Supporting information

Title:**Olefin Metathesis in the Design and Synthesis of a Globally Constrained Grb2 SH2 Domain Inhibitor**

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(S)-*N*-Acroyl-4-phenyl-2-oxazolidinone (9). To a solution of acrylic acid (5.19 g, 72 mmol) in 200 mL of anhydrous THF containing 7.28 g of *N*-methylmorpholine, was added pivaloyl chloride (8.68 g, 72 mmol) at 0 ˚C under argon, and the mixture was stirred at –78 ˚C for 1 hr. To this was added by cannula, a cooled solution of lithium (S)-4-phenyl-2-oxazolidinone, (prepared by addition of BuLi (1.6 M, 37.5 mL, 60 mmol) to a suspension of (S)-(+)-4-phenyl-2-oxazolidinone (9.79 g, 60 mmol) in 200 mL of anhydrous THF at –78 ˚C under argon with stirring for 30 min.). After being stirred at –78 ˚C for 2 hr, the resulting solution was raised to room temperature and stirred overnight. To the mixture was added100 mL of saturated NH_4Cl; THF was evaporated under reduced pressure and residue was extracted with ethyl acetate, washed with H_2O and saturated brine, and dried over Na_2SO_4. Concentration and purification by silica gel chromatography (hexanes and ethyl acetate, from 10:1 to 4:1) afforded 12.30 g of product **9** (79% yield). m.p. 88 ˚C; NMR ($CDCl_3$) δ 7.58~7.48 (1H, dd, *J* = 10.5, 16.8 Hz), 7.44~7.30 (5H, m), 6.53~6.46 (1H, dd, *J* = 1.71, 17.1 Hz), 5.92~5.87 (1H, dd, *J* = 1.7, 10.3 Hz), 5.53~5.48 (1H, dd, *J* =3.9, 8.6 Hz), 4.81 (1H, t, *J* = 8.8 Hz), 4.42~4.37 (1H, dd, *J* =3.9, 8.8 Hz).

Di-*tert*-butyl p-bromobenzylphosphite (10). To the solution of di-*tert*-butylphosphite (9.72 g, 50 mmol) in 150 mL of anhydrous THF was added BuLi (2.5 M in hexanes, 20 mL, 50 mmol) dropwise at –78 ˚C under Argon, and the solution was stirred at –78 ˚C for 30 min, then raised to 0 ˚C and stirred for an additional 1 hr. To the resulting solution was added a solution of 4-bromobenzyl bromide in 50 mL of anhydrous THF at 0 ˚C. After stirring for an additional 2 hr at the same temperature, the solution was raised to room temperature and stirred overnight. To the mixture was added 100 mL of H_2O was added to quench the reaction and THF was evaporated under reduced pressure. Residue was extracted with ethyl acetate, washed with water and saturated brine and dried over Na_2SO_4. Concentration and purification by silica gel chromatography (hexanes and ethyl acetate, from 10:1 to 4:1) afforded 16.5 g of product (**10**) as a white solid (91% Yield). NMR ($CDCl_3$) δ 7.42 (2H, d, *J* = 8.3 Hz), 7.16 (2H, dd, *J* = 2.4, 8.6 Hz), 2.99 (2H, d, *J* = 21.5 Hz), 1.43 (18H, s).

3-[(2E)-3-(4-{[bis(*tert*-butoxy)phosphono]methyl}phenyl)prop-2-enoyl](4S)-4-phenyl-1,3-oxazolidin-2-one (11). To a mixture of *N*-acroyl-(S)-4-phenyl-2-

oxazolidinone (**9**) (6.40 g, 27.8 mmol), di-*tert*-butyl p-bromobenzylphosphite (**10**) (10.10 g, 27.8 mmol), palladium acetate (309 mg) and tri-o-tolylphosphine, was added, 100 mL of anhydrous triethylamine and the resulting solution was refluxed under argon overnight. A significant amount of precipitate formed, with silvering of the flask wall. Triethylamine was evaporated and residue was dissolved in 150 mL of dichloromethane, and solid palladium compound was removed by filtration. The filtrate was washed with H_2O and brine, dried over Na_2SO_4, and evaporated to dryness to give a yellow solid. Crude product was recrystallized from a mixture of hexanes-EtOAc-CH_2Cl_2 to provide product **11** as a white solid (8.93 g. Additional product was recovered by chromatographic purification of the mother liquor (2.95 g) to provide a combined yield of 86%. m.p. 145-146 ˚C; NMR ($CDCl_3$) δ 7.92 (1H, d, *J* = 14.9 Hz), 7.77 (1H, d, *J* = 16.4 Hz), 7.53 (2H, d, *J* =7.6 Hz), 7.48~7.18 (7 H, m), 5.57 (1H, dd, *J* = 3.7, 8.5 Hz), 4.75 (1H, t, *J* = 8.8 Hz), 4.33 (1H, dd, *J* = 3.9, 8.8 Hz), 3.07 (2H, d, *J* = 21.7 Hz), 1.46 (18H, s); FAB-MS (+Ve): 500 (MH^+), 444 ($MH^+ - C_4H_8$), 388 ($MH^+ - 2C_4H_8$).

3-[(3R)-3-(4-{[bis(tert-butoxy)phosphono]methyl}phenyl)pent-4-enoyl](4S)-4-phenyl -1,3-oxazolidin-2-one [(R)-12]. To a slurry of cuprous thiophenoxide (1.73 g, 10 mmol) in 300 mL of anhydrous ether under argon at –40 ˚C, was added vinyl magnesium bromide in THF (1.0 M, 30 mLl, 30.0 mmol, 3 eq.) dropwise. The mixture was allowed to warm to –25 ˚C whereupon a color change (from brown to black-green) indicating the formation of complex $PhSCu(RMgX)_n$ was observed, The mixture was stirred at room temperature for additional 1 hr, then a pre-cooled (-40 ˚C) solution of **11** (4.10 g, 10 mmol) in 100 mL of anhydrous THF was added dropwise. The mixture was stirred at –40 ˚C with monitoring by TLC. At 3 hr, all starting material had been consumed and the mixture was poured into an ice-cooled NH_4Cl solution and solid cuprous salts were removed by filtration. THF was removed by evaporation and residue was extracted with ethyl acetate, washed with H_2O, saturated brine, and dried over Na_2SO_4. Concentration and purification by silica gel chromatography (hexanes : EtOAc from 4:1 to 2:1) afforded a white solid (2.97 g), which upon crystallization (hexanes : EtOAc 4:1) gave pure (R)-**12** in 56% yield. m.p. 155-156 ˚C; $[\alpha]^{26}_D$ = +55.7 (c 0.70, $CHCl_3$); NMR ($CDCl_3$) δ 7.41~7.10 (9H, m), 5.96 (1H, ddd, *J* = 6.6 Hz), 5.31 (1H, dd, *J* = 3.4, 8.5 Hz), 4.98 (1H, ddd, *J* = 1.2, 1.2, 10.4 Hz), 4.93 (1H, ddd, *J* = 1.2, 1.2, 17.1 Hz), 4.59 (1H, t, *J* = 8.8 Hz), 4.24 (1H, dd, *J* = 3.3, 9.0 Hz), 3.89 (1H, m), 3.49 (1H, dd, *J* = 8.1, 16.4 Hz), 3.33 (1H, dd, *i* = 7.1, 16.4 Hz), 3.01 (2H, d, *J* = 21.5 Hz), 1.43 (18H, s); FAB-MS (+VE): 472 (MH^+-C_4H_8), 416 (MH^+-$2C_4H_8$).

(3R)-3-(4-{[bis(*tert*-butoxy)phosphono]methyl}phenyl)pent-4-enoic acid (7). To thae solution of **12** (527 mg, 1 mmol) in 16 mL of THF-H_2O (3:1) at 0 ˚C was added H_2O_2 (30%, 509 µl, 5.0 mmol) via syringe over 1 min, then this was followed by addition of LiOH (84 mg, 2 mmol in 2 mL of H_2O). The mixture was stirred 0 ˚C for 1 hr, then the mixture was brought to ambient temperature and stirred overnight. Excess hydrogen peroxide as destroyed by addition of 628 mg of Na_2SO_3 (5.0 mmol) in 4.0 mL of H_2O, then THF was evaporated at 30 ˚C and residue was extracted with dichloromethane to remove Evans' reagent. The resulting aqueous solution was poured into 25 mLl of ice-cold 0.2 M HCl, and extracted with ethyl acetate, washed with ice-cold H_2O and brine and dried over Na_2SO_4. Taking to dryness under high vacuum, provided **7** as a foam (204

mg, 80% yield). m.p. 93-95 ˚C; $[\alpha]^{26}_{D}$ = +5.9 (c 1.13, CH_2Cl_2); NMR ($CDCl_3$) δ 7.22~7.17 (2H, dd, *J* = 2.2, 8.3 Hz), 7.14 (2H, d, *J* = 8.6 Hz), 5.99 (1H, m), 5.12~5.00 (2H, m), 3.85 (1H, m), 2.96 (2H, d, *J* = 21.5 Hz), 2.80 (1H, dd, *J* = 7.6, 15.1 Hz), 2.70 (1H, dd, *J* = 8.1, 15.4 Hz), 1.41 (9H, s), 1.40 (9H, s); FAB-MS (+VE): 381(M^+-1).

(4R)-3-pent-4-enoyl)-4-phenyl-1,3-oxazolidin-2-one (13). To a solution of 4-pentenoic acid (3.60g, 36 mmol) in 100 mL of anhydrous THF containing 3.64 g (36 mmol) of *N*-methylmorpholine was added pivaloyl chloride (4.34 g, 36 mmol) at –78 ˚C under argon. The mixture was stirred at –78 ˚C for 30 min, then raised to 0 ˚C and stirred for an additional 1 hr. The mixture was re-cooled to –78 ˚C and stirred for 15 min before adding via cannula, a solution of lithium oxazolidionoe [prepared from BuLi (1.6 M, 18.8 mL, 30 mmol) and (R)-(-)-4-phenyl-2-oxazolidinone (4.90 g, 30 mmol) in 200 mLl of anhydrous THF at –78 ˚C under argon, 30 min.] After stirring at –78 ˚C for 2 hr, the solution was raised to room temperature and stirred overnight. The reaction was quenched by addition of 100 mL of ice-cold H_2O; THF was evaporated under reduced pressure and residue was extracted with ethyl acetate, washed with H_2O and saturated brine and dried over Na_2SO_4. Concentration and purification by silica gel chromatography (hexanes and ethyl acetate, from 10:1 to 4:1) afforded 6.82 g of product (**13**) (70% yield). m.p. 70 ˚C; NMR ($CDCl_3$) δ 7.44~7.27 (5H, m), 5.89~5.73 (1H, ddt, *J* = 6.6, 10.3, 16.9 Hz), 5.44 (1H, dd, *J* = 3.7, 8.6 Hz), 5.10~4.95 (2H, m), 4.70 (1H, t, *J* = 8.8 Hz), 4.30 (1H, dd, *J* = 3.7, 9.0 Hz), 3.06 (2H, t, *J* = 7.1 Hz), 2.37 (2H, m); FAB-MS (+VE): 246 (MH^+); FAB HRMS calcd for $C_{14}H_{16}NO_3$: 246.1130 (MH^+); found: 246.1110.

(4R)-3-[(2S)-2-(naphthylmethyl)pent-4-enoyl)-4-phenyl-1,3-oxazolidin-2-one (14). To a solution of (R)-*N*-(4-pentenoic)-4-phenyl-2-oxazolidinone (**13**) (6.88 g, 27.3 mmol) in 150 mL of dry THF, was added a solution of LiHMDS (1.0 M in THF; 27.3 mL, 27.3 mmol) at –78 ˚C under argon. The resulting solution was stirred at –78 ˚C for 2 hr, then a pre-cooled solution of 1-(bromomethyl)-naphthalene (12.07 g, 54.3 mmol) in 50 mL of THF was added and the resulting solution was stirred at –78 ˚C for 4 hr, then the mixture was brought to ambient temperature and stirred overnight. The reaction was quenched by addition of 100 mL of ice-cold H_2O, and THF was evaporated under reduced pressure. Residue was extracted with ethyl acetate, washed with H_2O and saturated brine and dried over Na_2SO_4. Concentration and purification by silica gel chromatography (hexanes and ethyl acetate, from 20:1 to 6:1) afforded 9.26 g of product **14** (88% yield). m.p. 75 ˚C; $[\alpha]^{26}_D$ = -43.9 (c 0.90, $CHCl_3$); NMR ($CDCl_3$) δ 8.81 (1H, d, *J* = 7.8 Hz), 7.85 (1H, dd, *J* = 2.2, 6.8 Hz), 7.71 (1H, d, *J* = 8.1 Hz), 7.56~7.44 (2H, m), 7.30~7.20 (4H, m), 7.14 (1H, dd, *J* = 0.7, 6.8 Hz), 6.99 (2H, m), 5.93~5.76 (1H, ddt, *J* = 7.3, 10.0, 16.8 Hz), 5.40 (1H, dd, *J* = 4.2, 8.8 Hz), 5.14~5.05 (2H, m), 4.61 (1H, t, *J* = 8.8 Hz), 4.54 (1H, m), 4.14 (1H, dd, *J* = 4.2, 8.8 Hz), 3.42 (1H, dd, *J* = 8.3, 13.7 Hz), 3.17 (1H, dd, *J* = 6.6, 13.9 Hz), 2.52 (1H, m), 2.24 (1H, m); FAB-MS (+VE): 386 (MH^+); FAB HRMS calcd for $C_{25}H_{24}NO_3$: 386.1756 (MH^+); found: 386.1728.

(2S)-2-(naphthylmethyl)pent-4-en-1-ol (15). To a solution of $LiAlH_4$ (0.90 g, 95%, 22.5 mmol) in 100 mL of anhydrous THF at -78˚C, was added a pre-cooled solution of **14** (8.65 g, 22.5 mmol) in 50 mLl of dry THF at –78 ˚C. The mixture was stirred at –78 ˚C for 1 hr, then raised to 0 ˚C over 1 hr. After stirring at 0 ˚C (0.5 hr), thae clear solution resulted, which was cooled to –78 ˚C, and 15 mL of ethyl acetate was added to destroy remaining $LiAlH_4$. The reaction was quenched by addition of aqueous NH_4Cl at –78 ˚C, then the mixture was brought to ambient temperature, diluted with H_2O, extracted with ether, washed with H_2O and brine and dried over Na_2SO_4. Concentration and purification by silica gel chromatography (hexanes and ethyl acetate, from 20:1 to 10:1) afforded **15** as an oil (3.63 g, 70% yield). NMR ($CDCl_3$) δ 8.07 (1H, m), 7.87 (1H, m), 7.74 (1H, d, *J* = 7.8 Hz), 7.49 (2H, m), 7.39 (1H, m), 7.31 (1H, m), 5.88 (1H, m), 5.11 (2H, m), 3.61 (2H, d, *J* = 5.1 Hz), 3.16 (1H, dd, *J* = 7.8, 13.9 Hz), 3.06 (1H, dd, *J* = 6.6, 13.9 Hz), 2.30 ~2.20 (2H, m), 2.15~2.06 (1H, m); FAB-MS (+VE): 226 (M^+); FAB HRMS calcd for $C_{16}H_{18}O$: 226.1358 (M^+); found: 226.1339.

2-[(2S)-2-(naphthylmethyl)pent-4-enyl)]-benzo[c]azolidine-1,3-dione (16). To a solution **15** (3.49 g, 15.4 mmol) in 30 mL of THF, was added phthalimide (2.2 2g, 15.4 mmol) and triphenylphosphine (4.06 g, 15.4 mmol) at 0 ˚C, followed by diisopropyl azodicarboylate (3.13 g, 15.4 mmol). After stirring overnight at room temperature, THF was evaporated, and residue was purified by chromatography to provide **16** as a sticky oil (4.01 g, 73% yield). NMR ($CDCl_3$) δ 7.96 (1H, m), 7.82 (3H, m), 7.68 (3H, m), 7.46 (2H, m), 7.36 (2H, m), 5.93~5.77 (1H, ddt, *J* =7.1, 10.3, 17.1Hz), 5.15~5.00 (2H, m), 3.79 (1H, dd, *J* =7.6, 13.7 Hz), 3.69 (1H, dd, *J* =7.3, 13.7 Hz), 3.09 (2H, d, *J* = 7.3 Hz), 2.70 (1H, m), 2.15 (2H, m); FAB-MS (+VE): 356 (MH^+).

(2S)-2-(Naphthylmethyl)pent-4-enylamine (8). To the solution of **16** (3.94 g, 11.1 mmol) in 100 mL of ethanol containing 820 μl of H_2O, was added 867 mg (26.7

mmol) of hydrazine hydrate, and the resulting solution was refluxed under argon for 4 hr during which time a significant quantity precipitate formed. The solution was cooled to room temperature and solid was filtered off and washed with a small amount of ethanol. The combined organic solution was evaporated to dryness, and residue was purified by silica gel chromatography (hexanes and ethyl acetate, 2:1, with 1% v/v of 2M NH_3-MeOH) to provide **8** as an oil (1.92 g, 77% yield. $[\alpha]^{26}_{D}$ = -22.1 (c 1.0, $CHCl_3$); NMR ($CDCl_3$) δ 8.07 (1H, m), 7.86 (1H, m), 7.73 (1H, d, *J* = 8.1 Hz), 7.55~7.44 (2H, m), 7.40 (1H, t, *J* = 7.1 Hz), 7.31 (1H, m), 5.95~5.79 (1H, ddt, *J* = 7.1, 10.4, 17.1 Hz), 5.18~5.05 (2H, m), 3.07 (2H, d, *J* = 7.3 Hz), 2.72 (2H, d, *J* = 5.6 Hz), 2.30~2.10 (2H, m), 2.05~1.92 (1H, m); FAB-MS (+VE): 226 (MH^+).

(2S)-*N*-[(2S)-2-(Naphthylmethyl)pent-4-enyl]-2-[(tertbutoxy)carbonylamino]-3-carbamoylpropanamide (17). To the solution of amine **8** (1.92 g, 8.51 mmol) in DMF was added the pre-activated Boc-Asn [formed by the reaction of Boc-Asn (1.97 g, 8.51 mmol), HOBt (1.15 g, 8.5 1mmol), and DIPCDI (1.08 g, 8.51 mmol) in 20 mL of dry DMF, 10 min]. The resulting mixture was stirred at room temperature for 12 hr, then DMF was evaporated to provide a solid, which was washed with ethyl acetate (30 mL x 5) to give 3.44 g of pure **17**. Purification of the organic washes by silica gel flash chromatography (chloroform : methanol, from 20:1 to 9:1) provided additional **17** (112 mg), resulting in a combined yield 95%. m.p. 180-181 ˚C; NMR ($CDCl_3$) δ 8.03~7.96 (1H, m), 7.87~7.83 (1H, m), 7.72 (1H, d, *J* = 7.8 Hz), 7.55~7.30 (4H, m), 6.96 (1H, s, br.), 6.15~6.00 (1H, s, br.), 5.92~5.75 (2H, m), 5.36 (1H, s, br.), 5.18~5.05 (2H, m), 4.50~4.35 (1H, m), 3.25 (2H, m), 3.11~2.84 (3H, m), 2.56~2.47 (1H, dd, *J* = 6.4, 15.6 Hz), 2.12 (3H, m), 1.44 (9H, s); FAB-MS (+VE): 440 (MH^+), 384 (MH^+-C_4H_8).

(2S)-*N*-[(2S)-2-(naphthylmethyl)pent-4-enyl]-3-carbamoyl-2-({[(fluoren-9-ylmethoxy)carbonylamino]cyclohexyl}carbonylamino)propanamide (18). To a suspension of **17** (3.56 g, 8.08 mmol) in 20 mL of dichloromethane was added 15 mL of trifluoroacetic acid, and the resulting clear solution was stirred at room temperature for 1 hr, then dichloromethane and TFA were removed by evaporation. The residue was dissolved in 150 mL of ethyl acetate, neutralized with saturated $NaHCO_3$, and washed with brine. Drying over Na_2SO_4 and taking to dryness under high vacuum provide the intermediat N-deblocked free amine as an oil. [NMR ($CDCl_3$) δ 8.10~7.27 (7H, m), 5.87~5.65 (1H, m), 5.20~4.90 (2H, m), 3.95 (1H, m, br.), 3.40~2.60 (5H, m), 2.25~2.00 (4H, m).] Tp a solution of crude amine in 20 mL of anhydrous DMF was added a pre-activated solution of Fmoc-1-amino-cyclohexane carboxylic acid [formed by reaction of Fmoc-1-amino-cyclohexane carboxylic acid (3.11 g, 8.51 mmol), HOBt (1.15 g, 8.5 1mmol), DIPCDI (1.08 g, 8.51 mmol) in 20 mL of DMF, 10 min] The resulting mixture was stirred at room temperature for 12 hr, then DMF was evaporated and residue was dissolved in 200 mL of dichloromethane; washed with saturated $NaHCO_3$ followed by H_2O, and brine then dried over Na_2SO_4. Concentration and purification by silica gel chromatography (chloroform and methanol, from 20:1 to 9:1) afforded 4.09 g of **18** (70% yield). NMR ($CDCl_3$) δ 8.11 (1H, d, *J* = 8.1 Hz), 8.00 (1H, d, *J* = 8.1 Hz), 7.81~7.65 (4H, m), 7.48~7.19 (11H, m), 6.06 (1H, s, br.), 5.83~5.66 (1H, m), 5.27 (1H, s, br.), 5.23 (1H, s, br.), 5.07~4.90 (2H, m), 4.75 (1H, m), 4.31~4.01 (3H, m), 3.32~3.00 (4H, m), 2.89

(1H, dd, *J* = 5.1, 14.2 Hz), 2.43 (1H, dd, *J* = 4.4, 14.9 Hz), 2.16~1.53 (13H, m); FAB-MS (+VE): 687 (MH^+).

(3R)-*N*-{[*N*-((1S)-1-{*N*-[(2S)-2-(Naphthylmethyl)pent-4-enyl]carbamoyl}-2-carbamo-ylethyl)carbamoyl]cyclohexyl}-3-(4-{[bis(*ter*t-butoxy)phosphono]methyl} phenyl) pent-4-enamide (6). To **18** (4.09 g, 5.96 mmol) in 50 mL of acetonitrile was added 4.0 mL of piperidine and the resulting solution was stirred at room temperature for 2 hr. Solvent was evaporated, and residue was purified by silica gel chromatography to give free amine as 2.71 g (98% yield). NMR ($CDCl_3$) δ 8.89 (1H, d, *J* = 6.8 Hz), 7.98 (1H, m), 7.85 (1H, m), 7.72 (1H, d, *J* = 7.8 Hz), 7.55~7.26 (7H, m), 6.31 (1H, s, br.), 5.91~5.75 (1H, m), 5.54 (1H, s, br.), 5.13~5.07 (2H, m), 4.68 (1H, dd, *J* = 6.1, 10.7 Hz), 3.35~3.21 (2H, m), 3.08 (1H, dd, *J* = 6.6, 14.2 Hz), 2.97 (1H, dd, *J* = 6.4, 13.9 Hz), 2.83 (1H, dd, *J* = 4.4, 15.1 Hz), 2.56 (1H, dd, *J* = 6.5, 14.6 Hz), 2.17 (2H, d, *J* = 5.9 Hz), 2.05~1.23 (11H, m). To a solution of amine (376 g, 0,80 mmol) in 5 ml of dry DMF was added the pre-activated ester solution of **7** [formed by the reaction of **7** (306 mg, 0.80 mmol), HOBt (109 mg, 0.80 mmol), and DIPCDI (101 mg, 0.80 mmol) in 5 mL of anhydrous DMF, 10 min]. The resulting mixture was stirred at room temperature for 12 hr, then DMF was evaporated. Rresidue was dissolved in 50 mL of ethyl acetate, washed with saturated $NaHCO_3$, then H_2O, and brine and dried over Na_2SO_4. Concentration and purification by silica gel chromatography (chloroform and methanol, from 20:1 to 9:1) provided **6** as a foam (569 mg, 86% yield. NMR ($CDCl_3$) δ 8.05 (1H, d, *J* = 8.1 Hz), 7.85~7.64 (4H, m), 7.55~7.38 (4H, m), 7.15 (2H, dd, *J* = 2.4, 7.8 Hz), 6.99 (2H, d, *J* =, 8.1 Hz), 6.28 (1H, s, br.), 5.96~5.77 (3H, m), 5.41 (1H, s, br.), 5.13~4.90 (4H, m), 4.72 (1H, m), 3.73 (1H, m), 3.37 (1H, m), 3.22~2.91 (6H, m), 2.65~2.45 (2H, m), 2.30~2.01 (3H, m), 1.95~1.09 (11H, m), 1.43 (9H, s), 1.41 (9H, s); FAB-MS (+VE): 828 (M^+), 772 (M^+-C_4H_8), 716 (M^+-$2C_4H_8$)

2-[(9S,13S,17R)-8,11,20-triaza-17-(4-{[bis(*tert*-butoxy)phosphono]methyl}phenyl)-13-(naphthylmethyl)-7,10,19-trioxospiro[5.14]icos-15-en-9-yl]acetamide (20). To a solution of **6** (429 mg, 0.52 mmol) in 120 mL of anhydrous dichloromethane (deoxygenized with argon) was added via syringe, ruthenium catalyst **19** (180 mg, 0.22 mmol, 0.4 eq.) in 37 mL of dichloromethane. The solution was refluxed under argon for 60 hr. with monitoring by TLC.. Solvent was evaporated and residue was purified by silica gel chromatography (chloroform-ethyl acetate-methanol, from 2:1:0 to 14:7:1) to provide **20** as a solid (279 mg, 67% yield. m.p. 210 ˚C; NMR ($CDCl_3$) δ 8.30~8.00 (2H, m), 7.83 (1H, m), 7.69 (1H, d, *J* = 7.8 Hz), 7.59 (1H, m), 7.55~7.30 (4H, m), 7.25~7.05 (4H, m), 6.35 (1H, s, br.), 6.28 (1H, s, br.), 5.66 (1H, dd, *J* = 9.3, 14.4 Hz), 5.31 (1H, m), 5.08 (1H, s, br.), 4.66 (1H, m), 3.90~3.70 (2H, m), 3.62 (1H, m), 3.33~3.08 (2H, m), 3.06~2.88 (4H, m), 2.85~2.50 (4H, m), 2.37~1.15 (11H, m), 1.42 (18H, s); FAB-MS (+VE): 801 (MH^+), 745 (MH^+-C_4H_8), 689 (MH^+-$2C_4H_8$).

2-[(9S,13S,17R)-8,11,20-triaza-13-(naphthylmethyl)-7,10,19-trioxo-17-[4-(phosphonomethyl)phenyl]spiro[5.14]icos-15-en-9-yl]acetamide (5). Treatment of **20** (179 mg,) with a solution of TFA-triethylsilane-H_2O (3.7 mL-0.1 mL-0.2 mL) at room temperature, (1 hr) followed by evaporation of solvent and trituration with ether,

provided a precipitate, which was separated by centrifugation. Solid was resuspended in ether, and collected by centrifugation, then dried under high vacuum provide crude product (144 mg). Crude solid was dissolved in 16 mL of acetonitrile-water (1:1), and purified by HPLC to provide title compound **5** as a white solid (73 mg, 60% yield). m.p. 225 ˚C; NMR (DMSO-d_6): 8.40 (1H, s), 8.23 (1H, d, *J* = 7.8 Hz), 8.12 (1H, d, *J* = 8.1 Hz), 7.89 (1H, d, *J* =7.6 Hz), 7.75 (1H, m), 7.56~7.38 (6H, m), 7.15~7.02 (5H, m), 5.55 (1H, dd, *J* = 9.5, 14.2 Hz), 5.37 (1H, m), 4.27 (1H, m), 3.86 (1H, m), 3.59 (1H, dd, *J* = 5.6, 11.7 Hz), 3.16 (1H, dd, *J* = 5.7, 14.4 Hz), 2.95~2.30 (8H, m), 2.25~1.10 (13H, m); FAB-MS (+VE): 687.6 (M^+-H); FAB HRMS for $C_{37}H_{45}N_4O_7P$ cacld.: 687.2948 (M^+-H); found: 687.2958.