added crotonaldehyde (2.84 mL, 34.5 mmol). The reaction mixture was stirred at −78 °C for 25 h. The reaction mixture was quenched with a saturated aqueous solution of NH$_4$Cl. The aqueous layer was extracted two times with EtOAc. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. Purification by silica-gel column chromatography (hexane/EtOAc = 9:1~7:1~5:1) gave 8.46 g of 6 (81% yield, non-Evans syn:anti = 94:6 by $^1$H NMR analysis) as a slightly yellow oil: [α]$_D^{24}$ −265 (c 1.05, CHCl$_3$); $Rf$ 0.29 (hexane/EtOAc = 3:1); $^1$H NMR (400 MHz, CDCl$_3$) δ 7.39-7.23 (m, 5H), 5.76 (dd, $J = 2.9$, 8.5 Hz, 1H), 5.58 (qd, $J = 6.2$, 15.3 Hz, 1H), 5.46 (ddq, $J = 15.3$, 7.9, 1.4 Hz, 1H), 5.17 (dd, $J = 6.7$, 8.2 Hz, 1H), 4.70 (dd, $J = 8.5$, 8.9 Hz, 1H), 4.46 (ddd, $J = 2.5$, 7.9, 8.2 Hz, 1H), 4.42 (dd, $J = 2.9$, 8.9 Hz, 1H), 2.63 (br s, 1H), 2.11-2.02 (m, 1H), 1.56 (dd, $J = 1.4$, 6.2 Hz, 3H), 0.992 (d, $J = 6.7$ Hz, 3H), 0.931 (d, $J = 6.7$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 186.6, 174.3, 138.6, 129.7, 129.5, 129.2, 128.7, 125.8, 73.9, 73.6, 62.5, 53.7, 29.0, 20.8, 20.1, 17.8; IR (neat, cm$^{-1}$) 3444, 3064, 3031, 2962, 2730, 2520, 1954, 1880, 1695; HR-FABMS calcd for C$_{18}$H$_{24}$NO$_3$S: 334.1477, found: 334.1476.
Synthesis of 7

To a solution of 6 (15.3 g, 45.8 mmol) in MeOH (458 mL) was added NaOMe (5.44 g, 101 mmol) at rt, and then the resulting mixture was stirred at rt for 35 min. The reaction mixture was quenched by pouring into pH 7 phosphate buffer. The aqueous layer was extracted three times with CH$_2$Cl$_2$. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtrated, and concentrated under reduced pressure. Purification by silica-gel column chromatography (hexane/EtOAc = 5:1~4:1~3:1~0:1) gave 4.52 g of 7 (58% yield) as a colorless clear oil: $\left[\alpha\right]_D^{24} +28.9$ (c 1.02, CHCl$_3$); $R_f$ 0.55 (hexane/EtOAc = 3:2); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.74 (dq, $J = 15.2$, 6.2 Hz, 1H), 5.63 (ddq, $J = 7.2$, 15.2, 1.2 Hz, 1H), 4.33 (dt, $J = 3.9$, 7.2 Hz, 1H), 3.68 (s, 3H), 2.44 (dd, $J = 6.8$, 7.2 Hz, 1H), 2.06 (dqq, $J = 6.8$, 6.8, 6.8 Hz, 1H), 1.82 (d, $J = 3.9$ Hz, 1H), 1.71 (dd, $J = 1.2$, 6.2 Hz, 3H), 0.968 (d, $J = 6.8$ Hz, 3H), 0.951 (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.8, 130.7, 129.1, 72.1, 57.7, 51.1, 27.1, 21.1, 19.7, 17.7; IR (neat, cm$^{-1}$) 3448, 2693, 1734; HR-ESIMS calcd for C$_{10}$H$_{18}$O$_3$Na: 209.1148, found: 209.1151.
Synthesis of 8

\[
\begin{align*}
\text{7} & \quad 1) \text{TESOTf} \quad & \quad \text{8} \\
& \quad 2) \text{DIBAL} \\
& \quad 3) \text{Dess-Martin Periodinane}
\end{align*}
\]

To a solution of hydroxyester 7 (958 mg, 5.15 mmol) in distilled CH\(_2\)Cl\(_2\) (51.4 mL) were added distilled 2,6-lutidine (1.89 mL, 16.2 mmol), TESOTf (1.76 mL, 9.26 mmol) at \(-78^\circ\)C, and then the resulting mixture was stirred at that temperature for 35 min. The reaction mixture was quenched with a saturated aqueous solution of NaHCO\(_3\). The aqueous layer was extracted two times with CH\(_2\)Cl\(_2\). The combined organic layers were washed with brine, dried over Na\(_2\)SO\(_4\), filtrated, and concentrated under reduced pressure to afford crude silyloxyester.

To a solution of crude silyloxyester in distilled CH\(_2\)Cl\(_2\) (51.4 mL) was added DIBAL (0.98 M in hexane, 13.1 mL) at \(-78^\circ\)C, and then the reaction mixture was stirred at that temperature for 30 min. The reaction mixture was quenched with a Na\(_2\)SO\(_4\)·10H\(_2\)O, and allowed to warm to rt. This mixture was diluted with hexane, dry Na\(_2\)SO\(_4\), and Celite, and then stirred for 10 min. The resulting mixture was filtrated, and concentrated under reduced pressure. Purification by silica-gel column chromatography (hexane/i-Pr\(_2\)O = 10:1~5:1) gave 1.12 g of primary alchol (80% yield for the two steps, >95% dr by \(^1\)H NMR analysis) as a colorless clear oil.

To a solution of primary alcohol (4.09 g, 15.0 mmol) in distilled CH\(_2\)Cl\(_2\) (150 mL) was added Dess-Martin periodinane (12.7 g, 30.0 mmol) at 0 \(^\circ\)C, and then the resulting mixture was allowed to warm to rt, and stirred for 2 h. The reaction mixture was quenched with a saturated aqueous solution of NaHCO\(_3\), and Na\(_2\)S\(_2\)O\(_3\). The aqueous layer was extracted two times with CH\(_2\)Cl\(_2\). The combined organic layers were washed with brine, dried over Na\(_2\)SO\(_4\), filtrated, and concentrated under reduced pressure. Purification by silica-gel column chromatography (hexane/EtOAc = 40:1) gave 4.06 g of 8 (quantitative yield, >95% dr by \(^1\)H NMR analysis) as a colorless clear oil: \(Rf\) 0.68 (hexane/EtOAc = 5:1); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.69 (d, \(J = 4.2\) Hz, 1H), 5.67 (ddq, \(J = 0.7, 15.3, 6.6\) Hz, 1H), 5.51 (ddq, \(J = 7.6,\)
15.3, 1.5 Hz, 1H), 4.46 (ddd, $J = 0.7, 6.8, 7.6$ Hz, 1H), 2.24 (ddd, 4.2, 6.6, 6.8 Hz, 1H), 2.06 (dqq, $J = 6.6, 6.8, 6.8$ Hz, 1H), 1.70 (dd, $J = 1.5, 6.6$ Hz, 3H), 0.986 (d, $J = 6.8$ Hz, 3H), 0.936 (d, $J = 6.8$ Hz, 3H), 0.936 (t, $J = 7.9$ Hz, 9H), 0.577 (q, $J = 7.9$ Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 205.4, 131.2, 127.9, 72.4, 64.6, 25.7, 20.9, 19.9, 17.6, 6.8, 5.0; IR (neat, cm$^{-1}$) 2958, 2913, 2877, 2734, 1726; HR-ESIMS calcd for C$_{15}$H$_{30}$O$_2$NaSi: 293.1907, found: 293.1899.
Synthesis of 9

![Chemical Structure](image)

To a solution of dry THF (1.00 mL) were added $i$-Pr$_2$NH (0.0809 mL, 0.574 mmol) and $n$-BuLi (2.55 M in hexane, 0.216 mL) at 0 °C, and then the resulting mixture was stirred at that temperature for 50 min. After the reaction mixture was cooling to −78 °C, to this mixture was added cyclopentanone (0.0441 mL, 0.499 mmol) and stirred at that temperature for 2 h. Pre-cooled solutions of 8 (67.5 mg, 0.250 mmol) in distilled THF (1.50 mL) was added to the resulting mixture at −78 °C (Caution: 8 in THF had to cool to −78 °C before dropping into the reaction mixture to prevent an elimination of a hydroxyl group of 9), and then stirred at that temperature for 6 h. The reaction mixture was quenched with a saturated aqueous solution of NH$_4$Cl. The aqueous layer was extracted two times with EtOAc. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtrated, and concentrated under reduced pressure. Purification by silica-gel column chromatography (hexane/EtOAc = 50:1~40:1~30:1) gave 80.6 mg of 9 (91% yield) as a clear colorless oil: $R_f$ 0.59, 0.55 (hexane/EtOAc = 5:1); $^1$H NMR (400 MHz, CDCl$_3$) δ 5.71 (ddq, $J$ = 7.8, 15.4, 1.3 Hz, 0.2H), 5.66-5.55 (m, 1H), 5.47 (ddq, $J$ = 7.8, 15.1, 1.4 Hz, 0.8H), 4.55 (br d, $J$ = 1.5 Hz, 0.2H), 4.46 (dd, $J$ = 4.4, 7.8 Hz, 0.2H), 4.35 (dd, $J$ = 7.2, 7.8 Hz, 0.8H), 3.98-3.95 (m, 1H), 3.76 (t, $J$ = 1.5 Hz, 0.8H), 2.51-2.46 (m, 0.2H), 2.45-2.33 (m, 1.5H), 2.27-1.90 (m, 4.3H), 1.85-1.72 (m, 1.4H), 1.70-1.69 (m, 0.5H), 1.69 (dd, $J$ = 1.4, 6.4 Hz, 2.5H), 1.57-1.46 (m, 0.8H), 1.29-1.24 (m, 0.8H), 1.10 (d, $J$ = 7.1 Hz, 2.5H), 1.04 (d, $J$ = 6.8 Hz, 2.5H), 1.02 (d, $J$ = 7.1 Hz, 0.5H), 0.933 (t, $J$ = 8.0 Hz, 9H), 0.846 (d, $J$ = 6.8 Hz, 0.5H), 0.615-0.537 (m, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 224.7, 222.3, 133.0, 127.1, 127.0, 74.0, 73.9, 72.0, 71.3, 53.2, 52.6, 51.3, 51.0, 39.7, 38.6, 27.5, 27.3, 26.7, 25.7, 24.2, 20.8, 20.54, 20.47, 20.1, 17.8, 7.0, 6.8, 5.3, 4.9; IR (neat, cm$^{-1}$) 3506, 2956, 2913, 2876, 2732, 1723, 1672; HR-ESIMS calcd for C$_{20}$H$_{38}$O$_3$NaSi: 377.2482, found: 377.2495.
Synthesis of 10

To a solution of DMSO (4.99 mL, 70.1 mmol) in distilled CH$_2$Cl$_2$ (107 mL) was added (CF$_3$CO)$_2$O (4.89 mL, 35.2 mmol) at $-78^\circ$C, and then the resulting mixture was stirred at that temperature for 50 min. To this mixture was added a solution of the aldol adduct 9 (4.16 g, 11.7 mmol) in distilled CH$_2$Cl$_2$ (10.0 mL) at $-78^\circ$C, and then this mixture was stirred at that temperature for 2 h 15 min. To this mixture was added distilled Et$_3$N (14.7 mL, 106 mmol) at $-78^\circ$C, and then this mixture was allowed to warm to $-60^\circ$C, and stirred for 12 h. The reaction mixture was quenched with a saturated aqueous solution of NH$_4$Cl. The aqueous layer was extracted two times with EtOAc. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtrated, and concentrated under reduced pressure. Purification by silica-gel column chromatography (hexane/EtOAc = 50:1~40:1~10:1) gave 2.19 g of 1,3-diketone 10 (98% yield, a mixture of diastereomers by $^1$H NMR analysis) as a clear yellow oil: Rf 0.50 (hexane/EtOAc = 10:1); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 13.85 (br s, 0.7H), 13.82 (br s, 0.04H), 5.56 (dq, $J = 15.3$, 5.8 Hz, 0.8H), 5.48 (ddq, $J = 7.8$, 15.3, 1.0 Hz, 0.8H), 5.44-5.33 (m, 0.4H), 4.40-4.36 (m, 0.13H), 4.36 (dd, $J = 7.6$, 7.8 Hz, 0.8H), 4.26 (dd, $J = 7.8$, 8.3 Hz, 0.07H), 4.05 (s, 0.07H), 3.79 (dd, $J = 7.1$, 7.8 Hz, 0.13 H), 3.31 (dd, $J = 5.1$, 7.8 Hz, 0.07H), 3.24 (dd, $J = 5.5$, 10.3 Hz, 0.13H), 3.20 (dd, $J = 6.3$, 8.3 Hz, 0.07H), 2.63-2.44 (m, 2H), 2.42-2.38 (m, 1H), 2.26 (t, $J = 7.4$ Hz, 0.8H), 2.21 (t, $J = 7.6$ H, 0.07H), 2.20 (t, $J = 7.8$ Hz, 0.13H), 2.16-2.05 (m, 1H), 2.03-1.79 (m, 2.4H), 1.68 (dd, $J = 1.5$, 6.4 Hz, 0.39H), 1.64 (dd, $J = 1.0$, 5.8 Hz, 2.4H), 1.60 (dd, $J = 1.2$, 6.1 Hz, 0.21H), 0.962-0.863 (m, 15H), 0.724 (d, $J = 6.6$ Hz, 0.39H), 0.599-0.522 (m, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 213.1, 212.0, 207.3, 206.3, 205.9, 178.3, 132.6, 132.1, 129.9, 127.9, 127.3, 127.2, 112.5, 74.3, 73.7, 73.5, 66.1, 65.3, 63.3, 61.7, 57.7, 57.4, 57.1, 39.1, 38.6, 37.5, 27.5, 27.4, 26.8, 26.4, 25.18, 25.16, 21.3, 21.2, 21.1, 20.7, 20.6, 20.4, 19.9, 19.6, 19.0, 17.7, 17.6, 17.5, 15.2, 6.9, 6.81, 6.78, 5.4, 5.14,
5.10, 5.0, 4.9; IR (neat, cm⁻¹) 2957, 2914, 2876, 1743, 1703, 1654, 1609; HR-ESIMS calcd for C₂₀H₃₆O₃NaSi: 375.2325, found: 375.2323.
Synthesis of 11

0.01 N HCl in EtOH (12.6 mL) was added to the 1,3-diketone 10 (446 mg, 1.26 mmol) at rt, and then the reaction mixture was stirred at that temperature for 23 h 25 min. The reaction mixture was quenched with a saturated aqueous solution of NaHCO₃. The aqueous layer was extracted two times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by silica-gel column chromatography (hexane/EtOAc = 20:1~10:1) gave 266 mg of α,β-unsaturated ketone 11 (96% yield, >95% dr by ¹H NMR analysis) as a clear colorless oil: [α]D²⁵ –196 (c 0.99, CHCl₃); Rf 0.38 (hexane/EtOAc = 5:1); ¹H NMR (400 MHz, CDCl₃) δ 5.90 (ddq, J = 1.0, 15.3, 6.5 Hz, 1H), 5.74 (ddq, J = 7.1, 15.3, 1.5 Hz, 1H), 4.98-4.95 (m, 1H), 2.56-2.51 (m, 4H), 2.20-2.12 (m, 2H), 1.91 (quint, J = 7.6 Hz, 2H), 1.79 (ddd, J = 1.0, 1.5, 6.5 Hz, 3H), 1.01 (d, J = 6.6 Hz, 3H), 0.907 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 192.4, 176.6, 130.5, 126.0, 115.0, 84.8, 54.3, 32.6, 26.0, 25.5, 22.6, 19.4, 19.3, 17.9; IR (neat, cm⁻¹) 2960, 2872, 1659, 1615; HR-ESIMS calcd for C₁₄H₂₀O₂Na: 243.1355, found: 243.1356.
**Synthesis of 12**

To a solution of α,β-unsaturated ketone 11 (2.03 g, 9.19 mmol) in dry Et₂O (91.9 mL) was added LiAlH₄ (436 mg, 11.5 mmol) at 0 °C, and then the resulting mixture was stirred at that temperature for 35 min. The reaction mixture was quenched with Na₂SO₄·10H₂O, and allowed to warm to rt. This mixture was diluted with hexane and dry Na₂SO₄, and Celite, and then stirred for 10 min. The resulting mixture was filtrated, and concentrated under reduced pressure to afford crude allyl alcohol.

To a solution of crude allyl alcohol in distilled CH₂Cl₂ (91.9 mL) were added imidazole (2.50 g, 37.8 mmol), DMAP (112 mg, 0.919 mmol) and TESCl (3.07 mL, 18.4 mmol) at 0 °C, and then the reaction mixture was allowed to warm to rt and stirred for 17 h. The reaction mixture was quenched with a saturated aqueous solution of NaHCO₃. The aqueous layer was extracted two times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtrated, and concentrated under reduced pressure. Purification by silica-gel column chromatography (Silica Gel 60 N (spherical, neutral) 63-210 µm, hexane/i-Pr₂O = 100:1) gave 2.25 g of 12 (73% yield for the two steps, >95% dr by ¹H NMR analysis) as a colorless clear oil: [α]D²² +34.8 (c 0.71, MeOH); Rf 0.67 (hexane/EtOAc = 10:1); ¹H NMR (400 MHz, C₆D₆) δ 6.02 (ddq, J = 9.0, 15.1, 1.7 Hz, 1H), 5.18 (dq, J = 15.1, 6.6 Hz, 1H), 4.41 (dd, J = 4.4, 9.0 Hz, 1H), 3.78 (br s, 1H), 2.24-2.17 (m, 1H), 1.99-1.95 (m, 2H), 1.78-1.71 (m, 1H), 1.59-1.50 (m, 1H), 1.36-1.29 (m, 2H), 1.22 (dd, J = 1.7 6.6 Hz, 3H), 1.05 (m, 1H), 0.655 (t, J = 8.0 Hz, 9H), 0.605 (d, J = 6.4 Hz, 3H), 0.495 (d, J = 6.6 Hz, 3H), 0.302-0.240 (m, 6H); ¹³C NMR (100 MHz, C₆D₆) δ 153.1, 129.0, 127.6, 107.9, 78.5, 64.0, 50.2, 31.8, 31.6, 24.9, 21.7, 20.9, 20.3, 17.9, 7.4, 6.1; IR (neat, cm⁻¹) 2955, 2874, 2731, 1684; HR-ESIMS calcd for C₂₀H₃₆O₂NaSi: 359.2376, found: 359.2383.
Degassed solutions of 12 (23.1 mg, 0.0686 mmol) in distilled triglyme (2.75 mL) was heated 250 °C for 1 h in sealed tubes (Sealed tubes was washed with an aqueous solutions of KOH before use). The resulting mixture was cooled to rt, and added H$_2$O. The aqueous layer was extracted two times with EtOAc. The combined organic layers were washed with H$_2$O, brine, dried over Na$_2$SO$_4$, filtrated, and concentrated under reduced pressure. Purification by silica-gel column chromatography (Silica Gel 60 N (spherical, neutral) 63-210 µm, hexane/i-Pr$_2$O = 100:1) gave 19.3 mg of 13 (84% yield, >95% dr by $^1$H NMR analysis) as a colorless clear oil: [α]$_D^{24}$ +228 (c 0.99, CHCl$_3$); $R_f$ 0.50 (hexane/EtOAc = 10:1); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 5.64 (ddt, $J$ = 1.2, 10.3, 2.2 Hz, 1H), 5.48 (dt, $J$ = 10.3, 2.7 Hz, 1H), 4.05 (dd, $J$ = 1.2, 3.2 Hz, 1H), 2.37-2.23 (m, 2H), 2.20-2.11 (m, 2H), 1.94-1.85 (m, 4H), 1.68 (m, 1H), 0.969 (t, $J$ = 7.7 Hz, 12H), 0.917 (d, $J$ = 6.6 Hz, 3H), 0.911 (d, $J$ = 7.3 Hz, 3H), 0.693-0.631 (m, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 219.9, 131.0, 125.3, 69.1, 58.1, 45.0, 40.4, 33.9, 32.7, 26.9, 22.0, 20.9, 18.5, 15.1, 7.2, 5.8; IR (neat, cm$^{-1}$) 3030, 2958, 2912, 2876, 1736; HR-ESIMS calcd for C$_{20}$H$_{38}$O$_2$NaSi: 359.2376, found: 359.2363.
Synthesis of 14

To a solution of 13 (1.52 g, 4.51 mmol) in distilled CH₂Cl₂ (90.2 mL) was added Crabtree’s catalyst (363 mg, 0.451 mmol) at rt in the dark under argon atmosphere. The argon atmosphere was replaced by H₂ from a double balloon, and the reaction mixture was stirred at rt for 14 h. After the H₂ atmosphere was replaced by argon, the resulting mixture was concentrated under reduced pressure. Purification by silica-gel column chromatography (hexane/EtOAc = 10:1) gave 1.53 g of dihydroketone (quantitative yield) as a colorless clear oil.

To a solution of i-Pr₂NH (0.274 mL, 1.93 mmol) in dry THF (40.0 mL) was added n-BuLi (1.65 M in hexane, 1.10 mL) at 0 °C, and then the resulting mixture was stirred for 30 min. After the reaction mixture was cooling to –78 °C, dihydroketone (408 mg, 1.20 mmol) in dry THF (8.0 mL) was added to the reaction mixture. After the resulting mixture was stirred at –78 °C for 2 h, MeI (0.5 M in THF, 2.65 mL) was added to the reaction mixture, and then the reaction mixture was stirred at that temperature for 12 h. The reaction mixture was quenched with a saturated aqueous solution of NH₄Cl. The aqueous layer was extracted two times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtrated, and concentrated under reduced pressure. Purification by silica-gel column chromatography (hexane/i-Pr₂O = 15:1) gave 389 mg of 14 (90% yield) as a colorless clear oil: \( R_f \) 0.57 (hexane/EtOAc = 10:1); ¹H NMR (400 MHz, CDCl₃) \( \delta \) 3.80 (s, 0.7H), 3.71 (s, 0.3H), 2.25-1.70 (m, 6H), 1.60-1.53 (m, 1H), 1.50-1.30 (m, 5H), 1.05-0.962 (m, 12H), 0.867 (d, \( J = 6.1 \) Hz, 3H), 0.824-0.759 (m, 6H), 0.677-0.619 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) \( \delta \) 222.4, 74.7, 69.5, 59.1, 58.0, 47.0, 45.7, 43.9, 43.4, 34.94, 34.91, 31.9, 30.6, 30.4, 29.9, 28.7, 27.9, 27.7, 27.5, 23.0, 22.8, 21.3, 21.2, 20.8, 17.6, 16.9, 15.2, 13.4, 7.21, 7.17, 6.0, 5.9; IR (neat, cm⁻¹) 2956, 2876, 1725, 1459; HR-ESIMS calcd for C₂₁H₄₀O₂NaSi: 375.2689, found:
375.2692.
Synthesis of (+)-Gleenol (3)

To a solution of 14 (151 mg, 0.427 mmol) in THF (8.54 mL) was added LiAlH₄ (1.0 M in THF, 0.641 mL) at –78 °C, and then the resulting mixture was stirred at that temperature for 5 h. The reaction mixture was quenched with a saturated aqueous solution of NH₄Cl. The aqueous layer was extracted two times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtrated, and concentrated under reduced pressure to afford crude alcohol.

To a solution of crude alcohol in distilled pyridine (8.54 mL) was added MsCl (0.298 mL, 3.85 mmol) at 0 °C, and then the mixture was stirred at that temperature for 22 h. The reaction mixture was quenched with H₂O. The aqueous layer was extracted two times with CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄, filtrated, and concentrated under reduced pressure to afford crude mesylate.

To a solution of crude mesylate in distilled toluene (8.54 mL) was added DBU (0.766 mL, 5.12 mmol) at rt, and then the resulting mixture was stirred for 16 h at 150 °C in sealed tubes. The mixture were cooled to rt, and concentrated, filtrated by a pad of silica-gel (hexane/EtOAc = 300:1) to afford cyclopentene.

To a solution of cyclopentene in THF (8.54 mL) was added TBAF (1.0 M in THF, 2.56 mL) at 0 °C, and then the resulting mixture was allowed to warm to rt, and stirred for 17 h. The reaction mixture was diluted with Et₂O, and quenched with H₂O. The aqueous layer was extracted two times with Et₂O. The combined organic layers were washed with brine, dried over Na₂SO₄, filtrated, and concentrated under reduced pressure. Purification by silica-gel column chromatography (hexane/EtOAc = 7:1) gave 88.1 mg of (+)-3 (93% yield for the four steps, >95% by ¹H NMR analysis) as a colorless clear oil: [α]D²³ +24.8 (c 0.41, CHCl₃); Rf
0.17 (hexane/EtOAc = 10:1); $^1$H NMR (400 MHz, CDCl$_3$) δ 5.17 (tq, $J = 1.7, 1.4$ Hz, 1H), 3.54 (br s, 1H), 2.24-2.19 (m, 2H), 1.90 (ddd, $J = 7.0, 9.2, 13.2$ Hz, 1H), 1.80 (ddd, $J = 5.6, 8.1, 13.2$ Hz, 1H), 1.76-1.64 (m, 2H), 1.74 (dt, $J = 1.4, 1.2$ Hz, 3H), 1.59-1.43 (m, 2H), 1.33-1.23 (m, 2H), 1.17-1.03 (m, 2H), 0.922 (d, $J = 6.8$ Hz, 3H), 0.916 (d, $J = 6.8$ Hz, 3H), 0.749 (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 142.8, 125.6, 76.5, 58.9, 45.4, 36.3, 34.1, 34.0, 31.8, 29.3, 24.4, 21.2, 20.8, 17.0, 16.3; IR (neat, cm$^{-1}$)3480, 3041, 2925, 2730, 1718, 1656, 1462, 1377; HR-ESIMS calcd for C$_{15}$H$_{26}$ONa: 245.1878, found: 245.1875.

The enantiomeric excess of (+)-3 was determined by chiral HPLC analysis (DAICEL, CHIRALCEL OD-H, 0.5 mL/min, hexane:i-PrOH = 100:1, 210 nm, 30 °C) to be 97.8% ee.
Synthesis of 15

To a solution of (+)-3 (25.7 mg, 0.116 mmol) in distilled CH₂Cl₂ (2.32 mL) was added Dess-Martin periodinane (98.0 mg, 0.231 mmol) at rt, and stirred for 3 h. The reaction mixture was quenched with a saturated aqueous solution of NaHCO₃ and Na₂S₂O₃. The aqueous layer was extracted two times with CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄, filtrated, and concentrated under reduced pressure. Purification by silica-gel column chromatography (hexane/EtOAc = 20:1) gave 23.4 mg of 15 (92% yield, >95% dr by ¹H NMR analysis) as a colorless clear oil: [α]₀²³⁺2.2 (c 0.40, CHCl₃); Rf 0.55 (hexane/EtOAc = 10:1); ¹H NMR (400 MHz, CDCl₃) δ 5.31 (tq, J = 1.7, 1.5 Hz, 1H), 2.79 (ddd, J = 5.1, 9.6, 13.4 Hz, 1H), 2.31-2.22 (m, 2H), 2.19-2.01 (m, 3H), 1.72 (dt, J = 1.5, 1.2 Hz, 3H), 1.70-1.59 (m, 2H), 1.57-1.49 (m, 2H), 1.38-1.26 (m, 1H), 0.880 (d, J = 6.8 Hz, 3H), 0.876 (d, J = 6.8 Hz, 3H), 0.851 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 212.6, 144.9, 123.1, 69.7, 53.4, 43.6, 36.0, 31.8, 28.6, 28.2, 26.3, 21.5, 18.8, 17.0, 16.7; IR (neat, cm⁻¹) 2956, 2929, 2870, 1704, 1460, 1375; HR-ESIMS calcd for C₁₅H₂₅O: 221.1889, found: 221.1899.
Synthesis of 18

To a solution of 15 (505 mg, 2.29 mmol) in distilled pyridine (45.8 mL) was added MeONH$_2$·HCl (7.65 g, 91.6 mmol) at rt, and heated to 65 °C. The resulting mixture was stirred at that temperature for 72 h. The reaction mixture was diluted with Et$_2$O and H$_2$O. The aqueous layer was extracted two times with EtOAc. The combined organic layers were washed with brine, dried over Na$_2$SO$_4$, filtrated, and concentrated under reduced pressure.

Purification by silica-gel column chromatography (Silica Gel 60 N (spherical, neutral) 63-210 µm, hexane/EtOAc = 30:1) gave 555 mg of 18 (97% yield, >95% dr by $^1$H and $^{13}$C NMR analysis) as a colorless clear oil. The geometry of O-methyl oxime was determined by NOESY analysis, as shown below: [α]$_D$\textsuperscript{24} +50.0 (c 1.03, CHCl$_3$); $R_f$ 0.53 (hexane/EtOAc = 10:1); $^1$H NMR (400 MHz, CDCl$_3$) δ 5.55 (br s, 1H), 3.78 (s, 3H), 3.03 (ddd, $J$ = 2.9, 4.4, 11.5 Hz, 1H), 2.34-2.28 (m, 1H), 2.21-2.13 (m, 2H), 2.01-1.77 (m, 4H), 1.75 (s, 3H), 1.65-1.60 (m, 2H), 1.24 (ddd, $J$ = 3.2, 6.4, 13.5 Hz, 1H), 0.958 (d, $J$ = 6.4 Hz, 3H), 0.873 (d, $J$ = 6.8 Hz, 3H), 0.862 (d, $J$ = 6.6 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 164.9, 137.3, 131.2, 60.8, 58.4, 40.3, 38.0, 36.6, 35.9, 27.4, 25.5, 21.7, 21.22, 21.19, 17.0, 15.6; IR (neat, cm$^{-1}$) 2960, 2842, 2814, 1664, 1603, 1466, 1377; HR-FABMS calcd for C$_{16}$H$_{28}$NO: 250.2171, found: 250.2173.

NOESY analysis of O-methyl oxime 18.
Synthesis of 19

To a solution of 18 (206 mg, 0.826 mmol) in AcOH (16.5 mL) was added NaBH₃CN (571 mg, 9.08 mmol) at rt, and stirred at that temperature for 2 h 30 min. The reaction mixture was diluted with EtOAc, and quenched with H₂O. The aqueous layer was extracted two times with EtOAc. The combined organic layers were washed three times with a saturated aqueous solution of NaHCO₃, and washed with brine, dried over Na₂SO₄, filtrated, and concentrated under reduced pressure. Purification by silica-gel column chromatography (Silica Gel 60 N (spherical, neutral) 63-210 µm, hexane/i-Pr₂O = 20:1) gave 175 mg of 19 (84% yield, >95% dr by ¹H NMR analysis) as a colorless clear oil: [α]D²⁴ +21.1 (c 0.47, CHCl₃); Rf 0.48 (hexane/i-Pr₂O = 10:1); ¹H NMR (400 MHz, CDCl₃) δ 5.63 (br s, 1H), 5.27 (tq, J = 1.7, 1.4 Hz, 1H), 3.48 (s, 3H), 2.94 (dd, J = 2.6, 1.1 Hz, 1H), 2.27-2.17 (m, 2H), 2.15-2.05 (m, 1H), 1.82 (ddd, J = 4.2, 8.3, 13.2 Hz, 1H), 1.74 (d, J = 1.4 Hz, 3H), 1.71-1.67 (m, 1H), 1.62 (dq, J = 9.4, 6.5, 6.5 Hz, 1H), 1.48-1.38 (m, 2H), 1.26-1.16 (m, 1H), 1.14-0.99 (m, 2H), 0.955 (d, J = 6.5 Hz, 3H), 0.913 (d, J = 6.5 Hz, 3H), 0.722 (d, J = 6.5 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 142.3, 126.5, 67.4, 61.3, 58.2, 45.4, 36.5, 36.1, 34.4, 32.0, 29.3, 25.6, 21.5, 21.4, 17.0, 16.4; IR (neat, cm⁻¹) 2929, 2870, 2804, 1657, 1464, 1375; HR-EIMS calced for C₁₆H₂₃NO: 251.2249, found:251.2248.
Synthesis of 20

A solution of 19 (12.7 mg, 0.0505 mmol) in acetic formic anhydride (prepared from heating 1.60 mL HCOOH and 3.20 mL of (CH₃CO)₂O to 65 °C for 45 min under argon) was stirred at rt for 12 h. The reaction mixture was heated to 70 °C, and stirred for 96 h. After cooling to rt, the resulting mixture was concentrated under reduced pressure. Purification by silica-gel column chromatography (hexane/EtOAc = 10:1~5:1) gave 13.9 mg of 20 (98% yield, >95% dr by ¹H NMR analysis, a mixture of rotamer by ¹H and ¹³C NMR analysis) as a yellow clear oil: [α]D²⁴ +39.6 (c 0.55, CHCl₃); Rf 0.33 (hexane/EtOAc = 5:1); ¹H NMR (400 MHz, CDCl₃) δ 8.59 (s, 0.3H), 7.96 (s, 0.7H), 5.31 (tq, J = 1.7, 1.4 Hz, 0.7H), 5.29 (tq, J = 1.7, 1.4 Hz, 0.3H), 4.30 (d, J = 4.1 Hz, 0.3H), 3.87 (s, 2H), 3.81 (s, 1H), 3.33 (d, J = 4.1 Hz, 0.7H), 2.33-2.12 (m, 2H), 2.00-1.85 (m, 0.7H), 1.85-1.70 (m, 3H), 1.75 (d, J = 1.7 Hz, 2H), 1.72 (d, J = 1.7 Hz, 1H), 1.66-1.31 (m, 4H), 1.25-1.13 (m, 1.3H), 0.922 (d, J = 6.6 Hz, 2H), 0.912 (d, J = 6.6 Hz, 1H), 0.867 (d, J = 6.6 Hz, 1H), 0.850 (d, J = 6.6 Hz, 2H), 0.771 (d, J = 6.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 165.0, 159.9, 142.7, 142.4, 126.2, 125.9, 66.1, 64.7, 62.3, 61.4, 58.1, 57.7, 44.75, 44.66, 36.4, 36.2, 36.0, 34.1, 33.3, 32.1, 31.8, 29.5, 29.1, 26.5, 25.9, 21.8, 21.6, 21.0, 20.6, 16.9, 16.83, 16.78; IR (neat, cm⁻¹) 3041, 2956, 2870, 1682, 1462, 1369; HR-EIMS calcd for C₁₇H₂₉NO₂: 279.2198, found: 279.2197.
Synthesis of (−)-Axamide-3 (2)

To a solution of 20 (183 mg, 0.656 mmol) in THF (6.56 mL) was added SmI\(_2\) (0.1 M solution in THF, 19.7 mL, 1.97 mmol) at rt, and stirred at that temperature for 2 h 30 min. The reaction mixture was diluted with EtOAc, and quenched with a saturated aqueous solution of Na\(_2\)S\(_2\)O\(_3\). The aqueous layer was extracted with EtOAc. The organic layer was washed with brine, dried over Na\(_2\)SO\(_4\), filtrated, and concentrated under reduced pressure. Purification by silica-gel column chromatography (hexane/EtOAc = 3:1~1:1) gave 129 mg of (−)-2 (79% yield, a mixture of rotamer by \(^1\)H and \(^{13}\)C NMR analysis) as a amorphous solid: [α]\(_D\)\(^{23}\) −14.8 (c 0.20, CHCl\(_3\)); \(R_f\) 0.29, 0.19 (hexane/EtOAc = 3:1); \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 8.27 (d, \(J = 1.8\) Hz, 0.7H), 8.05 (d, \(J = 11.8\) Hz, 0.3H), 5.70 (dd, \(J = 11.4, 11.8\) Hz, 0.3H), 5.54 (dd, \(J = 1.8, 10.0\) Hz, 0.7H), 5.26 (m, 1H), 4.23 (br d, \(J = 10.0\) Hz, 0.7H), 3.31 (dd, \(J = 2.6, 11.4\) Hz, 0.3H), 2.32-2.10 (m, 2.5H), 1.89-1.82 (m, 1.5H), 1.76 (d, \(J = 1.0\) Hz, 0.7H), 1.74 (d, \(J = 1.0\) Hz, 2.3H), 1.69-1.61 (m, 0.7H), 1.57-1.49 (m, 3.3H), 1.44-1.26 (m, 3H), 1.23-1.02 (m, 1H), 0.96-0.85 (m, 6H), 0.78-0.73 (m, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 164.5, 161.2, 144.0, 143.8, 125.3, 125.2, 77.2, 59.3, 58.0, 57.8, 53.8, 44.1, 43.9, 35.9, 35.8, 35.5, 34.4, 33.4, 31.4, 31.1, 29.3, 28.6, 25.2, 24.9, 21.0, 20.7, 20.5, 16.75, 16.72, 16.0, 15.9; IR (neat, cm\(^{-1}\)) 3307, 3043, 2956, 2927, 2870, 1660, 1537, 1462, 1383; HR-FABMS calcd for C\(_{16}\)H\(_{28}\)NO: 250.2171, found: 250.2171.
Synthesis of (+)-Axisonitrile-3 (1)

To a solution of (-)-2 (2.6 mg, 0.0104 mmol) in distilled pyridine (0.20 mL) was added TsCl (7.0 mg, 0.0365 mmol) at rt, and stirred at that temperature for 3 h. The reaction mixture was quenched with a few chips of ice. The aqueous layer was extracted with Et₂O. The organic layer was washed two times with H₂O, dried over Na₂SO₄, filtrated, and concentrated under reduced pressure. Purification by silica-gel column chromatography (Silica Gel 60 N (spherical, neutral) 63-210 µm, hexane/i-Pr₂O = 20:1) gave 2.1 mg of (+)-1 (87% yield, >95% dr by ¹H NMR analysis) as a white solid: mp: 94-95 °C; [α]D²⁴ +54.4 (c 0.11, CHCl₃); Rf'0.45 (hexane/i-Pr₂O = 20:1); ¹H NMR (400 MHz, CDCl₃) δ 5.14 (q, J = 1.4 Hz, 1H), 3.59 (br s, 1H), 2.31-2.17 (m, 2H), 2.01-1.90 (m, 2H), 1.85-1.76 (m, 2H), 1.74 (d, J = 1.4 Hz, 3H), 1.59 (dq, J = 9.4, 6.7, 6.7 Hz, 1H), 1.51 (ddt, J = 13.4, 4.0, 3.5 Hz, 1H), 1.33 (ddt, J = 12.8, 4.0, 13.4 Hz, 1H), 1.20-1.11 (m, 1H), 1.06 (ddt, J = 12.8, 4.0, 13.4 Hz, 1H), 0.94 (d, J = 6.7 Hz, 3H), 0.91 (d, J = 6.7 Hz, 3H), 0.77 (d, J = 6.7 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 155.7, 144.8, 123.6, 64.5, 57.1, 43.8, 35.8, 34.9, 34.3, 31.2, 29.7, 24.9, 20.7, 20.3, 16.9, 16.1; IR (neat, cm⁻¹) 2925, 2131, 1541, 1456; HR-ESIMS calcd for C₁₆H₂₆N: 232.2055, found: 232.2059.