Supporting Information

A Stereocontrolled Synthesis of the C9-C19 Subunit of
(+)-Peloruside A

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General Information

All materials were used as received from a commercial supplier without further purification. All anhydrous reactions were performed using oven-dried or flame dried glassware, which was then cooled under nitrogen gas. Tetrahydrofuran (THF), toluene was distilled over Na/Ph₅CO under nitrogen atmosphere. Dichloromethane (CH₂Cl₂), hexane, acetonitrile, dimethylsulfoxide, dimethylformamide, triethylamine (TEA), 2,6-lutidine and diethyl ether (Et₂O) were dried over CaH₂ and distilled prior to use. 4 Å Molecular sieves were flame dried and then cooled under high vacuum prior to use. All reactions were monitored by E. Merck analytical thin layer chromatography (TLC) plates and analyzed with 254 nm UV light and/or anisaldehyde–sulfuric acid or potassium permanganate or PMA treatment. Silica gel for column chromatography was purchased from Acme (Silica Gel 60-120, 100-200 mesh). All ¹H and ¹³C NMR spectra were recorded in CDCl₃ using Gemini 200, Avance 300, Inova 400, Inova 500 spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) relative to residual CHCl₃ as an internal reference (¹H: δ 7.26 ppm, ¹³C: δ 77.00 ppm). Coupling constants (J) are reported in Hertz (Hz). Peak multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Enantiomeric excess were recorded using Waters HPLC instrument. For the preparation of dienol silyl ketene acetal an inert atmosphere filtration setup was employed. Sealed tube was purchased from Aldrich Company. Mass spectra were recorded using Waters Mass spectrometer. HPLC spectra were recorded
using Waters 2998 spectrometer. High resolution mass (HRMS) were recorded using Applied Bio-Sciences HRMS spectrometer and Thermo LTQ-Orbitrap mass spectrometer. All IR-spectra were recorded using Nexus 870-FT-IR Thermo Nicolet spectrometer.

**Experimental section**

**Compound 11.** To a suspension of NaH (4 g, 60% in Nujol, 100 mmol) in anhydrous THF (300 mL) cooled at 0 °C was added a solution of neopentyl glycol 10 (10.4 g, 100 mmol) in anhydrous THF (100 mL) dropwise over 30 minutes. The mixture was stirred for 16 h at rt during which a white color thick mono anion was formed. TBDPS-Cl (27.3 mL, 105 mmol) was added slowly at 0 °C over 20 minutes, the mixture stirred for an additional 3 h and quenched with aq NH₄Cl solution at 0 °C. The layers were separated and the aqueous layer extracted with ethyl acetate (3×200 mL). The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, concentrated and purified by column chromatography using hexanes/EtOAc (9:1, v/v) to afford pure mono protected alcohol 11 (29 g, 85 mmol) in 85% yield as a viscous oil. TLC Rₚ = 0.25 (15% EtOAc/Hexanes). IR (KBr): 3446, 3070, 2957, 2860, 1469, 1108, 821, 703, 506 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 7.69-7.40 (m, 4H), 7.46-7.38 (m, 6H), 3.51 (s, 2H), 3.47 (s, 2H), 1.06 (s, 9H), 0.89 (s, 6H). ¹³C NMR (75 MHz, CDCl₃): δ 135.6, 133.1, 129.7, 127.7, 71.9, 71.0, 37.0, 26.8, 21.4, 19.2. MS (ESI) 365 [M+Na]⁺. HRMS (ESI) m/z calcd for C₂₁H₃₀O₂NaSi 365.1912; found 365.1921.

**Compound 9.** The mixture of mono protected alcohol 11 (6.8 g, 20 mmol) and IBX (6.2 g, 24 mmol) in ethyl acetate (60 mL) was heated at reflux for 6 h. The solid material was
filtered and washed with ethyl acetate (2×30 mL). The combined filtrates were concentrated and the residue purified by flash column chromatography using hexanes/EtOAc (9:1, v/v) to afford pure aldehyde 9 (6.5 g, 19 mmol) in 95% yield as a viscous oil. TLC Rf = 0.35 (15% EtOAc/Hexanes). IR (KBr): 2959, 2932, 2859, 1706, 1471, 1427, 1110, 822, 704, 505 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ 9.55 (s, 1H), 7.62-7.58 (m, 4H), 7.42-7.34 (m, 6H), 3.60 (s, 2H), 1.06 (s, 6H), 1.03 (s, 9H). ¹³C NMR (75 MHz, CDCl₃): δ 205.6, 135.6, 133.0, 129.7, 127.7, 68.8, 48.3, 26.7, 19.2, 18.5. MS (ESI) 379 [K⁺].

**Compound 8.** To a solution of iPr₂NH (5.6 mL, 40.0 mmol) in anhydrous THF (40 mL) cooled at 0 °C was added n-BuLi (15.4 mL, 40.0 mmol, 2.6 M in hexane) over 5 minutes. The clear, colorless solution was stirred at 0 °C for 20 minutes and then cooled to -78 °C. Freshly distilled 2,2,6-trimethyl-[1,3]dioxine-4-one (4.7 mL, 36.0 mmol) was added neat over 10 minutes and the resulting yellowish solution was stirred at -78 °C for 60 minutes. Freshly distilled TMS-Cl (5.3 mL, 42 mmol) was added slowly over 10 min and the reaction mixture was stirred for an additional 30 minutes at -78 °C. The thick, orange suspension was allowed to warm to rt over 90 minutes and was then filtered over anhydrous Na₂SO₄ under nitrogen atmosphere. The filter cake was rinsed twice with anhydrous hexane (2×15 mL) and the clear, orange filtrate was concentrated under reduced pressure at low temperature (30-35 °C). The remaining red oil was distilled under reduced pressure (0.4 mm/Hg, 60 °C) to yield 8 (29.3 g, 78% yield) as a colorless liquid. The silyl ether 8 was stored at 0 °C and used within a week. ¹H NMR (300 MHz, CDCl₃): δ 4.55 (s, 1H), 4.00 (s, 1H), 3.80 (s, 1H), 1.53 (s, 6H), 0.26 (s, 9H).
**Anti-1,3-acetonide of 15.** To a solution of diol 15 (45 mg, 0.1 mmol) in anhydrous dichloromethane (2 mL) was added 2,2-dimethoxypropane (0.1 mL) and catalytic amounts of CSA. The mixture was stirred at rt for 1 h. Few drops of Et3N, enough to neutralize CSA, were added and the volatiles removed under reduced pressure. The residue was purified by column chromatography using 10% hexanes/EtOAc (v/v) as the eluent to afford the corresponding acetonide (45 mg, 0.095 mmol) in 95% yield. TLC \( R_f = 0.4 \) (20% EtOAc/Hexanes). IR (KBr): 2960, 2860, 1735, 1469, 1428, 1369, 1257, 1169, 1107, 822, 703, 505 cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta 7.73-7.64 \) (m, 4H), 7.48-7.37 (m, 6H), 4.2-4.15 (m, 1H), 3.87 (dd, \( J = 9.9, 5.9 \) Hz, 1H), 3.69 (s, 3H), 3.52 (d, \( J = 8.9 \) Hz, 1H), 3.33 (d, \( J = 8.9 \) Hz, 1H), 2.54 (dd, \( J = 15.9, 7.9 \) Hz, 1H), 2.43 (dd, \( J = 15.9, 4.9 \) Hz, 1H), 1.92-1.86 (m, 1H), 1.47-1.40 (m, 1H), 1.37 (s, 3H), 1.30 (s, 3H), 1.07 (s, 9H), 0.87 (s, 3H), 0.83 (s, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta 171.5, 135.7, 133.7, 129.5, 127.5, 100.5, 69.3, 69.0, 63.9, 51.6, 40.6, 38.7, 32.6, 26.9, 24.6, 24.1, 20.2, 19.4, 19.1. MS (ESI) 521 [M+Na]\(^+\). HRMS (ESI) \( m/z \) calcd for C\(_{29}\)H\(_{42}\)O\(_5\)NaSi 521.26937; found 521.26853.

**Compound 23.** To a stirred suspension of LiAlH\(_4\) (7.4 g, 200 mmol) in anhydrous THF (300 mL) cooled at -10 °C was added a solution of diethyl ethyl malonate 22 (18.8 g, 100 mmol) in THF (300 mL) dropwise over 30 minutes. The reaction mixture was stirred at rt for 16 h. The reaction mixture was cooled to -10 °C and an additional 200 mL of THF was added. The reaction was quenched with aq 20% NaOH solution followed by H\(_2\)O. This mixture was further diluted with THF (300 mL), filtered through a pad of Celite and the precipitated aluminum salts were washed with THF repeatedly until all the diol was removed from the aluminum salt (It required 6 to 8 times of washing). The combined
filtrates were concentrated under reduced pressure to give an yellow oil which was distilled under reduced pressure at 110 °C, to provide diol 23 as a colorless liquid (6.8 g, 65 mmol) in 65% yield. $^1$H NMR (500 MHz, CDCl$_3$): δ 3.82-3.69 (m, 2H), 3.62-3.58 (m, 2H), 1.64-1.56 (m, 1H), 1.32-1.24 (m, 2H), 0.92 (t, $J = 7.9$ Hz, 3H).

**Compound 24.** To a suspension of NaH (2 g, 60% in Nujol, 50 mmol) in anhydrous THF (100 mL) cooled at 0 °C was added a solution of diol 23 (5.2 g, 50 mmol) in anhydrous THF (100 mL) dropwise over 30 minutes. Stirring was continued for 16 h at rt. TBS-Cl (9 g, 60 mmol) in anhydrous THF (30 mL) was added at 0 °C slowly. After 3 h of stirring at rt, the reaction was quenched with aq NH$_4$Cl at 0 °C. The layers were separated and the aqueous layer was extracted with ethyl acetate (3×60 mL). The combined organic layers were washed with brine, dried over anhydrous Na$_2$SO$_4$, concentrated and the residue purified by column chromatography using hexanes/EtOAc (9:1, v/v) to afford alcohol 24 (7.7 g, 35 mmol) in 70% yield as a colorless oil. TLC $R_f = 0.15$ (20% EtOAc/Hexanexes).

IR (KBr): 3421, 3210, 2894, 1983, 1739, 1643, 1526, 1120, 709 cm$^{-1}$. $^1$H NMR (500 MHz, CDCl$_3$): δ 3.78 (dd, $J = 9.8$, 3.9 Hz, 1H), 3.69 (dd, $J = 9.8$, 3.0 Hz, 1H), 3.64-3.54 (m, 2H), 1.66-1.56 (m, 1H), 1.36-1.22 (m, 2H), 0.98-0.90 (m, 12H), 0.07 (s, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$): δ 67.0, 66.2, 43.5, 25.7, 20.5, 18.1, 11.6, -3.7, -5.7. MS (ESI) 241 [M+Na]$^+$. HRMS (ESI) $m/z$ calcd for C$_{11}$H$_{26}$O$_2$NaSi, 241.1599; found 241.1608.

**Compounds 25 and 26.** To a solution of racemic alcohol 24 (6.6 g, 30 mmol) and Amano lipase (0.50 g) in diisopropyl ether (90 mL) was added freshly distilled vinyl acetate (4 mL, 75 mmol). The heterogeneous mixture was stirred at rt for 12 h before being filtered through Celite to remove the enzyme. The filter cake was washed with Et$_2$O (2×40 mL) and the combined filtrates were concentrated under reduced pressure. Purification of the
residue by column chromatography using hexanes/EtOAc (95:5, v/v) afforded initially
(R)-acetate 26 (3.4 g, 13 mmol) in 43% yield as an oil and later (S)-alcohol 25 (2.7 gm,
12.3 mmol) in 41% yield as an oil. **Compound 26.** TLC Rf = 0.15 (20% EtOAc/Heaxnes).
\([\alpha]_D^{35} = +6.2 (c 1, CHCl_3).\) IR (KBr): 2890, 2856, 1798, 1734, 1640, 1529, 1109, 708 cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta 4.06 (d, J = 5.6 Hz, 2H), 3.60-3.54 (m, 2H), 2.04 (s, 3H), 1.78-1.64 (m, 1H), 1.42-1.24 (m, 2H), 0.98-0.88 (m, 12H), 0.03 (s, 6H).\) \(^{13}\)C NMR
(75 MHz, CDCl\(_3\)): \(\delta 171.2, 64.5, 62.3, 41.8, 25.8, 20.9, 20.7, 18.3, 11.4, -5.5.\) MS (ESI) 283 [M+Na]\(^+\). HRMS (ESI) \(m/z\) calcd for C\(_{13}\)H\(_{28}\)O\(_3\)NaSi 283.1705; found 283.1712.

**Compound 25.** \([\alpha]_D^{35} = -3.9 (c 1, CHCl_3),\) all other physical characteristics were identical
to compound 24.

**Compound epi-25.** To a solution of acetate 26 (3.1 g, 12 mmol) in MeOH (24 mL) was
added K\(_2\)CO\(_3\) (163 mg, 1.2 mmol). The reaction mixture was stirred for 2 h at rt. The
mixture was filtered through a pad of Celite and the filtrate concentrated in \textit{vacuo}. The
product was purified by column chromatography using hexanes/EtOAc (95:5, v/v) as the
eluent to afford alcohol \textit{epi}-25 (2.4 g, 11 mmol) in 92% yield. \([\alpha]_D^{37} = +4.4 (c 1, CHCl_3),\)
all other physical characteristics were identical to compound 25.

**Alcohol epi 33 by resolution.** Obtained by an identical route as detailed for racemic
alcohol 24. Yield 41%. TLC Rf = 0.24 (20% EtOAc/Hexanes). \([\alpha]_D^{37} = -5.3 (c 1.5,\)
CHCl\(_3\)). IR (KBr): 3420, 2959, 2931, 2858, 1467, 1109, 703 cm\(^{-1}\). \(^1\)H NMR (500 MHz,
CDCl\(_3\)): \(\delta 7.80-7.64 (m, 4H), 7.44-7.32 (m, 6H), 3.76 (dd, J = 11.0, 4.0 Hz, 1H), 3.35\)
(dd, J = 10.0, 4.0 Hz, 1H), 3.67-3.61 (m, 2H), 1.68-1.62 (m, 1H), 1.38-1.24 (m, 2H), 1.08\)
(s, 9H), 0.75 (t, J = 7.0 Hz, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta 135.5, 134.8, 129.8,\)
127.7, 67.2, 65.9, 43.8, 26.8, 20.5, 19.1, 11.7. MS (ESI) 365 [M+Na]+. HRMS (ESI) \textit{m/z} calcd for C_{21}H_{30}O_{2}NaSi 365.19073; found 365.19115.

\textit{Acetate via resolution.} Yield 43\%. TLC \textit{R}_{f} = 0.32 (20\% EtOAc/Hexanes). [\alpha ]_{D}^{37} = +2.9 (c 1.3, CHCl_{3}). IR (KBr): 2959, 2932, 1741, 1240, 1110, 703 cm\textsuperscript{-1}.\textsuperscript{1}H NMR (300 MHz, CDCl_{3}): \delta 7.74-7.62 (m, 4H), 7.48-7.32 (m, 6H), 4.18-4.09 (m, 2H), 3.72-3.58 (m, 2H), 1.98 (s, 3H), 1.80-1.68 (m, 1H), 1.48-1.30 (m, 2H), 1.03 (s, 9H), 0.87 (t, \textit{J} = 7.6 Hz, 3H).\textsuperscript{13}C NMR (75 MHz, CDCl_{3}): \delta 170.9, 135.5, 133.5, 129.5, 127.5, 64.3, 62.8, 41.8, 26.7, 26.5, 20.7, 19.2, 11.3. MS (ESI) 407 [M+Na]+. HRMS (ESI) \textit{m/z} calcd for C_{23}H_{33}O_{3}Si 385.21935; found 385.21866.

\textit{Compound 33.} Prepared by K\textsubscript{2}CO\textsubscript{3} catalyzed hydrolysis as described for compound 26. Yield 90\%. [\alpha ]_{D}^{37} = +5.1 (c 1.2, CHCl_{3}). The IR, NMR data were identical to that of \textit{epi}\textsuperscript{-33}. 
$^1$H NMR spectrum of Compound 11
$^{13}$C NMR spectrum of Compound 11

![C NMR spectrum of Compound 11](image)
$^1$H NMR spectrum of Compound 9
$^{13}$C NMR spectrum of Compound 9
$^1$H NMR spectrum of Compound 8
$^1$H NMR spectrum of Compound 12
$^{13}$C NMR spectrum of Compound 12
HPLC of Racemic compound 12
HPLC of compound 12
### Injection Summary Report

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$^1$H NMR spectrum of Compound 13
$^{13}$C NMR spectrum of Compound 13
$^1$H NMR spectrum of Compound 14
$^{13}$C NMR spectrum of Compound 14
$^1$H NMR spectrum of Compound 15
$^{13}$C NMR spectrum of Compound 15
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Compound 18
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$^1$H NMR spectrum of Acetate of Compound 33

HPLC of Racemic compound of Acetate of 33
HPLC of Acetate of compound 33
HPLC of Acetate of compound epi-33
$^{13}$C NMR spectrum of Acetate of Compound 33
$^1$H NMR spectrum of Compound 34
\(^{13}\text{C} \text{ NMR spectrum of Compound 34}\)
$^1$H NMR spectrum of Compound 35
$^{13}$C NMR spectrum of Compound 35
$^1$H NMR spectrum of Compound 36

![H NMR spectrum of Compound 36](image-url)
$^{13}$C NMR spectrum of Compound 36
$^1$H NMR spectrum of
Compound 31
$^{13}$C NMR spectrum of Compound 31
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$^{13}$C NMR spectrum of Compound 37
$^1\text{H} \text{ NMR spectrum of Compound 38}$
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Compound 41
$^{13}$C NMR spectrum of
Compound 41
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Compound 44
NOE for Compound 44
\( ^{13}\text{C} \) NMR spectrum of Compound 44
$^1$H NMR spectrum of Compound 45
NOE for Compound 45

[Chemical structure diagram of Compound 45]

Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry
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$^{13}$C NMR spectrum of Compound 45