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# Synthesis of (S)-2-Amino-1,1-diphenylbutan-4-ol; Conversion of an α-Amino Acid into an α-(Diphenylmethyl) Amine Without Loss of Optical Purity

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**Abstract:** The title amino-alcohol **4** is an intermediate for the preparation of chiral bicyclic amidines and guanidines, and also for polyamines with potential as ligands in enantioselective catalysis. It has been synthesized from (S)-methionine **1** via (S)-homoserine lactone **2** and amino-diol **3**. Hydrogenolysis of the doubly benzylic hydroxyl group in **3** proved non-trivial, but was eventually achieved through the application of catalytic transfer methodology to the bis-acetyl derivative **14**.

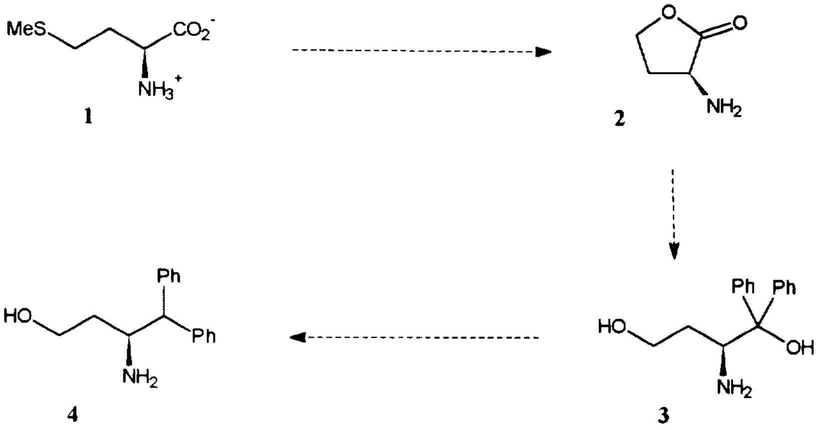
## Introduction

The proteinogenic α-amino acids constitute an important section of the "chiral pool", being inexpensive in the L-form (but available if necessary as the D enantiomers), structurally varied and chemically versatile.[1] In particular, as sources of nitrogen atoms attached to asymmetric centres, they have proved to be exceptionally useful starting materials for chiral reagents, auxiliaries and ligands.[2] Any high-yielding transformation of an α-amino acid carboxyl which proceeds without racemisation is thus of potential importance, especially if it generates a bulky substituent and may be applied to the synthesis of polyfunctional targets.

In the course of our programme on chiral bicyclic guanidines[3] and amidines,[4] the title amino-alcohol **4** was required as a central intermediate. It was clear that **4** could be obtained *via* a homoserine derivative such as lactone **2**, provided that the carboxyl/ester group could be elaborated into a diphenylmethyl substituent. There was, however, only limited precedent for this type of transformation, which is complicated by the need to maintain stereochemical integrity at the asymmetric centre. We now describe our studies on the synthesis of **4**, culminating in a workable large-scale preparation from (S)-methionine *via* **2** and including the non-trivial hydrogenolysis of benzhydrol **3**. We also show that **4** may be transformed into orthogonally protected diamines, which may serve as intermediates for the synthesis of a promising range of chiral ligands for enantioselective catalysis. The N-CH-CHPh$_2$ substructure, as present in **4**, has been employed in a range of potential pharmaceuticals, including thrombin inhibitors,[5] tachykinin antagonists,[6] neurotensin analogues,[7] endothelin antagonists[8] and analogues of the tricyclic antidepressants.[9] Our results should facilitate access to this unit for exploitation in medicinal chemistry and asymmetric synthesis.

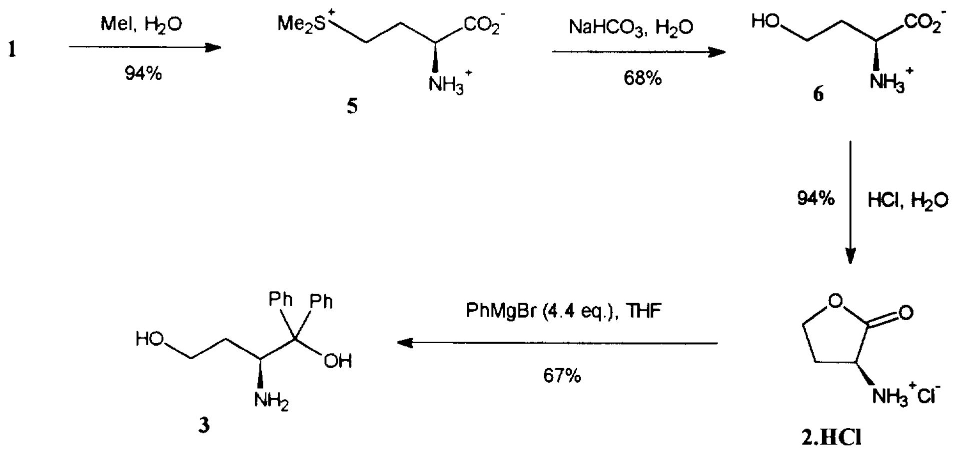
## Results and Discussion

Our proposed route to amino-alcohol **4** is shown in Scheme 1. As homoserine derivatives are too expensive for routine use in large-scale synthesis, we planned to prepare the lactone **2** from (S)-methionine **1** *via* S-alkylation and nucleophilic displacement of a dialkylsulphide, following literature precedent.[10] Addition of an arylmetal reagent would give amino-diol **3**, and hydrogenolysis of the "doubly benzylic" hydroxyl would give the target amine **4**.



**Scheme 1**

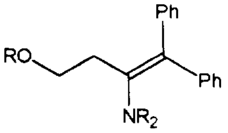
The first two transformations in Scheme 1 proved to be reasonably straightforward. Using the procedure of Baldwin *et al.* as a starting point,[10b,11] we developed a large-scale method for the conversion of (S)-methionine into (S)-homoserine lactone hydrochloride **2.HCl** *via* methiodide **5** and (S)-homoserine **6** in an overall yield of 60%, as shown in Scheme 2.[12]



**Scheme 2**

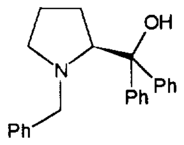
An important feature of our procedure is the control of pH during the conversion of **5** to **6** by treatment with aqueous sodium hydrogen carbonate. Addition of the base in a single portion, following the literature methods,[10b,12] sometimes gave satisfactory results. However on other occasions it resulted in product with seriously degraded enantiomeric purity (as low as 57% e.e., by analysis of MTPA derivatives[13] of the resulting lactone). Measurements taken during the course of the reaction revealed that, as might be expected, the addition of $NaHCO_3$ caused an initial rise in the pH which then fell as the reaction progressed and the base was required to neutralise the liberated HI. The initial pH varied to some degree (depending, presumably, on the purity of reagents and starting material, and the precision of weighing), and racemisation was observed on those occasions when the solution became significantly basic. The reaction progressed quite satisfactorily at pH = 6, and we found that enantiomerically pure material could be guaranteed if the base was added portionwise, such that this figure was never exceeded. The final conversion in Scheme 2, that of **2.HCl** into amino-diol **3**, was effected without incident through modification of a procedure previously applied to methyl valinate hydrochloride by Itsuno and co-workers.[14]

The third transformation in Scheme 1 required hydrogenolysis at a position with two activating phenyl groups, apparently a relatively favourable process. However, the presence of an amino group α to this centre introduced potential complications. Moreover, the requirement that enantiomeric purity be maintained placed an important mechanistic constraint on the transformation, in that it precluded elimination-hydrogenation sequences (*via* **7**) which in other circumstances would be acceptable. We could only find one previous example in which a diphenylcarbinol derived from an α-amino acid had been hydrogenolysed with retention of optical purity, the reduction of the proline-derived tertiary amine **8** with $Li/NH_3$.[15] Our initial attempts to apply this method to **3** were unsuccessful, the NMR spectra of crude products implying that over-reduction to cyclohexadienes had occurred. Although an indirect circumvention of this problem seemed possible, and was eventually developed (*vide infra*), we decided to seek a more convenient and efficient alternative.

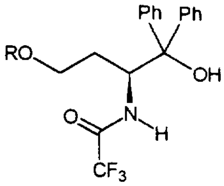


**7**

R = H or protecting group

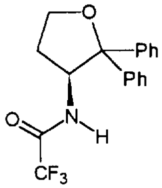


**8**

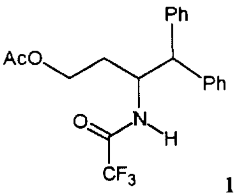


**9** R = H

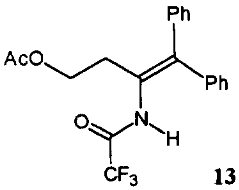
**10** R = Ac



**11**



**12**

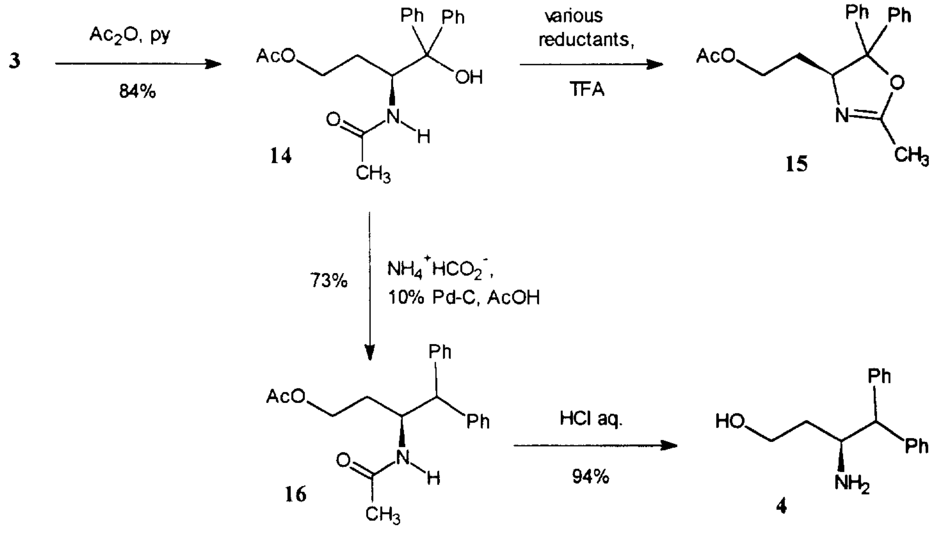


**13**

Attempted hydrogenolyses of unprotected **3** using a variety of literature procedures were uniformly unsuccessful. No reaction occurred under conventional conditions for Pd catalysis (10% $Pd\text{-}C/H_2/AcOH/$ trace

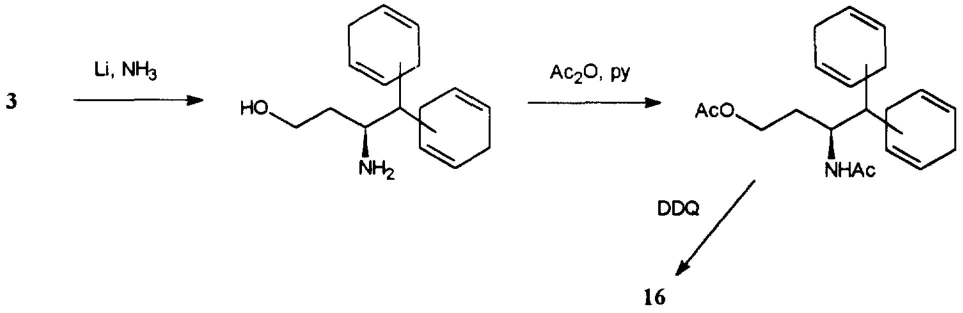
$H_2SO_4$),[16] on application of Olah's method for transfer hydrogenolysis (10% Pd-C/$AlCl_3$/cyclohexene),[17] or on treatment with sodium borohydride in trifluoroacetic acid (TFA),[18] presumably because of the deactivating effect of the α-amino group under acidic conditions. Lithium aluminium hydride[19] also yielded unchanged starting material, while $Et_3SiH$/TFA[20] and $Me_3SiCl$/NaI/$CH_3CN$[21] gave small quantities of unidentified products. Protection of the amino group as trifluoroacetyl did not improve matters. Attempted hydrogenolyses of diol **9** using Pd-C/$H_2$/EtOAc/TFA and $Et_3SiH$/TFA yielded tetrahydrofuran **11** as the only identified product. The *O*-acetyl derivative **10** was inert to a variety of Pd-catalysed methods, including Olah's transfer hydrogenolysis and the alternative of Ram and Spicer (10% Pd-C, $NH_4^+HCO_2^-$, AcOH).[22] Ionic hydrogenation of **10** ($Et_3SiH$/TFA) did yield a deoxygenated product **12**. Unfortunately it was racemic, accompanied by alkene **13**, and had clearly been formed by the elimination-addition mechanism (see above).

We next considered *N*-acetyl protection as an alternative to trifluoroacetyl, being less easily removable but less electron-withdrawing and (therefore) deactivating. Bis-acetylation of **3** was accomplished in good yield to give **14** (Scheme 3), which was then subjected to the range of hydrogenolysis methods. **14** was again inert to $H_2$/Pd-C/EtOAc, while any of the methods requiring TFA yielded a new unwanted side-product, the dihydro-oxazole **15**. However, we were pleased to find that, as shown in Scheme 3, the catalytic transfer method of Ram and Spicer[22] finally yielded a deoxygenated product **16** which showed optical activity. The enantiomeric purity of this compound could not, of course, be taken for granted. However, after deacetylation to our target **4**, bis-acylation with MTPA[13a] gave a derivative which was diastereomerically pure by $^{19}F$ NMR.[23]



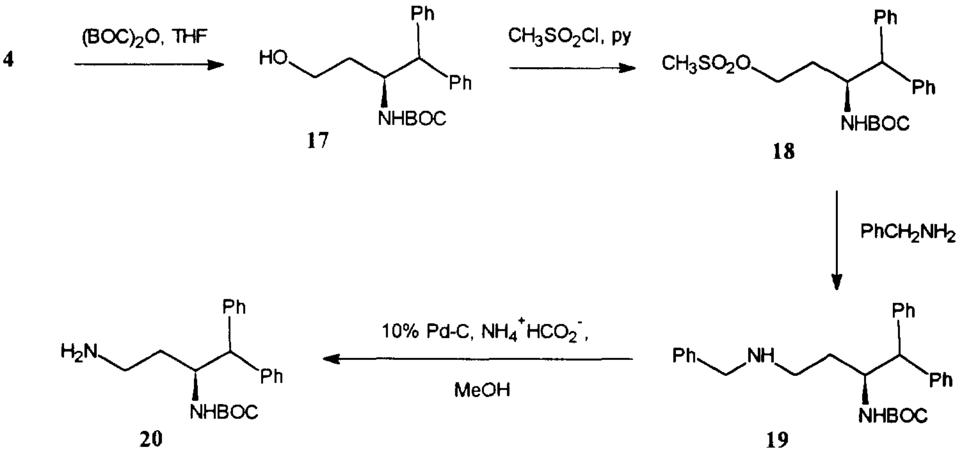
**Scheme 3**

As mentioned previously, a second route to **4** was developed based on the Li/$NH_3$ reduction of **3**. Although we were not able to prevent over-reduction of the aromatic rings in **3** when this procedure was employed, we found that bis-acetylation of the crude product followed by re-oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave enantiomerically pure **16** and thus, by implication, **4** (Scheme 4). However the yield of **16**, at 30%, was not competitive with that of the foregoing method.



**Scheme 4**

The stereogenic centre in **4** bears an unusually bulky, extended substituent, in addition to a hydrogen atom, a nitrogen, and a functionalised carbon chain. This combination would appear to be attractive for exploitation in the design and synthesis of chiral auxiliaries, or ligands for asymmetric catalysis. The reaction sequence in Scheme 5 provides an illustration of the possibilities. *N*-Protection of **4** with t-butyl pyrocarbonate proceeded in 86% yield, and was followed by *O*-mesylation to give **18** in 85% yield. Although there are limitations as to the usefulness of this compound under basic/nucleophilic conditions (see following paper),[3b] when treated with a large excess of benzylamine it gave **19** in 64% yield. Hydrogenolysis of the benzyl group yielded the monoprotected diamine **20** (66%). Removal of the BOC group in either **19** or **20** would give a diamine which, on chelation to a metal ion, would produce a complex with a large, asymmetrically-disposed steric barrier in its coordination sphere. A variety of related compounds could be prepared from **18** or **20**, or from analogues with alternative N-protection, including triamines as exemplified in the following paper.



**Scheme 5**

In conclusion, we have accomplished the synthesis of an unusual chiral amino-alcohol, in the course of which we have converted the carboxyl group of an α-amino acid into a bulky, extended diphenylmethyl group without affecting the asymmetric centre. The transformation of this compound into a hindered, chiral guanidine base is the subject of the following paper.

## Experimental Section

*General:* All solvents were distilled before use. When reactions were carried out under dry conditions $CH_2Cl_2$ was distilled from calcium hydride and THF from sodium/benzophenone. Extracts were dried with sodium sulphate unless otherwise stated. The $R_f$ values quoted are for thin-layer chromatography (TLC) on Merck DC-Fertigplatten Kieselgel F-254 plates. Flash column chromatography was performed on Merck Kieselgel 60 (particle size 0.040 - 0.063 mm). All melting points were obtained on a Gallenkamp melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 141 Polarimeter using the D line at 589 nm. $^1H$ NMR spectra were, unless otherwise stated, recorded in deuterated chloroform on a Bruker MSL-300 spectrometer (300.13 MHz) with tetramethylsilane as internal standard. $^{13}C$ NMR spectra were recorded in deuterated chloroform on the same instrument at 75.47 MHz using the central chloroform peak as reference (taken to be 77.00 p.p.m.). Signals were assigned with the assistance of the DEPT technique. $^{19}F$ NMR spectra were recorded in deuterated chloroform on the same instrument operating at 282.23 MHz. IR spectra were recorded neat, unless otherwise stated, on a Perkin-Elmer 883 spectrometer.

*(S)-Methionine methylsulphonium iodide* **5**. The procedure was based on that of Atkinson and Poppelsdorf[24] for the preparation of (R,S)-methionine methylsulphonium iodide. (S)-Methionine **1** (76.97 g, 0.516 mol) was suspended in distilled water (500 ml). Iodomethane (82.0 ml, 187 g, 1.32 mmol) was added, and the mixture was stirred at 35 - 40 °C for 20 hours. No suspended solid remained, and TLC indicated completion of reaction. The mixture was evaporated to dryness and the resulting solid was dissolved in water (200 ml). Ethanol (750 ml) was added, causing the precipitation of a white crystalline solid. The mixture was allowed to stand overnight to allow further precipitation. (S)-Methionine methylsulphonium iodide **5** (141.7 g, 94%), collected by filtration, was obtained as a white solid, m.p. 149 - 150 °C (lit.[24] m.p. 150 °C).

*(S)-Homoserine* **6**. (S)-Methionine methylsulphonium iodide **5** (20 g, 0.066 mol) was dissolved in water (30 ml) and heated under reflux. A solution of sodium hydrogen carbonate (5.5 g, 0.066 mol) in water (30 ml) was placed in a dropping funnel, and added dropwise until the pH of the solution rose to 6.0. The reaction was allowed to proceed until the pH dropped to 3.0, whereupon base was added as previously. This cycle was repeated until the reaction was complete (TLC analysis), after which the mixture was evaporated under reduced pressure to yield a thick syrup. This residue was dissolved in a minimum quantity of water (*ca.* 20 ml), with heating. Addition of acetone (40 ml) followed by ethanol (500 ml) caused immediate precipitation of (S)-homoserine as a white solid (5.4 g, 68%), m.p. 201 - 202 °C (dec) [lit.[25] m.p. 203 °C (dec)], $[\alpha]_D$ -8.2 (c = 3, $H_2O$) [lit.[25] -8.0 (c = 6, $H_2O$)].

*(S)-Homoserine lactone hydrochloride* **2.HCl**. (S)-Homoserine **6** (30.98 g, 0.26 mol) was dissolved in aqueous hydrochloric acid (2.4 M, 500 ml, 1.2 mol, 4.6 eq). The solution was heated under reflux for 3 h, and stirred at room temperature for 16 h. Most of the solvent was removed azeotropically with ethanol. The residue was cooled in ice and the solid which precipitated was collected by filtration and washed with cold ethanol to give (S)-homoserine lactone hydrochloride **2.HCl** (23.8 g, 67%) as a white solid. The filtrate was concentrated and cooled, and further product (4.99 g, 14%) was obtained as before. The process was repeated to obtain a third crop of product (4.25 g, 12%).and a fourth (0.74 g, 2%). Total yield = 94%, m.p. 202 °C (lit.[10b] m.p. 199 - 200 °C). Optical purity was confirmed by *N*-acylation with the acid chloride of (*R*)-(+)-MTPA,[13b] followed by $^{19}F$ NMR analysis (in comparison with material derived from racemic **2.HCl**).

*(S)-2-Amino-1,1-diphenylbutane-1,4-diol* **3**. Magnesium turnings (1.24 g, 51 mmol) were flame-dried under argon in a 250 ml 3-necked round-bottomed flask. Dry THF (20 ml) was added. A solution of bromobenzene (4.80 ml, 7.16 g, 45.6 mmol, 4.4 eq) in dry THF (20 ml) was added dropwise over 30 min. The mixture was heated under reflux for 1 h, and then cooled in ice. (S)-Homoserine lactone hydrochloride **2.HCl** (1.43 g, 10.4 mmol) was added portionwise over 7 min at 0 °C, and the mixture was stirred at 0 °C for a further 18 min. After stirring at room temperature for 17.5 h, ice was added portionwise until no further heating was observed. Aqueous hydrochloric acid (2 M, 100 ml) was added at 0 °C. The mixture was stirred at room temperature for 1 h. Aqueous ammonia (35%, 50 ml) was added, and the mixture was stirred at room temperature for 1 h. The mixture was filtered to give aminodiol **3** (1.78 g, 67%) as a white solid. Recrystallization from ethanol afforded colourless needles, m.p. 200 °C, $[\alpha]_D$ -26.0 (c = 0.26, EtOH), $R_f$ 0.47 (ethyl acetate - methanol, 2:1) (Found: C, 74.69; H, 7.55; N, 5.12. $C_{16}H_{19}NO_2$ requires C, 74.68; H, 7.44; N, 5.44%); $\nu_{max}/cm^{-1}$ (KBr disc) 3382, 3331, 3088, 2920, 1449, 1063, 975; $\delta_H$ ($d_6$-DMSO) 7.6 - 7.45 (4 H, m, arom H), 7.35 - 7.05 (6 H, m, arom H), 5.28 (1 H, br s, -CPh₂O*H*), 3.88 (1 H, dd, *J* 9.5 and 2.8 Hz, C*H*NH₂), 3.6 - 3.45 (2 H, m, C*H*₂OH), 1.55 - 1.2 (3 H, m, C*H*₂CH₂OH and -CH₂CH₂O*H*).

*(S)-2-Acetamido-4-acetoxy-1,1-diphenylbutan-1-ol* **14**. Aminodiol **3** (1.50 g, 5.8 mmol) was dissolved in pyridine (12 ml) and acetic anhydride (2.40 ml, 2.60 g, 25.4 mmol, 4.4 eq) was added. The solution was stirred at room temperature for 22.5 h. Aqueous HCl (2 M, 100 ml) was added and the acidic mixture was extracted with dichloromethane (3 x 100 ml). The combined organic extracts were dried and evaporated to yield **14** (1.67 g, 84%) as a colourless solid. Recrystallization from ethyl acetate - hexane afforded colourless spars, m.p. 175 °C, $[\alpha]_D$ -49.6° (c = 0.67, CHCl₃), $R_f$ 0.51 (ethyl acetate - hexane, 4:1) (Found: C, 70.42; H, 6.65; N, 4.05. $C_{20}H_{23}NO_4$ requires C, 70.36; H, 6.79; N, 4.10%); $\nu_{max}/cm^{-1}$ (CHCl₃) 3602, 3436, 1732, 1666; $\delta_H$ 7.55 - 7.45 (4 H, m, arom H), 7.35 - 7.1 (6 H, m, arom H), 6.06 (1 H, d, *J* 9.24 Hz, N*H*), 5.00 (1 H, ddd, *J* 9.25, 7.3 and 5.9 Hz, C*H*NHCOCH₃), 4.11 (2 H, t, *J* 6.5 Hz, C*H*₂OAc), 3.9 (1 H, br s, -C(Ph)₂O*H*), 2.04 (3 H, s, OCOC*H*₃ ), 1.9 -1.7, 1.77 (5 H, m, s, CHC*H*₂CH₂OAc and NHCOC*H*₃); $\delta_C$ 170.94, 170.85 (2 x *C*OCH₃), 145.50, 144.58 (arom C-1') 128.10, 127.89, 126.62, 126.56, 125.43, 125.22 (arom C), 80.46 [*C*(OH)Ph₂], 61.80 (*C*H₂OAc), 52.89 [Ph₂C(OH)*C*H], 29.33 (CH*C*H₂CH₂OAc), 22.53 (NHCO*C*H₃), 20.67 (OCO*C*H₃).

*(S)-4-Acetoxy-2-acetamido-1,1-diphenylbutane* **16**. To a solution of alcohol **14** (200 mg, 0.59 mmol) in glacial acetic acid (2 ml) was added palladium on activated charcoal (10%, 27 mg) and ammonium formate (187 mg, 5.1 eq.). The mixture was stirred at 110 °C until analysis by TLC indicated that the reaction was complete (8 hours). CH₂Cl₂ (50 ml) was added and the mixture was filtered through a plug of celi*te*. The solution was washed with saturated aqueous sodium carbonate (3 x 50 ml), water (50 ml), brine (30 ml), then dried and concentrated *in vacuo*. Recrystallisation from hexane gave the title compound **16** as white crystals (139 mg, 73%), m.p. 112 - 113 °C, $[\alpha]_D$ -32 (c = 5.00, CH₂Cl₂), $R_f$ 0.36 (CH₂Cl₂ - ethyl acetate, 3:1) (Found: C, 73.91, H, 7.15, N, 4.35. $C_{20}H_{23}NO_3$ requires C, 73.82, H, 7.12, N, 4.3%); $\nu_{max}/cm^{-1}$ 1722, 1641, 1540, 1245; $\delta_H$ 7.32 - 7.14 (10 H, m, arom H), 5.30 (1 H, d, *J* 10 Hz, CON*H*CH), 4.97 - 4.65 (1 H, ddd, CONHC*H*), 4.30 - 4.17 (2 H, m, OC*H*₂CH₂), 3.77 (1 H, d, *J* 10 Hz, C*H*Ph₂ ), 2.04 (3 H, s, OCOC*H*₃), 1.97 - 1.82 (2 H, m, OCH₂C*H*₂), 1.75 (3 H, s, NHCOC*H*₃); $\delta_C$ 171.02 (O*C*OCH₃), 169.77 (NH*C*OCH₃), 128.80, 128.54, 128.09, 128.05, 126.85, 126.69 (arom *C*H), 61.52 (O*C*H₂CH₂), 56.69 (*C*HPh₂), 48.94 (N*C*H), 32.72 (OCH₂*C*H₂), 23.18 (OCO*C*H₃) and 20.97 (NHCO*C*H₃).

*Preparation of* **16** *via Li/NH₃ reduction of* **3**. Liquid ammonia (*ca.* 50 ml) was distilled through a drying tower of potassium hydroxide into a solution of aminodiol **3** (61 mg, 0.24 mmol) in anhydrous THF (5 ml). Lithium wire (12 mg, 7.3 eq.) was then added causing the solution to turn blue. The reaction was quenched after ~20 min by the addition of ammonium chloride. The solvent was removed under reduced pressure and crude product (67 mg) was isolated from the resulting mixture by Soxhlet extraction. This material was then dissolved in pyridine (0.5 ml), and acetic anhydride (0.11 ml) was added. This mixture was stirred at room temperature for 4 days, after which the pH was adjusted to 1 with aq. HCl (2 M) and the solution extracted with $CH_2Cl_2$ (3 x 20 ml). Drying and evaporation yielded a crude product (52 mg). A solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (52 mg, 0.23 mmol) in benzene (0.8 ml) was added. The reaction was stirred at room temperature for 3 h and left to stand overnight. The mixture was then filtered, and the filtrate washed with aqueous sodium thiosulphate pentahydrate (1.6 g in 0.6 ml $H_2O$) and NaOH (2 M), dried and concentrated under reduced pressure to yield **16** (24 mg, 30%), $[\alpha]_D$ -32 (c = 5.00, $CH_2Cl_2$).

*(S)-2-Amino-1,1-diphenylbutan-4-ol* **4**. A mixture of **16** (240 mg, 0.702 mmol) and aqueous HCl (1.4 M, 3 ml) was heated to 100 °C, resulting in a homogeneous solution. After about 6 hours analysis by TLC indicated that the reaction was complete. The solution was basified by addition of solid NaOH, and extracted with $CH_2Cl_2$ (3 x 15 ml). The extract was washed with distilled water (20 ml), dried and evaporated to yield the amino-alcohol **4** as a colourless solid (159 mg, 94%). An analytical sample was obtained by recrystallisation from hexane - ethyl acetate, m.p. 64 - 65 °C, $[\alpha]_D$ 14.18 (c = 5.34, $CH_2Cl_2$) (Found: C, 79.78; H, 7.95; N:5.6. $C_{16}H_{19}NO$ requires C, 79.63; H, 7.94; N, 5.8%); $\delta_H$ 7.42-7.14 (10 H, m, arom H) 3.84 - 3.78 (2 H, m, $\mathrm{C}\mathit{H}\mathrm{Ph_2}$ and $\mathrm{H_2NC}\mathit{H}$), 3.7 (2 H, t, *J* 11.3 Hz, $\mathrm{HOC}\mathit{H}_2\mathrm{CH_2}$), 1.73-1.67 (1 H, m, $\mathrm{HOCH_2C}\mathit{H}_\mathrm{a}\mathrm{H_b}$), 1.52-1.4 (1 H, m, $\mathrm{HOCH_2CH_a}\mathit{H}_\mathrm{b}$); $\delta_C$ 142.67, 142.07 (arom C-1'), 128.99, 128.75, 128.18, 127.81, 126.82, 126.56 (arom *C*H), 62.83 ($\mathrm{HO}\mathit{C}\mathrm{H_2CH_2}$), 61.31 ($CHPh_2$), 55.94 ($H_2NCH$) and 35.51 ($\mathrm{HOCH_2}\mathit{C}\mathrm{H_2}$). Optical purity was confirmed by *N,O*-bis-acylation with the acid chloride of (*R*)-(+)-MTPA,[13a] followed by $^{19}F$ NMR analysis.[23]

*(S)-2-tert-Butoxycarbonylamino-1,1-diphenylbutan-4-ol* **17**. To a solution of (S)-2-amino-1,1-diphenylbutan-4-ol **4** (30 mg, 0.124 mmol) in anhydrous THF (2 ml) was added di-*tert*-butyl dicarbonate (28.7 µl, 0.125 mmol) under argon at 0 °C. The mixture was stirred at 0 °C for 0.5 hours and was then left stirring overnight at room temperature. The THF was removed under reduced pressure and the residue dissolved in ethyl acetate (5 ml). The resulting colourless solution was washed with dilute aqueous HCl (2 x 5 ml) and brine (5 ml), and dried. Evaporation of the solvent yielded the title compound **17** (36.4 mg, 86%) as a colourless solid which was used without further purification. A sample was prepared for analysis by recrystallising the crude material from hexane-ethyl acetate (3:1), m.p. 110 °C, $[\alpha]_D$ -57.6 (c = 1.36, $CH_2Cl_2$), $R_f$ 0.8 ($CH_2Cl_2$ - ethyl acetate, 3:1) (Found: C, 74.01; H, 8.1; N, 4.48. $C_{21}H_{27}N_1O_3$ requires C, 73.87; H, 7.97; N, 4.1%); $\nu_{max}/cm^{-1}$ (KBr disc) 3403, 1689, 1518, 1169; $\delta_H$ 7.5 - 7.15 (10 H, m, arom *H*), 4.72 - 4.6 (1 H, ddd, $\mathrm{NC}\mathit{H}\mathrm{CPh_2}$), 4.35 (1 H, d, *J* 10 Hz, $\mathrm{CON}\mathit{H}\mathrm{CH}$), 3.92 (1 H, d, *J* 10 Hz, $\mathrm{C}\mathit{H}\mathrm{Ph_2}$), 3.6 (2 H, t, *J* 11 Hz, $\mathrm{C}\mathit{H}_2\mathrm{OH}$), 1.89 - 1.76 (2 H, m, $\mathrm{C}\mathit{H}_2\mathrm{CH_2OH}$), 1.37 (9 H, s, $\mathrm{C}\mathit{H}_3$); $\delta_C$ 157.15 (*C*=O), 142.13, 141.78 (arom C-1'), 128.75, 128.59, 128.26, 128.11, 126.70, 126.63 (arom *C*H), 79.98 [$\mathrm{O}\mathit{C}\mathrm{(CH_3)_3}$], 58.74 ($\mathit{C}\mathrm{H_2OH}$), 56.92 ($\mathit{C}\mathrm{HPh_2}$), 49.29 (*C*HN), 37.33 ($\mathit{C}\mathrm{H_2CH_2OH}$), 27.40 ($\mathit{C}\mathrm{H_3}$).

*(S)-2-tert-Butoxycarbonylamino-4-methanesulphonyloxy-1,1-diphenylbutane* **18**. To a solution of alcohol **17** (129 mg, 0.38 mmol) in anhydrous pyridine (0.37 ml, 3.8 mmol, 10 eq.) was added methanesulphonyl chloride (29.4 µl, 0.38 mmol, 1 eq.) under argon, dropwise at -10 °C. The solution was stirred at -10 °C for a further 2.5 h. The pH of the reaction mixture was then adjusted to 1 by the addition of ice cold aqueous hydrochloric acid, causing the product to separate as an oil. The mixture was extracted with $CH_2Cl_2$ (3 x 15 ml) and the combined organic layers washed successively with ice cold $NaHCO_3$ aq. (20 ml), water (20 ml) and brine (20 ml). The extract was dried ($MgSO_4$) and the solvent removed under reduced

pressure to yield the mesylate **18** (136 mg, 85%) as a colourless oil which crystallised on standing, m.p. 75 - 77 °C, $[\alpha]_D$ -6.3 (c = 1.26, $CH_2Cl_2$); $\nu_{max}$/cm$^{-1}$ 1690, 1455, 1355, 1180, 1175; $\delta_H$ (80 MHz) 7.36 - 7.24 (10 H, m, arom *H*), 4.65 - 4.18 (1 H, ddd, NHC*H*), 4.25 (2 H, t, *J* 6 Hz, OC$H_2$), 3.94 (1 H, d, *J* 10 Hz, C*H*$Ph_2$) 2.97 (3 H, s, $SO_2CH_3$), 2.14 - 1.5 (2 H, m, $OCH_2CH_2$), 1.3 (9 H, s, C$H_3$); $\delta_C$ 153.67 (*C*=O), 140.18, 139.65 (arom C-1'), 128.17, 128.00, 127.80, 127.6, 127.23, 126.63 (arom *C*H), 79.4 [O*C*$(CH_3)_3$], 66.36 ($OCH_2$), 54.62 ($CHPh_2$), 51.51 (NCH), 37.06 ($SO_2CH_3$), 30.85 ($OCH_2CH_2$), 26.59 [OC$(CH_3)_3$]. .

***(S)-2-tert-Butoxycarbonylamino-4-benzylamino-1,1-diphenylbutane* 19**. A solution of mesylate **18** (200 mg, 0.48 mmol) in benzylamine (1 ml, 9.2 mmol, 19.2 eq.) was stirred at 60 °C for 8 h. The excess benzylamine was evaporated under reduced pressure, with addition of toluene and reevaporation to remove the last traces. The residue was then dissolved in $CH_2Cl_2$ (20 ml) and washed with $NaHCO_3$ aq. (20 ml), water (20 ml) and brine (20 ml). The organic phase was dried and evaporated to yield a yellow oil. The title compound **19** (130 mg, 63.5%) was isolated by flash chromatography eluting with ethyl acetate ($R_f$ 0.2 - 0.5) and used without further purification; $\nu_{max}$/cm$^{-1}$ 3303, 1701, 1452, 1169, 746; $\delta_H$ (80 MHz) 7.4 - 7.08 (15 H, m, arom C*H*), 4.13 (1 H, d, *J* 10 Hz, C*H*$Ph_2$), 3.63 (2 H, s, PhC$H_2$NH), 2.85 - 2.55 (2 H, m, NHC$H_2$$CH_2$), 1.95 - 1.75 (2 H, m, $NHCH_2CH_2$), 1.32 (9 H, s, C$H_3$); $\delta_C$ 142.5, 142, 140.6 (arom C-1'), 128.7, 128.35, 128.1, 128.08, 128.06, 127.8, 127.2, 126.8 (arom *C*H), 79.21 [O*C*$(CH_3)_3$], 56.45 (-$CHPh_2$), 54.1 ($PhCH_2NH$), 48.72 (NCH), 46.21 ($NCH_2CH_2$), 35.25 ($NCH_2CH_2$), 27.25 ($CH_3$).

***(S)-3-tert-Butoxycarbonylamino-4,4-diphenylbutylamine* 20**. Amine **19** (100 mg, 0.23 mmol) was added under argon to a reaction vessel containing palladium on activated charcoal (10%, 100 mg) covered by anhydrous methanol (3 ml). Ammonium formate (100 mg, 1.58 mmol, 6.9 eq.) was then added and the mixture refluxed for 8 hours. During the reaction a white solid collected on the inner walls of the reflux condenser. Analysis of this material showed that it was not derived from the starting material **19**. The catalyst was removed by filtering the reaction mixture through a plug of celite and the solvent was removed under reduced pressure. The title amine **20** (52 mg, 66%) was isolated by flash chromatography by eluting the faster running fractions with ethyl acetate and then washing the desired product off the baseline by the addition of methanol to the mobile phase. Analytically pure material was obtained by precipitation from a methanol solution by adding ethyl acetate, $[\alpha]_D$ -32.8 (c = 0.19, methanol) (Found: C, 81.89; H, 9.17; N, 8.99. $C_{21}H_{28}N_2O_2$ requires C, 81.77; H, 9.15; N, 9.08%); $\nu_{max}$/cm$^{-1}$ (KBr disk) 3389, 1691, 1522, 1171; $\delta_H$ ($CD_3OD$) 7.37 - 7.22 (10 H, m, arom C*H*), 4.65 (2 H, br s, N$H_2$), 4.5-3.92 (1 H, ddd, C*H*NH), 3.95 (1 H, d, *J* 10 Hz, C*H*$Ph_2$), 3.00 - 2.84 (2 H, m, C$H_2$$NH_2$), 1.8 - 1.56 (2 H, m, $CH_2CH_2NH_2$), 1.3 (9 H, s, C$H_3$); $\delta_C$ 153.22 (*C*=O), 141.1, 140.65 (arom C-1'), 128.51, 128.30. 128.15, 127.9, 127.4, 126.98 (arom *C*H), 79.6 [O*C*$(CH_3)_3$], 54.8 ($CHPh_2$), 49.6 (NCH) 48.2 ($NCH_2CH_2$), 35.2 ($NCH_2CH_2$), 26.9 ($CH_3$).

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