A Formal Synthesis of (−)-Paroxetine by Enantioselective Ring Enlargement of a Trisubstituted Prolinol

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Dedicated to Professor Marc Julia on the occasion of his 80th birthday

Keywords: Dehalogenation / Paroxetine / Piperidine / Prolinol / Ring expansion

A ring expansion and a radical dehalogenation have been used as the key steps in a formal total synthesis of (–)-paroxetine. The substituted piperidine ring precursor of (–)-paroxetine was generated by means of a stereoselective ring expansion of prolinol.

Introduction

Piperidine is the central structural feature of many biologically active compounds.[1−6] Substituted piperidines, more particularly 4-arylpiperidines, are important structural elements in a number of these compounds, possibly due to their similarity to the aryl alkylamine pharmacophore common in neurotransmitters such as serotonin [5-hydroxytryptamine, (5-HT)], dopamine (DA), noradrenaline (NA), and antagonists of opiate receptors. Drugs that modulate the physiological and pathophysiological actions of 5-HT are useful in the treatment of a variety of human diseases, including depression, anxiety, alcoholism, chronic pain, emesis, and eating disorders such as obesity and bulimia.[7] Such compounds are exemplified by the antipsychotic 5-HT-, and DA-antagonist haloperidol,[8] the analgesic opioid agonist meperidine,[9] and the selective serotonin reuptake inhibitor (SSRI) paroxetine [Paxil®, Deroxat®] (Figure 1).[10−11]

Paroxetine is an enantiomerically pure (−)-*trans*-3,4-disubstituted piperidine. The drug is used in the treatment of depression, obsessive compulsive disorder, and panic disorder.[12] Moreover, it has a reduced propensity to cause the side-effects usually associated with tricyclic antidepressants.[13] Because of its biological importance, several enantiocontrolled syntheses have been reported.[14−32]

The stereochemical configurations at the C-3 and C-4 positions of the piperidine ring are critical for the activity of this compound.[26] However, the synthetic methods usable for the preparation of 3,4-disubstituted piperidine derivatives are limited.[33−41]

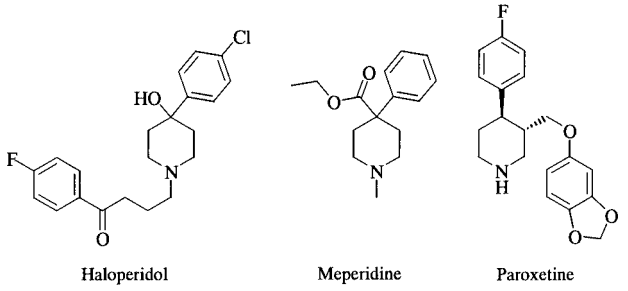
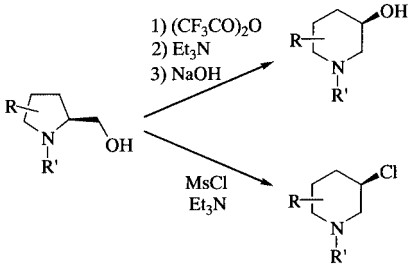


Figure 1. Selected 4-arylpiperidines

In the context of our studies on ring expansion reactions[42] of enantiomerically pure substituted prolinols to give enantiomerically pure substituted 3-hydroxypiperidines by use of trifluoroacetic anhydride,[43−45] or of substituted 3-chloropiperidines by use of mesyl chloride,[42,46] we would like to report the synthesis of (−)-paroxetine[47] (Scheme 1).



Scheme 1. Ring expansion reactions

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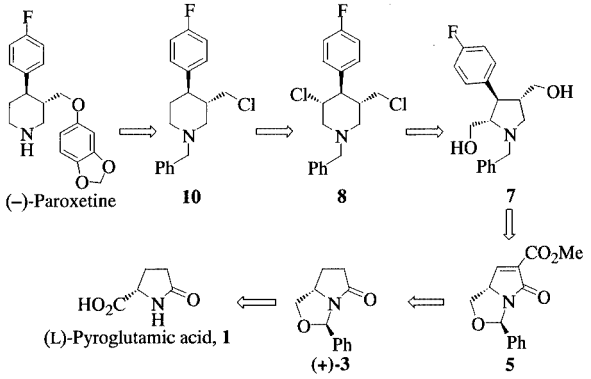
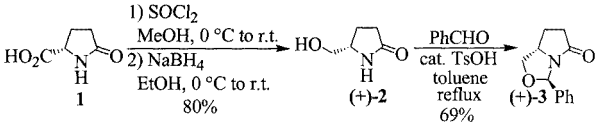
Results and Discussion

Since secondary chlorides are selectively reduced in preference to primary chlorides by nBu$_3$SnH in the presence of AIBN,[48] the synthesis of (−)-paroxetine was envisaged as proceeding from piperidine **10**, the result in turn of a chemoselective reduction of dichloride **8**. This compound would be produced from a ring expansion applied to prolinol **7**, which would in turn be derived from the unsaturated ester **5** by standard transformations. The last compound would be synthesized from L-pyroglutamic acid **1** via the known bicyclic lactam (+)-**3**[49] (Scheme 2).



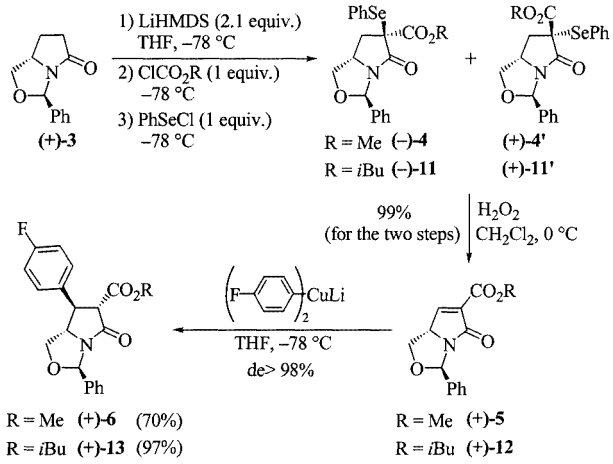
Scheme 2. Retrosynthetic analysis

Compound (+)-**3** was synthesized in three steps from L-pyroglutamic acid (**1**).[49] After treatment of L-pyroglutamic acid with thionyl chloride in methanol (88% yield), the corresponding methyl ester was reduced with $NaBH_4$ (EtOH, 0 °C to room temp., yield = 90%) and the amidoalcohol (+)-**2**[50] was protected with benzaldehyde in the presence of a catalytic amount of *p*-toluenesulfonic acid (TsOH). The optically pure bicyclic compound (+)-**3** was isolated in 69% yield ($[\alpha]_D^{20}$ = +237, c = 1.2, $CHCl_3$) (Scheme 3).



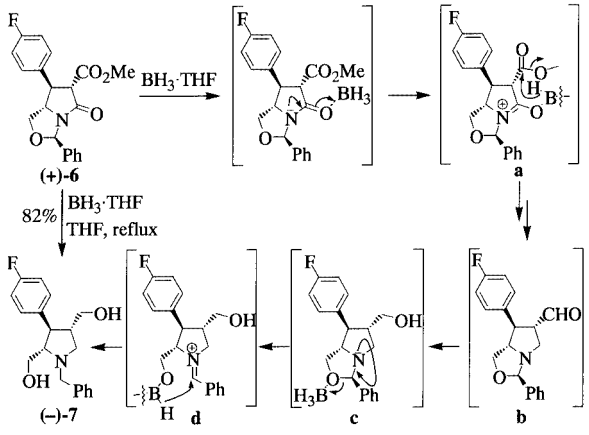
Scheme 3

In order to introduce the aromatic group present in (−)-paroxetine, compound (+)-**3** was transformed into the unsaturated ester (+)-**5** in two steps, via the seleno derivatives (−)-**4** and (+)-**4′**. The bicyclic compound (+)-**3** was deprotonated with an excess of LiHMDS (2.1 equiv.) and the resulting anion was quenched at −78 °C with methyl chloroformate (1 equiv., −78 °C, 1 h). The excess of base was capable of achieving a second deprotonation, and the newly formed anion was quenched with benzeneselenenyl chloride (1 equiv., −78 °C, 1.5 h) to produce, in a one-pot operation, the diastereomeric selenides (−)-**4** and (+)-**4′** in a ratio of 62:38. These two isomers were not separated or purified, but were directly oxidized with H_2O_2 [51] to afford the corresponding unsaturated ester (+)-**5** in nearly quantitative yield (99% overall yield for the two-step sequence). The conjugate addition of lithium bis(4-fluorophenyl)cuprate to (+)-**5** was achieved at −78 °C in THF to give compound (+)-**6** in 70% yield and with a diastereomeric excess superior to 98%[52] (Scheme 4). The relative *trans* stereochemistry of the substituents at C-3 and C-4 was established by ^{1}H NMR from the coupling constant between 3-H and 4-H (J = 10.7 Hz).



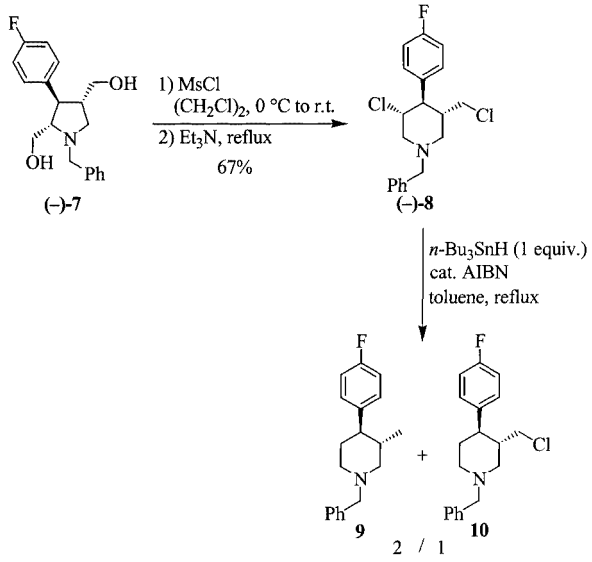
Scheme 4

Different reducing agents were investigated for the transformation of (+)-**6** into diol (−)-**7**. The best yield of (−)-**7** (82%) was obtained when (+)-**6** was treated with BH_3·THF in refluxing THF.[53] The unexpected reactivity of BH_3·THF towards the ester functionality of (+)-**6** can be explained by complexation of the oxygen atom of the lactam ring by the boron atom of BH_3·THF, which could produce the iminium ion **a**. Iminium ion **a** could be reduced to the corresponding amine, and an intramolecular reduction of the ester group could be achieved to produce aldehyde **b**, which could subsequently be reduced to the bicyclic alcohol **c**. The complexation of the oxazolidine by BH_3 could give rise to the iminium **d**, which would be reduced to produce diol (−)-**7** (Scheme 5). It is worth noting that the reduction of (+)-**6** to (−)-**7** was a very fast reaction, which probably means that the ester group was reduced first.



Scheme 5

Diol (−)-**7** was then treated with MsCl at 0 °C for 40 min, and the reaction mixture was then heated under reflux in the presence of Et_3N for 30 hours to produce the desired dichloropiperidine (−)-**8** in 67% yield. Dichloropiperidine (−)-**8** was treated, according to the literature procedure,[48] with nBu$_3$SnH (1 equiv.) in the presence of AIBN in refluxing toluene. Unfortunately, 3-methylpiperidine **9** was formed and could not be separated from the desired product **10**. These two compounds **9** and **10** were formed in a 2:1 ratio (determined by GC/MS). It is noteworthy that the use of tris(trimethylsilyl)silane [TTMSS] instead of nBu$_3$SnH also resulted in compounds **9** and **10** in a similar ratio, but the conversion was not complete (70%) (Scheme 6).

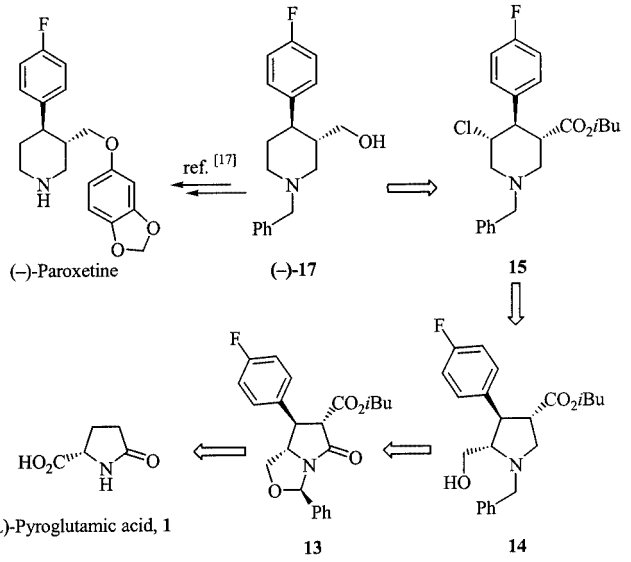


Scheme 6

Because of this disappointing result, the synthesis of (−)-paroxetine from the bicyclic isobutyl ester **13** was examined. This compound would be transformed into prolinol **14**, which, after treatment with MsCl, should undergo a ring expansion to produce piperidine **15**, which should be transformable into the precursor of (−)-paroxetine through (−)-**17**. As previously, prolinol **14** was to be synthesized from L-pyroglutamic acid (**1**) via the bicyclic lactam **13** (Scheme 7).

The synthesis of (+)-**13** from L-pyroglutamic acid (**1**) was similar to the synthesis of (+)-**6**, except that methyl chloroformate was replaced by isobutyl chloroformate. The compound was obtained in 52% overall yield from L-pyroglutamic acid (**1**) (Scheme 4). The sterically hindered ester was chosen to avoid its reduction during the oxazolidine ring opening of (+)-**13**. In order to obtain (−)-**14** from (+)-**13**, different reducing agents and conditions were examined. The results of these studies are summarized in Table 1.

When lactam (+)-**13** was reduced with $LiBEt_3H$ (Table 1, entry 1), the intermediate hemiaminal **13′** was formed, and was treated immediately with triethylsilane in the presence of $BF_3{\cdot}OEt_2$ or $TiCl_4$.[54] Under these conditions, a complex mixture resulted, from which neither lactam (+)-**13** nor



Scheme 7. Revised retrosynthetic analysis

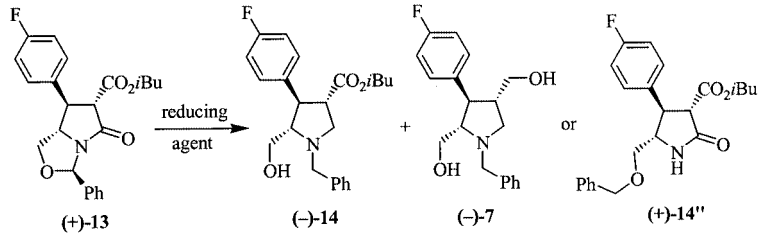
amino alcohol (−)-**14** could be isolated (Scheme 8). Since oxazolidines can be opened by Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ to produce *N*-alkylamino alcohols,[55] lactam (+)-**13** was treated with these reagents. In this case, amido alcohol **14′** was not formed, but the *O*-benzylated amido alcohol (+)-**14′′** was instead isolated in 95% yield (Scheme 8).

This result can be explained by the Lewis acid coordinating the oxygen atom of the lactam (+)-**13** (path b) and not the oxygen atom of the oxazolidine ring (path a) as previously observed for compound (+)-**6**. The lone-pair electrons of the oxygen atom of the oxazolidine ring participate in the formation of the imine-oxonium ion **f**, and this intermediate is then reduced with Et_3SiH (path b) (Scheme 9).

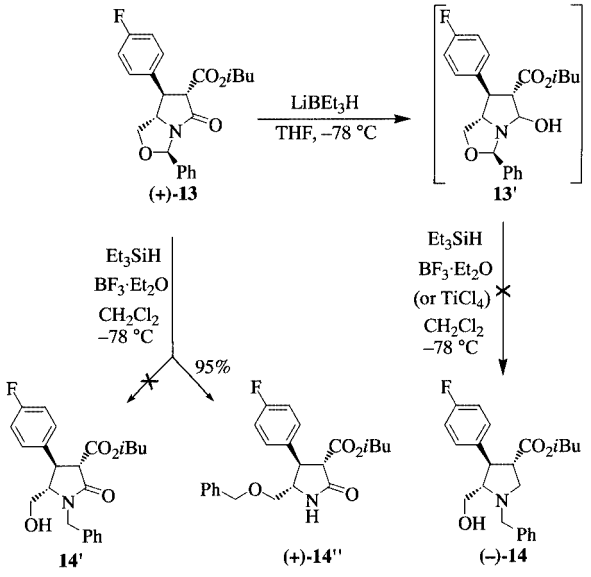
Under conditions developed previously, the bicyclic lactam (+)-**13** was treated with $BH_3{\cdot}THF$. When compound (+)-**13** was treated with 3 equivalents of $BH_3{\cdot}THF$ at 0 °C for 14 hours, the starting material was recovered unchanged (Table 1, entry 3). At room temperature, however, the expected compound (−)-**14** and the diol (−)-**7** were isolated in 27% and 54% yields, respectively (Table 1, entry 4). The best conditions for obtaining amino alcohol (−)-**14** were the use of 10 equivalents of $BH_3{\cdot}THF$ for 1.5 hour at room temperature. Under these conditions, (−)-**14** was isolated in 44% yield and diol (−)-**7** was isolated in 15% yield (Table 1, entry 5).

The ring expansion reaction was then studied on amino alcohol (−)-**14**. Thus, when (−)-**14** was treated with mesyl chloride (1.1 equiv.) at 0 °C in 1,2-dichloroethane for 50 min and then heated under reflux for 36 hours in the presence of triethylamine (3.1 equiv.), the expected trisubstituted 5-chloropiperidine (−)-**15** was isolated in 84% yield as a single diastereomer. The relative *trans* configuration of the substituents at C-4 and C-5 was established by NMR analysis (δ 5-H = 4.09 ppm, $J_{5\text{-Hax},4\text{-Hax}}$ = 10.7, $J_{5\text{-Hax},6\text{-Hax}}$ = 10.7, $J_{5\text{-Hax},6\text{-Heq}}$ = 4.4 Hz). The homoallylic cleavage of the C−Cl bond with tris(trimethylsilyl)silane

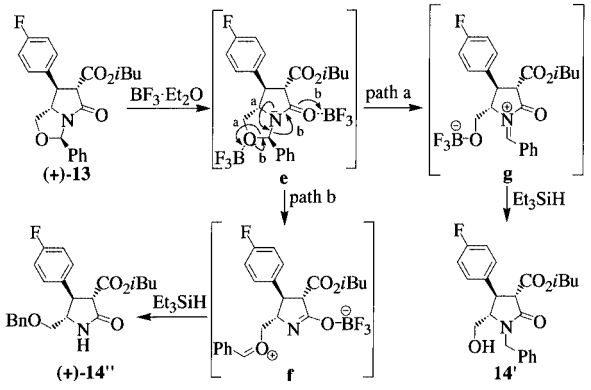
Table 1. Reagents and conditions for the synthesis of (−)-**14**



Entry	Reducing agent	Equiv.	Conditions	Products (yield)
1	$LiBEt_3H$ then	1		
	Et_3SiH, $BF_3{\cdot}OEt_2$	1	−78 °C	Degradation
2	Et_3SiH, $BF_3{\cdot}OEt_2$	2	−78 °C	(+)-**14**'' (95%)
3	$BH_3{\cdot}THF$	3	14 h, 0 °C	Starting material (+)-**13**
4	$BH_3{\cdot}THF$	3	60 h, 0 °C to room temp.	(−)-**14** (27%); (−)-**7** (54%)
5	$BH_3{\cdot}THF$	10	1.5 h, room temp.	(−)-**14** (44%); (−)-**7** (15%)

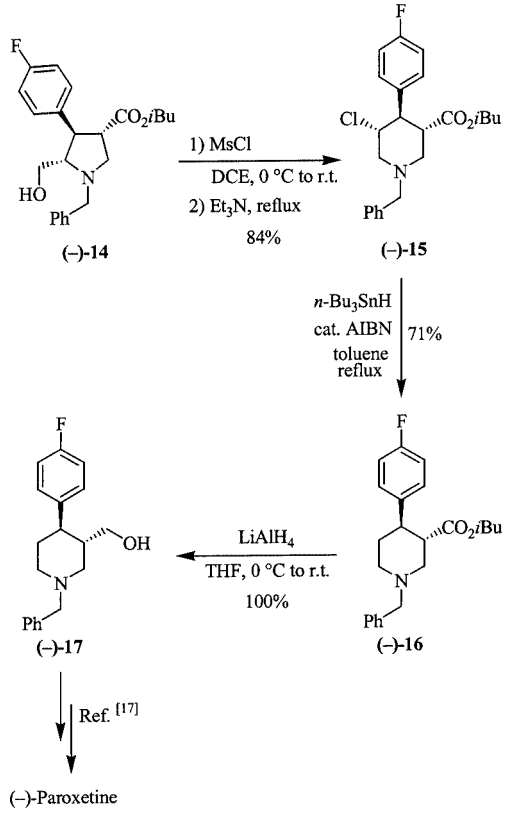


Scheme 8



Scheme 9

(TTMSS) or *n*-tributyltin hydride (nBu_3SnH) was examined. The best yield of (−)-**16** (71%) was obtained when (−)-**15** was treated with nBu_3SnH in the presence of AIBN in refluxing toluene.[56] The use of TTMSS afforded (−)-**16** in only 5% yield. The reduction of the ester group of (−)-**16** was achieved with $LiAlH_4$ in THF, which furnished the expected known piperidine (−)-**17**[17,23] [(−)-**17**·HCl: $[\alpha]_D^{20} = -10.6$, $c = 1$, MeOH; ref.[23] $[\alpha]_D^{20} = -10.3$, $c = 1$, MeOH] in quantitative yield (Scheme 10).



Scheme 10. Formal total synthesis of (−)-paroxetine

Conclusion

Compound (−)-**17**, a known precursor in the synthesis of (−)-paroxetine,[17] has been synthesized in ten steps from L-pyroglutamic acid (**1**), in an overall yield of 13.9% and with two key steps: an enantioselective ring expansion of prolinol induced by the mesyl chloride−Et_3N process and a homolytic cleavage of a C−Cl bond induced by n-Bu_3SnH. This transformation of the L-pyroglutamic acid (**1**) into amino alcohol (−)-**17** constitutes a formal synthesis of (−)-paroxetine.

Experimental Section

General Remarks: Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. THF and Et_2O were distilled from Na benzophenone-ketyl immediately prior to use. Amines and solvents were distilled from CaH_2 prior to use. Moisture-sensitive reactions were conducted in oven-dried glassware and under an argon atmosphere. Analytical thin-layer chromatography was performed on Merck precoated silica gel ($60F_{254}$) plates and flash column chromatography on Merck Kieselgel 60 (230−400 mesh). Melting points are uncorrected. IR: Perkin−Elmer 298 or Perkin−Elmer 1600. Optical rotations: Perkin−Elmer 343 polarimeter. Elemental analyses: Service Régional de Microanalyse de l'Université P. et M. Curie. HRMS: Centre de Spectrochimie de l'Ecole Normale Supérieure. NMR: Bruker AC 300 spectrometer (300 MHz and 75 MHz for ^1H and ^{13}C, respectively). Spectra were recorded in $CDCl_3$ as solvent, and chemical shifts (δ) were expressed in ppm relative to residual $CHCl_3$ at δ = 7.27 ppm for ^1H and to $CDCl_3$ at δ = 77.0 ppm for ^{13}C. MS: Mass spectra were obtained by GC/MS with electron impact ionization on a 5971 Hewlett Packard instrument at 70 eV; only selected ions are reported.

Methyl (3*S*,6*R*,7a*R*)-5-Oxo-3-phenyl-6-(phenylseleno)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxylate [(−)-4] and Methyl (3*S*,6*S*,7a*R*)-5-Oxo-3-phenyl-6-(phenylseleno)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxylate [(+)-4′]: A solution of (+)-**3**[49] (2.50 g, 12.3 mmol) in THF (50 mL) was added at −78 °C to a solution of LiHMDS (26.0 mL, 1 M in THF, 26.0 mmol, 2.1 equiv.) in THF (100 mL). The mixture was stirred at −78 °C for 30 min, and methyl chloroformate (0.95 mL, 12.0 mmol, 1 equiv.) was added dropwise. The solution was stirred for 1 h at −78 °C, and a solution of benzeneselenenyl chloride (2.5 g, 13.0 mmol, 1 equiv.) in THF (25 mL) was added. The mixture was stirred for 1.5 h at this temperature before addition of an aqueous HCl solution (1.2 N, 30 mL). The mixture was allowed to warm to room temp. and was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Although the 62:38 mixture of diastereomers (−)-**4** and (+)-**4′** (determined by ^1H NMR analysis) was carried on without purification, the following analytical data were obtained from a small-scale run with purification by flash column chromatography on silica gel (EtOAc/petroleum ether, 10:90).

Compound 4: M.p. 87 °C; R_f = 0.41 (EtOAc/petroleum ether, 20:80). $[\alpha]_D^{20}$ = −33.3 (c = 1.17, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1730, 1705, 1434, 1256, 1213, 745, 694 cm^{-1}. ^1H NMR: δ = 7.60 (dd, J = 8.1, 1.1 Hz, 2 H), 7.43−7.24 (6 H), 7.10 (m, 2 H), 6.24 (s, 1 H), 4.11 (dd, J = 8.1, 6.2 Hz, 1 H), 3.86 (s, 3 H), 3.47 (dd, J = 8.5, 8.1 Hz, 1 H), 3.18 (m, 1 H), 2.93 (dd, J = 14.3, 5.9 Hz, 1 H), 2.60 (dd, J = 14.3, 7.4 Hz, 1 H) ppm. ^{13}C NMR: δ = 171.7 (s), 169.3 (s), 138.1 (d), 137.9 (s), 130 (d), 129.0 (d), 128.7 (d), 128.3 (d), 126.0 (d), 125.8 (s), 87.0 (d), 72.0 (t), 57.5 (s), 55.6 (d), 53.7 (q), 36.5 (t) ppm. MS (EI): m/z (relative intensity) = 417 (64) [$M^{+\cdot}$], 415 (35) [$M^{+\cdot}$], 311 (100), 309 (49), 260 (67), 231 (47), 228 (31), 183 (67), 182 (32), 181 (33), 157 (48), 155 (31), 105 (67), 91 (45), 78 (38), 77 (62). $C_{20}H_{19}NO_4Se$ (416.33): calcd. C 57.70, H 4.60, N 3.36; found C 57.83, H 4.70, N 3.17.

Compound 4′: R_f = 0.27 (EtOAc/petroleum ether, 80:20). $[\alpha]_D^{20}$ = +221.8 (c = 2.71, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1729, 1710, 1435, 1374, 1255, 1226, 748, 693 cm^{-1}. ^1H NMR: δ = 7.68 (m, 2 H), 7.47−7.21 (8 H), 6.24 (s, 1 H), 4.15−3.99 (2 H), 3.71 (s, 3 H), 3.07 (m, 1 H), 3.05 (dd, J = 14.0, 7.0 Hz, 1 H), 2.15 (dd, J = 14.0, 5.9 Hz, 1 H) ppm. ^{13}C NMR: δ = 170.8 (s), 169.3 (s), 137.6 (s), 137.4 (d), 129.7 (d), 129.0 (d), 128.5 (d), 128.2 (d), 126.0 (s), 125.8 (d), 87.3 (d), 71.3 (t), 58.4 (s), 55.9 (d), 53.3 (q), 36.0 (t) ppm. MS (EI): m/z (relative intensity) = 417 (64) [$M^{+\cdot}$], 415 (35) [$M^{+\cdot}$], 311 (100), 309 (49), 260 (65), 231 (49), 228 (32), 183 (70), 182 (31), 181 (34), 157 (45), 155 (31), 105 (66), 91 (45), 78 (35), 77 (58).

Methyl (3*S*,7a*R*)-5-Oxo-3-phenyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]-oxazole-6-carboxylate [(+)-5]: An aqueous H_2O_2 solution (30%, 12.5 mL, 123.7 mmol, 10 equiv.) was added dropwise at 0 °C to a solution of the crude diastereoisomeric mixture of (−)-**4** and (+)-**4′** (5.1 g, 12.30 mmol) in CH_2Cl_2 (60 mL). The mixture was stirred at 0 °C for 45 min before being quenched with an aqueous HCl solution (1.2 N, 30 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 30 mL) and the combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution (2 × 40 mL) and brine (40 mL), dried over $MgSO_4$, filtered, and then concentrated under reduced pressure. Compound (+)-**5** (3.2 g, 12.3 mmol, 100% yield over two steps) was obtained as a yellow solid: m.p. 137 °C; R_f = 0.19 (EtOAc/petroleum ether, 40:60). $[\alpha]_D^{20}$ = +195.7 (c = 1.11, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1748, 1723, 1434, 1344, 1220, 1161, 1102, 702 cm^{-1}. ^1H NMR: δ = 8.00 (d, J = 1.8 Hz, 1 H), 7.53 (m, 2 H), 7.47−7.28 (3 H), 6.26 (s, 1 H), 4.62 (m, 1 H), 4.31 (dd, J = 7.7, 7.7 Hz, 1 H), 3.88 (s, 3 H), 3.49 (m, 1 H) ppm. ^{13}C NMR: δ = 171.3 (s), 161.1 (s), 154.7 (d), 137.9 (s), 131.9 (s), 128.6 (d), 128.3 (d), 125.9 (d), 87.6 (d), 67.3 (t), 62.1 (d), 52.2 (q) ppm. MS (CI^+, CH_4): m/z (relative intensity) = 260 (100) [M + H^+], 259 (6), 228 (25), 200 (11), 198 (3), 184 (9), 182 (6), 156 (26), 123 (3), 107 (13). HRMS (CI^+, CH_4) calcd. for $C_{14}H_{14}NO_4$ [[M + H]$^+$] 260.0923, found 260.0921.

Methyl (3*S*,6*S*,7*R*,7a*R*)-7-(4-Fluorophenyl)-3-phenyl-5-oxo-tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxylate [(+)-6]: n-Butyllithium (9.72 mL, 2.5 M in hexanes, 24.30 mmol, 10 equiv.) was added dropwise at −78 °C to a solution of 4-bromofluorobenzene (2.67 mL, 24.26 mmol, 10 equiv.) in THF (62 mL). The solution was stirred at −78 °C for 30 min and was then added dropwise by cannula to a suspension of copper iodide (2.31 g, 12.13 mmol, 5.0 equiv.) in THF (38 mL) at −78 °C. The resulting mixture was warmed slowly to −30 °C and stirred for 40 min at this temperature to give a clear orange solution. After the mixture had again been cooled to −78 °C, a solution of (+)-**5** (0.63 g, 2.43 mmol) in THF (38 mL) was added dropwise and the reaction mixture was stirred for 30 min before addition of a saturated aqueous NH_4Cl/NH_4OH (32%): 2:1 solution (75 mL). After 1 h of stirring, the deep blue aqueous layer was extracted with Et_2O (2 × 75 mL) and CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with aqueous NaOH (1 N, 2 × 50 mL) and brine (75 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (petroleum ether/EtOAc, 95:5, then 80:20) afforded (+)-**6** (0.61 g, 1.72 mmol, 70%

yield) as a pale yellow oil: R_f = 0.34 (EtOAc/petroleum ether, 20:80). $[\alpha]_D^{20}$ = +62.8 (*c* = 1.09, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1745, 1716, 1513, 1349, 1273, 1225, 1165, 701 cm^{-1}. ^1H NMR: δ = 7.53−7.43 (2 H), 7.42−7.29 (3 H), 7.25 (m, 2 H), 7.05 (m, 2 H), 6.43 (s, 1 H), 4.27−4.12 (2 H), 4.03 (d, *J* = 10.7 Hz, 1 H), 3.94 (m, 1 H), 3.89 (dd, *J* = 8.1, 5.9 Hz, 1 H), 3.77 (s, 3 H) ppm. ^{13}C NMR: δ = 170.6 (s), 168.2 (s), 162.1 (d, *J* = 247.2 Hz), 137.5 (s), 133.6 (d, *J* = 3.7 Hz), 128.7 (dd, *J* = 7.9 Hz), 128.6 (d), 128.3 (d), 125.8 (d), 115.9 (dd, *J* = 21.3 Hz), 87.3 (d), 70.6 (t), 63.6 (d), 59.0 (d), 52.6 (q), 49.1 (d) ppm. MS (EI): *m*/*z* (relative intensity) = 355 (0.03) [$M^{+\cdot}$], 297 (36), 296 (81), 267 (8), 149 (10), 148 (21), 123 (10), 122 (100), 121 (11), 117 (10), 109 (10), 105 (18), 91 (10), 90 (9), 77 (9).

(2*S*,3*R*,4*S*)-1-Benzyl-3-(4-fluorophenyl)pyrrolidine-2,4-bismethanol [(−)-7]: Borane−tetrahydrofuran complex (5.50 mL, 1 M in THF, 5.50 mmol, 5.2 equiv.) was added at room temp. to a solution of (+)-**6** (375 mg, 1.05 mmol) in THF (20 mL), and the mixture was heated at reflux for 19 h. The reaction mixture was cautiously quenched at 0 °C by addition of methanol until gas evolution stopped, and the solvents were evaporated. The residue was dissolved in methanol (20 mL) and heated at reflux for 1 h. The solution was concentrated in vacuo, methanol (20 mL) was added, and the solvents were evaporated. This procedure was repeated twice. The compound (−)-**7** (270 mg, 0.86 mmol, 82% yield) was obtained as a yellowish oil and was carried on without further purification: R_f = 0.50 (CH_2Cl_2/MeOH, 97:3). $[\alpha]_D^{20}$ = −53.3 (*c* = 1.05, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3377, 2926, 1604, 1511, 1225, 1160, 1047 cm^{-1}. ^1H NMR: δ = 7.39−7.17 (7 H), 7.01 (m, 2 H), 4.07 (d, *J* = 13.2 Hz, 1 H), 3.73 (dd, *J* = 11.6, 3.1 Hz, 1 H), 3.61 (dd, *J* = 10.5, 5.0 Hz, 1 H), 3.53 (dd, *J* = 10.5, 6.8 Hz, 1 H), 3.44 (dd, *J* = 11.6, 1.5 Hz, 1 H), 3.36 (d, *J* = 13.2 Hz, 1 H), 3.10 (dd, *J* = 9.2, 7.3 Hz, 1 H), 3.05 (dd, *J* = 9.9, 3.7 Hz, 1 H), 2.81 (dd, *J* = 10.3, 8.5 Hz, 1 H), 2.70 (ddd, *J* = 9.2, 2.9, 1.5 Hz, 1 H), 2.48−2.29 (3 H) ppm. ^{13}C NMR: δ = 161.8 (d, *J* = 245.0 Hz), 138.3 (d, *J* = 3.3 Hz), 138.2 (s), 129.5 (dd, *J* = 7.9 Hz), 128.6 (d), 128.5 (d), 127.3 (d), 115.5 (dd, *J* = 21.2 Hz), 73.8 (d), 65.4 (t), 58.2 (t), 57.9 (t), 56.8 (t), 48.2 (d), 46.6 (d) ppm. MS (EI): *m*/*z* (relative intensity) = 284 (73) [$M^{+\cdot}$ − $CH_2OH^{\cdot}$], 266 (5), 162 (9), 135 (4), 133 (3), 109 (4), 92 (8), 91 (100), 65 (5). HRMS (CI^+, CH_4) calcd. for $C_{19}H_{23}FNO_2$ [M + H]$^+$ 316.1713, found 316.1713.

(3*S*,4*R*,5*S*)-1-Benzyl-3-chloro-5-(chloromethyl)-4-(4-fluorophenyl)-piperidine [(−)-8]: Methanesulfonyl chloride (0.14 mL, 1.81 mmol, 2.10 equiv.) was added dropwise at 0 °C to a solution of (−)-**7** (270 mg, 0.86 mmol) in 1,2-dichloroethane (5.5 mL). The mixture was stirred for 40 min, and Et_3N (0.48 mL, 3.45 mmol, 4.0 equiv.) was added. The resulting solution was heated under reflux for 30 h and quenched with an aqueous NaOH solution (1 N, 2.5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (petroleum ether/CH_2Cl_2, 60:40) afforded (−)-**8** (203 mg, 0.58 mmol, 55% yield over two steps) as a yellow oil: R_f = 0.50 (petroleum ether/CH_2Cl_2, 63:47). $[\alpha]_D^{20}$ = −15.0 (*c* = 2.36, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1512, 1454, 1226, 1160, 832, 700 cm^{-1}. ^1H NMR: δ = 7.44−7.25 (5 H), 7.21 (m, 2 H), 7.03 (m, 2 H), 4.07 (ddd, *J* = 11.0, 11.0, 4.4 Hz, 1 H), 3.65 (d, *J* = 13.2 Hz, 1 H), 3.58 (d, *J* = 13.2 Hz, 1 H), 3.39−3.23 (2 H), 3.17−3.02 (2 H), 2.64 (m, 1 H), 2.35−2.13 (3 H) ppm. ^{13}C NMR: δ = 162.0 (d, *J* = 246.0 Hz), 137.4 (s), 135.1 (d, *J* = 3.0 Hz), 129.0 (d), 128.4 (d), 128.3 (dd, *J* = 6.7 Hz), 127.4 (d), 115.6 (dd, *J* = 21.4 Hz), 62.4 (t), 61.2 (t), 60.7 (d), 56.3 (t), 53.1 (d), 45.9 (t), 44.0 (d) ppm. MS (EI): *m*/*z* (relative intensity) = 355 (2) [$M^{+\cdot}$], 353 (10) [$M^{+\cdot}$], 351 (15) [$M^{+\cdot}$], 318 (24), 317 (15), 316 (69), 302 (17), 160 (11), 92 (12), 91 (100). HRMS (CI^+, CH_4) calcd. for $C_{19}H_{21}{}^{35}Cl_2FN$ [M + H]$^+$] 352.1035, found 352.1025 and calcd. for $C_{19}H_{21}{}^{35}Cl^{37}ClFN$ [M + H]$^+$ 354.1009, found 354.1003.

Isobutyl (3*S*,6*R*,7a*R*)-5-Oxo-3-phenyl-6-(phenylseleno)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxylate [(−)-11] and Isobutyl (3*S*,6*S*,7a*R*)-5-Oxo-3-phenyl-6-(phenylseleno)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxylate [(+)-11′]: *n*-Butyllithium (20.66 mL, 2.5 M in hexanes, 51.65 mmol, 2.1 equiv.) was added dropwise at −78 °C to a solution of HMDS (10.9 mL, 51.66 mmol, 2.1 equiv.) in THF (200 mL). After the mixture had been kept for 40 min at −78 °C, a solution of (+)-**3**[49] (5.00 g, 24.58 mmol) in THF (100 mL) was added dropwise. The mixture was stirred at −78 °C for 45 min, and isobutyl chloroformate (3.26 mL, 24.67 mmol, 1 equiv.) was added dropwise. The solution was stirred for 30 min at −78 °C and a solution of benzeneselenenyl chloride (4.79 g, 24.51 mmol, 1 equiv.) in THF (50 mL) was added. The reaction was stirred for 1.5 h at this temperature before addition of aqueous HCl (1.2 N, 100 mL). The mixture was allowed to warm to room temp. and extracted with Et_2O (3 × 100 mL).The combined organic layers were washed with brine (75 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Although the 62:38 mixture of diastereomers (−)-**11** and (+)-**11′** (determined by ^1H NMR analysis) was carried on without purification, the following analytical data were obtained from a small-scale run purified by flash column chromatography on silica gel (toluene/Et_2O, 99:1).

Compound 11: M.p. 88 °C; R_f = 0.60 (toluene/diethyl ether, 80:20). $[\alpha]_D^{20}$ = −12.1 (*c* = 1.00, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1732, 1696, 1401, 1256, 1220, 742, 691 cm^{-1}. ^1H NMR: δ = 7.57 (m, 2 H), 7.41−7.22 (6 H), 7.05 (m, 2 H), 6.21 (s, 1 H), 4.08 (dd, *J* = 8.1, 6.3 Hz, 1 H), 4.02 (d, *J* = 6.6 Hz, 1 H), 4.01 (d, *J* = 6.6 Hz, 1 H), 3.43 (dd, *J* = 8.5, 8.1 Hz, 1 H), 3.07 (m, 1 H), 2.92 (dd, *J* = 14.7, 5.9 Hz, 1 H), 2.56 (dd, *J* = 14.7, 7.4 Hz, 1 H), 2.02 (m, 1 H), 0.96 (d, *J* = 6.6 Hz, 3 H), 0.96 (d, *J* = 7.0 Hz, 3 H) ppm. ^{13}C NMR: δ = 171.9 (s), 168.8 (s), 138.1 (d), 138.0 (s), 129.8 (d), 129.0 (d), 128.6 (d), 128.3 (d), 126.0 (d), 125.9 (s), 87.0 (d), 72.8 (t), 72.1 (t), 57.9 (s), 55.6 (d), 36.4 (t), 27.7 (d), 19.0 (q) ppm. MS (EI): *m*/*z* (relative intensity) = 459 (60) [$M^{+\cdot}$], 457 (30) [$M^{+\cdot}$], 353 (37), 351 (19), 302 (61), 297 (100), 295 (50), 188 (58), 183 (49), 157 (48), 105 (85), 91 (53), 78 (50), 77 (61), 57 (56). $C_{23}H_{25}NO_4Se$ (459.09): calcd. C 60.25, H 5.50, N 3.05; found C 60.15, H 5.42, N 3.06.

Compound 11′: R_f = 0.67 (toluene/diethyl ether, 80:20) $[\alpha]_D^{20}$ = +147.7 (*c* = 1.64, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1716, 1252, 1225 cm^{-1}. ^1H NMR: δ = 7.68 (m, 2 H), 7.47−7.21 (8 H), 6.25 (s, 1 H), 4.07 (m, 2 H), 3.99−3.84 (2 H), 3.13−2.95 (2 H), 2.12 (dd, *J* = 13.8, 6.1 Hz, 1 H), 1.93 (m, 1 H), 0.88 (d, *J* = 6.6 Hz, 6 H) ppm. ^{13}C NMR: δ = 170.8 (s), 169.0 (s), 137.8 (s), 137.5 (d), 129.7 (d), 129.1 (d), 128.6 (d), 128.3 (d), 126.3 (s), 125.8 (d), 87.2 (d), 72.3 (t), 71.5 (t), 59.2 (s), 56.1 (d), 36.5 (t), 27.6 (d), 18.8 (q), 18.7 (q) ppm. MS (CI^+, CH_4): *m*/*z* (relative intensity) = 460 (100) [M + H$^+$], 458 (57) [M + H$^+$], 382 (9), 380 (5), 354 (30), 352 (17), 304 (24). HRMS (CI^+, CH_4) calcd. for $C_{23}H_{26}NO_4{}^{80}Se$ [M + H]$^+$ 460.1028, found 460.1031 and calcd. for $C_{23}H_{26}NO_4{}^{78}Se$ [M + H]$^+$ 458.1041, found 458.1030.

Isobutyl (3*S*,7a*R*)-5-Oxo-3-phenyl-5,7a-dihydro-1*H*,3*H*-pyrrolo[1,2-*c*]-oxazole-6-carboxylate [(+)-12]: Aqueous H_2O_2 (30%, 12.5 mL, 123.37 mmol, 5 equiv.) was added dropwise at 0 °C to a solution of the crude diastereoisomeric mixture of (−)-**11** and (+)-**11′** (11.22 g, 24.47 mmol) in CH_2Cl_2 (100 mL). The mixture was stirred at 0 °C for 30 min before being quenched by addition of an aqueous HCl solution (1.2 N, 50 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 50 mL) and the combined organic layers were washed

with a saturated aqueous $NaHCO_3$ (2 × 75 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and then concentrated under reduced pressure. Compound (+)-**12** (7.34 g, 24.36 mmol, 99% yield over 2 steps) was obtained as a yellow solid: m.p. 104 °C (EtOH); R_f = 0.41 (toluene/diethyl ether, 80:20). $[\alpha]_D^{20}$ = +193.2 (*c* = 1.03, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1740, 1347, 1225, 1166, 1112, 1018, 754 cm^{-1}. ^1H NMR: δ = 7.96 (d, *J* = 1.8 Hz, 1 H), 7.57−7.48 (2 H), 7.44−7.30 (3 H), 6.27 (s, 1 H), 4.63 (m, 1 H), 4.32 (dd, *J* = 8.1, 7.3 Hz, 1 H), 4.07 (d, *J* = 6.6 Hz, 2 H), 3.51 (dd, *J* = 8.5, 8.1 Hz, 1 H), 2.05 (m, 1 H), 1.00 (d, *J* = 6.6 Hz, 6 H) ppm. ^{13}C NMR: δ = 171.4 (s), 161.0 (s), 153.9 (d), 138.1 (s), 132.7 (s), 128.7 (d), 128.5 (d), 126.1 (d), 87.8 (d), 71.4 (t), 67.5 (t), 62.2 (d), 27.7 (d), 19.0 (q) ppm. MS (CI^+, CH_4): *m*/*z* (relative intensity) = 302 (100) [M + H^+], 246 (25), 228 (38), 224 (13), 196 (20), 140 (18), 107 (16). HRMS (CI^+, CH_4) calcd. for $C_{17}H_{20}NO_4$ [M + H]$^+$ 302.1392, found 302.1387.

Isobutyl (3*S*,6*S*,7*R*,7a*R*)-7-(4-Fluorophenyl)-5-oxo-3-phenyl-tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazole-6-carboxylate [(+)-13]: *n*-Butyllithium (14.60 mL, 2.5 M in hexanes, 36.50 mmol, 11 equiv.) was added dropwise at −78 °C to a solution of 4-bromofluorobenzene (4.02 mL, 36.52 mmol, 11 equiv.) in THF (60 mL). The solution was stirred at −78 °C for 30 min and was then added dropwise by cannula at −78 °C to a suspension of copper iodide (3.47 g, 18.22 mmol, 5.70 equiv.) in THF (30 mL). The resulting mixture was warmed slowly to −25 °C and stirred for 30 min at this temperature to give a clear orange solution. After the mixture had again been cooled to −78 °C, a solution of (+)-**12** (1.00 g, 3.32 mmol) in THF (36 mL) was added dropwise and the mixture was stirred for 2 h before being quenched with saturated aqueous NH_4Cl/NH_4OH (32%): 2:1 solution (100 mL). After 1 h of stirring, the deep blue aqueous layer was extracted with Et_2O (2 × 75 mL) and CH_2Cl_2 (50 mL). The combined organic layers were washed with an aqueous NaOH solution (1 N, 2 × 75 mL) and brine (75 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (petroleum ether/EtOAc, 95:5 then 80:20) afforded (+)-**13** (1.28 g, 3.22 mmol, 97% yield) as a white solid: m.p. 112 °C; R_f = 0.33 (petroleum ether/EtOAc, 90:10). $[\alpha]_D^{20}$ = +48.8 (*c* = 1.01, $CHCl_3$), IR (KBr): $\tilde{\nu}$ = 1740, 1716, 1513, 1350, 1225, 1162 cm^{-1}. ^1H NMR: δ = 7.53−7.29 (5 H), 7.25 (m, 2 H), 7.04 (m, 2 H), 6.44 (s, 1 H), 4.30−4.12 (2 H), 4.11−3.99 (2 H), 3.98−3.81 (3 H), 1.95 (m, 1 H), 0.91 (d, *J* = 6.6 Hz, 3 H), 0.90 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR: δ = 170.8 (s), 167.9 (s), 162.3 (d, *J* = 247.2 Hz), 137.7 (s), 133.8 (d, *J* = 3.7 Hz), 128.8 (dd, *J* = 7.9 Hz), 128.8 (d), 128.5 (d), 126.0 (d), 116.9 (dd, *J* = 22.0 Hz), 87.4 (d), 71.9 (t), 70.8 (t), 63.7 (d), 59.4 (d), 49.2 (d), 27.7 (d), 18.7 (q) ppm. MS (EI): *m*/*z* (relative intensity) = 397 (46) [$M^{+\cdot}$], 396 (44), 367 (15), 340 (16), 296 (27), 291 (25), 190 (29), 166 (100), 149 (81), 148 (34), 121 (29), 105 (43). $C_{23}H_{24}FNO_4$ (397.44): calcd. C 69.51, H 6.09, N 3.52; found C 69.39, H 6.13, N 3.39.

Isobutyl (3*S*,4*R*,5*S*)-1-Benzyl-4-(4-fluorophenyl)-5-(hydroxymethyl)-pyrrolidine-3-carboxylate [(−)-14]: Borane−tetrahydrofuran complex (1.3 mL, 1 M in THF, 1.30 mmol, 10 equiv.) was added to a solution of (+)-**13** (51 mg, 0.13 mmol) in THF (1 mL) at room temp. The mixture was stirred for 1.5 h and then cooled to 0 °C before being quenched with MeOH (3 mL). The solution was concentrated under reduced pressure and the residue was dissolved in methanol (5 mL) before being heated under reflux for 1 h. The reaction mixture was concentrated under reduced pressure and this procedure was repeated twice. The crude material was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 90:10). Compound (−)-**14** (22 mg, 0.06 mmol, 44% yield) was then obtained as a yellowish solid, and compound (−)-**7** (6 mg, 0.02 mmol, 15% yield) as a yellowish oil.

Compound 14: M.p. 71 °C; R_f = 0.35 (petroleum ether/EtOAc, 80:20). $[\alpha]_D^{20}$ = −54.6 (*c* = 1.91, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3448, 1730, 1511, 1226, 1175, 1160 cm^{-1}. ^1H NMR: δ = 7.40−7.17 (7 H), 7.01 (m, 2 H), 4.07 (d, *J* = 13.2 Hz, 1 H), 3.81 (dd, *J* = 10.7, 7.0 Hz, 1 H), 3.78 (dd, *J* = 10.7, 6.6 Hz, 1 H), 3.75−3.63 (2 H), 3.48−3.36 (2 H), 3.41(d, *J* = 13.2 Hz, 1 H), 3.06 (ddd, *J* = 9.2, 8.1, 4.8 Hz, 1 H), 2.89 (dd, *J* = 9.9, 9.2 Hz, 1 H), 2.77 (dd, *J* = 9.2, 1.5 Hz, 1 H), 2.44 (br. s, 1 H), 1.80 (m, 1 H), 0.79 (d, *J* = 6.6 Hz, 3 H), 0.78 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR: δ = 173.6 (s), 161.8 (d, *J* = 245.4 Hz), 138.1 (s), 136.9 (d, *J* = 3.7 Hz), 129.5 (dd, *J* = 7.9 Hz), 128.5 (d), 128.4 (d), 127.3 (d), 115.5 (dd, *J* = 21.4 Hz), 73.0 (d), 70.9 (t), 57.9 (t), 57.6 (t), 56.0 (t), 49.3 (d), 48.8 (d), 27.6 (d), 18.9 (q) ppm. MS (EI): *m*/*z* (relative intensity) = 354 (95) [$M^{+\cdot}$ − $CH_2OH^{\cdot}$], 340 (11), 311 (10), 253 (12), 252 (36), 162 (34), 91 (100). HRMS (CI^+, CH_4) calcd. for $C_{23}H_{29}FNO_3$ [M + H]$^+$ 386.2131, found 386.2130.

Isobutyl (3*R*,4*R*,5*S*)-5-[(Benzyloxy)methyl]-4-(4-fluorophenyl)-2-oxo-pyrrolidine-3-carboxylate [(+)-14′′]: $BF_3{\cdot}Et_2O$ (18 μL, 0.14 mmol, 1.1 equiv.) was added dropwise at −78 °C to a solution of (+)-**13** (50 mg, 0.13 mmol) and triethylsilane hydride (22 μL, 0.14 mmol, 1.1 equiv.) in CH_2Cl_2 (0.7 mL). The reaction mixture was stirred for 30 min at this temperature before further addition of Et_3SiH (22 μL, 0.14 mmol, 1.1 equiv.) and $BF_3{\cdot}Et_2O$ (18 μL, 0.14 mmol, 1.1 equiv.). The reaction mixture was stirred for 2 h at −78 °C and quenched with a saturated aqueous $NaHCO_3$ (1 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica gel (petroleum ether/EtOAc, 70:30) gave compound (+)-**14′′** (48 mg, 0.12 mmol, 95% yield) as a colourless oil: R_f = 0.53 (EtOAc/petroleum ether, 40:60). $[\alpha]_D^{20}$ = +6.1 (*c* = 2.10, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 3228, 1736, 1709, 1513, 1227, 1162 cm^{-1}. ^1H NMR: δ = 7.43−7.25 (5 H), 7.22 (m, 2 H), 7.04 (m, 2 H), 6.72 (br. s, 1 H), 4.53 (d, *J* = 11.8 Hz, 1 H), 4.48 (d, *J* = 11.8 Hz, 1 H), 4.10−3.76 (3 H), 3.74−3.36 (4 H), 1.93 (m, 1 H), 0.88 (d, *J* = 6.6 Hz, 3 H), 0.87 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR: δ = 170.5 (s), 168.7 (s), 162.1 (d, *J* = 246.6 Hz), 137.3 (s), 134.7 (d, *J* = 3.0 Hz), 129.1 (dd, *J* = 7.9 Hz), 128.5 (d), 127.9 (d), 127.7 (d), 116.0 (dd, *J* = 21.4 Hz), 73.5 (t), 72.1 (t), 71.7 (t), 59.3 (d), 56.4 (d), 46.3 (d), 27.6 (d), 18.9 (q) ppm. MS (CI^+, CH_4): *m*/*z* (relative intensity) = 400 (100) [M + H^+], 398 (20), 344 (6), 343 (4), 326 (12), 312 (5), 293 (3), 154 (2). HRMS (CI^+, CH_4) calcd. for $C_{23}H_{27}FNO_4$ [M + H]$^+$ 400.1924, found 400.1921.

Isobutyl (3*S*,4*R*,5*S*)-1-Benzyl-5-chloro-4-(4-fluorophenyl)piperidine-3-carboxylate [(−)-15]: Methanesulfonyl chloride (24 μL, 0.31 mmol, 1.1 equiv.) was added dropwise at 0 °C to a solution of (−)-**14** (110 mg, 0.28 mmol) in 1,2-dichloroethane (1.8 mL). The mixture was stirred for 50 min, and Et_3N (0.12 mL, 0.86 mmol, 3.1 equiv.) was added. The resulting solution was heated under reflux for 36 h and quenched with an aqueous NaOH solution (1 N, 0.5 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (petroleum ether/EtOAc, 95:5) afforded (−)-**15** (95 mg, 0.23 mmol, 84% yield) as a white solid: M.p. 77 °C; R_f = 0.35 (petroleum ether/EtOAc, 95:5). $[\alpha]_D^{20}$ = −5.2 (*c* = 1.06, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1728, 1513, 1229, 1186, 1150, 750 cm^{-1}. ^1H NMR: δ = 7.44−7.28 (5 H), 7.23 (m, 2 H), 7.03 (m, 2 H), 4.09 (ddd, *J* = 10.7, 10.7, 4.4 Hz, 1 H), 3.67 (dd, *J* = 10.7, 6.6 Hz, 1 H), 3.66 (s, 2 H), 3.57 (dd, *J* = 10.7, 6.6 Hz, 1 H), 3.37 (ddd, *J* = 11.4, 4.4, 1.5 Hz, 1 H), 3.15 (ddd,

J = 11.0, 3.3, 1.5 Hz, 1 H), 3.07−2.85 (2 H), 2.48−2.31 (2 H), 1.64 (m, 1 H), 0.71 (d, J = 6.6 Hz, 3 H), 0.70 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR: δ = 171.5 (s), 162.0 (d, J = 245.4 Hz), 137.1 (s), 135.2 (d, J = 3.0 Hz), 129.6 (dd, J = 7.9 Hz), 128.9 (d), 128.4 (d), 127.4 (d), 115.2 (dd, J = 31.4 Hz), 70.6 (t), 62.0 (t), 61.0 (t), 59.6 (d), 55.4 (t), 52.8 (d), 50.0 (d), 27.4 (d), 18.7 (q) ppm. MS (EI): *m*/*z* (relative intensity) = 405 (1) [M$^{+\cdot}$], 403 (3) [M$^{+\cdot}$], 369 (14), 368 (56), 354 (39), 314 (11), 312 (31), 276 (25), 91 (100). HRMS (CI$^+$, CH_4) calcd. for $C_{23}H_{28}{}^{35}ClFNO_2$ [M + H]$^+$ 404.1793, found 404.1788 and calcd. for $C_{23}H_{28}{}^{37}ClFNO_2$ [M + H]$^+$ 406.1773, found 406.1765.

Isobutyl (3*S*,4*R*)-1-Benzyl-4-(4-fluorophenyl)piperidine-3-carboxylate [(−)-16]: *n*Bu_3SnH (122 μL, 0.44 mmol, 1.1 equiv.) and AIBN (3 mg, 0.02 mmol, 0.05 equiv.) were added to a solution of (−)-**15** (161 mg, 0.40 mmol) in toluene (2.10 mL). The resulting solution was heated under reflux for 1.75 h and the toluene was evaporated. The crude product was then dissolved in CH_2Cl_2 (5 mL) and washed with a saturated aqueous KF solution (3 × 5 mL). The resulting organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography on silica gel (pentane, then pentane/CH_2Cl_2, 96:4, then pentane/Et_2O, 80:20) afforded compound (−)-**16** (105 mg, 0.28 mmol, 71% yield) as a colourless oil: R_f = 0.48 (pentane/diethyl ether, 80:20). $[\alpha]_D^{20}$ = −5.6 (c = 1.05, $CHCl_3$). IR (neat): $\tilde{\nu}$ = 1735, 1560, 1511, 1458, 1226, 1160 cm^{-1}. ^{1}H NMR: δ = 7.44−7.25 (5 H), 7.21 (m, 2 H), 6.98 (m, 2 H), 3.66 (dd, J = 10.7, 6.6 Hz, 1 H), 3.61 (s, 2 H), 3.59 (dd, J = 10.7, 6.6 Hz, 1 H), 3.17 (ddd, J = 11.0, 3.5, 1.5 Hz, 1 H), 3.02 (m, 1 H), 2.96−2.74 (2 H), 2.28 (dd, J = 11.0, 10.7 Hz, 1 H,), 2.17 (m, 1 H), 1.85 (m, 2 H), 1.65 (m, 1 H), 0.71 (d, J = 6.6 Hz, 6 H) ppm. ^{13}C NMR: δ = 173.2 (s), 161.6 (d, J = 244.1 Hz), 139.2 (d, J = 3.0 Hz), 138.0 (s), 129.0 (d), 128.7 (dd, J = 7.3 Hz), 128.2 (d), 127.1 (d), 115.1 (dd, J = 21.4 Hz), 70.3 (t), 62.9 (t), 56.1 (t), 53.5 (t), 49.5 (d), 44.7 (d), 33.3 (t), 27.4 (d), 18.7 (q) ppm. MS (EI): *m*/*z* (relative intensity) = 369 (13) [M$^{+\cdot}$], 296 (13), 279 (14), 278 (16), 268 (20), 232 (13), 146 (14), 132 (17), 120 (20), 119 (18), 91 (100). HRMS (EI) calcd. for $C_{23}H_{28}FNO_2$ 369.2104, found 369.2101.

(3*S*,4*R*)-[1-Benzyl-4-piperidin-3-yl-4-(4-fluorophenyl)]methanol [(−)-17]: A solution of (−)-**16** (103 mg, 0.28 mmol) in THF (1.00 mL) was added at 0 °C to a suspension of $LiAlH_4$ (23 mg, 0.57 mmol, 2 equiv.) in THF (0.15 mL). The mixture was allowed to warm at room temp. and stirred for 50 min before successive additions of water (3 μL), aqueous NaOH (3.75 N, 37 μL), and water (238 μL). After 1 h, the mixture was filtered through Celite and concentrated under reduced pressure. Purification of the crude material by flash column chromatography on silica gel ($CHCl_3$/MeOH, 97:3) afforded alcohol (−)-**17** (84 mg, 0.28 mmol, 100% yield) as a yellowish oil: R_f = 0.35 ($CHCl_3$/MeOH, 97:3). $[\alpha]_D^{20}$ = −15.8 (c = 1.05, $CHCl_3$) [for hydrochloride (−)-**17**·HCl $[\alpha]_D^{20}$ = −10.6 (c = 1.00, MeOH)]. IR (neat): $\tilde{\nu}$ = 3377, 1509, 1223, 833, 700 cm^{-1}. ^{1}H NMR: δ = 7.41−7.23 (5 H), 7.17 (m, 2 H), 6.98 (m, 2 H), 3.63 (d, J = 13.2 Hz, 1 H), 3.56 (d, J = 13.2 Hz, 1 H), 3.36 (dd, J = 11.0, 2.2 Hz, 1 H), 3.28−3.11 (2 H), 2.98 (m, 1 H), 2.34 (m, 1 H), 2.12−1.92 (3 H), 1.91−1.69 (3 H) ppm. ^{13}C NMR: δ = 161.4 (d, J = 244.1 Hz), 140.1 (d, J = 3.0 Hz), 137.9 (s), 129.3 (d), 128.8 (dd, J = 7.9 Hz), 128.2 (d), 127.1 (d), 115.3 (dd, J = 21.4 Hz), 63.9 (t), 63.4 (t), 57.2 (t), 53.8 (t), 44.2 (d), 44.1 (d), 34.4 (t) ppm. MS (EI): *m*/*z* (relative intensity) = 299 (27) [M$^{+\cdot}$], 298 (24), 268 (19), 208 (19), 176 (20), 120 (39), 91 (100); CI (CH_4): *m*/*z* (relative intensity) = 300 (100) [M + H$^+$], 283 (5), 282 (28), 281 (4), 280 (15), 222 (3), 204 (3), 154 (3).

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