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TETRAHEDRON: *ASYMMETRY*

Asymmetric syntheses of *trans*-3,4-disubstituted 2-piperidinones and piperidines

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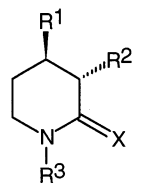
Abstract—A convenient and practical method for the preparation of chiral 4-aryl-2-piperidinone from 3-arylglutaric anhydride and (*S*)-methylbenzylamine is described. Acylation or alkylation at the α-carbon of the chiral 4-aryl-2-piperidinone product afforded chiral *trans*-3,4-disubstituted 2-piperidinone derivatives and reduction of the chiral 2-piperidinones with lithium aluminum hydride provided the corresponding enantiomerically pure *trans*-3,4-disubstituted piperidines. This methodology has been successfully applied to the synthesis of the anti-depressant paroxetine.

1. Introduction

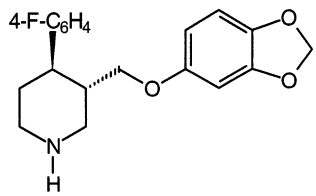
Chiral piperidine derivatives constitute many natural products and pharmacologically active compounds.[1,2] For example, as a *trans*-3,4-disubstituted piperidine derivative, paroxetine is a potent selective serotonin (5-hydroxytryptamine) re-uptake inhibitor and has been widely used as an anti-depressant and anti-Parkinson agent.[2,3] Chiral 2-piperidinones have been generally regarded as the precursors of the corresponding piperidines and δ-amino acids.

Several procedures have been used for the preparation of these chiral *trans*-3,4-disubstituted piperidines and their precursors. Physical and enzymatically assisted kinetic resolution are still the most common methods employed. For the preparation of homochiral paroxetine, methods such as the selective recrystallisation of diastereomeric salts,[3a–d,4] the biocatalytic kinetic resolution of racemic or prochiral esters,[3e–f] and a chiral auxiliary assisted asymmetric Michael addition[3g,h,5] have been reported. However, some racemic *trans*-3,4-piperidine derivatives could not be easily resolved because their diastereomeric salts did not form good enough crystals to be selectively crystallised,[4] and although enzymatic processes gave enantiomerically pure 3-substituted piperidine derivatives, the requisite use of chromatography for purification reduces the viability of large-scale processes.[6]

Recently, the asymmetric synthesis of specific chiral 3- or 4-substituted and 3,4-disubstituted 2-piperidinones has been published in the literature.[3g,h,5] These methodologies include the chiral auxiliary assisted Michael addition and the transformation of natural products. However, the synthetic methods available for the



trans-3,4-disubstituted piperidine (X = H, H) and 2-piperidinone (X = O)



trans-(-)-(3*S*,4*R*)-paroxetine

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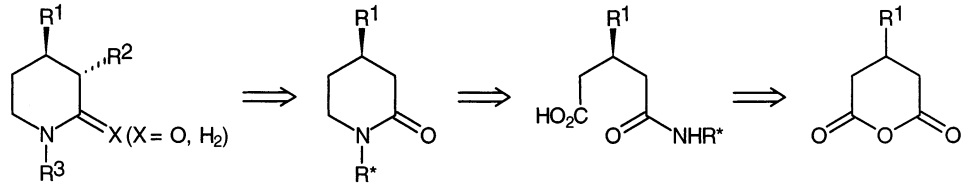


Scheme 1.

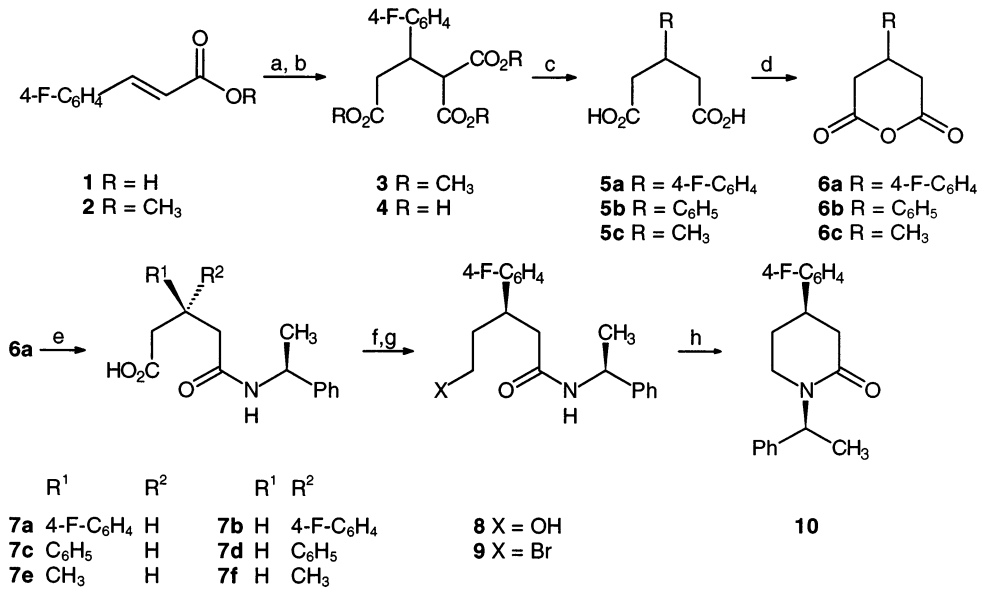
preparation of chiral 3,4-disubstituted 2-piperidinones and piperidines are still limited. Therefore, we decided to develop a convenient method for the preparation of chiral 2-piperidinones and their corresponding piperidine derivatives.

Herein, we report a chiral auxiliary assisted diastereoselective synthesis of chiral 4-substituted and *trans*-3,4-disubstituted 2-piperidinones from 3-substituted glutaric anhydrides and (*S*)-methylbenzylamine. As shown in Scheme 1, this new method can be used for the synthesis of chiral 4-aryl-2-piperidinones, *trans*-3,4-disubstituted 2-piperidinones and piperidines. The methodology developed was subsequently applied to the synthesis of homochiral paroxetine.

2. Results and discussion

The synthetic procedure is shown in Scheme 2. Diacid **5a** was prepared from 4-fluorocinnamic acid methyl ester **2** in three steps (Michael addition to ester **2**, hydrolysis of triester **3**, and decarboxylation of acid **4**).[7,8] The prochiral 3-substituted glutaric anhydrides **6a–6c** were then obtained by dehydration of the commercially available diacids **5a–5c** in acetyl chloride.[9] The anhydrides **6a** and **6b** were purified by recrystallisation and **6c** was purified by distillation.

Desymmetrisation of *meso*-3-substituted glutaric anhydrides **6a–6c** with (*S*)-methylbenzylamine (99% *e.e.*) was effected in toluene at −78°C (Scheme 2 and Table



Scheme 2. Reagents and conditions: (a) sodium methoxide, dimethyl malonate, methanol, reflux, 20 h, 70%; (b) 1N sodium hydroxide, reflux, 20 h; (c) concentrated hydrochloric acid, reflux, 20 h, 70% (two steps); (d) acetyl chloride, reflux, 20 h, 90%; (e) (*S*)-methylbenzylamine, triethylamine, toluene, −78°C, 10 h, room temperature 10 h, 70%; (f) triethylamine, isobutyl chloroformate, tetrahydrofuran, −78 to 0°C, 20 h; then, sodium borohydride, water, 0–25°C, 20 h, 86%; (g) phosphorus tribromide, concentrated hydrobromic acid, 0–25°C, 4 days, 70%; (h) sodium hydride, tetrahydrofuran, refluxed, 20 h, 85%.

Table 1. Yields and diastereoselectivities in the reactions of **6a–6c** with (*S*)-methylbenzylamine

Entry	Anhydrides	Major product	Yield (%)	Diastereoselectivity (de%)
1	**6a**	**7a**	70[a]	95[a]
2	**6b**	**7c**	67[a]	94[a]
3	**6c**	**7e**	76[a]	>99[a,b]

[a] The first crop of the recrystallised product.
[b] The crude product.

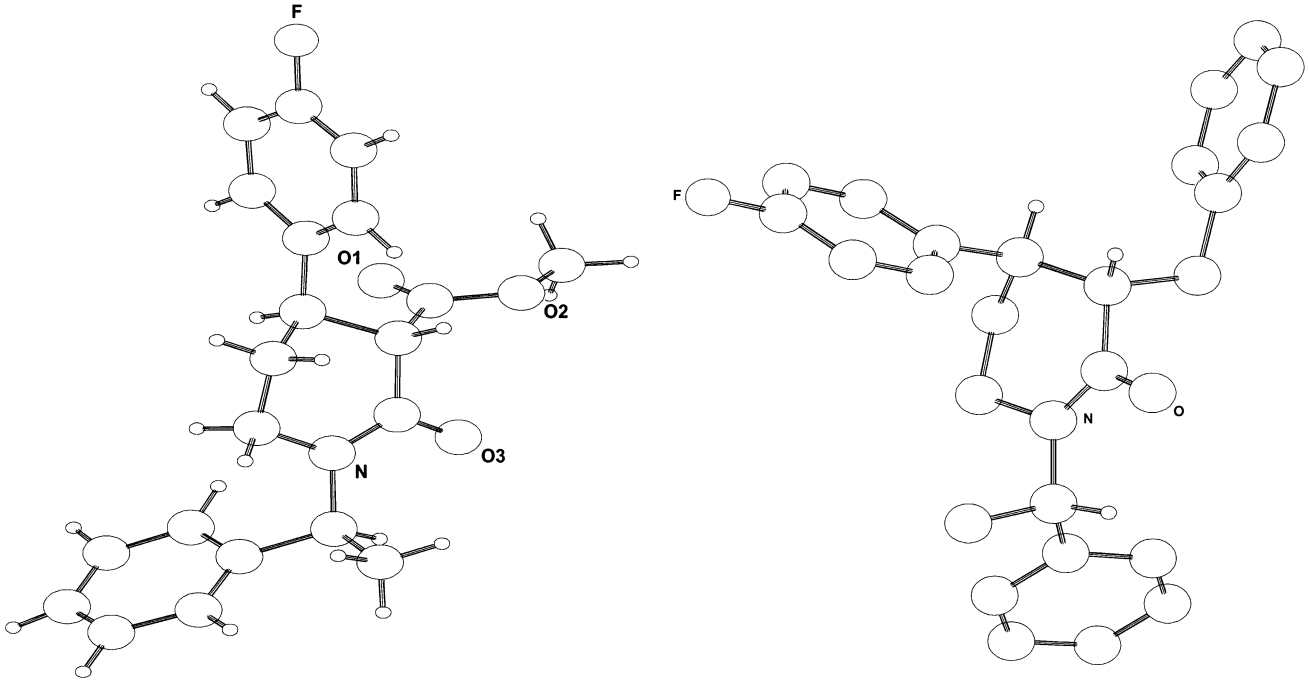


Figure 1. X-Ray crystal structures of compounds **11a** (left) and **11b** (right). Only hydrogens on the stereogenic carbon centres are displayed.

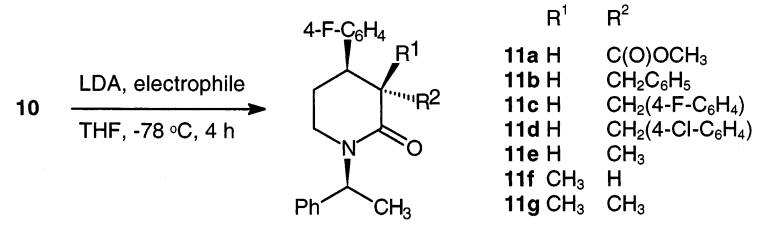
1) according to the procedure described by Karanewsky.[10] In the amidation of 3-arylglutaric anhydrides **6a**–**6b**, mixtures of hemiamides **7a** (or **7c**) and **7b** (or **7d**) were obtained in 98% yield. The major product was assigned as the hemiamides **7a** and **7c** according to a similar compound in the literature,[10] and the absolute configuration was later identified by X-ray crystallography of compounds **11a**–**11b** (Fig. 1). The proton NMR spectrum showed that the ratio of the two diastereomers **7a** and **7b** in the crude product was about 4.5–5.5:1 (60–70% *d.e.*, measured by relative integration of the methyl doublet). We found that selectivity was not improved even if 2 equivalents of (*S*)-methylbenzylamine was used, but the ratio of **7a**:**7b** was lowered to 2:1 if excess triethylamine (based on (*S*)-methylbenzylamine) was added. The diastereoselectivity of the crude **7c** was slightly lower, with a *d.e.* of 50–55%. The diastereomeric purity of the major products **7a** and **7c** was enhanced to a *d.e.* of 94–95% (67–70% yield) by one recrystallisation. The second and third crops which contained mixtures of diastereomers (e.g. **7a** and **7b**, 28% yield) were treated with concentrated hydrochloric acid, and the corresponding starting diacids **5a** and **5b** were recovered.

Amidation of 3-methylglutaric anhydride **6c** was much more selective under the same reaction conditions. No diastereomer **7f** was detected in the proton NMR spectrum of the crude product, and the hemiamide **7e** was obtained as the sole product with >99% *d.e.* in 76% yield after a single recrystallisation.

The carboxyl group of hemiamide **7a** was converted to the primary alcohol **8** in satisfactory yield by reduction of the corresponding mixed anhydride with sodium borohydride.[11] Bromination of alcohol **8** with phosphorus tribromide and hydrobromic acid then gave bromide **9** in moderate yield. Treatment of **9** with sodium hydride suspended in refluxing tetrahydrofuran afforded chiral 2-piperidinone **10** in 85% yield after recrystallisation. The proton NMR spectrum showed that the recrystallised 2-piperidinone **10** was diastereomerically pure with a *d.e.* of >99%.

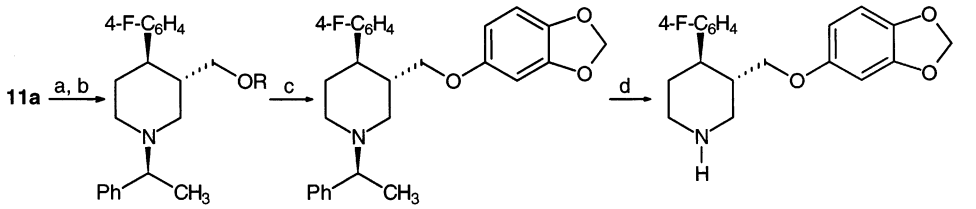
Alkylation or acylation at the α-carbon of 2-piperidinone **10** was effected by treatment with an excess of lithium diisopropylamide and 1.4–1.5 equivalents of methyl chloroformate or benzyl bromide. *trans*-3,4-Disubstituted 2-piperidinones **11a**–**11c** were obtained in good to moderate yields with excellent diastereoselectivity (Scheme 3). X-Ray crystallography and the ^{1}H NMR spectra of **11a**–**11b** (Fig. 1) showed that only the *trans*-diastereomer was obtained in each case. However, reactions with halides such as 4-substituted benzyl halides, methyl iodide and other alkyl iodides were unsatisfactory. For example, the yield was low if 4-chlorobenzyl bromide was used as an electrophile. Mixtures of 3-methyl and 3,3-dimethyl substituted 2-piperidinones **11e**–**11g** were obtained if 1.4 equivalents of methyl iodide was used, whilst only 3,3-dimethyl-2-piperidone **11g** was obtained if 2.4 equivalents of methyl iodide was added.

These homochiral *trans*-3,4-disubstituted 2-piperidinones **11** can be used as the precursors for the preparation of the corresponding chiral 3,4-disubstituted piperidines and δ-amino acids. The synthesis of chiral paroxetine, a 3,4-disubstituted piperidine derivative, exemplified the study (Scheme 4). Reduction of 2-piperidinone **11a** with lithium aluminum hydride provided 3-hydroxymethyl piperidine **12**. Protection of the hydroxyl group of compound **12**, followed by transformation of the resulting methanesulfonate **13** with sesamol and



Entry	electrophile	temp (°C)	product(s)	yield (%)	*d.e.* (%)
1	$CH_3OC(O)Cl$, 1.5 eq	-78	**11a**	78	99
2	$C_6H_5CH_2Br$, 1.4 eq	-78	**11b**	77	99
3	4-F-$C_6H_4CH_2Br$, 1.4 eq	-78	**11c**	40	99
4	4-Cl-$C_6H_4CH_2Br$, 1.4 eq	-78	**11d**	<5	--
5	CH_3I, 1.4 eq	-78	**11e/f/g**	68	--
6	CH_3I, 2.4 eq	-30	**11g**	75	--

Scheme 3.



Scheme 4. Reagents and conditions: (a) lithium aluminum hydride, tetrahydrofuran, reflux, 72 h, 65%; (b) methanesulfonyl chloride, dichloromethane, rt, 20 h; (c) (i) sesamol, sodium, propanol, reflux, 36 h; (ii) hydrochloric acid, 64%; (d) H_2, Pd–C, methanol, 68%.

sodium propoxide, provided aryl ether **14a** as an oily product. Ether **14a** was treated with hydrochloric acid, and hydrochloride salt **14b** was purified by recrystallisation. Hydrogenolysis removed the chiral auxiliary in ether **14b** to provide paroxetine hydrochloride salt **15** as an oily form. Although the recrystallised hydrochloride salt could be obtained from methanol and ether in 68% yield, some of the salt remained in the mother liquor. The recrystallised compound **15** had identical ^1H NMR spectrum and specific rotation value ($[\alpha]_D^{25}$ −88.6 (*c* 1.0, CH_3OH)) to an authentic sample of paroxetine extracted from commercial Seroxat® ($[\alpha]_D^{22}$ −89.4 (*c* 1.6, CH_3OH)). It is notable that the specific rotation value of paroxetine **15** obtained in this procedure is higher than that of Amat's compound ($[\alpha]_D^{22}$ +81.7 (*c* 1.3, CH_3OH)).[5a,b]

3. Conclusion

We have developed a convenient and practical four-step method for the preparation of diastereomerically pure 4-aryl-2-piperidinones **10** from 3-arylglutaric anhydride **6** and (*S*)-methylbenzylamine. Acylation or alkylation of **10** provided chiral *trans*-3,4-disubstituted 2-piperidinones **11a**–**11c** in good yield and excellent diastereoselectivity. These chiral *trans*-3,4-disubstituted 2-piperidinone derivatives can then be used as precursors for the preparation of the corresponding chiral piperidines and δ-amino acids. For example, reduction of 2-piperidinone **11a** with lithium aluminum hydride provided chiral piperidine **12**. This methodology has been successfully applied to the synthesis of the anti-depressant paroxetine, which was obtained in high enantiomeric purity using this methodology.

4. Experimental

4.1. General

All reactions were carried out under nitrogen unless otherwise stated. Tetrahydrofuran was dried by distillation from potassium benzophenone ketyl under a nitrogen atmosphere before use. Thin layer chromatography was performed on 0.2 mm aluminum sheets precoated with silica gel 60. Visualisation was achieved with UV light, 5% ninhydrin or 5% vanillin ethanolic solution. Flash chromatography was carried out using 0.040–0.063 mm (230–400 mesh) silica gel 60. The specific rotation values were measured at the sodium D-line (589 nm) and reported as $[\alpha]_D^{25}$ (*c* g/100 mL, solvent). Chemical shifts of proton and carbon-13 NMR spectra were reported in ppm relative to $Si(CH_3)_4$. Coupling constants are reported in Hz.

4.2. Dimethyl 3-(4-fluorophenyl)-2-methoxycarbonylpentanedioate 3

To a suspension of 4-fluorocinnamic acid **1** (25 g, 0.15 mol) in methanol (300 mL) at room temperature was added dropwise thionyl chloride (40 mL, 0.55 mol). The brown solution was stirred at room temperature for 18 h, and then evaporated to dryness. The crude compound was diluted with ethyl acetate, washed with saturated sodium hydrocarbonate and brine, and dried over magnesium sulfate. The viscous mass was distilled in vacuo to give the pure ester **2** (27 g, 99%).

To a solution of sodium (4.60 g, 0.20 mol) in methanol (100 mL) in an ice bath was added dropwise dimethyl malonate (27.0 g, 0.20 mol) in methanol (30 mL). After stirring for 20–30 min, a solution of ester **2** (27.0 g, 0.15 mol) in methanol (30 mL) was added dropwise into the solution at room temperature. The mixture was gently refluxed overnight, and then concentrated to dryness. The viscous mass was diluted with ethyl acetate and washed with a 1N hydrochloric acid solution. The aqueous solution was back extracted several times with ethyl acetate. The organic layer was combined, washed with brine solution, dried over magnesium sulfate and concentrated to afford the crude product **3** which was used directly for the next step or recrystallised from ethyl acetate and hexanes to afford a white solid (31.5 g, 67%): mp 77.5–78.0°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25 (m, 2H), 6.97 (t, $J=8.6$ Hz, 2H), 3.93 (td, $J=5.0$, 9.7 Hz, 1H), 3.74 (d, $J=9.9$ Hz, 1H), 3.75 (s, 3H), 3.54 (s, 3H), 3.50 (s, 3H), 2.86 (dd, $J=4.9$, 15.7 Hz, 1H), 2.72 (dd, $J=9.4$, 15.7 Hz, 1H).

4.3. 3-(4-Fluorophenyl)pentanedioic acid 5a

A suspension of triester **3** (31.5 g, 0.10 mol) in 2N aqueous sodium hydroxide (80 mL) was gently refluxed overnight. The solution was cooled to room temperature and acidified with concentrated hydrochloric acid to pH 0–1, and then refluxed overnight to effect complete decarboxylation. The aqueous solution was distilled to remove most of the water, then extracted with ethyl acetate. After drying over magnesium sulfate and evaporating the solvent, the crude product was recrystallised from ethyl acetate and hexanes to afford diacid **5a** (15.5 g, 68%): mp 146.0–146.5°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.23 (m, 2H), 6.96 (t, $J=8.6$ Hz, 2H), 5.47 (bs, 1H), 3.62 (m, 1H), 2.72 (dd, $J=6.8$, 15.6 Hz, 1H), 2.56 (dd, $J=8.2$, 15.7 Hz, 1H).

4.4. 4-(4-Fluorophenyl)dihydropyran-2,6-dione 6a

A suspension of diacid **5a** (40 g, 0.18 mol), in acetyl chloride (50 mL, 0.68 mol) was gently refluxed overnight. After evaporation of acetyl chloride, the viscous mass was dissolved in ethyl acetate, and then filtered through a silica gel pad. The solution was concentrated and diluted with ethyl acetate and hexanes, then kept in a freezer overnight. The white solid was collected and dried in vacuo to give the title compound (33 g, 90%): mp 98.5–99.0°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.25–7.00 (m, 4H), 3.40 (m, 1H), 3.11 (dd, $J=4.5$, 17.2 Hz, 1H), 2.83 (dd, $J=11.1$, 17.0 Hz, 1H). Anal. calcd for $C_{11}H_9FO_3$: C, 63.46; H, 4.36. Found: C, 63.37; H, 4.34%.

4.5. (3*S*,1′*S*)-3-(4-Fluorophenyl)-5-oxo-5-(1′-phenylethylamino)pentanoic acid 7a

To a solution of (*S*)-methylbenzylamine (99% *e.e.*, Acros or Aldrich 5.25 mL, 40.72 mmol) in toluene (200 mL) at −78°C was added dropwise a solution of anhydride **6a** (5.0 g, 24.02 mmol) in toluene (100 mL). Triethylamine (3.5 mL, 25.11 mmol) was then added dropwise. The mixture was stirred and allowed to warm to room temperature overnight. After evaporation of toluene, the mixture was stirred with a solution of 1N hydrochloric acid (50 mL), and then extracted with hot ethyl acetate. The organic extracts were combined, washed with brine, dried over magnesium sulfate and evaporated to dryness. The crude product was recrystallised to furnish the title compound as a colourless solid in the first crop (5.50 g, 70% yield, 95% *d.e.*): mp 195.0–195.5°C; $[\alpha]_D^{25}$ −78.8 (*c* 1.0, CH_3OH); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30–7.00 (m, 7H), 6.95 (t, $J=8.7$ Hz, 2H), 5.60 (m, 1H), 4.94 (quint, $J=6.9$ Hz, 1H), 3.58 (m, 1H), 2.75–2.25 (m, 4H), 1.26 (d, $J=6.9$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$/CD_3OD) δ 176.8, 173.6, 164.3, 145.8, 140.8, 131.6, 131.0, 129.7, 128.6, 117.8, 51.1, 45.3, 43.0, 41.1, 23.9. Anal. calcd for $C_{19}H_{20}FNO_3$: C, 69.29; H, 6.12; N, 4.25. Found: C, 69.07; H, 6.09; N, 3.83. The second and third crops were treated with concentrated hydrochloric acid to recover diacid **5a** (2.25 g, 28%).

4.6. (3*S*,1′*S*)-5-Oxo-3-phenyl-5-(1′-phenylethylamino)pentanoic acid 7c

Synthesised according to the procedure for **7a**, 67% yield, 94% *d.e.*, colourless solid: mp 181.0–181.2°C; $[\alpha]_D^{25}$ −81.2 (*c* 1.0, CH_3OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.20 (m, 6H), 7.17 (d, $J=6.9$ Hz, 2H), 7.13 (d, $J=7.1$ Hz, 2H), 5.49 (d, $J=7.8$ Hz, 1H), 5.00 (quint, $J=7.3$ Hz, 1H), 3.61 (quint, $J=6.3$ Hz, 1H), 2.81 (dd, $J=8.4$, 14.9 Hz, 1H), 2.70–2.60 (m, 2H), 2.52 (dd, $J=8.4$, 13.9 Hz, 1H), 1.25 (d, $J=6.8$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$/CD_3OD) δ 174.1, 170.8, 142.8, 142.2, 128.2, 128.1, 126.7, 126.5, 126.1, 125.7, 48.2, 42.4, 40.1, 38.9, 20.9. Anal. calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.52; H, 6.78; N, 4.41%.

4.7. (3*S*,1′*S*)-3-Methyl-5-oxo-5-(1′-phenylethylamino)pentanoic acid 7e

Synthesised according to the procedure for **7a**, 76% yield, 99% *d.e.*, colourless solid: mp 118.6–118.8°C; $[\alpha]_D^{25}$ −88.8 (*c* 1.0, CH_3OH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.26 (m, 5H), 6.03 (d, $J=7.4$ Hz, 1H), 5.16 (quint, $J=7.3$ Hz, 1H), 2.50–2.38 (m, 2H), 2.35 (dd, $J=6.2$, 14.2 Hz, 1H), 2.31 (dd, $J=6.6$, 14.2 Hz, 1H), 2.23 (dd, $J=6.7$, 13.9 Hz, 1H), 1.52 (d, $J=6.9$ Hz, 3H), 1.07 (d, $J=6.6$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$/CD_3OD) δ 175.2, 171.9, 143.3, 128.4, 127.1, 125.9, 48.6, 42.6, 40.6, 28.2, 21.7, 19.4. Anal. calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.59; H, 7.66; N, 5.49%.

4.8. (3*R*)-3-(4-Fluorophenyl)-5-hydroxypentanoic acid (1*S*)-1-phenylethylamide 8

To a solution of **7a** (5 g, 15.85 mmol) in tetrahydrofuran (200 mL) at room temperature was added triethylamine (3 mL, 21.52 mmol). The solution was stirred for 60 min at room temperature and then cooled to −78°C in a dry ice-acetone bath. To this solution was added dropwise isobutyl chloroformate (2.6 mL, 20.04 mmol). The suspension was stirred from −78°C to room temperature overnight. The mixture was filtered through a Celite and silica gel pad and washed with a small amount of tetrahydrofuran. To this solution in an ice bath was added sodium borohydride (2.0 g, 52.87 mmol), followed by dropwise addition of water (10 mL). Carbon dioxide gas was evolved violently. The reaction mixture was stirred for 2–4 h and filtered through a Celite pad. After evaporation of the solvent, the aqueous layer was extracted several times with ethyl acetate. The organic extracts were combined, washed with brine, dried over magnesium sulfate and concentrated. The solid was recrystallised from ethyl acetate and hexanes to afford the title compound as a colourless solid (4.3 g, 86%): mp 170.0–170.5°C; $[\alpha]_D^{25}$ −86.4 (*c* 1.0, CH_3OH); ^1H NMR (200 MHz, $CDCl_3$) δ 7.40–7.10 (m, 7H), 6.98 (t, $J=8.7$ Hz, 2H), 5.51 (br d, $J=7.7$ Hz, 1H), 5.00 (quint, $J=7.4$ Hz, 1H), 3.60–3.50 (m, 2H), 3.33 (m, 1H), 2.55 (dd, $J=6.6$, 14.2 Hz, 1H), 2.38 (dd, $J=8.6$, 14.2 Hz, 1H), 1.95–1.75 (m, 2H), 1.27 (d, $J=6.9$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 161.6, 142.9, 139.6, 128.9, 128.6, 127.4, 126.1, 115.4, 60.1, 48.6, 44.0, 38.9, 38.4, 21.3. Anal. calcd for $C_{19}H_{22}FNO_2$: C, 72.36; H, 7.03; N, 4.44. Found: C, 72.35; H, 6.83; N, 4.33%.

4.9. (3*S*)-5-Bromo-3-(4-fluorophenyl)pentanoic acid (1*S*)-1-phenylethylamide 9

To a solution of alcohol **8** (4.5 g, 14.27 mmol) in dry ethyl ether (250 mL) in an ice bath was added dropwise phosphorous tribromide (1.7 mL, 17.90 mmol). After stirring for 3 days in an ice bath, conc. hydrobromic acid (0.5 mL) was added to the mixture. The resulting solution was allowed to stir at room temperature overnight. Ice (100 mL) was added to quench the reaction. The white solid precipitate was collected, dissolved in ethyl acetate, washed with saturated sodium hydrogen carbonate solution and saturated brine. The organic layer was filtered through a silica gel pad. After evaporation of solvent, the crude solid was recrystallised from ethyl acetate and hexanes to afford the title compound as a white solid (3.8 g, 70%): mp 156.5–157.5°C; $[\alpha]_D^{25}$ −38.2 (*c* 1.0, CH_3OH); ^1H NMR (200 MHz, $CDCl_3$) δ 7.40–7.10 (m, 7H), 6.99 (m, 2H), 5.52 (br d, $J=7.6$ Hz, 1H), 4.98 (m, 1H), 3.35–3.20 (m, 2H), 3.05 (m, 1H), 2.51 (dd, $J=6.3$, 14.0 Hz, 1H), 2.37 (dd, $J=8.7$, 14.0 Hz, 1H), 2.25–2.05 (m, 2H), 1.25 (d, $J=6.9$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 161.8, 142.8, 137.7, 129.1, 128.6, 127.4, 126.1, 115.7, 48.6, 44.0, 40.6, 38.7, 30.9, 21.3. Anal. calcd for $C_{19}H_{21}BrFNO$: C, 60.33; H, 5.60; N, 3.70. Found: C, 60.57; H, 5.54; N, 3.82%.

4.10. (4*R*,1′*S*)-4-(4-Fluorophenyl)-1-(1′-phenylethyl)-piperidin-2-one 10

To a solution of **9** (3.5 g (9.25 mmol) in dry tetrahydrofuran (40 mL) at room temperature was added a suspension of sodium hydride (80% dispersion in mineral oil, 0.7 g, 23.33 mmol) in dry tetrahydrofuran (10 mL). The mixture was heated at 65–75°C overnight. After cooling to room temperature, the reaction mixture was slowly quenched in an ice bath with methanol (10 mL). After evaporation of solvent, the residue was diluted with ethyl acetate and then washed with brine. The organic layer was collected and filtered through a silica gel pad. After removal of solvent, the crude solid was recrystallised from ethyl acetate and hexanes to afford the title compound as colourless crystals (2.4 g, 87%): mp 163.5–164.0°C; $[\alpha]_D^{25}$ −108.4 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.36–7.25 (m, 5H), 7.13 (m, 2H), 7.00 (m, 2H), 6.18 (q, $J=7.08$ Hz, 1H), 3.16–2.87 (m, 2H), 2.87–2.69 (m, 2H), 2.55 (dd, $J=10.1$, 17.4 Hz, 1H), 2.05–1.78 (m, 2H), 1.51 (d, $J=7.1$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 161.6, 140.0, 139.3, 128.5, 128.0, 127.6, 127.4, 115.5, 49.8, 40.3, 39.6, 37.5, 30.3, 15.1. Anal. calcd for $C_{19}H_{20}FNO$: C, 76.74; H, 6.78; N, 4.71. Found: C, 76.93; H, 6.82; N, 4.30%.

4.11. (3*S*,4*R*,1′*S*)-4-(4-Fluorophenyl)-3-methoxycarbonyl-1-(1′-phenylethyl)piperidin-2-one 11a

To a stirred solution of lactam **10** (2 g, 6.72 mmol) in tetrahydrofuran (50 mL) at −78°C was added dropwise a solution of lithium diisopropylamide in cyclohexane (1.5 M, 19.5 mL, 29.25 mmol). After 1 h, methyl chloroformate (0.8 mL, 10.35 mmol) was added dropwise. The resultant solution was stirred at −78°C for 4 h and quenched at this temperature with aqueous ammonium chloride. The mixture was concentrated and the aqueous layer was extracted with ethyl acetate. The combined organic extract was washed with brine, dried over magnesium sulfate, filtered and concentrated to afford a yellow viscous oil which slowly solidified on standing. Recrystallisation from ethyl acetate and hexanes gave the title compound as white needles (1.85 g, 78%): mp 73.5–74.5°C; $[\alpha]_D^{25}$ −181.2 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.30 (m, 5H), 7.20–7.16 (m, 2H), 7.06–7.00 (m, 2H), 6.17 (q, $J=7.0$ Hz, 1H), 3.70 (s, 3H), 3.64 (d, $J=10.2$ Hz, 3H), 3.39 (td, $J=3.5$, 10.7 Hz, 1H), 3.17 (dt, $J=4.9$, 12.6 Hz, 1H), 2.88 (m, 1H), 2.05 (m, 1H), 1.96 (m, 1H), 1.57 (d, $J=7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 165.4, 161.9, 139.4, 137.4, 128.6, 128.3, 127.5, 115.7, 56.6, 52.3, 50.4, 41.4, 40.5, 29.4, 15.0. Anal. calcd for $C_{21}H_{22}FNO_3$: C, 70.97; H, 6.24; N, 3.94. Found: C, 70.97; H, 6.17; N, 4.01%.

4.12. (3*S*,4*R*,1′*S*)-4-(4-Fluorophenyl)-1-(1′-phenylethyl)-3-phenylmethylpiperidin-2-one 11b

Synthesised according to the procedure for **11a**. Recrystallisation from ethyl acetate and hexanes gave the title compound as colourless crystals (78% yield): mp 156.8–157.0°C; $[\alpha]_D^{25}$ −90.0 (*c* 1.0, $CHCl_3$); ^1H NMR (500

MHz, $CDCl_3$) δ 7.32–7.13 (m, 12H), 7.05 (t, $J=8.5$ Hz, 2H), 6.17 (q, $J=7.0$ Hz, 1H), 3.47 (dd, $J=5.2$, 13.7 Hz, 1H), 3.03–2.96 (m, 2H), 2.76–2.71 (m, 2H), 2.55 (m, 1H), 1.83–1.72 (m, 2H), 1.54 (d, $J=7.1$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.2, 162.0, 140.2, 139.7, 139.4, 130.4, 129.1, 128.7, 128.6, 127.9, 127.6, 127.2, 126.6, 115.9, 50.9, 49.5, 41.4, 41.0, 35.5, 31.3, 15.3. Anal. calcd for $C_{26}H_{26}FNO$: C, 80.59; H, 6.76; N, 3.61. Found: C, 80.77; H, 6.76; N, 3.48%.

4.13. (3*S*,4*R*,1′*S*)-4-(4-Fluorophenyl)-3-(4-fluorophenyl)-methyl-1-(1′-phenylethyl)piperidin-2-one 11c

Synthesised according to the procedure for **11a**. Recrystallisation from ethyl acetate and hexanes gave the title compound as colourless crystals (40% yield): mp 124.6–125.0°C; $[\alpha]_D^{25}$ −89.6 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.26 (m, 3H), 7.16 (d, $J=7.1$ Hz, 2H), 7.13–7.08 (m, 4H), 7.03 (t, $J=8.6$ Hz, 2H), 6.92 (t, $J=8.7$ Hz, 2H), 6.13 (q, $J=7.0$ Hz, 1H), 3.42 (dd, $J=4.9$, 13.8 Hz, 1H), 3.00–2.95 (m, 2H), 2.69–2.62 (m, 2H), 2.55 (m, 1H), 1.80–1.76 (m, 2H), 1.54 (d, $J=7.1$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 161.6, 161.6, 139.8, 139.2, 134.6, 131.4, 128.7, 128.4, 127.4, 127.3, 115.7, 114.9, 50.6, 49.2, 41.2, 40.7, 34.1, 31.2, 15.2. Anal. calcd for $C_{26}H_{25}F_2NO$: C, 77.01; H, 6.21; N, 3.45. Found: C, 77.07; H, 6.21; N, 3.27%.

4.14. (4*R*,1′*S*)-3,3-Dimethyl-4-(4-fluorophenyl)-1-(1′-phenylethyl)piperidin-2-one 11g

Synthesised according to the procedure for **11a** (with 2.4 equiv. of methyl iodide used as electrophile). Recrystallisation from ethyl acetate and hexanes gave the title compound as a colourless solid (75% yield): mp 102.2–102.6°C; $[\alpha]_D^{25}$ −31.6 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 7.12 (dd, $J=5.5$, 8.5 Hz, 2H), 7.01 (t, $J=8.6$ Hz, 2H), 6.16 (q, $J=7.0$ Hz, 1H), 3.18 (m, 1H), 2.84 (dd, $J=2.7$, 11.5 Hz, 1H), 2.78 (m, 1H), 2.17 (m, 1H), 1.90 (m, 1H), 1.56 (d, $J=7.1$ Hz, 3H), 1.30 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 162.6, 140.3, 136.9, 130.3, 128.5, 127.5, 127.3, 114.7, 50.4, 48.6, 42.9, 40.6, 27.0, 25.3, 22.2, 15.0. Anal. calcd for $C_{21}H_{24}FNO$: C, 77.51; H, 7.43; N, 4.30. Found: C, 77.90; H, 7.43; N, 4.18%.

4.15. (3*S*,4*R*,1′*S*)-4-(4-Fluorophenyl)-3-hydroxymethyl-1-(1′-phenylethyl)piperidine 12

To a suspension of lithium aluminum hydride (6 g, 158.10 mmol) in tetrahydrofuran (150 mL) under nitrogen in an ice bath was added dropwise a solution of ester **11a** (5.6 g, 15.67 mmol) in tetrahydrofuran (50 mL). The mixture was stirred under reflux for 3 days and treated with water (10 mL), 15% sodium hydroxide solution (6 mL), and water (25 mL) in an ice bath. After filtration of precipitates, the organic solution was washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo to afford the crude product as a pale yellow solid. Recrystallisation from ethyl acetate and hexanes gave the title compound as colourless crystals (3.2 g, 65%): mp 130.0–131.0°C; $[\alpha]_D^{25}$ −17.4 (*c* 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.40–7.10 (m, 7H), 7.05–6.90 (m, 2H), 3.51 (q, $J=6.78$ Hz, 1H), 3.45–3.34 (m, 2H), 3.23 (m, 1H), 2.89 (m, 1H), 2.20 (m, 1H), 2.05–1.80 (m, 4H), 1.80–1.65 (m, 2H), 1.44 (d, $J=6.8$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4, 143.2, 140.3, 128.8, 128.2, 127.8, 127.0, 115.3, 65.1, 63.9, 54.7, 50.6, 44.4, 34.6, 19.6. Anal. calcd for $C_{20}H_{24}FNO$: C, 76.65; H, 7.72; N, 4.47. Found: C, 76.86; H, 7.77; N, 4.58%.

4.16. (3*S*,4*R*,1′*S*)-3-(1,3-Benzodioxol-5-yloxy)methyl-4-(4-fluorophenyl)-1-(1′-phenylethyl)piperidine hydrochloride 14b

To a solution of **12** (2 g, 6.38 mmol) in dichloromethane (60 mL) in an ice bath was added dropwise triethylamine (1.65 mL, 11.84 mmol) and methanesulfonyl chloride (0.86 mL, 11.11 mmol). The mixture was stirred in an ice bath for 3 h and quenched with saturated sodium hydrogen carbonate solution (30 mL). The aqueous layer was extracted with dichloromethane. The combined organic extract was washed with brine, dried over magnesium sulfate and concentrated to furnish the mesylate **13** as a yellow viscous oil.

To a solution of sodium (0.28 g, 12.17 mmol) in propanol (20 mL) was added a solution of sesamol (3 g, 21.72 mmol) in propanol (30 mL). After gently refluxing for 30 min, the above prepared solution of mesylate **13** in propanol (50 mL) was added. The mixture was refluxed for 36 h, cooled to room temperature, and then quenched with ice water (30 mL). After evaporation of propanol, the aqueous layer was extracted with ethyl ether. The combined organic layer was washed with 1N sodium hydroxide solution, brine, dried over magnesium, filtered and then concentrated to afford the free amine **14a** as a red–brown viscous oil. The free amine was diluted with methanol (50 mL) and treated with concentrated hydrochloric acid (0.5 mL). The resultant solution was allowed to stand for several days and a yellow solid precipitate was collected, recrystallised from methanol and ethyl acetate to afford the hydrochloride salt as white needles (1.92 g, 64%). mp >250°C (decomposed); $[\alpha]_D^{25}$ −87.4 (*c* 1.0, CH_3OH); ^1H NMR (500 MHz, $CDCl_3$) δ 7.65–7.60 (m, 2H), 7.55–7.45 (m, 3H), 7.30–7.20 (m, 2H), 6.97 (t, $J=8.7$ Hz, 2H), 6.66 (d, $J=8.5$ Hz, 1 Hz), 6.34 (d, $J=2.5$ Hz, 1 Hz), 6.14 (dd, $J=2.5$, 8.5 Hz, 1H), 5.92 (s, 2H), 4.23 (quintet, $J=6.0$ Hz, 1H), 3.86 (m, 1H), 3.64 (dd, $J=2.3$, 9.6 Hz, 1H), 3.49 (dd, $J=3.9$, 9.6 Hz, 1H), 3.32 (m, 1H), 2.90–2.80 (m, 3H), 2.57 (m, 1H), 2.02 (d, $J=6.9$ Hz, 3H), 1.90 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 153.7, 148.2, 142.0, 136.9, 133.9, 123.0, 129.4, 129.2, 115.7, 107.9, 105.5, 101.2, 97.9, 67.6, 67.5, 54.6, 49.5, 41.2, 39.3, 29.9, 17.5. Anal. calcd for $C_{27}H_{29}ClFNO_3$: C, 69.00; H, 6.22; N, 2.98. Found: C, 69.36; H, 6.22; N, 3.07%.

4.17. Paroxetine hydrochloride or (3*S*,4*R*)-3-(1,3-benzodioxol-5-yloxy)methyl-4-(4-fluorophenyl)-piperidine hydrochloride 15

A suspension of **14b** (1.6 g, 3.49 mmol) and 10% Pd–C

(20 mg) in anhydrous methanol (140 mL) was stirred at room temperature under 1 atm. hydrogen gas for 48 h. The resulting suspension was filtered through Celite, washed with methanol and concentrated in vacuo. Crude paroxetine hydrochloride was obtained as a red viscous mass. Purification was accomplished by recrystallisation from methanol, ethyl ether and hexanes to afford paroxetine hydrochloride as pink crystals (0.85 g, 68%): mp 123–124°C (lit.[3c] 129–131°C); $[\alpha]_D^{25}$ −88.6 (*c* 1.0, CH_3OH); lit.[5] $[\alpha]_D^{22}$ −89.4 (*c* 1.6, CH_3OH)); ^1H NMR (500 MHz, $CDCl_3$) δ 7.35–7.25 (m, 2H), 7.05 (t, $J=8.5$ Hz, 2H), 6.68 (d, $J=8.4$ Hz, 1H), 6.40 (d, $J=2.3$ Hz, 1H), 6.18 (dd, $J=2.3$, 8.5 Hz, 1 Hz), 5.95 (s, 2H), 3.83 (d, $J=10.3$ Hz, 1H), 3.75 (d, $J=12.4$ Hz, 1H), 3.68 (d, $J=9.5$ Hz, 1H), 3.24 (m, 1H), 3.12 (m, 1H), 2.97 (td, $J=3.3$, 12.9 Hz, 1H), 2.75 (m, 1H), 2.50 (m, 1H), 2.01 (d, $J=13.1$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9, 153.7, 148.2, 142.0, 137.1, 128.9, 115.8, 107.9, 105.6, 101.2, 97.9, 67.5, 46.8, 44.5, 41.7, 39.4, 30.1.

4.18. X-Ray crystallography for compounds 11a and 11b

The crystals were grown from a mixture of dichloromethane and ethyl acetate at 25°C. Diffraction measurements were made on a Nonius CAD-4 diffractometer using graphite-monochromatised Mo Kα radiation ($\lambda=0.7107$ Å). Unit cell parameters were obtained by a least-squares fit to the automatically centred settings for 25 reflections. Intensity data were collected by using $\omega/2\theta$ scan mode. Corrections were made for Lorentz and polarisation effects. The structures were solved by direct methods SOLVER.[12a] All non-hydrogen atoms were located from the difference Fourier maps and were refined by full-matrix least-squares procedures. Hydrogen atoms were calculated and refined with an overall isotropic temperature factor. Calculations and full-matrix least-squares refinements were performed utilising the NRCVAX program package.[12b]

4.18.1. Crystal data for 11a. Crystal dimensions 0.46×0.58×0.58 mm were used for data collection. $C_{21}H_{22}FNO_3$, $fw=355.41$, monoclinic $C2$, $a=16.2213(22)$, $b=9.191(4)$, $c=13.022(3)$ Å, $\beta=96.887(16)°$, $V=1927.4(10)$ Å^3, $Z=4$, $D_{calcd}=1.225$ g cm^{-3}, μ(Mo Kα)$=0.825$ cm^{-1}. Unique reflections (3370) were obtained and 1994 observed reflections ($I>1\sigma(I)$) were used for refinement to give $R=0.080$ and $Rw=0.080$. These data are available in Supporting Information.

4.18.2. Crystal data for 11b. Crystal dimensions 0.49×0.42×0.31 mm were used for data collection. $C_{26}H_{26}FNO$, $fw=355.41$, orthorhombic $P2_12_12_1$, $a=10.1484(14)$, $b=10.294(4)$, $c=20.040(3)$ Å, $V=2093.6(8)$ Å^3, $Z=4$, $D_{calcd}=1.229$ g cm^{-3}, μ(Mo Kα)$=0.750$ cm^{-1}. Unique reflections (3677) were obtained and 2577 observed reflections ($I>1\sigma(I)$) were used for refinement to give $R=0.035$ and $Rw=0.037$. These data are available in Supporting Information.

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