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Enantioselective synthesis of 3-substituted-4-aryl piperidines useful for the preparation of paroxetine☆

K. S. Keshava Murthy,* Allan W. Rey* and Michael Tjepkema

Brantford Chemicals Inc., 34 Spalding Drive, Brantford, Ontario, Canada N3T 6B8

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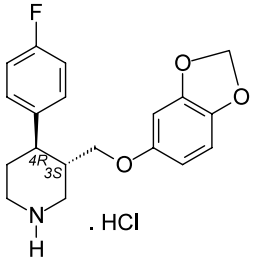
Abstract—The asymmetric conjugate addition reaction between 4-fluorophenylmagnesium bromide and various chiral α,β-unsaturated esters and enoylsultam substrates was explored to prepare a key intermediate useful in the preparation of paroxetine. The most selective auxiliary was found to be Oppolzer's (1*S*)-(−)-camphorsultam. Interestingly, the diastereoselection was opposite to that reported for acyclic enoylsultams.

The growth in the number of chiral pharmaceuticals coupled with both the need to reduce the cost of drug substances and to minimize waste streams has motivated research into finding more selective synthetic procedures. Paroxetine (**1**, Paxil®) is a good illustration of a chiral pharmaceutical that is useful for the treatment of depression and obsessive compulsive disorders.[2]

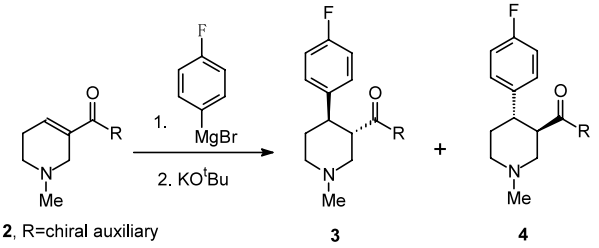


1, Paroxetine

Numerous syntheses of this potent and selective serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibitor have been reported by various workers.[3] Other methods to achieve the desired chirality at the C-3 and C-4 positions of the piperidine ring include biocatalytic methods, which rely on diastereoselective enzymatic hydrolyses of the ester functionality of various ester precursors,[4a,c–f] alcohol acylation[4b] and classical resolution of diastereomeric hydrobromide salts.[5a,c] A common deficiency of all the latter approaches is that 50% of the material is lost as the wrong isomer, which greatly diminishes their synthetic utility for scale-up.

To overcome these deficiencies and develop a scalable method to control the chirality at C-4 of the piperidine ring, we have explored the asymmetric conjugate addition reaction[6] between 4-fluorophenylmagnesium bromide and various chiral α,β-unsaturated esters and enoylsultams with the general formula **2** (Scheme 1). This reaction produced compounds **3**, a key intermediate in the synthesis of paroxetine, together with varying amounts of **4**. Compounds having the structure **3** can be elaborated into (−)-paroxetine using known chemistry.[5a,c] Various chiral auxiliaries were examined in order to achieve optimum selectivity. The results are summarized in Table 1.

The menthol-based Michael precursors of formula **2** (Table 1, entries 1–4) were prepared in near-quantitative yields by a modification of the procedure described by Meth-Cohn[7] via transesterification of arecoline in a toluene reaction medium using the requisite menthol or menthol-derived auxiliary (1.0 equiv.) together with



2, R=chiral auxiliary **3** **4**

Scheme 1. Conjugate addition reaction.

Keywords: Michael reaction; asymmetric synthesis; paroxetine; Grignard addition; camphorsultam.

☆ A patent covering aspects of this work has been issued. See Ref. 1.

* Corresponding authors. E-mail: kmurthy@brantfordchemicals.com; arey@brantfordchemicals.com

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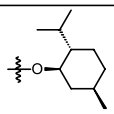
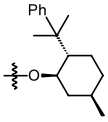
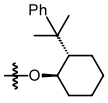
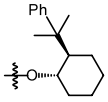
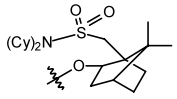
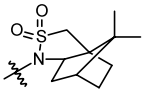
Table 1. Ratio of **3**:**4** for various auxiliaries

Entry	Auxiliary	R	**3**	**4**	Yield (%)
1	(-)-Menthol R		1.0	1.0	75
2	(-)-8-Phenylmenthol		3.7	1.0	76*
3	(1*R*,2*S*)-(-)-*trans*-Cumenecyclohexanol (TCC)		4.0	1.0	86*
4	(1*S*,2*R*)-(+)-*trans*-Cumenecyclohexanol (TCC)		1.0	4.0	86*
5	10-Dicyclohexylsulfamoyl-isoborneol		2.7	1.0	67
6	N-Camphorsultam		>9.8	<0.2	75

* Yield assessed by H NMR.

potassium *tert*-butoxide (0.05 equiv.). The reaction was driven to completion by distillation to azeotropically remove methanol. For the isoborneol-based auxiliary (entry 5), it was necessary to transesterify 10-dicyclohexylsulfamoylisoborneol with methylnicotinate (*n*-BuLi, THF) followed by quaternization (iodomethane) and reduction ($NaBH_4$).[8] The camphorsultam-based auxiliary (entry 6) was obtained using the procedure described by Ho and Mathre.[9]

For the 1,4-addition reactions a diethyl ether solution of 4-fluorophenylmagnesium bromide was typically added to a toluene solution of the Michael acceptor at 0 to −10°C. After the addition was complete, the reaction was quenched using saturated aqueous NH_4Cl and the organic phase was then washed with brine.[10] In terms of further elaboration to paroxetine, the stereochemistry at the C-3 position of the piperidine ring was controlled by the stereochemistry at C-4 by epimerization to the thermodynamically more stable C-3, C-4-*trans* isomer using catalytic potassium *tert*-butoxide in toluene. The only exception was when the camphorsultam auxiliary (entry 6) was used, where the C-3, C-4 *cis*-isomer was formed. All efforts to epimerize this compound were unsuccessful. However, other work has shown that the C-3, C-4 *cis*-compound can also be elaborated to paroxetine.[3n,5a,b]

The degree of asymmetric induction was assessed by ^1H NMR or HPLC analysis of the diastereomeric mixtures. For entries 1–4, the absolute stereochemistry at C-3 and C-4 of the piperidine rings was confirmed by comparison of their measured optical rotations with that of the known (3*S*,4*R*)-alcohol.[11] Thus, after epimerization, the compounds were reduced to *trans*-3-hydroxymethyl-4-(4′-fluorophenyl)piperidine ($LiAlH_4$ or REDAL®) and their optical rotations compared. For entry 5, the absolute stereochemistry was established by determination of the crystal structures of the major (3*S*,4*R*)- and minor (3*R*,4*S*)-diastereomers by single crystal X-ray analysis (Figs. 1 and 2[12]). For the camphorsultam auxiliary (entry 6), the absolute stereochemistry was determined by conversion to paroxetine hydrochloride using standard methodology.[5] The (3*S*,4*R*)-absolute configuration was confirmed by optical rotation comparison (−82.8°; lit.:[13] −88°).

Many different reaction conditions were examined to try to improve the yield and diasteroselection of these conjugate additions. For instance, in the case of the menthyl ester analog of arecoline (entry 1), the combined yield of the 1,4-adduct stereoisomers **3** and **4** (Scheme 1) was typically in the 65–75% range. For all of the auxiliaries examined, improvement of the

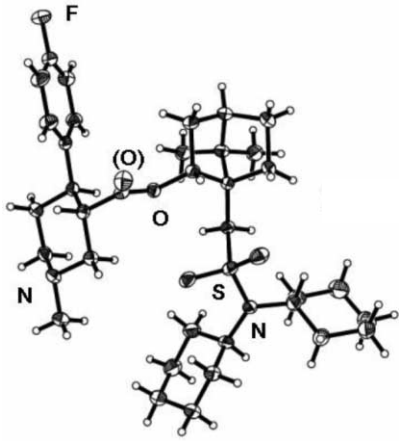


Figure 1. (3*S*,4*R*).

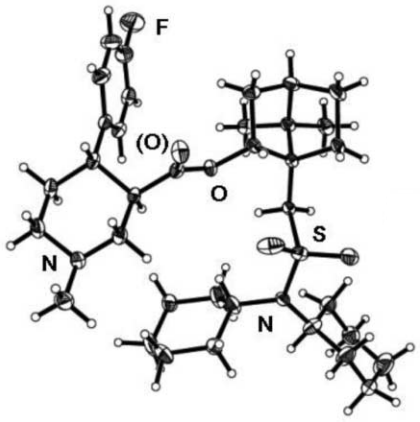


Figure 2. (3*R*,4*S*).

diastereoselection by changing the solvents (toluene, THF, ether), reaction temperatures (20 to −50°C), additives (copper(I) bromide–dimethylsulfide complex, TMEDA), nucleophiles, and Lewis acids used (TMS-Cl, $BF_3{\cdot}Et_2O$) was generally unsuccessful. However, it was found that by increasing the steric bulk of the auxiliary (cf. entries 2 and 3 versus entry 1), the selectivity increased significantly.

Even higher diastereoselection was achieved using the Oppolzer (1*S*)-(−)-(2,10)-camphorsultamoyl chiral auxiliary (entry 6), which afforded a high degree of stereocontrol. Surprisingly, the induction was the opposite of that predicted by the model developed by Oppolzer for similar acyclic unsaturated *N*-enoylsultams.[14] A similar observation was recently made by Cook[15] for the addition of *p*-tolylmagnesium bromide to the similar enoylsultam Michael precursor, *N*-ethyl-1,2,5,6-tetrahydropyridine-4-carboxylic acid. Also it is of interest to note that a conjugate addition strategy was used for the stereocontrolled synthesis of various 2-substituted-4-aryl piperidines from the corresponding 4,5-unsaturated-6-piperidinones.[16]

In conclusion, a highly stereoselective method for the preparation of a key synthetic precursor of paroxetine has been achieved by the asymmetric conjugate addition reaction.

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10. A 2 M solution of 4-fluorophenylmagnesium bromide in diethyl ether (4.42 mL, 8.84 mmol, 2.0 equiv.) was added to a solution of the *N*-enoyl camphorsultam **2** (R = 2,10-camphorsultamoyl, 1.50 g, 4.42 mmol) in toluene (30 mL) over a 10 minute period, while maintaining the temperature between 0 to −10°C. After a further 1 h at this temperature, the reaction mixture was quenched using saturated aqueous NH_4Cl. The layers were separated and the organic phase was washed with brine, filtered through Celite®, and the volatiles removed under reduced pressure. This afforded a crude solid which was further purified by silica gel chromatography (EtOAc) to provide 1.44 g (75% yield) of the *cis*-(3*R*,4*R*)-adduct. IR ($CHCl_3$): 3020, 1702, 1605, 1512, 1329, 909 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.31–7.18 (m, 2H), 7.01–6.88 (m, 2H), 3.72 (dd, 1H, $J = 7.3$, 5.0 Hz), 3.60 (br s, 1H), 3.32 (s, 2H), 3.25 (d, 1H, $J = 12.5$ Hz), 3.11 (d, 1H, $J = 5.9$ Hz), 3.01–2.74 (m, 2H), 2.48–2.18 (m, 2H), 2.28 (s, 3H), 2.01 (t, 1H, $J = 10.1$ Hz), 1.92–1.58 (m, 3H), 1.46–0.92 (m, 4H), 0.82 (s, 3H), 0.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.6, 161.7 (d, $J = 244.6$ Hz), 137.4, 129.4 (d, $J = 7.8$ Hz), 114.7 (d, $J = 21.0$ Hz), 65.3, 56.4, 55.9, 53.1, 47.7 47.3, 46.6, 45.3, 44.5, 42.1, 38.3, 32.8, 26.3 (2C), 20.0, 19.7; MS (DCI, NH_3): 435 ($M+H^+$, 100%), 371 ($M+H^+-SO_2$, 7.0%); HRMS calcd for $C_{23}H_{31}FN_2O_3S$ ($M+H^+$): 435.2119 amu. Found: 435.2112 amu.
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