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Synthesis of Enantiopure 3,4-Disubstituted Piperidines. An Asymmetric Synthesis of (+)-Paroxetine

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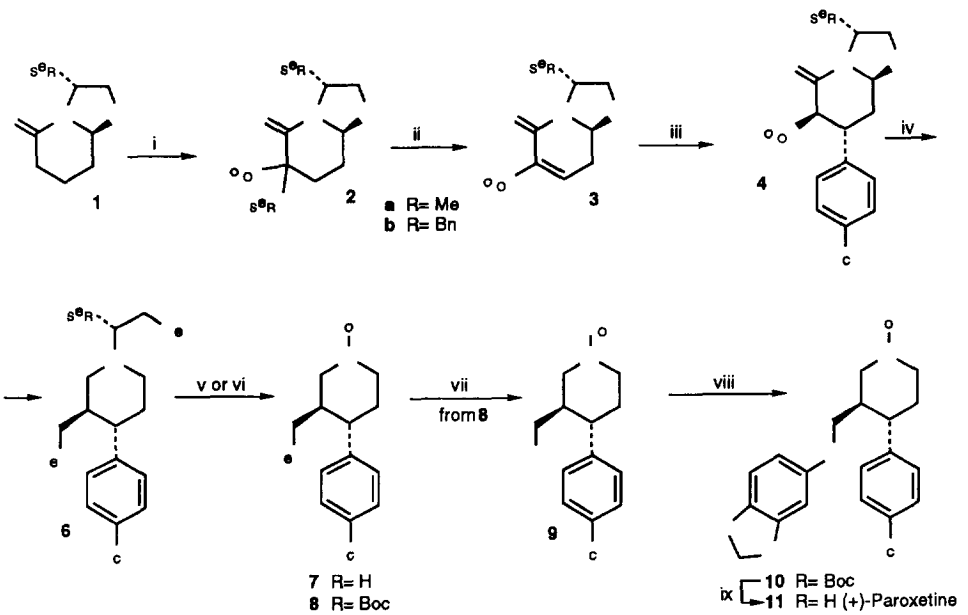
Abstract: An asymmetric synthesis of the 3,4-*trans*-disubstituted piperidine derivative (+)-paroxetine from the chiral non racemic lactam **1** is reported. The *p*-fluorophenyl substituent is introduced by conjugate addition to the unsaturated lactams **3** whereas the aryloxymethyl substituent at the 3-position is assembled by taking advantage of the activating alkoxycarbonyl group of **3**. Copyright © 1996 Elsevier Science Ltd

Paroxetine is a potent and selective inhibitor of 5-hydroxytryptamine uptake, with a reduced propensity to cause the side-effects usually associated with tricyclic antidepressants.[1] It is an enantiomerically pure [(-)-enantiomer] *trans*-3,4-disubstituted piperidine, and the only reported synthesis of this drug involves the resolution of an advanced racemic intermediate.[2]

In the context of our studies[3] on the synthesis of diversely substituted enantiopure piperidines from the chiral non-racemic lactam **1**, we report here an enantioselective synthesis of the (+)-enantiomer of paroxetine. This requires the stereoselective introduction of substituents at the piperidine 3- and 4-positions.

The *p*-fluorophenyl substituent at the piperidine 4-position was introduced by conjugate addition to the unsaturated lactams **3a** and **3b**. The alkoxycarbonyl group in **3** not only provides an additional activation towards the conjugate addition[4] but is also the precursor of the hydroxymethyl group required for the subsequent assembling of the aryloxymethyl substituent at the piperidine 3-position. The synthetic sequence is depicted in Scheme 1.

Bicyclic lactam **1**[3a] was converted to selenides **2a** (85%) and **2b** (77%) (diastereomeric mixtures) in a one-pot reaction involving the sequential treatment of **1** with lithium hexamethyldisilazide, methyl (or benzyl) chloroformate, and phenylselenenyl bromide.[5] Ozonolysis of selenides **2a** and **2b** gave the corresponding unsaturated lactams **3a** and **3b** which, without purification,[6] were allowed to react with lithium (*p*-fluorophenyl)cyanocuprate to give the *trans*-3,4-disubstituted piperidines **4a**[7] and **4b**[8] in 80% and 70% overall yield from **2a** and **2b**, respectively. Only minor amounts (< 5 %) of the *cis* isomers were detected by NMR. In the series **b**, it was demonstrated that the minor *cis* isomer was the epimer of **4b** at the C-3 position of the piperidine ring because the mixture of *cis-trans* esters was converted to a single enantiopure 4-substituted piperidine **5**[9] by debenzylation followed by decarboxylation [i) $NH_4^+HCO_2^-$, Pd-C, MeOH; ii) toluene, reflux].



Scheme 1. *Reagents and conditions:* i) HMDSLi (2.2 equiv), $ClCO_2R$ (1.0 equiv), -78°C, THF, then C_6H_5SeBr (1.4 equiv); ii) O_3, -78°C to 25°C, CH_2Cl_2; iii) (*p*-FC_6H_4)CuCNLi, -78°C, THF; iv) $LiAlH_4$-$AlCl_3$, THF, -78°C; v) H_2, $Pd(OH)_2$, MeOH; vi) H_2, $(Boc)_2O$, $Pd(OH)_2$, AcOEt; vii) MsCl, pyr, 10°C; viii) 3,4-(methylenedioxy)phenol, NaOMe, MeOH, reflux; ix) TFA, CH_2Cl_2.

The relative configuration within **4b** was determined by NOE experiments, thus confirming that the cuprate additions to **3b** proceed, as mentioned earlier,[3b] from the α face of the piperidine ring.

Treatment of **4a** with alane, generated *in situ* from $AlCl_3$ and $LiAlH_4$, accomplished the reduction of both the lactam carbonyl group and the ester function as well as the reductive cleavage of the oxazolidine ring to give the piperidine diol **6**[10] in 74% yield in a single synthetic step. The same diol **6** was obtained in 60% yield starting from the benzyl ester **4b**. The *trans* diequatorial relationship between the hydroxymethyl and *p*-fluorophenyl substituents was evident from the multiplicity and coupling constants of the piperidine protons in the ^{1}H-NMR spectrum.

The chiral auxiliary was removed by hydrogenolysis to give the secondary amine **7**, although from the synthetic standpoint it was more convenient to carry out this reaction in the presence of di-*tert*-butyl dicarbonate[11]. Under these conditions, the *N*-protected amine **8** was obtained in 73% yield. The aryl ether moiety of paroxetine was incorporated (57% overall yield) by mesylation of the hydroxy group of **8** followed by reaction of the resulting mesylate **9** with sodium 3,4-(methylenedioxy)phenoxide.

Finally, deprotection of the *N*-Boc derivative **10** with TFA provided (+)-paroxetine[12] in 94% yield. This synthetic material was identical in all respects (TLC in several solvent mixtures, IR, ^{1}H-NMR, ^{13}C-NMR) with an authentic sample of paroxetine extracted from commercial Seroxat® except for the sign of the optical rotation {$[\alpha]_D^{22}$ +81.7 (*c* 1.3, MeOH); sample from Seroxat® $[\alpha]_D^{22}$ -89.4 (*c* 1.6, MeOH)}.

The synthesis of (+)-paroxetine reported here further illustrates the potential of bicyclic lactam **1** for the synthesis of diversely substituted enantiopure piperidines.

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References and Notes

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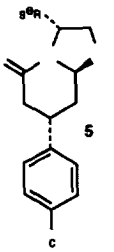
2. a) Christensen, J. A.; Squires, R. F.,Ger. Patent 2,404,113, **1974**; *Chem. Abs.* **1974**, *81*, 152011q. b) Christensen, J. A.; Squires, R. F., U. S. Patent 4,007,196, **1977**. c) Barnes, R. D.; Wood-Kaczmar, M. W.; Richanison, J. E.; Lynch, I. R.; Buxton, P. C.; Curzons, A. D., European Patent 0 223 403, **1987**.
3. (a) Amat, M.; Llor, N.; Bosch, J. *Tetrahedron Lett.* **1994**, *35*, 2223. (b) Amat, M.; Llor, N.; Hidalgo, J.; Hernández, A.; Bosch, J. *Tetrahedron: Asymmetry* **1996**, *7*, 977.
4. An alkoxycarbonyl group is necessary for the success of conjugate additions to unsaturated five-[4a,b] and six-membered[4c] lactams: (a) Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1992**, *57*, 3814. (b) Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1993**, *58*, 36. (c) Overman, L. E.; Robichaud, A. J. *J. Am. Chem. Soc.* **1989**, *111*, 300.
5. All yields are from material purified by column chromatography. Satisfactory analytical and/or spectral data were obtained for all new compounds.
6. Lactams **3** proved to be somewhat unstable, giving the corresponding 2-pyridones by opening of the oxazolidine ring.
7. **4a**: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 2.33 (ddd, *J*= 14.5, 9.0, 5.0 Hz, 1H, H-8); 2.43 (dt, *J*= 14.5, 4.5 Hz, 1H, H-8); 3.63 (td, *J*= 9.0, 4.5 Hz, 1H, H-7); 3.64 (s, 3H, CH_3); 3.64 (d, *J*= 9.0 Hz, 1H, H-6); 3.80 (dd, *J*= 8.5, 7.0 Hz, 1H, H-2); 4.50 (t, *J*= 8.5 Hz, 1H, H-2); 4.90 (t, *J*= 4.5 Hz, 1H, H-8a); 5.44 (t, *J*= 8.0 Hz, 1H, H-3); 6.94 (t, *J*= 8.5 Hz, 1H, *m*-FC_6H_4); 7.11 (dd, *J*= 8.5, 5.0 Hz, 1H, *o*-FC_6H_4); 7.16-7.22 (m, 3H, C_6H_5); 7.26 (m, 2H, C_6H_5). ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 33.1 (C-8); 37.2 (C-7); 52.2 (CH_3); 54.1 (C-6); 58.5 (C-3); 71.5 (C-2); 85.6 (C-8a); 115.5 ($J_{C\text{-}F}$= 21.0 Hz, *m*-FC_6H_4); 126.0 (*o*-C_6H_5); 127.6 (*p*-C_6H_5); 128.3 ($J_{C\text{-}F}$= 7.3 Hz, *o*-FC_6H_4); 128.6 (*m*-C_6H_5); 136.2 (*ipso*-C_6H_5); 139.2 (*ipso*-FC_6H_4); 161.5 ($J_{C\text{-}F}$= 245.0 Hz, *p*-FC_6H_4); 165.8 (C=O); 169.2 (C=O). $[\alpha]_D^{22}$ -37.1 (*c* 0.5, CH_2Cl_2).
8. **4b**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 2.31 (ddd, *J*= 14.5, 9.5, 5.0 Hz, 1H, H-8); 2.44 (dt, *J*= 14.5, 4.3 Hz, 1H, H-8); 3.62 (td, *J*= 9.5, 4.3 Hz, 1H, H-7); 3.75 (d, *J*= 9.5 Hz, 1H, H-6); 3.81 (dd, *J*= 8.8, 7.5 Hz, 1H, H-2); 4.51 (t, *J*= 8.8 Hz, 1H, H-2); 4.91 (t, *J*= 4.8 Hz, 1H, H-8a); 5.06 (d, *J*= 12.0 Hz, 1H, $CH_2C_6H_5$); 5.10 (d, *J*= 12.0 Hz, 1H, $CH_2C_6H_5$); 5.47 (t, *J*= 7.8 Hz, 1H, H-3); 6.97 (t, *J*= 8.5 Hz, 1H, *m*-FC_6H_4); 7.05-7.40 (m, 12H, Ar). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 33.4 (C-8); 37.3 (C-7); 54.6 (C-6); 58.6 (C-3); 67.0 ($CH_2C_6H_5$); 71.5 (C-2); 85.7 (C-8a); 115.6 ($J_{C\text{-}F}$= 21.0 Hz, *m*-FC_6H_4); 126.1 (*o*-C_6H_5); 135.2 (*ipso*-C_6H_5); 136.0 (*ipso*-C_6H_5); 139.3 (*ipso*-FC_6H_4); 161.2 ($J_{C\text{-}F}$= 245.0 Hz, *p*-FC_6H_4); 166.1 (C=O); 168.6 (C=O). $[\alpha]_D^{22}$ -52.2 (*c* 0.5, CH_2Cl_2).

9. **5**: ^{1}H-NMR ($CDCl_3$, 500 MHz) δ 2.17 (ddd, *J*= 13.5, 6.0, 4.0 Hz, 1H, H-8); 2.41 (ddd, 13.5, 7.5, 5.0 Hz, 1H, H-8); 2.75 (d, *J*=5.5 Hz, 2H, H-6); 3.43 (m, 1H, H-7); 3.69 (dd, *J*= 9.0 7.5 Hz, 1H, H-2); 4.48 (t, *J*= 8.5 Hz, 1H, H-2); 4.76 (t, *J*= 5.5 Hz, 1H, H-8a); 5.38 (t, *J*= 7.5 Hz, 1H, H-3); 7.05 (t, *J*= 8.5 Hz, 2H, *m*-FC_6H_4); 7.22 (m, 4H, Ar); 7.27 (m, 1H, Ar); 7.34 (m, 2H, Ar). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 33.67 (C-7); 34.6 (C-8); 37.3 (C-6); 58.2 (C-3); 72.0 (C-2); 86.1 (C-8a); 115.5 ($J_{C\text{-}F}$= 21.0 Hz, *m*-FC_6H_4); 125.8 (*o*-C_6H_5); 127.6 (*p*-C_6H_5); 128.1 ($J_{C\text{-}F}$= 7.3 Hz, *o*-FC_6H_4); 128.8 (*m*-C_6H_5); 137.5 (*ipso*-C_6H_5); 139.8 (*ipso*-FC_6H_4); 161.5 ($J_{C\text{-}F}$= 245.0 Hz, *p*-FC_6H_4); 168.8 (C=O). $[\alpha]_D^{22}$ +15.1 (*c* 0.5, CH_2Cl_2).



10. **6**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.65 (t, *J*= 11.0 Hz, 1H, H-2ax); 1.70-1.95 (m, 3H, H-3 and 2 H-5); 2.14 (t, *J*= 11.3, 4.6 Hz, 1H, H-4ax); 2.37 (td, *J*= 11.5, 3.3 Hz, 1H, H-6ax); 2.39 (br s, 2H, 2 OH); 2.95 (dm, *J*= 11.5 Hz, 1H, H-6eq); 3.09 (dd, *J*= 11.0, 7.3 Hz, 1H, CH_2O); 3.18 (dm, *J*= 11.0 Hz, 1H, H-2eq); 3.30 (dd, *J*= 11.0, 3.2 Hz, 1H, CH_2O); 3.63 (dd, *J*= 10.4, 5.0 Hz, 1H, NCHC*H*$_2$); 3.77 (dd, *J*= 10.4, 5.0 Hz, 1H, NCHC*H*$_2$); 4.04 (t, *J*= 10.4 Hz, 1H, NCH); 6.92 (t, *J*= 8.8 Hz, 2H, *m*-FC_6H_4); 7.06 (dd, *J*= 8.8, 5.6 Hz, 2H, *o*-FC_6H_4); 7.19 (m, 2H, C_6H_5); 7.32 (m, 2H, C_6H_5). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 35.0 (C-5); 44.2 (C-3); 44.6 (C-4); 49.3 (C-6); 53.2 (C-2); 60.0 (CHCH_2); 63.6 (CH_2O); 70.1 (NCH); 115.2 ($J_{C\text{-}F}$= 21.0 Hz, *m*-FC_6H_4); 127.9 (*p*-C_6H_5); 128.2 (*o*-C_6H_5); 128.6 ($J_{C\text{-}F}$= 7.3 Hz, *o*-FC_6H_4); 128.9 (*m*-C_6H_5); 135.1 (*ipso*-C_6H_5); 139.7 (*ipso*-FC_6H_4); 161.0 ($J_{C\text{-}F}$= 245.0 Hz, *p*-FC_6H_4). $[\alpha]_D^{22}$ +31.4 (*c* 0.5, MeOH).

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12. **11**: ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.75 (qd, *J*= 12.0, 4.0 Hz, 1H, H-5ax); 1.80 (m, 1H, H-5eq); 2.10 (m, 1H, H-3ax); 2.60 (td, *J*= 12.0, 5.0 Hz, 1H, H-4ax); 2.71 (t, *J*= 12.0 Hz, H-2ax); 2.77 (td, *J*= 12.0, 3.0 Hz, 1H, H-6ax); 3.21 (dm, *J*= 12.0 Hz, 1H, H-6eq); 3.42 (masked, 1H, H-2eq); 3.43 (dd, *J*= 9.5, 7.0 Hz, 1H, CH_2); 3.56 (dd, *J*= 9.5, 3.0 Hz, 1H, CH_2); 5.88 (s, 2H, OCH_2O); 6.12 (dd, *J*= 8.5, 2.5 Hz, 1H, H-6'); 6.33 (d, *J*= 2.5 Hz, 1H, H-2'); 6.61 (d, *J*= 8.5 Hz, 1H, H-5'); 6.98 (t, *J*= 8.8 Hz, 2H, *m*-FC_6H_4); 7.15 (dd, *J*= 8.8, 5.5 Hz, 2H, *o*-FC_6H_4). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 35.2 (C-5); 42.8 (C-3); 44.4 (C-4); 46.8 (C-6); 50.2 (C-2); 69.3 (CH_2O); 97.7 (C-2'); 100.9 (OCH_2O); 105.3 (C-6'); 107.6 (C-5'); 115.1 ($J_{C\text{-}F}$= 21.0 Hz, *m*-FC_6H_4); 128.5 ($J_{C\text{-}F}$= 7.3 Hz, *o*-FC_6H_4); 139.8 (*ipso*-FC_6H_4); 141.3 (C-3'); 147.9 (C-4'); 154.2 (C-1'); 160.5 ($J_{C\text{-}F}$= 245.0 Hz, *p*-FC_6H_4). Mp (maleate salt) 135-136°C (EtOH-ether) [Lit.[2a] 136-138°C (EtOH-ether)].

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