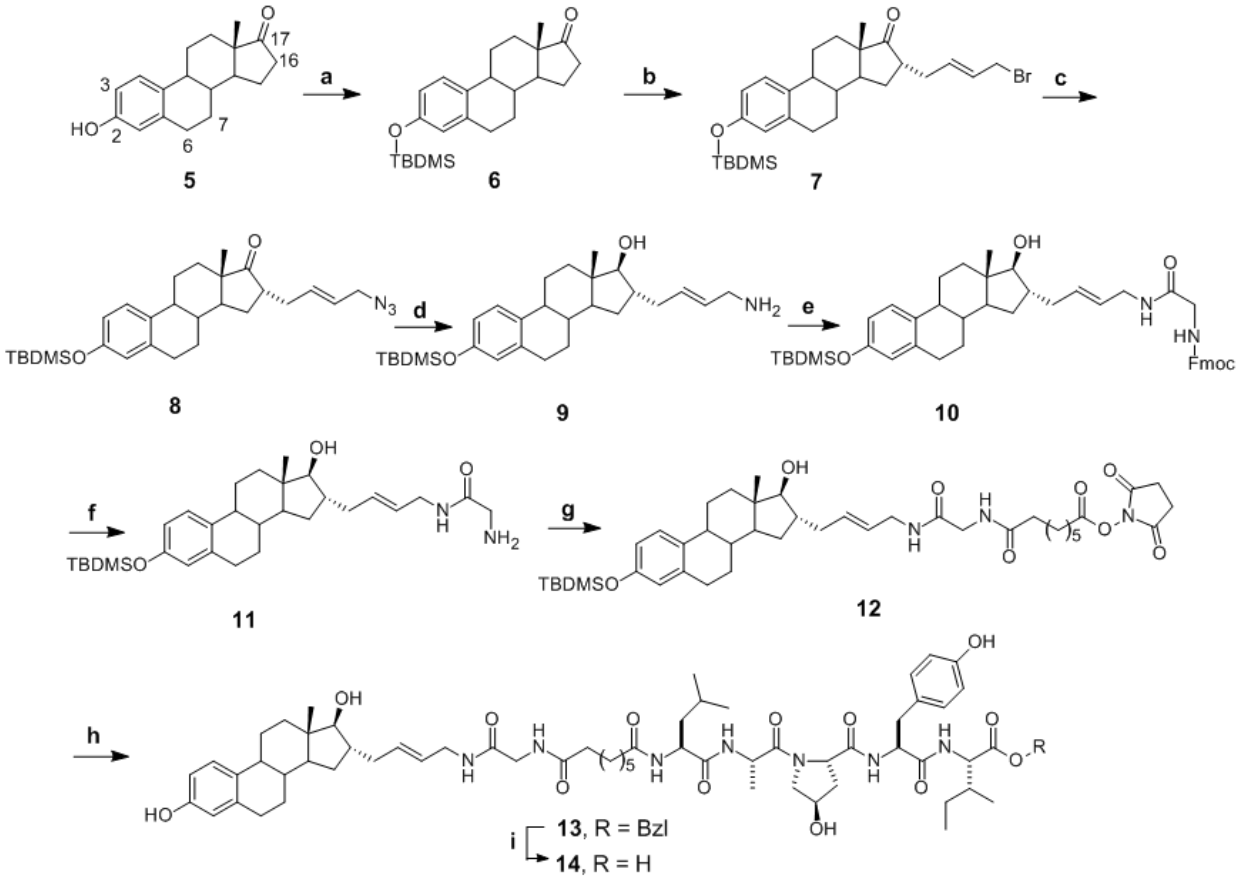
Supporting information

Scheme S.1. Synthesis of the C-16 derivatized estradiol-based PROTACs



Experimental:

Synthesis of 6: Estrone (1) (4.00 g, 0.0148 mol) and imidazole (3.00 g, 0.044 mol) were dissolved in 40 mL dichloromethane (CH_2Cl_2) and 15 ml DMF. tert-Butyldimethylsilyl chloride (TBDMS-Cl) (6.70g, 0.044mol) was added, and the solution was stirred at room temperature for 2 hours, after 2 hours solution was filtered through filter paper and solvent removed, the residue was dissolved in CH_2Cl_2 and column chromatography was performed using a 5:1 hexane:ethyl acetate mixture to yield a white solid (5.62 g, 99%). ^{1}H NMR ($CDCl_3$, 500 MHz): • 0.19 (s, 6H), 0.91 (s, 3 H), 0.98 (s, 9H), 2.84-2.87 (m, 2H), 6.57 (d, 2.5 Hz, 1 H), 6.62 (dd, *J* = 8.5, 2.5 Hz, 1 H), 7.13(d, *J* = 8 Hz, 1H)

Synthesis of 7: Under nitrogen, dry THF (6 mL) was added to a flask containing **6** (400.0 mg, 1.04 mmol) and the solution was cooled to 0 °C. Lithium diisopropylamide (LDA) (0.80 mL, 1.45 mmol) was then added drop-wise and the solution was stirred for an additional 0.5 h at 0 °C. The reaction was then cooled to -20 °C (NaCl, ice), and electrophile (1,4 dibromo-2-butene) (440.0 mg, 2.08 mmol, in 1 mL of

THF) was added drop-wise. The reaction mixture was stirred at -20 °C for 4 hrs, water was then added and mixture was extracted with three 50 ml portions of ethyl acetate. The organic phase was washed with brine and dried over (Na_2SO_4). Following filtration and solvent removal, residue was dissolved in CH_2Cl_2 and column chromatography was done using (10: l Hex: EtOAc) to give a thick yellow oil. Reaction was repeated 4 times with the same amounts for a total of 2.00 g of 3 yielding (1.2 g, 45%). 16• vs 16• 80:20. ^{1}H NMR ($CDCl_3$, 500 MHz): • 0.19 (s, 6 H), 0.96 (s, 3 H), 0.98 (s, 9 H), 2.82-2.85 (m, 2 H), 3.95 (d, *J* = 6.6 Hz, 2 H), 5.74 – 5.78 (m, 2 H), 6.57 (d, *J* = 3 Hz, 1 H), 6.63 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.12 (d, 1 H, *J* = 8.5 Hz, 1 H).

Synthesis of 8: Sodium azide (NaN_3) (520 mg, 7.64 mmol) was added to a flask containing **7** (960 mg, 1.91 mmol) and the contents were dissolved in THF (25ml), 2 ml water and 2 ml DMSO. The mixture was stirred at room temperature for 2 hrs after which, water was added and extraction was performed with EtOAc. The organic phase was washed with brine and dried over (Na_2SO_4). Following filtration and solvent removal, residue was dissolved in CH_2Cl_2 and column chromatography was done using (10: l Hex: EtOAc) to give a pale yellow oil (889 mg, 96 %). ^{1}H NMR ($CDCl_3$, 300MHz): • 0.19 (s, 6 H), 0.96 (s, 3 H), 0.98 (s, 9 H), 2.83 (m, 2H), 3.73 (d, *J* = 6.3 Hz, 2 H), 5.47-5.80 (m, 2 H), 6.56 (d, *J* = 2.4 Hz, 1H), 6.62 (dd, *J* = 8.3, 2.4 Hz, 1 H), 7.11 (d, *J* = 8.5 Hz, 1 H).

Synthesis of 9: MeOH was added to **8** (510 mg, 1.06 mmol) and cooled to 0 °C, after 10 min $NaBH_4$ (120 mg, 3.19 mmol) was added and reaction stirred for an additional 2.25 hr. MeOH was removed under reduced pressure, water was added and EtOAc was used for extraction. The organic phase was washed with brine and dried over (Na_2SO_4). Product was isolated as a white solid (250 mg, 49%) following column chromatography (10: l Hex: EtOAc). ^{1}H NMR ($CDCl_3$, 300MHz) • 0.19 (s, 6H), 0.82 (s, 3 H), 0.99 (s, 9H), 2.80 (m, 2 H), 3.33 (d, *J* = 7.8 Hz, 1H), 3.74 (d, J = 6.6 Hz, 2H), 5.56-5.88 (m, 2 H), 6.55 (d, *J* = 2.7 Hz, 1 H), 6.62 (dd, *J* = 8.5, 2.5 Hz, 1 H), 7.12 (d, *J* = 8.1 Hz, 1H).
The resulting compound (250 mg, 0.52 mmol) was then dissolved in dry THF (15ml) and then cooled to approximately -10°C. Excess lithium aluminum hydride (LAH) (100 mg, 2.60mmol) was slowly added and reaction was stirred for 2 hours. Reaction was then extracted with CH_2Cl_2 dried over Na_2SO_4 and purified via column chromatography CH_2Cl_2: MeOH (95:5). (159mg, 67%) of white solid was obtained. ^{1}H NMR ($CDCl_3$, 300 MHz) • 0.19 (s, 6H), 0.82 (s, 3 H), 0.98 (s, 9H), 2.78 - 2.80 (m, 2 H), 3.21-3.28 (m, 3 H) 5.58-5.63 (m, 2 H), 6.55 (d, *J* = 2 Hz, 1 H), 6.61 (dd, *J* = 8.1, 2.4 Hz, 1 H), 7.12 (d, *J* = 8.1 Hz, 1H).

Synthesis of 10: To a flask containing free amine **9** (136 mg, 0.30 mmol), was added Fmoc-Gly-OH (107mg, 0.360mmo1), HBTU (170 mg, 0.45 mmol) and HOBt (69 mg, 0.45 mmol). The reagents were dissolved in CH_2Cl_2 and excess DIPEA (310µl) was added and reaction stirred at room temperature

overnight. Column chromatography was performed using 1:1 Hex : EtoAC. (105 mg, 47%) of product was isolated as a clear oil. ^{1}H NMR ($CDCl_3$ 500 MHz) • 0.19 (s, 6H), 0.79 (s, 3H), 0.98 (s, 9H), 2.78 – 2.81 (m, 2H), 2.82 (s, 4H), 3.25 (d, *J* = 7 Hz, 1H), 3.77-3.89 (m, 4H), 4.23 (t, *J* = 6.7 Hz, 1H), 4.43 (d, *J* = 7 Hz, 2H), 5.47 - 5.70 (m, 2H), 6.27 (t, *J* = 5.4 Hz, 1H), 6.55 (d, *J* = 2.4 Hz, 1H), 6.62 (dd, *J* = 8.5, 2.4, 2.7 Hz, 1 H), 7.11 (d, *J* = 8.5 Hz, 1H),7.30 – 7.33 (m, 2H), 7.39 – 7.42 (m, 2H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.77 (d, *J* = 7.5 Hz, 2H).

Synthesis of 11: 20% piperidine in DMF (1.5ml) was added to **10** (105mg, 0.143mmol) and reaction was stirred at room temperature for 40 mins. Solvents were removed under high vacuum and column chromatography was performed using CH_2Cl_2: MeOH (95:5) to remove by products and the column was washed with MeOH to isolate 8 (49mg, 67%) as a white solid. Free amine confirmed by Kaiser test.

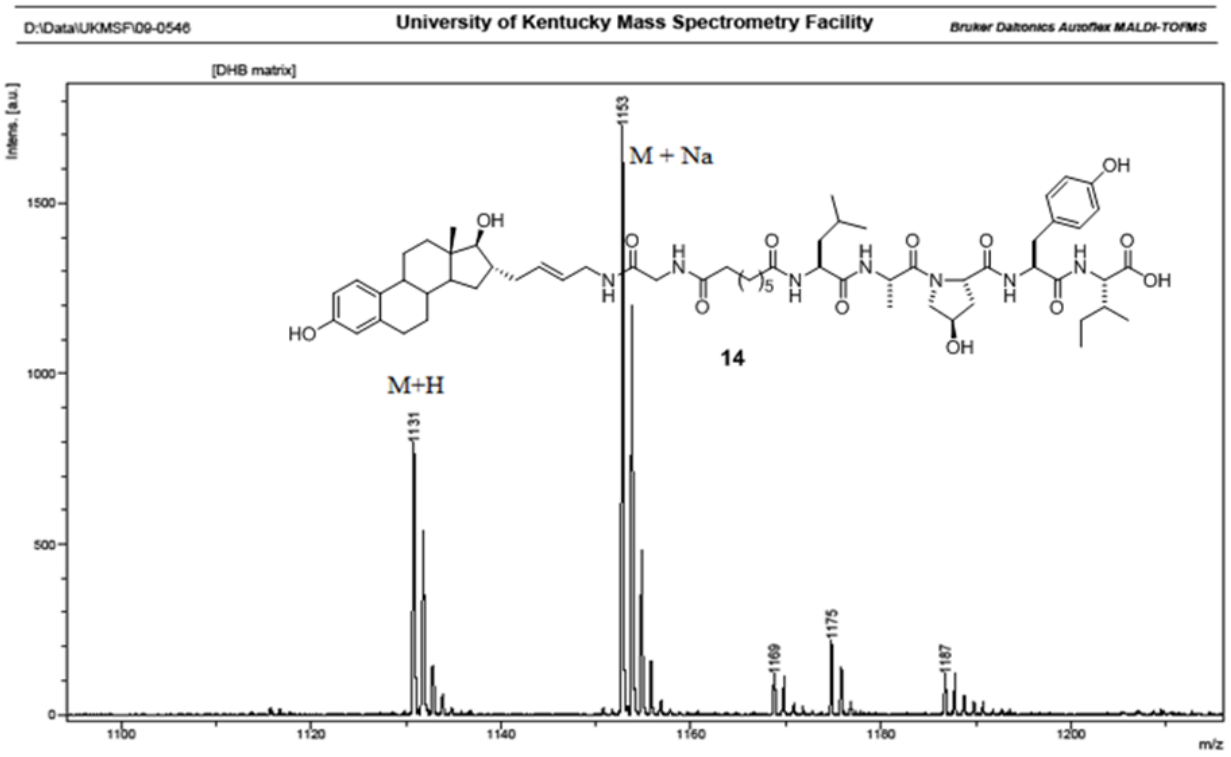
Synthesis of 12: Disuccinimidyl suberate (DSS) (70.0 mg, 0.191 mmol) was added to a flask containing **11** (49mg, 0.095mmol) and contents were dissolved in DMF (2.5 ml) and stirred at room temperature overnight. DMF was removed under high vacuum and CH_2Cl_2: MeOH (95:5) was used to purify the product via column chromatography. Compound **12** (27mg, 38%) was isolated as an oil. ^{1}H NMR ($CDCl_3$ 300 MHz) • 0.18 (s, 6H), 0.80 (s, 3H), 0.97 (s, 9H), 2.61 (t, *J* = 7.2 Hz, 2H), 2.78 – 2.84 (m, 6H), 3.27 (d, *J* = 7.2 Hz, 1H), 3.75-3.81 (m, 2H), 3.90 (d, *J* = 5.4 Hz, 2H), 5.44 - 5.70 (m, 2H), 6.33 (t, *J* = 5.4 Hz, 1H), 6.48 (t, J = 4.8 Hz, 1H), 6.55 (d, *J* = 2.4 Hz, 1H), 6.62 (dd, *J* = 8.5, 2.7, 2.4 Hz, 1 H), 7.11 (d, *J* = 8.5 Hz, 1H).

Synthesis of 13: HIF-1α pentapeptide-1, (26.0 mg, 0.035 mmol) was added to **12** (27.0 mg, 0.035 mmol), dissolved in DMF (2ml) and stirred under N_2 overnight at room temperature. Following removal of DMF under high vacuum, CH_2Cl_2: MeOH (95:5) was used to purify product as a white solid (22.5 mg, 47%). ^{1}H NMR ($CDCl_3$ 500 MHz) • 0.18 (s, 6H), 0.79 (s, 3H), 0.80-0.84 (m, 6H), 0.89-0.93 (m, 6H), 0.97 (s, 9H), 2.78 – 2.81 (m, 2H), 3.11 (dd *J* = 7, 3 Hz, 2H), 3.26 (d, *J* = 7 Hz, 1H), 3.55 (dd, *J* = 10.7, 2.7 Hz, 1H), 3.70-3.81 (m, 4H), 3.85 (d, *J* = 6 Hz, 2H), 4.36 – 4.55 (m, 6H), 4.60 (t, J = 7 Hz, 1H), 5.13 (s, 2H), 5.45 - 5.49 (m, 1H), 5.66 – 5.69 (m, 1H), 6.54 (d, *J* = 2.5 Hz, 1H), 6.60 (dd, *J* = 8.5, 2.5, Hz, 1 H), 6.87 (d, J = 8.5 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 1H), 7.09 (d, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 6.5 Hz, 1H), 7.30 – 7.38 (m, 6H), 7.39 (d, *J* = 7 Hz, 1H), 7.55 (d, *J* = 7.5 Hz, 1H).

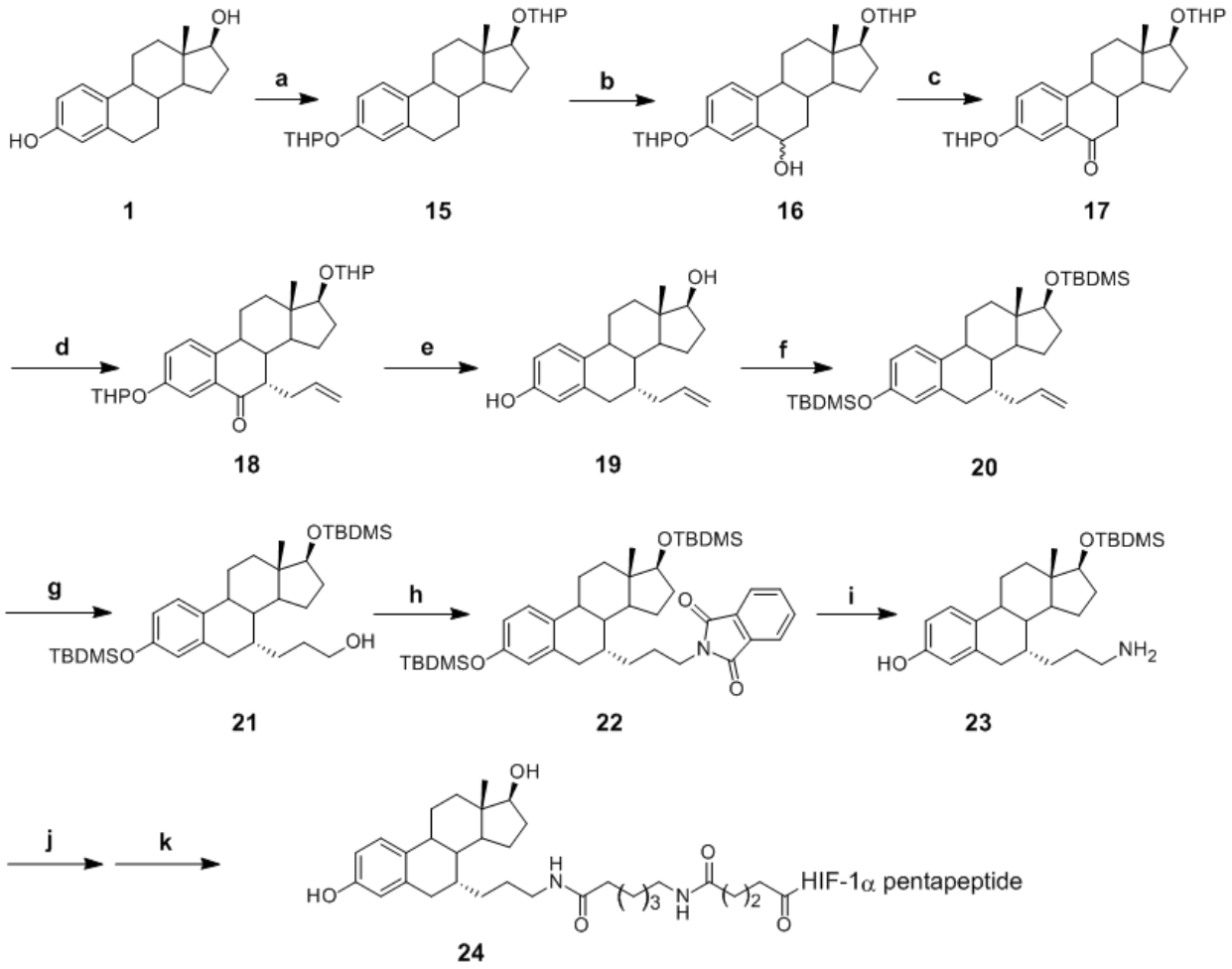
To obtain **13** the TBDMS protecting group was removed. THF (1ml) was added to **13** (22.5 mg, 0.016 mmol), followed by tertiary butyl ammonium fluoride in THF (TBAF) (14 µl, 0.048 mmol) and reaction was stirred at room temperature for 20 mins. Column chromatography was performed using CH_2Cl_2: MeOH (95:5) initially and then increasing MeOH concentrations to isolate **13** (20.6 mg, 100%) as a white solid. ^{1}H NMR ($CDCl_3$ 300 MHz) •: 0.79 (s, 3H), 0.80-0.84 (m, 6H), 0.89-0.93 (m, 6H), 2.78 – 2.81 (m,

2H), 3.11 (dd *J* = 7, 3 Hz, 2H), 3.26 (d, *J* = 7 Hz, 1H), 3.55 (dd, *J* = 10.7, 2.7 Hz, 1H), 3.75-3.86 (m, 4H), 4.39 – 4.57 (m, 6H), 5.13 (d, *J* = 5 Hz, 2H), 5.45 - 5.50 (m, 1H), 5.61 – 5.70 (m, 1H), 5.56 (d, *J* = 2.5, Hz, 1 H), 6.62 (dd, J = 8.5, 2.5 Hz, 1H), 6.76 (d, *J* = 8.5 Hz, 2H), 7.02 (d, J = 8.5 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 1H), 7.35 (s, 4H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 6.6 Hz, 1H). MS (MALDI, DHB) *m/z* 1219 (M+H, calcd for $C_{68}H_{95}N_7O_{13}$ requires 1217.70)

Synthesis of 14: To obtain K-2 an additional deprotection step was required to remove the benzyl protecting group from isoleucine. Compound 5 (16.6 mg, 0.0125 mmol) was dissolved in EtOAc and MeOH 1:1 ratio (2 ml) and to this was added 15% palladium on charcoal. Hydrogen was bubbled through the reaction mixture for 20 mins. The mixture was filtered through celite, concentrated under reduced pressure and dried under high vacuum to yield 16 mg of product, white solid. Product from hydrogenolysis (16 mg, 0.013 mmol) was dissolved in THF and TBAF in THF (0.039µl) was added. The mixture was stirred at room temperature for 20 mins. Column chromatography was performed using CH_2Cl_2: MeOH (95:5) initially and then increasing MeOH concentrations to isolate K-2 (14.0 mg, 89%) as a yellow solid. MS (MALDI, DHB) *m/z* 1131 (M+H, calcd for $C_{61}H_{91}N_7O_{13}$ requires 1129.67).



Scheme S.2. Synthesis of an estradiol containing the amine functional group at the C-7 position



Experimental:

Synthesis of 15: Estradiol (8.00 g, 29.4 mmol) was dissolved in CH_2Cl_2 (100 ml) and p-toluene sulfonic acid (TsOH) (56 mg, 0.29 mmol) was added followed by Dihydropyran (DHP) (13.3 ml, 146.8 mmol) and reaction was stirred at room temperature for 2 hours. After 2 hours water was added and product was extracted using ether. Column chromatography was performed to isolate THP protected products as clear oil (12 g, 94%). ^{1}H NMR ($CDCl_3$, 500 MHz): • 0.79, 0.81 (2s, 3H), 2.83-2.87 (m, 2H), 3.47-3.52 (m, 1H), 3.57-3.61 (m, 1H), 3.72 (t, *J* = 8.5 Hz, 1H), 3.89-3.97 (m, 2H), 4.64 - 4.65 (m, 1H), 5.38 - 5.39 (m, 1H), 6.78 (d, J = 2.5 Hz, 1H), 6.84 (dd, J = 8.5, 2.5 Hz, 1H), 7.22 (d, J = 8 Hz, 1H).

Synthesis of 16: To a -78 °C solution of 2.5 M *n*-BuLi in hexanes (30 mL, 75.0 mmol) in THF (50 mL) was added diisopropylamine (10.5 mL, 75.0 mmol), followed by 1 M KO*t*-Bu in THF (75.0 mL, 75.0 mmol) (yellow color change with addition of KO*t*-Bu). After 5 min, a solution of **15** (4.18 g, 9.49 mmol) in THF (20 mL) was added resulting in a dark red color reaction mixture which was stirred for 1.5 hours at -78

°C under N_2. The dry ice/acetone bath was replaced with an ice bath and trimethylborate ($BOMe_3$) (20 mL, 171.0 mmol) was slowly added. The reaction was stirred for an additional 2 hours at 0° C (reaction became turbid upon adition of trimethylborate). 35% H_2O_2 (25 mL) was then added and the reaction was stirred for 1 hour at room temperature after which time reaction was cooled to 0 °C, and 10% $Na_2S_2O_3$ (100 mL) was added. Product was extracted using EtOAc, dried over Na_2SO_4 and solvents were removed. The crude mixture was dissolved in CH_2Cl_2 and flash chromatography was don (3:1, Hex:EtOAc) to afford the 6-OH compound as a pale yellow foam (2.86 g, 66%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.79, 0.81 (2s, 3H), 3.45-3.49 (m, 1H), 3.56 - 3.59 (m, 1H), 3.68 – 3.73 (m, 1H), 3.87-3.93 (m, 2H), 4.63 - 4.67 (m, 1H), 4.78 – 4.81 (m, 1H), 5.40 - 5.43 (m, 1H), 6.92 (2dd, *J* = 8.5, 2.5 Hz, 1H), 7.17, 7.18 (2d, *J* = 8 Hz, 1H), 7.26 (d, *J* = 2.5 Hz, 1H).

Synthesis of 17: **16** (2.86 g, 6.26 mmol) was dissolved in CH_2Cl_2 (30 mL) and cooled to 0 °C, PCC (2.7 g, 12.5 mmol) was then added in portions within 15 min. After 15 min at 0 °C, the mixture was warmed to room temperature and stirred for 2 hours. The reaction was diluted with ether (50 mL) and then filtered through Florisil to remove the chromium salts. The solvent was evaporated and the residue was dissolved in CH_2Cl_2 and purified via flash chromatography (3:1, Hex: EtOAc) to yield 4 as a white foam (2.28 g, 80%). ^{1}H NMR ($CDCl_3$, 500 MHz): • 0.81, 0.82 (2s, 3H), 2.73 (dd, J = 16.5, 3.5 Hz, 1H), 3.47 – 3.52 (m, 1H), 3.58 – 3.62 (m, 1H), 3.73, 3.75 (2t, J = 8.5 Hz, 1H), 3.86-3.94 (m, 2H), 4.63 - 4.69 (m, 1H), 5.46 – 5.48 (m, 1H), 7.21 – 7.26 (2dd, *J* = 8.5, 3 Hz, 1H), 7.33, 7.34 (2d, *J* = 8.5 Hz, 1H), 7.71, 7.72 (2d, *J* = 3 Hz, 1H).

Synthesis of 18: Compound **17** (1.91 g, 4.20 mmol) was dissolved in dry THF and cooled to 0° C, then 1M KO*t*-Bu (4.6 ml, 4.60 mmol) was added and reaction was stirred under N_2 at 0 °C for 30 min and then cooled to -78°C. Allyl iodide (383 μL, 4.60 mmol) was then added dropwise to the solution and after 10 min the reaction was quenched with water and warmed to room temperature. The solvents were removed, redissolved in ether, and then passed through a plug of silica. After solvent was evaporated, the residue was dissolved in MeOH (25 mL), and several small pieces of sodium were added. The mixture was stirred for 2 hours at room temperature, and then quenched with water, the MeOH was evaporated, and the product was extracted from water with ether. The solvents were evaporated and the residue was dissolved in CH_2Cl_2 and purified by flash chromatography (5:1 Hex:EtOAc) to give **18** as a white foam (272 mg, 13%), recovered (4) 896 mg, corrected yield 25%. This process was repeated two more times with recovered starting material to provide a total (575 mg, overall uncorrected 28%, corrected 36%). ^{1}H NMR ($CDCl_3$, 500 MHz): • 0.80, 0.82 (2s, 3H), 3.47 – 3.52 (m, 1H), 3.60 – 3.62 (m, 1H), 3.74, 3.77 (2t, *J* = 8.5

Hz, 1H), 3.87-3.94 (m, 2H), 4.63 - 4.69 (m, 1H), 4.92 – 5.00 (m, 1H), 5.45 – 5.48 (m, 1H), 5.74 – 5.82 (m, 1H), 7.22 (2dd, *J* = 8.5, 2.5 Hz, 1H), 7.32, 7.34 (2d, *J* = 8.5 Hz, 1H), 7.69 (d, *J* = 2 Hz, 1H).

Synthesis of 19: Triethylsilane (Et_3SiH) (4.37 ml) was added to a solution of **18** (205 mg, 0.41 mmol) in CH_2Cl_2 and the mixture was cooled to 0 °C. $BF_3.Et_2O$ (15 ml) was added drop-wise and the mixture was warmed to room temp and stirred overnight (greenish-yellow color change). Reaction was then carefully hydrolyzed with 10% K_2CO_3 (72 ml) and filtered through a buccner funnel. The filtrate was extracted with CH_2Cl_2, dried over Na_2SO_4 and flash chromatography performed (1:1, Hex:EtOAc) to yield a white solid (116 mg, 90%). ^{1}H NMR ($CDCl_3$, 500 MHz): • 0.79 (s, 3H), 2.72 (d, *J* = 16 Hz, 1H), 2.83 (dd, *J* = 17, 5.5 Hz, 1H), 3.77 (t, *J* = 8.5 Hz, 1H), 4.91 - 5.00 (m, 1H), 5.74 – 5.82 (m, 1H), 6.54 (d, *J* = 3 Hz, 1H), 6.64 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.15 (d, *J* = 8.5 Hz, 1H).

Synthesis of 20: Imidazole (303 mg, 4.45 mmol) in CH_2Cl_2 and DMF (10 ml and 2 mL) was cooled to 0 °C for about 10 min, and then TBSCl (335 mg, 2.23 mmol) was added. The reaction was warmed to room temperature and a solution of **19** (116 mg, 0.37 mmol in 3 ml DMF) was added to the mixture. The reaction was stirred overnight at room temeprature. CH_2Cl_2 was removed via roto-vap and DMF via high vacuum, 0.1% K_2CO_3 (30 mL) was added and mixture extracted with CH_2Cl_2. The organic fractions were dried over Na_2SO_4 and passed through a short column (3:1 Hex:EtOAc) to yield **20** as a yellow oil (170 mg, 85%). ^{1}H NMR ($CDCl_3$, 500 MHz): • 0.03 (s, 3H), 0.04 (s, 3H), 0.18 (s, 6 H), 0.75 (s, 3H), 0.89 (s, 9H), 0.97 (s, 9H), 2.70 (d, *J* = 16 Hz, 1H), 2.83 (dd, *J* = 17, 5.5 Hz, 1H), 3.65 (t, *J* = 8.5 Hz, 1H), 4.88 – 4.98 (m, 1H), 5.74 – 5.82 (m, 1H), 6.52 (d, *J* = 2.5 Hz, 1H), 6.61 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H).

Synthesis of 21: A 0.5 M solution of 9-BBN in THF (3.14 mL, 1.57 mmol) was added to a solution of steroid **20** (170 mg, 0.31 mmol) in THF (10 mL). After stirring overnight at room temperature the reaction was cooled to 0 °C and quenched with 3 M KOH (2 mL), followed by 35% H_2O_2 (2 mL) after 5 min. The reaction was stirred for an addidional 3 h and saturated NaHCO3 was added. The mixture was extracted with CH_2Cl_2. The organic fractions were dried over Na_2SO_4 and evaporated in vacuo, and the residue was purified by flash chromatography (5:1 Hex:EtOAc) to provide **21** as a viscous oil (116 mg, 66%). ^{1}H NMR ($CDCl_3$, 300 MHz): • 0.02 (s, 3H), 0.03 (s, 3H), 0.19 (s, 6 H), 0.74 (s, 3H), 0.89 (s, 9H), 0.97 (s, 9H), 2.68 (d, *J* = 16 Hz, 1H), 2.88 (dd, *J* = 16.7, 5.5 Hz, 1H), 3.58 – 3.60 (m, 2H), 3.65 (t, *J* = 8.5 Hz, 1H), 6.53 (d, *J* = 2.5 Hz, 1H), 6.61 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H).

Synthesis of 22: To a cooled solution (0 °C) of PPh3 (97 mg, 0.415 mmol) in THF (5 mL) was added DIAD (dropwise) (77 µl, 0.415 mmol). A white precipitate of the ylide was observed, and the reaction was stirred for 40 min at 0 °C. A solution of **21** (116 mg, 0.207 mmol) and phthalimide (58 mg, 0.415

mmol) in THF (2 mL) was then added to the ylide. The reaction was stirred for 1 h at 0 °C and then at room temperature overnight. The solvent was evaporated in vacuo, and the residue was purified via flash chromatography (5:1 Hex:EtOAc) to give **22** as a white foam (118 mg, 83%). ^{1}H NMR ($CDCl_3$, 500 MHz): • 0.03 (s, 3H), 0.04 (s, 3H), 0.18 (s, 6 H), 0.74 (s, 3H), 0.89 (s, 9H), 0.99 (s, 9H), 2.67 (d, *J* = 16.5 Hz, 1H), 2.87 (dd, *J* = 17, 5 Hz, 1H), 3.55 – 3.68 (m, 3H), 6.52 (d, J = 2.5 Hz, 1H), 6.60 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 7.69 – 7.72 (m, 2H), 7.81 – 7.83 (m, 2H).

Synthesis of 23: Anhydrous hydrazine (800 μl) was added to a solution of **22** (118 mg, 0.171 mmol) in DME (1.6 mL) and EtOH (1.6 mL). The mixture was refluxed for 2 h, during which time slightly brown precipitate formed on the sides and the solution turned slightly green. The reaction was cooled, and 5% NaOH (1.6 mL) was added, dissolving the precipitate. After 30 min, water was added, and the solution was extracted with CH_2Cl_2, dried over Na_2SO_4. The solvent was evaporated in vacuo, and the residue was purified via flash chromatography (CH_2Cl_2: MeOH, 95:5) to give **23** as a white foam solid (56.7 mg, 76%). The TBDMS group at the 3-OH position is lost during this reaction. ^{1}H NMR ($CDCl_3$, 500 MHz): • 0.02 (s, 3H), 0.03 (s, 3H), 0.74 (s, 3H), 0.89 (s, 9H), 2.68 (d, *J* = 16.5 Hz, 1H), 2.88 (dd, *J* = 17, 5 Hz, 1H), 3.65 (t, J = 8.5 Hz, 1H), 6.50 (d, *J* = 2.5 Hz, 1H), 6.59 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H).

Synthesis of 24: Disuccinimidyl suberate DSS (12 mg, 0.033 mmol) was added to **23** (14.6 mg, 0.033 mmol) and dissolved in DMF (1ml) mixture was stirred at room temp overnight. DMF was removed via high vacuum and column was performed (95:5 CH_2Cl_2: MeOH) to give a white solid (5.7 mg, 25%). For this reaction two products were isolated having similar mobility on TLC. The upper product which was later identified by NMR to be the correct product was reactive while the other isomer was unreactive in subsequent reactions. ^{1}H NMR ($CDCl_3$, 500 MHz): • 0.03 (s, 3H), 0.04 (s, 3H), 0.73 (s, 3H), 0.89 (s, 9H), 2.12 (t, *J* = 7.5 Hz, 2H), 2.58 (t, *J* = 7.5 Hz, 2H), 2.65 (d, *J* = 16.5 Hz, 1H), 2.82 – 2.87 (m, 5H), 3.08 – 3.12 (m, 1H), 3.24 – 3.29 (m, 1H), 3.65 (t, *J* = 8.5 Hz, 1H), 5.76 (t, *J* = 5.5 Hz, 1H), 6.53 (d, *J* = 2.5 Hz, 1H), 6.61 (s, 1H), 6.64 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H).

To the resulting compound (5.7 mg, 0.008 mmol) HIF-1α pentapeptide (6 mg, 0.008 mmol) was added and dissolved in DMF (1.5 ml). The reaction was stirred at room temp overnight. Solvent was removed in vacuo and column chromatography was performed (95:5 CH_2Cl_2: MeOH) to yield a white solid (6.6 mg, 66%). ^{1}H NMR ($CDCl_3$, 500 MHz): • 0.03 (s, 3H), 0.04 (s, 3H), 0.74 (s, 3H), 0.79 – 0.85 (m, 6H), 0.87 – 0.95 (m, 6H), 0.89 (s, 9H), 1.13 – 1.33 (m, 13H), 1.31 (s, 9H), 2.63 (d, *J* = 16.5 Hz, 1H), 2.83 (dd, *J* = 16.5, 4.5 Hz, 1H), 2.97 – 3.10 (m, 3H), 3.23 – 3.27 (m, 1H), 3.56 (dd, *J* = 11.1, 3.9 Hz, 1H), 3.64 (t, *J* = 8.5 Hz, 1H), 3.75 (d, *J* = 11 Hz, 1H), 4.47 – 4.62 (m, 6H), 5.11 (2s, 2H), 6.53 (d, *J* = 2.5 Hz, 1H), 6.62

(dd, *J* = 8.5, 2.5 Hz, 1H), 6.66 (d, *J* = 8 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 2H), 7.05 (d, *J* = 8.5 Hz, 2H), 7.08 (d, *J* = 8.5 Hz, 1H), 7.30 – 7.37 (m, 4H), 7.51 (d, *J* = 7 Hz, 1H).

The resulting white solid (6.6 mg, 0.005 mmol) was dissolved in THF (0.5 ml) and TBAF in THF (3 drops) was added to remove TBDMS protecting group from O-17 position. Mixture was stirred at room temperature until starting material disappeared (5 days). Column chromatography was performed (CH_2Cl_2: MeOH 95:5) initially, then flushed with MeOH to isolate a white solid (2.5 mg, 42%). To the white solid TFA was added to remove both protecting groups (TBDMS and t-Bu). ^{1}H NMR ($CDCl_3$, 300 MHz): • 0.74 (s, 3H), 0.79 – 0.85 (m, 6H), 0.87 – 0.95 (m, 6H), 2.63 (d, *J* = 16.5 Hz, 1H), 2.83 (dd, *J* = 16.5, 4.5 Hz, 1H), 2.97 – 3.10 (m, 3H), 3.23 – 3.27 (m, 1H), 3.53 (dd, *J* = 11.1, 3.9 Hz, 1H), 3.64 (t, *J* = 8.5 Hz, 1H), 3.75 (d, *J* = 11 Hz, 1H), 4.36 – 4.54 (m, 6H), 5.14 (s , 2H), 6.53 (d, *J* = 2.5 Hz, 1H), 6.62 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.74 (d, *J* = 8 Hz, 1H), 7.02 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 1H), 7.25 (d, *J* = 8 Hz, 1H), 7.38 (s, 4H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.54 (d, *J* = 7 Hz, 1H). MS (MALDI, DHB) *m/z* 1172 ($M+Na^+$, calcd for $C_{65}H_{92}N_6O_{12}$ requires 1171.68).