Hormetic effects of binaphthyl phosphonothioates as pro-oxidants and antioxidants

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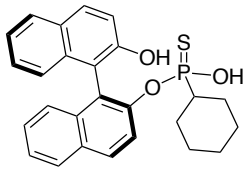
Supplementary Synthesis Section

General procedures for the synthesis of all the compounds

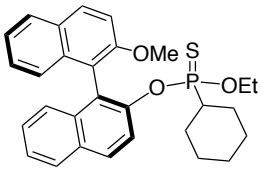
(S_{ax})-*O*-(2'-Hydroxy-[1,1'-binaphthalen]-2-yl)-*O*-hydrogencyclohexylphosphonothioate (KK243)



Chemical Formula: $C_{26}H_{25}O_3PS$
Exact Mass: 448.1262
Molecular Weight: 448.5168

To a 20 mL round-bottom flask were added phosphonothioate (218 mg, 0.50 mmol), LiOH (62 mg, 2.5 mmol), THF (1.0 mL) and water (1.0 mL), and the mixture was stirred at rt for 144 h. After that the mixture was added 1N HCl until pH reached 1 and it was extracted with Et_2O three times. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (Acetone : H_2O = 1 : 1, Rf = 0.14). The eluted fraction was concentrated to remove acetone and it was extracted with Et_2O three times. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated to give **KK243** (199 mg, 88%, dr = >95 : 5) as a colorless solid. mp: 175-178 ºC; IR (KBr): 3426, 3057, 2928, 2853, 1591, 1506, 1208, 1146, 988, 814, 748 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.84-1.00 (m, 5H), 1.26-1.49 (m, 6H), 7,09 (d, J = 8.6 Hz, 1H), 7.29-7.37 (m, 5H, Ar), 7.48-7.51 (m, 1H, Ar), 7.65-7.87 (m, 2H, Ar), 7.92-7.97 (m, 2H, Ar), 8.02 (d, J = 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 25.1, 25.2, 25.5, 25.8, 25.9, 42.9 (d, $^1J_{C\text{-}P}$ = 108.0 Hz, $\underline{C}HCH_2CH_2$), 115.0, 117.8, 121.8, 122.2, 123.9, 125.3, 125.8, 126.0, 126.9, 127.5, 128.0, 128.4, 129.3, 130.4, 130.6, 131.5, 133.7, 148.0, 148.1, 151.2; ^{31}P NMR ($CDCl_3$): δ 96.7 (s, major), 98.4 (s, minor); MS (EI) m/z 448 (M^+); HRMS Calcd for $C_{26}H_{25}O_3PS$: 448.1262, Found: 448.1241.

(S_{ax})-*O*-Ethyl *O*-(2'-methoxy-[1,1'-binaphthalen]-2-yl) cyclohexylphosphonothioate (KK255)

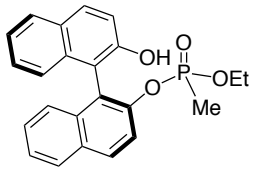


Chemical Formula: $C_{29}H_{31}O_3PS$
Exact Mass: 490.1732
Molecular Weight: 490.5978

To a 20 mL Schlenk tube were added (S_{ax})-4-cyclohexylbinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine-4-sulfide (111 mg, 0.25 mmol), ethanol (18 μL, 0.30 mmol), and THF (0.2 mL). The reaction mixture was added to NHMDS (1.0 M in THF, 0.30 mL, 0.30 mmol), and it was stirred at rt for 2 h. After that, the mixture was concentrated *in vacuo* followed by the addition of DMF (0.5 mL) and iodomethane (30 μL, 0.50 mmol), and the resulting solution was stirred at rt for 8 h. The reaction mixture was added to H_2O (2.0 mL), and it was extracted with EtOAc (5 mL × 3). The combined organic layer was washed with brine twice, dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography on silica gel (EtOAc:hexane = 1:10, Rf = 0.43) gave **KK255** (96 mg, 80%, >95:5 dr) as a colorless solid.

mp: 118-120 °C; IR (KBr): 2931, 2853, 1592, 1508, 1453, 1263, 981, 946, 810 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.59-0.82 (m, 5H), 0.95-1.05 (m, 1H), 1.19 (t, J = 7.1 Hz, 3H), 1.28-1.43 (m, 5H), 3.77 (s, 3H), 3.94-4.04 (m, 1H), 4.14-4.25 (m, 1H), 7.20-7.44 (m, 7H), 7.72 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 8.2 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.93 (d, J = 8.7 Hz, 1H), 7.98 (d, J = 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 16.2 (d, $^3J_{C\text{-}P}$ = 7.5 Hz), 25.2 (d, $^4J_{C\text{-}P}$ = 4.7 Hz), 25.5 (d, $^3J_{C\text{-}P}$ = 2.8 Hz), 25.6, 25.9 (d, $^2J_{C\text{-}P}$ = 8.5 Hz), 26.1 (d, $^2J_{C\text{-}P}$ = 8.5 Hz), 43.7 (d, $^1J_{C\text{-}P}$ = 111.8 Hz), 56.8, 62.7 (d, $^2J_{C\text{-}P}$ = 7.5 Hz), 113.8, 118.6, 121.7, 124.0, 125.1, 126.1, 126.2, 126.5, 126.8, 127.7, 128.2, 128.8, 129.2, 129.9, 131.1, 134.0, 134.1, 147.1, 147.2, 155.2; ^{31}P NMR ($CDCl_3$): δ 100.3 (s); MS (EI) m/z 490 (M^+); HRMS Calcd for $C_{29}H_{31}O_3PS$: 490.1732, Found: 490.1728.

(S_{ax})-*O*-Ethyl-(2'-hydroxy-[1,1'-binaphthalen]-2-yl)-methylphosphonate (KK304)



Chemical Formula: $C_{23}H_{21}O_4P$
Exact Mass: 392.1177
Molecular Weight: 392.3908

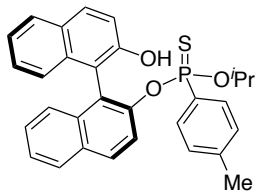
To a 10 mL two-necked flask were added (S_{ax})-4-methylbinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine-4-oxide (173 mg, 0.50 mmol) and sodium ethoxide (32 mg, 0.47 mmol), ethanol (1.0 mL) under Ar atmosphere. The reaction mixture was stirred for 10 min. After that, the mixture was added 1N HCl (1.0 mL) and it was extracted with Et_2O three times. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography on silica gel (EtOAc : hexane = 1 : 1, Rf = 0.28) gave diastereomers **KK304** (18 mg, 9%, dr = 92 : 8, The first fraction on TLC), (27 mg, 14%, dr = >5 : 95, The second fraction), (20 mg, 11%, dr = 40 : 60) as a colorless solid.

(dr = >5 : 95); mp: 80-83 °C; IR 3220, 3061, 2992, 1624, 1508, 1234, 1208, 1101, 1038, 990, 903,

822, 753 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.96 (d, J = 18.0 Hz, 3H, C<u>H</u>$_3$), 1.22 (t, J = 7.2 Hz, 3H, OCH$_2$C<u>H</u>$_3$), 3.99 (dq, J = 11.2 Hz, J = 7.2 Hz, 2H), 6.52 (br, 1H, O<u>H</u>), 7.02 (d, J = 8.1 Hz, 1H, Ar), 7.21-7.24 (m, 2H, Ar), 7.29-7.34 (m, 2H, Ar), 7.40 (d, J = 9.0 Hz, 1H, Ar), 7.43-7.47 (m, 1H, Ar), 7.51-7.54 (m, 1H, Ar), 7.84 (d, J = 8.1 Hz, 1H, Ar), 7.90-7.92 (m, 2H, Ar), 8.00 (d, J = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 11.1 (d, $^1J_{C\text{-}P}$ = 146.6 Hz, <u>C</u>H$_3$), 16.3 (d, $^3J_{C\text{-}P}$ = 6.6 Hz, OCH$_2$<u>C</u>H$_3$), 62.3 (d, $^2J_{C\text{-}P}$ = 6.6 Hz, O<u>C</u>H$_2$CH$_3$), 116.9, 120.1, 120.8, 123.8, 124.7, 125.8, 126.0, 126.7, 127.5, 128.1, 128.2, 129.3, 130.4, 130.8, 131.7, 133.7, 133.8, 147.5, 147.6, 152.5 (Ar); ^{31}P NMR ($CDCl_3$): δ 31.0 (s); MS (EI) m/z 392 (M^+); HRMS Calcd for $C_{23}H_{21}O_4P$: 392.1777, Found: 392.1158.

(dr = 92 : 8); ^{1}H NMR ($CDCl_3$): δ 0.74 (t, J = 7.2 Hz, 3H, OCH$_2$C<u>H</u>$_3$), 1.44 (d, J = 17.5 Hz, 3H, C<u>H</u>$_3$), 3.05 (ddq, J = 21.2 Hz, J = 7.2 Hz, J = 1.5 Hz, 1H, OC<u>H</u>$_2$CH$_3$), 3.41 (ddq, J = 21.5 Hz, J = 7.2 Hz, J = 1.5 Hz, 1H, OC<u>H</u>$_2$CH$_3$), 6.70 (br, 1H, O<u>H</u>), 7,14-7.18 (m, 3H, Ar), 6.93 (d, J = 8.5 Hz, 1H), 7.14-7.18 (m, 2H, Ar), 7.22-7.27 (m, 2H, Ar), 7.34 (d, J = 9.0 Hz, 1H), 7.37-7.42 (m, 2H, Ar), 7.77 (d, J = 8.1 Hz, 1H), 7.83 (d, J = 9.0 Hz, 1H), 7.86 (d, J = 8.5 Hz, 1H), 7.95 (d, J = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 12.2 (d, $^1J_{C\text{-}P}$ = 146.6 Hz, <u>C</u>H$_3$), 15.9 (d, $^3J_{C\text{-}P}$ = 6.6 Hz, OCH$_2$<u>C</u>H$_3$), 61.9 (d, $^2J_{C\text{-}P}$ = 6.6 Hz, O<u>C</u>H$_2$CH$_3$), 117.2, 120.1, 120.5, 123.9, 124.7, 126.0, 126.1, 126.9, 127.7, 128.1, 128.3, 129.4, 130.3, 131.0, 131.8, 134.0, 134.1, 147.2, 147.3, 152.7 (Ar); ^{31}P NMR ($CDCl_3$): δ 30.1 (s)

(S_{ax})-*O*-(2'-Hydroxy-[1,1'-binaphthalen]-2-yl) *O*-isopropyl *p*-tolylphosphonothioate (KK379)



Chemical Formula: $C_{30}H_{27}O_3PS$
Exact Mass: 498.1419
Molecular Weight: 498.5768

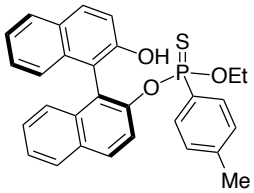
To a 20 mL Schlenk tube were added (S_{ax})-4-(p-tolyl)binaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine-4-sulfide (212 mg, 0.5 mmol), IPA (1.0 mL). The reaction mixture was added to sodium isopropoxide (0.66 M in IPA, 3.5 mL, 2.3 mmol), and the resulting solution was stirred at rt for 1 h. After that, the mixture was added to 3N HCl (1.0 mL), and it was extracted with Et_2O (5 mL × 3). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography on silica gel (EtOAc:hexane = 1:20, Rf = 0.50, 0.35) gave diastereomers of **KK379** (89 mg, 36%, 5:>95 dr, first fraction on TLC, major diastereomer), (50 mg, 20%, >95:5 dr, second fraction on TLC, minor diastereomer) as a colorless solid.

(5:>95 dr): mp: 161-162 °C; IR (KBr): 3526, 3059, 2976, 2925, 1598, 1210, 1117, 959, 818 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.51 (d, J = 6.3 Hz, 3H), 1.04 (d, J = 6.3 Hz, 3H), 2.41 (s, 3H), 4.04-4.17 (m,

1H), 5.55 (br, 1H), 7.08 (d, J = 8.1 Hz, 1H), 7.10 (d, J = 8.1 Hz, 1H), 7.20-7.34 (m, 6H), 7.40 (d, J = 9.0 Hz, 1H), 7.43-7.47 (m, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.84-7.90 (m, 3H), 7.92 (d, J = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 21.8, 22.9 (d, $^3J_{C\text{-}P}$ = 4.8 Hz), 23.7 (d, $^3J_{C\text{-}P}$ = 3.6 Hz), 72.5 (d, $^2J_{C\text{-}P}$ = 7.2 Hz), 115.6, 118.8, 120.9, 122.7, 123.7, 125.0, 125.8, 125.9, 126.8, 127.5, 128.1, 128.3, 129.1, 129.2, 129.4, 130.3, 130.6, 131.5, 131.6, 133.7, 134.0, 143.33, 143.35, 148.76, 148.81, 151.7; ^{31}P NMR ($CDCl_3$): δ 84.6 (s); MS (EI) m/z 498 (M^+); HRMS Calcd for $C_{30}H_{27}O_3PS$: 498.1419, Found: 498.1415.

(>95:5 dr): mp: 102-104 °C; IR (KBr): 3421,3057, 2978, 2925, 1215, 978, 814 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.06 (d, J = 6.3 Hz, 3H), 1.07 (d, J = 6.3 Hz, 3H), 2.32 (s, 3H), 4.43-4.52 (m, 1H), 5.12 (br, 1H), 6.93 (d, J = 8.1 Hz, 1H), 6.94 (d, J = 8.1 Hz, 1H), 7.13 (d, J = 9.0 Hz, 1H), 7.15 (d, J = 8.5 Hz, 1H), 7.22-7.34 (m, 6H), 7.43-7.47 (m, 1H), 7.59 (d, J =9.0 Hz, 1H), 7.73 (d, J =9.0 Hz, 1H), 7.76 (d, J = 8.1 Hz, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.99 (d, J = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 21.7, 23.60 (d, $^3J_{C\text{-}P}$ = 4.8 Hz), 23.64 (d, $^3J_{C\text{-}P}$ = 3.6 Hz), 72.5 (d, $^2J_{C\text{-}P}$ = 6.0 Hz), 114.9, 118.4, 121.8, 122.1, 123.5, 125.2, 125.8, 125.9, 126.6, 127.5, 127.9, 128.4, 128.6, 128.8, 129.2, 130.2, 130.5, 130.6, 131.6, 133.6, 133.8, 142.5, 142.6, 148.9, 149.0, 151.7; ^{31}P NMR ($CDCl_3$): δ 83.5 (s); MS (EI) m/z 498 (M^+); HRMS Calcd for $C_{30}H_{27}O_3PS$: 498.1419, Found: 498.1415.

(S_{ax})-*O*-Ethyl-(2'-hydroxy-[1,1'-binaphthalen]-2-yl)-(*p*-tolyl)phosphonothioate (KK387)

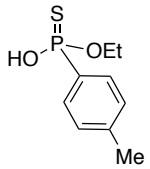


To a 20 mL reaction tube were added (S_{ax})-4-(*p*-tolyl)binaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine-4-sulfide (216 mg, 0.50 mmol) and ethanol (0.5 mL) under Ar atmosphere. The reaction mixture was cooled to 0 ℃. Then, lithium ethoxide generated from ethanol (0.5 mL) and *n*-BuLi (1.6 M hexane solution, 0.78 mL, 1.3 mmol) followed by concentrated *in vacuo.* in ethanol (0.5 mL) was added to the cooled solution through cannula, and it was stirred for 13 h. After that, the mixture was added 1N HCl (1.0 mL) and it was extracted with Et_2O three times. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography on silica gel (EtOAc : hexane = 1 : 20, Rf = 0.23) gave **KK387** (211 mg, 88%, dr = 94 : 6) as a colorless solid.

mp: 171 °C; IR (KBr): 3314, 3055, 2982, 1589, 1506, 1215, 1026, 981, 954, 821 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.12 (t, J = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 2.32 (s, 3H, $C\underline{H}_3$), 1.68 (d, J = 15.3 Hz, 1.2H, $C\underline{H}_3$), 3.21 (ddq, J = 21.5 Hz, 7.2 Hz, 2.5Hz, 0.6H, $OC\underline{H}_2CH_3$), 3.80 (ddq, J = 14.3 Hz, 7.2 Hz, 2.3 Hz, 1H, $OC\underline{H}_2CH_3$), 3.93 (ddq, J = 14.3 Hz, 7.2 Hz, 2.3 Hz, 1H, $OC\underline{H}_2CH_3$), 4.13 (ddq, J = 21.5 Hz, 7.2 Hz, 1.8 Hz, 0.6H, $OC\underline{H}_2CH_3$), 5.16 (br, 1H, O$\underline{H}$), 6.91 (d, J = 7.5 Hz, 1H), 6.92 (d,

J = 7.5 Hz, 1H), 7.12 (d, J = 9.2 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.24-7.35 (m, 4H, Ar), 7.47 (dd, J = 7.5 Hz, 7.5 Hz, 1H, Ar), 7.56-7.58 (m, 1H, Ar), 7.71 (d, J = 9.2 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 16.0 (d, $^3J_{C\text{-}P}$ = 8.4 Hz, $OCH_2\underline{C}H_3$), 21.7 ($\underline{C}H_3$), 63.1 (d, $^2J_{C\text{-}P}$ = 7.2 Hz, $O\underline{C}H_2CH_3$), 114.9, 118.4, 122.1, 123.6, 125.1, 125.9, 126.1, 126.7, 127.6, 127.9, 128.4, 128.7, 128.8, 129.2, 130.4, 130.5, 130.6, 131.7, 133.6, 133.8, 142.7, 148.7, 148.7, 151.7(Ar); ^{31}P NMR ($CDCl_3$): δ 86.5 (s), 96.2; MS (EI) m/z 484 (M^+); HRMS Calcd for $C_{29}H_{25}O_3PS$: 484.1262, Found: 484.1273.

O-Ethyl O-hydrogen p-tolylphosphonothioate (KK391)

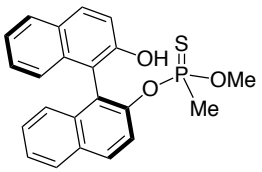


Chemical Formula: $C_9H_{13}O_2PS$
Exact Mass: 216.0374
Molecular Weight: 216.2348

To a test tube were added **KK387** (97 mg, 0.17 mmol), ^{t}BuOH (0.17 mL), and KOH aq. (8 M, 0.17 mL, 1.4 mmol), and it was stirred at rt for 48 h. After that, to the mixture were added 3N HCl (0.4 mL) and sat. $NaHCO_3$ aq. (1.0 mL). It was washed with CH_2Cl_2 (2 mL × 3). The aqueous phase was added 3N HCl until the pH reached to 1, and the resulting solution was extracted with CH_2Cl_2 (3 mL × 3). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated to give **KK391** (9 mg, 0.04 mmol, 24%) as a colorless liquid.

IR (KBr): 3459, 2983, 1604, 1122, 1036, 960, 685 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.34 (t, J = 6.9 Hz, 3H), 2.39 (s, 3H), 4.13-4.21 (m, 2H), 5.45-5.66 (br, 1H), 7.24 (d, J = 7.8 Hz, 1H), 7.25 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.80 (d, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 16.2 (d, $^3J_{C\text{-}P}$ = 7.5 Hz), 21.7, 62.7 (d, $^2J_{C\text{-}P}$ = 5.6 Hz), 129.1, 129.2, 130.8, 130.9, 142.9; ^{31}P NMR ($CDCl_3$): δ 81.0 (s); MS (EI) m/z 216 (M^+); HRMS Calcd for $C_9H_{13}O_2PS$: 216.0374, Found: 216.0368.

(S_{ax})-O-Ethyl-(2'-hydroxy-[1,1'-binaphthalen]-2-yl)-methylphosphonothioate (KK410)



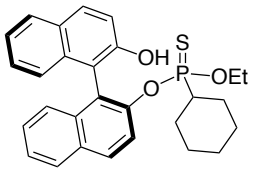
Chemical Formula: $C_{22}H_{19}O_3PS$
Exact Mass: 394.0793
Molecular Weight: 394.4248

To a 20 mL reaction tube were added (S_{ax})-4-methylbinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine-4-sulfide (183 mg, 0.50 mmol) and ethanol (0.5 mL) under Ar atmosphere. The reaction mixture was cooled to 0 ℃. Then, lithium ethoxide generated from ethanol (0.5 mL) and n-BuLi (1.6 M hexane solution, 0.78 mL, 1.3 mmol) followed by concentrated *in vacuo.* in ethanol (0.5 mL) was added to the cooled solution through cannula, and it was stirred for 2.5 h. After that, the mixture was added 1N HCl (1.0 mL) and it was extracted with Et_2O three times. The combined organic layer

was dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography on silica gel (EtOAc : hexane = 1 : 10, Rf = 0.38) gave **KK410** (181 mg, 88%, dr = 40 : 60) as a colorless solid.

mp: 125-126 °C; IR (KBr): 3530, 3053, 2979, 1618, 1589, 1506, 1216, 1039, 972, 906, 816, 753 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.91 (t, J = 7.2 Hz, 1.8H, $OCH_2C\underline{H}_3$), 1.21-1.28 (m, 3H, $C\underline{H}_3$, $OCH_2C\underline{H}_3$), 1.68 (d, J = 15.3 Hz, 1.2H, $C\underline{H}_3$), 3.21 (ddq, J = 21.5 Hz, 7.2 Hz, 2.5Hz, 0.6H, $OC\underline{H}_2CH_3$), 3.81 (ddq, J = 21.1 Hz, 7.2 Hz, 3.0 Hz, 0.4H, $OC\underline{H}_2CH_3$), 3.93 (ddq, J = 21.1 Hz, 7.2 Hz, 1.7 Hz, 0.4H, $OC\underline{H}_2CH_3$), 4.13 (ddq, J = 21.5 Hz, 7.2 Hz, 1.8 Hz, 0.6H, $OC\underline{H}_2CH_3$), 5.33-5.35 (br, 1H, O$\underline{H}$), 7.10-7.12 (m, 1H, Ar), 7.25-7.39 (m, 5H, Ar), 7.42-7.51 (m, 2H, Ar), 7.34-7.86 (m, 1H, Ar), 7.90-7.96 (m, 2H, Ar), 8.02-8.05 (m, 1H, Ar); ^{13}C NMR ($CDCl_3$): δ 15.8 (d, $^3J_{C-P}$ = 8.5 Hz, $OCH_2\underline{C}H_3$), 16.1 (d, $^3J_{C-P}$ = 8.5 Hz, $OCH_2\underline{C}H_3$), 21.6 (d, $^1J_{C-P}$ = 116.5 Hz, $\underline{C}H_3$), 23.1 (d, $^1J_{C-P}$ = 114.6 Hz, $\underline{C}H_3$), 62.0 (d, $^2J_{C-P}$ = 7.5 Hz, $O\underline{C}H_2CH_3$), 62.4 (d, $^2J_{C-P}$ = 7.5 Hz, $O\underline{C}H_2CH_3$), 115.0, 115.3, 118.5, 118.7, 121.7, 122.4, 122.7, 123.8, 124.9, 125.0, 125.9, 126.1, 126.9, 127.0, 127.7, 128.1, 128.4, 129.2, 129.2, 130.4, 130.6, 130.7, 130.8, 131.7, 133.6, 133.7, 133.7, 133.8, 148.3, 148.4, 148.5, 148.6, 151.7, 151.9 (Ar); ^{31}P NMR ($CDCl_3$): δ 95.5 (s, minor), 96.2 (s, major); MS (EI) m/z 408 (M^+); HRMS Calcd for $C_{23}H_{21}O_3PS$: 408.0949, Found: 408.0947. *R*p-KK410 $[\alpha]_D^{25}$ -26.348 °. KK410-*S*p $[\alpha]_D^{25}$ -34.791 °.

(S_{ax})-*O*-Ethyl-(2'-hydroxy-[1,1'-binaphthalen]-2-yl)-cyclohexylphosphonothioate (KK421)



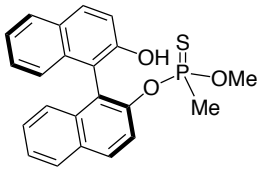
Chemical Formula: $C_{28}H_{29}O_3PS$
Exact Mass: 476.1575
Molecular Weight: 476.5708

To a 20 mL Schlenk tube were added (S_{ax})-4-cyclohexylbinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine-4-sulfide (215 mg, 0.50 mmol) and ethanol (0.5 mL) under Ar atmosphere. Then, lithium ethoxide generated from ethanol (0.5 mL) and *n*-BuLi (1.6 M hexane solution, 0.78 mL, 1.3 mmol) followed by concentrated *in vacuo.* in ethanol (0.5 mL) was added to the cooled solution through cannula, and it was stirred for 96 h at rt. After that, the mixture was added 1N HCl (3.0 mL) and it was extracted with Et_2O (5 mL × 3). The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography on silica gel (EtOAc : hexane = 1 : 20, Rf = 0.18) gave **KK421** (179 mg, 75%, dr = 84 : 16) as a colorless solid.

mp: 142-144 °C; IR (KBr): 3491, 2975, 2935, 2853, 1621, 1505, 1268, 1218, 985, 809, 754 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.89-0.95 (m, 5H, Cy), 1.05 (t, J = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 1.49-1.68 (m, 6H, Cy), 3.53-3.65 (m, 1H, $OC\underline{H}_2CH_3$), 3.94-4.04 (m, 1H, $OC\underline{H}_2CH_3$), 5.18 (br, 1H, O$\underline{H}$), 7.12

(d, J = 8.5 Hz, 1H), 7.25-7.36 (m, 4H, Ar), 7.46-7.50 (m, 1H, Ar), 7.62 (d, J = 9.0 Hz, 1H), 7.85 (d, J = 8.5 Hz, 1H), 7.90-7.96 (m, 2H, Ar), 8.02 (d, J = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 16.0 (d, $^3J_{C\text{-}P}$ = 7.2 Hz, $OCH_2\underline{C}H_3$), 44.2 (d, $^1J_{C\text{-}P}$ = 110.4 Hz, $C\underline{H}CH_2CH_2$), 25.5, 25.6, 25.8, 26.0, 26.2, 62.7 (d, $^2J_{C\text{-}P}$ = 7.2 Hz, $O\underline{C}H_2CH_3$), 114.9, 118.1, 122.1, 123.7, 125.3, 125.7, 126.0, 126.9, 127.6, 128.0, 128.4, 129.2, 130.3, 130.5, 131.5, 133.7, 133.8, 148.4, 148.5, 151.6 (Ar); ^{31}P NMR ($CDCl_3$): δ 102.1 (s, major), 109.7 (s, minor); MS (EI) m/z 476 (M^+); HRMS Calcd for $C_{28}H_{29}O_3PS$: 476.1575, Found: 476.1564.

(S_{ax})-*O*-(2'-Hydroxy-[1,1'-binaphthalen]-2-yl) *O*-methyl *p*-methylphosphonothioate (KK970)



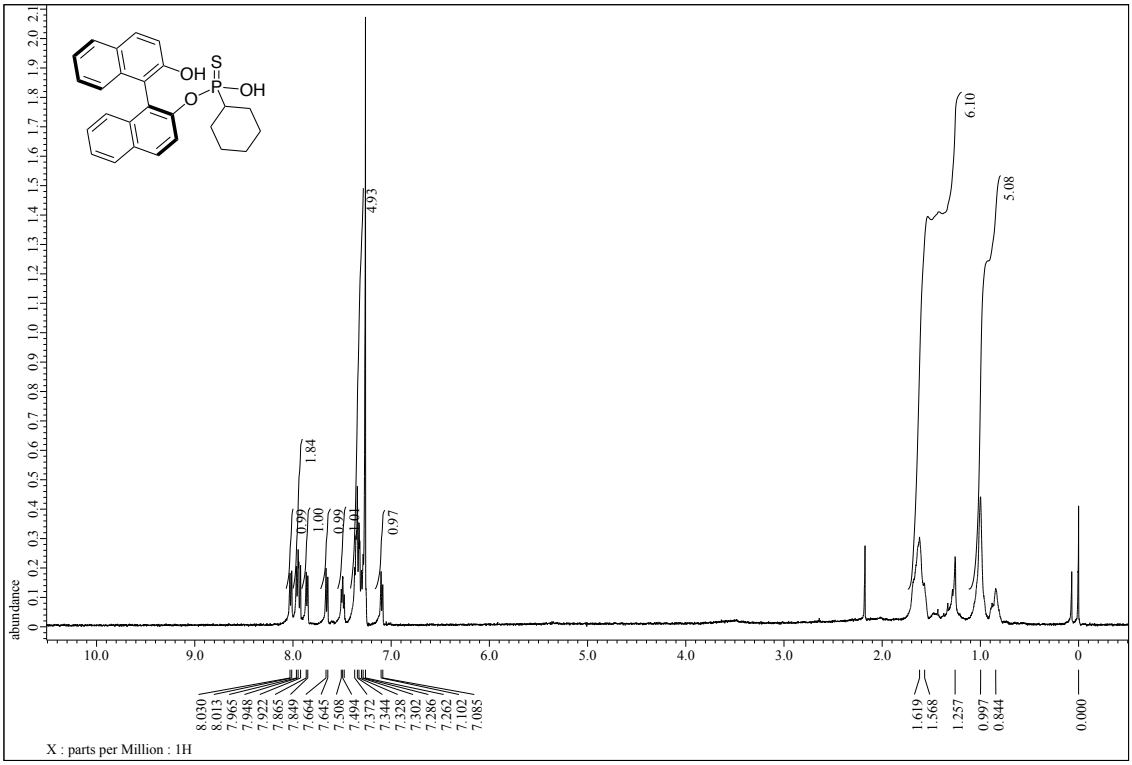
Chemical Formula: $C_{22}H_{19}O_3PS$
Exact Mass: 394.0793
Molecular Weight: 394.4248

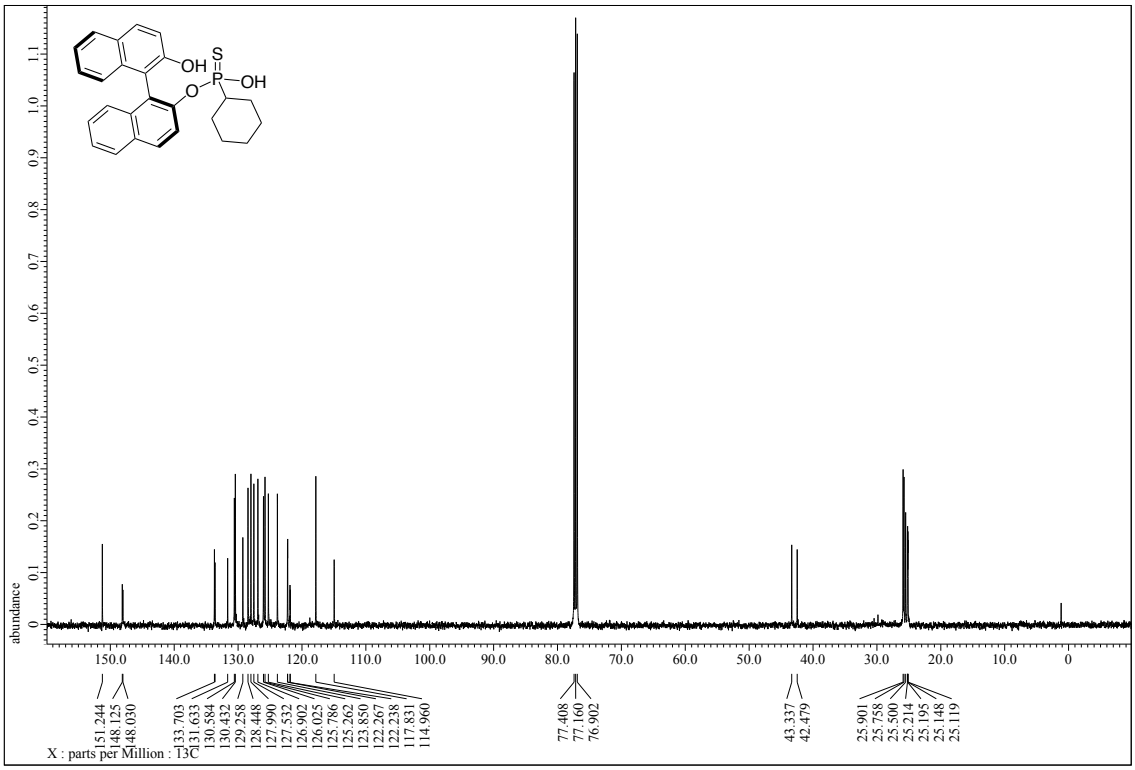
To a 20 mL Schlenk tube were added (S_{ax})-4-Methylbinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine-4-sulfide (189 mg, 0.50 mmol), methanol (20 μL, 0.5 mmol), and THF (0.5 mL). The reaction mixture was added to NHMDS (1.0 M in THF, 0.50 mL, 0.50 mmol), and the resulting solution was stirred at rt for 30 min. After that, the mixture was added to sat. NH_4Cl aq. and it was extracted with Et_2O (3 mL × 3). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by column chromatography on silica gel (EtOAc:hexane = 1:20, Rf = 0.15) gave KK970 (124 mg, 63%, >95:5 dr) as a colorless solid.

mp: 75-80 °C; IR (KBr): 3406, 3057, 2946, 1506, 1211, 1045, 985, 897, 813 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.66 (d, J = 15.7 Hz, 3H), 3.18 (d, J = 14.4 Hz, 3H), 5.24-5.39 (br, 1H), 7.11 (d, J = 8.1 Hz, 1H), 7.26-7.38 (m, 5H), 7.44-7.52 (m, 2H), 7.85-7.87 (m, 1H), 7.92 (d, J = 9.0 Hz, 1H), 7.96 (d, J = 8.1 Hz, 1H), 8.05 (d, J = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 22.5 (d, $^1J_{C\text{-}P}$ = 115.6 Hz), 52.0 (d, $^2J_{C\text{-}P}$ = 7.5 Hz), 114.9, 118.5, 121.8, 122.7, 123.8, 125.0, 125.9, 126.2, 127.0, 128.1, 128.4, 129.1, 130.5, 130.8, 131.8, 133.7, 133.8, 148.1, 148.2, 151.7; ^{31}P NMR ($CDCl_3$): δ 97.8 (s); MS (EI) m/z 394 (M^+); HRMS Calcd for $C_{22}H_{19}O_3PS$: 394.0793, Found: 394.0804.

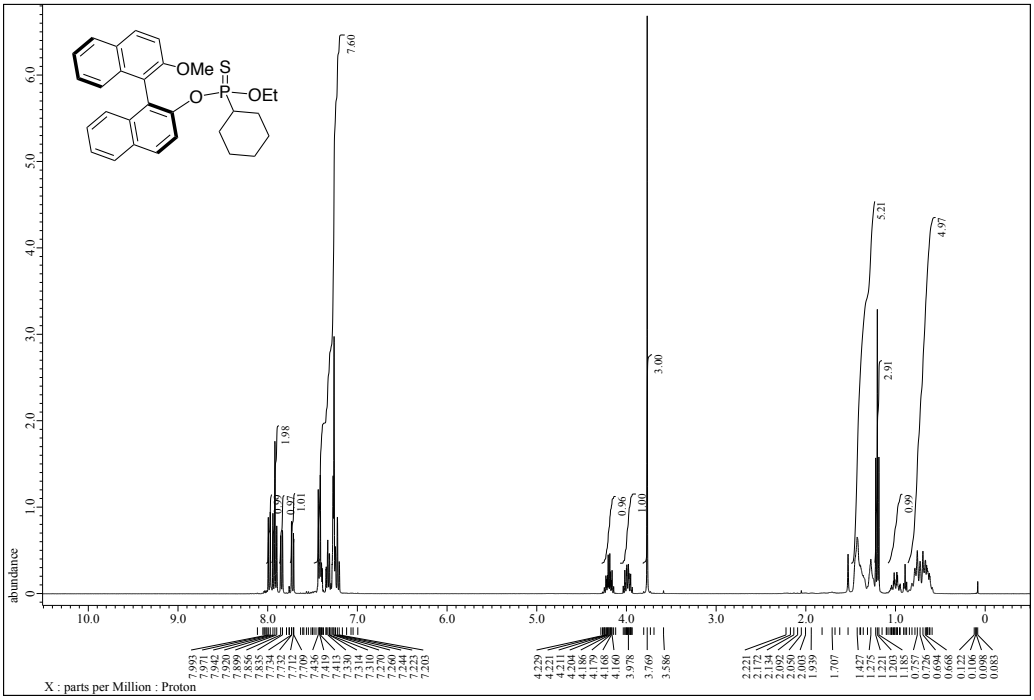
NMR Spectra

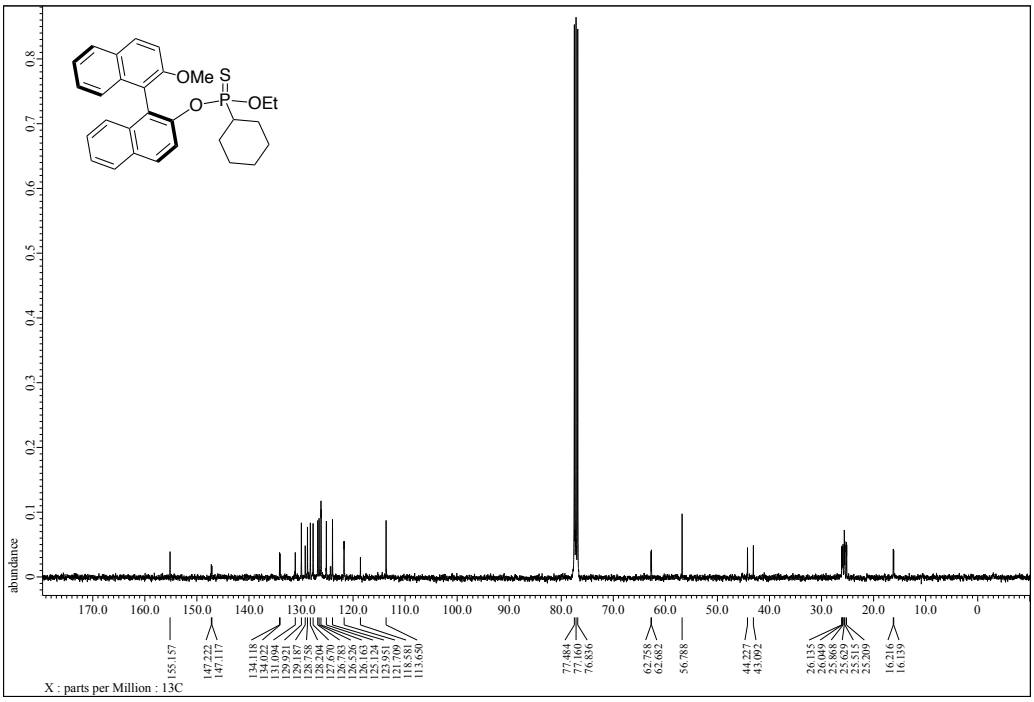
(S_{ax})-*O*-(2'-Hydroxy-[1,1'-binaphthalen]-2-yl) *O*-hydrogen-cyclohexylphosphonothioate (KK243)



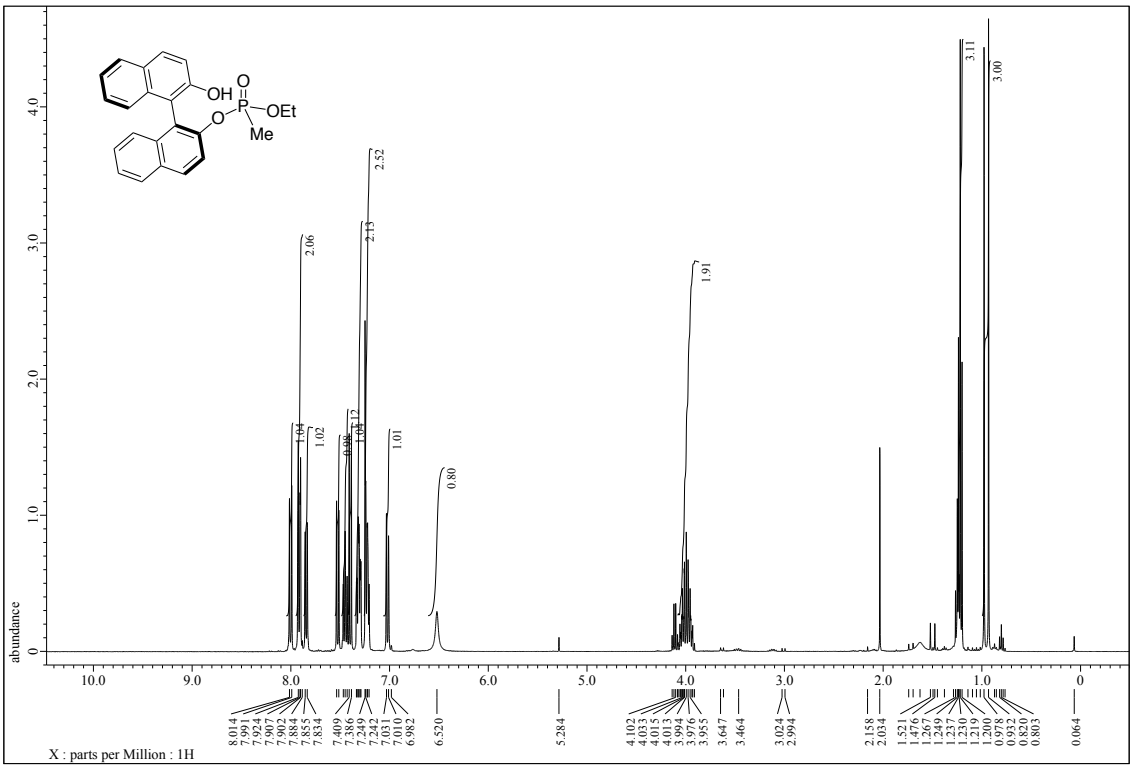


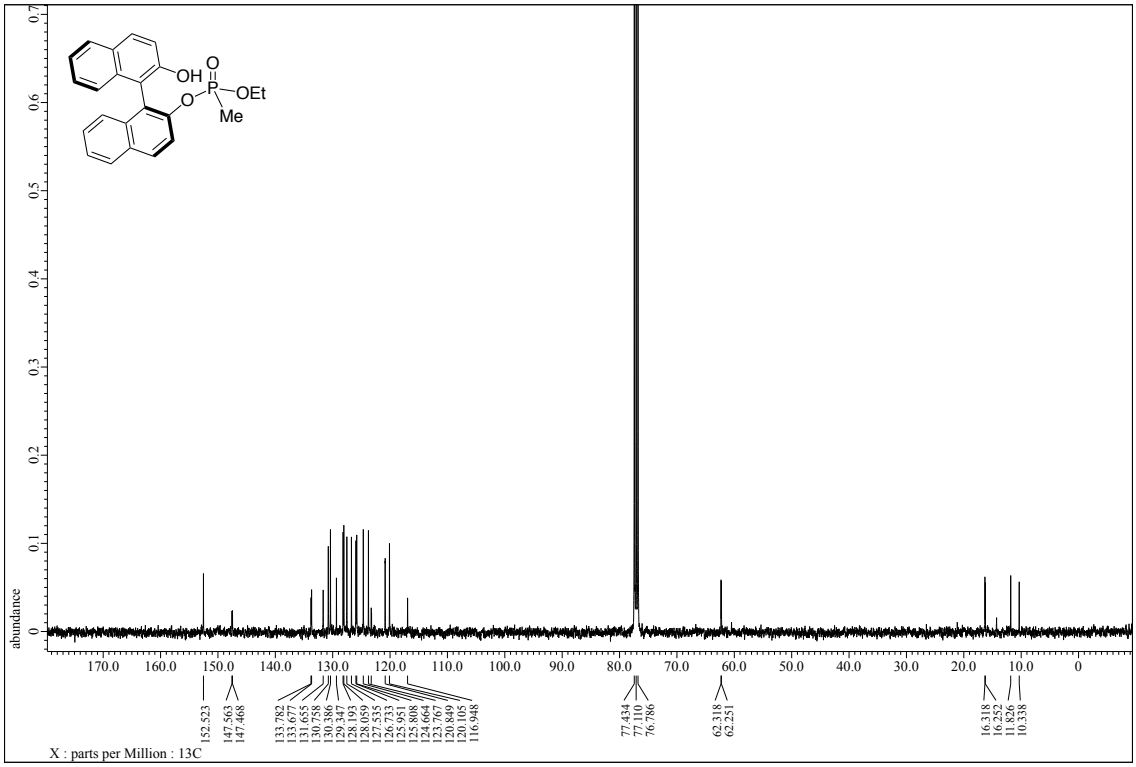
(S_{ax})-*O*-Ethyl *O*-(2'-methoxy-[1,1'-binaphthalen]-2-yl) cyclohexylphosphonothioate (KK255)



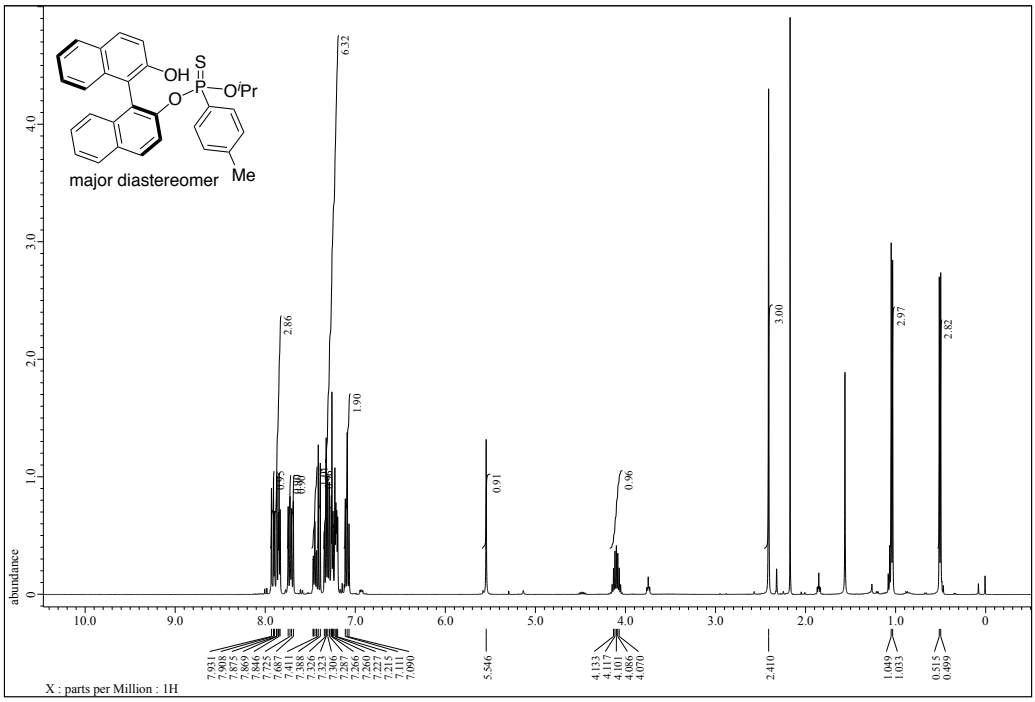


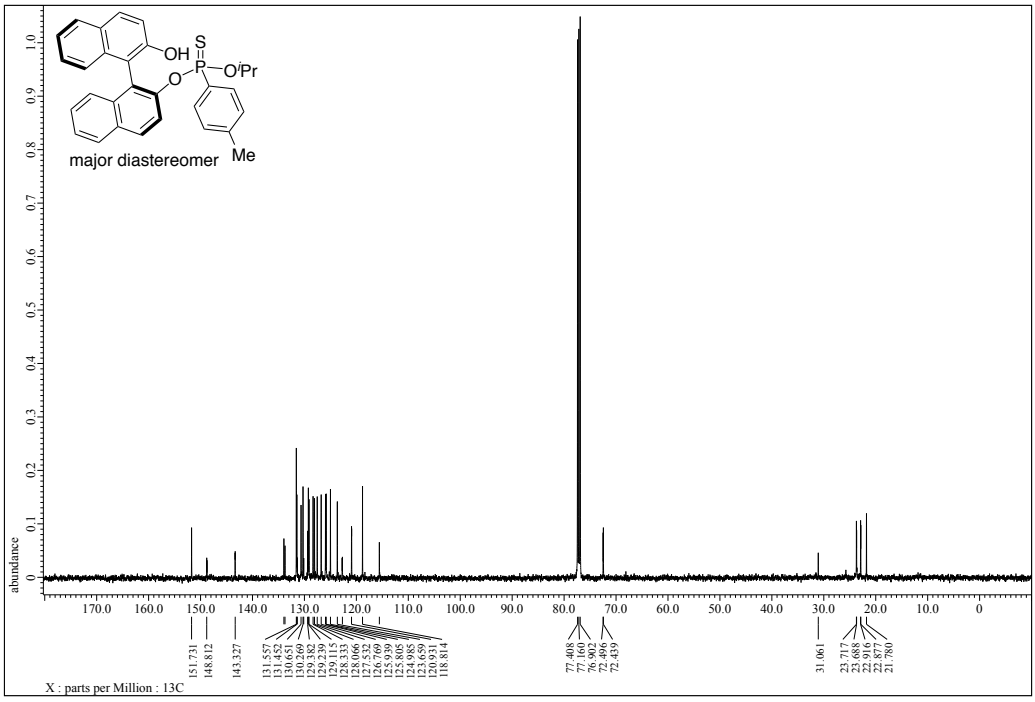
(S_{ax})-*O*-Ethyl-(2'-hydroxy-[1,1'-binaphthalen]-2-yl) methylphosphonate (KK304)



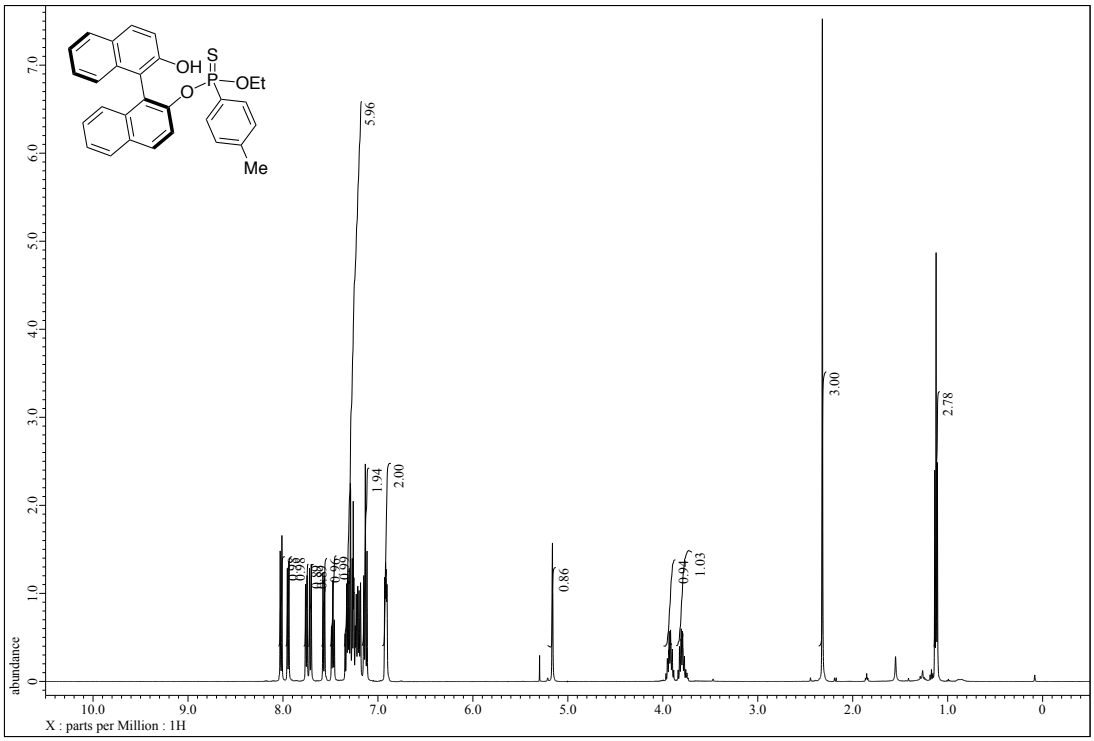


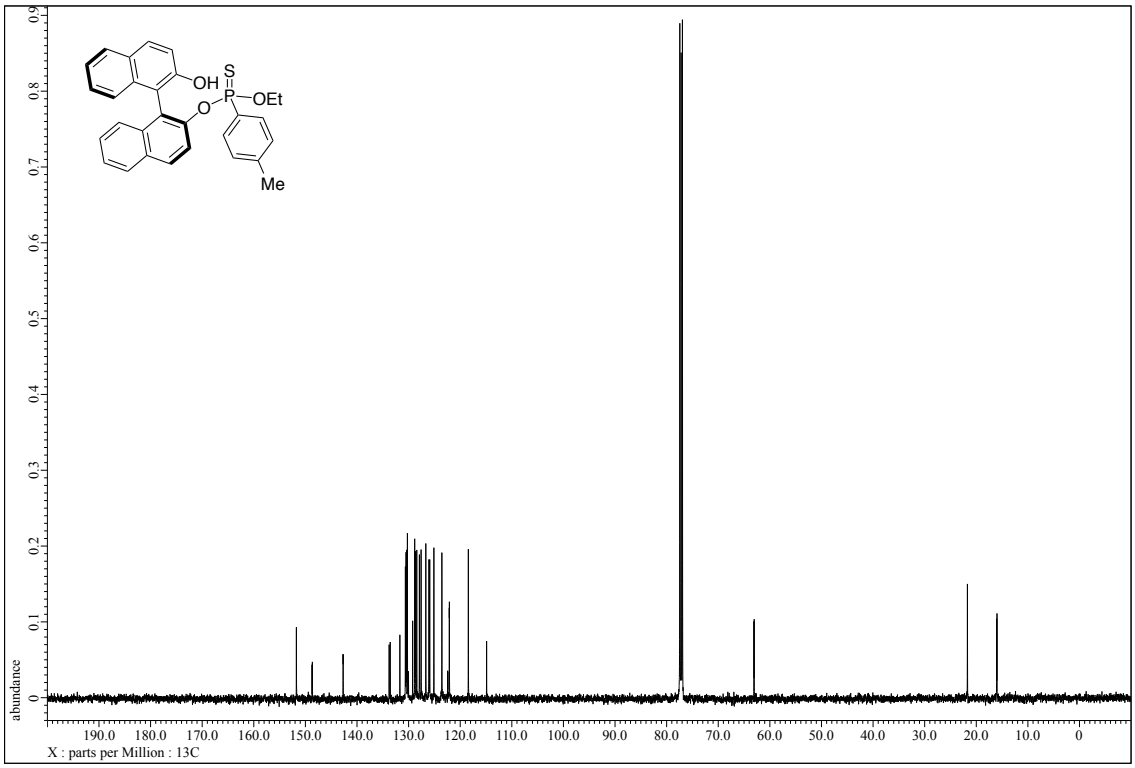
(S_{ax})-*O*-(2'-Hydroxy-[1,1'-binaphthalen]-2-yl) *O*-isopropyl *p*-tolylphosphonothioate (KK379)



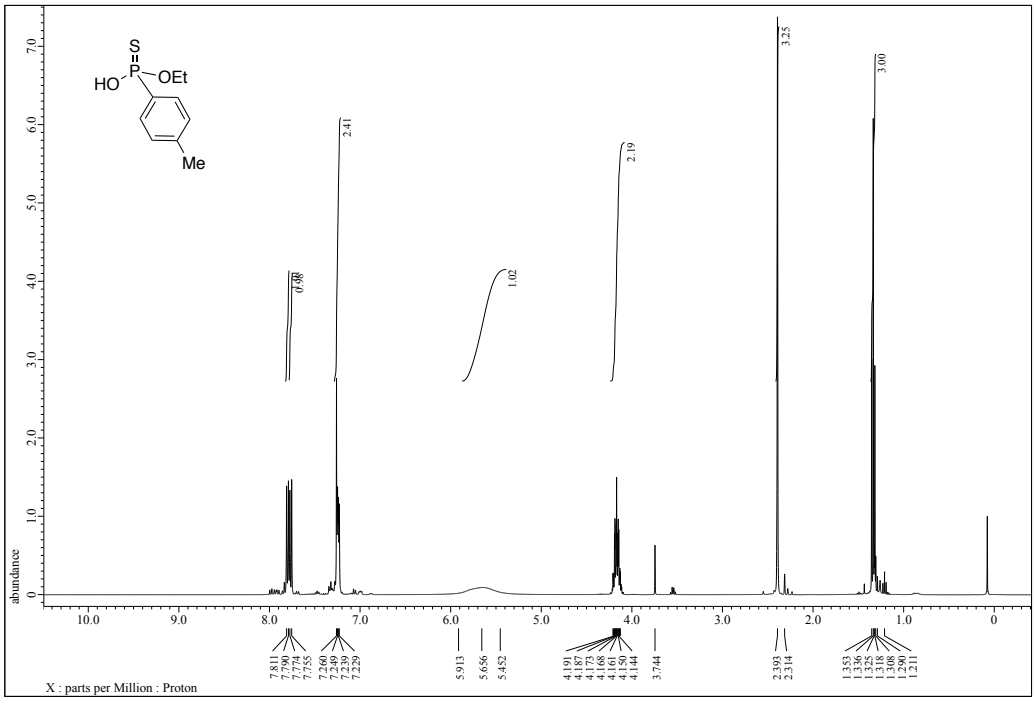


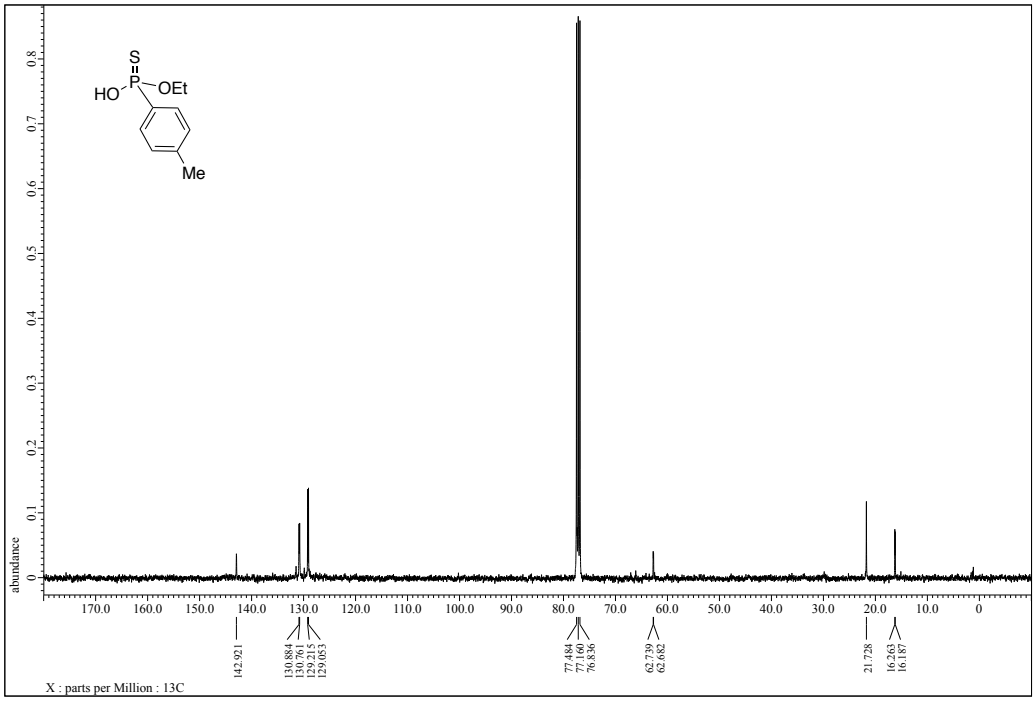
(S_{ax})-*O*-Ethyl-(2'-hydroxy-[1,1'-binaphthalen]-2-yl)-(*p*-tolyl)phosphonothioate (KK387)



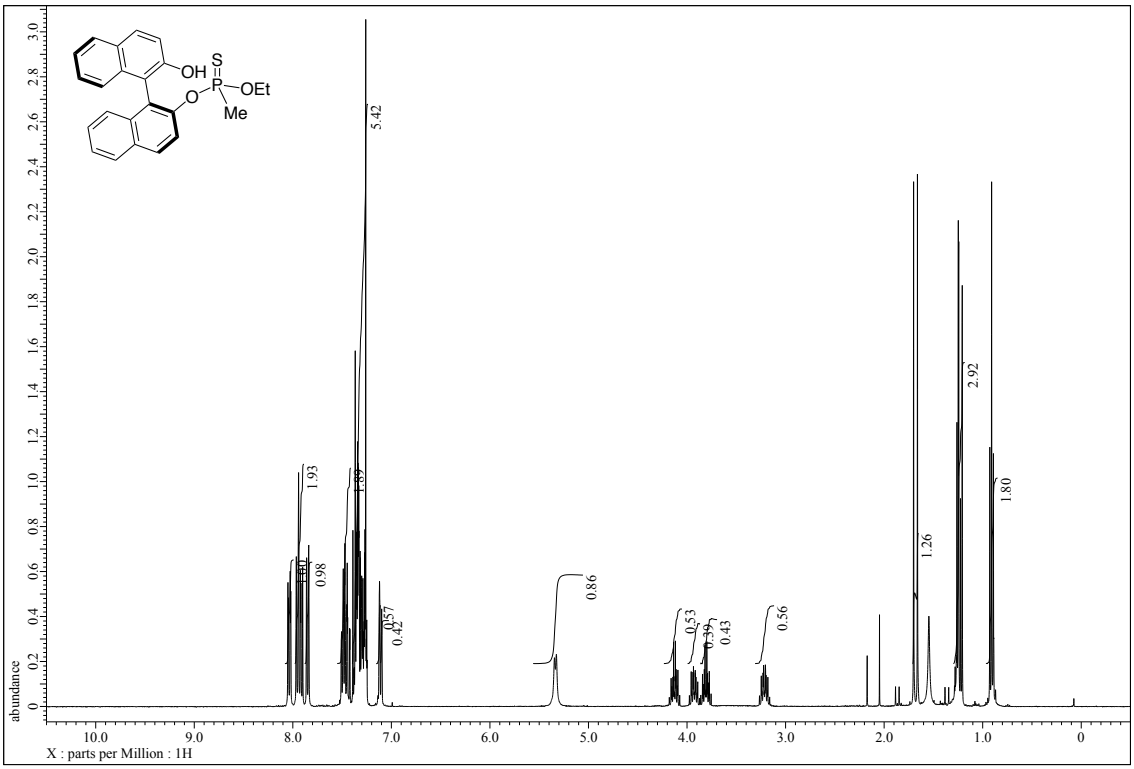


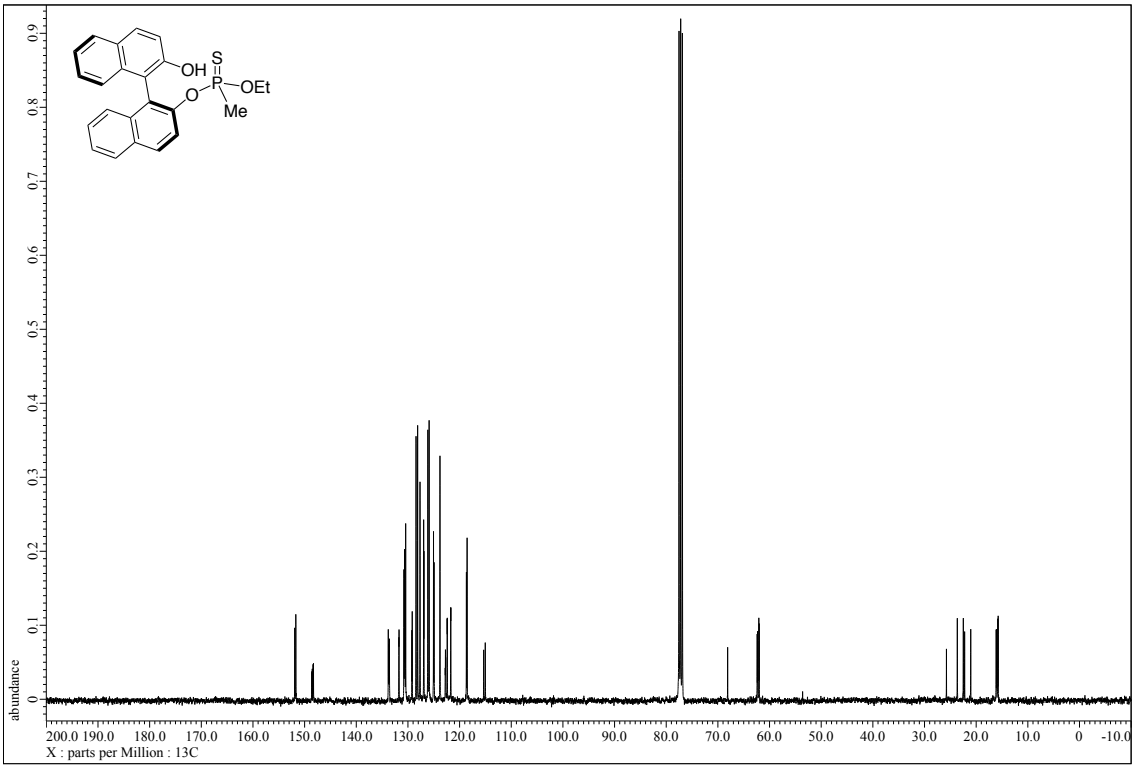
O-Ethyl *O*-hydrogen *p*-tolylphosphonothioate (KK391)



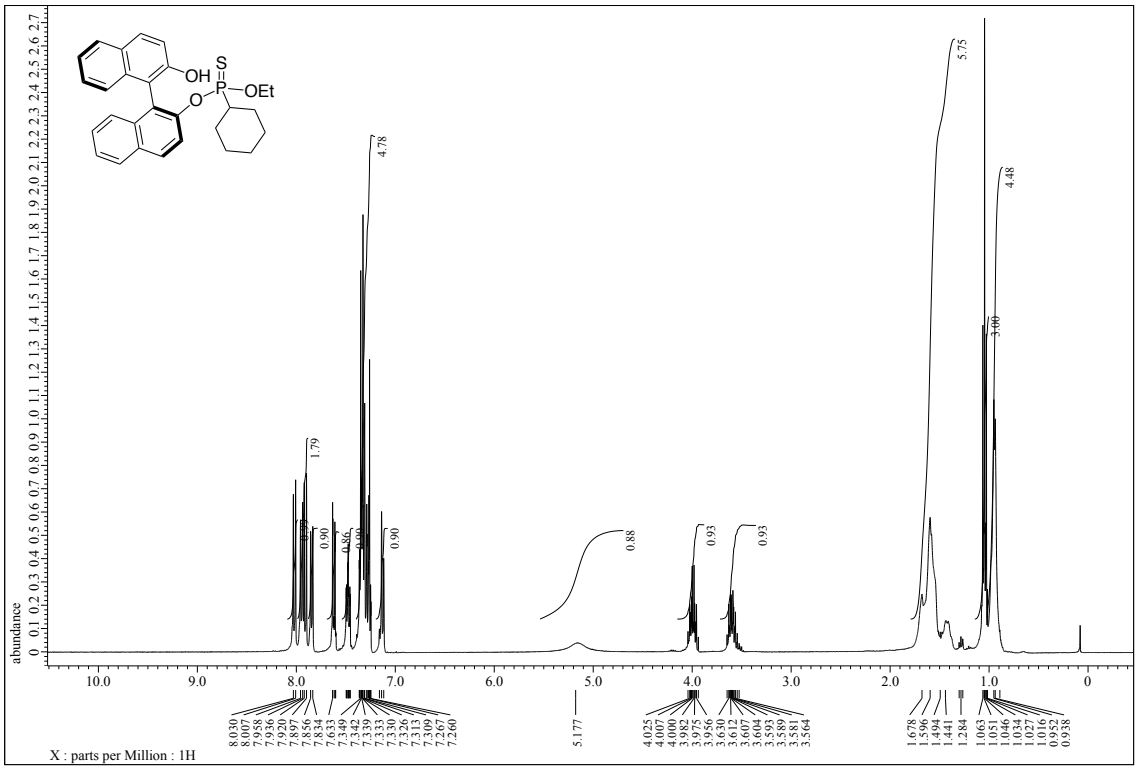


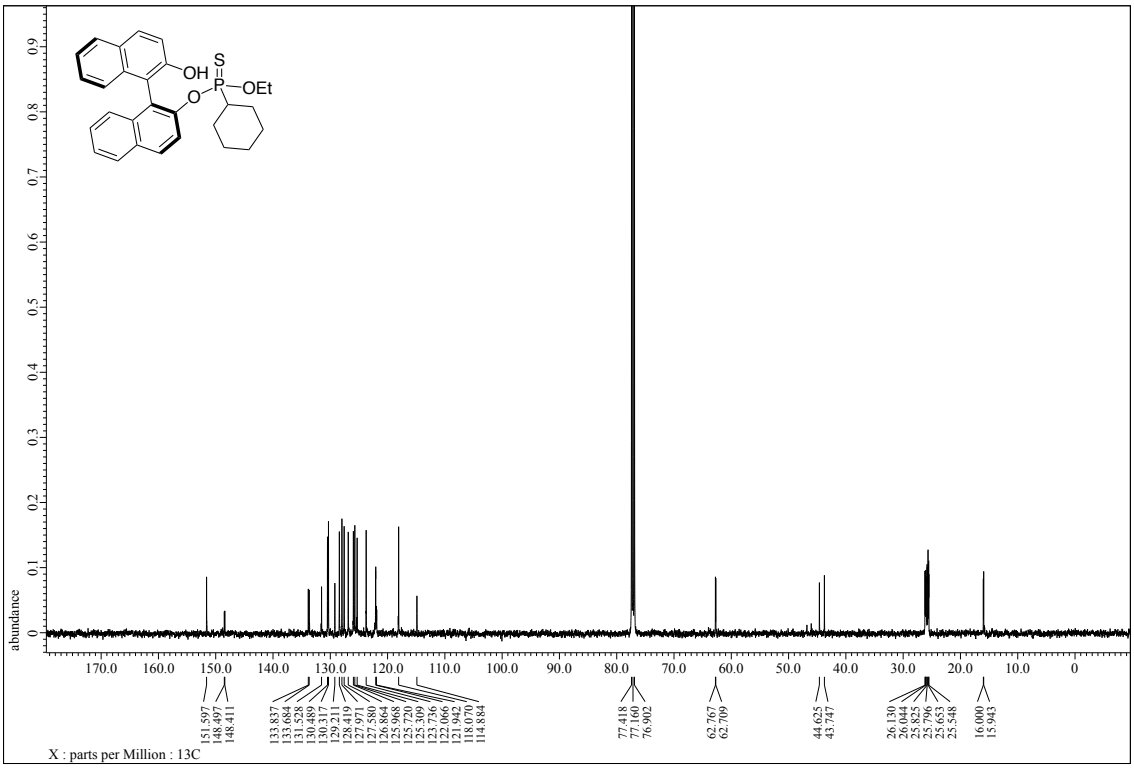
(S_{ax})-*O*-Ethyl-(2'-hydroxy-[1,1'-binaphthalen]-2-yl)-methylphosphonothioate (KK410)



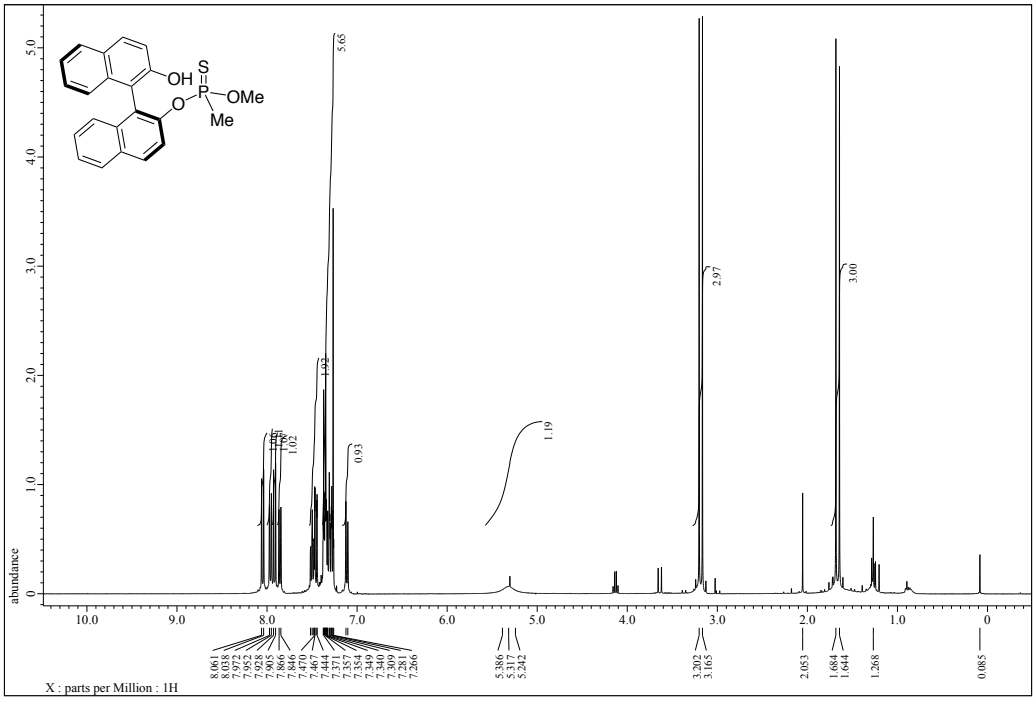


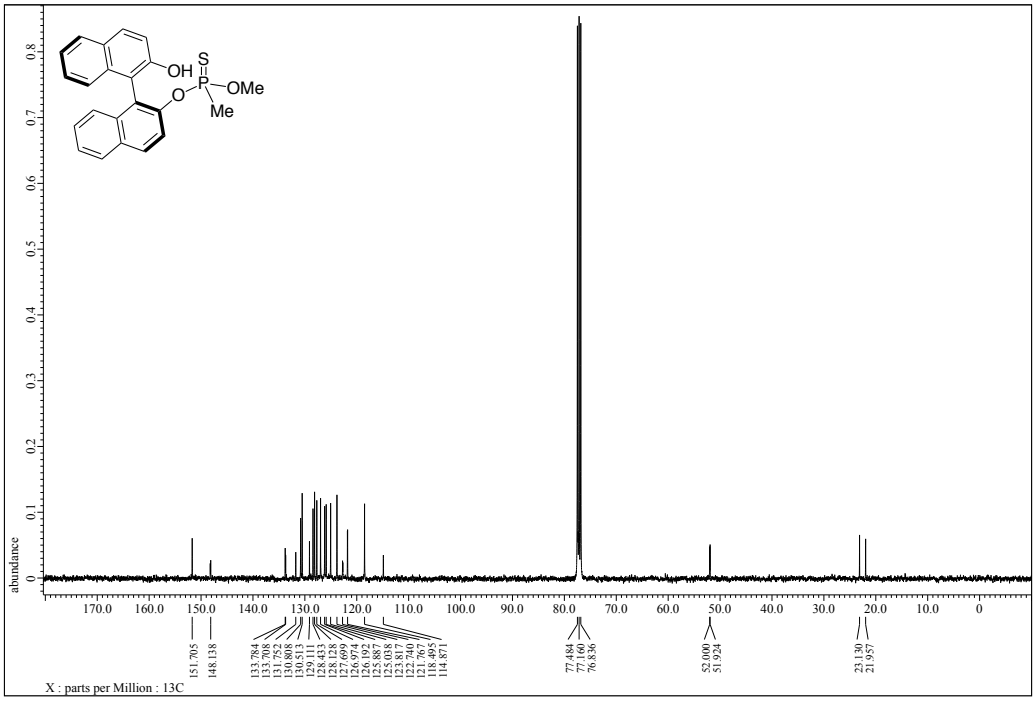
(S_{ax})-*O*-Ethyl-(2'-hydroxy-[1,1'-binaphthalen]-2-yl)-cyclohexylphosphonothioate (KK421)





(S_{ax})-*O*-(2'-Hydroxy-[1,1'-binaphthalen]-2-yl) *O*-methyl *p*-methylphosphonothioate (KK970)





Supplementary methods

Superoxide anion scavenging activity *in vitro*. The superoxide anions were measured using a SOD Assay Kit -WST according to the manufacturer's recommended protocol (Dojindo Laboratories, Cat# S311).

Supplementary results

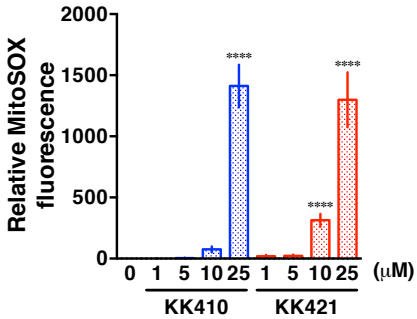


Fig. S1. Effects of concentration of KK410 and KK421 on intracellular superoxide anion production. HT22 cells were incubated with indicated concentrations of KK compounds for 8 h, and the generation of superoxide anion was determined as described in the "Materials and Methods" using the MitoSOX reagent (means ± SD; n=10; $^{****}p < 0.0001$ compared with control).

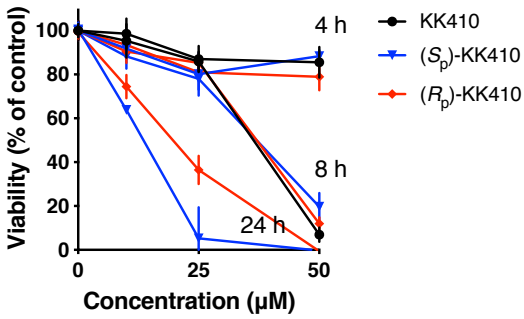


Fig. S2. Effects of chirality of KK410 on cell viability. HT22 cells were incubated with the indicated concentrations of test compounds for 4 h, 8 h, and 24 h and cell viability was determined by WST-8 assay. The data presented as the means ± SD of at least six independent cultures.

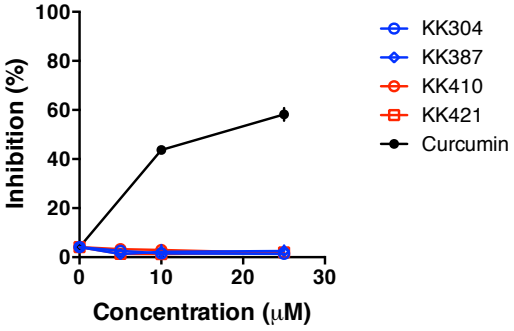
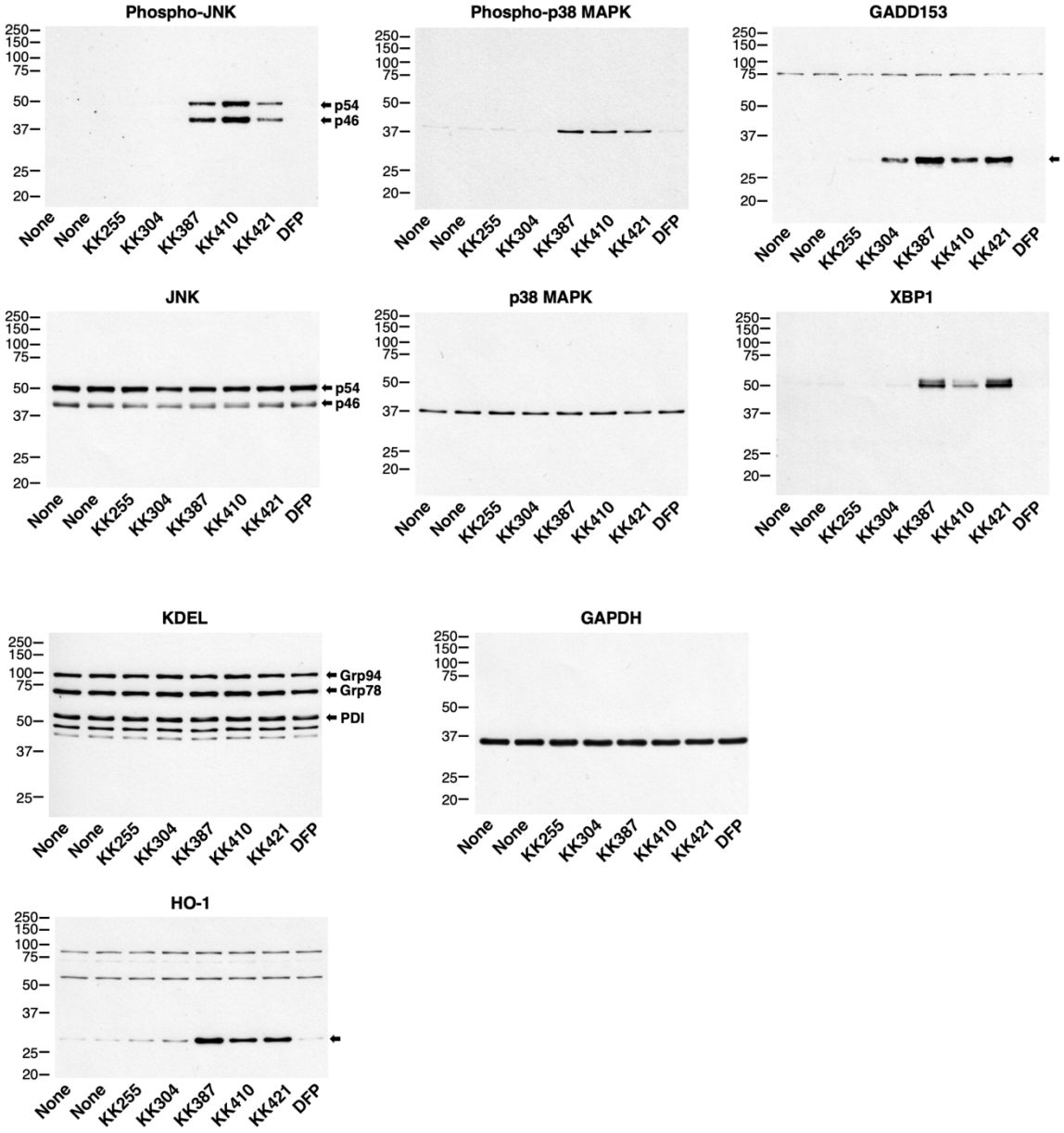


Fig. S3. Effects of KK304, KK387, KK410, and KK421 on superoxide anion scavenging activity *in vitro*. Superoxide anions were measured using a SOD Assay Kit WST according to the manufacturer's recommended protocol (Dojindo Laboratories, Cat# S311). The reduction of WST-1 to WST-1 formazan by superoxide anion was measured spectrophotometrically at 450 nm. Curcumin was used as a positive control of superoxide scavenger. The data are presented as the means ± SD for a representative experiment performed in triplicate. The experiments were repeated independently at least twice with comparable results.

Original uncropped blot images for Fig. 3A.