Supporting Information

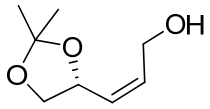
Design, Synthesis, and X-ray structure of substituted bis-Tetrahydrofuran (bis-THF)-derived Potent HIV-1 Protease Inhibitors

Arun K. Ghosh, Cuthbert D. Martyr, Melinda Steffey, Yuan-Fang Wang, Johnson Agniswamy, Masayuki Amano, Irene T. Weber, and Hiroaki Mitsuya

Contents

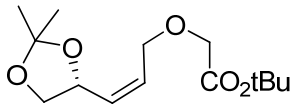
General Information

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400. IR spectra were recorded on a Mattson Genesis II FT-IR spectrometer. Optical rotations were recorded on a Perkin-Elmer 341 or an Autopol III automeric polarimeter. Anhydrous solvents were obtained as follow: Tetrahydrofuran and diethyl ether by distillation from sodium and benzophenone; dichloromethane from calcium hydride. All other solvents were reagent grade. All moisture sensitive reactions were carried out in a flame-dried flask under nitrogen atmosphere. Column chromatography was performed with Whatman 240-400 mesh silica gel under low pressure of 3-5 psi. Thin layer chromatography was carried out with E. Merck silica gel 60-F-254 plates.



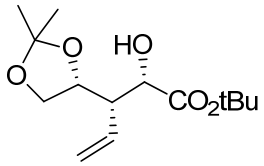
(2*Z*)-3-((4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (5):

Diisobutyl aluminum hydride (1 M in CH_2Cl_2, 27.5 mL, 27.5 mmol,) was slowly added to a cold solution (-78 ºC) of ethyl (2*Z*)-3-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-propenoate **4**, (2.5 g, 12.5 mmol) in dichloromethane (30 mL). The solution was allowed to stir for 15 min at -78 ºC (a color change from colorless to yellow and back to colorless indicates that the reaction is complete). A saturated solution of Rochelle's salt (20 mL) was added and the reaction mixture was warmed to room temperature. The reaction was stirred until both layers were clear. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 15 mL). The organic layers were combined, washed with brine and dried over $MgSO_4$. The solid was filtered out and the organic layer was concentrated under vacuum. The crude mixture was purified on silica gel using 20% ethyl acetate/hexanes to obtain alcohol **5** (1.9 g, 95% yield) as a colorless oil. R_f = 0.27 (40% ethyl acetate/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84 -5.81 (m, 1H), 5.55 (t, *J* = 8.5 Hz, 1H), 4.85 (q, *J* = 9.6 Hz, 1H), 4.28 (dd, *J* = 6.8, 7.3 Hz, 1H), 4.18 (d, *J* = 4.8 Hz, 1H), 4.08 (t, *J* = 6.5 Hz, 1H), 3.56 (t, *J* = 9.0 Hz, 1H), 2.12 (bs, 1H), 1.41 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$)**:** δ 133.1, 129.4, 109.4, 71.8, 69.4, 58.5, 26.6, 25.8



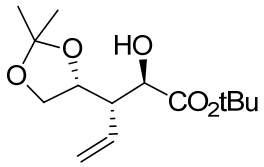
(2*Z*)-*tert*-Butyl 2-(3-((4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl))allyloxy)acetate (7)[1]:

To a round bottom flask charged with activated molecular sieves (6.0 g) was added a solution of substrate, **6** (4.00 g, 25.3 mmol) in acetonitrile, followed by *t*-butylbromoacetate (4.48 mL, 30.3 mmol), tetrabutylammonium iodide (1.12 g, 1.45 mmol) and cesium hydroxide monohydrate (5.10 g, 30.3 mmol) at room temperature. The reaction was allowed to stir for 24 h. The solid was filtered out and the solvent was concentrated under vacuum; the residue was purified by flash column chromatography (5% ethyl acetate/hexanes) to afford **7** (5.86 g, 85% yield) as a colorless oil. R_f = 0.57 (30% ethyl acetate/hexanes). $[\alpha]^{23}_D$ -3.30 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.78-5.74 (m, 1H), 5.61 – 5.66 (m, 1H), 4.83 (q, *J* = 7.4 Hz, 1H), 4.16- 4.20 (m, 2H), 4.09 (dd, *J* = 6.2, 2.0 Hz, 1H), 3.94 (d, *J* = 3.1 Hz, 2H), 3.54 (t, *J* = 8.1 Hz, 1H), 1.47 (s, 9H), 1.34 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 131.4, 129.5, 109.3, 81.6, 71.9, 69.4, 67.7, 66.5, 28.0, 26.6, 25.8.



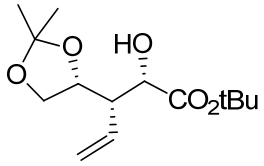
(2*S*,3*S*)-*tert*-Butyl 3-((4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl))-2-hydroxypent-4-enoate (9):

A solution of 1 M potassium *t*-butoxide (8.81 mL 8.81 mmol) in THF was added to a cold solution (-10 ºC) of **7** (2.00 g, 7.35 mmol) in THF (73 mL) and stirred for 1 h. The reaction was quenched with water (10 mL). The reaction mixture was diluted with ethyl acetate, the organic layer was separated and the aqueous layer was extracted with ethyl acetate (3x15 mL). The organic layers were combined, washed with brine and dry over $MgSO_4$. The solvent was concentrated under vacuum and the residue was purified with a gradient of 5% - 10% ethyl acetate/hexanes. The desired rearranged product **9** (1.26 g, 63% yield (17:1 dr)) was obtained as a colorless oil. R_f = 0.49 (30% ethyl acetate/hexanes). $[\alpha]^{23}_D$ + 4.85 (*c* 1.3, CH_2Cl_2); Major product: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81-5.75 (m, 1H). 5.16 (dd, *J* = 17.1, 10.3 Hz, 2H) 4.28 (q, *J* = 6.4 Hz, 1H),), 4.1 (q, *J* = 2.5 Hz, 1H), 4.05 (t, *J* = 6.2 Hz, 1H), 3.80 (t, *J* = 7.8 Hz, 1H), 3.08 (d, *J* = 4.7, 1H), 2.57-2.54 (m, 1H), 1.43 (s, 9H), 1.32 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 132.4, 119.6, 109.1, 82.7, 76.0, 71.2, 67.3, 50.3, 27.9, 26.8, 25.4.



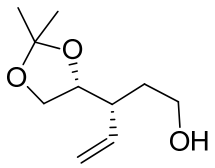
(2*R*,3*S*)-*tert*-Butyl 3-((4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxypent-4-enoate:

Minor product: $[\alpha]^{23}_{D}$ -25.2 (*c* 1.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.76 – 5.86 (m, 1H), 5.20 (dd, *J*= 17.2, 10.3 Hz, 2H), 4.36-4.32 (m, 1H), 4.06 -3.99 (m, 2H), 3.70 (t, *J* = 7.9, 1H), 3.0 (d, *J* = 8.2 Hz, 1H), 2.47-2.41 (m, 1H), 1.46 (s, 9H), 1. 29 (s, 3H), 1.23 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 133.3, 119.4, 109.0, 82.7, 74.7, 72.3, 67.2, 51.0, 27.9, 26.1, 25.3



(2*S*,3*S*)-*tert*-Butyl 3-((4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl))-2-hydroxypent-4-enoate (9) [2]:

A solution of LiHMDS (18 mL 1 M in THF, 18 mmol) was added to a cold solution (-45 ºC) of **7** (3.60 g, 13.2 mmol) in THF (100 mL). The reaction mixture was allowed to warm slowly to -30 ºC over 1 h. the reaction was quenched with saturated ammonium chloride (10 mL) extracted with ethyl acetate (3x20 mL) after warming to room temperature. The organic layers were combined washed with brine, dry over anhydrous $MgSO_4$ and reduce under vacuum. The residue was purified with a 5 - 10 percent gradient of ethyl acetate/hexanes. The desired rearranged product **9** (3.00 g, 83% yield) was obtained as a colorless oil. The spectral data was identical to the product obtained with potassium *t*-butoxide.

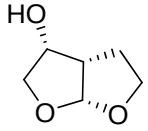


(3*R*)-3-((4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)pent-4-en-1-ol (10):

To a cold (-20 ºC) THF (25 mL) solution of **9** (2 g, 7.35 mmol) was added triethyl amine (3 mL, 22.1 mmol) followed by MsCl (0.7 mL, 8.81 mmol). The reaction was stirred for 2 h. The reaction was quenched with saturated ammonium chloride (10 mL) then extracted with ethyl

acetate (3x15 mL). The organic layers were combined and dried over anhydrous $MgSO_4$. The solvent was concentrated under vacuum and the crude mixture was purified using 10% ethyl acetate/hexanes to obtain the desired mesylated compound (2.4 g, 93% yield) as a colorless oil. R_f = 0.41 (30% ethyl acetate/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84-5.75 (m, 1H), 5.24 (dd, *J* = 17.2, 10.3 Hz, 2H), 4.97 (d, *J* = 3.1 Hz, 1H), 4.22 (q, *J* = 4.7 Hz, 1H), 4.09 (t, *J* = 6.2 Hz, 1H), 3.78 (t, *J* = 8.0 Hz, 1H), 3.07 (s, 3H), 2.79 - 2.74 (m, 1H), 1.46 (s, 9H), 1.33 (s, 3H), 1.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 131.3, 120.8, 109.4, 83.6, 78.1, 74.9, 66.9, 49.1, 39.2, 27.9, 26.4, 25.2.

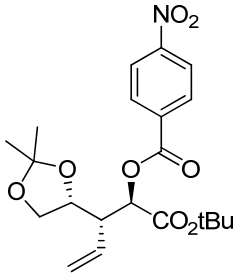
The mesylated compound above was dissolved (632 mg, 1.80 mmol) in THF (10 mL) at 0 ºC was added lithium aluminum hydride (288 mg, 7.2 mmol). The reaction was stirred for 30 min at 0 ºC then stirred for 6 h at room temperature. (A small aliquot of the reaction was quenched and checked by NMR to determine the reaction's progress). The reaction was cooled to 0 ºC and diluted with ethyl acetate. This was followed by the stepwise addition of 3N NaOH (0.5 mL) and H_2O (1 mL). The reaction was stirred until a white precipitate formed. $MgSO_4$ was added to the solution and the white solid was filtered out. The solvent was removed under vacuum and the crude was purified by flash column chromatography (gradient 10% - 20% ethyl acetate/hexanes) to give **10** (270 mg, 80% yield) as a colorless oil. R_f = 0.27 (40% ethyl acetate/hexanes). $[\alpha]^{23}_D$ -47.51 (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.71-5.64 (m, 1H), 5.12 (dd, *J* = 15.7, 10.3 Hz, 2H), 4.08 (q, *J* = 6.9 Hz, 1H), 3.98 (t, *J* = 6.3 Hz, 1H), 3.71 - 3.61 (m, 3H), 2.33 (m, 1H), 1.98 (bs, 1H), 1.69 - 1.60 (m, 2H), 1.33 (s, 3H), 1.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.3, 117.6, 108.9, 78.1, 67.1, 60.2, 43.6, 33.7, 26.2, 25.2



(3*R*,3*aS*,6*aR*)-Hexahydrofuro[2,3-*b*]furan-3-ol (11):

Into a cold a solution of **10** (2.6 g, 14 mmol) in CH_2Cl_2/MeOH (50 mL, 4:1 at -78 ºC) was bubbled a stream of ozone until a blue color persisted. The ozone stream was stopped and a stream of argon was bubbled through the reaction mixture to remove the excess ozone. Dimethyl sulfide (5.02 mL, 69.8 mmol) was added to the reaction and the mixture was warmed to room temperature and stirred an additional 3 h. The reaction mixture was carefully concentrated at (0

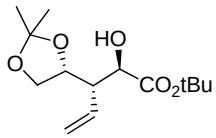
ºC) to remove any excess of dimethyl sulfide, then, 20 mL of $CHCl_3$, *p*-TsOH (90 mg, 0.473 mmol) and MeOH (0.5 µL) were added to the residue and the mixture was refluxed for 1 h. The reaction was again carefully concentrated and the residue was purified on silica gel (20% ether/hexanes to 40% ether/hexanes) to afford compound **11**, (1.45 g, 80 % yield) as a colorless oil. R_f = 0.2 (60% ethyl acetate/hexanes). $[\alpha]^{23}_D$ -13.2 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.67 (d, *J* = 5.1 Hz, 1H), 4.45 - 4.42 (m, 1H), 3.92-3.99 (m, 2H), 3.89 - 3.85 (m, 1H), 3.62 (dd, *J* = 9.1, 7.0 Hz, 1H), 2.87- 2.83 (m, 1H), 2.33-2.27 (m, 1H), 2.22 (d, *J* = 5.1 Hz, 1H), 1.81- 1.91 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 109.4, 73.0, 70.8, 69.8, 46.5, 24.8.



(2*S*,3*R*)-1-tert-Butoxy-3-((4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-1-oxopent-4-en-2-yl-4-nitrobenzoate (16)[3]:

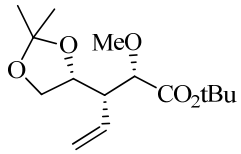
Into a cold (0 ºC) solution of **9** (0.29 g, 1.06 mmol) in THF (10 mL) was added triphenylphosphine (1.12 g, 4.25 mmol) p-nitrophenylbenzoic acid (0.71 g, 4.25 mmol) and diethyl azodicarboxylate (0.74 g, 4.25 mmol). The reaction was allowed to stir 24 h. The reaction was diluted with ethyl acetate (10 mL) and quenched with a saturated solution of sodium bicarbonate (10 mL). The reaction was extracted with ethyl acetate (3x15 mL). The organic layers were combined, washed with brine and dried over anhydrous sodium sulfate. The solvent was concentrated under vacuum and the crude mixture was purified on silica gel using 5% ethyl acetate/hexanes to obtain **17** (0.39 g, 87%) as a pale yellow solid. R_f = 0.24 (10% ethyl acetate/hexanes). $[\alpha]_{23}^{D}$ +2.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, *J* = 15.6, 2H), 8.22 (d, *J* = 15.6, 2H), 5.83-5.57 (m, 1H), 5.30 (dd, 17.2, 10.3 Hz, 2H), 5.11 (d, *J* = 7.3 Hz, 1H), 4.43 (q, *J* = 2.2 Hz, 1H), 4.09 (t, *J* = 6.34 Hz, 1H), 3.78 (t, 8.00 Hz, 1H), 2.80 - 2.79 (m, 1H), 1.45 (s, 9H), 1.41 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 163.9, 150.7, 134.8, 131.8, 130.9, 123.5, 120.5, 109.3, 83.0, 74.6, 73.9, 48.5, 27.9, 26.1, 25.2

Removal of Benzoate Ester and General Procedures for O-Methylation:



(2*R*,3*S*)-*tert*-Butyl -3-((4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxypent-4-enoate:

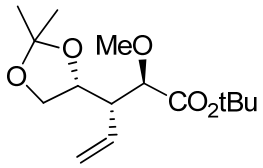
To a cold (0 ºC) solution of **16** (0.39 g, 0.93 mmol) in methanol was added potassium carbonate (260 mg, 1.85 mmol). The reaction was allowed to stir for 0.5 h. The reaction was quenched with a saturated ammonium chloride (5 mL) and the methanol was removed under vacuum. The solution was extracted with ethyl acetate (3x10 mL) and the combined organic layer was combined, washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under vacuum and the residue was purified on silica gel using 10% ethyl acetate/hexanes to obtain the free secondary alcohol (0.226 mg, 90% yield) as a white solid. $\mathbf{R_f}$ = 0.38 (30% ethyl acetate/hexanes). $[\alpha]_{23}^{D}$ -25.2 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85 - 5.78 (m, 1H), 5.21 (dd, *J* = 17.3, 10.3 Hz, 2H), 4.36 - 4.34 (m, 1H), 4.08 - 4.00 (m, 2H), 3.71 (t, *J* = 7.73 Hz, 1H), 2.97 (d, *J* = 8.1 Hz, 1H), 2.48 - 2.43 (m, 1H), 1.47 (s, 9H), 1.42 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 133.3, 119.0, 109.0, 82.7, 74.8, 72.3, 67.2, 51.0, 27.9, 26.1, 25.3



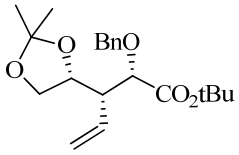
(2*S*,3*R*)-*tert*-Butyl 3-((4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-methoxypent-4-enoate (12):

To a cold (0 ºC) solution of **9** (200 mg, 0.73 mmol) and methyl iodide (90 μL) in THF (5 mL) was added sodium hydride (230 mg, 0.96 mmol). The reaction was allowed to stir for 2 h at 23 ºC then quenched with saturated ammonium chloride (5 mL). The reaction mixture was extracted with ethyl acetate (3x10 mL). The organic layers were combined, washed with brine and dried over anhydrous sodium sulfate. The solvent was reduced under vacuum and the residue was purified on silica gel to obtain **12** (190 mg, 90% yield) as a colorless oil. R_f = 0.62 (30% ethyl acetate/hexanes). $[\alpha]_{23}^{D}$ - 31.2 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81 - 5.75 (m, 1H), 5.13 (dd, 17.1, 10.3, 2H), 4.2 (q, *J* = 7.0 Hz, 1H), 3.98 (dd, *J* = 6.1, 2.0 Hz, 1H), 3.79 (t,

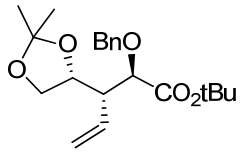
J = 3.79 Hz, 2H), 3.33 (s, 3H), 2.61-2.56 (m, 1H), 1.43 (s, 9H), 1.38 (s, 3H), 1.32 (s, 3H) ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 133.3, 119.1, 108.8, 81.6, 80.9, 75.5, 67.2, 58.3, 49.8, 28.0, 26.5, 25.4



(2*R*,3*R*)-*tert*-Butyl 3-((4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-methoxypent-4-enoate (17):
Follow the general procedure outlined for compound **12.** R_f = 0.7 (30% ethyl acetate/hexanes). $[\alpha]_{23}^{D}$ -22.4 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 5.75 - 5.22 (m, 1H), 5.16 (dd, *J* = 17.2, 10.3 Hz, 2H), 4.40 - 4.36 (m, 1H), 4.00 (t, *J* = 6.8 Hz, 1H), 3.65 (m, 2H), 3.37 (s, 3H), 2.44 - 2.38 (m, 1H), 1.45 (s, 9H), 1.38 (s, 3H), 1.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 170.5, 132.2, 120.1, 108.6, 81.9, 81.7, 73.9, 67.2, 57.9, 50.1, 28.0, 26.1, 25.3



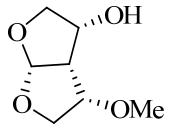
(2*S*,3*R*)-*tert*-Butyl 2-(benzyloxy)-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-enoate (13):
To a cold (0 ºC) solution of **9** (200 mg, 0.73 mmol), benzyl bromide (180 μL, 1.47 mmol) tetrabutyl ammonium bromide (270 mg, 0.07 mmol) in THF (5 mL) was added sodium hydride (23 mg, 0.95 mmol). The reaction was allowed to stir for 2 h at 23 ºC and then quenched with saturated ammonium chloride (5 mL). The reaction was extracted with ethyl acetate (3x10 mL). The organic layers were combined, washed with brine and dried over anhydrous sodium sulfate. The solvent was reduced under vacuum and the residue was purified on silica gel to obtain **13** (263 mg, 99% yield) as a colorless oil. R_f = 0.61 (20% ethyl acetate/hexanes). $[\alpha]_{23}^{D}$ -36.8 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.35-7.29 (m, 5H), 5.95-5.85 (m, 1H), 5.18 (dd, *J* = 17.2, 10.3 Hz, 2H) 4.75 (d, *J* = 11.5 Hz, 1H), 4.33 (d. *J* = 11.5 Hz, 1 H), 4.20 (q, *J* = 7.3, 1H), 3.85 (d, *J* = 3.5 Hz, 1H), 3.77 (dd, *J* = 6.1, 2.0 Hz, 1H), 3.66 (t, *J* = 7.7 Hz, 1H), 2.64-2.58 (m, 1H), 1.47 (s, 9H), 1.39 (s, 3H), 1.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 137.3, 133.5, 128.3, 128.2, 127.9, 119.1, 108.9, 81.7, 78.2, 75.6, 72.3, 67.2, 50.3, 28.1, 26.6, 25.4



(2*R*,3R)-*tert*-Butyl 2-(Benzyloxy)-3-((4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-enoate (18):

Follow the procedure outlined for compound **13**.

R_f = 0.58 (20% ethyl acetate/hexanes). $[\alpha]_{23}^{D}$ +32.3 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 - 7.29 (m, 5H), 5.76 - 5.71 (m, 1H), 5.73 (dd, *J* = 17.2, 10.3 Hz, 2H), 4.62 (d, *J* = 11.5 Hz, 1H), 4.44 (d, *J* = 11.5 Hz, 1H), 3.98 (t, *J* = 6.4 Hz, 1H), 3.88 (d, *J* = 9.5 Hz, 1H), 3.65 (t, *J* = 7.9 Hz, 1H), 2.54 - 2.51 (m, 1H), 1.44 (s, 9H), 1.37 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 137.3, 132.2, 128.3, 128.0, 127.8, 120.1, 108.5, 81.7, 79.8, 73.9, 72.3, 67.2, 49.9, 28.0, 26.1, 25.3

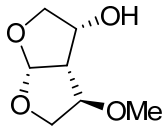


(3*R*,3*aR*,4*S*,6*aS*)-4-Methoxyhexahydrofuro[2,3-*b*]furan-3-ol (14):

To a cold (0 ºC) solution of **12** (100 mg, 0.35 mmol) in THF (5 mL) was added lithium aluminum hydride (28 mg, 0.73 mmol). The reaction was allowed to stir for 1 h at 23 ºC after which the reaction was cooled to 0 ºC and quenched by adding excess ethyl acetate, 1 N NaOH (0.5 mL), H_2O (0.5 mL). After a white precipitate formed magnesium sulfate was added and stirred for 15 min. The reaction mixture was filtered and concentrated under vacuum.

The crude mixture was taken up in DCM/MeOH (5 mL, 4:1) and a stream of ozonized oxygen was bubble through the solution until a blue color persisted. Argon was bubbled through the blue solution until the solution became clear. Dimethyl sulfide (130 μL, 1.75 mmol) was added to the reaction and the mixture was warmed to room temperature and stirred an additional 3 h. The reaction mixture was carefully concentrated at (0 ºC) to remove any excess of dimethyl sulfide, then, 5 mL of CH_2Cl_2, *p*-TsOH (6 mg, 0.04 mmol) and MeOH (0.5 μL) were added to the residue and the mixture was stirred for 2 h at room temperature. The reaction was again carefully concentrated and the residue was purified on silica gel (20% ether/hexanes to 50% ether/hexanes) to afford compound **14**, (30 mg, 54 % yield 2 steps) as a colorless oil. R_f = 0.20 (60% ethyl acetate/hexanes). $[\alpha]_{23}^{D}$ -35.9 (*c* 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.59 (d,

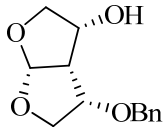
J = 5.5 Hz, 1H), 4.51 (m, 1H), 4.25 (m, 2H), 4.09 (dd, *J* = 5.9, 6.0 Hz, 1H), 3.97 - 3.89 (m, 3H), 3.43 (s, 3H), 2.91 - 2.85 (m, 1H) ^{13}C NMR (100 MHz, $CDCl_3$): δ 108.8, 82.9, 74.2, 73.7, 70.9, 58.1, 46.5



(3*R*,3*aR*,4*R*,6*aS*)-4-Methoxyhexahydrofuro[2,3-*b*]furan-3-ol (19):

Followed the general procedure outlined for compound **14**.

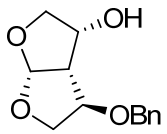
R_f = 0.26 (60% ethyl acetate/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): *δ*5.74 (d, *J* = 5.2 Hz, 1H), 4.51 - 4.46 (m, 1H), 4.23 (d, *J* = 3.5 Hz 1H), 4.03 (d, *J* = 10.2 Hz. 1H), 3.96 - 3.91 (m, 2H), 3.55 (dd, J = 6.7, 6.8 Hz, 1H), 3.29 (s, 3H), 2.95 (bs, 1H), 2.81 (dd, J = 5.25, 5.4 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 109.1, 80.67, 73.7, 73.3, 69.6, 56.4, 52.9



(3*R*,3*aR*,4*S*,6*aS*)-4-(Benzyloxy)hexahydrofuro[2,3-*b*]furan-3-ol (15):

Followed the general procedure outlined for compound **14**.

R_f = 0.43 (60% ethyl acetate/hexanes). $[\alpha]_{23}^{D}$ -22.9 (*c* 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.38 - 7.32- (m, 5H), 5.59 (d, *J* = 5.5 Hz, 1H), 4.66 (d, 11.5 Hz, 1H), 4.55 (d, 11.5 Hz, 1H), 4.48 - 4.44 (m, 2H), 4.28 (d, *J* = 6.3 Hz, 1H), 4.11 (dd, *J* = 6.8, 2.3 Hz, 1H), 3.97-3.92- (m, 3H), 2.88-2.83 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.4, 128.7, 128.5, 127.9, 108.7, 80.8, 74.4, 73.7, 73.2, 71.2, 46.6



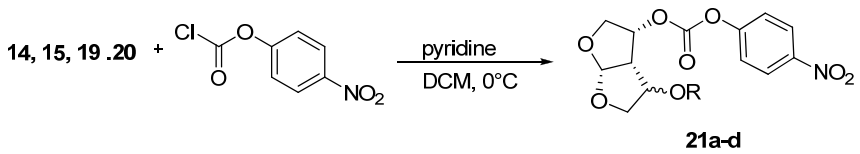
(3*R*,3*aR*,4R,6*aS*)-4-(Benzyloxy)hexahydrofuro[2,3-*b*]furan-3-ol (20):

Followed the general procedure outlined for compound **14**.

R_f = 0.52 (60% ethyl acetate/hexanes). $[\alpha]_{23}^{D}$ +58.6 (*c* 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.38-7.29 (m, 5H), 5.82 (d, *J* = 5.3 Hz, 1H), 4.56-4.46 (m, 4H), 4.12 (d, *J* = 10.2 Hz, 1H), 4.03

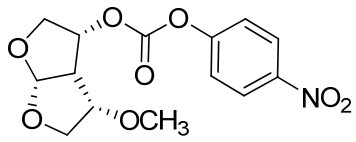
- 3.96 (m, 2H) 3.61 - 3.57 (dd, *J* = 6.9, 6.8 Hz, 1H), 2.91 (dd, *J* = 5.3, 5.4 Hz, 1H), 2.16 (bs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.7, 128.4, 127.7, 127.7, 109.2, 78.6, 74.2, 73.2, 71.1, 68.9, 55.4

Preparation of activated carbonates from polycyclic P2-ligands: 15, 16, 21, 22



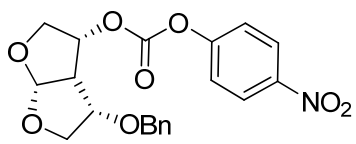
21a-d

To a solution of the corresponding ligand (**14**, **15**, **19**, and **20**) in dry CH_2Cl_2 was added pyridine (2.3 equiv). The resulting mixture was cooled to 0 ºC under argon and 4-nitrophenylchloroformate (2.2 equiv) was added in one portion. The resulting mixture was stirred at 0 ºC until completion. The reaction mixture was evaporated to dryness and the residue was purified by flash column chromatography on silica gel using a gradient of 20-40% ethyl acetate/hexanes to afford the desired ligand-activated carbonate **21a-d**.

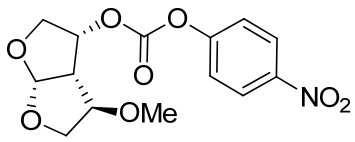


(3*R*,3*aR*,4*S*,6*aR*)-4-Methoxyhexahydrofuro[2,3-*b*]furan-3-yl 4-nitrophenyl carbonate (21a):

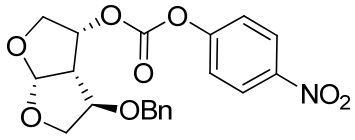
The reaction mixture was purified on silica gel using 40% ethyl acetate/hexanes. The desired activated alcohol was obtained as a white solid (33 mg, 80% yield). R_f = 0.12 (60% ethyl acetate/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, *J* = 10.3 Hz, 2H), 7.35 (d, *J* = 10.3 Hz, 2H), 5.72 (d, *J* = 5.1 Hz, 1H), 5.57 - 5.34 (m, 1H), 4.29-4.19 (m, 2H), 4.1 - 4.01 (m, 3H), 3.38 (s, 3H), 3.12 -3.07 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 152.1, 145.4, 125.2, 121.8, 108.6, 81.1, 77.4, 73.2, 70.7, 59.0, 46.2



(3*R*,3*aR*,4*S*,6*aR*)-4-(Benzyloxy)hexahydrofuro[2,3-*b*]furan-3-yl 4-nitrophenyl carbonate (21b): The reaction mixture was purified on silica gel using 20% ethyl acetate/hexanes. The desired activated alcohol was obtained as a white solid (41 mg, 80% yield). R_f = 0.42 (40% ethyl acetate/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, J = 7.1 Hz, 2H), 7.30 (bs, 5H), 6.95 (d, J = 7.1 Hz, 2H), 5.71 (d, J = 5.2 Hz, 1H), 5.61 - 5.58 (m, 1H), 4.41 (d, J = 11.2 Hz, 1H), 4.52 (d, J = 11.2 Hz, 1H), 4.42 (q, J = 7.6 Hz, 1H), 4.29 (dd, J = 2.7, 10.4 Hz, 1H), 4.13 - 4.07 (m, 3H), 3.11 - 3.06 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.3, 152.0, 145.1, 137.1, 128.4, 128.1, 127.9, 124.9, 121.7, 108.5, 79.3, 77.5, 73.7, 73.4, 70.8, 46.7



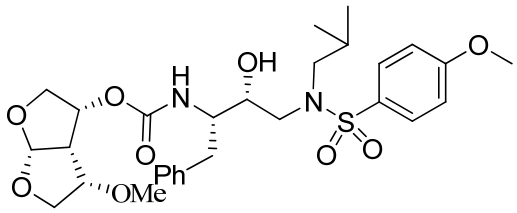
(3*R*,3*aS*,4*S*,6*aR*)-4-Methoxyhexahydrofuro[2,3-*b*]furan-3-yl 4-nitrophenyl carbonate (21c): The reaction mixture was purified on silica gel using 30% ethyl acetate/hexanes. The desired activated alcohol was obtained as a white solid (49 mg, 80% yield). R_f = 0.15 (30% ethyl acetate/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, J = 9.9 Hz, 2H), 7.38 (d, J = 10.2, 2H), 5.87 (d, J = 5.2 Hz, 1H), 5.32-5.37 (m, 1H), 4.17 - 4.12 (m, 3H), 4.10 (dd, J = 3.8, 5.6 Hz. 1H), 3.91 (dd, J = 5.57, 5.57 Hz, 1H), 3.34 (s, 3H), 3.13 - 3.10 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.0, 151.8, 145.6, 125.3, 121.5, 108.8, 80.8, 77.3, 73.5, 70.6, 56.6, 51.1



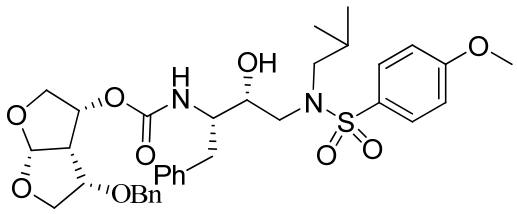
(3*R*,3*aS*,4*R*,6*aR*)-4-Methoxyhexahydrofuro[2,3-*b*]furan-3-yl 4-nitrophenyl carbonate (21d): The reaction mixture was purified on silica gel using 20% ethyl acetate/hexanes. The desired activated alcohol was obtained as a white solid (51 mg, 89% yield). R_f = 0.30 (30% ethyl acetate/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, J = 9.9 Hz, 2H), 7.34 - 7.27 (m, 7H), 5.91 (d, J = 4.0 Hz, 1H), 5.29-5.37 (m, 1H), 4.55 (s, 3H), 4.30 (J = 3.5 Hz, 1H), 4.20 - 4.14 (m, 2H), 4.08 (dd, J = 3.7, 3.8 Hz, 1H), 3.92 (dd, J = 5.7, 5.7 Hz, 1H), 3.20 (dd, J = 5.1, 5.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.9, 151.7, 145.5, 137.2, 128.5, 127.9, 127.5, 125.3, 121.5, 108.9, 78.5, 76.4, 74.0, 70.9, 70.4, 51.5

General procedure for the synthesis of HIV-1-protease inhibitors:

Isostere **22** was taken up in CH_3CN and cooled to 0 °C. *i*Pr_2EtN (5 equiv) was added, and the resulting solution was stirred for 5 min. A solution of the corresponding activated bis-THF ligand (**14, 15, 19** and **20**) in THF was added via cannula and the resulting solution was stirred at room temperature for 24 h to 3 days or until the reaction was complete. The solution was evaporated to dryness and the crude residue purified by flash column chromatography on silica gel to yield the desired inhibitor.

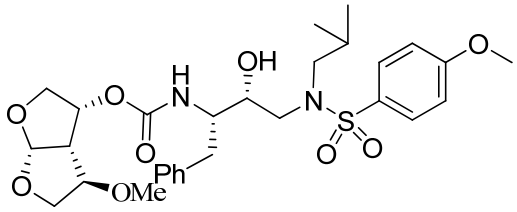


(*3R,3aS,4S,6aR*)-4-methoxyhexahydrofuro[2,3-*b*]furan-3-yl-(*2S,3R*)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-ylcarbamate, 23a: The reaction mixture was purified on silica gel using 40% ethyl acetate/hexanes. The desired inhibitor was obtained as an amorphous solid (20 mg, 55% yield). R_f = 0.12 (60% ethyl acetate/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 8.8, 2H), 7.34 – 7.13 (m, 6H), 6.97 (d, J = 8.9, 2H), 5.63 (d, J = 5.3, 1H), 5.44 – 5.37 (m, 1H), 4.88 (d, J = 8.9, 1H), 4.13 – 3.74 (m, 9H), 3.20 (s, 3H), 3.15 – 2.82 (m, 7H), 2.77 (dd, J = 13.4, 6.8, 1H), 1.85 – 1.70 (m, 1H), 0.88 (d, J = 6.6, 3H), 0.84 (t, J = 5.6, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 155.7, 137.1, 129.8, 129.6, 129.4, 128.4, 126.5, 114.2, 109.0, 80.7, 73.8, 72.9, 71.9, 71.3, 58.6, 58.5, 55.6, 54.6, 53.6, 46.4, 35.3, 27.1, 20.1, 19.7

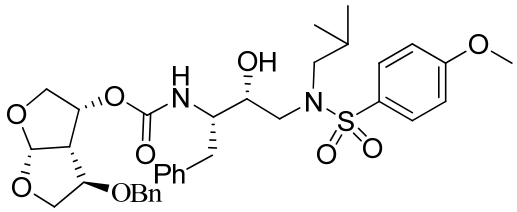


(*3R,3aS,4S,6aR*)-4-(benzyloxy)hexahydrofuro[2,3-*b*]furan-3-yl-(*2S,3R*)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-ylcarbamate, 23b: The reaction mixture was purified on silica gel using 40% ethyl acetate/hexanes. The desired inhibitor was

obtained as an amorphous solid (25 mg, 71% yield). R_f = 0.26 (50% ethyl acetate/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, *J* = 8.9, 2H), 7.36 – 7.13 (m, 10H), 6.97 (d, *J* = 8.9, 2H), 5.62 (d, *J* = 5.3, 1H), 5.46 – 5.40 (m, 1H), 4.72 (d, *J* = 9.0, 1H), 4.44 (q, *J* = 11.8, 2H), 4.26 (d, *J* = 7.8, 1H), 4.07 (dd, *J* = 9.9, 3.0, 1H), 3.98 – 3.88 (m, 3H), 3.86 (s, 3H), 3.82 – 3.69 (m, 2H), 3.66 (ddd, *J* = 8.6, 6.0, 2.9, 1H), 3.09 (dd, *J* = 15.2, 8.8, 1H), 2.96 – 2.83 (m, 4H), 2.73 (dd, *J* = 13.4, 6.6, 1H), 2.56 (dd, *J* = 13.9, 5.1, 1H), 1.82 – 1.55 (m, 1H), 0.87 (d, *J* = 6.6, 3H), 0.83 (d, *J* = 6.6, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9, 155.6, 137.5, 136.9, 129.8, 129.7, 129.4, 128.4, 127.9, 125.5, 114.2, 108.7, 78.3, 74.0, 73.1, 73.0, 71.6, 71.4, 58.6, 55.5, 54.3, 53.6, 46.8, 34.9, 27.1, 20.1, 19.7.



(*3R,3aS,4R,6aR*)-4-methoxyhexahydrofuro[2,3-*b*]furan-3-yl-(*2S,3R*)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-ylcarbamate, 23c: The reaction mixture was purified on silica gel using 40% ethyl acetate/hexanes. The desired inhibitor was obtained as an amorphous solid (28 mg, 77% yield). R_f = 0.14 (50% ethyl acetate/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ δ 7.71 (d, *J* = 8.8, 2H), 7.32 – 7.18 (m, 5H), 6.98 (d, *J* = 8.8, 2H), 5.74 (d, *J* = 5.2, 1H), 5.10 (dd, *J* = 21.2, 8.6, 2H), 4.00 – 3.82 (m, 7H), 3.77 (dd, *J* = 10.1, 3.7, 1H), 3.69 (dd, *J* = 9.8, 5.6, 2H), 3.41 (d, *J* = 3.3, 1H), 3.22 – 3.03 (m, 5H), 3.03 – 2.85 (m, 3H), 2.81 (dd, *J* = 13.5, 6.8, 2H), 1.84 (s, 1H), 0.92 (d, *J* = 6.6, 3H), 0.88 (d, *J* = 6.6, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 155.2, 137.6, 129.6, 129.4, 129.2, 128.5, 126.6, 114.3, 108.9, 80.9, 73.9, 72.8, 72.3, 71.0, 58.7, 56.2, 55.6, 55.3, 53.6, 51.0, 35.4, 27.2, 20.12, 19.88.



(*3R,3aS,4R,6aR*)-4-(benzyloxy)hexahydrofuro[2,3-*b*]furan-3-yl-(*2S,3R*)-3-hydroxy-4-(N-isobutyl-4-methoxyphenylsulfonamido)-1-phenylbutan-2-ylcarbamate, 23d: The reaction mixture was purified on silica gel using 40% ethyl acetate/hexanes. The desired inhibitor was

obtained as an amorphous solid (48 mg, 96% yield). R_f = 0.20 (40% ethyl acetate/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 7.1, 2H), 7.37 – 7.13 (m, 10H), 6.98 (d, *J* = 8.9, 2H), 5.79 (d, *J* = 5.2, 1H), 5.15 – 5.08 (m, 1H), 4.95 (d, *J* = 8.6, 1H), 4.37 (d, *J* = 11.8, 1H), 4.27 (d, *J* = 11.8, 1H), 4.07 – 3.91 (m, 2H), 3.91 – 3.79 (m, 6H), 3.70 (dd, *J* = 10.3, 4.1, 3H), 3.15 (dd, *J* = 15.2, 8.4, 1H), 2.98 (ddd, *J* = 16.4, 13.0, 7.7, 4H), 2.85 – 2.72 (m, 2H), 1.81 (dd, *J* = 14.0, 6.9, 1H), 0.92 (d, *J* = 6.6, 3H), 0.86 (t, *J* = 11.0, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 155.2, 137.7, 137.5, 129.6, 129.4, 129.3, 128.5, 128.3, 127.7, 127.4, 126.6, 114.3, 109.0, 79.2, 74.3, 72.7, 72.4, 71.1, 70.8, 58.7, 55.6, 55.2, 53.6, 51.6, 35.4, 27.2, 20.1, 19.8.

Determination of X-ray structures of HIV-1 protease-inhibitor complexes

The HIV-1 protease was expressed and purified as described.[4] The protease-inhibitor crystals were grown at room temperature by the hanging drop vapor diffusion method with well solutions of 1.2 M NaCl, 0.1M sodium citrate buffer (pH 5.5). The X-ray crystal structure was solved as described previously.[5] The crystallographic statistics are listed in Table 1. The coordinates and structure factors of the protease-GRL-04410A structure have been deposited in Protein Data Bank with code xxxx.

Table 1: Crystallographic data collection and refinement statistics

	PR_{WT}-GRL-044-10A (**23c**)
Space group	$P2_12_12$
Unit cell dimensions: (Å)	
a	58.44
b	86.11
c	46.03
Resolution range (Å)	50-1.40
Unique reflections	45,049
R_{merge} (%) overall (final shell)	8.0 (59.7)
I/σ(I) overall (final shell)	13.9 (2.1)
Completeness (%) overall (final shell)	96.6 (87.1)
Data range for refinement (Å)	10-1.40
R (%)	17.5
R_{free} (%)	23.0
No. of solvent atoms (total occupancies)	154 (105)

RMS deviation from ideality	
Bonds (Å)	0.010
Angle distance (Å)	0.029
Average B-factors (Å^2)	
Main-chain atoms	19.7
Side-chain atoms	26.3
Inhibitor atoms	18.0
Solvent atoms	27.9

References:

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