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Total synthesis of Fluoxetine & Duloxetine through an in situ imine formation/borylation/transimination and reduction approach

Adam D. J. Calow, Elena Fernández and Andrew Whiting

We report efficient, catalytic, asymmetric total syntheses of both (R)-Fluoxetine and (S)-Duloxetine from α,β-unsaturated aldehydes conducting five sequential one pot steps (imine formation / copper mediated β-borylation / transimination / reduction / oxidation) followed by the specific ether group formation which deliver to the desired products (R)-Fluoxetine in 45% yield (96% e.e.) and (S)-Duloxetine in 47% yield (94% e.e.).

Introduction

Fluoxetine 1 and Duloxetine 2, developed by Eli Lilly, are top-selling pharmaceuticals used for the treatment of major depressive disorder (MDD) and other conditions. Fluoxetine 1 belongs to the selective serotonin reuptake inhibitor (SSRI) class of anti-depressants and Duloxetine 2 to the serotonin-norepinephrine reuptake inhibitor (SNRI) class.

Due to the success and importance of these drugs, several groups have been interested in their preparation. An original asymmetric approach to Fluoxetine 1 was developed by Brown et al., using the chiral auxiliary disopinocamphenylchloroborane, for the asymmetric reduction of ketone precursors. Sharpless et al. also developed a route to Fluoxetine using an asymmetric epoxidation of an allylic alcohol, followed by ring-opening strategy. Corey et al. achieved an asymmetric reduction using the chiral oxazaborolidine (CBS reduction) in combination with borane to reduce a prochiral ketone in his approach. In recent years, the advancement of asymmetric catalytic hydrogenation has also proven highly effective for the asymmetric reduction of ketones (e.g. Noyori et al.) and, indeed, other groups have employed this methodology to the synthesis of both Fluoxetine 1 and Duloxetine 2.

It is interesting to note that Fluoxetine 1, despite being a chiral compound, is marketed as the racemic HCl-salt (Fig. 1). However, studies have revealed evidence of differing pharmacological and pharmacokinetic properties depending on the enantiomer of Fluoxetine 1. This evidence suggests that the (S)-enantiomer of Fluoxetine 1 is more active in the inhibition of serotonin than the (R)-enantiomer. Additionally, one of the major metabolites of Fluoxetine 1, norfluoxetine (demethylated Fluoxetine), is significantly more active as an inhibitor. In contrast, Duloxetine 2 is marketed as a single (S)-enantiomer.

Herein, we report an efficient, catalytic, asymmetric synthesis of Fluoxetine and Duloxetine with key steps that involves: 1) an in situ imine formation, 2) a copper-catalysed asymmetric β-borylation protocol that requires a specific bulky amine to block the imine functionality and prevent 1,2 addition versus 1,4 addition of the Cu-Bpin system, 3) a sequential transimination reaction, 4) a reduction of C=N bond and 5) a C-B oxidation protocol. Interestingly, since the asymmetry is induced in the second step by using a cheap chiral ligand ([R/S]-dimethyl-BINAP), another key point is the prevalence of the asymmetric induction along the following synthetic steps towards the target product.

Results and discussion

In recent years we have been interested in the preparation of γ-amino alcohols (e.g. 7)- via the β-borylation of α,β-unsaturated imines (e.g. 4-) because such γ-amino alcohols have applications as auxiliaries in synthetic and biochemical systems. In this context, we demonstrated a novel protocol for the asymmetric β-borylation of enal-derived α,β-unsaturated aldimes. This methodology owes its success to the sterically bulky N-benzhydryl substituent, which favours exclusive 1,4-boron addition (enals are prone to 1,2-boron addition to the carbonyl). The resulting β-boryl imines 5- can be reduced and oxidised in one-pot to yield N-benzhydryl γ-amino alcohols 7- with e.e. values up to 97% (Scheme 1).

We therefore became interested in applying our one-pot methodology (Scheme 2) to the total synthesis of some pharmaceuticals, such as Fluoxetine 1 and Duloxetine 2. By applying our retrosynthetic analysis to Fluoxetine 1, one can clearly see that γ-amino alcohol 7a is an appropriate precursor to Fluoxetine 1. Indeed, we considered that a debenzyldrylation, N-methylation and, finally, a nucleophilic
aromatic substitution would result in the target compound 1 (Scheme 2).

![Scheme 1 Asymmetric one-pot methodology towards chiral γ-amino alcohols.](image)

Initially, we prepared compound 7a from cinnamaldehyde 3a using CuCl/L0 or CuC/L1 (L0= PPh3 and L1=((R)-DM-BINAP) as the catalytic system. Our initial hypothesis to transform 7a into 1 required a debenzyhydrylation step using hydrogen over a palladium-on-carbon heterogeneous catalyst [Pd-C (10%)], because this has been employed for standard debenzyhydrylation in the literature [see Eqn. (1)]. However, using this methodology we encountered significant C-O bond hydrogenolysis, i.e., cleavage of the benzylic hydroxyl-group, which led to the formation of 10a as a significant product, in addition to the formation of the desired 8a. We therefore considered transfer hydrogenation as a suitable method, due to the practical ease of delivering stoichiometric amounts of hydrogen in situ from the decomposition of ammonium formate [see Eqn. (1)]. However, this resulted in the formation of a mixture of 7a, 8a, and 10a. Increased loadings of ammonium formate resulted in 10a being the primary product, with complete N-benzydryl group cleavage. Other milder methods, such as hydrogenation via Wilkinson’s catalysis and, indeed, refluxing TFA, resulted in no debenzyhydrylation. To our disappointment, conventional debenzyhydrylation methodologies appeared to be too harsh for substrate 7a due to the presence of the benzyl hydroxyl-group, which appears to undergo facile hydrogenolysis under palladium-catalysed hydrogenation conditions.

In addition to debenzyhydrylation, hydrolysis of compound 5a to the analogous aldehyde, with subsequent reductive amination using methylamine/NaBH4 (to yield 12a) was attempted and indeed did work, but due to the instability of the analogous β-boryl aldehyde the overall conversion in this case was low (<20%) and, hence, we needed to avoid the utilisation of such β-boryl aldehydes as intermediates in subsequent synthesis.

![Scheme 2 Retrosynthetic analysis of Fluoxetine 1.](image)

Continuing with the established one-pot methodology (Scheme 4), we therefore treated the intermediate β-boryl imine 5a with excess methylamine (4 equiv.), followed by in situ reduction using NaBH4/MeOH. Subsequently, solvent removal (to prevent MeOH oxidation to formaldehyde, which in the presence of γ-amino alcohols leads to the formation of 1,3-oxazines, as previously reported) and replacement with THF, followed by B-C oxidation with H2O2/NaOH of boronate 12a, gave the known precursor to Fluoxetine, γ-amino alcohol 9a [54% yield when using PPh3 L0 and 61% when using ((R)-DM-BINAP L1, see Scheme 4). This was achieved in five-steps, all of which were conducted in one-pot, without intermediate purification. Next, the addition of NaH to 9a resulted in the in situ generation of the analogous Na-alkoxide of 9a which, on addition of 4-chlorobenzotrifluoride at elevated temperature (100 °C, 3 h), gave Fluoxetine (rac)-1 in 74% yield [(R)]=90% e.e. when using L1] (Scheme 4). Determination of the enantiomeric excess was carried out by chiral HPLC on the Fluoxetine N-acyl compound 13a (see ESI), which is consistent with previously reported values of asymmetric induction (previously found to be 97% e.e.).

It is important to note that recent work described by Yun et al. on the asymmetric β-borylation of α,β-unsaturated amides 14, conducted to the formal synthesis of (S)-Fluoxetine with excellent enantioselectivity (99% e.e.) using in this case copper salts modified with a type of chiral josiphos ligand (Scheme 5). The intermediate compound 15 could be reduced...
using LiAlH₄ to give 9a in quantitative yields, which could be transformed to Fluoxetine using known procedures (e.g. Scheme 4).

With these results in hand, we turned our attention to the total synthesis of Duloxetine, which is marketed as the (S)-enantiomer. Enal 3b is not commercially available and therefore had to be prepared via reduction of the parent acid (DIBAL-H) to the analogous allylic alcohol, followed by oxidation to the aldehyde (without purification of the intermediate allylic alcohol) using Swern conditions.

Hence enal 3b (Scheme 6) was transformed in situ to the corresponding N-benzhydryl aldimine 4b in the presence of 3 Å molecular sieves and THF. After 9 hours, the imine was transferred directly to the pre-catalyst (copper salt, base, ligand and Bpin₂) mixture, followed by the addition of MeOH, to give the intermediate β-boryl aldimine 5b. Subsequent transamination was achieved through the addition of methylamine (in THF) which, after in situ borohydride reduction gave 12b. Again, to prevent the unwanted formation of oxazines (through in situ formaldehyde formation), the solvent was removed in vacuo prior to C-B oxidation and, hence, oxidation resulted in the formation of the known precursor γ-amino alcohol 9b in good yield [47% yield when using PPh₃, L₀ and 57% when using (S)-DM-BINAP L₂, see Scheme 6]. Finally, addition of NaH to 9b resulted in the in situ generation of the analogous alkoxyde of 9b which, on addition of 1-fluoronaphthalene at elevated temperature (70 °C, 1.5 h), gave Duloxetine (rac)-2 in 83% yield [(S)-2 in 94% e.e. when using L₂] (Scheme 6). The enantiomeric excess was again determined by chiral HPLC on the N-acetamide 13b of 2 (see ESI).

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Conclusions

In conclusion, we have developed an efficient, catalytic, asymmetric route to both (R)-Fluoxetine and (S)-Duloxetine (45 and 47% overall yield, 96 and 94% e.e., respectively) through the asymmetric copper mediated β-borylation of α,β-unsaturated imines. Although this strategy involves six steps, the first five-steps are conducted following a one-pot strategy. Importantly, the asymmetric induction provided by CuCl modified with a cheap chiral ligand (R/S)-DM-BINAP L₁/L₂, is high and is constant along the following transformation towards the targeted pharmaceuticals. Having demonstrated this approach, further applications are underway and will be communicated in due course.

Experimental

General experimental

All reagents were used as received from the supplier without further purification, unless stated. All solvents were used as received from the supplier, except THF (freshly distilled) and methanol (stored over molecular sieves). Molecular sieves, 3 Å 1-2 mm beads, were supplied from Alfa Aesar, and stored at 220 °C. Reactions were monitored by TLC analysis using P0LTFRAM® SIL G/UV254 (40 x
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Dispersion of 3-(Methylamino)-1-phenylpropan-1-ol (9a). Benzyldihydrazine (0.86 mL, 5.00 mmol) and cinnamaldehyde 3a (0.63 mL, 5.00 mmol) was added to a stirred solution of THF (20 mL) and oven-dried 3 Å-MS (5.0 g) for 6 h, to form the α,β-unsaturated imine 4a in situ. After 6 h, an aliquot of the solution containing the in situ-formed imine 4a (16.0 mL, 4.00 mmol) was transferred to a Schlenk-tube (under argon) containing CuCl (12.0 mg, 0.12 mmol), PPh 3 (62.9 mg, 0.24 mmol) or (R)-DM-BINAP (88.2 mg, 0.12 mmol), NaOr-Bu (34.6 mg, 0.36 mmol) and Bpin 3 (1.2 g, 4.4 mmol). After 5 min, MeOH (400 µL, 10.0 mmol) was added to the solution and the reaction was stirred overnight. Methylamine (8 mL, 16.0 mmol, 2 M THF solution) was added under argon and the resulting solution was stirred overnight. Methylamine (6 mL, 12.0 mmol, 2 M THF solution) was added under argon and the resulting solution was stirred for 1.5 h. NaBH 4 (0.34 g, 9.0 mmol) was added, followed by the drop-wise addition of MeOH (6.0 mL). The mixture was stirred for 3 h, followed by the removal of solvent under reduced pressure. THF (15 mL) was added to the resulting residue, followed by NaOH (1.8 mL, w/v 20%) and H 2O 2 (0.84 mL, w/w 35%), and the solution was heated to reflux for 1 h. After cooling, the resulting solution was partitioned between EtOAc and brine. The aqueous layer was extracted further with EtOAc (3x). The organic phase was separated and dried over anhydrous MgSO 4. After filtration the organic phase was removed under reduced pressure to yield a crude product. Purification by silica gel chromatography (DCM → DCM : MeOH : NEt 3, 5 : 1 : 1%) gave the pure product as an yellow oil 9b on standing [241 mg, 47% when using PPh 3 and 292 mg, 57% when using (S)-DM-BINAP]: 1 H-NMR (400 MHz, CDCl 3): δ 7.20 (dd, J = 5.0, 1.2 Hz, 1H), 7.06 (dd, J = 5.0, 3.4, 1H), 6.93-6.91 (m, 1H), 5.19 (dd, J = 8.4, 3.2 Hz, 1H), 4.68-4.32 (bs, 1H), 3.02-2.83 (m, 2H), 2.45 (s, 3H), 2.05-1.86 (m, 2H) ppm. 13 C-NMR (101 MHz, CDCl 3): δ 149.7, 126.6, 123.7, 122.3, 71.9, 50.1, 36.8, 35.9 ppm. LRMS (ESI+) [M+H] + calculated 310.1419, found 310.1419. All spectroscopic values are consistent with those obtained in the literature. 27

Synthesis of Fluoxetine, N-methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propan-1-amine (1). 3-(Methylamino)-1-phenylpropan-1-ol (9a) (330 mg, 2.00 mmol) was dissolved in dry dimethylacetamide (2.8 mL) and transferred to an oven-dried Schlenk-tube and purged with Ar. NaH (100 mg, 2.2 mmol, 60% in mineral oil) was transferred directly to the solution and heated (70 °C under Argon for 30-40 min, or until hydrogen evolution had ceased. 4-Chlorobenzotri fluoride (354 µL, 2.4 mmol) was added under argon, and the resulting solution was heated (100 °C) for 3 h. On cooling, the solution was partitioned between toluene and H 2O and washed (3x H 2O). The organic phase was separated and dried over anhydrous MgSO 4. After filtration the organic phase was removed under reduced pressure to yield a crude product. Purification by silica gel chromatography (DCM → DCM : MeOH : NEt 3, 5 : 1 : 1%) gave the pure product as a yellow oil 1 (458 mg, 74%): 1 H-NMR (400 MHz, CDCl 3): δ 7.43 (d, J = 8.6 Hz, 2H), 7.39-7.24 (m, 5H), 6.90 (d, J = 8.6 Hz, 2H), 5.31 (dd, J = 8.2, 4.7 Hz, 1H), 2.79-2.69 (m, 2H), 2.43, (s, 3H), 2.26-1.95 (m, 2H) ppm. 13 C-NMR (101 MHz, CDCl 3): δ 160.5, 141.0, 128.8, 127.9, 126.8, 126.7, 125.8, 115.8, 78.6, 48.2, 38.6, 29.7 ppm. LR-MS (ESI+) 309.3 (57%), HRS-MS (ESI+) Calculated [C 17 H 14 NOF 3 ] + 310.1419, found 310.1411, [α] d 20 = +3.5 (1.0, HCCl 4 ). Enantiomeric excess was determined by derivatisation to 13a. All spectroscopic values are consistent with those obtained in the literature. 27

Synthesis of Duloxetine, Methyl[(3-naphthalene-1-yl)-oxy]-3-(thiophen-2-yl)propylamine (2). 3-(Methylamino)-1-(thiophen-2-yl)propan-1-ol (9b) (150 mg, 0.87 mmol) was dissolved in dry DMSO (3.0 mL) and transferred to an oven-dried Schlenk-tube and purged...
with Argon. NaH (43.5 mg, 0.96 mmol, 60% in mineral oil) was transferred directly to the solution and heated (60 °C) under Argon for 1.5 h, or until hydrogen evolution had ceased. 1-Fluorophenanthrene (154 µL, 1.2 mmol) was added under argon, and the resulting solution was heated (70 °C) for 1.5 h. On cooling, the solution was partitioned between toluene and H₂O and washed (3x H₂O). The organic phase was separated and dried over anhydrous MgSO₄. After filtration the organic phase was removed under reduced pressure to yield a crude yellow oil. Purification by silica gel chromatography (DCM → DCM : MeOH : EtOAc 1:1:1) yielded a yellow oil (220 mg, 96%). IR (neat): ν 3052, 2928, 2850, 1516, 1323, 1245, 1108, 835 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 8.38-8.33 (m, 1H), 7.80-7.76 (m, 1H), 7.51-7.46 (m, 2H), 7.39 (d, J = 8.3 Hz, 1H), 7.29 (d, J = 7.9 Hz, 1H), 7.21 (dd, J = 5.0, 1.2 Hz, 1H), 7.06 (d, J = 3.5 Hz, 1H), 6.94 (dd, J = 5.0, 3.5 Hz, 1H), 6.86 (d, J = 7.2 Hz, 1H), 5.79 (dd, J = 7.7, 5.3 Hz, 1H), 2.88-2.79 (m, 2H), 2.51-2.40 (m, 2H), 2.44 (s, 3H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 153.0, 145.3, 134.6, 127.5, 126.3, 126.2, 125.7, 125.2, 124.7, 124.2, 121.1, 121.1, 100.7, 74.8, 48.4, 39.1, 36.6 ppm. LRMS (ESI⁺) [M+H⁺]⁺ 298.0. HRMS (ESI⁺) calculated [C₁₇H₁₇NO₃H⁺]⁺ 298.1266, found 298.1263.

with silica gel chromatography (Hexane : DCM : MeOH, 9 : 1) gave 13a as a yellow oil (220 mg, 96%). IR (neat): ν 3052, 2928, 2850, 1516, 1323, 1245, 1108, 835 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 7.42 (d, J = 8.5 Hz, 2H), 7.38-7.27 (m, 5H), 6.89 (d, J = 8.4 Hz, 2H), 5.21 (dd, J = 8.6, 4.3 Hz, 1H), 3.63-3.51 (m, 2H), 2.97 (s, 3H), 2.25-2.09 (m, 2H), 2.04 (s, 2H) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 170.6, 160.3, 140.7, 129.1, 128.3, 126.9, 126.8, 125.7, 125.5, 115.6, 78.4, 47.1, 37.4, 36.6, 21.1 ppm. LRMS (ESI⁻) [M-H⁻]⁻ 351.9. HRMS (ESI⁻) calculated [C₁₇H₁₇NO₃F⁺H⁻]⁻ 352.1524 found 352.1515.

**Synthesis of (S)-3-(thiophen-2-yl)propylacetamide (13a).** Dufloxetine 2 (166 mg, 0.56 mmol, DCM (3 mL), acetic anhydride (1 mL) and pyridine (1 mL) were combined and allowed to stir over night. The resulting solution was diluted in DCM (30 mL) and washed with HCl (3 x 10 mL, w/v 20%) and water (3 x). The organic layer was separated and dried over anhydrous MgSO₄. Filtration followed by the removal of

Note: The text continues with similar descriptions of chemical syntheses and characterization data, followed by an acknowledgments section. The full document contains detailed procedures, spectral data, and references for each step of the synthesis.
23 This β-boryl aldehyde eliminates to give cinnamaldehyde during column chromatography, as reported in the literature: I. Ibrahem, P. Breistein and A. Córdova, Angew. Chem. Int. Ed., 2011, 50, 12036-12041.
Graphical abstract

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