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A Formal Synthesis of (3S, 4R) (-)-fermoxetine and (3S, 4R) (-)-paroxetine from Enantioselective Desymmetrisation of N-Benzyl Imides

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Abstract
Enantioselective reduction of *N*-benzyl 4-substituted glutarimides employing oxazaborolidine catalyst **3** derived from *cis*-1-amino-indan-2-ol occurred in moderate yield and excellent ee. This has led to the formal synthesis of two antidepressants (-)-fermoxetine **1** and (-)-paroxetine **2**.
Keywords: Enantioselective, desymmetrisation, imides, glutarimides, fermoxetine, paroxetine

Introduction

Recently we have reported an efficient strategy of desymmetrisation of a number of *N*-Bn glutarimides employing an oxazaborolidine catalyst giving access to the corresponding chiral *N*-Bn 2-piperidinones in good yields and excellent enantioselectivities (Kutama & Jones, 2015). Two of the chiral piperidin-2-ones are used in this work for the formal synthesis of two important antidepressants (-)-fermoxetine **1** and (-)-paroxetine **2**. (-)-Paroxetine hydrochloride marketed as Paxil/Seroxat, and (-)-femoxetine are selective serotonin reuptake inhibitors used in the treatment of depression, obsessive compulsive disorder, and panic. (-)-Paroxetine hydrochloride was reported to have generated sales in excess of over $1.0 billion/year (Liu, *et. al.,* 2001, Yu, *et. al*., 2000). There have been a number of reported syntheses of these two pharmaceuticals showing different ways of enantioselective constructions of the (3*S*)- and (4*R*)-stereogenic centres (Kim, M *et. al.*, 2010). These ways include kinetic resolutions (Sugi, K. *et. al*. 2000, De Gonzalo, G. *et. al.*, 2001), chiral auxiliaries (Amat, M *et. al.*, 1996), chiral bases (Johnson, T. A. *et. al.*, 2001, 2002), the use of chiral pool (Cossy, J. *et. al.*, 2001), enantioselective catalysis (Senda, T. *et. al*., 2001, Taylor, M. S and Jacobsen, E. N., 2003) and enzymatic asymmetrisations (Yu, M. S. *et. al*., 2000).

The desymmetrisation methodology has also been employed as an effective way of constructing these two stereogenic centres in paroxetine by some research groups. Yu *et al*. employed a porcine liver esterase (PLE) mediated asymmetric desymmetrisation of glutaric acid bis methyl ester (Yu, M. S. *et. al*., 2000). Liu *et al*. used desymmetrisation of 3-substituted glutaric anhydride with (*S*)-methylbenzylamine (Liu, L. T. *et. al*., 2001) while Ikariya and co-workers (Ikariya, T and co-workers, 2007) and Simpkins and co-workers (Simpkins, S. N and co-workers, 2003) in separate works employed desymmetrisation of glutarimides for the synthesis of (-)-paroxetine.
In this work we have reported the enantioselective reduction of *N*-benzyl 4-substituted glutarimides employing oxazaborolidine catalyst **3** derived from cis-1-amino-indan-2-ol and their subsequent functionalization to the (*3S, 4R*) chiral lactams as yet another convenient route to the construction of the two important stereogenic centres in these important pharmaceuticals.

Experimental

All solvents were obtained dry from a Grubbs dry solvent system and glassware was flame dried and cooled under vacuum before use. ^{1}H and ^{13}C NMR spectra were measured using $CDCl_3$ or DMSO as solvent unless otherwise stated, on a Brüker 250 or 400 MHz machine with an automated sample changer (unless otherwise stated). Chemical shifts for carbon and hydrogen are given on the scale relative to TMS (tetramethylsilane, δ = 0 ppm). Coupling constants were measured in Hz. ^{13}C NMR spectra were recorded using the JMOD method. Infrared spectra were recorded on a Perkin-Elmer 1600 FT-IR machine using 0.5mm NaCl cells and mass spectra were recorded on a Kratos instrument using electrospray technique unless otherwise stated.

General Procedure for the asymmetric reduction of glutarimides using *B*-Me catalyst 3 followed by conversion to the corresponding lactam

A suspension of (1*R*, 2*S*)-*cis*-amino-2-indanol (0.15 g, 1.00 mmol) in dry toluene (3 cm^3) was treated with trimethylboroxine (0.05 cm^3, 0.33 mmol) and allowed to stir under nitrogen for 30 mins. Dry toluene (5 cm^3) was added and the reaction distilled until approximately 2 cm^3 of solvent remained. This procedure was repeated twice after which the final volume of toluene was removed under pressure to give a yellow solid. Dry dichloromethane (5 cm^3) was added to give a stock solution of the *B*-Me catalyst **3**. The catalyst (0.5 cm^3, 10 mol %) was added to the solution of the glutarimide substrate (1.00 mmol) in dry dichloromethane (30 cm^3) followed by a drop-wise addition of BH_3.THF (1 cm^3, 1.00 mmol). The solution was then allowed to stir at room

temperature for 24 hours. The reaction was finally quenched by addition of MeOH (2 cm^3) and 1M HCl (2 cm^3), extracted with CH_2Cl_2 (3 × 15 cm^3), dried over $MgSO_4$ and filtered. The solvent was evaporated *in vacuo* to give the crude hydroxy-lactam as a white powder which was immediately re-dissolved in CH_2Cl_2 (30 cm^3) and treated with TFA (1 cm^3) and triethylsilane (1 cm^3) in CH_2Cl_2 (5 cm^3). This mixture was allowed to stir at rt for 1 h, after which the solution was added to an ice-water mixture (15 cm^3) followed by extraction with CH_2Cl_2 (3 × 15 cm^3). The combined organic extracts were washed with saturated $NaHCO_3$ (3 × 15 cm^3), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give a crude white solid, which was purified via flash column chromatography eluting with EtOAc : petroleum ether (40-60) (7:3).

4(*R*)-1-(Phenylmethyl)-4-phenylpiperidin-2-one 5
Using glutarimide **4** (0.30 g, 1.00 mmol) the title compound was obtained as a white solid using general procedure above (0.16 g, 60% over 2 steps) Mpt 80 – 82 °C [lit.(T. A. Johnson *et. al*., 2002) 88 – 90 °C]; $[\alpha]_D^{20}$ + 33.0 (*c* 1.1, $CHCl_3$; 90% ee), lit.(T. Senda *et. al*., 2001) $[\alpha]_D^{20}$ + 35.0 (*c* 1.1, $CHCl_3$); ν_{max} (ATR) / cm^{-1} 1619, 1494; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.97 (1H, dtd, *J* 13.2, 10.8, 6.0, CH*H*), 2.07 – 2.14 (1H, m, CH*H*), 2.63 (1H, dd, *J* 17.5, 11.0, CH*H*), 2.83 (1H, ddd, *J* 17.5, 5.2, 2.0, CH*H*), 3.13 (1H, tdd, *J* 11.0, 5.2, 3.1, C*H*Ph), 3.26 – 3.37 (2H, m, 2 × CH*H*), 4.59 (1H, d, *J* 14.5, NCH*H*), 4.77 (1H, d, *J* 14.5, NCH*H*), 7.21 – 7.39 (10H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 30.3 (*C*H_2), 38.7 (*C*H), 39.5 (*C*H_2), 46.4 (*C*H_2), 50.0 (*C*H_2), 126.5 (2 × Ar*C*H), 126.8 (Ar*C*H), 127.5 (Ar*C*H), 128.2 (2 × Ar*C*H), 128.6 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 137.1 (Ar*C*), 143.4 (Ar*C*), 169.3 (*C*=O); *m/z* (EI$^+$) 265 (100%, M^+ $C_{18}H_{19}NO$), 174 (12), 131 (32), 104 (230), 131 (32), 91 (70). Chiral HPLC, Lux 3u CELLULOSE-2, 20% IPA in hexane @ 1.0 mL min^{-1}, t_R (major) 23.5 min and (minor) 26.1 min. All data are in accordance with literature. (T. A. Johnson *et al*., 2002, T. Senda *et. al*., 2001, S.-S. Jin *et. al*., 2012).

4(*R*)-1-(Phenylmethyl)-4-(4-fluorophenyl)piperidin-2-one 9
Using glutarimide **8** (0.30 g, 1.00 mmol) the title compound was obtained as a white solid using general procedure above (0.15 g, 54% over 2 steps) Mpt 114 – 116 °C; $[\alpha]_D^{20}$ + 30.0 (*c* 1.1, $CHCl_3$; 92% ee), lit. $[\alpha]_D^{20}$ + 33.0 (*c* 1.07, $CHCl_3$); ν_{max} (ATR) / cm^{-1} 3071, 2927, 1625, 1601, 1510; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.87 – 1.97 (1H, m, CH*H*), 2.07 – 2.10 (1H, m, CH*H*), 2.57 (1H, dd, *J* 17.4, 11.0, CH*H*), 2.83 (1H, dd, *J* 17.4, 3.4, CH*H*), 3.09 – 3.14 (1H, m, C*H*), 3.25 – 3.36 (2H, m, 2 × CH*H*), 4.57 (1H, d, *J* 14.5, NCH*H*), 4.77 (1H, d, *J* 14.5, NCH*H*), 7.03 [2H, $(AX)_2$, ArC*H*], 7.18 [2H, $(AX)_2$, ArC*H*], 7.28 – 7.38 (5H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 30.3 (*C*H_2), 38.0 (*C*H), 39.6 (CH_2), 46.2 (CH_2), 50.0 (CH_2), 115.5 (d, $J_{C\text{-}F}$ 21.2, 2 × Ar*C*H), 127.5 (Ar*C*H), 128.0 (d, $J_{C\text{-}F}$ 7.8, 2 × Ar*C*H), 128.2 (2 × Ar*C*H), 128.7 (2× Ar*C*H), 137.1 (Ar*C*), 139.1 (d, $J_{C\text{-}F}$ 3.0, Ar*C*), 161.7 (d, $J_{C\text{-}F}$ 245.0, Ar*C*), 169.1 (*C*=O); *m/z* (TOF MS ES$^+$) 284.1437 (100%, MH^+ $C_{18}H_{19}FNO$ requires 284.1451). Chiral HPLC, CHIRAL PAK IA, 7% IPA in hexane @ 1.0 mL min^{-1}, t_R (minor) 38.2 min and (major) 40.0 min. All data are in accordance with literature. (Senda, T. *et. al*., 2001, Chaubey, N. R. and Gosh, S. K. 2012).

General Procedure for the synthesis of 3-substituted *N*-Bn-4-phenylpiperidin-2-ones 6 and 10 (Sébastien, B. *et. al*., 2010)
Diisopropylamine (1.10 cm^3, 7.50 mmol) was added to a flask containing dry THF (5.10 cm^3) under N_2 atmosphere at - 78 °C and stirred gently. *n*-BuLi (3.80 cm^3, 7.50 mmol, 2.0 M in hexane) was added drop-wise and the mixture stirred at - 78 °C for 10 mins to give the LDA stock solution (7.50 mmol / 10 cm^3 solution). The LDA (2.00 cm^3, 1.50 mmol) from the stock solution was added drop-wise to a solution of the *N*-benzyl substrate **5** or **9** (0.27 g, 1.00 mmol) in dry THF (5.00 cm^3) under N_2 atmosphere. The solution was allowed to stir at - 78 °C for 20 mins. Then the electrophile ethyl chloroformate (1.00 equiv.) was slowly added and the mixture stirred at - 78 °C for 2 h, allowed to warm to room temperature slowly and further stirred for 18 h. The reaction was quenched by slow addition of saturated $NaHCO_3$ (10 cm^3), concentrated *in vacuo* and extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give a crude yellow oily solid, which was purified via flash column chromatography eluting with EtOAc : petroleum ether (40-60) (3:7).

(3*S*, 4*R*)-1-Benzyl-2-oxo-4-phenylpiperidine-3-ethyl carboxylate 6
Using general procedure above starting with the phenyl lactam **5** (0.38 g, 1.00 mmol) and ethyl chloroformate (0.10 cm^3, 1.00 mmol) as the electrophile, a yellow oily solid was obtained which was purified via flash column chromatography eluting with EtOAc : DCM : petroleum ether (2:1:7) to afford the title compound as yellow solid in 10:1 diastereomeric ratio (0.24 g, 71%) Mpt 140 – 142 °C; $[\alpha]_D^{20}$ + 3.0 (*c* 0.1, $CHCl_3$); ν_{max} (ATR) / cm^{-1} 3029, 2929, 2927, 1733, 1635; ^{1}H NMR (400 MHz; $CDCl_3$) **Major diastereomer** δ_H 1.12 (3H, t, *J* 7.1, CH_3), 2.00 – 2.11 (2H, m, 2 × CH*H*), 3.30 (1H, ddd, *J* 11.0, 5.3, 3.2, C*H*Ph), 3.39 – 3.50 (2H, m, 2 × CH*H*), 3.66 (1H,

d, *J* 11.0, C*H*CO), 4.12 (2H, q, *J* 7.1, CH_2), 4.56 (1H, d, *J* 14.5, NCH*H*), 4.79 (1H, d, *J* 14.5, NCH*H*), 7.22 [2H, $(AX)_2$, ArC*H*], 7.29 – 7.39 (8H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 14.0 (*C*H_3), 29.3 (*C*H_2), 42.6 (*C*H), 46.2 (*C*H_2), 50.3 (*C*H_2), 56.5 (*C*H), 61.2 (*C*H_2), 126.9 (2 × Ar*C*H), 127.3 (Ar*C*H), 127.6 (Ar*C*H), 128.2 (2 × Ar*C*H), 128.7 (2 × Ar*C*H), 128.2 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 136.7 (Ar*C*), 141.4 (Ar*C*), 166.0 (O*C*=O), 170.1 (N*C*=O); *m/z* (TOF MS ES$^+$) 338.1758 (100%, MH$^+$ $C_{21}H_{24}NO_3$ requires 338.1756).

(3*S*, 4*R*)-1-Benzyl-2-oxo-4-(4-fluorophenyl)piperidine-3-ethyl carboxylate 10

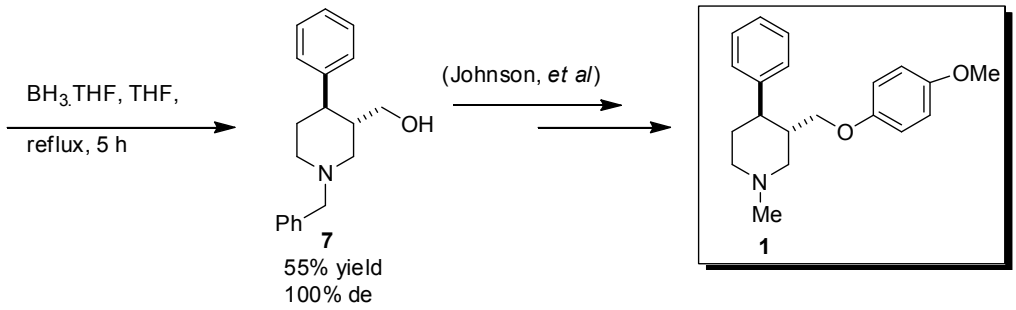
Using general procedure above, starting with the 4-(*p*-fluorophenyl) lactam **9** (0.36 g, 1.00 mmol) and ethyl chloroformate (0.10 cm^3, 1.00 mmol) as the electrophile, a yellow oily solid was obtained which was purified via flash column chromatography eluting with EtOAc : DCM : petroleum ether (40-60) (2:1:7) to afford the title compound as yellow solid in 10:1 diastereomeric ratio (0.22 g, 62%) Mpt 148 – 150 ^{o}C; $[\alpha]_D^{20}$ + 3.5 (*c* 0.1, $CHCl_3$); ν_{max} (ATR) / cm^{-1} 2933, 1734, 1640, 1605; ^{1}H NMR (400 MHz; $CDCl_3$) **Major diastereomer** δ_H 1.14 (3H, t, *J* 7.1, C*H*$_3$), 1.98 – 2.09 (2H, m, 2 × CH*H*), 3.30 (1H, ddd, *J* 11.0, 5.4, 2.9, C*H*Ph), 3.39 – 3.49 (2H, m, 2 × CH*H*), 3.59 (1H, d, *J* 11.0, C*H*CO), 4.13 (2H, q, *J* 7.1, CH_2), 4.53 (1H, d, *J* 14.5, NCH*H*), 4.81 (1H, d, *J* 14.5, NCH*H*), 7.02 [2H, $(AX)_2$, ArC*H*], 7.18 [2H, $(AX)_2$, ArC*H*], 7.28 – 7.39 (5H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 14.0 (*C*H_3), 29.4 (*C*H_2), 41.9 (*C*H), 46.2 (*C*H_2), 50.3 (*C*H_2), 56.7 (*C*H), 61.3 (*C*H_2), 115.7 (d, $J_{C\text{-}F}$ 21.4, 2 × Ar*C*H), 127.6 (Ar*C*H), 128.2 (2 × Ar*C*H), 128.4 (d, $J_{C\text{-}F}$ 8.0, 2 × Ar*C*H), 128.7 (2 × Ar*C*H), 136.6 (Ar*C*), 137.1 (Ar*C*), 161.9 (d, $J_{C\text{-}F}$ 245.5, Ar*C*), 165.8 (O*C*=O), 170.0 (N*C*=O); *m/z* (TOF MS ES$^+$) 356.1645 (100%, MH$^+$ $C_{21}H_{23}FNO_3$ requires 356.1662).

(3*S*, 4*R*)-1-(Phenylmethyl)-3-(hydroxymethyl)-4-phenylpiperidine 7

BH_3.THF (3 equiv.) was added to a solution of the piperidin-2-one **6** (0.22 g, 0.65 mmol) in dry THF. The mixture was heated at reflux for 5 h and cooled to room temperature. Distilled H_2O (2 cm^3) was slowly added and the resultant solution was extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give the crude material which was purified via flash column chromatography to obtain the title compound as a white solid as a single diastereomer (0.10 g, 55%) Mpt 106 – 108 ^{o}C; $[\alpha]_D^{20}$ - 22.2 (*c* 2.0, $CHCl_3$); ν_{max} (ATR) / cm^{-1} 3063 (broad), 3030, 2926, 2867, 2353, 2277, 1646, 1602; ^{1}H NMR (400 MHz; $CDCl_3$) δ_H 1.68 – 1.73 (2H, m, 2 × CH*H*), 2.30 (1H, td, *J* 11.9, 4.3, PhC*H*), 2.62 – 2.80 (3H, m, 2 × CH*H* and C*H*), 2.39 – 2.98 (1H, m, CH*H*), 3.03 – 3.06 (1H, m, CH*H*), 3.17 – 3.24 (2H, m, 2 × CH*H*), 3.40 (1H, app dd, *J* 11.0, 3.0, O*H*), 4.17 (2H, s, NCH_2), 7.24 – 7.44 (10H, m, ArC*H*); ^{13}C NMR (100 MHz; $CDCl_3$) δ_C 29.4 (*C*H_2), 39.3 (*C*H), 43.2 (*C*H), 56.4 (*C*H_2), 59.3 (*C*H_2), 63.2 (*C*H_2), 70.6 (*C*H_2), 126.9 (Ar*C*H), 127.5 (2 × Ar*C*H), 128.3 (2 × Ar*C*H), 128.8 (2 × Ar*C*H), 129.1 (Ar*C*H), 130.3 (Ar*C*), 133.2 (2 × Ar*C*H), 143.2 (Ar*C*); *m/z* (TOF MS ES$^+$) 282 (100%, MH$^+$ $C_{19}H_{24}NO$). All data are in accordance with literature (Johnson, T. A. *et. al*., 2002).

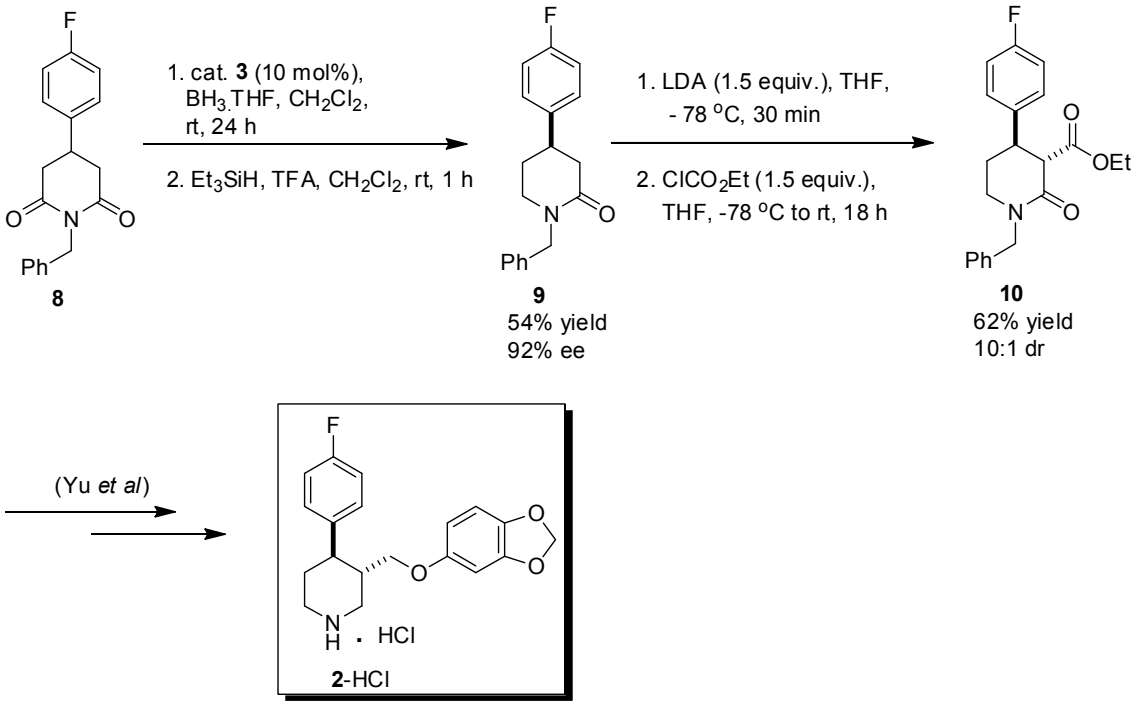
Results and discussions

The route leading to the formal synthesis of (*3S, 4R*) (-)-fermoxetine is represented in Scheme 1. The *N*-benzyl glutarimide **4** was obtained from benzaldehyde in four steps from a procedure described from our earlier work (Kutama and Simon, 2015). The enantioselective reduction of the glutarimide was carried out successfully using 10 mol% of the oxazaborolidine catalyst **3** at room temperature using BH_3.THF as the reducing agent to give the corresponding hydroxy-lactam which was further reduced to give the corresponding lactam **5** by reaction with Et_3SiH / TFA in 60% yield (over 2 steps) and 90% ee (Kutama and Simon, 2015). The C-3 enantioselective functionalization of *N*-Bn lactam **5** was successfully achieved by first treating the lactam with LDA for 30 minutes and quenching with ethyl chloro formate as the electrophile to obtain the carboxylate intermediate **6** in 71% yield and 10:1 dr. Subsequent borane reduction of the carboxylate compound gave the alcohol **7** in 55% yield as a single diastereomer (Scheme 1). The alcohol intermediate **7** could be converted to (-)-femoxetine **1** in four steps by the method of Johnson, T. A (Johnson, T. A *et al*., 2002).



Scheme 1. Formal synthesis of (3*S*, 4*R*) (-)-fermoxetine 1

Scheme 2 below represents the formal synthesis of (3*S*, 4*R*) (-)-paroxetine in form of its hydrochloride salt. The 4-(*p*-fluorophenyl) lactam **9** obtained as the desymmetrisation product from the corresponding glutarimide **8** in 54% yield (over 2 steps) and 92% ee provided direct access to (-)-paroxetine **2**. Deprotonation of the lactam **9** and quenching with ethyl chloroformate provided the corresponding carboxylate **10** in 62% (over 2 steps) and 10:1 diastereomeric ratio. The carboxylate intermediate **10** could then be converted to (-)-paroxetine **2**-HCl in four steps by the method of Yu *et al*. (Yu, M. S. *et. al*., 2000)



Scheme 2. Formal synthesis of (3*S*, 4*R*) (-)-paroxetine 2

Conclusion

In conclusion, a formal synthesis of two important antidepressants (3*S*, 4*R*)-(-)-femoxetine and (3*S*, 4*R*)-(-)-paroxetine from enantioselective desymmetrisation of imides and their subsequent functionalization to install the

3S, *4R* stereogenic centres has been developed. The desymmetrisation proceeded with moderate yield and excellent enantioselectivity while the functionalization gave good yield and excellent diastereoselectivity.

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