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A new route to 3,4-disubstituted piperidines: formal synthesis of (−)-paroxetine and (+)-femoxetine

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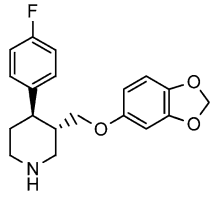
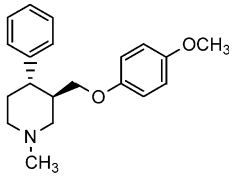
Abstract—A new route to 3,4-disubstituted piperidines was developed using chiral 1,4-dihydropyridines as key intermediates, the synthetic utility of which was demonstrated by formal synthesis of (−)-paroxetine and (+)-femoxetine.

3-Substituted-4-arylpiperidines[1] such as (−)-paroxetine,[2] (+)-femoxetine,[3] and their analogues are a significantly important class of serotonin (5-hydroxytryptamine) reuptake inhibitors. Therefore, extensive efforts have been made for the efficient synthesis of (−)-paroxetine[4–10] and (+)-femoxetine.[4d,f,10f,11] The reported syntheses are based on the following representative strategies: (i) cyclization of chiral linear compounds[4] (ii) expansion of chiral five-membered rings[5] (iii) asymmetric nucleophilic addition to α,β-unsaturated δ-lactams or piperidine derivatives[6] (iv) desymmetrization of *meso*-glutalimides[7] (v) kinetic resolution of intermediate esters[8] or optical resolution of piperidine derivatives.[9] However, little has been known of approaches using pyridine derivatives as substrates despite their easy availability.

We have previously reported a new method for the synthesis of chiral 1,4-dihydropyridines by face-selective nucleophilic addition reaction to an intermediate pyridinium salt.[12] In this letter, we report a new entry for the formal synthesis of (−)-paroxetine and (+)-femoxetine by using the chiral 1,4-dihydropyridines as key intermediates. In addition, the syntheses of the stereoisomers of the piperidine precursors are also described.

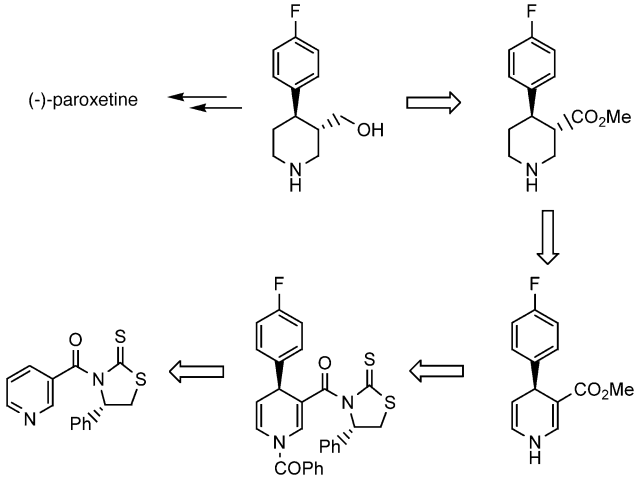


(-)-paroxetine



(+)-femoxetine

Scheme 1 outlines a retrosynthetic analysis of (−)-paroxetine. Introduction of a 4-fluorophenyl group at the 4-position is performed by a face-selective addition to a pyridinium salt. After removal of the chiral auxiliary, hydrogenation of the double bonds and isomerization of the resulting *cis*-piperidine ester will provide *trans*-3,4-disubstituted piperidine. Transformation of the ester moiety to a hydroxymethyl group affords a reported precursor[8e,9b] of (−)-paroxetine. Similar retrosynthetic



Scheme 1. Retrosynthetic analysis of (−)-paroxetine.

Keywords: (−)-Paroxetine; (+)-Femoxetine; Face-selective addition; Cation–π interaction; 1,4-Dihydropyridine.
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analysis can be applied to the formal synthesis of (+)-femoxetine using a chiral auxiliary with an opposite configuration to that used for (−)-paroxetine synthesis.

First, we examined face-selective addition of a cuprate toward nicotinic amide **1** according to our reported method.[12] The addition of a cuprate generated from 4-fluorophenyllithium and CuBr·SMe_2 toward a pyridinium salt produced from **1** with methyl chloroformate gave 1,4-adduct **2a** in 69% yield with 95% de. When benzoyl chloride was used instead of methyl chloroformate for the activation of the pyridine nucleus, the stereoselectivity was improved to give **2b**[13] in 99% de. These good stereoselectivities can be explained by the addition of a nucleophile from the less hindered side of the intermediary cation–π complex[14] as shown in Scheme 2.

Removal of the chiral auxiliary was accomplished by treatment with NaOMe in CH_2Cl_2 to yield ester **3** (Scheme 3). It is worthwhile noting that the recovered chiral auxiliary is reusable for the synthesis of **1**. Hydrogenation of dihydropyridine **3** in the presence of PtO_2 in EtOH proceeded regioselectively to give tetrahydropyridine **4**. When the reduction was allowed to continue for six days, simultaneous reduction of both double bonds of dihydropyridine **3** proceeded and provided a 4:1 mixture of *cis*- and *trans*-piperidines **5**. On the other hand, further reduction of the remained double bond of **4** was accomplished by use of CH_2Cl_2–AcOH (4:1) as a mixed solvent to afford a 15:1 mixture of *cis*- and *trans*-piperidines **5**. The cis-selectivity can be explained based on the optimized geometry of **4** by AM1 calculations[15] (Fig. 1); the pseudo-axial aryl group effectively hinders

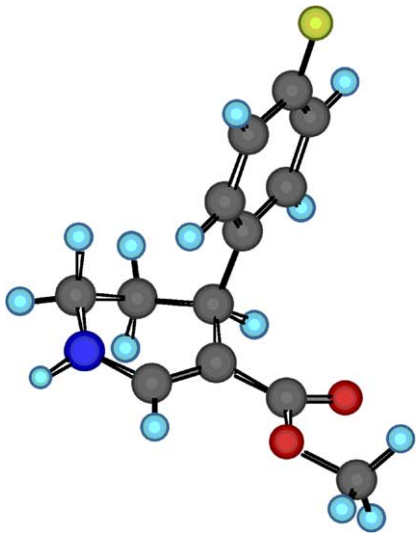
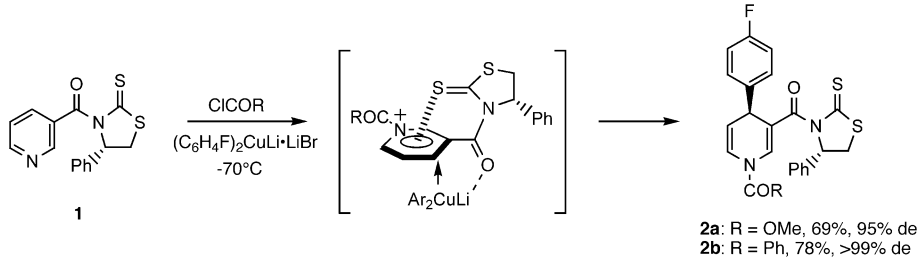
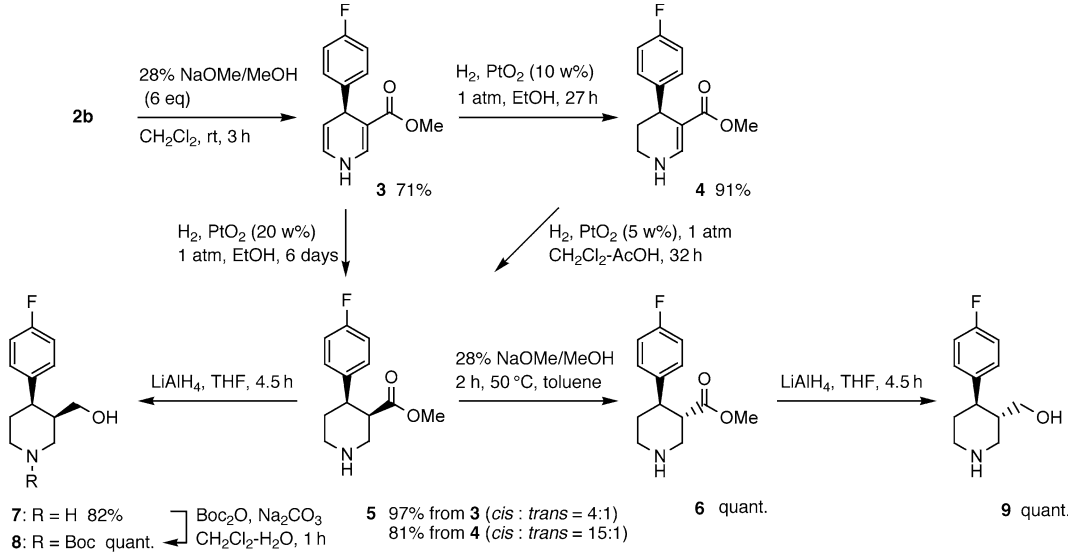


Figure 1. Optimized structure of **4**.



Scheme 2. Face-selective addition reaction to a pyridinium intermediate.



Scheme 3.

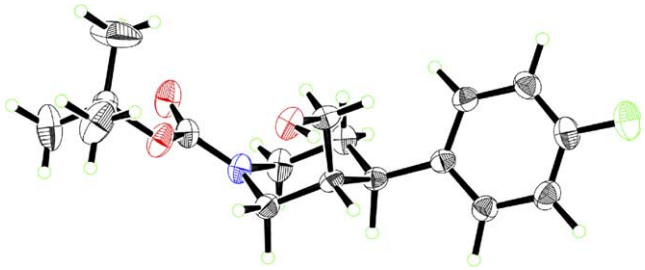


Figure 2. ORTEP drawing for **8**.

one side of the double bond, which would cause the hydrogenation from the less crowded side.

Isomerization of *cis*-piperidine **5** into *trans*-piperidine **6** was achieved in quantitative yield by treatment with NaOMe at 50 °C in toluene. Reduction of the ester moiety of **6** provided alcohol **9**, which is the reported precursor of (−)-paroxetine. All spectral data of **9** were in agreement with those reported,[8e] and the specific rotation was close to that reported ($[\alpha]_D^{23}$ −21.7, *c* 0.41, MeOH; lit.:[8e] $[\alpha]_D^{25}$ −24.3, *c* 0.46, MeOH). Similar reduction of *cis*-piperidine **5** afforded *cis*-alcohol **7**. The relative configuration of *cis*-product **7** was confirmed by X-ray structural analysis after conversion to *N*-Boc derivative **8**.[16] X-ray structure clearly shows *cis*-orientation of the two groups as shown in Figure 2.[17]

The formal synthesis of (+)-femoxetine was also accomplished according to a similar procedure to the formal synthesis of (−)-paroxetine (Scheme 4). Addition of phenyl cuprate to the nicotinic amide **10** possessing an opposite absolute configuration to that of **1** gave 1,4-adduct **11** in 90% de. This was used for the next reaction without further purification due to the difficulty of the separation of the diastereomers by column chromatography. Removal of the chiral auxiliary with NaOMe afforded **12** in 69% yield. Hydrogenation of both double bonds with PtO_2 in MeOH led to a tetrahydropiperidine **13**, which was further reduced in CH_2Cl_2–AcOH to give a 9:1 mixture of *cis* and *trans*-piperidines **14**. When the reduction was carried out in MeOH for four days at rt, simultaneous reduction of both double bonds of **12** proceeded and yielded **14** in 65% yield (a 4:1 mixture of *cis*- and *trans*-piperidines). After isomerization of **14** to *trans*-ester with NaOMe, the ester was transformed into *trans*-alcohol **15** by reduction with $LiAlH_4$. N-Protection of **15** afforded reported *N*-Boc-piperidine **16**, a precursor of (+)-femoxetine, recrystallization of which gave optically pure crystals. All spectral data of **16** were in agreement with those reported[4f] ($[\alpha]_D^{23}$ +6.5, *c* 0.4, MeOH; lit.:[4f] $[\alpha]_D^{22}$ +6.4, *c* 0.4, MeOH).

It has been known that the enantiomers and diastereomers of (−)-paroxetine and (+)-femoxetine exhibit different activities toward 5-HT uptake inhibition;[10f,18] therefore, it is quite important to establish a synthetic route for all of the diastereomers of 3,4-disubstituted piperidines in pure form. The fact that the present method can provide all of the four stereoisomers for 3,4-disubstituted piperidine as described above indicates its synthetic utility.

In summary, we have described a new route to the formal total synthesis of (−)-paroxetine and (+)-femoxetine by using chiral 1,4-dihydropyridines as key intermediates. This method can provide all of the stereoisomers of a 3,4-disubstituted piperidine. Further application to the synthesis of multi-substituted piperidines is in progress.

Acknowledgements

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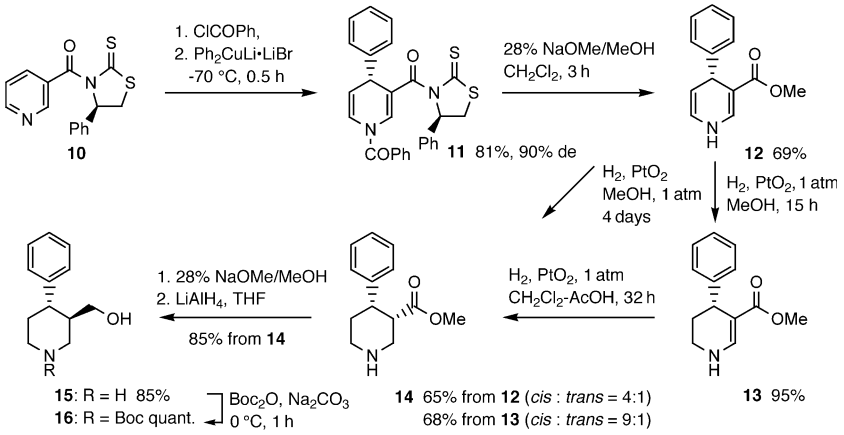

Scheme 4.

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13. Compound **2b**: $[\alpha]_D^{27}$ −216.6 (*c* 0.54, MeOH); IR (neat): 3064, 1717, 1695, 1557, 1473 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (s, 1H), 7.65–6.88 (m, 15H), 5.24–5.23 (m, 2H), 4.75 (d, 1H, $J = 4.4$ Hz), 3.39 (dd, 1H, $J = 7.4$, 11.0 Hz), 3.18 (dd, 1H, $J = 6.4$, 11.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.5, 169.9, 167.5, 162.9, 160.3, 139.6, 138.0, 137.0, 131.9, 131.8, 128.8, 128.8, 128.7, 128.6, 126.4, 120.3, 115.4, 115.2, 113.9, 71.5, 38.9, 38.1; HRMS: calcd for $C_{28}H_{21}N_2O_2FS_2$: 500.1029, found: 500.1092.
14. Yamada, S.; Misono, T.; Tsuzuki, S. *J. Am. Chem. Soc.* **2004**, *126*, 9862–9872.
15. AM1 calculations were performed by using Spartan 04'.
16. Compound **8**: Mp 145–147 °C; $[\alpha]_D^{27}$ +72.6 (*c* 0.38, MeOH); IR (KBr): 3448, 3032, 1668, 1601, 1345, 1263, 1229, 1257, 1114, 1028, 835, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.11 (dd, $J = 5.4$, 8.4 Hz, 2H), 6.99 (t, $J = 8.4$ Hz, 2H), 4.39 (d, $J = 13.6$ Hz, 1H), 4.29 (br d, $J = 10.4$ Hz, 1H), 3.40 (br s, 1H), 3.17–3.14 (m, 1H), 3.04 (dt, $J = 4.2$, 13.0 Hz, 1H), 3.00–2.86 (m, 2H), 2.11 (br s, 1H), 2.02–1.88 (ddd, $J = 4.6$, 13.0, 26.0 Hz, 1H), 1.65 (br d, $J = 10.8$ Hz, 1H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5, 160.0, 135.5, 128.3, 128.2, 115.2, 115.0, 80.5, 57.7, 45.5, 42.6, 28.4, 25.2.
17. Crystal data and structure refinement for **8**: Data were collected on a Rigaku AFC7R diffractometer with Cu-Kα radiation ($\lambda = 1.54178$ Å). The structures were solved by direct methods with SHELXS-93 and refined by full-matrix least-squares on F^2 using SHELXL-97. Compound **8**: $C_{17}H_{24}NO_3F$, $M = 309.37$, monoclinic, $P2_1$, $\mu = 0.735$ mm^{-1}, $a = 11.740(3)$, $b = 9.615(2)$, $c = 7.6352(13)$ Å, $\beta = 99.36(2)$, $V = 850.4(3)$ $Å^3$, $T = 296$ K, $Z = 2$, $D_c = 1.208$ g cm^{-1}. A total of 2548 reflections were collected and 1988 are unique ($R_{int} = 0.0222$). *R*1 and *wR*2 are 0.0398 [$I > 2\sigma(I)$] and 0.1393 (all data), respectively. Crystallographic data (excluding structure factors) for the structures in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 282601. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.jp].
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