mmol) of bromotrimethylsilane. After 72 h, the resulting clear solution was evaporated at 25° C. and the residue dissolved in 5 mL of THF. To this stirred solution was added 180 mg (1.1 mmol) of dried, finely ground potassium iodide and 3 mg (0.01 mmol) of 18-crown-6. The resulting slurry was heated to reflux for 20 h, evaporated and then stirred for 1 h with 8 mL (4 mmol) of 0.5M potassium hydroxide solution. The solution was lyophilized and then purified by MPLC (2.5×20 cm column of Mitsubishi Kasei Sepadbeads SP-207SS resin): 11.5 mL fractions, 7 mL/min flow rate, eluted with 200 mL of water and then a gradient prepared from 400 mL of water and 450 mL of 2:1 acetonitrile/water). Fractions 20–34 were collected and lyophilized to give title salt as a white solid, 505 mg, 85% yield.

IR (KBr pellet) 3422, 2959, 2930, 2870, 1653, 1497, 1202, 1080, 968 cm^{-1}.

^1H NMR (D_2O, 400 MHz) δ7.45 (d, 2H, J=8.6 Hz) 7.43 (d, 2H, J=8.6 Hz) 7.39 (d, 2H, J=8.1 Hz) 7.15 (d, 2H, J=8.1 Hz) 6.44 (m, 2H) 2.98 (dm, 1H, J=13.2 Hz) 2.87 (tm, 1H, J=13.6 Hz) 2.68 (m, 1H) 2.44 (t, 2H, J=6.0 Hz) 1.46 (dq, 2H, J=6.0 Hz) 0.73 (t, 3H, J=6.0 Hz) ppm.

Anal. Calc'd for $C_{19}H_{20}K_3O_6PS.2.2\ H_2O$: C, 40.45; H, 4.36; P, 5.49; S, 5.68 Found: C, 40.11; H, 4.70; P, 5.18; S, 5.95.

MS (FAB, +ions) m/e 563 (M+K), 525 (M+H), 487 (M−K+2H).

EXAMPLE 7

α-Phosphono-4'-Propyl[1,1'-biphenyl]-4-butanesulfonic acid, tripotassium salt

A. α-(Diethoxyphosphinyl)-4'-propyl[1,1'-biphenyl]-4-butanesulfonic acid, cyclohexyl ester

To a nitrogen-purged solution of 1.30 mg (2.37 mmol) of Example 6 Part B compound in 50 mL of ethyl acetate in a 500 mL one-neck round bottom flask was attached a hydrogen-filled rubber bladder of approximately 1 L capacity. The reaction mixture was vigorously stirred for 16 h, purged with nitrogen, filtered through Celite and the filtrate evaporated. The oily residue was redissolved in dichlormethane, filtered through a 0.75μ (micron) filter and re-evaporated to give title compound as a colorless oil, 1.28 g, 98% yield. The product was used without further purification.

B. α-Phosphono-4'-propyl[1,1'-biphenyl]-4-butanesulfonic acid, tripotassium salt

To a stirred solution of 1.14 g (2.06 mmol) of Part A compound in 10 mL of dichloromethane under argon at room temperature was added 1.10 mL (8.3 mmol) of bromotrimethylsilane. After 24 h, the resulting clear solution was evaporated at 25° C. and the residue dissolved in 10 mL of THF. To this stirred solution was added 340 mg (2.1 mmol) of dried, finely ground potassium iodide and 5 mg (0.02 mmol) of 18-crown-6. The resulting slurry was heated to reflux for 24 h, evaporated and then stirred for 1 h with 8 mL (8 mmol) of 1.0M potassium hydroxide solution. The solution was lyophilized and then purified by MPLC (2.5×20 cm column of Mitsubishi Kasei Sepadbeads SP207SS resin): 11.5 mL fractions, 7 mL/min flow rate, eluted with 200 mL of water and then a gradient prepared from 400 mL of water and 450 mL of 1:1 acetonitrile/water). Fractions 27–31 were collected and lyophilized to give title compound as a white solid, 450 mg, 39% yield.

IR (KBr pellet) 3432, 2957, 2930, 2870, 1636, 1499, 1198, 1080, 1049, 966 cm^{-1}.

^1H NMR (D_2O, 400 MHz) δ7.47 (d, 2H, J=7.5 Hz) 7.46 (d, 2H, J=7.3 Hz) 7.28 (d, 2H, J=7.5 Hz) 7.21 (d, 2H, J=7.3 Hz) 2.86 (dm, 1H, J=18.4 Hz) 2.58 (m, 2H) 2.49 (t, 2H, J=7.2 Hz) 1.85 (m, 4H) 1.50 (m, 2H) 0.78 (t, 3H, J=6.0 Hz) ppm.

Anal. Calc'd for $C_{19}H_{22}K_3O_6PS.1.9\ H_2O$: C, 40.68; H, 4.64; P, 5.52; S, 5.72 Found: C, 40.69; H, 5.00; P, 5.46; S, 6.00.

MS (ion spray, +ions) m/e 495 (M−3K+4H+2CH_3CN), 492 (M−2K+3H+CH_3CN), 489 (M−K+2H), 454 (M−3K+4H+CH_3CN), 451 (M−2K+3H), 413 (M−3K+4H).

EXAMPLE 8

4-(2-Phenylethoxy)-α-phosphonobenzenebutanesulfonic acid, dipotassium salt

A. 4-(2-Phenylethoxy)benzenepropanoic acid, 2-phenylethyl ester

To a stirred solution of 5.00 g (30.1 mmol) of 4-hydroxybenzenepropanoic acid, 8.0 mL of 2-phenylethanol (67 mmol) and 16.3 g (61 mmol) of triphenyl-phosphine in 50 mL of THF at −10° C. under argon was added a solution 12.0 mL (61 mmol) of diisopropyl diazodicarboxylate in 50 mL of THF over the course of 4 hours. The resulting light yellow solution was allowed to warm to room temperature, stirred 16 h and then evaporated. The oily residue was triturated in 500 mL of hot hexane until a precipitate formed. The solids were filtered off and treated with an additional 100 mL of hot hexane. The filtrates were combined and concentrated. Purification of the residue by flash chromatography (5×20 cm column, 3:2 dichloromethane/hexanes as elutent) gave 6.51 g, 58% yield, of title compound as a colorless oil.

B. 1-(3-Iodopropyl)-4-(2-phenylethoxy)benzene

To a stirred solution of 6.20 g (16.6 mmol) of Part A compound in 50 mL of THF at room temperature under argon was added a 1M solution of lithium aluminum hydride (9.0 mL, 2.2 equivalents) in THF. After 2 h, the reaction was quenched with 1M sodium potassium tartrate solution and extracted twice with ether. The organic extracts were dried ($MgSO_4$) and evaporated.

The residue was stirred in 25 mL of dichloromethane at 0 ° C. under argon with 2.8 mL (20 mmol) of triethyl amine. To this solution was added, over 20 min, 1.3 mL (17 mmol) of methanesulfonyl chloride. After an additional 20 min, the reaction mixture was diluted with dichloromethane and washed twice with 10% citric acid. The organic extracts were dried ($MgSO_4$) and evaporated.

The resulting yellow oil was stirred at reflux under argon in a solution of 25 mL of acetone containing 3 g (20 mmol) of sodium iodide. After 16 h, the reaction mixture was cooled and diluted with an iced solution of 5% aqueous sodium bisulfite. After two extractions with hexane, the extracts were dried ($MgSO_4$) and evaporated. Purification on silica gel (5×20 cm column, 1:7 dichloromethane/hexanes as elutent) gave 4.13 g, 68%, of Part B compound from Part A compound.

C. α-(Diethoxyphosphinyl)-4-(2-phenylethoxy) benzenebutanesulfonic acid, cyclohexyl ester

To a stirred slurry of 120 mg (3.0 mmol, 60% mineral oil dispersion) of sodium hydride in 3 mL of DMF under argon at −20° C. was added a solution of 1.12 g (3.56 mmol, 1.3 equiv.) of Example 1A, Part B sulfonate in 1 mL of DMF. After addition was complete, the reaction was warmed to room temperature and stirred for 30 min. To the resulting solution was added a solution of 1.00 g (2.73 mmol) of Part B compound in 1 mL of DMF. The reaction was stirred for 16 h, diluted with ether and washed once with 10% citric

acid and thrice with water. The organic phase was dried ($MgSO_4$) and evaporated. Purification by chromatography on silica gel (5×20 cm column) eluted with 1:19 ether/dichloromethane gave title compound as a colorless oil, 935 mg, 62% yield.

D. 4-(2-Phenylethoxy)-α-phosphonobenzenebutanesulfonic acid, dipotassium salt

To a stirred solution of 648 mg (1.2 mmol) of Part C compound in 5 mL of dichloromethane under argon at room temperature was added 620 mL (3.0 mmol) of bis (trimethylsilyl)trifluoroacetamide and then 620 mL (6.9 mmol) of bromotrimethylsilane. After 16 h, the resulting clear solution was evaporated at 25° C. and the residue dissolved in 6 mL of THF. To this stirred solution was added 250 mg (1.5 mmol) of dried, finely ground potassium iodide and 3 mg (0.01 mmol) of 18-crown-6. The resulting slurry was heated to reflux for 24h, evaporated and then stirred for 1 h with 8 mL (4 mmol) of 0.5M potassium hydroxide solution. The solution was lyophilized and then purified by MPLC (2.5×20 cm column of Mitsubishi Kasei Sepadbeads HP-20 resin): 11.5 mL fractions, 7 mL/min flow rate, eluted with 200 mL of water and then a gradient prepared from 400 mL of water and 450 mL of 2:1 acetonitrile/water). Fractions 25–32 were collected and lyophilized to give title salt as a white solid, 385 mg, 57% yield.

IR (KBr pellet) 3434, 3088, 2936, 2868, 1636, 1512, 1198, 1076, 966 cm^{-1}.

^1H NMR (D_2O, 400 MHz) δ7.21 (m, 5H) 7.09 (d, 2H, J=8.6 Hz) 6.76 (d, 2H, J=8.6 Hz) 4.15 (t, 2H, J=6.4 Hz) 2.91 (t, 2H, J=6.4 Hz) 2.77 (dm, 1H, J=18.0 Hz) 2.44 (m, 2H) 1.67 (m, 2H) ppm.

Anal. Calc'd for $C_{18}H_{21}K_2O_7PS.3.75\ H_2O$: C, 38.73; H, 5.15; P, 5.55; S, 5.74 Found: C, 38.73; H, 5.10; P, 5.24; S, 5.51.

MS (FAB, +ions) m/e 567 (M+2K–H), 529 (M+K).

EXAMPLE 9

6-(Hexyloxy)-α-phosphono-2-naphthalenebutanesulfonic acid, dipotassium salt

A. 2-Bromo-6-(hexyloxy)naphthalene

To a stirred solution of 4.46 g (20.0 mmol) of 6-bromo-2-naphthalenol (obtained from Aldrich Chemical Company (#B7,340-6) and used without purification), in 20 mL of DMF at room temperature under argon was added 480 mg (20 mmol) of 95% sodium hydride over the course of 15 min. The resulting light yellow solution was stirred 30 min and 3.5 mL (22 mmol) of 1-bromohexane was added. The reaction was heated to 50° C. and stirred for 60 min. The reaction was quenched with ice water, the resultings solids filtered, washed with water and dried in vacuo at 60° C. Purification of the residue by chromatography on silica gel (5×20 cm column, hexanes as elutant) gave 5.00 g, 81% yield, of title compound as a colorless oil.

B. α-Ethenyl-6-(hexyloxy)-2-naphthalenemethanol

To a stirred solution of 2.23 g (7.25 mmol) of Part A compound in 25 mL of THF under argon at −78° C. was added a solution of 8.5 mL (14.5 mmol) of 1.7M t-butyllithium in pentane over 10 min. After 15 min, a yellow slurry had formed. This was warmed to 0° C. and the resulting organic solution was stirred for 30 min. To this reaction mixture was added 550 mL (9.5 mmol, 1.3 equivalents) of freshly distilled acrolein at a rate to keep the temperature below 5° C. After an additional 30 min, the reaction was quenched with saturated ammonium chloride solution, extracted twice with ether, dried ($MgSO_4$) and evaporated. Recrystallization from hexanes gave title compound as a white solid, mp 47°–48° C., 1.83 g, 89%.

C. α-Ethenyl-6-(hexyloxy)-2-naphthalenemethanol, acetate ester

To a solution of 1.43 g (5.0 mmol) of Part B compound and 1.1 mL (8 mmol) of triethylamine in 15 mL of CH_2Cl_2 at room temperature under argon was added 0.7 mL (6.6 mmol) of acetic anhydride and 20 mg (0.16 mmol) of 4-dimethylaminopyridine. After 10 min, the reaction mixture was evaporated, diluted with ether, washed once with 10% citric acid, once with water, once with saturated sodium bicarbonate solution, dried ($MgSO_4$) and evaporated to give title compound as a colorless oil, 1.54 g, 94%. The compound was used without further purification for the subsequent reaction.

D. (E)-1-(Diethoxyphosphinyl)-4-[6-(hexyloxy)-2-naphthalenyl]-3-butenesulfonic acid, cyclohexyl ester

To a stirred solution of 1.47 g (4.5 mmol) of Part C compound, 1.55 mL (6.6 mmol, 1.5 equiv.) of bis (trimethylsilyl)acetamide, 1.85 g (5.85 mmol, 1.3 equiv.) of Example 1A, Part B sulfonate and 125 mg (0.5 mmol) of triphenylphosphine in 10 mL of THF under argon was added 270 mg (0.24 mmol) of tetrakis(triphenylphosphine) palladium. The resulting mixture was heated to reflux for 1 hour. The reaction was cooled, evaporated, diluted with ether and washed once with 10% citric acid and thrice with water. The organic phase was dried ($MgSO_4$) and evaporated. Purifica-tion by flash chromatography on silica gel (5×20 cm column) eluted with 1:24 ether/dichloromethane gave title compound as a colorless oil, 1.06 g, 41% yield.

E. α-(Diethoxyphosphinyl)-6-(hexyloxy)-2-naphthalenebutanesulfonic acid, cyclohexyl ester

To an argon-purged solution of 965 mg (1.66 mmol) of Part D compound and 100 mg of 10% palladium-on-carbon in 15 mL of ethyl acetate in a 500 mL one-neck round bottom flask was attached a hydrogen-filled rubber bladder of approximately 1 L capacity. The reaction mixture was vigorously stirred for 16 h, purged with nitrogen, filtered through Celite and the filtrate evaporated. The oily residue was redissolved in dichlormethane, filtered through a 0.75μ (micron) filter and re-evaporated to give title compound as a colorless oil, 950 mg, 98% yield. The product was used without further purification.

F. 6-(Hexyloxy)-α-phosphono-2-naphthalenebutanesulfonic acid, dipotassium salt

To a stirred solution of 885 mg (1.52 mmol) of Part E compound in 10 mL of dichloromethane under argon at room temperature was added 800 μL (8.9 mmol) of bromotrimethylsilane. After 18 h, the resulting clear solution was evaporated at 25° C. and the residue dissolved in 15 mL of THF. To this stirred solution was added 320 mg (1.9 mmol) of dried, finely ground potassium iodide and 3 mg (0.01 mmol) of 18-crown-6. The resulting slurry was heated to reflux for 24h, evaporated and then stirred for 1 h with 9 mL (4.5 mmol) of 0.5M potassium hydroxide solution. The solution was lyophilized and then purified by MPLC (2.5×20 cm column of Mitsubishi Kasei Sepadbeads CHP-20P resin): 11.5 mL fractions, 7 mL/min flow rate, eluted with 200 mL of water and then a gradient prepared from 400 mL of water and 450 mL of 1:1 acetonitrile/water). Fractions 44–52 were collected and lyophilized to give title compound as a white solid, 475 mg, 53% yield.

IR (KBr pellet) 3434, 3057, 2932, 2861, 1653, 1605, 1181, 1076, 966 cm^{-1}.

^1H NMR (D_2O, 400 MHz) δ7.60 (d, 1H, J=9 Hz) 7.56 (s, 1H) 7.52 (d, 1H, J=8.3 Hz) 7.32 (d, 1H, J=8.3 Hz) 7.00 (s, 1H) 6.94 (d, 1H, J=9.0 Hz) 3.78 (t, 2H, J=6.4 Hz) 2.83 (dm, 1H, J=18.0 Hz) 2.65 (m 2H) 1.89 (m 4H) 1.48 (m 2H) 1.16 (m 2H) 1.07 (m 4H) 0.67 (t 2H, J=5.5 Hz) ppm.

Anal. Calc'd for $C_{20}H_{27}K_2O_7PS.3.81\ H_2O$: C, 40.76; H, 5.92; P, 5.26; S, 5.44 Found: C, 40.76; H, 5.81; P, 5.35; S, 5.35.

MS (FAB, +ions) m/e 559 (M+K), 521 (M+H).

EXAMPLE 10

4-[(5-Methyl-4-hexenyl)oxy]-α-phosphonobenzenebutanesulfonic acid, tripotassium salt

A. 5-Methyl-4-hexenoic acid, 1,1-dimethylethyl ester

To a stirred solution of 20.0 mL (142 mmol) of diisopropylamine in 160 mL of THF under argon at −10° C. was added a solution of 56 mL (140 mmol) of 2.5M n-butyllithium in hexane at a rate to keep the temperature below 0° C. The resulting light yellow solution was stirred 15 min and to this reaction mixture was added 20 mL (115 mmol) of HMPA. After an additional 10 min, the reaction was cooled to −75° C. and 18.8 mL (140 mmol) of 1,1-dimethylethanol, acetate ester was added at a rate to keep the temperature below −60° C. The resulting colorless solution was stirred for 30 min and 20 g (134 mmol) of 4-bromo-2-methyl-2-butene was added over 10 min. The reaction was stirred at −75° C. for 6 h and then warmed to room temperature. After 16 h, the reaction was quenched with saturated ammonium chloride solution, extracted twice with ether, dried ($MgSO_4$) and evaporated. Purification by distillation (b.p. 64°–67° C. @6 mmHg) gave title compound as a colorless oil, 20.1 g, 82% yield.

B. 5-Methyl-4-hexen-1-ol

To a stirred slurry of 1.71 g (45.1 mmol) of lithium aluminum hydride in 50 mL of ether under nitrogen at 0° C. was added a solution of 15.5 g (84 mmol) of Part A compound in 20 mL of ether over 20 min. The reaction was warmed to room temperature and stirred. After 24 h, the reaction was quenched with 1M sodium potassium tartrate solution, extracted twice with 50 mL portions of ether, dried ($MgSO_4$) and filtered. The extract was distilled at atmospheric pressure through a 10 cm Vigreau column until the head temperature reached 80° C. The residue was purified by vacuum distillation (b.p. 76°–77° C. @14 mmHg) to give title compound as a colorless oil, 9.06 g, 94% yield.

C. 4-[(5-Methyl-4-hexenyl)oxy]benzenepropanoic acid, ethyl ester

To a stirred solution of 1.14 g (10.0 mmol) of Part B compound, 1.94 g (10.0 mmol) of ethyl 4-hydroxyphenyl-3-propanoate and 2.62 g (10.0 mmol) of triphenylphosphine in 20 mL of THF at −10° C. under nitrogen was added a solution 2.0 mL (10 mmol) of diisopropyl diazodicarboxylate in 20 mL of THF over the course of 2 hours. The resulting light yellow solution was allowed to warm to room temperature, stirred 16 h and then evaporated. The oily residue was triturated in 500 mL of hot hexane until a precipitate formed. The solids were filtered off and treated with an additional 100 mL of hot hexane. The filtrates were combined and concentrated. Purification of the residue by flash chromatography (5×15 cm column, 1:1 dichloromethane/hexanes as elutent) gave 2.58 g, 89% yield, of title compound as a colorless oil.

D. 4-[(5-Methyl-4-hexenyl)oxy]benzenepropanol

To a stirred solution of 2.28 g (7.85 mmol) of Part C compound in 15 mL of THF at room temperature under nitrogen was added a 1M solution of lithium aluminum hydride (4.5 mL, 2.4 equivalents) in THF. After 20 min, the reaction was quenched with 1M sodium potassium tartrate solution and extracted twice with ether. The organic extracts were dried ($MgSO_4$) and evaporated twice from hexanes to give 1.88 g of title compound, 96% yield, as a colorless oil.

E. 1-(3-Iodopropyl)-4-[(5-methyl-4-hexenyl)oxy]benzene

To a stirred solution of 1.86 g (7.5 mmol) of Part D compound, 1.96 g (7.5 mmol) of triphenylphosphine and 1.13 g (16.5 mmol) of imidazole in 25 mL of THF at room temperature under nitrogen was added 1.91 g (7.5 mmol) of solid iodine, portionwise, over 30 min. After an additional 10 min, the reaction mixture was diluted with hexanes and washed once with saturated sodium bisulfite solution. The organic extracts were dried ($MgSO_4$) and evaporated. Purification by flash chromatography (5×12 cm column, 1:4 dichloromethane/hexanes as elutent) gave 2.26 g, 84%, of title compound.

F. α-(Diethoxyphosphinyl)-4-[(5-methyl-4-hexenyl)oxy]benzenebutanesulfonic acid, cyclohexyl ester

To a stirred slurry of 120 mg (3.0 mmol, 60% mineral oil dispersion) of sodium hydride in 3 mL of DMF under argon at −10° C. was added a solution of 1.12 g (3.56 mmol, 1.3 equiv.) Example 1A, Part B sulfonate in 1 mL of DMF. After addition was complete, the reaction was warmed to room temperature and stirred for 30 min. To the resulting solution was added a solution of 1.00 g (2.79 mmol) of Part E compound in 1 mL of DMF. The reaction was stirred for 16 h, diluted with ether and washed once with 10% citric acid and thrice with water. The organic phase was dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica gel (5×20 cm column) eluted with 3:47 ether/dichloromethane gave title compound as a colorless oil, 685 mg, 45% yield.

G. 4-[(5-Methyl-4-hexenyl)oxy]-α-phosphonobenzenebutanesulfonic acid, tripotassium salt

A solution of 680 mg (1.25 mmol) of Part F compound in 10 mL of methanol under argon at room temperature was saturated with ammonia gas. The flask containing the reaction mixture was sealed and heated to 75° C. After 16 h, the reaction was cooled to room temperature and evaporated under dry conditions. The residue was dissolved in 10 mL of dichloromethane and 1.7 mL (6.4 mmol) of bis(trimethylsilyl)trifluoroacetamide and then 670 μL (5.0 mmol) of bromotrimethylsilane was added. After 24 h, the resulting clear solution was evaporated at 25° C. and then stirred for 1 h with 8 mL (4 mmol) of 0.5M potassium hydroxide solution. The solution was lyophilized and then purified by MPLC (2.5×20 cm column of Mitsubishi Kasei Sepadbeads HP-20 resin): 11.5 mL fractions. 7 mL/min flow rate, eluted with 200 mL of water and then a gradient prepared from 400 mL of water and 450 mL of 3:1 acetonitrile/water). Fractions 25–31 were collected and lyophilized to give title salt as a white solid, 504 mg, 74% yield.

IR (KBr pellet) 3432, 2963, 2928, 2866, 1636, 1512, 1242, 1202, 1080, 966 cm^{-1}.

^1H NMR (D_2O, 400 MHz) δ7.09 (d, 2H, J=8.5 Hz) 6.77 (d, 2H, J=8.5 Hz) 5.06 (t, 1H, J=6.7 Hz) 3.85 (t, 1H, J=6.4 Hz) 2.79 (ddd, 1H, J=4.3, 6.0, 18.0 Hz) 2.45 (m 2H) 1.98 (m 2H) 1.77 (m 4H) 1.61 (m 2H) 1.52 (s 3H) 1.43 (s 3H) ppm.

Anal. Calc'd for $C_{17}H_{24}K_3O_7PS.1.33\ H_2O$: C, 37.49; H, 4.93; P, 5.69; S, 5.89 Found: C, 37.48; H, 5.28; P, 5.62; S, 5.64.

MS (FAB, +ions)m/e 559 (M+K), 521 (M+H), 483 (M−K+2H).

EXAMPLE 11

1-Phosphono-1-pentadecanesulfonic acid, tripotassium salt

A. (Diethoxyphosphinyl)methanesulfonic acid, 1-methylethyl ester

To a rapidly stirred solution of 8.28 g (60 mmol) of isopropyl methanesulfonate in 150 mL of THF at −73° C.

(internal temp.) was added 25 mL (60 mmol) of 2.4M n-butyllithium dropwise over 20 min. The internal temperature was not allowed to rise above –69° C. throughout the course of the addition. After an additional 15 min., 5.17 g (30 mmol) of freshly distilled diethyl chlorophosphate was added at a rate to keep the solution temperature below –69° C. The reaction mixture was stirred for 0.3 h at –73° C. and for 0.5 h at –40° C. when it was quenched with 125 mL of saturated NH_4Cl solution. The reaction mass was warmed to room temperature and the THF removed under reduced pressure. The remainder was partitioned between methylene chloride and water (3×75 mL). The extracts were dried (Na_2SO_4), concentrated, and purified by flash chromatography (350 g silica gel) eluting with 1:1 methylene chloride/ether to provide 5.20 g (67%) of title compound as a colorless oil.

TLC Silica gel (1:1 methylene chloride/ether) R_f=0.37.

^1H NMR ($CDCl_3$, 270 MHz) δ5.05 (sept, 1H, J=6.0 Hz) 4.20 (quint, 4H, J=7.0 Hz) 3.75 (d, 2H, J=17.5 Hz) 1.50 (d, 6H, J=6.0 Hz) 1.40 (t, 6H, J=7.5 Hz) ppm.

B. 1-(Diethoxyphosphinyl)pentadecanesulfonic acid, 1-methylethyl ester

To a suspension of 0.10 g (4.38 mmol) of NaH in 7 mL of dry DMF at 0° C. under argon was added 1.20 g (4.38 mmol) of Part A compound over 5 min. to give a yellow solution. The reaction was allowed to warm to room temperature and stir for 0.5 h when 0.55 g (2.00 mmol) of tetradecanyl bromide was added in one portion. The reaction mixture was stirred for 24 h when it was quenched with 20 mL of saturated NaCl solution and diluted with 50 mL of ether. The layers were separated, the organics dried (Na_2SO_4) and evaporated to provide a crude oil. Flash chromatography was performed on 100 g of silica gel eluting with 3:7 ethyl acetate/hexane to provide 0.30 g (31%) of title compound in the form of a pale yellow oil.

TLC Silica gel (1:1 ethyl acetate/hexanes) R_f=0.50.

IR (film) 2924, 2853, 1466, 1358, 1260, 1177, 1053, 1024, 930 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz) δ5.05 (sept., 1H, J=6.0 Hz) 4.20 (m, 4H) 3.35 (dr, 1H, J=20.0, 6.4 Hz) 2.10 (m, 2H) 1.45 (m, 2H) 1.40 (d, 6H, J=6.5 Hz) 1.30 (t, 6H, J=7.3 Hz) 1.20 (m, 22H) 0.85 (t, 3H, J=6.5 Hz) ppm.

Mass Spec (CI, +ions) m/e 488 ($M+NH_4$), 471 (M+H), 347 ($M+H-SO_3C_3H_8$).

C. 1-Phosphono-1-pentadecanesulfonic acid, tripotassium salt

To a stirred solution of 0.25 g (0.53 mmol) of Part B compound in 5 mL of dichloromethane at 0° C. and in the dark was added 4.24 g (2.12 mmol) of iodotrimethylsilane. The reaction was allowed to stir for 16 h when the solvent was evaporated and the semisolid residue pumped (≈1 mm pressure) for 0.5 h. The residue was dissolved by adding 3 mL of 1M (3.0 mmol) KOH solution and freeze dried to provide an off white solid. The solid was purified by MPLC on a column of CHP20P gel (2.5 cm diam.×15 cm height) eluting with water (100 mL) followed by a gradient created by the gradual addition of 400 mL of acetonitrile to a reservoir of 250 mL of water. Approximately 7 mL fractions were collected. The acetonitrile was removed under reduced pressure and the aqueous solution was lyophilized to provide 0.15 g (62%) of title salt as a white lyophilate.

TLC Silica gel (6:3:1 n-propanol/conc. ammonia/water) R_f=0.40.

IR (KBr) 3443, 2920, 2851, 1653, 1468, 1215, 1163, 1045, 966 cm^{-1}.

^1H NMR (D_2O, 300 MHz) δ2.80 (dt, 1H, J=19.0, 6.0 Hz) 1.85 (m, 2H) 1.50 (m, 2H) 1.20 (m, 22H) 0.90 (t, 3H, J=6.0 Hz) ppm.

Mass Spec (FAB, +ions) m/e 525 (M+K), 487 (M+H).

Anal. Calc'd for $C_{15}H_{30}O_6K_3PS$+2.19 H_2O: C, 34.24; H, 6.59; P, 5.89; S, 6.09 Found: C, 34.03; H, 6.88; P, 5.57; S, 6.02.

EXAMPLE 12

(E)-10,14-Dimethyl-1-phosphono-9,13-pentadecadiene-1-sulfonic acid, dipotassium salt

A. Dichloro[μ-[1-hexanolato(2-)-C_6:O_1]]dimagnesium

To a stirred solution of 11.00 g (80.0 mmol) of 6-chloro-1-propanol (Aldrich) in 20 mL of THF at –20° C. was added 27.0 mL (81.0 mmol) of 3.0M methylmagnesium chloride in THF dropwise over 25 minutes. After 0.5 hours at –20° C., the reaction was allowed to warm to room temperature and 2.88 g (118.0 mmol) of magnesium turnings were added and the reaction was heated to reflux. The reaction was initiated by adding a few crystals of iodine at the start of reflux and after 1 hour of heating. After 2 hours at reflux the reaction was cooled to room temperature providing the Grignard solution. The molarity of the reaction mixture was determined by titration: 5.20 mL (2.60 mmol) of a 0.5M solution of 2-propanol in benzene was slowly added to a blood red solution of 2–2'-biquinoline (indicator) in benzene and 2.0 mL of the freshly prepared Grignard solution. The endpoint color was light green and the molarity was determined to be 1.3M.

B. (E)-9,13-Dimethyl-8,12-tetradecadiene-1-ol

A solution of 21.5 mL (28.0 mmol) of 1.3M Part A Grignard reagent in THF and 5.0 mL of KMPA at 0° C. was treated dropwise with 1.21 g (7.0 mmol) of geranyl chloride in 7 mL of THF over 7 minutes. After the addition the reaction was allowed to warm to room temperature and stir for 2 hours, at which point the reaction was diluted with ether and quenched with 50 mL (50.0 mmol) of 1M HCl solution. The organic layer was washed two times with NH_4Cl solution, dried over $MgSO_4$ and evaporated to provide a crude oil. Flash chromatography was performed on 125 g of silica gel packed, loaded and eluted with 1:4 ethyl acetate/hexanes to provide 1.10 (66%) of title alcohol as an amber oil.

TLC Silica gel (1:9 ethyl acetate:hexane) R_f=0.20.

IR (CCl_4 solution) 3636, 2928, 2854, 1450, 1377, 1055 cm^{-1}.

^1H NMR ($CDCl_3$, 270 MHz): δ5.40 (q, 2H, J=7.0 Hz), 3.69 (t, 2H, J=7.0 Hz), 2.25–1.85 (m, 8H), 1.75 (s, H), 1.70 (s, 6H), 1.65 (m, 2H), 1.39 (s, 7H) ppm.

MS (CI, NH_3, +ions) 256 ($M+NH_4$).

C. (E)-9,13-Dimethyl-8,12-tetradecadien-1-yl iodide

To a stirred solution of 1.10 g (4.62 mmol) of Part B alcohol and 1.40 mL (10.00 mmol) of triethylamine in 10 mL of methylene chloride at 0° C. was added 0.37 mL (4.80 mmol) of methanesulfonyl chloride dropwise over 15 minutes. After 1 hour at 0° C. the reaction was diluted with ether and washed with aqueous solutions of NH_4Cl, $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to provide 1.42 g (~4.5 mmol) of the crude mesylate. The residual oil was dissolved in 25 mL of acetone and treated with 3.00 g (20.0 mmol) of NaI. The resulting suspension was heated to reflux for 4 hours and diluted with ether, washed with brine, dried over $MgSO_4$, and concentrated to provide a yellow oil. Flash chromatography was performed on 100 g of silica gel packed, loaded and eluted with hexanes to provide 1.10 g (68% overall yield) of title iodide in the form of a colorless oil.

TLC Silica gel (hexanes) R_f=0.45.

IR (CCl_4 solution) 2962, 2928, 2854, 1450, 1375, cm^{-1}.

^1H NMR ($CDCl_3$, 270 MHz): δ5.41 (q, 2H, J=7.0 Hz), 3.47 (t, 2H, J=7.0 Hz), 2.40–2.20 (m, 6H), 2.11 (quint., 2H, J=7.0 Hz), 1.97 (s, 3H), 1.89 (s, 6H), 1.60 (m, 8H) ppm.

MS (CI, NH_3, +ions) 366 ($M+NH_4$), 348 (M).

D. (E)-α-(Diethyoxyphosphinyl)-10,14-dimethyl-9,13-pentadecadiene-1-sulfonic acid, cyclohexyl ester

To a stirred suspension of 191 mg (4.77 mmol, 2 eq.) of sodium hydride (as a 60% mineral oil dispersion) in 2 mL of dry dimethylformamide (DMF) at 0° C. was added a solution of 1.50 g (4.77 mmol, 2 eq.) of Example 1A Part B sulfonate in 3 mL of DMF dropwise over 7 min. The solution was warmed to RT and stirred for 50 min. To the resulting clear yellow solution was added a solution of 831 mg (2.39 mmol, 1 eq.) of Part C iodide in 3 mL of dry DMF dropwise over 5 min. The reaction was stirred at RT for 16 h diluted with ether (100 mL) and washed with water (50 mL). The aqueous layer was extracted with ether (2×20 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to afford 1.77 g of a yellow oil. Flash chromatography was performed on 300 g of silica gel eluting with 30% ethyl acetate in hexanes. Fractions (40 mL each) containing clean product by TLC were pooled and concentrated to afford, after high vac (0.25 mmHg) removal of solvent remnants, 782 mg (61%) of title compound as a clear yellow oil.

TLC Silica gel (10% ether in CH_2Cl_2): R_f 0.50.

E. (E)-10,14-Dimethyl-1-phosphono-9,13-pentadecadiene-1-sulfonic acid, dipotasium salt

To a solution of 515 mg (0.96 mol, 1 eq.) of Part D compound in 10 mL of methanol at 0° C. was bubbled ammonia until the solution was saturated. The reaction tube was then sealed and heated at 75° C. for 16 h. The reaction mixture was allowed to cool to RT and then concentrated. The oily residue was dried by coevaporation with toluene (2×). High vac (0.25 mmHg) removal of solvent remnants afforded 480 mg of light yellow oil.

To a solution of the yellow oil in 4 mL of dry dichloromethane at RT was added 636 μL (4.81 mmol, 5 eq.) of 2,4,6-collidine all at once. To the resulting clear light yellow solution was added 890 μL (6.74 mmol, 7 eq.) of bromotrimethylsilane (TMSBr) dropwise over 3 min. As the TMSBr was added a white precipitate formed and upon completion of TMSBr addition, 1 mL of dichloromethane was added to the thick reaction mixture to facilitate stirring. After 17 h at RT the reaction was concentrated and the resulting semisolid was placed on high vac (0.25 mm Hg) for 1 h. The residue was dissolved by adding 4.8 mL (5 eq.) of 1M potassium hydroxide followed by 10 mL of water and lyophilized to afford an off-white lyophilate. The lyophilate was purified by MPLC on a column of CHP20P (2.5 cm×25 cm) eluting initially with 150 mL of water followed by a gradient formed by the gradual addition of 400 mL of 30% acetonitrile in water to a reservoir containing 400 mL of 10% acetonitrile in water. Fractions containing clean product by HPLC (Method 8) were pooled and concentrated. The semisolid residue was taken up in water, filtered, concentrated and finally triturated with acetone to afford, after high vac (0.025 mm Hg) removal of acetone remnants, 207 mg (43%) of title salt in the form of a white solid.

TLC silica gel (5:4:1 n-propanol:ammonium hydroxide:water): R_f 0.39

IR (KBr) 3450(br), 2920, 2851, 1462, 1215, 1080, 1040 cm^{-1}.

^1H NMR (D_2O, 300 MHz) δ5.01 (t, 1H, J=7.6 Hz) 4.96 (t, 1H, J=7.0 Hz) 2.87 (dt, 1H, J=18.1, 5.4 Hz) 1.90 (m, 2H) 1.82 (m, 6H) 1.49 (s, 3H) 1.43 (m, 2H) 1.42 (s, 6H) 1.15 (bs, 8H) ppm.

^{13}C NMR (D_2O, 75.6 MHz) δ135.7 132.7 125.5 124.7 61.0 (d, J_{CP}=126 Hz) 39.4 29.6 29.4 29.2 (d, J_{CP}=7 Hz) 29.1 29.1 28.1 27.2 26.3 25.3 17.4 15.6 ppm

MS (FAB, +ions) m/z 473 (M+H), 511 (M+K), 549 (M−H+K).

Anal. Calc'd for $C_{17}H_{31}O_6PSK_2.1.4\ H_2O$: C, 41.01; H, 6.84; S, 6.44; P, 6.22 Found: C, 41.19; H, 6.52; S, 6.30; P, 5.95

EXAMPLE 13

(E,E)-6,10,14-Trimethyl-1-phosphono-5,9,13-pentadecatriene-1-sulfonic acid, phenyl ester, dipotassium salt

A. Methanesulfonic acid, phenyl ester

To a solution of 40.0 g (0.42 mol, 1 sq.) of phenol in 250 mL of dichloromethane at 0° C. was added 250 mL (1.8 mol, 4.2 sq.) of triethylamine. After 5 min, 49.3 mL (0.64 mol, 1.5 sq.) of methanesulfonyl chloride was added dropwise over 20 min. The resulting cloudy yellow solution was warmed to RT and stirred for 14 h. The reaction was partitioned between ether (250 mL) and water (100 mL) and the resulting organic layer was washed with cold 6N hydrochloric acid (2×200 mL). The combined aqueous layers were extracted with ether (2×50 mL) and the combined organic layers were washed with water (100 mL), saturated sodium bicarbonate (200 mL), brine (200 mL), dried ($MgSO_4$) and concentrated. Recrystallization of the orange solid from isopropanol afforded 44.94 g (61%) of the title compound as light yellow crystals; mp 58.0°–58.5° C.

TLC Silica gel (25% ethyl acetate in hexanes): R_f 0.29.

B. (Diethoxyphosphinyl)methanesulfonic acid, phenyl ester

To a turbid solution of 174 mL (0.174 mol, 1 eq.) of potassium bis(trimethylsilyl)amide (20% by weight in tetrahydrofuran (THF) from Callory Chem.) at −88° C. (internal temperature) was added a solution of 30.0 g (0.174 mol, 1 eq.) of Part A compound in 75 mL of dry THF at a rate to keep the internal temperature below −85° C. (addition took 20 min). The reaction was stirred for 5 min at −85° C. then 15.2 mL (104 mmol, 0.6 eq.) of freshly distilled diethylchlorophosphate was added dropwise at a rate that kept the temperature below −72° C. (addition took 13 min). After stirring at −65° C. for 1h, the reaction was quenched at −65° C. by the addition of a solution of 9.97 mL (0.174 mol, 1 eq.) of acetic acid in 25 mL of THF over 5 min. The resulting solution was warmed to RT and the majority of the solvent was removed in vacuo. The residue was partitioned between dichloromethane (300 mL) and water (100 mL). The aqueous layer was extracted with dichloromethane (2×20 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated to afford 43.82 g of solid/liquid mixture. The product was isolated by flash chromatography on silica gel (1000 g) eluting with 7:3 ethyl acetate: hexanes. Fractions (40 mL each) containing clean product by TLC were pooled to afford 17.19 g (54%) of title compound as a white solid; m.p. 50.5°–51.5° C.

TLC Silica gel (10% ether in dichloromethane): R_f 0.38.

C. (E,E)-1-(Diethyoxyphosphinyl)-6,10,14-trimethyl-5,9,13-pentadecatriene-1-sulfonic acid, phenyl ester

To a suspension of 333 mg (8.32 mmol, 2 eq.) of sodium hydride (60% mineral oil dispersion) in 5 mL of dry dimethylformamide (DMF) at 0° C. was added a solution of 2.56 g (8.32 mmol, 2 eq.) of Part B compound in 5 mL of dry DMF. The hetero-geneous bubbling solution was warmed to RT and stirred for 30 min. To the resulting homogeneous yellow solution was added a solution of 1.50 g (4.16 mmol, 1 eq.) of Example 1 Part C iodide in 5 mL of dry DMF and

the reaction was stirred for 41 h at RT. The reaction was diluted with ether (150 mL) and washed with water (50 mL). The aqueous layer was extracted with ether (2×15 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated to afford 3.11 g of a yellow oil. The product was isolated via flash chromatography on silica gel (200 g) eluting with 35% ethyl acetate in hexanes. Fractions (40 mL each) containing clean product by TLC were pooled and concentrated to afford 1.39 g (62%) Of title compound as a clear light yellow oil.

TLC Silica gel (10% ether in hexanes): R_f 0.66.

D. (E,E)-6,10,14-Trimethyl-1-phosphono-5,9,13-pentadecatriene-1-sulfonic acid, phenyl ester, dipotassium salt

To a solution of 500 mg (0.92 mmol, 1 eq.) of Part C compound in 4 mL of dichloromethane at RT was added 367 μL (2.8 mmol, 3 eq.) of 2,4,6-collidine followed by 488 μL (3.7 mmol, 4 eq.) of bromotrimethylsilane (TMSBr). After 28 h an additional 100 μL (0.76 mmol, 0.8 eq.) of TMSBr was added to consume intermediate monoester. After 18 h (46 h total), reaction mixture was concentrated and placed on high vac (0.25 mmHg) for 2 h. The resulting yellow oil was dissolved by adding 1.9 mL (1.9 mmol, 2.1 eq.) of 1M potassium hydroxide. The resulting cloudy solution (pH 8.42) was lyophilized and the light brown lyophilate was chromatographed on a column of CHP20 (2.5 cm×25 cm) eluting initially with 150 mL of water then with a gradient formed by the gradual addition of mL of acetonitrile to a reservoir containing mL of water. Fractions containing clean product by HPLC were pooled and concentrated. The residue was taken up in a minimal amount of water, filtered and lyophilized to afford 411 mg of title salt in the form of an off-white lyophilate.

TLC Silica gel (7:2:1 n-propanol:ammonium hydroxide:water): R_f 0.38.

IR (KBr): 3410 (br), 2965, 2924, 1636, 1487, 1339, 1194, 1148, 1098 cm^{-1}.

^1H NMR (D_2O, 400 MHz) δ7.10 (m, 4H) 6.99 (t, 1H, J=7.1 Hz) 4.97 (t, 1H, J=6.4 Hz) 4.74 (m, 2H) 3.42 (dr, 1H, J=17.1, 5.6 Hz) 2.08 (m, 2H) 1.98 (m, 1H) 1.88 (m, 1H) 1.68–1.47 (m, 10H) 1.37 (s, 3H) 1.29 (s, 3H) 1.20 (s, 3H) 1.17 (s, 3H) ppm.

^{13}C NMR (D_2O, 75.6 MHz) δ148.8 135.7 134.4 130.4 130.0 127.0 124.4 124.3 124.3 122.4 62.3 (d, J_{CP}=107 Hz) 39.8 39.6 29.0 (d, J_{CP}=5 Hz) 28.1 27.5 26.8 26.7 25.3 17.3 15.9 15.7 ppm.

MS (FAB, +ions): m/z 523 $(M-K+2H)^+$, 561 $(M+H)^+$, 599 $(M+K)^+$.

Anal. Calc'd for $C_{24}H_{35}O_6PSK_2$·0.84 H_2O: C, 50.05; H, 6.42; P, 5.38; S, 5.72 Found: C. 50.05; H, 6.74; P, 5.11; S, 5.45

EXAMPLE 14

(E,E)-9,13,17-Trimethyl-1-phosphono-8,12,16-octadecatriene-1-sulfonic acid, tripotassium salt

A. Dichloro[μ-[1-propanolato(2-)-C_3:O_1]]dimagnesium

A modification of the procedure of G. Cahiez et al was employed (Tetrahedron Letters, 1978, 3013–4): To a stirred solution of 1.89 g (20 mmol) of 3-chloropropanol in 20 mL of THF under argon at –20° C. was added 10 mL (20 mmol) of 2M phenylmagnesium chloride in THF over 15 minutes. After 10 minutes at 20° C., the reaction was allowed to warm to RT, 730 mg (30 mmol) of magnesium turnings were added and the reaction was heated to reflux. Two 40 μL portions of 1,2-dibromoethane were added, the first portion injected at the start of reflux, and the second after 1 hour. After refluxing for a total of 2 hours, the reaction was allowed to cool to RT and was diluted with 37 mL of THF for a theoretical concentration of 0.3M.

B. (E,E)-8,12,16-Trimethyl-7,11,15-hentadecatrien-1-ol

Copper (I) iodide (18 mg, 0.097 mmol) was added to a solution of Example 1 Part C iodide (3.50 g, 9.72 mmol) in THF (50 mL) under argon, and the mixture was cooled to 0° C. The Part A Grignard solution (23.4 mL, 0.5M in THF, 11.7 mmol) was added dropwise over 10 min, and the resultant cloudy white reaction was stirred at 0° C. for 10 min. The ice bath was removed and the reaction was stirred at RT for 1 h. Isopropanol (1.5 mL) was added dropwise slowly to quench the reaction, followed by addition of 1M $KHSO_4$ (30 mL). The mixture was stirred for 5 min at RT, whereupon two layers separated. Diethyl ether (250 mL) was added, and the organic layer was washed with water (20 mL), saturated NH_4Cl (50 mL), and brine (50 mL), then dried over $MgSO_4$. Evaporation gave a yellow oil which was purified by flash chromatography on 100 g silica gel eluting with 15:85 EtOAc/hexanes to give title compound (2.62 g, 92%) as a colorless oil.

C. (E,E)-17-Iodo-2,6,10-trimethyl-2,6,10-heptadecatriene

A solution of iodine (861 mg, 3.39 mmol) in THF (4 mL) was added dropwise to a solution of Part B compound (900 mg, 3.08 mmol), triphenylphosphine (888 mg, 3.39 mmol), and imidazole (461 mg, 6.78 mmol) in THF (10 mL) under argon at RT. The reaction became slightly exothermic during addition. The resultant brown reaction mixture was stirred at RT for 5 min, diluted with hexane (70 mL) and washed with 10% aqueous sodium bisulfite and brine (10 mL each), then dried over $MgSO_4$. Silica gel (4 g) was added to the filtrate, and the solvent was evaporated to give a white solid. Purification by flash chromatography on 50 g silica gel eluting with hexane gave title compound (1.19 g, 96%) as a colorless oil.

D. (E,E)-1-(Diethoxyphosphinyl)-9,13,17-trimethyl-8,12,16-octadecatriene-1-sulfonic acid, cyclohexyl ester

A solution of Example 1A, Part B sulfonate (958 mg, 3.05 mmol) in DMF (2 mL) was added dropwise over 5 min to a suspension of dry sodium hydride (67 mg, 2.79 mmol) in DMF at –15° C. under argon (note: H_2 evolution). The cooling bath was removed and the suspension was stirred at RT for 1 h, whereupon a clear yellow solution was obtained. A solution of Part C compound (1.02 g, 2.54 mmol) in DMF (3 mL) was added dropwise over 3 min, and the reaction was stirred at RT for 23 h. The reaction was quenched by addition of saturated NH_4Cl (2 mL), and the resultant mixture was partitioned between diethyl ether (100 mL) and water (20 mL). The organic layer was washed with water (10 mL) and brine (50 mL), then dried over $MgSO_4$. Evaporation gave an opaque oil which was purified by flash chromatography on 125 g silica gel eluting with 20:80 EtOAc/hexane followed by 30:70 EtOAc/hexane to give title compound (981 mg, 66%) as a colorless oil.

E. (E,E)-9,13,17-Trimethyl-1-phosphono-8,12,16-octadecatriene-1-sulfonic acid, tripotassium salt

Ammonia was bubbled through a solution of Part D compound (876 mg, 1.49 mmol) in methanol (20 mL) at 0° C. for 15 min. The reaction mixture was then heated at 75° C. in a sealed tube for 20 h, cooled to RT, and concentrated in vacuo to give a yellow gum. The crude product was dissolved in CH_2Cl_2 (7 mL) under argon. Bis(trimethylsilyl) trifluoroacetamide (2.0 mL, 7.45 mmol) was added and the reaction was stirred at RT for 10 min. Bromotrimethylsilane (786 mL, 5.96 mmol) was added dropwise and the resultant cloudy yellow reaction mixture was stirred at RT for 22 h. Additional bromotrimethylsilane (197 mL, 1.49 mmol) was

added to the clear yellow solution and the reaction was stirred for another 18 h at RT. The reaction was concentrated in vacuo then pumped at high vacuum for 1 h to give a yellow oil, which was dissolved in 1N KOH (7.5 mL, 7.5 mmol) and stirred at RT for 2 h. The resultant heterogeneous yellow mixture was lyophilized to give a tan solid, which was purified by chromatography on CHP20P gel (2.5×20 cm column) eluting with water followed by a gradient created by the gradual addition of acetonitrile to a reservoir of water. The product fractions were concentrated to approximately a 10 mL volume, then lyophilized. The white solid was dissolved in water (600 mL) and acetone (2 mL) was added. The white semi-solid which precipitated was washed with acetone (3×2 mL) then pumped at high vacuum to give title salt (517 mg, 62%) as a white solid.

TLC Silica gel (6:3:1 n-propanol/NH_4OH/H_2O): R_f=0.21

IR (KBr) 2924, 2855, 1624, 1449, 1383, 1213, 1148, 1092, 1044, 966, 714 cm^{-1}.

^1H NMR (D_2O, 300 MHz) δ5.04 (m, 3H) 2.76 (ddd, 1H, J=18.3, 5.9, 4.9 Hz) 1.84 (m, 12H) 1.50 (s, 3H) 1.44 (s, 3H) 1.42 (s, 6H) 1.40 (m, 2H) 1.17 (br s, 6H) ppm.

^{13}C NMR (D_2O, 75 MHz) δ135.15 131.56 125.27 124.53 124.44 61.69 (d, J=123 Hz) 39.54 39.46 29.85 29.72 29.60 29.26 28.71 27.86 26.49 25.29 15.66 ppm.

MS (FAB, +ions) m/z 527 (M+2H−K), 565 (M+H), 603 (M+K).

Anal. Calc'd for $C_{21}H_{36}K_3O_6PS$.1.0 equiv H_2O: C, 43.27; H, 6.57; P, 5.31; S, 5.50. Found: C, 42.93; H, 6.93; P, 5.03; S, 5.87.

EXAMPLE 15

(E,E)-1-(Ethoxyhydroxyphosphinyl)-6,10,14-trimethyl-5,9,13-pentadecatriene-1-sulfonic acid, dipotassium salt

To a solution of 0.44 g (0.80 mmol) of Example 1A Part C compound and 10 mL of methanol in a sealable tube at 0° C. was added NH_3 (g) until the solution was saturated. The tube was sealed and placed in an oil bath at 70° C. for 24 h, at which point the tube was opened and the volatiles removed under reduced pressure. The remainder was dissolved in dry ethanol and evaporated two times (2×10 mL) leaving an amber oil. The oil was dissolved in 4.0 mL of a 1:1 ethanol/water solution and treated with 0.45 g (8.00 mmol) of potassium hydroxide. The mixture was heated to 80° C. for 72 h when the solvent was evaporated and the residue pumped (≈0.5 mm pressure) for 0.5 h. The remainder was purified by MPLC on a column of CHP20P gel (2.5 cm diam.×20 cm height) eluting with water (150 mL) followed by a gradient created by the gradual addition of 400 mL of acetonitrile to a reservoir of 350 mL of water. Approximately 7 mL fractions were collected. Pure fractions were combined and the acetonitrile was removed under reduced pressure. The aqueous solution was lyophilized to provide 0.30 g (74%) of title salt as a white lyophilate.

TLC Silica gel (6:3:1 n-propanol/conc. ammonia/water) R_f=0.55.

IR (KBr) 3459, 3052, 2969, 2926, 2859, 1636, 1445, 1383, 1221, 1105, 1190, 1055, 1038, 945 cm^{-1}.

^1H NMR (D_2O, 400 MHz) δ5.19 (t, 1H, J=7.0 Hz) 5.11 (q, 2H, J=6.5 Hz) 3.90 (m, 2H) 3.00 (dt, 1H, J=18.4, 6.0 Hz) 2.10–1.80 (m, 12H) 1.61 (s, 3H) 1.56 (s, 3H) 1.54 (s, 6H) 1.55 (m, 2H) 1.17 (t, 3H, J=7.2 Hz) ppm.

Mass Spec (FAB, +ions) m/e 551 (M+K), 513 (M+H).

Anal. Calc'd for $C_{20}H_{35}O_6K_2PS$: C, 46.85; H, 6.88; P, 6.04; S, 6.25 Found: C, 46.76; H, 6.89; P, 5.67; S, 6.60.

EXAMPLE 16

(E)-8,12-Dimethyl-1-phosphono-7,11-tridecadiene-1-sulfonic acid, dipotassium salt

A. (E)-7,11-Dimethyl-6,10-dodecadienoic acid, 1,1-dimethylethyl ester

To a stirred solution of 1.10 mL (7.71 mmol) of freshly distilled diisopropylamine in 7.0 mL of THF under argon at −78° C. was added 3.20 mL (5.14 mmol) of 1.6M n-butyllithium in hexanes to give a pale yellow solution. The solution was allowed to warm to 0° C. for 15 minutes then cooled again to −78° C., at which time 693 μL (5.14 mmol) of t-butylacetate (t-BuOAc) was added neat. After an additional 15 minutes at −78° C., 1.79 mL (10.28 mmol) of HMPA was added followed by the addition of 1.50 g (5.14 mmol) of Example 2, Part F iodide in 5 mL of THF dropwise over 5 minutes. The reaction was stirred at −78° C. for 2 hours at which time it was warmed to room temperature, diluted with 50 mL of ether and quenched with saturated NH_4Cl. The organic layer was washed with water, brine, dried ($MgSO_4$) and evaporated to provide 1.39 g of a pale yellow oil. Flash chromatography was performed on 100 g of silica gel eluting with hexane (1 L) and 9:1 hexane/EtOAc (1 L). Product fractions were combined and evaporated to provide 1.15 g (92%) of title compound as a pale yellow oil.

TLC Silica gel (9:1 hexane/ethyl acetate) R_f=0.70.

IR (CCl_4) 2976, 2928, 2857, 1732, 1454, 1368, 1155 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ5.20 (t, 1H, J=6.9 Hz), 5.18 (t, 1H, J=6.9 Hz), 2.30 (t, 2H, J=7.3 Hz), 2.14 (m, 2H), 2.08 (m, 4H), 1.77 (s, 3H), 1.69 (m+s, 8H), 1.53 (s, 9H), 1.47 (m, 2H) ppm.

MS (CI-NH_3, +ions) m/e 298 (M+NH_4), 281 (M+H).

B. (E)-7,11-Dimethyl-6,10-dodecadien-1-ol

To a stirred solution of 234 mg (6.16 mmol) of lithium aluminum hydride in 10 mL of ether at 0° C. under argon was added dropwise over 10 minutes 1.15 g (4.10 mmol) of Part A ester. The reaction was stirred for 1 hour at which time it was quenched by the following: 234 μL of water, 234 μL of 15% NaOH in water and 700 μL of water. The granular mixture was stirred and dried (Na_2SO_4) for 0.5 hours at which time the mixture was filtered through a celite cake and the cake was washed with ether followed by dichloromethane. The filtrate was evaporated to provide 834 mg of a colorless oil. Flash chromatography was performed on 100 g of silica gel eluting with 1:1 hexane/EtOAc (1 L). Pure product fractions were combined and evaporated to provide 824 mg (96%) of title alcohol as a colorless oil.

TLC Silica gel (9:1 hexane/ethyl acetate) R_f=0.15.

IR (CCl_4) 3300, 2928, 2856, 1450, 1377, 1151, 1107, 1055 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ5.13 (t, 1H, J=7.0 Hz), 5.10 (t, 1H, J=7.0 Hz), 3.63 (t, 2H, J=6.5 Hz), 2.10 (m, 2H), 2.01 (m, 4H), 1.68 (s, 3H), 1.60 (s, 6H), 1.56 (m, 2H), 1.36 (m, 4H) ppm.

MS (CI-NH_3) m/e 228 (M+NH_4).

C. (E)-12-Iodo-2,6-dimethyl-2,6-dodecadiene

To a stirred solution of 820 mg (3.90 mmol) of Part B alcohol in 8 mL of THF under argon at room temperature was added 3.07 g (11.71 mmol) of triphenylphosphine, 797 mg (11.71 mmol) of imidazole and 1.98 g (7.81 mmol) of iodine. After 1 hour, the brown solution was diluted with ether and washed with saturated sodium sulfite, brine, dried ($MgSO_4$) and evaporated. Flash chromatography was performed on 100 g of silica gel eluting with hexane. Pure product fractions were combined and evaporated to provide 913 mg (73%) of title iodide as a colorless oil.

TLC Silica gel (Hexane) R_f=0.46.

IR (CCl_4) 2922, 2853, 1449, 1383 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ5.22 (t, 1H, J=6.5 Hz), 5.19 (t, 1H, J=6.5 Hz), 3.29 (t, 2H, J=7.0 Hz), 2.14 (m, 2H), 2.09 (m, 4H), 1.93 (quint, 2H, J=7.0 Hz), 1.78 (s, 3H), 1.70 (s, 6H), 1.45 (m, 4H) ppm.

MS (CI-NH_3, +ions) m/e 338 (M+NH_4), 320 (M).

D. (E)-1-(Diethoxyphosphinyl)-8,12-dimethyl-7,11-tridecadiene-1-sulfonic acid, cyclohexyl ester

To a stirred suspension of 187 mg (4.68 mmol, 1.5 eq.) of sodium hydride (as a 60% mineral oil dispersion) in 1.5 mL of dry dimethylformamide (DMF) at 0° C. was added a solution of 1.47 g (4.68 mmol, 1.5 eq.) of Example 1A Part B compound in 2 mL of DMF dropwise over 5 min. The solution was warmed to RT and stirred for 30 min. To the resulting clear yellow solution was added a solution of 1.00 g (3.12 mmol, 1 eq.) of Part C iodide in 3 mL of dry DMF dropwise over 5 min. The reaction was stirred at RT for 70 h, diluted with ether (100 mL) and washed with water (50 mL). The aqueous layer was extracted with ether (2×15 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to afford 1.14 g of a yellow oil. Flash chromatography was performed on 250 g of silica gel eluting with 30% ethyl acetate in hexanes. Fractions (40 mL each) containing clean product by TLC were pooled and concentrated to afford, after high vac (0.25 mmHg) removal of solvent remnants, 410 mg (26%) of title compound as a clear yellow oil.

TLC Silica gel (10% ether in CH_2Cl_2): R_f 0.49.

E. (E)-8,12-Dimethyl-1-phosphono-7,11-tridecadiene-1-sulfonic acid, dipotassium salt

To a solution of 400 mg (0.79 mol, 1 eq.) of Part D compound in 8 mL of methanol in a sealable tube at 0° C. was bubbled ammonia until the solution was saturated. The reaction tube was then sealed and heated at 75° C. for 17 h. The reaction mixture was allowed to cool to RT and then concentrated. The oily residue was dried by coevaporation with toluene (2×). High vac (0.25 mmHg) removal of solvent remnants a light yellow oil.

To a solution of the yellow oil in 5 mL of dry dichloromethane at RT was added 522 μL (3.95 mmol, 5 eq.) of 2,4,6-collidine. To the resulting clear light yellow solution was added 729 μL (5.53 mmol, 7 eq.) of bromotrimethylsilane (TMSBr) dropwise over 4 min. As the TMSBr was added a white precipitate formed and the reaction became exothermic. An ice bath was used to cool reaction mixture until addition of TMSBr was complete. After 16 h at RT the reaction was concentrated and the resulting semisolid was placed on high vac (0.25 mm Hg) for 2 h. The residue was dissolved by adding 4.95 mL (6.3 eq.) of 1M potassium hydroxide followed by 5 mL of water and lyophilized to afford an off-white lyophilate. The lyophilate was purified by MPLC on a column of CHP20P (2.5 cm×25 cm) eluting initially with 150 mL of water followed by a gradient formed by the gradual addition of 400 mL of 50% acetonitrile in water to a reservoir containing 400 mL of 10% acetonitrile in water. Fractions containing clean product by HPLC were pooled and concentrated. The semisolid residue was taken up in water, filtered, concentrated and finally triturated with acetone to afford, after high vac (0.025 mm Hg) removal of acetone remnants, 305 mg (77%) of title salt as a white solid.

TLC silica gel (5:4:1 n-propanol:ammonium hydroxide:water): R_f 0.39

IR (KBr): 3450(br), 2924, 2855, 1653, 1447, 1209, 1148, 1044 cm^{-1}.

^1H NMR (D_2O, 300 MHz) δ5.10 (t, 1H, J=6.9 Hz) 5.03 (t, 1H, J=6.5 Hz) 2.73 (ddd, 1H, J=17.9, 6.5, 4.6 Hz) 1.95 (m, 2H) 1.86 (m, 4H) 1.75 (m, 2H) 1.52 (s, 3H) 1.46 (s, 6H) 1.41 (m, 2H) 1.18 (m, 4H) ppm.

^{13}C NMR (D_2O, 75.6 MHz) δ136.4 133.7 125.6 124.7 6.18 (d, J_{CP}=121 Hz) 39.0 29.5 (d, J_{CP}=7 Hz) 29.2 29.0 28.7 27.5 26.0 25.0 17.2 15.5 ppm

MS (FAB, +ions): m/z 445 (M+H), 483 (M+K), (M−H+2K)

Anal. Calc'd for $C_{15}H_{27}O_6PSK_2.3.2\ H_2O$: C, 35.87; H, 6.70; S, 6.38; P, 6.17 Found: C, 35.91; H, 6.30; S, 6.11; P, 6.10

EXAMPLE 17

α-Phosphono[1,1'-biphenyl]-4-heptanesulfonic acid, tripotassium salt

A. 4-(6-Iodohexyl) [1,1'-biphenyl]

A(1). 6-([1,1'-Biphenyl]-4-yl)-6-hexyn-1-ol

To suspension of 0.361 g (2.04 mmol, 0.02 eq) of palladium chloride and 1.07 g (4.08 mmol, 0.04 eq) of triphenylphosphine in 300 mL of diethylamine at room temperature was added 26.1 g (112 mmol, 1.1 eq) of 4-bromobiphenyl (from Aldrich) followed by 0.766 g (4.08 mmol, 0.04 eq) of copper (I) iodide (99.999% pure, from Aldrich). After 5 min, 10.0 g (102 mmol, 1.0 eq) of 5-hexyn-1-ol (from Aldrich) was added neat. After 43 h, the reaction was concentrated and the residue was partitioned between water (250 mL) and CH_2Cl_2 (250 mL). The aqueous solution was extracted with CH_2Cl_2 and the combined organic solutions were concentrated. To remove the catalyst the residue was filtered through silica gel (40 g) eluting initially with CH_2Cl_2, then with CH_2Cl_2 containing 2% EtOAc. Concentration afforded 31.9 g of a brownish orange solid which was chromatographed on silica gel (400 g) eluting with 2% EtOAc in CH_2Cl_2 (4 L), then 4% EtOAc in CH_2Cl_2 (2 L). The isolated solid was then recrystallized from chloroform/hexanes to afford 16.2 g (64%) of the title compound as a white solid; m.p. 64.0°–64.5° C.

TLC Silica gel (25% EtOAc in hexanes): R_f 0.14.

A(2). [1,1'-Biphenyl]-4-hexanol

To a solution of 9.0 g (36 mmol, 1 eq) of Part A(1) alcohol in 100 mL of THF was added 300 mg (0.36 mmol, 0.01 eq) of 10% palladium on activated carbon. The resulting heterogeneous mixture was placed under an H_2 atmosphere at RT After 67 h, the reaction was filtered through Celite and the filter cake was washed with Et_2O and CH_2Cl_2. Concentration afforded 9.07 g (99%) of the title compound as a fluffy white solid; m.p. 77.0°–77.5° C.

TLC Silica gel (25% EtOAc in hexanes): R_f 0.19.

A(3). 4-(6-Iodohexyl) [1,1'-biphenyl]

To a solution of 7.00 g (28 mmol, 1.0 eq) of Part A(2) biphenylhexanol in 30 mL of dry THF were added 8.66 g (33 mmol, 1.2 eq) of triphenylphosphine and 4.50 g (66 mmol, 2.4 eq) of imidazole. To the resulting homogeneous solution was added dropwise a solution of 8.38 g (33 mmol, 2.4 eq) of iodine in 40 mL of dry THF over 25 min. After 45 min, the reaction was diluted with Et_2O and washed with 10% aqueous sodium bisulfite, brine and dried ($MgSO_4$) The solution was filtered and the volume was reduced approximately by 50%. Silica gel (35 g) was added and the remainder of the solvent was removed. The product adsorbed onto silica gel was loaded onto a pre-equilibrated column (hexanes) of silica gel (20 g) and eluted with hexanes. Fractions containing clean product were pooled and concentrated to afford 9.40 g (94%) of the title compound as a clear, colorless oil.

TLC Silica gel (25% EtOAc in hexanes): R_f 0.69.

B. α-(Diethoxyphosphinyl)[1,1'-biphenyl]-4-heptanesulfonic acid, phenyl ester

To a stirred suspension of 329 mg (8.23 mmol, 2 eq.) of sodium hydride (as a 60% mineral oil dispersion) in 3 mL of dry dimethylformamide (DMF) at 0° C. was added a solution of 2.54 g (8.23 mmol, 2 eq.) of Example 13 Part B compound in 6 mL of DMF dropwise over 10 min. The solution was warmed to RT and stirred for 30 min. To the resulting clear yellow solution was added a solution of 1.50 g (4.12 mmol, 1 eq.) of Part A iodide in 6 mL of dry DMF dropwise over 5 min. The reaction was stirred at RT for 43 h, diluted with ether (200 mL) and washed with water (100 mL). The aqueous layer was extracted with ether (2×25 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to afford 3.36 g of a yellow oil. Flash chromatography was performed on 400 g of silica gel eluting with 40% ethyl acetate in hexanes. Fractions (40 mL each) containing clean product by TLC were pooled and concentrated to afford, after high vac (0.25 mmHg) removal of solvent remnants, 1.06 g of a clear yellow oil, as well as 742 mg of the desired product contaminated with dialkylated material. The contaminated material was rechromatographed on 200 g of silica gel and the clean product was combined with the previously isolated product to afford 1.375 g (61%) of title compound as a clear light yellow oil.

TLC Silica gel (10% ether in CH_2Cl_2): R_f 0.57.

C. α-Phosphono[1,1'-biphenyl]-4-heptanesulfonic acid, tripotassium salt

To a solution of 600 mg (1.1 mmol, 1 eq.) of Part B compound in 5 mL of dioxane at RT was added 1.1 mL (1.1 mmol, 1 eq.) of 1M potassium hydroxide. The initially turbid solution became homogeneous within 2 h. After 19 h, starting material was still evident by TLC as well as a lower Rf spot (presumably due to over hydrolysis). An additional 1.1 mL (1.1 mmol, 1 eq.) of KOH was added and reaction was stirred for 16 h (35 h total) at RT. The reaction mixture was concentrated and the residual yellow oil was co-evaporated with toluene (4×) to remove water and placed on high vac (0.25 mmHg) for 2 h to afford a yellow solid.

To a heterogeneous solution of the yellow solid in 5 mL of dry dichloromethane at RT was added 1.45 mL (11.0 mmol, 10 eq.) of bromotrimethylsilane (TMSBr) dropwise over 3 min. As the TMSBr was added the solution began to clear and upon completion of TMSBr addition the reaction was nearly homogeneous. After 17 h, an additional 750 μL (5.7 mmol, 5.1 eq.) of TMSBr was added to complete consumption of the intermediate monoester. After 22 h (39 h total) at RT, the reaction was concentrated and the resulting oil was placed on high vac (0.25 mm Hg) for 13 h. The residue was dissolved by adding 4.4 mL (4.4 mmol, 4 eq.) of 1M potassium hydroxide followed by 20 mL of water and sonicating at 40° C. for 10 min. The crude product was purified by MPLC on a column of CHP20P (2.5 cm×25 cm) eluting initially with 150 mL of water followed by a gradient formed by the gradual addition of 400 mL of acetonitrile in water to a reservoir containing 400 mL of water. Fractions containing clean product were pooled and concentrated. The semisolid residue was taken up in water, filtered and lyophilized to afford 243 mg (39%) of a white lyophilate.

TLC silica gel (5:4:1 n-propanol: ammonium hydroxide:water): R_f 0.38.

IR (KBr): 3403(br), 2928, 2857, 1651, 1202, 1163, cm^{-1}.

^1H NMR (D_2O, 300 MHz): δ7.52 (d, 2H, J=7.8 Hz) 7.45 (d, 2H, J=8.0 Hz) 7.35 (t, 2H, J=7.5 Hz) 7.24 (t, 1H, J=8.0 Hz) 7.22 (d, 2H, J=8.0 Hz) 2.73 (ddd, 1H, J=17.8, 6.6, 4.4 Hz) 2.51 (t, 2H, J=7.5 Hz) 1.74 (m, 2H) 1.48 (m, 2H) 1.39 (m, 2H) 1.20 (bs, 4H) ppm.

^{13}C NMR (D_2O, 75.6 MHz): δ143.4 140.6 137.9 129.4 129.3 127.6 127.0 126.9 61.8 (d, J_{CP}=121 Hz) 34.7 30.9 29.5 (d, J_{CP}=6 Hz) 29.1 28.7 28.5 ppm.

MS (FAB): m/z 489 $(M-K+2H)^+$, 527 $(M+H)^+$.

Anal. Calcd for $C_{19}H_{22}O_6PSK_3.2.31\ H_2O$: C, 40.15; H, 4.72; S, 5.64; P, 5.45 Found: C, 40.15; H, 4.89; S, 5.60; P, 5.47

EXAMPLE 18

(E)-4-(4'-Pentyl[1,1'-biphenyl]-4-yl)-1-phosphono-3-butene-1-sulfonic acid, tripotassium salt

A. α-Ethenyl-4'-pentyl[1,1'-biphenyl]-4-methanol, acetate ester

To a stirred solution of 3.03 g (10.0 mmol) of 4-bromo-4'-pentyl[1,1'-biphenyl] in 20 mL of THF under argon at −78° C. was added a solution of 12.5 mL (21.2 mmol) of 1.7 M t-butyllithium in pentane over 1 h. A dark-colored slurry had formed. This was warmed to 0° C. and the resulting organic solution was stirred for 25 min. To this reaction mixture was added 0.8 mL (12 mmol, 1.2 equivalents) of freshly distilled acrolein at a rate to keep the temperature below 5° C. After an additional 30 min, the reaction was quenched with saturated ammonium chloride solution, extracted twice with ether, dried ($MgSO_4$) and evaporated. The resulting yellow solid was dissolved in 50 mL of dichloromethane and stirred under argon. To this solution was added 2.5 mL (18 mmol) of triethylamine, 1.5 mL (15 mmol) of acetic anhydride and 20 mg (0.16 mmol) of 4-N,N-dimethylaminopyridine at room temperature. After 14 h, the reaction mixture was evaporated, redissolved in ether, washed once with 10% citric acid, once with water and once with saturated sodium bicarbonate solution. The extract was dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica gel (5×25 cm column, 2:3 dichloromethane/hexanes as elutent) gave title compound as a colorless oil, 2.20 g, 68% yield.

B. (E)-1-(Diethoxyphosphinyl)-4-(4'-pentyl[1,1'-biphenyl-4-yl)-3-butene-1-sulfonic acid, 1-methylethyl ester

To a stirred solution of 1.50 g (4.65 mmol) of Part B compound, 2.7 mL (10.7 mmol, 2.3 equiv.) of bis (trimethylsilyl)acetamide, 2.5 g (9.3 mmol, 2.0 equiv.) of Example 11, Part A sulfonate and 125 mg (0.5 mmol) of triphenylphosphine in 10 mL of THF under argon was added 270 mg (0.24 mmol) of tetrakis(triphenylphosphine) palladium. The resulting mixture was heated to 45° C. for 2 hour. The reaction was cooled, evaporated, diluted with ether and washed once with 10% citric acid and thrice with water. The organic phase was dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica gel (5×20 cm column) eluted with 4:96 ether/dichlo-romethane gave title compound as a colorless oil, 1.65 g, 66% yield.

C. (E)-4-(4'-Pentyl[1,1'-biphenyl]-4-yl)-1-phosphono-3-butene-1-sulfonic acid, tripotassium salt

A solution of 670 mg (1.24 mmol) of Part B compound in 10 mL of methanol under argon at room temperature was saturated with ammonia gas. The flask containing the reaction mixture was sealed and heated to 75° C. After 16 h, the reaction was cooled to room temperature and evaporated under dry conditions. The residue was dissolved in 10 mL of dichloromethane and 560 μL (6.4 mmol) of bis (trimethylsilyl)trifluoroacetamide and then 670 μL (5.0 mmol) of bromotrimethylsilane was added. After 24 h, the resulting clear solution was evaporated at 25° C. and then stirred for 1 h with 8 mL (4 mmol) of 0.5M potassium hydroxide solution. The solution was lyophilized and then purified by MPLC (2.5×20 cm column of Mitsubishi Kasei

Sepadbeads HP-20 resin): 11.5 mL fractions, 7 mL/min flow rate, eluted with 200 mL of water and then a gradient prepared from 400 mL of water and 450 mL of 3:1 acetonitrile/water). Fractions 42–50 were collected and lyophilized to give title salt as a white solid, 505 mg, 85% yield.

IR (KBr pellet) 3430, 2928, 2855, 1636, 1497, 1202, 1078, 968 cm^{-1}.

^1H NMR (D_2O, 400 MHz) δ7.28 (m, 4H) 7.21 (d, 2H, J=7.1 Hz) 6.88 (d, 2H, J=7.3 Hz) 6.40 (m, 2H) 2.94 (dm, 1H, J=17.1 Hz) 2.82 (m, 1H) 2.67 (m, 1H) 2.25 (t, 2H, J=5.5 Hz) 1.27 (dq, 2H, J=6.0 Hz) 0.98 (m, 4H) 0.58 (t, 3H, J=6.8 Hz.) ppm.

Anal. Calc'd for $C_{21}H_{24}K_3O_6PS.2.2\ H_2O$: C, 42.58; H, 4.83; P, 5.23; S, 5.41 Found: C, 42.18; H, 5.19; P, 5.63; S, 5.42.

MS (FAB, +ions) m/e 591 (M+K), 553 (M+H), 515 (M–K+2H).

EXAMPLE 19

α-Phosphono-4'-Pentyl[1.1'-biphenyl]-4-butanesulfonic acid, tripotassium salt

A. α-(Diethoxyphosphinyl)-4'-propyl[1,1'-biphenyl]-4-butanesulfonic acid, 1-methylethyl ester

To an argon-purged solution of 550 mg (1.02 mmol) of Example 18 Part B compound and 100 mg of 10% palladium-on-carbon in 25 mL of ethyl acetate in a 200 mL one-neck round bottom flask was attached a hydrogen-filled rubber bladder of approximately 1 L capacity. The reaction mixture was vigorously stirred for 16 h, purged with nitrogen, filtered through Celite and the filtrate evaporated. The oily residue was triturated in hexanes and re-evaporated to give title compound as a colorless oil, 545 mg, 99% yield. The product was used without further purification.

B. α-Phosphono-4'-pentyl[1,1'-biphenyl]-4-butanesulfonic acid, tripotassium salt

To a stirred solution of 520 mg (1.00 mmol) of Part A compound in 5 mL of dichloromethane under argon at room temperature was added 400 μL (4.5 mmol) of bromotrimethylsilane. After 18 h, the resulting clear solution was evaporated at 25° C. and the residue dissolved in 10 mL of THF. To this stirred solution was added 330 mg (2 mmol) of dried, finely ground potassium iodide and 3 mg (0.01 mmol) of 18-crown-6. The resulting slurry was heated to reflux for 24h, evaporated and then stirred for 1 h with 6 mL (4.5 mmol) of 0.5M potassium hydroxide solution. The solution was lyophilized and then purified by MPLC (2.5×20 cm column of Mitsubishi Kasei Sepadbeads CHP-20P resin): 11.5 mL fractions, 7 mL/min flow rate, eluted with 200 mL of water and then a gradient prepared from 400 mL of water and 450 mL of acetonitrile). Fractions 26–31 were collected and lyophilized to give title salt as a white solid, 400 mg, 69% yield.

IR (KBr pellet) 3424, 3088, 2928, 2859, 1663, 1499, 1202, 1082, 1049, 966 cm^{-1}.

^1H NMR (D_2O, 400 MHz) 7.34 (d, 1H, J=7.7 Hz) 7.31 (d, 1H, J=7.8 Hz) 7.18 (d, 1H, J=7.8 Hz) 7.02 (d, 1H, J=7.7 Hz) 2.80 (dt, 1H, J=17.8, 5.1 Hz) 2.35 (t, 1H, J=7.0 Hz) 1.81 (m, 4H) 1.36 (m, 2H) 1.06 (m, 4H) 0.63 (t, 2H, J=6.8 Hz) ppm.

Anal. Calc'd for $C_{21}H_{26}K_3O_6PS.1.42\ H_2O$: C, 43.46; H, 5.01; P, 5.34; S, 5.52 Found: C, 43.46; H, 4.93; P, 5.37; S, 5.25.

MS (FAB, +ions) m/e 593 (M+K), 555 (M+H), 517(M–K+2H).

EXAMPLE 20

4-(2-Naphthalenyl)-α-phosphonobenzenebutanesulfonic acid, tripotassium salt

A. 2-(4-Bromophenyl)naphthalene

To a stirred solution of 4.14 g (20.0 mmol) of 2-bromonaphthalene in 50 mL of THF at –78° C. under nitrogen was added a solution of 23.5 mL (40.0 mmol, 1.7 M in pentane) of t-butyllithium over 10 minutes. The resulting slurry was stirred for 30 minutes and then warmed to 0° C. for 15 minutes. To this deep indigo solution was added a solution of 3.50 g (25.6 mmol) of thrice-fused zinc chloride in 25 mL of THF. The resulting light yellow solution was warmed to room temperature and stirred for 1 hour. After cooling to –78° C., a solution of 5.66 g (20.0 mmol) 1-bromo-4-iodobenzene and 300 mg (0.26 mmol) of tetrakis(triphenylphosphine)palladium in 20 mL of THF was added over the course of 15 minutes. After an additional 20 min, the cooling bath was removed, the reaction stirred at room temperature for 16 hours and then quenched with 50 mL of 2M hydrochloric acid. The mixture was extracted thrice with ether, the extracts combined, washed once with saturated sodium bicarbonate solution and once with 10% sodium thiosulfate. The organic extract was dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel (5×25 cm column, hexanes as elutent) to give 4.05 g (72%) of title compound as a white solid, mp 121°–123° C.

B. α-Ethenyl-4-(2-naphthalenyl)benzenemethanol, acetate ester

To a stirred solution of 2.59 g (9.13 mmol) of Part A compound in 20 mL of THF at –78° C. under nitrogen was added a solution of 10.8 mL (18.4 mmol, 1.7M in pentane) of t-butyllithium over 20 minutes. The resulting magenta slurry was warmed to 0° C. and stirred for 1 h. To the resulting solution was added 0.8 mL (14 mmol) of freshly distilled acrolein over 5 min. The resulting light yellow solution was stirred for 1 hour and then quenched with saturated ammonium chloride. The mixture was extracted twice with ether, dried ($MgSO_4$) and evaporated to give a white solid.

The solid was dissolved in 50 mL of dichloromethane, stirred under nitrogen at room temperature and treated with 2.0 mL (14.4 mmol) of triethylamine, 1.23 mL (13 mmol) of acetic anhydride and 50 mg (0.4 mmol) of DMAP. After 16 h, the reaction mixture was evaporated, redissolved in ether and washed once with 10% citric acid solution, once with brine and once with saturated sodium bicarbonate solution. The organic phase was dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel (5×20 cm column, 1:1 dichloromethane/hexanes as elutent) to give 1.83 g (66% from Part A compound) of title compound as a white solid, mp 61°–63° C.

C. (E)-1-(Diethoxyphosphinyl)-4-[4-(2-naphthalenyl) phenyl]-3-butene-1-sulfonic acid, 1-methylethyl ester

To a stirred solution of 1.55 g (5.13 mmol) of Part B compound, 2.75 mL (12.9 mmol, 2.5 equivalents) of bis (trimethylsilyl)acetamide, 2.81 g (10.2 mmol, 2.0 equivalents) of Example 11, Part A sulfonate and 125 mg (0.48 mmol) of triphenylphosphine in 10 mL of THF under nitrogen was added 270 mg (0.24 mmol) of tetrakis (triphenylphosphine)-palladium. The resulting mixture was heated to 45° C. for 2 h. The reaction was cooled and evaporated and pumped at room temperature @ 0.2 Torr for 24 hours. The residue was diluted with dichloromethane and evaporated onto 5 g of silica gel. Purification by flash

chromatography on silica gel (5×20 cm column) eluted with 1:16 ether/dichloromethane gave title compound as a yellow oil, 950 mg, 36% yield.

D. α-(Diethoxyphosphinyl)-4-(2-naphthalenyl) benzenebutanesulfonic acid, 1-methylethyl ester

To a nitrogen-purged solution of 950 mg (1.85 mmol) of Part C compound and 350 mg of 10% Pd/C in 25 mL of ethyl acetate in a 200 mL one-neck round bottom flask was attached a hydrogen-filled rubber bladder of approximately 1 L capacity. The reaction mixture was vigorously stirred for 16 h, purged with nitrogen, filtered through Celite and the filtrate evaporated. The oily residue was redissolved in dichlormethane, filtered through a 0.75 m filter and re-evaporated to give title compound as a colorless oil, 960 mg, 100% yield. The product was used without further purification.

E. 4-(2-Naphthalenyl)-α-phosphonobenzencbutanesulfonic acid, tripotassium salt

To a stirred solution of 950 mg (1.81 mmol) of Part D compound in 10 mL of dichloromethane under nitrogen at room temperature was added 1.4 mL (10.5 mmol) of bromotrimethylsilane. After 24 h, the resulting clear solution was evaporated at 25° C. and the residue dissolved in 10 mL of THF. To this stirred solution was added 0.5 g (3 mmol) of dried, finely ground potassium iodide and 6 mg (0.02 mmol) of 18-crown-6. The resulting slurry was heated to reflux for 20 h, evaporated and then stirred for 1 h with 12 mL (6 mmol) of 0.5M potassium hydroxide solution. The solution was lyophilized and then purified by MPLC (2.5×20 cm column of CHP20P resin): 11.5 mL fractions, 7 mL/min flow rate, eluted with 200 mL of water and then a gradient prepared from 400 mL of water and 450 mL of 2:1 acetonitrile/water). Fractions 66–72 were collected and lyophilized to give title salt as a white solid, 560 mg, 55% yield.

IR (KBr pellet) 3418, 3055, 2934, 2864, 1661, 1503, 1339, 1196, 1078, 966 cm^{-1}.

^1H NMR (D_2O, 400 MHz) δ7.68 (s, 1H) 7.57 (m, 3H) 7.37 (dd, 1H, J=1.3, 8.6 Hz) 7.31 (d, 1H, J=8.1 Hz) 7.27 (m, 2H) 7.14 (d, 1H, J=8.1 Hz) 2.82 (ddd, 1H, J=2.1, 6.4, 17.5 Hz) 2.56 (m, 2H) 1.74 (m, 4H) ppm.

MS (FAB, +ions) m/e 573 (M+K), 535 (M+H), 497 (M−K+2H).

Anal. Calc'd for $C_{20}H_{18}K_3PSO_6.1.3H_2O$: C, 43.04; H, 3.72; P, 5.55; S, 5.74 Found: C, 43.04; H, 3.86; P, 5.79; S, 6.09.

EXAMPLE 21

4-Phenoxy-α-phosphonobenzenebutanesulfonic acid, tripotassium salt

A. α-Ethenyl-4-phenoxybenzenemethanol

tert-Butyllithium (24.5 mL, 1.7M in pentane, 42.2 mmol) was added dropwise over 30 min to a solution of 4-bromodiphenyl ether (5.00 g, 20.1 mmol) in THF (50 mL) at −78° C. under argon. The cooling bath was removed and the bright yellow reaction mixture was warmed to 0° C. over 20 min. The reaction was stirred at 0° C. for 30 min, at which time a tan-colored solution developed. Freshly distilled acrolein (1.6 mL, 24 mmol) was added dropwise over 5 min. The colorless reaction mixture was stirred at 0° C. for 15 min, then quenched by addition of saturated NH_4Cl (10 mL). The mixture was diluted with diethyl ether (200 mL) and the organic layer was washed with water (20 mL) and brine (50 mL), then dried over $MgSO_4$. Evaporation gave a crude oil which was purified by flash chromatography on silica gel (400 g) eluted with a step gradient of 10:90 EtOAc/hexane to 15:85 EtOAc/hexane to 20:80 EtOAc/hexane to provide title compound (3.31 g, 73%) as a colorless oil.

B. α-Ethenyl-4-phenoxybenzenemethanol, acetate ester

Acetic anhydride (1.7 mL, 18 mmol) and 4-dimethylaminopyridine (18 mg, 0.15 mmol) were added to a solution of Part A alcohol (3.30 g, 14.6 mmol) and triethylamine (4.1 mL, 29.2 mmol) in CH_2Cl_2 (50 mL), and the reaction was stirred at RT under argon for 1.5 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with water (10 mL) and brine (20 mL), then dried over $MgSO_4$. Evaporation gave a yellow oil which was purified by flash chromatography on silica gel (100 g) eluted with 30 10:90 EtOAc/hexane to give title compound (3.83 g, 98%) as a pale yellow oil.

C. (E)-1-(Diethoxyphosphinyl)-4-(4-phenoxyphenyl)-3-butene-1-sulfonic acid, 1-methylethyl ester

Tetrakis(triphenylphosphine)palladium (200 mg, 0.17 mmol) was added to a mixture of Part B compound (1.50 g, 5.60 mmol), Example 11, Part A compound (3.07 g, 11.2 mmol), bis(trimethylsilyl)acetamide (2.76 mL, 11.2 mmol), and triphenylphosphine (73 mg, 0.28 mmol) in THF (20 mL). The reaction was heated at reflux for 45 min, cooled to RT, and concentrated in vacuo to give a gold-colored oil. The crude product was purified by flash chromatography on silica gel (150 g) eluted with a gradient of 40:60 EtOAc/hexane to 50:50 EtOAc/hexane to afford title compound (914 mg, 34%) as a colorless oil.

D. α-(Diethoxyphosphinyl)-4-phenoxybenzenebutanesulfonic acid, 1-methylethyl ester

A mixture of Part C compound (900 mg, 1.87 mmol) and 10% palladium on carbon (50 mg) in EtOAc (6 mL) was stirred at RT under an atmosphere of H_2 (balloon) overnight (18 h), then was filtered through a pad of Celite with the aid of EtOAc. Evaporation gave title compound (855 mg, 94%) as a colorless oil.

E. 4-Phenoxy-α-phosphonobenzenebutanesulfonic acid, tripotassium salt

Ammonia gas was bubbled through a solution of Part D compound (780 mg, 1.61 mmol) in methanol (15 mL) for 15 min at RT. During the saturation, the solution turned yellow and became slightly exothermic. The reaction mixture was heated at 75° C. in a sealed tube overnight (17 h), then was cooled to RT. The reaction was concentrated in vacuo, and the residue was azeotroped with toluene (2×10 mL) to give a thick yellow syrup.

The crude product was dissolved in CH_2Cl_2 (5 mL) under argon and bromotrimethylsilane (1.5 mL, 11.3 mmol) was added dropwise. The cloudy yellow reaction was stirred at RT overnight, concentrated in vacuo, and pumped at high vacuum for 3 h.

The crude residue was dissolved in 1N KOH (8.1 mL, 8.1 mmol) and stirred at RT for 30 min. The reaction was heterogeneous. Additional 1N KOH (1.6 mL, 1.6 mmol) was added along with water (5 mL). The still heterogeneous reaction mixture was lyophilized to give a beige solid, which was purified by chromatography on CHP20P gel (2.5×20 cm column) eluted with water followed by a gradient created by the gradual addition of acetonitrile to a reservoir of water. The product fractions were concentrated to approximately a 5 mL volume, then lyophilized to provide title salt (488 mg, 61%) as a white solid.

TLC (silica gel) (6:3:1 n-propanol/NH_4OH/H_2O): R_f=0.15

IR (KBr) 3042, 2936, 2864, 1663, 1589, 1507, 1489, 1240, 1198, 1076, 966 cm^{-1}.

^1H NMR (D_2O, 400MHz) δ7.27 (t, 2H, J=7.9 Hz) 7.19 (d, 2H, J=8.3 Hz) 7.04 (t, 1H, J=7.5 Hz) 6.91 (d, 2H, J=7.7 Hz) 6.87 (d, 2H, J=8.3 Hz) 2.79 (dm, 1H) 2.52 (m, 2H) 2.00–1.63 (m, 4H) ppm.

^{13}C NMR (D_2O, 75 MHz) δ157.22 154.56 138.96 130.15 130.08 123.66 119.04 118.57 61.69 (d, J=120 Hz) 34.74 31.53 (d, J=7 Hz) 28.61 (d, J=2 Hz) ppm.

MS (FAB, +ions) m/z 463 (M+2H−K), 501 (M+H), 539 (M+K).

Anal. Calc'd for $C_{16}H_{16}K_3O_7PS$.1.0 equiv H_2O: C, 37.05; H, 3.50; P, 5.97; S, 6.18. Found: C, 36.77; H, 3.86; P, 6.42; S, 6.48.

EXAMPLE 22

1-Phosphono-7-(4-propylphenoxy)-1-heptanesulfonic acid, tripotassium salt

A. 1-[(6-Bromohexyl)oxy]-4-propylbenzene

A solution of diisopropylazodicarboxylate (2.12 g, 10.5 mmol) in THF (25 mL) was added via syringe pump over 1.5 h to a mixture of 4-propylphenol (purchased from Aldrich Chemical Co.) (1.36 g, 10.0 mmol), 6-bromo-1-hexanol (purchased from Aldrich Chemical Co.) (1.81 g, 10.0 mmol), and triphenylphosphine (2.75 g, 10.5 mmol) in THF (25 mL) at 0° C. under argon. The slightly yellow reaction was stirred at 0° C. for 30 min, whereupon additional triphenylphosphine (262 mg, 1.00 mmol) was added, followed by addition of diisopropylazodicarboxylate (200 mL, 1.0 mmol) over 30 min. The reaction was allowed to warm to RT, at which time silica gel (15 g) was added. The mixture was concentrated in vacuo and the white powder obtained was purified by flash chromatography on silica gel (150 g) eluted with a step gradient of hexane to 2:98 EtOAc/hexane. The slightly impure product obtained was rechromatographed on silica gel (150 g) eluted with 1:99 EtOAc/hexane to give title compound (2.00 g, 67%) as a colorless oil.

B. 1-[(6-Iodohexyl)oxy]-4-propylbenzene

A mixture of Part A compound (1.85 g, 6.19 mmol), sodium iodide (4.65 g, 31.0 mmol), and anhydrous sodium bicarbonate (520 mg, 6.19 mmol) in methyl ethyl ketone (15 mL) was brought to reflux and maintained at that temperature for 2 h, then allowed to cool to RT. The solvent was removed from the colorless reaction in vacuo and the residue was partitioned between diethyl ether (70 mL) and water (20 mL). The organic layer was washed with water (10 mL) and brine (10 mL), then dried over $MgSO_4$. Evaporation gave title compound (2.09 g, 98%) as a opaque oil.

C. 1-(Diethoxyphosphinyl)-7-(4-propylphenoxy)-1-heptanesulfonic acid, cyclohexyl ester

A solution of Example 1A, Part B sulfonate (4.65 g, 14.8 mmol) in DMF (5 mL) was added dropwise over 5 min to a suspension of dry sodium hydride (283 mg, 11.8 mmol) in DMF (5 mL) at −15° C. under argon (note: H_2 evolution). The cooling bath was removed and the suspension was stirred at RT for 30 min, whereupon a clear yellow solution was obtained. A solution of Part B iodide (2.04 g, 5.90 mmol) in DMF (10 mL) was added dropwise over 5 min, and the reaction was stirred at RT overnight. The reaction was quenched by addition of saturated NH_4Cl (10 mL), and the resultant mixture was partitioned between diethyl ether (50 mL) and water (50 mL). The aqueous layer was extracted with diethyl ether (50 mL). The organic extracts were combined and washed with water (20 mL) and brine (2×20 mL), then dried over $MgSO_4$. Evaporation gave a yellow oil which was purified by flash chromatography on silica gel (200 g) eluted with 30:70 EtOAc/hexane to give title compound (2.12 g, 68%) as a colorless oil.

D. 1-Phosphono-7-(4-propylphenoxy)-1-heptanesulfonic acid, tripotassium salt

Ammonia gas was bubbled through a solution of Part C compound (810 mg, 1.52 mmol) in methanol (15 mL) for 10 min at RT. During the saturation, the solution turned yellow and became slightly exothermic. The reaction mixture was heated at 75° C. in a sealed tube overnight (20 h), then cooled to RT. The reaction was concentrated in vacuo, and the residue was azeotroped with toluene (2×10 mL) to give a white semi-solid.

The crude product prepared above was dissolved in CH_2Cl_2 (8 mL) under argon and bromotrimethylsilane (1.4 mL, 10.6 mmol) was added dropwise. The cloudy yellow reaction was stirred at RT overnight (19 h), concentrated in vacuo, and pumped at high vacuum for 3 h.

The crude residue prepared above was dissolved in 1N KOH (7.6 mL, 7.6 mmol) and stirred at RT for 15 min, diluted with water (5 mL), then lyophilized to give a white solid. Purification was performed by chromatography on CHP20P gel (2.5×20 cm column) eluted with water followed by a gradient created by the gradual addition of acetonitrile to a reservoir of water. The product fractions were concentrated to approximately a 5 mL volume, then lyophilized to provide title salt (406 mg, 53%) as a white solid.

TLC (silica gel) (6:3:1 n-propanol/NH_4OH/H_2O): R_f=0.21

IR (KBr) 2932, 2868, 1636, 1512, 1200, 1074, 966 cm^{-1}.

^{1}H NMR (D_2O, 300 MHz) δ7.05 (d, 2H, J=8.4 Hz) 6.79 (d, 2H, J=8.4 Hz) 3.90 (t, 2H, J=6.6 Hz) 2.72 (ddd, 1H, J=4.5, 6.3, 17.8 Hz) 2.37 (t, 2H, J=7.5 Hz) 1.93 −1.10 (m, 12H) 0.71 (t, 3H, J=7.3 Hz) ppm.

^{13}C NMR (D_2O, 75 MHz) δ156.24 136.23 129.78 115.03 69.14 61.76 (d, J=120 Hz) 36.41 29.42 (d, J=7 Hz) 28.92 28.63 28.54 25.24 24.31 13.07 ppm.

MS (FAB, +ions) m/z 509 (M+H), 547 (M+K).

Anal. Calc'd for $C_{16}H_{24}K_3O_7PS$.1.6 equiv H_2O: C, 35.75; H, 5.10; P, 5.76; S, 5.97. Found: C, 35.79; H, 5.49; P, 5.54; S, 5.95.

α-Phosphono-4-(4-propylphenoxy) benzenebutanesulfonic acid, tripotassium salt

A. 4-(4-Propylphenoxy)benzaldehyde

Anhydrous potassium carbonate (14.9 g, 0.12 mol) was added to a mixture of 4-propylphenol (13.6 g, 0.10 mol) and 4-fluorobenzaldehyde (12.4 g, 0.10 mol) in N,N-dimethylacetamide (100 mL) under argon. The heterogeneous mixture was brought to reflux, maintained at that temperature for 5 h, then cooled to RT. Water (100 mL) and CH_2Cl_2 (100 mL) were added, resulting in a tri-phase system. The bottom layer was removed; the middle layer was dried over $MgSO_4$; and, the top layer was extracted with CH_2Cl_2 (100 mL) and dried over $MgSO_4$. The dried layers were combined and concentrated in vacuo at 50° C. to give an orange oil. The crude product was purified by distillation to give title compound (16.6 g, 69%) as a colorless oil. bp 133°–150° C. (0.2 mm Hg)

B. α-Ethenyl-4-(4-propylphenoxy)benzenemethanol, acetate ester

A solution of Part A compound (2.00 g, 8.33 mmol) in THF (15 mL) was added dropwise over 10 min to a solution of vinylmagnesium bromide (9.2 mL, 1.0M in THF, 9.2 mmol) in THF (15 mL) at −40° C. under argon. The reaction was warmed to −20° C. over 30 min, whereupon the heterogeneous mixture went to clear yellow. Additional vinylmagnesium bromide (1.5 mL, 1.0M in THF, 1.5 mmol) was added dropwise. The reaction was stirred at −20° C. for 10 min, then quenched by addition of saturated NH_4Cl (10 mL). The solvent was removed in vacuo, and the mixture was diluted with diethyl ether (50 mL). The organic layer was washed with water (10 mL), 1N HCl (10 mL), and brine (20 mL), then dried over $MgSO_4$. Evaporation gave the alcohol (2.6 g) as a yellow oil.

Acetic anhydride (0.94 mL, 10.0 mmol), triethylamine (2.3 mL, 16.7 mmol), and 4-dimethylaminopyridine (10 mg, 0.08 mmol) were added to a solution of the crude alcohol in CH_2Cl_2 (30 mL) under argon. The yellow reaction was stirred at RT for 2.5 h, diluted with CH_2Cl_2 (50 mL), and washed with water and brine (20 mL each), then dried over $MgSO_4$. Evaporation gave a heterogeneous yellow oil, which was purified by flash chromatography on silica gel (150 g) eluted with 3:97 EtOAc/hexane to give title compound (1.85 g, 72%) as a pale yellow oil.

C. (E)-1-(Diethoxyphosphinyl)-4-[4-(4-propylphenoxy) phenyl]-3-butene-1-sulfonic acid, 1-methylethyl ester

Tetrakis(triphenylphosphine)palladium (196 mg, 0.17 mmol) was added to a mixture of Part B compound (1.74 g, 5.61 mmol), Example 11, Part A compound (3.07 g, 11.2 mmol), bis(trimethylsilyl)acetamide (2.8 mL, 11 mmol), and triphenylphosphine (73 mg, 0.28 mmol) in THF (20 mL). The reaction was heated at 45° C. for 3 h, cooled to RT, and concentrated in vacuo to give a yellow oil. The crude product was purified by flash chromatography on silica gel (200 g) eluted with a step gradient of 30:70 EtOAc/hexane to 40:60 EtOAc/hexane to afford title compound (706 mg, 24%) as a colorless oil.

D. 1-(Diethoxyphosphinyl)-4-(4-propylphenoxy) benzenebutanesulfonic acid, 1-methylethyl ester

A mixture of Part C compound (700 mg, 1.34 mmol) and 10% palladium on carbon (40 mg) in EtOAc (5 mL) was stirred at RT under an atmosphere of H_2 (balloon) overnight, then was filtered through a pad of Celite with the aid of CH_2Cl_2. Evaporation gave title compound (669 mg, 95%) as a colorless oil.

E. α-Phosphono-4-(4-propylphenoxy) benzenebutanesulfonic acid, tripotassium salt

Ammonia gas was bubbled through a solution of Part D compound (610 mg, 1.16 mmol) in methanol (10 mL) for 10 min at RT. During the saturation, the solution turned yellow and became slightly 10 exothermic. The reaction mixture was heated at 75° C. in a sealed tube overnight (20 h), then cooled to RT. The reaction was concentrated in vacuo, and the residue was azeotroped with toluene (2×10 mL) to give a pale yellow oil.

The crude product prepared above was dissolved in CH_2Cl_2 (6 mL) under argon and bromotrimethylsilane (1.1 mL, 8.1 mmol) was added dropwise. The cloudy yellow reaction was stirred at RT overnight (19 h), concentrated in vacuo, and pumped at high vacuum for 3 h.

The crude residue prepared above was dissolved in 1N KOH (5.8 mL, 5.8 mmol) and stirred at RT for 15 min, diluted with water (5 mL), then lyophilized to give a white solid. Purification was performed by chromatography on CHP20P gel (2.5×20 cm column) eluted with water followed by a gradient created by the gradual addition of acetonitrile to a reservoir of water. The product fractions were concentrated to approximately a 5 mL volume, then lyophilized to provide title salt (445 mg, 71%) as a white solid.

TLC (silica gel) (6:3:1 n-propanol/NH_4OH/H_2O): R_f=0.18

IR (KBr) 2959, 2870, 1503, 1240, 1200, 1078, 966 cm^{-1}.

^1H NMR (D_2O, 400 MHz) δ7.16 (d, 2H, J=8.6 Hz) 7.10 (d, 2H, J=8.6 Hz) 6.83 (2d, 4H, J=6.4, 6.8 Hz) 2.79 (ddd, 1H, J=4.3, 6.2,. 16.9 Hz) 2.50 (m, 2H) 2.42 (t, 2H, J=7.5 Hz) 1.97 –1.62 (m, 4H) 1.45 (sextet, 2H, J=7.5 Hz) 0.73 (t, 3H, J=7.5 Hz) ppm.

^{13}C NMR (D_2O, 75 MHz) δ154.93 138.64 130.01 118.70 118.63 61.54 (d, J=120 Hz) 36.56 34.73 31.51 (d, J=7 Hz) 28.52 24.27 13.06 ppm.

MS (FAB, +ions) m/z 543 (M+H), 581 (M+K).

Anal. Calc'd for $C_{19}H_{22}K_3O_7PS$.2.0 equiv H_2O: C, 39.43; H, 4.53; P, 5.35; S, 5.54. Found: C, 39.63; H, 4.70; P, 5.18; S, 5.50.

EXAMPLE 24

(E,E)-1-(Diethoxyphosphinyl)-6,10,14-trimethyl-5,9, 13-pentadecatriene-1-sulfonic acid, sodium salt

To a solution of 0.50 g (0.91 mmol) of Example 1A Part C compound and 10 mL of methanol in a sealable tube at 0° C. was added NH_3 (g) until the solution was saturated. The tube was sealed and placed in an oil bath at 70° C. for 24 h, at which point the tube was opened and the volatiles removed under reduced pressure. The remainder was dissolved with 1.20 mL (1.20 mmol) of 1N sodium hydroxide solution. The compound was purified by MPLC by loading the basic solution on a column of CHP20P gel (2.5 cm diam.×20 cm height) and eluting with water (150 mL) followed by a gradient created by the gradual addition of 400 mL of acetonitrile to a reservoir of 350 mL of water. Approximately 7 mL fractions were collected. Pure fractions (#30–34) were combined and the acetonitrile was removed under reduced pressure. The aqueous solution was lyophilized to provide 0.39 g (87%) of title salt as an amber oil.

TLC Silica gel (6:3:1 n-propanol/conc. ammonia/water) R_f=0.80.

IR (CHC_{13}) 3459, 2969, 2926, 2859, 1647, 1445, 1236, 1165, 1098, 1069, 1034, 970 cm^{-1}.

^1H NMR (CD_3OD, 300 MHz) δ5.15 (m, 4.18 (quint., 4H, J=7.0 Hz) 3.22 (dr, 1H, J=18.4, 6.0 Hz) 2.10–1.80 (m, 12H) 1.70 (s, 3H) 1.65 (s, 3H) 1.60 (s, 6H) 1.60 (m, 2H) 1.30 (t, 3H, J=7.0 Hz) ppm.

Mass Spec (FAB, +ions) m/e 509 (M+Na).

Anal. Calc'd for $C_{22}H_{40}O_6NaPS$-0.73 H_2O: C, 53.91; H, 8.31; P, 6.32; S, 6.54 Found: C, 53.91; H, 8.23; P, 6.17; S, 6.33.

EXAMPLE 25

(E)-6-Methyl-10-phenyl-1-phosphono-5-decene-1-sulfonic acid, tripotassium salt

A. 5-Methyl-9-phenyl-non-4-en-1-ol

To a solution of 1.5 g (4.26 mmol) of the Example 35, Part B iodide in 10 mL of THF at 0° C. was added 12.9 mL (25.8 mmol) of benzylmagnesium chloride in THF (purchased from Aldrich Chemical) followed by 10 mg (catalyst) of copper (I) iodide. The reaction was stirred at 0° C. for 1 h, and at room temperature for 3 h. The reaction was diluted with ether and aqueous NH_4Cl solution. The organic fraction was washed with water and brine, dried ($MgSO_4$) and concentrated to provide 2.70 g of a crude oil. The oil was purified by flash chromatography (250 g of silica gel) eluting with 8:2 ethyl acetate/hexane to provide 1.10 g (99%) of title compound as a colorless oil.

TLC Silica gel (8:2 hexane/ethyl acetate) R_f=0.29.

B. (E)-(9-Iodo-5-methyl-5-nonenyl)benzene

A solution of 980 mg (4.22 mmol) of Part A alcohol in 10 mL of methylene chloride and 0.76 mL (5.49 mmol) of triethylamine at 0° C. was treated with 0.39 mL (5.07 mmol) of methanesulfonyl chloride dropwise over 0.2 h. The reaction mixture was stirred for 1.0 h when it was quenched with saturated aqueous $KHSO_4$ solution and diluted with ether. The layers were separated and the organic fraction was washed with solutions of $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to provide the mesylate as a pale yellow oil.

The crude mesylate was diluted with 100 mL of acetone and treated with 3.65 g (24.39 mmol) of NaI at room temperature for 48 h. The mixture was diluted with 200 mL of a hexane/water mixture. The organic fraction was extracted with $NaHSO_3$, brine, dried ($MgSO_4$) and concentrated to provide a colorless oil. The oil was purified by flash chromatography (50 g of silica gel) eluting with 8:2 ethyl acetate/hexane to provide 1.05 g (76%) of title compound as a colorless oil.

TLC Silica gel (8:2 hexane/ethyl acetate) R_f=0.64.

C. (E)-1-(Diethoxyphosphinyl)-6-methyl-10-phenyl-5-decene-1-sulfonic acid, cyclohexyl ester

To a stirred solution of 0.93 g (2.95 mmol) of Example 1A Part B compound in 3 mL DMF at −20° C. was added 51 mg (2.13 mmol) of sodium hydride. After the hydrogen evolution diminished, the reaction was brought to RT and stirred for 10 minutes. When hydrogen evolution subsided completely, 0.56 g (1.64 mmol) of Part B iodide was added and the reaction stirred 24 hours before storing at −80° C. for 30 hours. The reaction was quenched with 10 mL of saturated aqueous ammonium chloride solution, diluted with ether (150 mL) and water (75 mL). The aqueous layer was removed and the organics washed with saturated sodium chloride. The combined aqueous layers were back extracted with ether and the combined organic fractions dried (over sodium sulfate) and evaporated. The crude material was purified by flash chromatography on silica gel (60g), packed, loaded, and eluted with 60:40 hexane/ethyl acetate. The pure fractions (#8–18) were combined and concentrated to yield 0.55 g (64%) of title compound as a clear oil.

TLC Silica gel (60:40 hexane/ethyl acetate) R_f=0.25.

MS (CI, +ions) m/e 529 (M+H), 546 ($M+NH_4$).

IR (KBr) 2934, 2858, 1452, 1454, 1260, 1194, 1053, 1024, 928 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ7.18 (t, 2H, J=7.5 Hz) 7.08 (d, 3H, J=7.5 Hz) 5.03 (t, 1H, J=7.0 Hz) 4.76 (m, 1H) 4.14 (m, 4H) 3.35 (dr, 1H, J=19.7, 6.5 Hz) 2.53 (t, 2H, J=7.7 Hz) 2.05 (m, 2H) 1.95 (m, 5H) 1.77–1.17 (m, 16H) 1.50 (s, 3H) 1.28 (t, 6H, J=8.0 Hz) ppm.

D. (E)-6-Methyl-10-phenyl-1-phosphono-5-decene-1-sulfonic acid, tripotassium salt

To a solution of 0.496 g (1.93 mmol) of Part C triester in 10 mL methanol in a sealable tube was added ammonia gas at 0° C. until saturated. The tube was then sealed and heated at 65° C. for 24 hours. The tube was opened and the solution evaporated to a glassy oil which was evaporated from toluene two times and dried under high vacuum, leaving an amber oil. The residue was dissolved in 3.5 mL methylene chloride and treated sequentially with 1.53 mL (11.55 mmol) of collidine and 1.78 mL (13.47 mmol) of bromotrimethylsilane bromide. The reaction mass was stirred at RT under argon for 24 hours, at which point an additional 0.254 mL (13.47 mmol) of collidine and 0.508 mL (3.86 mmol) of bromotrimethylsilane were added. After 45 hours at room temperature, the reaction was quenched with 6.95 mL (6.95 mmol) of 1N KOH and lyophilized. The remainder was purified by MPLC on a column of CHP-20P gel (2.5 cm diameter×21 cm height), eluting with water (100 mL), followed by a gradient formed by the gradual addition of 400 mL acetonitrile to a reservoir of 350 mL water. Approximately 10 mL fractions were collected. Pure fractions (#30–32) were combined, concentrated to 0.36 g, and passed through a column of 30 g (153 meq) AG 50W-XG (K^+ form) with water. The potassium salt eluted in fractions 1 to 4, which were lyophilized, providing a granular powder. The lyophilate was diluted in 150 μL water and triturated with 2 mL portions of acetone three times. The product was dried under high vacuum for three days, yielding 259 mg (26%) of title salt as a pale beige powder.

IR (KBr) 3424, 2932, 2857, 1653, 1200, 1080, 966 cm^{-1}.

MS (Ion Spray, +ions) 429 (M−2K+3H), 467 (M−K+2H), 505 (M+H).

^1H NMR (300 MHz, D_2O) δ7.25 (m, 5H) 5.25 (t, 1H, J=6.5 Hz) 2.85 (dr, 1H, J=19.0, 6.0 Hz) 2.60 (t, 2H, J=8.5 Hz) 2.00 (m, 6H) 1.53 (s, 3H) 1.53 (m, 4H) 1.40 (quint, 2H, J=6.4 Hz) ppm.

Anal. Calc'd. for $C_{17}H_{24}K_3PO_6S$·2.1 H_2O: C, 37.64; H, 5.24; P, 5.71; S, 5.91 Found: C, 37.64; H, 5.19; P, 5.34; S, 6.09

EXAMPLE 26

4-(3-Phenylpropyl)-α-phosphonobenzenebutanesulfonic acid, tripotassium salt

A. 4-(1-Hydroxy-3-phenyl-2-propynyl)benzoic acid, methyl ester

To a stirred solution of 4.40 mL (40.0 mmol) of phenylpropyne in 30 mL of THF under nitrogen at −75° C. was added a solution of 16 mL (40 mmol) of 2.5M n-butyllithium in hexane over 20 min. The resulting light yellow solution was warmed to 0° C. and stirred for 30 min. This solution was added via syringe to a slurry of 6.25 g (38.0 mmol) of methyl 4-formylbenzoate in 30 mL of THF at −30° C. over 20 min. The resulting light yellow solution was warmed to room temperature and stirred for 30 min. The reaction was quenched with saturated ammonium chloride solution, extracted twice with ether, dried ($MgSO_4$) and evaporated. Purification by flash chromato-graphy (5×15 cm column, 1:19 ether/dichloromethane as elutent) gave title compound as a white solid, mp 48°–50° C., 9.36 g, 88% yield.

B. 4-(3-Phenylpropyl)benzoic acid, methyl ester

A 500 mL Parr vessel was charged with 3.11 g (11.7 mmol) of Part A compound in 100 mL of methanol and purged with a rapid stream of nitrogen for 15 min. The solution was treated with 0.5 g of Pearlman's catalyst (20% $Pd(OH)_2$ on carbon, 31% H_2O). This mixture was agitated for 16 h at an initial hydrogen pressure of 42 psi. Total hydrogen uptake was 15 psi. The reaction was purged with nitrogen, filtered through Celite and evaporated. The oily residue was dissolved in dichloromethane, dried ($MgSO_4$) and filtered to give title compound as a colorless oil, 2.85 g, 97% yield. The material was used without further purification.

C. 4-(3-Phenylpropyl)benzaldehyde

To a stirred solution of 2.80 g (11.0 mmol) of Part B compound in 20 mL of methanol under nitrogen at room temperature was added 22 mL (22 mmol) of 1M NaOH solution. The milky solution was heated to 60° C. for 2 h. The resulting clear solution was cooled and 1M HCl solution was added to bring the reaction mixture to pH 2. The resulting solids were collected, washed with water and dried in vacuo at 60° C. to give 2.55 g (96%) of the carboxylic acid of the Part B compound.

This solid was dissolved in 25 mL of dichloromethane under nitrogen and 1.4 mL (15 mmol) of oxalyl chloride followed by 0.1 mL of DMF. The resulting vigorously bubbling solution was stirred for 1 h and then evaporated. The semi-solid residue was dissolved in 25 mL of benzene under nitrogen and 170 mg (0.15 mmol) of tetrakis (triphenylphosphine)palladium was added. To this stirring solution at room temperature was added 11.1 mL (34 mmol) of tributyltin hydride over 20 min. The solution turns yellow and warms autogenously to 40° C. After 1 h, the reaction

was treated with 40 mL of 10% aqueous potassium fluoride and stirred vigorously for 30 min. The reaction mass was filtered, the filtrate diluted with ether, washed with water, and the organic layer separated, dried ($MgSO_4$) and evaporated onto 10 g of silica gel. Purification by flash chromatography (5×20 cm column, 45:55 dichloromethane/hexanes as elutent) gave 2.15 g, 87% yield (84% yield from Part B compound), of title compound as a colorless oil.

D. α-Ethenyl-4-(3-phenylpropyl)benzenemethanol, acetate ester

To a stirred slurry of 11.0 mL (11.0 mmol, 1M in THF) of vinyl magnesium bromide in 20 mL of THF at −40° C. under argon was added a solution of 1.95 g (8.7 mmol) of Part C compound in 10 mL of THF over 20 min. The resulting pale yellow solution was warmed to room temperature, stirred for 2 h and then quenched with saturated ammonium chloride solution. The reaction mixture was extracted twice with ether. The extracts were combined, dried ($MgSO_4$) and evaporated. The resulting yellow oil was dissolved in 20 mL of dichloromethane at room temperature under nitrogen and 2.2 mL (16 mmol) of triethylamine and 1.4 mL (15 mmol) of acetic anhydride were added, followed by 100 mg (0.4 mmol) of DMAP. After 30 minutes, the reaction mixture was diluted with ether, washed twice with 10% citric acid, once with brine and once with saturated sodium bicarbonate. The organic phase was dried ($MgSO_4$) and evaporated onto 10 g of silica gel. Purification by flash chromatography (5×25 cm column, 2:3 dichloromethane/hexanes as elutent) gave 7.12 g, 92%, of title compound as a colorless oil.

E. (E)-1-(Diethoxyphosphinyl)-4-[4-(3-phenylpropyl) phenyl]-3-butene-1-sulfonic acid, 1-methylethyl ester

To a stirred solution of 1.33 g (4.52 mmol) of Part D compound, 2.5 mL (10 mmol, 2.2 equiv.) of bis (trimethylsilyl)acetamide, 2.48 g (9.0 mmol, 2.0 equiv.) of Example 11 Part A sulfonate and 125 mg (0.5 mmol) of triphenyl-phosphine in 20 mL of THF under argon was added 270 mg (0.24 mmol) of tetrakis(triphenylphosphine) -palladium. The resulting mixture was heated to reflux for 30 min. The reaction was cooled, evaporated, diluted with ether and washed once with 10% citric acid and thrice with water. The organic phase was dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica gel (5×25 cm column) eluted with 2:23 ether/dichloro-methane gave title compound as a colorless oil, 1.10 g, 55% yield.

F. α-(Diethoxyphosphinyl)-4-(3-phenylpropyl) benzenebutanesulfonic acid, 1-methylethyl ester

To an argon-purged solution of 890 mg (1.75 mmol) of Part E compound and 100 mg of 10% palladium-on-carbon in 20 mL of ethyl acetate in a 500 mL one-neck round bottom flask was attached a hydrogen-filled rubber bladder of approximately 1 L capacity. The reaction mixture was vigorously stirred for 16 h, purged with nitrogen, filtered through Celite and the filtrate evaporated. The oily residue was redissolved in dichlormethane, filtered through a 0.75μ filter and re-evaporated to give title compound as a colorless oil, 865 mg, 99% yield. The product was used without further purification.

G. 4-(3-Phenylpropyl)-α-phosphonobenzenebutanesulfonic acid, tripotassium salt

To a stirred solution of 860 mg (1.7 mmol) of Part F compound in 10 mL of dichloromethane under argon at room temperature was added 700 μL (5.3 mmol) of bromotrimethylsilane. After 24 h, the resulting clear solution was evaporated at 25° C. and the residue dissolved in 10 mL of THF. To this stirred solution was added 560 mg (3.4 mmol) of dried, finely ground potassium iodide and 3 mg (0.01 mmol) of 18-crown-6. The resulting slurry was heated to reflux for 24 h, evaporated and then stirred for 1 h with 6 mL (6 mmol) of 1.0M potassium hydroxide solution. The solution was lyophilized and then purified by MPLC (2.5×20 cm column of Mitsubishi Kasei Sepadbeads HP-20 resin): 11.5 mL fractions, 7 mL/min flow rate, eluted with 200 mL of water and then a gradient prepared from 400 mL of water and 450 mL of 2:1 acetonitrile/water). Fractions 38–48 were collected and lyophilized to give title salt as a white solid, 640 mg, 69% yield.

IR (KBr pellet) 3428, 3084, 2934, 2859, 1659, 1514, 1196, 1107, 1084, 966 cm^{-1}.

^1H NMR (D_2O, 400 MHz) δ7.10 (m, 9H) 2.76 (din, 1H, J=17.3 Hz) 2.45 (m, 6H) 1.74 (m, 6H)ppm.

Anal. Calc'd for $C_{20}H_{18}K_3O_6PS.1.1\ H_2O$: C, 41.77; H, 4.46; P, 5.67; S, 5.87 Found: C, 41.77; H, 4.68; P, 5.46; S,6.08.

MS (FAB, +ions) m/e 565 (M+K), 527 (M+H), 489 (M−K+2H).

EXAMPLE 27

(E,E)-1-(Hydroxymethylphosphinyl)-6,10,14-trimethyl-5,9,13-pentadecatriene-1-sulfonic acid, dipotassium salt

A. Chloromethylphosphinic acid, ethyl ester

To a solution of 15.0 g (98.6 mmol, 1 eq) of diethyl methylphosphonate in 20 mL of dry benzene at room temperature was added 20.5 g (98.6 mmol, 1 eq) of phosphorus pentachloride as a solid all at once. The reaction became very exothermic and began to reflux. Stirring was discontinued and the flask was cooled to 0° C. After 5 minutes, the ice bath was removed and the reaction mixture was warmed to room temperature and stirred for 2 hours, then heated at reflux for 1 hour. After cooling to room temperature, the reaction mixture was concentrated. High vacuum (0.1 mmHg) removal of phosphorus oxychloride (POC_{13}, a volatile by-product of the reaction; Note 1) and any solvent remnants for 13 h afforded 3.42 g of a cloudy yellow liquid which was used without purification or characterization.

Note 1: The product is volatile and the lengthy high vacuum exposure resulted in loss of a significant amount of the desired chlorophosphonate.

B. (Ethoxymethylphosphinyl)methanesulfonic acid, cyclohexyl ester

To a solution of 8.55 g (48.0 mmol, 1 eq) of Example 1A Part A mesylate in 200 mL of dry THF at −75° C. was added 19.2 mL (48.0 mmol, 1 eq) of n-butyllithium (2.5M hexane solution) dropwise at a rate that kept the temperature below −72° C. (addition time 35 min). The resulting clear light yellow solution was stirred for 10 min at −74° C. A solution of 3.42 g of Part A chloride in 20 mL of dry THF was added dropwise at a rate that again kept the temperature below −72° C. (addition time 40 min). The resulting brown reaction mixture was stirred for 90 min at −74° C. and then quenched by addition of a solution of 2.75 mL (48.0 mmol, 1 eq) of glacial acetic acid in 10 mL of THF over 5 min. The solution was warmed to room temperature and concentrated. The viscous brown residue was taken up in dichloromethane (200 mL), washed with water (100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated to afford after high vac removal of solvent remnants 9.26 g of a viscous brown oil. The desired product was isolated by flash chromatography on silica gel (1000 g) eluting initially with ethyl acetate (5 L) followed by 10% ethanol in ethyl acetate (2 L). Fractions (40 mL) containing the clean product were pooled and

concentrated to afford 3.91 g of title compound as a viscous yellow oil (57% assuming starting phosphonyl chloride was pure).

TLC Silica gel (Ethyl acetate): R_f 0.36.

C. (E,E)-1-(Ethoxymethylphosphinyl)-6,10,14-trimethyl-5, 9,13-pentadecatriene-1-sulfonic acid, cyclohexyl ester

To a suspension of 222 mg (5.6 mmol, 2 eq) of sodium hydride (as a 60% mineral oil dispersion) in 1 mL of dry dimethylformamide (DMF) at 0° C. was added dropwise a solution of 1.58 g (5.6 mmol, 2 eq) of Part B compound in 3 mL of dry DMF. The vigorously bubbling solution was stirred for 5 min at 0° C. followed by 30 min at room temperature. To the resulting homogeneous brown solution was added a solution of 1.0 g (2.8 mmol, 1 eq) of Example 1 Part C iodide in 3 mL of DMF. After 16 h at room temperature, the reaction was quenched by adding 25 mL of water. The heterogeneous solution was partitioned between ether (100 mL) and brine (25 mL). The aqueous layer was extracted with ether (4×20 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated to afford after high vac (0.25 mmHg) removal of solvent remnants 1.49 g of crude product as a light brown oil. The desired product was isolated via flash chromatography on silica gel (250 g) eluting with 9% isopropanol in hexanes. Fractions (40 mL each) containing clean product were pooled and concentrated to afford 813 mg of title compound (56%) as a light yellow oil.

TLC Silica gel (15% isopropanol in hexanes): R_f 0.34.

D. (E,E)-1-(Hydroxymethylphosphinyl)-6,10,14-trimethyl-5,9,13-pentadecatriene-1-sulfonic acid, dipotassium salt

Into a solution of 800 mg (1.55 mmol, 1 eq) of Part C compound in 10 mL of dry methanol (MeOH) at 0° C. was bubbled gaseous ammonia until the solution was saturated. The tube was sealed with a threaded teflon cap fitted with an O-ring and heated at 75° C. for 17 h. The volatiles were removed in vacuo and the oily residue was co-evaporated twice with toluene before placing on high vac (0.25 mmHg) for three hours. To the resulting clear yellow oil was added 8 mL of dry CH_2Cl_2 followed by 2.04 mn (15.5 mmol, 10 eq) of dry 2,4,6-collidine. To the resulting light yellow clear solution was added 2.04 (15.5 mmol, 10 eq) of bromotrimethylsilane (TMSBr) and the resulting white heterogeneous mixture was stirred at room temperature. After 16 h, the reaction mixture was concentrated and placed on high vac (0.25 mmHg) for 3 h. The resulting yellow white solid was dissolved by adding 7.3 mL (7.3 mmol, 4.7 eq) of 1M potassium hydroxide (pH 12.35), frozen and lyophilized. The light brown lyophilate was dissolved in water and chromatographed on a column of CHP20P (2.5 cm×25 cm) eluting initially with water (150 mL) followed a gradient formed by the gradual addition of acetonitrile (400 mL) to a reservoir containing water (400 mL). No fractions (10 mL each) containing clean product by were obtained. The fractions containing approximately 2% of an impurity (which eluted just before the desired product) were pooled, concentrated and rechromatographed using the same conditions. Fractions containing clean product by HPLC were concentrated and the residual waxy residue was triturated with acetone to afford 274 mg of title salt (37%) as a white solid.

TLC Silica gel (7:2:1 n-propanol:ammonium hydroxide:water): R_f 0.47.

^1H NMR (D_2O, 300 MHz): δ5.09 (t, 1H, J=6.8 Hz) 5.01 (t, 1H, J=6.9 Hz) 4.98 (t, 1H, J=6.8 Hz) 2.75 (dr, 1H, J=15.0, 5.6 Hz) 1.90 (m, 10H) 1.76 (m, 2H,) 1.51 (s 3H) 1.47 (s 3H) 1.44 (s, 6 H_s) 1.43 (m, 2H) 1.21 (d 3H, J=14.3 Hz) ppm.

^{13}C NMR (D_2O, 75.6 MHz): δ136.7 136.3 133.0 124.8 124.8 124.7 63.0 (d, J_{CP}=81 Hz) 39.4 39.3 29.6 (d, J_{CP}=5 Hz) 27.8 26.9 26.4 26.3 25.3 17.4 16.0 (d, J_{CP}=98 Hz) 15.7 ppm.

IR (KBr) 2922, 2857, 1213, 1188, 1088, 1034 cm^{-1}.

MS (FAB, +ions) m/z 483 (M+H), 445 (M+2H–K), 407 (M+3H–2K).

Anal. Calcd. for $C_{19}H_{33}O_5PSK_2$: C, 47.28; H, 6.89; P, 6.42; S, 6.64 Found: C, 47.30; $H_{0\ 6.92}$; P, 6.04; S, 6.94

EXAMPLE 28

(E,E)-1-(Hydroxyphosphinyl)-6,10,14-trimethyl-5,9, 13-pentadecatriene-1-sulfonic acid, dipotassium salt

A. (E,E)-6,10,14-Trimethyl-5,9,13-pentadecatriene-1-sulfonic acid, ethyl ester

n-Butyllithium (11.1 mL, 2.5M in hexanes, 27.8 mmol) was added dropwise over 15 min to a solution of ethyl methanesulfonate (5.17 g, 41.7 mmol) in THF (50 mL) at –78° C. under argon. The clear colorless reaction mixture was stirred at –78° C. for 20 min, whereupon a solution of Example 1 Part C iodide (5.00 g, 13.9 mmol) in THF (10 mL) was added dropwise over 10 min. The reaction was warmed to –60° C. (internal temperature) and stirred at that temperature for 1.5 h. The reaction was then warmed to –20° C. over 2 h, then quenched by addition of saturated NH_4Cl (20 mL). Diethyl ether (300 mL) was added, and the organic layer was washed with water (2×50 mL) and brine (10 mL), then dried over $MgSO_4$. Evaporation gave a yellow oil, which was purified by flash chromatography on silica gel (200 g) eluting with a step gradient of 5:95 to 8:92 EtOAc/hexane to provide title compound (3.61 g, 73%) as a colorless oil.

B. (E,E)-1-(Ethoxyphosphinyl)-6,10,14-trimethyl-5,9,13-pentadecatriene-1-sulfonic acid, ethyl ester

n-Butyllithium (2.7 mL, 2.5M in hexanes, 6.7 mmol) was added dropwise to a solution of Part A compound (2.00 g, 5.62 mmol) in THF (15 mL) at –78° C. under argon. The yellow reaction was stirred at –78° C. for 30 min, whereupon diethyl chlorophosphite (2.4 mL, 16.9 mmol) was added rapidly in one portion. The colorless reaction was stirred at –78° C. for 1 h, then allowed to warm to RT over 2.5 h. The reaction was diluted with anhydrous diethyl ether (50 mL). Water (10 mL) was then added, and the resultant biphase mixture was stirred vigorously at RT for 1 h. The aqueous layer was removed, and the organic layer was washed with water (10 mL) and brine (15 mL), then dried over $MgSO_4$. Evaporation gave a colorless oil, which was purified by flash chromatography on CC_7 buffered silica gel (250 g) eluting with a step gradient of 25:75 to 35:65 to 45:55 EtOAc/hexane to give title compound (2.07 g, 82%) as a colorless oil as a 1:1 mixture of diastereomers.

C. (E,E)-1-(Hydroxyphosphinyl)-6,10,14-trimethyl-5,9,13-pentadecatriene-1-sulfonic acid, dipotassium salt

Potassium iodide (317 mg, 1.91 mmol) was added to a solution of Part B compound (816 mg, 1.82 mmol) in acetone (10 mL) under argon. As the mostly insoluble potassium iodide reacted, the product precipitated out of the reaction mixture. The white heterogeneous reaction was stirred at RT overnight, concentrated in vacuo, then pumped at high vacuum to give a white solid.

The crude sulfonate salt was dissolved in 1N KOH (3.6 mL, 3.6 mmol), then chromatographed on CHP-20P gel (2.5×20 cm column) eluting with water followed by a gradient created by the gradual addition of acetonitrile to a reservoir of water. The product fractions were concentrated in vacuo to give an opaque white gum. Acetone (2 mL) was added and the product was precipitated out as a solid. The solid was filtered, washed with acetone (2×5 mL), then pumped at high vacuum to give title salt (507 mg, 60%) as a white solid.

TLC (silica gel) (7:2:1 n-propanol/NM_4OH/H_2O): R_f=0.43

IR (KBr) 2928, 2857, 2288, 1202, 1094 cm^{-1}.

^1H NMR (D_2O, 400 MHz) δ7.02 (d, 1H, J=548 Hz) 5.12 (t, 1H, J=6.8 Hz) 5.06 (t, 1H, J=6.8 Hz) 5.04 (t, 1H, J=6.8 Hz) 2.85 (dr, 1H, J=6.4, 13.7 Hz) 2.03–1.85 (m, 10H) 1.78 (m, 2H) 1.54 (s, 3H) 1.49 (s, 3H) 1.47 (s, 6H) 1.44 (m, 2H) ppm.

^{13}C NMR (D_2O, 100 MHz) δ136.53 135.96 132.67 124.60 124.55 124.47 62.42 (d, J=81 Hz) 39.29 39.18 28.41 (d, J=6 Hz) 27.56 26.23 26.19 25.15 24.93 17.24 15.55 ppm.

MS (ES, +ions) m/z 393 (M+3H–2K), 410 [(M+2H–2K)+NH_4], 427 [(M+2H–2K)+NH_3+NH_4], 431 (M+2H–K), 448 [(M+2H–K)+NH_3], 469 (M+H).

Anal. Calc'd for $C_{18}H_{31}K_2O_5PS$: C, 46.13; H, 6.67; P, 6.61; S, 6.84. Found: C, 46.18; H, 6.68; P, 6.28; S, 7.17.

EXAMPLE 29

4-(Phenylmethyl)-α-phosphonobenzenebutanesulfonic acid, tripotassium salt

A. 1-Bromo-4-(phenylmethyl)benzene

To a stirred solution of 21 mL (42 mmol, 2.0M in THF) of benzylmagnesium chloride at room temperature under nitrogen was added a solution of 6.80 g (50.0 mmol) of thrice-fused zinc chloride in 50 mL of THF. The resulting tan slurry was stirred for 1 hour. To this slurry was added 10.0 g (35.3 mmol) 1-bromo-4-iodobenzene and 450 mg (0.4 mmol) of tetrakis(tri-phenylphosphine)palladium in 30 mL of THF. The reaction was stirred at room temperature for 16 hours and then quenched with 50 mL of 2M hydro-chloric acid. The mixture was extracted thrice with hexanes, the extracts combined, washed once with saturated sodium bicarbonate solution and once with 10% sodium thiosulfate. The organic extract was dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel (5×25 cm column, hexanes as elutent) to give 7.05 g (80%) of title compound as a colorless oil.

B. α-Ethenyl-4-(phenylmethyl)benzenemethanol, acetate ester

To a stirred solution of 2.47 g (10.0 mmol) of Part A compound in 30 mL of THF at –60° C. under nitrogen was added a solution of 12 mL (20 mmol, 1.7M in pentane) of t-butyllithium over 20 minutes. The resulting deep red solution was warmed to 0° C. and stirred for 30 min. To the resulting solution was added 1.0 mL (18 mmol) of freshly distilled acrolein over 5 min. The resulting light yellow solution was stirred for 30 min, quenched with saturated ammonium chloride. The mixture was extracted twice with ether, dried ($MgSO_4$) and evaporated to give a colorless oil.

The solid was dissolved in 30 mL of dichloromethane, stirred under nitrogen at room temperature and treated with 2.2 mL (15.8 mmol) of triethylamine, 1.3 mL (14 mmol) of acetic anhydride and 50 mg (0.4 mmol) of DMAP. After 30 min, the reaction mixture was evaporated, redissolved in ether and washed once with 10% citric acid solution, once with brine and once with saturated sodium bicarbonate solution. The organic phase was dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel (5×15 cm column, 1:1 dichloromethane/hexanes as elutent) to give 2.51 g (94% from Part A compound) of title compound as a colorless oil.

C. (E)-1-(Diethoxyphosphinyl)-4-[4-(phenylmethyl)phenyl]-3-butene-1-sulfonic acid, cyclohexyl ester

To a stirred solution of 1.45 g (5.44 mmol) of Part B compound, 2.5 mL (11.7 mmol, 2.15 equivalents) of bis (trimethylsilyl)acetamide, 3.14 g (10.0 mmol, 1.8 equivalents) of Example 1A Part B sulfonate and 270 mg (1.0 mmol) of triphenylphosphine in 15 mL of THF under nitrogen was added 600 mg (0.53 mmol) of tetrakis (triphenylphosphine)palladium. The resulting mixture was heated to reflux for 1 h. The reaction was cooled and evaporated and pumped at room temperature @ 0.2 Torr for 24 hours. The residue was diluted with dichloromethane and evaporated onto 5 g of silica gel. Purification by flash chromatography on silica gel (5×25 cm column) eluted with 1:13 ether/dichloromethane gave title compound as a yellow oil, 1.65 g, 58% yield.

D. α-(Diethoxyphosphinyl)-4-(phenylmethyl) benzenebutanesulfonic acid, cyclohexyl ester

To a nitrogen-purged slurry of 1.15 g (2.2 mmol) of Part C compound and 120 mg of 10%Pd/C in 50 mL of ethyl acetate in a 200 mL one-neck round bottom flask was attached a hydrogen-filled rubber bladder of approximately 1 L capacity. The reaction mixture was vigorously stirred for 16 h, purged with nitrogen, filtered through Celite and the filtrate evaporated. The oily residue was redissolved in dichloromethane, filtered through a 0.75μ filter and re-evaporated to give title compound as a colorless oil, 1.15 g, 99% yield. The product was used without further purification.

E. 4-(Phenylmethyl)-α-phosphonobenzenebutanesulfonic acid, tripotasisum salt

To a stirred solution of 1.15 g (2.20 mmol) of Part D compound in 10 mL of dichloromethane under nitrogen at room temperature was added 1.0 mL (7.5 mmol) of bromotrimethylsilane. After 24 h, the resulting clear solution was evaporated at 25° C. and the residue dissolved in 10 mL of THF. To this stirred solution was added 830 mg (5 mmol) of dried, finely ground potassium iodide and 6 mg (0.02 mmol) of 18-crown-6. The resulting slurry was heated to reflux for 20 h, evaporated and then stirred for 1 h with 7 mL (7 mmol) of 1M potassium hydroxide solution. The solution was lyophilized and then purified by MPLC (2.5×20 cm column of Mitsubishi Kasei Sepadbeads CHP20P resin): 11.5 mL fractions, 7 mL/min flow rate, eluted with water. Fractions 29–55 were collected and lyophilized to give title salt as a white solid, 840 mg, 76% yield.

IR (KBr pellet) 3426, 3063, 2934, 2864, 1636, 1198, 1074, 966 cm^{-1}.

^1H NMR (D_2O, 400 MHz) δ7.16 (m, 5H) 7.08 (d, 2H,J=8.3, H_3) 7.05 (d, 2H,J=8.3, H_2) 3.78 (s, 2H) 2.72 (ddd, 1H, J=3.9, 6.4, 18 Hz) 2.45 (m, 2H) 1.75 (m, 4H) ppm.

MS (FAB, +ions) m/e 536 (M+K), 499 (M+H), 461 (M–K+2H).

Anal. Calc'd for $C_{17}H_{18}K_3PSO_6.1.1H_2O$: C, 39.33; H, 3.94; P, 5.97; S, 6.18 Found: C, 39.33; H, 4.06; P, 5.71; S, 5.89.

EXAMPLE 30

(E,E)-1-[Hydroxy(methoxymethyl)phosphinyl)-6,10,14-trimethyl-5,9,13-pentadecatriene-1-sulfonic acid, dipotassium salt

A. (Methoxymethyl)phosphonic acid, diethyl ester

To a sample of 17.90 mL (0.104 mol) of triethylphosphite at –78° C. under argon was added dropwise 8.50 mL (0.104 mol) of bromomethyl methyl ether. The mixture slowly warmed to RT and stirred for 24 h, when it was fractionally distilled (bp 100° C., 5 mm) to provide 16.22 g (98%) of title compound as a pale yellow oil.

TLC Silica gel (Ethyl acetate) R_f=0.50.

B. Chloro(methoxymethyl)phosphinic acid, ethyl ester

To a solution of 5.0 g (27.6 mmol, 1 eq) of Part A compound in 5 mL of dry benzene at 0° C. was added 5.75 g (27.6 mmol, 1 eq) of phosphorus pentachloride as a solid in one portion. The resulting heterogeneous solution was stirred at 0° C. for 5 min, then warmed to room temperature and stirred for 5 min. The resulting homogeneous solution was heated at reflux for 1 h, cooled to room temperature and concentrated. The residue was co-evaporated twice with benzene followed by exposure to high vacuum (0.25 mmHg) for 1 h to afford 4.52 g (95%) of title compound as a yellow liquid which was used in the next step without purification.

C. [Ethoxy(methoxymethyl)phosphinyl]methanesulfonic acid, cyclohexyl ester

To a solution of 9.84 g (55.2 mmol, 2.1 eq) of Example 1A Part A mesylate compound in 200 mL of dry tetrahydrofuran (THF) at −75° C. (internal temperature) was added dropwise via syringe 22.1 mL (55.2 mmol, 2.1 eq) of a 2.5M n-butyllithium solution in hexanes at a rate that kept the temperature below −71° C. (over 40 min). The resulting solution was stirred for 5 min at −75° C. A solution of 4.52 g (26.2 mmol, 1 eq) of freshly prepared Part B compound in 20 mL of THF was added dropwise at a rate to keep the temperature below −71° C. (over 30 min) and the resulting light brown solution was stirred at −75° C. for 1 h. The reaction was quenched by addition of a solution of 3.16 mL (55.2 mmol, 2.1 eq) of glacial acetic acid in 15 mL of THF over 5 min, then allowed to warm to room temperature. The solution was concentrated and the viscous residue was taken up in dichloromethane (250 mL), washed with water (100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated to afford 12.4 g of a light brown oil. The desired product was isolated by flash chromatography on silica gel (250 g) eluting with ethyl acetate. The fractions containing product by TLC were combined and concentrated to afford a solid which was contaminated by an unknown impurity as evidenced by extraneous peaks in the ^1H NMR spectrum. The solid was recrystallized from hexanes/chloroform to afford 5.04 g (61%) of the title compound as a white solid, m.p. 78.5°–79.5° C.

TLC Silica gel (ethyl acetate) R_f 0.40.

D. (E,E)-1-[Ethoxy(methoxymethyl)phosphinyl]-6,10,14-trimethyl-5,9,13-pentadecatriene-1-sulfonic acid, cyclohexyl ester

To a suspension of 222 mg (5.6 mmol, 2 eq) of sodium hydride (as a 60% dispersion in mineral oil) in 1 mL of dry dimethylformamide (DMF) at 0° C. was added a solution of 1.74 g (5.6 mmol, 2 eq) of Part C compound in 4 mL of DMF dropwise over 10 min. The bubbling heterogeneous mixture was allowed to warm to room temperature and stir for 30 min. To the resulting homogeneous solution was added a solution of 1.0 g (2.8 mmol, 1 eq) of Example 1 Part C iodide in 3 mL of DMF. After 20 h, the reaction was diluted with brine (25 mL). The resulting cloudy solution was extracted with ether (1×100 mL, 3×15 mL), dried ($MgSO_4$) and concentrated to afford 1.64 g of a yellow oil. The desired product was isolated by flash chromatography on silica gel (250 g) eluting with 40% ethyl acetate in hexanes. Fractions containing clean product by TLC were pooled and concentrated to afford 801 mg (52%) of title compound as a viscous yellow oil.

TLC Silica gel (1:1 ethyl acetate:hexanes): R_f 0.23.

E. (E,E)-1-[Hydroxy(methoxymethyl)phosphinyl)-6,10,14-trimethyl-5,9,13-pentadecatriene-1-sulfonic acid, dipotassium salt

To a solution of 600 mg of Part D compound in 12 mL of dry methanol at 0° C. was introduced ammonia until the solution was saturated. The tube was sealed with a threaded teflon cap fitted with an O-ring and heated at 75° C. for 16 h. The volatiles were removed in vacuo and the oily residue was co-evaporated twice with toluene before placing on high vac (0.25 mmHg) for three hours. To the resulting clear yellow oil was added 7 mL of dry CH_2Cl_2 followed by 806 μL (6.1 mmol, 4.5 eq) of dry 2,4,6-collidine. To the resulting light yellow clear solution was added 1.25 mL (9.5 mmol, 7 eq) of bromotrimethylsilane (TMSBr) and the resulting white heterogeneous mixture was stirred at room temperature. After 21 h, the reaction mixture was concentrated and placed on high vac (0.25 mmHg) for 30 min. The resulting yellow white solid was dissolved by adding 7.0 mL (7.0 mmol, 5.2 eq) of 1M potassium hydroxide, and the resulting solution was frozen and lyophilized. The light brown lyophilate was dissolved in water and chromatographed on a column of CHP20P (2.5 cm×25 cm) eluting initially with water (150 mL) followed a gradient formed by the gradual addition of a 63% solution of acetonitrile in water (400 mL) to a reservoir containing water (400 mL). No fractions (10 mL each) containing clean product by HPLC were obtained. The fractions containing approximately 2% of an impurity (which eluted just before the desired product) were pooled, concentrated and rechromatographed using a step gradient. After eluting with water (150 mL) the column was eluted with 15% acetonitrile in water (300 mL) followed by 20% acetonitrile in water (500 mL). Fractions containing pure product by HPLC were concentrated and the residual waxy residue was triturated with acetone to afford 245 mg of title salt (35%) as a white solid.

TLC Silica gel (7:2:1 n-propanol:ammonium hydroxide:water): R_f 0.42.

^1H NMR (D_2O, 300 MHz): δ5.06 (t, 1H, J=6.8 Hz) 4.98 (t, 1H, J=6.9 Hz) 4.96 (t, 1H, J=7.2 Hz) 3.56 (dd, 1H, J=12.9, 6.9 Hz) 3.40 (dd, 1H, J=12.9, 7.5 Hz) 3.23 (s, 3H) 2.92 (m, C_{18}) 1.83 (m, 12H) 1.49 (s, 3H) 1.46 (s, 3H) 1.43 (m, 2H) 1.41 (s, 6H)ppm.

^{13}C NMR (D_2O, 75.6 MHz): δ136.3 135.7 132.3 124.6 70.9 (d, J_{CF}=116 Hz) 60.8 (d, J_{CF}=12 Hz) 59.9 (d, J_{CF}=81 Hz) 39.5 39.4 29.5 (d, J_{CF}=5 Hz) 27.7 26.5 26.4 26.3 (d, J_{CF}=4 Hz) 25.3 17.4 15.7 ppm.

IR (KBr): 3437, 2926, 1449, 1200, 1076, 1030 cm^{-1}.

MS (FAB, +ions) m/z 551 (M+K), 513 (M+H).

Anal. Calc'd for $C_{20}H_{35}O_6PSK_2$.0.55 H_2O: C, 45.96; H, 6.96; P, 5.93; S, 6.13 Found: C, 45.96; H, 6.80; P, 5.54; S, 6.50

EXAMPLE 31

(E,E)-1-[Hydroxy(hydroxymethyl)phosphinyl)-6,10,14-trimethyl-5,9,13-pentadecatriene-1-sulfonic acid, dipotassium salt

Potassium iodide (370 mg, 2.23 mmol) was added to a solution of Example 28 Part B compound (950 mg, 2.12 mmol) in acetone (10 mL) under argon. As the mostly insoluble potassium iodide reacted, the product precipitated out of the reaction mixture. The white heterogeneous reaction was stirred at RT overnight, concentrated in vacuo, then pumped at high vacuum to give a white solid.

A heterogeneous mixture of the sulfonate salt paraformaldehyde (254 mg, 8.48 mmol), and diisopropylethylamine (184 mL, 1.06 mmol) in absolute ethanol (7 mL) was heated at 60° C. under argon. After 15 min, the reaction went from milky white to clear and colorless. After 7 h at 60° C., the reaction was allowed to cool to RT. The reaction was concentrated in vacuo, then pumped at high vacuum to give a white semi-solid.

Aqueous KOH (6.4 mL, 1N, 6.4 mmol) was added to the mono-ester prepared above. The initially white foamy dispersion was stirred at RT under argon overnight, after which time the reaction was clear and colorless. The reaction mixture was chromatographed on CHP20P gel (2.5×20 cm column) eluting with water followed by a gradient created by the gradual addition of acetonitrile to a reservoir of water. The product fractions were concentrated in vacuo to give an opaque white gum. Acetone (5 mL) was added and the product was precipitated out as a solid. The solid was filtered, washed with acetone (3×5 mL), then pumped at high vacuum to give the title product (520 mg, 49%) as a white solid.

TLC (silica gel) (7:2:1 n-propanol/NH_4OH/H_2O): R_f=0.36

IR (KBr) 3430, 2926, 1636, 1449, 1204, 1078, 1024 cm^{-1}.

^1H NMR (D_2O, 400 MHz) δ5.12 (t, 1H, J=6.6 Hz) 5.05 (t, 1H, J=6.8 Hz) 5.03 (t, 1H, J=7.7 Hz) 3.76 (dd, 1H, J=4.3, 14.4 Hz) 3.53 (dd, 1H, J=6.6, 14.4 Hz) 2.98 (ddd, 1H, J=4.7, 6.8, 13.3 Hz) 1.88 (m, 10H) 1.75 (m, 2H) 1.55–1.35 (m, 2H) 1.53 (s, 3H) 1.48 (s, 3H) 1.46 (s, 6H,) ppm.

^{13}C NMR (D_2O, 100 MHz) δ136.35 135.78 132.37 124.56 60.65 (d, J=109 Hz) 60.49 (d, J=78 Hz) 39.34 39.24 29.30 (d, J=6 Hz) 27.69 26.35 26.28 26.10 25.17 17.24 15.56 ppm.

Mass Spec (FAB, +ions) m/z 499 (M+H), 537 (M+K).

Anal. Calc'd for $C_{19}H_{33}K_2O_6PS$: C, 45.76; H, 6.67; P, 6.21; S, 6.43. Found: C, 45.41; H, 6.92; P, 6.47; S, 6.77.

EXAMPLE 32

(E,E)-7,11,15-Trimethyl-2-phosphono-6,10,14-hexadecanriene-2-sulfonic acid, tripotassium salt

A. (E,E)-7,11,15-Trimethyl-2-(diethoxyphosphinyl)-6,10,14-hexadecatriene-2-sulfonic acid, cyclohexyl ester

To a suspension of 47 mg (1.2 mmol, 1.1 eq) of sodium hydride (as a 60% mineral oil dispersion) in 1 mL of dry DMF at 0° C. was added a solution of 580 mg (1.1 mmol, 1 eq) of Example 1A Part C compound in 2 mL of DMF over 1 min. The bubbling solution was allowed to warm to RT and stirred for 30 min. To the resulting yellow homogeneous solution of anion at RT was added 264 μL (4.2 mmol, 4 eq) of methyl iodide over 1 min. After 16 h, the turbid yellow reaction mixture was diluted with ether (100 mL) and washed with brine (50 mL). The aqueous layer was extracted with ether (2×15 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated to afford 583 mg of a light yellow cloudy oil. ^1H NMR of the crude oil indicated no unalkylated starting material was present. The desired product was isolated via flash chromatography on silica gel (75 g) eluting with 35% ethyl acetate in hexanes. Fractions containing the desired product by TLC were pooled and concentrated to afford 418 mg (68%) of title compound as a clear viscous oil.

TLC Silica gel (10% ether in CH_2Cl_2): R_f 0.46.

B. (E,E)-7,11,15-Trimethyl-2-phosphono-6,10,14-hexadecatriene-2-sulfonic acid, tripotassium salt

To a solution of 408 mg of Part A compound in 8 mL of dry methanol at 0° C. was introduced ammonia until the solution was saturated. The tube was sealed with a threaded teflon cap fitted with an O-ring and heated at 75° C. for 17 h. The volatiles were removed in vacuo and the oily 10 residue was co-evaporated twice with toluene before placing on high vac (0.25 mmHg) for three hours. To the resulting clear yellow oil was added 4 mL of dry CH_2Cl_2 followed by 769 μL (5.8 mmol, 8 eq) of dry 2,4,6-collidine. To the resulting light yellow clear solution was added 768 μL (5.8 mmol, 8 eq) of bromotrimethylsilane (TMSBr) and the resulting white heterogeneous mixture was stirred at room temperature. After 84 h, the reaction mixture was concentrated and placed on high vac (0.25 mmHg) overnight. The resulting yellow white solid was dissolved by adding 5.0 mL (5.0 mmol, 6.8 eq) of 1M potassium hydroxide (DH 12.45) and 5 mL of water and the resulting solution (pH 12.35) was frozen and lyophilized. The light brown lyophilate was dissolved in water and chromatographed on a column of CHP20P (2.5 cm×25 cm) eluting initially with water (150 mL) followed a gradient formed by the gradual addition of acetonitrile (400 mL) to a reservoir containing water (400 mL). Fractions (10 mL each) were collected and analyzed by HPLC (Method 8). One fraction contained material ≧98% pure. This fraction was concentrated, taken up in a minimum volume of water, filtered and preciptated using acetone. The resulting solid was dryed on high vac to afford 134 mg of an off-white solid which did not pass elemental analysis. The >95% material from the column above was rechromatographed on CHP20P under isocratic conditions with 20% acetonitrile in water. Fractions containing ≧98% material were combined with the >98% material obtained from the first column, dissolved in water and concentrated. The resulting glassy solid was triturated with acetone to afford, after high vacuum removal of the acetone remnants, 94 mg title salt in the form of an off-white solid (24%).

TLC Silica gel (5:4:1 n-propanol:ammonium hydroxide:water): R_f 0.24.

^1H NMR (D_2O, 300 MHz): δ5.08 (m, 1H) 4.98 (m, 1H) 4.95 (m, 1H) 1.86 (m, 12H) 1.49 (s, 3H) 1.45 (s, 3H) 1.43 (m) 1.42 (s, 6H) 1.28 (d, J=13.6 Hz) ppm.

^{13}C NMR (D_2O, 75.6 MHz): δ136.2 135.8 132.3 125.1 124.7 62.3 (d, J_{CP}=126 Hz) 39.5 39.4 34.2 28.8 26.5 26.4 25.3 24.9 (d, J_{CP}=3 Hz) 18.2 17.4 15.8 15.7 ppm.

IR (KBr): 3434, 2928, 1452, 1202 cm^{-1}.

MS (FAB, +ions) m/z 499 (M+2H −K), 521 (M−K+Na+H), 537 (M+H).

Anal. Calc'd for $C_{19}H_{32}O_6PSK_3.0.5\ H_2O$: C, 41.81; H, 6.09; P, 5.67 Found: C, 42.20; H, 6.41; P, 4.94.

EXAMPLE 33

4'-(2-Methyl-1-propenyl)-α-phosphono[1,1'-biphenyl]-4-butanesulfonic acid, tripotassium salt

A. 1-Bromo-4-(2-methyl-1-propenyl]benzene

To a stirred slurry of 17.29 g (40.0 mmol) of isopropyltriphenylphosphonium iodide and 500 mg (2 mmol) of 18-crown-6 in 100 mL of THF under nitrogen at 5° C. was added 4.50 g (40.0 mmol) of potassium t-butoxide over 5 min. the resulting deep red-orange slurry was stirred 10 min and then a solution of 6.50 g (35.0 mmol) 4-bromobenzaldehyde in 40 mL of THF was added at a rate to keep the temperature below +10° C. The resulting bright yellow slurry was stirred for 20 min and then poured into 300 mL of hexanes. The solids were filtered off and the filtrate evaporated. This residue was purified by flash chromatography (5×15 cm column) and eluted with hexanes to provide 5.66 g (77%) of title bromide as a colorless oil.

TLC Silica gel (hexanes) R_f=0.32.

^1H NMR ($CDCl_3$, 270 MHz) δ7.40 (d, 2H, J=8.4 Hz) 7.05 (d, 2H, J=8.4 Hz) 6.17 (s, 1H) 1.88 (s, 1H) 1.81 (s, 1H) ppm.

Anal. Calc'd for $C_{10}H_{11}Br$: C, 56.90; H, 5.25 Found: C, 56.83; H, 5.22.

MS (CI-NH_3, −ions) m/e 209 (M−H).

B. 4'-(2-Methyl-1-propenyl)[1,1'-biphenyl]-4-carboxylic acid, methyl ester

To a stirred solution of 52 mL (88.4 mmol, 1.7M in pentane) of t-butyllithium at −78° C. under argon was added

a solution of 7.92 g (37.5 mmol) of Part A bromide in 15 mL of THF over 10 minutes. The resulting deep red slurry was stirred for 1 hour, warmed to −22° C. and a solution of 6.16 g (45.2 mmol) of thrice-fused zinc chloride in 40 mL of THF was added over 20 minutes. The light yellow, faintly turbid solution was stirred for 1 hour and then cannulated into a stirred solution of 7.04 g (26.9 mmol) of methyl 4-iodobenzoate and 600 mg (0.52 mmol) of tetrakis (triphenylphosphine)palladium in 30 mL of THF at −22° C. under argon. After the addition was complete, the reaction was warmed to room temperature and stirred for 16 hours. The reaction mixture was diluted with ether, washed successively with 1M hydrochloric acid, saturated sodium bicarbonate and saturated sodium sulfite solution. The organic extract was dried ($MgSO_4$) and evaporated to give a dark brown solid. Recrystallization from methanol gave title ester as a light yellow solid, mp 66°–68° C., 6.13 g, 86% yield.

C. 4'-(2-Methyl-1-propenyl)[1,1'-biphenyl]-4-methanol

To a stirred solution of 3.00 g (11.3 mmol) of Part B ester in 10 mL of THF at room temperature under nitrogen was added 6.0 mL of lithium aluminum hydride solution (1.0 M in THF, 6.0 mmol). After 1 hour, the reaction was quenched with 1 mL of brine and then sufficient 1M hydrochloric acid to bring the solution to pH 1. The resulting mixture was extracted twice with ether, the combined extracts washed with saturated sodium bicarbonate solution, dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica gel (5×10 cm column, 3:97 ether/dichloromethane as elutent) gave title alcohol as a colorless oil, 2.42 g, 90% yield.

D. 4-(Bromomethyl)-4'-(2-methyl-1-propenyl)[1,1'-biphenyl]

To a stirred solution of 2.82 g of triphenylphosphine (8.4 mmol) and 2.33 g (9.79 mmol) of Part C alcohol in 30 mL of dichloromethane under argon at −40° C. was added 1.92 g (11.7 mmol) of N-bromosuccinimide over 20 minutes. After 1 hour, the reaction mixture was evaporated onto 10 g of silica gel. Purification by flash chromatography on silica gel (5 ×20 cm column, 12% CH_2Cl_2 in hexanes as the elutent) gave title bromide as a colorless oil, 2.75 g, 93% yield.

E. 4'-(2-Methyl-1-propenyl)[1,1'-biphenyl]-4-propanoic acid, 1,1-dimethylethyl ester

To a stirred solution of 1.01 mL (7.2 mmol) of diisopropylamine in 15 mL of THF at −5° C. under argon was added 2.8 mL (7.0 mmol, 2.5M in hexane) of n-butyllithium at a rate to keep the temperature below 0° C. After stirring the resulting pale yellow solution for 15 minutes, 3.0 mL (17 mmol) of hexamethylphosphoramide was added. After an additional 15 minutes, the deep yellow solution was cooled to −78° C. and 0.98 mL (7.2 mmol) of t-butyl acetate was added over the course of 5 minutes. The solution was stirred for 30 minutes and then a solution of 1.75 g (5.8 mmol) of Part D bromide in 10 mL of THF was added over 5 minutes. The reaction mixture was stirred for 8 hours at −78° C., quenched with 10% citric acid solution and extracted twice with ether. The extracts were combined, washed twice with water, once with saturated sodium bicarbonate solution, dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica gel (5×20 cm column, 1:1 hexanes/dichloromethane as elutent) gave title ester as a white foamy solid, 1.85 g, 95% yield.

F. 4'-(2-Methyl-1-propenyl)[1,1'-biphenyl]-4-propanol

To a stirred solution of 1.08 g (3.20 mmol) of Part E ester in 5 mL of THF at room temperature under nitrogen was added 2.0 mL of lithium aluminum hydride solution (1.0 M in THF, 2.0 mmol). The reaction was heated to reflux for 1 hour, quenched with 1 mL of brine and then sufficient 1 M hydrochloric acid to bring the solution to pH 1. The resulting mixture was extracted twice with ether, the combined extracts washed with saturated sodium bicarbonate solution, dried ($MgSO_4$) and evaporated. The oily residue was passed through a 2 cm high pad of silica gel, eluting with dichloromethane to give title alcohol as a white solid, 0.824 g, 97% yield.

G. 4-(3-Iodopropyl)-4'-(2-methyl-1-propenyl)[1,1'-biphenyl]

To a stirred solution of 813 mg (3.05 mmol) of Part F alcohol, 882 mg (3.36 mmol) of triphenylphosphine and 440 mg (6.4 mmol) of imidazole in 20 mL of THF was added a solution of 813 mg (3.2 mmol) of iodine in 10 mL of THF over 20 min. After 10 min, the light yellow reaction mixture was diluted with hexanes and washed once each with 10% sodium bisulfite solution, water and brine. The organic layer was dried ($MgSO_4$) and evaporated onto 5 g silica gel. Purification by flash chromatography on silica gel (5×5 cm column) eluted with dichloromethane gave title iodide, 1.11 g (97%) as a white solid, mp 58°–61° C.

H. 4'-(2-Methyl-1-propenyl)-α-phosphono-[1,1'-biphenyl]-4-butanesulfonic acid, cyclohexyl ester

To a stirred slurry of 85 mg (2.1 mmol, 60% mineral oil dispersion) of sodium hydride in 3 mL of DMF under argon at −10° C. was added a solution of 670 mg (2.4 mmol, 1.3 equiv.) of Example 1A Part B compound in 1 mL of DMF. After addition was complete, the reaction was warmed to room temperature and stirred for 30 min. To the resulting solution was added a solution of 700 mg (1.86 mmol) of Part G compound in 1 mL of DMF. The reaction was stirred for 16 h, diluted with ether and washed once with 10% citric acid and thrice with water. The organic phase was dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica gel (5×20 cm column) eluted with 1:24 ether/dichloromethane gave title salt as a colorless oil, 610 mg, 62% yield.

I. 4'-(2-Methyl-1-propenyl)-α-phosphono-[1,1'-biphenyl]-4-butanesulfonic acid, tripotassium salt

A solution of 500 mg (0.89 mmol) of Part H ester in 15 mL of methanol under argon at room temperature was saturated with ammonia gas. The flask containing the reaction mixture was sealed and heated to 75° C. After 16 h, the reaction was cooled to room temperature and evaporated under dry conditions. The residue was dissolved in 10 mL of dichloromethane and 0.59 mL (4.5 mmol) of 2,4,6-collidine and then 940 mL (7.1 mmol) of bromotrimethylsilane was added. After 24 h, the resulting clear solution was evaporated at 25° C. and then stirred for 1 h with 8 mL (4 mmol) of 0.5M potassium hydroxide solution. The solution was lyophilized and then purified by MPLC (2.5×20 cm column of Mitsubishi Kasei Sepadbeads HP-20 resin): 11.5 mL fractions, 7 mL/min flow rate, eluted with water and then a gradient prepared from 400 mL of water and 450 mL of 2:1 acetonitrile/water). Fractions 39–48 were collected and lyophilized to give title salt as a white solid, 310 mg, 62% yield.

IR (KBr pellet) 3403, 2967, 2932, 1653, 1497, 1184, 1051, 966 cm^{-1}.

^1H NMR (D_2O, 400 MHz) δ7.45 (d, 2H, J=8.1 Hz) 7.44 (d, 2H, J=8.1 Hz) 7.25 (d, 2H, J=8.1 Hz) 7.19 (d, 2H, J=8.1 Hz) 6.17 (s, 1H) 2.78 (dr, 1H, J=5, 18 Hz) 2.54 (m, 2H) 1.77–1.91 (m, 4H) 1.74 (s, 3H) 1.69 (s, 3H)ppm.

Anal. Calc'd for $C_{20}H_{22}K_3O_6PS.1.5\ H_2O$: C, 42.46; H, 4.45; P, 5.47; S, 5.67 Found: C, 42.35; H, 4.80; P, 5.20; S, 6.06.

Mass Spec (FAB, +ions) m/e 577 (M+K), 539 (M+H), 501 (M−K+2H).

EXAMPLE 34

4'-Butyl-α-phosphono[1,1'-biphenyl]-4-butanesulfonic acid, tripotassium salt

A. 4'-Butyl[1,1'-biphenyl]-4-propanoic acid, ethyl ester

To a stirred solution of 3.20 g (15.0 mmol) of 1-bromo-4-butylbenzene (Aldrich Chemical Company #33, 576-2) at −78° C. under argon was added, dropwise over 30 min, 18.0 mL (30.6 mmol, 1.7M in pentane) of t-butyllithium solution. The resulting light yellow solution was warmed to 0° C. and stirred for 1 h. To this solution was added 3.4 g (25 mmol) of thrice-fused zinc chloride in 20 mL of THF. The resulting slurry was stirred for 30 min and then a solution of 2.0 g (6.5 mmol) of 4-iodobenzenepropanoic acid, ethyl ester (Example 43, Part B) and 0.4 g (0.35 mmol) of tetrakis (triphenylphosphine)-palladium(0) in 5 mL of THF was added. The reaction was stirred for 16 h, diluted with ether and washed once with 10% citric acid. The organic phase was dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica gel (5×20 cm column) eluted with 1:1 hexanes/dichloromethane gave title compound as a colorless oil, 1.79 g , 91% yield.

B. 4'-Butyl[1,1'-biphenyl]-4-propanol

To a stirred solution of 1.72 g (5.54 mmol) of Part A ester in 10 mL of THF at room temperature under argon was added, over the course of 2 min, a solution of 4 mL (4 mmol, 1M in THF) of lithium aluminum hydride. The resulting solution was stirred for 16 h. The reaction was quenched with 1M sodium potassium tartrate and extracted twice with ether. The ether extracts were dried over $MgSO_4$, filtered and evaporated. Recrystallization from hexanes provided title alcohol as a white solid, 1.19 g, 80% yield, mp 62°–64° C.

C. 4'-Butyl[1,1'-biphenyl]-4-propyl iodide

To a stirred solution of 1.19 g (4.43 mmol) of Part B alcohol, 1.16 g (4.43 mmol) of triphenylphosphine, and 0.66 g (7.4 mmol) of imidazole in 15 mL of THF under argon at room temperature was added a solution of 1.12 g (4.7 mmol) of iodine in 5 mL of THF, dropwise over 20 min. After addition was complete, the reaction was diluted with hexanes and washed once with saturated sodium bisulfite solution. The organic phase was dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica gel (5×20 cm column) eluted with dichloromethane gave title iodide as a white waxy solid, 1.52 g, 91% yield.

D. 4'-Butyl-α-(dieythoxyphosphinyl)[1,1'-biphenyl]-4-butanesulfonic acid, cyclohexyl ester

To a stirred slurry of 190 mg (4.75 mmol, 60% mineral oil dispersion) of sodium hydride in 5 mL of DMF under argon at −10° C. was added a solution of 1.66 g (5.28 mmol) of Example 1A Part B sulfonate in 2 mL of DMF. After addition was complete, the reaction was warmed to room temperature and stirred for 30 min. To the resulting solution was added a solution of 1.00 g (2.64 mmol) of Part C iodide in 5 mL of DMF. The reaction was stirred for 16 h, diluted with ether and washed once with 10% citric acid and thrice with water. The organic phase was dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica gel (5×25 cm column) eluted with 3:47 ether/dichloromethane gave title compound as a colorless oil, 0.825 g, 55% yield.

E. 4'-Butyl-α-Phosphono[1,1'-biphenyl]-4-butanesulfonic acid, tripotassium salt

To a stirred solution of 0.82 g (1.55 mmol) of Part F ester in 5 mL of dichloromethane under argon at room temperature was added 0.62 mL (4.7 mmol) of bromotrimethylsilane. After 24 h, the resulting clear solution was evaporated at 25° C. and the residue dissolved in 10 mL of THF. To this stirred solution was added 0.8 g (5 mmol) of dried, finely ground potassium iodide and 5 mg (0.015 mmol) of 18-crown-6. The resulting slurry was heated to reflux for 24 h, evaporated and then stirred for 1 h with 5 mL (5 mmol) of 1.0M potassium hydroxide solution. The solution was lyophilized and then purified by MPLC (2.5×20 cm column of CHP-20P resin): 11.5 mL fractions, 6 mL/min flow rate, eluted with 250 mL of water, then a gradient of 450 mL of 3:1 acetonitrile/water into 450 mL of water). Fractions 32–40 were collected and lyophilized to give title salt as a white solid, 425 mg, 49% yield.

IR (KBr pellet) 3424, 3027,2957, 2930, 2859, 1653, 1499, 1200, 1078, 966 cm^{-1}.

^1H NMR (D_2O, 400 MHz) δ7.47 (d, 2H, J=8.1 Hz) 7.46 (d, 2H, J=8.1 Hz) 7.27 (d, 2H, J=8.1 Hz) 7.21 (d, 2H, J=8.6 Hz) 2.79 (ddd, 1H, J=17.5, 5.6, 3.8 Hz) 2.55 (m, 4H) 1.92 (m, 4H) 1.46 (m, 2H) 1.19 (m, 4H) 0.75 (t, 3H, J=7.5 Hz) ppm.

Anal. Calc'd for $C_{20}H_{24}K_3O_6PS.0.75\ H_2O$: C, 43.34; H, 4.64; P, 5.59; S, 5.78 Found: C, 43.01; H, 4.88; P, 5.16; S, 6.21.

Mass Spec (FAB, +ions)m/e 579 (M+K), 541 (M+H), 503 (M−K+2H), 465 (M−2K+3H).

EXAMPLE 35

(E)-6-Methyl-1-phosphono-9-(4-propylphenyl)-5-nonene-1-sulfonic acid, tripotassium salt

A. Bromo(4-propylphenyl)magnesium

A solution of 30.80 mL (0.20 mol) of 1-bromo-4-propylbenzene in 50 mL dry THF was added to 9.60 g (0.40 mol) of magnesium turnings in 200 mL THF at a rate to maintain low reflux. After the addition was complete, the reaction was heated to 55° C. for one hour. The THF solution was transferred via cannula to a sure-seal bottle and sealed for storage. Titration of 3.00 mL of the title Grignard reagent with 1N isopropanol in toluene against 2,2'-biquinoline as an indicator required volumes of 5.4 and 5.3 mL, indicating the concentration to be 1.74N.

B. 2,2-Dimethylpropanoic acid, (E)-8-iodo-5-methyl-4-octen-1-yl ester

The above iodide is prepared as described in Example 35 Part A.

C. (E)-5-Methyl-8-(4-propylphenyl)-4-octen-1-ol

A solution of 2.15 g (6.10 mmol) of Part B iodide in 10 mL THF at 0° C. was treated with 10 mg (1 mol %) of copper iodide and 21.00 mL (36.60 mmol) of the 1.74N solution of Part A Grignard reagent. The mixture was stirred for one hour at 0° C. and fifteen hours at RT, at which time an additional 7.00 mL (12.00 mmol) of Part A Grignard reagent were added. After twenty four hours, the reaction was chilled to 0° C. and quenched with 105 mL ammonium chloride and diluted with 200 mL ether and 1.00 mL ammonium hydroxide. The aqueous fraction was removed and the organics were washed with ammonium chloride solution (3×30 mL), water (2×30 mL), saturated sodium chloride (30 mL), dried (sodium sulfate), and concentrated. The resulting oil was purified by flash chromatography on silica gel packed, loaded, and eluted with 85:15 hexane/ethyl acetate. Pure fractions (#67-100) were combined and concentrated to yield 1.11 g (69%) of title alcohol as a clear oil.

TLC (7:3 hexane/ethyl acetate) R_f=0.18.

MS (CI, NH_3, +ions) m/e 261 (M+H), 278 ($M+NH_4$).

IR (neat) 3335, 2959, 2932, 2861, 1898, 1669, 1539, 1456, 1379, 1059, 802 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) δ7.11 (s, 4H) 5.19 (t, 1H, J=7.5 Hz) 3.66 (t, 2H, J=6.4 Hz) 2.58 (m, 4H) 2.12 (q, 2H, J=7.5 Hz) 2.05 (t, 2H, J=7.5 Hz) 1.76 (m, 2H) 1.64 (m, 4H) 1.63 (s, 3H) 0.97 (t, 3H, J=7.5 Hz) ppm.

D. (E)-1-(8-Iodo-4-methyl-4-octen-1-yl)-4-propylbenzene

A solution of 1.11 g (4.20 mmol) of Part C alcohol in 5 mL CH_2Cl_2 at 0° C. was treated sequentially with 10 mg (2.5 mol %) of 4-dimethylaminopyridine, 0.36 mL (5.50 mmol) of triethylamine, and 0.77 mL (4.70 mmol) of methanesulfonyl chloride. The reaction was allowed to stir at room temperature for 80 minutes before diluting with ether. The organic solution was washed with water (2×25 mL), saturated sodium chloride, dried (sodium sulfate), and evaporated to a clear oil. The oil was dissolved in 20 mL acetone and stirred with 1.92 g (12.80 mmol) of sodium iodide for fifteen hours. The reaction was driven to completion by heating at 50° C. for three more hours, then concentrated to a slurry, which was redissolved solved in hexane and water. The aqueous layer was removed, and the organic layer was washed with water, saturated sodium sulfite, saturated sodium chloride, dried (sodium sulfate), and evaporated. The resulting yellow oil was purified by flash chromatography on silica gel (100 g), packed, loaded, and eluted with hexane. Pure fractions were combined and concentrated to yield 1.04 g (67%) of title iodide as a clear oil.

TLC (85:15 hexane/ethyl acetate): R_f=0.70.

MS (CI, NH_3, +ions) m/e 270 (M+H).

IR (film) 2957, 2930, 2859, 1514, 1456, 1445, 1379, 1341, 1316, 1227, 1202, 1165, 1092, 1020, 839, 820, 802, 739 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) δ7.24 (s, 4H) 5.24 (t, 1H, J=7.5 Hz) 3.33 (t, 2H, J=7.0 Hz) 2.69 (q, 4H, J=6.0 Hz) 2.26 (q, 2H, J=7.2 Hz) 2.18 (t, 2H, J=7.5 Hz) 2.01 (quint, 2H, J=7.0 Hz) 1.86 (m, 2H) 1.78 (s, 3H) 1.77 (m, 2H) 1.09 (t, 3H, J=7.2 Hz) ppm.

E. (E)-1-(Diethoxyphosphinyl)-6-methyl-9-(4-propylphenyl)-5-nonenesulfonic acid, cyclohexyl ester

To a solution of 1.53 g (4.87 mmol) of Example 1A Part B sulfonaCe in 4.00 mL DMF at −20° C. was added 84.5 mg (3.25 mmol) of sodium hydride. The reaction was stirred at −20° C. until hydrogen evolution diminished, and at RT until gas evolution subsided completely, when 1.0 g (2.71 mmol) of Part D iodide in 1.0 mL DMF was added. After stirring at RT for 23 hours, the reaction was quenched with 5 mL ammonium chloride and diluted with ether and water. The aqueous layer was removed and the organic layer was washed with saturated sodium chloride. The combined aqueous fractions were back extracted with ether, and the combined organic fractions were dried (sodium sulfate) and concentrated to an oil (1.84 g). The crude product was purified by flash chromatography on silica gel (140 g), packed, loaded, and eluted with 70:30 hexane/ethyl acetate. Pure fractions (#57-103) were combined and concentrated to yield 0.58 g (38%) of title compound as a clear oil.

TLC (7:3 hexane/ethyl acetate) R_f=0.18.

MS (CI, NH_3, +ions) m/e 557 (M+H), 574 ($M+NH_4$).

IR (film) 2934, 2863, 1614, 1452, 1354, 1262, 1175, 1053, 1024, 972, 930, 866, 828, 802, 758 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) δ7.01 (s, 4H) 5.05 (t, 1H, J=6.6 Hz) 4.76 (m, 1H) 4.15 (m, 4H) 3.35 (dt, 1H, J=19.6 Hz, 6.2 Hz) 2.46 (m, 4H) 2.04 (m, 2H) 1.94 (m, 6H) 1.62 (m, 8H) 1.52 (s, 3H) 1.43 (m, 1H) 1.31 (m, 5H) 1.27 (t, 6H, J=6.8 Hz) 0.86 (t, 3H, J=7.3 Hz) ppm.

F. (E)-6-Methyl-1-phosphono-9-(4-propylphenyl)-5-nonene-1-sulfonic acid, tripotassium salt

A solution of 0.57 g (1.02 mmol) of Part E compound in 10 mL methanol in a sealable tube was chilled to 0° C. and saturated with ammonia gas. The tube was then sealed and heated at 65° C. for twenty four hours. After cooling, the tube was opened and the methanol evaporated. The residue was dissolved in toluene and evaporated twice (2×10 mL), leaving a glassy oil. The oil was dissolved in 2.00 mL of methylene chloride and treated sequentially with 1.38 mL (5.20 mmol) of bistrimethylsilyl trifluoroacetamide and 0.83 mL (6.24 mmol) of trimethylsilyl bromide. The reaction stirred for hours, at which point the organics were removed under vacuum, and the residue treated with 6.00 mL (6.00 mmol) of 1N KOH and lyophilized. The crude product was purified by MPLC on a column of CHP-20P gel (2.5 cm diam.×25 cm height) eluting with water (100 mL) followed by a gradient created by the gradual addition of 400 mL acetonitrile to a resevoir of 350 mL water. Approximately 7 mL fractions were collected. Pure fractions (#41–45) were combined and concentrated to yield 348 mg (64%) of a waxy solid, which was triturated with acetone (3×2.00 mL) and dried on high vacuum to yield 270 mg (50%) of title compound, as an off-white solid.

TLC (5:4:1 n-propanol/ammonium hydroxide/water) R_f=0.22.

MS (FAB, +ions) 533 (M+H), 457 (M+H−K).

IR (KBr) 3235, 2934, 2872, 1653, 1458, 1144, 1098, 1052, 964 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz) δ7.07 (s, 4H) 5.16 (m, 1H) 2.76 (m, 1H) 2.42 (m, 4H) 1.79 (m, 6H) 1.53 (m, 2H) 1.48 (s, 3H) 1.43 (m, 2H) 0.74 (t, 2H, J=7.3 Hz) ppm.

Anal. Calc'd for $C_{19}H_{28}O_6PSK_3$-H_2O: C, 41.43; H, 5.49; S, 5.82; P, 5.62; Found C, 41.43; H, 5.72; S, 6.23; P, 5.29.

EXAMPLE 35A

2,2-Dimethylpropanoic acid, (E)-8-iodo-5-methyl-4-octen-1-yl ester

(1). 2,2-Dimethylpropanoic acid, (E)-5,9-dimethyl-4,8-decadienyl ester

To a solution of 10.00 g (54.94 mmol) of Example 2 Part D alcohol in 50 mL of dichloromethane at 0° C. was added 0.67 g (5.50 mmol) of 4-dimethylaminopyridine (DMAP) and 11.49 mL (82.41 mmol) of triethylamine followed by the addition of 8.12 mL (65.93 mmol) of trimethylacetyl chloride over 15 min. The reaction mixture was stirred for 1 h at 0° C. and 2.5 h at room temperature. The suspension was diluted with 200 mL of dichloromethane and 300 mL of water. The layers were separated and the organic fraction was washed with solutions of $KHSO_4$, $NaHCO_3$ and NaCl, dried ($MgSO_4$) and concentrated to provide title compound as a colorless liquid.

TLC Silica gel (8:2 hexanes/ethyl acetate) R_f=0.25.

(2). 2,2-Dimethylpropanoic acid, (E)-8-bromo-9-hydroxy-5,9-dimethyl-4-decenyl ester

To a solution of 10.00 g (37.59 mmol) of Part (1) ester in 100 mL of a solution of 7:3 t-butanol/water at 0° C. was added 6.69 g (37.59 mml) of N-bromosuccinimide portionwise with the aid of a solid addition funnel over 0.5 h. The reaction mixture was stirred at 0° C. for 3 h, diluted with 300 mL of ether, washed with solutions of K_2CO_3 and NaCl, dried ($MgSO_4$) and concentrated. The residue obtained was purified by flash chromatography (800 g of silica gel) eluting with 9:1 hexanes/ethyl acetate to provide 11.30 g (63%) of title alcohol as a colorless oil.

TLC Silica gel (8:2 hexanes/ethyl acetate) R_f=0.42.

(3). 2,2-Dimethylpropanoic acid, (E)-8,9-epoxy-5,9-dimethyl-4-decenyl ester

To a stirred solution of 11.00 g (30.30 g) of Part (2) alcohol in 100 mL of THF at −78° C. was added 21.68 mL