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Enantioenriched synthesis of Escitalopram using lithiation–borylation methodology

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This paper is dedicated with deep admiration to Professor Gilbert Stork, a true gentleman and outstanding scientist, on the occasion of his 90th birthday

Keywords:
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Escitalopram
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Carbamate
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ABSTRACT

The asymmetric synthesis of Escitalopram has been completed using a lithiation–borylation reaction as the key step. Suitably functionalized enantioenriched carbamate (er 98:2) and boronic ester coupling partners were prepared and following deprotonation with *s*-BuLi and borylation, the tertiary alcohol was obtained in 42% yield and 93:7 er. The lithiation–borylation reaction was found to tolerate nitrile, benzylic alcohol and *N*-Boc functionalities. The tertiary alcohol was converted to Escitalopram in three further steps.

1. Introduction

Escitalopram is a Selective Serotonin Reuptake Inhibitor (SSRI) antidepressant. Developed by Lundbeck, it rapidly achieved blockbuster status generating over $1.5B sales in 2010.[1,2] Originally marketed as a racemate, Citalopram, it was later found that the (*S*)-enantiomer (Escitalopram) was significantly more potent than both the (*R*)-enantiomer and the racemic mixture.[3]

Having recently developed lithiation–borylation methodology for the synthesis of enantioenriched tertiary alcohols we were keen to explore the applications of this transformation in the asymmetric synthesis of a complex, and challenging target.[4] This would help establish the scope and limitations of the methodology.

A number of syntheses of Escitalopram have been reported that rely on a resolution to obtain enantiopure material (Scheme 1). In these syntheses a double Grignard addition is used to elaborate lactone **3**[5] and then either resolution of the diol (±)-**2a** and cyclization, or cyclization and resolution of cyclic ether (±)-**1** is used to give the enantioenriched product.[1,6] Resolution by co-crystallization with (+)-di-*p*-toluoyl-D-tartaric acid [(+)-DPTTA **6**] has been used to give both the enantioenriched diol (*S*)-**2a** and ether (*S*)-**1**.[1,6d–g] Enzymatic resolution by either acylation of the benzyl alcohol (±)-**2a** (R=H) or deacylation of the benzyl acetate (±)-**2b** (R=Ac) have also been used to give the enantioenriched diol (*S*)-**2a**.[6b,c]

An impressive enantioselective synthesis of Escitalopram has been reported by Albert (Scheme 2).[7] Here the diaryl ketone **7** was initially complexed with methyl boronic acid and *N*-methylpseudoephedrine **8**. Subsequent addition of the amino Grignard reagent **10** to the complexed ketone **9** occurred with high selectivity leading to the tertiary alcohol (*S*)-**11** in 77% yield and 92% ee. The ee was further enhanced to 99.3% by resolution with (+)-DPTTA **6**.

As with previous syntheses we envisaged that Escitalopram could be made via the diol (*S*)-**12**. In turn, the diol (*S*)-**12**, being a tertiary alcohol, could be obtained through a lithiation–borylation reaction of the enantioenriched benzyl carbamate (*S*)-**13** and an aryl boronic ester (Fig. 1). Not only would this represent a convergent synthesis, but it would also enable us to test the functional group compatibility of the lithiation–borylation reaction. We envisaged that two boronic esters **14** and **15** could be used. Boronic ester **14** would require late-stage functionalization of the benzylic position to allow ring-closing ether formation and boronic ester **15**, which incorporated a protected benzylic alcohol, ready-primed for ring-closure. Careful choice of protecting group on the benzylic alcohol would allow this otherwise incompatible

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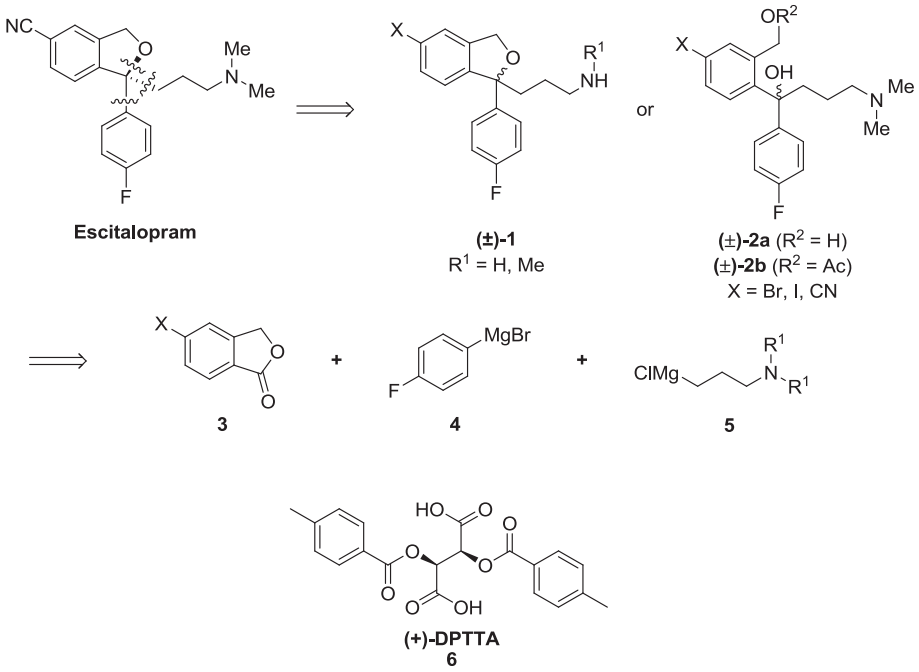
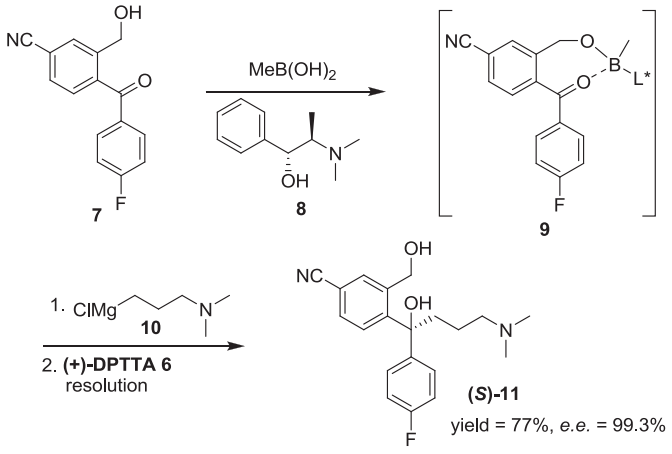


Scheme 1. Previous synthesis of Escitalopram using resolution.



Scheme 2. Enantioselective synthesis of Escitalopram.

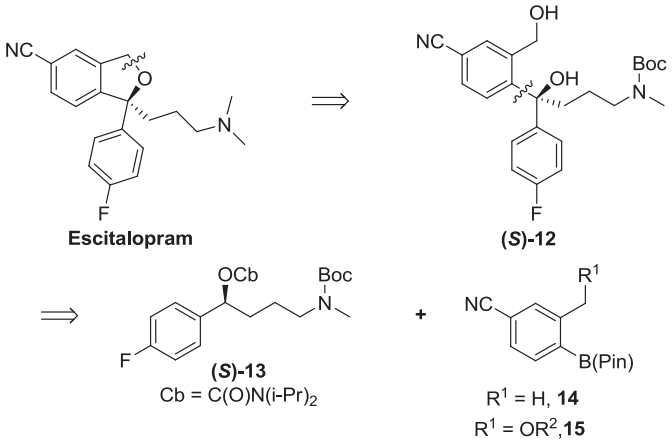
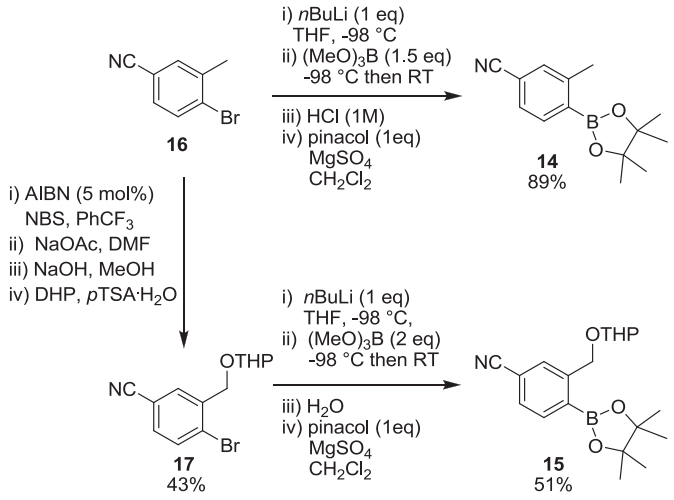


Fig. 1. Retrosynthetic analysis of Escitalopram.

functionality to be used in the lithiation–borylation reaction, and also act as a leaving group for the ring-closing etherification. For these reasons we chose the THP protecting group.

2. Results and discussion

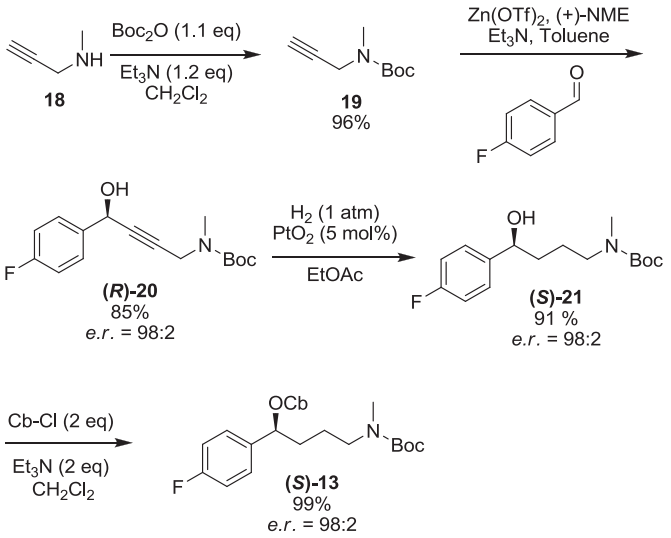
The synthesis of Escitalopram began with the preparation of the coupling partners needed for the lithiation–borylation reaction, boronic esters **14** and **15**, and the enantioenriched carbamate (*S*)-**12**. Boronic ester **14** was readily synthesized in two steps, in a single pot, from aryl bromide **16** (Scheme 3). Using the method of Hall,[8] lithium–halogen exchange at −98 °C, to prevent addition of the organolithium to the nitrile, and quenching with trimethoxyborane gave an intermediate boronic ester. Transesterification with pinacol, via the boronic acid, gave the target pinacol boronic ester in 89% yield over the two steps. Boronic ester **15** was prepared by a similar lithium–halogen exchange, following benzylic oxidation and THP



Scheme 3. Synthesis of boronic esters **14** and **15**.

protection of the benzyl alcohol, in a slightly reduced yield compared to the non-oxygenated boronic ester **14**. This was due to partial hydrolysis of the THP group followed by intramolecular trapping of the alcohol to give a cyclic boronic ester.

The enantioenriched carbamate (*S*)-**13** was prepared in four steps from propargylamine **18** (Scheme 4). Boc-protection of the commercially available propargylamine **18** and zinc-mediated addition of the alkyne to 4-fluorobenzaldehyde using (+)-*N*-methylephedrine ((+)-NME) as a chiral ligand on zinc gave the enantioenriched alcohol (*R*)-**20** with an er of 98:2. The asymmetric alkyne addition was developed by Carreira and had previous been employed for the addition of *N*,*N*-dibenzylpropargylamine to aldehydes.[9] Here the methodology was extended to include the addition of *N*-Boc protected amines. Hydrogenation using PtO_2 and carbamoylation gave the enantioenriched carbamate (*S*)-**13** in 74% yield over the four steps and with 98:2 er.



Scheme 4. Synthesis of enantioenriched carbamate (*S*)-**13**.

With both of the coupling partners prepared, we turned our attention to the key lithiation–borylation reaction. This would be a significant test of the methodology as both the required boronic esters **14** and **15** bear significant functionality. Boronic ester **14** incorporates a nitrile group, which could be susceptible to attack by the lithiated carbamate and an *ortho*-methyl group, which could sterically hinder attack at the boronic ester. Boronic ester **15** is even more sterically hindered. The carbamate (*S*)-**13** also bears functionality, which could hinder the reaction. The electrophilic Boc-group could trap the lithiated carbamate in an intramolecular manner or decrease the nucleophilicity of the organolithium by coordination of the amine or carbonyl groups.

In practice, lithiation of carbamate (*S*)-**13** with *s*-BuLi, followed by addition of the boronic ester **14** and further addition of $MgBr_2$/MeOH gave the enantioenriched tertiary alcohol (*S*)-**22** in 42% isolated yield and excellent 93:7 er after oxidation (Scheme 5). The starting carbamate was reisolated in 27% yield. These conditions were developed to maximize the er of the reaction since the intermediate boronate complex is prone to reversibility, and the lithiated carbamate generated undergoes competing racemization and readdition to the boronic ester.[4c] The addition of $MgBr_2$/MeOH not only reprotonates any lithiated carbamate generated by the reverse process thereby preventing racemization and recombination but it also promotes the 1,2-metallate rearrangement. In the absence of $MgBr_2$ the tertiary alcohol was obtained in lower yield (21%). The slight decrease in er of the product alcohol (*S*)-**22** compared to the carbamate arises from a small degree of competing inversion in the attack of the lithiated carbamate on the boronic ester **14** (it occurs predominantly with retention).[4c] In addition to the tertiary alcohol, we also observed a significant amount of phenol **23**. This came from lithiation *ortho* to fluorine, followed by trapping of the boronic ester and oxidation to the phenol. In an attempt to counter the *ortho*-lithiation we added TMEDA during the deprotonation as it was hoped this would inhibit the precomplexation of *s*-BuLi to the fluorine and so prevent the *ortho*-lithiation.[10] Pleasingly, this completely stopped *ortho*-lithiation, but now gave another side product; the lactam **24**.

Lithiation–borylation using the more functionalized boronic ester **15** was also successful (Scheme 5). Once again, the addition of TMEDA in the deprotonation step stopped any *ortho*-lithiation but competing formation of the corresponding lactam was observed. We found it beneficial to add the boronic ester at −98 °C to prevent addition of the lithiated carbamate to the aromatic nitrile.

With the tertiary alcohol (*S*)-**22a** in hand we turned our attention to benzylic oxidation and cyclization to form the cyclic ether (*S*)-**25**. Initial attempts focused on the radical bromination of the benzylic methyl group. However, no conditions were found to effect the benzylic bromination using either AIBN or light as the radical initiator. Fortunately, basic $Pb(OAc)_4$ and I_2 successfully mediated the intramolecular etherification but in low yield, although importantly, without racemization of the tertiary alcohol. Our synthesis was completed by Boc-deprotection and reductive amination to give Escitalopram (Scheme 6).

In order to address the low yield in the cyclization reaction of tertiary alcohol (*S*)-**22a** we decided to complete an additional synthesis of Escitalopram using the more functionalized tertiary alcohol (*S*)-**22b** from the lithiation–borylation reaction using boronic ester **15** (Scheme 7). In this case, acid-catalyzed THP-deprotection with concomitant Boc-deprotection and intramolecular ether cyclization gave a mixture of ether (*S*)-**26** and diol (*S*)-**12**, arising from THP-deprotection alone. It is worth highlighting that the careful choice of the THP and Boc protecting groups allowed both deprotection reactions to be carried out in a single step and the acidic conditions mediate simultaneous ring-closing etherification. Presumably any adventitious water present prevents complete ether formation. However, this mixture was subjected to N-methylation and the free diol was cyclized using mesyl chloride and base to give Escitalopram in 62% overall yield from (*S*)-**22b**.

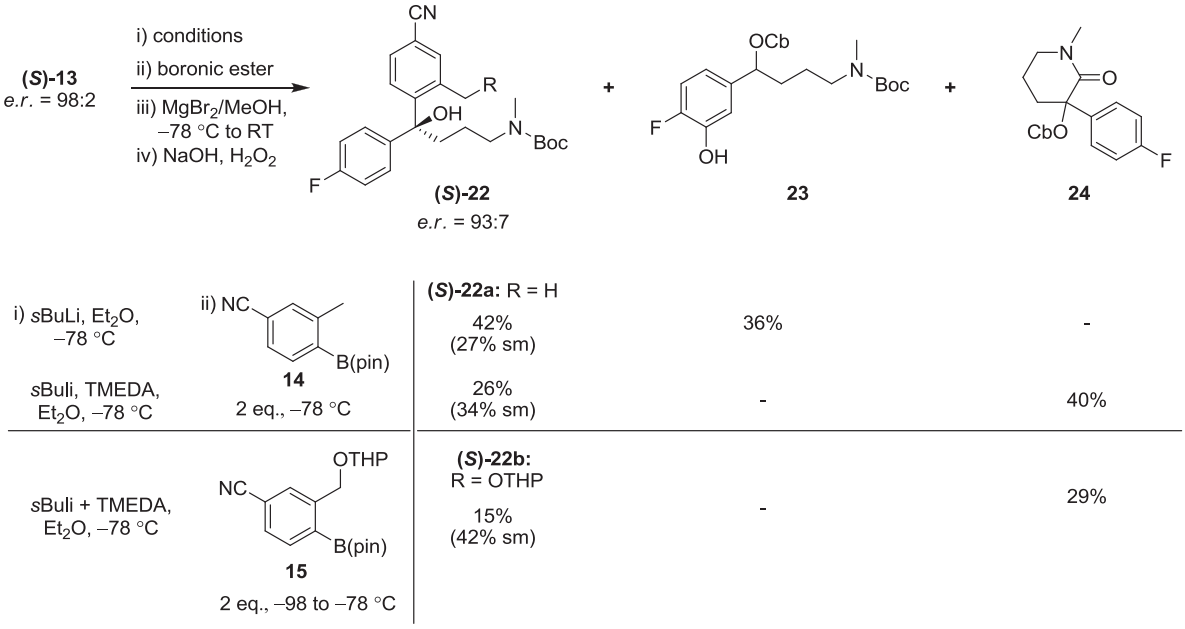
3. Conclusion

In this paper we set out to test the applicability of the lithiation–borylation reaction for the synthesis of a highly functionalized target molecule, Escitalopram. Using a novel set of disconnections, the lithiation–borylation reaction was successfully applied to two syntheses of Escitalopram. Pleasingly, we found that boronic esters bearing functionality susceptible to nucleophilic attack (aromatic nitrile and benzylic alcohol) and a carbamate with both chelating substituents and a *N*-Boc protecting group were tolerated in the lithiation–borylation reaction. However, caution needs to be taken when using aromatic substituents that can direct *ortho*-lithiation as competing aromatic lithiation can occur during deprotonation of the carbamate. In our case, *ortho*-lithiation to fluorine was observed. The addition of TMEDA in the deprotonation step of the reaction was found to inhibit such *ortho*-lithiation.

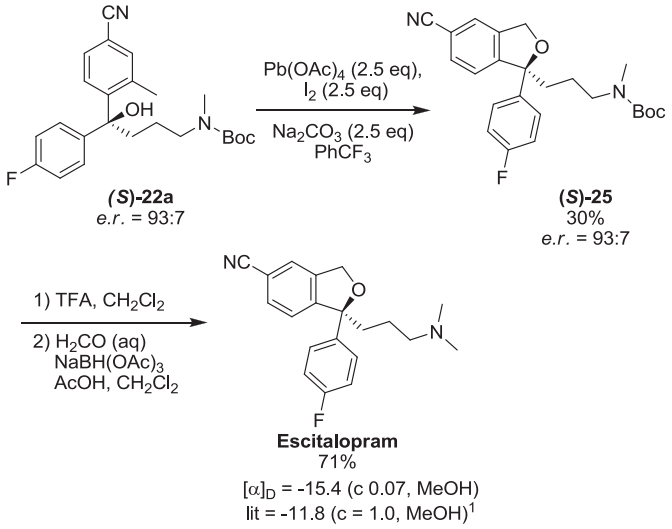
4. Experimental

4.1. General methods

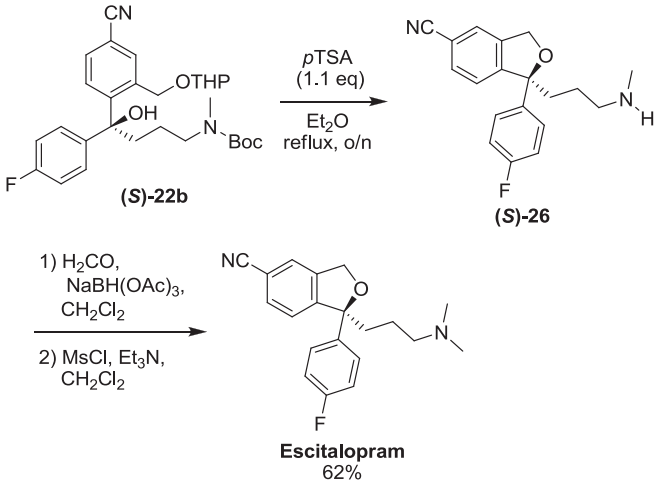
All air and moisture sensitive manipulations were performed either under argon using standard Schlenk techniques. Anhydrous



Scheme 5. Key lithiation–borylation to construct the tertiary alcohol (*S*)-**22**.



Scheme 6. Cyclization and methylation to give Escitalopram.



Scheme 7. Alternative synthesis of Escitalopram using the more functionalized tertiary alcohol (*S*)-**22b**.

solvents were purified by means of a Grubbs-type solvent system.[11] In addition, Et_2O was stored over oven dried 4 Å molecular sieves under argon for at least 16 h prior to use. All reagents and solvents were used as purchased if not otherwise stated. Melting points were determined with a Kofler hot stage apparatus and were not corrected. Mass spectrometry was carried out by the University of Bristol Mass Spectrometry service. Elemental analysis was carried out by the University of Bristol Microanalysis service. Optical rotations were obtained using a Perkin–Elmer 241MC polarimeter at the sodium D line (589 nm) and are reported as follows: $[\alpha]_D^T$, concentration (g/100 mL), and solvent. NMR spectra were acquired on either a Jeol Lambda 300 (^{1}H: 300 MHz, ^{11}B: 96 MHz), a Varian 400 (^{1}H: 400 MHz, ^{13}C: 101 MHz) or a Varian 500 (^{13}C: 126 MHz) NMR spectrometer. ^{1}H and ^{13}C NMR spectra were referenced to external tetramethylsilane via the residual *protio* solvent (^{1}H) or the solvent itself (^{13}C). All chemical shifts are reported in parts per million. Infrared spectra were recorded using a Perkin–Elmer Spectrum 100 FT-IR spectrometer with an ATR diamond cell, irradiating between 4000 cm^{-1} and 600 cm^{-1}. Chiral HPLC separations were done using an Agilent 1100 series high performance liquid chromatography units using HP Chemstation for LC or LC-MS.

4.2. Preparation of compound 14

Using a modification of the procedure by Hall and co-workers,[8] *n*-BuLi (1.6 M, 7.5 mL, 12.0 mmol) was added drop-wise to a solution of 4-bromo-3-methylbenzonitrile (2.34 g, 12.0 mmol) in anhydrous THF (24 mL) at −98 °C. The mixture was stirred at −98 °C for 10 min and trimethylborate (2.0 mL, 18 mmol) was added drop-wise. The reaction mixture was kept at −98 °C for 30 min before being warmed to room temperature and stirred for a further 15 min. Aqueous HCl (1 M, 5 mL, 5 mmol) was added and the mixture was stirred for 15 min before being diluted with H_2O (20 mL) and extracted with EtOAc (3×20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. Pinacol (1.42 g, 12.0 mmol) and $MgSO_4$ (1.44 g, 12.0 mmol) were

added to a solution of the residue dissolved in CH_2Cl_2 (25 mL). The mixture was stirred for 15 h at room temperature, $MgSO_4$ removed by filtration and the filtrate concentrated in vacuo. The product was purified by column chromatography (5% EtOAc/petroleum ether) to give the *boronic ester* **14** (2.59 g, 89%) as needles (petroleum ether); [Found: C, 69.44; H, 7.68, N, 5.61. $C_{14}H_{18}NO_2B$ requires C, 69.17; H, 7.46; N, 5.76%]; mp=139.5–140.5 °C (petroleum ether); ν_{max} (neat): 2969, 2235, 1347, 1146, 1062 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.83 (1H, d, *J* 8.0 Hz, Ar*H*), 7.41–7.47 (2H, m, Ar*H*), 2.56 (3H, s, Ar–*Me*), 1.36 (12H, s, 2× C*Me*$_2$); δ_C (101 MHz, $CDCl_3$) 145.6, 136.1, 132.6, 128.0, 119.0, 113.9, 84.1, 24.8, 21.9; δ_B (96 MHz, $CDCl_3$): 30.7; *m*/*z* (EI): 243 (M^+, 10), 228 (80), 84 (100); HRMS (EI): M^+, found 243.1440. $C_{14}H_{18}NO_2B$ requires 243.1431.

4.3. Preparation of compound 27

Using a modification of the procedure by Baker and co-workers,[12] 1,1′-azobis(cyclohexanecarbonitrile) (0.343 g, 1.41 mmol) was added to a solution of 4-bromo-3-methylbenzonitrile (2.75 g, 14.1 mmol) and *N*-bromosuccinimide (2.75 g, 15.5 mmol) in α,α,α-trifluorotoluene (70 mL). The mixture was heated to reflux for 18 h. Upon cooling to room temperature, H_2O (75 mL) was added and the mixture extracted with CH_2Cl_2 (3×50 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. NaOAc (5.76 g, 70.0 mmol) was added to a solution of the residue in dimethyl formamide (45 mL) and the mixture was heated to 90 °C for 18 h. Upon cooling to room temperature, H_2O (100 mL) was added and the mixture was extracted with EtOAc (3×75 mL). The combined organic phases were washed with brine (75 mL), dried ($MgSO_4$) and concentrated in vacuo. Aqueous NaOH (2 M, 7.1 mL, 14.2 mmol) was added to a solution of the residue in MeOH (60 mL) and the mixture was stirred for 4 h. The solution was concentrated to ¼ of its volume in vacuo and the mixture was extracted with EtOAc (3×50 mL). The combined organic phases were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo. The product was purified by column chromatography (20% EtOAc/petroleum ether) to give the alcohol **27** (1.51 g, 51%) as needles (hexane); mp=152–154 °C (hexane); δ_H (400 MHz, DMSO-d_6): 7.83–7.86 (1H, m, Ar*H*); 7.81 (1H, d, *J* 8.2 Hz, Ar*H*), 7.68 (1H, dd, *J* 8.2, 2.1 Hz, Ar*H*), 5.69 (1H, t, *J* 5.6 Hz, O*H*), 4.53 (2H, d, *J* 5.6 Hz, CH_2); δ_C (101 MHz, DMSO-d_6): 143.1, 133.4, 131.9, 131.0, 126.6, 118.3, 110.6, 62.1. The data were consistent with those reported by Baker and co-workers.[12]

4.4. Preparation of compound 17

para-Tolylsulfonic acid monohydrate (52.0 mg, 0.270 mmol) was added to a solution of **27** (0.575 g, 2.73 mmol) and dihydro-2*H*-pyran (0.29 mL, 3.27 mmol) in anhydrous CH_2Cl_2 (5.5 mL) and the mixture was stirred at room temperature for 15 h. Saturated aqueous $NaHCO_3$ (10 mL) was added and the mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3×15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The product was purified by column chromatography (10% EtOAc/petroleum ether) to give the *bromide* **17** (0.666 g, 83%) as needles (petroleum ether); [Found: C, 53.01; H, 4.80, N, 4.74. $C_{13}H_{14}NO_2Br$ requires C, 52.72; H, 4.76; N, 4.73%]; mp=61–63 °C (petroleum ether); ν_{max} (neat): 2941, 2232, 1465, 1121, 1022 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.80–7.86 (1H, m, Ar*H*), 7.64 (1H, d, *J* 8.2 Hz, Ar*H*), 7.42 (1H, dd, *J* 8.2, 2.1 Hz, Ar*H*), 4.82 (1H, d, *J* 14.4 Hz, ArCH_aH_b), 4.79 (1H, t, *J* 3.4 Hz, C*H*), 4.54 (1H, d, *J* 14.4 Hz, ArCH-$_aH_b$), 3.87 (1H, ddd, *J* 11.5, 8.7, 3.2 Hz, OC$H_aH_bCH_2$), 3.54–3.62 (1H, m, OCH$_aH_b$CH$_2$), 1.51–1.98 (6H, m, OCH$_2$CH_2CH_2CH_2); δ_C (126 MHz, $CDCl_3$) 140.0, 133.2, 131.6, 131.5, 127.2, 118.4, 111.5, 98.6, 67.6, 62.2, 30.3, 25.3, 19.2; *m*/*z* (CI): 296 (MH^+, 30), 212 (45), 85 (100); HRMS (CI): MH^+, found 296.0294. $C_{13}H_{15}NO_2Br$ requires 296.0286.

4.5. Preparation of compound 15

n-BuLi (1.6 M, 3.3 mL, 5.24 mmol) was added drop-wise to a solution of **17** (1.55 g, 5.24 mmol) in anhydrous THF (15 mL) at −98 °C. The mixture was stirred at −98 °C for 15 min and trimethylborate (1.23 mL, 10.5 mmol) was added drop-wise. The reaction mixture was kept at −98 °C for 40 min before being warmed to room temperature and stirred for a further 1 h H_2O (5.0 mL) was added and the mixture was stirred for 1 h. The mixture was diluted with H_2O (15 mL) and extracted with EtOAc (3×20 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. Pinacol (0.619 g, 5.24 mmol) and $MgSO_4$ (0.628 g, 5.24 mmol) were added to a solution of the residue dissolved in CH_2Cl_2 (20 mL). The mixture was stirred for 15 h at room temperature, $MgSO_4$ removed by filtration and the filtrate concentrated in vacuo. The product was purified by column chromatography (10% EtOAc/petroleum ether) to give the *boronic ester* **15** (0.915 g, 51%) as an amorphous solid (hexanes); [Found: C, 66.65; H, 7.88, N, 4.19. $C_{19}H_{26}BNO_4$ requires C, 66.49; H, 7.64; N, 4.08%]; mp=64–65 °C (hexanes); ν_{max} (neat): 2946, 2225, 1340, 1264, 1113, 1029 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.87 (1H, d, *J* 7.7 Hz, Ar*H*), 7.82–7.84 (1H, m, Ar*H*), 7.54 (1H, dd, *J* 7.7, 1.6 Hz, Ar*H*), 4.97 (1H, d, *J* 13.6 Hz, ArCH_aH_b), 4.82 (1H,d, *J* 13.6 Hz, ArH$_aH_b$), 4.77 (1H, t, *J* 3.4 Hz, CH), 3.89 (1H, ddd, *J* 11.5, 8.5, 3.3 Hz, OCH_aH_b), 3.53–3.59 (1H, m, OCH$_aH_b$), 1.51–1.96 (6H, m, OCH$_2$CH_2CH_2CH_2), 1.35 (12H, s, 2× CMe$_2$); δ_C (101 MHz, $CDCl_3$) 146.2, 136.0, 130.3, 129.6, 119.0, 114.2, 98.2, 84.3, 67.4, 62.0, 30.5, 25.4, 24.8, 24.8, 19.3; δ_B (96 MHz, $CDCl_3$): 30.4; *m*/*z* (CI): 344 (MH^+, 50), 260 (80), 85 (100); HRMS (CI): found 344.2026. $C_{19}H_{17}NO_4B$ requires 344.2033.

4.6. Preparation of compound 19

Di-*tert*-butyl dicarbonate (14.0 mL, 65.3 mmol) was added to a solution of **18** (4.10 g, 59.4 mmol) and Et_3N (9.1 mL, 65.3 mmol) in CH_2Cl_2 (120 mL). The mixture was stirred at room temperature for 15 h before being diluted with H_2O (50 mL). Saturated aqueous $NaHCO_3$ (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3×100 mL). The combined organic phases were washed with water (100 mL), dried ($MgSO_4$) and concentrated in vacuo to give the alkyne **19** (10.0 g, 100%) as a pale yellow oil; The product was used without further purification. δ_H (400 MHz, $CDCl_3$), 4.05 (2H, br s, CH_2), 2.92 (3H, s, N*Me*), 2.22 (1H, t, *J* 2.4 Hz, C*H*), 1.41 (9H, s, C*Me*$_3$); δ_C (101 MHz, $CDCl_3$) 155.2, 80.1, 79.2, 71.2, 37.9, 33.4, 28.3. The data were consistent with those reported by Paul and co-workers.[13]

4.7. Preparation of compound (*R*)-20

$Zn(OTf)_2$ (0.517 g, 1.42 mmol) was dried in vacuo (0.5 mbar) at 120 °C for 3 h (+)-*N*-methylephedrine (0.214 g, 1.19 mmol), Et_3N (0.17 mL, 1.23 mmol) and anhydrous toluene (1.5 mL) were added and the mixture was stirred at room temperature for 3 h. Alkyne **19** (0.190 g, 1.23 mmol) was added and the mixture stirred for 15 min. The mixture was cooled to 5 °C and 4-fluorobenzaldehyde (0.10 mL, 0.95 mmol) was added. After stirring at 5 °C for 16 h, H_2O (10 mL) was added and the mixture was extracted with EtOAc (3×10 mL). The combined organic phases were washed with brine (15 mL), dried ($MgSO_4$) and concentrated in vacuo. The product was purified by column chromatography (20% EtOAc/petroleum ether) to give the *alcohol* (*R*)-**20** (0.120 g, 85%, er=98:2) as a colourless oil; $[\alpha]_D^{21}$ −16.0 (*c* 1.1, $CHCl_3$); ν_{max} (neat): 3385, 2978, 1673, 1391, 1222, 1148 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.40–7.56 (2H, m, Ar*H*), 6.96–7.10 (2H, m, Ar*H*), 5.45 (1H, d, *J* 3.5 Hz, C*H*), 4.10 (2H, br s, NCH_2), 2.89 (3H, s, N*Me*), 1.44 (9H, s, C*Me*$_3$); δ_C (101 MHz, $CDCl_3$) 162.5 (d, J_F 246.0 Hz), 155.3, 136.5, 128.4 (d, J_F 7.8 Hz), 115.2 (d, J_F 21.8 Hz), 83.3, 82.0, 80.3, 63.7, 38.3, 33.6, 28.3; *m*/*z* (ESI) 316 (MNa^+), 260; HRMS

(ESI): MNa^+, found 316.1319428. $C_{16}H_{20}NO_3FNa$ requires 316.1306110.

4.8. Preparation of compound (*S*)-21

PtO_2 (16 mg, 0.070 mmol) was added to a solution of alcohol (*R*)-**20** (0.418 g, 1.43 mmol) in EtOAc (8 mL). The mixture was purged with nitrogen (×3) then hydrogen (×3) before being stirred under hydrogen (1 atm) for 15 h. The mixture was filtered through Celite, which was washed with EtOAc (30 mL), and the filtrate was concentrated in vacuo. The product was purified by column chromatography (20% EtOAc/petroleum ether) to give the *alcohol* (*S*)-**21** (0.385 g, 91%, er=98:2) as pale yellow needles (hexanes); $[\alpha]_D^{22}$ −16.0 (*c* 1.5, $CHCl_3$); mp=81–83 °C (hexanes); ν_{max} (neat): 3416, 2934, 1664, 1395, 1215, 1155, 1078 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.28–7.35 (2H, m, Ar*H*), 7.02 (2H, t, *J* 8.6 Hz, Ar*H*), 4.70 (1H, s, C*H*), 3.31 (1H, br s, NCH_aH_b), 3.21 (1H, br s, NCH_aH_b), 2.80 (3H, s, N*Me*), 1.50–1.74 (4H, m, $CHCH_2CH_2$), 1.43 (9H, br s, CMe_3); δ_C (126 MHz, $CDCl_3$) 162.1 (d, *J* 246 Hz), 155.9, 140.6, 127.4 (d, J_F 7.8 Hz), 115.1 (d, J_F=21.5 Hz), 79.3, 73.5, 48.2, 35.9, 34.0, 28.4, 23.9; *m*/*z* (ESI): 320 (MNa^+), 264; HRMS (ESI): MNa^+, found 320.1632429. $C_{16}H_{24}NO_3FNa$ requires 320.1631870.

4.9. Preparation of compound (*S*)-13

Et_3N (0.46 mL, 3.00 mmol) was added to a solution of (*S*)-**21** (0.447 g, 1.50 mmol) and *N*,*N*-diisopropylcarbamoyl chloride (0.492 g, 3.00 mmol) in CH_2Cl_2 (15 mL) and the mixture was heated to reflux for 6 days. Upon cooling to room temperature, H_2O (30 mL) and saturated aqueous $NaHCO_3$ (20 mL) were added and the mixture was extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The product was purified by column chromatography (30% EtOAc/petroleum ether) to give the *carbamate* (*S*)-**13** (0.609 g, 99%, er=98:2) as a colourless oil; $[\alpha]_D^{24}$ −3.2 (*c* 0.6, $CHCl_3$); ν_{max} (neat): 2971, 1685, 1366, 1286, 1134, 1047 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.23–7.35 (2H, m, Ar*H*), 6.94–7.08 (2H, m, Ar*H*), 5.67 (1H, t, *J* 6.8 Hz, OC*H*), 4.03 (1H, br s, NC*H*), 3.79 (1H, br s, NC*H*), 3.20 (2H, br s, NCH_2), 2.78 (3H, s, N*CMe*), 1.82–1.99 (1H, m, $CHCH_aH_b$), 1.65–1.82 (1H, m, $CHCH_aH_b$), 1.42 (9H, br s, CMe_3), 1.32–1.64 (2H, m, NCH_2CH_2), 1.06–1.32 (12H, m, $N(CHMe_2)_2$); δ_C (126 MHz, $CDCl_3$) 162.1 (d, J_F 246 Hz), 155.7, 154.8, 137.1, 128.1 (d, J_F 7.8 Hz), 115.2 (d, J_F 21.5 Hz), 79.2, 75.5, 48.2, 45.8, 34.0, 33.9, 28.4, 24.0, 21.1; *m*/*z* (CI): 425 (MH^+, 8), 224 (95), 180 (100); HRMS (CI): MH^+ found 425.2805, $C_{23}H_{38}N_2O_4F$ requires 425.2816.

4.10. Preparation of compound (*S*)-22a

s-BuLi (1.3 M, 0.16 mL, 0.210 mmol) was added drop-wise to a solution of (*S*)-**13** (67.4 mg, 0.164 mmol) in anhydrous Et_2O (0.8 mL) cooled to −78 °C. The mixture was stirred at −78 °C for 30 min before **14** (87.8 mg, 0.328 mmol in anhydrous Et_2O (1.2 mL)) was added drop-wise. The solution maintained at −78 °C for 1 h. Magnesium bromide (0.83 M in MeOH, 0.40 mL, 0.328 mmol) was added drop-wise before warming to room temperature and stirring the reaction mixture for 15 h. A solution of BHT in anhydrous THF (~1 mg/mL, 0.4 mL) was added to the reaction mixture, which was subsequently cooled to 0 °C. A pre-cooled solution of aqueous NaOH (2 M, 0.67 mL) and aqueous H_2O_2 (30%, 0.45 mL) was added to the mixture at 0 °C. The mixture was stirred for 16 h at room temperature before being diluted with water (10 mL). The mixture was extracted with Et_2O (3×10 mL) and the combined organic phases were washed with brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. The product was purified by column chromatography (30% EtOAc/petroleum ether) to give the *alcohol* (*S*)-**22a** (29.7 mg, 44%, er=93:8) as needles (hexane/EtOAc); $[\alpha]_D^{25}$ −17.2 (*c* 1.0, $CHCl_3$); mp=151–153 °C (hexane/EtOAc); ν_{max} (neat): 3422, 2934, 2229, 1669, 1222, 1156 cm^{-1}; δ_H (300 MHz, $CDCl_3$): 7.81 (1H, d, *J* 7.9 Hz, Ar*H*); 7.53 (1H, d, *J* 8.0 Hz, Ar*H*), 7.36 (1H, s, Ar*H*), 7.12–7.26 (m, 2H, Ar*H*), 6.96 (2H, t, *J* 8.4 Hz, Ar*H*), 4.05 (1H, br s, O*H*), 3.34 (1H, br s, NCH_aH_b), 3.23 (1H, br s, NCH_aH_b), 2.77 (3H, s, N*Me*), 2.29 (1H, dt, *J* 14.1, 7.2, 7.2 Hz, $OCCH_aH_b$), 2.06–2.22 (1H, m, $OCCH_aH_b$), 2.01 (3H, s, Ar*Me*), 1.34–1.58 (2H, m, NCH_2CH_2), 1.42 (9H, s, CMe_3); δ_C (126 MHz, $CDCl_3$): 161.6 (d, J_F 249 Hz), 156.7, 149.5, 141.7, 138.9, 135.6, 129.0, 127.6 (d, J_F 7.8 Hz), 126.9, 118.8, 114.9 (d, J_F 15.4 Hz), 111.1, 79.7, 77.8, 48.9 (NCH_2 rotamer), 48.1 (NCH_2), 38.1 ($OCCH_2$ rotamer), 36.7 ($OCCH_2$), 34.0, 28.3, 21.9, 21.3; *m*/*z* (CI): 339 (MH^+−*t*-BuO, 98), 295 (100); HRMS (ESI): MNa^+, found 435.2061220. $C_{24}H_{29}N_2O_3FNa$ requires 435.2054421.

4.11. Preparation of compound 23

s-BuLi (1.3 M, 0.24 mL, 0.312 mmol) was added drop-wise to a solution of (±)-**13** (0.116 g, 0.282 mmol) in anhydrous Et_2O (1 mL) cooled to −78 °C. The mixture was stirred at −78 °C for 15 min before **14** (0.98 M in anhydrous Et_2O, 0.43 mL, 0.423 mmol) was added drop-wise. The solution was stirred at −78 °C for 1 h before warming and stirring at room temperature for 2 h. A pre-cooled solution of aqueous NaOH (2 M, 1.33 mL) and aqueous H_2O_2 (30%, 0.51 mL) was added to the mixture at 0 °C. The mixture was stirred for 16 h at room temperature before being diluted with water (5 mL). The mixture was extracted with Et_2O (3×5 mL) and the combined organic phases were washed with brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo. The product was purified by column chromatography (30% EtOAc/petroleum ether) to give the *phenol* **23** (54.6 mg, 44%) as a colourless oil; ν_{max} (neat): 3264, 2973, 1665, 1301, 1159 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.00 (1H, dd, J_H 8.4 Hz, J_F 10.3 Hz, Ar*H*); 6.95 (1H, dd, J_H 2.1 Hz, J_F 8.4 Hz, Ar*H*), 6.79 (1H, ddd, J_H 8.4, 2.1 Hz, J_F 4.5 Hz, Ar*H*), 6.19 (1H, d, J_F 22.2 Hz, O*H*), 5.60 (1H, t, *J* 6.8 Hz, OC*H*), 4.07 (1H, br s, NC*H*), 3.80 (1H, br s, NC*H*), 3.20 (2H, br s, NCH_2), 2.78 (3H, s, N*Me*), 1.82–1.93 (1H, m, $OCHCH_aH_b$), 1.66–1.77 (1H, m, $OCHCH_aH_b$), 1.52 (2H, s, NCH_2CH_2), 1.43 (9H, s, CMe_3), 1.22 (12H, br s, 2× $CHMe_2$); δ_C (101 MHz, $CDCl_3$) 155.8, 155.1, 150.6 (d, J_F 241 Hz) 143.9 (d, J_F 14.0 Hz), 137.9, 118.1 (d, *J* 3.9 Hz), 115.7 (d, J_F 5.5 Hz), 115.6 (d, J_F 25.7 Hz), 79.4, 75.9, 48.3, 45.9, 34.0, 33.9, 28.4, 23.9, 21.1; *m*/*z* (CI): 340 (MH^+−Boc, 45), 196 (80) 57 (100); HRMS (ESI): found 463.2597190. $C_{23}H_{37}N_2O_5FNa$ requires 463.257816.

4.12. Preparation of compound 24

s-BuLi (1.3 M, 0.10 mL, 0.130 mmol) was added drop-wise to a solution of (±)-**13** (0.2 M in anhydrous Et_2O, 0.61 mL, 0.122 mmol) and TMEDA (0.02 mL, 0.134 mmol) cooled to −78 °C. The mixture was stirred at −78 °C for 3 h before CD_3OD (0.05 mL) was added. The mixture was warmed to room temperature and diluted with water (2 mL). The mixture was extracted with Et_2O (3×2 mL) and the combined organic phases were concentrated in vacuo. The product was purified by column chromatography (95% CH_2Cl_2, 4% MeOH, 1% Et_3N) to give the *lactam* **24** (13.9 mg, 33%) as a colourless oil; ν_{max} (neat): 2934, 1658, 1303, 1046 cm^{-1}: δ_H (400 MHz, $CDCl_3$): 7.38–7.50 (2H, m, Ar*H*), 6.99–7.10 (2H, m, Ar*H*), 4.12 (1H, br s, NC*H*), 3.70 (1H, br s, NC*H*), 3.63 (1H, td, *J* 12.0, 4.5 Hz, NCH_aH_b), 3.28 (0.5H, dt, *J* 5.2, 1.9 Hz, $CbOCCH_aH_b$), 3.25 (0.5H, dt, *J* 5.1, 1.9 Hz, $CbOCCH_aH_b$), 3.09 (3H, s, N*Me*), 3.03–3.13 (1H, m, NCH_aH_b), 2.18 (0.5H, td, *J* 3.5, 1.9 Hz, $CbOCCH_aH_b$), 2.15 (0.5H, td, *J* 3.5, 1.9 Hz, $CbOCCH_aH_b$), 1.64–1.82 (2H, m, NCH_2CH_2), 1.15–1.32 (12H m, 2× $CHMe_2$); δ_C (101 MHz, $CDCl_3$): 168.8, 162.2 (d, J_F 247 Hz), 154.4, 137.6 (d, J_F 3.1 Hz), 128.8 (d, J_F 7.8 Hz), 114.9 (d, J_F 21.0 Hz), 81.1, 50.0, 46.6, 45.3, 35.3, 35.2, 21.2, 20.0; *m*/*z* (CI): 351 (MH^+, 50), 206 (100); HRMS (CI): found 351.2078. $C_{19}H_{28}N_2O_3F$ requires 351.2084.

4.13. Preparation of compound (*S*)-25

Iodine (70.3 mg, 0.277 mmol) was added to a suspension of (*S*)-**22a** (45.7 mg, 0.111 mmol), lead tetraacetate (0.123 g, 0.277 mmol) and Na_2CO_3 (29.4 mg, 0.277 mmol) in α,α,α-trifluorotoluene (3 mL). The mixture was stirred at 70 °C for 20 h before being cooled to room temperature. Aqueous sodium thiosulfate (1.0 M, 10 mL) was added and the mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The product was purified by column chromatography (30% EtOAc/petroleum ether) to give the *carbamate* (*S*)-**22a** (13.5 mg, 30%, er=93:8) as a pale yellow oil; ν_{max} (neat): 2926, 2230, 1690, 1508, 1168 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.61 (1H, d, *J* 7.8 Hz, Ar*H*); 7.52 (1H, s, Ar*H*), 7.34–7.44 (2H, m, Ar*H*), 7.38 (1H, d, *J* 7.9 Hz, Ar*H*), 6.95–7.08 (2H, m, Ar*H*), 5.20 (1H, d, *J* 13.0 Hz, OCH_aH_b), 5.15 (1H, d, *J* 13.0 Hz, OCH_aH_b), 3.20 (2H, br s, NCH_2), 2.76 (3H, s, N*Me*), 2.17 (1H, ddd, *J* 14.2, 11.4, 4.8 Hz, $OCCH_aH_b$), 2.00–2.12 (1H, m, $OCCH_aH_b$), 1.32–1.54 (2H, m, NCH_2CH_2), 1.41 (9H, br s, CMe_3); δ_C (126 MHz, $CDCl_3$) 162.1 (d, J_F=247 Hz), 155.8, 149.3, 140.3, 139.4, 131.9, 126.7 (d, J_F=7.8 Hz), 125.2, 122.6, 118.6, 115.4 (d, J_F=21.5 Hz), 111.8, 90.9, 79.3, 71.3, 48.3, 38.3, 34.0, 28.4, 22.4; *m*/*z* (ESI): 433 (MNa^+), 411 (MH^+); HRMS (ESI): MNa^+, found 433.1906700. $C_{24}H_{27}N_2O_3FNa$ requires 433.1897920.

4.14. Preparation of Escitalopram

Trifluoroacetic acid (35 μl, 0.460 mmol) was added to a solution of a solution of (*S*)-**25** (13.5 mg, 0.033 mmol) in CH_2Cl_2 (1 mL) and the mixture was stirred at room temperature for 4 h. Saturated aqueous $NaHCO_3$ (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (1 mL) and aqueous formaldehyde (37%, 0.02 mL, 0.753 mmol), $NaBH(OAc)_3$ (13.9 mg, 0.066 mmol) and acetic acid (0.02 mL, 0.329 mmol) were added and the mixture was stirred at room temperature for 16 h. Saturated aqueous $NaHCO_3$ (5 mL) was added and the mixture was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The product was purified by column chromatography (95% CH_2Cl_2, 4% MeOH, 1% Et_3N) to give the amine Escitalopram (7.6 mg, 71%) as a yellow oil; $[\alpha]_D^{25}$ −15.4 (*c* 0.1, MeOH), lit.=−11.8 (*c* 1.0, MeOH);[1] δ_H (400 MHz, $CDCl_3$): 7.61 (1H, d, *J* 7.9 Hz, Ar*H*); 7.51 (1H, s, Ar*H*), 7.40–7.48 (3H, m, ArH), 6.95–7.07 (m, 2H, ArH), 5.21 (1H, d, *J* 13.0 Hz, OCH_aH_b), 5.15 (1H, d, *J* 13.0 Hz, OCH_aH_b), 2.40 (2H, t, *J* 7.1 Hz, NCH_2), 2.26 (6H, s, NMe_2), 2.13–2.33 (2H, m, CCH_2), 1.35–1.61 (2H, m, NCH_2CH_2); δ_C (101 MHz, $CDCl_3$): 162.0 (d, J_F 246 Hz); 149.3, 140.2, 139.3, 131.9, 126.7 (d, J_F 7.8 Hz), 125.2, 122.8, 118.6, 115.4 (d, J_F 21.8 Hz), 111.8, 91.0, 71.3, 59.1, 44.8, 38.7, 21.6. The data were consistent with those reported by Boegesoe and co-workers.[1]

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.09.142.

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