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Full Paper

Total Synthesis

Total Asymmetric Synthesis of (+)-Paroxetine and (+)-Femoxetine

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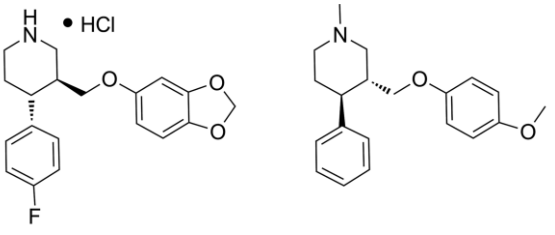
Abstract: Total, asymmetric synthesis of (+)-Paroxetine and (+)-Femoxetine, selective serotonin reuptake inhibitors, used for the treatment of depression, anxiety, and panic disorders is reported. The key step is organocatalytic Michael addition of aldehydes to trans-nitroalkenes realized in bath or continues flow. High efficiency and selectivity in the Michael addition was achieved by application of Wang resin-supported Hayashi–Jørgensen catalyst.

Introduction

Depression is a common debilitating mental disorder, that produces negative consequences in the lives of more than 300 million people all over the world, and additional hundreds of thousands people of all ages are diagnosed with depression every year. Depression is ranked as the single largest contributor to global disability, as well as a leading cause of suicide deaths, which number close to 800 000 per year.[1] Depression and its treatment has an enormous effect on the economy. It is estimated to cost the U.S. about $210 billion a year in productivity loss and health care needs. Global revenue for antidepressants was about $14.5 billion in 2014 and is projected to grow to nearly $17 billion by 2020.[2]

(–)-Paroxetine hydrochloride is an active ingredient of Paxil®, Seroxat®, which is approved by FDA for treatment of depression resistant to other antidepressants, depression complicated by anxiety, panic disorder, social and general anxiety disorder, obsessive-compulsive disorder, premenstrual dysphoric disorder, premature ejaculation, and hot flashes of menopause in women with breast cancer.[3] The mechanism of paroxetine action results from selective inhibition of the reuptake of serotonin by blocking the serotonin transporter. The other property paroxetine has is its ability to block muscarinic receptors, which causes the drug to have anticholinergic effects. The importance for this in clinical practice is that central anticholinergic effects can trigger cognitive impairment in the elder.[4] Although it was approved for medical treatment in the U.S. in 1992 worldwide net sales strongly increase year by year.[5] In 2006, paroxetine was the fifth-most prescribed antidepressant in the U.S. retail market, with more than 19.7 million prescriptions. In 2007 paroxetine was ranked 94th on the list of bestselling drugs, with over $1 billion in sales.

(+)-Femoxetine is related selective serotonin reuptake inhibitor, which was developed as a potent antidepressant by Danish pharmaceutical company Ferrosan in 1975. However, its development was halted to focus attention on paroxetine instead, given femoxetine's inability to be administered as a daily pill.[6]



(-)-Paroxetine hydrochloride (+)-Femoxetine

Because of the medicinal importance of paroxetine and femoxetine, the synthesis of this *trans*-3,4-disubstituted piperidines derivative has attracted many researchers at academia as well as in industry. The most commonly used strategies for the stereo- and enantioselective synthesis of paroxetine and femoxetine are based on enzymatic asymmetric desymmetrization,[7] chiral auxiliary,[8] asymmetric catalysis,[9] chiral pool[10] and chiral base.[11] These methods have proven effective, however their main drawback results from relatively long and complicated synthetic sequence. Wherefore, it is still necessary to find an alternative and improved process for paroxetine and femoxetine manufacturing that would be more competitive and cost-efficient.

Very recently, we demonstrated that functionalized, optically active cyclic nitrones or pyrrolidines can be obtained in a simple and highly efficient manner via organocatalytic Michael addition of aldehydes to *trans*-nitroalkenes and subsequent reductive cyclization.[12–14] This methodology was successfully applied, as a key step in the asymmetric total synthesis of methdilazine, BZN molecule, and asenapine.

Considering the chemical structure of paroxetine and femoxetine as a *trans*-3,4-disubstituted piperidine ring systems. conceptually, we visualized that they can be built form correspond-

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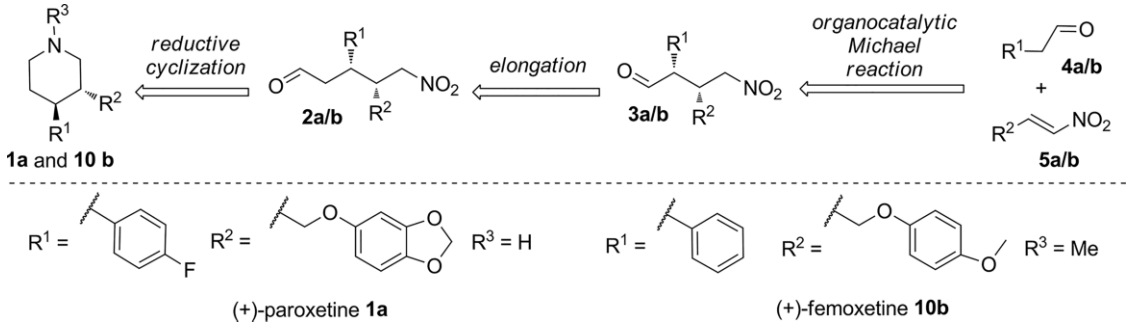


Scheme 1. Retrosynthetic analysis of (+)-paroxetine **1a** and (+)-femoxetine **10b**.

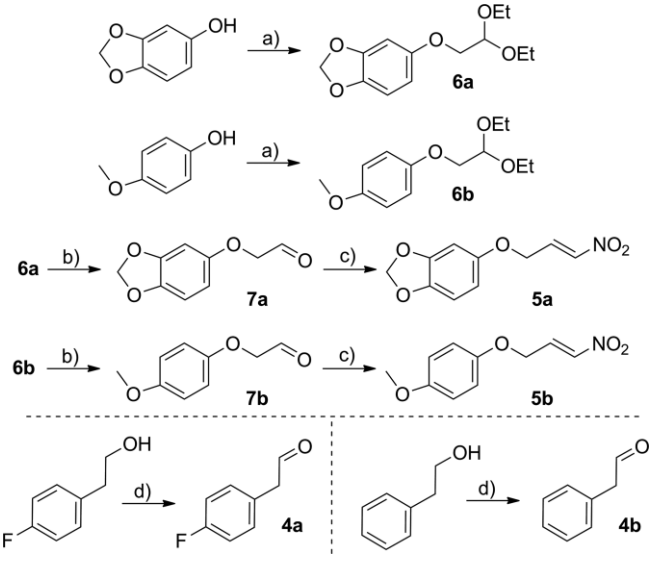
ing δ-nitroaldehyde **2a/b** via reductive cyclization reaction. δ-nitroaldehyde **2a/b** can be obtained from γ-nitroaldehyde **3a/b** via one-carbon elongation reaction. In turn, synthon **3a/b** could be obtained via organocatalytic Michael addition of aldehydes **4a/b** to *trans*-nitroalkene **5a/b** (Scheme 1).

On the basis of the above analysis, the proposed synthetic strategy seems to be short and simple with high atom economy. Moreover, the undoubted advantage is that both stereogenic center at C3 and C4 are installed in one step. The application of the (*S*)-α,α-diphenylprolinol trimethylsilyl ether (Hayashi–Jørgensen catalyst **cat. 1**) as a catalyst for Michael addition reaction should lead to (+)-paroxetine **1a** and (+)-femoxetine **10b**. Successful execution of this strategy will naturally allow one to synthesize (–)-paroxetine and (–)-femoxetine by simply switching of the catalyst.

Results and Discussion

The study started with the preparation of nitroalkene **5a** and aldehyde **4a** – acceptor and donor in Michael addition reaction (Scheme 2). The first step in the synthesis of **5a** consists of transformation of commercially available sesamol to acetal **6a**. The reaction proceeds in 95 % yield in the presence of sodium hydride and bromoacetaldehyde diethyl acetal in boiling 1,4-dioxane. Subsequent hydrolysis of acetal **6a** promoted by *p*-toluenesulfonic acid (10 mol-%) in a mixture of acetone and water (9:1) provided to aldehyde **7a**. Then aldehyde **7a** was submitted to Henry reaction with nitromethane and catalytic amount of *N*,*N*,*N*,*N*-tetramethylguanidine in toluene. Subsequent addition of methanesulfonyl chloride and triethylamine to the intermediate nitro alcohol effected elimination to give the desired nitro olefin **5a** in good overall yield 62 %. In turn, aldehyde **4a** was obtained in 98 % yield from commercially available 2-(4-fluorophenyl)ethanol via Dess–Martin oxidation. The same reaction sequence was used for the preparation of nitroalkane **5b**, and aldehyde **4b**. **5b** was obtained in overall yield 48 % started from commercially available 4-methoxyphenol, and the aldehyde **4b** was obtained in 94 % started from 2-phenylethan-1-ol (Scheme 2).

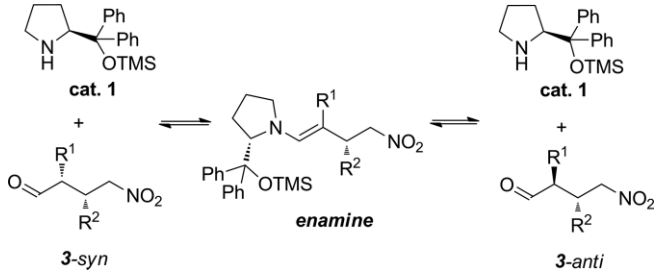
With the desired Michaele acceptor **5a/b** and donor **4a/b** in hand, we initiated the study of the organocatalytic Michaele addition reaction leading to γ-nitroaldehyde **3a/b**. Based on our



Scheme 2. *Reagents and conditions*: a) bromoacetaldehyde diethyl acetal (1.1 equiv.), K_2CO_3 (1.1 equiv.), DMF, 140° C, overnight, **6a** 95 %, **6b** 97 %; b) TsOH (10 mol-%), acetone/H_2O (10:1), 90 min; c) i. $MeNO_2$ (10 equiv.), *N*,*N*,*N*,*N*-tetramethylguanidine (10 mol-%), toluene, 0[°] C, 90 min; ii. MsCl (1.5 equiv.), Et_3N (1.5 equiv.), 0[°] C, 40 min, **5a** 62 % (4 steps, starting from sesamol) **5b** 48 % (4 steps, starting from 4-methoxyphenol); d) Dess–Martin periodinate (1.2 equiv.), CH_2Cl_2, r.t., 30 min, **4a** 98 %, **4b** 94 %.

experience, the reaction between nitro olefin **5a** and aldehyde **4b** was performed in chloroform in the presence of 10 mol-% of the Hayashi–Jørgensen catalyst **cat. 1**. and benzoic acid (20 mol-%) as an additive, at ambient temperature. The reaction was complete within 1 h, and the corresponding γ-nitroaldehyde **3a** was isolated in an excellent yield of 93 %, with high stereoselectivity (*ee* 87 %, *syn* isomer), as an inseparable mixture of diastereoisomers in *syn*/*anti* ratio 1.3:1. A comparable result was obtained in an analogous Michael addition between **5b** and **4b**. The reaction was complete within 30 min, provided to γ-nitroaldehyde **3b** in an excellent 90 % yield, high stereoselectivity (*ee* 90 %, *syn* isomer), and low diastereoselectivity (*syn*/*anti* ratio 1.2:1). Based on our previous experience, we reasoned that the low diastereselectivity observed in Michael addition catalyzed by Hayashi–Jørgensen catalyst **cat. 1** might result from epimerization of α-substituted γ-nitroaldehydes. The isomerization process occurs when the products remain in contact with the catalyst for an extended period of time, after turnover

is completed. The γ-nitroaldehydes with high *syn*/*anti* ratio react with the catalyst, a low steady-state concentration of the enamine is rapidly established, and the equilibration between *syn* and *anti* continues until thermodynamic ratio is reached (Scheme 3). This effect, intensively studied and explained by Blackmond,[15] has been confirmed by our group.[12–14]



Scheme 3. Reversible enamine formation between **cat. 1**, **3-*syn***, and **3-*anti***.

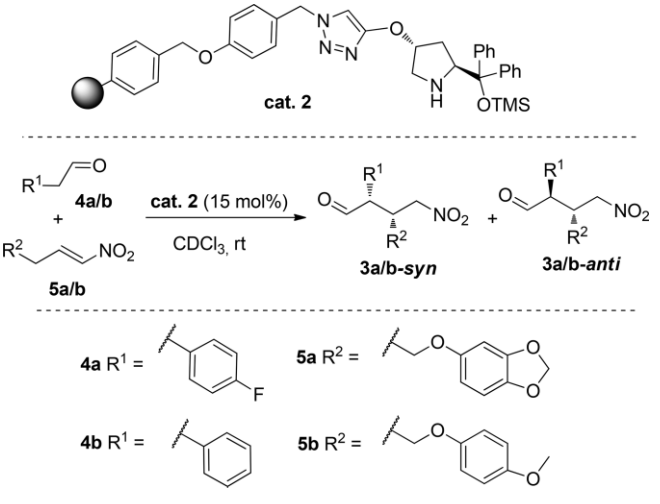
In order to verify this hypothesis we conducted a ^{1}H-NMR experiment in which we expected to observe the diastereomeric ratio decreasing in time during Michael addition reaction. The reaction between **4a** and **5a** was performed in deuterated chloroform in the presence of 10 mol-% of the Hayashi–Jørgensen catalyst **cat. 1** and benzoic acid (20 mol-%) as an additive, at ambient temperature. After 40 min, we observed 95 % conversion to the desired γ-nitroaldehyde **3a** with *syn*/*anti* ratio 3:1. After complete conversion of starting aldehyde **4a**, we began to observe decrease in the *syn*/*anti* ratio to 2:1, and the equilibration between *syn* and *anti* continued until the *syn*/*anti* ratio reached equilibrium at 1.3:1, and didn't change in extra time (see supporting information, Scheme 1). Moreover, we found that the isomerization progresses not only after turnover is completed, but also during purification by column chromatography. When crude γ-nitroaldehyde **3a** with *syn*/*anti* ratio 3:1 was purified on silica gel column chromatography, the *syn*/*anti* ratio of the obtained product decreased to 1.3:1.

Analogue isomerization effect was observed in the Michael addition between **4b** and **5b** catalyzed by 10 mol-% of the Hayashi–Jørgensen catalyst **cat. 1**. At the moment of complete conversion the *syn*/*anti* ratio of γ-nitroaldehyde **3b**, was established at 3.5:1 and it decreased during 24 h to equilibrium reached at 1.2:1 (see supporting information, Scheme 2).

Bearing in mind that in order to maintain the high diastereomeric ratio, the catalyst has to be removed from the reaction mixture immediately after complete conversion of substrates, and the product should be used for the next step without purification, we reasoned that this drawback could be mitigated by replacing batch operation with a continuous flow process involving a suitable immobilized catalyst. This approach should ensure minimal contact time between product and catalyst, moreover continuous flow technologies have recently attracted attention in modern synthetic chemistry as they offer several advantages over conventional batch procedures, including improved heat and mass transfer, efficient mixing of substrates and shorter reaction times.[16] Although the potential of carrying out asymmetric organocatalytic reactions in continuous flow was recognized at the end of 2000 by Lectka and coworkers[17,18] examples regarding the use of enantioselective organocatalyzed reactions in continuous flow are still scarce,[19] and the field of continuous-flow asymmetric organocatalyzed reactions is still in its infancy. For the best of our knowledge there are only two literature precedents for the organocatalytic Michael addition of aldehydes to nitroolefins in continuous-flow. In both examples solid-supported peptides have been applied as catalysts.[20,21]

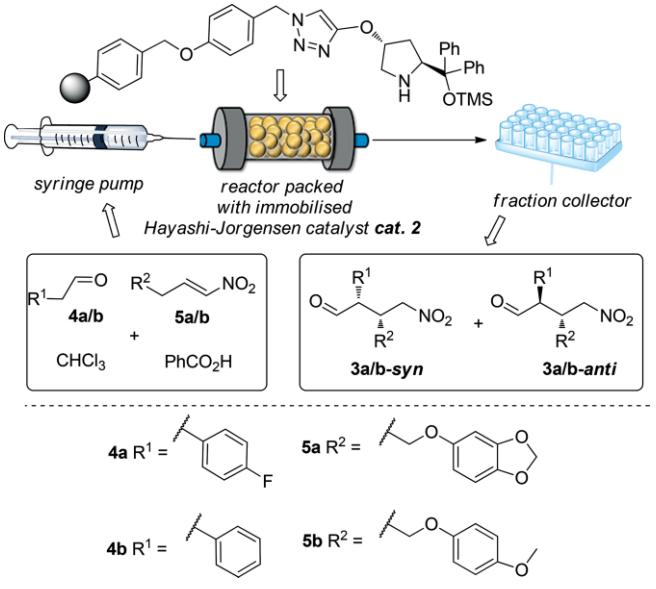
In our studies we proposed application of heterogeneous catalytic system based on an insoluble Wang resin as a solid support for the Hayashi–Jørgensen catalyst **cat. 2**. Only recently we demonstrated that this catalytic system is highly efficient in stereoselective Michael addition reaction leading to γ-nitroaldehydes with high yield, enantio- and diastereoselectivity.[13] Moreover, the catalyst could be easily recovered and reused in the next catalytic cycle without significant loss of catalytic activities and stereoselectivities.

We began our investigation into organocatalytic Michael addition in continuous flow with examination of the catalytic efficiency of the immobilized Hayashi–Jørgensen catalyst **cat. 2**. in standard bath operation. For this purpose, the Michael addition between **4a** and **5a** was performed in deuterated chloroform in the presence of 15 mol-% of **cat. 2** and 20 mol-% of benzoic acid as an additive, at ambient temperature. After 4 h we observed complete conversion to the desired product **3a** with *syn*/*anti* ratio 4.6:1, and *ee* 93 % (*syn* isomer). In turn, the reaction between **4b** and **5b** under the same reaction condition provides to corresponding γ-nitroaldehyde **3b** with *syn*/*anti* ratio 3.6:1, and *ee* 89 % (*syn* isomer) (Scheme 4). In both cases, after simple filtration, catalyst **cat. 2** was recovered in 100 % yield, and crude γ-nitroaldehydes **3a** and **3b** with perfect purities as judged by NMR spectroscopy were carried out the subsequent elongation reaction.



Scheme 4. *Reagents and conditions*: **4a/b** (1.5 equiv.), **5a/b** (1.0 equiv.), catalyst **cat. 2** (15 mol-%)(catalyst loading 1.0 mmol/g), $CDCl_3$, r.t.; **3a**, 100 % conversion[a] after 4 h, *syn*/*anti** 4.6:1, *ee*[b] 93 % (*syn* isomer); **3b**, 100 % conversion* after 5 h, *syn*/*anti**3.6:1, *ee*[b] 89 % (*syn* isomer); [a]determined by ^{1}H-NMR; [b] determined by HPLC.

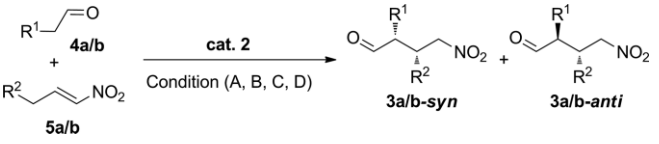
Encouraged by the results, in the next step we investigated the behavior of catalyst **cat.2** in the flow Michael addition between **4a/b** and **5a/b**. For this purpose, a simple homemade flow setup had been constructed consisting of feeding stream connected to a syringe pump and column packed with immobilized Hayashi–Jørgensen catalyst **cat. 2**. The column outcome was connected to the fraction collector (Scheme 5).



Scheme 5. Continues flow system for the organocatalytic Michael addition reaction catalyzed by Wang resin solid support Hayashi–Jørgensen catalyst **cat. 2**.

The study started with an adjustment of the optimal flow rate means fine-tuning of the residence time on the catalyst bed; complete conversion without isomerization. The best results were obtained in the Michael addition between **4a** and **5a** with a flow rate 0.005 mL min^{-1}. A complete conversion to the desired product **3a** with *syn/anti* ratio approximately 3.2:1 was achieved during total operation time, however more than 16 h were required to pump 5 mL of the starting material through the system (Table 1, entry 1–5). In contrast, when a flow rate of 0.5 mL min^{-1} was used, 1 h 40 min were sufficient for a single run, high *syn/anti* ratio 4.5:1 was observed, but the conversion dropped to 17 %. As a compromise, the flow rate was set to 0.01 mL min^{-1} to achieve a conversion not exceeding 50 % and syn/anti ratio 3.8:1. Next, the catalytic robustness was investigated. For this purpose, the reaction was performed with a double amount of substrates, under optimal flow rate 0.005 mL min^{-1}. To our delight, catalyst **cat. 2** remained active for most of the reaction time leading to obtaining the desired product **3a** with complete conversion and *syn/anti* ratio approximately 4.0:1. However, after 9 h the catalytic activity slightly decreased (Table 1, entry 6–10). For further optimization, the temperature impact was investigated. A significant increase in *syn/anti* ratio of approximately 6.6:1 was observed when the reaction between **4a** and **5a** was performed at 0° C with a flow rate 0.005 mL min^{-1}, however the conversion range was from 56 to 45 % (Table 1 entry 11–16). Finally, the reaction between **4b** and **5b** was performed in optimal reaction condition (flow rate 0.005 mL min^{-1}) to achieve complete conversion to desired product **3b** with *syn/anti* ratio approximately 3.0:1 (Table 1, entry 17–20).

Table 1. Optimization of the Michael addition reaction between aldehydes **4a/b** and nitroolefins **5a/b** catalyzed by Wang resin solid support Hayashi–Jørgensen catalyst **cat. 2** in continues flow.

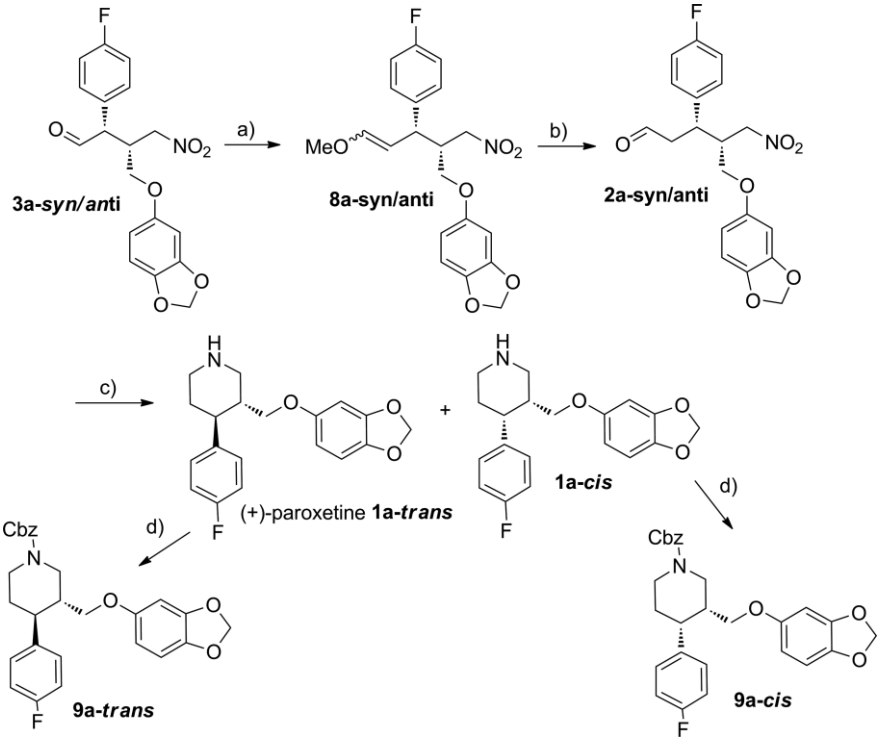


Entry	Reagent and condition	Reaction time [h]	Conversion [%][a]	syn/anti[a]
1	A	4	100	2.9:1
2	A	6	100	3.0:1
3	A	9	100	3.2:1
4	A	11	100	3.3:1
5	A	15	98	3.3:1
6	B	3	100	3.3:1
7	B	5	100	3.7:1
8	B	7	100	3.8:1
9	B	9	89	4.0:1
10	B	11	73	4.2:1
11	C	4	56	6.5:1
12	C	6	53	6.5:1
13	C	8	51	6.6:1
14	C	10	49	6.6:1
15	C	12	47	6.7:1
16	C	14	45	6.7:1
17	D	7	100	2.7:1
18	D	9	100	2.9:1
19	D	11	100	3.0:1
20	D	15	100	3.2:1

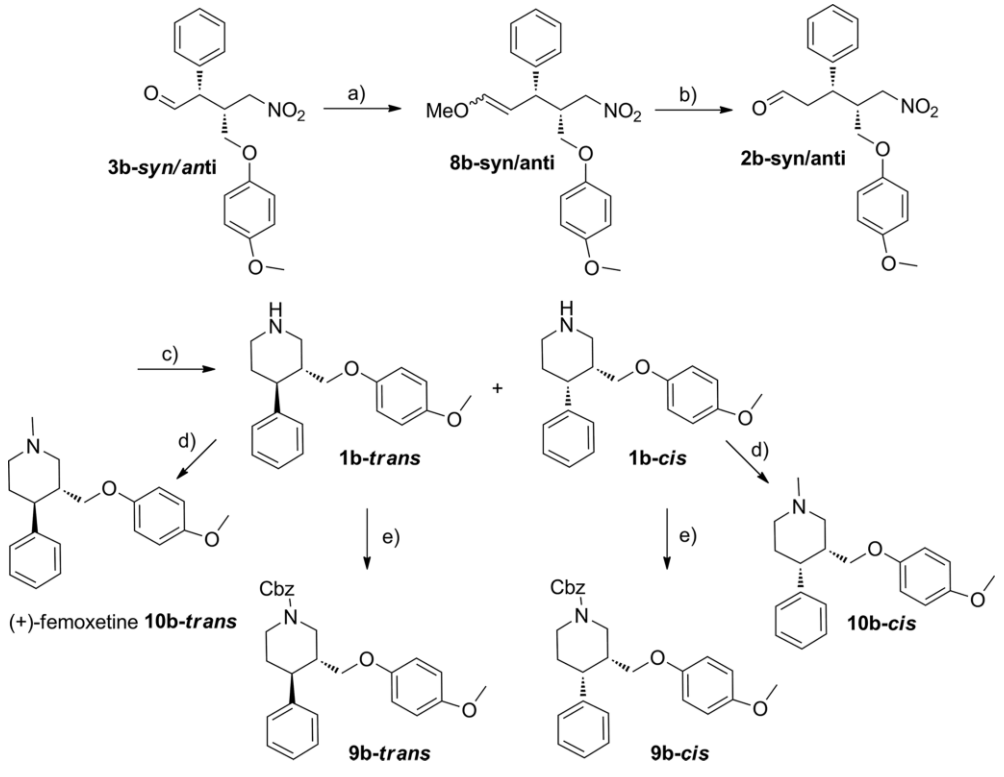
[a] *Reagent and Condition:* **A: 5a** (20 mg, 1.0 equiv.), **4a** (25 mg, 2.0 equiv.), $PhCO_2H$ (2.2 mg, 20 mol-%), **cat. 2** (13.4 mg, 15 mol-%)(catalyst loading 1.0 mmol/g), $CHCl_3$ (5 mL), r.t., total operation time (16 h 40 min.), flow rate 0.005 mL min^{-1}; **B: 5a** (40 mg, 1.0 equiv.), **4a** (50 mg, 2.0 equiv.), $PhCO_2H$ (4.4 mg, 20 mol-%), **cat. 2** (13.4 mg, 7.5 mol-%)(catalyst loading 1.0 mmol/g), $CHCl_3$ (5 mL), r.t., total operation time (16 h 40 min.), flow rate 0.005 mL min^{-1}; **C: 5a** (40 mg, 1.0 equiv.), **4a** (50 mg, 2.0 equiv.), $PhCO_2H$ (4.4 mg, 20 mol-%), **cat. 2** (13.4 mg, 7.5 mol-%)(catalyst loading 1.0 mmol/g), $CHCl_3$ (5 mL), 0° C, total operation time (16 h 40 min.), flow rate 0.005 mL min^{-1}; **D: 5b** (20 mg, 1.0 equiv.), **4b** (23 mg, 2.0 equiv.), $PhCO_2H$ (2.2 mg, 20 mol-%), **cat. 2** (14.3 mg, 15 mol-%)(catalyst loading 1.0 mmol/g), $CHCl_3$ (5 mL), r.t., total operation time (16 h 40 min.), flow rate 0.005 mL min^{-1}; [a] determined by ^{1}H-NMR.

It is worth emphasizing that, *ee* ratio remains constant in investigated flow condition, and does not differ from that obtained in bath procedure.

Having established the suitable conditions in the organocatalytic Michael addition catalyzed by a solid supported Hayashi–Jørgensen catalyst **cat. 2**, we were ready to examine transformation of γ-nitroaldehyde **3a** into the desired (+)-paroxetine **1a-*trans***. For this purpose, the requisite one-carbon elongation was achieved by using a Wittig olefination of the crude mixture of γ-nitroaldehyde **3a** with methoxymethyltriphenylphosphoniumchloride in the presence of LiHMDS. After short column chromatography corresponding product **8a** was obtained in overall yield 68 % after two steps as a mixture of E/Z and *syn/anti* isomers. Subsequent hydrolysis of olefin **8a** promoted



Scheme 6. *Reagents and conditions*: a) (methoxymethyl)-triphenylphosphonium chloride (5.0 equiv.), LiHMDS (1.0 M in THF)(4.8 equiv.), THF, 0[°] C, 1 h, 68 % (after two steps); b) 5 M aq. HCl, THF, bp, 1 h; c) Zn powder (25.0 equiv.), MeOH:AcOH (1:1), 0[°] C to r.t., 24 h, **1a-trans** 52 % (after two steps), **1a-cis** 12 % (after two steps); d) Et_3N (1.0 equiv.), benzyl chloroformate (1.0 equiv.), CH_2Cl_2, 0[°] C to r.t., 24 h, **9a-*trans*** (71 %, *ee* 80 %), **9a-*cis*** (71 %, *ee* 53 %).



Scheme 7. *Reagents and conditions*: a) (methoxymethyl)-triphenylphosphonium chloride (5.0 equiv.), LiHMDS (1.0 M in THF)(4.8 equiv.), THF, 0[°] C, 1 h, 62 % (after two steps); b) 5 M aq. HCl, THF, bp, 1 h; c) Zn powder (25.0 equiv.), MeOH:AcOH (1:1), 0[°] C to r.t., 24 h, **1b-*trans*** 45 % (after two steps), **1b-*cis*** 14 % (after two steps); d) $NaCNBH_3$ (3.0 equiv.), formaldehyde (37 %) (1.5 equiv.), AcOH (one drop), MeOH, 0[°] C to r.t., overnight, **10b-*trans*** (96 %), **10b-*cis*** (95 %); e) Et_3N (1.0 equiv.), benzyl chloroformate (1.0 equiv.), CH_2Cl_2, 0[°] C to r.t., 24 h, **9b-*trans*** (72 %, *ee* 75.4 %), **9b-*cis*** (73 %, *ee* 51.8 %).

by hydrochloric acid in boiling THF was provided to aldehyde **2a** as an inseparable mixture of *syn*/*anti* isomer. Aldehyde **2a** turned out to be unstable, and it decomposed during purification on column chromatography. **2a** was not purified, but after aqueous workup it was subjected directly to the final reductive cyclization step. The reductive cyclization reaction was performed with Zn powder (25 equiv.) in a mixture of acetic acid and methanol (1:1) at 0° C to room temperature over 24 h. After workup, the obtained mixtures of diastereomeric paroxetine were separated to single isomers by column chromatography to afford (+)-paroxetine **1a-*trans*** in overall yield 52 %, and 4-*epi*-(+)-Paroxetine **1a-*cis*** in overall yield 12 % after two steps. The relative configuration of both **1a-*trans*** and **1a-*cis*** isomers was confirmed on the basis of the analysis of NOE experiments. The optical purity of **1a-*trans*** and **1a-*cis*** was established after transformation to corresponding Cbz derivatives **9a-*trans*** and **9a-*cis***, and it was found to be 80 % for **9a-*trans***, and 53 % for **9a-*cis*** (Scheme 6).

The same reaction sequence as shown in Scheme 7 was used for the preparation of (+)-femoxetine **10b**. The crude mixture of γ-nitroaldehyde **3b** (*syn*/*anti* 3:1) was submitted Wittig olefination leading to mixture of E/Z and *syn*/*anti* **8b** in overall yield 62 % after two steps. Then, hydrolysis of olefin **8b** with hydrochloric acid yielded δ-nitroaldehyde **2b**, which was used directly for the next step without purification. Based on the previous experiment, the treatment of δ-nitroaldehyde **2b** with zinc powder (25.0 equiv.) in a mixture of acetic acid and methanol gave the mixture of diastereomeric piperidines which were separated to single isomers by column chromatography to afford **1b-*trans*** in overall yield 45 %, and **1b-*cis*** in overall yield 14 % after two steps. The relative configuration of the isomer **1b-*trans*** and **1b-*cis*** was confirmed on the basis of the analysis of NOE experiments, in turn optical purity was establish for Cbz derivatives **9b-*trans*** (*ee* 75 %) and **9b-*cis*** (*ee* 52 %). In the final methylation step, piperidine **1b-*trans*** was treated with formaldehyde followed by $NaCNBH_3$ in the presence of a catalytic amount of acetic acid in methanol to furnish (+)-femoxetine **10b** in 96 % yield. The analogues transformation for **1b-*cis*** lead to 4-*epi*-(+)-femoxetine **10b-*cis*** in yield 95 %.

Conclusions

In summary, asymmetric total synthesis of (+)-paroxetine and (+)-femoxetine involving organocatalytic Michael addition reaction as the key step has been reported. As it has been demonstrated, high efficiency, selectivity, and robustness in asymmetric Michael reactions catalyzed by immobilized Hayashi–Jørgensen catalyst was achieved in batch as well as in continues flow. The target molecules were obtained with an overall yield of 35 % (4 steps started from Michael addition) and 80 % *ee* for (+)-paroxetine, and 27 % (5 steps started from Michael addition) and 75 % *ee* for (+)-femoxetine. An equally important advantage over the methods developed so far lies in the simple route procedure employment of a readily available and inexpensive substrate. The synthetic strategy presented above can be regarded as a general method for preparation of piperidine core structure having two *trans*-substituents at C3 and C4.

Experimental Section

The synthesis of Hayashi–Jørgensen Catalyst (cat. 1)

The Hayashi-Jorgensen Catalyst **cat. 1** was obtained according to the literature procedure.[12]

The synthesis of Wang Resin-Supported Hayashi–Jørgensen Catalyst (cat. 2)

The Wang resin-supported Hayashi-Jorgensen Catalyst **cat. 2** was obtained according to the literature procedure.[13]

Synthesis of Nitroolefins 5a and 5b. General Procedure.

To a solution of sesamol or 4-methoxyphenol (14.48 mmol), in dry DMF (15 mL), potassium carbonate (2.2 g, 15.93 mmol, 1.1 equiv.) and bromoacetaldehyde diethyl acetal (2.4 mL, 15.93 mmol, 1.1 equiv.) were added under argon. The reaction mixture was heated to reflux and stirred overnight. After complete conversion of the starting alcohol (TLC control, 1:3 AcOEt/hexanes), the reaction mixture was diluted with AcOEt (20 mL) and washed with H_2O (20 mL). After phase separation, the aqueous layer was washed with AcOEt (3 × 10 mL). The combined organic layers were washed with H_2O (30 mL) and brine (30 mL), dried with Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude product **6a** (3.498 g, 95 %) or **6b** (3.375 g, 97 %), which was used to the next step without purification.

5-(2,2-Diethoxyethoxy)benzo[*d*][1,3]dioxole (6a); brown oil; R_f = 0.52 (1:3 AcOEt/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.69 (d, J = 8.5 Hz, 1H), 6.52 (d, J = 2.5 Hz, 1H), 6.34 (dd, J = 8.5, 2.5 Hz, 1H), 5.91 (s, 2H), 4.80 (t, J = 5.2 Hz, 1H), 3.93 (d, J 5.2 Hz, 2H), 3.75 (dq, J = 9.3, 7.1 Hz, 2H), 3.63 (dq, J = 9.3, 7.0 Hz, 2H), 1.24 (t, J = 7.1 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 154.2, 148.2, 141.9, 107.9, 105.9, 101.2, 100.5, 98.4, 69.5, 62.5, 15.3; HRMS (ESI-TOF) *m/z* calcd. for $C_{13}H_{18}NaO_2$ [M + Na^+] 277.1052, found 277.1047.

1-(2,2-Diethoxyethoxy)-4-methoxybenzene (6b); brown oil; R_f = 0.53 (1:3 AcOEt/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 6.88–6.85 (m, 2H), 6.84–6.80 (m, 2H), 4.81 (t, J = 5.2 Hz, 1H), 3.96 (d, J = 5.2 Hz, 2H), 3.80–3.73 (m, 5H), 3.63 (dq, J = 9.4, 7.0 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 154.0, 152.8, 115.7, 114.6, 100.6, 69.3, 62.5, 55.7, 15.3; HRMS (ESI-TOF) *m/z* calcd. for $C_{13}H_{20}NaO_4$ [M + Na^+] 263.1259, found 263.1254.

To a solution of **6a** or **6b** (14.0 mmol), in acetone/H_2O (10:1, 15 mL), *p*-toluenesulfonic acid (241 mg, 1.4 mmol, 10 mol-%) was added. The reaction mixture was heated to 65° C, and stirred until complete conversion of substrate **6a** or **6b** (TLC control, 1:3 AcOEt/hexanes). After that, the mixture was cooled to room temperature, diluted with Et_2O (20 mL) and H_2O (20 mL). After phase separation, the aqueous layer was washed with Et_2O (3 × 10 mL). The combined organic layers were washed brine (30 mL), dried with Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude aldehyde **7a** or **7b**, which was used directly to the next step without purification.

2-(Benzo[*d*][1,3]dioxol-5-yloxy)acetaldehyde (7a); brown oil; R_f = 0.13 (1:3 AcOEt/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.83 (t, J = 1.0 Hz, 1H), 6.71 (d, J = 8.2 Hz, 1H), 6.53 (d, J = 2.4 Hz, 1H), 6.28 (dd, J = 8.5, 2.5 Hz, 1H), 5.94 (s, 2H), 4.50 (d, J 1.0 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 199.4, 153.1, 148.6, 142.7, 108.0, 105.6, 101.4, 98.4, 73.7; HRMS (ESI-TOF) *m/z* calcd. for $C_{10}H_{12}NaO_5$ [M + MeOH + Na^+] 235.0582, found 235.0576.

2-(4-Methoxyphenoxy)acetaldehyde (7b); brown oil; R_f = 0.13 (1:3 AcOEt/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.85 (t, J = 1.1 Hz, 1H), 6.86–6.85 (m, 4H), 4.52 (d, J = 1.0 Hz, 2H), 3.77 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 199.8, 154.7, 151.8, 115.7, 114.9, 73.5, 55.7;

HRMS (ESI-TOF) *m/z* calcd. for $C_{10}H_{14}NaO_4$ [M + MeOH + Na^+] 221.0790, found 221.0784.

To a solution of aldehyde **7a** or **7b** (14.0 mmol) in 50 mL of dry toluene, nitromethane (7.58 mL, 140 mmol, 10.0 equiv.) and *N*,*N*,*N*,*N*-tetramethylguanidine (177 μL, 1.4 mmol, 10 mol-%) were added at 0 °C under argon. The resulting solution was stirred at the same temperature for 90 min, until complete conversion of aldehyde **7a** or **7b** (TLC control, 1:2 AcOEt/hexanes). Then MsCl (1.625 mL, 21 mmol, 1.5 equiv.) and Et_3N (2.927 mL, 21 mmol, 1.5 equiv.) were added at 0 °C and the reaction mixture was stirred for additional 40 min at the same temperature. Progress of the reaction was monitored by TLC (1:2 AcOEt/hexanes). After complete conversion, the reaction mixture was quenched with sat. aq. $NaHCO_3$ (50 mL). and diluted with AcOEt (50 mL). After phase separation, the aqueous layer was washed with AcOEt (3 × 30 mL). The combined organic layers were washed with brine (100 mL), dried with anhydr. Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude product **5a** or **5b**, which was purified by silica gel column chromatography, and then additionally recrystallized from Et_2O/hexanens (1:9).

(*E*)-5-((3-Nitroallyl)oxy)benzo[*d*][1,3]dioxole (5a); yellow crystal; m.p. 92–93° C; isolated yield 62 % (4 steps, starting from sesamol); R_f = 0.48 (1:2 AcOEt/hexanes); column chromatography (1:4 AcOEt/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.37 (dt, *J* = 13.3, 3.5 Hz, 1H), 7.30 (dt, *J* = 13.3, 2.1 Hz, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 6.51 (d, *J* = 2.5 Hz, 1H), 6.33 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.95 (s, 2H), 4.73 (dd, *J* = 3.4, 2.1 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 152.9, 148.6, 142.7, 140.3, 136.7, 108.1, 105.9, 101.4, 98.3, 64.7; HRMS (ESI-TOF) *m/z* calcd. for $C_{10}H_9NNaO_5$ [M + Na^+] 246.0378, found 246.0373.

(*E*)-1-Methoxy-4-((3-nitroallyl)oxy)benzene (5b); yellow crystal; m.p; 64–65° C isolated yield 48 % (4 steps, starting from 4-methoxyphenol); R_f = 0.47 (1:2 AcOEt/hexanes); column chromatography (1:4 AcOEt/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.38 (dt, *J* = 13.3, 3.5 Hz, 1H), 7.32 (dt, *J* = 13.3, 2.1 Hz, 1H), 6.87–6.85 (m, 4H), 4.75 (dd, *J* = 3.5, 2.2 Hz, 2H), 3.78 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 154.7, 151.6, 140.2, 137.0, 115.7, 114.9, 64.5, 55.7; (ESI-TOF) *m/z* calcd. for $C_{10}H_{11}NNaO_4$ [M + Na^+] 232.0586, found 232.0580.

Synthesis of Aldehyde 4a and 4b. General Procedure.

To a solution of Dess–Martin periodinane (3.563 g, 8.4 mmol, 1.2 equiv.) in dry CH_2Cl_2 (20 mL), solution of 2-(4-fluorophenyl)ethan-1-ol or 2-phenylethan-1-ol (7.0 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise under argon at 0 °C. The reaction mixture was stirred at the same temperature for ca. 30 min. After complete conversion of substrate (TLC control, 1:3 AcOEt/hexanes), the reaction was quenched with sat. aq. $NaHCO_3$ (20 mL) and sat. aq. $Na_2S_2O_3$ (20 mL). The aqueous layer was washed with Et_2O (2 × 20 mL). The combined organic layers were washed sequentially with sat. aq. $NaHCO_3$ (20 mL), H_2O (3 × 20 mL) and brine (20 mL), dried with Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the aldehyde **4a** or **4b**, which was used directly to the next step without purification.

2-(4-Fluorophenyl)acetaldehyde (4a); colorless oil; R_f = 0.48 (1:3 AcOEt/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.74 (t, *J* = 2.2 Hz, 1H), 7.20–7.16 (m, 2H), 7.08–7.03 (m, 2H), 3.68 (d, *J* = 2.1 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 199.0, 162.2 (d, *J* = 246.0 Hz), 131.2 (d, *J* = 8.0 Hz), 127.6 (d, *J* = 2.8 Hz), 115.9 (d, *J* = 21.5 Hz), 49.6; HRMS (ESI-TOF) *m/z* calcd. for C_8H_7FNaO [M + Na^+] 161.0379, found 161.0374.

2-Phenylacetaldehyde (4b); colorless oil; R_f = 0.50 (1:3 AcOEt/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.75 (t, *J* = 2.4 Hz, 1H), 7.44–7.20 (m, 5H), 3.69 (d, *J* = 2.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 199.4, 131.9, 129.6, 129.0, 127.4, 50.6; HRMS (ESI-TOF) *m/z* calcd. for C_8H_8NaO [M + Na^+] 143.0473, found 143.0469.

Organocatalytic Michael Addition Reaction between 3a/b and 4a/b Catalyzed by Wang Resin-Supported Hayashi-Jorgensen Catalyst (cat. 2). General procedure in bath.

To a solution of nitroalkene **5a** or **5b** (0.45 mmol, 1.0 equiv.) in 3 mL of $CDCl_3$, Wang resin-supported Hayashi–Jørgensen catalyst **cat. 2** (68 mg, 0.068 mmol, 15 mol-%)(catalyst loading 1.0 mmol/g), benzoic acid (11 mg, 0.09 mmol, 20 mol-%) and a solution of aldehyde **4a** or **4b** (0.68 mmol, 1.5 equiv.) in 3 mL of $CDCl_3$ were added. The resulting mixture was stirred at room temperature until complete conversion of starting nitroalkene **5a/b** (reaction progress was monitored by TLC 1:3 AcOEt/hexanes and ^{1}H-NMR). Then, the catalyst **cat. 2** was filtered; washed with $CHCl_3$ (3 × 2 mL), and then dried in a high vacuum to afford 68 mg (100 %) of the recovered catalyst. The combined $CHCl_3$ filtrates were concentrated under reduced pressure to give crude γ-nitroaldehyde **3a** or **3b**, which were used for the next step without further purification.

Organocatalytic Michael Addition Reaction between 3a/b and 4a/b Catalyzed by Wang Resin-Supported Hayashi-Jorgensen Catalyst (cat. 2). General procedure in continues flow.

The Wang resin-supported Hayashi–Jørgensen catalyst **cat. 2** (13.4 mg, 0.0134 mmol)(catalyst loading 1.0 mmol/g), was placed in the fritted PTFE tube (0.3 mm ID, 6 cm length, 4.24 μL). The stationary phase was swollen and equilibrated by pumping $CHCl_3$ at a flow rate of 0.1 mL min^{-1} for 30 min through the system. Then a solution of nitroalkane **5a** or **5b** (0.09 mmol, 1.0 equiv.), aldehyde **4a** or **4b** (0.135 mmol, 1.5 equiv.) and benzoic acid (0.018 mmol, 20 mol-%) in $CHCl_3$ (5 mL) was pumped at a flow rate of 0.005 mL min^{-1} for 16 h 40 min. The solution flowing out of the system was collected for the time period indicated for each round (see Table 1). All volatile components of the collected mixture were removed on at reduced pressure and the obtained residue was used to determined conversion and diastereoselectivity by ^{1}H NMR spectroscopy. Pure conjugate addition product **3a** or **3b** was used for the next step without further purification.

(2*S*,3*R*)-4-(Benzo[d][1,3]dioxol-5-yloxy)-2-(4-fluorophenyl)-3-(nitromethyl)butanal; (3a-*syn*) and **(3a-*anti*)**; Inseparable mixture of diastereomers *syn*/*anti*; yellow oil; R_f = 0.31 (1:4 AcOEt/hexanes); major isomer **3a-*syn***: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.73–9.71 (m, 1H), 7.24–7.07 (m, 4H), 6.64 (d, *J* = 8.5 Hz, 1H), 6.34 (d, *J* = 2.5 Hz, 1H), 6.14 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.91–5.90 (m, 2H), 4.77 (dd, *J* = 13.1, 7.5 Hz, 1H), 4.69 (dd, *J* = 13.1, 4.5 Hz, 1H), 4.01 (d, *J* = 9.4 Hz, 1H), 3.78 (dd, *J* = 9.7, 3.6 Hz, 1H), 3.53 (dd, *J* = 9.7, 5.0 Hz, 1H), 3.31–3.25 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 197.7, 162.8 (d, *J* = 248.8 Hz), 153.3, 148.3, 142.4, 131.5 (d, *J* = 8.2 Hz), 127.6, 116.7 (d, *J* = 21.6 Hz), 108.0, 105.8, 101.3, 98.1, 74.3, 66.2, 56.3, 38.0; minor isomer **3a-*anti***: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.70 (d, *J* = 1.3 Hz, 1H), 7.24–7.06 (m, 4H), 6.70 (dd, *J* = 8.2, 4.1 Hz, 1H), 6.47 (d, *J* = 2.5 Hz, 1H), 6.30 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.93 (s, 2H), 4.35 (d, *J* = 3.2 Hz, 1H), 4.35–4.34 (m, 1H), 4.14–4.09 (m, 1H), 4.07 (dd, *J* = 9.7, 1.0 Hz, 1H), 4.00–3.98 (m, 1H), 3.45–3.39 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 197.0, 162.9 (d, *J* = 249.4 Hz), 153.3, 148.4, 142.4, 131.4 (d, *J* = 8.2 Hz), 127.6, 117.0 (d, *J* = 21.6 Hz), 108.0, 105.9, 101.3, 98.2, 74.1, 66.5, 56.3, 37.9; HRMS (ESI-TOF) *m/z* calcd. for $C_{10}H_{16}FNNaO_6$ [M + Na^+] 384.0858, found 384.0854; HPLC (Chiralcel OZ-H, 10 % *i*PrOH 90 % *n*-hexane, flow rate: 1.0 mL min^{-1},λ = 220 nm, 5 °C; 69 min, 76 min minor isomer (*anti*), 83 min, 95 min major isomer (*syn*).

(2*S*,3*R*)-4-(4-Methoxyphenoxy)-3-(nitromethyl)-2-phenylbutanal (3b-*syn*) and **(3b-*anti*)**; Inseparable mixture of diastereomers;

syn/anti; yellow oil; R_f = 0.32 (1:4 AcOEt/hexanes); major isomer **3b-*syn***: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.73–9.72 (m, 1H), 7.40–7.32 (m, 3H), 6.84–6.82 (m, 2H), 6.79–6.74 (m, 2H), 6.69–6.66 (m, 2H), 4.79 (dd, *J* = 13.1, 7.4 Hz, 1H), 4.71 (dd, *J* = 13.1, 4.6 Hz, 1H), 4.02–3.99 (m, 1H), 3.81 (dd, *J* = 9.7, 3.7 Hz, 1H), 3.73 (s, 3H), 3.56 (dd, *J* = 9.7, 5.3 Hz, 1H), 3.35–3.29 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 198.1, 154.4, 152.1, 133.0, 129.9, 129.6, 128.7, 115.7, 114.7, 74.4, 66.1, 57.2, 55.7, 38.1; **3b-*anti***: ^{1}H NMR (600 MHz, $CDCl_3$) δ = 9.71 (d, *J* = 1.4 Hz, 1H), 7.45–7.33 (m, 4H), 7.25–7.21 (m, 2H), 7.21–7.17 (m, 2H), 6.83 (s, 1H), 4.37 (dd, *J* = 13.6, 8.3 Hz, 1H), 4.33 (dd, *J* = 13.6, 4.3 Hz, 1H), 4.14 (dd, *J* = 9.8, 5.0 Hz, 1H), 4.07 (dd, *J* = 9.7, 1.2 Hz, 1H), 4.04–4.00 (m, 1H), 3.76 (s, 3H), 3.50–3.44 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 197.4, 154.5, 152.2, 131.9, 129.9, 129.7, 128.9, 115.7, 114.8, 74.3, 66.4, 57.1, 55.7, 37.8; (ESI-TOF) *m/z* calcd. for $C_{18}H_{19}NNaO_5$ [M + Na^+] 352.1161, found 352.1155; OZ-H, 10 % *i*PrOH 90 % *n*-hexane, flow rate: 1.0 mL min^{-1},λ = 220 nm, 5 °C; 32 min, 38 min minor isomer (*anti*), 45 min, 53 min major isomer (*syn*).

Synthesis of Paroxetine and Femoxetine. General Procedure.

Synthesis of Enol Ether 8a/b. General Procedure.

To a solution of (methoxymethyl)triphenylphosphonium chloride (1.7 g, 5.0 mmol, 5.0 equiv.) in 10 mL of dry THF, LiHMDS solution (1.0 M in THF)(4.8 mL, 4.8 mmol, 4.8 equiv.) was added dropwise under argon at 0 °C. The reaction mixture was stirred for 30 min at the same temperature, and then a solution of crude γ-nitroaldehyde **3a** or **3b** (1.0 mmol) in dry THF (10 mL) was added dropwise. The resulting mixture was stirred at the same temperature for ca. 30 min, until TLC analysis (1:4 AcOEt/hexanes) revealed consumption of the **3a/b**. After that, the reaction was quenched with sat. aq. NH_4Cl (20 mL). The aqueous layer was washed with AcOEt (3 × 10 mL). The combined organic layers were washed with brine (30 mL), dried with Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the residue, which was purified by short silica gel column chromatography (1:8 AcOEt/hexanes) to afford inseparable mixture of E/Z-enol ether **8a-*syn/anti*** (68 % after two steps) or **8b-*syn/anti*** (62 % after two steps), which was used directly for the next step.

5-(((2*R*,3*R*)-3-(4-Fluorophenyl)-5-methoxy-2-(nitromethyl)pent-4-en-1yl)oxy)benzo[d][1,3]dioxole; E/Z-(8a-*syn*) and **E/Z-(8a-*anti*)**; Inseparable mixture of diastereomers; yellow oil; R_f = 0.52 (1:4 AcOEt/hexanes); HRMS (ESI-TOF) *m/z* calcd. for $C_{20}H_{20}FNNaO_6$ [M + Na^+] 412.1172, found 412.1151.

1-Methoxy-4-(((2*R*,3*R*)-5-methoxy-2-(nitromethyl)-3-phenylpent-4-en-1-yl)oxy)benzene; E/Z-(8b-*syn*) and **E/Z-(8b-*anti*)**; Inseparable mixture of diastereomers; yellow oil; R_f = 0.53 (1:4 AcOEt/hexanes); HRMS (ESI-TOF) *m/z* calcd. for $C_{20}H_{23}NNaO_5$ [M + Na^+] 380.1474, found 380.1463.

Synthesis of Aldehyde 2a/b. General Procedure.

Obtained enol ether **8a** or **8b** was dissolved in THF (4 mL) and 5 M aq. HCl (1 mL) was added. The reaction mixture was refluxing until TLC analysis revealed complete hydrolysis of the starting enol ether **8a/b** (ca. 1 hours). Then the reaction was cooled to room temperature, diluted with AcOEt (10 mL) and neutralized with sat. aq. $NaHCO_3$ (20 mL). After phase separation, the aqueous layer was washed with AcOEt (3 × 10 mL). The combined organic layers were washed with brine (30 mL), and then dried with Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude aldehyde **2a** or **2b**, which was used directly to the next step without purification.

(3*S*,4*R*)-5-(Benzo[d][1,3]dioxol-5-yloxy)-3-(4-fluorophenyl)-4-(nitromethyl)pentanal; (2a-*syn*) and **(2a-*anti*)**; Inseparable mixture of diastereomers *syn/anti*; yellow oil; R_f = 0.33 (1:3 AcOEt/hexanes); HRMS (ESI-TOF) *m/z* calcd. for $C_{19}H_{18}FNNaO_6$ [M + Na^+] 398.1016, found 398.1010.

(3*S*,4*R*)-5-(4-Methoxyphenoxy)-4-(nitromethyl)-3-phenylpentanal (2b-*syn*) and **(2b-*anti*)**; Inseparable mixture of diastereomers *syn/anti*; yellow oil; R_f = 0.35 (1:3 AcOEt/hexanes); (ESI-TOF) *m/z* calcd. for $C_{20}H_{25}NNaO_6$ [M + MeOH + Na^+] 398.1580, found 398.1558.

General Procedure for Reductive Cyclization Reaction. Synthesis of (+)-Paroxetine 1a and 1b.

To a solution of aldehyde **2a** or **2b** (0.42 mmol) in 2 mL of MeOH, acetic acid (2.0 mL) was added, the mixture was cooled to 0 °C, and then Zn powder (686 mg, 10.5 mmol, 25.0 equiv.) was added in portion. The reaction was warmed gradually to room temperature and stirred overnight. Then the reaction was quenched with 4 M aq. NaOH to pH = 12, and diluted with AcOEt (5 mL). After phase separation, the aqueous layer was washed with AcOEt (5 × 3 mL). The combined organic layers were dried with Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude mixture of piperidines **1a-*trans*** and **1a-*cis*** or **1b-*trans*** and **1b-*cis***, which were separated by silica gel column chromatography (5:95 Et_3N/AcOEt).

(+)-Paroxetine (1a-*trans*); yellow oil isolated yield 52 % (after 2 steps, starting from **2a**); R_f = 0.08 (5:95 Et_3N/AcOEt); $[\alpha]_D^{22}$= +78.9 (c= 2.3; $CHCl_3$); ^{1}H NMR (600 MHz, C_6D_6) δ = 6.79–6.75 (m, 2H), 6.73–6.68 (m, 2H), 6.47 (d, *J* = 8.5 Hz, 1H), 6.38 (d, *J* = 2.5 Hz, 1H), 5.99 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.24 (d, *J* = 1.4 Hz, 1H), 5.23 (d, *J* = 1.3 Hz, 1H), 3.32 (dd, *J* = 9.4, 2.9 Hz, 1H), 3.24 (dd, *J* = 12.0, 3.5 Hz, 1H), 3.18 (dd, *J* = 9.3, 7.2 Hz, 1H), 2.80 (d, *J* = 11.9 Hz, 1H), 2.43 (t, *J* = 11.4 Hz, 1H), 2.38–2.33 (m, 1H), 2.28–2.22 (m, 1H), 1.85–1.79 (m, 1H), 1.47–1.41 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 161.89 (d, *J* = 243.9 Hz), 155.0, 148.8, 142.2, 140.5 (d, *J* = 3.2 Hz), 129.06 (d, *J* = 7.7 Hz), 115.52 (d, *J* = 21.0 Hz), 108.2, 105.9, 101.1, 98.2, 69.7, 50.6, 47.2, 44.8, 43.1, 35.6; HRMS (ESI-TOF) *m/z* calcd. for $C_{19}H_{21}FNO_3$ [M + H^+] 330.1505, found 330.1504.

4-*epi*-(+)-Paroxetine (1a-*cis*); yellow oil; isolated yield 12 % (after 2 steps, starting from **2a**); R_f = 0.11 (5:95 Et_3N/AcOEt); $[\alpha]_D^{22}$= +49.9 (c= 0.6; $CHCl_3$); ^{1}H NMR (600 MHz, C_6D_6) δ = 6.76–6.72 (m, 2H), 6.71–6.67 (m, 2H), 6.47 (d, *J* = 8.5 Hz, 1H), 6.45 (d, *J* = 2.4 Hz, 1H), 6.11 (dd, *J* = 8.5, 2.4 Hz, 1H), 5.23 (d, *J* = 1.2 Hz, 1H), 5.22 (d, *J* = 1.2 Hz, 1H), 4.17 (t, *J* = 9.4 Hz, 1H), 3.38 (dd, *J* = 9.1, 3.4 Hz, 1H), 3.26 (d, *J* = 11.8 Hz, 1H), 2.85 (d, *J* = 11.7 Hz, 1H), 2.52 (dt, *J* = 13.0, 3.9 Hz, 1H), 2.47 (dd, *J* = 11.8, 2.5 Hz, 1H), 2.30 (td, *J* = 11.7, 2.5 Hz, 1H), 2.06–2.00 (m, 1H), 1.57 (ddd, *J* = 25.0, 12.7, 4.2 Hz, 1H), 1.21–1.20 (m, 1H); ^{13}C NMR (126 MHz, C_6D_6) δ = 161.8 (d, *J* = 244.0 Hz), 155.2, 148.8, 142.0, 139.8 (d, *J* = 3.2 Hz), 128.81 (d, *J* = 7.6 Hz), 115.28 (d, *J* = 21.0 Hz), 108.2, 106.3, 101.0, 98.4, 65.7, 48.5, 47.2, 43.0, 40.5, 26.8; HRMS (ESI-TOF) *m/z* calcd. for $C_{19}H_{21}FNO_3$ [M + H^+] 330.1505, found 330.1504.

(3*R*,4*S*)-3-((4-Methoxyphenoxy)methyl)-4-phenylpiperidine; (1b-*trans*); colorless oil; isolated yield 45 % (after 2 steps, starting from **2b**); R_f = 0.09 (5:95 Et_3N/AcOEt); $[\alpha]_D^{22}$= +65.5 (c= 2.9; $CHCl_3$); ^{1}H NMR (600 MHz, C_6D_6) δ = 7.12–7.03 (m, 4H), 7.01–6.97 (m, 1H), 6.63–6.61 (m, 2H), 6.61–6.58 (m, 2H), 3.51 (dd, *J* = 9.4, 2.9 Hz, 1H), 3.38 (dd, *J* = 12.0, 3.5 Hz, 1H), 3.34 (dd, *J* = 9.3, 7.7 Hz, 1H), 3.25 (s, 3H), 2.84 (d, *J* = 12.0 Hz, 1H), 2.51 (t, *J* = 11.4 Hz, 1H), 2.46–2.35 (m, 2H), 2.07–2.01 (m, 1H), 1.61–1.54 (m, 2H); ^{13}C NMR (151 MHz, C_6D_6) δ = 154.0, 153.3, 144.7, 128.5, 126.3, 115.3, 114.5, 69.3, 54.8, 50.6, 47.1, 45.5, 42.8, 35.5; (ESI-TOF) *m/z* calcd. for $C_{19}H_{24}NO_2$ [M + H^+] 298.1807, found 298.1812.

(3*R*,4*S*)-3-((4-Methoxyphenoxy)methyl)-4-phenylpiperidine; (1b-*cis*); colorless oil; isolated yield 14 % (after 2 steps, starting from **2b**); R_f = 0.11 (5:95 Et_3N/AcOEt); $[\alpha]_D^{22}$= +59.2 (c= 0.9; benzene); ^1H NMR (600 MHz, C_6D_6) δ = 6.90–6.86 (m, 2H), 6.80–6.77 (m, 1H), 6.77–6.74 (m, 2H), 6.43–6.40 (m, 2H), 6.39–6.36 (m, 2H), 4.06 (t, *J* = 9.5 Hz, 1H), 3.32 (dd, *J* = 9.1, 3.0 Hz, 1H), 3.14 (d, *J* = 11.8 Hz, 1H), 3.00 (d, *J* = 4.8 Hz, 3H), 2.64 (d, *J* = 11.7 Hz, 1H), 2.47 (dt, *J* = 13.0, 4.1 Hz, 1H), 2.31 (dd, *J* = 11.8, 2.4 Hz, 1H), 2.12 (td, *J* = 11.7, 2.6 Hz, 1H), 2.00–1.94 (m, 1H), 1.49 (ddd, *J* = 24.9, 12.7, 4.2 Hz, 1H), 1.11 (dd, *J* = 12.8, 2.6 Hz, 1H); ^{13}C NMR (151 MHz, C_6D_6) δ = 153.9, 153.5, 144.0, 128.2, 127.1, 126.0, 115.5, 114.5, 65.0, 54.8, 48.3, 47.1, 43.6, 40.3, 26.5; (ESI-TOF) *m/z* calcd. for $C_{19}H_{24}NO_2$ [M + H^+] 298.1807, found 298.1775.

General procedure for *N*-methylation reaction. Synthesis of (+)-Femoxetine 10b.

To a solution of piperidine **1b-*trans*** or **1b-*cis*** (60 mg, 0.2 mmol) in MeOH (2 mL), 37 % aq. solution of formaldehyde (23 μL, 0.31 mmol, 1.5 equiv.) and acetic acid (one drop) were added. The resulting solution was then cooled to 0 °C, $NaCNBH_3$ (38 mg, 0.61 mmol, 3.0 equiv.) was added, and the reaction mixture was warmed to room temperature and stirred overnight. After complete conversion of the starting amines **1b-*trans*/*cis*** (TLC control, 5:95 MeOH/CH_2Cl_2), the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with 15 % aq. solution of NaOH (5 mL) and sat. aq. NaCl (5 mL). The organic layer was dried with Na_2SO_4 and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography (5:95 MeOH/CH_2Cl_2) to afford 60 mg (96 %) of **(+)-femoxetine (10b-*trans*)** or 59 mg (95 %) **of 4-*epi*-(+)-femoxetine (10b-*cis*)**.

(+)-Femoxetine (10b-*trans*); colorless oil; $[\alpha]_D^{22}$= +76.2 (c= 2.0; $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 7.30–7.26 (m, 2H), 7.23–7.17 (m, 3H), 6.78–6.73 (m, 2H), 6.69–6.65 (m, 2H), 3.73 (s, 3H), 3.62 (dd, *J* = 9.4, 3.0 Hz, 1H), 3.49 (dd, *J* = 9.4, 7.5 Hz, 1H), 3.25 (dd, *J* = 11.3, 2.2 Hz, 1H), 2.99 (d, *J* = 11.2 Hz, 1H), 2.44 (td, *J* = 11.7, 4.2 Hz, 1H), 2.37 (s, 3H), 2.35–2.27 (m, 1H), 2.11–2.00 (m, 2H), 1.94 (ddd, *J* = 24.7, 12.4, 3.9 Hz, 1H), 1.85 (ddd, *J* = 13.3, 6.7, 2.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 153.7, 153.1, 144.1, 128.6, 127.5, 126.5, 115.4, 114.5, 69.5, 59.7, 56.3, 55.7, 46.5, 44.4, 41.9, 34.3; (ESI-TOF) *m/z* calcd. for $C_{20}H_{26}NO_2$ [M + H^+] 312.1964, found 312.1953.

4-*epi*-(+)-Femoxetine (10b-*cis*); colorless oil; $[\alpha]_D^{22}$= +23.9 (c= 0.8; $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ = 7.35–7.29 (m, 2H), 7.25–7.19 (m, 3H), 6.74–6.69 (m, 2H), 6.64–6.60 (m, 2H), 4.22 (t, *J* = 9.5 Hz, 1H), 3.72 (s, 3H), 3.52 (dd, *J* = 9.1, 3.4 Hz, 1H), 3.21 (d, *J* = 11.3 Hz, 1H), 3.04 (d, *J* = 7.4 Hz, 1H), 2.96–2.90 (m, 1H), 2.40–2.34 (m, 1H), 2.30 (s, 3H), 2.21–2.16 (m, 1H), 2.14–2.06 (m, 1H), 1.83–1.76 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 153.5, 153.2, 128.4, 127.3, 126.3, 115.5, 114.4, 65.8, 57.7, 56.4, 55.7, 46.5, 42.5, 40.5, 29.7, 26.0; (ESI-TOF) *m/z* calcd. for $C_{20}H_{26}NO_2$ [M + H^+] 312.1964, found 312.1961.

General Procedure for Cbz Protection. Synthesis of 9a-*trans*/*cis* and 9a-*trans*/*cis*.

To a solution of piperidine **1a-*trans*/*cis*** or **1b-*trans*/*cis*** (0.3 mmol) in 3 mL of dry CH_2Cl_2, Et_3N (42 μL, 0.3 mmol, 1.0 equiv.) and benzyl chloroformate (43 μL, 0.3 mmol, 1.0 equiv.) were added at 0 °C under argon. The reaction mixture was warmed gradually to room temperature and stirred overnight. After complete conversion of the starting piperidine **1a-*trans*/*cis*** or **1b-*trans*/*cis*** (TLC control, 5:95 Et_3N/AcOEt), the reaction mixture was diluted with CH_2Cl_2 (5 mL) and quenched with sat. 1 M aq. HCl (3 mL). After phase separation, the organic layer was washed with brine (50 mL), and then dried with Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography.

Benzyl (3*R*,4*R*)-3-((benzo[d][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidine-1-carboxylate (9a-*cis*); colorless oil; isolated yield 71 %; column chromatography (1:6 AcOEt/hexanes); $[\alpha]_D^{23}$= +42.3 (c= 0.4; $CHCl_3$); *ee* 53 % (determined by HPLC); ^1H NMR (500 MHz, $CDCl_3$) δ = 7.25–7.19 (m, 4H), 7.19–7.14 (m, 3H), 7.02 (t, *J* = 8.6 Hz, 2H), 6.59 (d, *J* = 8.5 Hz, 1H), 6.25 (mj, 1H), 6.05 (d, *J* = 7.5 Hz, 1H), 5.87 (s, 2H), 5.17–4.93 (m, 2H), 4.64–4.58 (m, 1H), 4.54–4.43 (m, 1H), 3.76 (t, *J* = 9.4 Hz, 1H), 3.53–3.38 (m, 1H), 3.15–3.06 (m, 2H), 2.97–2.85 (m, 1H), 2.38–2.26 (m, 1H), 2.06–1.94 (m, 1H), 1.78 (d, *J* = 11.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 161.6 (d, *J* = 245.2 Hz), 154.2, 148.1, 141.6, 138.2 (d, *J* = 2.5 Hz), 128.53 (d, *J* = 7.9 Hz), 128.4, 127.8, 115.4 (d, *J* = 21.2 Hz), 107.8, 101.0, 67.2, 46.0, 44.3, 42.5, 40.0, 29.7; HRMS (ESI-TOF) *m/z* calcd. for $C_{27}H_{26}FNNaO_5$ [M + Na^+] 486.1693, found 486.1676; HPLC (Chiralcel OD-H, 10 % *i*PrOH 90 % *n*-hexane, flow rate: 1.0 mL min^{-1}, λ = 220 nm); 33 min minor isomer (3*S*,4*S*), 42 min major isomer (3*R*,4*R*).

Benzyl (3*R*,4*S*)-3-((benzo[d][1,3]dioxol-5-yloxy)methyl)-4-(4-fluorophenyl)piperidine-1-carboxylate (9a-*trans*); colorless oil; isolated yield 71 %; column chromatography (1:6 AcOEt/hexanes); $[\alpha]_D^{22}$= +24.1 (c= 1.6; $CHCl_3$); *ee* 80 % (determined by HPLC); ^1H NMR (500 MHz, $CDCl_3$) δ = 7.41–7.30 (m, 5H), 7.16–7.10 (m, 2H), 7.01–6.95 (m, 2H), 6.62 (d, *J* = 8.5 Hz, 1H), 6.35 (d, *J* = 2.0 Hz, 1H), 6.13 (dd, *J* = 8.4, 2.1 Hz, 1H), 5.88 (s, 1H), 5.18 (s, 2H), 4.51 (s, 1H), 4.33 (s, 1H), 3.61 (dd, *J* = 9.4, 2.5 Hz, 1H), 3.46 (dd, *J* = 9.4, 6.4 Hz, 1H), 2.90 (t, *J* = 12.1 Hz, 1H), 2.71 (t, *J* = 10.0 Hz, 1H), 2.09–1.98 (m, 1H), 1.87–1.80 (m, 1H), 1.79–1.67 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 161.6 (d, *J* = 244.8 Hz), 155.3, 148.2, 141.7, 138.9 (d, *J* = 3.2 Hz), 136.8, 128.7 (d, *J* = 7.8 Hz), 128.5, 128.0, 127.9, 115.5 (d, *J* = 21.2 Hz), 107.8, 105.6, 101.1, 98.0, 68.7, 67.2, 47.4, 44.5, 43.9, 29.7; HRMS (ESI-TOF) *m/z* calcd. for $C_{27}H_{26}FNNaO_5$ [M + Na^+] 486.1693, found 486.1691; HPLC (Chiralcel OD-H, 10 % *i*PrOH 90 % *n*-hexane, flow rate: 1.0 mL min^{-1}, λ = 220 nm); 30 min major isomer (3*R*,4*S*), 35 min minor isomer (3*S*,4*R*).

Benzyl (3*R*,4*R*)-3-((4-methoxyphenoxy)methyl)-4-phenylpiperidine-1-carboxylate (9b-*cis*); colorless oil; isolated yield 73 %; column chromatography (1:8 AcOEt/hexanes); $[\alpha]_D^{22}$= +61.1 (c= 1.4; $CHCl_3$); *ee* 52 % (determined by HPLC); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.41–7.12 (m, 10H), 6.71 (d, *J* = 8.9 Hz, 2H), 6.58 (d, *J* = 8.6 Hz, 2H), 5.18–4.88 (m, 2H), 4.64 (d, *J* = 13.4 Hz, 1H), 4.59–4.39 (m, 1H), 3.81 (t, *J* = 9.6 Hz, 1H), 3.73 (s, 3H), 3.58–3.44 (m, 1H), 3.11 (d, *J* = 12.9 Hz, 2H), 3.01–2.86 (m, 1H), 2.36 (s, 1H), 2.14–1.95 (m, *J* = 9.3 Hz, 1H), 1.95–1.71 (m, *J* = 12.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.9, 155.8, 153.7, 152.9, 142.6, 128.6, 128.4, 1278, 127.2, 126.6, 115.3, 114.5, 67.1, 55.7, 46.0, 44.4, 43.2, 40.0; HRMS (ESI-TOF) *m/z* calcd. for $C_{27}H_{29}NNaO_4$ [M + Na^+] 454.1994, found 454.1968; HPLC (Chiralcel AS-H, 10 % *i*PrOH 90 % *n*-hexane, flow rate: 1.0 mL min^{-1}, λ = 220 nm); 19 min minor isomer (3*S*,4*S*), 21 min major isomer (3*R*,4*R*).

Benzyl (3*R*,4*S*)-3-((4-methoxyphenoxy)methyl)-4-phenylpiperidine-1-carboxylate (9b-*trans*); colorless oil; isolated yield 72 %; column chromatography (1:8 AcOEt/hexanes); $[\alpha]_D^{22}$= +22.0 (c= 1.2; $CHCl_3$); *ee* 75 % (determined by HPLC); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.43–7.14 (m, 10H), 6.75 (d, *J* = 9.1 Hz, 2H), 6.67 (d, *J* = 9.0 Hz, 1H), 5.19 (s, 2H), 4.62–4.52 (m, *J* = 11.6 Hz, 1H), 4.40–4.28 (m, 1H), 3.73 (s, 3H), 3.65 (dd, *J* = 9.5, 2.7 Hz, 1H), 3.50 (dd, *J* = 9.4, 6.9 Hz, 1H), 2.90 (t, *J* = 12.2 Hz, 2H), 2.70 (t, *J* = 9.8 Hz, 1H), 2.18–2.05 (m, 1H), 1.91–1.66 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.3, 153.9, 152.9, 143.3, 136.9, 128.7, 128.5, 128.0, 127.9, 127.4, 127.0, 126.8, 115.5, 114.6, 68.6, 67.1, 55.7, 47.5, 44.8, 44.6, 41.8; HRMS (ESI-TOF) *m/z* calcd. for $C_{27}H_{29}NNaO_4$ [M + Na^+] 454.1994, found 454.1985;

HPLC (Chiralcel OD-H, 10 % *i*PrOH 10 % *n*-hexane, flow rate: 1.0 mL min^{-1}, λ = 220 nm); 20 min major isomer (3*R*,4*S*), 25 min minor isomer (3*S*,4*R*).

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Total Synthesis

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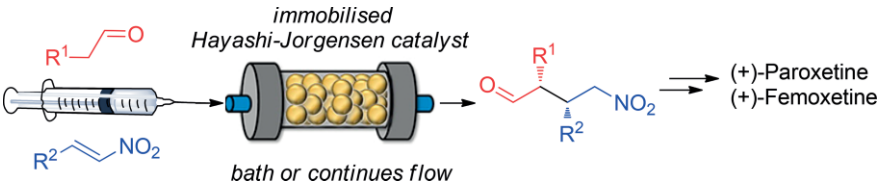
Total Asymmetric Synthesis of (+)-Paroxetine and (+)-Femoxetine



Total, asymmetric synthesis of (+)-Paroxetine and (+)-Femoxetine is reported. The key step is organocatalytic Michael addition of aldehydes to *trans*-nitroalkenes realized in bath or continues flow. High efficiency and selectivity in the Michael addition was achieved by application of Wang resin-supported Hayashi–Jørgensen catalyst.

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