EXAMPLE 177

[3aR-[2(R*),3aα,7aβ]]-[1-[[(Dimethylamino) thioxomethyl]thio]-4-(3-phenoxyphenyl)butyl] octahydro-1,3-dimethyl-2–1H-1,3,2-benzodiazaphosphole, 2-oxide

and

[3aR-[2(S*),3aα,7aβ]]-[1-[[(Dimethylamino) thioxomethyl]thio]-4-(3-phenoxyphenyl)butyl]-octahydro-1,3-dimethyl-2–1H-1,3,2-benzodiazaphosphole, 2-oxide

A. [3aR-(3aα,7aβ)]-2-[[[(Dimethylamino)thioxomethyl]thio]]octahydro-1,3-dimethyl-1H-1,3,2-benzodiazaphosphole, 2-oxide

To a stirred solution of 502 mg (2.48 mmol) of Example 175 Part B compound in 10 mL of THF under argon at –78° C. was added 1.09 mL (2.73 mmol) of a 2.5N solution of n-butyllithium in hexanes dropwise over 10 minutes. After stirring at –78° C. for one hour, 87 mg (2.73 mmol) of sulfur was added via a solid addition tube, and temperature of the reaction was raised to –20° C. over 1 hour. The reaction mixture was treated with 0.93 mL (6.69 mmol) of triethylamine and 276 mg (2.23 mmol) of dimethylthiocarbamoyl chloride at –20° C., stirred for 5 minutes, then allowed to warm to room temperature. The mixture was diluted with ether and washed with water. The aqueous layer was back extracted with ether and the organics were combined, dried and concentrated to afford 558 mg of an oil. The crude product was purified by flash chromatography on silica gel (50 g) eluted with 96:4 ethyl acetate/methanol. Pure fractions were combined and concentrated to yield 337 mg (47%) of title compound as a clear oil.

TLC (Silica gel, 9:1 ethyl acetate/methanol) R_f=0.35.

MS (CI, +ions) 332 (M+H).

^{31}P NMR ($CDCl_3$, 121 MHz) 37.7 ppm.

B. 3aR-[2(R*),3aα,7aβ]]-[1-[[(Dimethylamino) thioxomethyl]thio]-4-(3-phenoxyphenyl)butyl]octahydro-1,3-dimethyl-2–1H-1,3,2-benzodiazaohosohole, 2-oxide

To a stirred solution of 89 mg (0.28 mmol) of Part A compound in 1 mL of THF under argon at –78° C. was added 122 μL (0.31 mmol) of a 2.5N solution of n-butyllithium in hexanes dropwise over 10 mintues. After 90 minutes at –78° C., 0.096 mL (0.55 mmol) of hexamethylphosphoramide was added, followed by 98 mg (0.30 mmol) of 3-(3-phenoxyphenyl)propyliodide in 1 mL of THF. After 28 hours at –78° C., the reaction was quenched with methanol and allowed to reach room temperature. The mixture was concentrated, then dissolved in ether and washed with water and brine, dried over sodium sulfate, and concentrated to afford 129 mg of a yellow oil. The crude product was purified by flash chromatography on silica gel (15 g) eluted with 98:2 ethyl acetate/methanol. Fractions (#11–19) containing pure material were combined and concentrated to yield 50 mg (34%) of title α-(R) isomer as a clear oil.

TLC (Silica gel, 9:1 ethyl acetate/methanol) R_f=0.45.

C. [3aR-[2(S*),3aα,7aβ]]-[1-[[(Dimethylamino) thioxomethyl]thio]-4-(3-phenoxyphenyl)butyl]octahydro-1,3-dimethyl-2-1H-1,3,2-benzodiazaphosDhole, 2-oxide

Fractions #21–30 were combined and concentrated to provide 10 mg (7%) of title isomer as a clear oil.

TLC (Silica gel, 9:1 ethyl acetate/methanol) R_f=0.39.

MS (CI, +ions) 532 (M+H).

^{31}p NMR ($CDCl_3$, 121 MHz) 39.3 ppm.

The Parts B and C compounds may then be 10 separated and subjected to acid hydrolysis and then oxidation and salt formation as described in Example 175 to form the title compound of Examples 175 and 176.

EXAMPLE 178

[3aR-[2(R*),3aα,7aβ]]-[1-[[(Dimethylamino) thioxomethyl]thio]-4-(3-phenoxyphenyl)butyl] octahydro-1,3-dimethyl-2–1H-1,3,2-benzodiazaphosphole, 2-oxide

A. [3aR-(3aα,7aβ)]-Octahydro-1,3-dimethyl-1H-1,3,2-benzodiazaphosoholeo 2-oxide

To a stirred solution of 497 mg (3.49 mmol) of Example 175 Part A (R,R)-diamine and 1.07 mL (7,89 mmol) of triethylamine in 25 mL of tetrahydrofuran (THF) under argon at –78° C. was added dropwise over 5 minutes 335 μL (3.84 mmol) of phosphorus trichloride. The cloudy solution was allowed to warm to room temperature and was filtered under argon through a pad of celite and magnesium sulfate. The filtrate was chilled to –78° C. under argon and treated with 536 μL of triethylamine and 63 μL (3.49 mmol) of water. The mixture was allowed to warm to room temperature and was filtered under argon through a pad of celite and magnesium sulfate and concentrated to provide 544 mg (82%) of title compound as a yellow oil.

^{31}P NMR ($CDCl_3$, 121 MHz) δ27.3 ppm.

B. [3aR-[2(R*),3aα,7aβ)]-Octahydro-1,3-dimethyl-2-[4-(3-phenoxyphenyl)-1-[(trimethylsilyl)oxy]butyl]-1H-1,3,2-benzodiazaphosohole, 2-oxide

C. [3aR-[2(S*),3aα,7aβ)]-Octahydro-1,3-dimethyl-2-[4-(3-phenoxyphenyl)-1-[(trimethylsilyl)oxy]butyl]-1H-1,3,2-benzodiazaphosphole, 2-oxide

A solution of 544 mg (2.89 mmol) of Part A compound and 534 mg (2.22 mmol) of 3-phenoxybenzenebutanal (Example 180 Part B) in 5 mL of methylene chloride under argon was treated with 814 μL (3.33 mmol) of bis [trimethylsilyl) acetamide at room temperature and stirred for 17 hours. The reaction was quenched with water and extracted with methylene chloride (3×35 mL). The combined organics were washed with brine, dried (sodium sulfate), and concentrated to provide 875 mg of a yellow oil. The crude product mixture was purified by flash chromatography on silica gel (80 g) eluted with 2 L of 9:1 hexane/acetone followed by 2 L of 85:15 hexane/acetone and 1.5 L of 8:2 hexane/acetone. Fractions containing the more polar α-(R) isomer (title B) were combined and concentrated to yield 135 mg (14%) of title B compound as a clear oil.

TLC Silica gel (1:1 hexane/acetone) R_f=0.29.

^{31}P NMR ($CDCl_3$, 121 MHz) δ41.1 ppm.

Fractions #85–96 were combined and concentrated to yield 112 mg (12%) of the pure Part C α-(S)isomer.

TLC Silica gel (1:1 hexane/acetone) R_f=0.31.

^{31}P NMR ($CDCl_3$, 121 MHz) δ27.3 ppm.

D. [3aR-[2(R*),3aα,7aβ)]-Octahydro-2-[1-hydroxy-4-(3-phenoxyphenyl)butyl]-1,3-dimethyl-1H-1,3,2-benzodiazaphosphole, 2-oxide

To a stirred solution of 125 mg (0.20 mmol) of Part B isomer in 1 mL of THF was added 0.29 mL (0.29 mmol) of a 1.0N solution of tetrabutylammonium fluoride in THF. After stirring for three hours at room temperature, the mixture was diluted with ether, washed with saturated sodium bicarbonate, brine, dried (sodium sulfate), and concentrated to provide 104 mg of a white solid. The crude product was purified by flash chromatography on silica gel (15 g) eluted with 97.5:2.5 ethyl acetate/methanol. Clean fractions (#41–71) were combined and concentrated to yield 100 mg (93%) of title compound as a white solid. m.p. 122°–125° C.

TLC Silica gel (1:1 hexane/acetone) R_f=0.44.

^{31}P NMR ($CDCl_3$, 121 MHz) δ41.1 ppm.

E. [3aR-[2(R*),3aα,7aβ]]-[1-[[(Dimethylamino) thioxomethyl]thio]-4-(3-phenoxyphenyl)butyl]octahydro-1, 3-dimethyl-2–1H-1,3,2-benzodiazaphosDhole, 2-oxide

To a stirred suspension of 56 mg (0.13 mmol) of Part D compound, 30 mg (0.09 mmol) of dimethyldithiocarbamic acid, zinc salt, and 47 mg (0.18 mmol) of triphenylphosphine in 1 mL of THF at 0° C. under argon was added a solution of 52 μL (0.27 mmol) of diisopropyl azodicarboxylate in 0.5 mL of THF over fifteen minutes. The reaction was stirred at room temperature for 45 hours, then diluted with ether and quenched with water. The organics were washed with brine, dried (sodium sulfate), and concentrated to provide 150 mg of an oil. The crude product was purified by flash chromatography on silica gel (15 g) eluted with ethyl acetate. Pure fractions were combined and concentrated to yield 15 mg (21%) of title compound as a film, the α-(R)-isomer.

TLC Silica gel (1:1 hexane/acetone) R_f=0.20. Note: This is identical to Example 175 Part D compound and is the precursor to the Example 176 compound.

MS (CI, +ions) 532 (M+H).

^{31}P NMR ($CDCl_3$, 121 MHz) a 41.2 ppm.

EXAMPLE 179

(S)-(−)-3-Phenoxy-α-phosphonobenzenebutanesulfonic acid, tripotassium salt

A. [3aR-(3aα,7aβ)]-2-Chlorooctahydro-1,3-dimethyl-1H-1, 3,2-benzodiazaphosphole, 2-oxide

A solution of 4.72 g (33.20 mmol) of Example Part A diamine and 12.63 g (125.0 mmol) of triethylamine in 50 mL of toluene at 0° C. was treated with 5.00 g (33.20 mmol) of phosphorus oxychloride dropwise over 15 min. The reaction mixture was stirred for 10 min. at 0° C. and warmed to RT. After 3 h the solids were filtered off and the filtrate concentrated to a slurry. The slurry was purified by flash chromatography (100 g of silica gel) eluting with 15:85 acetone/toluene to provide 6.50 g (88%) of title chloride as a low melting solid.

TLC Silica gel (1:4 acetone/toluene) R_f=0.30.

^{1}H NMR ($CDCl_3$, 300 MHz): δ2.85 (td, 1H, J=10.8, 3.0 Hz) 2.67 (d, 3H, J=10.0 Hz) 2.55 (d+m, 4H, J=18.0 Hz) 2.05 (m, 2H) 1.85 (m, 2H) 1.35 (m, 4H) ppm.

^{13}C NMR ($CDCl_3$, 75.6 MHz): δ63.5 (d, J=7.0 Hz) 62.5 (d, J=10.0 Hz) 28.0 27.5 (d, J=7.0 Hz) 27.0 (d, J=7.0 Hz) 24.0 23.9 ppm.

^{31}P NMR ($CDCl_3$, 121.7 MHz): δ36.6 ppm

B. [3aR-(3aα,7aβ)]-Octahydro-1,3-dimethyl-1H-1,3,2-benzodiazaphosphole-2-methanesulfonic acid, ethyl ester, 2-oxide

To a rapidly stirred solution of 6.20 g (50.0 mmol) of ethyl methanesulfonate in 150 mL of THF at −73° C. (internal temperature) was added 20 mL (50 mmol) of 2.5M n-butyllithium dropwise over 20 min (The internal temperature was not allowed to rise above −69° C. throughout the addition of n-BuLi). After an additional 30 min., 5.56 g (25.0 mmol) of freshly prepared Part A chloride in 25 mL of THF 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 3 h at −30° C. The reaction mixture was poured into 250 mL of a rapidly stirring mixture of 1:1 saturated aqueous $NaHCO_3$ solution/ethyl acetate. The mixture was partitioned between ethyl acetate and water (3×75 mL). The organic extracts were dried (Na_2SO_4) and concentrated to an oil. The oil was purified by flash chromatography (200 g silica gel) eluting with methylene chloride (600 mL) followed by 93:7 dichloromethane/isopropanol (1000 mL) to provide 6.60 g (85%) of title compound as a low melting solid.

TLC Silica gel (1:9 2-propanol/dichloromethane) R_f=0.58.

IR (KBr) 2947, 2878, 1478, 1451, 1348, 1258, 1236, 1215, 1165, 1123, 1026, 1005, 918 cm^{-1}.

Mass Spec (CI-NH_3, +ions) m/e 638 (2M+NH_4), 621 (2M+H), 328 (M+NH_4), 311 (M+H).

Anal. Calc'd for $C_{11}H_{23}N_2O_4PS$: C, 42.57; H, 7.47; N, 9.03; P, 9.89; S, 10.33 Found: C, 42.95; H, 7.55; N, 9.10; P, 9.81; S, 10.59.

$[\alpha]_D^{20}$=−79° $CHCl_3$, (c=1)

^{1}H NMR ($CDCl_3$, 300 MHz): δ4.35 (q, 2H, J=6.9 Hz) 3.82 (t, 1H, J=14.1 Hz) 3.73 (t, 1H, J=15.0 Hz) 2.93 (td, 1H, J=9.0, 2.0 Hz) 2.80 (td, 1H, J=9.0, 2.0 Hz) 2.67 (d, 3H, J=8.0 Hz) 2.63 (d 3H, J=8.0 Hz) 2.05 (m, 2H) 1.85 (m 2H) 1.40 (t 3H, J=7.0 Hz) 1.30 (m 4H) ppm.

^{13}C NMR ($CDCl_3$, 75.6 MHz): δ67.0 64.3 (d, J=6.8 Hz) 62.8 (d, J=9.0 Hz) 46.3 (d, J=102.0 Hz) 28.7 (d, J=2.0 Hz) 27.8 (d, J=10.5 Hz) 27.7 (d, J=8.3 Hz) 27.4 (d, J=4.5 Hz) 24.0 23.9 ppm.

^{31}P NMR ($CDCl_3$, 121.7 MHz): δ26.7 ppm

C. [3aR-(3aα,7aβ)]-Octahydro-1,3-dimethyl-1H-1,3,2-benzodiazaphosphole-2-methanesulfonic acid, tetrabutylammonium salt, 2-oxide

A suspension of 5.00 g (16.12 mmol) of Part B compound and 6.02 g (16.29 mmol) of tetrabutylammonium iodide in 30 mL of anhydrous THF at RT was stirred for 10 min. at 0° C. and warmed to RT. After 30 h the clear solution was concentrated to a thick oil. The oil was dried under vacuum (0.009 nun Hg) overnight. The honey-like oil was used without further purification.

^{1}H NMR (CD_3OD, 300 MHz): δ3.55 t, 1H, J=14.1 Hz) 3.50 (t, 1H, J=14.1 Hz) 3.30 (m, 8H) 3.00 (m, 1H) 2.67 (m, 1H) 2.62 (d, 3H, J=10.0 Hz) 2.58 (d, 3H, J=10.0 Hz) 2.05 (t_{br}, 2H, J=10.0 Hz) 1.85 (m, 2H) 1.70 (m, 8H) 1.40 (m, 12H) 1.05 (t, 12H, J=8.0 Hz) ppm.

^{13}C NMR ($CDCl_3$, 75.6 MHz): δ64.1 (d, J=6 Hz) 63.0 (d, J=6.8 Hz) 48.4 (d, J=107 Hz) 29.0 (d, J=2.0 Hz) 28.9 (d, J=4.5 Hz) 27.9 (d, J=10 Hz) 24.2 (d, J=18 Hz) 13.6 ppm.

^{31}P NMR (CD_3OD, 121.7 MHz): δ35.4 ppm

Mass Spec (FAB, +ions) m/e 242 (Bu_4N).

Mass Spec (high res., FAB, −ions)

Calcd for $C_9H_{18}O_4N_2PS$: 281.0725 Found: 281.0717

$[\alpha]_D^{20}$=−33.8° $C.H_3OH$ (c=1)

D. (S)-(−)-3-phenoxy-α-phosphonobenzenebutanesulfonic acid, tripotassium salt

To a slurry of 3.29 g (6.29 mmol) of Part C compound in 20 mL of dry THF at −90° C. (internal temperature) under argon was added 3.0 mL (7.50 mmol) of 2.5M n-BuLi in hexanes to give a yellow solution. After 0.5 h at −90° C. the solution was treated with 2.10 g (6.29 mmol) of 3-(3-phenoxyphenyl)propyl iodide in 6 mL of THF at such at rate to keep the internal temperature below −85° C. The reaction mixture was stirred at −90° C. for 3 h when it was gradually warmed to −74° C. overnight. The mixture was quenched with 360 uL of acetic acid in 3 mL of THF and allowed to warm to RT. The mixture was concentrated and acidified with 12 mL of 2M HCl solution (24 mmol). The reaction mass was extracted with hexane, the aqueous layer was heated to 80° C. for 3 hours and then diluted with 2-propanol until a clear solution resulted. After heating an additional hour the solvent was evaporated and the residue pumped (=0.5 mm pressure) for 0.5 h. The remainder was dissolved

in 30 mL (30 mmol) of 1M KOH solution and freeze dried to provide a cream colored solid. The solid was diluted with water and eluted through 24 g of AG50X8 (63 meq, K^+ form) ion exchange resin. Final purification was accomplished by MPLC on a column of CHP20P gel (125 mL) eluting with water (200 mL) followed by a gradient created by the gradual addition of 500 mL of acetonitrile to a reservoir of 500 mL of water. Approximately 10 mL fractions were collected. Pure fractions were pooled, the acetonitrile was removed under reduced pressure and the aqueous solution lyophilized to provide 1.48 g (47%) of title compound as a white lyophilate.

TLC Silica gel (6:3:1 propanol/ammonium hydroxide/water) R_f=0.2

Chiral HPLC analysis of enantiomeric excess was performed on a ChromTech α-acid glycoprotein (α1-AGP) column: isocratic 85% 0.1M KH_2PO_4/15% CH_3CN, (pH 4.6) in isocratic mode.

For this sample title compound (S)-isomer: retention time=10.3 min. 94% Example 176 compound (R)-isomer: retention time=19.0 min. 6% Therefore, the enaniomeric excess is 88%.

Anal. Calc'd for $C_{16}H_{16}O_7PSK_3$+2.2 H_2O: C, 35.54; H, 3.81; P, 5.73; S, 5.93 Found: C, 35.54; H, 3.98; P, 5.42; S, 6.30.

EXAMPLE 180

(R)-(+)-3-Phenoxy-α-phosphonobenzenebutanesulfonic acid, tripotassium salt

A. 4-(3-Phenoxyphenyl)butyl alcohol

A(1) 3-Phenoxybenzyl alcohol

Sodium borohydride (961 mg, 25.3 mmol) was added in one portion to a solution of 3-phenoxybenzaldehyde (10.0 g, 50.5 mmol) in methanol (150 mL) at RT under argon. Once the bubbling ceased, the reaction was stirred at RT for 5 min, then adjusted to pH 6 with glacial acetic acid (about 1 mL). The reaction was concentrated in vacuo to give a residue, which was partitioned between EtOAc (200 mL) and saturated $NaHCO_3$ (50 mL). The organic layer was washed with water and brine (50 mL each), then dried over $MgSO_4$. Evaporation gave title compound (10.1 g, 100%) as a tan oil.

A(2) 3-Phenoxybenzylbromide

Phosphorus tribromide solution (11.0 mL, 1M in CH_2Cl_2, 11.0 mmol) was added over 5 min to a solution of Part 1(A) alcohol (2.00 g, 10.0 mmol) in CH_2Cl_2 (30 mL) under argon at RT. The yellow reaction was stirred at RT for 10 min, diluted with CH_2Cl_2 (100 mL), and washed with saturated $NaHCO_3$ (2×30 mL). The organic layer was dried over $MgSO_4$. Evaporation gave a pale yellow oil, which was purified by flash chromatography on silica gel (75 g) eluting with 10:90 CH_2Cl_2/hexane to provide title bromide (1.57 g, 60%) as a yellow oil.

A(3) 4-(3-Phenoxyphenylbutyl alcohol

A Grignard solution of $ClMg(CH_2)_3OMgCl$ (19.2 mL, 0.6M in THF, 11.5 mmol) was added to a mixture of Part A(2) bromide (1.51 g, 5.74 mmol) and copper(I) iodide (11 mg, 0.057 mmol) in THF (10 mL) at 0° C. under argon over a period of 5 min. The dark green reaction was stirred at 0° C. for 30 min, then quenched by dropwise addition of 2-propanol (2 mL). The reaction was diluted with diethyl ether (100 mL) and washed with 1N $KHSO_4$ (2×50 mL). The aqueous layers were back-extracted with diethyl ether (20 mL). The combined organic layers were dried over $MgSO_4$. Evaporation gave a pale yellow oil, which was purified by flash chromotography on silica gel (100 g) eluting with 30:70 EtOAc/hexane to provide title alcohol (1.10 g, 79%) as a colorless oil.

B. 3-Phenoxybenzenebutanal

To a stirred solution of 3.4 mL (48.6 mmol) of methyl sulfoxide in 50 mL of CH_2Cl_2 under argon at −78° C. was added 3.9 mL (44.5 mmol) of oxalyl chloride dropwise over 5 min. The reaction was stirred at −78° C. for 0.5 h at which time 9.8 g (40.4 mmol) of Part A alcohol in 15 mL of CH_2Cl_2 was added dropwise. The reaction was stirred at −78° C. for 20 min, warmed to −30° C. for 5 min, cooled back down to −78° C. and treated with 22.6 mL (162 mmol) of triethylamine. The reaction gradually warmed to −20° C. and was quenched with 150 mL of water. The mixture was diluted with a 1:1 mixture of hexanes/ethyl acetate and the layers were separated. The organics were dried over Na_2SO_4 and evaporated to dryness to provide 8.8 g (91%) of title compound as a pale yellow oil.

TLC Silica gel (70:30 hexanes/ethyl acetate) R_f=0.40.

C. 4,6-Dimethyl-2-[3-(3-phenoxyphenyl)propyl]-1,3-dioxane

To a solution of 5.6 g (23.33 mmol) of Part B aldehyde in 25 mL of benzene was added 2.4 g (23.33 mmol) of (2S,4S)-(+)-pentanediol and a 50 mg (0.36 mol) of p-toluenesulfonic acid. The reaction was refluxed for 2 h using a Dean-Stark trap for the azeotropic removal of water. The reaction was diluted with ethyl acetate, washed with sat. $NaHCO_3$ solution, water, dried over $MgSO_4$ and evaporated to provide a crude yellow oil. Flash chromatography was performed on 300 g of silica gel eluting with 90:10 hexanes/ethyl acetate. Pure product fractions were combined and evaporated to provide 5.5 g (72%) of title compound as a colorless oil.

TLC Silica gel (90:10 hexanes/ethyl acetate) R_f=0.21.

$[\alpha]_D^{20}$−13.1° (c=1 CH_2Cl_2)

MS (CI-NH_3, +ions) m/e 344 (M+NH_4), 326 (M).

D. [R-[R*[R*(R*)]]]-α-(3-Hydroxy-1-methylbutoxy)-3-phenoxybenzenebutanephosphonic acid, diethyl ester

(Yokomatsu, T., Shibuya, S., Tetrahedron *Asymmetry* 1992, 3, 377–8).

To a solution of 2.9 mL (16.87 mmol) of triethyl phosphite in 7 mL of CH_2Cl_2 at −78° C. under argon was added dropwise 1.5 mL (13.50 mmol) of titanium (IV) chloride. The resulting orange solution was stirred at −78° C. for 0.5 h at which time 2.2 g (6.75 mmol) of Part C compound in 5 mL of CH_2Cl_2 was added dropwise over 0.5 h (internal temperature of the reaction maintained at −68° C.). The reaction was stirred for 48 h at −78° C. at which time the reaction was poured into 200 mL of a 1:1 mixture of $NaHCO_3$/ethyl acetate and extracted. The organics were washed with water, brine, dried ($MgSO_4$) and evaporated to provide 2.0 g of a crude oil. Flash chromatography was performed on 200 g of silica gel eluting with 4:1 dichloromethane/acetone. Pure product fractions were pooled and evaporated to provide 1.5 g (48%) of title compound as a colorless oil.

TLC Silica gel (4:1 dichloromethane/acetone) R_f=0.24.

$[\alpha]_D^{20}$+15.8 (c=1 CH_2Cl_2)

IR (Film, CH_2Cl_2) 3410, 3040, 2969, 2870, 1584, 1487, 1447, 1385, 1250, 1215, 1163, 1047 cm^{-1}.

^{31}P NMR ($CDCl_3$, 121 MHz, ref. to 10% H_3PO_4, 0 ppm): 24.20 ppm.

HRMS (EI, +ions) m/z Calculated for $C_{25}H_{37}O_6P$: M^+ 464.2328 Found: 464.2316

E. (R)-α-Hydroxy-3-phenoxybenzenebutanephosphonic acid, diethyl ester

To a solution of 3 mL (6.00 mmol) of 2.0M oxalyl chloride in CH_2Cl_2 in 3.5 mL of CH_2Cl_2, under argon at

–70° C., was added dropwise 535 μL (7.54 mmol) of DMSO (exothermic). This mixture was stirred at –70° C. for 15 min at which time 1.4 g (3.02 mmol) of Part D compound in 5 mL of CH_2Cl_2 was added dropwise. The reaction was stirred at –70° C. for 1 h, treated with 1.7 mL of triethylamine and allowed to warm to RT. The reaction was quenched with water and diluted with a 1:1 mixture of hexanes/ethyl acetate. The organics were dried ($MgSO_4$) and evaporated to provide 1.4 g of a crude oil. The crude oil was treated with 14 mL of dioxane, 70 mg (0.37 mmol, 5%) of p-toluenesulfonic acid, 1.4 mL of water and refluxed for 0.5 h then cooled to RT. The mixture was diluted with a 1:1 mixture of water/$NaHCO_3$ and extracted 3 times with CH_2Cl_2. The organics were dried ($MgSO_4$) and evaporated to provide 1.2 g of a pale yellow oil. Flash chromatography was performed on 100 g of silica gel eluting with 4:1 dichloromethane/acetone. Pure product fractions were combined and evaporated to provide 690 mg (60%) of title compound as a colorless oil.

$[\alpha]_D^{20}$–5.9° (c=1, $CHCl_3$)

TLC Silica gel (4:1 dichloromethane/acetone) R_f=0.23.

IR (Film, CH_2Cl_2) 3306, 2982, 1584, 1485, 1445, 1385, 1250, 1215, 1163, 1142, 1096, 1051, 1026, 966 cm^{-1}.

^1H (300 MHz, $CDCl_3$): δ7.30–6.70 (m, 9H) 4.15 (m, 4H) 3.95 (m, 1H) 3.87 (m, 1H) 2.61 (m, 2H) 1.95 (m, 1H) 1.70 (m, 3H) 1.30 (t, 6H, J=7.1 Hz) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ157.2, 157.0, 144.1, 129.6, 129.4, 123.3,122.9,118.9, 118.6, 116.2, 67.5 (d, J=161 Hz), 62.6 (d, J=6.8 Hz), 62.4 (d, J=6.8 Hz), 35.2, 30.8, 27.2 (d, J=12.8 Hz), 16.4 (d, J=4.5 Hz) ppm.

^{31}P NMR (121 MHz, $CDCl_3$, ref. to 10% H_3PO_4, 0 ppm): 25.28 ppm.

HRMS (FAB, +ions) m/z Calculated for $C_{20}H_{28}O_5P$: $(M+H)^+$=379.1675 FOUND: 379.1692

Anal. Calcd. for $C_{20}H_{27}PO_5$+0.50 mol H_2O. Effective MW=387.40. C, 62.00; H, 7.28; P, 7.99 Found: C, 62.00; H, 7.05; P, 8.13.

F. (R)-α-[[(Dimethylamino)thioxomethyl]thio]-3-phenoxybenzenebutanephosphonic acid

To a stirred slurry of 415 mg (1.10 mmol) of Part E compound, 585 mg (2.23 mmol) of triphenylphosphine and 252 mg (0.82 mmol) of dimethyldithiocarbamic acid, zinc salt, in 3 mL of THF at 0° C. under argon was added 446 mg (2.21 mmol) of diisopropyl diazodicarboxylate in 2 mL of THF over the course of 20 minutes. The resulting light yellow solution was allowed to warm to room temperature and stirred for 16 hours. The reaction mixture was then evaporated and immediately purified by flash chromatography (5×15 cm column, eluting with 1:3 ether/dichloromethane). Fractions containing both the product and an impurity were collected, concentrated and re-chromatographed (5×15 cm column, 85:15 ethyl acetate/hexane). The resulting yellow oil still contained ca. 8–10% of diisopropyl dicarbazide as an impurity. The yield of title compound was 490 mg (82% of 91% pure material).

$[\alpha]_D^{20}$=24.5° (c=0.99, $CHCl_3$)

G. (R)-(+)-3-Phenoxy-α-phosphonobenzenebutanesulfonic acid, tripotassium salt

To a stirred solution of 410 mg (0.851 mmol) of Part F compound in 3 mL of CH_2Cl_2 at room temperature under argon was added 0.7 mL (5.3 mmol) of bromotrimethylsilane. The nearly colorless solution was stirred for 16 hours and then evaporated at less than 25° C. The residue was dissolved in 10 mL of dry methanol and stirred for 1 hour. Re-evaporation gave 358 mg (99%) of the diacid as a colorless glass.

To a solution of 0.326 g (0.77 mmol, 1 eq) of the diacid in 50 mL of 98% formic acid was added 4.2 mL (38 mmol, 50 eq) of 30% hydrogen peroxide in water. The reaction became cloudy after 0.5 min and a precipitate formed after ~2 min. After 1 h, the reaction was cooled to 0° C. and the excess peroxide was decomposed by the slow addition of 40 mL of 1N potassium sulfite. The solution was concentrated and the residue was coevaporated twice with water. The residue was dissolved in 10 mL of water and the pH of the solution (pH~3) was brought to pH 12 with 1N potassium hydroxide. The solution was then chromatographed on CHP-20P gel (2.5 cm×25 cm) eluting with water. Fractions containing product were analyzed by HPLC, then pooled and concentrated to afford a clear waxy residue which was dissolved in water, filtered and lyophilized to afford 201 mg (48%) of title compound.

TLC Silica gel (6:3:1 n-propanol:ammonium hydroxide:water): R_f 0.21.

Chiral HPLC analysis of enantiomeric excess was performed on a ChromTech α-acid glycoprotein (α_1-AGP) column, eluted with 85% 0.1M KH_2PO_4, 15% CH_3CN, pH 4.6 in isocratic mode.

For title compound: ret. time 18.5 min, 98.95% (R)-enantiomer ret. time 11.2 min, 1.05% (S)-enantiomer therefore 97.9% enantiomeric excess of the (R)-isomer.

Anal. Calc'd for $C_{16}H_{16}O_7PSK_3$+2.5 H_2O: C, 35.19; H, 3.88; P, 5.67; S, 5.87 Found: C, 35.19; H, 3.54; P, 5.32; S, 6.27.

EXAMPLE 181

(S)-(–)-3-Phenoxy-α-phosphonobenzenebutanesulfonic acid, 1-adamantanamine (1:2) salt

A sample of the (R)-(-)-trisalt (94:6, (S):(R)) prepared in Example 179 (70 mg, 0.14 mmol) was stirred with 3 g of Ag50-X8 ion exchange resin (7.5 meq, H^+ form) for 1 h in 5 mL of water and 3 mL of methanol. The mixture was slowly eluted through an additional column of Ag50-X8 ion exchange resin (1 g, 2.5 meq, H^+ form) with 1:1 methanol/water. Approximately 3 mL fractions were collected. Fractions #2 to 7 were pooled, the methanol was removed under reduced pressure and the aqueous solution lyophilized to provide 54 mg (100%) of the free acid form of the title salt as a thin film.

The free acid 54 mg, 0.14 mmol) in 3 mL of a 1:1 methanol/water solution was treated with 39 mg (0.28 mmol, 2 eq) of adamantanamine and the mixture stirred for 0.5 h. The mixture was concentrated to a white solid. The solid was recrystallized from hot water and 2-propanol. The white granules were collected to yield 79 mg (85%) of title salt as a 97:3 mixture of (S):(R) enantiomers. The recrystallization procedure was repeated to provide 66 mg (85%) of title salt, as a white solid, mp 248°–252° C. The two recrystalizations from hot 2-propanol/water improved the ratio of (S):(R) enantiomers from 94:6 to 98:2 determined by HPLC as described on the α-acid glycoprotein column.

TLC Silica gel (6:3:1 n-propanol/conc. ammonia/water) R_f=0.30.

IR (KBr) 3426, 3086, 3065, 3036, 2915, 2855, 1609, 1582, 1485, 1233, 1215, 1175, 1022, 882 cm^{-1}.

^1H NMR (CD_3OD, 400 MHz): δ7.30 (t, 2H, J=8.1 Hz) 7.20 (t, 1H, J=8.0 Hz) 7.07 (t, 1H, J=6.2 Hz) 6.95 (m, 3H) 6.86 (s, 1H) 6.73 (dd, 1H, J=8.5, 2.5 Hz) 3.05 (dr, 1H, J=18.0, 6.2 Hz) 2.65 (m, 2H) 2.15 (s+m, 8H) 2.00 (m, 2H) 1.90 (s, 12H) 1.75 (d, 6H, J=12.0 Hz) 1.68 (d, 6H, J=12.0 Hz) ppm.

Mass Spec (FAB, +ions) m/e 689 (M+H); (FAB, –ions) m/e 385 (M–2($C_9H_{17}N$)+H).

Anal. Calc'd for $C_{36}H_{53}O_7N_2PS+1.00\ H_2O$: C, 61.17; H, 7.84; N, 3.96; P, 4.38; S, 4.54. Found: C, 61.26; H, 7.90; N, 4.00; P, 4.27; S, 4.74.

Regeneration of Metal Salt

Title salt (60 mg, 0.08 mmol) was stirred with 1.5 mL of Ag50-X8 ion exchange resin (2.5 meq, K^+ form) for 2 h in 3 mL of water and 1 mL of methanol (pH=7). The mixture was slowly eluted through an additional column of Ag50-X8 ion exchange resin (1.5 mL, 2.5 meq, K^+ form) with 1:1 methanol/water. Product containing fractions were pooled, the methanol was removed under reduced pressure and the aqueous solution lyophilized to provide 38 mg (95%) of the tripotassium salt as a white lyophilate.

Chiral HPLC analyis of enantiomeric excess was performed on a ChromTech α-acid glycoprotein (α1-AGP) column eluted with isocratic 85% 0.1M KH_2PO_4, 15% CH_3CN, pH 4.6.

For this sample,

Example 181 (S)-isomer: retention time=9.5 min. 98%

Example 180 (R)-isomer: retention time≈19.0 min. 2%, therefore a 96% enantiomeric excess of the (S)-isomer.

EXAMPLE 182

(S)-(−)-3-Phenoxy-(1-phosphonobenzenebutanesulfonic acid, (S)-(1-methylbenzylamine (1:2) salt

A sample of the (−)-isomer (Example 175) (70 mg, 0.14 mmol) was stirred with 3 g of Ag50-X8 ion exchange resin (7.5 meq, H^+ form) for 1 h in 5 mL of water and 3 mL of methanol. The mixture was slowly eluted through an additional column of Ag50-X8 ion exchange resin (1 g, 2.5 meq, H+ form) with 1:1 methanol/water. Approximately 3 mL fractions were collected. Fractions #2 to 7 were pooled, the methanol was removed under reduced pressure and the aqueous solution lyophilized to provide 54 mg (100%) of the free acid form of the title salt as a thin film. The free acid was used without further characterization.

The free acid in 3 mL of a 1:1 methanol/water solution was treated with 36 uL (0.28 mmol, 2 eq) of (S)-(−)-(1-methylbenzylamine under argon. The mixture was stirred for 0.5 h and concentrated to an oil. Recrystallization from 3 mL of hot acetonitrile and 3 drops of water followed by slow evaporation to dryness provided 60 mg (73%) of title diamine salt as needles. mp 160°–163° C.

$[\alpha]_D^{20}$=−8.0° (methanol, c=1)

IR (KBr) 3447, 3050, 3038, 2938, 2762, 1613, 1582, 1566, 1489, 1242, 1213, 1182, 1163, 1072, 1044, 1022, 924, 702 cm^{-1}.

Mass Spec (FAB, +ions) m/e 629 (M+H); (FAB, −ions) m/e 385 (M−2($C_8H_{11}N$)+H).

^1H NMR (3:1 DMSO:CD_3OD, 300 MHz): δ7.58–7.30 (m, 12H) 7.25 (t, 1H, J=8.0 Hz) 7.10 (t, 1H, J=8.0 Hz) 7.00 (d, 3H, J=9.0 Hz) 6.85 (m, 1H) 6.75 (dd, 1H, J=7.0, 2.0 Hz) 4.40 (q, 2H, J=6.5 Hz) 2.80 (dt, 1H, J=19.0, 5.8 Hz) 2.57 (m, 2H) 1.80 (m, 4H) 1.55 (d, 6H, J=6.5 Hz) ppm.

The needles were subjected to X-ray crystallographic studies, which demonstrated that the (−)-isomer had the (S)-stereochemistry at the α-carbon.

EXAMPLE 183

(S)-α-[Bis[(2,2-dimethyl-1-oxopropoxy)methoxy] phosphinyl]-3-phenoxybenzenebutanesulfonic acid, monopotassium salt

A. (S)-3-Phenoxy-α-phosphonobenzenebutanesulfonic acid, trisilver salt

A solution of Example 175 product (1.66 g, 3.32 mmol) in water (17 mL) was added over 30 min via syringe pump to a vigorously stirred solution of silver nitrate (2.02 g, 11.9 mmol) in water (17 mL) under argon at RT in the dark. A white precipitate resulted immediately upon addition. Following addition, additional water (5 mL) was added to aid stirring, and the thick slurry was stirred vigorously at RT for 15 min then filtered through a porosity D (10–20 μm) glass fritted funnel. The solid was washed with water (2×40 mL) and diethyl ether (2×40 mL) then air-dried for 15 min. The product was further dried by pumping under high vacuum in the dark overnight to give title compound (2.28 g, 97%) as a beige solid.

B. (S)-α-[Bis[(2,2-dimethyl-1-oxopropoxy)methoxy] phosphinyl]-3-phenoxybenzenebutanesulfonic acid, monopotassium salt

A suspension of Part A compound (2.12 g, 3.00 mmol) and activated 4A molecular sieves (2.1 g) in CH_2Cl_2 (25 mL) was stirred at RT in the dark under argon for 45 min. Anhydrous anisole (1.6 mL, 15.0 mmol) was added and the reaction was placed in a 20° C. water bath. To the suspension was added a solution of 2,2-dimethylpropanoic acid, iodomethyl ester (2.18 g, 9.00 mmol) in CH_2Cl_2 (5 mL) dropwise slowly over 15 min via syringe pump ensuring that the reaction temperature remained below 30° C. The reaction turned bright yellow during addition. The heterogeneous reaction was stirred vigorously at RT in the dark for 40 min. then filtered through Celite with the aid of CH_2Cl_2 (200 mL). Evaporation of the filtrate gave 3.3 g of the crude triester α-[bis[(2,2-dimethyl-1-oxopropoxy)methoxy] phosphinyl]-3-phenoxybenzenebutanesulfonic acid, (2,2-dimethyl-1-oxopropoxy)methyl ester as a yellow liquid.

The crude triester was dissolved in CH_3CN/water (4:1, 40 mL) to give an opaque solution containing a small amount of yellow precipitate. The reaction was stirred at RT and progress of the solvolysis was monitored by ^1H NMR (disappearance of the t-$BuCO_2CH_2$-sulfonate signal at 5.8 ppm [in d6-DMSO]). When no sulfonate ester remained (8 h) the reaction was partitioned between EtOAc (150 mL) and saturated KCl (20 mL). The resultant biphasic mixture was filtered to remove the yellow precipitate. The organic layer was washed with 1M potassium phosphate (pH=6.0, 2×20 mL) and saturated KCl (5 mL), then dried over anhydrous KCl. Evaporation followed by pumping under high vacuum for 1.5 h gave 2.0 g of a colorless oil.

CHP20P gel was stirred with 0.5M potassium phosphate buffer (pH=5.0, 1000 mL) for 4 h, then packed (5×25 cm column) and flushed with water (500 mL). The column was equilibrated with 5:95 CH_3CN/water (1.5 L).

The crude product was dissolved in CH_3CN (5 mL), then water (10 mL) was added. The solution was adjusted to pH 5.0 with 1M potassium phosphate buffer (pH=7.0). The product solution was chromatographed on CHP20P gel prepared above (25 mL fractions), eluted with 5:95 CH_3CN/H_2O (250 mL) followed by a gradient created by the gradual addition of 80:20 CH_3CN/H_2O (1200 mL) to a reservoir of 5:95 CH_3CN/H_2O (1200 mL)). Fractions 55–62 were combined and concentrated to a volume of 100 mL consisting almost entirely of water. The aqueous solution (pH=3.2) was adjusted slowly to pH=5.0 with 1M potassium phosphate (pH=7.0), then concentrated to dryness. The resultant residue was dissolved in CH_3CN/H_2O (1:4, 10 mL) and lyophilized to give title compound (1.12 g, 57%) as a white lyophilate.

TLC (silica gel)(10:90MeOH/CH_2Cl_2) R_f 0.25

Chiral purity was determined by HPLC on a Chrom Tech α-acid glycoprotein column, with isocratic elution of 10 mM

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