Synthesis of New Optically Active Bis- and Tris(phosphines)

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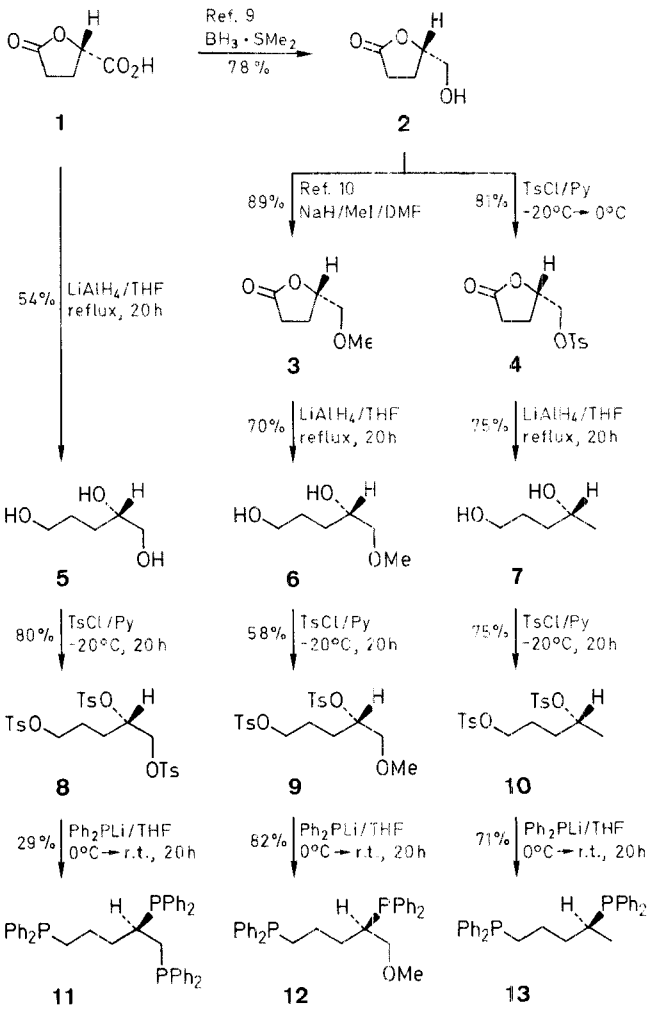
The synthesis of new optically active alkanediylbis- and alkanetriyltris(diphenylphosphines) is described. Easily accessible optically pure lactones and carboxylic acids are reduced to the alcohols, tosylated and reacted with lithium diphenylphosphide to give the corresponding phosphines.

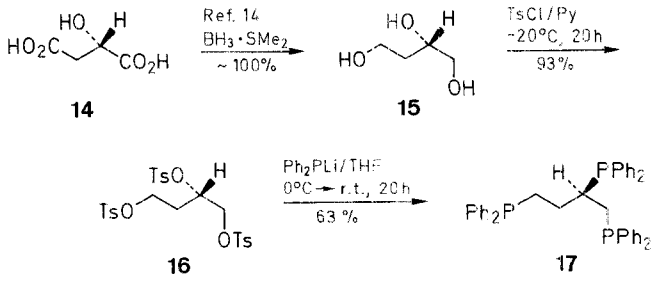
Optically active chelating phosphines are the most efficient and widely used ligands in enantioselective catalysis by transition-metal complexes.[1-3] In recent years interest has focussed on ligands containing further functional groups supposed to participate in the formation of the diastereoisomeric transition state and to increase the stereoselectivity.[4-7] We now report on the synthesis of some potentially tridentate ligands.

The starting material for the synthesis of phosphines **11–13** is (*S*)-(+)-5-oxotetrahydrofuran-2-carboxylic acid (**1**), prepared from L-glutamic acid.[8] The carboxylic acid **1** is reduced by borane–dimethyl sulfide to (*S*)-(+)-5-hydroxymethyl-2-oxotetrahydrofuran (**2**),[9] which is easily converted to the methyl ether **3**[10] or the tosyl derivative **4**[9] (Scheme **A**). The compounds **1**, **3**, and **4** are reduced to the alcohols **5–7**, respectively. In this reaction the tosyl group of **4** is eliminated by reductive cleavage[11] (Scheme **A**). The treatment of the alcohols **5–7** with *p*-toluenesulfonic acid in dry pyridine leads to the tosylates **8–10** (Scheme **A**). The crystalline phosphines **11–13** are obtained by substitution of the tosylate groups by diphenylphosphide (Scheme **A**), a reaction known to proceed with inversion of configuration at an asymmetric carbon atom.[12,13]



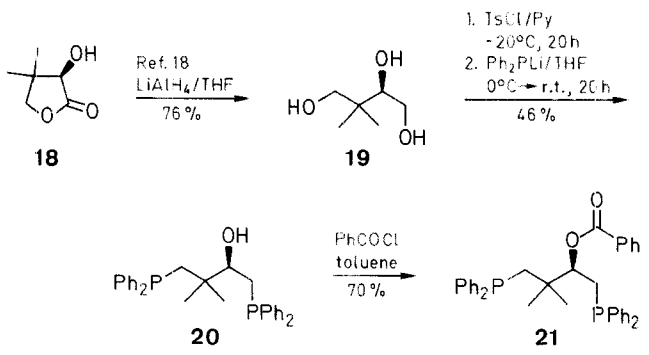
Scheme **A**

Reduction of L-malic acid **14** by means of borane–dimethyl sulfide affords the triol **15** in quantitative yield,[14] which is tosylated to give compound **16**. Phosphinylation of the tosylate groups in **16** results in the 1,2,4-tris(diphenylphosphine) **17** (Scheme **B**), the lower homologue of the 1,2,5-triphosphine **11**.



Scheme **B**

Unexpectedly, no tris(phosphine) is accessible from (*R*)-(−)-pantolactone **18**. Tosylation of the triol **19**[15] affords a crude, viscous oil. Without further purification, the oil is converted with lithium diphenylphosphide to the pure bis(phosphine) **20**. The hydroxy group in the backbone of compound **20** can easily be esterified with benzoyl chloride to give **21** (Scheme **C**).



Scheme C

The preparation of phosphines was carried out in an atmosphere of nitrogen. All organic solvents were dried according to standard procedures. Those used in the preparation of phosphines were distilled under nitrogen. Silica gel was rigorously dried *in vacuo* and kept under nitrogen.

(*S*)-(+)-5-Hydroxymethyl-2-oxotetrahydrofuran (2):
This compound is prepared from **1**[8] according to Ref. 9; yield: 78%; $[\alpha]_D^{20}$ + 31.6° (c = 3, EtOH) (Lit. 16 $[\alpha]_D^{26}$ + 31.3°).

(*S*)-(+)-5-Methoxymethyl-2-oxotetrahydrofuran (3):
This compound is prepared from **2** according to Ref. 10; yield: 89%; $[\alpha]_D^{20}$ + 26.6° (*c* = 1, $CHCl_3$) (Lit.[10] $[\alpha]_D^{20}$ + 27.9°).

(*S*)-(+)-5-Tosyloxymethyl-2-oxotetrahydrofuran (4):
Tosyl chloride (40.0 g, 0.21 mol) is added in small portions to a solution of **2** (12.7 g, 0.11 mol) in dry pyridine (80 mL) at − 20 °C. After 14 h the

Table 1. Alcohols **5–7** Prepared

Lactone	$LiAlH_4$ (mol)	Alcohol	Yield (%)	bp (°C)/mbar[a]	$[\alpha]_D$[b] (c, EtOH)	Molecular Formula or Lit. Data	^{1}H-NMR ($CDCl_3$/TMS)[c] δ, J (Hz)	^{13}C-NMR ($CDCl_3$/TMS)[d] δ	MS m/z (M^+)
1	0.26	**5**	54	150/0.01	−15.1° (4.8)	bp 115–136 °C[16] (0.013 mbar)	1.29–1.71 (m, 4H, CH_2); 2.81 (t, 1H, J = 1, OH); 3.33–3.63 (m, 6H, CH + OCH_2 + OH); 3.70 (d, 1H, J = 4, OH)	–	–
3	0.1	**6**	70	110/0.01	−9.0° (1.0)	$C_6H_{14}O_3$[e] (134.2)	1.43–1.74 (m, 4H, CH_2); 3.26–3.42 (m, 2H, OCH_2); 3.38 (s, 3H, OCH_3); 3.55–3.68 (m, 4H, OCH_2 + OH); 3.71–3.84 (m, 1H, OH)	28.77 (CH_2); 30.23 (CH_2); 58.95 (OCH_3); 62.24 (OCH_2); 69.99 (CH); 77.12 (OCH_2)	134
4	0.39	**7**	75	100/0.01	−9.5° (43.9)	$[\alpha]_D^{22}$ −11°[11] (c = 38, EtOH)	1.19 (d, 3H, J = 6, CH_3); 1.50–1.68 (m, 4H, CH_2); 3.59–3.68 (m, 2H, OCH_2); 3.78–3.85 (m, 1H, CH); 3.87–4.36 (m, 2H, OH)	23.25 (CH_3); 28.93 (CH_2); 35.93 (CH_2); 62.26 (OCH_2); 67.55 (CH)	104

[a] Kugelrohr distillation, bath temperature is given.
[b] Measured at room temperature with a Perkin-Elmer polarimeter 241.
[c] Recorded at 250 MHz on a Bruker 250 spectrometer.
[d] Recorded at 23 MHz on a Bruker WH 90 spectrometer.
[e] calc. C 53.70 H 10.52
found 53.56 10.37

Table 2. Tosylates **8–10** and **16** Prepared

Compound	Yield (%)	mp (°C)	$[\alpha]_D$[a] (c, solvent)	Molecular Formula[b]	^{1}H-NMR ($CDCl_3$/TMS)[c] δ, J (Hz)	^{13}C-NMR ($CDCl_3$/TMS)[d] δ	MS m/z (M^+)
8	80	oil	−6.4° (4.2, $CHCl_3$)	$C_{26}H_{30}O_9S_3$ (582.7)	1.53–1.71 (m, 4H, CH_2); 2.46 (s, 9H, CH_3); 3.89–4.01 (m, 4H, OCH_2); 4.55–4.60 (m, 1H, CH); 7.31–7.81 (m, 12H_{arom})	21.18 (CH_3); 21.57 (2C, CH_3); 24.06 (CH_2); 27.06 (CH_2); 69.42 (2C, OCH_2); 77.84 (OCH); 127.69–145.32 (m, 18C_{arom})	582
9	58	oil	+7,6° (1.6, EtOH)	$C_{20}H_{26}O_7S_2$ (442.5)	1.56–1.73 (m, 4H, CH_2); 2.45 (s, 6H, CH_3); 3.18 (s, 3H, OCH_3); 3.26–3.41 (m, 2H, OCH_2); 3.96–3.98 (m, 2H, OCH_2); 4.55–4.63 (m, 1H, CH); 7.31–7.78 (m, 8H_{arom})	21.57 (2C, CH_3); 24.37 (CH_2); 27.48 (CH_2); 59.00 (OCH_3); 69.76 (OCH_2); 73.10 (OCH_2); 80.41 (OCH); 127.72 (2C_{arom}); 127.77 (2C_{arom}); 129.71 (2C_{arom}); 129.92 (2C_{arom}); C_{arom}); 132.93 (C_{arom}); 134.07 (C_{arom}); 144.77 (C_{arom}); 144.88 (C_{arom})	442
10	75	49–51	+5.5° (1.3, $CHCl_3$)	$C_{19}H_{34}O_6S_2$ (412.5)	1.18 (d, 3H, J = 7, CH_3); 1.57–1.63 (m, 4H, CH_2); 2.44 (s, 3H, CH_3); 2.45 (s, 3H, CH_3); 3.92–3.97 (m, 2H, OCH_2); 4.53–4.60 (m, 1H, CH); 7.31–7.78 (m, 8H_{arom})	20.68 (CH_3); 21.54 (2C, CH_3); 24.39 (CH_2); 32.32 (CH_2); 69.73 (OCH_2); 79.22 (OCH); 127.56 (2C_{arom}); 127.74 (2C_{arom}); 129.92 (4C_{arom}); 132.95 (C_{arom}); 134.22 (C_{arom}); 144.75 (C_{arom}); 144.90 (C_{arom})	412
16	93	102–103	−28.7° (1.0, $CHCl_3$)	$C_{25}H_{28}O_9S_3$ (568.6)	1.97 (dt, 2H, J = 6, CH_2); 2.46 (s, 9H, CH_3); 3.83–4.08 (m, 4H, OCH_2); 4.65–4.73 (m, 1H, CH); 7.26–7.74 (m, 12H_{arom})	21.59 (3C, CH_3); 30.74 (CH_2); 65.30 (OCH_2); 69.29 (OCH_2); 74.91 (OCH); 127.77–130.00 (12C_{arom}); 132.51–132.72 (3C_{arom}); 145.14–145.45 (3C_{arom})	568

a Measured at room temperature with a Perkin-Elmer polarimeter 241.
[b] Satisfactory microanalyses obtained: C ± 0.38, H ± 0.42; exception: **16**:C + 0.65.
[c,d] Refers to footnotes c, d in Table 1

mixture is warmed up to 0 °C. Slow addition of water initiates crystallization of the tosylate and then water (250 mL) is added more rapidly. The product is filtered, dried *in vacuo*, and recrystallized from MeOH; yield: 81%; mp 85–86 °C; $[\alpha]_D^{20}$ +45.8° (*c* = 2, $CHCl_3$) (Lit.[9] $[\alpha]_D^{20}$ +47.0°).

(*S*)-(−)-1,2,4-Butanetriol (15):
This compound is prepared from **14** according to Ref. 14; yield: ~100%; $[\alpha]_D^{25}$ −26.6° (*c* = 1, MeOH) (Lit.[14], $[\alpha]_D^{20}$ −28°).

(*R*)-(−)-3,3-Dimethyl-1,3,4-butanetriol (19):
This compound is prepared from **18** according to Ref. 18; yield: 76%; $[\alpha]_D^{25}$ −14.9° (*c* = 1, EtOH) (Lit.[18] $[\alpha]_D^{22}$ −16.0°).

Preparation of Alcohols 5–7 from Lactones; General Procedure:
The appropriate lactone **1**,**3** or **4** (0.1 mol) is dissolved in THF (150 mL) and added dropwise to a cooled suspension of $LiAlH_4$ in THF (200 mL), using the amounts given in Table 1. After refluxing for 20 h the mixture is cooled by means of an ice bath and carefully neutralized with 20% H_2SO_4 to pH 7. The white granular suspension is filtered and the solid is washed with THF (100 mL). Evaporation of the solvent yields a colorless oil, which is purified by Kugelrohr distillation (Table 1).

Preparation of Tosylates 8–10, 16 from Alcohols; General Procedure:
A solution of the appropriate alcohol **5**–**7** or **15** (50 mmol) in pyridine (60 mL) is cooled to −20 °C and 1.5 equiv of tosyl chloride per hydroxy group are added in small portions within a period of 5 min. After stirring for 20 h the mixture is warmed up to 0 °C and H_2O (100 mL) is added dropwise. The mixture is extracted with $CHCl_3$ (100 mL), the organic phase is washed with water (50 mL), dried (Na_2SO_4), and the solvent is evaporated. The crude viscous oils are sufficiently pure for further reactions (Table 2).

Tosylate **16** is obtained in crystalline form from the reaction mixture and is recrystallized from *i*-PrOH/EtOH. The viscous oil of tosylate **10** crystallizes on trituration with water in a mortar and is purified by recrystallization from MeOH.

Preparation of Phosphines 11–13, 17 and 20 from Tosylates; General Procedure:
A 1 M solution of lithium diphenylphosphide[19] in THF is added dropwise to a stirred solution of the tosylate (30 mmol) in THF (100 mL) at 0 °C until the mixture remains deeply red from unreacted lithium diphenylphosphide. After stirring for 20 h at room temperature the solution is quenched with H_2O (20 mL) and the organic phase is

Table 3. Phosphines **11**–**13**, **17**, **20** and **21** Prepared

Compound	Yield (%)	mp (°C)	$[\alpha]_D$[a] (*c*, solvent)	Molecular Formula[b]	^{1}H-NMR ($CDCl_3$/TMS)[c] δ, *J* (Hz)	^{13}C-NMR ($CDCl_3$/TMS)[d] δ, *J* (Hz)	^{31}P-NMR ($CDCl_3$/H_3PO_4)[e] δ, *J* (Hz)	MS *m/z* (M^+)
11	29	91–93	+68.8° (1.6, toluene)	$C_{41}H_{39}P_3$ (624.7)	1.56–2.25 (m, 9H, CH_2 + CH); 7.13–7.46 (m, 30H, H_{arom})	23.34 (dd, $^2J_{PC}$ = 17, $^3J_{PC}$ = 11, CH_2); 28.20 (d, $^1J_{PC}$ = 12, PCH_2); 30.29 (dd, $^2J_{PC}$ = $^3J_{PC}$ = 15, CH_2); 32.36 (m, CH, PCH_2); 126.62–139.29 (m, 36C_{arom})	−19.65 (d., $^3J_{PP}$ = 23); −15.37 (s); −2.21 (d, $^3J_{PP}$ = 23)	624
12	82	88–91	+5.2° (0.96, toluene)	$C_{30}H_{32}OP_2$ (470.5)	1.45–1.73 (m, 4H, CH_2); 1.88–2.02 (m, 2H, CH_2); 2.44–2.48 (m, 1H, CH); 3.11–3.19 (m, 1H, PCH_2); 3.17 (s, 3H, OCH_3); 3.35–3.44 (m, 1H, OCH_2); 7.28–7.49 (m, 20H_{arom})	24.21 (dd, $^2J_{PC}$ = 16, $^3J_{PC}$ = 11, CH_2); 28.18 (d, $^1J_{PC}$ = 12, PCH_2); 30.93 (dd, $^2J_{PC}$ = 16, $^3J_{PC}$ = 13, CH_2); 36.49 (d, $^1J_{PC}$ = 13, CH); 58.56 (s, OCH_3); 72.82 (d, $^2J_{PC}$ = 16, OCH_2); 126.68–139.15 (m, 24C_{arom})	−15.03; −8.83	470
13	71	74–75	−16.4° (1.3, $CHCl_3$)	$C_{29}H_{30}P_2$ (440.5)	0.97 (dd, 3H, $J_{H,H}$ = 7, J_{PH} = 15, CH_3); 1.35–1.44 (m, 2H, CH_2); 1.60–1.66 (m, 2H, CH_2); 1.91–2.01 (m, 2H, PCH_2); 2.26–2.31 (m, 1H, CH); 7.28–7.48 (m, 20H_{arom})	16.06 (d, $^2J_{PC}$ = 16, CH_3); 23.82 (dd, $^2J_{PC}$ = 16, $^3J_{PC}$ = 12, CH_2); 28.01 (d, $^1J_{PC}$ = 13, PCH_2); 29.74 (d, $^1J_{PC}$ = 11, CH); 34.80 (dd, $^2J_{PC}$ = 18, $^3J_{PC}$ = 13, CH_2); 126.99–139.07 (m, 24C_{arom})	−5.03; 0.01	440
17	63	oil	+77.4° (1.0, $CHCl_3$)	$C_{40}H_{37}P_3$ (610.7)	1.84–1.98 (m, 3H, PCH, CH_2); 2.15–2.34 (m, 4H, CH_2); 7.15–7.46 (m, 30H_{arom})	25.46 (dd, $^2J_{PC-2}$ = $^2J_{PC-4}$ = 12; 26.62–27.46 (m); 30.07 (dd, $^1J_{PC}$ = 12, $^3J_{PC}$ = 17); 33.68 (dd, $^1J_{PC}$ = 10, $^2J_{PC}$ = 18); 126.45–139.30 (m, 36C_{arom})	−19.52 (d, $^3J_{PP}$ = 20); −14.29 (s); −3.55 (d, $^3J_{PP}$ = 20)	610
20	46	oil	−50.8° (3.2, $CHCl_3$)	$C_{30}H_{32}OP_2$ (470.5)	0.94 (s, 3H, CH_3); 0.97 (s, 3H, CH_3); 2.04–2.43 (m, 5H, PCH_2, OH); 3.56 (m, 1H, CH); 7.10–7.48 (m, 20H_{arom})	3.70 (d, $^3J_{PC}$ = 10, CH_3); 25.01 (d, $^3J_{PC}$ = 10, CH_3); 31.97 (d, $^1J_{PC}$ = 10, PCH_2); 38.30 (d, $^1J_{PC}$ = 2, PCH_2); 38.92 (dd, $^2J_{PC}$ = $^3J_{PC}$ = 6, H_3CCCH_3); 75.60 (dd, $^2J_{PC}$ = 13, $^3J_{PC}$ = 7, CH); 127.83–139.89 (m, 24C_{arom})	−21.80; −17.28	470
21	70	92–96	−9.5° (1.8, $CHCl_3$)	$C_{37}H_{36}O_2P_2$ (574.6)	1.04 (s, 6H, CH_3); 2.08–2.49 (m, 4H, PCH_2); 5.31 (m, 1H, CH); 7.18–7.89 (m, 25H_{arom})	24.73 (d, $^3J_{PC}$ = 8, 2C, CH_3); 29.46 (d, $^1J_{PC}$ = 10, PCH_2); 37.38 (d, $^1J_{PC}$ = 9, PCH_2); 39.34 (dd, $^2J_{PC}$ = 12, $^3J_{PC}$ = 8, H_3CCCH_3); 78.21 (dd, $^2J_{PC}$ = 11, $^3J_{PC}$ = 7, CH); 126.97–137.15 (m, 30C_{arom}); 366.82 (s, CO_2)	−24.42; −19.66	574

[a] Measured at room temperature with a Perkin-Elmer polarimeter 241.
[b] Satisfactory microanalyses obtained: C ±0.40, H ±0.12.
[c,d] Refers to footnotes c, d in Table 1.
[e] Recorded on a Bruker WM 250 spectrometer.

separated. The solvent is evaporated and the crude product is chromatographed on a silica gel column (20 cm × 3.5 cm; 70–230 mesh) using toluene (400 mL) as eluent. After evaporation of the solvent, diphenylphosphine is distilled off (100 °C/0.01 mbar) to yield a colorless oil. Phosphines **11–13** crystallize on trituration with MeOH (Table 3).

(*R*)-(−)-2-Benzoyloxy-3,3-dimethyl-1,4-bis(diphenylphosphino)butane (21):

A solution of phosphine **20** (12.1 g, 25.7 mmol) in toluene (60 mL) is cooled to 0 °C and benzoyl chloride (4 mL, 34.5 mmol) is added. After stirring the mixture for 10 min at room temperature, the solvent is evaporated. Trituration of the remaining yellow oil with petroleum ether (bp 40–60 °C) yields colorless crystals. The partly oxidized product is dissolved in benzene (20 mL) and reduced in an autoclave with an excess of trichlorosilane (3 mL) to pure phosphine **21**, which is again crystallized from petroleum ether.

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