Synthesis of sparteine-like chiral diamines and evaluation in the enantioselective lithiation-substitution of *N*-(*tert*-butoxycarbonyl)pyrrolidine

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Supporting Information:

Experimental procedures for the synthesis of **34**, **37**, *rac*-**25**, **39**, *rac*-**41**, (*R*)-**41**, **44**, (+)-**24** and **(*S*)-48•CSA**.

General:

Xylene was dried over calcium hydride and distilled before use. In the 1H NMR spectra, the symbol * indicates that the signal disappears after a D_2O shake.

Octahydro-2*H*-quinolizin-2-one 34

A solution of bis ester **33** (3.9 g, 14.3 mmol) in xylene (14 cm^3) was added dropwise over 3 h to a stirred solution of sodium hydride (1.4 g of a 60 wt% dispersion in mineral oil, 35.9 mmol) and EtOH (0.08 cm^3, 1.2 mmol) in refluxing xylene (67 cm^3) under nitrogen. After stirring for 2 h at reflux, the mixture was cooled to 0 °C and acetic acid (2.4 g, 6.0 mmol) was added. Then, after

warming to room temperature, water (7.0 cm^3) was added and the mixture was extracted with 6 M hydrochloric acid (3 × 20 cm^3). The combined aqueous extracts were stirred and heated at reflux for 16 h. After cooling to room temperature, the solution was carefully neutralised with solid potassium carbonate until gas evolution stopped and the solution was saturated. The solid was removed by filtration and washed with Et_2O (20 cm^3). The aqueous filtrate was extracted with Et_2O (3 × 10 cm^3). The combined Et_2O extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave amino ketone **34** (1.4 g, 65%) as a colourless oil, bp 67-73 °C/1.0 mmHg (lit.,[1] 64-66 °C/0.5 mmHg); R_F(97:3 CH_2Cl_2-MeOH) 0.35. Spectroscopic data identical to that reported in the literature.[2]

(1*S,2*R**,8*R**)-10-Methyl-6,10-diazatricyclo[6.3.1.$0^{2,6}$]dodecan-12-one 37**

Methylamine (1.1 cm^3 of a 2.0 M solution in MeOH, 2.2 mmol) was added dropwise to a stirred solution of amino ketone **30** (296 mg, 2.1 mmol), paraformaldehyde (194 mg, 6.5 mmol) and acetic acid (0.1 cm^3) in MeOH (2.4 cm^3) at room temperature under nitrogen. The resulting solution was heated at reflux for 16 h. After cooling to room temperature, the solvent was evaporated under reduced pressure and 50% aqueous potassium hydroxide solution (10 cm^3) was added to the residue. The aqeuous mixture was extracted with Et_2O (3 × 20 cm^3) and the combined Et_2O extracts were dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product. Purification by Kugelrohr distillation gave diazatricyclic ketone **37** (121 mg, 29%) as a colourless oil, bp 130-140 °C/0.8 mmHg (lit.,[3] 135-145 °C/0.8 mmHg); R_F(4:1 $CHCl_3$-MeOH) 0.1. Spectroscopic data identical to that reported in the literature.[3]

(1*S,2*R**,8*R**)-10-Methyl-6,10-diazatricyclo[6.3.1.$0^{2,6}$]dodecane *rac*-25**

A solution of diazatricyclic ketone **37** (3.7 g, 19.3 mmol), hydrazine hydrate (4.9 cm^3, 101 mmol) and potassium hydroxide (14.0 g, 245 mmol) in diethylene glycol (40 cm^3) under nitrogen was stirred and heated at reflux (230 °C) using a

silicone oil bath for 2 h. Then, the volatile components were removed by distillation for 1 h at 190 °C. The reaction mixture was cooled to room temperature and combined with the previously distilled fraction. Water (90 cm^3) was added and the aqueous mixture was extracted with Et_2O (4 × 30 cm^3). The combined Et_2O extracts were washed with 20% aqueous sodium hydroxide solution (4 × 30 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude diamine *rac*-**25** (3.3 g, 95%) as a colourless oil. Spectroscopic data identical to that reported in the literature.[3]

***ortho*-Bromobenzophenone 39**

A solution of *ortho*-bromobenzoyl chloride (4.25 cm^3, 32.0 mmol) in benzene (20 cm^3) was added dropwise to a stirred suspension of aluminium chloride (4.68 g, 35.0 mmol) in benzene (30 cm^3) at room temperature under nitrogen. The resulting mixture was heated at reflux for 5 h. After cooling to room temperature, water (15 cm^3) and then 12 M hydrochloric acid (5 cm^3) were carefully added. Then, EtOAc (50 cm^3) was added, the two layers were separated and the aqeuous layer was extracted with EtOAc (2 × 50 cm^3). The combined EtOAc extracts were washed with brine (50 cm^3), 1 M aqueous sodium hydroxide solution (50 cm^3) and brine (50 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Trituration with petrol-Et_2O gave ketone **39** (6.56 g, 79%) as pale yelow trigonal prisms, mp 40.8-41.0 °C (lit.,[4] 40-41 °C); R_F(6:1 petrol-EtOAc) 0.5. Spectroscopic data identical to that reported in the literature.[4]

1-(2-Bromophenyl)-1-phenylprop-2-yn-1-ol *rac*-41

A solution of *ortho*-bromobenzophenone **39** (7.9 g, 30.4 mmol) in THF (20 cm^3) was added dropwise to a stirred solution of ethynylmagnesium bromide (80 cm^3 of a 0.5 M solution in THF, 40.0 mmol) at room temperature under nitrogen. The resulting solution was heated at reflux for 16 h. After cooling to room temperature, the solution was carefully poured into a mixture of ice (50 cm^3),

water (150 cm^3) and 12 M hydrochloric acid (5 cm^3). Then, the aqueous mixture was extracted with Et_2O (3 × 100 cm^3) and the combined Et_2O 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 (3:1) as eluent gave alcohol *rac*-**41** (6.0 g, 70%) as a brown solid, mp 55-56 °C; R_F(3:1 petrol-EtOAc) 0.3; $n_{max}(CHCl_3)/cm^{-1}$ 3585 (OH), 3304 (C≡CH), 1026 and 980; d_H(270 MHz; $CDCl_3$) 8.02 (1 H, dd, *J* 1.5 and 8.0), 7.57 (1 H, dd, *J* 1.0 and 8.0), 7.54-7.50 (2 H, m), 7.41-7.31 (4 H, m), 7.21 (1 H, dt, *J* 2.0 and 7.5), 3.28 (1 H, d, *J* 0.5, C≡CH) and 2.90* (1 H, d, *J* 0.5, OH); d_C(67.9 MHz; $CDCl_3$) 142.7 (*ipso*-Ar), 141.4 (*ipso*-Ar), 134.8, 129.6, 128.5, 128.4, 128.1, 127.1, 126.7, 121.8 (*ipso*-Ar), 84.1 (*C*≡CH), 76.3 (C≡*C*H) and 74.6 (COH); *m/z* (EI) 207 [100%, M^+ – Br][Found: $^{79}M^+$, 284.9907. $C_{15}H_{10}{}^{79}BrO$ requires *M*, 284.9915].

(*R*)-1-(2-Bromophenyl)-1-phenylprop-2-yn-1-ol 41

(–)-Sparteine (4.0 cm^3, 20.3 mmol) was added dropwise to a solution of alcohol *rac*-**41** (5.8 g, 20.3 mmol) in acetone (20 cm^3) at room temperature. After allowing some of the solvent to evaporate over 16 h, colourless crystals formed. Petrol (10 cm^3) was added and the crystals were collected by filtration and washed with petrol (3 × 40 cm^3). Then, the crystals were dissolved in a mixture of Et_2O (150 cm^3) and 2 M hydrochloric acid (100 cm^3). The two layers were separated and the aqueous layer was extracted with Et_2O (2 × 80 cm^3). The combined Et_2O extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give alcohol (*R*)-**41** (2.6 g, 45%) as a brown oil, $[\alpha]_D$ –108.3 (*c* 1.0 in MeOH). To the combined petrol washes, a mixture of Et_2O (150 cm^3) and 2 M hydrochloric acid (150 cm^3) were added. The two layers were separated and the aqueous layer was extracted with Et_2O (2 × 80 cm^3). The combined Et_2O extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give alcohol (*S*)-**41** (3.3 g, 55%) as a brown oil, $[\alpha]_D$ +86.5 (*c* 1.0 in MeOH).

Using the procedure described above, alcohol (*R*)-**41** {2.6 g, $[\alpha]_D$ –108.3 (*c* 1.0 in

MeOH), 9.0 mmol} and (–)-sparteine (1.8 cm^3, 9.0 mmol) in acetone (12 cm^3) gave alcohol (*R*)-**41** (2.05 g, 36% from *rac*-**41**) as a brown oil, $[\alpha]_D$ –122.9 (*c* 1.1 in MeOH).

Using the procedure described above, alcohol (*R*)-**41** {2.05 g, $[\alpha]_D$ –122.9 (*c* 1.1 in MeOH), 7.2 mmol} and (–)-sparteine (1.4 cm^3, 7.2 mmol) in acetone (9 cm^3) gave alcohol (*R*)-**41** (1.75 g, 30% from *rac*-**41**, >99% ee by chiral HPLC) as a brown oil, identical spectroscopically to *rac*-**41**, $[\alpha]_D$ –123.6 (*c* 1.1 in MeOH)(lit.,[5] –114 (*c* 0.2 in MeOH)); HPLC: Chiralcel OD-H, 5% ^{i}PrOH in heptane, 1.0 cm^3 min^{-1}, 215 nm, 11.2 [(*R*)-**41**], 12.6 [(*S*)-**41**].

(1*R*,5*S*,12*S*)-3-Methoxycarbonyldecahydro-1,5-methanopyrido[1,2-a][1,5]diazocin-8-one 44

Methyl chloroformate (1.1 cm^3, 13.4 mmol) was added dropwise over 10 min to a stirred solution of (–)-cytisine **42** (2.32 g, 12.2 mmol) and triethylamine (1.9 cm^3, 13.4 mmol) in CH_2Cl_2 (49 cm^3) at 0 °C under nitrogen. After stirring for 5 h at room temperature, the solvent was evaporated under reduced pressure. EtOAc (30 cm^3) was added to the residue and the solids were removed by filtration. The filtrate was evaporated under reduced pressure to give the crude pyridone **43**. A suspension of crude pyridone **43** and platinum(IV) oxide (132 mg, 0.60 mmol) in EtOH (36 cm^3) was stirred at room temperature under a hydrogen atmosphere (balloon) for 30 h. The solids were removed by filtration through Celite and the filter cake was washed with 9:1 CH_2Cl_2-MeOH (100 cm^3). The filtrate was evaporated under reduced pressure to give the crude lactam **44** (3.07 g, 99%) as a white solid, identical spectroscopically to that reported in the accompanying paper and sufficiently pure for use in the next step.

(1*R*,2*S*,9*S*)-11-Methyl-7,11-diazatricyclo[7.3.1.$0^{2,7}$]tridecane or (1*R*,5*S*,12*S*)-3-Methyldecahydro-1,5-methanopyrido[1,2-a][1,5]diazocine (+)-24

Lithium aluminium hydride (3.35 g, 83.9 mmol) was added in one portion to a

stirred solution of lactam **44** (3.36 g, 13.3 mmol) in THF (52 cm^3) at 0 °C under nitrogen. The resulting suspension was heated at reflux for 16 h. After cooling to 0 °C, Et_2O (20 cm^3) was added followed by the portionwise addition (CARE) of solid hydrated sodium sulfate until effervescence ceased. The solids were removed by filtration through Celite and the filter cake was washed with 9:1 CH_2Cl_2-MeOH (150 cm^3). The filtrate was dried (Na_2SO_4) and evaporated under reduced pressure to give the crude product as a brown oil. Purification by Kugelrohr distillation gave diamine (+)-**24** (2.27 g, 88%) as a colourless oil, identical spectroscopically to *rac*-**24**, bp 110-120 °C/0.5 mmHg.

2-(2-Hydroxyethyl)piperidine Camphosulfonate (*S*)-48•CSA

A solution of 2-piperidine ethanol *rac*-**48** (7.03 g, 54.4 mmol) in EtOH (10 cm^3) was added dropwise to a stirred solution of (1*S*)-(+)-camphorsulfonic acid (12.90 g, 54.4 mmol) in EtOH at 0 °C. After warming to room temperature, the solution was stirred for 19 h. Then, the solvent was evaporated under reduced pressure and Et_2O (50 cm^3) was added. The resulting precipitate was collected by filtration. To the filtrate, Et_2O (30 cm^3) was added the resulting precipitate was collected by filtration. The combined solids were dissolved in hot ethanol (20 cm^3) and the undissolved solids were removed by filtration. After standing for 48 h at 4 °C, the very small amount of salt (*S*)-**48**•CSA (colourless crystals, 25 mg, 0.2%, mp 166-168 °C) that had formed were collected by filtration. Then, the filtrate was evaporated under reduced pressure and the remaining white solid was dissolved in hot EtOH (10 cm^3). After standing for 1 h at 4 °C, the very small amount of salt (*S*)-**48**•CSA (colourless crystals, 45 mg, 0.3%, mp 160-162 °C) that had formed were collected by filtration. After standing for a further 2 h at 4 °C, the crystals formed were collected by filtration to give salt (*S*)-**48**•CSA (2.31 g, 12%) as a white solid, mp 158-160 °C (lit.,[6] 167-168 °C); $[\alpha]_D$ +28.1 (*c* 1.1 in $CHCl_3$)(lit.,[6] +34.0 (*c* 1.0 in $CHCl_3$)).

References for supporting information:

1. N. J. Leonard, R. W. Fulmer and A. S. Hay, *J. Am. Chem. Soc.*, 1956, **78**, 3457.
2. A. Barco, S. Benetti, C. De Risi, P. Marchetti, G. P. Pollini and V. Zanirato, *Eur. J. Org. Chem.*, 2001, 975.
3. J. R. Harrison, P. O'Brien, D. W. Porter and N. M. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3623.
4. P. J. Wagner, J. H. Sedon and A. Gudmunsdottir, *J. Am. Chem. Soc.*, 1996, **118**, 746.
5. F. Toda, K. Tanaka and H.Ueda, *Tetrahedron Lett.*, 1981, **22**, 4669.
6. C. Morley, D. W. Knight and A. C. Share, *J. Chem. Soc.,Perkin Trans. 1*, 1994, 2903.