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PREPARATION OF 4-(4-FLUOROPHENYL)-1-METHYL-3-METHYLENEPIPERIDINE BY MICROWAVE-ASSISTED ELIMINATION REACTION

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Paroxetine **1** is a selective serotonine-reuptake inhibitor (Paxil, Seroxat) used in the treatment of depression [1] and Parkinson's disease [2]. Its industrial synthesis [3] proceeds *via* racemic *trans*-4-(4-fluorophenyl)-3-hydroxymethyl-1-methylpiperidine, which undergoes optical resolution to provide a desirable (3*S*,4*R*)-enantiomer **2a** and its antipode **2b** whose enantiomeric purity can be improved by a reverse enrichment procedure [4]. Transformations of **2b** proceeding through 'temporary destruction' of asymmetric centres is challenging particularly in respect to the possibility of converting the unwanted (3*R*,4*S*)-enantiomer into the desirable one with the opposite absolute configuration.

The more accessible of the two chiral centers in **2b** appears to be that on C-3. It can be readily attacked by a strong base in an elimination reaction to furnish (4*S*)-4-(4-fluorophenyl)-3-methylene-1-methylpiperidine **7b** which can be further transformed into an achiral intermediate **8** (Fig. 1).

In an attempt to improve the yields of elimination we decided to employ a supported solvent-free microwave methodology [6]. Dehydration of **2b** was attempted on acidic clays (KSF, K-10) and calcined alumina, on basic alumina, basic alumina impregnated with KF, neutral alumina and neutral alumina/KF under microwave irradiation.

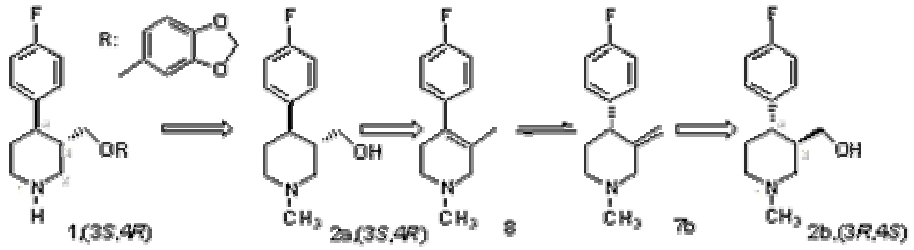

Figure 1.

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