Diastereoselective conjugate addition of organocuprates to chiral racemic olefinic amido esters. Formal total synthesis of paroxetine

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The diastereoselective conjugate addition of an organocopper reagent to a chiral racemic olefinic amido ester has been used as the key step in a formal total synthesis of paroxetine.

Introduction

A large number of piperidine containing compounds, either natural or synthetic, are of biological and medicinal interest.[1] Consequently, the development of methods for the synthesis of optically active substituted piperidines has been the subject of considerable synthetic efforts.[2] General strategies for the synthesis of enantio-enriched, substituted piperidines utilizing amino acids, chiral catalysts or auxiliaries[2a,3] and focusing on asymmetric carbon substitution at the C-2 and C-6 positions have been developed.[3,4] Methods providing substitutions at C-3, C-4 and C-5 of the piperidine ring are quite limited.[2a,3,5] For our part, we were interested in the synthesis of *trans*-3,4-disubstituted piperidines[6] as these structures are present in (−)-paroxetine[7,8] and (+)-femoxetine[8,9] (Fig. 1), which are related to serotonin (5-hydroxytryptamine) reuptake inhibitors, which have been used clinically for the treatment of depression, obsessive compulsive disorder and panic disorder.[10] Due to the importance of its biological properties, several syntheses of these compounds have been achieved.[5a,c,d,11]

The stereochemical configuration at the C-3 and C-4 positions of the piperidine ring are critical for the activity of these compounds.[11k] Here, we would like to report that 3,4-disubstituted piperidines and more particularly, paroxetine, can be obtained by diastereoselective conjugate addition of an organocopper compound to chiral racemic cyclic olefinic amido esters. The conjugated addition of cuprates to asymmetric shielded enoates[12] has developed into an important and well-known method for assembling structurally complex organic molecules. Outstanding results were obtained by Helmchen and Wegner[13] on the conjugate addition of organocopper compounds to enoates of the camphor derived chiral auxiliaries **A*** or **B*** (Fig. 2), which generally proceed with high diastereoselectivity and in good yields.[14]

In connection with the formal synthesis of paroxetine, we investigated the preparation of chiral racemic olefinic amido carboxylate **5**, which could be synthetized from δ-valerolactam and camphor auxiliary **A*** according to the retrosynthetic scheme (Scheme 1).

Results and discussion

Treatment of *N*-Boc δ-valerolactam **1**[15] with LiHMDS at −78 °C (1.3 equiv., THF) followed by the addition of methyl chloroformate afforded the corresponding methyl amidocarboxylate **2**[16] in 93% yield. The transesterification of **2** with the chiral racemic auxiliary **A*** was achieved in the presence of DMAP (1.7 equiv.) and 4 Å molecular sieves in refluxing toluene.[17a] The desired compound **3** was obtained as a mixture of two diastereomers in a 65:35 ratio with a maximum yield of 50%. It is worth noting that the ring-opened product **3′** was also isolated as a mixture of two diastereomers in a 70:30 ratio with yields between 22% and 82% (Scheme 2).

The formation of **3** and **3′** can be explained by the generation of the ketene intermediates[17] **I** and **II** according to Scheme 3. The abstraction of the acidic proton in **2** by DMAP can produce either ketene **I** (path a) or ketene **II** (path b). These two ketenes can be trapped by a nucleophile such as **A*** to produce **3** and **3′**, respectively. It is worth noting that when compound **3′** was treated with DMAP, ketene **III** was probably not formed, as compound **3** was not formed (Scheme 3).

The amido ester **3** was then transformed into the key unsaturated compound **5** by using an oxidative deselenylation reaction. Several basic conditions were examined for the synthesis

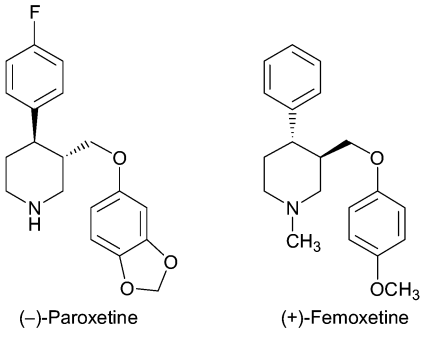


Fig. 1 Serotonin reuptake inhibitors.

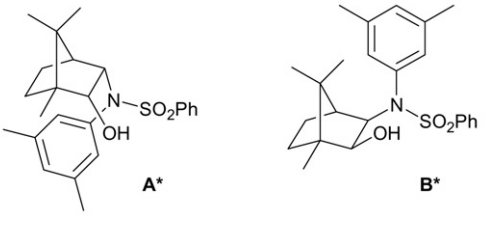
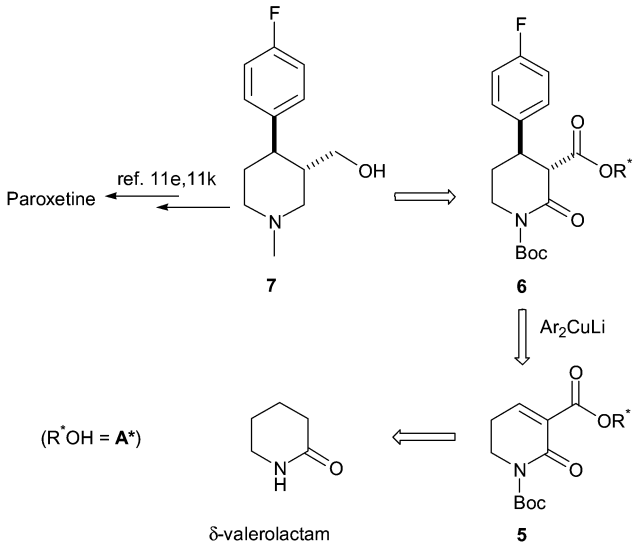


Fig. 2 Camphor derived chiral auxiliaries.



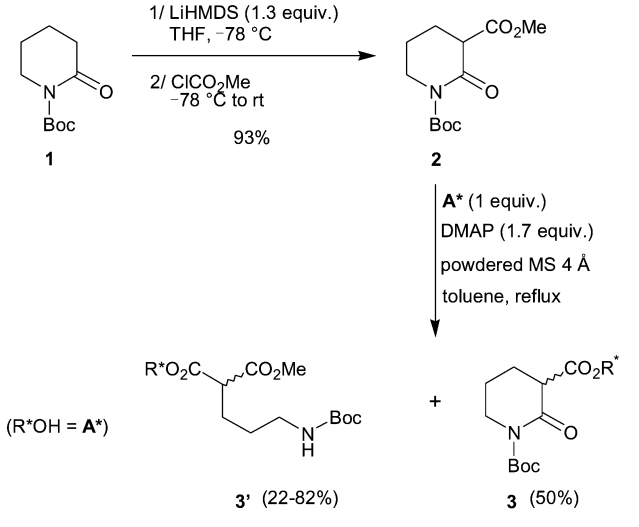
Scheme 1 Retrosynthetic analysis.

of the seleno compound **4** by using phenylselenyl chloride (PhSeCl). The results are summarized in Table 1. Treatment of **3** with NaH or KH at room temperature, followed by addition of PhSeCl, did not produce the desired compound **4** (Table 1, entries 1 and 2). However, when the anion of **3** was generated by NaH in the presence of HMPA in refluxing THF for 1 h, followed by the addition of PhSeCl, compound **4** was isolated as a mixture of two diastereomers in a 75:25 ratio in 48% yield (Table 1, entry 3). This yield was increased to 53% or 68% for a 75% conversion of **3** when the reaction mixture was sonicated for 15 min to 1 h at room temperature (Table 1, entries 4 and 5).

Subsequent oxidation of selenide **4** using H_2O_2 provided the desired α,β-unsaturated ester **5** in quantitative yield (Scheme 4).

Because **5** is a valuable material, the conjugate addition of the 4-fluorophenyl on the achiral unsaturated lactam **9** was studied. This compound was prepared from δ-valerolactam in 3 steps with an overall yield of 74% (Scheme 5).

As 1,4-addition products can be obtained by treatment of α,β-unsaturated carbonyl compounds with Grignard reagents, 4-fluorophenylmagnesium bromide was added to **9** in ether at −10 °C. Under these conditions, a complex mixture of non-identified products was obtained and the desired product **10** was not formed. The addition of a catalytic amount of $CuBr{\cdot}SMe_2$ to the Grignard reagent, in ether, did not produce



Scheme 2 Synthesis of chiral racemic amido ester **3**.

compound **10**. By changing the solvent to THF and cooling the reaction to −78 °C, compound **10** was obtained as a single isomer in 30% yield. The yield of **10** was further increased to 67% when lithium (4-fluorophenyl)cyanocuprate in THF was added at −78 °C and the temperature was raised to 0 °C. The best yield in **10** (80%) was obtained by using lithium di(4-fluorophenyl)cuprate in THF at −78 °C and raising the temperature to 0 °C. The results are summarized in Table 2. It is worthy of note that the *trans* isomer was the only detected compound. The relative *trans* configuration of the aromatic group and the benzyl carboxylic group was determined by the value of the coupling constants between H_3 and H_4 [H_3: 3.67 (d, 1H, J = 11.8 Hz); H_4: 3.44 (ddd, 1H, J = 11.8, 11.4 and 4 Hz)].

According to these results, lithium di(4-fluorophenyl)cuprate was added to **5** at −78 °C and the temperature was raised to 0 °C. Under these conditions, **6** was obtained in 65% yield without any control of the diastereoselectivity. On the contrary, when the reaction was performed at −78 °C for 2 h, compound **6** was obtained in 80% yield and only one diastereomer was obtained (d:r > 98:2). The relative stereochemistry of the substituants of the piperidine ring at C_3 and C_4 was determined by NOE experiments. NOE effects were observed between H_7 (7.48–7.27 ppm) and H_3 (d, 3.93 ppm) and $H_{5\beta}$ (m, 2.44 ppm). Furthermore, NOE effects were observed between H_4 (m, 4.08 ppm) and $H_{5\alpha}$ (m, 1.99–1.82 ppm), indicating that H_3 and H_4 are antiperiplanar (Fig. 3).

However, the relative configuration between the chiral auxiliary and the substituants of the piperidine could not be established as no NOE effects were observed with the protons of the auxiliary. The relative configuration of the substituents in compound **6** was established by X-ray diffraction analysis (Fig. 4).[18]

These analyses showed that during the conjugate addition, compound **5** was attacked by the organocopper reagent on its less sterically hindered face of the *s-trans* enoate double bond. To control the diastereoselectivity of the nucleophilic attack, the temperature has to be maintained to −78 °C to favour the π-stacking interaction between the olefin and the aromatic group present in **5** (Scheme 6).

Alternatively, the *trans* relationship between the substituents at C_3 and C_4 on the piperidine ring can be explained by an *in situ* epimerisation at C_3, which would lead to the thermodynamically more stable isomer.

The formal synthesis of (±)-paroxetine was completed as follows: piperidine **6** was reduced by $LiAlH_4$ in refluxing THF to produce the known amino alcohol **7** in 85% yield for which spectral data are in accordance with those reported in the literature[11d] (Scheme 6).

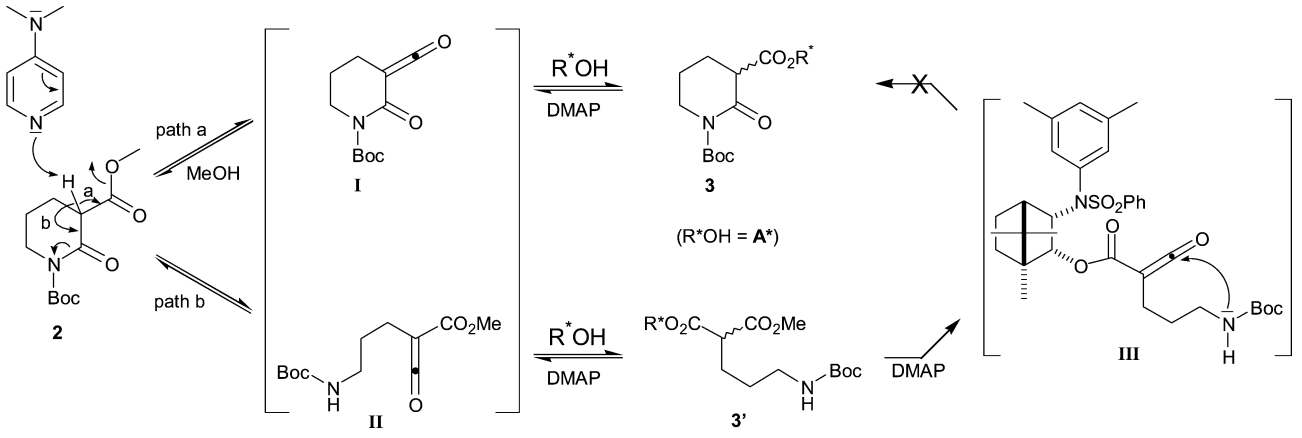
Conclusion

As compound **7** was transformed to paroxetine,[11e,11k] the transformation of *N*-Boc protected δ-valerolactam **1** to **7** in 6 steps constitutes a formal synthesis of paroxetine (Scheme 7). Futhermore, the use of the chiral auxiliary **A*** in an enantiomerically pure form would furnish (−)-paroxetine.

Experimental

General methods

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 under an argon atmosphere. Analytical thin-layer chromatography was performed on Merck precoated silica gel ($60F_{254}$) plates and flash column chromatography was accomplished on Merck Kieselgel 60



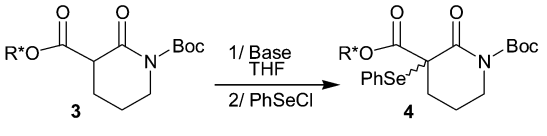
Scheme 3 Proposed mechanism and intermediates leading to **3** and **3′**.

(230–400 mesh). Melting points are uncorrected. IR spectra were taken on Perkin–Elmer 298 or Perkin–Elmer 1600 instrucments. Elemental analyses were performed by the Service Régional de Microanalyse de l'Université P. et M. Curie. HRMS spectra were acquired by the Centre de Spectrochimie Organique de l'Université P. et M. Curie or the Centre de Spectrochimie de l'Ecole Normale Supérieure. NMR spectra were recorded on a Bruker AC 300 spectrometer (300 MHz and 75 MHz for ^{1}H and ^{13}C, respectively) in $CDCl_3$ as solvent, and chemical shifts are expressed in ppm relative to residual $CHCl_3$ at $\delta = 7.27$ for ^{1}H and to $CDCl_3$ at $\delta = 77.1$ for ^{13}C. 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.

Syntheses

1-(*tert*-Butoxycarbonyl)piperidin-2-one, 1[15]. To a solution of δ-valerolactam (6.0 g, 60.5 mmol), DMAP (1.85 g, 15.1 mmol, 0.2 equiv.) and Boc_2O (26.4 g, 121.0 mmol, 2.0 equiv.) in CH_2Cl_2 (70 mL) at room temperature was added Et_3N (17.8 mL, 127.7 mmol, 2.1 equiv.). The solution was stirred for 32 h before being quenched with aqueous 1.2 N HCl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3×20 mL); the combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution (20 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (cyclohexane–EtOAc 80:20) to give compound **1** (9.71 g, 48.7 mmol, 81% yield) as a colorless low melting point solid. Mp 36 °C; R_f 0.40 (cyclohexane–EtOAc 70:30); IR (KBr) 1713, 1302, 1249, 1159, 1138 cm^{-1}; ^{1}H NMR δ 3.66 (m, 2H), 2.50 (m, 2H), 1.90–1.74 (4H), 1.53 (s, 9H); ^{13}C NMR δ 171.1 (s), 152.4 (s), 82.5 (s), 46.0 (t), 34.6 (t), 27.7 (q), 22.5 (t), 20.2 (t); EI MS m/z (relative intensity) 199 ($M^{+\bullet}$, 0.3), 144 (52), 126 (21), 100 (38), 99 (31), 98 (31), 82 (24), 57 (100), 56 (38), 55 (30).

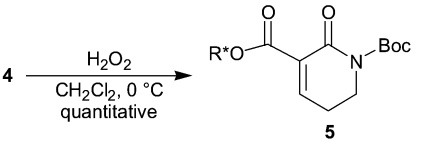
Table 1 Conditions for the synthesis of **4**



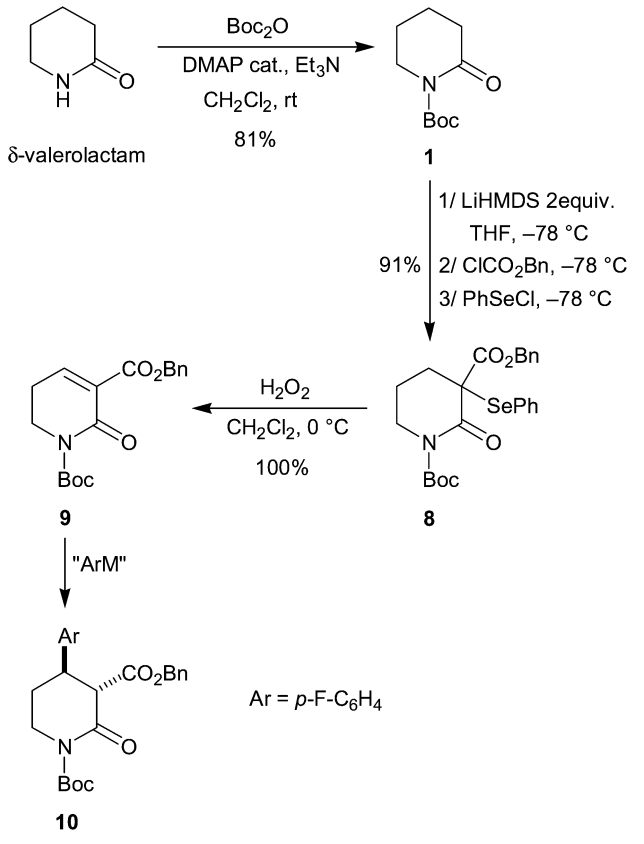
Entry	Basic conditions	% Conversion	% Yield
1	KH, rt	0	—
2	NaH, rt	0	—
3	NaH, HMPA, reflux	100	48
4	NaH, HMPA, rt sonication (15 min)	75	53
5	NaH, HMPA, rt sonication (1 h)	75	68

Methyl 1-(*tert*-butoxycarbonyl)-2-oxopiperidine-3-carboxylate, 2[16]. To a solution of LiHMDS (6.5 mL, 1 M in THF, 6.5 mmol, 1.3 equiv.) in THF (20 mL) at −78 °C was added dropwise a solution of **1** (1.00 g, 5.02 mmol) in THF (23 mL). The resulting solution was stirred at −78 °C for 70 min. Methyl chloroformate (0.5 mL, 6.5 mmol, 1.3 equiv.) was added and the reaction mixture was allowed to warm to room temperature over 17 h. Aqueous 1.2 N HCl solution (5 mL) was then added followed by ether (20 mL) and water (10 mL). The organic layer was separated and the aqueous layer was extracted with ether (2×20 mL) and CH_2Cl_2 (20 mL). The combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution (30 mL) and brine (30 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude product, a pale red oil, was purified by flash column chromatography on silica gel (cyclohexane–EtOAc 85:15) to give compound **2** (1.21 g, 4.70 mmol, 93% yield) as a pale yellow oil. R_f 0.40 (cyclohexane–EtOAc 70:30); IR (neat) 1773, 1718, 1369, 1294, 1255, 1149 cm^{-1}; ^{1}H NMR δ 3.75 (s, 3H), 3.71–3.59 (2 H), 3.51 (dd, $J = 8.8$ and 7.0 Hz, 1H), 2.26–1.70 (4H), 1.51 (s, 9H); ^{13}C NMR δ 170.3 (s), 167, 2 (s), 152.5 (s), 83.3 (s), 52.5 (q), 51.2 (d), 45.7 (t), 27.9 (q), 24.1 (t), 20.9 (t); EI MS m/z (relative intensity) 257 ($M^{+\bullet}$, 0.4), 216 (71), 215 (58), 184 (66), 156 (39), 145 (38), 124 (51), 113 (53), 57 (100).

(1*S,2*R**,3*S**,4*R**)-3-[(3,5-Dimethylphenyl)(phenylsulfonyl)-amino]-1,7,7-trimethylbicyclo[2.2.1]-hept-2-yl 1-(*tert*-butoxycarbonyl)-2-oxopiperidine-3-carboxylate, 3, and (1*S**,2*R**,3*S**,4*R**)-3-[(3,5-Dimethylphenyl)(phenylsulfonyl)amino]-1,7,7-trimethylbicyclo-[2.2.1]hept-2-yl 5-[(*tert*-butoxycarbonyl)amino]-2-(methoxycarbonyl)pentanoate, 3′.** A mixture of compound **2** (100 mg, 0.37 mmol, 1.95 equiv.), alcohol **A*** (80 mg, 0.19 mmol), DMAP (40 mg, 0.33 mmol, 1.7 equiv.) and 4 Å molecular sieves in toluene (1 mL) was refluxed for 20 h. The formed methanol was distilled continously. The reaction mixture was concentrated under reduced pressure and ether



Scheme 4 Synthesis of chiral racemic ester **5**.



Scheme 5 Preparation of lactam **10**.

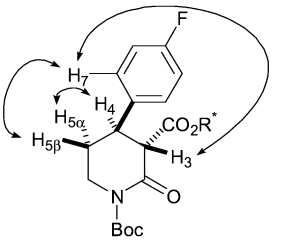


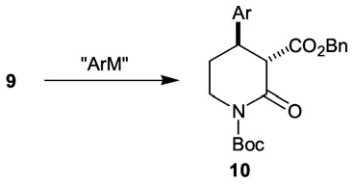
Fig. 3 NOE effects.

(2 mL) was added. The organic layer was washed with an aqueous 1.2 N HCl solution (1 mL), with brine (1 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel (EtOAc–cyclohexane 15:85) to give compound **3** (60 mg, 0.09 mmol, 65:35 mixture of diastereomers, 50% yield) as a white solid and compound **3′** (28 mg, 0.04 mmol, 70:30 mixture of diastereomers, 22% yield) as a solid.

Compound **3**. Mp 94 °C; R_f 0.44 (EtOAc–cyclohexane 30:70); IR (KBr) 1773, 1741, 1720, 1367, 1353, 1300, 1251, 1168, 1146, 1090 cm^{-1}; ^1H NMR δ 7.51 (m, 1H), 7.40–7.31 (4H), 7.13 (br s, 0.35H), 7.04 (br s, 0.65H), 6.85 (br s, 0.35H), 6.83 (br s, 0.65H), 5.92 (br s, 0.65H), 5.61 (br s, 0.35H), 5.51 (d, J = 8.8 Hz, 0.35H), 5.40 (d, J = 8.8 Hz, 0.65H), 4.19 (dd, J = 8.8 and 3.3 Hz, 1H), 3.86 (m, 0.65H), 3.75–3.57 (2.35H), 2.61 (m, 0.35H), 2.39–1.74 (4.30H), 2.34 (s, 1.05H), 2.30 (s, 1.95H), 2.04 (s, 1.95H), 1.99 (s, 1.05H), 1.73–0.72 (4.35H), 1.51 (s, 3.15H), 1.50 (s, 5.85H), 1.02 (s, 3H), 0.90 (s, 3H), 0.81 (s, 1.95H), 0.77 (s, 1.05H); ^{13}C NMR (major isomer) δ 169.6 (s), 167.9 (s), 152.1 (s), 139.2 (s), 138.2 (s), 137.0 (s), 136.8 (s), 132.5 (d), 129.2 (d), 128.1 (d), 128.0 (d), 127.6 (d), 82.8 (s), 77.2 (d), 59.2 (d), 51.4 (d), 51.3 (s), 49.5 (d), 45.9 (t), 45.6 (s), 27.9 (q), 26.8 (t), 23.5 (t), 21.1 (t), 20.9 (q), 19.5 (t), 19.3 (q), 14.0 (q); ^{13}C NMR (minor isomer) δ 169.0 (s), 167.4 (s), 152.6 (s), 138.2 (s), 138.3 (s), 136.6 (s), 136.1 (s), 132.6 (d), 130.4 (d), 129.4 (d), 128.4 (d), 127.3 (d), 82.7 (s), 77.1 (d), 59.1 (d), 52.4 (d), 51.8 (s), 49.2 (d), 46.1 (t), 45.4 (s), 27.9 (q), 26.5 (t), 24.0 (t), 21.3 (t), 21.1 (q), 19.5 (t), 19.2 (q), 14.3 (q); MS CI$^+$ (NH_3) m/z (relative intensity) 656 ($M + NH_4^+$, 14), 500 (56), 499 (100), 498 (12), 399 (22), 274 (14), 256 (51), 200 (11), 144 (12), 100 (10); Anal. calcd for $C_{35}H_{46}N_2O_7S$: C, 65.81; H, 7.26; N, 4.38; found C, 65.85; H, 7.29; N, 4.25.

Compound **3′**. Mp 75 °C; R_f 0.34 (EtOAc–cyclohexane 30:70); IR (KBr) 3410, 1758, 1735, 1712, 1446, 1365, 1354, 1252, 1170, 1092 cm^{-1}; ^1H NMR δ 7.53 (m, 1H), 7.45–7.32 (4H), 7.16 (br s, 0.3H), 7.00 (br s, 0.7H), 6.89 (br s, 0.3H), 6.86 (br s, 0.7H), 5.97 (br s, 0.7H), 5.76 (br s, 0.3H), 5.45 (d, J = 8.8 Hz, 0.3H), 5.40 (d, J = 8.8 Hz, 0.7H), 4.87 (br s, 0.3H), 4.70 (br s, 0.7H), 4.23 (ddd, J = 8.8, 8.8 and 3.7 Hz, 1H), 3.78 (s, 3H), 3.54 (dd, J = 15.4 and 7.7 Hz, 1H), 3.29–3.09 (2H), 2.37 (s, 0.9H), 2.32 (s, 2.1H), 2.08 (s, 2.1H), 2.05 (s, 0.9H), 2.06–1.78 (2.7H), 1.75–1.49 (2.3H), 1.41 (s, 6.3H), 1.40 (s, 2.7H), 1.32–1.02 (4H), 0.90–0.77 (9H); ^{13}C NMR (major isomer) δ 170.3 (s), 168.9 (s), 156.0 (s), 139.2 (s), 138.7 (s), 138.3 (s), 136.9 (s), 132.5 (d), 129.3 (d), 129.1 (d), 128.2 (d), 128.1 (d), 127.7 (d), 79.0 (s), 77.3 (d), 59.0 (d), 52.3 (q), 51.5 (s), 51.3 (d), 49.6 (d), 45.7 (s), 40.1 (t), 28.4 (q), 28.0 (t), 26.6 (t), 25.6 (t), 21.2 (q), 21.0 (q), 19.5 (q), 19.3 (q), 14.0 (q); ^{13}C NMR (minor isomer) δ 169.8 (s), 168.9 (s), 156.0 (s), 139.2 (s), 138.5 (s), 137.2 (s), 136.9 (s), 132.5 (d), 130.5 (d), 129.6 (d), 128.3 (d), 128.2 (d), 127.3 (d), 79.0 (s), 76.0 (d), 58.9 (d),

Table 2 Reagents and conditions of the 1,4-addition reaction



Entry	ArM	Solvent	Temperature/°C	% Yield
1	*p*-F–C_6H_4MgBr	Et_2O	–10 to RT	—
2	*p*-F–C_6H_4MgBr CuBr·Me_2S cat.	Et_2O	–78	—
3	*p*-F–C_6H_4MgBr CuBr·Me_2S cat	THF	–78	30
4	*p*-F–$C_6H_4Cu(CN)Li$	THF	–78 to 0	67
5	$(p\text{-F–}C_6H_4)_2CuLi$	THF	–78 to 0	80

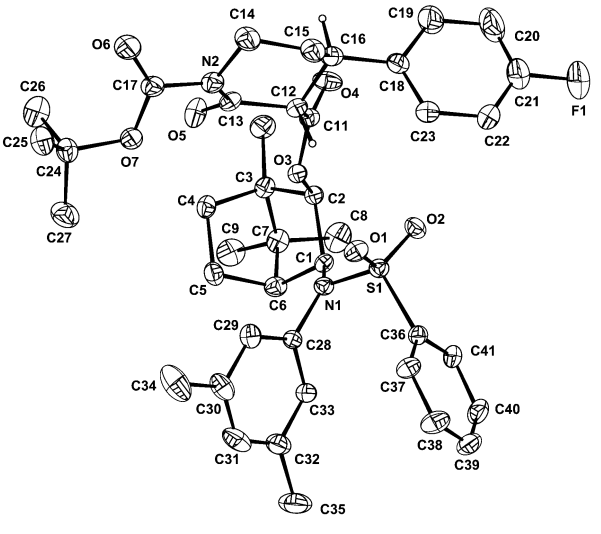
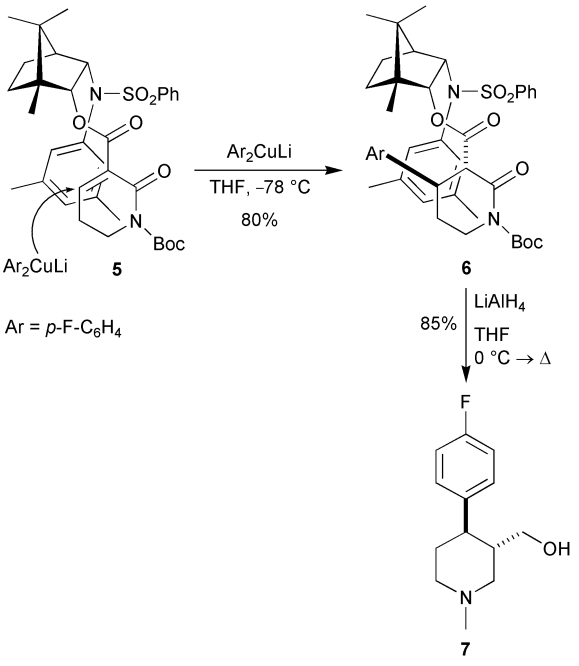


Fig. 4 ORTEP plot for compound **6**.



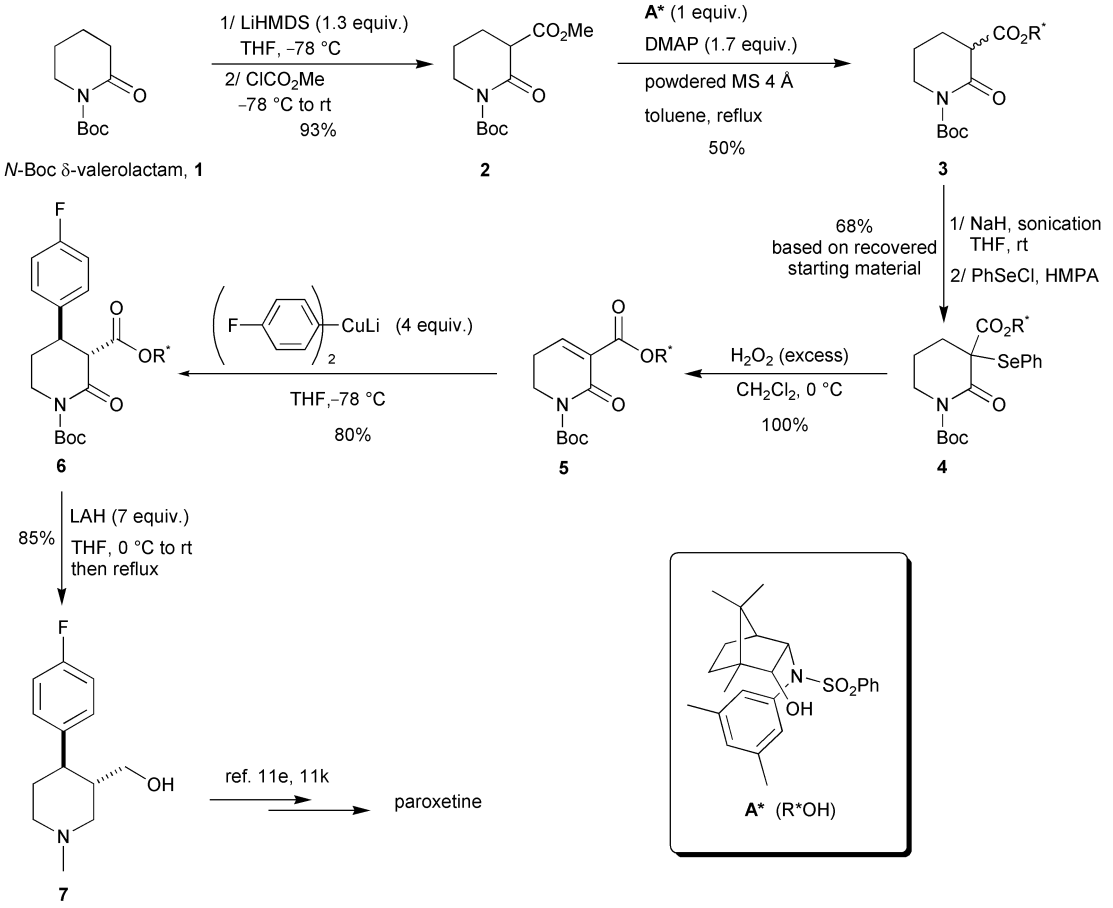
Scheme 6 Synthesis of the known amino alcohol **7**.

52.4 (d), 52.2 (q), 51.5 (s), 49.2 (d), 45.7 (s), 40.1 (t), 28.4 (q), 28.0 (t), 27.4 (t), 26.1 (t), 21.2 (q), 21.0 (q), 19.6 (q), 19.3 (q), 14.3 (q). MS (CI^+, CH_4) m/z (relative intensity) 671 ($M+H^+$, 6), 615 (45), 532 (33), 531 (100), 475 (35), 457 (59), 274 (37), 256 (60), 158 (38), 124 (39). HRMS (CI^+, CH_4) calcd for $C_{36}H_{51}N_2O_8S$ [$(M+H)^+$] 671.3366; found 671.3372.

(1*S,2*R**,3*S**,4*R**)-3-[(3,5-Dimethylphenyl)(phenylsulfonyl)-amino]-1,7,7-trimethylbicyclo[2.2.1]-hept-2-yl 1-(tert-butoxycarbonyl)-2-oxo-3-(phenylseleno)piperidine-3-carboxylate, 4.** To a suspension of NaH (37 mg, 60% in oil, 0.92 mmol, 2.0 equiv.) in THF (1.5 mL) at room temperature was added dropwise a solution of **3** (0.3 g, 0.47 mmol) in THF (1.5 mL). The mixture was stirred at room temperature for 1 h and under sonication for an additional hour. HMPA (0.29 mL, 1.67 mmol, 3.50 equiv.) and a solution of phenylselenyl chloride (0.18 g, 0.94 mmol, 2.0 equiv.) in THF (2.8 mL) were then added and the reaction mixture was stirred for 3 days at room temperature before being quenched with a saturated aqueous NH_4Cl solution (2 mL). The organic layer was then washed with a saturated aqueous $NaHCO_3$ solution (2 mL) and brine (2 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude product by flash column chromatography on silica gel (cyclohexane–EtOAc 85:15) gave compound **4** (0.19 g, 0.24 mmol, 75:25 mixture of diastereomers) in 68% yield based on recovered starting material (25%), as a yellow solid.

Major diastereomer. R_f 0.65 (EtOAc–cyclohexane 15:85). ^1H NMR δ 7.73 (m, 2H), 7.52 (m, 2H), 7.44–7.27 (7H), 6.83 (br s, 1H), 5.63 (dd, $J = 1.5$ and 8.5 Hz, 1H), 5.46 (br s, 1H), 4.20 (m, 1H), 3.91 (m, 1H), 3.60 (ddd, $J = 12.5$, 10.3 and 5.1 Hz, 1H), 2.39 (s, 3H), 2.34–1.51 (5H), 1.96 (s, 3H), 1.57 (s, 9H), 1.50–0.76 (4H), 1.09 (s, 3H), 1.06 (s, 3H), 0.80 (s, 3H). ^{13}C NMR δ 170.5 (s), 167.9 (s), 151.6 (s), 138.9 (s), 138.5 (s), 138.3 (d), 136.4 (s), 136.0 (s), 132.5 (d), 131.7 (d), 129.4 (d), 128.6 (d), 128.5 (d), 128.0 (d), 127.9 (d), 127.2 (d), 82.4 (s), 77.7 (d), 59.4 (d), 56.7 (s), 52.3 (s), 49.3 (d), 47.0 (t), 45.6 (s), 31.3 (t), 29.7 (t), 28.1 (q), 26.6 (t), 21.1 (q), 20.9 (q), 20.5 (t), 19.7 (q), 19.2 (q), 14.6 (q).

Minor diastereomer. R_f 0.41 (EtOAc–cyclohexane 15:85). ^1H NMR δ 7.88 (m, 2H), 7.67 (br s, 1H), 7.62–7.48 (3H),



Scheme 7 Formal total synthesis of paroxetine.

7.48–7.29 (5H), 6.92 (br s, 1H), 5.78 (br s, 1H), 5.59 (d, $J = 8.8$ Hz, 1H), 4.36 (dd, $J = 8.8$ and 2.9 Hz, 1H), 3.64 (m, 1H), 3.22 (ddd, $J = 12.5$, 10.3 and 4.8 Hz, 1H), 2.75 (m, 1H), 2.43 (s, 3H), 2.23 (ddd, $J = 14.0$, 11.4 and 4.6 Hz, 1H), 2.09 (s, 3H), 2.03–1.42 (5H), 1.48 (s, 9H), 1.24–0.95 (2H), 1.06 (s, 3H), 0.90 (s, 3H), 0.81 (s, 3H); ^{13}C NMR δ 169.4 (s), 168.3 (s), 152.7 (s), 138.6 (d), 138.5 (s), 137.2 (s), 136.7 (s), 132.4 (d), 131.9 (d), 129.6 (d), 129.3 (d), 128.6 (d), 128.2 (d), 126.9 (d), 82.8 (s), 78.4 (d), 58.7 (s), 57.4 (d), 51.7 (s), 48.9 (d), 46.5 (t), 45.8 (s), 33.3 (t), 30.1 (t), 27.9 (q), 26.9 (t), 21.2 (q), 21.0 (q), 20.8 (t), 19.7 (q), 19.2 (q), 14.4 (q).

Mixture of diastereomers. IR (KBr) 1772, 1723, 1368, 1354, 1281, 1255, 1167, 1147, 604 cm^{-1}; MS (CI$^+$, NH_3) m/z (relative intensity) 795 ($M + H^+$, 0.1), 793 ($M + H^+$, 0.05), 540 (8), 415 (28), 399 (50), 275 (17), 274 (83), 272 (16), 107 (29); HRMS (CI$^+$, NH_3) calcd for $C_{41}H_{51}N_2O_7S^{80}Se$ ($M + H^+$) 795.2586; found 795.2595. Calcd for $C_{41}H_{51}N_2O_7S^{78}Se$ ($M + H^+$) 793.2600; found 793.2603.

(1*S,2*R**,3*S**,4*R**)-3-[(3,5-Dimethylphenyl)(phenylsulfonyl)-amino]-1,7,7-trimethylbicyclo[2.2.1]-hept-2-yl 1-(*tert*-butoxycarbonyl)-2-oxo-1,2-5,6-tetrahydropyridine-3-carboxylate, 5.** To a solution of **4** (310 mg, 0.39 mmol) in CH_2Cl_2 (4 mL) at 0 °C was added dropwise a 30% aqueous H_2O_2 solution (3.0 mL, 29.7 mmol, 76 equiv.). The mixture was stirred at 0 °C for 4 h before being quenched with an aqueous 1.2 N HCl solution (2 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 2 mL) and the combined organic layers were washed with a saturated aqueous $NaHCO_3$ solution (2 × 5 mL), brine (5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Compound **5** (250 mg, 0.39 mmol, 100% yield) was obtained as a yellow solid. Mp 97 °C; R_f 0.35 (EtOAc–petroleum ether 30:70); IR (KBr) 1748, 1715, 1353, 1312, 1286, 1258, 1150 cm^{-1}; ^{1}H NMR δ 7.81 (dd, $J = 4.4$ and 4.4 Hz, 1H), 7.53 (m, 1H), 7.42–7.33 (4H), 6.97 (br s, 1H), 6.85 (br s, 1H), 5.87 (br s, 1H), 5.50 (d, $J = 9.2$ Hz, 1H), 4.25 (m, 1H), 4.07–3.85 (2H), 2.64–2.55 (2H), 2.31 (s, 3H), 2.04 (s, 3H), 1.96 (m, 1H), 1.81–0.77 (4H), 1.57 (s, 9H), 1.06 (s, 3H), 0.94 (s, 3H), 0.83 (s, 3H); ^{13}C NMR δ 163.4 (s), 160.3 (s), 152.4 (s), 148.1 (d), 139.1 (s), 138.2 (s), 137.0 (s), 136.8 (s), 132.6 (d), 131.0 (s), 129.5 (d), 129.4 (d), 128.2 (d), 128.1 (d), 127.7 (d), 83.1 (s), 77.1 (d), 59.4 (d), 51.5 (s), 49.6 (d), 45.7 (s), 43.3 (t), 29.7 (t), 28.1 (q), 27.1 (t), 24.7 (t), 21.1 (q), 21.0 (q), 19.6 (q), 19.4 (q), 14.3 (q); MS (CI$^+$, CH_4) m/z (relative intensity) 637 ($M + H^+$, 5), 536 (29), 537 (88), 414 (77), 412 (29), 397 (54), 396 (100), 274 (45), 273 (100), 124 (31); HRMS (CI$^+$, NH_3) calcd for $C_{35}H_{45}N_2O_7S$ ($M + H^+$) 637.2947; found 637.2945.

(1*S,2*R**,3*S**,4*R**)-3-[(3,5-Dimethylphenyl)(phenylsulfonyl)-amino]-1,7,7- trimethylbicyclo[2.2.1]-hept-2-yl 1-(*tert*-butoxycarbonyl)-2-oxo-4-(4-fluorophenyl)piperidine-3-carboxylate, 6.** To a solution of 4-fluorophenyl bromide (70 μL, 0.62 mmol, 8.0 equiv.) in THF (1,6 mL) at −78 °C was added *n*-butyllithium dropwise (0.25 mL, 2.5 M in hexanes, 0.62 mmol, 8.0 equiv.). The solution was stirred at −78 °C for 30 min and then added dropwise *via* cannula to a suspension of copper iodide (60 mg, 0.31 mmol, 4.0 equiv.) in THF (1 mL) at −78 °C. The mixture was allowed to warm slowly to −25 °C and stirred for 30 min to give a clear orange solution, which was cooled to −78 °C. A solution of **5** (50 mg, 0.08 mmol) in THF (1 mL) was then added dropwise and the reaction mixture was stirred 2 h at −78 °C before being quenched with a saturated aqueous NH_4Cl–NH_4OH (32%) 2:1 solution (2 mL). After 1 h stirring, the deep blue aqueous layer was extracted with Et_2O (2 × 4 mL) and CH_2Cl_2 (4 mL). The combined organic layers were washed with an aqueous 1 N NaOH solution (2 × 5 mL) and brine (5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane–EtOAc 95:5) afforded **6** (46 mg, 0.06 mmol, 80% yield) as a white solid. Mp 215–217 °C; R_f 0.25 (EtOAc–cyclohexane 10:90); IR (KBr) 1742, 1730, 1708, 1332, 1297, 1185, 1163 cm^{-1}; ^{1}H NMR δ 7.54 (m, 1H), 7.48–7.27 (6H), 7.06 (br s, 1H), 7.03 (m, 2H), 6.81 (br s, 1H), 5.86 (br s, 1H), 5.43 (d, $J = 8.5$ Hz, 1H), 4.23 (dd, $J = 8.5$ and 3.3 Hz, 1H), 4.08 (m, 1H), 3.93 (d, $J = 5.1$ Hz, 1H), 3.83 (ddd, $J = 13.2$, 6.6 and 4.8 Hz, 1H), 3.66 (ddd, $J = 13.2$, 9.2 and 4.0 Hz, 1H), 2.44 (m, 1H), 2.27 (s, 3H), 2.00 (s, 3H), 1.99–1.82 (2H), 1.74 (m, 1H), 1.54 (s, 9H), 1.34–0.99 (3H), 1.03 (s, 3H), 0.89 (s, 3H), 0.81 (s, 3H); ^{13}C NMR δ 168.8 (s), 167.3 (s), 161.7 (d, $J = 244.8$ Hz), 152.1 (s), 138.8 (s), 138.7 (d, $J = 3.7$ Hz), 138.3 (s), 137.1 (s), 136.9 (s), 132.5 (d), 130.1 (d), 129.4 (d), 128.8 (dd, $J = 7.9$ Hz), 128.2 (d), 127.5 (d), 115.6 (dd, $J = 21.4$ Hz), 83.1 (d), 78.0 (s), 59.0 (d), 57.4 (d), 51.2 (s), 49.2 (d), 45.8 (s), 43.5 (t), 39.7 (d), 30.5 (t), 28.0 (q), 26.7 (t), 21.1 (q), 20.9 (q), 19.5 (q), 19.4 (t), 19.3 (q), 14.4 (q); MS (CI$^+$, NH_3) (relative intensity)750 ($M + NH_4^+$, 11), 634 (37), 633 (92), 593 (20), 493 (40), 415 (29), 414 (100), 274 (23), 174 (20); HRMS (CI$^+$, NH_3) calcd for $C_{41}H_{50}FN_2O_7S$ ($M + H^+$) 733.3323; found 733.3317.

(3*S,4*R**)-4-(4-Fluorophenyl)-1-methylpiperidine-3-methanol, 7.** To a suspension of $LiAlH_4$ (28 mg, 0.7 mmol, 7 equiv.) in THF (0.2 mL) was added a solution of **6** (74 mg, 0.1 mmol) in THF (0.2 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 20 min. After refluxing for 5 h, the reaction mixture was quenched with water (4 μL), an aqueous 15% NaOH solution (43 μL) and water (140 μL) at 0 °C. After 1 h, the solution was filtered and the aluminium salts were extracted with hot EtOAc (3 × 1 mL). The combined organic layers were concentrated under reduced pressure and the resulting yellow oil was purified by flash column chromatography on silica gel (EtOAc–MeOH 90:10). Compound **7** was obtained (19 mg, 0.08 mmol, 85% yield) as a colorless oil. R_f 0.12 (EtOAc–MeOH 95:5); IR (neat) 3354, 1511, 1468, 1224, 1159, 1066, 1024, 831, 733 cm^{-1}; ^{1}H NMR δ 7.12 (m, 2H), 6.95 (m, 2H), 4.37 (br s, 1H), 3.31 (dd, $J = 10.7$ and 2.8 Hz, 1H), 3.21 (m, 1H), 3.08 (dd, $J = 10.7$ and 7.7 Hz, 1H), 2.86 (m, 1H), 2.23 (s, 3H), 2.22 (m, 1H), 2.04–1.66 (5H); ^{13}C NMR δ 161.2 (d, $J = 244.1$ Hz), 139.8 (d, $J = 3.1$ Hz), 128.6 (dd, $J = 7.8$ Hz), 114.7 (dd, $J = 21.0$ Hz), 62.9 (t), 59.5 (t), 56.0 (t), 46.2 (q), 44.2 (d), 43.5 (d), 34.0 (t); EI MS m/z (relative intensity) 223 ($M^{+\bullet}$, 100), 222 (75), 192 (56), 167 (10), 133 (16), 109 (23), 101 (10), 100 (66), 96 (13), 71 (16), 70 (27), 58 (22), 57 (14).

Benzyl 1-(*tert*-butoxycarbonyl)-2-oxo-3-(phenylseleno)piperidine-3-carboxylate, 8. To a solution of HMDS (4.45 mL, 21.06 mmol, 2.1 equiv.) in THF (100 mL) at −78 °C was added *n*-butyllithium dropwise (8.45 mL, 2.5 M in hexanes, 21.12 mmol, 2.1 equiv.). After 20 min at −78 °C, a solution of **1** (2.00 g, 10.04 mmol) in THF (40 mL) was added dropwise. The mixture was stirred at −78 °C for 35 min and benzyl chloroformate (1.43 mL, 10.02 mmol, 1 equiv.) was added dropwise. The solution was stirred for 30 min at −78 °C and a solution of phenylselenyl chloride (1.92 g, 10.02 mmol, 1 equiv.) in THF (20 mL) was added. The reaction was stirred for 2 h at this temperature before being quenched by the addition of an aqueous 1.2 N HCl solution (40 mL). The mixture was warmed to room temperature and was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude product by flash column chromatography on silica gel (cyclohexane–EtOAc 85:15) gave the compound **8** (4.45 g, 9.11 mmol, 91% yield) as a yellow oil. R_f 0.68 (EtOAc–cyclohexane 30:70); IR (neat) 1771, 1718, 1369, 1278, 1257, 1148, 744, 694 cm^{-1}; ^{1}H NMR δ 7.52 (m, 2H), 7.41–7.29 (6H), 7.25 (m, 2H), 5.26 (d, $J = 12.3$ Hz, 1H), 5.15 (d, $J = 12.3$ Hz, 1H), 3.60 (ddd, $J = 13.2$, 8.1 and 5.1 Hz, 1H), 3.38 (m, 1H), 2.24

(m, 1H), 2.00 (ddd, J = 13.6, 10.1 and 5.7 Hz, 1H), 1.88–1.56 (2H), 1.52 (s, 9H); ^{13}C NMR δ 169.2 (s), 167.6 (s), 152.6 (s), 138.4 (d), 135.1 (s), 129.6 (d), 128.6 (d), 128.4 (d), 128.2 (d), 128.0 (d), 126.3 (s), 83.3 (s), 67.6 (t), 56.8 (s), 45.2 (t), 31.7 (t), 27.9 (q), 20.8 (t); EI MS m/z (relative intensity) 389 [$M^{+\bullet} - CO_2$ and $-(CH_3)_2C{=}CH_2$, 18], 387 [$M^{+\bullet} - CO_2$ and $-(CH_3)_2C{=}CH_2$, 9], 314 (5), 312 (4), 226 (26), 224 (13), 158 (38), 157 (28), 99 (29), 91 (100), 79 (19), 78 (57), 77 (41); Anal. calcd for $C_{24}H_{27}NO_5Se$: C, 59.02; H, 5.57; N, 2.87; found C, 58.98; H, 5.68; N, 2.90.

Benzyl 1-(*tert*-butoxycarbonyl)-2-oxo-1,2,5,6-tetrahydropyridine-3-carboxylate, 9. To a solution of **8** (4.45 g, 9.11 mmol) in CH_2Cl_2 (45 mL) at 0 °C was added dropwise a 30% aqueous H_2O_2 solution (3.8 mL, 37.6 mmol, 4 equiv.). The mixture was stirred at 0 °C for 15 min before being quenched by addition of an aqueous 1.2 N HCl solution (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 $NaHCO_3$ solution (2 × 75 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Compound **9** (3.03 g, 9.14 mmol, 100% yield) was obtained as a yellowish oil. R_f 0.31 (EtOAc–cyclohexane 30:70); IR (neat) 1771, 1747, 1718, 1398, 1312, 1288, 1264, 1157, 754 cm^{-1}; ^{1}H NMR δ 7.49 (t, J = 4.2 Hz, 1H), 7.45–7.24 (5H), 5.27 (s, 2H), 3.84 (t, J = 6.3 Hz, 2H), 2.48 (m, 2H), 1.54 (s, 9H); ^{13}C NMR δ 163.4 (s), 159.7 (s), 152.2 (s), 149.1 (d), 135.3 (s), 130.1 (s), 128.3 (d), 128.1 (d), 128.0 (d), 83.2 (s), 68.8 (t), 42.8 (t), 27.8 (q), 24.5 (t); MS (CI$^+$, CH_4) m/z (relative intensity) 332 ($M + H^+$, 10), 276 (65), 260 (34), 233 (55), 232 (100), 230 (24), 169 (17), 131 (22); HRMS (CI$^+$, CH_4) calcd for $C_{18}H_{22}NO_5$ [$(M + H)^+$] 332.1498; found 332.1502.

Benzyl 1-(*tert*-butoxycarbonyl)-4-(4-fluorophenyl)-2-oxopiperidine-3-carboxylate, 10. To a solution of 4-fluorophenyl bromide (1.67 mL, 15.17 mmol, 10.25 equiv.) in THF (39 mL) at −78 °C was added *n*-butyllithium dropwise (6.08 mL, 2.5 M in hexanes, 15.20 mmol, 10.27 equiv.). The solution was stirred at −78 °C for 30 min and added dropwise *via* cannula to a suspension of copper iodide (1.45 g, 7.61 mmol, 5.14 equiv.) in THF (24 mL) at −78 °C. The mixture was allowed to warm slowly to −25 °C and stirred for 30 min to give a clear orange solution, which was cooled to −78 °C. A solution of **9** (0.49 g, 1.48 mmol) in THF (24 mL) was added dropwise and the resulting reaction mixture was stirred 1.5 h before being quenched with a saturated aqueous NH_4Cl–NH_4OH (32%) 2:1 solution (50 mL). After 1 h stirring, the deep blue aqueous layer was extracted with Et_2O (2 × 50 mL) and CH_2Cl_2 (30 mL). The combined organic layers were washed with an aqueous 1 N NaOH solution (2 × 25 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (cyclohexane–EtOAc 90:10 then 80:20) afforded **10** (0.50 g, 1.17 mmol, 80% yield) as a white solid. Mp 134 °C (ether); R_f 0.31 (EtOAc–cyclohexane 20:80); IR (KBr) 1770, 1748, 1311, 1244, 1224, 1143 cm^{-1}; ^{1}H NMR δ 7.35–7.20 (3H), 7.15–7.02 (4H), 6.93 (m, 2H), 5.11 (d, J = 12.1 Hz, 1H), 5.01 (d, J = 12.1 Hz, 1H), 3.90 (ddd, J = 12.9, 5.1 and 4.8 Hz, 1H), 3.68 (ddd, J = 12.9, 11.4 and 4.4 Hz, 1H), 3.67 (d, J = 11.8 Hz, 1H), 3.44 (ddd, J = 11.8, 11.4 and 4.0 Hz, 1H), 2.16 (dddd, J = 14.0, 4.0, 4.0 and 4.0 Hz, 1H), 2.02 (dddd, J = 14.0, 11.4, 11.4 and 4.8 Hz, 1H), 1.55 (s, 9H); ^{13}C NMR δ 168.6 (s), 166.7 (s), 161.9 (d, J = 246.0 Hz), 152.5 (s), 136.7 (d, J = 3.7 Hz), 135.3 (s), 128.4 (dd, J = 7.9 Hz), 128.3 (d), 128.1 (d), 128.0 (d), 115.7 (dd, J = 21.4 Hz), 83.7 (s), 67.0 (t), 59.1 (d), 45.5 (t), 41.9 (d), 29.9 (t), 27.9 (q); MS (CI$^+$, NH_3) m/z (relative intensity) 445 ($M + NH_4^+$, 1), 346 (20), 345 (94), 329 (21), 328 (100), 211 (57), 194 (74); HRMS (CI$^+$, CH_4) calcd for $C_{24}H_{30}FN_2O_5$ [$(M + NH_4)^+$] 445.2139; found 445.2131; Anal. calcd for $C_{24}H_{26}FNO_5$: C, 67.43; H, 6.13; N, 3.28; found C, 67.43; H, 6.04; N, 3.29.

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