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Ring expansion: formal total synthesis of (−)-paroxetine

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Abstract—A ring expansion and a radical dehalogenation have been used as the key steps in a formal total synthesis of (−)-paroxetine. A stereoselective ring expansion of prolinol generated the substituted piperidine ring precursor of (−)-paroxetine.

4-Arylpiperidine is an important structural element in a number of biologically active compounds, possibly due to the similarity to aryl alkylamine pharmacophore common to neurotransmitters like serotonin [5-hydroxytryptamine (5-HT)], dopamine (DA), noradrenaline (NA) and to antagonists of opiate receptors. Drugs that modulate the physiological and pathophysiological actions of 5-HT are useful or potentially useful in the treatment of a variety of human diseases, including depression, anxiety, alcoholism, chronic pain, emesis and eating disorders such as obesity and bulimia.[1] Such compounds can be exemplified by the antipsychotic 5-HT- and DA-antagonists, haloperidol,[2] the analgesic opioid agonist, meperidine,[3] and the selective serotonin reuptake inhibitor (SSRI), paroxetine **1** [Paxil®, Seroxat®] (Fig. 1).[4]

This drug is used in the treatment of depression, obsessive compulsive disorder and panic disorder. Moreover, it had a reduced propensity to cause the side-effects usually associated with tricyclic antidepressants.[5] Paroxetine is an enantiomerically pure (−)-*trans*-3,4-disubstituted piperidine. Due to its biological importance, several enantiocontrolled syntheses have been disclosed.[6]

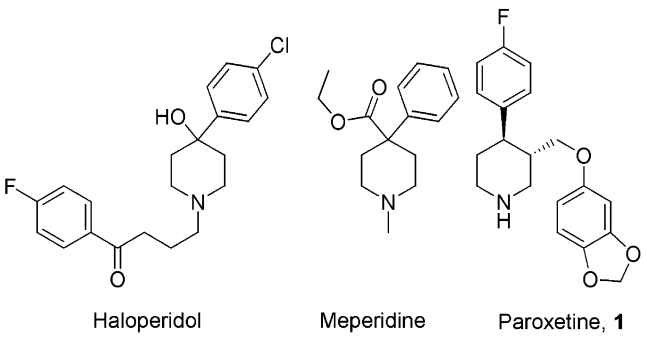
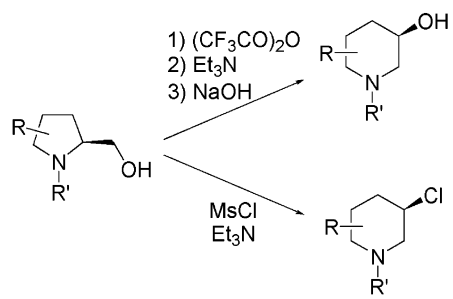


Figure 1. Selected 4-arylpiperidines.

In the context of our studies on ring expansion reactions[7] of enantiomerically pure substituted prolinols to enantiomerically pure substituted 3-hydroxypiperidines[7,8] or substituted 3-chloropiperidines[7,9] (Scheme 1), we report here a formal enantioselective synthesis of the (−)-paroxetine.

The retrosynthetic analysis shown in Scheme 2 envisions aminoalcohol (−)-**9**, a known precursor of the (−)-paroxetine **1**,[6a] arising from optically pure substituted 3-chloropiperidine (−)-**7**, which would be derived from (L)-pyroglutamic acid via the known bicyclic lactam (+)-**2**.[10]

Enantiomerically pure bicyclic lactam (+)-**2** ($[\alpha]_D$ = +237, *c* 1.2, $CHCl_3$), obtained in three steps from (L)-pyroglutamic acid,[10] was treated with an excess of LiHMDS (2.1 equiv., THF, −78°C, 40 min) which



Scheme 1. Ring expansion reactions.

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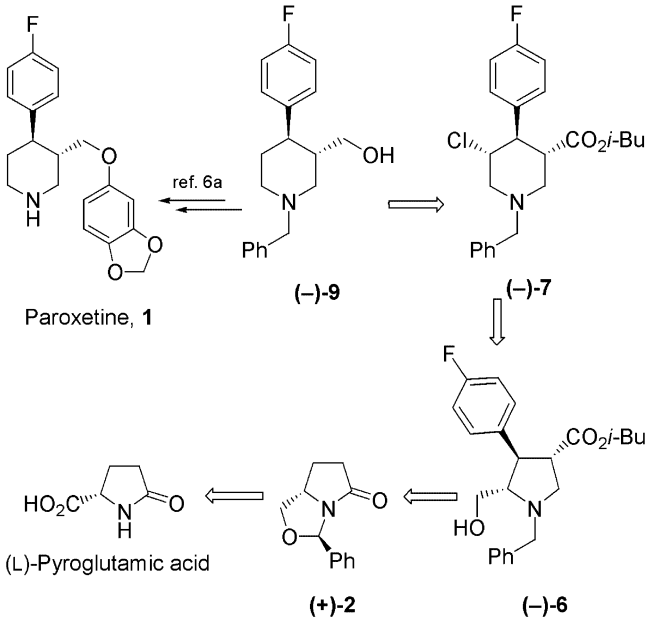
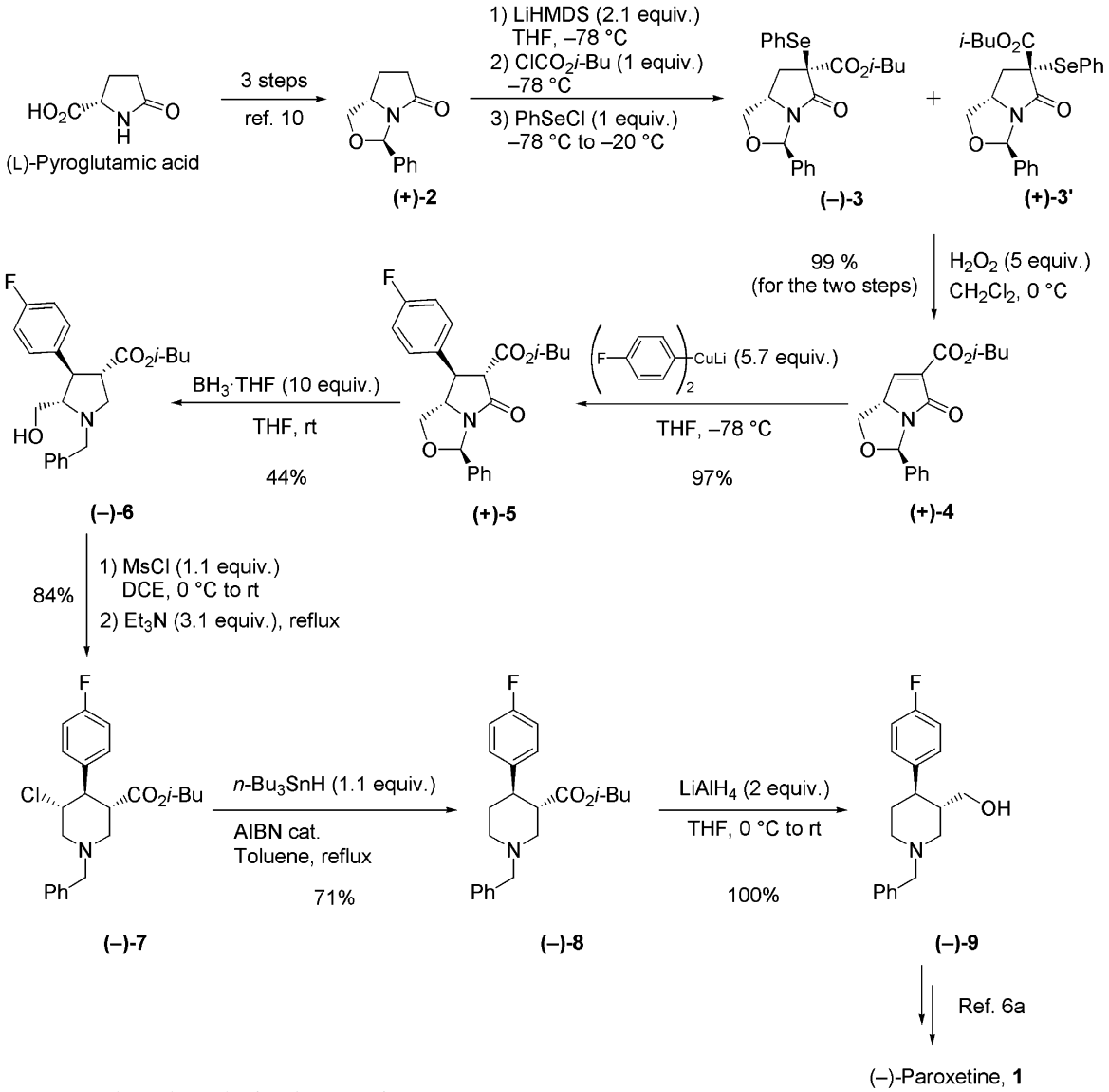


Scheme 2. Retrosynthetic analysis.

allowed the formation of the selenoesters (–)-**3** and (+)-**3′** in a one-pot reaction (ratio (–)-**3**/(+)-**3′** = 62/38) involving successive addition of isobutyl chloroformate (1 equiv., –78°C, 45 min) and phenylselenyl chloride (1 equiv., –78°C to –20°C, 1.2 h). The phenylselenoesters were not purified but treated directly with H_2O_2 (5 equiv., CH_2Cl_2, 0°C, 30 min)[11] and the unsaturated bicyclic lactam (+)-**4** was isolated in 99% yield (overall yield from the bicyclic lactam (+)-**2**). The unsaturated bicyclic lactam (+)-**4** was allowed to react diastereoselectively with lithium di(4-fluorophenyl)cuprate (5.7 equiv., –78°C, 2 h) to give the conjugate addition product, the all-*trans* trisubstituted pyrrolidinone (+)-**5**, in 97% yield.[12] Reduction of (+)-**5** with BH_3·THF (10 equiv., THF, 0°C, 1.5 h), which also causes the cleavage of the C–O bond of the oxazolidine ring, led to the prolinol (–)-**6** (44% yield). Ring expansion of prolinol (–)-**6** by addition of mesyl chloride (1.1 equiv., DCE, 0°C to rt, 1 h) followed by the addition of Et_3N (3.1 equiv., reflux, 2 days) provided the expected trisubstituted 3-chloropiperidine (–)-**7**[13] in 84% yield. The relative stereochemistry of the chloride and the aryl



Scheme 3. Formal total synthesis of paroxetine.

group was determined by examination of the ^{1}H NMR coupling constants between the C-4 and C-5 protons.[14] Reduction of (−)-**7** with *n*-Bu_3SnH (1.1 equiv., toluene, reflux, 2 h) in the presence of a catalytic amount of AIBN[15] gave the amino ester (−)-**8** in 71% yield. Finally, the known precursor (−)-**9**[16] of the (−)-paroxetine was obtained by reducing (−)-**8** by LAH (2 equiv., THF, 0°C to rt, 50 min) in quantitative yield (Scheme 3).

Since the piperidine (−)-**9** has been converted into (−)-paroxetine,[6a] the present transformation of the known bicyclic lactam (+)-**2** into the aminoalcohol (−)-**9** (seven steps, 25% overall yield) constitutes a new formal synthesis of (−)-paroxetine.

Our work demonstrates that *trans*-3,4-disubstituted piperidines can be obtained with high stereoselectivity employing a stereospecific ring expansion applied to prolinol which uses a mesyl chloride–Et_3N process and a *n*-Bu_3SnH mediated reduction of 3-chloropiperidine. Application of this procedure to other complex products is currently underway.

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13. (−)-**7**: R_f = 0.35 (petroleum ether/EtOAc, 95/5). $[\alpha]_D$ = −5.2 (*c* 1.06/$CHCl_3$). Mp 77°C. IR (KBr): 1728, 1513, 1229, 1186, 1150, 750 cm^{-1}. ^{1}H NMR δ 7.44–7.28 (5H), 7.23 (m, 2H), 7.03 (m, 2H), 4.09 (ddd, 1H, *J* = 10.7, 10.7 and 4.4 Hz), 3.67 (dd, 1H, *J* = 10.7 and 6.6 Hz), 3.66 (s, 2H), 3.57 (dd, 1H, *J* = 10.7 and 6.6 Hz), 3.37 (ddd, 1H, *J* = 11.4, 4.4 and 1.5 Hz), 3.15 (ddd, 1H, *J* = 11.0, 3.3 and 1.5 Hz), 3.07–2.85 (2H), 2.48–2.31 (2H), 1.64 (m, 1H), 0.71 (d, 3H, *J* = 6.6 Hz), 0.70 (d, 3H, *J* = 6.6 Hz). ^{13}C NMR δ 171.5 (s), 162.0 (d, *J* = 245.4 Hz), 137.1 (s), 135.2 (d, *J* = 3.0 Hz), 129.6 (dd, *J* = 7.9 Hz), 128.9 (d), 128.4 (d), 127.4 (d), 115.2 (dd, *J* = 31.4 Hz), 70.6 (t), 62.0 (t), 61.0 (t), 59.6 (d), 55.4 (t), 52.8 (d), 50.0 (d), 27.4 (d), 18.7 (q). EI MS *m*/*z* (relative intensity): 405 ($M^{+\bullet}$, 1), 403 ($M^{+\bullet}$, 3), 369 (14), 368 (56), 354 (39), 314 (11), 312 (31), 276 (25), 91 (100). HRMS (CI^+, CH_4) calcd for $C_{23}H_{28}^{35}ClFNO_2$ [(M+H)$^+$]: 404.1793; found: 404.1788. Calcd for $C_{23}H_{28}^{37}ClFNO_2$ [(M+H)$^+$]: 406.1773; found: 406.1765.
14. The *trans* stereochemistry was assigned on the basis of mechanistic considerations and spectroscopic data (H-5: δ = 4.09 ppm, $J_{H5ax\text{-}H6ax}$ = 10.7 Hz, $J_{H5ax\text{-}H4ax}$ = 10.7 Hz, $J_{H5ax\text{-}H6eq}$ = 4.4 Hz).
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