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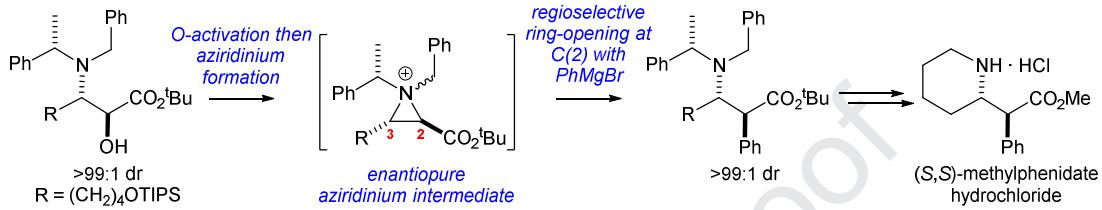

The asymmetric synthesis of (*S*,*S*)-methylphenidate hydrochloride via ring-opening of an enantiopure aziridinium intermediate with phenylmagnesium bromide

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Dedicated to Professor Stephen G. Davies in recognition of his outstanding contributions to the field of organic chemistry.

Abstract

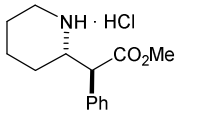
The key step in our synthetic strategy towards (*S*,*S*)-methylphenidate hydrochloride employs the ring-opening of an in situ formed aziridinium intermediate. Treatment of an α-hydroxy-β-amino ester with methanesulfonic anhydride promoted aziridinium formation and the subsequent addition of phenylmagnesium bromide resulted in stereospecific and regioselective ring-opening to give the corresponding α-phenyl-β-amino ester with overall retention of configuration. Subsequent functional group manipulation followed by N-deprotection and cyclization generated the piperidine ring within the target compound, and transesterification gave (*S*,*S*)-methylphenidate hydrochloride in only 8 steps from 1,5-pentanediol, in 15% overall yield. These results demonstrate the synthetic utility of enantiopure aziridinium intermediates as substrates for the generation of stereodefined C–C bonds, and crucially this methodology provides access to α-substituted-β-amino ester substrates that are not accessible via enolate alkylation chemistry. The strategy reported herein is potentially applicable to all possible stereoisomers of methylphenidate as well as differentially substituted analogues.

Key words: methylphenidate; ritalin; asymmetric synthesis; lithium amide; aziridinium; α-aryl-β-amino acid

1. Introduction

Racemic *threo*-methylphenidate hydrochloride **1**·HCl, sold under the tradename Ritalin®, is a dopamine re-uptake inhibitor commonly prescribed as a treatment for attention deficit hyperactivity disorder (ADHD) in children and adolescents (Fig. 1).[1] Whilst the drug is typically supplied as a racemate, the (+)-enantiomer

has been determined to be about thirteen times more pharmacologically active than its antipode.[2,3] Furthermore, *threo*-methylphenidate **1**·HCl has also undergone evaluation for its therapeutic potential for the treatment of cocaine addiction and narcolepsy.[4] Several syntheses of enantiopure *threo*-methylphenidate hydrochloride **1**·HCl have been reported via a number of distinct approaches.[5,6] Protocols for the resolution of *threo*-methylphenidate **1** by enzymatic hydrolysis as well as classical resolution methods have also been developed,[7] and there have also been reports of various synthetic analogues of methylphenidate hydrochloride **1**·HCl being evaluated for their biological activity.[8]



(±)-*threo*-methylphenidate hydrochloride (Ritalin®) **1**·HCl

Fig. 1. The structure of (±)-*threo*-methylphenidate hydrochloride (Ritalin®) **1**·HCl.

We have previously explored the utility of enantiopure aziridinium species as versatile intermediates in asymmetric synthesis,[9] and envisaged that the stereospecific and regioselective ring-opening of an aziridinium intermediate with an organometallic reagent could be incorporated as a key step in an asymmetric synthesis of (*S*,*S*)-methylphenidate hydrochloride **1**·HCl. This strategy relied upon the manipulation of a suitably protected α-hydroxy-β-amino ester: substrates which are readily accessible using our diastereoselective aminohydroxylation protocol.[10] ζ-Silyloxy-α-hydroxy-β-amino ester **2** was selected as a suitable substrate for this synthesis as removal of the *O*-silyl protecting group would reveal a synthetic handle for subsequent cyclisation to give the piperidine ring within the target compound. Activation of the α-hydroxyl group within **2** as a leaving group was expected to promote displacement by the adjacent amino group [with inversion of configuration at C(2)] to give the corresponding aziridinium **3**.[9] Subsequent in situ ring-opening of aziridinium **3** with an organometallic reagent was anticipated to proceed preferentially at the C(2)-position [again with inversion of configuration at C(2)], distal to the alkyl substituent and proximal to the electronically activating α-carbonyl of the ester moiety,[11] to give the corresponding α-phenyl-β-amino ester **4** with overall retention of configuration. Subsequent *O*-silyl deprotection and manipulation of the resultant hydroxyl group was expected to facilitate cyclisation to give the corresponding piperidine **6**, which could be converted into (*S*,*S*)-methylphenidate hydrochloride **1**·HCl upon transesterification under acidic conditions (Fig. 2).

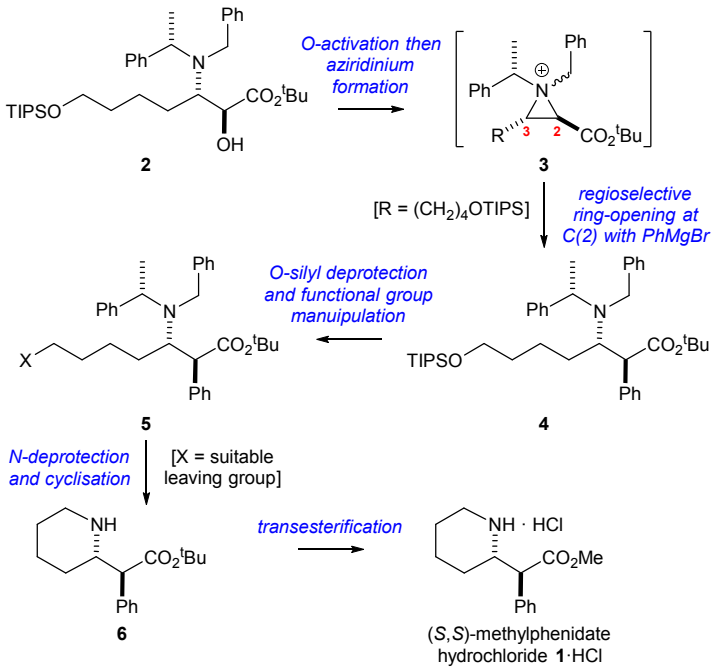
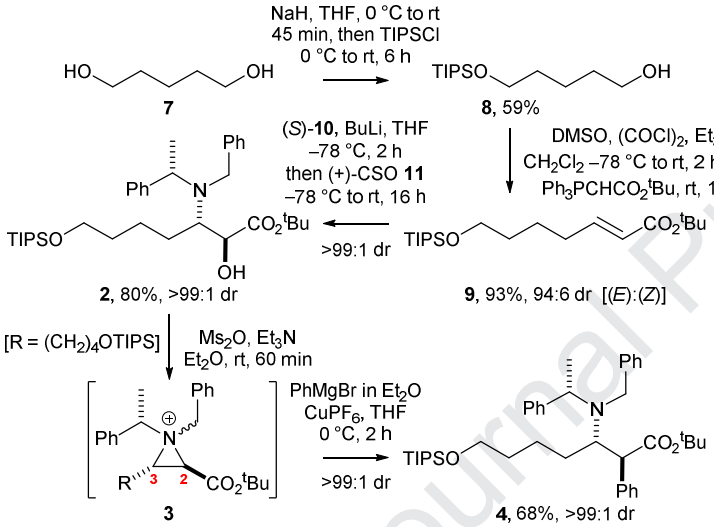


Fig. 2. Proposed asymmetric synthesis of (*S*,*S*)-methylphenidate hydrochloride **1**·HCl.

2. Results and discussion

The requisite ζ-silyloxy-α-hydroxy-β-amino ester **2** was prepared in three steps from commercially available 1,5-pentanediol **7**. Mono-protection of **7** upon treatment with NaH and TIPSCl gave **8** in 59% yield, and Swern oxidation of **8** followed by Wittig olefination of the resultant aldehyde gave α,β-unsaturated ester **9** in 93% yield (from **8**) and 94:6 dr [(*E*):(*Z*)]. The configuration of the major diastereoisomer was assigned from the diagnostic value of the ^{3}J coupling constant between the two olefinic protons ($^{3}J_{2,3}$ = 15.6 Hz) in the ^{1}H NMR spectrum. The mixture of olefin isomers was carried through the next step to give, following diastereoselective aminohydroxylation upon sequential treatment of **9** with lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide (*S*)-**10** and (+)-(camphorsulfonyl)oxaziridine [(+)-CSO] **11**,[10] 2,3-*anti*-α-hydroxy-β-amino ester **2** as a single diastereoisomer (>99:1 dr). Following purification by flash column chromatography, **2** was isolated in 80% yield and >99:1 dr. The 2,3-*anti*-relative configuration within **2** was assigned by analogy to the well-established outcome of this aminohydroxylation procedure,[10] and this assignment was supported by ^{1}H NMR ^{3}J coupling constant analysis ($^{3}J_{2,3}$ = 1.8 Hz for **2**).[12] Elaboration of **2** to the corresponding α-phenyl-β-amino ester **4** was undertaken next. Under the optimised conditions for aziridinium ion formation,[9] α-hydroxy-β-amino ester **2** was treated with Ms_2O and Et_3N then aziridinium intermediate **3** was reacted with PhMgBr in the presence of $CuPF_6$, which gave α-phenyl-β-amino ester **4** as the sole reaction product. After chromatographic purification of the crude reaction mixture, **4** was isolated in 68% yield and >99:1 dr (Scheme 1). The relative 2,3-*anti*-configuration within α-phenyl-β-amino ester **4** was

unambiguously established via single crystal X-ray diffraction analysis (Fig. 3),[13] with the absolute (*S*,*S*,*S*)-configuration of **4** being assigned from the known (*S*)-configuration of the α-methylbenzyl fragment. The determination of a Flack *x* parameter[14] of −0.02(2) for the structure of **4** confirmed this assignment. The exclusive formation of **4** in this reaction is entirely consistent with our mechanistic hypothesis, whereby the Grignard reagent regioselectively reacts at the C(2) position within aziridinium **3**.[15] This stereospecific C–C bond forming reaction was conducted on a ~3 g scale, demonstrating the robustness of this methodology for the α-arylation of β-amino esters, a transformation that is not possible using standard enolate alkylation chemistry.



Scheme 1.

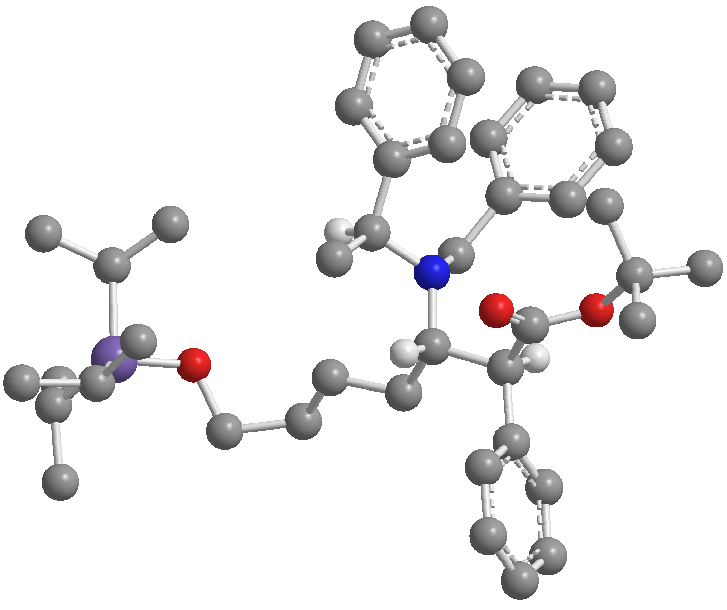
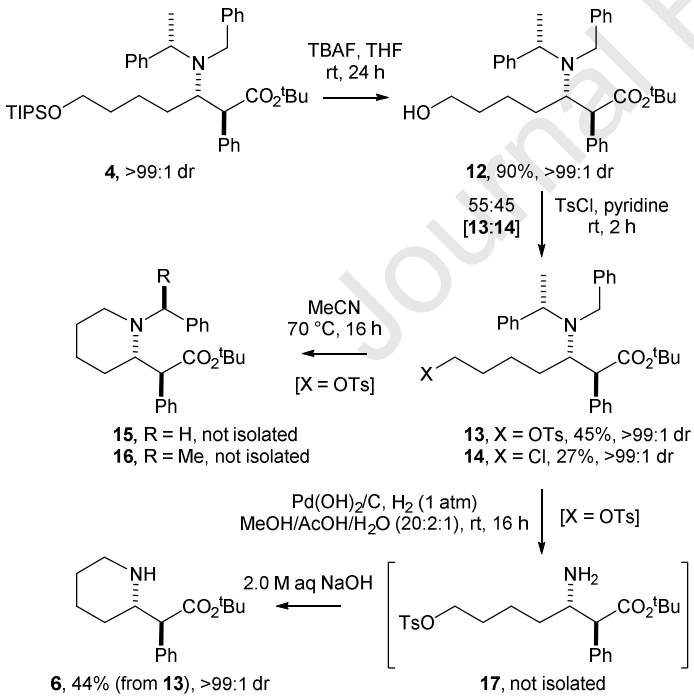


Fig. 3. X-ray crystal structure of (*S*,*S*,*S*)-**4** (selected H atoms have been omitted for clarity).

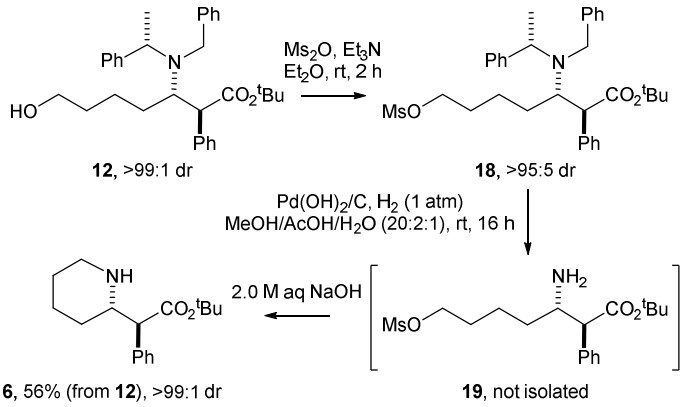
O-Silyl deprotection of **4** upon treatment with TBAF proceeded to give alcohol **12** in 90% isolated yield. Subsequent treatment of **12** with TsCl in pyridine gave the corresponding tosylate **13** in 45% yield and >99:1 dr. The low yield of this transformation was due to the competitive formation of the corresponding chloride **14**, which represented 45% of the crude reaction mixture and was isolated in 27% yield (Scheme 2). We have previously shown that ω-sulfonyloxy substituted amines undergo cyclisation to the corresponding quaternary ammonium intermediate followed by S_N1-type loss of a benzyl fragment upon heating in MeCN.[16,17] However, under these conditions, tosylate **13** did not react to give either of the potential piperidine products **15** (R = H) or **16** (R = Me), and only starting material **13** was recovered. With heat-induced cyclisation of tosylate **13** having proved unsuccessful the next strategy was to convert **13** to the corresponding primary amine **17** prior to cyclisation. Hydrogenolysis of tertiary amine **13** in the presence of Pearlman's catalyst [$Pd(OH)_2$/C] gave primary amine **17**, and immediate treatment of the crude reaction mixture with 2.0 M aq NaOH returned piperidine **6** in 44% yield (from **13**) and >99:1 dr (Scheme 2).



Scheme 2.

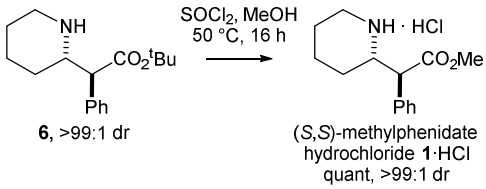
The generation of piperidine **6** in 20% yield over the three steps from alcohol **12** demonstrates the viability of this strategy of *O*-activation, hydrogenolysis, and cyclisation. Efforts therefore turned to increasing the overall yield of this sequence of reactions. Mesylation of alcohol **12** upon treatment with Ms_2O and Et_3N gave **18** (>95:5 dr) as the only observed product in the crude reaction mixture. Subsequent hydrogenolysis of

18 followed by treatment of the resultant primary amine **19** with 2.0 M aq NaOH gave piperidine **6** in a much improved 56% yield over three steps from alcohol **12** (Scheme 3).



Scheme 3.

Finally, transesterification of the *tert*-butyl ester moiety within **6** upon reaction with $SOCl_2$ and MeOH gave (*S*,*S*)-methylphenidate hydrochloride **1**·HCl in quantitative yield and >99:1 dr (Scheme 4). As the lithium amide reagent used for the conjugate addition reaction was >99:1 er, our sample of **1**·HCl was inferred as being >99:1 er, along with all intermediates en route, as epimerisation was not observed at any stage in the synthesis. The specific rotation of our sample of **1**·HCl {$[\alpha]_D^{25}$ −65.0 (*c* 1.0 in MeOH)} was in general agreement with literature values {lit.[7b] $[\alpha]_D^{20}$ −85.0 (*c* 1.0 in MeOH); lit.[5b] $[\alpha]_D^{20}$ −81.8 (*c* 1.38 in MeOH)}, and the ^{1}H and ^{13}C NMR spectroscopic data for this sample of **1**·HCl were also in complete accord with the literature.[5b,7b] The assigned relative and absolute configuration of (*S*,*S*)-**1**·HCl were unambiguously confirmed via single crystal X-ray diffraction analysis (Fig. 4),[13] with the Flack *x* parameter[14] for the structure of **1**·HCl being determined as +0.02(3).



Scheme 4.

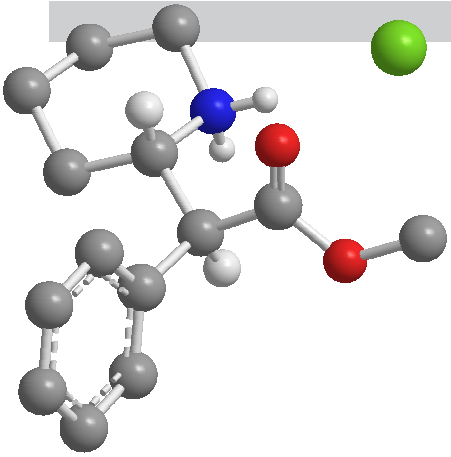


Fig. 4. X-ray crystal structure of (*S*,*S*)-methylphenidate hydrochloride (*S*,*S*)-**1**·HCl (selected H atoms have been omitted for clarity).

3. Conclusion

In conclusion, (*S*,*S*)-methylphenidate hydrochloride was synthesised in 15% yield over 8 steps from commercially available 1,5-pentanediol. The key step in the synthesis employed the regioselective and stereospecific ring-opening of an enantiopure aziridinium intermediate with phenylmagnesium bromide. This synthesis demonstrates the synthetic utility of enantiopure aziridiniums as substrates for the generation of stereodefined C–C bonds, and provides access to substrates that are not accessible via enolate alkylation chemistry. The strategy reported herein is potentially applicable to all possible stereoisomers of methylphenidate as well as differentially substituted analogues.

4. Experimental

4.1. General Experimental

Reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. BuLi was purchased as a solution in hexanes and titrated against diphenylacetic acid before use. Solvents were dried according to the procedure outlined by Grubbs and co-workers.[20] Water was purified by an Elix® UV-10 system. All other reagents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$ or $NaSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), iodine, 1% aq $KMnO_4$, or 10% ethanolic phosphomolybdic acid. Flash column chromatography was performed on Kieselgel 60 silica.

Melting points were recorded on a Gallenkamp Hot Stage apparatus. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g/100 mL. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer using an ATR module. Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated. Spectra were recorded at rt. The field was locked by external referencing to the relevant deuteron resonance. $^1H-^1H$ COSY, $^1H-^{13}C$ HMQC, and $^1H-^{13}C$ HMBC analyses were used to establish atom connectivity. Low-resolution mass spectra were recorded on either a VG MassLab 20–250 or a Micromass Platform 1 spectrometer. Accurate mass measurements were run on either a Bruker MicroTOF internally calibrated with polyalanine, or a Micromass GCT instrument fitted with a Scientific Glass Instruments BPX5 column (15 m × 0.25 mm) using amyl acetate as a lock mass.

4.2. 5-(Triisopropylsilyloxy)pentan-1-ol 8

1,5-Pentanediol **7** (7.50 g, 72.0 mmol) was added dropwise to a stirred suspension of NaH (60% dispersion in mineral oil, 2.88 g, 72.0 mmol) in THF (144 mL) at 0 °C, and the resultant mixture was stirred at rt for 45 min. TIPSCl (15.4 mL, 72.0 mmol) was then added at 0 °C and the resultant mixture was allowed to warm to rt and stirred at rt for 6 h. H_2O (125 mL) was then added and the reaction mixture was extracted with Et_2O (3 × 125 mL). The combined organic extracts were washed with brine (125 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 5:1 increased to 1:1) gave **8** as a colourless oil (11.1 g, 59%);[18] δ_H (400 MHz, $CDCl_3$) 0.97−1.16 (21H, m, Si(C*H*Me_2)$_3$), 1.38−1.48 (2H, m, C(3)H_2), 1.51−1.67 (4H, m, C(2)H_2, C(4)H_2), 3.62−3.73 (4H, m, C(1)H_2, C(5)H_2).

4.3. *tert*-Butyl (*E*)-7-(triisopropylsilyloxy)hept-2-enoate 9

DMSO (12.1 mL, 171 mmol) was added dropwise to a stirred solution of $(COCl)_2$ (7.20 mL, 85.1 mmol) in CH_2Cl_2 (190 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 20 min. A solution of **8** (11.1 g, 42.5 mmol) in CH_2Cl_2 (120 mL) at −78 °C was then added via cannula and the resultant mixture was stirred at −78 °C for 30 min. Et_3N (35.6 mL, 256 mmol) was then added dropwise and the resultant mixture was stirred at −78 °C for 30 min, then allowed to warm to rt and stirred at rt for 30 min. $Ph_3PCHCO_2{}^tBu$ (16.0 g, 42.5 mmol) was then added and the resultant mixture was stirred at rt for 18 h, before being diluted with H_2O (600 mL) and extracted with CH_2Cl_2 (3 × 300 mL). The combined organic extracts were

sequentially washed with satd aq $NaHCO_3$ (300 mL) and brine (300 mL), then concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O, 50:1 increased to 5:1) gave **9** as a yellow oil (14.0 g, 93%, 94:6 dr [(*E*):(*Z*)]); ν_{max} 2942 (C−H), 2866 (C−H), 1717 (C=O), 1654 (C=C); δ_H (400 MHz, $CDCl_3$) Data for major (*E*)-diastereoisomer: 1.01−1.14 (21H, m, Si(C*H*Me_2)$_3$), 1.48 (9H, s, CMe_3), 1.48−1.66 (4H, m, C(5)H_2, C(6)H_2), 2.20 (2H, app qd, *J* 7.0, 1.6, C(4)H_2), 3.63−3.74 (2H, m, C(7)H_2), 5.74 (1H, dt, *J* 15.6, 1.6, C(2)*H*), 6.86 (1H, dt, *J* 15.6, 7.0, C(3)*H*); δ_C (100 MHz, $CDCl_3$) Data for major (*E*)-diastereoisomer: 11.9 (Si*C*HMe_2), 18.0 (SiCH*Me*$_2$), 24.5 (*C*(5)), 28.2 (C*Me*$_3$), 31.9 (*C*(4)), 32.4 (*C*(6)), 63.0 (*C*(7)), 80.0 (*C*Me_3), 123.1 (*C*(2)), 148.0 (*C*(3)), 166.2 (*C*(1)); *m/z* (ESI^+) 379 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{20}H_{40}NaO_3Si^+$ ($[M+Na]^+$) requires 379.2639; found 379.2641.

4.4. *tert*-Butyl (*S*,*S*,*S*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-7-(triisopropylsilyloxy)heptanoate 2

n-BuLi (2.5 M in hexanes, 4.36 mL, 10.9 mmol) was added dropwise to a stirred solution of (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amine (*S*)-**10** (13.3 g, 62.9 mmol, >99:1 er) in THF (300 mL) at −78 °C. The resultant mixture was stirred at −78 °C for 30 min, then a solution of **9** (14.0 g, 39.3 mmol, 94:6 dr [(*E*):(*Z*)]) in THF (90 mL) at −78 °C was added dropwise via cannula. The resultant mixture was stirred at −78 °C for a further 2 h then (+)-CSO **11** (15.4 g, 67.2 mmol) was added. The reaction mixture was allowed to warm to rt and stirred at rt for 16 h, then concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (150 mL) and 10% aq citric acid (150 mL). The aqueous layer was extracted with two portions of CH_2Cl_2 (100 mL) and the combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (200 mL) and brine (200 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30–40 °C petrol/Et_2O, 13:1) gave **2** as a pale yellow oil (18.5 g, 80%, >99:1 dr); $[\alpha]_D^{25}$ +21.3 (*c* 1.0 in $CHCl_3$); ν_{max} 3503 (O−H), 2941 (C−H), 2865 (C−H), 1720 (C=O); δ_H (400 MHz, $CDCl_3$) 1.03−1.12 (21H, m, Si(C*H*Me_2)$_3$), 1.30 (3H, d, *J* 6.9, C(α)*Me*), 1.43 (9H, s, CMe_3), 1.37−1.51 (3H, m, C(6)H_2, C(5)H_A, C(4)H_A) 1.57−1.71 (2H, m, C(5)H_B, C(4)H_B), 2.89 (1H, d, *J* 6.0, O*H*), 3.23 (1H, ddd, *J* 8.8, 4.5, 1.8, C(3)*H*), 3.64−3.71 (3H, m, NC$H_A$$H_B$Ph, C(7)$H_2$), 3.87 (1H, dd, *J* 6.0, 1.8, C(2)*H*), 3.94 (1H, q, *J* 6.9, C(α)*H*), 4.26 (1H, d, *J* 15.5, NC$H_A$$H_B$Ph), 7.18−7.50 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.1 (Si(*C*HMe_2)$_3$), 18.1 (Si(CH*Me*$_2$)$_3$), 19.5 (C(α)*Me*), 23.3 (*C*(5)), 27.4 (*C*(4)), 28.0 (C*Me*$_3$), 33.3 (*C*(6)), 51.1 (N*C*H_2Ph), 58.4 (*C*(α)), 58.8 (*C*(3)), 63.4 (*C*(7)), 71.2 (*C*(2)), 82.4 (*C*Me_3), 126.4, 127.0, 128.1, 128.1, 128.2, 128.2 (*o*,*m*,*p*-

Ph), 142.6, 143.0 (*i-Ph*), 174.4 (*C*(1)); *m/z* (ESI$^+$) 584 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{58}NO_4Si^+$ ([M+H]$^+$) requires 584.4130; found 584.4139.

4.5. *tert*-Butyl (*S*,*S*,*S*)-2-phenyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-7-(triisopropylsilyloxy)heptanoate 4

Ms_2O (3.85 g, 25.7 mmol) was added to a stirred solution of **2** (4.30 g, 8.56 mmol, >99:1 dr) and Et_3N (4.62 mL, 38.5 mmol) in Et_2O (350 mL) and the resultant mixture was stirred at rt for 60 min. The reaction mixture was then cooled to 0 °C and $CuPF_6$ (1.38 g, 4.28 mmol) and PhMgBr (3.0 M in Et_2O, 24.5 mL, 85.6 mmol) were sequentially added, and the resultant mixture was stirred at 0 °C for 2 h. Satd aq NH_4Cl (80 mL) was added, and the reaction mixture was diluted with H_2O (400 mL) and extracted with Et_2O (3 × 300 mL), then the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O 75:1) gave **4** as a white solid (3.23 g, 68%, >99:1 dr); mp 84−86 °C; $[\alpha]_D^{25}$ −21.9 (*c* 1.0 in $CHCl_3$); ν_{max} 2942 (C−H), 2865 (C−H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 0.48−0.66 (1H, m, C(5)H_A), 1.00−1.09 (22H, m, C(4)H_A, Si(C*HMe*$_2$)$_3$), 1.10−1.21 (3H, m, C(5)H_B, C(6)H_2), 1.24−1.35 (1H, m, C(4)H_B), 1.38 (3H, d, *J* 6.9, C(α)*Me*), 1.42 (9H, s, C*Me*$_3$), 3.30−3.43 (2H, m, C(7)H_2), 3.39 (1H, d, *J* 9.7, C(2)*H*), 3.63 (1H, ddd, *J* 9.7, 6.9, 4.9, C(3)*H*), 3.69−3.83 (2H, m, NCH_2Ph), 4.14 (1H, q, *J* 6.9, C(α)*H*), 7.12−7.38 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.0 (Si(*C*HMe$_2$)$_3$), 18.1 (Si(CH*Me*$_2$)$_3$), 20.8 (C(α)*Me*), 24.3 (*C*(5)), 28.0 (C*Me*$_3$), 30.0 (*C*(4)), 33.3 (*C*(6)), 50.4 (N*C*H$_2$Ph), 58.3 (*C*(2)), 62.0 (*C*(3)), 62.2 (*C*(α)), 63.2 (*C*(7)), 80.1 (*C*Me$_3$), 126.3, 126.7, 127.0, 127.8, 127.9, 128.1, 128.2, 128.6, 129.1 (*o*,*m*,*p-Ph*), 137.7, 142.7, 144.9 (*i-Ph*), 172.8 (*C*(1)); *m/z* (ESI$^+$) 644 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{41}H_{62}NO_3Si^+$ ([M+H]$^+$) requires 644.4493; found 644.4480.

4.5.1. X-ray crystal structure determination for *tert*-butyl (*S*,*S*,*S*)-2-phenyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-7-(triisopropylsilyloxy)heptanoate 4

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[19]

X-ray crystal structure data for **4** [$C_{41}H_{61}NO_3Si$]:[13] M = 644.03, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 7.87519(15) Å, b = 11.8183(3) Å, c = 41.2585(6) Å, V = 3840.00(13) Å^3, Z = 4, μ = 0.811 mm^{-1},

colourless prism, crystal dimensions = 0.11 × 0.11 × 0.23 mm^3. A total of 7943 unique reflections were measured for $4 < \theta < 76$ and 7472 reflections were used in the refinement. The final parameters were $wR_2 = 0.085$ and $R_1 = 0.039$ [$I>-3.0\sigma(I)$], with Flack x parameter = –0.02(2).[14]

4.6. *tert*-Butyl (*S*,*S*,*S*)-2-phenyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-7-hydroxyheptanoate 12

TBAF (1.0 M in THF, 25.1 mL, 25.1 mmol) was added to a stirred solution of **4** (3.23 g, 5.02 mmol, >99:1 dr) in THF (33 mL) at rt and the resultant mixture was stirred at rt for 24 h. H_2O (100 mL) was then added and the reaction mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were then dried and concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O 3:2) gave **12** as a white solid (2.21 g, 90%, >99:1 dr); mp 97−100 °C; $[\alpha]_D^{25}$ −25.0 (*c* 1.0 in $CHCl_3$); ν_{max} 3375 (O−H), 3028 (C−H), 2976 (C−H), 1723 (C=O); δ_H (400 MHz, $CDCl_3$) 0.42−0.54 (1H, m, C(5)H_A), 0.84 (1H, app t, *J* 5.8, C(6)H_A), 0.89−1.16 (3H, m, C(4)H_A, C(5)H_B, C(6)H_B), 1.20−1.32 (1H, m, C(4)H_B), 1.37 (3H, d, *J* 7.0, C(α)*Me*), 1.43 (9H, s, CMe_3), 3.27(2H, app q, C(7)H_2), 3.39 (1H, d, *J* 9.8, C(2)*H*), 3.59 (1H, ddd, *J* 9.8, 6.7, 4.9, C(3)*H*), 3.73 (1H, d, *J* 15.2, NC$H_A$$H_B$Ph), 3.85 (1H, d, *J* 15.2, NC$H_A$$H_B$Ph), 4.19 (1H, q, *J* 7.0, C(α)*H*), 7.13−7.45 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.8 (C(α)*Me*), 23.9 (*C*(5)), 28.0 (CMe_3), 29.6 (*C*(4)), 32.7 (*C*(6)), 49.8 (NCH_2Ph), 58.4 (*C*(2)), 62.4 (*C*(3)), 62.4 (*C*(α)), 62.6 (*C*(7)), 80.2 (*C*Me_3), 126.4, 126.8, 127.1, 127.9, 128.0, 128.2, 128.3, 128.6, 129.0 (*o*,*m*,*p*-*Ph*), 137.8, 142.7, 144.8 (*i*-*Ph*), 172.8 (*C*(1)); *m/z* (ESI^+) 488 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{32}H_{42}NO_3^+$ ($[M+H]^+$) requires 488.3159; found 488.3154.

4.7. *tert*-Butyl (*S*,*S*,*S*)-2-phenyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-7-(*p*-toluenesulfonyloxy)heptanoate 13 and *tert*-butyl (*S*,*S*,*S*)-2-phenyl-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-7-chloroheptanoate 14

TsCl (59.0 mg, 0.312 mmol) was added to a stirred solution of **12** (51.0 mg, 0.104 mmol, >99:1 dr) in pyridine (1.0 mL) and the resultant mixture was stirred at rt for 2 h, then concentrated in vacuo. Purification via flash column chromatography (eluent 30−40 °C petrol/Et_2O 75:1 increased to 10:1) gave **14** as a colourless oil (14 mg, 27%, >99:1 dr); $[\alpha]_D^{25}$ –23.1 (*c* 1.0 in $CHCl_3$); ν_{max} 3028 (C−H), 2975 (C−H), 1723 (C=O); δ_H (400 MHz, $CDCl_3$) 0.52−0.67 (1H, m, C(5)H_A), 0.93–1.05 (1H, m, C(4)H_A), 1.05−1.17 (1H, m, C(5)H_B), 1.19–1.32 (3H, m, C(4)H_B, C(6)H_2), 1.37 (3H, d, *J* 7.0, C(α)*Me*), 1.43 (9H, s, CMe_3), 3.07–3.26 (2H, m, C(7)H_2), 3.41 (1H, d, *J* 9.8, C(2)*H*), 3.54−3.62 (1H, m, C(3)*H*), 3.74 (1H, d, *J* 15.2, NC$H_A$$H_B$Ph),

3.85 (1H, d, *J* 15.2, NCH$_A$*H*$_B$Ph), 4.19 (1H, q, *J* 7.0, C(α)*H*), 7.11–7.42 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.2 (C(α)*Me*), 25.3 (*C*(5)), 28.2 (C*Me*$_3$), 29.5 (*C*(4)), 32.8 (*C*(6)), 44.9 (*C*(7)), 50.1 (N*C*H$_2$Ph), 58.3 (*C*(2)), 62.3 (*C*(3)), 62.5 (*C*(α)), 80.4 (*C*Me$_3$), 126.6, 127.0, 127.3, 128.1, 128.2, 128.2, 128.4, 128.6, 129.1 (*o,m,p-Ph*), 137.8, 142.8, 144.8 (*i-Ph*), 172.9 (*C*(1)); *m/z* (ESI$^+$) 506 ([M(^{35}Cl)+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{41}{}^{35}ClNO_2{}^+$ ([M(^{35}Cl)+H]$^+$) requires 506.2820; found 506.2820. Further elution (eluent 30−40 °C petrol/Et$_2$O 10:1) gave **13** as a colourless oil (30 mg, 45%, >99:1 dr); $[\alpha]_D^{25}$ −26.8 (*c* 1.0 in $CHCl_3$); ν_{max} 3028 (C−H), 2974 (C−H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 0.40−0.56 (1H, m, C(5)*H*$_A$), 0.79−1.02 (2H, m, C(5)*H*$_B$, C(4)*H*$_A$), 1.04−1.29 (3H, m, C(6)*H*$_2$, C(4)*H*$_B$), 1.33 (3H, d, *J* 7.0, C(α)*Me*), 1.42 (9H, s, C*Me*$_3$), 2.45 (3H, s, Ar*Me*), 3.37 (1H, d, *J* 9.7, C(2)*H*), 3.52 (1H, ddd, *J* 9.7, 7.0, 4.6, C(3)*H*), 3.65 (2H, app tt, *J* 6.7, 3.3, C(7)*H*$_2$), 3.69 (1H, d, *J* 15.2, NC*H*$_A$H$_B$Ph), 3.81 (1H, d, *J* 15.2, NCH$_A$*H*$_B$Ph), 4.14 (1H, q, *J* 7.0, C(α)*H*), 7.03−7.84 (19H, m, *Ar*, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.0 (C(α)*Me*), 21.6 (Ar*Me*), 23.5 (*C*(5)), 28.0 (C*Me*$_3$), 28.8 (*C*(6)), 29.4 (*C*(4)), 50.0 (N*C*H$_2$Ph), 58.0 (*C*(2)), 61.9 (*C*(3)), *C*(α)), 70.3 (*C*(7)), 80.3 (*C*Me$_3$), 126.5, 126.9, 127.1, 127.9, 128.0, 128.0, 128.3, 128.4, 128.9, 129.8 (*Ar*, *o,m,p-Ph*), 137.6, 142.6, 144.5, 144.7 (*Ar*, *i-Ph*), 172.7 (*C*(1)); *m/z* (ESI$^+$) 642 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{39}H_{48}NO_5S^+$ ([M+H]$^+$) requires 642.3248; found 642.3249.

4.8. *tert*-Butyl (*S,S*)-2-phenyl-2-(piperidin-2'-yl)ethanoate 6

Method A: A mixture of **13** (135 mg, 0.210 mmol, >99:1 dr) and Pd(OH)$_2$/C (50.0 mg, 20% *w*/*w*) in MeOH/H$_2$O/AcOH (20:2:1, 4.00 mL) was stirred under H$_2$ (1 atm) for 16 h then filtered through celite (eluent MeOH) and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL) and washed with 2.0 M aq NaOH (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/MeOH 60:1) gave **6** as a pale yellow oil (25 mg, 44% from **13**, >99:1 dr); $[\alpha]_D^{25}$ −33.7 (*c* 1.0 in $CHCl_3$); ν_{max} 2931 (C−H), 2854 (C−H), 1720 (C=O); δ_H (400 MHz, $CDCl_3$) 0.93−1.05 (1H, m, C(3')*H*$_A$), 1.12−1.27 (2H, m, C(3')*H*$_B$, C(4')*H*$_A$), 1.35 (9H, s, C*Me*$_3$), 1.38−1.49 (1H, m, C(5')*H*$_A$), 1.54−1.60 (1H, m, C(5')*H*$_B$), 1.61−1.72 (1H, m, C(4')*H*$_B$), 2.48 (1H, app s, N*H*), 2.70 (1H, td, *J* 11.8, 2.9, C(6')*H*$_A$), 3.04–3.10 (2H, m, C(6')*H*$_B$, C(2')*H*), 3.37 (1H, d, *J* 10.0, C(2)*H*), 7.21−7.33 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.4 (*C*(4')), 25.9 (*C*(5')), 27.9 (C*Me*$_3$), 29.7 (*C*(3')), 46.9 (*C*(6')), 59.0 (*C*(2')), 59.4 (*C*(2)), 81.1 (*C*Me$_3$), 127.2, 128.5, 128.5 (*o,m,p-Ph*), 137.0 (*i-Ph*), 172.7 (*C*(1)); *m/z* (ESI$^+$) 276 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{26}NO_2{}^+$ ([M+H]$^+$) requires 276.1958; found 276.1956.

Method B − Step 1: Ms_2O (267 mg, 1.53 mmol) was added to a stirred solution of **12** (250 mg, 0.510 mmol, >99:1 dr) and Et_3N (0.30 mL, 2.3 mmol) in Et_2O (5.0 mL) at rt and stirred at rt for 2 h. The reaction mixture was then diluted with H_2O (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried and concentrated in vacuo to give **18** as a pale yellow oil (290 mg, >95:5 dr); δ_H (400 MHz, $CDCl_3$) 0.48−0.62 (1H, m, C(5)H_A), 0.94–1.08 (2H, m, C(4)H_A, C(5)H_B), 1.15–1.31 (3H, m, C(4)H_B, C(6)H_2), 1.36 (3H, d, *J* 6.9, C(α)*Me*), 1.43 (9H, s, CMe_3), 2.89 (3H, s, SO_2Me), 3.41 (1H, d, *J* 9.7, C(2)*H*), 3.52–3.60 (1H, m, C(3)*H*), 3.74 (1H, d, *J* 15.2, NCH_AH_BPh), 3.80–3.90 (3H, m, C(7)H_2, NCH_AH_BPh), 4.19 (1H, q, *J* 6.9, C(α)*H*), 7.02–7.54 (15H, m, *Ph*).

Method B − Step 2: The sample of **18** from the previous step was dissolved in MeOH/AcOH/H_2O (20:2:1, 5 mL). $Pd(OH)_2$/C (100 mg, 20% w/w) was added and the reaction mixture was stirred under H_2 (1 atm) at rt for 16 h then filtered through celite (eluent MeOH) and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL) and the resultant solution was washed with 2.0 M aq NaOH (5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic extracts were dried and concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/MeOH 75:1) gave **6** as a yellow oil (79 mg, 56% from **12**, >99:1 dr).

4.9. Methyl (*S*,*S*)-1-phenyl-2-[*N*-(1')-piperidin-2'-yl]ethanoate hydrochloride [(*S*,*S*)-methylphenidate hydrochloride] 1·HCl

Method A: $SOCl_2$ (50 μL, 0.63 mmol) was added to a stirred solution of **6** (68 mg, 0.21 mmol, >99:1 dr) in MeOH (5.0 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 30 min. The reaction mixture was then heated at 50 °C for 16 h before being concentrated in vacuo to give (*S*,*S*)-methylphenidate hydrochloride **1**·HCl as a white solid (67 mg, quant, >99:1 dr); mp 214−219 °C; {lit.[5b] mp 222−224 °C; lit.[7b] mp 219−221 °C}; $[\alpha]_D^{25}$ −65.0 (*c* 1.0 in MeOH); {lit.[5b] $[\alpha]_D^{20}$ −85.0 (*c* 1.0 in MeOH); lit.[7b] $[\alpha]_D^{20}$ −81.8 (*c* 1.38 in MeOH)}; ν_{max} 3657 (N−H) 2981 (C−H), 1740 (C=O); δ_H (400 MHz, MeOH-d_4) 1.17–1.34 (1H, m, C(3')H_A), 1.32–1.48 (2H, m, C(5')H_A, C(3')H_B), 1.50–1.65 (1H, m, C(4')H_A), 1.66–1.75 (1H, m, C(5')H_B), 1.79 (1H, d, *J* 14.6, C(4')H_B), 3.01 (1H, td, *J* 12.8, 3.3, C(6')H_A), 3.34 (1H, m, C(6')H_B), 3.63 (3H, s, O*Me*), 3.69–3.81 (2H, m, C(2)*H*, C(2')*H*), 7.15–7.36 (5H, m, *Ph*); δ_C (100 MHz, MeOH-d_4) 22.8 (*C*(4')), 23.4 (*C*(5')), 27.8 (*C*(3')), 46.7 (*C*(6')), 53.4 (O*Me*), 55.4 (*C*(2)), 59.3 (*C*(2')), 129.6, 129.8, 130.5 (*o*,*m*,*p*-*Ph*), 135.1 (*i*-*Ph*), 173.3 (*C*(1)); *m/z* (ESI^+) 234 ($[M-Cl]^+$, 100%); HRMS (ESI^+) $C_{14}H_{20}NO_2^+$ ($[M-Cl]^+$) requires 234.1489; found 234.1488.

Method B: $SOCl_2$ (35 μL, 0.44 mmol) was added to a stirred solution of **6** (44 mg, 0.14 mmol) in MeOH (3.5 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 30 min. The reaction mixture was then heated at 50 °C for 16 h before being concentrated in vacuo. The residue was dissolved in H_2O (5 mL) and the resultant solution was washed with Et_2O (10 mL). 1.0 M aq NH_4OH (5 mL) was added to the aqueous layer, which was then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), then dried and concentrated in vacuo. Purification via flash column chromatography (eluent $CHCl_3$/MeOH, 75:1) gave (*S*,*S*)-methylphenidate **1** as a colourless oil (18 mg, 48% from **6**, >99:1 dr);[5i] $[\alpha]_D^{25}$ −54.1 (*c* 0.68 in MeOH); {lit.[5i] $[\alpha]_D^{26}$ −58.8 (*c* 0.68 in MeOH)}; ν_{max} 3657 (N−H), 2981 (C−H), 2854 (C−H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 0.81–1.03 (1H, m, C(3')H_A), 1.14–1.29 (2H, m, C(5')H_A, C(3')H_B), 1.33–1.47 (1H, m, C(4')H_A), 1.51–1.63 (1H, m, C(4')H_B), 1.62–1.74 (1H, m, C(5')H_B), 1.98 (1H, app s, N*H*), 2.69 (1H, td, *J* 11.9, 2.9, C(6')H_A), 3.00–3.18 (2H, m, C(2')*H*, C(6')H_B), 3.44 (1H, d, *J* 10.0, C(2)*H*), 3.64 (3H, s, O*Me*), 7.20–7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.5 (*C*(5')), 26.3 (*C*(4')), 30.2 (*C*(3')), 47.1 (*C*(6')), 52.1 (O*Me*), 58.9 (*C*(2)), 59.1 (*C*(2')), 127.6, 128.7, 128.8 (*o*,*m*,*p*-*Ph*), 136.6 (*i*-*Ph*), 174.0 (*C*(1)); *m/z* (ESI^+) 234 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{14}H_{20}NO_2^+$ ($[M+H]^+$) requires 234.1489; found 234.1488. A sample of **1** (16.9 mg) was treated with HCl (2.0 M in Et_2O) and concentrated in vacuo to give (*S*,*S*)-methylphenidate hydrochloride **1**·HCl as a white solid (19.5 mg, quant from **1**, >99:1 dr); $[\alpha]_D^{25}$ –67.0 (*c* 1.0 in MeOH); {lit.[5b] $[\alpha]_D^{20}$ −85.0 (*c* 1.0 in MeOH); lit.[7b] $[\alpha]_D^{20}$ −81.8 (*c* 1.38 in MeOH)}.

4.9.1. X-ray crystal structure determination for (*S*,*S*)-methylphenidate hydrochloride 1·HCl

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[19]

X-ray crystal structure data for **1**·HCl [$C_{14}H_{20}ClNO_2$]:[13] M = 269.77, monoclinic, space group $P\ 2_1$, a = 9.3195(4) Å, b = 7.2618(3) Å, c = 11.0016(7) Å, β = 109.277(6)°, V = 702.80(7) Å^3, Z = 2, μ = 2.36 mm^{-1}, colourless block, crystal dimensions = 0.12 × 0.18 × 0.18 mm^3. A total of 2916 unique reflections were measured for $4 < \theta < 77$ and 2710 reflections were used in the refinement. The final parameters were wR_2 = 0.135 and R_1 = 0.088 [I>–3.0σ(I)], with Flack x parameter = +0.02(3).[14]

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[11] The regioselectivity of ring-opening of 2,3-disubstituted aziridinium ions is a complex process, which can be affected by a range of factors including electronic, stereoelectronic and steric effects. We have also shown that the relative configuration of the C(2) and C(3) stereogenic centres is important in determining the regioselectivity of ring-opening for this class of aziridinium ions. See Ref 9d.

[12] For *anti*-α-hydroxy-β-amino esters ^{1}H NMR $^{3}J_{2,3}$ coupling constants of ~4.0 Hz are usually observed whereas values of ~10.0 Hz are indicative of *syn*-α-hydroxy-β-amino esters; see: Ref 9c.

[13] Crystallographic data (excluding structure factors) for **1**·HCl and **4** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 1951733 and 1951734, respectively.

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[15] The regioselectivity in this reaction is in contrast to that of ring-opening of similar aziridinium species with H_2O, which is presumably dictated by electronic effects in the positively charged transition state; see Refs 9a and 9d.

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- Asymmetric synthesis of (*S*,*S*)-methylphenidate hydrochloride in 15% overall yield in only 8 steps from 1,5-pentanediol
- Stereospecific and regioselective ring-opening of an in situ formed aziridinium intermediate with phenylmagnesium bromide
- Conversion of an α-hydroxy-β-amino ester into the corresponding α-phenyl-β-amino ester with overall retention of configuration
- Enantiopure aziridinium intermediates as substrates for the generation of stereodefined C–C bonds, providing access to α-substituted-β-amino ester substrates that are not accessible via enolate alkylation chemistry

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: