Supporting information.

Synthesis and asymmetric hydrogenation of (3*E*)-1-benzyl-3-[(2-oxopyridin-1(2*H*)-yl)methylidene]piperidine-2,6-dione.

Alexander A. Bisset,[a] Akira Shiibashi,[b] Jasmine L. Desmond,[a] Allan Dishington,[c] Teyrnon Jones,[c] Guy J. Clarkson, [a] Takao Ikariya[b] and Martin Wills.[a*]

a Department of Chemistry, The University of Warwick, Coventry, CV4 7AL, UK. Fax: 24 7652 4112; Tel: 24 7652 3260; E-mail: m.wills@warwick.ac.uk

b Department of Applied Chemistry, Graduate School of Science and Engineering, Tokyo Institute of Technology, 2-12-1-E4-1 O-okayama, Meguro-ku, Tokyo 152-8552, Japan

c *AstraZeneca, Oncology Innovative Medicines, Alderley Park, Macclesfield, Cheshire, England. SK10 4TG, UK.*

1) Experimental details.

General:

All reactions unless otherwise stated were run under an atmosphere of nitrogen in glassware (round bottomed flasks or schlenk tubes). Room temperature refers to ambient room temperature (20-22 °C), and 0 °C refers to an ice slush bath. Heated experiments were conducted using thermostatically controlled oil baths. Reactions were monitored by thin layer chromatography (TLC) using aluminium backed silica gel 60 (F254) plates, visualised using UV254 nm and PMA, potassium permanganate and ninhydrin dips as appropriate. Flash column chromatography was carried out routinely using 60 Å silica gel. NMR spectra were recorded on 300, 400 MHz and 700 MHz spectrometers as indicated. Chemical shifts are reported in δ units, parts per million downfield from TMS. Coupling constants (J) are reported in Hertz. IR spectra were recorded on an FTIR instrument fitted with a golden gate single reflection diamond attenuated total reflection top plate. Mass spectra were recorded on an ESI mass spectrometer unless otherwise indicated. Determinations of enantiomeric excesses were made by chiral GC or HPLC and specific conditions are listed where appropriate. Optical rotations were measured on an polarimeter. Hydrogenations were carried out in a bench-top hydrogenator if the required pressure was > 1atm. Data collection and processing was carried out on a four-circle diffractometer system with Ruby CCD area detector or by the UK X-ray data centre.

1-Benzylpiperidine-2,6-dione **5.**

Glutaric anhydride (1.26 g, 11.06 mmol) was added to NEt_3 (1.54 mL, 11.06 mmol) in THF (40 cm^3) at 0 °C. Benzylamine (1.21 mL, 11.06 mmol) in THF (40 cm^3) was added dropwise to the first mixture over 1 h, which was cooled to 0 °C. The mixture was heated to 75 °C and left stirring for 24 h before hydrochloric acid (1 M, 40 cm^3) was added. Following extraction

with ethyl acetate (3 x 55 cm^3), the organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give the intermediate $BnNHCO(CH_2)_3CO_2H$ (2.34 g, 10.58 mmol, 96 % yield) as a white solid; (found (EI): M^+ + Na, 244.0944. $C_{12}H_{15}NNaO_3$ requires MH^+, 244.0944); ν_{max} 3303, 3031, 2954, 1693, 1638, 1543, 1453, 1260 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.36-7.25 (5H, m), 5.81 (1H, s), 4.42 (2H, d, *J* 5.5), 2.44 (2H, t, *J* 7.0), 2.31 (2H, t, *J* 7.0), 1.99 (2H, q, *J* 7.0,); δ_C (75 MHz, $CDCl_3$) 177.68, 172.32, 137.95, 128.75, 127.83, 127.61, 43.71, 35.21, 33.00, 20.68; m/z (ESI) 222.0 (M^+ + 1). The data was in agreement with that reported in the literature.[1] The intermediate $BnNHCO(CH_2)_3CO_2H$ (2.34 g, 10.58 mmol) was added to acetyl chloride (60 mL) and was then heated to 65 °C. The mixture was heated to 65 °C and left stirring for 10 h before the mixture was allowed to cool to room temperature. Acetyl chloride was removed under reduced pressure before the product was purified by column chromatography (hexane – 70/30 hexane / ethyl acetate) to give product **5** (1.93 g, 9.52 mmol, 86 %) as a yellow oil; (found (EI): M^+ + H, 204.1028. $C_{12}H_{14}NO_2$ requires MH^+, 204.1019); ν_{max} 3034, 2964, 1760, 1723, 1669, 1456, 1168 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.35-7.32 (5H, m), 4.95 (2H, s), 2.68 (4H, t, *J* 6.5), 2.41 (2H, q, *J* 6.5); δ_C (75 MHz, $CDCl_3$) 173.48, 136.81, 128.81, 128.31, 127.38, 42.57, 32.80, 17.03; m/z (ESI) 204.0 (M^+ + 1), 226.0 (M^+ + 23). The data was in agreement with that reported.[1a,b]

(Z)-1-Benzyl-3-(hydroxymethylene)piperidine-2,6-dione **6**.

Under an inert atmosphere, dry ethanol (1.60 cm^3, 27.44 mmol) was added dropwise to a suspension of 60 % NaH in oil (1.10 g, 27.58 mmol) in Et_2O (32.0 cm^3) at 0 °C and left stirring for 20 min or until evolution of hydrogen had ceased. In a second flask, imide **5** (2.0 g, 9.85 mmol) and ethyl formate (1.35 cm^3, 16.75 mmol) were added to Et_2O (32.0 cm^3). This mixture was transferred dropwise to the first flask over 1 h at 0 °C, then left warming to room temperature and stirred for 16 h before extraction with water (2 x 40 cm^3). The aqueous

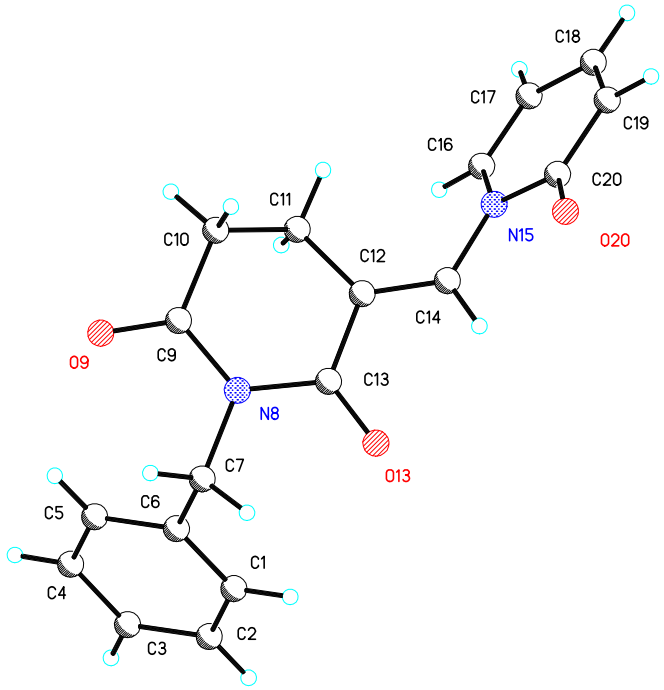
and concentrated under reduced pressure to give the intermediate $BnNHCO(CH_2)_3CO_2H$ (2.34 g, 10.58 mmol, 96 % yield) as a white solid; (found (EI): M^+ + Na, 244.0944. $C_{12}H_{15}NNaO_3$ requires MH^+, 244.0944); ν_{max} 3303, 3031, 2954, 1693, 1638, 1543, 1453, 1260 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.36-7.25 (5H, m), 5.81 (1H, s), 4.42 (2H, d, *J* 5.5), 2.44 (2H, t, *J* 7.0), 2.31 (2H, t, *J* 7.0), 1.99 (2H, q, *J* 7.0,); δ_C (75 MHz, $CDCl_3$) 177.68, 172.32, 137.95, 128.75, 127.83, 127.61, 43.71, 35.21, 33.00, 20.68; m/z (ESI) 222.0 (M^+ + 1). The data was in agreement with that reported in the literature.[1] The intermediate $BnNHCO(CH_2)_3CO_2H$ (2.34 g, 10.58 mmol) was added to acetyl chloride (60 mL) and was then heated to 65 °C. The mixture was heated to 65 °C and left stirring for 10 h before the mixture was allowed to cool to room temperature. Acetyl chloride was removed under reduced pressure before the product was purified by column chromatography (hexane – 70/30 hexane / ethyl acetate) to give product **5** (1.93 g, 9.52 mmol, 86 %) as a yellow oil; (found (EI): M^+ + H, 204.1028. $C_{12}H_{14}NO_2$ requires MH^+, 204.1019); ν_{max} 3034, 2964, 1760, 1723, 1669, 1456, 1168 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.35-7.32 (5H, m), 4.95 (2H, s), 2.68 (4H, t, *J* 6.5), 2.41 (2H, q, *J* 6.5); δ_C (75 MHz, $CDCl_3$) 173.48, 136.81, 128.81, 128.31, 127.38, 42.57, 32.80, 17.03; m/z (ESI) 204.0 (M^+ + 1), 226.0 (M^+ + 23). The data was in agreement with that reported.[1a,b]

(Z)-1-Benzyl-3-(hydroxymethylene)piperidine-2,6-dione **6**.

Under an inert atmosphere, dry ethanol (1.60 cm^3, 27.44 mmol) was added dropwise to a suspension of 60 % NaH in oil (1.10 g, 27.58 mmol) in Et_2O (32.0 cm^3) at 0 °C and left stirring for 20 min or until evolution of hydrogen had ceased. In a second flask, imide **5** (2.0 g, 9.85 mmol) and ethyl formate (1.35 cm^3, 16.75 mmol) were added to Et_2O (32.0 cm^3). This mixture was transferred dropwise to the first flask over 1 h at 0 °C, then left warming to room temperature and stirred for 16 h before extraction with water (2 x 40 cm^3). The aqueous extracts were acidified with weak aqueous HCl, followed by extraction with Et_2O (3 x 50

(E)-1-Benzyl-3-((2-oxopyridin-1(2H)-yl)methylene)piperidine-2,6-dione **4** and C-O isomer **8**. Under nitrogen, **7** (1.32 g, 3.43 mmol) was added to a solution of 2-hydroxypridine (0.98 g, 10.30 mmol) and NEt_3 (1.67 cm^3, 12.02 mmol) in dry toluene (42.0 cm^3). The mixture was heated with a reflux condenser to 125 ^{0}C for 20 h with stirring. Removal of the solvent under reduced pressure gave the crude product as dark black tar which was purified by column chromatography (10/90 hexane/ethyl acetate) to give **4** (0.687 g, 2.23 mmol, 65 % yield) as a dark brown solid; Mp 138 – 144 ^{0}C; (found (EI): M^+ + H, 309.1235. $C_{18}H_{17}N_2O_3$ requires $M+H^+$, 309.1234); ν_{max} 3020, 2960, 1720, 1660, 1630, 1580, 1520, 1440, 1250, 730, 680 cm^{-1}; δ_H (400 MHz, $CDCl_3$); 7.97 (1 H, s), 7.43-7.35 (3 H, m), 7.34-7.22 (3 H, m), 7.10 (1 H, dd, *J* 7.0, 2.0), 6.62 (1 H, d, *J* 9.0 Hz), 6.24 (1 H, td, *J* 7.0, 1.5 Hz), 5.04 (2 H, s), 2.78-2.64 (4 H, m); δ_C (101 MHz, $CDCl_3$) 170.86, 165.16, 161.51, 140.25, 136.75, 136.34, 135.50, 128.73, 128.33, 127.46, 124.50, 121.90, 106.39, 43.37, 31.40, 20.91; *m/z* (ESI) 309.1 (M^+ + 1), 331.1 (M^+ + 23).

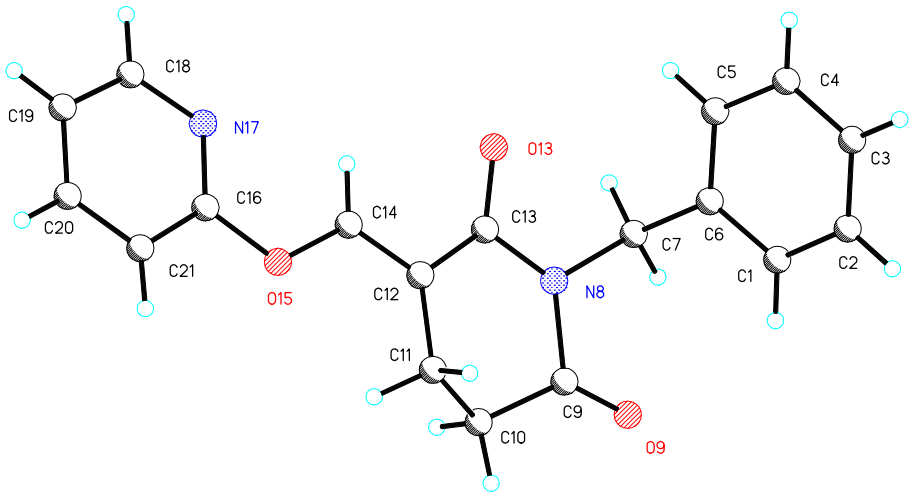
Crystallographic data for **4** (CCDC873751). $C_{18}H_{16}N_2O_3$, M = 308.33, Monoclinic, space group P21/c, a = 13.8161(4), b = 9.6613(2), c = 11.7717(3) Å, α = 90 deg., β = 107.2680(10) deg., γ = 90 deg. U = 1500.48(7) $Å^3$ (by least squares refinement on 9224 reflection positions), T =120(2) K, lambda = 071073 Å, Z = 4, D(cal) = 1.365 Mg/m^3, F(000) = 648. mυ(MoK-α) = 0.094 mm^{-1}. Crystal character: colourless block. Crystal dimensions 0.60 x 0.38 x 0.05 mm. 20600 reflections measured, 3425 unique [R(int) = 0.0430].



Initially, at shorter reaction times, the *O*-substituted isomer **8** was also isolated in varying yields from the reaction mixture following column chromatography (hexane- 50/50 hexane / ethylacetate) and recrystallisation (EtOH) as a colourless crystalline product; (found (EI): M^+ + H, 309.1248. $C_{18}H_{17}N_2O_3$ requires MH^+, 309.1234,); ν_{max} 3020, 2960, 1710, 1690, 1660, 1580, 1250, 720, and 690 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 8.82 (1 H, s), 8.25 (1 H, dd, *J* 5.0, 1.5), 7.75 - 7.71 (1 H, m), 7.44-7.15 (5 H, m), 7.13-7.09 (1 H, m), 6.94 (1 H, d, *J* 8.5), 5.04 (2 H, s), 2.84-2.79 (2 H, m), 2.75-2.70 (2 H, m); δ_C (126 MHz, $CDCl_3$) 148.47, 147.45, 139.83, 128.77, 128.34, 127.29, 120.25, 111.30, 43.01, 31.76, 17.75; *m/z* (ESI) 309.1 (M^+ + 1), 331.1 (M^+ + 23).

Crystallographic data for **8** (CCDC873752). $C_{18}H_{16}N_2O_3$, M = 308.33, Monoclinic, space group P21/c, a = 14.0338(5) b = 8.3474(3), c = 13.1017(3) Å, α = 90 deg., β = 96.381(2)

deg., γ = 90 deg. U = 1525.30(8) $Å^3$ (by least squares refinement on 13564 reflection positions), T =298(2) K, lambda = 0.71073 Å, Z = 4, D(cal) = 1.343 Mg/m^3, F(000) = 648. mυ(MoK-α) = 0.093 mm^{-1}. Crystal character: pale block. Crystal dimensions 0.58 x 0.38 x 0.25 mm. 27338 reflections measured, 3487 unique [R(int) = 0.0544].



In further experiments, long reaction times (20 h as opposed to 10 h) were found to result in an absence of O-substituted product **8** (Table 3). To determine if the N-product **4** was a thermodynamically favoured product, a separate isomerisation experiment was carried out. An mixture of **4**, **8,** and 2-hydroxypyridine were combined under the same reaction conditions and found to form only the N-substituted product. This suggests that isomerisation occurs between the two O- and N- compounds, forming the thermodynamically favoured product, **4**.[2,3]

Table 3: Yields of products **4** and **8**.

Run code	**Scale / g**	**N-product 4 / %**	**O-product 8 / %**	**Reaction Time / h**
ALX17	0.45	14	25	10

ALX33	0.45	32	12	10
ALX41	0.28	75	0	20
ALX49	1.32	65	0	20
ALX161	4.18	48	0	20
ALX321	1.54	62	0	20

Procedure for the isomerisation of N- and O- substituted Compounds

Under nitrogen, NEt_3 (0.15 cm^3, 1.09 mmol) was added to a mixture containing **4** (67 mg, 0.218 mmol), **8** (44 mg, 0.143 mmol), and 2-hydroxypridine (42 mg, 0.436 mmol) in dry toluene (3.0 cm^3). The mixture was heated with a reflux condenser to 125 ^{0}C for 20 h with stirring. Removal of the solvent by reduced pressure gave the crude product which contained the *N*-substituted product **4** as the major product, and only a trace of the *O*- substituted product **8** (as determined by ^{1}H NMR analysis).

*Procedure for the transfer hydrogenation of **4**.*

Alkene **4** (10 mg, 3.2 x 10^{-2} mmol) was added to a solution of [Ru(*S,S*)*teth*-TsDPEN] **9b** (0.6 mg, 9.7 x 10^{-4} mmol) in dry ethanol (0.6 cm^3) at 28 ^{0}C before formic acid:triethylamine (5:2) (33 μL) was added. The solution was stirred at 28 ^{0}C for 5 days before saturated aqueous hydrogen carbonate (1.0 cm^3) was added. Following extraction with DCM (3 × 2.0 cm^3), the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product which was purified by chromatography (10/90 hexane / ethyl acetate) to give compound **10** as an oil (8 mg, 2.6 x 10^{-2} mmol, 81 % yield) which was identified by ^{1}H NMR. The product was found to be racemic (compared with authentic sample; see next paragraph). Full characterisation data for **10** is given in a later section.

*Procedure for the transfer hydrogenation of **4** with Ru(TsEN) **9a**.*

Under nitrogen, $[Ru(cymene)Cl_2]_2$ (0.4 mg, 6.5 x 10^{-4} mmol) and TsEN (0.8 mg, 2.8 x 10^{-3} mmol) were added to a mixture of dry ethanol (1.0 cm^3) and formic acid triethylamine (5:2) (78 μL) at 28 ^{0}C and left to stir for 20 min. Alkene **4** (20 mg, 6.5 x 10^{-2} mmol) was added and the solution was stirred at 28 ^{0}C for 5 days before saturated aqueous hydrogen carbonate (1.0 cm^3) was added. Following extraction with DCM (3 × 2.0 cm^3), the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to yield **10** as an oil (18 mg, 89 % yield, 5.8 x 10^{-2} mmol) which was identified by ^{1}H NMR. Full characterisation data for **10** is given in a later section.

(S)-1-Benzyl-3-((2-oxopyridin-1(2H)-yl)methyl)piperidine-2,6-dione **10** and reduction product **13**.

Under nitrogen, a solution of thoroughly dried alkene **4** (0.78 g, 2.53 mmol) and $[Rh(COD)(Et\text{-}DuPHOS)]BF_4$ (50.7 mg, 76.7 x 10^{-3} mmol) in dry DCM (10.14 cm^3) was degassed three times. The solution was divided equally into five glass test tubes which were used in the hydrogenation procedure. To the stirred solutions, the hydrogenation was performed at 20 °C under 25 bar hydrogen for 5 days. The reaction mixture was passed through a short silica gel column (10/90 hexane / ethyl acetate) to remove the catalyst, yielding product (*S*)-**10** (0.75 g, 2.42 mmol, 96 % yield) as a colourless solid; Mp 124 - 126 ^{0}C (found (EI): M^+ + Na, 333.1208. $C_{18}H_{18}N_2NaO_3$ requires MNa^+, 333.1300); ν_{max} 3035, 2953, 1724, 1657, 1584, 1540, 1455, 1160 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.42 (1 H, dd, *J* 7.0, 2.0), 7.37-7.19 (6 H, m), 6.55 (1 H, d, *J* 9.0), 6.14 (1 H, t, *J* 7.0), 4.97 (1 H, d, *J* 14.0), 4.89 (1 H, d, *J* 14.0), 4.38 (1 H, dd, *J* 13.0, 6.0), 4.16 (1 H, dd, *J* 13.0, 6.0), 3.11 (1 H, dt, *J* 18.0, 6.0), 2.85 (1 H, dt, *J* 18.0, 3.5), 2.63 (1 H, m), 2.10 (1 H, m), 1.74 (1 H, dq, *J* 13.0, 5.0); δ_C (100 MHz, $CDCl_3$) 173.30, 171.68, 162.84, 139.78, 138.68, 136.92, 128.49, 128.34, 127.39,

120.71, 105.89, 50.17, 41.98, 40.95, 32.24, 21.10; *m/z* (ESI) 311.1 (M^+ + 1), 333.1 (M^+ + 23); (Chiracel IA, 25 cm x 4.6 mm column, iPrOH : hexane 15 : 85, 1 mL/min, T = 20 ^{0}C, *S* isomer 23.5 min, *R* isomer 55.8 min.) 90 % ee; $[\alpha]_D^{25}$ + 11.1 (***c***1.00 in $CHCl_3$). Configuration was subsequently determined by analysis of compound (*R*)-**23**.

During other experiments, over-reduction to lactam **13** was observed. This crude mixture of **10** and **13** could not be separated by chromatography. Subsequently, the ee of **10** in these cases was not determined by direct HPLC analysis but by hydrogenation of the mixture to **13**, from which the ee was determined by HPLC analysis. The ee of this sample was taken to as an indirect indication of the ee of compound **10**. The experimental procedure for this analysis is shown in the next section.

(S)-1-Benzyl-3-((2-oxopiperidin-1-yl)methyl)piperidine-2,6-dione **13**.

Under nitrogen, a solution of an inseparable mixture of (*S*)-**10** and (*S*)-**13** (89 % and 11 % respectively, as determined by ^{1}H NMR analysis; (15.0 mg, 4.8 x 10^{-2} mmol) and palladium on charcoal (2.6 mg, 2.4 x 10^{-3} mmol, 10 % Pd / w) in dry MeOH (1.00 cm^3) was hydrogenated at room temperature under 5 bar hydrogen overnight. The catalyst was removed by filtration with celite and the reaction mixture was passed through a short silica gel column (10/90 hexane / ethyl acetate) to yield the product, (*S*)-**13** (15 mg, 0.048 mmol, > 99 % yield) as a colourless waxy solid (full characterisation is listed in the next section); enantiomeric excess determined by HPLC analysis (Chiracel IA, 25 cm x 4.6 mm column, IPA : hexane 30 : 70, 1 mL/min, T = 15 ^{0}C, *S* isomer (major) 10.28 min., *R* isomer (minor) 23.26 min.) 94.5 % ee; $[\alpha]_D^{25}$ + 55.1 (***c*** 0.1 in $CHCl_3$). Full characterization data for **20** is given in the next section. The HPLC of the racemic sample (see below) was used to determine the position of the peaks for analysis.

Racemic-1-benzyl-3-((2-oxopiperidin-1-yl)methyl)piperidine-2,6-dione **10**.

A short reaction time allowed isolation of the reduction of the C=C bond before subsequent reduction of the pyridone ring. Under nitrogen, a solution of **4** (30 mg, 9.7 x 10^{-2} mmol) and palladium on charcoal (21 mg, 9.7 x 10^{-3} mmol, 5 % Pd / w) in dry MeOH (0.2 cm^3) and dry DCM (0.2 cm^3) was hydrogenated at room temperature under a balloon of hydrogen for 30 min before the catalyst was removed by filtration with celite and the reaction mixture was passed through a short silica gel column (10/90 hexane / ethyl acetate) to yield the product, (±)-**10** (20 mg, 6.5 x 10^{-2} mmol, 67 % yield) as a colourless solid.

Racemic 1-benzyl-3-((2-oxopyridin-1-yl)methyl)piperidine-2,6-dione **13**.

A longer reaction time and higher pressure resulted in reduction of both the C=C bond and the pyridone ring. Under nitrogen, a solution of **4** (50.0 mg, 0.16 mmol) and palladium on charcoal (8.6 mg, 8.11 x 10^{-3} mmol, 10 % Pd / w) in dry MeOH (2.50 cm^3) was hydrogenated at room temperature under 5 bar hydrogen overnight. The catalyst was removed by filtration with celite and the reaction mixture was passed through a short silica gel column (10/90 hexane / ethyl acetate) to yield the crude product, (±)-**13** (46 mg, 0.15 mmol, 90 % yield) as a colourless waxy solid; found (EI): M^+ + Na, 337.1522. $C_{18}H_{22}N_2NaO_3$ requires MNa^+, 337.1500); ν_{max} 3031, 2945, 1721, 1670, 1629, 1452, 1163 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.37-7.20 (5 H, m), 4.99-4.90 (2 H, m), 3.87 (1 H, dd, *J* 13.5, 7.5), 3.59 (1 H, dd, *J* 13.5, 6.0), 3.32 - 3.43 (1 H, m), 3.23-3.13 (1 H, m), 2.85 - 2.97 (2 H, m), 2.66-2.55 (1 H, m), 2.42-2.33 (2 H, m), 2.08-1.97 (1 H, m), 1.85-1.66 (5 H, m); δ_C (75 MHz, $CDCl_3$) 173.53, 172.07, 170.59, 137.10, 128.58, 128.30, 127.34, 48.90, 47.52, 42.90, 40.97, 32.23, 31.58, 23.19, 21.13, 20.71; *m/z* (ESI) 315.2 (M^+ + 1), 338.1 (M^+ + 23+1).

Procedure for the screening of asymmetric hydrogenation ligands.

Under nitrogen, a solution of thoroughly dried alkene **4** (30.0 mg, 0.10 mmol) in dry DCM (0.39 cm^3) was purged with argon for 30 min before $[Rh(COD)Cl]_2$ (0.8 mg, 1.6 x 10^{-3} mmol) and the ligand (3.0 x 10^{-3} mmol) were added. To the stirred solution, the hydrogenation was performed at 30 °C under 25 bar hydrogen for 5 days. The reaction mixture was purified by silica gel column chromatography (10/90 hexane /ethyl acetate) to separate reaction products where applicable, yielding products **10** and / or product **13** as determined by ^1H NMR and analysed for enantiomeric excess by HPLC (conditions as described above). Results are given in Table 2. The highest ee for this transformation was obtained using Taniaphos SL-T002-1 **17** under the same conditions as described above. In this case the ee of exclusive product **13** was 98 % (*R*) and was determined by direct HPLC analysis following purification by flash chromatography): (Chiracel IA, 25 cm x 4.6 mm column, iPrOH : hexane 15 : 85, 1 mL/min, T = 15 ^{0}C, *S* isomer 31.5 min, *R* isomer 57.3 min.) 98 % ee. The configuration was subsequently determined by analysis of compound (*R*)-**20**.

*Compound **19**.*

Under nitrogen, **7** (0.46 g, 1.19 mmol) was added to a solution of pyrrolidine (0.20 cm^3, 2.39 mmol) and NEt_3 (0.41 cm^3, 2.96 mmol) in dry toluene (14.0 cm^3) and the mixture stirred at 125 ^{0}C for 8 h. The mixture was concentrated under reduced pressure the crude product as dark black oil which was purified by column chromatography (10/90 hexane / ethyl acetate) to give the product **19** (0.119 g, 0.42 mmol, 35 %), as an dark oil; (found (EI): M^+ + Na, 307.1410. $C_{17}H_{20}N_2NaO_2$ requires M^+, 307.1417); ν_{max} 3020, 2955, 1716, 1668, 1608, 1152 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.64 (1 H, s), 7.33-7.08 (5 H, m), 4.94 (2 H, s), 3.50-3.40 (4 H,

m), 2.72 (2 H, t, *J* 7.0), 2.52 (2 H, t, *J* 7.0), 1.88-1.77 (4 H, m); δ_C (101 MHz, $CDCl_3$) 172.68, 168.92, 146.75, 138.55, 128.37, 128.20, 126.82, 92.99, 51.70, 42.93, 33.03, 25.37, 19.25.; *m/z* (ESI) 307.1 (M^+ + 23).

(R)-1-((1-Benzyl-6-oxopiperidin-3-yl)methyl)pyridin-2(1H)-one **20** *and minor isomer* **22**.

Under nitrogen, a solution of imide (*S*)-**10** (90 % ee, Table 2, entry 4) (200 mg, 0.645 mmol) in dry ethanol (6.0 cm^3) was acidified to approximately pH 7 with HCl (20 μL, 0.8 M) and cooled to 0 ^{0}C. To the stirred solution, $NaBH_4$ (73 mg, 1.93 mmol) was added portionwise at 10 min intervals. Throughout the reaction HCl (20 μL, 0.8 M) was added in 10 min intervals to maintain the reaction at approximately pH 7. After 40 min, the reaction was neutralised and saturated aqueous sodium hydrocarbonate (10.0 cm^3) was added. Following extraction with DCM (3 x 5 cm^3), the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude intermediate product **21** (~200 mg) as a slightly orange oil. Approximate conversion was deduced by ^{1}H NMR analysis. No further purification was attempted. Under nitrogen, the crude intermediate product **21** was added to Et_3SiH (512 μL, 3.21 mmol) in TFA (1.14 cm^3) and dry DCM (1.14 cm^3). The mixture was heated to 45 ^{0}C and stirred for 5 h before saturated aqueous sodium hydrocarbonate (10 cm^3) was carefully added. Following extraction with DCM (3 x 10 cm^3), the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product which was purified by column chromatography (95/5 ethyl acetate / methanol) to give the major amide (*R*)-**20** (65 mg, 0.220 mmol, 34 % yield from imide (*S*)-**10**) as a colourless oil; found (EI): M^+ + Na, 319.1417. $C_{18}H_{20}N_2NaO_2$ requires MNa^+, 319.1417); ν_{max} 3066, 2929, 1650, 1629, 1580, 1451 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.30-7.14 (6 H, m), 6.82 (1 H, dd, *J* 7.0, 2.0), 6.47 (1 H, d, *J* 9.0), 5.99 (1 H, t, *J* 7.0), 4.65 (1 H, d, *J* 14.5), 4.36 (1 H, d, *J* 14.5), 3.79-3.67 (2 H, m), 3.17 (1 H, dd, *J* 12.0, 5.0), 2.94 (1 H, dd, *J* 12.0, 9.0), 2.50 (1 H, dt, *J* 18.0, 5.5), 2.44-

2.31 (2 H, m), 1.77 - 1.89 (1 H, m), 1.56 (1 H, dtd, *J* 13.5, 10.0, 6.5); δ_C (176 MHz, $CDCl_3$) 169.19, 162.58, 139.60, 137.60, 136.96, 128.69, 128.29, 127.54, 121.30, 105.97, 52.21, 50.19, 49.58, 33.05, 30.58, 24.83; m/z (ESI) 319.2 (M^+ + Na); $[\alpha]_D^{25}$ + 8.8 (***c*** 0.7 in $CHCl_3$) 20 % ee (*R*) (reported[4] $[\alpha]_D^{24}$ + 31.3 (***c*** 0.8, $CHCl_3$) 98 % ee *(R)*). Because the ee of **20** could not be determined directly using GC or HPLC methods available to us, it was established by chiral HPLC of **23** as described below, spectroscopic data matching that reported in the literature.[4]

An attempt was made by column chromatography (10/90 hexane /ethyl acetate) to fully purify the minor amide **22** (varying yields, commonly a 3:1 ratio of **20:22** in the crude product) however this could not be fully purified. Data for **22** obtained from this mixture; δ_H (400 MHz, $CDCl_3$) 7.53 (1 H, dd, *J* 7.0, 2.0), 7.38-7.20 (6H, m, Ar), 6.55 (1 H, d, *J* 9.0), 6.16-6.10 (1H, m), 4.60-4.51 (2H, m), 4.45-4.40 (2H, m), 3.22-3.16 (1H, m), 2.90-2.82 (1H, m), 2.08-2.00 (1H, m), 1.90-1.82 (1H, m), 1.80-1.68 (1H, m), and 1.60-1.50 (2H, m).

Racemic 1-((1-benzyl-6-oxopiperidin-3-yl)methyl)piperidin-2-one **23** and regiosiomer **24**.

Under nitrogen, a solution of imide (±)-**13** (56.0 mg, 0.19 mmol) in dry ethanol (1.70 cm^3) was acidified to approximately pH 7 with HCl (~ 5 μL, 0.8 M) and cooled to 0 ^{0}C. To the stirred solution, $NaBH_4$ (13.5 mg, 0.36 mmol) was added portion-wise at 10 min intervals. Throughout the reaction, HCl (~5 μL, 0.8 M) was added in 10 min intervals to maintain the reaction at approximately pH 7. After 40 min the reaction was neutralised and saturated aqueous sodium hydrocarbonate (1.00 cm^3) was added. Following extraction with DCM (3 x 1 cm^3), the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude intermediate product (52.5 mg) as a slightly orange oil. No further purification was attempted. Under nitrogen, the crude intermediate product (53.0 mg, 0.17 mmol) was

added to Et_3SiH (134 µL, 0.84 mmol) in TFA (0.30 mL) and dry DCM (0.30 cm^3). The mixture was heated to 40 ^0C and stirred for 5 h before saturated aqueous sodium hydrocarbonate (1 cm^3) was added. Following extraction with DCM (3 x 1 cm^3), the organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give the crude product which was purified by column chromatography (95:5 ethyl acetate / methanol) to give the minor amide (±)-**24** (10.5 mg, 0.04 mmol, 20 % yield) as a colourless oil; found (EI): M^+ + Na, 323.1733. $C_{18}H_{24}N_2NaO_2$ requires MNa^+, 323.1730); ν_{max} 3080, 2928, 1624, 1590, 1456 cm^{-1}; δ_H (700 MHz, $CDCl_3$) 7.28-7.14 (5 H, m), 4.54-4.48 (2 H, m), 4.09-4.01 (1 H, m), 3.44 (1 H, dd, *J* 13.5, 5.0), 3.39-3.31 (1 H, m), 3.21-3.09 (3 H, m), 2.67-2.59 (1 H, m), 2.37-2.28 (2 H, m), 1.90-1.83 (1 H, m), 1.79 (1 H, dtd, *J* 13.0, 6.5, 2.5), 1.76-1.69 (2 H, m), 1.66-1.46 (4 H, m); δ_C (176 MHz, $CDCl_3$) 170.84, 170.42, 137.15, 128.60, 127.99, 127.36, 50.37, 48.15, 48.01, 47.45, 40.42, 32.38, 24.62, 23.28, 21.20; m/z (ESI) 301.2 (M^+ + 1), 323.2 (M^+ + 23) and the major amide (±)-**23** (15.0 mg, 0.05 mmol, 28 % yield) as a colourless oil; found (EI): M^+ + H, 301.1922. $C_{18}H_{25}N_2O_2$ requires MH^+, 301.1911); ν_{max} 2950, 1631, 1453 cm^-1; δ_H (400 MHz, $CDCl_3$) 7.36-7.21 (5 H, m), 4.72 (1 H, d, *J* 15.0), 4.44 (1 H, d, *J* 15.0), 3.78-3.71 (1 H, m), 3.38-3.30 (1 H, m), 3.22 (1 H, dd, *J* 13.5, 7.5), 3.19-3.11 (2 H, m), 3.00-2.95 (1 H, m), 2.64-2.54 (1 H, m), 2.49-2.38 (1 H, m), 2.37-2.31 (1 H, m), 2.25-2.12 (1 H, m), 1.89 - 1.80 (2 H, m), 1.79 - 1.69 (4 H, m), 1.50 - 1.62 (1 H, m); δ_C (176 MHz, $CDCl_3$) 170.18, 169.51, 137.06, 128.59, 128.15, 127.39, 50.36, 50.14, 49.78, 48.98, 32.67, 32.23, 31.19, 25.33, 23.26, 21.22; m/z (ESI) 301.2 (M^+ + 1), 323.2 (M^+ + 23). This sample was used in chiral HPLC to confirm the retention times of the enantiomers. The HPLC data is given in the following section.

(S)-1-((1-Benzyl-6-oxopiperidin-3-yl)methyl)piperidin-2-one **23**.

Under nitrogen, a solution of asymmetric product (*R*)-**20** (20% ee) (16.0 mg, 0.05 mmol) and palladium on charcoal (6.0 mg, 2.7 x 10^{-3} mmol, 5 % Pd / w) in dry MeOH (0.90 cm^3) was hydrogenated at room temperature under 5 bar hydrogen overnight. The catalyst was removed by filtration with celite and the reaction mixture was passed through a short silica gel column (10/90 hexane /ethyl acetate) to yield the crude product, (*S*)-**23** (15 mg, 0.050 mmol, 100 % conversion) as a colourless oil; enantiomeric excess determined by HPLC analysis (Chiracel IA, 25 cm x 4.6 mm column, IPA : hexane 95 : 5, 0.8 mL/min, T = 15 ^{0}C, *R* isomer (minor) 15.40 min., *S* isomer (major) 18.56 min.) 20 % ee. The racemic standard was used to establish the positions of the required peaks.

References.

1. (a) Burdzhiev, N. T.; Stanoeva, E. R. *Tetrahedron* **2006**, *62*, 8318-8326. (b) Zhang, J.; Senthilkumar, M.; Ghosh, S. C.; Hong S. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 6391-6395. (c) Cook, G. L.; Church, F. M. *J. Phys Chem.* **1957**, *61*, 458-462.

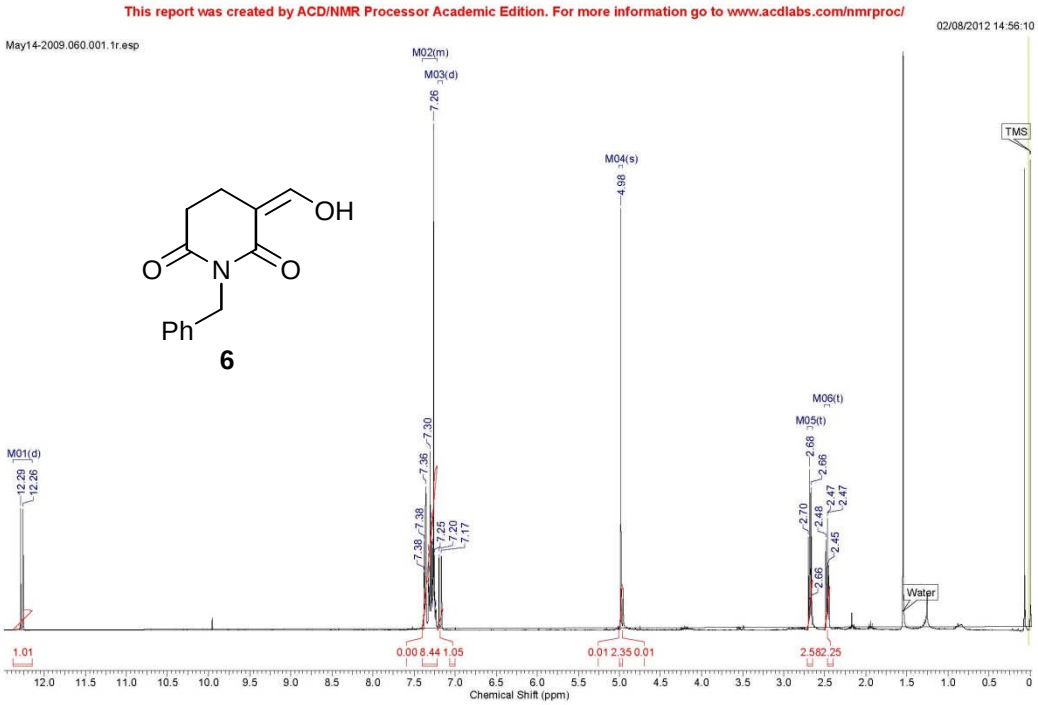
2. P. S. Mariano and R. B. Kromml, *Tetrahedron* 1978, **34**, 2609-2616.

3. A. McKillop and M. J. Ielesko, *Tetrahedron Lett.* 1968, **48**, 4945-4948.

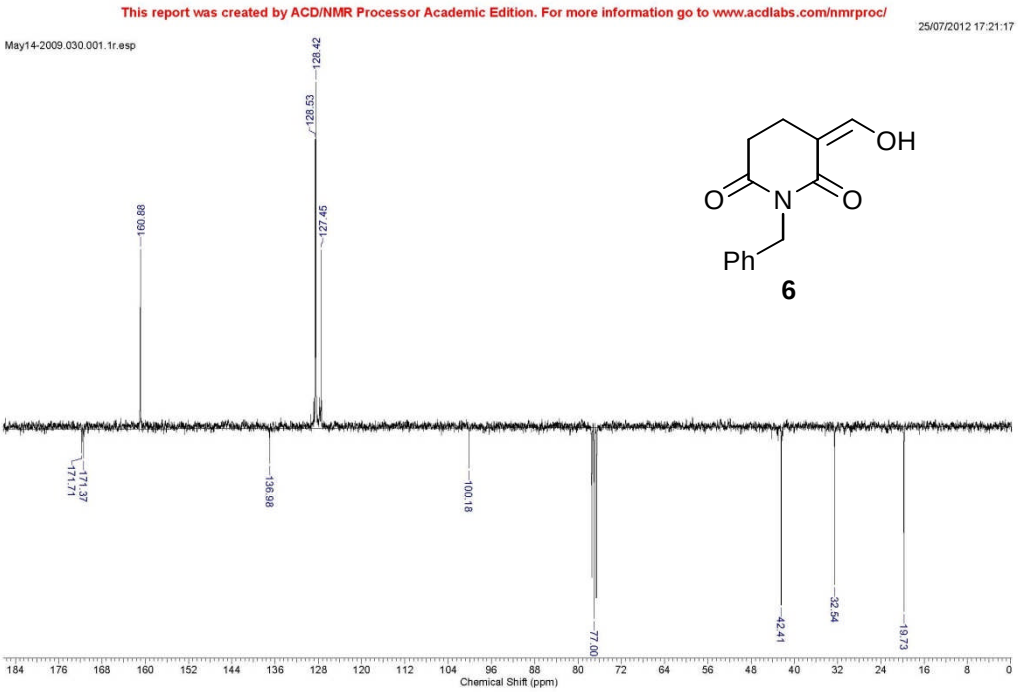
4. (a) D. Gray and T. Gallagher, *Angew. Chem. Int. Ed.* 2006, **45**, 2419-2423. (b) C. Botuha, C. M. S. Galley and T. Gallagher, *Org. Biomol. Chem.* 2004, **2**, 1825-1826. (c) C. Hirschhauser, C. A. Haseler and T. Gallagher, *Angew. Chem. Int. Ed.* 2011, **50**, 5162-5165.

2) ^{1}H and ^{13}C NMR Spectra of Novel Compounds.

(Z)-1-Benzyl-5-(hydroxymethylene)piperidine-2,6-dione, ***6***.

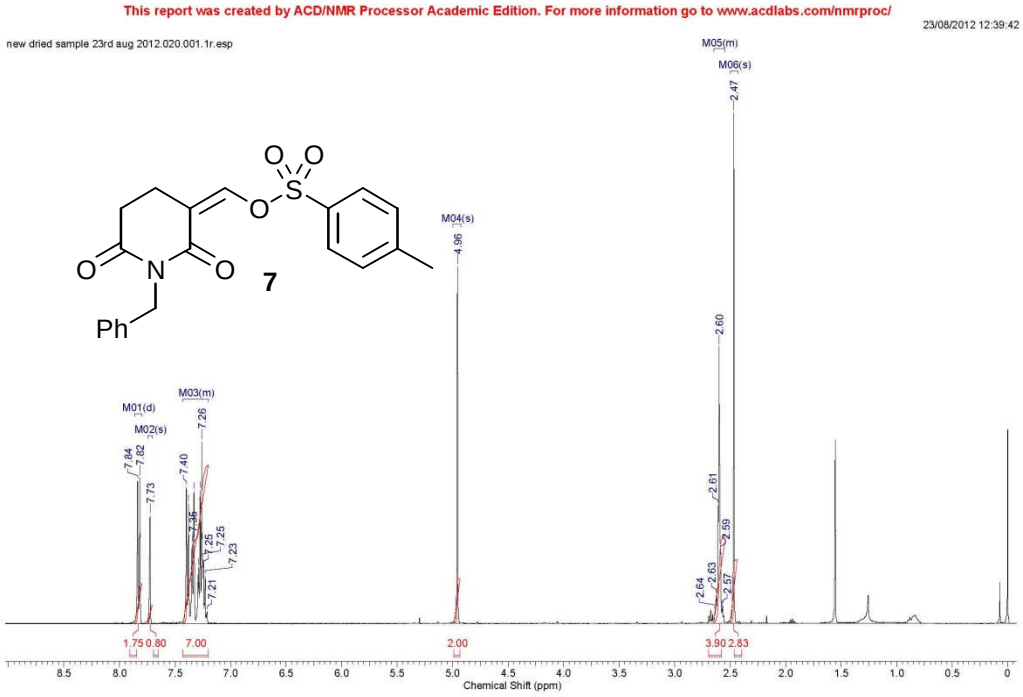


^{1}H NMR spectrum of ***6****, 300 MHz, $CDCl_3$.*

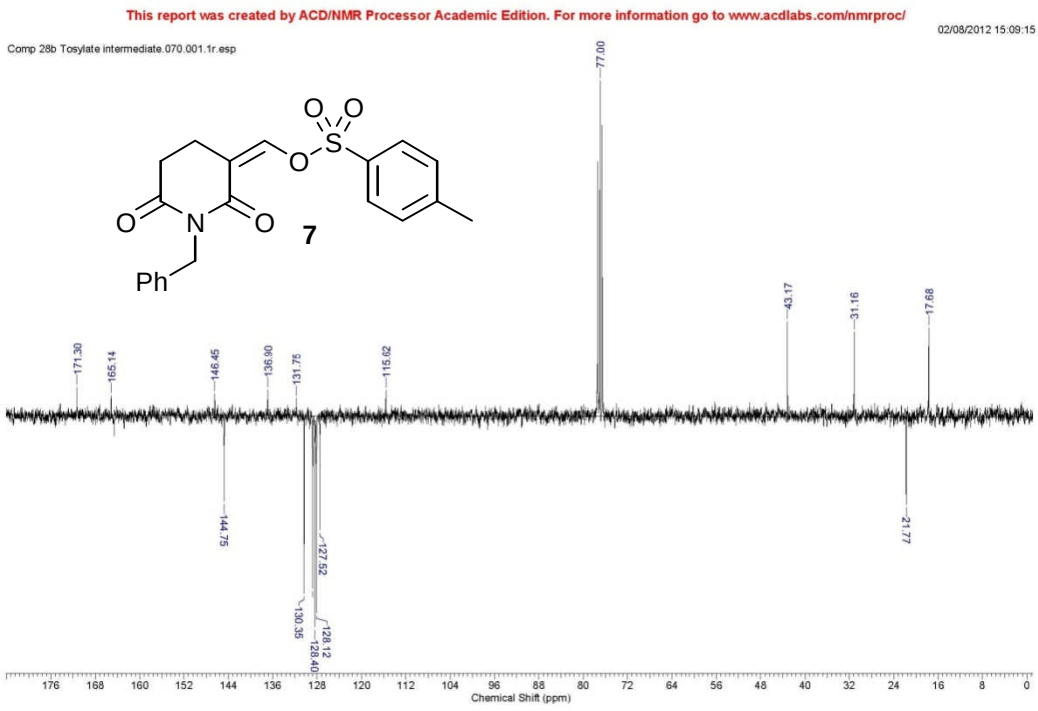


^{13}C NMR spectrum of ***6****,* 75 MHz, $CDCl_3$.

*(1-Benzyl-2,6-dioxopiperidin-3-ylidene)methyl-11-methylbenzene sulfonate, **7**.*

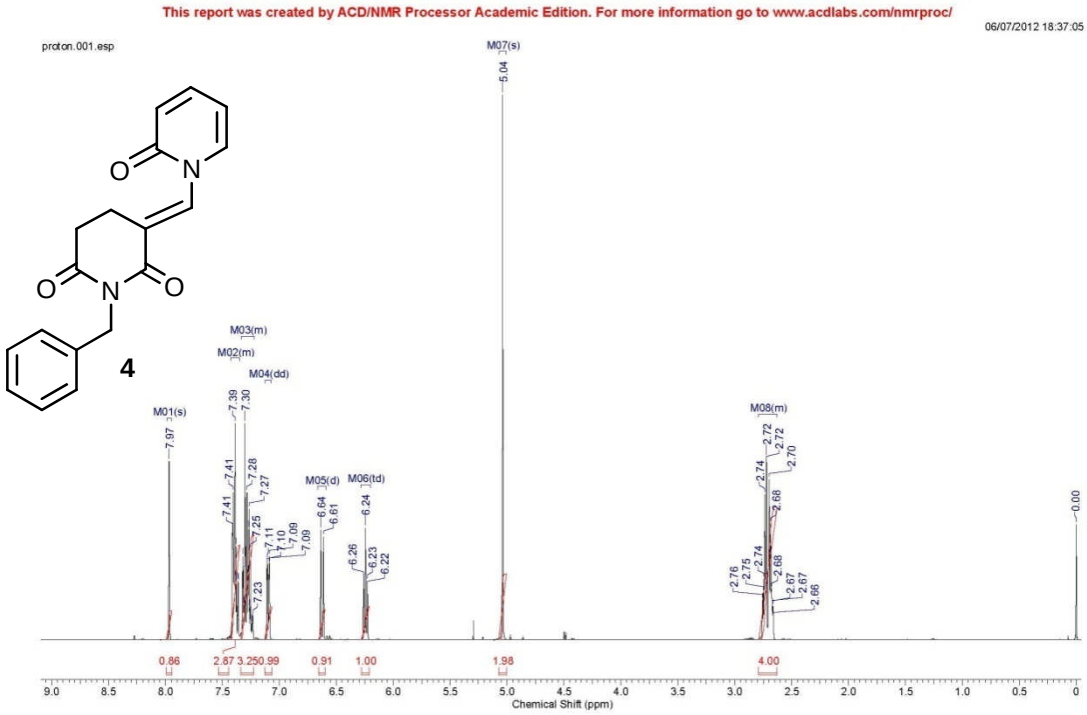


*^{1}H NMR spectrum of **7**, 400 MHz, $CDCl_3$.*

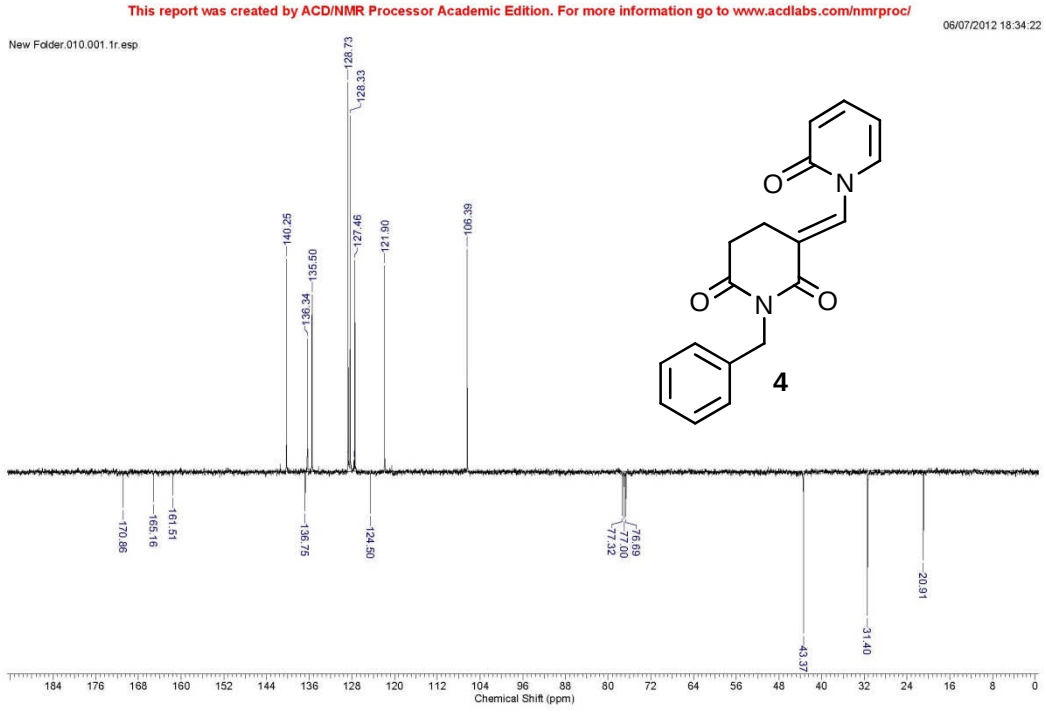


*^{13}C NMR spectrum of **7**,* 75 MHz, $CDCl_3$.

(E)-1-Benzyl-4-((2-oxopyridin-1(2H)-yl)methylene)piperidine-2,6-dione, ***4****.*

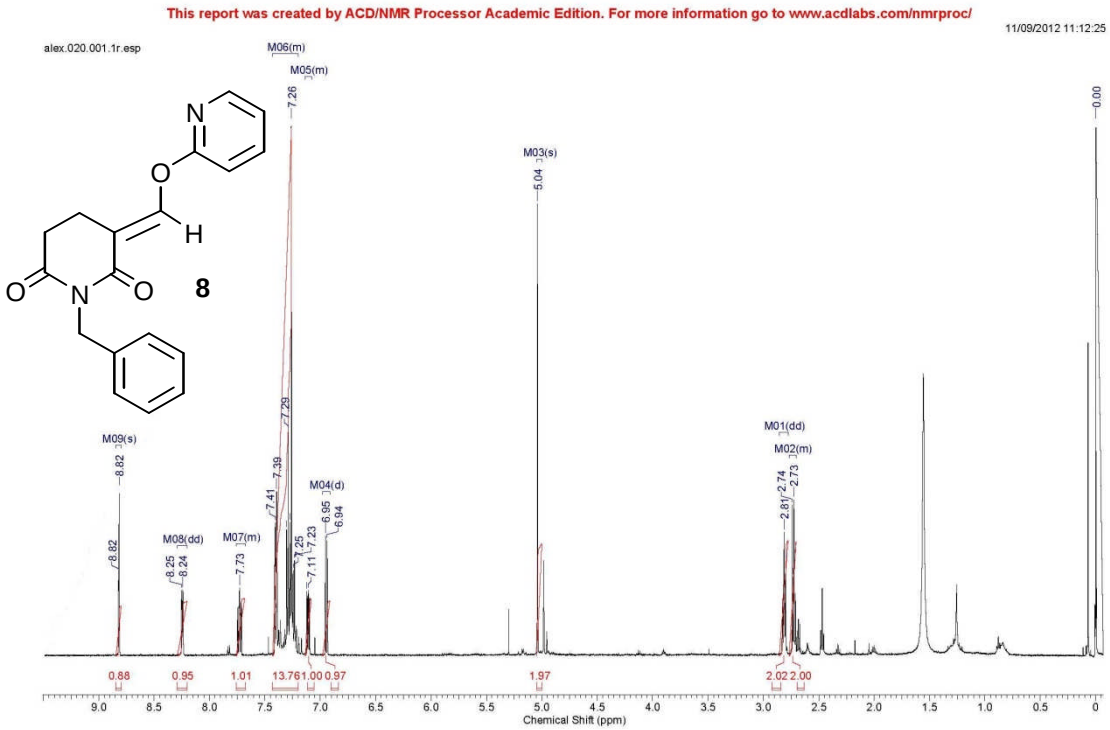


[1]H NMR spectrum of ***4****, 400 MHz, CDCl*$_3$*.*

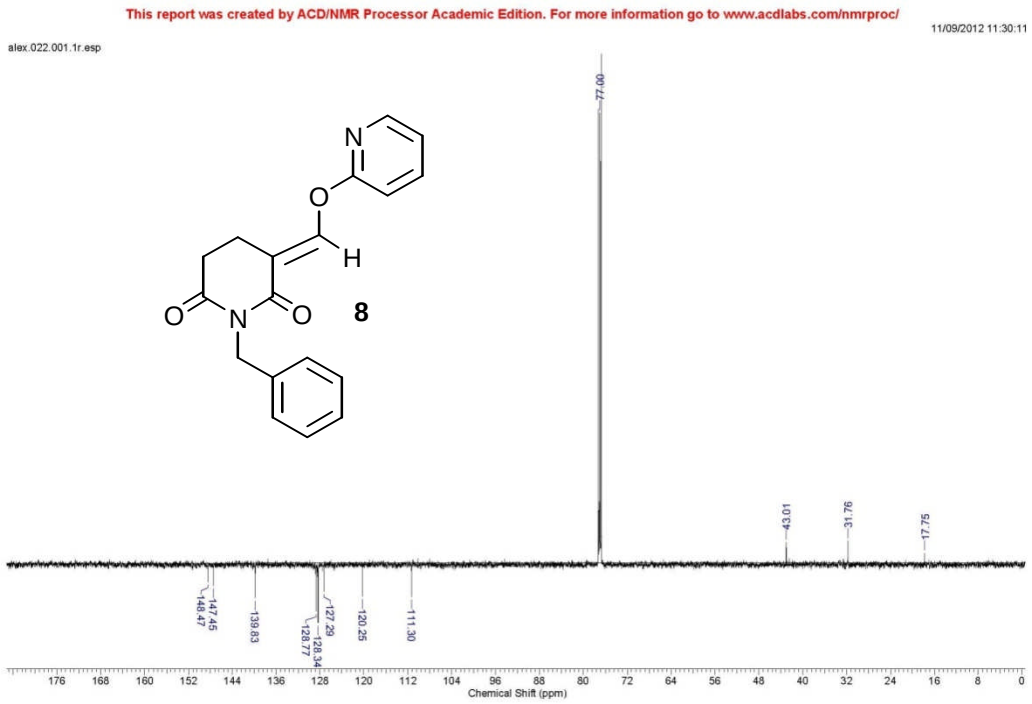


[13]C NMR spectrum of ***4****,* 100 MHz, $CDCl_3$.

1-Benzyl-3-[(pyridin-2-yloxy)methyl]piperidine-2,6-dione, ***8****.*

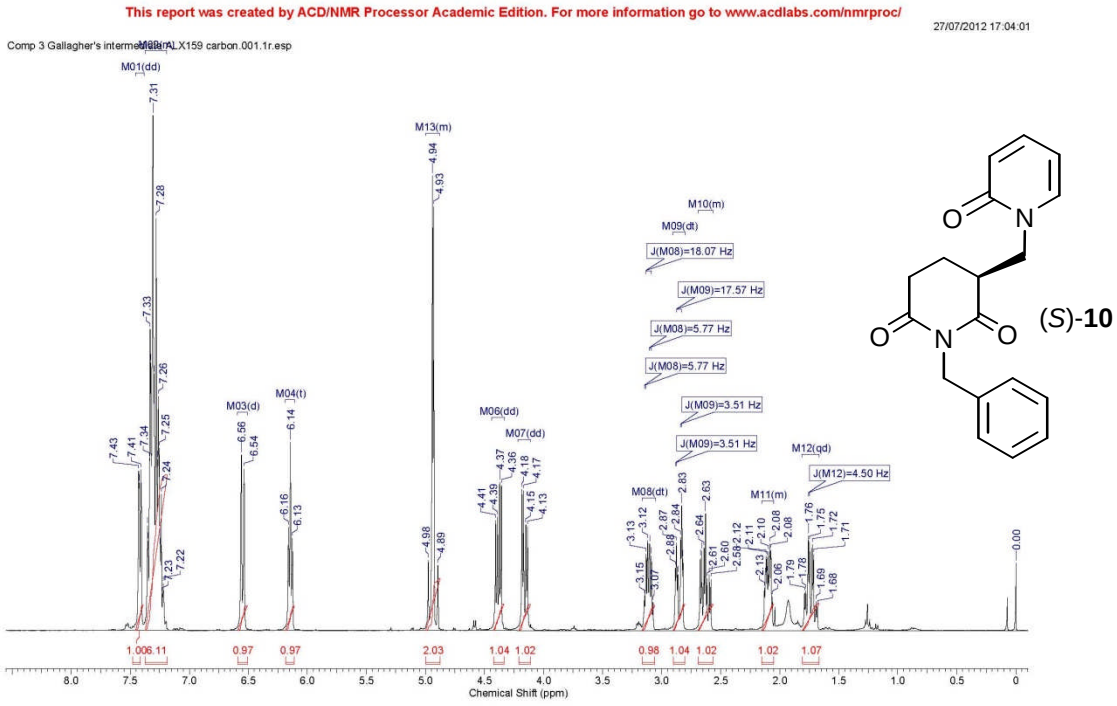


^{1}H NMR spectrum of ***8****, 500 MHz, $CDCl_3$.*

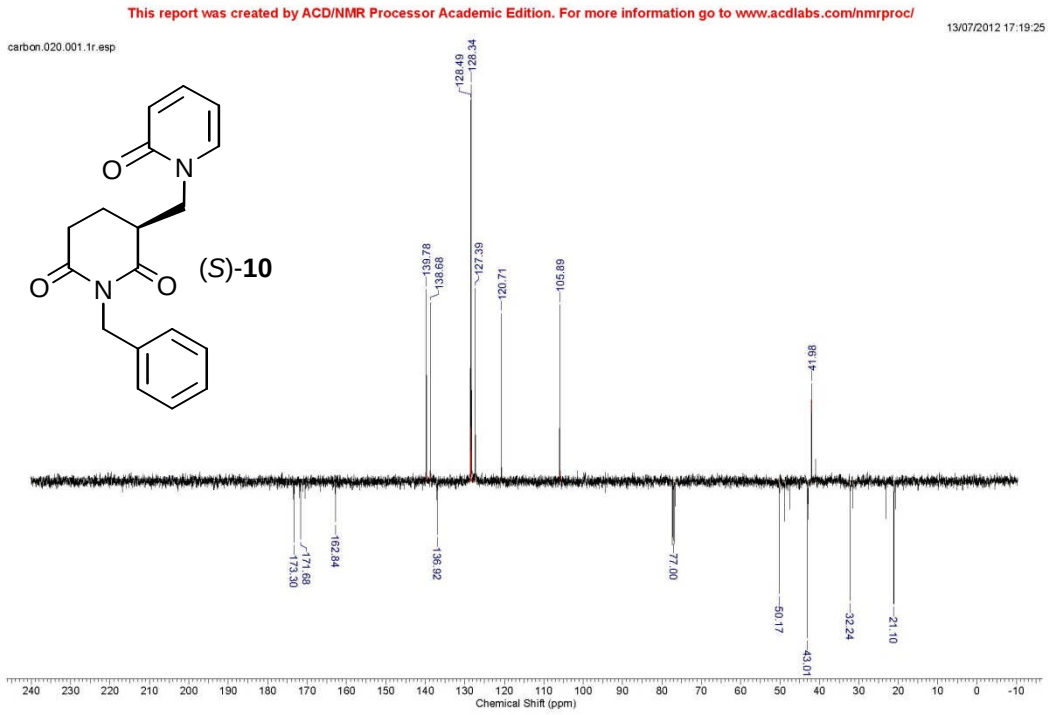


^{13}C NMR spectrum of ***8****, 126 MHz, $CDCl_3$.*

*(S)-1-Benzyl-4-((2-oxopyridin-1(2H)-yl)methyl)piperidine-2,6-dione, (S)-**10**.*

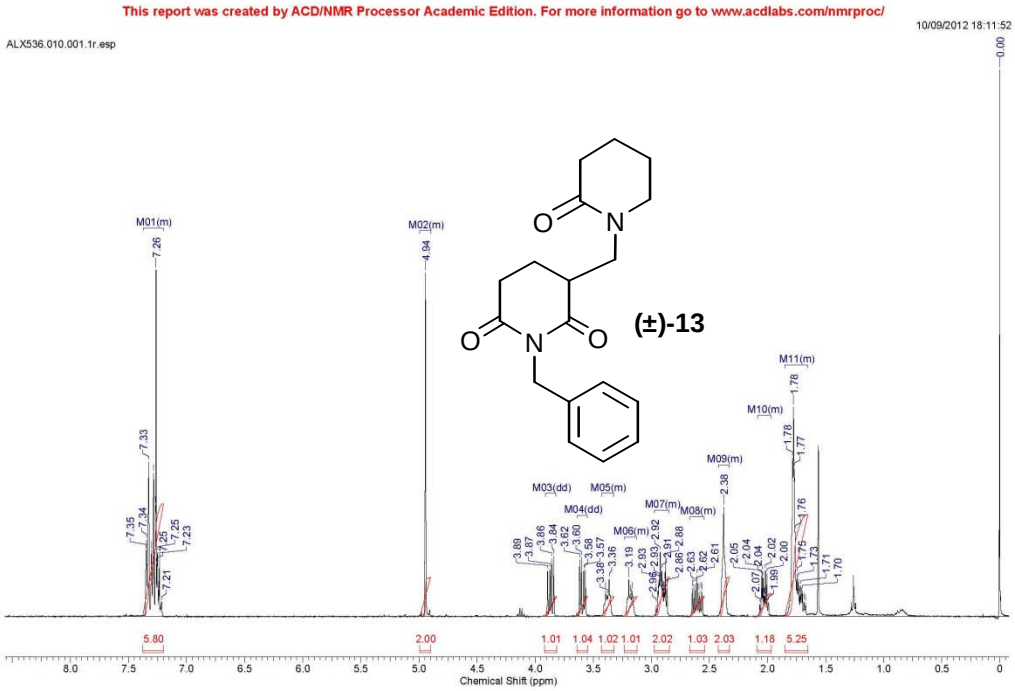


*^{1}H NMR spectrum of (S)-**10**, X MHz, $CDCl_3$*

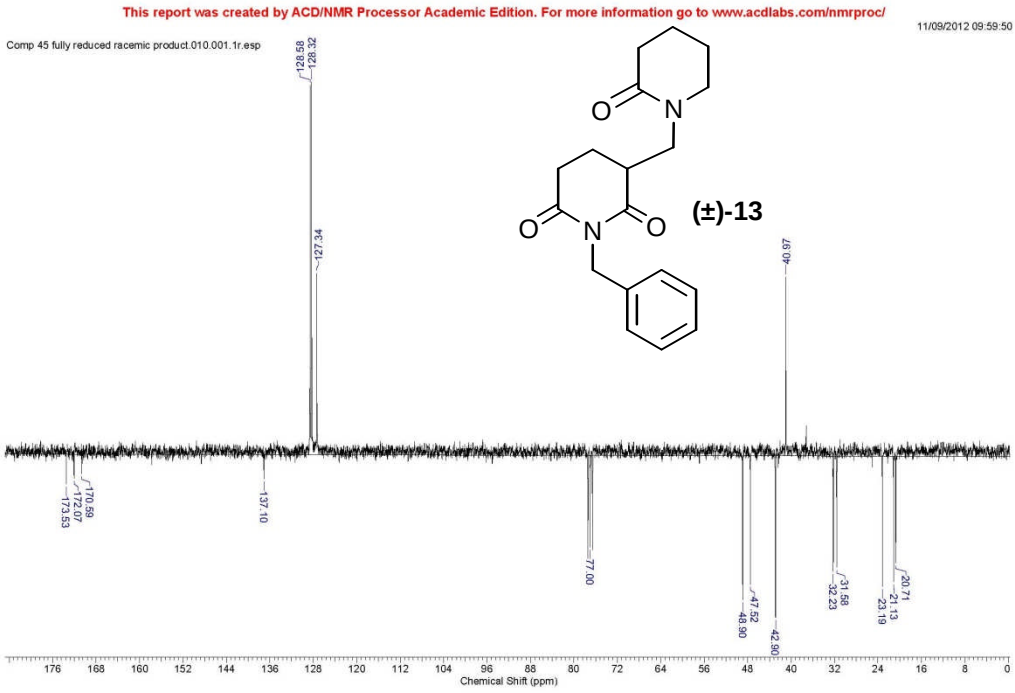


*^{13}C NMR spectrum of (S)-**10**,* 75 MHz, $CDCl_3$.

*1-Benzyl-4-((2-oxopyridin-1-yl)methyl)piperidine-2,6-dione, (±)-**13**.*

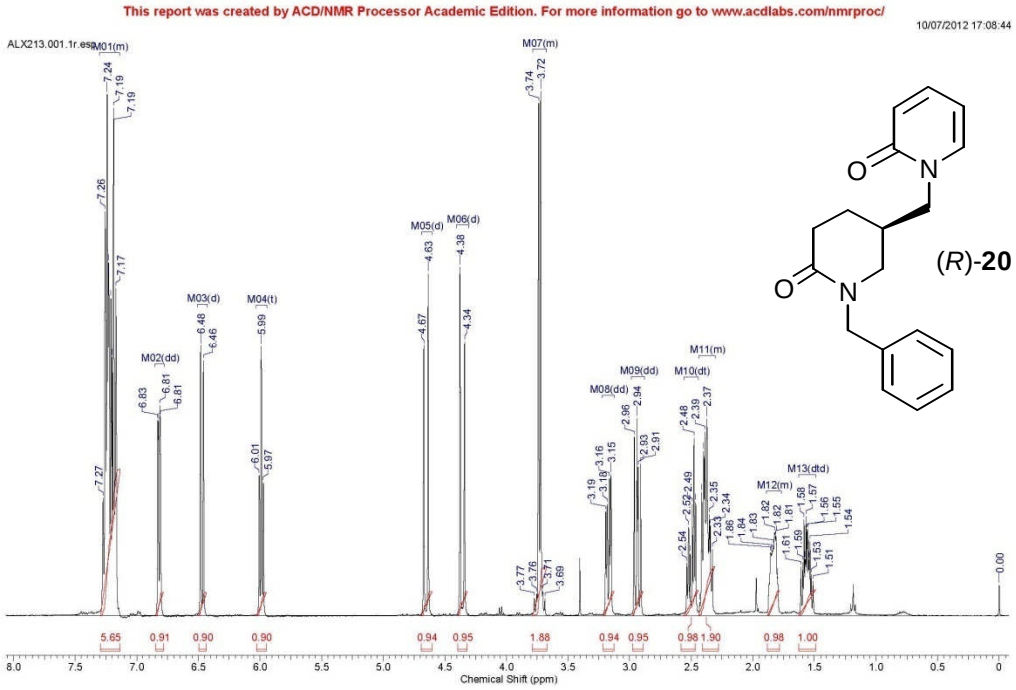


*^{1}H NMR spectrum of (±)-**13**, 300 MHz, $CDCl_3$.*

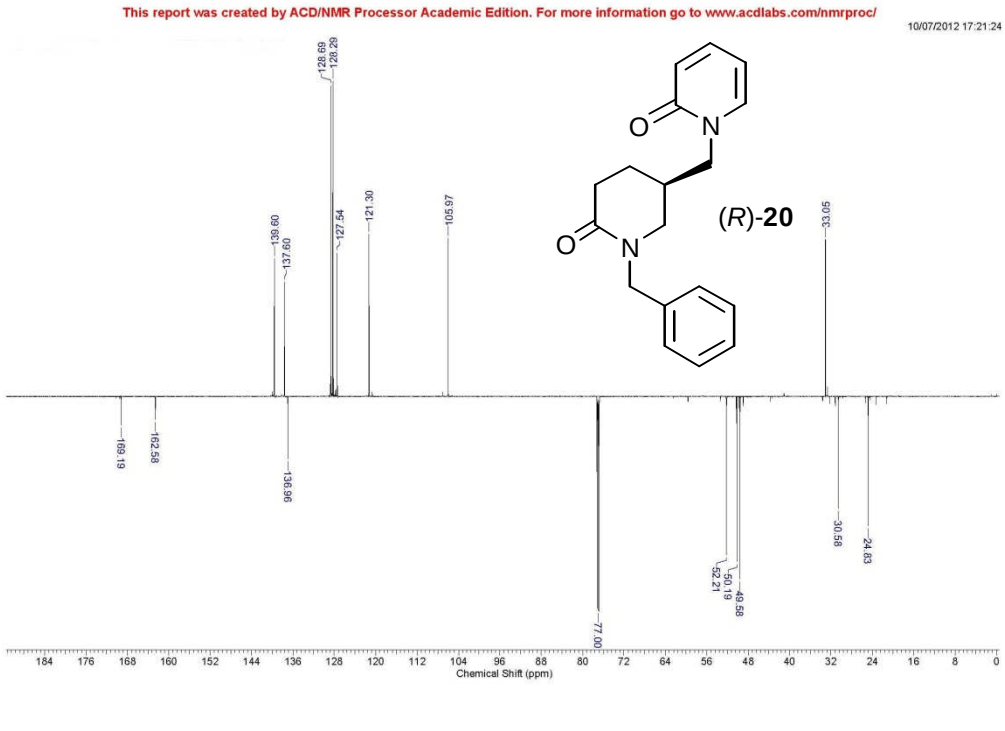


*^{13}C NMR spectrum of (±)-**13**,* 75 MHz, $CDCl_3$.

*(R)-1-((1-Benzyl-6-oxopiperidin-3-yl)methyl)pyridin-2(1H)-one, (R)-**20**.*

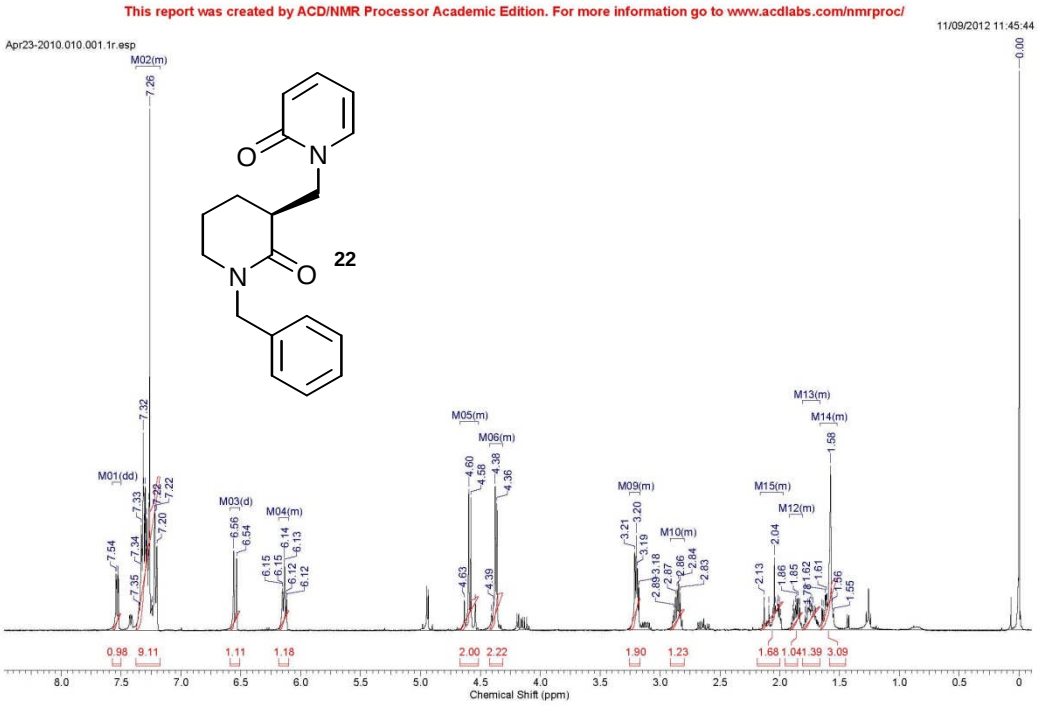


*^{1}H NMR spectrum of (R)-**20**, 700 MHz, $CDCl_3$.*



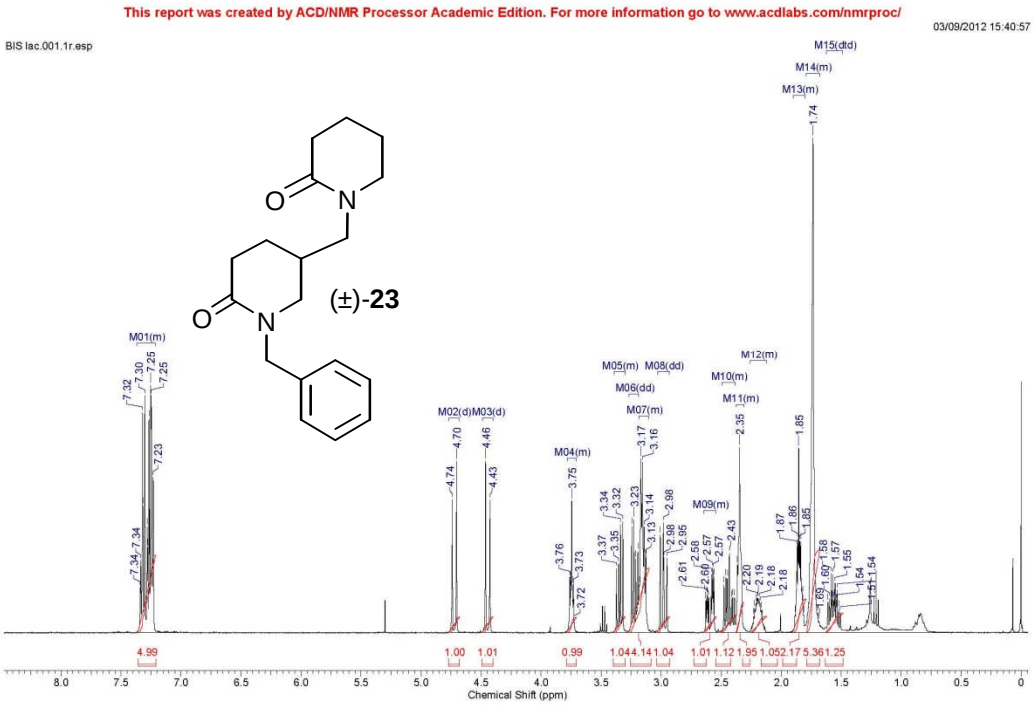
*^{13}C NMR spectrum of (R)-**20**, 176 MHz, $CDCl_3$.*

1-[(1-Benzyl-2-oxopiperidin-3-yl)methyl]pyridin-2(1*H*)-one, ***22***.

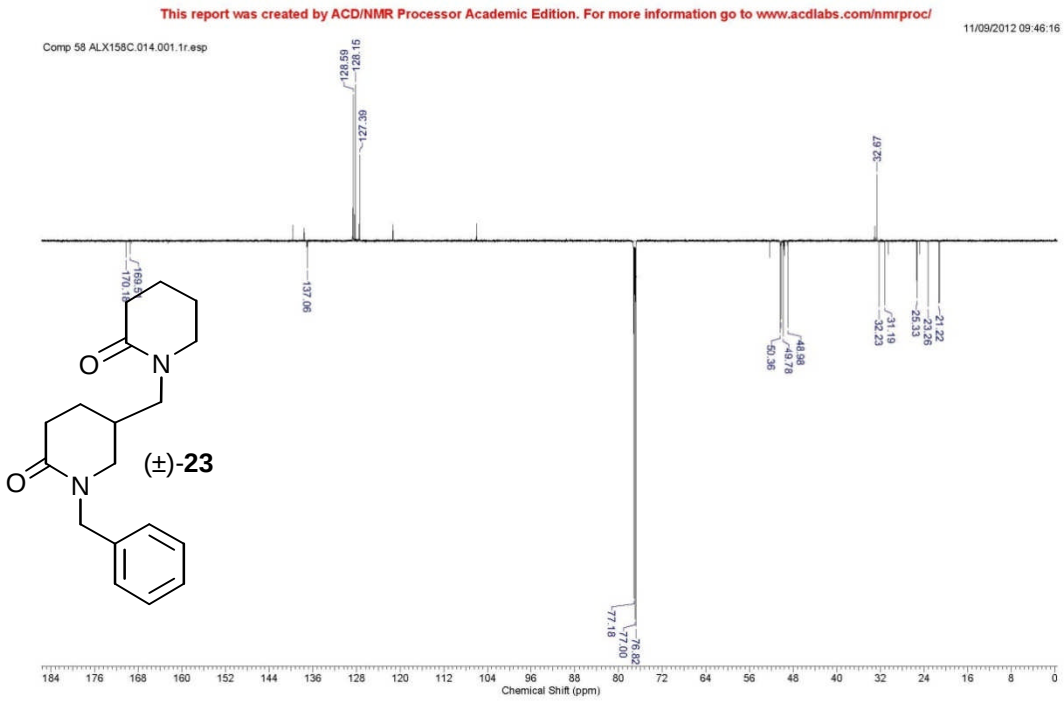


*^{1}H NMR spectrum of **22**, 300 MHz, $CDCl_3$.Compound **22** was a minor component in reduction reactions of **10**, which gave **20** as the major product. It was formed in small amounts and not fully purified from a small amount of unreacted **10**, which is visible in the spectrum above.*

*(S)-1-((1-Benzyl-6-oxopiperidin-3-yl)methyl)piperidin-2-one, (±)-**23**.*

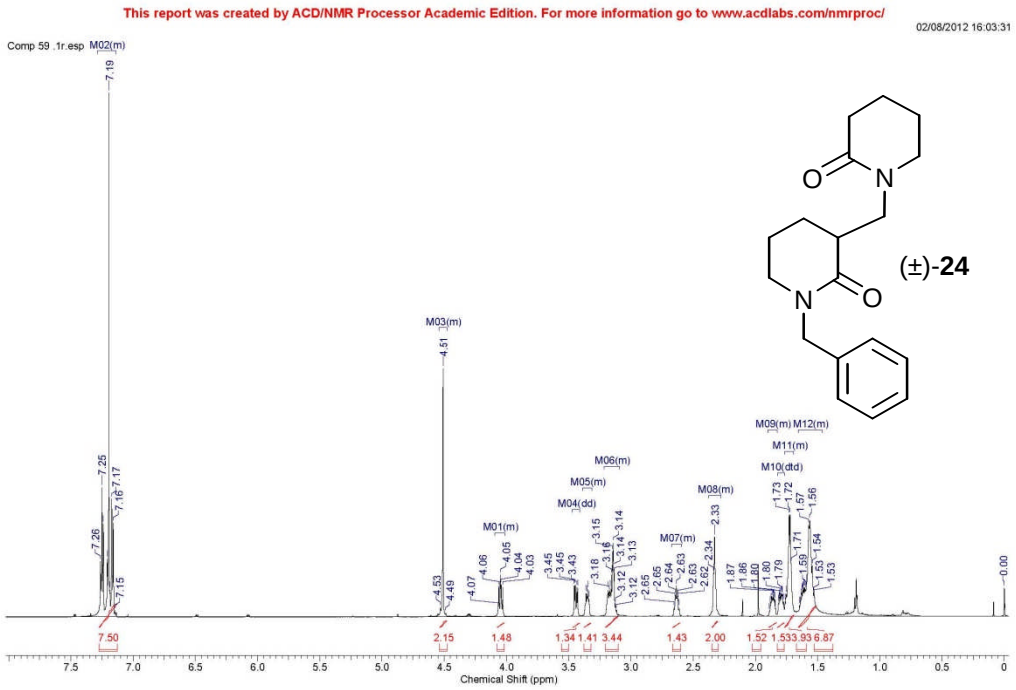


*^{1}H NMR spectrum of (±)-**23**, 700 MHz, $CDCl_3$.*

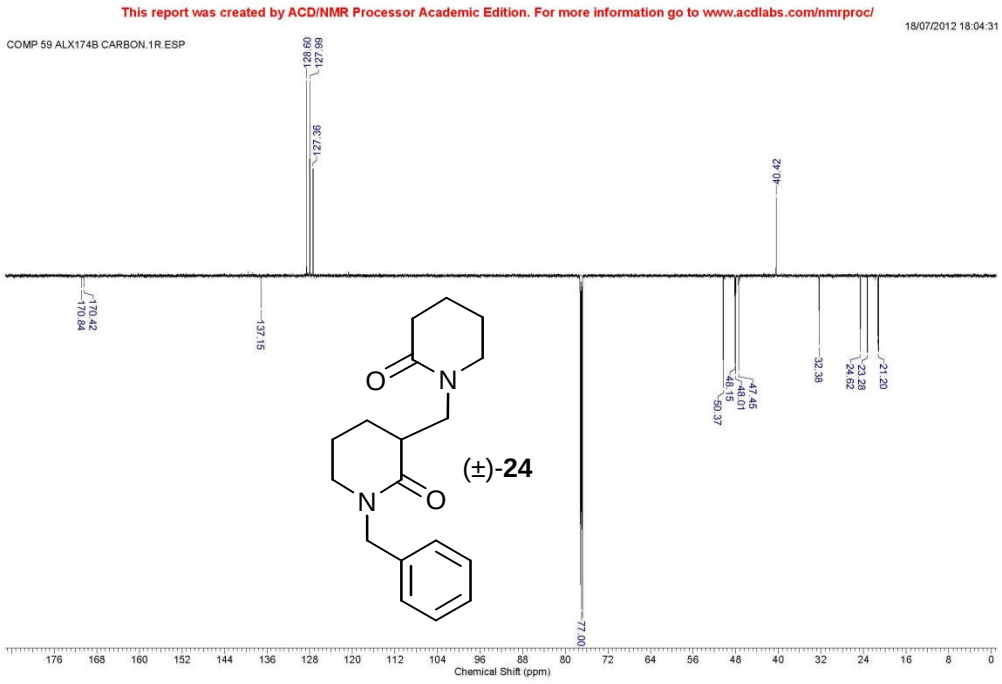


*^{13}C NMR spectrum of (±)-**23**, 176 MHz, $CDCl_3$.*

*Regioisomer, (±)-**24***

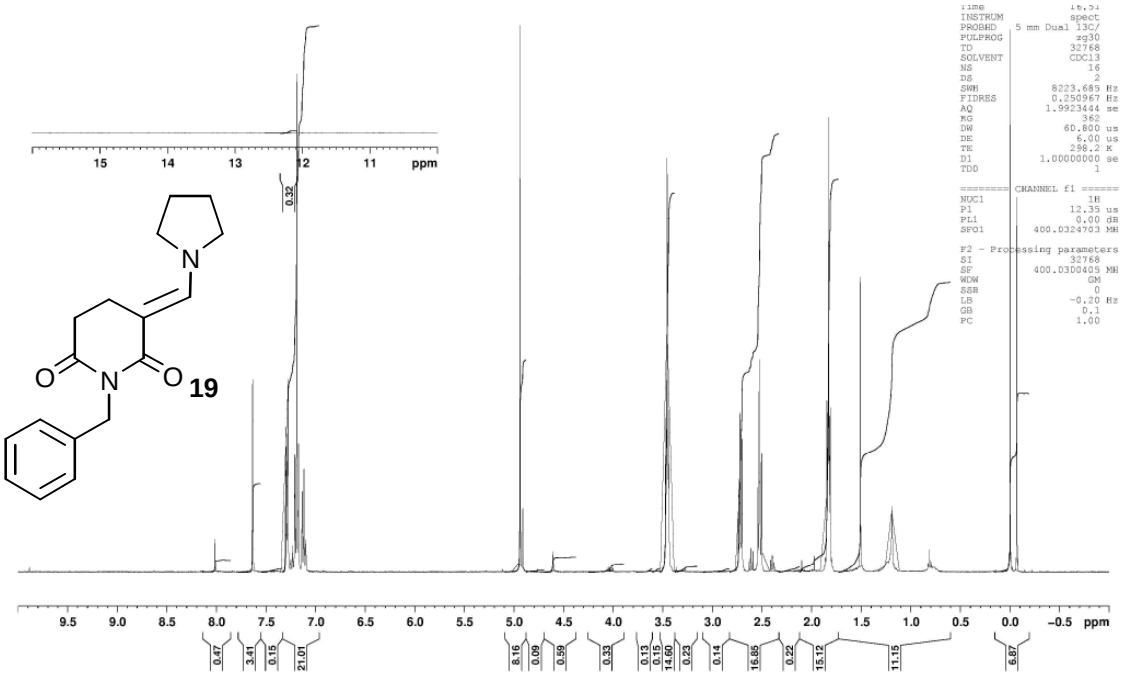


*^{1}H NMR spectrum of (±)-**24**, 700 MHz, $CDCl_3$.*

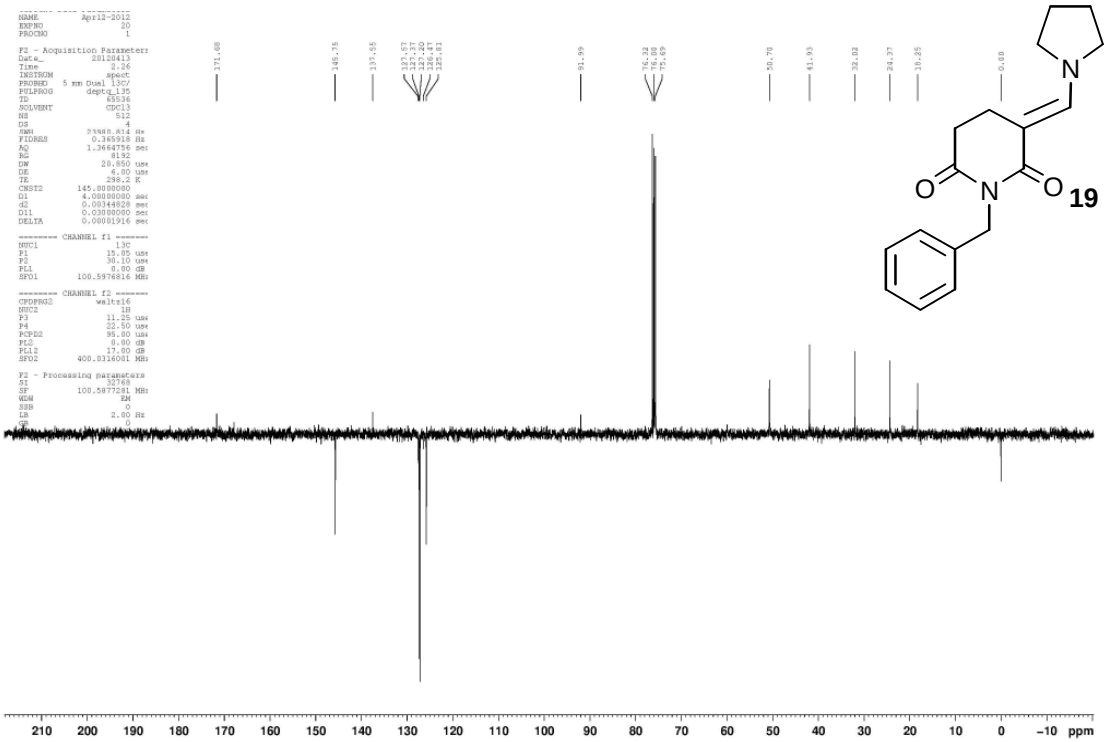


*^{13}C NMR spectrum of (±)-**24**, 176 MHz, $CDCl_3$.*

*Pyrrolidine compound **19**.*



^{1}*H NMR spectrum of **19**,* 400 MHz, $CDCl_3$.



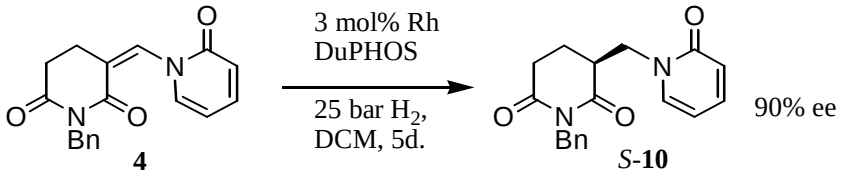
^{13}*C NMR spectrum of **19**,* 101 MHz, $CDCl_3$.

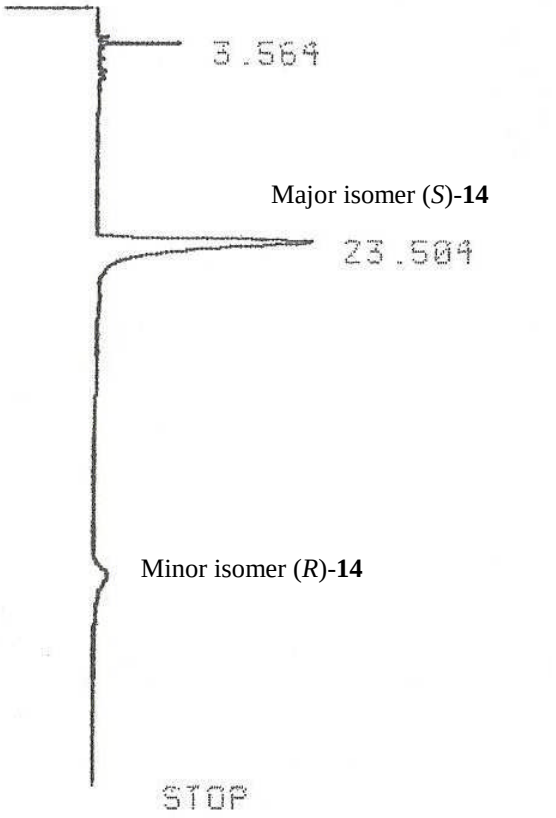
3. Chiral HPLC Chromatographs of 10, 13 and 23.

*HPLC Chromatographs for Imide (S)-**10***

Determination of ee of **10**.

Experiment ALX 199.





Reaction ALX 199

Entry 2, Table 2.

85 : 15 Hexane : IPA

1.0 mL / min

IA Column

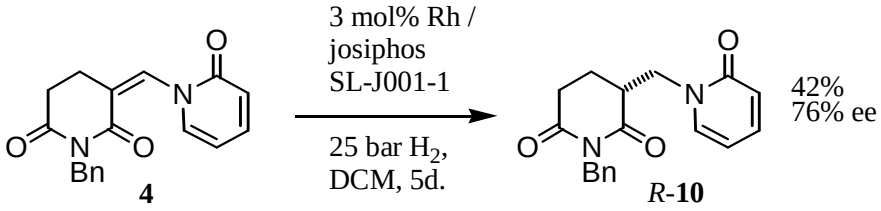
25 ºC

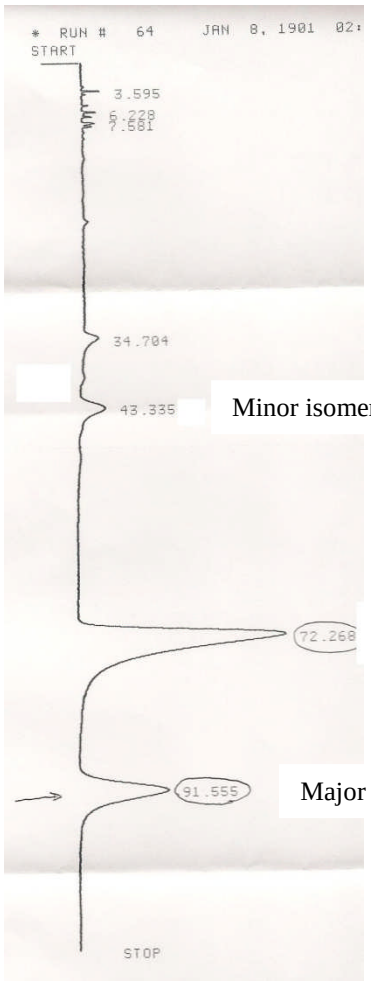
*HPLC chromatograph of (S)-**10**, obtained from reaction ALX 199.*

Compound (*S*)-**10** was obtained by the hydrogenation of compound **4**. The major and minor peaks constitute the *S* and *R* isomers of **10** respectively. The absolute configuration of the major enantiomer of (*S*)-**10** was determined via compound **23**.

HPLC Chromatographs for Lactam 10.

Determination of ee of **10**.





Minor isomer (*S*)-**14**

Peak B: Starting material, **4**

Major isomer (*R*)-**14**

Entry 3, Table 2.

Josiphos SL-J001-1

Reaction ALX 176

90 : 10 Hexane : IPA

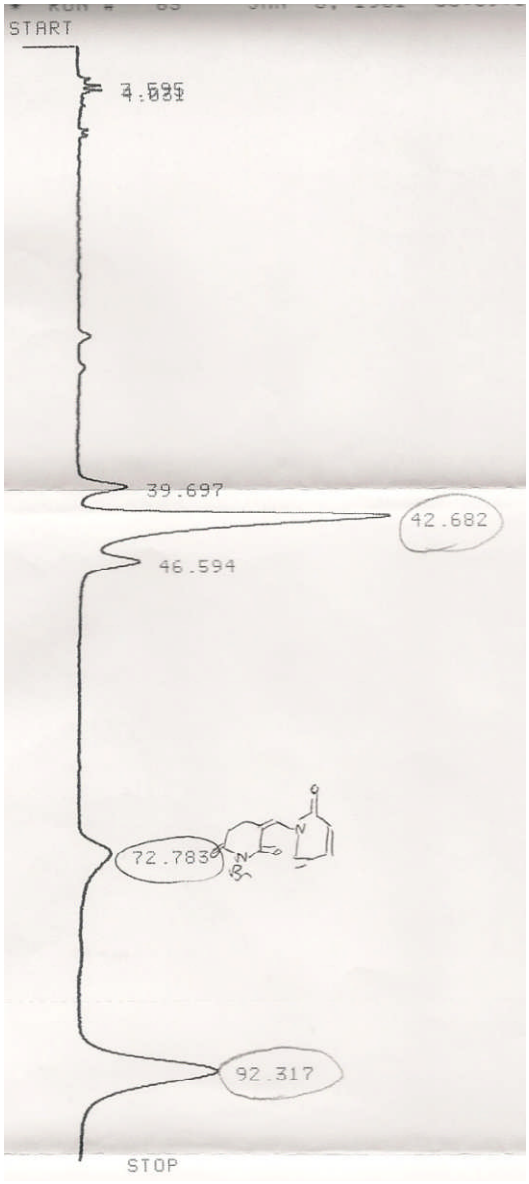
1 mL / min

IA Column

20 °C

76 % ee

*HPLC chromatograph of an inseparable mixture of (R)-**10** and **4**, obtained from reaction ALX176.* The major and minor peaks constitute the *R* and *S* isomers of **10** respectively. Peak B is the starting material, **4**. The HPLC chromatograph of the racemic standard used to establish the position of the required peaks is shown below.



Racemic Standard of 10

90 : 10 Hexane : IPA

1 mL / min

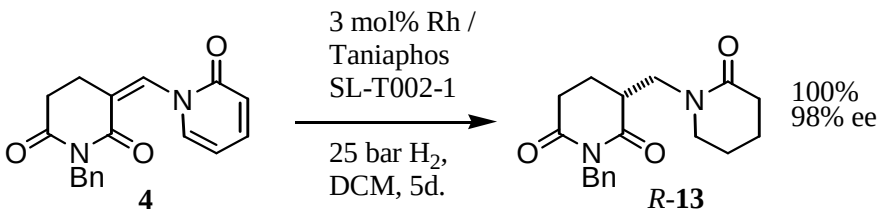
IA Column

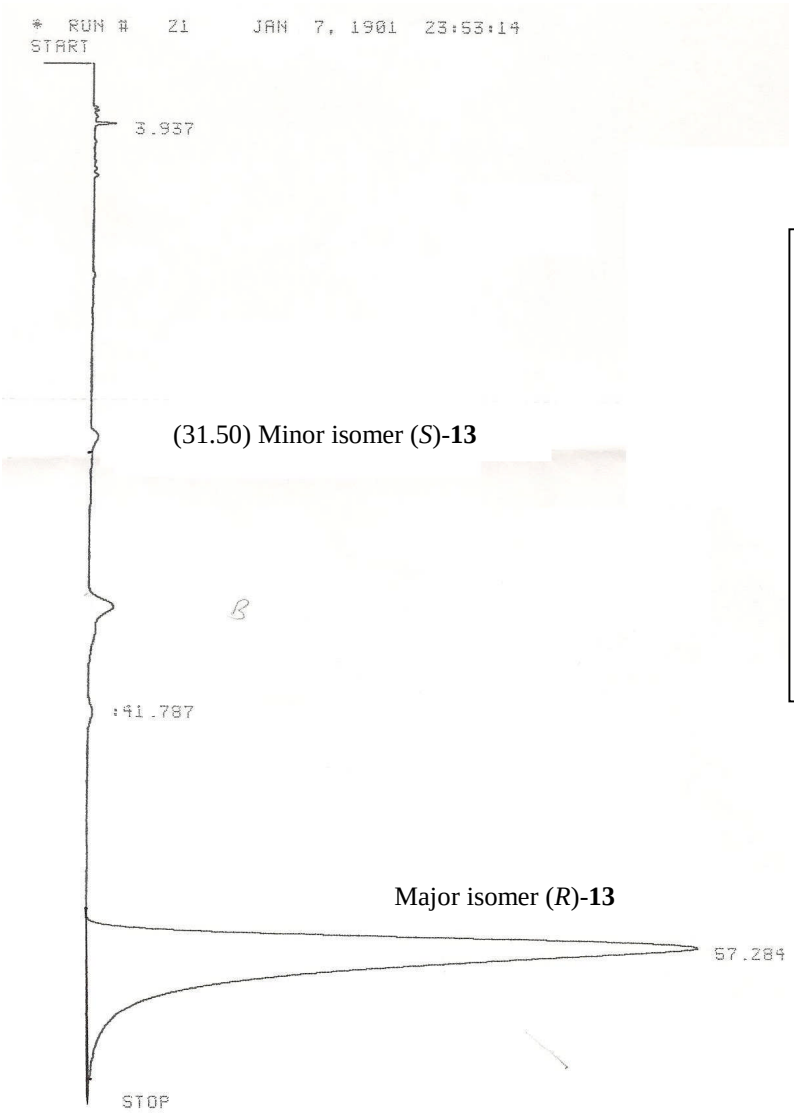
20 °C

*HPLC chromatograph of (±)-**10**. Used to establish the positions of the required peaks in the analysis of reductions.*

HPLC Chromatographs for Lactam **13**.

*Determination of ee of **13**.*





Entry 6, Table 2.

Taniaphos SL-T002-1

Reaction ALX 187

85 : 15 Hexane : IPA

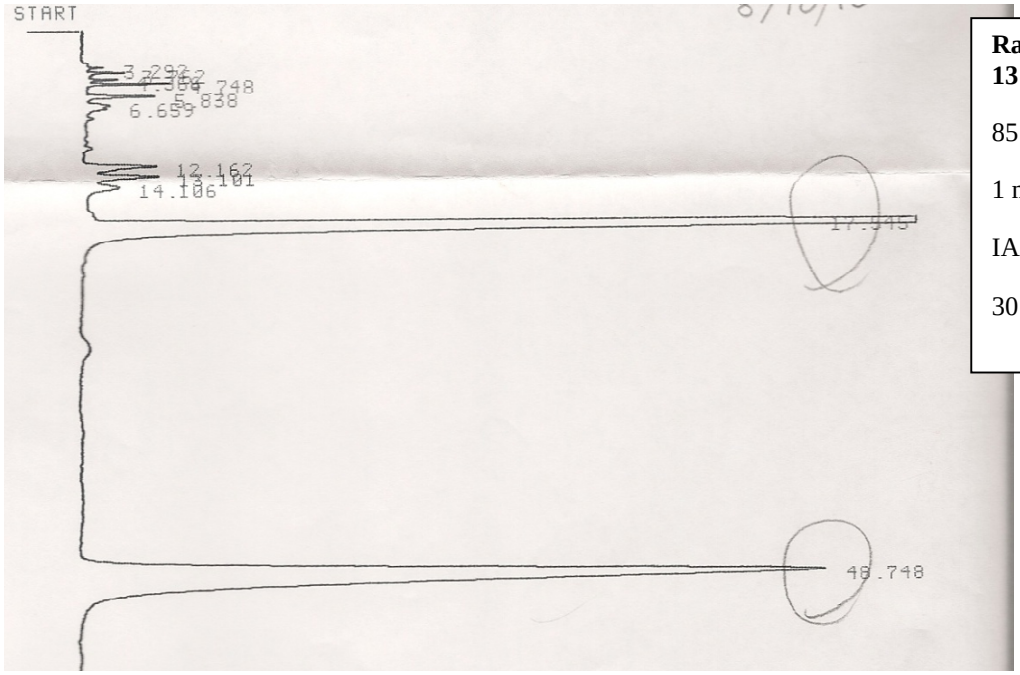
1 mL / min

IA Column

15 ºC

98 % ee

*HPLC chromatograph of (R)-**13**, obtained from reaction ALX187. The major and minor peaks constitute the R and S isomers of **13** respectively. The HPLC chromatograph of the racemic standard used to establish the position of the required peaks is shown below.*



Racemic Standard of 13

85 : 15 Hexane : IPA

1 mL / min

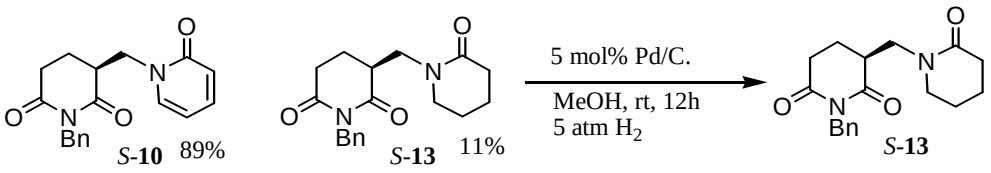
IA Column

30 °C

*HPLC chromatograph of (±)-**13**. Used as a racemic standard to establish the positions of the required peaks in the analysis of reductions. Retention times vary slightly due to variation in temperature in this example.*

HPLC Chromatographs for imide 10 via reduction to 13.

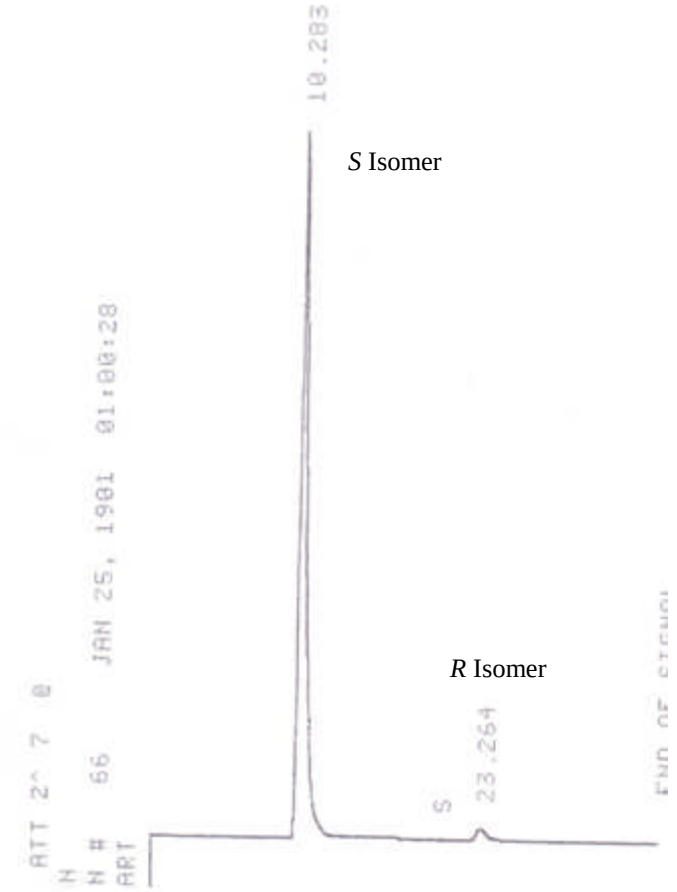
Hydrogenation of sample ALX 54 (from Table 2, entry 1) using indirect method.



S-**10** 89% *S*-**13** 11% *S*-**13**

Inseparable mixure from asymmetric reduction.

Peaks were assigned by comparison with a reference sample of the racemic compound.

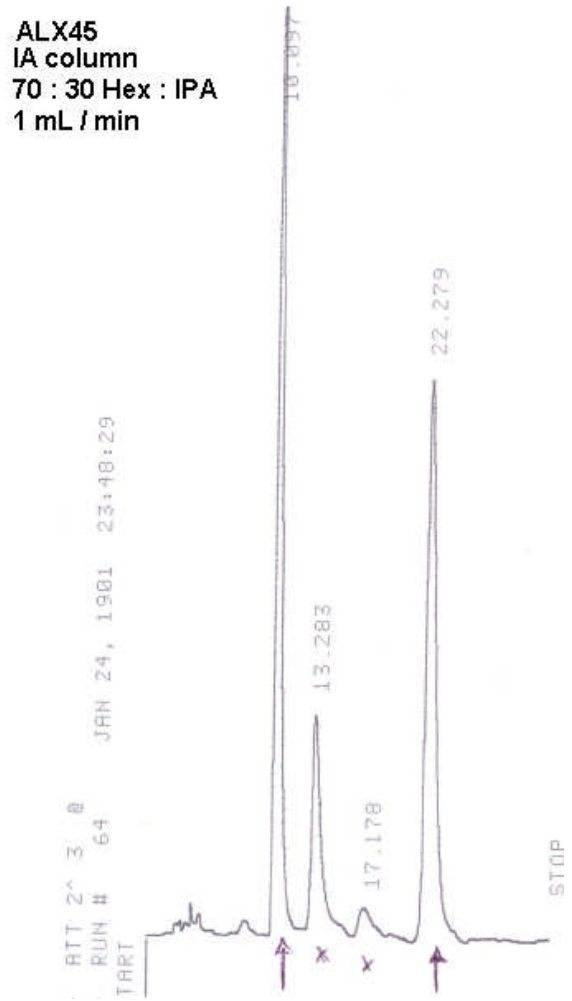


Reaction ALX 54
70 : 30 Hexane : IPA
1 mL / min
IA Column
15 °C
94.5 % ee (*S*)

*HPLC chromatograph of (S)-**13**, used in the analysis of reaction ALX54 (*Scheme 3*)*

Experiment ALX54 resulted in an inseparable mixture of **10** and **13** (ratio 89:11, Table 2 entry 1). This prevented the direct determination of the ee of **10** by HPLC analysis due to poor resolution of peaks. This mixture was hydrogenated and the resulting product **23** was analysed by HPLC and used to indirectly determine the ee of **10**.

The major and minor peaks constitute the *S* and *R* isomers of **13** respectively. The HPLC chromatograph of the racemic standard used to establish the position of the required peaks is shown below.



Racemic Standard 13

70 : 30 Hexane : IPA

1 mL / min

IA Column

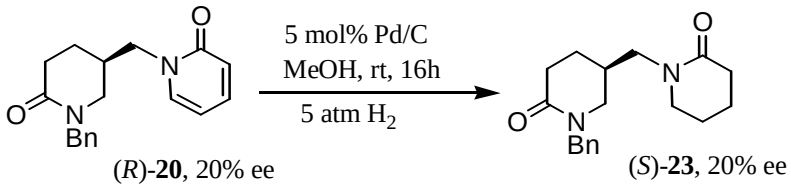
15 °C

*HPLC chromatograph of (±)-**13**.*

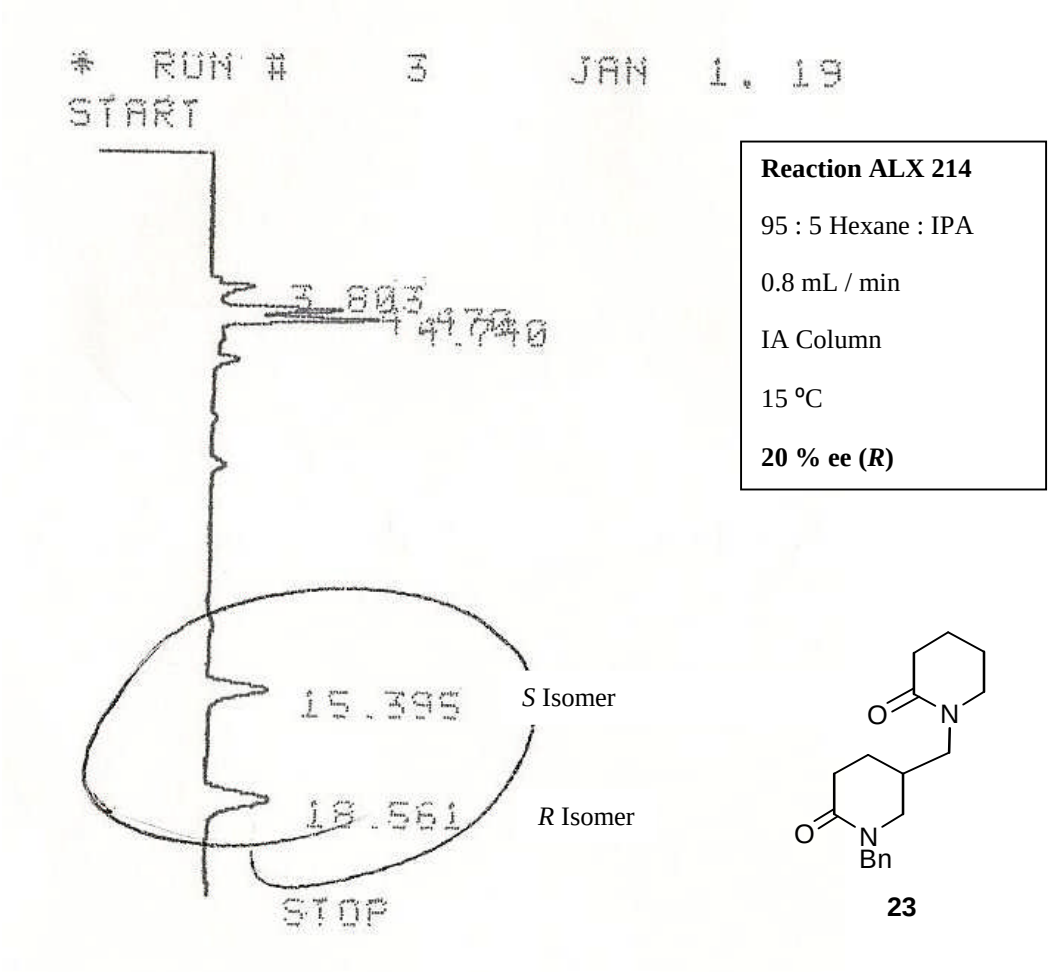
This compound was used as a racemic standard to establish the positions of the required peaks in the analysis of sample ALX 54.

HPLC Chromatographs for Lactam 23.

Experiment ALX 214.



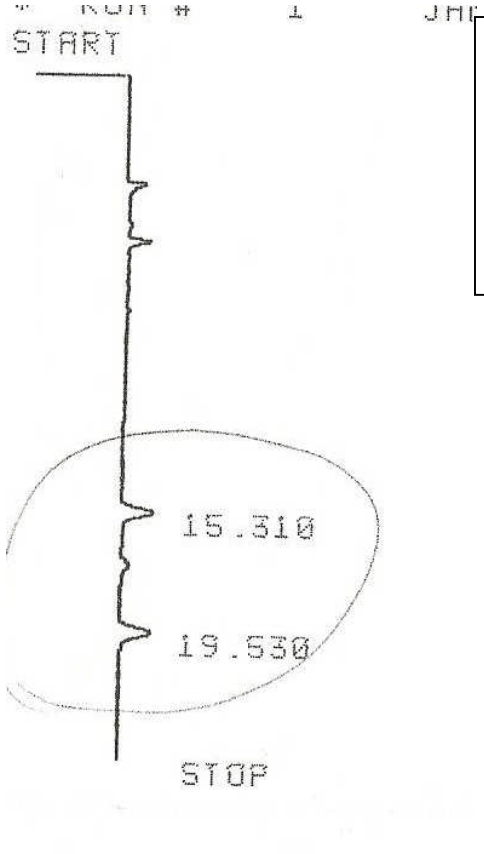
(*R*)-**20**, 20% ee (*S*)-**23**, 20% ee



*HPLC chromatograph of (S)-**23**, obtained from reaction ALX214.*

The ee of compound **20** was obtained indirectly through the analysis of compound **23** because **20** could not be resolved directly. Compound **23** was obtained by the hydrogenation of compound **20** (from imide reduction of compound **10** featured in Table 2, entry 2).

The major and minor peaks constitute the *R* and *S* isomers of **23** respectively. The absolute configuration of the major enantiomer was established by comparison of optical rotation of **20** with that reported. The HPLC chromatograph of the racemic standard used to establish the position of the required peaks is shown below.



Racemic Standard 23

95 : 5 Hexane : IPA

0.8 mL / min

IA Column

15 °C

*HPLC chromatograph of (±)-**23**.*