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Synthesis of new, highly hindered C_2-symmetric *trans*-(2*S*,5*S*)-disubstituted pyrrolidines

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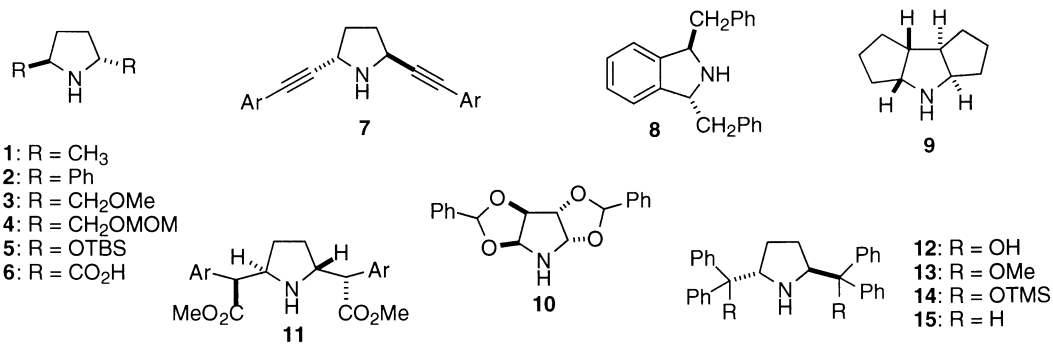
Abstract—*trans*-(2*S*,5*S*)-(1,1-Diphenylmethyl)pyrrolidine has been prepared from the corresponding diester in four steps and 54% overall yield. Key steps involve the nucleophilic addition of an organomagnesiun reagent to a carbonyl compound promoted by cerium(III) chloride and the reductive removal of benzylic trimethylsilyloxyl groups with Me_3SiCl–NaI–MeCN and water.

1. Introduction

2,5-Disubstituted pyrrolidines with a C_2 axis of symmetry constitute an important class of chiral auxiliaries.[1] The 2,5-dimethyl derivative **1**, introduced by Whitesell for enantioselective alkylation of chiral enamines,[2] was one of the first chiral auxiliaries. Since then **1** has been widely used to obtain excellent selectivities in radical cyclisations,[3] carbon radical additions to amides,[4,5] alkylation or condensation of lithium enolates derived from a vinylogous urethane,[6] Claisen rearrangement,[7] [2+2] and [4+2]-cycloadditions,[8–11] enantioselective deprotonation[12] and additions to arene–manganese complexes.[13] The first enantioselective synthesis of **1** was reported by Schlessinger starting from D- or L-alanine[14] and was later improved by Welch and co-workers.[15] More recently, a very concise synthesis starting from *N*-Boc pyrrolidine has been developed by Beak using enantioselective deprotonation strategies although this has not been extended to other derivatives.[16]

However, one of the most popular ways to obtain **1** in an enantiomerically pure form involves using enantiomerically pure (2,5)-hexanediol, obtained by enzymatic reduction[17] or enzymatic resolution,[18] followed by amination of the corresponding mesylate. This strategy was applied recently by Chong in the synthesis of pyrrolidine **2**,[19] and has also been reexamined by Steel.[20] The more hindered amine **2** has recently been shown to be a very efficient chiral auxiliary in asymmetric thio-Claisen rearrangements,[21] Diels–Alder reactions[22] and as a new class of chiral chelating ligand for palladium-catalysed allylic alkylations.[23] Another class of commonly employed chiral auxiliaries, are the *O*-protected derivatives of *trans*-2,5-bis(hydroxymethyl)pyrrolidine, **3**–**5**, which were introduced by Katsuki,[24] and their synthetic value in many asymmetric processes has been demonstrated including alkylation or condensation of carboxyamide enolates,[25,26] [2,3] Wittig rearrangements,[27] addition and reduction reactions of α-ketoamides,[28,29] Diels–Alder reactions of acrylamides[30] and carbamylnitroso[31] compounds, the



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α-iodination of enamides[32] and iodolactonisation reactions.[33] Several enantioselective syntheses of these *trans*-2,5-disubstituted pyrrolidines have been reported by lipase-catalysed kinetic resolution[34–36] or by using optically active starting materials such as D-mannitol,[37] (*S*)-*O*-benzylglycidol,[38] homochiral glycidyl triflate[39] or pyroglutamate esters in the synthesis of pyrrolidine 2,5-dicarboxylic acid **6**.[40–42] Other notable examples of such C_2-symmetric chiral pyrrolidines include *trans*-2,5-bis(arylethynyl)pyrrolidines **7**,[43] *trans*-1,3-dibenzylisoindoline **8**,[44] tricyclamine **9**,[45] (2*S*,5*S*)-bishydroxymethyl-(3*R*,4*R*)-bishydroxypyrrolidine **10**[46,47] and amine **11** which was obtained efficiently through a C–H insertion reaction on *N*-Boc pyrrolidine using a chiral rhodium catalyst.[48]

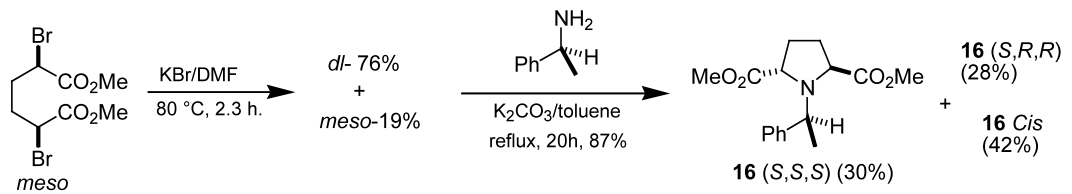
In the course of another project involving the chiral amine-catalysed asymmetric epoxidation of unsubstituted alkenes,[49] we became interested in the synthesis of C_2-symmetric chiral amines **12**–**15**. Of the possible strategies involving the formation of pyrrolidine rings,[50] we chose the convenient synthesis of each enantiomer of the 2,5-disubstituted pyrrolidines by reaction of dimethyl-2,5-dibromoadipate with (*S*)-(−)-1-phenylethylamine as a chiral auxiliary. The *cis*-isomer and the two diastereomeric *trans*-pyrrolidines **16** have been easily separated by chromatographic separation and crystallisation.[51] Using this method 1-[(*S*)-1-phenylethyl]-(2*S*,5*S*)-bis(methoxycarbonyl)pyrrolidine **16** was easily obtained (Scheme 1).

2. Results and discussion

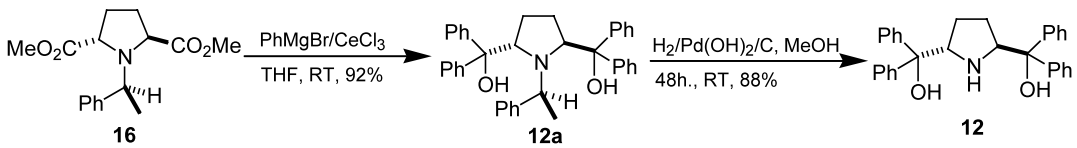
The synthesis of 2,5-disubtituted pyrrolidine **12** was realised in two steps from diester (*S*,*S*)-**16** (Scheme 2). The synthesis of **12** by reaction of the hydrochloride salt of the unprotected diester **16** with phenylmagnesium bromide had been reported by Shi to proceed in poor yield (35%).[52,53] In our case complete degradation of **16** was observed with phenylmagnesium bromide. We therefore considered alternative organometallic reagents and were delighted to find that the use of in situ-generated organocerium reagent,[54,55] gave the corresponding tertiary-alcohol **12a** in very high yield (92%) and showed the efficiency of this reagent in the synthesis of the considerably hindered substrate. Hydrogenolysis of **12a** afforded amine **12** in 88% yield after recrystallisation.

The chiral amine **13** was obtained in a good yield from the diol **12a** by *O*-methylation followed by hydrogenolysis (Scheme 3). The alcohol groups were readily converted to their methyl ethers by treatment with sodium hydride and methyl iodide in THF at reflux overnight. The protected amino ether **13a** and the compound resulting from mono-alkylation were isolated in 83% and 12% yield after separation by column chromatography. The deprotection by hydrogenation of **13a** gave rise to the corresponding aminoether **13** in 83% yield.

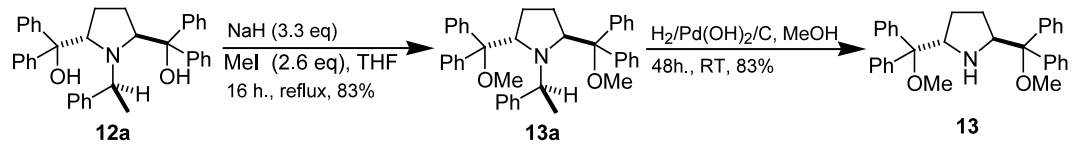
Several approaches were considered for the synthesis of amine **15** involving the reductive dehydroxylation of either the unprotected or protected amine **12a**. The first conditions we tried involved treating these compounds with excess triethylsilane and boron trifluoride etherate[56] (Et_3SiH–$BF_3{\cdot}Et_2O$) or trifluoroacetic acid[57] (Et_3SiH–CF_3CO_2H) in dichloromethane at room temperature. In both cases no dehydroxylated product was observed and a substantial amount of starting material was recovered. When the reactions were performed either at reflux or using an excess of reagents, decomposition occurred. Recently, Dondoni reported that the reduction of a ketol phosphonate, which was unsuccessful using Et_3SiH–$BF_3{\cdot}Et_2O$, could be promoted by replacing the boron with a silicon Lewis acid.[58] How-



Scheme 1.



Scheme 2.



Scheme 3.

ever, using the same system (Et_3SiH–TMSOTf), with diol **12a**, no dehydroxylated product was observed but the mono-silylated compound **14a** was isolated in 78% yield instead. Addition of 1,8-bis(dimethylamino)naphthalene as a proton sponge to avoid protonation of the nitrogen atom (which could prevent the dehydroxylation reaction) led to the formation of **14a** in 56% isolated yield with 34% of the double silylation product **14b**. Starting from the unprotected diol **12**, a similar result was observed, with the formation of the doubly silylated compound **14** in 89% isolated yield with none of the dehydroxylated product observed (Scheme 4).

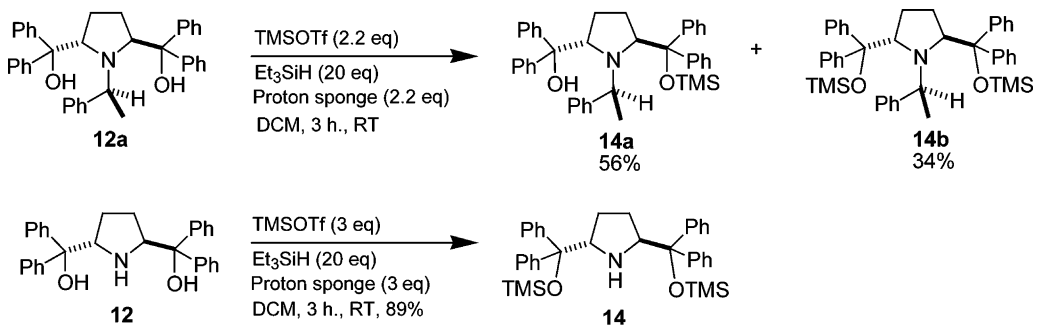
As triethylsilane was unreactive, we moved to a reductive method for removal of the benzylic hydroxyl or trimethylsilyloxyl group with Me_3SiCl–NaI–MeCN reagent. This alternative procedure, reported by Utaka,[59] involves the formation of an intermediate iodide followed by reduction with in situ generated HI. As the protected amine **12a** was only sparingly soluble in the reaction medium we instead started from the silylated compound **14**, which had been obtained in high yield from amine **12** using TMSOTf and 1,8-bis(dimethylamino)naphthalene. The reaction of **14** with Me_3SiCl–NaI–MeCN reagent and water as a proton source gave the corresponding reduced amine **15** in good yield after purification by flash chromatography (Scheme 5).

The relative configuration was confirmed by X-ray crystallographic analysis showing that no epimerisation had occurred during the synthesis (Fig. 1). Crystallographic data (excluding structure factors) for the structure in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 177283.

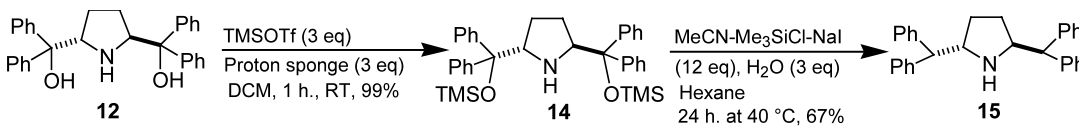
3. Conclusions

In conclusion, we have developed an efficient synthesis of amine **15** in four steps and 54% overall yield from 1-[(*S*)1 - phenylethyl] - (2*S*,5*S*) - bis(methoxycarbonyl)-pyrrolidine **16**. Advantages of this route include reagent availability and procedural simplicity using mild conditions. The use of an organocerium reagent was critical to the success of the synthesis and demonstrated its superiority over alternative organometallic reagents in the synthesis of hindered substrates. Furthermore, tertiary hydroxyl groups at the benzylic positions were reductively removed via conversion to trimethylsilyloxy groups followed by the use of Me_3SiCl–NaI–MeCN reagent and water. This new class of highly hindered C_2-symmetric pyrrolidine derivatives **12**–**15** will no doubt find wide application in asymmetric synthesis and are currently being investigated in amine-catalysed epoxidation processes in our laboratory.

Figure 1. The ORTEP drawing of compound **15**.



Scheme 4. Proton sponge: 1,8-bis(dimethylamino)naphthalene.



Scheme 5. Proton sponge: 1,8-bis(dimethylamino)naphthalene.

4. Experimental

All reactions involving air or moisture sensitive species were performed in oven-dried glassware under N_2. THF was freshly distilled from potassium/benzophenone. Products were purified by column chromatography on Merck silica gel 60 (eluents given in brackets). Sodium iodide was dried in the oven at 140°C under vacuum prior to use. Other commercially available reagents were used as received from the supplier. Melting points were measured on Reichert apparatus. ^{1}H and ^{13}C NMR spectra were recorded using Delta/GX 270 and 250, Lambda 300 or Amx 400 instruments in $CDCl_3$ unless otherwise stated and are referenced to the appropriate solvent signal or using Me_4Si as internal standard. Chemical shifts are given in ppm. IR spectra were obtained using a Perkin–Elmer 1600 instrument on KBr plates. Mass spectra were recorded on KRATOS MS25, MS80 mass spectrometers using electron impact (EI, 20–50 eV), chemical ionisation (CI) or fast atom bombardment (FAB). Optical rotations were determined by digital polarimeter using a Perkin–Elmer 241 MC instrument. Elemental analyses were performed by the University of Bristol and the University of Sheffield.

4.1. 1-[(*S*)-1-Phenylethyl]-(2*S*,5*S*)-bis(methoxycarbonyl)-pyrrolidine 16

The synthesis of 1-[(*S*)-1-phenylethyl]-(2*S*,5*S*)-bis-(methoxycarbonyl)pyrrolidine **16** was performed according to the method reported by Yamamoto[51] by reaction of dimethyl 2,5-dibromoadipate with (*S*)-(−)-1-phenylethylamine. $[\alpha]_D^{22}$ −104.3 (*c* 1.01 in $CHCl_3$) (lit.[51] $[\alpha]_D^{22}$ −107.0, *c* 1.5 in $CHCl_3$).^{1}H NMR (270 MHz, $CDCl_3$, TMS): $\delta_H = 1.28$ (d, 3H, CH_3, $J = 6.7$ Hz), 1.73–1.89 (m, 2H, CH_2), 2.23–2.40 (m, 2H, CH_2), 3.64 (s, 6H, 2×OCH_3), 3.75–3.79 (m, 2H, 2×CH), 3.99 (q, 1H, C*H*CH_3, $J = 6.7$ Hz), 7.18–7.36 (m, 5H, aromatic H). ^{13}C NMR (67.9 MHz, $CDCl_3$, TMS): $\delta_C = 23.5$ (CH*C*H_3), 29.3 (2×CH_2), 51.5 (*C*HCH_3), 59.9 (2×CH), 62.9 (2×OCH_3), 127.2, 127.4, 128.4, 144.7 (aromatic C), 175.9 (2×C=O).

4.2. 1-[(*S*)-1-Phenylethyl]-*trans*-(2*S*,5*S*)-bis(hydroxydiphenylmethyl)pyrrolidine 12a

Cerium chloride ($CeCl_3 \cdot 7H_2O$) (22.4 g, 60.0 mmol) and a magnetic stirrer were placed in a 500 mL two-necked flask. Most of the water was removed in vacuo (0.1 Torr) by immersing the flask in an oil bath and heating slowly to 135°C over a 2 h period. The magnetically stirred white solid was then heated overnight at 135°C. While the flask was still hot, nitrogen gas was introduced and the flask was cooled in an ice bath. Dry THF (200 mL) was added with stirring and the suspension was stirred for 2 h at room temperature. The flask was again immersed in an ice bath and phenylmagnesium bromide (1.00 M solution in THF, 60 mL, 60 mmol) was added. After stirring the solution at 0°C for 1.5 h, a solution of diester **16** (2.91 g, 10.0 mmol) in dry THF (15 mL) was added. Stirring was continued for 1 h at 0°C and then at room temperature overnight. The reaction mixture was treated with water (300 mL) containing acetic acid (14 mL). The aqueous phase was extracted with EtOAc (4×400 mL) and the combined extracts were washed with brine (3×100 mL), aqueous $NaHCO_3$ solution (2×100 mL), brine (1×100 mL) and dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure to give a yellow solid. The solid was triturated with a mixture of EtOAc/petroleum ether (10/90) (100 mL) and the solvent removed by filtration. The same operation was repeated twice affording a white solid, which was then dried under vacuum at 50°C for 15 h yielding the protected diol **12a** (4.99 g, 92%): mp 210–211°C; $[\alpha]_D^{22}$ −105.3 (*c* 1.50 in $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$, TMS): $\delta_H = 1.48$ (d, 3H, CH_3, $J = 6.7$ Hz), 1.61–1.83 (m, 2H, CH_2), 1.91–2.12 (m, 2H, CH_2), 2.94 (br s, 2H, 2×OH), 3.82 (br s, 2H, 2×CH), 4.43 (q, 1H, C*H*CH_3, $J = 6.7$ Hz), 6.58–6.67 (m, 2H, aromatic H), 7.05–7.48 (m, 23H, aromatic H). ^{13}C NMR (67.9 MHz, $CDCl_3$, TMS): $\delta_C = 15.5$ (CH_3), 27.1 (2×CH_2), 55.6 (*C*HCH_3), 68.5 (2×*C*HCH_2), 78.3 [2×C(OH)], 126.4, 126.7, 126.8, 126.9, 127.0, 127.7, 127.9, 128.0, 128.5 (aromatic C), 144.9, 145.7, 147.0 (aromatic q. C). IR (KBr disc): 3448 (OH), 3058, 3025, 2972 (CH), 1493, 1447, 1064, 1064, 746, 702 cm^{-1}. MS (CI): *m*/*z* (rel. intensity) 540 ([M$^+$+1], 20), 356 (34), 183 (88), 105 (100). Elemental analysis: $C_{38}H_{37}NO_2$ requires C, 84.57; H, 6.91; N, 2.60. Found C, 84.05; H, 6.92; N, 2.51%.

4.3. *trans*-(2*S*,5*S*)-Bis(hydroxydiphenylmethyl)-pyrrolidine 12

A solution of (*S*,*S*)-**12a** (1.89 g, 3.50 mmol) in MeOH (50 mL) was hydrogenated over 20% $Pd(OH)_2$/C (455 mg). The air was removed gently by vacuum before introducing H_2 and the mixture was then stirred at room temperature for 48 h. The catalyst was removed by filtration through Celite and the cake washed with MeOH (100 mL) to remove impurities. A second wash with EtOAc (250 mL) and evaporation of this solvent under reduced pressure gave a white solid, which was recrystallised from ethyl acetate. After recrystallisation, the white solid was partially dissolved in CH_2Cl_2 and the solvent evaporated to remove the remaining ethyl acetate.[52] This solid was dried under vacuum at 50°C for 15 h affording the unprotected diol **12** (1.49 g, 88%): mp 234–235°C; $[\alpha]_D^{22}$ −106.6 (*c* 1.50 in $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$, TMS): $\delta_H = 1.44$–1.76 (m, 5H, 2×CH_2 and NH), 3.47 (br s, 2H, 2×OH), 4.35 (m, 2H, 2×CH), 7.11–7.50 (m, 20H, aromatic H). ^{13}C NMR (67.9 MHz, $CDCl_3$, TMS): $\delta_C = 27.3$ (2×CH_2), 64.8 (2×CH), 78.9 [2×C(OH)], 126.2, 126.8, 127.1, 127.4, 128.5, 128.8 (aromatic C), 145.9, 147.1 (aromatic q. C). MS (FAB): *m*/*z* (rel. intensity) 436 ([M$^+$+1], 100), 252 (28), 136 (64), 131 (33).

4.4. 1-[(*S*)-1-Phenylethyl]-*trans*-(2*S*,5*S*)-bis(1-methoxy-1,1-diphenylmethyl)pyrrolidine 13a

Diol (*S*,*S*)-**12a** (808 mg, 1.50 mmol) was dissolved in anhydrous THF (5 mL) in a 25 mL two-necked flask equipped with a magnetic stirrer and condenser under N_2. The solution was cooled with an ice bath and the

flask flushed with N_2. NaH (60% in oil, 200 mg, 5.00 mmol) was then introduced carefully in one portion. The solution was stirred for 1.5 h at room temperature then MeI (0.24 mL, 4.00 mmol) was added. The mixture was heated under reflux for 15 h. Excess NaH was hydrolysed with aqueous NH_4Cl solution. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3×50 mL). The combined extracts were washed with brine (2×20 mL) and dried over Na_2SO_4. After filtration, the solvent was removed by rotary evaporator affording a white solid. Column chromatography on silica gel (EtOAc/petroleum ether; 20/80) afforded (*S*,*S*)-**13a** (710 mg, 83%) as a white solid: R_f=0.67; mp 71–72°C; $[\alpha]_D^{22}$ −78.6 (*c* 1.50 in $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.10–1.25 (br s, 3H, CHC*H*$_3$), 1.50–4.00 (br s, 12H), 4.60–4.80 (br s, 1H, C*H*CH$_3$), 6.95–7.67 (m, 25H, aromatic H). ^{1}H NMR (400 MHz, DMSO at 80°C): δ_H=1.18 (d, 3H, CHC*H*$_3$, *J*=6.7 Hz), 1.60–1.87 (m, 4H, CH_2CH_2), 2.63 (br s, 6H, 2×OCH_3), 3.71 (br s, 2H, 2×CH), 4.63 (q, 1H, C*H*CH$_3$, *J*=6.7 Hz), 7.05–7.40 (m, 25H, aromatic H). ^{13}C NMR (400 MHz, DMSO at 80°C): δ_C=16.1 (CH*C*H$_3$), 28.5 (2×CH_2), 52.2 (*C*HCH$_3$), 55.8 (2×OCH_3), 67.5 (2×CH), 86.3 (2×CPh_2), 125.7, 126.9, 127.1, 127.5, 129.0, 129.1, 129.8 (aromatic C), 142.9, 143.1, 146.1 (aromatic q. C). IR (KBr disc): 3057, 3025, 2935 (CH); 1493, 1447, 1074, 746, 701 cm^{-1}. MS (FAB): *m*/*z* (rel. intensity)=568 ([M$^+$+1], 14), 370 (100), 234 (23), 197 (30), 131 (40). Elemental analysis: $C_{40}H_{41}NO_2$ requires C, 84.62; H, 7.28; N, 2.47. Found C, 84.48; H, 7.43; N, 2.31%. The compound resulting from monoalkylation was isolated as a white solid (113 mg, 13%): R_f=0.41; mp 69–72°C; $[\alpha]_D^{22}$ −90.5 (*c* 1.47 in $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.21 (d, 3H, CHC*H*$_3$, *J*=6.4 Hz), 1.60–2.00 (m, 4H, CH_2CH_2), 2.76 (s, 3H, OCH_3), 3.10 (br s, 1H, OH), 3.51–3.80 (m, 2H, 2×CH), 4.55 (q, 1H, C*H*CH$_3$, *J*=6.4 Hz), 6.55–6.75 (m, 2H, aromatic H), 6.90–7.65 (m, 23H, aromatic H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_C=15.4 (CH*C*H$_3$), 27.4 and 28.8 (2×CH_2), 53.0 (*C*HCH$_3$), 55.5 (OCH_3), 66.9 and 67.8 (2×CHN), 78.5 [C(OH)], 85.2 (*C*OCH$_3$), 126.5, 126.6, 126.7, 126.8, 126.9, 127.0, 127.1, 127.4, 127.5, 127.6, 127.8, 127.9, 128.2, 128.8, 129.1 (aromatic C), 143.1, 143.7, 145.3, 146.0, 146.8 (aromatic q. C). IR (KBr disc): 3057, 3024, 2987 (CH), 1493, 1447, 1075, 756, 700 cm^{-1}. MS (FAB): *m*/*z* (rel. intensity)=554 ([M$^+$+1], 49), 370 (100), 356 (77), 234 (41), 197 (33). Elemental analysis: $C_{39}H_{39}NO_2$ requires C, 84.59; H, 7.10; N, 2.53. Found C, 84.41; H, 7.23; N, 2.38%.

4.5. *trans*-(2*S*,5*S*)-Bis(1-methoxy-1,1-diphenylmethyl)-pyrrolidine 13

A solution of (*S*,*S*)-**13a** (1.00 g, 1.76 mmol) in MeOH (30 mL) was hydrogenated over 20% $Pd(OH)_2$/C (325 mg). The air was removed gently by vacuum before introducing H_2 and the mixture was then stirred at room temperature for 48 h. After removing the catalyst by filtration through Celite, the solvent was removed under reduced pressure to give a white solid, which was purified by column chromatography on silica gel (EtOAc/petroleum ether; 20/80) (680 mg, 83%): R_f= 0.50; mp 48–50°C; $[\alpha]_D^{22}$ −106.6 (*c* 1.52 in $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ_H=1.00–1.50 (m, 4H, CH_2–CH_2), 1.95 (br s, 1H, NH), 2.98 (s, 6H, 2×OCH_3), 3.71–3.82 (m, 2H, 2×CH), 7.21–7.44 (m, 20H, aromatic H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ_C=26.8 (2×CH_2), 51.4 (2×OCH_3), 62.3 (2×CH), 85.7 (2×*C*OCH$_3$), 127.0, 127.1, 127.2, 127.5, 129.2, 129.5 (aromatic C), 141.5, 142.7 (aromatic q. C). IR (KBr disc): 3056, 2988, 2903 (CH), 1492, 1445, 1075, 757, 701 cm^{-1}. MS (CI): *m*/*z* (rel. intensity)=464 ([M$^+$+1], 61), 266 (53), 234 (80), 197 (100), 131 (68), 105 (70), 77 (33). Elemental analysis: $C_{32}H_{33}NO_2$ requires: C, 82.90; H, 7.17; N, 3.02. Found: C, 82.88; H, 7.25; N, 2.86%.

4.6. 1-[(*S*)-1-Phenylethyl]-*trans*-(2*S*,5*S*)-(1-hydroxy-1,1-diphenylmethyl)-(1-trimethylsilyloxy-1,1-diphenylmethyl)pyrrolidine 14a

To a stirred solution of diol (*S*,*S*)-**12a** (270 mg, 0.50 mmol), 1,8-bis(dimethylaminonaphthalene) (236 mg, 1.10 mmol), triethylsilane (1.58 mL, 5.00 mmol) and anhydrous CH_2Cl_2 (1.5 mL) was added and trimethylsilyl triflate (0.20 mL, 1.10 mmol) dropwise under nitrogen. The mixture was stirred at room temperature for 3 h and then neutralised with a mixture of CH_2Cl_2 (40 mL) and Et_3N (0.4 mL). The solvent was removed under reduced pressure to obtain a yellow solid, which was purified by column chromatography on silica gel (EtOAc/petroleum ether; 15/85). The first compound eluted was the corresponding double-silylated compound **14b** (125 mg, 36%) as a white solid. R_f=0.80; mp 73–75°C; $[\alpha]_D^{22}$ +37.9 (*c* 1.53 in $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ_H=−0.38 (s, 9H, OSiCH$_3$), 0.00 (s, 9H, OSiMe$_3$), 1.35–1.54 [m, 4H, CH_3 and C*H*(H)], 2.10–2.26 [m, 3H, CH_2 and C*H*(H)], 4.05–4.17 (m, 1H, NCH), 4.30–4.38 (m, 1H, NCH), 4.45 (q, 1H, C*H*CH$_3$, *J*=6.6 Hz), 6.64–7.35 (m, 23H, aromatic H), 7.75–7.74 (m, 2H, aromatic H). ^{13}C NMR (75.5 MHz, $CDCl_3$, TMS): δ_C=1.8 and 2.5 (2×$SiMe_3$), 17.4 (CH_3), 28.8 and 29.0 (CH_2–CH_2), 55.2 (*C*HCH$_3$), 67.4 and 70.9 (2×CHN), 84.5 and 87.7 (2×*C*OSiMe$_3$), 124.6, 125.7, 126.5, 126.8, 127.1, 127.4, 127.6, 127.7, 128.6, 129.3, 130.4, 144.6 (aromatic C), 145.5, 146.7, 147.1, 148.4 (aromatic q. C). IR (KBr disc): 3059, 2958, 1493, 1445, 1252, 1117, 1060, 881, 838, 700 cm^{-1}. MS (CI): *m*/*z* (rel. intensity)=684 ([M$^+$+1], 22), 668 (48), 428 (85), 308 (29), 255 (100), 234 (32), 131 (46), 105 (60), 91 (21), 73 (35). Elemental analysis: $C_{44}H_{53}NO_2Si_2$ requires: C, 77.25; H, 7.81; N, 2.05. Found: C, 77.66; H, 7.81; N, 1.88%. The corresponding monosilylated compound **14a** was obtained as a white solid (160 mg, 52%). R_f=0.45; mp 69–72°C; $[\alpha]_D^{22}$ −38.8 (*c* 1.58 in $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$, TMS): δ_H=0.00 (s, 9H, $SiMe_3$), 1.54 (d, 3H, CH_3, *J*=6.8 Hz), 1.70–1.86 (m, 1H, C*H*(H)), 2.10–2.37 (m, 3H, CH_2 and C*H*(H)), 3.47 (br s, 1H, OH), 3.50–3.63 (m, 1H, NCH), 4.16–4.27 (m, 1H, NCH), 4.54 (q, 1H, C*H*CH$_3$, *J*=6.8 Hz), 6.51–6.61 (m, 2H, aromatic H), 6.86–6.98 (m, 2H, aromatic H), 7.06–7.56 (m, 21H, aromatic H). ^{13}C NMR (67.9 MHz, $CDCl_3$, TMS): δ_C=2.6 ($SiMe_3$), 16.3 (CH_3), 27.4 and 28.9 (CH_2CH_2), 55.1 (*C*HCH$_3$), 67.9 and 69.4 (CHN), 78.5 [C(OH)], 84.4 (COSi), 126.3, 126.5, 126.6, 126.7, 126.8, 127.4, 127.43, 127.5, 127.60, 127.62, 127.7, 127.9, 128.1 (aromatic C), 144.7, 146.2, 146.5, 146.8, 146.9

(aromatic q. C). IR (KBr disc): 3472 (OH), 3017, 2968 (CH), 1493, 1446, 1253, 1216, 1109, 1072, 1049, 1020, 880, 839, 746, 702 cm^{-1}. MS (CI): m/z (rel. intensity) = 612 ([M^++1], 68), 596 (19), 508 (47), 428 (58), 400 (25), 356 (77), 255 (50), 234 (66), 183 (62), 131 (42), 105 (100), 91 (22). Elemental analysis: $C_{41}H_{45}NO_2Si$ requires: C, 80.48; H, 7.41; N, 2.29. Found: C, 80.53; H, 7.44; N, 2.21%.

4.7. *trans*-(2*S*,5*S*)-Bis(1-trimethylsilyloxy-1,1-diphenylmethyl)pyrrolidine 14

To a stirred solution of diol (*S*,*S*)-**12** (676 mg, 1.55 mmol), 1,8-bis(dimethylaminonaphthalene) (996 mg, 4.65 mmol) and anhydrous CH_2Cl_2 (4.7 mL) was added and trimethylsilyl triflate (0.845 mL, 4.65 mmol) dropwise under nitrogen. The mixture was stirred at room temperature for 1 h and was then neutralised with a mixture of CH_2Cl_2 (40 mL) and Et_3N (0.4 mL). The solvent was removed under reduced pressure to obtain a yellow solid, which was purified by column chromatography on silica gel (EtOAc/petroleum ether; 10/90). R_f = 0.43; mp 146–148°C; $[\alpha]_D^{22}$ −137.9 (*c* 1.51 in $CHCl_3$). ^1H NMR (270 MHz, $CDCl_3$, TMS): δ_H = −0.01 (s, 18H, 2×$SiMe_3$), 1.18–1.35 (m, 2H, CH_2), 1.53–1.72 (m, 2H, CH_2), 2.15 (br s, 1H, NH), 3.91–4.02 (m, 2H, 2×CHN), 7.23–7.51 (m, 20H, aromatic H). ^{13}C NMR (67.9 MHz, $CDCl_3$, TMS): δ_C = 2.3 (2×$SiMe_3$), 26.9 (2×CH_2), 65.2 (2×CHN), 83.7 (2×CO), 126.6, 126.9, 127.4, 127.6, 128.4 (aromatic C), 146.1, 146.8 (aromatic q. C). IR (KBr disc): 3019, 2956, 2895 (CH), 1492, 1446, 1251, 1217, 1100, 1072, 1025, 890, 840, 768, 741, 703 cm^{-1}. MS (CI): m/z (rel. intensity) = 580 ([M^++1], 17), 564 (20), 400 (21), 255 (32), 234 (100), 131 (52), 73 (42). Elemental analysis: $C_{36}H_{45}NO_2Si_2$ requires: C, 74.56; H, 7.82; N, 2.42. Found: C, 74.54; H, 7.97; N, 2.33%.

4.8. *trans*-(2*S*,5*S*)-Bis(1,1-diphenylmethyl)pyrrolidine 15

The silylated compound (*S*,*S*)-**14** (290 mg, 0.50 mmol) was added to a mixture of Me_3SiCl (0.767 mL, 6.00 mmol), NaI (900 mg, 6.00 mmol), anhydrous acetonitrile (0.38 mL, 6.00 mmol) and anhydrous hexane (1.5 mL). After the addition of water (0.036 mL, 2.00 mmol), the reaction was stirred for 24 h at 40°C. After cooling to room temperature, the mixture was dissolved in CH_2Cl_2 (40 mL) and cooled with an ice bath. This reaction was then neutralised by dropwise addition of a mixture of CH_2Cl_2 (40 mL) and Et_3N (0.4 mL). The organic layer was washed with water (5×30 mL) and dried over Na_2SO_4. After filtration and concentration under reduced pressure a brown oil was obtained which was purified by column chromatography on silica gel (EtOAc/petroleum ether; 25/75) to obtain a yellow solid (136 mg, 67%). A portion of this solid was recrystallised from EtOAc/petroleum ether. R_f = 0.30; mp 132–133°C; $[\alpha]_D^{22}$ +22.7 (*c* 1.31 in $CHCl_3$). ^1H NMR (270 MHz, $CDCl_3$, TMS): δ_H = 1.42–1.60 (m, 2H, CH_2), 1.71 (br s, 1H, NH), 1.81–1.96 (m, 2H, CH_2), 3.76 (d, 2H, 2×C*H*Ph_2, *J* = 10.2 Hz), 3.96–4.08 (m, 2H, 2×CHN), 7.08–7.29 (m, 20H, aromatic H). ^{13}C NMR (67.9 MHz, $CDCl_3$, TMS): δ_C = 30.2 (2×CH_2), 58.1 (2×*C*HPh_2), 60.5 (2×CHN), 126.4, 126.5, 128.1, 128.3, 128.5, 128.6 (aromatic C), 143.4 (4×aromatic q. C). IR (KBr disc): 3018, 2970, 2916 (CH), 1495, 1450, 1404, 1215, 764, 703, 668 cm^{-1}. MS (CI): m/z (rel. intensity) = 404 ([M^++1], 46), 236 (100), 167 (24), 91 (28), 79 (8). Elemental analysis: $C_{30}H_{29}N$ requires: C, 89.29; H, 7.24; N, 3.47. Found: C, 89.49; H, 7.79; N, 3.49%.

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