Supporting Information
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Concise Synthesis of (−)-Axenol by Using Stereocontrolled Allylic Substitution

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General Methods

The $^1$H NMR (300 or 400 MHz) and $^{13}$C NMR (75 MHz) spectra were measured in CDCl$_3$ using SiMe$_4$ ($\delta = 0$ ppm), residual CHCl$_3$ ($\delta = 7.26$ ppm), and the center line of CDCl$_3$ triplet ($\delta = 77.1$ ppm) as internal standards, respectively.

(1S,3R,6S)-6-Isopropyl-3-methyl-2-oxocyclohexyl benzoate (5)

![Structure of 1S,3R,6S-6-Isopropyl-3-methyl-2-oxocyclohexyl benzoate (5)]

To an ice-cold solution of monobenzoate 9 (1.19 g, 4.32 mmol) in acetone (20 mL) was added Jones reagent (4.0 M in H$_2$O) dropwise until orange color persisted (ca. 1.5 mL). The mixture was stirred at 0 °C further for 30 min, and diluted with $i$-PrOH with vigorous stirring. The resulting precipitate was removed by filtration through a pad of Celite. The filtrate was concentrated to give a residue, which was diluted with saturated NaHCO$_3$ and EtOAc. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined extracts were washed with saturated NaHCO$_3$ and brine, dried over MgSO$_4$, and concentrated to give ketone 5 (1.16 g, 98%) as a colorless oil, which was used for the next reaction without further purification: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.90 (d, $J = 6.9$ Hz, 3 H), 1.00 (d, $J = 6.9$ Hz, 3 H), 1.08 (d, $J = 6.6$ Hz, 3 H), 1.35 (dq, $J = 3.6$, 13.2 Hz, 1 H), 1.64 (dq, $J = 3.6$, 13.2 Hz, 1 H), 1.90 (dq, $J = 13.8$, 3.4 Hz, 1 H), 1.96–2.21 (m, 3 H), 2.55 (sept, $J = 6.4$ Hz, 1 H), 5.28 (dd, $J = 11.9$, 1.4 Hz, 1 H), 7.46 (t, $J = 7.4$ Hz, 2 H), 7.58 (tt, $J = 7.4$, 1.5 Hz, 1 H), 8.08–8.13 (m, 2 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 13.9 (+), 16.1 (+), 20.4 (+), 22.9 (−), 27.4 (+), 34.4 (−), 43.8 (+), 49.4 (+), 79.0 (+), 128.3 (+), 129.7 (−), 129.8 (+), 133.1 (+), 165.8 (−), 206.1 (−). [$\alpha$]$_D^{20}$ −78.5 (c 1.16, CHCl$_3$). HRMS (FAB) calcd for C$_{17}$H$_{23}$O$_3$ [(M + H)$^+$] 275.1647, found 275.1646.
(1S,3R,6S,Z)-2-(2-Ethoxy-2-oxoethylidene)-6-isopropyl-3-methylcyclohexyl benzoate (10)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{OBz} & \quad \text{OBz} \\
5 & \quad 10
\end{align*}
\]

To an ice-cold solution of \(i\)-Pr₂NH (0.110 mL, 0.783 mmol) in THF (2 mL) was added \(n\)-BuLi (1.60 M in hexane, 0.370 mL, 0.592 mmol). The mixture was stirred at 0 °C for 30 min, cooled to −78 °C and ethyl (trimethylsilyl)acetate (0.140 mL, 0.769 mmol) was added to it dropwise. The solution was stirred at −78 °C for 1 h, and ketone 5 (83.0 mg, 0.303 mmol) in THF (1 mL) was added dropwise. The solution was allowed to warm to rt over 5 h, and diluted with saturated \(\text{NH}_4\text{Cl}\) and \(\text{EtOAc}\) with vigorous stirring. The layers were separated and the aqueous layer was extracted with \(\text{EtOAc}\) three times. The combined extracts were washed with brine, dried over \(\text{MgSO}_4\), and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford ester 10 (83.4 mg, 80%) as a colorless oil: \(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \(\delta\) 0.86 (d, \(J = 6.6\) Hz, 3 H), 1.06 (d, \(J = 6.3\) Hz, 3 H), 1.14 (t, \(J = 7.2\) Hz, 3 H), 1.26 (d, \(J = 6.9\) Hz, 3 H), 1.30–1.51 (m, 2 H), 1.64–2.03 (m, 4 H), 2.39–2.52 (m, 1 H), 3.81 (dq, \(J = 11.1, 7.2\) Hz, 1 H), 4.01 (dq, \(J = 11.1, 7.2\) Hz, 1 H), 5.76 (s, 1 H), 6.45 (d, \(J = 5.7\) Hz, 1 H), 7.45 (t, \(J = 7.5\) Hz, 2 H), 7.56 (tt, \(J = 7.5, 1.7\) Hz, 1 H), 8.03–8.09 (m, 2 H); \(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)) \(\delta\) 14.0 (+), 18.6 (+), 20.5 (−), 20.6 (+), 21.3 (+), 26.7 (+), 30.6 (−), 38.2 (+), 47.7 (+), 60.4 (−), 72.5 (+), 117.5 (+), 128.4 (+), 129.8 (+), 130.4 (−), 133.0 (+), 154.2 (−), 165.4 (−), 167.0 (−). \([\alpha]_D^{20}\) +62.5 (c 0.78, CHCl\(_3\)). HRMS (FAB) calcd for C\(_{21}\)H\(_{29}\)O\(_4\) [(M + H)+] 345.2066, found 345.2071.

(1S,3R,6S,Z)-2-(2-Hydroxyethylidene)-6-isopropyl-3-methylcyclohexanol (11)

\[
\begin{align*}
\text{O} & \quad \text{OH} \\
\text{OBz} & \\
10 & \quad 11
\end{align*}
\]

To a solution of ester 10 (81.4 mg, 0.236 mmol) in THF (4 mL) was added DIBAL (1.02 M in hexane, 1.40 mL, 1.43 mmol) at −40 °C. The solution was allowed to warm to 0 °C
over 2 h, and diluted with saturated Rochelle salt and EtOAc. The resulting mixture was stirred at rt overnight. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined extracts were washed with brine, dried over MgSO₄, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford diol 11 (45.0 mg, 96%) as white solids: ¹H NMR (300 MHz, CDCl₃) δ 0.86 (d, J = 6.9 Hz, 3 H), 0.93 (d, J = 7.2 Hz, 3 H), 0.98–1.10 (m, 1 H), 1.06 (d, J = 6.6 Hz, 3 H), 1.17–1.32 (m, 1 H), 1.42–1.53 (m, 1 H), 1.71 (dq, J = 12.9, 3.9 Hz, 1 H), 1.79 (dq, J = 12.3, 3.9 Hz, 1 H), 1.96–2.22 (m, 2 H), 2.91 (br s, 1 H), 3.37 (br s, 1 H), 4.10 (d, J = 9.6 Hz, 1 H), 4.27 (dd, J = 12.0, 6.5 Hz, 1 H), 4.32 (dd, J = 12.0, 6.5 Hz, 1 H), 5.46 (t, J = 6.5 Hz, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 16.2 (+), 19.1 (+), 21.1 (+), 22.5 (–), 26.1 (+), 35.5 (–), 38.1 (+), 51.4 (+), 58.5 (–), 75.6 (+), 117.9 (+), 150.9 (–). [α]D₂⁰ –18.1 (c 1.20, CHCl₃). HRMS (FAB) calcd for C₁₂H₂₂O₂Na [(M + Na)+] 221.1517, found 222.1518.

2-((2S,3S,6R,Z)-2-Hydroxy-3-isopropyl-6-methylcyclohexylidene)ethyl picolinate (15)

To a solution of diol 11 (110 mg, 0.553 mmol) in CH₂Cl₂ (8 mL) were added picolinic acid (75.2 mg, 0.611 mmol), Et₃N (0.155 mL, 1.11 mmol), DMAP (33.4 mg, 0.273 mmol), and 2-chloro-1-methylpyridinium iodide (211 mg, 0.825 mmol). The solution was stirred at rt overnight, and diluted with brine with vigorous stirring. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ three times. The combined extracts were washed with brine, dried over MgSO₄, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford picolinate 15 (144 mg, 86%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 0.87 (d, J = 6.9 Hz, 3 H), 0.97–1.14 (m, 1 H) 1.07 (d, J = 6.6 Hz, 3 H), 1.21–1.36 (m, 1 H), 1.47–1.58 (m, 1 H), 1.60 (s, 1 H), 1.70–1.84 (m, 2 H), 2.00–2.20 (m, 2 H), 3.55 (d, J = 3.9 Hz, 1 H), 4.26 (dd, J = 9.2, 3.9 Hz, 1 H), 5.18 (dd, J = 12.1, 6.9 Hz, 1 H), 5.39 (dd, J = 7.8, 6.9 Hz, 1 H), 5.52 (dd, J = 12.1, 7.8 Hz, 1 H), 7.49 (ddd, J = 7.8, 4.8, 1.2 Hz, 1 H), 7.86 (dt, J = 1.7, 7.8 Hz, 1 H), 8.15 (dt, J = 7.8, 1.2 Hz, 1 H), 8.77 (dm, J = 4.8 Hz, 1 H); ¹³C NMR (75 MHz,
CDCl₃ δ 16.5 (+), 19.6 (+), 21.1 (+), 22.0 (−), 26.0 (+), 34.6 (−), 37.9 (+), 50.5 (+), 63.2 (−), 75.1 (+), 114.5 (+), 125.2 (+), 127.0 (+), 137.1 (+), 148.2 (−), 149.8 (+), 151.6 (−), 165.8 (−). [α]D²¹ +8.7 (c 0.32, CHCl₃). HRMS (FAB) calcd for C₁₈H₂₆NO₃ [(M + H)+] 304.1913, found 304.1912.

2-((2S,3S,6R,Z)-3-Isopropyl-6-methyl-2-((trimethylsilyl)oxy)cyclohexylidene)ethyl picolinate (6b)

To a solution of picolinate 15 (112 mg, 0.370 mmol) in CH₂Cl₂ (4 mL) were added I₂ (10.7 mg, 0.0422 mmol) and HMDS (0.117 mL, 0.551 mmol) dropwise. The solution was stirred at rt for 2 h, and diluted with saturated Na₂S₂O₃ with vigorous stirring. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ three times. The combined extracts were washed with brine, dried over MgSO₄, and concentrated to give TMS ether 6b (131 mg, 94%) as a pale yellow oil, which was used for the next reaction without further purification: ¹H NMR (300 MHz, CDCl₃) δ 0.15 (s, 9 H), 0.78 (d, J = 6.9 Hz, 3 H), 0.91 (d, J = 6.9 Hz, 3 H), 1.02–1.22 (m, 1 H), 1.09 (d, J = 6.9 Hz, 3 H), 1.16–1.30 (m, 1 H), 1.41–1.51 (m, 1 H), 1.72–1.83 (m, 2 H), 1.92–2.16 (m, 2 H), 4.09 (d, J = 8.4 Hz, 1 H), 5.20–5.40 (m, 3 H), 7.48 (ddd, J = 7.6, 4.8, 1.6 Hz, 1 H), 7.85 (dt, J = 1.8, 7.6 Hz, 1 H), 8.16 (d, J = 7.6 Hz, 1 H), 8.78 (dm, J = 4.8 Hz, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 0.1 (+), 17.2 (+), 19.4 (+), 21.7 (+), 21.8 (−), 25.2 (+), 35.0 (−), 38.5 (+), 51.7 (+), 63.9 (−), 75.1 (+), 115.1 (+), 125.1 (+), 126.7 (+), 136.9 (+), 148.4 (−), 149.0 (−), 149.8 (+), 165.2 (−). [α]D²¹ −54.0 (c 0.67, CHCl₃). HRMS (FAB) calcd for C₂₁H₃₄NO₃Si [(M + H)+] 376.2308, found 376.2302.

(−)-Axenol (4)
The experimental procedure is given in the text.

(Z)-2-((2S,3S,6R)-3-Isopropyl-6-methyl-2-((trimethylsilyl)oxy)cyclohexylidene)ethyl pivalate (i)

To a solution of diol 11 (43.4 mg, 0.219 mmol) in pyridine (2 mL) was added PivCl (0.0330 mL, 0.271 mmol). The solution was stirred at rt overnight, and diluted with saturated NaHCO₃ with vigorous stirring. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ three times. The combined extracts were washed with brine, dried over MgSO₄, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford the corresponding pivalate (46.8 mg, 76%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 0.85 (d, J = 6.9 Hz, 3 H), 0.92 (d, J = 7.2 Hz, 3 H), 0.99–1.10 (m, 1 H), 1.06 (d, J = 6.6 Hz, 3 H), 1.16–1.33 (m, 1 H), 1.19 (s, 9 H), 1.39–1.52 (m, 1 H), 1.68–1.82 (m, 2 H), 1.99–2.15 (m, 2 H), 3.37 (d, J = 3.9 Hz, 1 H), 4.20 (dd, J = 8.7, 3.9 Hz, 1 H), 4.80 (dd, J = 12.0, 6.6 Hz, 1 H), 5.07–5.23 (m, 2 H).

To a solution of the above product (43.6 mg, 0.154 mmol) in CH₂Cl₂ (2 mL) were added I₂ (4.4 mg, 0.017 mmol) and HMDS (0.050 mL, 0.24 mmol) dropwise. The solution was stirred at rt for 1.5 h, and diluted with saturated Na₂S₂O₃ with vigorous stirring. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ three times. The combined extracts were washed with brine, dried over MgSO₄, and concentrated to give the TMS ether i (49.4 mg, 90%) as a pale yellow oil, which was used for the next reaction without further purification: ¹H NMR (300 MHz, CDCl₃) δ 0.12 (s, 9 H), 0.78 (d, J = 6.9 Hz, 3 H),
0.90 (d, J = 6.9 Hz, 3 H), 1.01–1.14 (m, 1 H), 1.10 (d, J = 6.9 Hz, 3 H), 1.21 (s, 9 H), 1.24–1.30 (m, 1 H), 1.34–1.42 (m, 1 H), 1.69–1.95 (m, 3 H), 2.04–2.16 (m, 1 H), 4.13 (d, J = 7.8 Hz, 1 H), 4.86 (d, J = 6.3 Hz, 2 H), 5.14 (t, J = 6.3 Hz, 1 H).

**(1S,3R,6S,Z)-6-Isopropyl-3-methyl-2-(5-methylhex-5-en-1-ylidene)cyclohexanol (iii)**

\[
\text{OTMS} \quad \text{OPiv} \quad \text{OTMS} \quad \text{OH}
\]

To an ice-cold suspension of TMS ether \(i\) (14.3 mg, 0.0403 mmol) were added a solution of Li\(_2\)CuCl\(_4\) (0.10 M in THF, 0.080 mL, 0.0080 mmol) and a solution of (3-methylbut-3-en-1-yl)magnesium bromide (0.57 M in THF, 0.215 mL, 0.123 mmol) dropwise over 20 min. The resulting solution was stirred at rt overnight, and diluted with saturated NH\(_4\)Cl and EtOAc with vigorous stirring. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined extracts were washed with brine, dried over MgSO\(_4\), and concentrated to give the S\(_2\)N product \(ii\), which was used for the next reaction without further purification.

The above product in H\(_2\)O-AcOH-THF (0.72 mL, 3:5:10) was stirred at rt for 2.5 h, and diluted with saturated NaHCO\(_3\) and CH\(_2\)Cl\(_2\) with vigorous stirring. The layers were separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) three times. The combined extracts were washed with brine, dried over MgSO\(_4\), and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford alcohol \(iii\) (7.3 mg, 72% from TMS ether \(i\)) as a pale yellow oil: \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 0.87 (d, \(J = 6.9\) Hz, 3 H), 0.94 (d, \(J = 6.6\) Hz, 3 H), 1.18–1.78 (m, 8 H), 1.20 (d, \(J = 7.2\) Hz, 3 H), 1.72 (s, 3 H), 1.90–2.00 (m, 1 H), 2.03 (t, \(J = 7.5\) Hz, 2 H), 2.16 (q, \(J = 7.5\) Hz, 2 H), 2.21–2.33 (m, 1 H), 4.57 (br s, 1 H), 4.68 (br s, 1 H), 4.71 (br s, 1 H), 5.29 (t, \(J = 7.5\) Hz, 1 H); \(^1\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 19.0, 19.5, 21.8, 22.5, 23.1, 26.4, 26.8, 28.3, 29.4, 37.5, 37.8, 48.5, 70.2, 110.0, 127.5, 142.2, 146.0.
NOE, CDCl₃, 400 MHz

10
5

$\text{H NMR, CDCl}_3, 300 \text{ MHz}$

$\text{APT, CDCl}_3, 75 \text{ MHz}$

S9
\[ \text{1H NMR, CDCl}_3, \text{300 MHz} \]

\[ \text{APT, CDCl}_3, \text{75 MHz} \]
$^1$H NMR, CDCl$_3$, 300 MHz

APT, CDCl$_3$, 75 MHz
$^{1}$H NMR
CDCl$_3$, 300 MHz

APT, CDCl$_3$, 75 MHz
$^{1}H$ NMR
CDCl$_3$, 300 MHz

APT, CDCl$_3$, 75 MHz

S13
$^1$H NMR, CDCl$_3$, 300 MHz

APT, CDCl$_3$, 75 MHz

S14
$^1$H NMR
CDCl$_3$, 300 MHz

APT, CDCl$_3$, 75 MHz
$^{1}$H NMR
CDCl$_3$, 300 MHz

Piv ester of 11

$^{1}$H NMR
CDCl$_3$, 300 MHz

S16
$^1$H NMR
CDCl$_3$, 300 MHz

$^{13}$C NMR, CDCl$_3$, 75 MHz