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An optimised synthetic approach to a chiral derivatising agent and the utilisation of a dimerisation reaction in the synthesis of a novel C2-symmetric diphosphine ligand

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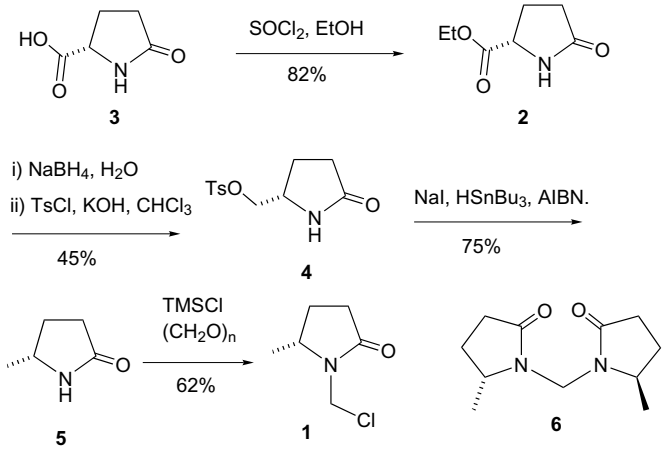
Abstract—We report an optimised synthetic approach to the chiral derivatising agent (5*R*)-methyl-1-(chloromethyl)-2-pyrrolidinone. In addition, the observation of an unwanted dimerisation product is turned to our advantage by providing a method for the synthesis of a new class of C2-symmetric chiral diphosphine.

1. Introduction

During the course of a project directed towards the asymmetric synthesis of cyclic amines via C=N reduction,[1] we required reagent **1** for its use as a chiral derivatising agent.[2–5] This compound was originally prepared by the cyclisation and esterification of glutamic acid in refluxing ethanol with an acid catalyst.[2] Attempts to replicate this procedure gave the desired ester in low yield. It was found that intermediate **2** was more easily accessed from pyroglutamic acid **3** using the method described by Silverman (Scheme 1).[6]

2. Results and discussion

We have developed an optimised route to **1**; pyroglutamic acid **3** was suspended in ethanol and thionyl chloride added dropwise. Removal of the solvent in vacuo and reduced pressure distillation gave ethyl ester **2** in 82% yield. Ester **2** was reduced to the primary alcohol using sodium borohydride in water following the method of Smith et al.[2] The solution was then concentrated to approximately half of the original volume and a biphasic mixture prepared by adding chloroform, KOH, TsCl and the phase transfer catalyst *tetra-n*-butylammonium hydrogen sulfate. After vigorous stirring, tosylate **4** could be isolated in 45% yield for the two steps. The tosyl group was converted to the iodide by an in situ Finkelstein reaction and radical removal of the iodide using tributyltin hydride to give lactam **5** in 75% yield after distillation.



Scheme 1. Synthesis of chloromethyl amide **1**.

Chloromethylation was carried out by heating **5** in TMSCl and *para*-formaldehyde at 50 °C to give **1** in 62% yield after distillation.

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During the course of this work, we made an unexpected observation: Smith's original procedure required the heating of **5**, TMSCl and *para*-formaldehyde at reflux;[2] but in our hands this led to a single product with a singlet at 4.83 ppm, which appeared to integrate to one proton. It was suspected that the chloromethylated product **1** was reacting with lactam **5** to dimerise the lactam through a methylene bridge; the singlet at 4.83 ppm was assigned as the methylene CH_2.

The compound was crystalline and a single crystal was grown for X-ray crystallographic analysis, the structure was confirmed as **6** (Fig. 1).

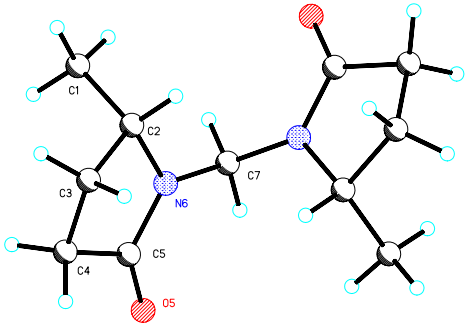
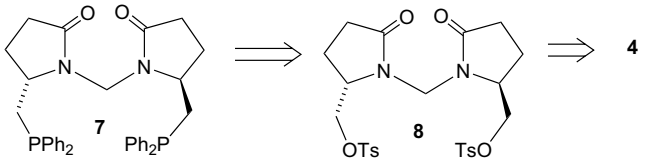


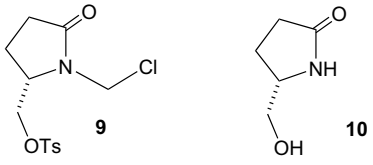
Figure 1. X-ray crystallographic structure of **6**.

In view of this result we decided to investigate the use of the dimerisation of **5** to give **6** in the preparation of novel diphosphine ligands from this reaction.[7] The diphosphine we wished to investigate was compound **7**, which we thought we may be able to prepare from ditosylate **8**. It was anticipated that **8** could be formed from the reaction of **4** with *para*-formaldehyde and TMSCl (Scheme 2).



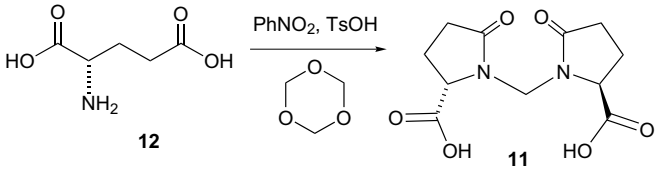
Scheme 2. Retrosynthesis of diphosphine **7**.

Tosylate **4** was a product of the synthesis of the chiral derivitising agent **1** and when treated with TMSCl and *para*-formaldehyde appeared to form the chloromethylated adduct **9** but failed to form the desired dimer **8**. Excessive heating to try and drive the reaction resulted in decomposition of intermediate **8**.



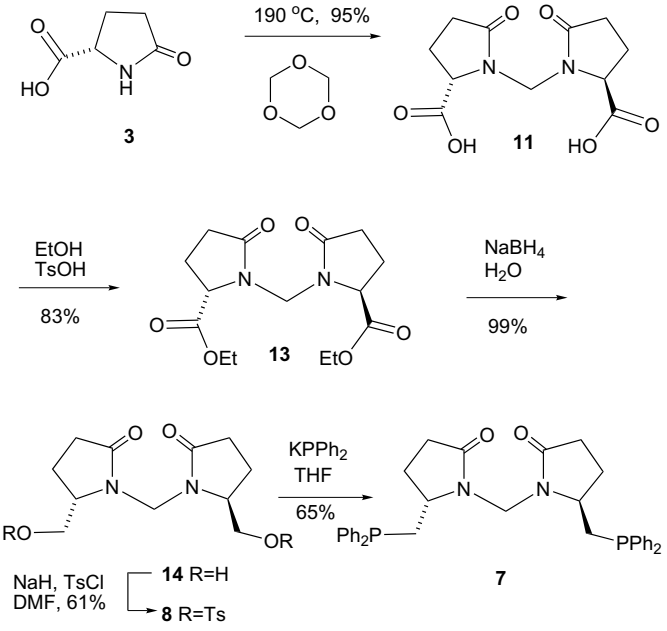
Attempts were also made to dimerise ester **2** and alcohol **10** but these only resulted in decomposition products.

In 1980, Rigo and co-workers[7a] reported the synthesis of diacid **11** from glutamic acid **12** and trioxane in nitrobenzene at 150 °C. We attempted to follow this procedure but only recovered small amounts of diacid **11**, coupled with the arduous task of steam distilling off the nitrobenzene made this procedure unappealing (Scheme 3).



Scheme 3. One pot approach to dimer.

A successful approach to **7** is shown in Scheme 4. It was discovered that heating pyroglutamic acid **3** and trioxane together without solvent at 190 °C resulted in the formation of the desired diacid as a white crystalline solid in 95% yield. The reaction was worked up by distilling off excess trioxane, cooling to room temperature, crushing the solid to a fine powder and then washing the powder in a sintered funnel with EtOAc to remove any remaining trioxane (Scheme 4). It should be noted that the synthesis of **11** through the use of aqueous formaldehyde has also been reported.[7e]



Scheme 4. Synthetic approach to diphosphine **7**.

To confirm the structure of **11**, single crystals were grown for X-ray crystallographic analysis (Fig. 2).

The crystal data showed that **11** formed an interesting secondary structure in the solid state, connected by the hydrogen bonding of the acid OH and the amide C=O to form H-bonded strands (Fig. 3).

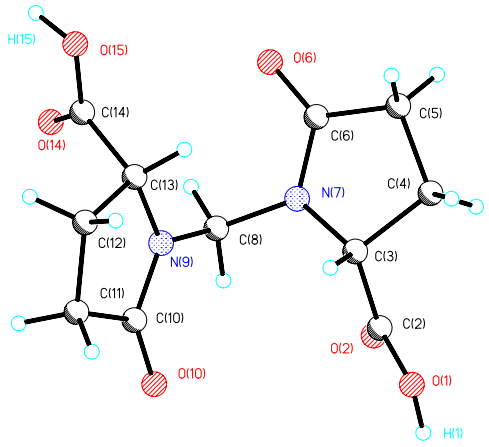


Figure 2. X-ray crystallographic structure of **11**.

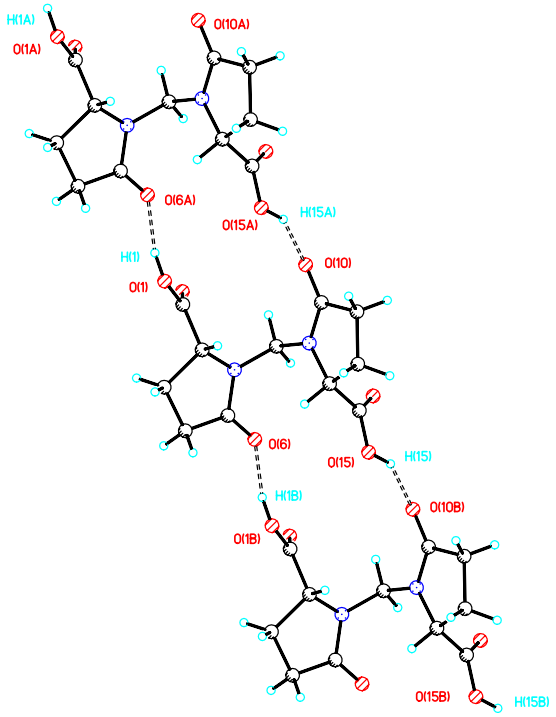


Figure 3. Extended structure of **11**.

The diagram in Figure 3 shows the hydrogen bonded network running parallel to the *X*-axis of the cell formed by the carboxylic acid dimer. The H-bonded strands run in opposite directions. These also form a hydrogen bonded network with adjacent strands (not illustrated).

Diacid **11** was converted to diester **13** by refluxing in EtOH with a catalytic amount of *p*-TsOH overnight; removal of the solvent gave a white crystalline solid which could be recrystallised from EtOAc/hexanes to give pure **13** in 83% yield. Diester **13** was reduced to diol **14** by $NaBH_4$ in water. The inorganics were precipitated by the addition of acetone and filtered off. Removal of the water in vacuo to approximately a third of the volume and the addition of further acetone precipitated more solids that were filtered off. This procedure was repeated once more before removal of all the water to leave diol **14** as a white moisture sensitive solid in 99% yield.

Diol **14** was converted to ditosylate **8** by treatment with NaH in DMF followed by tosyl chloride at 0 °C. After aqueous work-up, the tosylate could be crystallised from EtOAc/hexanes in 61% yield. Ditosylate **8** was treated with two equivalents of potassium diphenylphosphine in THF at −78 °C. A 50:50 mixture of EtOAc/hexanes was added to the crude reaction mixture and the resulting slurry filtered through a short path of silica. Removal of the solvent gave a white oil which on trituration with diethyl ether gave diphosphine **7** as a white solid in 65% yield.

The structure of **7** was confirmed by X-ray crystallographic analysis of the phosphine oxide, which was generated by air oxidation, in a quantitative yield (Fig. 4).

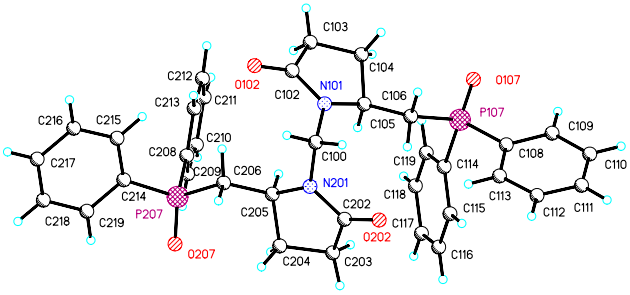


Figure 4. X-ray crystallographic structure of **7** dioxide.

3. Conclusion

In conclusion, a novel bidentate phosphine ligand has been prepared from pyroglutamic acid in five steps and in 31% overall yield. Ruthenium and rhodium complexes were prepared using this ligand and tested for activity in the hydrogenation of acetophenone. Unfortunately, the complexes gave poor results for this substrate, possibly due to the instability of the complexes under the reaction conditions. Ligand **7** is currently being investigated in other transition metal mediated reactions and the results will be reported in due course.

4. Experimental

4.1. General

The ^{1}H NMR, ^{13}C NMR and ^{31}P NMR spectra were recorded at 300, 75 and 121 MHz, respectively, using $CDCl_3$ as a solvent, and were reported in ppm relative to $CHCl_3$ (δ 7.26) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ 77.00) for ^{13}C NMR. Flash chromatography(FC) was carried out with silicagel 60 (230–400 mesh). All solvents and commercially available chemicals, including amino acid precursors were used as received.

4.2. Synthesis of ethyl-(2*S*)-5-oxopyrrolidine 2

To a suspension of (*S*)-pyroglutamic acid **3** (50.0 g, 0.39 mol) in EtOH (650 mL) was added dropwise $SOCl_2$

(45.7 g, 28 mL, 0.39 mol). The resulting solution was stirred for 1 h, neutralised (pH 7) with saturated $NaHCO_3$ and extracted with $CHCl_3$ (3×250 mL). The combined organics were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give a green oil which was purified by reduced pressure distillation to afford ethyl-(2*S*)-5-oxopyrrolidine **2** (49.1 g, 82%) as a white solid; mp 49–51 °C (lit.[8] 54–55 °C); $[\alpha]_D^{22} = -6.8$ (*c* 0.03, EtOH) [lit.[8] $[\alpha]_D^{22} = -7.1$ (*c* 0.06, EtOH)]; (found: C, 53.42; H, 7.06; N, 8.94. $C_7H_{11}NO_3$ requires C, 53.49; H, 7.05; N, 8.91); ν_{max} (neat)/cm^{-1} 3206, 2982, 2341, 1742 and 1693; δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.23 (1H, br s, N*H*), 4.29–4.17 (1H, m, C*H*) 4.24 (2H, q, *J* 7.0, OCH_2), 2.52–2.32 (3H, m, $COCH_2CH_aH_b$), 2.27–2.15 (1H, m, $COCH_2CH_aH_b$) and 1.31 (3H, t, *J* 7.0, CH_3); δ_C (75 MHz; $CDCl_3$) 178.7 (C_q), 172.5 (C_q), 61.9 (CH_2), 55.9 (CH), 29.7 (CH_2), 25.1 (CH_2) and 14.5 (CH_3); *m*/*z* (EI) 157.0740 ($C_7H_{11}NO_3$ requires 157.0738) 158 (5%), 84 (100) and 56 (10).

4.3. Synthesis of [(2*S*)-5-oxopyrrolidin-2-yl]methyl-4-methylbenzenesulfonate 4 (adapted from Smith et al.[2])

To a solution of ethyl-(2*S*)-5-oxopyrrolidine **2** (15.7 g, 100.0 mmol) in water (50 mL) was added dropwise a solution of $NaBH_4$ (2.2 g, 58.0 mmol) in water (50 mL) over a period of 30 min. The resulting solution was warmed to rt and stirred for a further 1 h. Acetone (10 mL) was added dropwise at 0 °C and stirred for 30 min. The reaction was concentrated to ca. 40 mL, KOH (7.0 g, 125.0 mmol), TsCl (19.1 g, 100.0 mmol), Bu_4NSO_4 (1 g, 2.94 mmol) and $CHCl_3$ (150 mL) were added and the reaction stirred vigorously for 18 h. The phases were separated and the aqueous phase extracted with DCM (3×100 mL). The combined organics were dried (Na_2SO_4) and the solvent was removed in vacuo to give a white solid which was recrystallised from hot toluene to afford [(2*S*)-5-oxopyrrolidin-2-yl]methyl-4-methylbenzenesulfonate **4** (12 g, 45%) as fine white needles; mp 126–128 °C (lit.[2] 129–130 °C); $[\alpha]_D^{22} = -6.5$ (*c* 0.013, EtOH) [lit.[2] $[\alpha]_D^{22} = -7.1$ (*c* 1, EtOH)]; (found: C, 53.42; H, 7.06; N, 8.94. $C_7H_{11}NO_3$ requires C, 53.49; H, 7.05; N, 8.91); ν_{max} (neat)/cm^{-1} 3206, 2982, 2341, 1742 and 1693; δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.80 (2H, d, *J* 8.5, AA′ of AA′BB′ Ar*H*), 7.38 (2H, d, *J* 8.5, AA′ of AA′BB′ Ar*H*), 6.19 (1H, br s, N*H*), 4.05 (1H, dd, *J* 9.5 and 3.5, OCH_aH_b), 3.97–3.86 (2H, m, $OCH_aH_b + NCH$), 2.48 (3H, s, CH_3), 2.29–2.21 (3H, m, $COCH_2CH_aH_b$) and 1.85–1.75 (1H, m, $COCH_2CH_aH_b$); δ_C (100 MHz; $CDCl_3$) 178.2 (C_q), 145.8 (C_q), 132.8 (C_q), 130.5 (CH), 128.3 (CH), 72.4 (CH_2), 53.0 (CH), 29.6 (CH_2), 23.2 (CH_2) and 22.1 (CH_3); *m*/*z* (EI+) 269.0739 ($C_{12}H_{15}NO_4S$ requires 269.0722) 270 (10%), 239 (20) and 84 (100).

4.4. Synthesis of (5*R*)-5-methylpyrrolidin-2-one 5

To a solution of [(2*S*)-5-oxopyrrolidin-2-yl]methyl-4-methylbenzenesulfonate **4** (18.0 g, 67.2 mmol), NaI (19.8 g, 134.2 mmol), tributyltin hydride (21.0 g, 19.2 mL, 72.0 mmol) in DME (600 mL) was added AIBN (0.1 g, 0.61 mmol). The mixture was heated at reflux for 12 h and cooled to rt. The white precipitate was filtered off and washed with Et_2O (2×300 mL) and the filtrate concentrated under reduced pressure to give a green oil which was purified by flash column chromatography (SiO_2, DCM–MeOH, 100:0→90:10) to afford (5*R*)-5-methylpyrrolidin-2-one **5** (4.2 g, 75%) as a colourless oil; $[\alpha]_D^{22} = +15.8$ (*c* 0.023, EtOH) [lit.[2] $[\alpha]_D^{22} = +16.0$ (*c* 1, EtOH)]; ν_{max} (neat)/cm^{-1} 3217, 2965, 1677 and 1274; δ_H (400 MHz; $CDCl_3$; Me_4Si) 6.83 (1H, br s, N*H*), 3.78 (1H, quintet, *J* 7.0, C*H*), 2.40–2.19 (3H, m, $COCH_2CH_aH_b$), 1.70–1.59 (1H, m, $COCH_2CH_aH_b$), and 1.22 (3H, t, *J* 7.0, CH_3); (75 MHz; $CDCl_3$) 178.4 (C_q), 49.9 (CH), 30.5 (CH_2), 28.8 (CH_2) and 21.9 (CH_3); *m*/*z* (EI+) 100 (60%) and 84 (100).

4.5. Preparation of (5*R*)-methyl-1-(chloromethyl)-2-pyrrolidinone 1

To a solution of (5*R*)-5-methylpyrrolidin-2-one **5** (0.65 g, 6.6 mmol) in TMSCl (3 mL) was added *para*-formaldehyde (0.22 g, 6.8 mmol), the resulting suspension was heated to 50 °C for 2 h. Excess TMSCl was removed under reduced pressure to give the crude product which was purified by bulb-to-bulb distillation to afford (5*R*)-methyl-1-(chloromethyl)-2-pyrrolidinone **1** as a colourless oil (0.59 g, 61%); $[\alpha]_D^{22} = +106.9$ (*c* 0.021, $CHCl_3$) [lit.[2] $[\alpha]_D^{22} = +109.9$ (*c* 0.032, $CHCl_3$)]; ν_{max} (neat)/cm^{-1} 2970, 1701, 1386 and 1255; δ_H (400 MHz; $CDCl_3$) 5.61 (1H, d, *J* 10.4, $ClCH_aH_b$), 4.87 (1H, d, *J* 10.4, $ClCH_aH_b$), 3.86 (1H, sex, *J* 7.0, C*H*), 2.49–2.22 (3H, m, $COCH_2CH_aH_b$), 1.67–1.37 (1H, m, $COCH_2CH_aH_b$) and 1.32 (3H, d, *J* 7.0, CH_3); δ_C (100 MHz; $CDCl_3$) 176.1 (C_q), 52.4 (CH), 51.7 (CH_2), 30.6 (CH_2), 27.2 (CH_2) and 19.7 (CH_3); *m*/*z* (EI+) 147.0469 ($C_6H_{10}NO^{35}Cl$ requires 147.0451) 147 (3%), 132 (13%), 112 (100%) and 84 (35%).

4.6. Synthesis of (5*R*)-5-methyl-1-{[(2*R*)-2-methyl-5-oxopyrrolidin-1-yl]methylpyrrolidin-2-one 6

Procedure. Colourless crystalline plates; mp 110–112 °C; $[\alpha]_D^{22} = +207.7$ (*c* 0.48, $CHCl_3$); (found: C, 62.86; H, 8.60; N, 13.16. $C_{11}H_{18}N_2O_2$ requires C, 62.83; H, 8.63; N, 13.32); ν_{max} (neat)/cm^{-1} 3356, 2964, 2861, 2358, 1677 and 1370; δ_H (300 MHz; $CDCl_3$; Me_4Si) 4.83 (2H, s, NCH_2N), 3.56 (2H, sextet, *J* 6.2, $2 \times CH_3CH$), 2.40–2.29 (4H, m, $2 \times COCH_2$), 2.19–2.10 (2H, m, $2 \times CHCH_aH_b$), 1.68–1.58 (2H, m, $2 \times CH_2CH_aH_b$) and 1.31 (6H, d, *J* 6.2, $2 \times CH_3$); δ_C (100 MHz; $CDCl_3$) 176.1 (C_q), 52.6 (CH), 44.3 (CH_2), 30.4 (CH_2), 26.9 (CH_2) and 19.9 (CH_3); *m*/*z* (EI+) 210.1368 ($C_{11}H_{18}N_2O_2$ requires 210.1368) 210 (27%), 112 (77%), 111 (100%), 98 (52%) and 83 (37%).

4.7. Synthesis of L-(+)-1,1′-methylenebis[5-oxo-2-pyrrolidinecarboxylic acid] 11

L-(+)-Pyroglutamic acid **3** (25.0 g, 0.19 mol) and trioxane (17.4 g, 0.19 mol) were heated to 180 °C for 3 h. Excess trioxane was removed by distillation and the mixture was then cooled to rt. The white solid was crushed to a fine powder and washed with AcOH (20 mL) and EtOAc (50 mL) to afford L-(+)-1,1′-methylenebis[5-oxo-2-pyrrolidinecarboxylic acid **11** (25.0 g, 95%) as a fine white powder; mp 290–295 °C (decomp., water) (lit.[7a] 312 °C, decomp.); $[\alpha]_D^{22} = +104.0$ (*c* 0.022, H_2O) [lit.[7a] $[\alpha]_D^{22} = +105.7$ (*c* 0.009, H_2O)]; (found: C, 48.80; H, 5.23; N, 10.41. $C_{11}H_{14}N_2O_6$ requires C, 48.89; H, 5.22; N, 10.37); ν_{max}

(neat)/cm^{-1} 2980, 2359, 1732, 1629 and 1158; δ_H (300 MHz; DMSO) 13.10 (2H, br s, $2\times CO_2H$), 4.70 (2H, s, NCH_2N), 4.12–4.02 (2H, m, $2\times NCH$), 2.37–2.20 (6H, m, $2\times COCH_2CH_aH_b$) and 1.94–1.85 (2H, m, $CHCH_aH_b$); δ_C (75 MHz; DMSO) 176.1 (C_q), 173.5 (C_q), 57.5 (CH), 46.8 (CH_2), 29.1 (CH_2) and 22.6 (CH_2); *m/z* (EI+) 271.0929 ($C_{11}H_{15}N_2O_6$ requires 271.0930), 271 (100%).

4.8. Synthesis of L-(+)-1,1′-methylenebis[5-oxo-2-pyrrolidinecarboxylic acid ethyl ester] 13

L-(+)-1,1′-Methylenebis[5-oxo-2-pyrrolidinecarboxylic acid **11** (5.0 g, 18.5 mmol) and *p*-TsOH (0.1 g, 0.6 mmol) were suspended in EtOH (50 mL) and heated at reflux for 16 h. The solution was cooled to rt and the solvent removed under reduced pressure, the crude was redissolved in DCM (100 mL) and washed with saturated $NaHCO_3$ (20 mL), dried over Na_2SO_4 and the solvent removed under reduced pressure to afford L-(+)-1,1′-methylenebis[5-oxo-2-pyrrolidinecarboxylic acid ethyl ester] **13** (5.0 g, 83%) as a white solid; mp 112–114 °C (toluene) (lit.[9] 117 °C); $[\alpha]_D^{22}=+52.7$ (*c* 0.0204, EtOH) (lit.[9] $[\alpha]_D^{22}=+55.6$); (found: C, 55.15; H, 6.76; N, 8.42. $C_{15}H_{22}N_2O_6$ requires C, 55.21; H, 6.79; N, 8.58); ν_{max} (neat)/cm^{-1} 2986, 2360, 1738, 1692, 1196 and 1033; δ_H (300 MHz; $CDCl_3$; Me_4Si) 4.82 (2H, s, NCH_2N), 4.39 (2H, dd, *J* 5.4 and 2.6, $2\times NCH$), 4.25 (4H, q, *J* 7.2, $2\times OCH_2CH_3$), 2.45–2.31 20 (6H, m, $2\times COCH_2CH_aH_b$), 2.14–2.06 (2H, m, $2\times CHCH_aH_b$) and 1.32 (6H, t, *J* 7.3, $2\times OCH_2CH_3$); δ_C (75 MHz; $CDCl_3$) 176.3 (C_q), 171.6 (C_q), 61.6 (CH_2), 59.2 (CH), 48.3 (CH_2), 28.9 (CH_2), 23.0 (CH_2) and 14.1 (CH_3); *m/z* (EI+) 326 (100%), 252 (45) and 169 (50).

4.9. Synthesis of L-(+)-1,1′-methylenebis[5-hydroxymethyl-2-pyrrolidinone] 14

To a stirred solution of L-(+)-1,1′-methylenebis[5-oxo-2-pyrrolidine carboxylic acid ethyl ester] **13** (13.5 g, 41.4 mmol) in EtOH/water (135 mL/13.5 mL) was added $NaBH_4$ (4.72 g, 124 mmol) in 1 portion. The suspension was stirred for 12 h, cooled to 0 °C, acetone (100 mL) was added and stirred for a further 2 h. The white solids were filtered off and washed with cold EtOH (50 mL). The filtrate was reduced by half under reduced pressure and acetone (50 mL) added to the residue. The white precipitate was filtered off and washed with cold EtOH (25 mL). The filtrate was evaporated under reduced pressure to afford L-(+)-1,1′-methylenebis[5-hydroxymethyl-2-pyrrolidinone] **14** (9.9 g, 99%) as a colourless oil; $[\alpha]_D^{22}=+91.3$ (*c* 0.0145, H_2O); ν_{max} (neat)/cm^{-1} 3329, 1657, 1410 and 1212; δ_H (300 MHz; D_2O) 4.75 (2H, s, NCH_2N), 3.81 (2H, dd, *J* 12.6 and 3.4, $2\times OCH_aH_b$), 3.62–3.56 (2H, m, $2\times NCH$), 3.50 (2H, dd, *J* 12.6 and 2.5 $2\times OCH_aH_b$), 2.48–2.25 (4H, m, $2\times COCH_2$), 2.14–2.00 (2H, m, $2\times CHCH_aH_b$) and 1.91–1.80 (2H, m, $2\times CHCH_aH_b$); δ_C (100 MHz; D_2O) 179.9 (C_q), 60.3 (CH_2), 57.9 (CH), 45.0 (CH_2), 30.2 (CH_2) and 20.2 (CH_2); *m/z* (EI+) 243.1344 ($C_{11}H_{19}N_2O_4$ requires 243.1344), 243 (20%).

4.10. Synthesis of L-(+)-1,1′-methylenebis[toluene-4-sulfonic acid (*S*)-5-oxo-pyrrolidin-2-ylmethyl ester] 8

To a cooled (0 °C) stirred suspension of washed (hexanes) NaH (0.29 g, 12.1 mmol) in DMF (14 mL) was added a solution of L-(+)-1,1′-methylenebis[5-hydroxymethyl-2-pyrrolidinone] **14** (1.4 g, 5.8 mmol) in DMF (14 mL). The resulting suspension was stirred for 1 h at 0 °C before toluene-4-sulfonyl chloride (2.3 g, 12.1 mmol) was added in small portions over a period of 2 h. The reaction was quenched by the addition of water (10 mL) and extracted with EtOAc (4×25 mL). The combined organics were washed with water (2×10 mL) and brine (10 mL), dried ($NaSO_4$) and the solvent removed in vacuo to afford a yellow oil. The crude was purified by flash column chromatography (SiO_2, EtOAc–MeOH, 95:5) to give L-(+)-1,1′-methylenebis[toluene-4-sulfonic acid (*S*)-5-oxo-pyrrolidin-2-ylmethyl ester] **8** as a white crystalline solid; mp 116–117 °C (toluene); $[\alpha]_D^{22}=+52.6$ (*c* 0.0204, EtOH); (found: C, 54.47; H, 5.48; N, 5.09. $C_{15}H_{22}N_2O_6$ requires C, 54.53; H, 5.49; N, 5.09); ν_{max} (neat)/cm^{-1} 2923, 1698, 1356, 1171, 951 and 856; δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.78 (4H, AA′ of AA′BB′ *J* 8.2, Ar*H*), 7.38 (4H, BB′ of AA′BB′ *J* 8.2, Ar*H*), 4.42 (2H, dd, *J* 11.1, 3.4, $2\times OCH_aH_b$), 4.38 (2H, s, NCH_2N), 4.01 (2H, dd, *J* 10.9, 2.0, $2\times OCH_aH_b$), 3.76–3.70 (2H, m, $2\times NCH$), 2.46 (6H, s, $2\times CH_3$) and 2.49–1.90 (8H, m, $2\times CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 176.8 (C_q), 145.8 (C_q), 132.7 (C_q), 130.5 (CH), 128.3 (CH) 68.6 (CH_2), 55.7 (CH), 44.7 (CH_2), 29.8 (CH_2), 22.1 (CH_3) and 21.4 (CH_2); *m/z* (EI+) 551.1506 ($C_{25}H_{31}N_2O_8S_2$ requires 551.1522) 550 (20%), 364 (19), 281 (100), 205 (25), 154 (35) and 90 (54).

4.11. Synthesis of L-(+)-1,1′-Methylenebis[5-diphenylphosphino-2-pyrrolidinone] 7

To a stirred solution of L-(+)-1,1′-methylenebis[toluene-4-sulfonic acid (*S*)-5-oxo-pyrrolidin-2-ylmethyl ester] **8** (1.28 g, 2.3 mmol) in THF was added dropwise a 0.5 mol solution potassium diphenylphosphine (1.56 g, 13.9 ml, 6.9 mmol) in THF. The reaction was stirred for 1 h, diluted with EtOAc–hexanes (50:50, 10 mL) and filtered through a pad of silica. The solvent was removed under reduced pressure to give a colourless oil, which was triturated with Et_2O to give a white solid. This was washed with Et_2O (2×5 mL) to afford L-(+)-1,1′-methylenebis[5-diphenylphosphino-2-pyrrolidinone] **7** (0.86 g, 65%) as a white powder; mp 158–160 °C; $[\alpha]_D^{22}=+83.6$ (*c* 0.031, EtOH); ν_{max} (neat)/cm^{-1} 3064, 2928, 1683, 1377 and 737; δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.53–7.30 (20H, m, $20\times ArH$), 4.76 (2H, s, NCH_2N), 3.26–3.14 (2H, m, $2\times NCH$), 2.98 (2H, dt, *J* 13.0, 3.2, $2\times PCH_aH_b$), 2.43 (2H, ddd, *J* 15.3, 9.8 and 5.7, $2\times PCH_aH_b$) and 2.20–1.82 (8H, m, $2\times CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 175.2 (C_q), 137.7 (C_q, d, *J* 11.0), 136.2 (C_q, *J* 12.6), 133.1 (CH, d, *J* 20.1), 132.3 (CH, d, *J* 19.0), 128.9 (CH), 128.6 (CH), 128.4 (CH, d, *J* 1.7), 128.3 (CH, d, *J* 1.6), 53.5 (CH, d, *J* 20.1), 43.4 (CH_2), 31.7 (CH_2, d, *J* 14.4), 30.0 (CH_2, d, *J* 2.2) and 24.6 (CH_2, d, *J* 10.9); δ_P (121.51 MHz; $CDCl_3$) −24.86; *m/z* (EI+) 577.2169 ($C_{25}H_{35}N_2O_2P_2$ requires 577.2174), 578 (20%), 393 (40), 377 (45), 296 (100) and 183 (60).

4.12. X-ray crystallographic data for 6

$C_{11}H_{18}N_2O_2$, $M = 210.27$, Tetragonal, space group $P4(3)2(1)2$, $a = 6.8307(4)$, $b = 6.8307(4)$, $c = 24.495(2)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $U = 1142.89(13)$ Å^3 (by least squares refinement on 2637 reflection positions), $T = 180(2)$ K, $\lambda = 0.71073$ A, $Z = 4$, $D(\text{cal}) = 1.222$ g/cm^3, $F(0\,0\,0) = 456$. $\mu(\text{MoK-}\alpha) = 0.085$ mm^{-1}. Crystal character: colourless block. Crystal dimensions $0.22 \times 0.12 \times 0.08$ mm. *Data collection and processing*: Siemens SMART (Siemens, 1994) three-circle system with CCD area detector. The crystal was held at 180(2) K with the Oxford Cryosystem Cryostream Cooler (Cosier and Glazer, 1986). Maximum theta was 25.00°. The hkl ranges were −7/8, −5/8, −29/28. 5817 reflections measured, 1006 unique [R(int) = 0.1100]. Absorption correction by semi-empirical from equivalents; minimum and maximum transmission factors: 0.53; 0.96. No crystal decay. *Structure analysis and refinement*: Systematic absences indicated either space group $P4(3)2(1)2$ or $P4(1)2(1)2$. The former was chosen on the basis of intensity statistics and shown to be correct by successful refinement. The structure was solved by direct methods using SHELXS (Sheldrick, 1990) (TREF) with additional light atoms found by Fourier methods. Hydrogen atoms were added at calculated positions and refined using a riding model with freely rotating methyl groups. Anisotropic displacement parameters were used for all non-H atoms; H-atoms were given isotropic displacement parameters equal to 1.2 (or 1.5 for methyl hydrogen atoms) times the equivalent isotropic displacement parameter of the atom to which the H-atom is attached. The chirality was established from the known chirality of the compound but the anomalous scattering was insufficiently large for this to be checked independently. C7 of the molecule lies on the two-fold axis (4a) so there is only half a molecule in the asymmetric unit and so four molecules per cell. R_1 [For 767 reflections with $I > 2\sigma(I)$] = 0.0673, $wR_2 = 0.1225$. Data/restraints/parameters 1006/0/71. Extinction coefficient 0.066(9). Refinement used SHELXTL.[10]

4.13. X-ray crystallographic data for 11[11]

$C_{11}H_{14}N_2O_6$, $M = 270.24$, monoclinic, space group $P2(1)$, $a = 7.9622(8)$, $b = 9.1728(12)$, $c = 9.1731(12)$ Å, $\alpha = 90°$, $\beta = 112.952(4)°$, $\gamma = 90°$, $U = 616.92(13)$ Å^3 (by least squares refinement on 2893 reflection positions), $T = 180(2)$ K, $\lambda = 0.71073$ Å, $Z = 2$, $D(\text{cal}) = 1.455$ g/cm^3, $F(0\,0\,0) = 284$. $\mu(\text{MoK-}\alpha) = 0.120$ mm^{-1}. Crystal character: colourless block. Crystal dimensions $0.38 \times 0.20 \times 0.14$ mm. *Data collection and processing*: Siemens SMART (Siemens, 1994) three-circle system with CCD area detector. The crystal was held at 180(2) K with the Oxford Cryosystem Cryostream Cooler (Cosier and Glazer, 1986). Maximum theta was 28.76°. The hkl ranges were −10/9, −10/12, −11/12. 3928 reflections measured, 2407 unique [R(int) = 0.0379]. Absorption correction by semi-empirical from equivalents; minimum and maximum transmission factors: 0.55; 0.96. No crystal decay. *Structure analysis and refinement*: Systematic absences indicated space group $P2(1)$ or $P2(1)/m$. The former was chosen because of the known chirality of the system and shown to be correct by successful refinement. The structure was solved by direct methods using SHELXS (Sheldrick, 1990) (TREF) with additional light atoms found by Fourier methods. Hydrogen atoms were added at calculated positions and refined using a riding model with freely rotating methyl groups. Anisotropic displacement parameters were used for all non-H atoms; H-atoms were given isotropic displacement parameters equal to 1.2 (or 1.5 for methyl hydrogen atoms) times the equivalent isotropic displacement parameter of the atom to which the H-atom is attached. The chirality was established from the known chirality of the compound but the anomalous scattering was insufficiently large for this to be checked independently. Floating origin constraints were generated automatically. R_1 [For 1758 reflections with $I > 2\sigma(I)$] = 0.0407, $wR_2 = 0.0832$. Data/restraints/parameters 2407/1/179. Extinction coefficient 0.006(3). *Note*: The asymmetric unit contains a dicarboxylic acid. This forms hydrogen bonded ribbons (shown in Fig. 3) which run parallel to the a axis of the cell. There are close contacts between these ribbons. Refinement used SHELXTL.[10]

4.14. X-ray crystallographic data for 7

The asymmetric unit contains the compound as the bis phosphine oxide. The unit cell contains four such molecules. $C_{35}H_{36}N_2O_4P_2$, $M = 610.60$, orthorhombic, space group $P2(1)2(1)2(1)$, $a = 8.5543(11)$, $b = 18.463(2)$, $c = 19.916(3)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $U = 3145.5(7)$ Å^3 (by least squares refinement on 7415 reflection positions), $T = 180(2)$ K, $\lambda = 0.71073$ Å, $Z = 4$, $D(\text{cal}) = 1.289$ g/cm^3, $F(0\,0\,0) = 1288$. $\mu(\text{MoK-}\alpha) = 0.180$ mm^{-1}. Crystal character: colourless block. Crystal dimensions $0.22 \times 0.20 \times 0.06$ mm. *Data collection and processing*: Siemens SMART (Siemens, 1994) three-circle system with CCD area detector. The crystal was held at 180(2) K with the Oxford Cryosystem Cryostream Cooler (Cosier and Glazer, 1986). Maximum theta was 28.87°. The hkl ranges were −11/10, −23/23, −25/23. 20,277 reflections measured, 7572 unique [R(int) = 0.0744]. Absorption correction by semi-empirical from equivalents; minimum and maximum transmission factors: 0.63; 0.96. No crystal decay. *Structure analysis and refinement*: Systematic absences indicated space group $P2(1)2(1)2(1)$ and shown to be correct by successful refinement. The structure was solved by direct methods using SHELXS (Sheldrick, 1990) (TREF) with additional light atoms found by Fourier methods. Hydrogen atoms were added at calculated positions and refined using a riding model with freely rotating methyl groups. Anisotropic displacement parameters were used for all non-H atoms; H-atoms were given isotropic displacement parameters equal to 1.2 (or 1.5 for methyl hydrogen atoms) times the equivalent isotropic displacement parameter of the atom to which the H-atom is attached. The chirality was established from the known chirality of the compound and checked by refinement of a delta-f″ multiplier. Absolute structure parameter $x = -0.02(13)$. R_1 [For 4680 reflections with $I > 2\sigma(I)$] = 0.0769, $wR_2 = 0.1639$. Data/restraints/parameters 7572/0/389. Extinction coefficient 0.0017(6). Largest difference Fourier peak and hole 0.380 and −0.451 e A^{-3}. Refinement used SHELXTL.[10]

Additional material for all X-ray analyses available from the Cambridge Crystallographic Data Centre comprises H-atom coordinates, thermal parameters and the remaining bond lengths and angles. The following crystal structures have been deposited at the Cambridge Crystallographic Data Centre: CCDC 636611 (**6**); CCDC 636612 (**11**); CCDC 636613 (**7**).

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References

1. (a) Williams, G. D.; Pike, R. A.; Wade, C. E.; Wills, M. *Org. Lett.* **2003**, *5*, 4227–4230; (b) Williams, G. D.; Wade, C. E.; Wills, M. *Chem. Commun.* **2005**, 4735–4737.
2. Smith, M. B.; Dembofsky, B. T.; Son, Y. C. *Org. Chem.* **1994**, *59*, 1719–1725.
3. Latypov, S. K.; Riguera, R.; Smith, M. B.; Polivkova, J. *J. Org. Chem.* **1998**, *63*, 8682–8688.
4. Chen, P.; Tao, S.; Smith, M. B. *Synth. Commun.* **1998**, *28*, 1641–1648.
5. Chen, P.; Suh, D.-J.; Smith, M. B. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1317–1322.
6. Silverman, R. B.; Levy, M. A. *J. Org. Chem.* **1980**, *45*, 815–818.
7. (a) Miquel, C.; Pigache, P.; Rigo, B. *J. Heterocycl. Chem.* **1980**, *17*, 1447–1453; (b) Cauliez, P.; Rigo, B.; Fasseur, D.; Couturier, D. *J. Heterocycl. Chem.* **1991**, *28*, 1143–1146; (c) Rigo, B.; Lelier, J. P.; Kolocouris, N. *Synth. Commun.* **1986**, *16*, 1587–1591; (d) Rigo, B.; De Quillarcq, J.; Fossaert, E.; Kolocouris, N. *J. Heterocycl. Chem.* **1984**, *21*, 1393–1396; (e) Stark, J. B.; Goodman, A. E. *J. Am. Chem. Soc.* **1952**, *74*, 4966–4967.
8. Khim, S.-K.; Cederstrom, E.; Ferri, D. C.; Marinano, P. S. *Tetrahedron* **1996**, *52*, 3195–3222.
9. Kanao, S. *Chem. Abstr.* **1952**, *46*, 11044.
10. Sheldrick, G. M. SHELXTL ver 5.1, **1997**, Bruker Analytical X-ray Systems, Madison, Wis. USA.
11. The X-ray crystallographic structure of this compound has been reported: Jones, F. T.; Palmer, K. J.; Black, D. R. *Anal. Chem.* **1953**, *25*, 1929–1930.
12. Fletcher, D. A.; McMeeking, R. F.; Parkin, D. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 746.