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Diastereoconvergent Synthesis of (-)-Paroxetine

Delfino Chamorro-Arenas, [a]‡ Lilia Fuentes, [a]‡ Leticia Quintero, [a] Silvano Cruz-Gregorio, [a] Herbert Höpfl, [b] and Fernando Sartillo-Piscil * [a]

Abstract: A diastereoconvergent approach to (-)-paroxetine from diastereomeric 3,4-epoxy-2-piperidones is reported. For this synthesis, the regioselective and stereodivergent Cu(I)-catalyzed epoxide ring-opening of the epoxyamide precursors to give the 4-fluorophenyl-2-piperidone skeleton with the correct absolute configuration, is crucial. Using CuBr·SMe_2 as catalyst, the epoxide ring-opening reaction is achieved with inversion of the configuration, whilst the configuration is retained when CuI is employed.

Introduction

Many 4-arylpiperidines belong to a selected group of synthetic alkaloids pharmacologically actives (*e.g.*, haloperidol, femoxetin, and (-)-paroxetine; see Figure 1) that can modulate the physiological and pathophysiological actions of neurotransmitters such as serotonin and dopamine.[1a] In particular, (-)-paroxetine hydrochloride, also known by the trade names Paxil® and Seroxat®, [1b,c] is a *trans*-3,4-disubstituted piperidine derivative that acts as a selective serotonine reuptake inhibitor (SSRI). Therefore, is a drug used worldwide not only as antidepressant, but also in the treatment of several other disorders (*i.e.,* obsessive compulsive disorder, panic disorder and, post-traumatic stress disorder).[2]

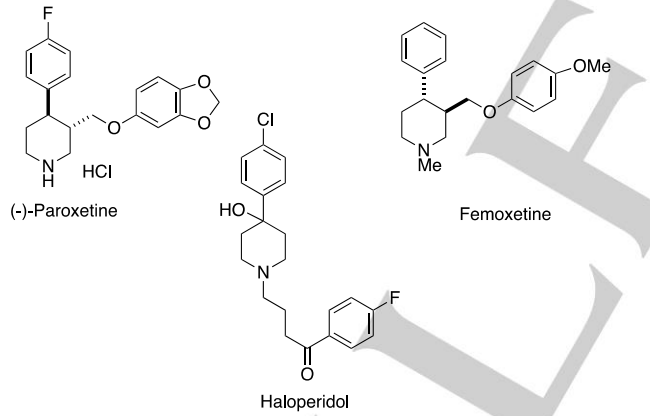
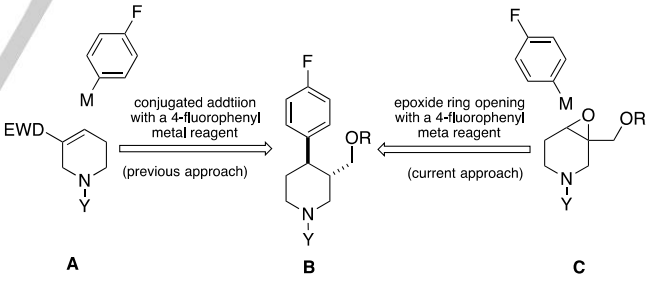


Figure 1. Selected 4-arylpiperidines pharmacologically actives

Since the (-)-paroxetine is one of the most important non-natural alkaloid commercially available for use in humans, the organic synthesis community has been focused on developing a number of efficient approaches for its total synthesis.[3] The use of chiral pools,[4] chiral auxiliaries,[5-7] asymmetrization of a prochiral dicarbonyl intermediate,[8] enzymatic resolution methodologies[9] and asymmetric catalysis[10,11] are the most common strategies for the stereo- and enantioselective synthesis of this *trans*-3,4-disubstituted piperidine. Because of the location and orientation of the *p*-fluorophenyl group within the piperidine ring is responsible for the biological activity,[12] many synthesis of the (-)-paroxetine are based on the development of efficient methods for the introduction of this function. Although the selected chemical operation for attaching the *p*-fluorophenyl group is the conjugated addition reaction of the corresponding 4-fluorophenyl metal reagent onto an α,β- unsaturated substrate (e.g., **A**, Scheme 1),[4,5,10b,i] addition of lithium cuprates towards pyridinium salts,[7a] addition of Grignard reagents onto 4-piperidones[9g], Heck reaction,[13] and Co-catalyzed arylation[14] are further synthetic methodologies employed for this purpose.

Herein, as part of our studies on the use of sodium chlorite as oxidant agent in the synthesis of 2,3-epoxyamides from allylamines and its application in the synthesis of alkaloids biologically actives,[15] a new strategy to achieve the *trans*-4-(4-fluorophenyl)-3-piperidinemethanol skeleton (**B**) is described. This method is based on an epoxide ring opening reaction of a chiral 3,4-epoxy-2-piperidone (e.g., **C**) as starting material. Glycidic amide **C** is easily obtained in multigram quantities from simple substrates and using environmentally friendly reagents (Scheme 1).



Scheme 1. Common (**A**) and current strategy (**C**) for the preparation of the *trans*-4-(4-fluorophenyl)-3-piperidinemethanol skeleton (**B**) of (-)-paroxetine

Results and Discussion

For this approach, the regio- and stereoselective ring-opening of epoxyamide **1a** with the corresponding Grignard reagent via a S_N2 displacement by means of a Cu(I)-catalyzed reaction is crucial. Deoxygenation of the tertiary hydroxyl group in **2** (Barton-McCombie reaction) is a second key step, especially because the *trans*-configuration of the substituents at C3 and C4 must be created at this stage (**3**). Incorporation of the sesamol group (5-benzodioxolol) to **3**, reduction of the carbonyl group and removal of the chiral auxiliary of **4** would finally provide the target product (Scheme 2).

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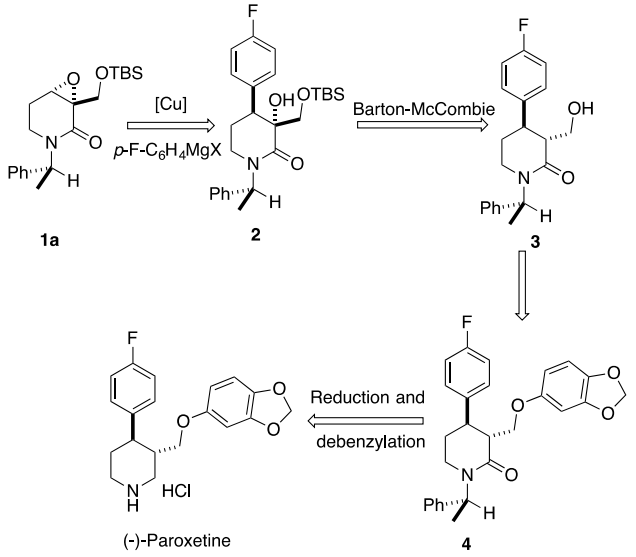
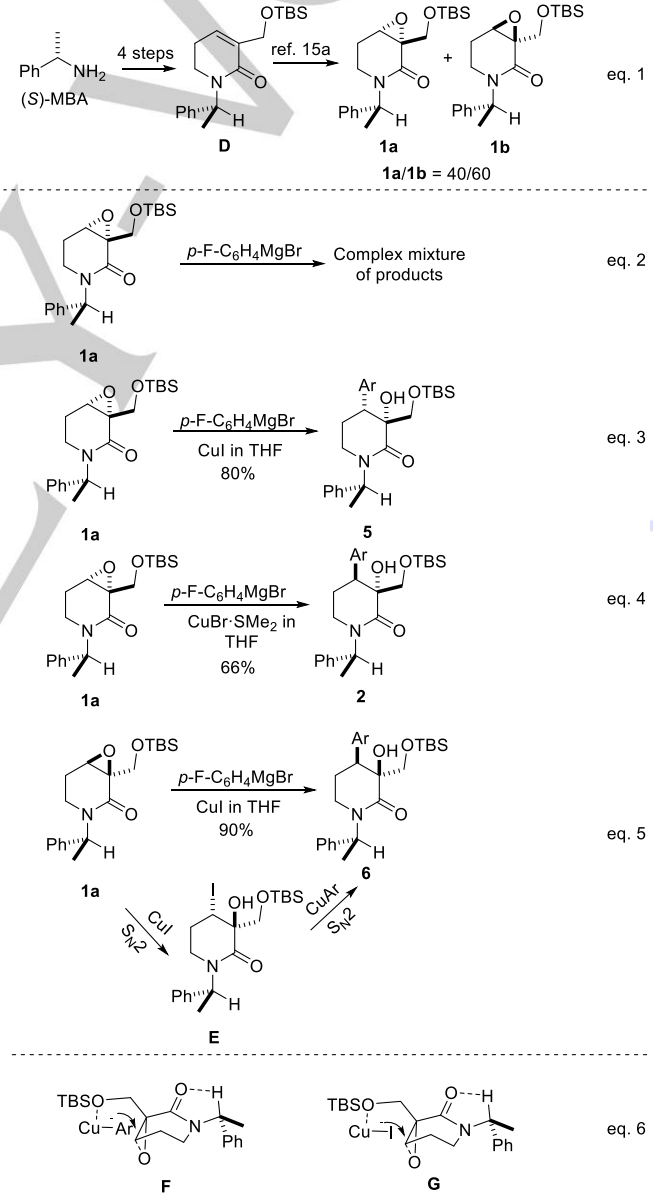


Scheme 2. General synthetic strategy for the preparation of enantiomerically pure (-)-paroxetine starting from the easily accessible glycidic amide **1a**

In order to test this proposal, the starting epoxyamide **1a** was prepared along with the diastereomeric congener **1b** in multigram scale from the corresponding allyl amine **D,** which was prepared in four steps with only two column-chromatographic steps from commercially available (*S*)-methylbenzylamine (MBA) (Scheme 3, eq. 1).[15a,b] Epoxyamide **1a** was treated with *p*-F-C_6H_4MgBr in THF under catalyst-free conditions; however, only a complex mixture of byproducts was observed (Scheme 3, eq. 2). Interestingly, when using CuI as catalyst,[16] not only a regioselective epoxide ring-opening occurred, but also complete retention of the configuration was achieved (**5**) (Scheme 3, eq. 3). Moreover, when epoxyamide **1a** was tested with CuBr•SMe_2 as catalyst under the same reactions conditions, the expected intermediate **2** was obtained in good yield following the usual S_N2 mechanism (Scheme 3, eq. 4). Intrigued by this apparent stereodivergence in the epoxide ring-opening reaction of epoxyamide **1a** mediated by Cu(I), epoxyamide **1b** was tested with CuI and the epoxide ring-opening reaction occurred in high yield and complete retention of the configuration (**6**). This unexpected retention in the configuration at C4 can be explained by a premature S_N2 epoxide ring-opening mediated by CuI to give, in the first instance, the respective *trans*-halohydrin **E**,[17] which by the subsequent S_N2 substitution with the aryl cuprate provides the piperidonemethanol **6** in good yield (Scheme 3, eq. 5). Additionally, the regio- and steredivergent ring-opening reaction of **1a** can also be explained by considering the chelation complexes **F** and **G** as the key intermediates for both: inversion and retention of the configuration in the epoxide ring-opening reaction. Aryl group in **F** is prone for S_N2 attack to give directly compound **2**. On the other hand, and the iodine atom in **G** is attached temporally (**E**), and by another subsequent S_N2 reaction, mediated by aryl cuprate, compound **6** is formed (Scheme 3, eq. 6). The presence of an C−H•••O intramolecular hydrogen interaction between the benzylic hydrogen atom and the oxygen atom from carbonyl group[18,15b] might exert a stabilization effect on the key intermediates **F** and **G**.

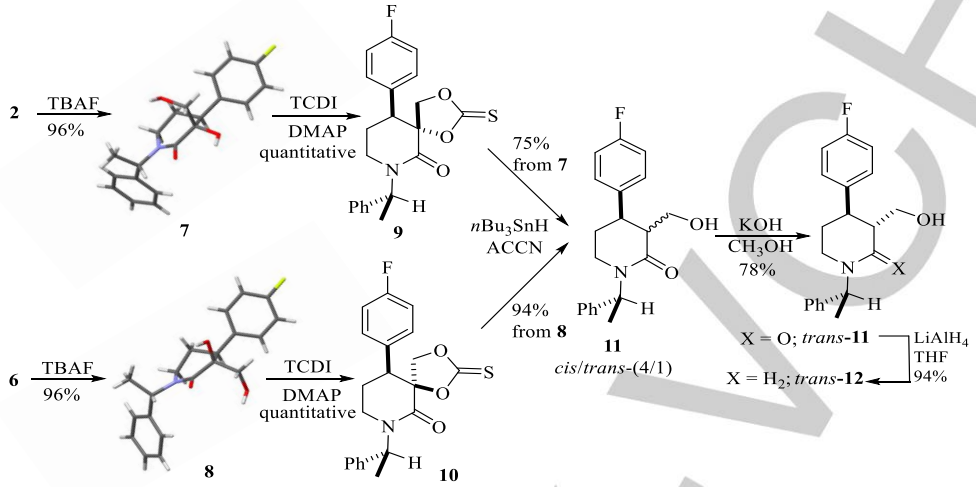
This diastereodivergent epoxide ring-opening of epoxyamides **1a** and **1b** mediated by arylcuprates provides an expedient opportunity for developing a convergent strategy for the preparation of (-)-paroxetine from either **1a** or **1b**. The selective double oxidation of allylamines to 2,3-epoxyamides (i.e., **A** → **1a** and **1b**) proceeds in high yields and in a multigram scale, but only poor stereoselectivity has been achieved so far.[15] Consequently, starting from **2** and **6**, which both have the required absolute configuration at the C4 atom, the synthesis of (-)-paroxetine can be achieved by a diastereoconvergent approach.

Attempts for the deoxygenation of the tertiary alcohols **2** and **6** under classical Barton-McCombie[19] conditions failed, because the respective xanthates (not shown) either decompose or hydrolyze to the respective alcohol precursors. Therefore, the deoxygenation was performed via cyclic thiocarbonates.[20] For this purpose, compounds **2** and **6** were desilylated with tetra-n-butylammonium fluoride (TBAF) to diols **7** and **8**, respectively. Fortunately, both compounds gave crystalline materials suitable for single-crystal X-ray diffraction analysis (see Supporting Information), which allowed to confirm the Cu(I)-induced stereodivergence in the epoxide-ring opening.



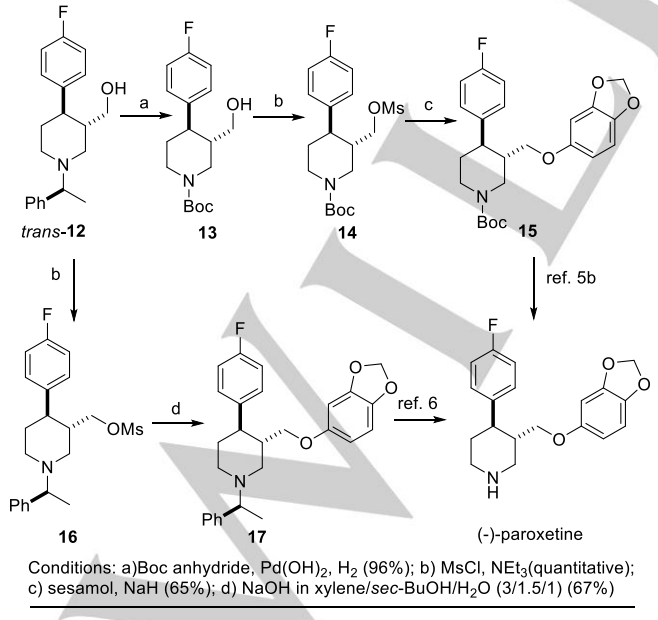
Scheme 3. Synthesis of 2,3-epoxyamides **1a** and **1b** from (*S*)-MBA (eq. 1). Diastereodivergent epoxide ring-opening of the epoxyamide precursors **1a** and **1b** with *p*-F-C_6H_4MgBr catalyzed with Cu(I) (eqs. 2-5). Key intermediates **F**

and **G** that showcase the regio-and stereoselective epoxide ring-opening of **1a** and **1b** (eq. 6).



Scheme 4. Diastereoconvergent synthesis of **11** starting from **2** and **6**

Diols **7** ann **8** were then transformed quantitatively with 1,1'-thiocarbonyldiimidazole (TCDI) in the presence of 4-dimethylaminopyridine (DMAP) tot he corresponding cyclic thiocarbonates **9** and **10**. Without further purification, the thiocarbonates **9** and **10** were treated with *n*Bu_3SnH and ACCN in refluxing toluene to give, in both cases, a *cis*/*trans* mixture of 4-(4-fluorophenyl)-3-piperidonemethanol **11** in good yield with an approximate 4/1 ratio. Thermodynamic equilibration of *cis*/*trans*-**11** mixture to exclusively the *trans*-diaThe regioselectivity of the deoxygenation reaction in stereoisomer **11** was achieved with a methanolic solution of KOH at reflux temperature (Scheme 4).



Scheme 5. Completion of the synthesis of the target product starting from *trans*-**12**

Having in hands the *trans*-4-(4-fluorophenyl)-3-piperidinemethanol (*trans*-**12**), completion of the (-)-paroxetine was achieved following two different pathways. The first one followed the final steps of Amat's paroxetine synthesis,[5] consisting in the simultaneous debenzylation/protection protocol to obtain **13**, which was then with methanesulfonyl chloride (MsCl) transformed into the corresponding mesylate **14** followed by a substitution reaction with sesamol in the presence of NaH. Removal of the Boc protecting group from **15** yielded (-)-paroxetine quantitatively. The second route to (-)-paroxetine partially followed a modified version of Liu's approach.[6] In the first instance, sesamol was incorporated via mesylate formation (**12** → **16** → **17**), giving after debenzylation of **17** the target product (Scheme 5).

Conclusions

By taking advantage from a diastereodivergent copper-catalyzed regioselective ring-opening of diastereomeric 2,3-epoxyamides with a Grignard reagent, an efficient protocol could be established for the synthesis of (-)-paroxetine. The principles of the current strategy provide valuable elements for further applications to the synthesis of other biologically important 3,4-disubustituted piperidines.

Acknowledgements

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Experimental Section

General Considerations NMR spectra were obtained in a 500 MHz Bruker spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C). All samples were analyzed in $CDCl_3$ with TMS as internal reference using a relative scale in parts per millon (ppm) for the chemical shift (δ) and Hz for coupling constants (J). Splitting patterns are designated as follow: s, singlet; d, doublet; q, quartet; m, multiplet; dd, doublet doublet; br, broad; and their combinations. Optical rotation of the compounds was measured on a Perkin-Elmer model 241 polarimeter on the *D*-line of sodium (589 nm) and expressed in degrees; the measurements were performed at a temperature of 20 °C and the concentration of the sample was expressed in g/100 mL. The FAB^+ and EI mass spectra were recorded on a JOEL JMS AX505HA spectrometer. The melting points were determined with a Fischer-Scientific fusiometer in capillary tube.

(3*S*,4*S*)-3-[((*tert*-Butyldimethylsilyl)oxy)methyl]-4-(*p*-fluorophenyl)-3-hydroxy-1-[(*S*)-1-phenylethyl]piperidin-2-one (6). A mixture of CuI (0.52 g, 2.76 mmol) and *p*-fluorophenylmagnesium bromide (5.53 mL, 11.06 mmol, 2M) was stirred at room temperature for 2 h. Then, a solution of epoxyamide **1b**[15] (1.0 g, 2.76 mmol) in THF (2.8 mL) was added dropwise into the reaction mixture during 1.5 h. The resulting reaction mixture was stirred for 3.5 h at room temperature. The reaction mixture was quenched with a saturated solution of ammonium chloride (5 mL) and the aqueous phase was extracted with EtOAc (4 x 10 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc 9:1) to give 1.14 g (90%) of **6** as a colorless syrup. $[\alpha]_D^{20}$ -14.8 (c = 2.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.11 (s, 6H), 0.95 (s, 9H), 1.57 (d, J = 7.0 Hz, 3H), 1.83 (dq, J = 13.0, 3.5 Hz, 1H), 2.25 (dddd, J = 13.0, 11.5, 11.5, 4.5 Hz, 1H), 2.72 (d, J = 1.5 Hz, 1H), 2.78 (ddd, J = 12.5, 11.0, 4.0 Hz, 1H), 3.08 (ddd, J = 12.5, 4.5, 3.5 Hz, 1H), 3.29 (d, J = 9.0 Hz, 1H), 3.40 (dd, J = 12.5, 3.5 Hz, 1H), 3.95 (d, J = 9.0 Hz, 1H), 5.97 (q, J = 7.0 Hz, 1H), 6.99 (m, 2H), 7.24 (m, 2H), 7.32 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: -5.5, -5.3, 14.7, 18.3, 25.8, 25.9, 41.5, 42.6, 51.5, 66.1, 75.2, 114.7 (d, J = 21.1 Hz), 127.4, 127.6, 128.4, 130.7 (d, J = 7.6 Hz), 135.3 (d, J = 3.2 Hz), 139.3, 161.8 (d, J = 243.5 Hz), 171.9. HRMS-FAB (*m/z*): $[M + H]^+$ calcd for $C_{26}H_{37}FNO_3Si$, 458.2527; found 458.2541.

(3*R*,4*R*)-3-[((*tert*-Butyldimethylsilyl)oxy)methyl]-4-(*p*-fluorophenyl)-3-hydroxy-1-[(*S*)-1-phenylethyl]piperidin-2-one (5). Starting from epoxyamide **1a** and by using the same procedure as for **6**, compound **5** was obtained in 80% yield, as a colorless syrup. $[\alpha]_D^{20}$ = -145.26 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.08 (s, 3H), 0.11 (s, 3H), 0.94 (s, 9H), 1.55 (d, J = 7.5 Hz, 3H), 1.79 (dq, J = 13.5, 3.5 Hz, 1H), 2.12 (dddd, J = 13.0, 11.5, 11.5, 4.5 Hz, 1H), 2.72 (d, J = 1.0 Hz, 1H), 2.99 (ddd, J = 12.5, 4.5, 3.5 Hz, 1H), 3.27 (td, J = 11.5, 3.5 Hz, 1H), 3.31 (d, J = 12.5 Hz, 1H), 3.48 (dd, J = 13.0, 3.0 Hz, 1H), 3.91 (d, J = 8.5 Hz, 1H), 6.08 (q, J = 7.5 Hz, 1H), 6.97 (t, J = 8.5 Hz, 2H), 7.21 (m, 2H), 7.35 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.5, -5.4, 15.8, 18.1, 25.8, 25.8, 41.2, 42.8, 50.8, 65.9, 75.3, 114.8 (d, J = 20.9 Hz), 127.1, 127.4, 128.5, 130.7 (d, J = 7.8 Hz), 135.3 (d, J = 3.3 Hz), 140.1, 161.8 (d, J = 243.4 Hz), 172.3. HRMS-FAB (*m/z*): $[M + H]^+$ calcd for $C_{26}H_{37}FNO_3Si$, 458.2527; found 458.2544.

(3*S*,4*S*)-3-(((*tert*-Butyldimethylsilyl)oxy)methyl)-3-hydroxy-4-iodo-1-((*S*) phenylethyl)piperidin-2-one (E). A mixture of CuI (104.74 mg, 0.55 mmol) and *p*-fluorophenylmagnesium bromide (0.27 mL, 0.55 mmol, 2M) was stirred at room temperature for 2 h. Then, a solution of epoxyamide **1b** (200.0 mg, 0.55 mmol) in THF (1 mL) was added dropwise into the reaction mixture during 0.5 h. The resulting reaction mixture was stirred for 6.5 h. at room temperature. The reaction was quenched with a saturated solution of ammonium chloride (3 mL) and the aqueous phase was extracted with EtOAc (4 x 10 mL). The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc 10:1) to yield 0.097 g (36%) of **E** as a yellow oil. $[\alpha]_D^{20}$ = -67.59 (c = 1.03, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.11 (s, 3H), 0.12 (s, 3H), 0.90 (s, 9H) 1.55 (d, J = 7.0 Hz, 3H), 2.34 (m, 1H), 2.81 (m, 1H), 2.88 (m, 1H), 3.21 (m, 1H), 3.66 (s, 1H), 4.02 (dd, J = 9.7, 1.2 Hz, 1H), 4.13 (d, J = 10.0 Hz, 1H), 4.53 (dd, J = 12.3, 3.7 Hz, 1H), 5.98 (q J = 7.0 Hz, 1H), 7.31 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.4 -5.4, 15.3, 18.3, 26.0, 30.6, 31.9, 42.1, 51.6, 72.3, 74.0, 127.4, 127.5, 128.5, 139.1, 168.0. HRMS-FAB (m/z): [M + H]+ calcd for C20H33NO3SiI, 490.1274; found 490.1291.

(3*R*,4*S*)-3-[((*tert*-Butyldimethylsilyl)oxy)methyl]-4-(*p*-fluorophenyl)-3-hydroxy-1-[(*S*)-1-phenylethyl]piperidin-2-one (2). A mixture of $CuBr{\bullet}SMe_2$ (0.22 g, 1.10 mmol) and *p*-fluorophenylmagnesium bromide (2.21 mL, 4.42 mmol, 2M) was stirred at room temperature for 2 h. Then, a solution of epoxyamide **1a** (0.40 g, 1.10 mmol) in THF (1.5 mL) was added dropwise into the reaction mixture. The resulting reaction mixture was stirred for 7 h. at room temperature. The reaction was quenched with a saturated solution of ammonium chloride (3 mL) and the aqueous phase was extracted with EtOAc (4 x 10 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc 14:1) to yield 0.33 g of **2** (66%) as a colorless syrup. $[\alpha]_D^{20}$ = -46.25 (c = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.02 (d, J = 1.5 Hz, 6H), 0.92 (s, 9H), 1.57 (d, J = 7.0 Hz, 3H), 1.78 (m, 1H), 2.86 (td, J = 12.0, 5.0 Hz, 1H), 3.01 (dddd J = 12.5, 11.5, 11.5, 5.5 Hz, 1H), 3.14 (dd, J = 13.5, 2.5 Hz, 1H), 3.27 (m, 2H), 3.54 (m, 2H), 6.15 (q, J = 7.0 Hz, 1H), 7.00 (m, 2H), 7.34 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ -5.8, -5.7, 15.4, 18.1, 23.9, 25.8, 41.0, 46.3, 51.0, 67.2, 74.3, 114.7 (d, J = 20.9 Hz), 127.5, 127.6, 128.5, 130.1(d, J = 7.6 Hz), 135.2 (d, J = 3.4 Hz), 139.5, 161.9 (d, J = 243.6 Hz), 172.9. HRMS-FAB (*m/z*): $[M + H]^+$ calcd for $C_{26}H_{37}FNO_3Si$, 458.2527; found 458.2536.

(3*S*,4*S*)-4-(*p*-Fluorophenyl)-3-hydroxy-3-(hydroxymethyl)-1-[(*S*)-1-phenylethyl]piperidin-2-one (8). To a solution of **6** (0.315 g, 0.69 mmol) in THF (8 mL) at room temperature was added TBAF (1.37 mL, 1.37 mmol, 1M). The reaction mixture was stirred for 3 h. Then, H_2O (4 mL) was added and the aqueous phase was extracted with EtOAc (4 x 10 mL). The combined organic phases were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (hexane/EtOAc, 1:1) to afford 0.227 g of **8** (96%) as a colorless crystal. Mp = 134-136 °C. $[\alpha]_D^{20}$ = -31.17 (c = 1.01, $CHCl_3$). ^{1}H NMR (500 MHz $CDCl_3$) δ: 1.57 (d, J = 7.0 Hz, 3H), 1.86 (ddt, J = 13.5, 5.0, 4.0 Hz, 1H), 2.37 (dddd, J = 13.5, 11.5, 10.0, 5.5 Hz, 1H), 2.78 (ddd, J = 12.5, 10.0, 5.0 Hz, 1H), 2.97 (dd, J = 11.5, 3.3 Hz, 1H), 3.20 (ddd, J = 12.5, 5.5, 4.0 Hz, 1H), 3.50 (dd, J = 11.5, 10.0 Hz, 1H), 3.62 (s, 1H), 3.69 (dd, J = 11.3, 3.3 Hz, 1H), 3.86 (dd, J = 10.0, 3.0 Hz, 1H), 6.01 (q, J = 7.0 Hz, 1H), 6.98 (m, 2H), 7.22 (m, 2H), 7.30 (m, 3H), 7.37 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.9, 25.6, 40.5, 43.6, 50.9, 66.8, 73.2, 114.9 (d, J = 20.9 Hz), 127.5, 127.7, 128.6, 130.7 (d, J = 7.8 Hz), 134.9 (d, J = 3.2 Hz), 139.2,

161.9 (d, *J* = 244.0 Hz), 172.8. HRMS-EI (*m/z*) $[M]^+$ calcd. for $C_{20}H_{22}FNO_3$, 343.1584; found 343.1573.

(3*R*,4*S*)-4-(*p*-Fluorophenyl)-3-hydroxy-3-(hydroxymethyl)-1-[(*S*)-1-phenylethyl]piperidin-2-one (7). Starting from compound **2** and by using the same procedure as for **8**, 0.226 g of compound **7** was obtained (96%) as a colorless crystal. Mp = 155-157 °C. $[\alpha]_D^{20}$ = -103.77 (*c* = 1.02, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 1.59 (d, *J* = 7.5 Hz, 3H), 2.14 (m, 1H), 2.22 (m, 1H), 2.92 (ddd, *J* = 12.5, 9.0, 5.5 Hz, 1H), 3.00 (br, 1H), 3.20 (d, *J* = 10.5, 5.0 Hz, 1H), 3.25 (m, 1H), 3.29 (d, *J* = 11.5 Hz, 1H), 3.71 (d, *J* = 11.0 Hz, 1H), 4.10 (s, 1H), 6.08 (q, *J* = 7.5 Hz, 1H), 7.00 (t, *J* =8.5 Hz, 2H), 7.21 (m, 2H), 7.35 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 15.4, 24.8, 40.0, 45.9, 50.8, 66.0, 73.5, 115.13 (d, *J* = 21.0 Hz), 127.4, 127.7, 128.7, 130.0 (d, *J* = 7.8 Hz), 134.2 (d, *J* = 3.4 Hz), 139.2, 161.9 (d, *J* = 244.4 Hz), 173.0. HRMS-FAB (*m/z*) [M + H]$^+$ calcd for $C_{20}H_{23}FNO_3$ 344.1662; found 344.1661.

(3,4-*cis*/*trans*)-(4*R*)-4-(*p*-Fluorophenyl)-3-(hydroxymethyl)-1-[(*S*)-1-phenylethyl]piperidin-2-one (*cis*/*trans*-11). To a solution of diol **8** (0.48 g, 1.40 mmol) and DMAP (0.40 g, 3.34 mmol) in $CHCl_3$ (50 mL) at room temperature was stirred for 10 min. Next, a solution of 1,1´-thiocarbonyldiimidazole (0.29 g, 1.67 mmol) in $CHCl_3$ (50 mL) was added via cannula. The reaction mixture was stirred for 5 h. The solvent was evaporated under reduced pressure and H_2O (10 mL) was added to the residue. The aqueous phase was extracted with EtOAc (5 x 15mL). The combined organic phases were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The crude reaction was submitted to the next reaction without further purification. A solution of the reaction crude and ACCN (0.47 g, 1.95 mmol) in toluene (245 mL) was heated to reflux before to add Bu_3SnH (0.60 mL, 2.23 mmol). The reaction mixture was refluxed for 40 min. The reaction mixture was cooled to ambient temperature, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (hexane/EtOAc, 2:1) to give 0.44 g of the diastereoisomeric mixture *cis*/*trans*-**11** (94%) in approximate 5:1 ratio.
Following the same procedure starting from diol **7**, 0.34 g of the diastereoisomeric mixture *cis*/*trans*-**11** (75%) in approximate 3:1 ratio, was isolated.

(3*R*,4*R*)-4-(*p*-Fluorophenyl)-3-(hydroxymethyl)-1-[(*S*)-1-phenylethyl]piperidin-2-one (*cis*-11). White solid. Mp = 133-135 °C. $[\alpha]_D^{20}$ = -40.97 (*c* = 1.03, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 1.56 (d, *J* = 7.0 Hz, 3H), 1.87 (m, 1H), 2.08 (ddt, *J* = 13.0, 8.0, 5.0 Hz, 1H), 2.82 (ddd, *J* = 13.0 6.2, 5.0 Hz, 1H), 2.91 (ddd, *J* = 9.0, 6.5, 4.5 Hz, 1H), 3.09 (ddd, *J* = 13.0 8.5, 5.0 Hz, 1H), 3.35 (m, 2H), 3.82 (t, *J* = 10.0, 1H), 3.99 (d, *J* = 8.0 Hz, 1H), 6.17 (q, *J* = 7.0 Hz, 1H), 6.99 (t, *J* = 8.5 Hz, 2H), 7.09 (m, 2H), 7.33 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 14.9, 29.2, 38.3, 39.6, 46.8, 49.9, 62.2, 115.3 (d, *J* = 21.1 Hz), 127.1, 127.4, 128.4, 129.0 (d, *J* = 7.8 Hz), 136.0 (d, *J* = 3.3 Hz), 139.7, 161.5 (d, *J* = 244.1 Hz) 172.5. HRMS-FAB (*m/z*) [M + H]$^+$ calcd for $C_{20}H_{23}FNO_2$, 328.1713; found 328.1705.

(3*S*,4*R*)-4-(*p*-Fluorophenyl)-3-(hydroxyl methyl)-1-[(*S*)-1-phenylethyl]piperidin-2-one (*trans*-11). Mp = 148-150 °C. $[\alpha]_D^{20}$ = -79.06 (*c* = 1.02, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 1.56 (d, *J* = 7.0 Hz, 3H), 1.92 (m, 2H), 2.63-2.73 (m, 2H), 2.80 (ddd, *J* = 12.5, 8.5, 7.0 Hz, 1H), 3.18 (dt, *J* =12.5, 4.0 Hz, 1H), 3.60 (ddd, *J* = 11.0, 7.0, 3.2 Hz, 1H), 3.68 (ddd, *J* =11.0, 9.0, 3.5 Hz, 1H), 4.13 (dd, *J* = 7.5, 3.5 Hz, 1H), 6.15 (q, *J* = 7.0 Hz, 1H), 7.01 (t, *J* = 8.5 Hz, 2H), 7.14 (m, 2H), 7.34 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 15.2, 30.9, 40.3, 40.9, 49.9, 50.1, 62.4, 115.7 (d, *J* = 21.2 Hz), 127.4, 127.5, 128.5 (d, *J* = 7.8 Hz), 128.6, 138.5 (d, *J* = 3.2 Hz), 139.5, 161.7 (d, *J* = 244.1 Hz), 172.1. HRMS-FAB (*m/z*) [M + H]$^+$ calcd for $C_{20}H_{23}FNO_2$; 328.1713 found 328.1707.

Procedure for epimerization of *cis*-11 to *trans*-11.
A solution of *cis/trans*-**11** mixture (0.10 g, 0.30 mmol) in MeOH (4 mL) was added an aqueous solution of KOH (0.30 mL, 0.30 mmol, 1 M) and heated to reflux temperature for 40 min. The solvent was removed under reduced pressure, and H_2O (2 mL) was added. The aqueous phase was extracted with EtOAc (5 x 5 mL). The combined organic phases were dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ EtOAc, 3:1) to obtain 0.079 g (78%) of compound *trans*-**11**.

((3*S*,4*R*)-4-(*p*-Fluorophenyl)-3-(hydroxymethyl)-1-(1-(*S*)-phenylethyl))piperidin (*trans*-12). A mixture of *trans*-**11** (0.083 g, 0.25 mmol) and $LiAlH_4$ (0.043 g, 1.13 mmol) in THF (3 mL) was heated to reflux temperature for 1 h. After this time, the mixture was cooled to 0 °C and H_2O (2 mL) was added dropwise until a salt formation was observed. Then, the resulting solids were washes with EtOAc (5 x 5 mL) and the organic phase was dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 3:1) to obtain 0.075 g of *trans*-**12** (94%) as a withe solid. Mp = 129-131 °C. $[\alpha]_D^{20}$ = -14.23 (*c* = 1.06, $CHCl_3$), lit.[5b] $[\alpha]_D^{20}$ = -17.4 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 1.44 (d, *J* = 6.5 Hz, 3H), 1.72 (m, 2H), 1.92 (m, 2H), 2.02 (m, 1H), 2.25 (td, *J* = 11.0, 5.0 Hz, 1H), 2.91 (m, 1H), 3.23 (dd, *J* =10.5, 6.5 Hz, 1H), 3.36 (ddd, *J* = 10.5, 3.5, 2.0 Hz, 1H), 3.40 (dd, *J* =10.5, 3.5 Hz, 1H), 3.51 (q, *J* = 6.5 Hz, 1H), 6.96 (t, *J* = 8.5 Hz, 2H), 7.15 (m, 2H), 7.26 (m, 1H), 7.33 (m, 4H) ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 19.5, 34.6, 44.4, 44.5, 50.8, 54.5, 64.2, 65.0, 115.3 (d, *J* = 20.8 Hz), 126.9, 127.8, 128.1, 128.8 (d, *J* = 7.7 Hz), 140.2 (d, *J* = 3.2 Hz), 143.1, 161.4 (d, *J* = 242.7 Hz). HRMS-FAB (*m/z*) [M + H]$^+$ calcd for $C_{20}H_{25}FNO$, 314.1920; found 314.1910.

(3*S*,4*R*)-1-(*tert*-Butoxycarbonyl)-4-(*p*-fluorophenyl)-3-(hydroxymethyl)piperidine (13). To a solution of *trans*-**12** (0.032 g, 0.10 mmol), Boc anhydride (0.040 g, 0.18 mmol) and $Pd(OH)_2$ (0.013 g, at 20 wt. %) in EtOAc (1.5 mL) was stirred under 100 psi of H_2 for 11 h. After this time, the reaction mixture was filtered over celite and rinsed with EtOAc. The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (hexanes/EtOAc, 3:1) to afford 0.030 g (96%) as a colorless viscous liquid. $[\alpha]_D^{20}$ = -5.01 (*c* = 1.87, MeOH), lit.[5b] $[\alpha]_D^{20}$ = -6.8 (*c* = 1.75, MeOH)). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 1.25 (s, 9H), 1.64 (m, 1H), 1.78 (m, 2H), 2.54 (m, 1H), 2.70 (t, *J* = 12.0 Hz, 1H), 2.77 (br, 1H), 3.25 (dd, *J* = 11.0, 6.5 Hz, 1H), 3.43 (dd, *J* = 11.0, 3.0 Hz, 1H), 4.20 (br, 1H) 4.36 (br, 1H), 6.99 (m, 2H), 7.15 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 28.4, 34.0, 43.8, 44.0, 63.0, 79.7, 128.7 (d, *J* = 20.9 Hz), 128.7 (d, *J* = 7.9 Hz), 139.4 (d, *J* = 3.2 Hz), 154.9, 161.5 (d, *J* = 243.1 Hz).

(3*S*,4*R*)-3-[(1,3-Benzodioxol-5-yloxy)methyl]-1-(*tert*-Butoxycarbonyl)-4-(*p*-fluorophenyl)piperidine (15). To a solution of **13** (0.047 g, 0.15 mmol) and MsCl (13 µ, 0.17 mmol) in CH_2Cl_2 (3.0 mL) at room temperature was added Et_3N (21 µ, 0.15 mmol). The reaction mixture was stirred for 1.5 h, next, H_2O (1.5 mL) was added and the organic phase was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic phases were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the reaction crude of **14** was submitted to the next reaction without further purification. A solution of NaH (15 mg, 0.37 mmol,

60% dispersion in mineral oil) and sesamol (33 mg, 0.24 mmol) in THF (1.5 mL) was stirred for 1 h. at room temperature. Next, the reaction crude of **14** in THF (1.5 mL) was added into the reaction mixture. Finally, the resulting mixture was heated to reflux temperature for 6 h. After cooling to ambient temperature, H_2O (3 mL) was added and extracted with EtOAc (5 x 8 mL). The combined organic extracts were dried over Na_2SO_4 and the residue was purified by column chromatography on silica gel (hexane/EtOAc, 10:1) to obtain 42.4 mg (65%) of **15** as colorless oil. $[\alpha]_D^{20}$ = -23.46 (*c* = 0.47, MeOH), lit.[5b] $[\alpha]_D^{20}$ = -25.1 (*c* = 1.0, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 1.50 (s, 9H), 1.70 (m, 1H), 1.80 (m, 1H), 2.02 (m, 1H), 2.67 (td, *J* = 12.5, 3.7 Hz, 1H), 2.81 (m, 2H), 3.44 (dd, *J* = 9.5. 6.5 Hz, 1H), 3.60 (dd, *J* = 9.5, 3.0 Hz, 1H), 4.24 (br, 1H), 4.44 (br, 1H), 5.89 (s, 2H), 6.13 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.35 (d, *J* = 2.5 Hz, 1H), 6.63 (d, *J* = 8.5 Hz, 1H), 6.98 (m, 2H), 7.14 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 28.5, 33.9, 41.9, 44.0, 68.7, 79.7, 98.0, 101.1, 105.5, 107.8, 115.5 (d, *J* = 21.0 Hz), 128.7 (d, *J* = 7.8 Hz), 139.1 (d, *J* = 3.3 Hz), 141.6, 148.1, 154.2, 154.8, 161.6 (d, *J* = 243.1 Hz).

(3*S*,4*R*)-3-[(1,3-Benzodioxol-5-yloxy)methyl]-4-(*p*-fluorophenyl)-1-(1-(*S*)-phenylethyl)piperidine (17). To a solution of *trans*-**12** (0.068 g, 0.22 mmol) and MsCl (18 µ, 0.24 mmol) in CH_2Cl_2 (4 mL) at room temperature was added Et_3N (28 µ, 0.21 mmol). The reaction mixture was stirred for 3 h before to add H_2O. The organic phase was extracted with EtOAc (4 x 5 mL), the combined organic layer was dried over Na_2SO_4 and filtered; the solvent was removed under reduced pressure. The residue (**16**) was submitted to the next reaction without further purification. To the reaction crude of **16** was added a mixture of xylene/2-butanol (3 mL/1.5 mL), and a solution of sesamol (0.041g, 0.30 mmol) and NaOH (0.037 g, 0.97 mmol) in H_2O (1 mL). The reaction mixture was heated to reflux temperature for 18 h. The resulting reaction mixture was cooled to ambient temperature, extracted with EtOAc (5 x 5 mL) and the combined organic layer was dried over Na_2SO_4 and concentrate under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 10:1) to obtain 0.063 g (67%) of **17** as a colorless oil. $[\alpha]_D^{20}$ = -67.61 (*c* = 1.0, $CHCl_3$), ^{1}H NMR (500 MHz, $CDCl_3$) *δ* 1.44 (d, *J* = 7.0 Hz, 3H), 1.74 (m, 2H), 1.93 (td, *J* = 11.0, 3.5, 1H), 2.02 (t, *J* = 11.0, 1H), 2.22 (m, 1H), 2.38 (td, *J* = 11.0, 5.0 Hz, 1H), 2.92 (m, 1H), 3.42 (m, 2H), 3.51 (q, *J* = 7.0 Hz, 1H), 3.57 (dd, *J* = 9.5, 3.0 Hz, 1H), 5.87 (s, 2H), 6.12 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.33 (d, *J* = 2.5 Hz, 1H), 6.62 (d, *J* = 8.5 Hz, 1H), 6.95 (t, *J* = 8.5 Hz, 2H), 7.14 (m, 2 H), 7.26 (m, 1H), 7.33 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 19.6, 34.6, 42.4, 44.3, 50.9, 54.8, 64.9, 69.7, 97.9, 101.0, 105.5, 107.8, 115.3 (d, *J* = 21.0 Hz), 126.8, 127.7, 128.1, 128.8 (d, *J* = 7.7 Hz), 139.9 (d, *J* = 3.1 Hz), 141.4, 143.4, 148.1, 154.4, 161.4 (d, *J* = 242.5 Hz). HRMS-FAB (*m/z*) [M + H]$^+$ calcd for $C_{27}H_{29}FNO_3$, 434.2131; found 434.2102.

(-)-**Paroxetine**

To a solution of **15** (37 mg, 0.09 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise 0.5 mL of CF_3CO_2H (6.38 mmol). The resulting reaction mixture was stirred for 20 min at room temperature. Then, a saturated aqueous solution of $NaHCO_3$ was added and the aqueous phase was extracted with CH_2Cl_2 (4 x 5 mL). The combined organic phases were dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (EtOAc:MeOH, 1:1) to afford 21 mg (75%) of (-)-paroxetine as a colorless oil; $[\alpha]_D^{20}$ = -79.7 (*c* = 1.0, MeOH) lit.[5b] (-)-paroxetine $[\alpha]_D^{20}$ = -80.8 (*c* = 1.25, MeOH). (-)-Paroxetine was dissolved in MeOH (0.5 mL) and a solution of HCl (0.01 mL, 10%) was added. The solvent was removed under reduced pressure and purification was accomplished by recrystallization from methanol, ethyl ether and hexanes to afford paroxetine hydrochloride as colorless crystals. Mp = 121-123°C, lit.[6] = 123-124°C. $[\alpha]_D^{20}$ = -84.0 (*c* = 0.27, MeOH), lit.[6] $[\alpha]_D^{20}$ = -88.0 (*c* = 1.0, MeOH). NMR spectroscopy match perfectly with those reported in the literature.

Supporting information for this article (Experimental procedures and characterization data, NMR spectra, crystallographic data in CIF format (CCDC 1541564-1541565), selected crystallographic data and perspective views of the molecular structures for **7** and **8**) is available on the WWW under:

Keywords: 2,3-Epoxyamides • Convergent synthesis • Stereodivergence • Alkaloids

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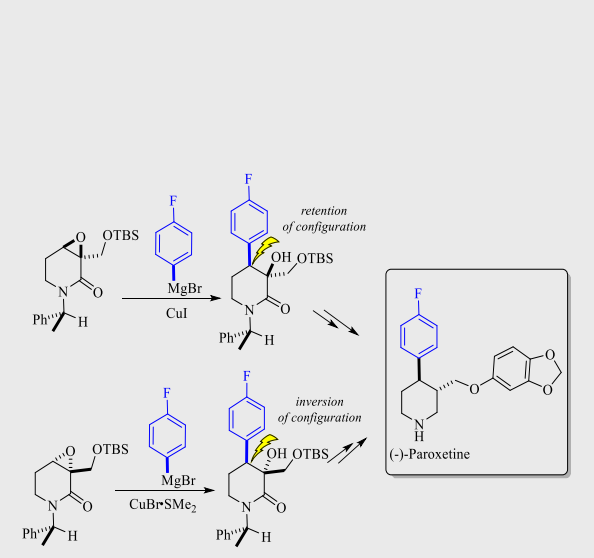
Layout 1:

FULL PAPER

By featuring a diastereodivergent copper-catalyzed regioselective ring-opening of diastereomeric 2,3-epoxyamides, a diastereoconvergent synthesis of (-)-paroxetine is presented.



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Diastereoconvergent Synthesis of (-)-Paroxetine

* De Novo Synthesis of (-)-Paroxetine