Supporting Information

Synthesis, X-ray Analysis, and Biological Evaluation of a New Class of Stereopure Lactam Based HIV-1 Protease Inhibitors

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1 EXPERIMENTAL SECTION

1.1 General Information

Analytical thin layer chromatography was performed using Merck aluminum sheets precoated with silica gel 60 F_{254}. Column chromatography was performed on Merck silica gel 60 (40-63 μm). The microwave reactions were performed in a Biotage Initiator producing controlled irradiation at 2450 MHz with a power of 0–300 W. Reaction temperatures were determined using the built-in on-line IR-sensor. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury Plus instruments; ^{1}H at 399.9 MHz and ^{13}C at 100.6 MHz at 25 °C. Chemical shifts for ^{1}H and ^{13}C were referenced to $CHCl_3$ and $CDCl_3$ for those samples with neat $CDCl_3$ as solvent, respectively. For those samples with CD_3OD as solvent chemical shifts were referenced to CD_2HOD (^{1}H) or CD_3OD (^{13}C). Analytical RPHPLC-MS was performed on a Gilson HPLC system with a Finnigan AQA quadropole low-resolution mass spectrometer in positive or negative ESI mode using a Onyx Monolithic C18 4.6 x 50mm 5μm (Phenomenex) or ACT C4 4.6 x 50mm, 5μm column with MeCN in 0.05% aqueous HCOOH as mobile phase at a flow rate of 4 mL/min. Preparative RPLC-MS was performed on a Gilson HPLC system using a Zorbax SB-C8, 5 μm 21.2 × 150 mm (Agilent technologies) column, with MeCN in 0.05% aqueous HCOOH as mobile phase at a flow rate of 10-15 mL/min or with MeCN in 0.1% aqueous TFA as mobile phase at a flow rate of 5 mL/min. Analytical GC-MS was performed on a Varian Saturn 2100T equipped with a CP-Sil 8 CB Low Bleed (30 m x 0.25 mm, 0.25 μm) or with a CP-Sil 5 CB Low Bleed (30 m x 0.25 mm, 0.25 μm) using a 40–300 °C temperature gradient and EI ionization. Exact molecular masses were determined on Micromass Q-Tof2 mass spectrometer equipped with an electrospray ion source. Optical rotations were obtained on a Perkin-Elmer 241 polarimeter, specific rotations ($[\alpha]_D$) are reported in deg/dm and the concentration (*c*) is given in g/100 mL in the specified solvent. Analytische Laboratorien, Lindlar, Germany performed elemental analyses. All protease inhibitors were >95% pure according to ^{1}H NMR, LC-UV (254 nm and 214 or 220 nm), and LC-MS (TIC).

1.1.1 Abbreviatins

DMPU	1,3-dimethyltetrahydropyrimidin-2(1H)-one
LDA	Lithiumdiisopropylamide
DCM	Dichloromethane
DME	1,2-Dimethoxyethane
MeCN	Acetonitrile
$[bmim]BF_4$	The ionic liquid 1-butyl-3methylimidazolium tetrafluoroborate
NMM	N-methylmorpholine
EDCI	*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride
TBAHS	tetrabutylammonium hydrogen sulfate

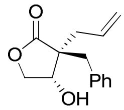
1.1.2 Chemicals

All starting materials and reagents were commercially available and used as received.
Compounds **5b**[1] and **11**[2] were synthesized and characterized as previously preported.

1.2 Chemistry

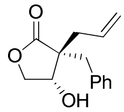
1.2.1 General Procedure A: Dialkylation to Form 2a–d

To a solution of Lactone **1a** or **1b** and DMPU (2.5 equiv) in anhydrous THF was added LDA (2.05 equiv) at approximately -50 °C, then 1.05 equiv allyl bromide for **2a** and **2c** (or benzyl bromide for **2b** and **2d**) was added to the mixture after 5 min at approximately -50 °C. The solution was stirred at approximately -40 °C for 1 h. Then another 1.2 equiv LDA was added to the mixture at approximately -40 °C. After 5 minutes 1.1 equiv benzyl bromide for **2a** and **2c** (or allyl bromide for **2b** and **2d**) was added at approximately -40 °C and stirred at approximately -40 °C to -30 °C for 1 h. The temperature was allowed to slowly increase up to -20 °C. The solution was quenched with aqueous NH_4Cl and extracted with ethyl acetate. The organic layer was dried with $MgSO_4$, concentrated and the crude product was purified by silica flash chromatography using 20–35% ethyl acetate in petroleum ether as eluent to give **2a–d** in 2–49% isolated yields.



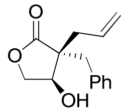
(3*S*,4*S*)-3-Allyl-3-benzyl-4-hydroxydihydrofuran-2(3H)-one (2a)

Compound **2a** was prepared according to general procedure A, using lactone **1a** (5.00 g, 48.97 mmol), dry DMPU (15.69 g, 122.4 mmol), 100 mL dry THF, LDA (51.4 mL, 2M in hexanes), allyl bromide (6.223 g, 51.43 mmol) and followed by a second addition of 29.4 mL LDA and benzyl bromide (9.212 g, 53.87 mmol). The temperature was kept at -50 °C throughout the reaction and a mechanic stirrer was used. The crude product was purified by gradient dry column vacuum chromatography using 10–90% ethyl acetate in isohexane as eluent to give 5.62 g **2a** in 49% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35–7.23 (m, 3H), 7.21–7.16 (m, 2H), 6.0 (ddt, *J* = 7.4, 10.1, 17.5 Hz, 1H), 5.24–5.15 (m, 2H), 4.38 (ddd, *J* = 1.6, 4.7, 10.9 Hz, 1H), 3.82 (dd, *J* = 4.7, 9.7 Hz, 1H), 3.69 (dd, *J* = 6.2, 9.7 Hz, 1H), 2.96 (d, *J* = 13.7 Hz, 1H), 2.81 (d, *J* = 13.7 Hz, 1H), 2.52–2.40 (m, 2H), 2.19 (d, *J* = 5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.0, 135.8, 133.2, 129.8, 128.7, 127.3, 119.7, 72.2, 71.7, 51.5, 40.3, 35.8; ESI-MS: m/z 233 $[M+H]^+$, 465 $[2\times M+H]^+$; $[\alpha]_{589}^{26}$ = -1.0° (c, 1.05, $CHCl_3$); Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94; Found: C, 72.11; H, 6.83.



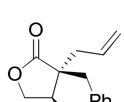
(3*R*,4*S*)-3-Allyl-3-benzyl-4-hydroxydihydrofuran-2(3H)-one (2b)

Compound **2b** was prepared according to general procedure A, using lactone **1a** (1.021 g, 10.00 mmol), DMPU (3.205 g, 25.00 mmol), 50 mL dry THF, 11.4 mL LDA (11.4 mL, 1.8 M in THF), benzyl bromide (1.796 g, 10.50 mmol) and followed by a second addition of 6.67 mL LDA (1.8 M in THF) and allyl bromide (1.331 g, 11.00 mmol). The crude product was purified by silica flash chromatography using 20–35% ethyl acetate in petroleum ether as eluent to give 0.035 g **2b** in about 2% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34–7.20 (m, 5H), 5.83–5.70 (m, 1H), 5.18–5.08 (m, 2H), 4.43–4.36 (m, 1H), 4.26 (dd, *J* = 6.4, 9.6 Hz, 1H), 3.67-3.60 (m, 1H), 3.08–2.96 (m, 2H) 2.38–2.24 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.8, 136.4, 132.5, 130.7, 128.6, 127.1, 120.1, 72.8, 71.5, 51.8, 39.0, 36.2; ESI-MS: m/z 233$[M+H]^+$, 465 $[2\times M+H]^+$.



(3*R*,4*R*)-3-Allyl-3-benzyl-4-hydroxydihydrofuran-2(3H)-one (2c)

Compound **2c** was prepared according to general procedure A, using lactone **1b** (2.042 g, 20.00 mmol), DMPU (6.410 g, 50.00 mmol), 100 mL dry THF, LDA (22.8 mL, 1.8M in THF), allyl bromide (2.541 g, 21.00 mmol) and followed by a second addition of 13.3 mL LDA (1.8 M in THF) and benzyl bromide (3.762 g, 22.00 mmol). The crude product was purified by silica flash chromatography using 20–35% ethyl acetate in petroleum ether as eluent to give 1.532 g **2c** in 33% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36–7.24 (m, 3H), 7.22–7.16 (m, 2H), 6.08–5.94 (m, 1H), 5.32–5.22 (m, 2H), 4.50–4.42 (m, 1H), 3.91 (dd, *J* = 4.8, 9.6 Hz, 1H), 3.75 (dd, *J* = 6.0, 9.6 Hz, 1H), 3.04 (d, *J* = 13.6 Hz, 1H), 2.88 (d, *J* = 13.6 Hz, 1H), 2.64–2.48 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.0, 136.0, 133.5, 130.0, 128.9, 127.6, 120.0, 72.7, 71.7, 51.7, 40.6, 36.0; ESI-MS: m/z 233 $[M+H]^+$, 465 $[2\times M+H]^+$; $[\alpha]_{589}^{26}$ = +1.7° (c, 1.01, $CHCl_3$); Anal. Calcd for $C_{14}H_{16}O_3 \times 1/5\ H_2O$: C, 71.28; H, 7.01; Found: C, 71.48; H, 6.90.

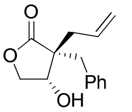


(3*S*,4*R*)-3-Allyl-3-benzyl-4-hydroxydihydrofuran-2(3H)-one (2d)

Compound **2d** was prepared according to general procedure A, using lactone **1b** (1.021 g, 10.00 mmol), DMPU (3.205 g, 25.00 mmol), 50 mL dry THF, LDA (11.4 mL, 1.8M in THF), benzyl bromide (1.796 g, 10.50 mmol) and followed by a second addition of 6.67 mL LDA (1.8 M in THF) and allyl bromide (1.331 g, 11.00 mmol). The crude product was purified by silica flash chromatography using 20–35% ethyl acetate in petroleum ether as eluent to give 0.1154 g **2d** in 5% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40–7.15 (m, 5H), 5.85–5.75 (m, 1H), 5.25–5.10 (m, 2H), 4.50–4.36 (m, 1H), 4.29 (dd, *J* = 6.4, 9.6 Hz, 1H), 3.75–3.65 (m, 1H), 3.15–3.00 (m, 2H), 2.45-2.24 (m, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 178.9, 136.4, 132.5, 130.7, 128.5, 127.1, 120.1, 72.7, 71.5, 51.8, 39.0, 36.2; ESI-MS: m/z 233 [M+H]$^+$, 465 [2×M+H]$^+$.

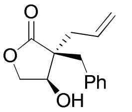
1.2.2 General procedure B: alternative route to 2b and 2d

The dialkylated **2a** or **2c** (1.0 equiv.) was oxidized to the corresponding ketone using Dess-Martin reagens (1.1 equiv) in DCM at room temperature for 1 h. The reaction mixture was extracted twice with water/DCM. The organic layers were combined and concentrated under reduce pressure. Then 30 mL THF was added to the crude followed by NaBH$_4$ (1.5 equiv.) and 0.3 mL methanol. The reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with NH$_4$Cl and extracted with DCM (3 × 30 mL). The organic layers were combined, dried with MgSO$_4$ and concentrated under reduced pressure. The crude product was purified by silica flash chromatography using ethyl acetate in petroleum ether as eluent to give **2d:2a** (5.9:1) and **2b:2c** (5.7:1) in 92% and 85% isolated yield respectively.



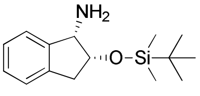
(3*R*,4*S*)-3-Allyl-3-benzyl-4-hydroxydihydrofuran-2(3H)-one (2b)

Compound **2b** was prepared according to general procedure B, using **2c** (2.152 mmol, 0.500 g), Dess-Martin reagent (2.367 mmol, 1.004 g) in DCM (40 mL). The reduction was performed using the crude ketone, NaBH$_4$ (3.228 mmol, 0.122 g) in THF (30 mL) and MeOH (0.3 mL). The crude product was purified by silica flash chromatography using 20–40% ethyl acetate in petroleum ether as eluent to give 0.360 g **2b** and 0.063 g **2c** in a 5.7:1 ratio and in 85% isolated yield (**2b**+**2c**).



(3*S*,4*R*)-3-Allyl-3-benzyl-4-hydroxydihydrofuran-2(3H)-one (2d)

Compound **2d** was prepared according to general procedure B, using **2a** (3.33 mmol, 0.7731 g), Dess-Martin reagent (3.66 mmol, 1.553 g) in DCM (35 mL). The reduction was performed using the crude ketone, NaBH$_4$ (5.000 mmol, 0.189 g) in THF (30 mL) and MeOH (0.3 mL). The crude product was purified by silica flash chromatography using 25–35% ethyl acetate in petroleum ether as eluent to give 0.608 g **2d** and 0.103 g **2a** in a 5.9:1 ratio and in a 92% isolated yield (**2d**+**2a**).



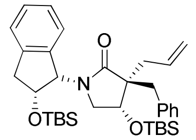
(1*S*,2*R*)-2-((*tert*-Butyldimethylsilyl)oxy)-2,3-dihydro-1H-inden-1-amine (3)

To a stirred solution of 1-amino-2-indanol (4.228 g, 28.34 mmol) in dry DCM (100 mL) under N$_2$ (g) atmosphere at 0 °C, triethylamine (11.8 mL, 85.03 mmol) was added drop-wise, subsequently followed by the drop-wise addition of TBSOTf (9.8 mL, 42.51 mmol) under vigorous stirring. The reaction was allowed to reach room temperature and was stirred for 3 h. The reaction was quenched with NH$_4$Cl, diluted with 100 mL DCM and washed with 2 x 100 mL NH$_4$Cl (aq. sat.). The organic phase was dried over MgSO$_4$ (s), concentrated and the remaining crude was purified by gradient dry column vacuum chromatography (*iso*-hexane:EtOAc:Et$_3$N 3:1.9:0.1) to give 5.8 g of **3** in 78% isolated yield as a transparent oil. ^{1}H NMR (CDCl$_3$, 400 MHz) δ7.42–7.37 (m, 1H), 7.24–7.17 (m, 3H), 4.44 (ddd, *J* = 4.9, 5.3, 5.9 Hz, 1H), 4.1 (dd, *J* = 0.7, 5.3 Hz, 1H), 3.01 (dd, *J* = 5.9, 15.8 Hz, 1H), 2.88 (dd, *J* = 4.9, 15.8 Hz, 1H), 1.77 (bs, 2H), 0.90 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ144.2, 140.2, 127.6, 126.7, 124.9, 124.7, 75.2, 59.5, 39.2, 25.8, 18.2, -4.8, -4.6; ESI-MS: m/z 263[M+H]$^+$.

1.2.3 General procedure C: Formation of Compounds 4a–d

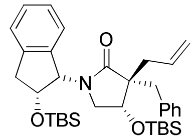
A 0.2–0.5 mL process vial was charged with **2a–d**, 1.9–2.4 equiv **3** and 1.0 equiv [bmim]BF$_4$ and irradiated under microwave irradiation at 180 °C for 35 min. The reaction mixture was then dissolved in ~30 mL DCM and washed with 10 mL water and 10 mL aqueous NH$_4$Cl solution. The organic fraction was dried with MgSO$_4$ and concentrated under reduced pressure. Next, the reaction mixture was dissolved in 20–30 mL dry DCM and 8.0

equiv triethylamine was added. After 5–10 min 4.0 equiv TBSOTf was added to the solution at ~0 °C. The solution was stirred at room temperature overnight. If full conversion was not achieved, the solution was concentrated again and extracted with DCM/water or diethyl ether/water, more triethylamine was added followed by TBSOTf until full conversion was achieved. Then the reaction mixture was extracted with DCM/water and dried with $MgSO_4$. The crude product was purified by silica flash chromatography using 5–25% ethyl acetate in petroleum ether or 0–4% methanol in DCM as eluent to give to give 50–72% isolated yields of **4a–d**.



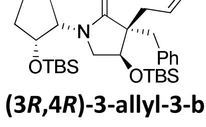
(3*S*,4*S*)-3-Allyl-3-benzyl-4-((*tert*-butyldimethylsilyl)oxy)-1-((1*S*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)-2,3-dihydro-1H-inden-1-yl)pyrrolidin-2-one (4a)

Compound **4a** was prepared according to general procedure C, using **2a** (0.2604 g, 1.121 mmol), **3** (0.5705 g 2.165 mmol), [bmim]BF_4 (0.2534 g, 1.121 mmol), triethylamine (2.722 g, 26.90 mmol) and TBSOTf (2.666 g, 10.09 mmol). The crude product was purified by silica flash chromatography using 0–4% methanol in DCM as eluent to give 0.4262 g of **4a** in 64% isolated yield. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.46–7.32 (m, 9H), 6.26–6.14 (dddd, *J* = 6.8, 8.0, 10.6, 17.0 Hz, 1H), 5.82 (d, *J* = 6.8 Hz, 1H), 5.34 (dd, *J* = 2.3, 17.0 Hz, 1H), 5.25 (dd, *J* = 2.3, 10.1 Hz, 1H), 4.8 (dt, *J* = 5.4, 6.8 Hz, 1H), 4.47 (t, *J* = 7.5 Hz, 1H), 3.71 (dd, *J* = 7.6, 8.9 Hz, 1H), 3.31 (d, *J* = 13.6 Hz, 1H), 3.29 (dd, *J* = 6.8, 16.1 Hz, 1H), 3.04 (dd, *J* = 5.4, 16.1 Hz, 1H), 2.96 (dd, *J* = 7.5, 8.9 Hz, 1H), 2.88, (d, *J* = 13.6 Hz, 1H), 2.60 (ddt, *J* = 1.2, 6.7, 13.8 Hz, 1H), 2.53 (ddt, *J* = 1.2, 8.0, 13.8 Hz, 1H), 1.00 (s, 9H), 0.94 (s, 9H), 0.20 (s, 3H), 0.16 (s, 3H), 0.05 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 175.6, 140.2, 138.6, 137.6, 134.8, 130.7, 128.2, 127.0, 126.4, 125.6, 124.8, 118.0, 73.4, 69.8, 57.2, 52.7, 50.0, 41.2, 40.1, 37.2, 25.7, 25.6, 17.8, 17.7, -4.1, -4.8, -5.1, -5.2; ESI-MS: m/z 592 $[M+H]^+$; $[\alpha]^{22}_{589}$ = +34.0° (c, 1.09, $CHCl_3$) Anal. Calcd for $C_{35}H_{53}N1O_3Si_2 \times H_2O$: C, 68.91; H, 9.09; N, 2.30; Found: C, 68.69; H, 9.37; N, 2.21.



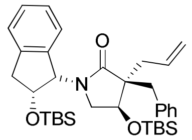
(3*R*,4*S*)-3-Allyl-3-benzyl-4-((*tert*-butyldimethylsilyl)oxy)-1-((1*S*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)-2,3-dihydro-1H-inden-1-yl)pyrrolidin-2-one (4b)

Compound **4b** was prepared according to general procedure C, using **2b** (0.0500 g, 0.2152 mmol), **3** (0.1134 g 0.4304 mmol), [bmim]BF_4 (0.0520 g, 0.2301 mmol), triethylamine (0.1743 g, 1.722 mmol), TBSOTf (0.2275 g, 0.8608 mmol) and 0.12 mL dioxane as solvent. The crude product was purified by silica flash chromatography using 0–4% methanol in DCM as eluent to give 0.067 g **4b** in 53% isolated yield. ^1H NMR ($CDCl_3$, 400 MHz) *δ* 7.46–7.38 (m, 2H), 7.30–7.10 (m, 6H), 7.00–6.94 (m, 1H), 5.94–5.80 (m, 2H), 5.45 (d, *J* = 6.4 Hz, 1H), 5.18–5.08 (m, 2H), 4.68–4.60 (m, 1H), 4.45 (t, *J* = 8.4 Hz, 1H), 3.22 (t, *J* = 8.4 Hz, 1H), 3.12 (d, *J* = 13.2 Hz, 1H), 3.05 (dd, *J* = 16.4, 6.0 Hz, 1H), 2.81 (dd, *J* = 16.4, 3.2 Hz, 1H), 2.73 (d, *J* = 13.2 Hz, 1H), 2.60–2.50 (m, 2H), 2.37 (dd, *J* = 14.0, 8.8 Hz, 1H), 0.96(s, 9H), 0.86 (s, 9H), -0.11(s, 3H), -0.09(s, 3H), -0.06 (s, 3H), -0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 175.3, 140.3, 138.5, 138.1, 135.1, 131.7, 128.2, 128.0, 126.7, 126.5, 125.8, 125.0, 118.5, 74.5, 71.5, 57.8, 53.1, 50.7, 41.7, 41.6, 38.6, 26.2, 26.1, 18.33, 18.26, -4.7, -4.5, -4.1, -4.0; ESI-MS: m/z 592 $[M+H]^+$; $[\alpha]^{24}_{589}$ = +30.0° (c, 2.02, $CHCl_3$); Anal. Calcd for $C_{35}H_{53}N_1O_3Si_2$: C, 71.01; H, 9.02; N, 2.37; Found: C, 70.68; H, 9.14; N, 2.18.



(3*R*,4*R*)-3-allyl-3-benzyl-4-((*tert*-butyldimethylsilyl)oxy)-1-((1*S*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)-2,3-dihydro-1H-inden-1-yl)pyrrolidin-2-one (4c)

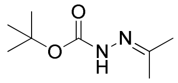
Compound **4c** was prepared following general procedure C, using **2c** (0.1000 g, 0.4304 mmol), **3** (0.2268 mg 0.8608 mmol), [bmim]BF_4 (0.1070 g, 0.4734 mmol), triethylamine (1.045 g, 10.32 mmol), TBSOTf (2.274 g, 8.604 mmol), 2,6-Lutidine (0.7360 g, 6.869 mmol) and 0.10 mL dioxane as solvent were used. The crude product was purified by silica flash chromatography using 5–20% ethyl acetate in petroleum ether as eluent to give 0.1835 g of **4c** in 72% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30–7.14 (m, 8H), 7.08–7.02 (m, 1H), 6.45 (d, *J* = 7.6 Hz, 1H), 6.18–6.06 (m, 1H), 5.63 (d, *J* = 6.4 Hz, 1H), 5.20–5.10 (m, 2H), 4.72–4.64 (m, 1H), 4.06 (t, *J* = 7.6 Hz, 1H), 3.33 (d, *J* = 13.6 Hz, 1H), 3.17(dd, *J* = 9.6, 7.2 Hz, 1H), 3.07 (dd, *J* = 16.4, 6.4 Hz, 1H), 2.84–2.74 (m, 2H), 2.56–2.40 (m, 3H), 0.88 (s, 9H), 0.87 (s, 9H), -0.14 (s, 3H), 0.12 (s, 3H), 0.09 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.6, 140.6, 138.6, 138.4, 135.1, 130.7, 128.3, 128.2, 127.1, 126.5, 125.0, 124.5, 117.7, 74.5, 69.4, 57.9, 53.0, 50.4, 41.2, 39.9, 37.7, 26.1, 25.8, 18.3, 18.0, -4.9, -4.6, -4.3, -4.2; ESI-MS: m/z 592 $[M+H]^+$; $[\alpha]_{589}^{25}$ = +3.9° (c, 1.61, $CHCl_3$); Anal. Calcd for $C_{35}H_{53}N_1O_3Si_2$: C, 71.01; H, 9.02; N, 2.37; Found: C, 70.83; H, 8.91; N, 2.22.



(3*S*,4*R*)-3-Allyl-3-benzyl-4-((*tert*-butyldimethylsilyl)oxy)-1-((1*S*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)-2,3-dihydro-1H-inden-1-yl)pyrrolidin-2-one (4d)

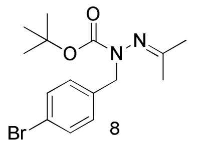
Compound **4d** was prepared following general procedure C, using **2d** (0.1154 g, 0.497 mmol), **3** (0.3100 g, 1.177 mmol), [bmim]BF_4 (0.1050 g, 0.4646 mmol), triethylamine (1.405 g, 13.89 mmol), TBSOTf (1.835 g, 6.943 mmol) and 0.10 mL dioxane as solvent. The crude product was purified by silica flash chromatography using 10–25% ethyl acetate in petroleum ether as eluent. **4d** as well as monoprotected product were isolated. The monoprotected analogue of **4d** was treated with more triethylamine (0.0874 mL, 0.6270 mmol) and TBSOTf (0.0553 g, 0.2093 mmol) and was stirred at room temperature overnight and purified once more by silica flash chromatography using 10–25% ethyl acetate in petroleum ether as eluent. All together 0.150 g **4d** was produced in 50% isolated yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35–7.20 (m, 8H), 7.05–7.00 (m, 1H), 5.80–5.65 (m, 2H), 5.20–5.08 (m, 2H), 4.80–4.70 (m, 1H), 4.33 (dd, *J* = 7.6, 8.4 Hz, 1H), 3.33 (dd, *J* = 8.4, 9.6 Hz, 1H), 3.20–3.08 (m, 2H), 3.04–2.88 (m, 3H), 2.52–2.44 (m, 1H), 2.10 (dd, *J* = 8.8, 14.0 Hz, 1H), 0.93 (s, 9H), 0.89 (s, 9H), 0.17 (s, 3H), 0.12 (s, 3H), 0.09 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.6, 140.7, 139.0, 137.6, 135.1, 131.3, 128.2, 127.8, 127.2, 126.4, 125.3, 124.2, 118.6, 75.1, 70.9, 58.2, 51.5, 50.1, 41.2, 37.7, 37.0, 26.1, 25.9, 18.3, 18.1, -4.1, -4.2, -4.5, -4.6; ESI-MS: m/z 592 $[M+H]^+$; $[\alpha]_{589}^{24}$ = -10.2° (c, 1.83, $CHCl_3$); Anal. Calcd for $C_{35}H_{53}N_1O_3Si_2$: C, 71.01; H, 9.02; N, 2.37; Found: C, 70.82; H, 9.11; N, 2.24.

1.2.4 Synthesis of the prime side scaffold



***tert*-Butyl 2-(propan-2-ylidene)hydrazinecarboxylate (7)**

To a solution of **6** (5.00 g, 37.8 mmol) in acetone (40 mL) were added $MgSO_4$ (1.00 g, 8.31 mmol) and AcOH (0.20 mL). The resulting mixture was refluxed at 56 °C for 1 h under nitrogen atmosphere and then cooled to 25 °C. The resulting white suspension was filtered off to remove $MgSO_4$. The filter cake was washed with acetone (1 × 10 mL). The combined filtrates were concentrated under vacuum. The obtained residue was triturated with *iso*-hexane (2 × 10 mL) and dried under vacuum to give 6.41 g of **7** as white crystals in 98% yield. The compound was used in the next step without any additional purification. Mp: 86–87 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (br s, 1H), 2.04–2.01 (m, 3H), 1.81–1.79 (m, 3H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.1, 150.3, 81.2, 28.6, 28.4, 28.2, 25.6, 16.2. ESI-MS: m/z 173 $[M+H]^+$, 345 $[2\times M+H]^+$.



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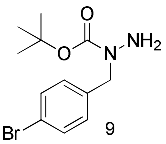
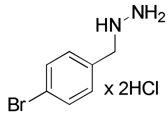


9

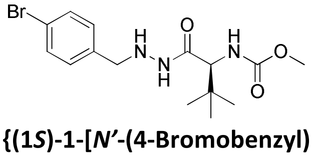
***tert*-Butyl 1-(4-bromobenzyl)-2-(propan-2-ylidene)hydrazinecarboxylate (8) and *tert*-butyl 1-(4-bromobenzyl)hydrazinecarboxylate (9)**

To a solution of **7** (6.41 g, 37.2 mmol) in anhydrous toluene (100 mL) were added thoroughly crushed KOH (3.13 g, 55.8 mmol) and TBAHS (1.26 g, 3.72 mmol). The reaction mixture was stirred at 50 °C for 20 min under nitrogen atmosphere after which 4-bromobenzyl bromide (11.15 g, 44.64 mmol) was added. The resulting mixture was stirred at 100 °C for 3 h. The reaction mixture was gradually cooled to 25 °C after which water (50 mL) was added and the product was partitioned between the aqueous and organic layers. The aqueous layer was washed with ethyl acetate (3 × 20 mL) and the combined organic layers were washed with brine (3 × 20 mL), dried over sodium sulfate and concentrated under reduced pressure to yield crude **8** as a golden yellow oil. ESI-MS: m/z 341 [M+H]$^+$, 343 [M+2+H]$^+$, 681 [2×M+H]$^+$, 683 [2×M+2+H]$^+$, 685 [2×M+4+H]$^+$. The crude product was purified by silica flash chromatography using 5–30% ethyl acetate in *iso*-hexane as eluent to give 10.3 g of a mixture of **8** and **9** as pale yellow oil in a 1:1 ratio according to NMR. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48–7.39 (m, 4H), 7.20–7.15 (m, 4H) 4.62 (s, 2H), 4.50 (s, 2H), 2.03 (s, 3H), 1.73 (s, 3H), 1.48 (s, 9H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.7, 156.9, 137.4, 137.2, 131.8, 131.6, 130.3, 129.8, 121.4, 121.2, 81.2, 81.0, 54.1, 53.5, 28.61, 28.55, 24.9, 20.1; ESI-MS: m/z 341 [M+H]$^+$, 343 [M+2+H]$^+$, 681 [2×M+H]$^+$, 683 [2×M+2+H]$^+$, 685 [2×M+4+H]$^+$ for **8**, *m/z* 301 [M+H]$^+$, 303 [M+2+H]$^+$, 601 [2×M+H]$^+$, 603 [2×M+2+H]$^+$, 605 [2×M+4+H]$^+$ for **9**.



(4-Bromobenzyl)hydrazine dihydrochloride (10)

To a solution of conc. HCl (1.07 g, 29.3 mmol) in THF (15 mL) were added a mixture of **8** and **9** (5.00 g) and refluxed at 68 °C for 3 h. The reaction mixture was concentrated under reduced pressure to yield a white slurry. The residue obtained was triturated with *iso*-hexane (2 × 20 mL) and dried under vacuum to yield **10** as white crystals (4.00 g). Mp: 194–195 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.36 (br s, 1H), 7.56 (d, J = 8.4 Hz, 2H,), 7.49–7.36 (m, 2H), 4.00 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6 + 2 drops of $CDCl_3$): δ 135.2, 132.2, 131.9, 130.7, 122.0, 53.4. ESI-MS: m/z 201 [M]$^+$, 203 [M+2]$^+$.



{(1*S*)-1-[*N'*-(4-Bromobenzyl)hydrazinocarbonyl]-2,2-dimethylpropyl}carbamic acid methyl ester (5a)

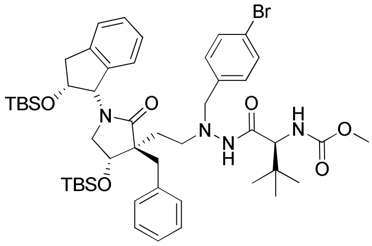
A 250 mL round bottom flask under nitrogen was charged with **10** (3.62 g, 13.2 mmol), **11** (1.79 g, 9.46 mmol), HOBt (1.45 g, 9.46 mmol) and anhydrous DCM (35 mL). The reaction vessel was covered with an aluminum foil, cooled to 0 °C and stirred. To this mixture NMM (4.78 g, 47.3 mmol) was added and the mixture was stirred for 30 min at 0 °C. Thereafter EDCI (2.36 g, 12.3 mmol) was added and the reaction mixture was gradually warmed to 25 °C and stirred for 15 h. Water was added to the reaction mixture and the organic layer was separated. The aqueous phase was washed with DCM (2 × 10 mL) and the combined organic layers were washed with brine (2 × 25 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by silica flash chromatography using 25–55% ethyl acetate in *iso*-hexane as eluent to give 2.70 g of **5a** as off-white crystals in 77% isolated yield. The overall isolated yield of **5a** from **6** was calculated as 61%. Mp: 50–51 °C; ^{1}H NMR (400 MHz, CD_3OD): δ 7.45 (dt, J = 2.3, 8.8 Hz, 2H), 7.29 (dt, J = 2.3, 8.8 Hz, 2H), 3.91 (d, J = 2.7 Hz, 2H), 3.82 (s, 1H), 3.64 (s, 3H), 0.91 (s, 9H); ^{13}C NMR (100 MHz, CD_3OD): δ 171.8, 138.5, 132.6, 132.1, 122.3, 63.0, 55.6, 52.9, 35.3, 27.1; ESI-MS: m/z 372 [M+H]$^+$, 374 [M+2+H]$^+$, 743 [2×M+H]$^+$, 745 [2×M+2+H]$^+$, 747 [2×M+4+H]$^+$; $[\alpha]^{22}_D$ = -26.9 (c = 0.84, MeOH).

1.2.5 General procedure D: Formation of Compounds 12a, 12d and 13a–d

To the solution of **4a**–**d** in THF/H_2O (3:1) was added 0.05 equiv OsO_4, 4.0–8.0 equiv $NaIO_4$ and the reaction mixture was stirred overnight at room temperature. If full conversion was not achieved, more $NaIO_4$ (8 equiv) was added and the reaction mixture was stirred overnight at room temperature. Next, the reaction mixture was diluted with 20 mL ethyl acetate, quenched with 15 mL NaS_2O_3 (aq. sat.) and extracted. The aqueous layer was then extracted two more times with ethyl acetate (2 x 10 mL). The organic layers were combined and dried over $MgSO_4$, concentrated and purified on silica gel with 10–35% ethyl acetate in petroleum ether to give crude aldehyde intermediates **v**–**viii**.

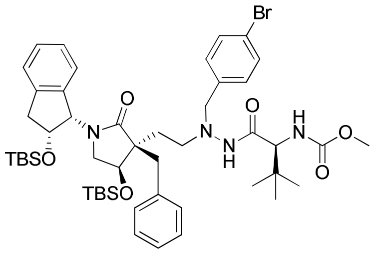
Bromohydrazide **5a** was added to the corresponding aldehyde. Then about 15 mL dry THF was added to the mixture together with 2.0 equiv acetic acid. After 10 min stirring at room temperature 4.0 equiv $Na(OAc)_3BH$ was added. The mixture was stirred overnight at room temperature. The reaction was quenched with NH_4Cl (aq. sat.), extracted with ethyl acetate (3 x 15–20 mL), dried with $MgSO_4$, concentrated and purified on silica gel using 20–45 % ethyl acetate in petroleum ether as eluent to give the crude TBS-protected compound of **13a**–**d** and products **12a** and **12d**.

The crude TBS-protected compound was dissolved in 1.0 mL THF and 10.0 equiv of TBAF was added to the solution which was stirred overnight. The solution was concentrated, 10-15 mL water was added and the mixture was extracted with DCM (3 x 15 mL). The combined organic layers were dried with $MgSO_4$, concentrated under reduced pressure and the crude product was purified by silica flash chromatography using 4–5% methanol in DCM as eluent to give **13a**–**d** in 34–60% isolated yields. Alcohols of **14a** and **14d** were obtained as side products in the syntheses of **13a** and **13d** respectively.



Methyl ((*S*)-1-(2-(2-((3*R*,4*S*)-3-benzyl-4-((*tert*-butyldimethylsilyl)oxy)-1-((1*S*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)-2,3-dihydro-1H-inden-1-yl)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-bromobenzyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (12a)

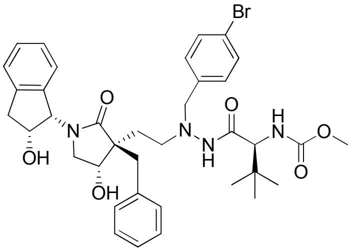
Compound **12a** was prepared following general procedure D (but without the final deprotecting step) using **4a** (0.3180 g, 0.5371 mmol), OsO_4 (0.0135 g, 0.0531 mmol), $NaIO_4$ (1.838 g, 8.5926 mmol) in 15 mL THF:H_2O (3:1). A fast silica gel column was run with 15-35% ethyl acetate in petroleum ether to isolate the aldehyde. Thereafter hydrazide **5a** (0.1535 g, 0.4130 mmol), $Na(OAc)_3BH$ (0.3501 g, 1.652 mmol), acetic acid (0.0496 g, 0.8253 mmol) were added according to general procedure D. The reaction mixture was stirred at room temperature overnight. More $Na(OAc)_3BH$ (0.260 g, 1.227 mmol) was added and the reaction mixture was stirred at room temperature for another 4 h. The reaction was quenched according to general procedure D. Next, the crude product was purified by silica flash chromatography using 20–45 % ethyl acetate in petroleum ether as eluent and thereafter extended purification by silica flash chromatography using 30–35% ethyl acetate in petroleum ether as eluent to give 0.1805 g of **12a** in 35% isolated yield. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, J = 8.0 Hz, 2H), 7.35–7.05 (m, 11H), 6.67 (br s, 1H), 5.58 (d, J = 6.8 Hz, 1H), 4.75–4.60 (m, 1H), 4.25–4.15 (m, 1H), 3.99 (d, J = 13.2 Hz, 1H), 3.82 (d, J = 13.2 Hz, 1H), 3.80–3.60 (m, 5H), 3.15 (dd, J = 16.0, 7.6 Hz, 1H), 3.04 (d, J = 13.6, 1H), 3.00–2.80 (m, 3H), 2.72 (d, J = 13.6 Hz, 1H), 2.65–2.50 (m, 1H), 1.90–1.60 (m, 2H), 0.87 (s, 9H), 0.78 (s, 9H), 0.70 (s, 9H), 0.06 (s, 3H), -0.10 (s, 3H), -0.15 (s, 3H), -0.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.2, 169.4, 157.0, 140.6, 138.9, 137.2, 135.0, 131.54, 131.46, 130.8, 129.1, 128.4, 127.6, 126.8, 125.6, 125.2, 121.7, 72.9, 70.3, 61.7, 61.2, 57.2, 52.6, 52.5, 52.1, 50.2, 41.1, 40.2, 34.4, 29.2, 26.6, 25.9, 25.7, 18.1, 17.9, -4.3, -4.6, -5.0, -5.1; ESI-MS: m/z 949 $[M+H]^+$, 951 $[M+H]^+$; $[\alpha]^{28}_{589}$ = +45.3° (c, 0.10, $CHCl_3$); Anal. Calcd for $C_{49}H_{73}N_4O_6BrSi_2 \times 0.5\ H_2O$: C, 61.35; H, 7.78; N, 5.84; Found: C, 61.14; H, 7.67; N, 5.64.



Methyl ((*S*)-1-(2-(2-((3*R*,4*R*)-3-benzyl-4-((*tert*-butyldimethylsilyl)oxy)-1-((1*S*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)-2,3-dihydro-1H-inden-1-yl)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-bromobenzyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (12d)

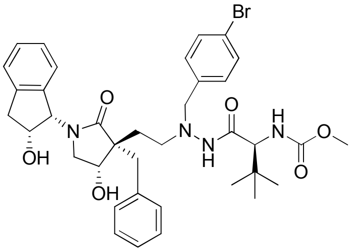
Compound **12d** was prepared following general procedure D (but without the final deprotecting step) using **4d** (0.2640 g, 0.4460 mmol), OsO_4 (0.0056 g, 0.0223 mmol), $NaIO_4$ (0.6816 g, 3.1865 mmol) in 20 mL THF:H_2O (3:1). A fast silica gel column was run with 15–35% ethyl acetate in petroleum ether to isolate the aldehyde. Thereafter hydrazide **5a** (0.0878 g, 0.2360 mmol), $Na(OAc)_3BH$ (0.200 g, 0.9438 mmol), acetic acid (0.0284 g, 0.4725 mmol) were added according to general procedure D. The crude product was purified by silica flash chromatography using 20–45 % ethyl acetate in petroleum ether as eluent to give 0.120 g of **12d** in 54%

isolated yield. ^{1}H NMR (CD$_3$OD, 400 MHz) δ 7.35–7.10 (m, 13H), 5.55 (d, J = 6.0 Hz, 1H), 4.82–4.75 (m, 1H), 4.38 (t, J = 7.6 Hz, 1H), 3.87 (d, J = 12.8 Hz, 1H), 3.75 (d, J = 12.8 Hz, 1H), 3.69 (s, 1H), 3.61 (s, 3H), 3.42–3.35 (m, 1H), 3.25–3.10 (m, 2H), 3.00–2.75 (m, 5H), 1.90–1.65 (m, 2H), 0.90 (s, 9H), 0.87 (s, 9H), 0.76 (s, 9H), 0.18 (s, 3H), 0.12 (s, 3H), 0.05 (s, 3H), -0.02 (s, 3H); ^{13}C NMR (CD$_3$OD, 100 MHz) δ 177.8, 171.3, 158.8, 142.0, 139.4, 138.3, 137.9, 132.2, 132.1, 129.7, 128.8, 128.4, 127.5, 126.3, 125.4, 122.1, 76.1, 73.0, 62.9, 61.0, 59.5, 53.8, 52.8, 52.1, 51.3, 42.0, 37.4, 35.2, 31.0, 26.9, 26.6, 26.3, 19.0, 18.8, -3.9, -4.1, -4.5, -4.6; ESI-MS: m/z 949 [M+H]$^+$, 951 [M+H]$^+$; $[\alpha]^{27}_{589}$ = +28.5° (c, 0.37, CHCl$_3$); Anal. Calcd for C$_{49}$H$_{73}$N$_4$O$_6$BrSi$_2$: C, 61.93; H, 7.74; N, 5.90; Found: C, 61.72; H, 7.82; N, 5.81.



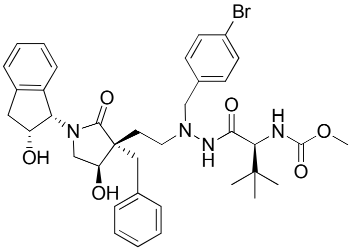
Methyl ((*S*)-1-(2-(2-((3*R*,4*S*)-3-benzyl-4-hydroxy-1-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-bromobenzyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (13a)

Compound **13a** was prepared following general procedure D, using **4a** (0.1000 g, 0.1689 mmol), OsO$_4$ (0.0021 g, 0.0085 mmol), NaIO$_4$ (0.2892 g, 1.352 mmol) in 15 mL THF:H$_2$O (3:1). A fast silica gel column was run with 10–35% ethyl acetate in petroleum ether to isolate the intermediate aldehyde [**v**]. Thereafter hydrazide **5a** (0.0312 g, 0.0839 mmol), Na(OAc)$_3$BH (0.1068 g, 0.5040 mmol) and acetic acid (0.0151 g, 0.2512 mmol) were added according to general procedure D. The crude product was purified by silica flash chromatography using 10–40 % ethyl acetate in petroleum ether as eluent to give the TBS protected compound. Deprotection was performed using TBAF (0.421 mL, 1.8 M in THF) followed by purification by silica flash chromatography using 4–5% methanol in DCM as eluent to give 0.023 g of **13a** in 38% isolated yield. ^{1}H NMR (CD$_3$OD/CDCl$_3$, 400 MHz) δ 7.39 (d, J = 8.8 Hz, 2H), 7.30–7.00 (m, 11H), 5.37 (d, J = 5.6 Hz, 1H), 4.60–4.50 (m, 1H), 3.87 (d, J = 12.4 Hz, 1H), 3.72–3.56 (m, 6H), 3.20–3.20 (m, 2H), 2.94–2.84 (m, 3H), 2.82–2.70 (m, 2H), 2.61 (d, J = 13.6 Hz, 1H), 1.98–1.72 (m, 2H), 0.79 (s, 9H); ^{13}C NMR (CD$_3$OD/CDCl$_3$ 100 MHz) δ 177.9, 170.3, 157.6, 140.9, 137.6, 136.9, 135.4, 131.6, 130.5, 128.6, 128.4, 127.3, 127.0, 125.5, 125.4, 121.9, 73.5, 70.5, 61.8, 61.4, 59.2, 54.3, 52.5, 52.1, 51.5, 40.6, 39.9, 34.3, 28.5, 26.3; ESI-MS: m/z 721 [M+H]$^+$, 723 [M+2+H]$^+$; $[\alpha]^{24}_{589}$ = -49.0° (c, 0.64, CHCl$_3$); Anal. Calcd for C$_{37}$H$_{45}$N$_4$O$_6$Br × 1.5 H$_2$O: C, 59.35; H, 6.46; N, 7.48; Found: C, 59.18; H, 6.14; N, 7.16.



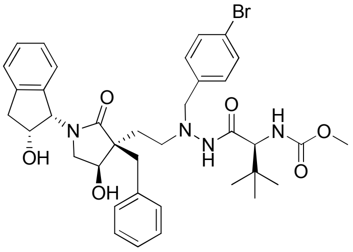
Methyl ((*S*)-1-(2-(2-((3*S*,4*S*)-3-benzyl-4-hydroxy-1-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-bromobenzyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**13b**)

Compound **13b** was prepared following general procedure D, using **4b** (0.1250 g, 0.2111 mmol), OsO$_4$ (0.0026 g, 0.0107 mmol), NaIO$_4$ (0.3615 g, 1.690 mmol) in 15 mL THF:H$_2$O (3:1). A fast silica gel column was run with 10–35% ethyl acetate in petroleum ether to isolate the intermediate aldehyde. Thereafter hydrazide **5a** (0.0266 g, 0.0716 mmol), Na(OAc)$_3$BH (0.0911 g, 0.4299 mmol) and acetic acid (0.0129 g, 0.2150 mmol) were added according to general procedure D. The crude product was purified by silica flash chromatography using 20–40 % ethyl acetate in petroleum ether as eluent to give the TBS protected compound. Deprotection was performed using TBAF (0.543 mL, 1.8 M in THF) followed by purification by silica flash chromatography using 4–5% methanol in DCM as eluent to give 0.023 g of **13b** in 62% isolated yield. ^{1}H NMR (CD$_3$OD, 400 MHz) δ 7.44–7.34 (m, 4H), 7.30–7.14 (m, 7H), 7.08–7.00 (m, 1H), 6.33 (d, J = 7.6 Hz, 1H), 5.32 (d, J = 6.4 Hz, 1H), 4.70–4.55 (m, 2H), 4.15–3.95 (m, 1H), 3.75–3.60 (m, 5H), 3.28–3.05 (m, 3H), 3.05–2.90 (m, 2H), 2.85 (dd, J = 4.0, 16.4 Hz, 1H), 2.75–2.60 (m, 2H), 1.95–1.80 (m, 2H), 0.85 (s, 9H); ^{13}C NMR (CD$_3$OD, 100 MHz) δ 178.7, 172.0, 159.0, 142.1, 139.3, 138.6, 137.2, 132.7, 132.3, 132.2, 129.4, 129.1, 127.7, 127.5, 126.7, 126.2, 122.3, 74.0, 72.0, 63.0, 61.7, 59.9, 55.1, 54.3, 52.9, 51.5, 41.1, 38.0, 34.9, 33.4, 26.9; ESI-MS: m/z 721 $[M+H]^+$, 723 $[M+2+H]^+$; $[\alpha]^{24}_{589}$ = +16.6° (c, 1.53, $CHCl_3$); Anal. Calcd for $C_{37}H_{45}N_4O_6Br$ × 1.3 H_2O: C, 59.64; H, 6.44; N, 7.52; Found: C, 59.43; H, 6.04; N, 7.24.



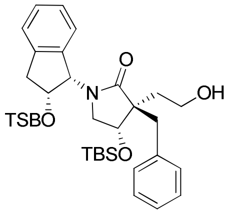
Methyl ((*S*)-1-(2-(2-((3*S*,4*R*)-3-benzyl-4-hydroxy-1-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-bromobenzyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**13c**)

Compound **13c** was prepared following general procedure D, using **4c** (0.1000 g, 0.1690 mmol), OsO_4 (0.0021 g, 0.0085 mmol), $NaIO_4$ (0.4342 g, 2.030 mmol) in 15 mL THF:H_2O (3:1). A fast silica gel column was run with 10-35% ethyl acetate in petroleum ether to isolate the intermediate aldehyde. Thereafter hydrazide **5a** (0.0270 g, 0.0727 mmol), $Na(OAc)_3BH$ (0.1836 g, 0.8664 mmol) and acetic acid (0.0087 g, 0.1450 mmol) were added according to general procedure D. The crude product was purified by silica flash chromatography using 20–40 % ethyl acetate in petroleum ether as eluent to give the TBS protected compound. Deprotection was performed using TBAF (0.421 mL, 1.8 M in THF) followed by purification by silica flash chromatography using 4–5% methanol in DCM as eluent to give 0.024 g of **13c** in 46% isolated yield. ^1H NMR (CD_3OD, 400 MHz) δ 7.40 (d, *J* = 8.4 Hz, 2H), 7.36–7.16 (m, 9H), 7.08–7.00 (m, 1H), 6.48 (d, *J* = 8.0 Hz, 1H), 5.46 (d, *J* = 6.4 Hz, 1H), 4.70–4.60 (m, 1H), 4.09 (t, *J* = 7.6 Hz, 1H), 3.95 (d, *J* = 13.2 Hz, 1H), 3.84 (d, *J* = 13.2 Hz, 1H), 3.73 (s, 1H), 3.65 (s, 3H), 3.25–3.10 (m, 4H), 3.10–2.95 (m, 1H), 2.90–2.80 (m, 2H), 2.65 (d, *J* = 13.2Hz, 1H), 2.05–1.80 (m, 2H), 0.82 (s, 9H); ^{13}C NMR (CD_3OD, 100 MHz) δ 178.3, 171.8, 159.0, 142.4, 138.91, 138.89, 137.2, 132.8, 132.2, 131.6, 129.6, 129.4, 128.0, 127.8, 126.3, 125.8, 122.3, 74.2, 69.6, 63.0, 62.2, 59.8, 54.5, 54.2, 52.8, 51.4, 41.8, 41.0, 34.9, 31.2, 26.9; ESI-MS: m/z 721 $[M+H]^+$, 723 $[M+2+H]^+$; $[\alpha]^{24}_{589}$ = -1.4° (c, 1.09, MeOH); Anal. Calcd for $C_{37}H_{45}N_4O_6Br$ × 1.75 H_2O: C, 59.00; H, 6.49; N, 7.44; Found: C, 59.23; H, 6.09; N, 7.04.



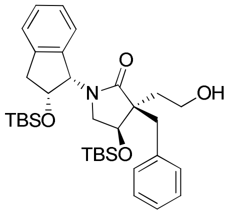
Methyl ((*S*)-1-(2-(2-((3*R*,4*R*)-3-benzyl-4-hydroxy-1-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-bromobenzyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**13d**)

Compound **13d** was prepared following general procedure D, using **4d** (0.1000 g, 0.1690 mmol), OsO_4 (0.0021 g, 0.0085 mmol), $NaIO_4$ (0.4342 g, 2.030 mmol) in 15 mL THF:H_2O (3:1). A fast silica gel column was run with 15–35% ethyl acetate in petroleum ether to isolate the intermediate aldehyde. Thereafter hydrazide **5a** (0.0210 g, 0.0565 mmol), $Na(OAc)_3BH$ (0.1206 g, 0.5691 mmol) and acetic acid (0.0102 g, 0.1697 mmol) were added according to general procedure D. The crude product was purified by silica flash chromatography using 20–40 % ethyl acetate in petroleum ether as eluent to give the TBS protected compound. Deprotection was performed using TBAF (0.320 mL, 1.8 M in THF) followed by purification by silica flash chromatography using 4–5% methanol in DCM as eluent to give 0.014 g **13d** in 34% isolated yield. ^1H NMR (CD_3OD, 400 MHz) δ 7.44–7.36 (m, 2H), 7.32–7.12 (m, 10H), 7.03 (d, *J* = 6.4 Hz, 1H), 5.49 (d, *J* = 6.8 Hz, 1H), 4.68–4.60 (m, 1H), 4.54–4.44 (m, 1H), 3.97 (d, *J* = 13.2 Hz, 1H), 3.76–3.64 (m, 5H), 3.34 (d, *J* = 10.0 Hz, 1H), 3.22–3.12 (m, 2H), 3.05 (d, *J* = 13.2 Hz, 1H), 2.94–2.84 (m, 2H), 2.84–2.74 (m, 2H), 1.80–1.60 (m, 2H), 0.75 (s, 9H); ^{13}C NMR (CD_3OD, 100 MHz) δ 178.5;, 172.6, 159.1, 142.6, 139.2, 138.7, 137.5, 132.4, 132.3, 132.1, 129.6, 128.7, 128.4, 127.3, 126.5, 125.7, 122.4, 74.5, 72.1, 63.3, 62.5, 59.7, 54.7, 53.5, 52.8, 48.4, 41.2, 36.7, 29.9, 26.9; ESI-MS: m/z 721 $[M+H]^+$, 723 $[M+2+H]^+$; $[\alpha]^{20}_{589}$ = -66.5° (c, 0.04, CH_3OH) Anal. Calcd for $C_{37}H_{45}N_4O_5$ × 1.5 H_2O + 0.5 MeOH: C, 58.89; H, 6.59; N, 7.33; Found: C, 58.91; H, 6.23; N, 6.96.



(3*R*,4*S*)-3-Benzyl-4-((*tert*-butyldimethylsilyl)oxy)-1-((1*S*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)-2,3-dihydro-1H-inden-1-yl)-3-(2-hydroxyethyl)pyrrolidin-2-one (**14a**)

Compound **14a** was isolated as a side product in the first syntheses of **13a**. The compound **14a** was isolated by silica flash chromatography using 10–40 % ethyl acetate in petroleum ether as eluent followed by extended purification on RP-HPLC using 80–100% acetonitrile in water as eluent giving 0.0128 g **14a** in 11% isolated yield calculated from **4a**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35–7.15 (m, 9H), 5.64 (d, *J* = 6.8 Hz, 1H), 4.75–4.65 (m, 1H), 4.19 (t, *J* = 6.0 Hz, 1H), 4.10–4.02 (m, 1H), 3.84–3.76 (m, 1H), 3.63 (dd, *J* = 6.4, 9.6 Hz, 1H), 3.22–3.10 (m, 2H), 2.94–2.74 (m, 3H), 2.45 (br s, 1H), 2.00–1.88 (m, 1H), 1.85–1.70 (m, 1H), 0.80 (s, 9H), 0.77 (s, 9H), 0.06 (s, 3H), -0.10 (s, 3H), -0.12 (s, 3H), -0.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.2, 140.4, 138.2, 137.2, 130.8, 128.8, 128.6, 127.7, 126.9, 125.9, 125.0, 73.3, 70.2, 59.2, 57.7, 52.7, 50.5, 41.4, 38.9, 33.5, 26.0, 25.6, 18.2, 18.0, -5.0, -4.98, -4.5, -4.2; ESI-MS: m/z 596 $[M+H]^+$; $[\alpha]^{24}_{589}$ = +0.9° (c, 0.60, $CHCl_3$); Anal. Calcd for $C_{34}H_{53}N_1O_4Si_2 \times H_2O$: C, 66.51; H, 9.03; N, 2.28; Found: C, 66.47; H, 9.03; N, 2.28.

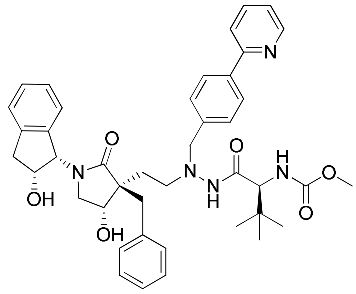


(3*R*,4*R*)-3-Benzyl-4-((*tert*-butyldimethylsilyl)oxy)-1-((1*S*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)-2,3-dihydro-1H-inden-1-yl)-3-(2-hydroxyethyl)pyrrolidin-2-one (**14d**)

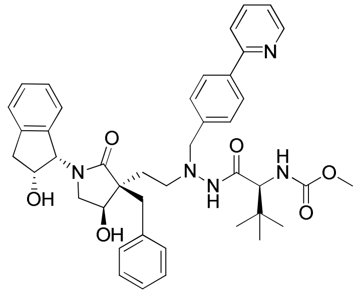
Compound **14d** was as a side product in the first syntheses of **13d**. The compound **14d** was isolated by silica flash chromatography using 15–35 % ethyl acetate in petroleum ether as eluent followed by extended purification on RP-HPLC using 80–100% acetonitrile in water as eluent giving 0.048 g of **14d** in 53% isolated yield calculated from **4d**. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30–7.20 (m, 8H), 7.10–7.05 (m, 1H), 5.64 (d, *J* = 6.0 Hz, 1H), 4.75–4.66 (m, 1H), 4.31 (t, *J* = 8.0 Hz, 1H), 3.82–3.60 (m, 2H), 3.33 (dd, *J* = 8.0, 10.0 Hz, 1H), 3.18 (dd, *J* = 7.6, 10.0 Hz, 1H), 3.11 (dd, *J* = 8.0, 16.0 Hz, 1H), 2.97 (s, 2H), 2.91 (dd, *J* = 4.4, 16.0 Hz, 1H), 2.00–1.90 (m, 1H), 1.72–1.60 (m, 1H), 0.90 (s, 9H), 0.86 (s, 9H), 0.14 (s, 3H), 0.08 (s, 3H), 0.06 (s, 3H), 0.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.7, 140.5, 138.7, 137.3, 131.2, 128.4, 127.9, 127.4, 126.5, 125.2, 124.3, 74.9, 72.2, 59.0, 58.4, 51.5, 50.3, 41.2, 36.7, 35.4, 26.1, 25.8, 18.3, 18.1, -4.7, -4.6, -4.3, -4.1; ESI-MS: m/z 596 $[M+H]^+$; $[\alpha]^{24}_{589}$ = -10.5° (c, 0.60, $CHCl_3$); Anal. Calcd for $C_{34}H_{53}N_1O_4Si_2 \times H_2O$: C, 66.51; H, 9.03; N, 2.28; Found: C, 66.80; H, 9.02; N, 2.30.

1.2.6 General procedure E: Formation of compounds 13e–f

Compound **14a** or **14d** was oxidized using 1.2 equiv Dess-Martin reagent in 10 mL dry DCM. The mixture was stirred at room temperature for 1 h. Then another 5 mL DCM was added and the reaction was quenched with 10 mL NH_4Cl (aq,. sat.) and 2 mL $Na_2S_2O_3$ (aq,. sat.) and extracted. The aqueous layers were extracted with DCM (2 x 15 mL), all organic layers were combined, dried with $MgSO_4$ and concentrated under reduced pressure. 4-(2-pyridinyl)-benzhydrazide (**5b**), dry THF and 2.0 equiv acetic acid were added to the mixture and stirred for 15 minutes at room temperature. Next 4.0 equiv of $Na(OAc)_3BH$ was added and the mixture was stirred overnight. The reaction was quenched with NH_4Cl (aq,. sat.) and extracted with EtOAc (3 x 15 mL), dried with $MgSO_4$ and concentrated. The crude reaction mixture was purified by silica flash chromatography using 30–70 % ethyl acetate in petroleum ether as eluent, THF (1.0 mL) and 10.0 equiv TBAF was added and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated, water was added to the mixture before it was extracted with DCM (3 x 15 mL). The organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The crude products were purified by silica flash chromatography using 3–5% methanol in ethyl acetate as eluent to give **13e** and **13f** in 48% and 38% isolated yield respectively.



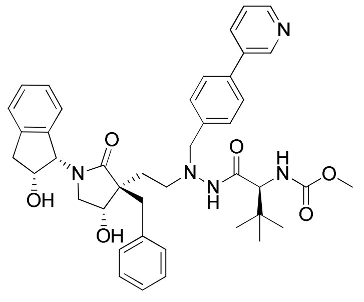
Methyl ((*S*)-1-(2-(2-((3*R*,4*S*)-3-benzyl-4-hydroxy-1-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-(pyridin-2-yl)benzyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (13e)
Compound **13e** was prepared according to general procedure E, using alcohol **14a** (0.0350 g, 0.0589 mmol), Dess-Martin reagent (0.0299 g, 0.0702 mmol), **5b** (0.0230 g, 0.0620 mmol), AcOH (0.007 mg, 0.1164 mmol), $Na(OAc)_3BH$ (0.0496 g, 0.2341 mmol) and 1.0 M TBAF (0.332 mL) in THF. The crude product was purified by silica flash chromatography using 3–5% methanol in ethyl acetate as eluent to give 0.0201 g **13e** in 48% isolated yield. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.59 (d, J = 4.8 Hz, 1H), 7.95–7.80 (m, 4H), 7.54 (d, J = 8.4 Hz, 2H), 7.40–7.30 (m, 1H), 7.30–7.10 (m, 9H), 5.47 (d, J = 6.0 Hz, 1H), 4.65–4.55 (m, 1H), 4.20–4.10 (m, 1H), 4.01 (d, J = 12.8 Hz, 1H), 3.92 (d, J = 12.8 Hz, 1H), 3.77 (s, 1H), 3.55 (s, 3H), 3.42 (dd, J = 6.0, 10.8 Hz, 1H), 3.15 (dd, J = 6.8, 16.4 Hz, 1H), 3.10–3.00 (m, 2H), 2.94–2.80 (m, 3H), 2.74 (d, J = 13.6 Hz, 1H), 2.00–1.82 (m, 2H), 0.82 (s, 9H); ^{13}C NMR (CD_3OD, 100 MHz) δ 179.1, 171.8, 159.0, 158.6, 150.3, 142.3, 139.7, 139.2, 138.9, 138.3, 131.5, 131.3, 129.5, 129.2, 128.1, 128.0, 127.6, 126.43, 126.4, 123.7, 122.5, 74.3, 71.4, 63.0, 62.8, 59.9, 54.7, 53.8, 52.7, 52.3, 41.2, 40.9, 35.1, 29.2, 27.0; ESI-MS: m/z 720 $[M+H]^+$; $[\alpha]_{589}^{20}$ = -22.5° (c, 0.15, CH_3OH); Anal. Calcd for $C_{42}H_{49}N_5O_6$ × 1.25 H_2O: C, 67.95; H, 6.99; N, 9.44; Found: C, 67.82; H, 6.70; N, 9.21.



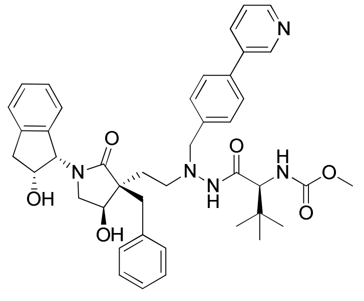
Methyl ((*S*)-1-(2-(2-((3*R*,4*R*)-3-benzyl-4-hydroxy-1-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-(pyridin-2-yl)benzyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**13f**)
Compound **13f** was prepared according to general procedure E, using alcohol **14d** (0.0480 g, 0.0805 mmol), Dess-Martin reagent (0.0410 g, 0.0966 mmol), **5b** (0.030 g, 0.0810 mmol), AcOH (0.0097 mg, 0.1620 mmol), $Na(OAc)_3BH$ (0.0682 g, 0.3218 mmol) and 0.332 mL TBAF (1.0 M in THF). The crude product was purified by silica flash chromatography using 5% methanol in ethyl acetate as eluent to give 0.0220 g **13f** in 38% isolated yield. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.59 (d, J = 4.4 Hz, 1H), 7.90–7.82 (m, 3H), 7.79 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.40–7.10 (m, 8H), 7.05–6.90 (m, 2H), 5.47 (d, J = 6.4 Hz, 1H), 4.65–4.60 (m, 1H), 4.55–4.45 (m, 1H), 4.06 (d, J = 13.6 Hz, 1H), 3.83 (d, J = 13.6 Hz, 1H), 3.77 (s, 1H), 3.64 (s, 3H), 3.40–3.30 (m, 1H), 3.20–3.10 (m, 2H), 3.05 (d, J = 13.6 Hz, 1H), 2.95–2.75 (m, 4H), 1.80–1.65 (m, 2H), 0.76 (s, 9H); ^{13}C NMR (CD_3OD, 100 MHz) δ 178.5, 172.6, 159.1, 158.6, 150.3, 142.5, 139.7, 139.3, 139.2, 138.9, 138.7, 132.1, 130.9, 129.5, 128.7, 128.2, 128.0, 127.3, 126.4, 125.7, 123.7, 122.5, 74.5, 72.1, 63.3, 63.1, 59.6, 54.5, 53.5, 52.8, 41.2, 36.8, 34.8, 29.8, 26.9; ESI-MS: m/z 720 $[M+H]^+$; $[\alpha]_{589}^{20}$ = -67.8° (c, 0.15, CH_3OH); Anal. Calcd for $C_{42}H_{49}N_5O_6$ × 1.5 H_2O: C, 67.54; H, 7.02; N, 9.38; Found: C, 67.82; H, 7.09; N, 9.27.

1.2.7 General procedure F: Formation of compounds 13g–j, 19b–d, by Suzuki–Miyaura cross-coupling

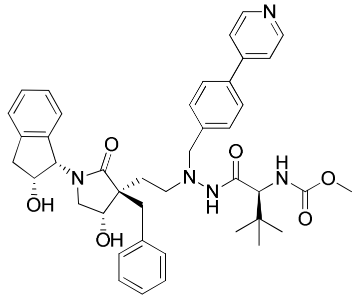
A 2 mL process vial was charged with **12a**, **12d** or **18**, Herrmann's palladacycle (0.1 equiv), K_2CO_3 (3.3 equiv), aryl boronic acid (3.3 equiv), $[HP(tBu)_3]BF_4$ (0.2 equiv), DME 0.9 mL and water 0.2 mL. The vessel was sealed under air and was irradiated with microwaves to 140 °C for 20 min. The reaction tube was thereafter allowed to reach room temperature and after adding 10 mL water the mixture was extracted with DCM (3 x 15 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. Next the mixture was dissolved in 1.0 mL THF, 10 equiv TBAF (1.0 M in THF) was added and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated, 10 mL water was added and then extracted with DCM (3 x 15 mL) and ethyl acetate (15 mL × 2). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica flash chromatography using 4–5% methanol in DCM as eluent to give inhibitors **13g–j** in 59–74% isolated yields, **19b**–**d** in 30-45% isolated yields.



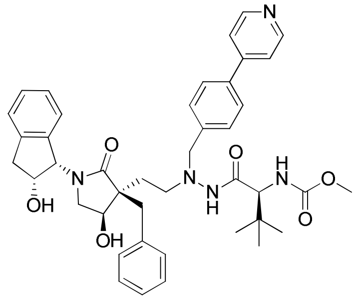
Methyl ((*S*)-1-(2-(2-((3*R*,4*S*)-3-benzyl-4-hydroxy-1-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-(pyridin-3-yl)benzyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**13g**)
Compound **13g** was prepared according to general procedure F, using **12a** (0.0500 g, 0.0526 mmol), Hermann's palladacycle (0.0049 g, 0.0053 mmol), K_2CO_3 (0.0240 g, 0.1736 mmol), 3-pyridylboronic acid (0.0214 g, 0.1741 mmol), $[HP(t\text{-Bu})_3]BF_4$ (0.0031 g, 0.0105 mmol), DME (0.9 mL) and water (0.2 mL) followed by TBAF (0.526 mL, 1.0 M in THF). The crude product was purified by silica flash chromatography using 4–5% methanol in DCM as eluent followed by re-crystallization from DCM/diethyl ether to give 0.024 g **13g** in 63% isolated yield. ^1H NMR (CD_3OD, 400 MHz) δ 8.75 (s, 1H), 8.49 (d, *J* = 4.0 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.60–7.45 (m, 5H), 7.30–7.10 (m, 9H), 5.47 (d, *J* = 6.0 Hz, 1H), 4.65–4.55 (m, 1H), 4.20–4.10 (m, 1H), 4.00 (d, *J* = 12.8 Hz, 1H), 3.92 (d, *J* = 12.8 Hz, 1H), 3.76 (s, 1H), 3.56 (s, 3H), 3.42 (dd, *J* = 6.0, 10.8 Hz, 1H), 3.15 (dd, *J* = 6.8, 16.4 Hz, 1H), 3.10–3.00 (m, 2H), 2.96–2.80 (m, 3H), 2.76 (d, *J* = 13.6 Hz, 1H), 2.00–1.85 (m, 2H), 0.81 (s, 9H); ^{13}C NMR (CD_3OD, 100 MHz) δ 179.1, 171.8, 159.0, 148.7, 148.3, 142.3, 139.2, 138.5, 138.3, 137.9, 136.5, 131.7, 131.6, 129.5, 129.2, 128.1, 128.0, 127.6, 126.42, 126.4, 125.5, 74.3, 71.4, 63.0, 62.7, 59.9, 54.6, 53.9, 52.7, 52.3, 41.2, 40.9, 35.1, 29.3, 27.0; ESI-MS: m/z 720 $[M+H]^+$; $[\alpha]_{589}^{20}$ = -21.3° (c, 0.10, CH_3OH); Anal. Calcd for $C_{42}H_{49}N_5O_6 \times 1.75\ H_2O$: C, 67.13; H, 7.04; N, 9.32; Found: C, 67.19; H, 6.65; N, 8.94.



Methyl ((*S*)-1-(2-(2-((3*R*,4*R*)-3-benzyl-4-hydroxy-1-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-(pyridin-3-yl)benzyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**13h**)
Compound **13h** was prepared according to general procedure F, using **12d** (0.0500 g, 0.0526 mmol), Hermann's palladacycle (0.0049 g, 0.0053 mmol), K_2CO_3 (0.0240 g, 0.1736 mmol), 3-pyridylboronic acid (0.0214 g, 0.1714 mmol), $[HP(t\text{-Bu})_3]BF_4$ (0.0031 g, 0.0105 mmol), DME (0.9 mL) and water (0.2 mL) followed by TBAF (0.526 mL, 1.0 M in THF). The crude product was purified by silica flash chromatography using 4–5% methanol in DCM as eluent to give 0.0222 g **13h** in 59% isolated yield. ^1H NMR (CD_3OD, 400 MHz) δ 8.73 (s, 1H), 8.50 (d, *J* = 4.4 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.60–7.45 (m, 5H), 7.30–7.10 (m, 7H), 7.10–6.95 (m, 2H), 5.48 (d, *J* = 6.4 Hz, 1H), 4.70–4.60 (m, 1H), 4.60–4.45 (m, 1H), 4.07 (d, *J* = 13.2 Hz, 1H), 3.85–3.70 (m, 2H), 3.64 (s, 3H), 3.40–3.30 (m, 1H), 3.20–3.10 (m, 2H), 3.05 (d, *J* = 14.4 Hz, 1H), 3.00–2.75 (m, 4H), 1.80–1.65 (m, 2H), 0.75 (s, 9H); ^{13}C NMR (CD_3OD, 100 MHz) δ 178.5, 172.6, 159.1, 148.7, 148.3, 142.6, 139.2, 138.7, 138.6, 138.4, 137.9, 136.5, 132.1, 131.4, 129.6, 128.7, 128.2, 128.1, 127.3, 126.4, 125.6, 125.5, 74.5, 72.2, 63.3, 63.0, 59.6, 54.6, 53.5, 52.8, 41.2, 36.8, 34.7, 29.9, 26.9; ESI-MS: m/z 720 $[M+H]^+$; $[\alpha]_{589}^{20}$ = -60.3° (c, 0.11, CH_3OH); Anal. Calcd for $C_{42}H_{49}N_5O_6 \times H_2O$: C, 68.36; H, 6.97; N, 9.49; Found: C, 68.35; H, 6.99; N, 9.35.

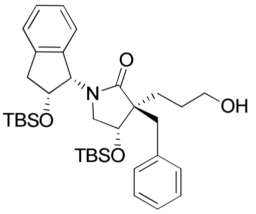


Methyl ((*S*)-1-(2-(2-((3*R*,4*S*)-3-benzyl-4-hydroxy-1-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-(pyridin-4-yl)benzyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**13i**)
Compound **13i** was prepared according to general procedure F, using **12a** (0.0500 g, 0.0526 mmol), Hermann's palladacycle (0.0049 g, 0.0053 mmol), K_2CO_3 (0.0240 g, 0.1736 mmol), 4-pyridylboronic acid (0.0214 g, 0.1741 mml), $[HP(t\text{-}Bu)_3]BF_4$ (0.0031 m, 0.0105 mmol), DME (0.9 mL) and water (0.2 mL) followed by TBAF (0.526 mL, 1.0 M in THF). The crude product was purified by silica flash chromatography using 4–5% methanol in DCM as eluent to give 0.028 g **13i** in 74% isolated yield. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.60–8.45 (m, 2H), 7.75–7.60 (m, 4H), 7.55 (d, *J* = 7.6 Hz, 2H), 7.30–7.10 (m, 9H), 5.47 (d, *J* = 6.4 Hz, 1H), 4.66–4.56 (m, 1H), 4.18–4.12 (m, 1H), 4.01 (d, *J* = 13.2 Hz, 1H), 3.92 (d, *J* = 13.2 Hz, 1H), 3.76 (s, 1H), 3.56 (s, 3H), 3.43 (dd, *J* = 6.0, 10.8 Hz, 1H), 3.20–3.00 (m, 3H), 2.96–2.80 (m, 3H), 2.75 (d, *J* = 13.6 Hz, 1H), 2.02–1.82 (m, 2H), 0.81 (s, 9H); ^{13}C NMR (CD_3OD, 100 MHz) δ 179.0, 171.8, 158.9, 150.7, 150.4, 142.3, 139.7, 139.2, 138.3, 138.0, 131.7, 131.5, 129.5, 129.2, 128.1, 128.0, 127.6, 126.41, 126.39, 123.0, 74.3, 71.8, 63.0, 62.7, 59.9, 54.6, 54.0, 52.7, 52.3, 41.2, 40.9, 35.0, 29.3, 26.9; ESI-MS: m/z 720 $[M+H]^+$; $[\alpha]^{20}_{589}$ = -17.7° (c, 0.11, $CHCl_3$); Anal. Calcd for $C_{42}H_{49}N_5O_6 \times 1.5\ H_2O$: C, 67.54; H, 7.02; N, 9.38; Found: C, 67.22; H, 6.73; N, 9.01.



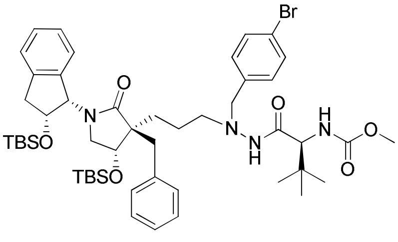
Methyl ((*S*)-1-(2-(2-((3*R*,4*R*)-3-benzyl-4-hydroxy-1-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-2-oxopyrrolidin-3-yl)ethyl)-2-(4-(pyridin-4-yl)benzyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (**13j**)
Compound **13j** was prepared according to general procedure F, using **12d** (0.0500 g, 0.0526 mmol), Hermann's palladacycle (0.0049 mg, 0.0053 mmol), K_2CO_3 (0.0240 mg, 0.1736 mmol), 3-pyridylboronic acid (0.0214 mg, 0.1741 mmol), $[HP(t\text{-}Bu)_3]BF_4$ (0.0031 mg, 0.0105 mmol), DME (0.9 mL) and water (0.2 mL). The vessel was sealed under air and irradiated with microwaves to 140 °C for 25 min. Work-up according to general procedure F followed by deprotection using TBAF (0.526 mL, 1.0 M in THF). The crude product was purified by silica flash chromatography using 4–5% methanol in DCM as eluent to give 0.0250 g **13j** in 66% isolated yield. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.55 (d, *J* = 5.2 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.70–7.60 (m, 4H), 7.30–6.80 (m, 9H), 5.48 (d, *J* = 6.4 Hz, 1H), 4.70–4.60 (m, 1H), 4.60–4.48 (m, 1H), 4.08 (d, *J* = 13.6 Hz, 1H), 3.85–3.70 (m, 2H), 3.64 (s, 3H), 3.40–3.30 (m, 1H), 3.20–3.10 (m, 2H), 3.05 (d, *J* = 13.6 Hz, 1H), 3.00–2.75 (m, 4H), 1.85–1.65 (m, 2H), 0.74 (s, 9H); ^{13}C NMR (CD_3OD, 100 MHz) δ 178.5, 172.6, 159.1, 150.6, 150.4, 142.6, 139.9, 139.2, 138.7, 138.1, 132.1, 131.4, 129.6, 128.7, 128.2, 128.0, 127.3, 126.4, 125.7, 123.1, 74.5, 72.2, 63.3, 63.0, 59.6, 54.7, 53.5, 52.8, 41.2, 36.8, 34.7, 29.9, 26.9; ESI-MS: m/z 720 $[M+H]^+$; $[\alpha]^{20}_{589}$ = -58.8° (c, 0.10, CH_3OH); Anal. Calcd for $C_{42}H_{49}N_5O_6 \times 1.5\ H_2O$: C, 67.54; H, 7.02; N, 9.38; Found: C, 67.76; H, 6.90; N, 9.26.

1.2.8 Three-carbon spacer – Compounds 19a–e



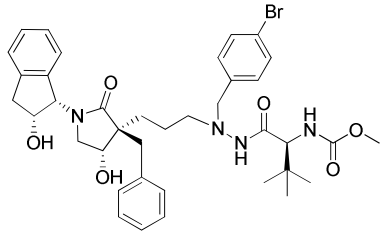
(3*S*,4*S*)-3-Benzyl-4-((*tert*-butyldimethylsilyl)oxy)-1-((1*S*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)-2,3-dihydro-1H-inden-1-yl)-3-(3-hydroxypropyl)pyrrolidin-2-one (16)

A dry 2-necked round bottom flask were charged with **4a** (1.400 g, 2.364 mmol) and dry THF (23 mL). 9-BBN (10.4 mL, 5.203 mmol) was thereafter added drop wise and stirred vigorously at room temperature. The reaction was thereafter refluxed at 80 °C for 6 h. The reaction mixture was allowed to reach room temperature. A mixture of 2M NaOH (aq., 12.0 mL), H_2O_2 (30% in water, 6.1 mL) and ethanol (4 mL) were added drop wise and the reaction mixture was stirred at room temperature for 2 h before it was diluted with EtOAc (30 mL). The organic phase was washed with NH_4Cl (aq., sat.) (2 × 50 mL) followed by extraction of the combined aqueous phases with EtOAc (1 × 30 mL). The organic phases were dried with $MgSO_4$, concentrated under reduced pressure and the crude residue was purified using gradient dry column vacuum chromatography with ethyl acetate in isohexane as eluent giving **16** in 78 % isolated yield as a transparent oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28–7.16 (m, 9H); 5.64 (d, *J* = 6.9 Hz, 1H), 4.67 (ddd, *J* = 5.7, 6.9, 6.9 Hz, 1H), 4.29 (dd, *J* = 6.7, 7.4 Hz, 1H), 3.66–3.62 (m, 2H), 3.59 (dd, *J* = 7.4, 9.2 Hz, 1H), 3.13 (ddd, *J* = 0.7, 6.9, 16.1 Hz, 1H), 3.12 (d, *J* = 13.7 Hz, 1H), 2.87 (dd, *J* = 5.6, 16.1 Hz, 1H), 2.75 (dd, *J* = 6.9, 9.2 Hz, 1H), 2.74 (d, *J* = 13.7 Hz, 1H), 1.91–1.78 (m, 1H), 1.75–1.64 (m, 3H), 0.79 (s, 9H), 0.78 (s, 9H), 0.05 (s, 3H), -0.06 (s, 3H), -0.13 (s, 3H), -0.15 (s, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 176.6, 140.3, 138.5, 137.5, 130.7, 128.4, 128.2, 127.2, 126.5, 125.4, 124.9, 73.3, 70.0, 63.5, 57.3, 52.1, 50.4, 41.2, 40.2, 28.6, 27.9, 25.8, 25.6, 17.9, 17.8, -4.1, -4.8, -5.1, -5.2; ESI-MS: m/z 610 $[M+H]^+$; $[\alpha]^{22}_{589}$ = +16.0° (c, 5.8, $CHCl_3$); Calcd. HRMS for $C_{35}H_{55}NO_4Si_2$: 610.3748; found: 610.3763.



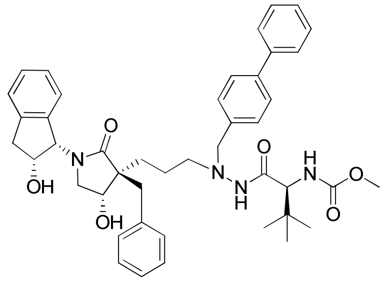
Methyl ((*S*)-1-(2-(3-((3*S*,4*S*)-3-benzyl-4-((*tert*-butyldimethylsilyl)oxy)-1-((1*S*,2*R*)-2-((*tert*-butyldimethylsilyl)oxy)-2,3-dihydro-1H-inden-1-yl)-2-oxopyrrolidin-3-yl)propyl)-2-(4-bromobenzyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (18)

A solution of 50% SO_3Py (0.7311 g, 2.2975 mmol) in DMSO (4 mL) was slowly added to a solution of **16** (0.4670 g, 0.7656 mmol) and Et_3N (0.54 mL, 3.828 mmol) in dry DCM (2 mL) stirred at 0 °C. The reaction mixture was allowed to reach room temperature and was stirred for 3 h. The reaction was quenched with 10 mL H_2O and diluted with 25 mL diethyl ether. The mixture was washed with $Na_2S_2O_3$ (aq., sat.) (2 × 15 mL) and NH_4Cl (aq., sat.) (1 × 15 mL). The aqueous phases were combined and extracted with diethyl ether (25 mL). The combined organic phases were dried with $MgSO_4$ and concentrated under reduced pressure. The crude mixture was diluted in toluene and concentrated under reduced pressure at 45 °C (repeated three times) to remove remaining pyridine. The crude material was transferred to round bottom flask containing **5a** (0.4655 g, 0.7656 mmol), acetic acid (0.29 mL, 0.0051 mmol) in dry THF (16 mL) and with 4Å molecular sieves. The mixture was stirred at room temperature for 20 minutes before addition of $Na(OAc)_3BH$ (0.6490 g, 3.062 mmol). The reaction was stirred at 35 °C for 3 h. Next the mixture was quenched with 15 mL NH_4Cl (aq., sat.) and extracted with EtOAc (3 x 15 mL). The organic phases were combined, dried with $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by gradient dry column vacuum chromatography using ethyl acetate in isohexane or diethyl ether in isohexane as eluent giving 0.250 g **18** in 35% isolated yield.^{1}H NMR ($CDCl_3$, 400 MHz) δ7.40 (d, *J* = 8.4 Hz, 2H), 7.15-7.29 (m, 13H), 5.64(dd, *J* = 6.9, 12.1 Hz, 1H), 4.66 (dt, *J* = 5.8, 6.9 Hz, 1H), 4.21-4.31 (m, 1H), 3.98-4.08 (m, 1H), 3.61 (s, 3H), 3.55-3.68 (m, 2H), 3.05-3.19 (m, 2H), 2.90 (dd, *J* = 0.9, 5.7 Hz, 1H), 2.86 (dd, *J* = 0.9, 5.7 Hz, 1H), 2.66-2.77 (m, 3H), 1.49-1.84 (m, 5H), 0.86 (s, 9H), 0.77-0.80 (m, 18H), 0.05 (s, 3H), -0.06 (s, 3H), -0.13 (s, 3H), -0.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.3, 171.5, 158.8, 141.8, 139.3, 138.7, 138.0, 132.4, 132.3, 131.8, 129.8, 129.4, 128.5, 127.7, 126.4, 126.2, 122.1, 74.5, 71.2, 62.8, 61.5, 58.9, 58.8, 53.6, 52.7, 51.7, 42.2, 40.6, 35.1, 30.4, 27.0, 26.5, 26.2, 23.1, 18.8, 18.7, -3.8, -4.3, -4.7, -4.9; ESI-MS: m/z 963 [M+H]$^+$, 965 [M+2+H]$^+$; $[\alpha]^{22}_{589}$ = +21.5° (c, 7.4, CH_3OH); HRMS for $C_{50}H_{75}BrN_4O_6Si_2$: 963.4487; found: 963.4494.



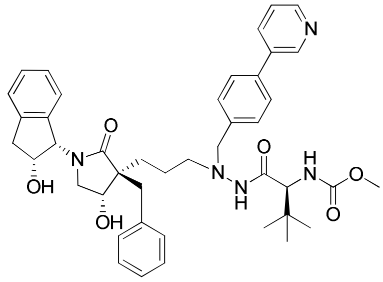
Methyl ((*S*)-1-(2-(3-((3*S*,4*S*)-3-benzyl-4-hydroxy-1-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-2-oxopyrrolidin-3-yl)propyl)-2-(4-bromobenzyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (19a)

Compound **19a** was prepared by deprotecting **18** (0.0303 g, 0.0314 mmol) with 1 mL TBAF (1.0 M in THF). The reaction mixture was stirred at room temperature overnight. The reaction was quenched with NH_4Cl (aq. sat.) (4 mL) and extracted with DCM (3 × 2 mL). The combined organic layers were washed once with NH_4Cl (aq. sat.) (2 mL) and concentrated. The crude reaction mixture was dissolved in MeCN/water and purified using RP-HPLC 35–70% MeCN in 0.1% aqueous THF as mobile phase at 5 mL/min and freeze dried to give 0.014 g **19a** in 61 % isolated yield. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.45–7.38 (m, 2H), 7.36–7.31 (m, 2H), 7.28–7.16 (m, 9H), 5.49 (d, J = 6.3 Hz, 1H), 4.62 (dt, J = 4.7, 6.5 Hz, 1H), 4.21 (dd, J = 4.7, 6.5 Hz, 1H), 3.96 (m, 2H), 3.74 (s, 1H), 3.55 (s, 3H), 3.41 (dd, J = 6.6, 10.5 Hz, 1H), 3.17 (dd, J = 6.7, 16.3 Hz, 1H), 3.05 (d, J = 13.7 Hz, 1H), 2.90 (d, J = 4.4, 10.3 Hz, 1H), 2.85 (d, J = 4.5, 16.2 Hz, 1H), 2.93–2.79 (m, 2H), 2.77 (d, J = 13.7 Hz, 1H), 1.90–1.79 (m, 1H), 1.78–1.63 (m, 3H), 0.79 (s, 9H); ^{13}C NMR (CD_3OD, 100 MHz) δ 179.3, 171.8, 158.9, 142.3, 139.1, 138.8, 137.8, 132.5, 132.2, 131.5, 129.5, 129.2, 128.1, 127.5, 126.5, 126.4, 122.1, 74.2, 71.0, 63.0, 62.0, 59.8, 59.4, 54.3, 52.7, 52.6, 41.2, 40.6, 35.0, 29.6, 26.9, 26.3, 23.0; ESI-MS: m/z 735 [M+H]$^+$, 737 [M+2+H]$^+$ $[\alpha]^{22}_{589}$ = -42.9° (c, 7.4, CH_3OH); Anal. Calcd for $C_{38}H_{47}N_4O_6Br \times ½\ H_2O$: C, 61.28; H, 7.00; N, 7.53; Found: C, 61.08; H, 6.33; N, 7.38.



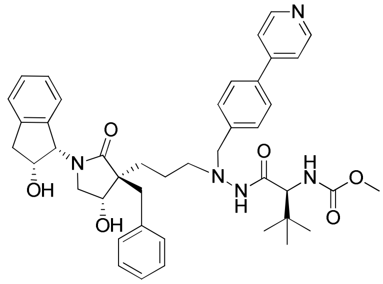
Methyl ((*S*)-1-(2-([1,1'-biphenyl]-4-ylmethyl)-2-(3-((3*S*,4*S*)-3-benzyl-4-hydroxy-1-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-2-oxopyrrolidin-3-yl)propyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (19b)

Compound **19b** was prepared according to general method E using **18** (0.0449 g, 0.0466 mmol), Herrmann's palladacycle (0.0044 g, 0.0047 mmol), K_2CO_3 (0.0213 g, 0.1538 mmol), phenylboronic acid (0.0188 g, 0.1538 mmol) and $[HP(t\text{-}Bu)_3]BF_4$ (0.0025 g, 0.0087 mmol). The reaction mixture was irradiated with microwaves to 140 °C for 25 min followed by work up according to the general method E. The reaction mixture was then treated with 1.0 M TBAF in THF (0.699 mL, 0.699 mmol) and stirred at 65 °C for 5 h. The reaction mixture was then extracted with ethyl acetate / diethyl ether (50:50), washed three times with brine, dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica flash chromatography using 2% methanol in DCM followed by purification on RP-HPLC using 35–95% acetonitrile in water and 75 min gradient time to give 0.0153 g **19b** in 45% isolated yield. ^{1}H NMR (CD_3OD, 400 MHz) δ 7.59–7.56 (m, 2H), 7.54–7.47 (m, 4H), 7.45–7.39 (m, 2H), 7.36–7.29 (m, 1H), 7.27–7.16 (m, 9H), 5.49 (d, *J* = 6.2 Hz, 1H), 4.62 (dt, *J* = 4.7, 6.4 Hz, 1H), 4.21 (dd, *J* = 4.7, 6.2 Hz, 1H), 3.96 (m, 2H), 3.77 (s, 1H), 3.46 (s, 3H), 3.42 (dd, *J* = 6.4, 10.3 Hz, 1H), 3.16 (dd, *J* = 6.2, 16.4 Hz, 1H), 3.06 (d, *J* = 13.7 Hz, 1H), 2.91 (dd, *J* = 4.7, 10.5 Hz, 1H),2.88–2.81 (m, 2H), 2.85 (dd, *J* = 4.7, 16.4 Hz, 1H), 2.77 (d, *J* = 13.7 Hz, 1H), 1.91–1.65 (m, 3H), 0.78 (s, 9H); ^{13}C NMR (CD_3OD, 100 MHz) δ 179.3, 171.7, 158.9, 142.3, 142.3, 141.7, 139.1, 138.8, 137.5, 131.6, 131.1, 129.8, 129.5, 129.2, 128.2, 128.1, 127.9, 127.8, 127.5, 126.5, 126.3, 74.2, 71.0, 63.0, 62.5, 59.8, 59.4, 54.4, 52.6, 41.2, 40.5, 35.0, 29.6, 26.9, 23.0; ESI-MS: m/z 733 [M+H]$^+$; $[\alpha]^{21}_{589}$ = -37.9° (c, 0.22, CH_3OH); Calcd. HRMS for $C_{44}H_{52}N_4O_6$ 733.3965, found 733.3956.



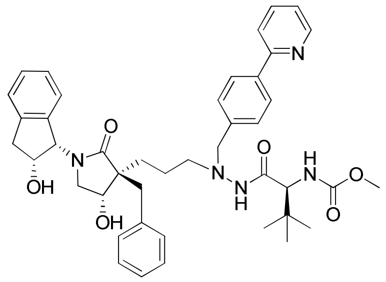
Methyl ((*S*)-1-(2-(3-((3*S*,4*S*)-3-benzyl-4-hydroxy-1-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-2-oxo-pyrrolidin-3-yl)propyl)-2-(4-(pyridin-3-yl)benzyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (19c)

Compound **19c** was prepared according to general method E using **18** (0.0300 g, 0.0311 mmol), $Pd(OAc)_2$ (0.00056 g, 0.0025 mmol), instead of Herrmann's palladacycle, K_2CO_3 (0.0129 g, 0.0933 mmol), 3-pyridylboronic acid (0.0191 g, 0.1555 mmol) and $[HP(t\text{-}Bu_3)]BF_4$ (0.0014 g, 0.0050 mmol) and H_2O (0.1 mL) in dimethylacetamide (0.5 mL), instead of DME. The vial was sealed under air and was irradiated with microwaves to 105 °C for 1.5 h. The reaction mixture was allowed to reach room temperature and was then diluted with ethyl actetate (10 mL) and extracted with NaCl (aq. sat.) (2 × 10 mL). the organic layer was concentrated under reduced pressure and roughly purified using dry column vacuum chromatography with 0–100% ether in isohexane followed by 0–20% ethyl acetate in diethyl ether as eluents. The fractions containing the TBS-protected product were combined and concentrated under reduced pressure. The TBS-protected product was then deprotected using TBAF (0.55 mL, 1M solution in THF) in THF (2 mL). The reaction mixture was stirred at room temperature for 6 h. The reaction was quenched with NaCl (aq. sat.) and extracted with a diethyl ether:ethyl acetate mixture (70:30). The organic layer was concentrated and the crude was purified using dry column vacuum chromatography with 0–95% ethyl acetate in diethyl ether as eluent. Extended purifications using RP-HPLC with 25–50% acetonitrile in H_2O as eluent gave 0.015 g **19c** in 35% isolated yield. ^1H NMR (CD_3OD, 400 MHz) δ 8.79 (dd, *J* = 0.9, 2.3 Hz, 1H), 8.52 (dd, *J* = 1.6, 4.9 Hz, 1H), 8.06 (ddd, *J* = 1.6, 2.4, 8.0 Hz, 1H), 7.58–7.56 (m, 4H), 7.51 (ddd, *J* = 0.9, 4.9, 8.0 Hz, 1H), 7.28–7.15 (m, 9H), 5.49 (d, *J* = 6.3 Hz, 1H), 4.62 (ddd, *J* = 4.7, 6.4, 6.6 Hz, 1H), 4.21 (dd, *J* = 4.6, 6.4 Hz, 1H), 4.01 (d, *J* = 12.8 Hz, 1H), 3.95 (d, *J* = 12.8 Hz, 1H), 3.76 (s, 1H), 3.46 (s, 3H), 3.42 (dd, *J* = 6.6, 10.4 Hz, 1H), 3.16 (dd, *J* = 6.6, 16.4 Hz, 1H), 3.06 (d, *J* = 13.6 Hz, 1H), 2.91 (dd, *J* = 4.8, 10.4 Hz, 1H), 2.86–2.81(m, 2H), 2.77 (d, *J* = 13.6 Hz, 1H), 1.93–1.63 (m, 5H), 0.78 (s, 9H); ^{13}C NMR (CD_3OD, 100 MHz) δ 179.3, 171.7, 158.8, 148.7, 148.3, 142.3, 139.1, 138.9, 138.8, 138.5, 137.7, 136.4, 131.6, 131.5, 129.4, 129.2, 128.1, 127.9, 127.5, 126.5, 126.3, 125.4, 74.2, 71.0, 62.9, 62.4, 59.8, 59.5, 54.7, 54.4, 52.6, 41.2, 35.0, 30.9, 26.9, 23.0, 21.7; ESI-MS: m/z 368 $[M+H]^{2+}$, 734 $[M+H]^+$; $[\alpha]^{21}_{589}$ = -12.0° (c, 0.75, CH_3OH); Calcd. HRMS for $C_{43}H_{51}N_5O_6$ 734.3918, found 734.3935.



Methyl ((*S*)-1-(2-(3-((3*S*,4*S*)-3-benzyl-4-hydroxy-1-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-2-oxo-pyrrolidin-3-yl)propyl)-2-(4-(pyridin-4-yl)benzyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (19d)

Compound **19d** was prepared according to general method E using **18** (0.0450 g, 0.0467 mmol), Herrmann's palladacycle (0.0044 g, 0.0047 mmol), K_2CO_3 (0.0213 g, 0.1541 mmol), 4-pyridylboronic acid (0.0189 g, 0.1541 mmol) and $[HP(tBu_3)]BF_4$ (0.0027 g, 0.0093 mmol) in 0.2 mL H_2O and 0.9 mL DME. The vessel was sealed under air and was irradiated with microwaves to 140 °C for 25 min. The reaction mixture was allowed to reach room temperature and was extracted with water and DCM. Organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. Next the mixture was treated with 0.467 mL 1.0 M TBAF solution in THF and stirred at room temperature overnight. Since deprotection was not completed another 0.400 mL TBAF (1.0 M in THF) was added and stirred at room temperature overnight. Yet another 1.0 mL TBAF (1.0 M in THF) was added and the mixture was stirred at 65 °C for 72 h. The reaction was allowed to reach room temperature, was quenched with NH_4Cl (aq. sat.) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed once with NH_4Cl (aq. sat.) where after the aqueous phases were extracted carfully with ethyl acetate (3 × 10 mL). The combined ethyl acetate fractions were dried with $MgSO_4$ and concentrated under reduced pressure. The crude reaction mixture was extensively prurified on RP-HPLC using 10–55% acetonitrile in water as eluent to give 0.0103 g **19d** in 30% isolated yield. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.82 (d, J = 7.0 Hz, 2H), 8.34 (d, J = 7.0 Hz, 2H), 7.90 (d, J = 8.5 Hz, 2H), 7.71 (d, J = 8.5 Hz, 2H), 7.28-7.14 (m, 9H), 5.48 (d, J = 6.2 Hz, 1H), 4.61 (dt, J = 4.7, 6.2 Hz, 1H), 4.21 (dd, J = 4.7, 6.2 Hz, 1H), 4.04 (m, 2H), 3.74 (s, 1H), 3.47 (s, 3H), 3.42 (dd, J = 6.2, 10.1 Hz, 1H), 3.15 (dd, J = 7.0, 16.4 Hz, 1H), 3.05 (d, J = 14.0 Hz, 1H), 2.94-2.81 (m, 4H), 2.77 (d, J = 14.0 Hz, 1H), 1.93-1.61 (m, 4H), 0.77 (s, 9H); ^{13}C NMR (CD_3OD, 100 MHz) δ 179.2, 171.7, 158.8, 158.2, 143.7, 143.2, 142.3, 139.1, 138.7, 135.0, 131.8, 131.5, 129.4, 129.1, 128.8, 128.0, 127.4, 126.4, 126.3, 125.0, 74.1, 70.9, 63.0, 62.3, 59.8, 59.5, 54.3, 52.6, 41.2, 40.5, 34.9, 29.5, 26.8, 23.0; ESI-MS: m/z 368 $[M+H]^{2+}$, 734 $[M+H]^+$; $[\alpha]^{22}_{589}$ = -13.0° (c, 5.3, CH_3OH); Calcd. HRMS for $C_{43}H_{51}N_5O_6$: 734.3918, found 734.3935.



Methyl ((*S*)-1-(2-(3-((3*S*,4*S*)-3-benzyl-4-hydroxy-1-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-2-oxo-pyrrolidin-3-yl)propyl)-2-(4-(pyridin-2-yl)benzyl)hydrazinyl)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (19e)
Compound **19e** was prepared using **18** (0.0705 g, 0.0731 mmol), 2-(tributylstannyl)-pyridyl (0.1345 g, 0.3656 mmol), $Pd(PPh_3)_2Cl_2$ (0.0026 g, 0.0037 mmol), CuO (0.0058 g. 0.0732 mmol) in DMF (1.4 mL). The 2 mL microwave process vial was sealed under air and was irradiated with microwaves to 105 °C for 2 h. The reaction mixture was allowed to reach room temperature and was concentrated under reduced pressure. The crude mixture was first roughly purified using dry column vacuum chromatography with ether in isohexane as eluent. Next, the crude product was deprotected using 0.5 mL TBAF (1M solution in THF) in THF (4 mL) at room temperature overnight. The crude mixture was purified using dry column vacuum chromatography with 0–100% ethyl acetate in isohexane followed by 0–40% diethyl ether in ethyl acetate as eluents. Extended purification was performed on RP-HPLC using 25–80% acetonitrile in water giving 0.0115 g **19e** in 16% isolated yield. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.62 (ddd, J = 0.9, 1.8, 4.9 Hz, 1H), 7.97 (t, J = 7.74 Hz, 1H), 7.87 (dt, J = 1.9, 8.5 Hz, 2H), 7.81 (dt, J = 1.1, 8.0 Hz, 1H), 7.57 (d, J = 8.5 Hz, 2H), 7.42 (ddd, J = 1.2, 4.9, 7.4 Hz, 1H), 7.28-7.15 (m, 9H), 5.49 (d, J = 6.3 Hz, 1H), 4.62 (ddd, J = 4.7, 6.5, 12.9 Hz, 1H), 4.21 (dd, J = 4.7, 6.5 Hz, 1H), 4.03 (d, J = 13.1 Hz, 1H), 3.97 (d, J = 13,1 Hz, 1H), 3.77 (s, 1H), 3.45 (bs, 1H), 3.42 (dd, J = 6.5, 10.4 Hz, 1H), 3.15 (dd, J = 6.6, 16.4 Hz, 1H), 3.06 (d, J = 13.6 Hz, 1H), 2.90 (dd, J = 4.9, 10.4 Hz, 1H), 2.88-2.81(m, 3H), 2.78 (d, J = 13.6 Hz, 1H), 1.93-1.64 (m, 4H), 0.78 (s, 9H);. ^{13}C NMR (CD_3OD, 100 MHz) δ 179.3, 171.7, 158.9, 158.2, 149.5, 142.3, 140.2, 139.9, 139.8, 139.1, 138.6, 131.6, 131.1, 129.4, 129.4, 128.1, 128.0, 127.5, 126.5, 126.4, 124.0, 123.0, 74.2, 71.0, 63.0, 62.4, 59.8, 59.4, 54.4, 52.6, 41.2, 40.6, 35.0, 29.6, 26.9, 23.0; ESI-MS: m/z 368 $[M+H]^{2+}$, 734 $[M+H]^+$; $[\alpha]^{22}_{589}$ = -11,7° (c, 4.7, CH_3OH); Calcd. HRMS for $C_{43}H_{51}N_5O_6$: 734.3918, Found: 734.3923.

2 Biological evaluation

2.1 *HIV protease inhibition*

The HIV-1 protease was cloned and heterologously expressed in *Escherichia coli* and purified as described elsewhere.[3] The K_i values for the synthesized compounds were determined from two individual measurements by a fluorometric assay using the fluorescent substrate DABCYL-©-Abu-Ser-Gln-ASN-Tyr-Pro-Ile-Val-Gln-EDANS (Bachem, Bubendorf, Switzerland).[4] Measurements were performed in 96-well plates with a Fluoroskan plate reader (Labsystems, Helsinki, Finland). Excitation and emission wavelengths were 355 and 500 nm, respectively. All incubations were performed at 30 °C in 0.1 M sodium acetate-1 M NaCl-1 mM dithiothreitol (DTT)-1 mM EDTA-3% DMSO at pH 5.0 with 5 µM substrate. In order to allow substrate and inhibitor to be dissolved completely, all components (300 µL) were preincubated for at least 20 min before the reaction was started by adding enzyme. Initial rates were measured over 5 min. Data were analyzed by nonlinear regression by using SIMFIT and an equation for tightly binding inhibitors. The kinetic constants (k_{cat} and K_m) were determined by using the spectrophotometric assay with a chromophoric peptide substrate. The substrate concentration was varied over as wide a range as permitted with respect to sensitivity and soluability. The kinetic constants were estimated by nonlinear regression analysis by using SIMFIT and the equation for simple Michaelis-Menten kinetics. Assay variability was checked by inclusion of a known inhibitor and the standard deviation for the enzyme assays was ±50% of the mean.

2.2 In vitro anti-HIV activity

The in vitro anti-HIV activity was assayed in MT4 cells according to a previously published procedure[4] using the colorimetric XTT assay to monitor the cytopathogenic effects.

2.3 Determination of cytotoxicity

MT4 cells were maintained in RPMI supplemented with 10% heat inactivated fetal calf serum, penicillin (100 U/mL) and streptomycin (100 µg/mL). Briefly, compounds in serial dilutions were added to MT4 cells (2 x 10^4 cells/well) in microplates. After five days of incubation at 37 °C, the number of viable cells in each well was assessed by using a soluble formazan (XTT) assay[5] and the concentration causing 50% decrease in cell proliferation (CC_{50}) was determined.

2.4 Caco-2 cell penetration assay

The transport was measured in one direction (apical to basolateral compartment). In the assay 0.1 mL of the apical 1X HBSS buffer (pH 7.4) with a final concentration of 10 µM test compound (0.5% DMSO), was added to the apical compartment and after 60 minutes samples were withdrawn from the basolateral compartment. The basolateral buffer (0.6 mL) contained 1% BSA and 1X HBSS.

2.5 Metabolic stability

1 µM test compound was incubated with human liver microsomes (0.5 mg/ml) in phosphate buffer (100 mM, pH 7.35). After 10 min of pre-incubation at 37 °C the enzymatic reaction was initiated by addition of NADPH (1 mM final concentration) and incubated at 37 °C for 30 min. The incubations were performed in triplicates and the final concentration of solvent in the assay was 0.5% acetonitrile. The reactions were terminated by addition of an equal volume of ice-cold acetonitrile containing an internal standard and centrifuged (10 min 20000 x G, 7°). The disappearance of test compound was monitored by LC/MS/MS and the intrinsic clearance value (Cl_{int}) was calculated using.

$$Cl_{int} = \frac{\ln 2 \times [ml\ in\ incubation]}{t_{½} \times [mg\ protein\ in\ incubation}, t_{½} = \frac{\ln 2}{k}$$

3 X-ray analysis

3.1 Inhibitors co-crystallized with HIV-1 Protease

Crystals of HIV-1 protease mutant L63P, V82T, I84V with inhibitors were produced as described before.[6] Data was collected at Maxlab, Lund, beamline I911-2 and was processed with Mosflm[7] and scaled using SCALA[8]. As a starting model for molecular replacement 1AJV was used. All structure refinement was carried out in CNS[9] and Refmac[10,11] and model building in O[12] and Coot.[13] The final R_{cryst} (R_{free}) for **13i**, **19d**, and **19b** were 20.1% (24.5%), 23.5% (25.6%), and 22.3% (25.3%) respectively. All images were produced using a combination of O[12] and Molray.[14]

3.2 *Table of statistics for the crystallographic structure determination*

Values within parenthesis correspond to the highest resolution bin. Molprobity[15] was used to calculate the Ramachandran statistics, residues with bad bonds, residues with bad angles, and poor rotamers.

Data collection	**13i**	**19b**	**19d**
Wavelength (Å)	1.038	1.000	1.000
Resolution range (Å) (outer shell)	19.3-1.8 (1.9-1.8)	21.5-1.8 (1.9-1.8)	12.5-1.5 (1.6-15)
No. of measured reflections	80420	98022	165841
No. of unique reflections	18880	21277	37738
Average multiplicity (outer shell)	4.3 (4.1)	4.6 (4.5)	4.4 (4.4)
Completeness (outer shell) (%)	86.3 (89.7)	95.8 (98.3)	99.4 (99.8)
Mean I/sigma(I) (outer shell)	17.3 (7.7)	15.9 (6.1)	15.6 (6.5)
R-merge (outer shell)	0.074 (0.15)	0.067 (0.22)	0.061 (0.23)
R-p.i.m. (outer shell)(%)	0.038 (0.075)	0.030 (0.10)	0.032 (0.12)
Crystal parameters			
Space group	$P2_12_12$	$P2_12_12$	$P2_12_12$
Unit cell lengths	a=58.4, b=86.0, c=46.5	a=58.4, b=86.5, c=46.3	a=58.1, b=86.4, c=46.2
Unit cell angles	α=90, β =90, γ=90	α=90, β =90, γ=90	α=90, β =90, γ=90
Mosaicity (deg.)	0.60	0.75	0.60
Refinement statistics			
Resolution range (Å) (outer shell)	19.3-1.8 (1.83-1.8)	20.9-1.8 (1.9-1.8)	12.5-1.5 (1.6-15)
No. of reflections, target set	18873	20178	35727
No. of reflections, test set	951	1051	1903
R-conventional (%)	0.201 (0.233)	0.223 (0.238)	0.235
R-free (%)	0.245 (0.297)	0.253 (0.251)	0.256
No. of non-hydrogen atoms	1497	1709	1724
No. of solvent water molecules	191	143	175
Mean B factor, protein	13.6	16.0	12.8
Coordinate error, Luzzati plot e.s.d	0.22	0.22	0.21

R_{merge} and $R_{p.i.m}$ are defined a ${}^{a}R_{merge}=\Sigma_h\Sigma_l\ |I_{hl}-\langle I_h\rangle| /\Sigma_h\Sigma_l\langle I_h\rangle$, ${}^{b}R_{P.I.M} =\Sigma_{hkl}[1/(N-1)]^{1/2}\Sigma_i|I_i(hkl)-\langle I(hkl)\rangle| /\Sigma_{hkl}\Sigma_i I(hkl)$ respectively.

3.3 X-ray crystallization

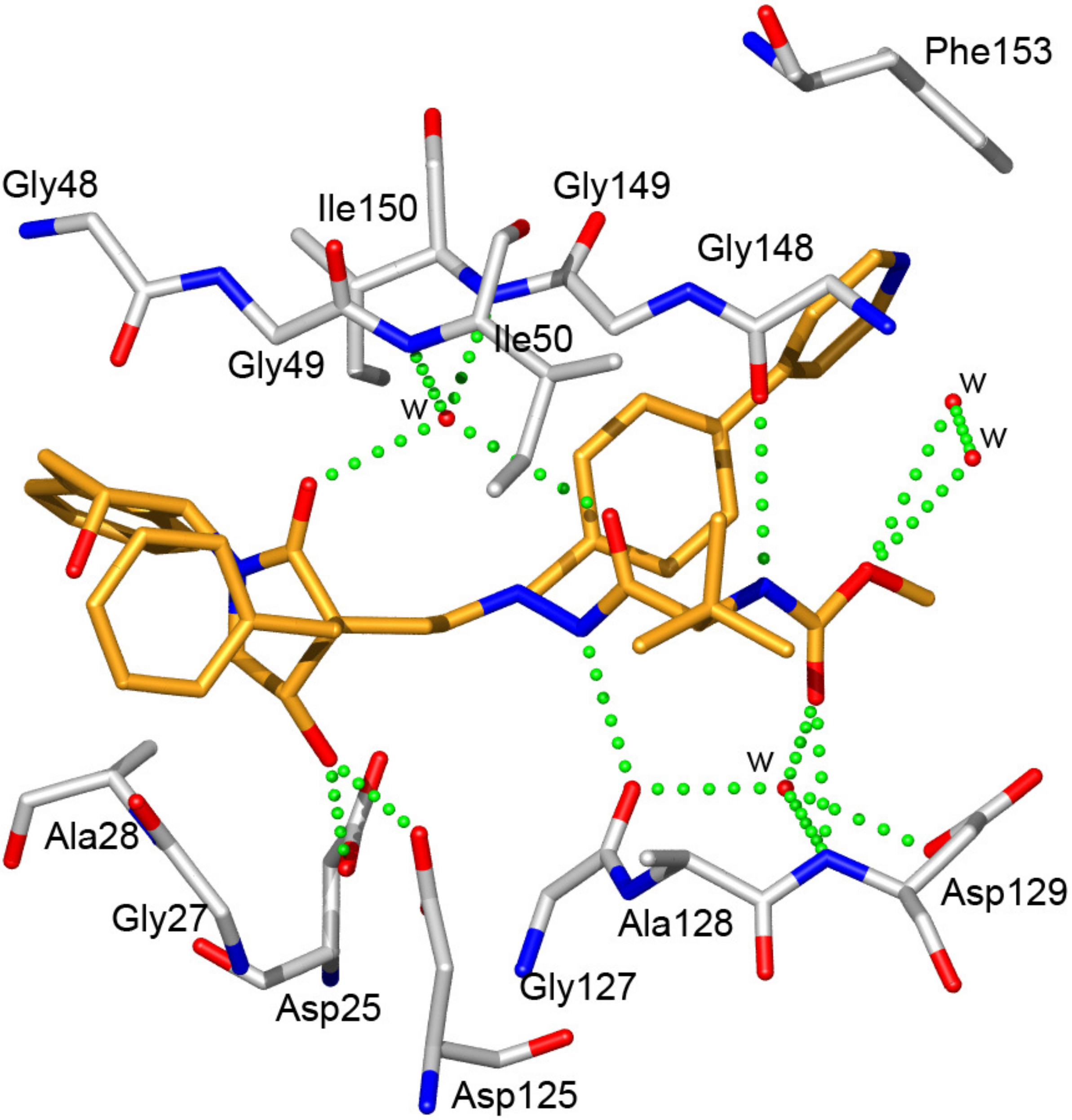


Figure S- 1. The overall conformations and binding pattern of compound **13i** (PDB code 2uxz).

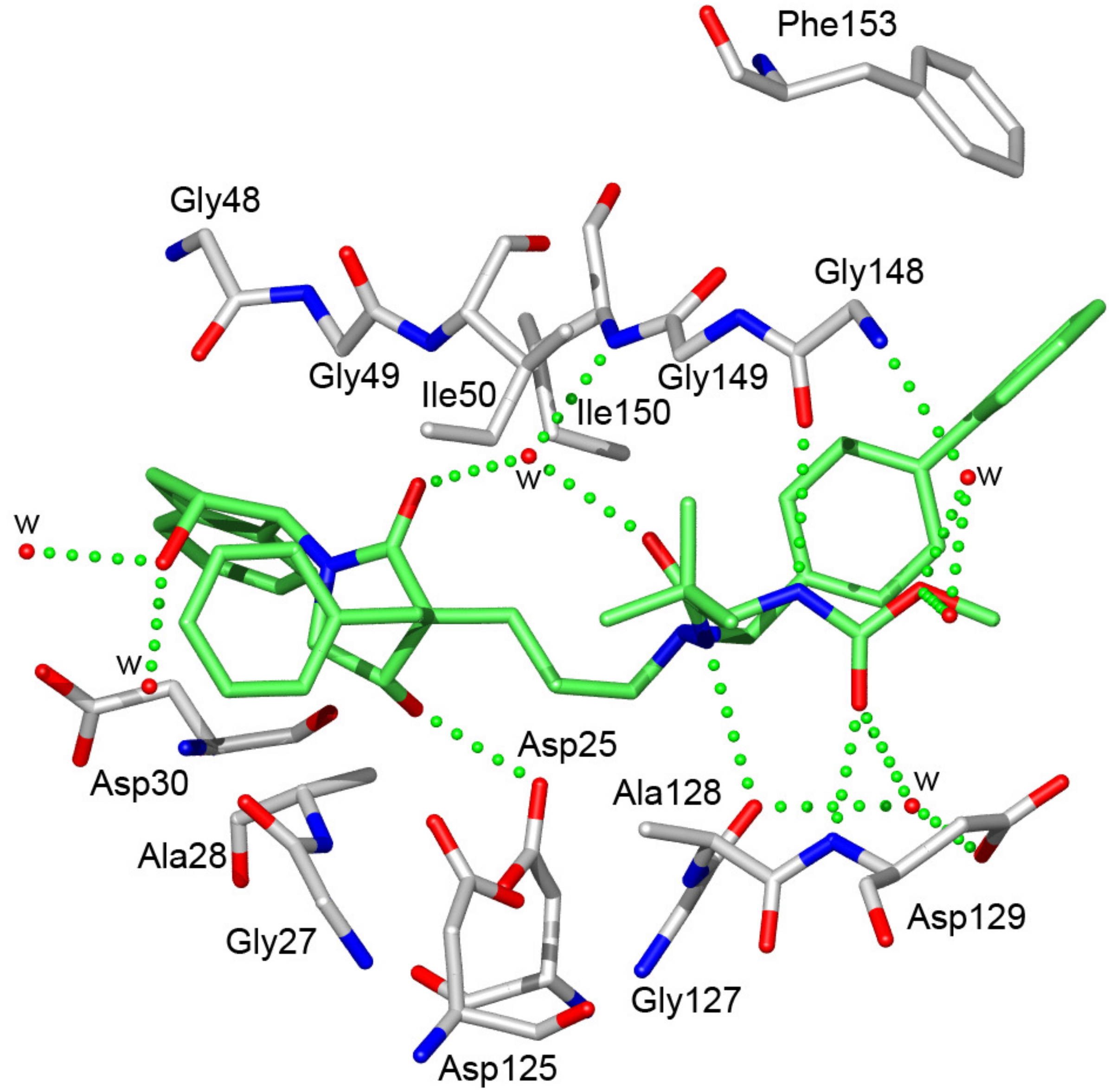


Figure S- 2 The overall conformations and binding pattern of compound **19b** (PDB code 4a6b).

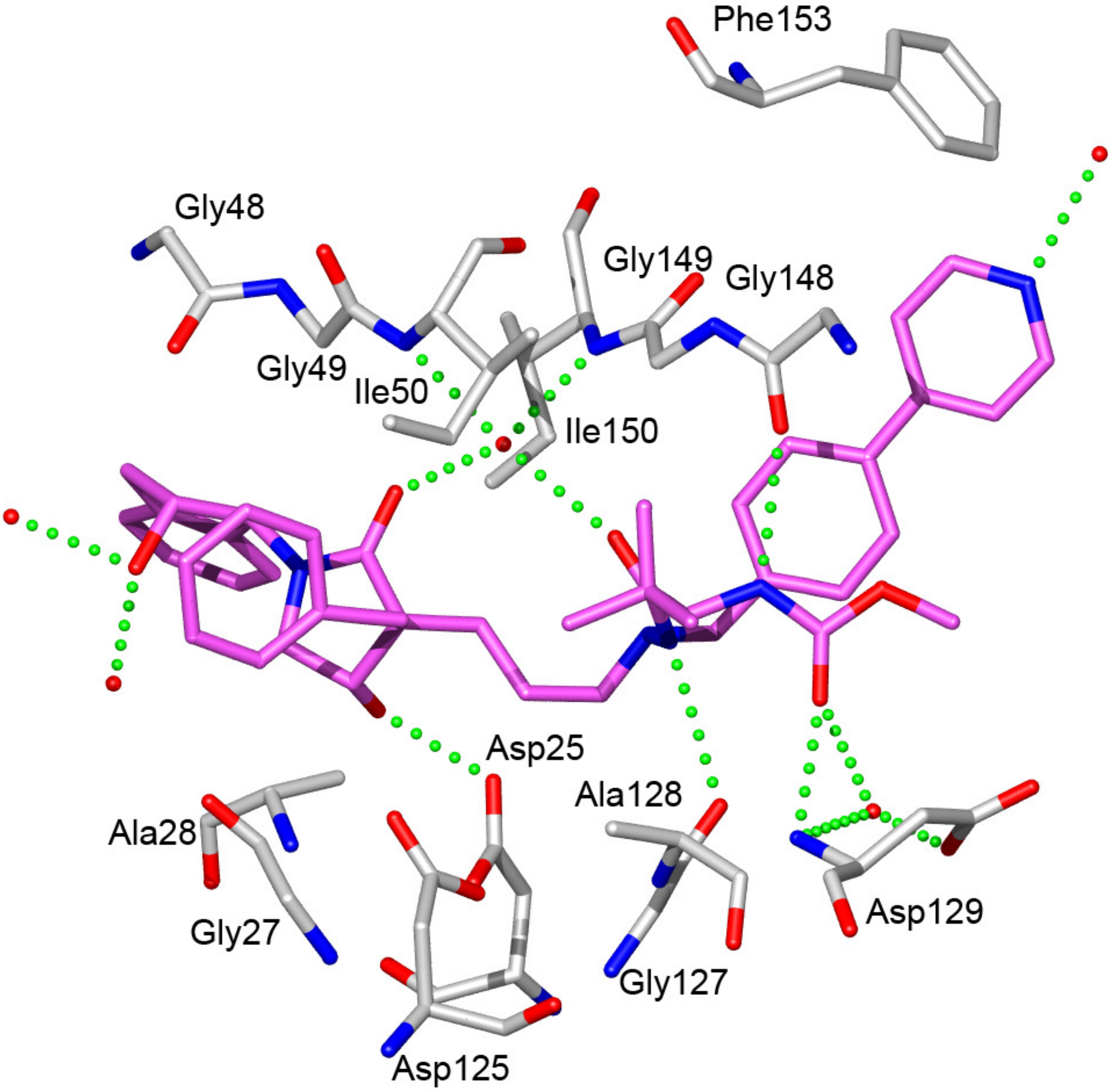


Figure S- 3. The overall conformations and binding pattern of compound **19d** (PDB code 4a6c).

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