Synthesis of chiral organophosphorous ligands based on transformations of methyl 3,4-*O*-isopropylidene-L-threonate

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Chiral organophosphorous compounds which are of interest as ligands for metallocomplex catalysts for enantioselective transformations were synthesized from methyl 3,4-*O*-isopropylidene-L-threonate.

Key words: methyl 3,4-*O*-isopropylidene-L-threonate, ligands; enantioselectivity.

It is known that the efficiency of metallocomplex catalysts for enantioselective reactions depends to a considerable extent on the nature of the chiral ligands, among which organophosphorous compounds are the most important.[1,2] Methods of synthesis of these compounds have been developed using transformations of carbohydrates,[3] esters of L- and D-tartaric acids,[4] amino acids,[5,6] monoterpenes,[7] and binaphthyl derivatives.[8]

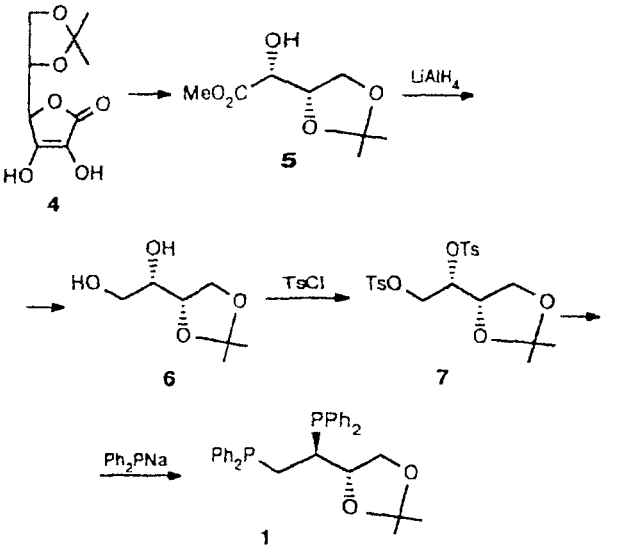
In a contituation of the studies in this area, we synthesized optically active bisphosphine (**1**) and bisphosphinites (**2** and **3**), which are structurally similar to the bidentate ligand DIOP.[4] The product of oxidative cleavage of 5,6-*O*-isopropylidene-L-ascorbic acid (**4**), methyl 3,4-*O*-isopropylidene-L-threonate (**5**), which has been described earlier, was used as the starting chiral compound.[9]

Methyl ester **5** was reduced with $LiAlH_4$ to give diol (**6**), whose structure was confirmed by its ^1H NMR spectrum. Tosylation of compound **6** gave ditosylate (**7**) in a 62% yield. The target bis(diphenylphosphino)isopropylidenedioxybutane **1** was obtained by the reaction of compound **7** with sodium diphenylphosphinide[4] (Scheme 1). The signals of the carbons linked to tosyloxy groups observed in the ^{13}C NMR spectrum of ditosylate **7** (δ 67.20 and 78.57), undergo, in the case of bisphosphine **1**, typical upfield shifts (C(4) and C(3), (δ 32.65 and 33.60, respectively).

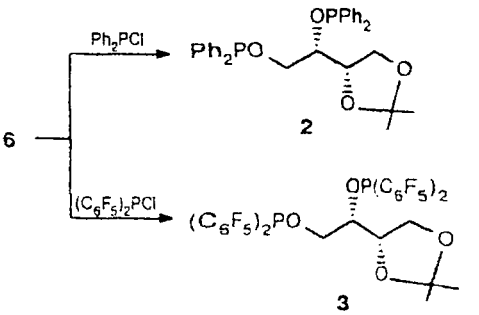
Optically active bisphosphinites **2** and **3** were synthesized from diol **6** and either Ph_2PCl or $(C_6F_5)_2PCl$, respectively (Scheme 2).

Complexes (**9**—**11**) were prepared by treating of compounds **1**—**3** with di-μ-chlorobis(1,5-cyclooctadiene)dirhodium (**8**) in the presence of $NaClO_4$. We performed a preliminary estimation of their catalytic activity using hydrogenation of itaconic acid (**12**) and its methyl ester as an example. It turned out that the hydrogenation of compound **12** for 2.5 h, catalyzed by either complex **9** or **10**, resulted in optically inactive 2-methylsuccinic acid, which was isolated as its dimethyl ester (**13**), in 62 and 27% yields, respectively (Scheme 3). An increase in the reaction time (to 24 h) does not substantially affect the yield of acid **13**, but, at the same time,

Scheme 1



Scheme 2



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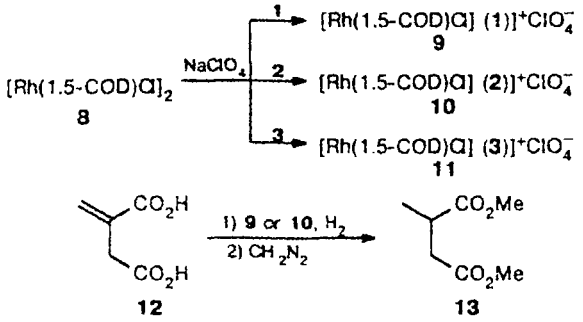
leads to the accumulation of unidentified polar products. These products seem to be formed as a result of catalytic di- and trimerization of itaconic acid. A mixture of similar products was obtained in the hydrogenation of compound **12** in the presence of complex **11**.

Scheme 3



All three complexes were inactive in the hydrogenation of dimethyl itaconate.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200 instrument (operating at 200.13 and 50.32 MHz, respectively) in $CDCl_3$. Chemical shifts (^{1}H) are referenced to Me_4Si as the internal standard. The ^{19}F NMR spectrum was recorded on a Bruker WP-200 SY (188.28 MHz) in CCl_4 and C_6F_6 was used as the internal standard. Optical rotation was measured on Perkin—Elmer 241C and Polamat A polarimeters. GLC analysis of the products of hydrogenation (in the form of their methyl esters) was carried out on a Shimadzu-9A chromatograph using a glass capillary column (25 m×0.2 mm) and liquid phase PEG-20M. The course of the reaction was monitored by TLC on Silufol plates. All operations with complexes **8** and **9** were conducted under dry argon, and dry solvents were used.

1,2-*O*-Isopropylidene-L-threitol (6). A solution of compound **5** (5 g, 26 mmol) in 20 mL of dry Et_2O was added dropwise to a stirred suspension of $LiAlH_4$ (1.4 g, 36 mmol) in 300 mL of dry Et_2O. The reaction mixture was heated under reflux for 4 h and chilled to 20 °C. Ethyl acetate (30 mL), water (5 mL), and 3 mL of a 4 *M* aqueous NaOH solution were then added to the resulting mixture. The precipitate that formed was filtered off, the organic layer was separated, and the aqueous layer was extracted with ether (3×50 mL). The organic layer and the combined extracts were dried with Na_2SO_4, concentrated, and the residue was chromatographed (SiO_2, ethyl acetate—hexane, 4 : 1). Compound **6** (2.4 g, 75%) was obtained, $[\alpha]_D^{20}$ +3.5° (*c* 4.0, $CHCl_3$). ^{1}H NMR, δ: 1.26 and 1.36, (both s, 6 H, Me_2C); 2.63 (br s, 1 H, OH); 2.85 (br s, 1 H, OH); 3.59 (m, 3 H, H(3), H(4a), H(4b)); 3.83 (dd, 1 H, H(1a), J_{gem} = 8.5 Hz, $J_{1a,2}$ = 6.2 Hz); 3.99 (t, 1 H, H(1b), J_{gem} = $J_{4b,2}$ = 8.5 Hz); 4.13 (m, 1 H, H(2)).

3,4-*O*-Isopropylidene-1,2-di-*O*-tosyl-L-threitol (7). Freshly crystallized TsCl (0.8 g, 4.9 mmol) was added to a cooled (0 °C) solution of compound **6** (0.3 g, 1.5 mmol) in 2 mL of freshly distilled pyridine and stirred at 0 °C for 48 h. The reaction mixture was then diluted with 10 mL of ethyl acetate, the precipitate was filtered off, and the filtrate was washed with water, dried with Na_2SO_4, and concentrated. The residue was chromatographed (SiO_2, ethyl acetate—hexane, 1 : 1). Ditosylate **7** (0.35 g, 62%) was obtained, m.p. 70—72 °C (ethyl acetate—hexane), $[\alpha]_D^{20}$ +12.1° (*c* 0.8, $CHCl_3$). ^{1}H NMR, δ: 1.22 and 1.30 (both s, 6 H, Me_2C); 2.43 (s, 6 H, MeAr); 3.75 (dd, 1 H, H(4a), J_{gem} = 10.0 Hz, $J_{4a,3}$ = 6.1 Hz); 3.96 (dd, 1 H, H(4b), J_{gem} = 10.0 Hz, $J_{4b,3}$ = 5.9 Hz); 4.05 (dd, 1 H, H(1a), J_{gem} = 11.5 Hz, $J_{1a,2}$ = 6.5 Hz); 4.20 (dd, 1 H, H(1b), J_{gem} = 11.0 Hz, $J_{1b,2}$ = 5.6 Hz); 4.26 and 4.61 (both m, 2 H, H(2), H(3)); 7.29—7.74 (m, 8 H, Ar). ^{13}C NMR, δ: 21.80 (CH_3Ar), 24.30, 26.30 ($(CH_3)_2$C), 63.40 (C(4)), 67.20 (C(1)), 74.30 (C(3)), 78.57 (C(2)), 109.79 (Me_2C), 128.08, 129.90, 132.03, 132.05, 145.47, 145.73 (Ar).

(2*S*,3*S*)-3,4-Bis(diphenylphosphino)-1,2-*O*-isopropylidenebutane-1,2-diol (1). Metallic sodium (0.3 g, 16 mg-at.) was added to a solution of PPh_2Cl (0.9 g, 4 mmol) in 6 mL of dry 1,4-dioxane under dry argon. The reaction mixture was heated to 120 °C, stirred at this temperature for 6 h until a bright yellow color persisted, and chilled to 0 °C. A solution of ditosylate **7** (97 g, 2.1 mmol) in 4 mL of dry THF was then added, the resulting mixture was stirred for 2 h at 20 °C and passed through a column packed with SiO_2 under argon using dry benzene as the eluant. The eluate was concentrated and the residue was crystallized to give bisphosphine **1** (0.4 g, 42%), m.p. 92—94 °C (EtOH), $[\alpha]_D^{20}$+20.3° (*c* 0.07, $CHCl_3$). ^{13}C NMR, δ: 24.84, 26.64 ($(\underline{C}H_3)_2$C), 32.65 (C(4)), 33.60 (C(3)), 67.26 (C(1)), 76.52 (C(2)), 109.33 ($Me_2\underline{C}$), 128.45, 128.62, 128.79, 130.80, 130.91, 131.11, 131.25, 131.78, 131.88, 132.68, 133.45, 134.00 (Ph). Found (%): C, 72.60; H, 6.30; P, 11.82. $C_{31}H_{32}O_2P_2$. Calculated (%): C, 72.69; H, 6.92; P, 12.44.

1,2-Di-*O*-diphenylphosphino-3,4-*O*-isopropylidene-L-threitol (2). PPh_2Cl (0.64 g, 2.9 mmol) and freshly distilled pyridine (0.3 g, 3.7 mmol) were added to a solution of compound **6** (0.23 g, 1.5 mmol) in 5 mL of dry THF. The reaction mixture was stirred at 20 °C for 3 h, diluted with 5 mL of ethyl acetate, washed with water; the organic layer was dried with Na_2SO_4 and concentrated. The resulting residue was chromatographed (SiO_2, ethyl acetate—hexane, 1 : 1) to give compound **2** (1.0 g, 78%), $[\alpha]_D^{20}$ +2.8° (*c* 1.8, $CHCl_3$). ^{13}C NMR, δ: 24.99, 26.09 ($(\underline{C}H_3)_2$C), 63.78, 65.26 (C(4), C(1)), 74.63, 74.82 (C(2), C(3)), 109.79 ($Me_2\underline{C}$), 128.28, 128.40, 128.59, 128.63, 128.77, 129.63, 129.88, 130.44, 131.34, 131.54, 131.69, 131.76, 131.89, 132.21, 132.31, 132.43, 132.69 (Ph). Found (%): C, 70.24; H, 6.10, P, 11.56: $C_{31}H_{32}O_4P_2$. Calculated (%): C, 70.19; H, 6.03; P, 11.68.

1,2-Di-*O*-bis(pentafluorophenyl)phosphino-3,4-*O*-isopropylidene-L-threitol (3). Under the conditions of the synthesis of compound **2**, compound **3** (1.1 g, 80%) was obtained from compound **6** (0.23 g, 1.5 mmol) and $(C_6F_5)_2PCl$ (1.16 g, 2.9 mmol), $[\alpha]_D^{20}$ +0.43° (*c* 4.0, $CHCl_3$). ^{19}F NMR, δ: 2.68 (m, 8 *o*-F, C_3F_5); 17.17 (m, 4 *p*-F, C_6F_5); 32.16 (m, 8 *m*-F, C_6F_5). Found (%): C, 41.79; H, 1.24; F, 42.50; P, 6.78: $C_{31}H_{12}F_{20}O_4P_2$. Calculated (%): C, 41.82; H, 1.36; F, 42.67; P, 6.69.

Complex 9. $NaClO_4$ (0.02 g, 0.16 mmol) was added to a suspension of complex **8** (0.04 g, 0.08 mmol) in 1 mL of acetone, and the resulting mixture was stirred at 20 °C for 15 min. A solution of bisphosphine **1** (0.12 g, 0.25 mmol) in 0.5 mL of acetone was then added dropwise and the reaction mixture was stirred at 20 °C for 0.5 h. The mixture was filtered, the precipitate was washed with 1 mL of acetone, and

the filtrate was concentrated. The residue was crystallized to give compound **9** (0.08 g, 64%) as yellow crystals, m.p. 158 °C (decomp., acetone—ether). Found (%): C, 57.02; H, 5.64; Cl, 4.12; P, 6.42; Rh, 11.93; $C_{39}H_{44}ClO_6P_2Rh$. Calculated (%): C, 57.89; H, 5.48; Cl, 4.38; P, 7.66; Rh, 12.71.

Complex 10. Under the conditions of the synthesis of compound **9**, complex **10** (0.3 g, 75%) was obtained from complex **8** (0.12 g, 0.25 mmol), $NaClO_4$ (0.06 g, 0.5 mmol), and bisphosphinite **2** (0.26 g, 0.5 mmol), light-yellow crystals, m.p. 182 °C (decomp., CH_2Cl_2). ^1H NMR, δ: 1.22 and 1.24 (both s, 6 H, Me_3C); 1.84—2.48 (m, 8 H, (1,5-COD)); 3.08 (m, 1 H, H(2)); 3.92—4.18 (m, 3 H, H(1a), H(1b), H(4a)); 4.27 (m, 4 H (1,5-COD); 4.45 (dd, 1 H, H(4b), J_{gem} = 11.7 Hz, $J_{4b,3}$ = 6.2 Hz); 4.71 (m, 1 H, H(3)); 7.32—7.93 (m, 20 H, Ph). Found (%): C, 55.32; H, 5.20; Rh, 12.42: $C_{39}H_{44}ClO_8P_2Rh$. Calculated (%): C, 55.69; H, 5.27; Rh, 12.23.

Complex 11. A solution of $NaClO_4$ (0.03 g, 0.28 mmol) in 1.5 mL of water and a solution of bisphosphinite **3** (0.25 g, 0.28 mmol) in 1 mL of CH_2Cl_2 were added to a solution of complex **8** (0.07 g, 0.14 mmol) in 1 mL of CH_2Cl_2. The reaction mixture was stirred at 20 °C for 5 h. The aqueous layer was separated, and the organic layer was washed with water (3×2 mL), dried with Na_2SO_4, and concentrated. The residue was crystallized to yield compound **11** (0.27 g, 80%) in the form of dark-red crystals, m.p. 92 °C (decomp., CH_2Cl_2). Found (%): C, 38.87; H, 1.78; Rh, 8.03: $C_{39}H_{24}ClF_{20}O_8P_2Rh$. Calculated (%): C, 39.01; H, 2.01; Rh, 8.57.

Hydrogenation of itaconic acid (12). A solution of acid **12** (0.5 g, 3.8 mmol) and freshly distilled Et_3N (0.01 mL, 0.076 mmol) were added to a solution of complex **9** (0.038 mmol) in 2 mL of dry THF in an atmosphere of hydrogen. The mixture was shaken for 2.5 h at 1 atm (20 °C), and then passed through a column with SiO_2 using Et_2O as the eluant. The eluate was concentrated, and the residue was treated with an ethereal solution of diazomethane. The solvent was distilled off, and the residue was chromatographed (SiO_2, hexane). Dimethyl (±)-2-succinate **13** (0.3 g, 62%) was obtained. When hydrogenation was conducted with complex **10**, the yield of compound **13** was 27%.

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