A New Sparteine Surrogate for Asymmetric Deprotonation of *N*-Boc Pyrrolidine

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Supporting Information Available: Full experimental procedures and characterisation data.

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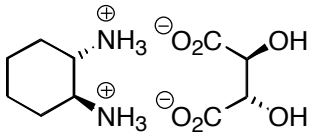
General

Water is distilled water. Where necessary, solvents were dried on a MBraun SPS solvent purification system or distilled before use. Et_2O and THF were freshly distilled from sodium and benzophenone. *s*-BuLi was titrated against *N*-benzylbenzamide or by acid/base double titration before use. Petrol refers to the fraction of petroleum ether with a boiling point range of 40-60 °C. Diamines used in lithiation reactions were distilled from CaH_2 before use. All reactions were carried out under oxygen-free nitrogen or argon using oven-dried and/or flame dried glassware. Flash column chromatography was carried out using Fluka Silica gel 60 (0.035-0.070 mm particle size). Thin layer chromatography was carried using Merck F_{254} aluminium-backed silica plates. For Kügelrohr distillations, the oven temperatures are quoted.

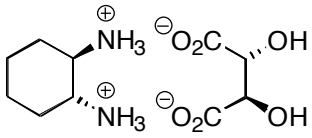
Proton (270 MHz or 400 MHz) and carbon (100.6 MHz) NMR spectra were recorded on a Jeol EX 270 or a Joel ECX-400 instrument using an internal deuterium lock. All samples were recorded in $CDCl_3$. Chemical shifts are quoted in parts per million and referenced to $CHCl_3$ (7.27 for ^1H NMR and 77.0 for ^{13}C NMR spectroscopy). Carbon NMR spectra were recorded with broadband proton decoupling and were assigned using DEPT and HSQC experiments. Infra-red spectra were recorded on an ATI Matteson Genesis FT-IR spectrometer. Chemical ionisation and high resolution mass spectra were recorded on a Fisons Analytical (VG) Autospec spectrometer. Electrospray ionisation low and high resolution mass spectra were recorded on a Bruker Daltronics micrOTOF spectrometer.

Optical rotations were recorded at rt on a Jasco DIP-370 polarimeter (using the sodium D line; 259 nm) and $[\alpha]_D$ given in units of 10^{-1} deg cm^3 g^{-1}. Chiral stationary phase HPLC was performed on one of three systems: a Gilson system with 712 controller software and a 118 UV/Vis diode array detector or on a Waters system with a Waters 255 pump and a Waters 2487 UV detector or an Agilent 1200 series chromatograph using the column indicated for individual compounds. Chiral stationary phase GC was performed on either an Agilent 6890 gas chromatograph using the column indicated for individual compounds or a Perkin Elmer Autosystem XL gas chromatograph. Melting points were measured on a Gallenkamp melting point apparatus.

Full experimental procedures and characterisation data



(*S*,*S*)-**5**



(*R*,*R*)-**5**

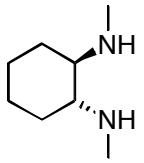
(1*S*,2*S*)-Cyclohexane-1,2-diamine 2,3-dihydroxysuccinate salt (*S*,*S*)-5 and (1*R*,2*R*)-Cyclohexane-1,2-diamine 2,3-dihydroxysuccinate salt (*R*,*R*)-5

Trans (±)-1,2 cyclohexane diamine (20.00 mL, 100.00 mmol) was added dropwise to a stirred solution of D-tartaric acid (12.51 g, 50.00 mmol) in water (45 mL) under air, such that the internal temperature did not exceed 70 °C (during this time a white precipitate forms, but this disappears by the point of complete addition). Then, AcOH (5 mL) was added dropwise such that the internal temperature did not exceed 90 °C. The resulting solution was allowed to cool to 5 °C over 4 h and kept at 5 °C for 2 h (refrigerator). The solids were removed by filtration and the filter-cake was washed with cold water (≤ 5 °C, 20 mL) and MeOH (5 x 10 mL) (Washings kept separate). The resulting white solid was sucked dry to give the (1*S*,2*S*) cyclohexane diamine D-tartaric acid salt (*S*,*S*)-**5** (22.75 g, ≥95%, ≥99:1 er by chiral shift ^{1}H NMR spectroscopy of the TMCDA derivative); mp 283-284 °C (lit.,[1] 280-284 °C). The aqueous filtrate was combined with the aqueous washings and cooled to 0 °C. L-tartaric acid (12.51 g, 50.00 mmol) was then added portionwise to the solution over 5 min. The resulting solution was stirred at 0 °C for 4 h. The solids were removed by filtration and the filter-cake was washed with cold water (≤ 5 °C, 20 mL) and MeOH (5 x 10 mL). The resulting white solid was sucked dry to give the (1*R*,2*R*) cyclohexane diamine L-tartaric acid salt (*R*,*R*)-**5** (19.05 g, 90%, ≥99:1 er by chiral shift ^{1}H NMR spectroscopy of the TMCDA derivative); 275-276 °C (lit.,[1] 273 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (s, 2H, $C(O)_2CHOH$), 3.22-3.12 (m, 2H, 2 x $CHNH_3^+$), 2.04-1.92 (m, 2H, 2 x CH_AH_BCHN), 1.72-1.60 (m, 2H, 2 x CH_AH_BCHN), 1.41-1.27 (m, 2H, 2 x $CH_AH_BCH_2$), 1.25-1.11 (m, 2H, 2 x $CH_AH_BCH_2$). Spectroscopic data consistent with that reported in the literature.[1]

The er of each salt was determined by conversion to TMCDA and ^{1}H NMR spectroscopy in the presence of 2,2,2 trifluoro-1-(9-anthryl)-ethanol using the following procedure: TMCDA (1 mg) was dissolved in $CDCl_3$ (0.2 mL) in a NMR sample tube, and to this a solution of (*R*)-(–)-2,2,2-trifluoro-1-(9-

anthryl)-ethanol (2.8 mg) in $CDCl_3$ (0.3 mL) was added. ^1H NMR spectroscopy then gave the er of TMCDA and hence tartaric acid salt **5**.

(1*R*,2*R*)-N^1,N^2-Dimethylcyclohexane-1,2-diamine (*R,R*)-6

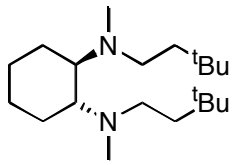


(*R,R*)-**6**

A solution of NaOH (12.24 g, 306.0 mmol) in water (20 mL) and methylchloroformate (6.20 mL, 80.34 mmol) were simultaneously added to a stirred suspension of L-tartaric acid salt (*R,R*)-**5** (10.01 g, 37.9 mmol) in toluene (50 mL) at 0 °C under air. This led to the formation of a gel-like precipitate. The resulting mixture was stirred at rt for 48 h. Then, $CHCl_3$ (50 mL) was added and the solids were removed by filtration and washed with $CHCl_3$ (2 x 25 mL). Water (25 mL) was added to the filtrate and the two layers were separated. The aqueous layer was extracted with $CHCl_3$ (2 x 50 mL). The combined organics were dried (K_2CO_3) and evaporated under reduced pressure to give the crude carbamate (8.69 g, ≥99% crude yield, ≥95% purity by ^1H NMR spectroscopy) as a white solid, ^1H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 6H, 2 x OMe), 3.40-3.36 (m, 2H, 2 x NHC*H*), 2.09-1.98 (m, 2 H, NHCHCH_2), 1.78-1.66 (m, 2H, NHCHCH_2), 1.35-1.11 (m, 4H, CH_2CH_2). A solution of the crude carbamate (max. 37.9 mmol) in THF (60 mL) was added dropwise *via* a dropping funnel to a stirred suspension of $LiAlH_4$ (7.20 g, 189.6 mmol) in THF (60 mL) at 0 °C under N_2. The resulting solution was stirred and heated at reflux for 40 h. Then, the solution was cooled to 0 °C and Et_2O (50 mL) was added, followed by the portionwise addition of $Na_2SO_4 \cdot 10H_2O$ (36.0 g). The resulting mixture was then stirred at rt for 1 h. The solids were removed by filtration through a pad of Celite® and were washed with 24:1 CH_2Cl_2-MeOH (2 x 50 mL). The combined organics were dried (K_2CO_3) and evaporated under reduced pressure to give crude diamine (*R,R*)-**6** (5.39 g, ≥99% crude yield) as a yellow oil, ^1H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 6H, 2 x NMe), 2.12-2.04 (m, 2H, 2 x NCH), 2.02-1.97 (m, 2H, NCHCH_2), 1.75-1.64 (m, 2H, NCHCH_2), 1.27-1.13 (m, 2H, CH_2), 1.01-

0.84 (m, 2H, CH_2). Spectroscopic data consistent with that reported in the literature.[3] The crude product was used in the next step without further purification (≥95% purity by ^{1}H NMR spectroscopy).

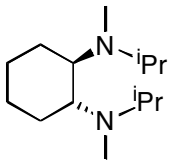
(1*R*,2*R*)-*N*^{1},*N*^{2}-Dimethyl-*N*^{1},*N*^{2}-bis(3,3-dimethylbutyl)cyclohexane-1,2-diamine (*R*,*R*)-4



(*R*,*R*)-**4**

A solution of *t*-butylacetylchloride (10.76 mL, 77.5 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a stirred biphasic mixture of crude diamine (*R*,*R*)-**6** (max. 37.9 mmol) in CH_2Cl_2 (50 mL) and NaOH (7.06 g, 176.5 mmol) in water (25 mL) at 0 °C under air. The resulting mixture was stirred at rt for 40 h. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (5 x 100 mL). The combined organic extracts were dried (K_2CO_3) and evaporated under reduced pressure to give the bis-amide as a white solid. A solution of the crude bis-amide in THF (60 mL) was added dropwise *via* a dropping funnel to a stirred suspension of $LiAlH_4$ (7.20 g, 189.6 mmol) in THF (60 mL) at 0 °C under N_2. The resulting solution was stirred and heated at reflux for 40 h. Then, the solution was cooled to 0 °C and Et_2O (50 mL) was added, followed by the portionwise addition of $Na_2SO_4 \cdot 10H_2O$ (36.0 g). The resulting mixture was then stirred at rt for 1 h. The solids were removed by filtration through a pad of Celite® and washed with 24:1 CH_2Cl_2-MeOH (2 x 50 mL). The combined organic extracts were dried (K_2CO_3) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by Kügelrohr distillation gave diamine (*R*,*R*)-**6** (8.42 g, 72% over 4 steps) as a colourless oil, bp 180-190 ºC/1.5 mm Hg (lit.,[2] 150 ºC/1.0 mm Hg); $[\alpha]_D$ –38.1 (*c* 1.0 in $CHCl_3$) (lit.,[3] $[\alpha]_D$ –31.1 (*c* 1.02 in $CHCl_3$)); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58-2.36 (m, 6H, 2 x NCH_2 and 2 x NCH), 2.25 (s, 6H, 2 x NMe), 1.83-1.63 (m, 4H, 2 x NCHCH_2), 1.39 (t, *J* = 8.0 Hz, 4 H, 2 x CH_2CMe_3), 1.20-1.06 (m, 4H, 2 x CH_2), 0.90 (s, 18 H, 2 x CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 62.6 (NCH), 50.1 (NCH_2), 42.2 (*C*H_2CMe_3), 37.0 (NMe), 29.8 (*C*Me_3), 29.6 (C*Me*$_3$), 25.9 (CH_2), 25.1 (CH_2), Spectroscopic data consistent with that reported in the literature.[3]

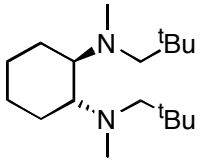
(1*R*,2*R*)-N^1,N^2-Diisopropyl-N^1,N^2-dimethylcyclohexane-1,2-diamine (*R*,*R*)-2



(*R*,*R*)-**2**

Acetone (206 μL, 2.82 mmol) was added to a stirred solution of diamine (*R*,*R*)-**6** (104 mg, 0.73 mmol) in CH_2Cl_2 (3 mL) at rt under N_2. The resulting solution was stirred at rt for 5 min and $NaBH(OAc)_3$ (604 mg, 2.83 mmol) was added portionwise over 5 min. The resulting mixture was stirred at rt for 16 h. Then, water (5 mL) and CH_2Cl_2 (5 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a colourless oil. A solution of the crude product in toluene (1 mL) was added to a solution of HCl in EtOH (prepared by adding acetyl chloride (61 μL, 0.88 mmol) to EtOH (389 μL)) at 0 ºC. Petrol was then added until a cloudy solution resulted. After 1 h at 0 ºC, the solid was collected by filtration and washed with petrol (2 x 2 mL). The solid was dissolved in hexane (5 mL) and 2 M $NaOH_{(aq)}$ (5 mL) was added and the two layers were separated and the aqueous layer was extracted with hexane (4 x 5 mL) and the combined organic extractss were dried ($MgSO_4$) and evaporated under reduced pressure to give diamine (*R*,*R*)-**2** (122 mg, 74%) as a colourless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.93 (septet, J = 6.5 Hz, 2 H, 2 x NC*H*Me$_2$), 2.65-2.56 (m, 2H, 2 x NCH), 2.20 (s, 6H, 2 x NMe), 1.81-1.71 (m, 2H, 2 x NCHCH_AH_B), 1.14-1.07 (m, 2H, CH_2), 1.06 (d, J = 6.5 Hz, 6H, CH*Me*$_2$), 1.02 (d, J = 6.5 Hz, 6H CH*Me*$_2$). Spectroscopic data consistent with that reported in the literature.[4] Diamine (*R*,*R*)-**2** was purified by Kügelrohr distillation before use: bp 180 °C/1.5 mm/Hg.

(1*R*,2*R*)-*N*^{1},*N*^{2}-Dimethyl-*N*^{1},*N*^{2}-dineopentylcyclohexane-1,2-diamine (*R*,*R*)-3



(*R*,*R*)-**3**

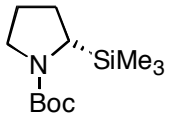
Trimethylacetaldehyde (1.93 mL, 17.80 mmol) was added to a stirred solution of diamine (*R*,*R*)-**6** (623 mg, 4.39 mmol) in CH_2Cl_2 (25 mL) at rt under N_2. The resulting solution was stirred at rt for 5 min and $NaBH(OAc)_3$ (3.77 g, 17.80 mmol) was added portionwise over 5 min. The resulting mixture was stirred at rt for 16 h. Then, water (30 mL) and CH_2Cl_2 (20 mL) were added and the two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 50 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a colourless oil. A solution of the crude product in toluene (5 mL) was added to a solution of HCl in EtOH (prepared by adding acetyl chloride (364 μL, 5.18 mmol) to EtOH (2.3 mL)) at 0 ºC. Petrol was then added until a cloudy solution resulted. After 1 h at 0 ºC, the solid was collected by filtration and washed with petrol (2 x 5 mL). The solid was dissolved in hexane (20 mL) and 2 M $NaOH_{(aq)}$ (20 mL) was added and the two layers were separated and the aqueous layer was extracted with hexane (4 x 20 mL) and the combined organic extractss were dried ($MgSO_4$) and evaporated under reduced pressure to give diamine (*R*,*R*)-**3** (777 mg, 63%) as a colourless oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37-2.32 (m, 2H, 2 x NCH), 2.34-2.30 (m, 4H, C*H*$_2$CMe$_3$), 2.29 (s, 6H, 2 x NMe), 1.78 (br dt, *J* = 13.5, 3.0 Hz, 2H, NCHC*H*$_A$H$_B$), 1.71-1.62 (m, 2H, NCHCH$_A$*H*$_B$), 1.29-1.15 (m, 2H, 2 x C*H*$_A$H$_B$), 1.10-1.01 (m, 2H, 2 x CH$_A$*H*$_B$), 0.89 (s, 18H, 2 x CMe$_3$). Spectroscopic data consistent with that reported in the literature.[2] Diamine (*R*,*R*)-**3** was purified by Kügelrohr distillation before use: bp 210 °C/2.5 mm/Hg (lit.,[2] 120 ºC/1 mm/Hg).

General Procedure for lithiation/electrophilic trapping of *N*-Boc pyrrolidine 7

s-BuLi (1.61 mL of a 1.27 M solution in cyclohexane, 2.04 mmol) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **7** (1.57 mmol) and the diamine (1.75 mmol) in Et_2O (5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 3 h. Then, Me_3SiCl (358 μL, 2.82 mmol) was added

dropwise and the reaction mixture was allowed to warm to rt and stirred at rt for 16 h. Saturated $NH_4Cl_{(aq)}$ (5 mL) was added and the mixture stirred for 20 min at rt. The two layers were separated and the aqueous layer was extracted with Et_2O (5 x 5 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product.

(*S*)-2-Trimethylsilylpyrrolidine-1-carboxylic acid *tert*-butyl ester (*S*)-8



(*S*)-**8**

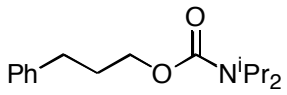
Using the general procedure for lithiation/electrophilic trapping, *s*-BuLi (1.05 mL of a 1.10 M solution in cyclohexane, 1.16 mmol), *N*-Boc pyrrolidine **7** (157 μL, 0.90 mmol), diamine (*R,R*)-**4** (361 mg, 1.16 mmol) and Me_3SiCl (252 μL, 1.98 mmol) after 3 h lithiation in Et_2O (3 mL) gave the crude product as a yellow oil. Purification by flash column chromatography on silica with petrol-Et_2O (95:5) as eluent gave pyrrolidine (*S*)-**8** (166 mg, 72%, 95:5 er by chiral GC) as a colourless oil, $[\alpha]_D$ +76.7 (*c* 1.0 in $CHCl_3$)(lit.,[5] $[\alpha]^{20}_D$ +71.8 (*c* 2.6 in $CHCl_3$) for (*S*)-**8** of 98:2 er); R_F(95:5 petrol-Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.36-3.39 (br m, 1H, NCH), 3.38-3.06 (br m, 2H, NCH_2), 2.12-1.92 (br m, 1H, CH_AH_B), 1.89-1.65 (br m, 3H, CH_AH_B and CH_2), 1.47 (s, 9H, CMe_3), 0.06 (s, 9H, $SiMe_3$); GC: Betadex 120, 30 m x 0.25 mm i.d.(β-cyclodextrin) T 91 °C isothermal, He carrier gas at 12 psi constant pressure, 103 min [(*S*)-**8**], 105 min [(*R*)-**8**] and recovered *N*-Boc pyrrolidine **7** (10 mg, 7%) as a colourless oil. Spectroscopic data consistent with that reported in the literature.[5]

Using the general procedure for lithiation/electrophilic trapping, *s*-BuLi (560 μL of a 1.20 M solution in cyclohexane, 0.67 mmol), *N*-Boc pyrrolidine **7** (73 μL, 0.42 mmol) and diamine (*R,R*)-**2** (153 mg, 0.67 mmol) and Me_3SiCl (189 μL, 1.47 mmol) after 3 h lithiation in Et_2O (2 mL) gave the crude product as a yellow oil. Purification by flash column chromatography on silica with petrol-Et_2O (95:5) as eluent gave

pyrrolidine (*S*)-**8** (31 mg, 29%, 50:50 er by chiral GC) as a colourless oil and recovered *N*-Boc pyrrolidine **7** (30 mg, 42%) as a colourless oil.

Using the general procedure for lithiation/electrophilic trapping, *s*-BuLi (710 μL of a 1.20 M solution in cyclohexane, 0.85 mmol), *N*-Boc pyrrolidine **7** (93 μL, 0.53 mmol), diamine (*R,R*)-**3** (239 mg, 0.85 mmol), and Me_3SiCl (160 μL, 1.26 mmol) after 3 h in Et_2O (2 mL) gave the crude product as a yellow oil. Purification by flash column chromatography on silica with petrol-Et_2O (95:5) as eluent gave pyrrolidine (*S*)-**8** (4 mg, 4%, 50:50 er by chiral GC) as a colourless oil and recovered *N*-Boc pyrrolidine **7** (47 mg, 51%) as a colourless oil.

3-Phenylpropyl *N,N*-diisopropylcarbamate 9



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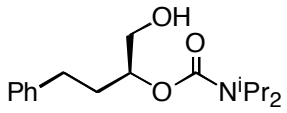
A solution of diisopropylcarbamoyl chloride (2.16 g, 13.21 mmol) in Et_2O (10 mL) was added dropwise over 10 min to a stirred solution of NaH (579 mg of 60% wt dispersion in mineral oil, 14.47 mmol, pre-washed with Et_2O (3 x 10 mL)) and 3-phenyl-1-propanol (1.70 mL, 12.58 mmol) in Et_2O (30 mL) at rt under N_2. The resulting mixture was stirred at rt for 16 h. Then, 2 M $HCl_{(aq)}$ (30 mL) was added and the resulting mixture was stirred vigorously for 5 min. The two layers were separated and the aqueous layer was extracted with Et_2O (4 x 30 mL). The combined organic extracts were dried (2:1 Na_2SO_4-$NaHCO_3$) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with petrol-Et_2O (5:1) as eluent gave carbamate **9** (2.77 g, 84%) as a colourless oil; R_F(5:1 petrol-Et_2O) 0.35; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.27 (m, 2H, Ph), 7.23-7.17 (m, 3H, Ph), 4.28-3.58 (br m, 2 x NCH), 4.13 (t, J = 6.5 Hz, 2H, OCH_2), 2.73 (t, J = 8.0 Hz, 2H, CH_2Ph), 2.03-1.95 (m, 2H, CH_2), 1.23 (d, J = 7.0 Hz, 12H, 2 x NCHMe_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.7

(C=O), 141.5 (*ipso*-Ph), 128.4 (Ph), 128.3 (Ph), 125.8 (Ph), 63.9 (OCH_2), 45.7 (NCH), 32.5 (CH_2), 30.8 (Me), 21.0 (CH_2). Spectroscopic data consistent with that reported in the literature.[6]

Diisopropylcarbamic acid (*S*)-1-hydroxymethyl-3-phenyl-propyl ester (*S*)-10

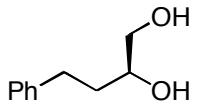


(*S*)-**10**

s-BuLi (1.38 mL of a 1.12 M solution in cyclohexanes, 1.54 mmol) was added dropwise to a stirred solution of diamine (*S,S*)-**4** (478 mg, 1.54 mmol) in Et_2O (2 mL) at –78 ºC under Ar. After stirring for 30 min at –78 ºC, a solution of carbamate **9** (279 mg, 1.06 mmol) in Et_2O (2 mL) was added dropwise over 1 min. The resulting solution was stirred at –78 ˚C for 5 h. Then, a stream of CO_2 was bubbled into the solution for 1 h. The solution was then allowed to warm to rt over 10 min. Water (4 mL) and concentrated $HCl_{(aq)}$ (1 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude acid as a colourless oil. BH_3·DMS (3.50 mL of a 2 M solution in THF, 7.00 mmol) was added dropwise over 2 min to a stirred solution of the crude acid (max. 1.06 mmol) at 0 ˚C under Ar. The resulting solution was allowed to warm to rt over 15 min and stirred at rt for 16 h. Then, the solution was cooled to 0 ˚C and MeOH (20 mL) was added over 10 min. The resulting solution was then stirred at rt for 1 h and then stirred and heated at reflux for 1 h. After being allowed to cool to rt, the solvent was evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with petrol-EtOAc (1:1) as eluent gave alcohol (*S*)-**10** (259 mg, 84%, 84:16 er by chiral HPLC of the diol obtained after $LiAlH_4$ reduction) as a white solid, mp 56-57 ˚C, (lit.,[6] 55-57 ˚C); R_F(1:1 petrol-EtOAc) 0.3; $[\alpha]_D$ –20.7 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.26 (m, 2H, Ph), 7.24-7.16 (m, 3H, Ph), 4.93-4.84 (m, 1H, CHO), 4.19-4.00 (m, 2H, C*H*Me_2), 3.76 (dd, *J* = 12.0, 3.0 Hz, 1H, C$H_A$$H_B$OH), 3.69 (dd, *J* = 12.0, 3.0 Hz, 1H, C$H_A$$H_B$OH), 2.80-2.64 (m, 2H, C$H_2$Ph), 2.01-1.82 (m, 2H, CH_2), 1.25 (d, *J* = 7.0 Hz, 12H, 4 x CH*Me*); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.5 (C=O), 141.4 (*ipso*-Ph), 128.5 (Ph), 128.3 (Ph), 126.1 (Ph), 76.4 (CHO), 66.2 (CH_2O), 46.3 (CHN), 45.6

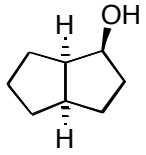
(CHN), 33.1 (CH_2), 31.9 (CH_2). 21.3 (CHMe_2) 20.6 (CHMe_2). Spectroscopic data consistent with that reported in the literature.[6]

(*S*)-4-Phenylbutane-1,2-diol



$LiAlH_4$ (175 mg, 4.55 mmol) was added portionwise to a stirred solution of alcohol (*S*)-**10** (259 mg, 0.89 mmol) in THF (20 mL) at 0 ˚C under Ar. The resulting solution was stirred and heated at reflux for 18 h. After being allowed to cool to rt, the solution was cooled to 0 ˚C and $Na_2SO_4 \cdot 10H_2O$ (1.0 g) was added portionwise. The resulting suspension was then stirred at rt for 1 h. The solids were removed by filtration through a pad of Celite® and washed with CH_2Cl_2 (25 mL), 1:1 CH_2Cl_2-MeOH (25 mL) and MeOH (25 mL). The combined organic extracts were evaporated under reduced pressure to give the crude product as a white oil. Purification by flash column chromatography on silica with CH_2Cl_2-MeOH (19:1) as eluent gave (*S*)-4-phenylbutane-1,2-diol (73 mg, 50%, 84:16 er by chiral HPLC) as a colourless oil, R_F(19:1 CH_2Cl_2-MeOH) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.28 (m, 2H, Ph), 7.23-7.19 (m, 3H, Ph), 3.75-3.69 (m, 1H, C*H*OH), 3.65 (dd, *J* = 11.0, 3.0 Hz, 1H, CH_AH_BOH), 3.46 (dd, *J* = 11.0, 7.5 Hz, 1H, CH$_A$$H_B$OH), 2.83-2.65 (m, 2H), 1.79-1.72 (m, 2H); Chiral HPLC: Daicel Chiralcel OD, 1:4 v/v *i*PrOH-hexane, 0.5 mL min^{-1}, 254 nm, 14.5 min [(*R*)] 18.5 min [(*S*)]. Spectroscopic data consistent with that reported in the literature.[6]

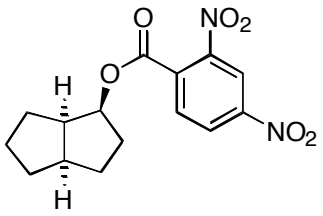
(*S*)-Octahydropentalen-1-ol 12



12

s-BuLi (1.46 mL of a 1.12 M solution in cyclohexanes, 1.64 mmol) was added dropwise to a stirred solution of diamine (*R,R*)**-4** (507 mg, 1.64 mmol) in Et_2O (2 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 30 min and then a solution of cyclooctene oxide **11** (154 mg, 1.22 mmol) in Et_2O (2 mL) was added dropwise over 2 min. The resulting solution was stirred at –78 °C for 5 h and then allowed to warm to rt and stirred at rt for 16 h. The solution was cooled to 0 °C and 2 M $HCl_{(aq)}$ (10 mL) was added. The two layers were separated and the aqueous layer was extracted with EtOAc (4 x 10 mL). The combined organic extracts were washed with saturated $NaHCO_{3(aq)}$ (10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a colourless oil. Purification by flash column chromatography on silica with petrol-Et_2O (7:3) as eluent gave alcohol **12** (141 mg, 92%, 50:50 er by chiral HPLC of the dinitrobenzoate) as a colourless oil, R_F(1:1 petrol-Et_2O) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17-4.13 (m, 1H, C*H*OH), 2.45-2.35 (m, 2H, 2 x CH), 1.81-1.07 (m, 11H, 5 x CH_2 and OH). Spectroscopic data consistent with that reported in the literature.[7]

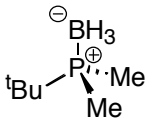
2,4-Dinitro-benzoic acid (*S*)-(octahydro-pentalen-1-yl) ester



2,4-Dinitrobenzoic acid (170 mg, 0.81 mmol) was added in one portion to a stirred solution of alcohol **12** (68 mg, 0.54 mmol), DMAP (6 mg, 0.05 mmol) and DCC (133 mg, 0.65 mmol) in CH_2Cl_2 (5 mL) under Ar at 0 °C. The resulting solution was stirred at rt for 72 h. Then, the solids were removed by filtration and washed with CH_2Cl_2 (2 x 5 mL). The combined filtrate was evaporated to give the crude product as a

yellow solid. Purification by flash column chromatography on silica with petrol-Et_2O (3:2) as eluent the gave ester (167 mg, 97%, 50:50 er by chiral HPLC) as a yellow oil, R_F(1:1 petrol-Et_2O) 0.8; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 2.0 Hz, 1H, ArCH), 8.53 (dd, *J* = 8.5, 2.0 Hz, 1H, ArCH), 7.96 (d, *J* = 8.5 Hz, 1H, ArCH), 5.37 (dd, *J* = 12.5, 6.5 Hz, 1H, CHO), 2.28-2.67 (m, 1H, CH), 2.59-2.46 (m, 1H, CH), 1.98-1.19 (m, 10H, CH_2); Chiral HPLC: Daicel Chiralpak AD-H, 3:7 v/v MeOH-hexane + 0.2% *i*PrOH, 5 mL min^{-1}, 254 nm, 0.92 min and 1.63 min (*ent*). Spectroscopic data consistent with that reported in the literature.[7]

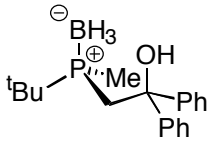
***tert*-Butyldimethylphosphine borane 13**



13

MeMgBr (46.5 mL of a 3 M solution in Et_2O, 139.6 mmol) was added dropwise over 1 h to a stirred solution of *t*-butyldichlorophosphine (10.0 g, 62.9 mmol) in THF (120 mL) at –10 °C under Ar. The resulting cloudy solution was stirred at rt for 5 h and then cooled to –10 °C. Then, BH_3•DMS (38.0 mL of a 2 M solution in THF, 76.0 mmol) was added dropwise over 20 min. The solution was stirred at rt for 1 h and poured onto a mixture of ice (150 g) and concentrated $HCl_{(aq)}$ (15 mL). The mixture was extracted with EtOAc (4 x 50 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a white solid. Purification by recrystallisation from hexane (40 mL) gave phosphine borane **13** (6.12 g, 74%) as a white solid, mp 163-164 °C (lit.,[8] 160-163 °C); R_F(4:1 petrol-Et_2O) 0.4; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (d, *J* = 10.0 Hz, 6H, PMe), 1.13 (d, *J* = 14.0 Hz, 9H, CMe_3), 0.41 (qd, *J* = 95.0, 13.0 Hz, 3H, BH_3). Spectroscopic data consistent with that reported in the literature.[8]

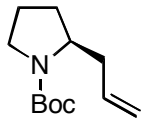
(*R*)-*P*-(2,2-Diphenyl-2-hydroxyethyl)-*P*-methyl-*tert*-butylphosphine borane (*R*)-14



(*R*)-**14**

s-BuLi (1.00 mL of a 1.12 M solution in cyclohexanes, 1.49 mmol) was added dropwise to a stirred solution of diamine (*S,S*)-**4** (464 mg, 1.49 mmol) in Et_2O (2 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 30 min and then a solution of phosphine borane **13** (138 mg, 1.05 mmol) in Et_2O (2 mL) was added dropwise over 2 min. The resulting solution was stirred at –78 °C for 3 h. Then, a solution of benzophenone (229 mg, 1.29 mmol) in Et_2O (1 mL) was added dropwise. The resulting mixture was allowed to warm to rt and stirred at rt for 16 h. 1 M $HCl_{(aq)}$ (2 mL) was added and the two layers were separated. The aqueous layer was extracted with Et_2O (5 x 5 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a white solid. Purification by flash column chromatography on silica with petrol-EtOAc (95:5) as eluent gave alcohol (*R*)-**14** (309 mg, 99%, 60:40 er by chiral HPLC) as a white solid, mp 110-112 °C (lit.,[9] 116.5-117.5 °C); R_F(95:5 petrol-EtOAc) 0.2; $[\alpha]_D$ –2.5 (*c* 1.0 in $CHCl_3$) (lit.,[9] $[\alpha]_D$ –14.9 (*c* 0.47 in $CHCl_3$) for (*R*)-**14** of 96:4 er); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.44 (m, 4H, Ph), 7.38-7.28 (m, 4H, Ph), 7.28-7.20 (m, 2H, Ph), 4.58 (s, 1H, OH), 2.89 (t, *J* = 14.5 Hz, 1H C(OH)CH_AH$_B$), 2.68 (dd, *J* = 14.5, 7.0 Hz, 1H C(OH)CH$_A$$H_B$), 1.80 (d, *J* = 13.5 Hz, 9H, CMe_3), 1.07-0.07 (m, 3H, BH_3), 0.75 (d, *J* = 10.0 Hz, 3H, PMe); Chiral HPLC: Daicel Chiralcel OD, 1:19 v/v *i*-PrOH-hexane, 0.5 mL min^{-1}, 254 nm, 10.5 min [(*R*)-**14**] 12.5 min [(*S*)-**14**]. Spectroscopic data consistent with that reported in the literature.[10]

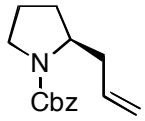
(*S*)-*tert*-Butyl 2-allylpyrrolidine-1-carboxylate 15



15

s-BuLi (0.98 mL of a 1.20 M solution in cyclohexane, 1.18 mmol) was added dropwise over 1 min to a stirred solution of the *N*-Boc pyrrolidine **7** (160 μL, 0.91 mmol) and diamime (*S,S*)-**4** (366 μL, 1.18 mmol) in Et_2O (3.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 3 h. Then, CuCN•2LiCl (758 μL of a 0.6 M solution in THF, 0.46 mmol) was added dropwise and the resulting solution was stirred at –78 °C for 1 h. Then, allyl bromide (142 μL, 1.64 mmol) was added dropwise and the reaction mixture was allowed to warm to rt and stirred at rt for 16 h. $NH_4OH_{(aq)}$ (0.5 mL), saturated $NH_4Cl_{(aq)}$ (4.5 mL) and Et_2O (5 mL) were added and the mixture stirred at rt for 20 min. The solids were removed by filtration through a pad of Celite® and the filter cake was washed with Et_2O (5 mL). The two layers of the filtrate were separated and the blue aqueous layer was extracted with Et_2O (3 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with petrol-EtOAc (85:15) as eluent gave allyl pyrrolidine **15** (150 mg, 78%, 85:15 er by chiral HPLC) as a colourless oil, R_F(9:1 petrol-EtOAc) 0.2; $[\alpha]^{24}_D$ –35.1 (*c* 0.95 in $CHCl_3$) (lit.,[11] $[\alpha]^{24}_D$ –32.4 (*c* 1.56 in $CHCl_3$) for (*S*)-**15** of ≥ 99:1 er); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.74 (ddt, *J* = 17.5, 10.0, 7.0 Hz, 1H, C*H*=CH_2), 5.05 (d, *J* = 17.5 Hz, 1H, *trans*-CH=C$H_A$$H_B$), 5.03 (d, *J* = 10.0 Hz, 1H, *cis*-CH=$CH_A$$H_B$), 3.88-3.73 (br m, 1H, CHN), 3.41-3.36 (m, 2H, CH_2N), 2.55-2.42 (m, 1H, C$H_A$$H_B$CH=$CH_2$), 2.16-2.05 (m, 1H, $CH_A$$H_B$CH=$CH_2$), 1.94-1.66 (m, 4H, 2 x CH_2), 1.46 (s, 9H, CMe_3); Chiral HPLC: Chiralcel OD, 99:1 hexane:*i*-PrOH, 0.1 mLmin^{-1}, 44.07 min [(*R*)-**15**], 47.38 min [(*S*)-**15**]. Spectroscopic data consistent with that reported in the literature.[12]

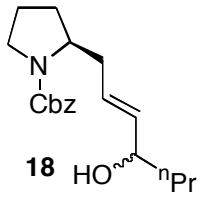
(*S*)-Benzyl 2-allylpyrrolidine-1-carboxylate 16



16

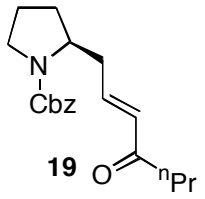
TFA (1 mL, 13.46 mmol) was added dropwise to a stirred solution of pyrrolidine (*S*)-**15** (145 mg, 0.69 mmol) in CH_2Cl_2 (5 mL) at rt under Ar. The resulting solution was stirred at rt for 3 h and the solvent was evaporated under reduced pressure to give the crude product as a yellow oil. To a stirred solution of the crude product in CH_2Cl_2 (2 mL) at 0 °C under Ar, Et_3N (288 μL, 2.07 mmol) and benzyl chloroformate (128 μL, 0.90 mmol) were added dropwise. The resulting mixture was allowed to warm to rt and stirred at rt for 8 h. CH_2Cl_2 (5 mL) and water (5 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 10 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with petrol-EtOAc (9:1) as eluent gave allyl pyrrolidine (*S*)-**16** (168 mg, 99% over 2 steps) as a colourless oil, $[\alpha]^{24}_D$ –30.2 (*c* 1.15 in $CHCl_3$) (lit.,[13] $[\alpha]^{24}_D$ –38.7 (*c* 1.13 in $CHCl_3$) for (*S*)-**16** of ≥ 99:1 er); R_F(9:1 petrol-EtOAc) 0.3; ^{1}H NMR (400 MHz, $CDCl_3$) rotamers present δ 7.41-7.28 (m, 5H, Ph), 5.84-5.64 (m, 1H, C*H*=CH_2), 5.23-4.97 (m, 4H, CH=CH_2 and CH_2Ph), 3.98-3.85 (m, 1H, NCH), 3.53-3.36 (m, 2H, NCH_2), 2.65-2.39 (m, 1H, C$H_A$$H_B$CH=$CH_2$), 2.23-2.08 (m, 1H, $CH_A$$H_B$CH=$CH_2$), 1.99-1.70 (m, 4H, 2 x CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) approx 1:1 mixture of rotamers, δ 154.9 and 154.7 (C=O), 137.1 and 136.9 (*ipso*-Ph), 135.0 and 134.8 (*C*H=CH_2), 128.4 and 127.8 and 127.7 (Ph), 117.3 and 117.2 (CH=*C*H_2), 66.6 and 66.4 (*C*H_2Ph), 57.2 and 56.7 (NCH), 46.8 and 46.5 (NCH_2), 38.9 and 38.0 (*C*H_2CH=CH_2), 30.0 and 29.1 (CH_2), 23.6 and 22.8 (CH_2). Spectroscopic data consistent with that reported in the literature.[13]

(*S*)-Benzyl 2-((*E*)-4-hydroxyhept-2-enyl)pyrrolidine-1-carboxylate 18



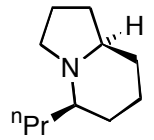
Grubbs' 2nd generation catalyst (28 mg, 0.033 mmol) was added in one portion to a stirred solution of the allyl-pyrrolidine **16** (160 mg, 0.65 mmol) and 1-hexen-3-ol **17** (157 μL, 1.31 mmol) in CH_2Cl_2 (4.5 mL) at rt under Ar. The resulting mixture was stirred at rt for 6 h before a second portion of Grubb's 2nd generation catalyst (10 mg, 0.012 mmol) was added. The resulting mixture was stirred at rt for a further 10 h. Then, the solvent was removed under reduced pressure to give the crude product as a brown oil. Purification by flash column chromatography on silica with petrol-EtOAc (7:3 to 1:1) as eluent gave alcohol **18** (161 mg, 78%) as a yellow oil, R_F(1:1 petrol-EtOAc) 0.53; IR (neat) 3435 (OH), 1695 (C=O), 1425 (C=C) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) mixture of diastereoisomers/rotamers δ 7.43-7.25 (m, 5H, Ph), 5.68-5.36 (m, 2H, CH=CH), 5.23-5.04 (m, 2H, CH_2Ph), 4.10-3.97 (m, 1H, C*H*OH), 3.97-3.81 (m, 1H, NCH), 3.53-3.31 (m, 2H, NCH_2), 2.57-2.32 (m, 1H, CH_AH$_B$CH=CH), 2.23-2.05 (m, 1H, CH$_A$$H_B$CH=CH), 1.98-1.67 (m, 4H, 2 x CH_2), 1.58-1.21 (m, 4H, 2 x CH_2), 0.92 (t, J = 7.5 Hz, 3H, Me); ^{13}C NMR (400 MHz, $CDCl_3$) mixture diastereoisomers/rotamers δ 154.9 (C=O), 137.0 (*ipso*-Ph), 136.1 and 136.0 (=CH), 128.4 (Ph), 127.9 (Ph), 127.8 (Ph), 127.3 (=CH), 72.6 and 72.5 (COH), 66.7 and 66.4 (*C*H_2Ph), 57.3 and 56.8 (NCH), 46.8 and 46.4 (NCH_2), 39.3 (*C*H_2CH=CH), 37.2 and 36.5 (CH_2), 30.0 and 29.4 (CH_2), 23.6 and 22.8 (CH_2), 18.6 (CH_2), 14.0 (Me). Spectroscopic data consistent with that reported in the literature.[14]

(*S*)-Benzyl 2-((*E*)-4-oxohept-2-enyl)pyrrolidine-1-carboxylate 19



Dess-Martin periodinane (422 mg, 1.00 mmol) was added in one portion to a stirred solution of alcohol **18** (142 mg, 0.45 mmol) in CH_2Cl_2 (4 mL) at rt under Ar. The resulting mixture was stirred at rt for 1 h. Then, CH_2Cl_2 (7 mL) and a solution of $Na_2S_2O_3$ (1.0 g) in 5% $NaHCO_{3(aq)}$ (10 mL) were added. The resulting mixture was stirred at rt for 15 min. The two layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with petrol-EtOAc (85:15) as eluent gave ketone **19** (111 mg, 72%) as a colourless oil, $[\alpha]^{24}_D$ –74.6 (*c* 0.33 in $CHCl_3$); R_F(5:1 petrol-EtOAc) 0.36; IR (neat) 2962 (CH), 1697 (C=O), 1627 (C=O), 1411 (C=C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) approx 2:3 mixture of rotamers δ 7.46-7.23 (m, 5H, Ph), 6.86-6.84 (m, 1H, C*H*=CH(CO)), 6.12 (d, *J* = 16.0 Hz, 0.6H, CH=C*H*(CO)), 6.05 (d, *J* = 16.0 Hz, 0.4H CH=C*H*(CO)), 5.15 (br s, 0.8H, CH_2Ph), 5.13 (br s, 1.2H, CH_2Ph), 4.08-3.94 (m, 1H, NCH), 3.55-3.34 (m, 2H, NCH_2), 2.79-2.67 (m, 0.6H, C$H_A$$H_B$CH=CH), 2.61-2.52 (m, 0.4H, C$H_A$$H_B$CH=CH), 2.50 (t, *J* = 7.5 Hz, 1.2H, C(O)CH_2), 2.45 (t, *J* = 7.0 Hz, 0.8H, C(O)CH_2), 2.41-2.26 (m, 1H, $CH_A$$H_B$CH=CH) 2.04-1.77 (m, 3H, CH_2 and CH), 1.75 (m, 3H, CH and CH_2), 0.93 (t, *J* = 7.5 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) approx 2:3 mixture of rotamers δ 200.3 (C=O), 154.8 (C=O), 143.0 and 142.5 (*C*H=CH(CO)), 136.9 (*ipso*-Ph), 132.4 (CH=*C*H(CO)), 128.5 (Ph), 128.0 (Ph), 127.9 (Ph), 127.8 (Ph), 66.9 and 66.6 (*C*H_2Ph), 56.7 and 56.1 (NCH), 46.8 and 46.5 (NCH_2), 42.2 and 41.9 (C(O)*C*H_2), 37.6 and 36.8 (*C*H_2CH=CH), 30.4 and 29.6 (NCH*C*H_2), 23.6 and 22.9 (NCH_2*C*H_2), 17.6 and 17.5 (*C*H_2Me), 13.7 (Me); MS (ESI) *m/z* 338 [(M + Na)$^+$, 100], 316 [(M + H)$^+$, 33]; HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{19}H_{25}NO_3$, 338.1732; found 338.1727.

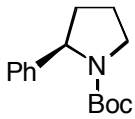
(–)-(5*R*,9*R*)-Octahydro-5-propylindolizine ((–)-indolizidine 167B))



(–)-Indolizidine 167B

A suspension of 10% (w/w) Pd/C (40 mg, 0.038 mmol) in MeOH (2 mL) was added to stirred solution of ketone **19** (60 mg, 0.19 mmol) in MeOH (1 mL) at rt under N_2. The flask was evacuated and back-filled with N_2 three times. Then, the flask was evacuated and back-filled with H_2. The resulting mixture was stirred at rt under H_2 for 16 h. Then, CH_2Cl_2 (20 mL) was added and the solids were removed by filtration through a pad of Celite® and washed with CH_2Cl_2 (2 x 5 mL). The filtrate was evaporated under reduced pressure to give the crude product as a yellow/browm oil. Purification by flash column chromatography on a pad of Et_3N-deactivated silica with petrol-EtOAc (1:1 → 0:1) as eluent gave (–)-indolizidine 167B (26 mg, 81%) as a yellow oil, $[\alpha]^{24}_D$ –89.5 (*c* 0.2 in CH_2Cl_2) (lit.,[15] $[\alpha]^{24}_D$ –115 (*c* 1.17 in CH_2Cl_2) for (–)-indolizidine 167B of ≥ 99:1 er); R_F(1:1 petrol-EtOAc) on Et_3N deactivated silica 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.28 (td *J* = 9.0, 2.0 Hz, 1H, NCH), 2.06-1.54 (m, 10H, 4 x CH_2, NCH and CH), 1.54-1.67 (m, 7H, CH and 3 x CH_2), 0.90 (t, *J* = 7.0 Hz, 3H, Me); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 65.2 (NCH), 63.7 (NCH), 51.3 (NCH_2), 36.5 (CH_2), 30.5 (CH_2), 30.4 (CH_2), 30.3 (CH_2), 20.3 (CH_2), 19.1 (CH_2), 14.4 (Me). Spectroscopic data is consistent with that reported in the literature.[15]

(*R*)-*tert*-Butyl 2-phenylpyrrolidine-1-carboxylate 20

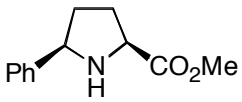


20

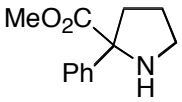
s-BuLi (1.32 mL of a 1.30 M solution in cyclohexane, 1.75 mmol) was added dropwise to a stirred solution of *N*-Boc pyrrolidine **7** (307 μL, 1.75 mmol) and (–)-sparteine (402 μL, 1.75 mmol) in Et_2O (3.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 3 h. Then, $ZnCl_2$ (1.04 mL of a 1.0 M solution in Et_2O, 1.04 mmol) was added dropwise and the resulting solution was stirred at –78 °C

for 30 min. Then, the solution was allowed to warm to rt over 15 min, followed by stirring at rt for 20 min. Then, bromobenzene (153 μL, 1.46 mmol) and a mixture of $^{t}Bu_3PHBF_4$ (25 mg, 0.09 mmol) and $Pd(OAc)_2$ (16 mg, 0.07 mmol) were added. The resulting mixture was stirred at rt for 16 h. $NH_4OH_{(aq)}$ (150 μL) was added and the mixture stirred at rt for 1 h. The solids were removed by filtration through a pad of Celite® and washed with Et_2O (20 mL). The filtrate was washed with 1 M $HCl_{(aq)}$ (15 mL) and water (2 x 15 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with CH_2Cl_2 as eluent gave pyrrolidine (*R*)-**20** (307 mg, 81%, 95:5 er by chiral HPLC) as a colourless oil that solidifies of standing, mp 58-60 °C (lit.,[16] 61.9-62.7 °C); $[\alpha]^{24}_{D}$ +83.2 (*c* 0.7 in acetone) (lit.,[16] $[\alpha]^{24}_{D}$ +85.3 (*c* 0.019 in acetone)); $R_F(CH_2Cl_2)$ 0.25; ^{1}H NMR (400 MHz, $CDCl_3$) rotamers present δ 7.33-7.26 (m, 2H, Ph), 7.25-7.13 (m, 3H, Ph), 5.03-4.90 (br m, 0.33H, NC*H*Ph), 4.83-4.70 (m, 0.66H, NC*H*Ph), 3.72-3.45 (m, 2H, NCH_2), 2.42-2.20 (br m, 1H, CH_AH_B), 1.99-1.77 (m, 3H, CH_AH_B and CH_2), 1.46 (s, 3H, CMe_3), 1.18 (s, 6H, CMe_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) rotamers present δ 154.5 (C=O), 145.1 (*ipso*-Ph), 128.1 (2 x Ph), 125.5 (Ph), 79.1 (CMe_3), 61.3 and 60.6 (*C*HPh), 47.0 (NCH_2), 36.0 (CH_2), 28.5 and 28.1 (CMe_3), 23.4 (CH_2), 23.39 (CH_2); Chiral HPLC: Chiralpak AD, 99:1 hexane/*i*-PrOH, 0.5 mLmin^{-1}, 9.40 min [(*R*)-**20**] and 11.84 min [(*S*)-**20**].[16]

(2*S*,5*R*)-Methyl 5-phenylpyrrolidine-2-carboxylate *cis*-22 and methyl 2-phenylpyrrolidine-2-carboxylate 23



cis-**22**

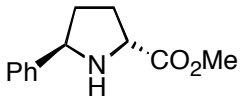


23

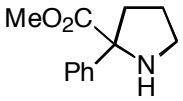
s-BuLi (1.28 mL of a 1.20 M solution in cyclohexane, 1.53 mmol) was added dropwise to a stirred solution of pyrrolidine (*R*)-**20** (250 mg, 0.96 mmol) and diamine (*S,S*)-**4** (475 mg, 1.53 mmol) in Et_2O (2.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 6 h. Then, a stream of CO_2 was bubbled into the solution for 1 h and the solution was allowed to warm to rt and stirred at rt for 16 h. 1 M $HCl_{(aq)}$ (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (5 x 10 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated

under pressure to give the crude acids as a pale yellow oil. To a stirred solution of the crude acid in 1:1 MeOH-toluene (14 mL) at 0 °C under Ar trimethylsilyldiazomethane (534 μL of a 2 M solution in hexanes, 1.07 mmol) was added dropwise. The resulting solution was stirred at rt for 1 h. Acetic acid (11 μL, 0.2 mmol) was added dropwise and the solvent was evaporated under reduced pressure to give the crude methyl esters. To a stirred solution of the crude methyl esters in CH_2Cl_2 (2.5 mL) at 0 °C under Ar TFA (250 μL, 3.25 mmol) was added dropwise. The resulting solution was stirred at rt for 3 h. CH_2Cl_2 (2.5 mL) and 1 M $NaOH_{(aq)}$ (5 mL) were added and the resulting layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with petrol-EtOAc (7:3) as eluent gave *cis*-pyrrolidine *cis*-**22** (51 mg, 33% over 3 steps, ≥ 99:1 er by chiral HPLC) as a pale yellow oil, $[\alpha]^{24}_D$ +14.7 (*c* 0.45 in CH_2Cl_2) (lit.,[17] $[\alpha]^{24}_D$ +15.3 (*c* 1.22 in CH_2Cl_2) for (2*S*,5*R*)-**22**); R_F(7:3 petrol-EtOAc) 0.15; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.5 Hz, 2H, *o*-Ph), 7.36 (t, *J* = 7.5 Hz, 2H, *m*-Ph), 7.30 (d, *J* = 7.5 Hz, 1H *p*-Ph), 4.31 (dd, *J* = 10.0, 6.0 Hz, 1H, NCH), 4.06 (dd, *J* = 9.0, 4.5 Hz, 1H, NCH), 3.80 (s, 3H, Me), 2.39-2.35 (m, 3H, CH_2 and CH_AH$_B$), 1.84-1.73 (m, 1H, CH$_A$$H_B$); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 175.5 (C=O), 143.1 (*ipso*-Ph), 128.5 (Ph), 127.3 (Ph), 126.7 (Ph), 63.5 (NCH), 60.0 (NCH), 52.2 (Me), 34.1 (CH_2), 30.5 (CH_2). Chiral HPLC: Chiralpak AD 95:5 Hexane/*i*-PrOH, 0.5 mLmin^{-1}, 22.71 min [(2*R*,5*S*)-**22**], 26.48 min [(2*S*,5*R*)-**22**] and amine **23** (18 mg, 22% over 3 steps) as a pale yellow oil, $[\alpha]^{24}_D$ –7.1 (*c* 0.9 in $CHCl_3$); R_F(7:3 petrol-EtOAc) 0.16; IR (neat) 2953 (CH), 2926 (CH), 2855 (CH), 1730 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.50 (m, 2H, *o*-Ph), 7.33 (t, *J* = 7.5 Hz, 2H, *m*-Ph), 7.24 (t, *J* = 7.5 Hz, 1H, *p*-Ph), 3.69 (s, 3H, OMe), 3.16-3.06 (m, 2H, NCH_2), 2.76 (ddd, *J* = 12.5, 8.0, 5.0 Hz, 1H, NC(Ph)CH_AH$_B$), 2.59-1.97 (br m, 1H, NH), 2.09 (dt, *J* = 12.5, 8.5 Hz, 1H, NC(Ph)CH$_A$$H_B$), 1.95-1.76 (m, 2H, CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.0 (C=O), 142.6 (*ipso*-Ph), 128.2 (Ph), 127.2 (Ph), 126.0 (Ph), 72.2 (N*C*Ph), 52.7 (OMe), 45.7 (NCH_2), 36.6 (CH_2), 24.5 (CH_2); MS (ESI) *m*/*z* 228 [(M + Na)$^+$, 5], 206 [(M + H)$^+$, 20], 146 [(M – CO_2Me)$^+$ 100]; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{15}NO_2$, 206.1181; found 205.1176. Spectroscopic data of *cis*-**22** consistent with that reported in the literature.[17]

(2*R*,5*R*)-Methyl 5-phenylpyrrolidine-2-carboxylate *trans*-24 and methyl 2-phenylpyrrolidine-2-carboxylate 23



trans-**24**

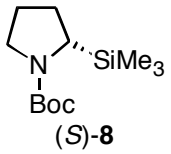


23

s-BuLi (1.50 mL of a 1.20 M solution in cyclohexane, 1.80 mmol) was added dropwise to a stirred solution of pyrrolidine (*R*)-**20** (294 mg, 1.13 mmol) and (–)-sparteine (413 μL, 1.80 mmol) in Et_2O (2.5 mL) at –78 °C under Ar. The resulting solution was stirred at –78 °C for 6 h. Then, a stream of CO_2 was bubbled into the solution for 1 h and the solution was allowed to warm to rt and stirred at rt for 16 h. 1 M $HCl_{(aq)}$ (10 mL) and EtOAc (10 mL) were added and the two layers were separated. The aqueous layer was extracted with EtOAc (5 x 10 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated under pressure to give the crude acids as a pale yellow oil. To a stirred soluition of the crude acids 1:1 MeOH-toluene (7 mL) at 0 °C under Ar, trimethylsilyldiazomethane (713 μL of a 2 M solution in hexanes, 1.42 mmol) was added dropwise. The resulting solution was stirred at rt for 1 h. Acetic acid (13 μL, 0.23 mmol) was added dropwise and the solvent was evaporated under reduced pressure to give the crude methyl esters. To a stirred solution of the crude methyl esters in CH_2Cl_2 (3 mL) at 0 °C under Ar, TFA (300 μL, 3.89 mmol) was added dropwise. The resulting solution was stirred at rt for 2 h. CH_2Cl_2 (5 mL) and 1 M $NaOH_{(aq)}$ (5 mL) were added and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (4 x 5 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product as a yellow oil. Purification by flash column chromatography on silica with petrol-EtOAc (7:3) as eluent gave *trans*-pyrrolidine *trans*-**24** (67 mg, 27% over 3 steps) as a pale yellow oil, $[\alpha]^{24}_D$ +84.8 (*c* 0.7 in CH_2Cl_2) (lit.,[18] $[\alpha]^{24}_D$ +82.0 (*c* 1.00 in CH_2Cl_2) for (2*R*,5*R*)-**24**); R_F(7:3 petrol-EtOAc) 0.2; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.36 (m, 2H, *o*-Ph), 7.33 (t, *J* = 7.5 Hz, 2H, *m*-Ph), 7.24 (t, *J* = 7.5 Hz, 1H *p*-Ph), 4.37 (dd, *J* = 8.5, 6.0 Hz, 1H, NCH), 4.06 (dd, *J* = 8.5, 6.0 Hz, 1H, NCH), 3.77 (s, 3H, Me), 2.36 (dtd, *J* = 13.0, 8.5, 4.0 Hz, 1H, CH), 2.21 (ddddd, *J* = 12.0, 8.0, 6.5, 4.0, 0.5 Hz, 1H, CH), 2.00 (dddd, *J* = 13.0, 8.5, 8.0, 6.0 Hz, 1H, CH), 1.75 (dq, *J* = 12.0, 8.5 Hz, 1H, CH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 176.3 (C=O), 144.3 (*ipso*-Ph), 128.3 (Ph), 126.8 (Ph), 126.4 (Ph), 61.7 (NCH), 59.4 (NCH), 52.1 (OMe), 34.5 (CH_2), 29.7 (CH_2) and **23** (44 mg, 27% over 3 steps) as a pale

yellow oil, $[\alpha]^{24}_{D}$ –44.5 (*c* 0.05 in $CHCl_3$). Spectroscopic data for *trans*-**24** consistent with that reported in the literature.[19]

Representative GC/HPLC data



(*S*)-**8**

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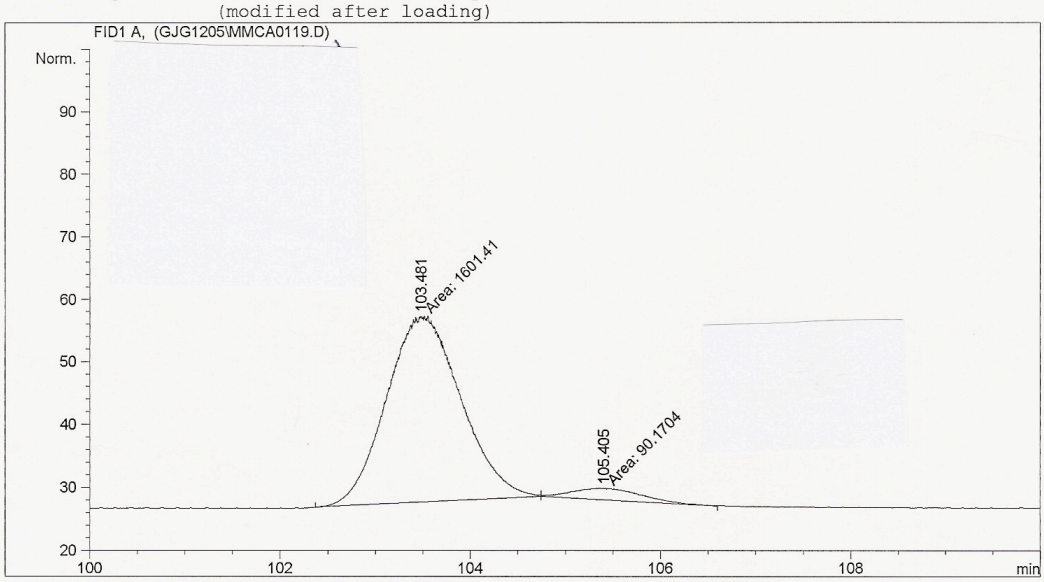


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Sample Amount         :      1.00000  [ng/ul]   (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
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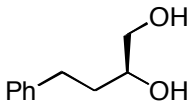
Instrument 1 4/21/2006 2:17:38 PM darren Page 1 of 2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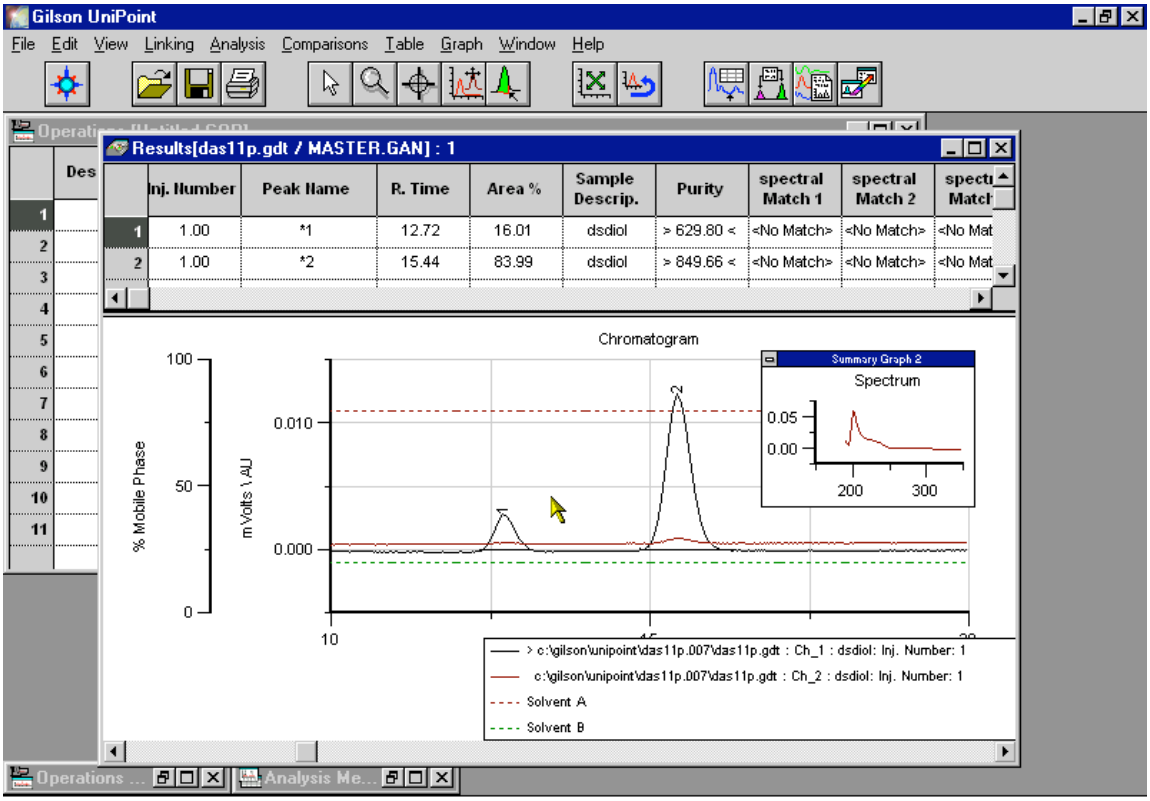
Gilson UniPoint
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Solvent B
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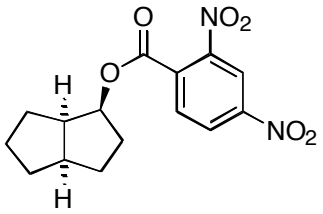

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Operator: John Burnett

Vial Number: 9
Injection Volume: 10.000 ul

Sample Name: 59M-0000-556-001
Column: AD-H
Mobile Phase: 30%MeOH/IPAm
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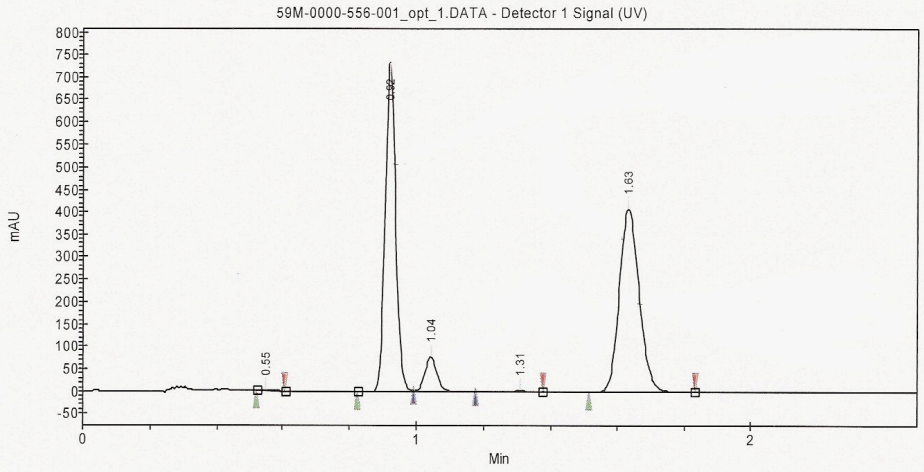

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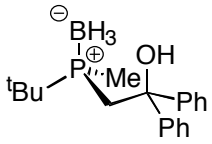
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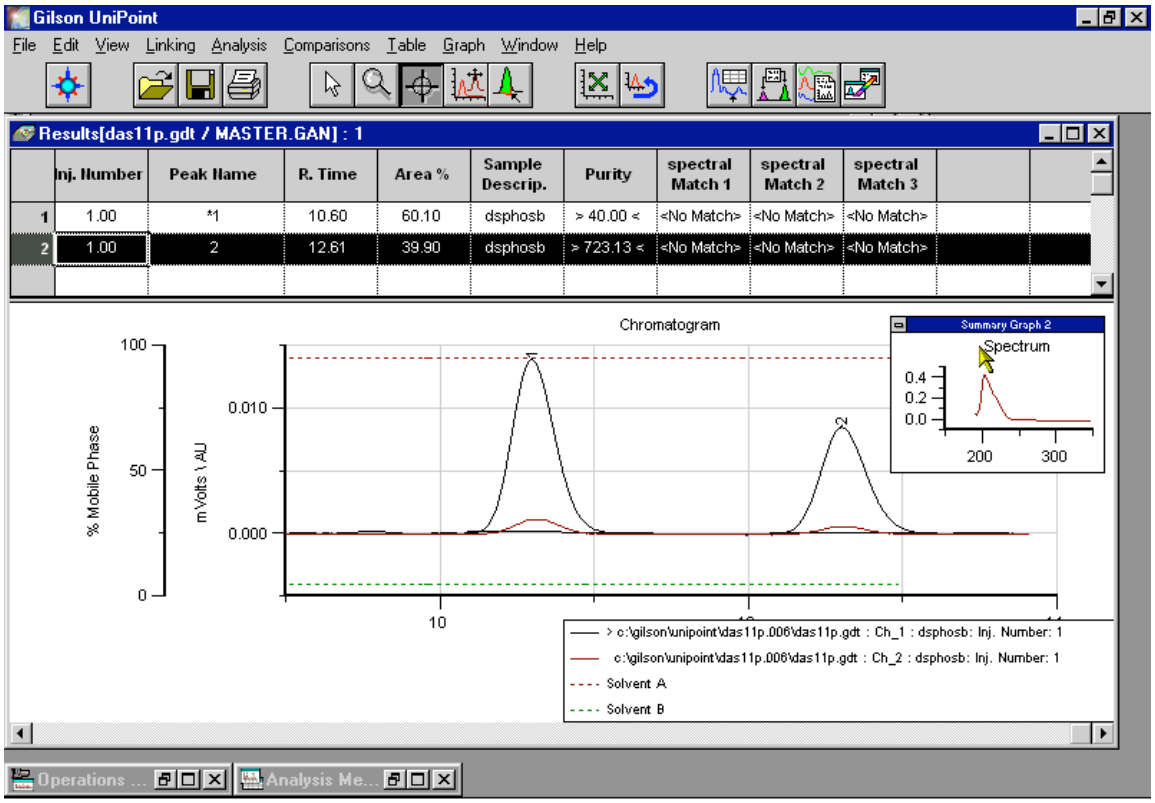
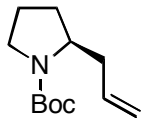
Ph

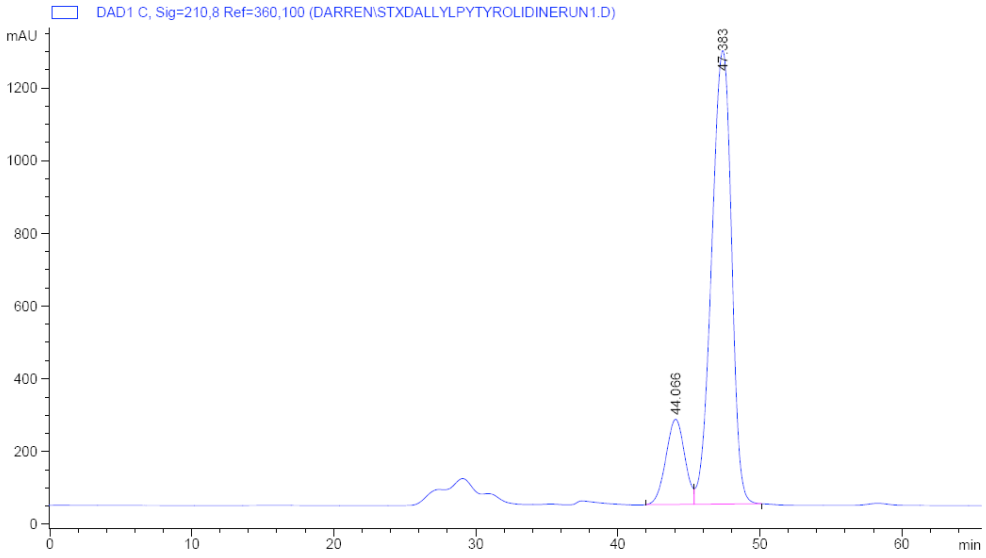
(*R*)-**14**


Gilson UniPoint
File Edit View Linking Analysis Comparisons Table Graph Window Help
Results[das11p.gdt / MASTER.GAN] : 1
Inj. Number | Peak Name | R. Time | Area % | Sample Descrip. | Purity | spectral Match 1 | spectral Match 2 | spectral Match 3
1 | 1.00 | *1 | 10.60 | 60.10 | dsphosb | > 40.00 < | <No Match> | <No Match> | <No Match>
2 | 1.00 | 2 | 12.61 | 39.90 | dsphosb | > 723.13 < | <No Match> | <No Match> | <No Match>
Chromatogram
Summary Graph 2
Spectrum
0.4
0.2
0.0
200
300
100
50
0
% Mobile Phase
0.010
0.000
mVolts \ AU
10
> c:\gilson\unipoint\das11p.006\das11p.gdt : Ch_1 : dsphosb: Inj. Number: 1
c:\gilson\unipoint\das11p.006\das11p.gdt : Ch_2 : dsphosb: Inj. Number: 1
Solvent A
Solvent B
Operations ...
Analysis Me...

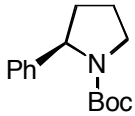


15

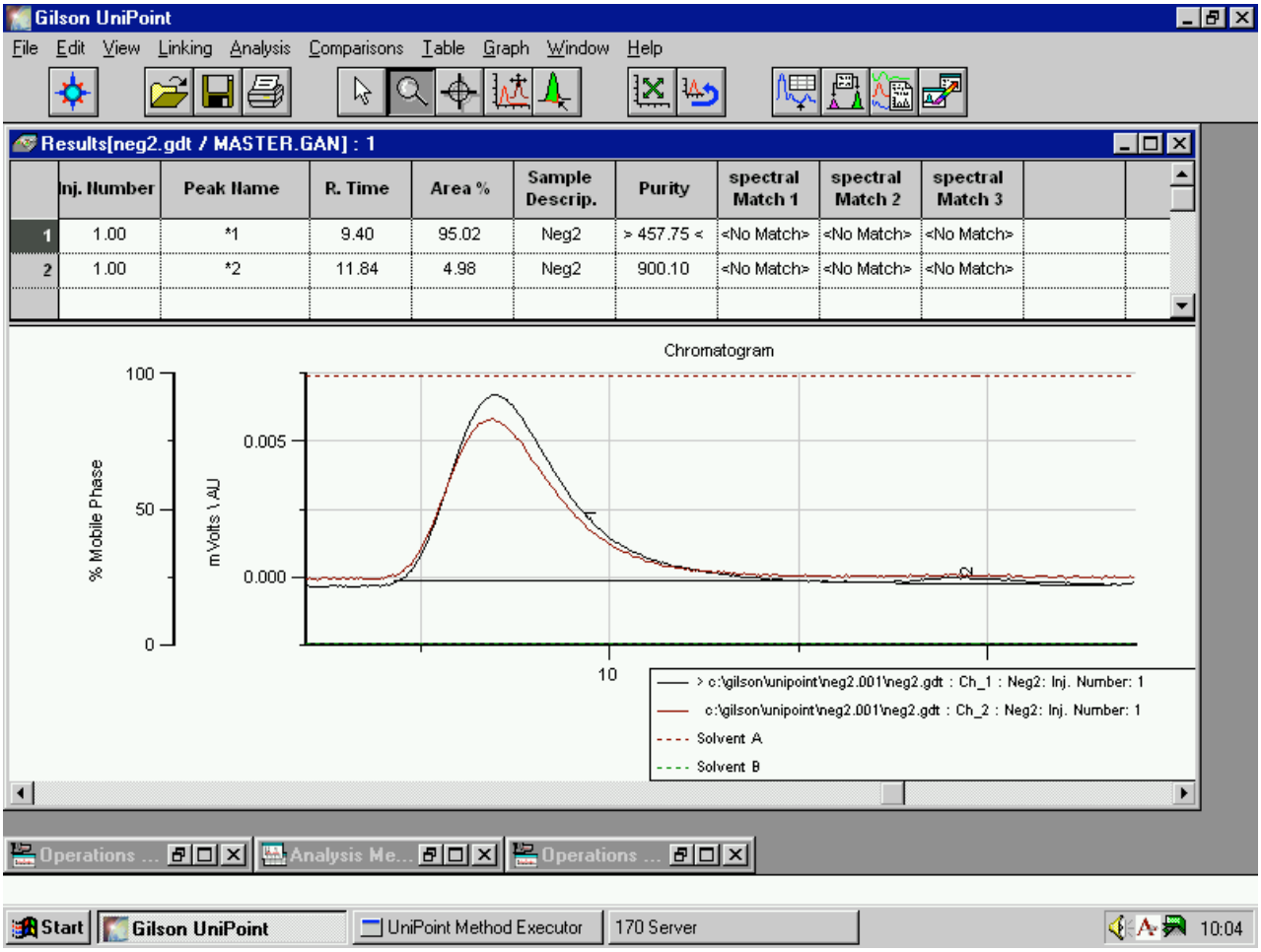
```
Data File C:\CHEM32\1\DATA\DARREN\STXDALLYLPYTYROLIDINERUN1.D
Sample Name: DS8.83.Prun1

    ========================================================================
    Acq. Operator   : Darren
    Acq. Instrument : Instrument 1                    Location : Vial 1
    Injection Date  : 8/20/2007 12:43:26 PM
    Acq. Method     : C:\CHEM32\1\METHODS\DARREN\ALLYLPYRROLIDINEO.5EQCU.M
    Last changed    : 8/20/2007 12:42:13 PM by Darren
    Analysis Method : C:\CHEM32\1\DATA\DARREN\STXDALLYLPYTYROLIDINERUN1.D\DA.M (
                      ALLYLPYRROLIDINEO.5EQCU.M)
    Last changed    : 8/20/2007 1:49:12 PM by Darren
    Method Info     : allybocpyrrolidine method 2

    Sample Info     : OD column 0.1 ml/min flow, 1:99 IPA:Hexane, 2 bar,  ds8
                      /83/prun1
```

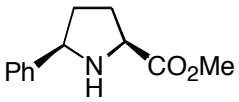



```
    ========================================================================
                              Area Percent Report
    ========================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 C, Sig=210,8 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  44.066 BV    1.4335 2.17321e4   234.43938  15.1971
       2  47.383 VB    1.5488 1.21270e5  1246.79138  84.8029

    Totals :                  1.43002e5  1481.23076

    ========================================================================
```


Ph
N
Boc

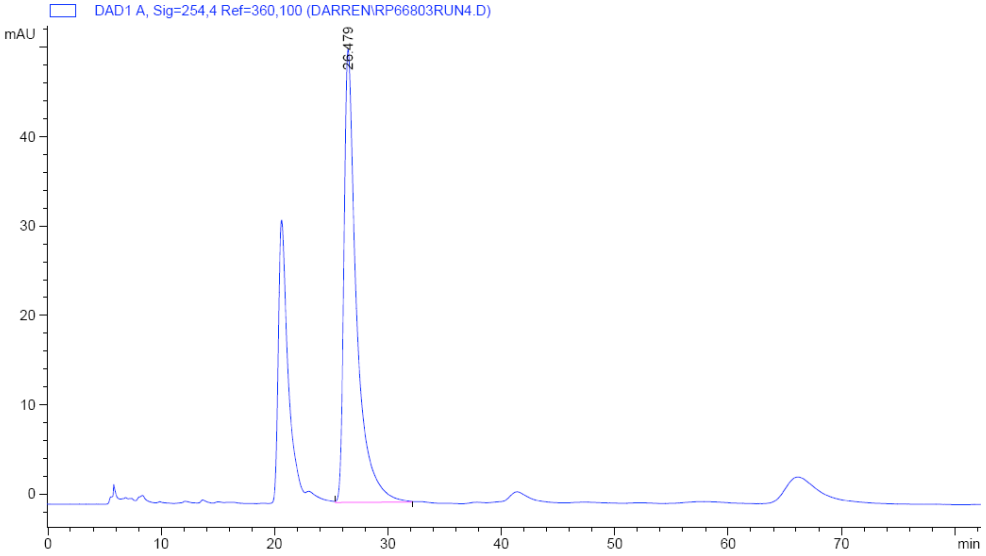
20


Gilson UniPoint
File Edit View Linking Analysis Comparisons Table Graph Window Help
Results[neg2.gdt / MASTER.GAN] : 1
Inj. Number | Peak Name | R. Time | Area % | Sample Descrip. | Purity | spectral Match 1 | spectral Match 2 | spectral Match 3
1 | 1.00 | *1 | 9.40 | 95.02 | Neg2 | > 457.75 < | <No Match> | <No Match> | <No Match>
2 | 1.00 | *2 | 11.84 | 4.98 | Neg2 | 900.10 | <No Match> | <No Match> | <No Match>
Chromatogram
% Mobile Phase
mVolts \ AU
100
50
0
0.005
0.000
10
> c:\gilson\unipoint\neg2.001\neg2.gdt : Ch_1 : Neg2: Inj. Number: 1
c:\gilson\unipoint\neg2.001\neg2.gdt : Ch_2 : Neg2: Inj. Number: 1
Solvent A
Solvent B
Operations ...
Analysis Me...
Operations ...
Start
Gilson UniPoint
UniPoint Method Executor
170 Server
10:04

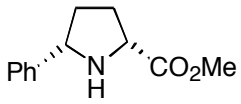


cis-**22**

```
Data File C:\CHEM32\1\DATA\DARREN\RP66803RUN4.D
Sample Name: ds other/p4run1

    ========================================================================
    Acq. Operator   : Darren
    Acq. Instrument : Instrument 1                    Location : Vial 1
    Injection Date  : 7/27/2007 2:44:24 PM
    Acq. Method     : C:\CHEM32\1\METHODS\DARREN\RP66803STUFF1.M
    Last changed    : 7/27/2007 2:33:33 PM by Darren
                      (modified after loading)
    Analysis Method : C:\CHEM32\1\DATA\DARREN\RP66803RUN4.D\DA.M (RP66803STUFF1.M)
    Last changed    : 9/21/2007 4:57:54 PM by Jule
                      (modified after loading)
    Method Info     : RP 66803NH

    Sample Info     : AD column 0.5 ml/min flow, 5:95 IPA:Hexane, 11 bar ds 8
                      /other
```



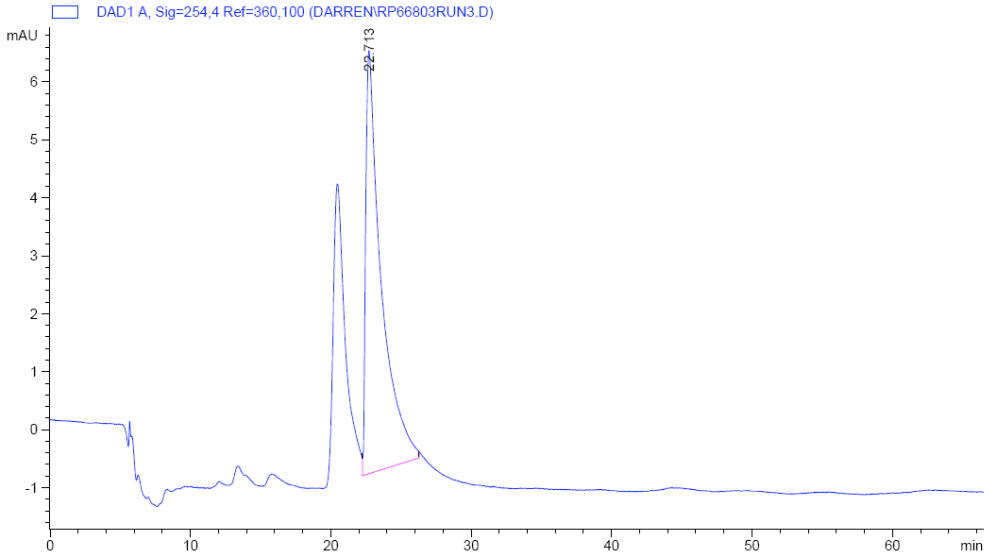

```
    ========================================================================
                           Area Percent Report
    ========================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 A, Sig=254,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  26.479 BB    1.1078 3913.66919   50.74343 100.0000

    Totals :                  3913.66919   50.74343


    ========================================================================

Instrument 1 9/21/2007 4:58:30 PM Jule                          Page   1 of 1
```



ent-cis-**22**

independently synthesised

```
Data File C:\CHEM32\1\DATA\DARREN\RP66803RUN3.D
Sample Name: ds 8.71/p4run1

    ======================================================================
    Acq. Operator   : Darren
    Acq. Instrument : Instrument 1                    Location : Vial 1
    Injection Date  : 7/27/2007 1:27:03 PM
    Acq. Method     : C:\CHEM32\1\METHODS\DARREN\RP66803STUFF1.M
    Last changed    : 7/27/2007 1:25:13 PM by Darren
                      (modified after loading)
    Analysis Method : C:\CHEM32\1\DATA\DARREN\RP66803RUN3.D\DA.M (RP66803STUFF1.M)
    Last changed    : 9/21/2007 4:59:48 PM by Jule
                      (modified after loading)
    Method Info     : RP 66803NH

    Sample Info     : AD column 0.5 ml/min flow, 5:95 IPA:Hexane, 11 bar ds 8
                      /71/p4
```




```
    ======================================================================
                            Area Percent Report
    ======================================================================

    Sorted By             :      Signal
    Multiplier            :      1.0000
    Dilution              :      1.0000
    Use Multiplier & Dilution Factor with ISTDs


    Signal 1: DAD1 A, Sig=254,4 Ref=360,100

    Peak RetTime Type  Width     Area      Height     Area
      #   [min]        [min]   [mAU*s]     [mAU]       %
    ----|-------|----|-------|----------|----------|--------|
       1  22.713 VB    1.0403  560.62384    7.29767 100.0000

    Totals :                   560.62384    7.29767
```

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