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 added 100 mL of saturated NH4Cl; THF was evaporated under reduced pressure and residue was extracted with ethyl acetate, washed with H2O and saturated brine, and dried over Na2SO4. 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 (CDCl3) 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-butyl phosphite (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 H2O 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 Na2SO4. 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 (CDCl3) 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 H2O and brine, dried over Na2SO4 and evaporated to dryness to give a yellow solid. Crude product was recrystallized from a mixture of hexanes-EtOAc-CH2Cl2 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 (CDCl3) 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+ - C4H8), 388 (MH+ - 2C4H8).

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 mL, 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 NH4Cl solution and solid cuprous salts were removed by filtration. THF was removed by evaporation and residue was extracted with ethyl acetate, washed with H2O, saturated brine, and dried over Na2SO4. 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; [α]26D = +55.7 (c 0.70, CHCl3); NMR (CDCl3) 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 = 7.1, 16.4 Hz), 3.01 (2H, d, J = 21.5 Hz), 1.43 (18H, s); FAB-MS (+Ve): 472 (MH+-C4H8), 416 (MH+-2C4H8).

(3R)-3-(4-{(bis(tert-butoxy)phosphono)methyl}phenyl)pent-4-enoic acid (7). To the solution of 12 (527 mg, 1 mmol) in 16 mL of THF-H2O (3:1) at 0 °C was added H2O2 (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 H2O). 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 Na2SO3 (5.0 mmol) in 4.0 mL of H2O, 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 mL of ice-cold 0.2 M HCl, and extracted with ethyl acetate, washed with ice-cold H2O and brine and dried over Na2SO4. Taking to dryness under high vacuum, provided 7 as a foam (204
mg, 80% yield). m.p. 93-95 °C; $[\alpha]^2_D = +5.9$ (c 1.13, CH$_2$Cl$_2$); NMR (CDCl$_3$) $\delta$ 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$_2$O; THF was evaporated under reduced pressure and residue was extracted with ethyl acetate, washed with H$_2$O and saturated brine and dried over Na$_2$SO$_4$. 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$_3$) $\delta$ 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 H2O, and THF was evaporated under reduced pressure. Residue was extracted with ethyl acetate, washed with H2O and saturated brine and dried over Na2SO4. 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, CHCl3); NMR (CDCl3) \(\delta\) 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 C25H24NO3: 386.1756 (MH+); found: 386.1728.

(2S)-2-(naphthylmethyl)pent-4-en-1-ol (15). To a solution of LiAlH4 (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 mL 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), the clear solution resulted, which was cooled to –78˚C, and 15 mL of ethyl acetate was added to destroy remaining LiAlH4. The reaction was quenched by addition of aqueous NH4Cl at –78˚C, then the mixture was brought to ambient temperature, diluted with H2O, extracted with ether, washed with H2O and brine and dried over Na2SO4. 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 (CDCl3) \(\delta\) 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 C16H18O: 226.1358 (M+); found: 226.1339.

2-[(2S)-2-(naphthylmethyl)pent-4-enyl]-benzo[c]azolidine-1,3-dione (16). To a solution of LiAlH4 (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 mL 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), the clear solution resulted, which was cooled to −78 °C, and 15 mL of ethyl acetate was added to destroy remaining LiAlH4. The reaction was quenched by addition of aqueous NH4Cl at −78 °C, then the mixture was brought to ambient temperature, diluted with H2O, extracted with ether, washed with H2O and brine and dried over Na2SO4. 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 (CDCl3) \(\delta\) 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 H2O, 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 NH3-MeOH) to provide 8 as an oil (1.92 g, 77% yield. [α]26D = -22.1 (c 1.0, CHCl3); NMR (CDCl3) 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, 8.51 mmol), 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 (CDCl3) 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+-C4H8).

(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 NaHCO3, and washed with brine. Drying over Na2SO4 and taking to dryness under high vacuum provide the intermediat N-deblocked free amine as an oil. [NMR (CDCl3) 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).] To 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, 8.51 mmol), and 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 NaHCO3 followed by H2O, and brine then dried over Na2SO4. 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 (CDCl3) 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
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 (CDCl₃) 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 = 6.6, 14.2 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. Residue was dissolved in 50 mL of ethyl acetate, washed with saturated NaHCO₃, then H₂O, and brine and dried over Na₂SO₄. 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 (CDCl₃) 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⁺-C₄H₈), 716 (M⁺-2C₄H₈)

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 (CDCl₃) δ 8.30~8.00 (2H, m), 7.83 (1H, 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⁺-C₂H₆), 689 (MH⁺-2C₂H₆).
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-d6): 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 C37H45N4O7P cacld.: 687.2948 (M+-H); found: 687.2958.